SYNTHESIS OF α-THIO-β-CHLOROACRYLAMIDES INCLUDING CONTINUOUS PROCESSING AND APPLICATION TO THE FORMATION OF SULFUR CONTAINING HETEROCYCLES

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TABLE OF CHAPTERS

DECLARATION BY CANDIDATE

I hereby confirm that the body of work described within this thesis for the degree of Doctor of Philosophy, is my own research work, and has not been submitted for any other degree, either in University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

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Valérie M. Y. Cacheux Date: 23th March 2018

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ABSTRACT

α-Thio-β-chloroacrylamides are formed from the analogous α-thioamides through an oxidative reaction cascade. In this work, enhanced insight into the mechanistic pathway leading to these highly functionalised compounds has been achieved, in addition to demonstration of their potential as intermediates in the synthesis of pharmaceutically significant heterocycles.

The first chapter is an extensive literature review of the synthesis of sulfur containing heterocycles including 1,4-oxathiin, 1,4-dithiin, 1,4-thiazine and 1,4-benzothiazine derivatives. After an initial brief discussion of the importance of these compounds as therapeutic agents, common synthetic strategies and more exotic approaches are described. In some instances, the mechanisms involved in these transformations are outlined.

The second chapter focuses on a detailed investigation of a series of α-thio-β-chloroacrylamides and of the intermediates involved in the reaction cascade leading to their formations. A previously unseen pathway leading to the β-chlorosulfide has been revealed. The advantages associated with used of a continuous flow process enabled for the first time the scale up of the α-thio-β-chloroacrylamide transformation. Notably, the reaction cascade can be controlled through this continuous system, leading to selective recovery of individual components from the reaction. Efficient rapid quantification of reaction products, intermediates, starting material and by-products within the process through HPLC underpinned the development of an efficient flow process.

The third chapter discusses the synthesis of a range of functionalised α-thio-β-chloroacrylamides. The stereoselectivity and the efficiency of the transformation involved were seen to be highly sensitive to the precursor substituents and the solvent system employed. These novel derivatives enabled formation of 1,4-oxathiin, 1,4-thiazine and 1,4-benzothiazine derivatives *via* intramolecular cyclisation processes. Extension of the strategy to dithiin synthesis has also been investigated. The novel thiazine synthesised in this project was subsequently derivatised providing a broad range of new thiomorpholines. Investigation into the potential of these sulfur containing heterocycles as anti-cancer agents is described.

ABBREVIATIONS

%	Percentage
µL	Microlitre
µm	Micrometer
µM	Micromolar
^{1}H	Proton
^{13}C	Carbon (13)
2D	Two dimensional
α	Alpha
Å	Angstrom
ABq	AB quartet
Abs.	Absolute
Ac	Acetate
aq.	Aqueous
Ar	Aryl
AZT	Azidothymidine
β	Beta
B^{-}	Base
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
br.	broad
Bu	Butyl
n-BuLi	*n*-Butyllithium
t-BuOK	Potassium *tert*-butoxide
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^{o}C	Celsius degrees
ca.	Circa (approximately)
CCl_4	Tetrachloromethane
$CDCl_3$	Deuterated chloroform
cf.	Compare

cod	1,5-Cyclooctadiene
*m*CPBA	3-Chloroperoxybenzoic acid
Cq	Quaternary carbon
d	Chemical shift
Δ	Reflux
	Delta
d	Deuterated
d	Doublet
D_2O	Deuterated water
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublets of doublets
ddd	Doublets of doublets of doublets
DIEA	*N*,*N*-Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dt	Doublet of triplets
DTP	Developmental therapeutics program
e^-	electron
E	Entgegen
EDPBT	1,1'-(Ethane-1,2-diyl)dipyridium bistribromide
ELSD	Evaporative light scattering detector
Eq	Number of equivalent
ERK	Extracellular signal-regulated kinases
ES+	Positive electrospray ionization
ES-	Negative electrospray ionization

ESI	Electrospray ionization
Et	Ethyl
et al.	and others
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
Exp	experiment
FVP	Flash vacuum pyrolysis
g	gram
GABA	Gamma-aminobutyric acid
GI_{50}	Drug concentration at which 50% of growth is inhibited
h	Hour
H	Proton
HeLa	Henrietta Lacks
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
*h*v	Light
Hz	Hertz
i.e.	That is
J	Coupling constant
K	Kelvin
L	Liter
LC	Liquid chromatography
LC_{50}	Drug concentration at which 50% of cells are killed
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
Lit.	Literature
LR	Lawesson's reagent

LRMS	Low resolution mass spectrometry
m	*meta*
m	Multiplet
M	Mol/L
	Molecule
m/z	mass-to-charge ratio
MCF-7	Michigan cancer foundation-7
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Millilitre
mm	Millimeter
mmol	Millimole
MMPP	Magnesium monoperoxyphthalate
mol	Mole
mp	Melting point
MW	Microwave
NaH	Sodium hydride
NaOEt	Sodium ethoxide
Nap	Naphthalene
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NCI	National cancer institute
NCI-60	National cancer institute 60-cell line screening
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHC	*N*-Heterocyclic carbene
nm	Nanometer
NMR	Nuclear magnetic resonance

NOESY	Nuclear overhauser effect spectroscopy
Nu^-	Nucleophile
o	*ortho*
[omim]NO_3	1-Methyl 3-octylimidazolium nitrate
p	*para*
Pac	Phenacyl
PFA	Perfluoroalkoxy alkane
PGR	Plant growth regulator
Ph	Phenyl
Phth	Phthalimides
pKa	Acid dissociation constant
ppm	Parts per million
Prot	Protecting group
PSI	Pounds per square inch
PT	Proton transfer
PTSA	*p*-Toluenesulfonic acid
q	Quartet
®	Registered trademark
rt	Room temperature
RT	Reverse transcriptase
TLC	Thin layer chromatography
TMS	Tetramethylsilane
σ	Sigma
s	Singlet
SCE	Saturated Calomel Electrode
SCl_2	Sulfur dichloride
SM	Starting material
S_N	Nucleophilic substitution
t	*tertio*
t	Triplet
T	Temperature

TBAF	Tetra *n*-butylammonium fluoride
td	Triplet of doublets
TFA	Trifluoroacetic acid
TGI	Drug concentration at which total growth inhibition occurs
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TNF	Tumor necrosis factor
Tol	Toluene
tt	Triplet of triplets
U.S.	United State
USA	United State of America
UV	Ultra violet
V	Volt
n_{max}	Frequency of maximum absorption
via	Through or By way of
vs	Versus
X	Halogen
Z	Zusammen
$ZnCl_2$	Zinc chloride

CHAPTER 1

Synthesis of 1,4-oxathiin, 1,4-dithiin and 1,4-thiazine derivatives

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1. INTRODUCTION

Sulfur containing heterocyclic compounds have been extensively studied.[1-5] The synthesis of benzothiazines,[6-8] phenoxathiins,[9] thiazines[8, 10-14] and oxathiins[11] has been reviewed. However, in addition to 1,4-derivatives, these literature reviews also include discussion on the 1,2- and 1,3-derivatives, or focus on particular chemistry involved in the synthetic process and, therefore are not exhaustive. The goal of this review is to summarise the current state of knowledge for the synthesis of sulfur containing 1,4-heterocycles, including 1,4-oxathiin, 1,4-thiazine, 1,4-benzothiazine and 1,4-dithiin derivatives (Figure 1). Because of their promising diverse biological activities, extensive synthetic studies have been reported for these derivatives.

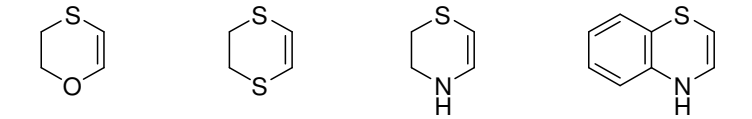


Figure 1

Since the discovery of Vitavax (Figure 2), a fungicide for preventing and controlling cereal smut and wheat rust in 1966, the chemistry of 1,4-oxathiins derivatives has attracted considerable attention by agrochemists and medicinal chemists.[15,16]

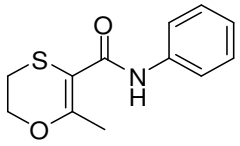
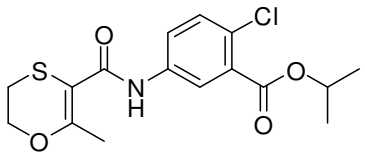


Figure 2

Subsequently, syntheses of analogues of Vitavax were performed, some of which have also become commercial fungicides.[16-19] Other analogues are used as anti-HIV agents,[20,21] and also as non-nucleoside reverse transcriptase inhibitors (*e.g.* oxathiine carboxanilide UC84, Figure 3).[22,23]

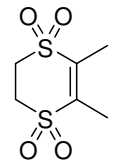


UC84

Figure 3

The 1,4-oxathiins and analogues also display a range of activity such as adrenoreceptor antagonists[24,25] and oestrogen receptor modulators.[26]

1,4-Dithiin is a ring system found in numerous biologically active compounds such as Dimethipin, a commercial plant growth regulator (Figure 4).[27] In addition to the herbicidal and PGR activities,[28-32] this scaffold also displays antimicrobial and antifungal activities.[29,33-36]



Dimethipin

Figure 4

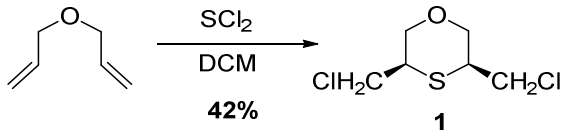
1,4-Thiazine and 1,4-benzothiazines derivatives are well known for their biological properties such as antifungal,[37] antibacterial,[38-43] antihypertensive,[44] anti-inflammatory,[45-47] anticancer,[48-50] anticonvulsant,[51] anthelmintic,[52] anti-HIV,[53] antimalarial,[54] etc. The 1,4-thiazine ring system is also known to play an important role in pigments and dyestuffs.[55-57]

2. SYNTHESIS OF 1,4-OXATHIIN DERIVATIVES

A wide range of synthetic routes are described for the 1,4-oxathiin scaffold formation. These can be classified according to the precursors employed; mercaptoethanols, mercaptoketones, 1,3-oxathiolanes or oxathianes. Also, use of sulfur dichloride and sulfenyl chloride as an external sulfur source is described in this section.

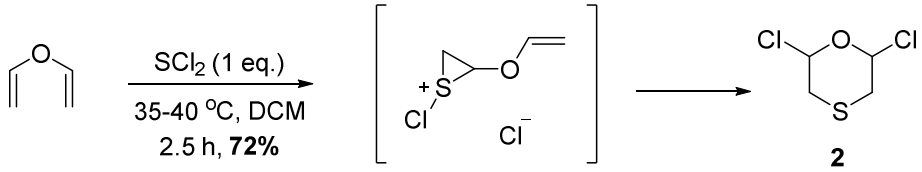
A. Using sulfur dichloride

In 1968, Lautenschlaeger reported the electrophilic addition of sulfur dichloride to diallyl ether leading to oxathianes **1** in 42% yield (Scheme 1).[58] For this transformation, no isomeric products of different size were observed.



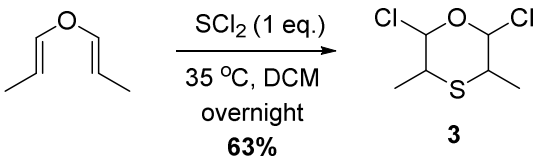
Scheme 1

The method was extended by Schoufs employing divinyl ether as diolefin, giving the cyclic derivative **2** in 72% yield, when the reaction was performed at 35-40 °C (Scheme 2).[59] *Cis* and *trans* derivatives were produced, and the isomeric ratio appeared to be strongly dependent on the solvent used, ranging from *trans* : *cis* 75 : 25 to 50 : 50. The solvent system also affected the yield of the transformation ranging from 30% to 77%. At lower reaction temperature (- 60 °C) polymeric products resulting from intermolecular addition were mainly obtained, along with ~10% of **2**.



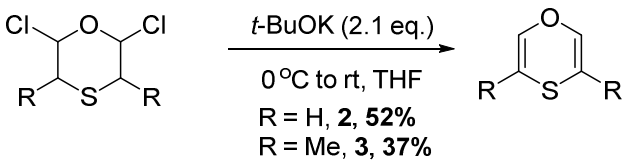
Scheme 2

When the reaction was performed with di-1-propenyl ether, much slower transformation was observed and a mixture of isomers **3** resulted (Scheme 3).



Scheme 3

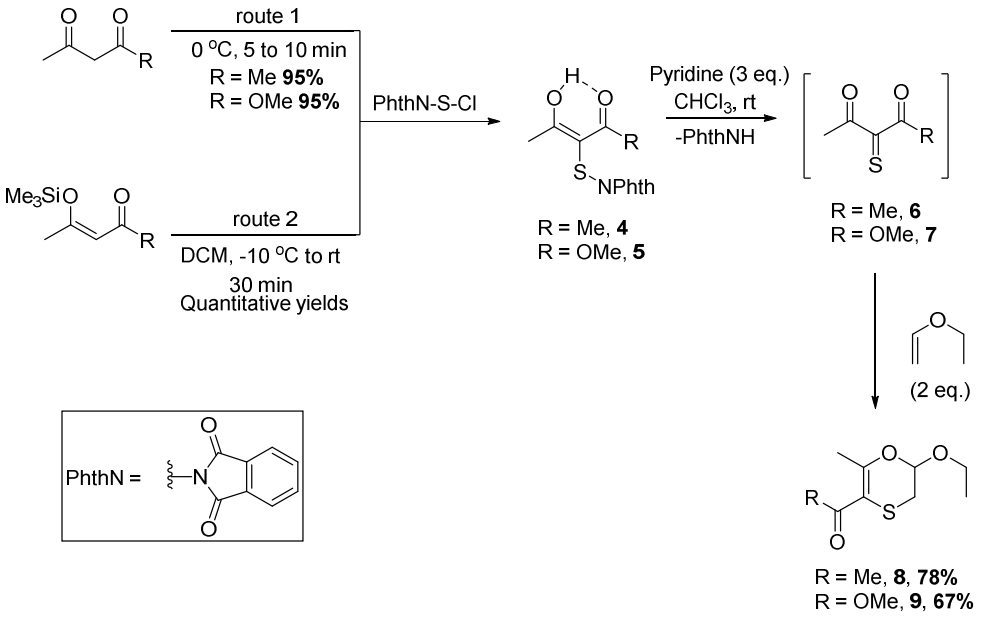
The corresponding 1,4-oxathiins of oxathianes **2** and **3** are easily accessible by hydrochloric acid elimination using *t*-BuOK in low to moderate yields (Scheme 4).



Scheme 4

B. From dithioester precursors

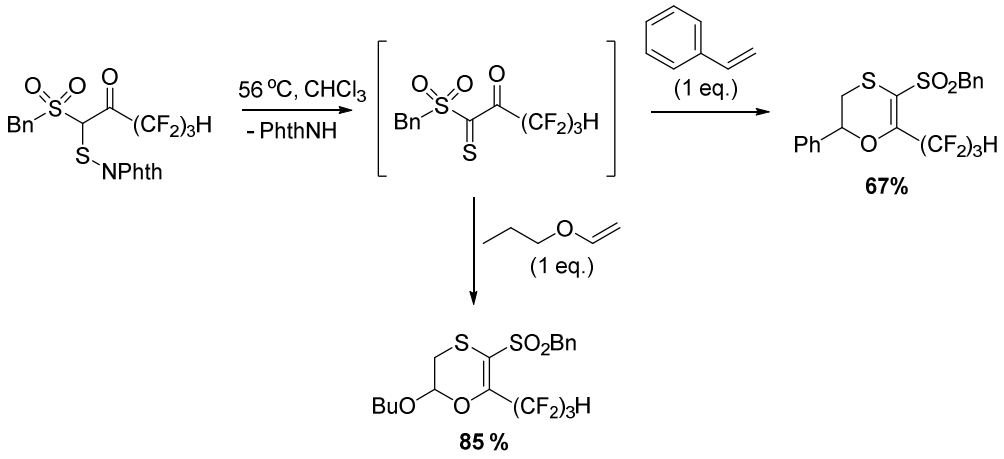
Capozzi *et al.* reported the formation of the 1,4-oxathiin heterocyclic system from α,α'-dioxothiophthalimides **4** and **5** with pyridine (Scheme 5).[60] The engendered α,α'-dioxothiones **6** and **7** undergo chemo- and regiospecific inverse electron demand Diels-Alder reactions with electron-rich alkenes. The employed α,α'-dioxothiophthalimides **4** and **5** could be generated by addition of phthalimidosulfenyl chloride either to an excess of acetylacetone or methyl acetoacetate (route 1, Scheme 5), or to an equimolar amount of silyl derivatives at -10 °C (route 2, Scheme 5).[61] Generation of **6** and **7** in the presence of ethyl vinyl ether afforded 1,4-oxathiins **8** and **9** in 78 and 67% yield respectively. The ring system formation was rationalized *via* the cycloaddition of thiones acting as dienes with the vinyl ether dienophiles. The formation of the cycloadducts as single compounds indicates that the reaction is regiospecific.



Scheme 5

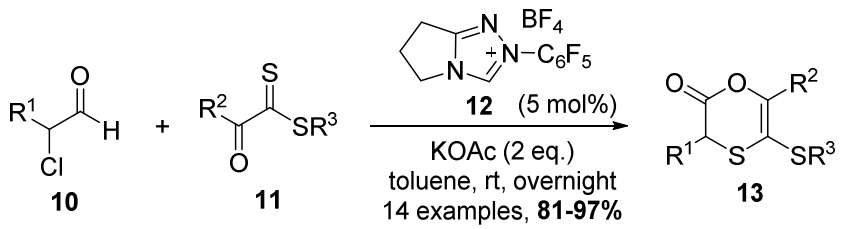
A large range of dienophiles can be employed for this transformation giving access to a wide series of 1,4-oxathiin derivatives. Thus, enol ethers, silyl enol ethers, vinyl sulfides and 2-vinylpyrrolidones are good dienophiles for cycloadditions with thiones **6** and **7**. In each case the cycloaddition is regiospecific and the cyclic adducts were isolated in good to excellent yield. The ketone carbonyl of the thiones is linked to the hetero-substituted carbon of the dienophile, and in all the cases the cycloaddition is chemoselective with the exclusive participation of the ketone carbonyl.

Derived from this study, Yemets *et al.*[62] developed a method from the phthalimidothio derivative allowing the synthesis of new fluorine containing 1,4-oxathiins (Scheme 6).



Scheme 6

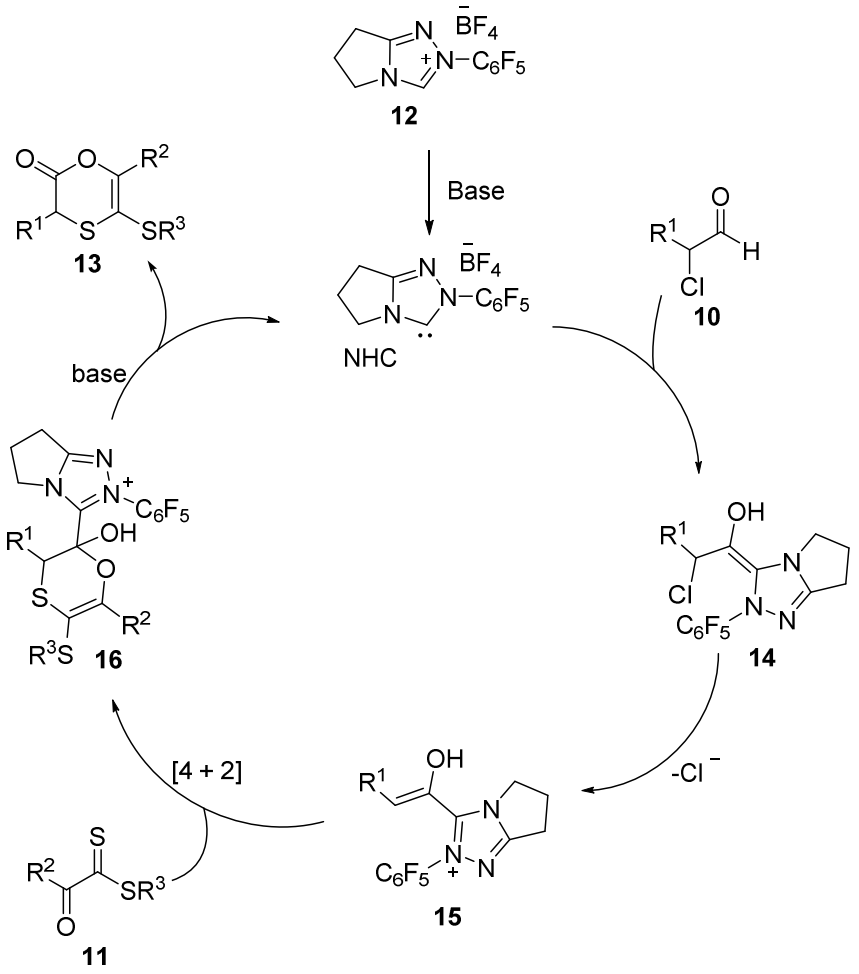
Recently, Wang *et al.* described [4+2] annulation of α-chloroaldehydes **10** with dithioesters **11** yielding the 1,4-oxathiin **13** under *N*-heterocyclic carbene (NHC) catalysis (Scheme 7).[63] The *N*-pentafluorophenyltriazolium **12** was found to produce the most efficient NHC catalyst for this transformation. The method developed provides **13** in excellent yields with large scope of substituents tolerated.



R^1 = Bn, n-Pr, n-Hex, n-Hep, i-Pr
R^2 = Ph, 4-ClC_6H_4, p-Tol, 3-ClC_6H_4, o-Tol, 2-Nap
R^3 = Bn, n-Bu, CH_2-α-Nap, CH_2-β-Nap

Scheme 7

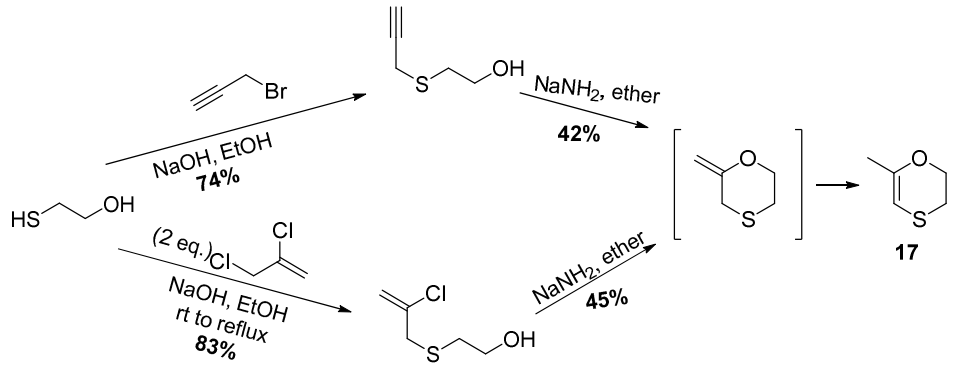
The proposed mechanism for the catalytic reaction is outlined in Scheme 8. First, addition of NHC to **10** generates the intermediate **14**, which gives **15** by elimination of chloride. Further [4+2] annulation of the enolate **15** with dithioester **11** produces **16**. Final fragmentation yields the 1,4-oxathiin **13** with regeneration of the NHC catalyst.



Scheme 8

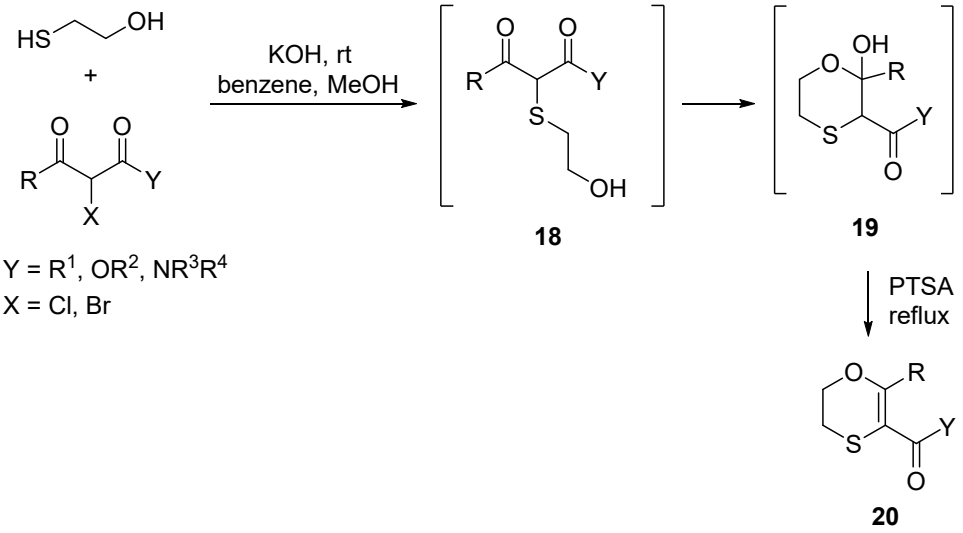
C. From mercaptoethanol

β,ɤ-Unsaturated-β'-hydroxy sulfides can be employed for the base-mediated preparation of oxathiin rings.[64,65] Treatment of 2-propargylthioethanol or a 2-(2-haloallylthio)ethanol with sodium amide in ether gave the thermodynamic endo-olefin **17** as the only cyclic product (Scheme 9).



Scheme 9

A common method for the preparation of oxathiin heterocycles is the condensation of 1,2-mercaptoethanol with a 2-halogenated-1,3-dicarbonyl compound under basic conditions, followed by mild acid promoted ring closure (Scheme 10). The reaction proceeds through two intermediates, **18** and **19**, neither of which require isolation.[66]



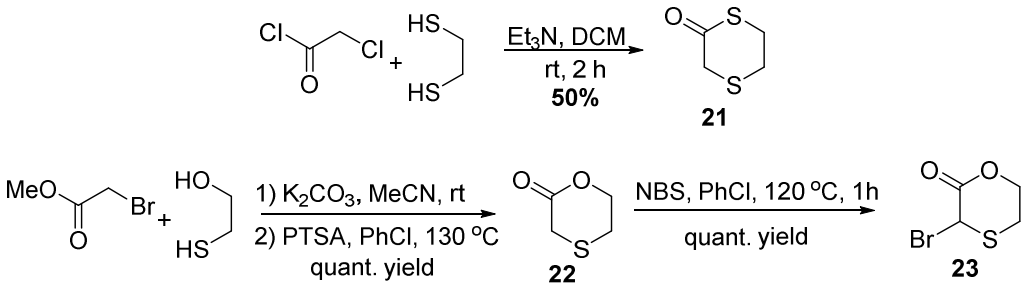
Scheme 10

The reaction between the 1,2-mercaptoethanol and 2-halogenated-1,3-dicarbonyl proceeds readily at ambient temperature in the presence of either an organic or inorganic base (such as carbonate or pyridine). The intermediate **18** cyclises readily to **19**, followed by dehydration to yield product **20**.

This procedure, originally patented for the preparation of Vitavax® and Plantavax® was recently extended to the solid supported synthesis of biologically active perfluoro oxathiins.[67]

Hiroi *et al.* reported the synthesis of 1,4-dithiane **21** from 1,2-ethanedithiol and chloroacetyl chloride on a small scale (Scheme 11).[68] Hellberg *et al.* extended the scope to the synthesis of 1,4-oxathiane **22**.[69,70] Equal amounts of mercaptoethanol and methyl bromoacetate react conveniently in the presence of potassium carbonate in acetonitrile, or sodium hydride in chlorobenzene, to give the corresponding methyl 2-(2-hydroxyethylthio) acetate in quantitative yield. The ring closure of the adduct to **22** is performed at 130 °C in the presence of catalytic amounts of *p*-toluenesulfonic acid.

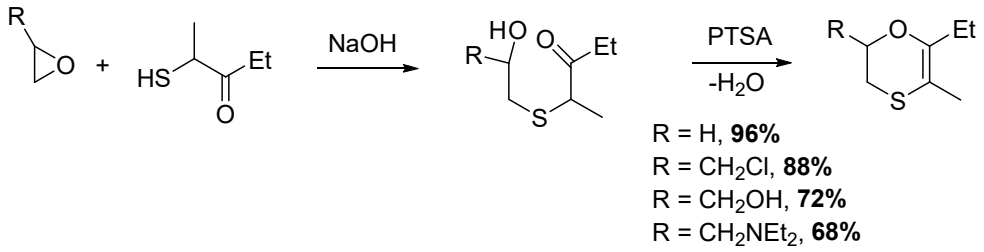
Further, functionalization of the generated oxathiane **22** can be performed easily when reacted with NBS giving the halo-derivative **23** in quantitative yield (Scheme 11).[71,72]



Scheme 11

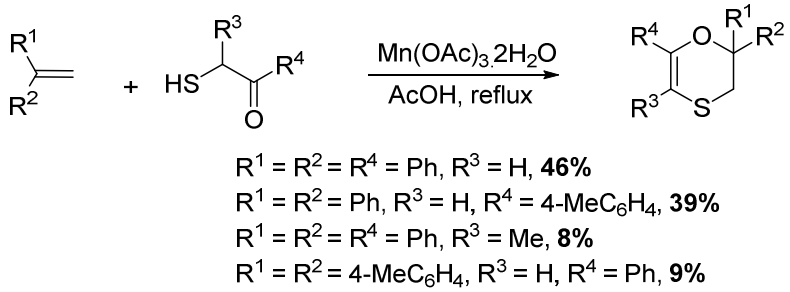
D. From mercaptoketone precursors

The reaction of oxiranes with α-mercaptoketones represents a further general approach to the synthesis of poly-substituted 1,4-oxathiin derivatives. The procedure developed by Asinger *et al.*[17] in 1971 allowed the formation of the internal double bond by a facile base-catalysed dehydratation (Scheme 12). The regio- and/or the stereoselectivity of the reaction was not discussed and the products were afforded in good to excellent yields. A wide range of substituents are tolerated, some examples of which are shown in Scheme 12.



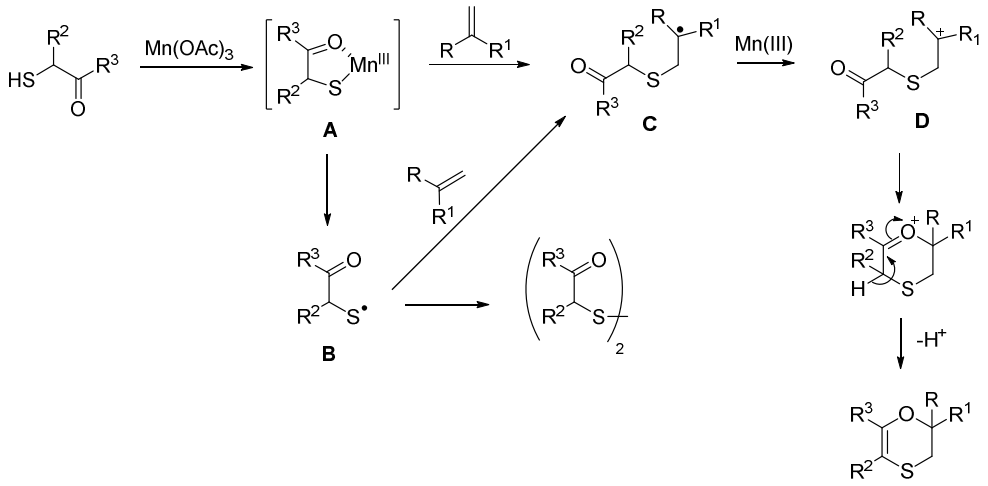
Scheme 12

Nguyen *et al.*[73] reported another approach by a Mn(III)-based reaction. Treatment of 1,1-disubstituted ethenes with α-mercaptoketones by manganese(III) acetate in acetic acid provided the 1,4-oxathiin derivative in poor to moderate yields (Scheme 13).



Scheme 13

It is envisaged that during the first step a complex **A** was formed by a ligand-exchange process between manganese(III) acetate with α-mercaptoketones (Scheme 14). Subsequently, the interaction of an alkene and **A** itself[18] or free thiyl radical **B** derived from the decomposition of **A** would produce a tertiary carbon radical **C**.[19,20] Although the formation of complex **A** was not established, isolation of the disulfide from the reaction mixture was seen and supports the intermediacy of **A** (30-50% yield). Oxidation of the radical **C** by manganese(III) acetate would give the corresponding carbocation **D**. Subsequent cyclisation and β-proton elimination would give the 2,3-dihydro-1,4-oxathiins.

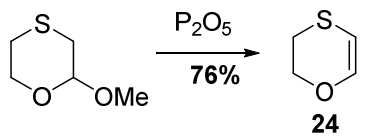


Scheme 14

E. From oxathiane

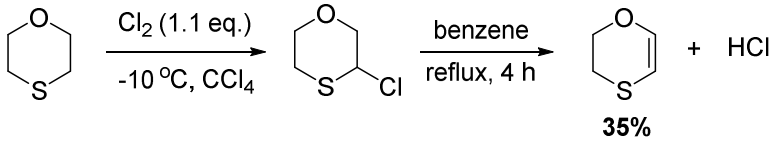
Few methods describe the transformation of a saturated 1,4-oxathiane ring to an oxathiin system.

In 1952, Parham *et al.* reported the synthesis of 1,4-oxathiin **24** by acid catalysed dealkoxylation of 2-methoxy-1,4-oxathiane with a small quantity of phosphorus pentoxide in 76% yield (Scheme 15).[74]



Scheme 15

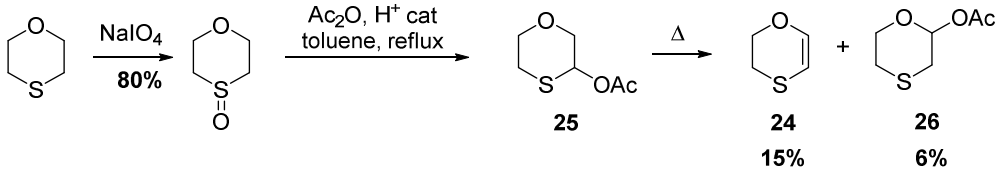
Another method employed α-chlorination of the oxathiane in tetrachloromethane to give the corresponding 3-chlorothioxane by rearrangement of the sulfonium chloride intermediate (Scheme 16).[75] Then, hydrogen chloride elimination under reflux conditions in benzene gave the 1,4-oxathiin derivative in 35% yield.



Scheme 16

The method described previously (*cf. Section 2.A.*, Scheme 4) also allows to access the 1,4-oxathiins from the chlorinated oxathiane using *t*-BuOK.[59]

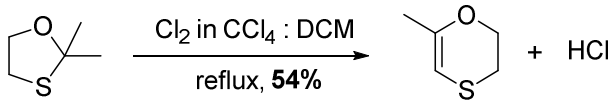
Hronowski and Szarek[76] described the synthesis of the 1,4-oxathiin **24** from the sulfoxide oxathiane derivative using the Pummerer reaction with *p*-toluenesulfonic acid monohydrate under reflux conditions in toluene (Scheme 17). Under these conditions, 3-acetoxy-1,4-oxathiane **25** is formed first, which then eliminates acetic acid to produce 1,4-oxathiin **24** as the main compound, followed by the appearance of 2-acetoxy derivative **26** (Scheme 17).



Scheme 17

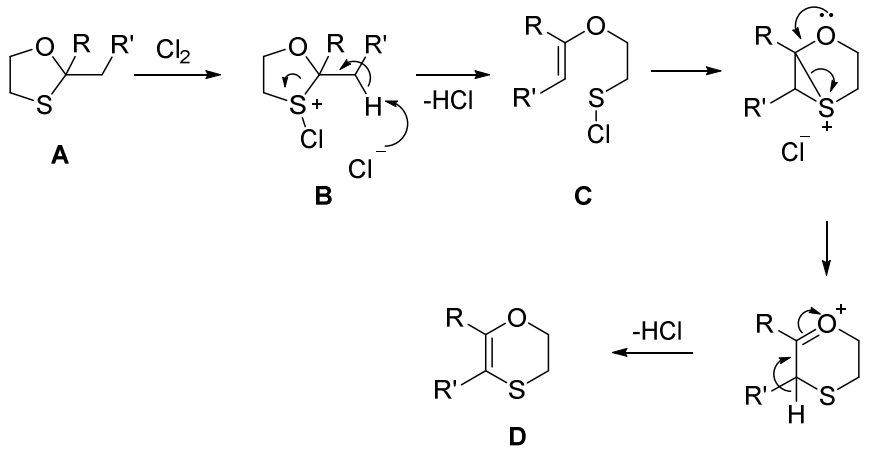
F. From 1,3-oxathiolane

Synthesis of 1,4-oxathiins from 1,3-oxathiolane rings is extensively reported. This transformation was firstly described by Wilson and Huang in 1965 who demonstrated that treatment of 2,2-dimethyl-1,3-oxathiolane with chlorine afforded the 2-methyl-1,4-oxathiin in 54% yield (Scheme 18).[77]



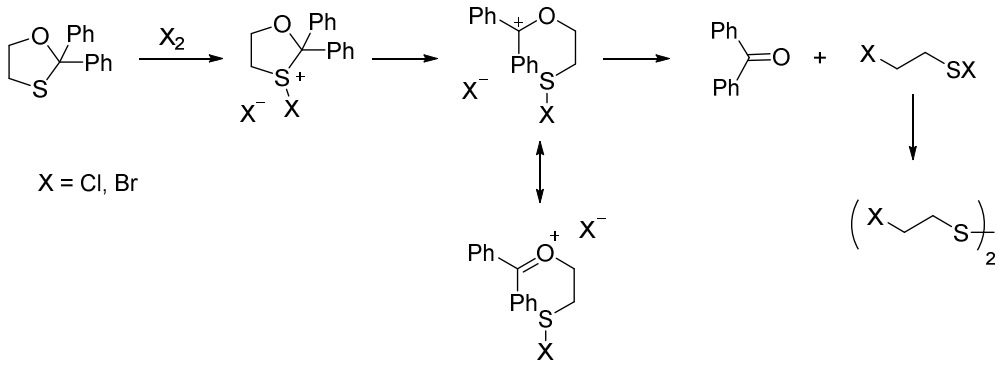
Scheme 18

The initial chlorination of 1,3-oxathiolanes **A** in a mixed solvent of methylene chloride and tetrachloromethane led to chlorosulfonium chloride **B** which was heated under reflux to promote the ring opening generating the sulfenyl chloride **C** which, in turn, gives rise to the six membered ring *via* a bicyclic episulfonium salt (Scheme 19).



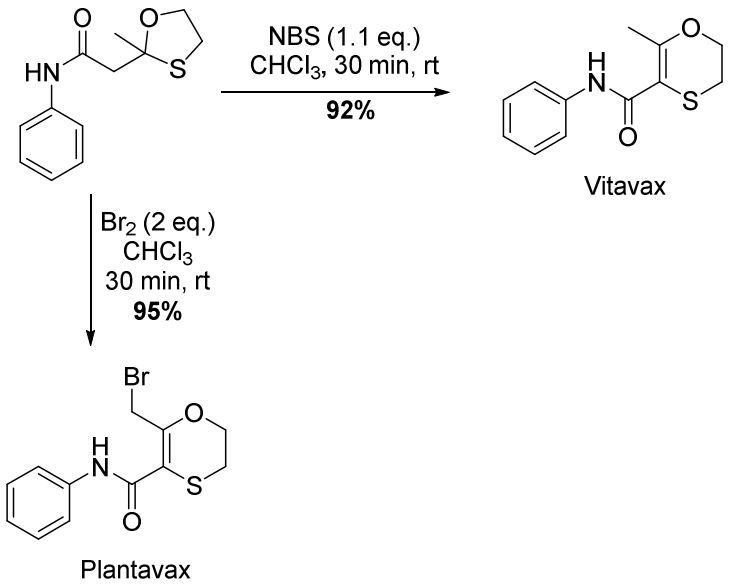
Scheme 19

This mechanism was corroborated by the same author who demonstrated that without hydrogens at C-2 of the oxathiolane ring, chlorination afforded the ketone and 1,2-mercaptoethanol without formation of the ring (Scheme 20).[78]



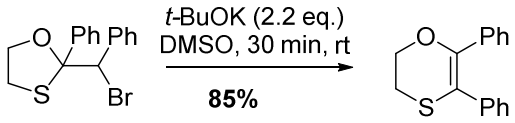
Scheme 20

Several authors extended the scope of this transformation,[79-81] which was further optimised for the synthesis of Vitavax® and Plantavax® with excellent yield (Scheme 21).[82]



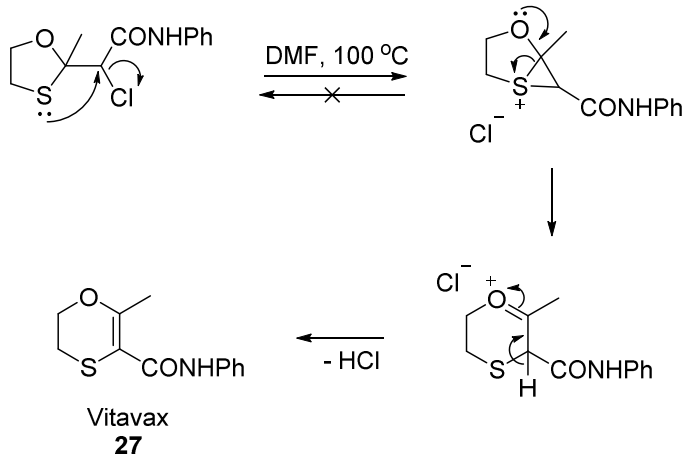
Scheme 21

A similar method described by Mattay involved elimination and rearrangement of the halogenated 1,3-oxathiolanes by means of potassium *tert*-butoxide in dimethyl sulfoxide at room temperature to yield 1,4-oxathiins in at least 80% yield (Scheme 22).[83] The yields decrease markedly if a chloride derivative is employed.



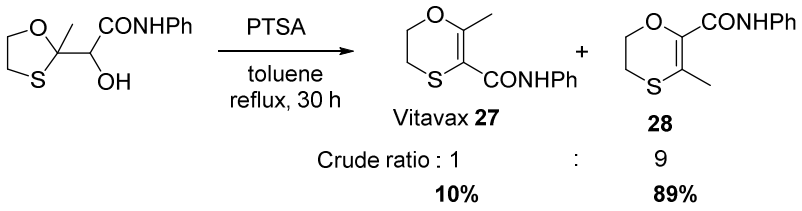
Scheme 22

Park *et al.* proposed a mechanism for this transformation with formation of an episulfonium salt as the key intermediate, and extended the scope to the synthesis of Vitavax® **27** (Scheme 23).[84]



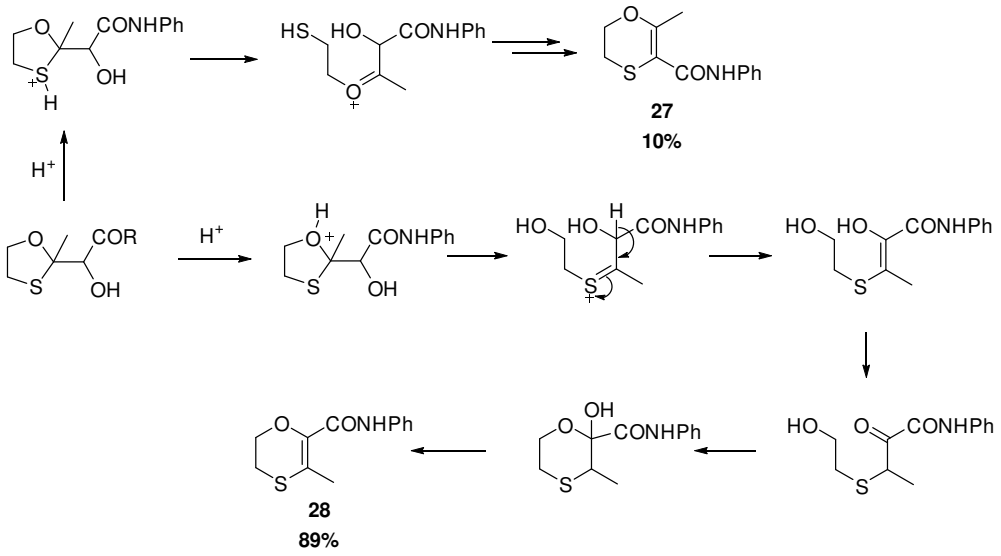
Scheme 23

Interestingly, the acid catalyzed dehydration of a mixture of diastereoisomers of β-hydroxy-1,3-oxathiolane produced a mixture of **27** and **28** in a ratio 1 : 9 respectively (Scheme 24).[85]



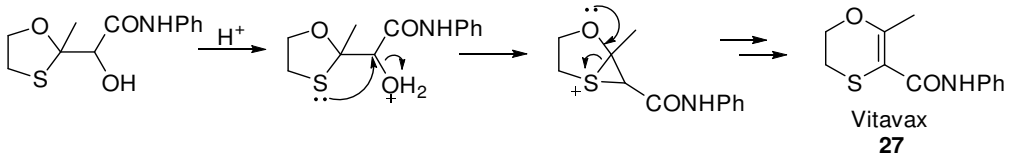
Scheme 24

The authors describe that the ring opening appears to be the crucial step of the reaction sequence described Scheme 25. Since ethers are more basic than thioether,[86] the oxygen would be protonated in preference to the sulfur in the oxathiolane ring. As a result, the ring opening occur selectively with C-O bond cleavage to yield **27** as the main product.



Scheme 25

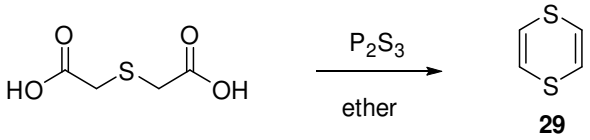
Alternatively, the minor product Vitavax® **27** could possibly be formed from the C-S bond cleavage of the sulfur protonated oxathiolanes as shown above in Scheme 23. However, **27** may also results from displacement of the β-hydroxy group by neighboring sulfur to form the thiiranium ion (Scheme 26).



Scheme 26

3. SYNTHESIS OF 1,4-DITHIIN DERIVATIVES

In 1890, Levi first reported that condensation of thiodiglycolic acid and phosphorus trisulfide (P_2S_3) resulted in the formation of 1,4-dithiadiene **29**, a substance which he called 'biophene' (Scheme 27).[87]

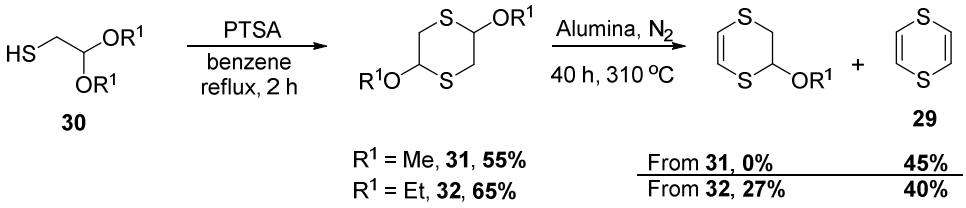


Scheme 27

Evidence cited by Levi for the proposed structure was sulfur analysis and positive indophene test with isatin and sulfuric acid. Also, the product underwent Friedel-Craft acylation, by reaction with acyl halide in the presence of aluminum chloride into the corresponding methyl ketone and phenyl ketone, and on the basis of these data, Levi concluded that the derivative is aromatic in character.

In 1950, Parham *et al.* modified the procedure described by Levi by the use of tetraphosphorus heptasulphide (P_4S_7) and phosphorus pentasulfide (P_2S_5) in place of P_2S_3 and by further temperature variation.[74] During this study, no evidence of formation of the derivative **29** reported by Levi was obtained.

In the same study, Parham *et al.* reported the cyclisation of di-alkyl-mercaptoacetal **30** in refluxing benzene yielding a mixture of *cis* and *trans* dithiane **31** or **32** with moderate yields (Scheme 28).[74] Dealkoxylation of the mixture of dithiane diastereoisomers over alumina at 310 °C occurred readily to give 1,4-dithiadiene **29** in 40-45% yield, depending on the substituent in the precursor. The structures were confirmed by elemental analysis.

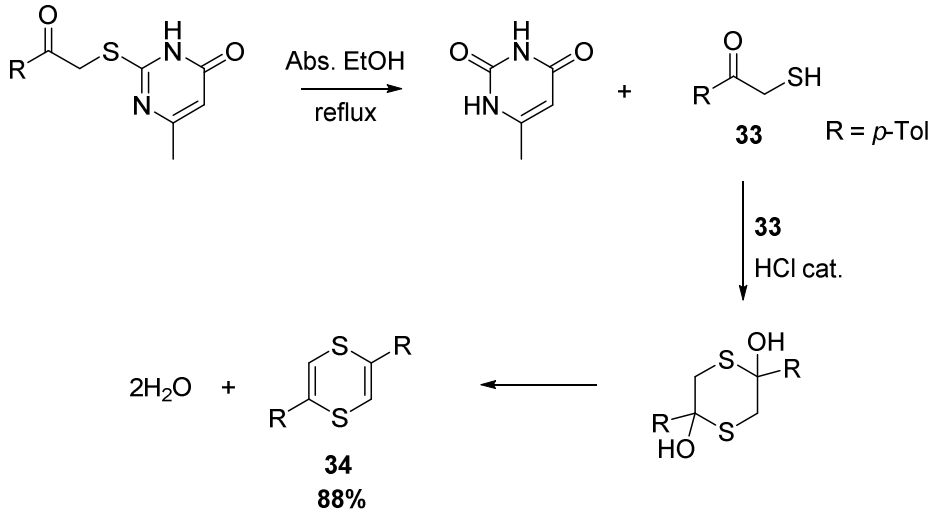


Scheme 28

A. From α-mercaptoketone

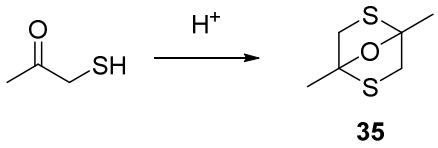
In 1913, Johnson *et al.* reported preparation of the 2,5-dithiadiene **34** by self-condensation of α-mercaptoketones (Scheme 29).[88] Hydrolysis of the pyrimidine generates first the 4-methyluracyl and the mercaptoacetophenone **33**. The latter is unstable in the presence of hydrochloric acid and undergoes condensation forming a dithiane derivative which then leads to dithiene **34** in 88% yield. This reaction corroborated the early work reported by Steude in 1891, who prepared this type of ring structure by hydrolyzing ethyl thioacetoacetoacetate.[89] Baker and Barkenbus investigated the scope of the transformation and observed that R must

be an aryl group and that the nature of the aryl group had little effect on the reaction yield.[90] However, substitution on the α-carbon made the condensation more difficult, α-methyl phenacyl mercaptan giving a very small yield of the product, while α-phenyl phenacyl mercaptan did not produce the 1,4-dithiene.



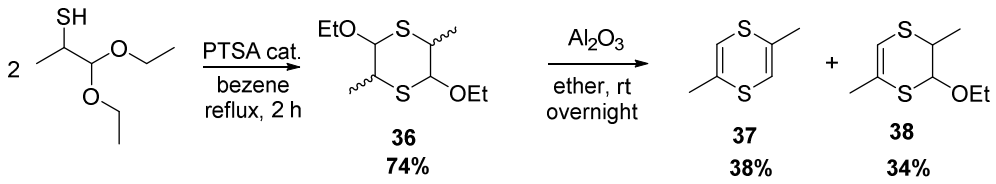
Scheme 29

Attempts to prepare alkyl substituted dithiadienes by the self-condensation of α-mercaptoketones interestingly generates 2,5-dimethyl 2,5-endoxy-1,4-dithiane **35** (Scheme 30).[91]



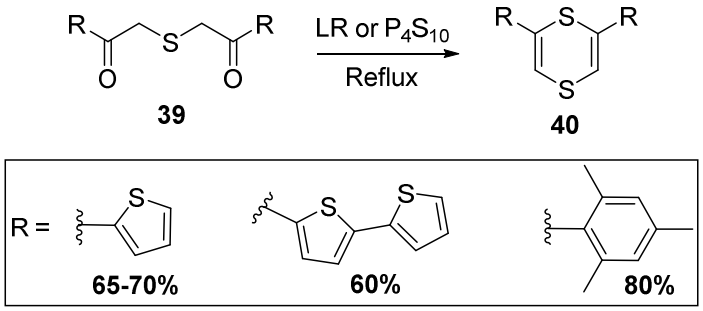
Scheme 30

2,5-Dimethyl-1,4-dithiadiene **37** has however been prepared by cyclisation of the diethylacetal of α-mercaptopropional in refluxing benzene affording initially **36** in 74% yield, followed by treatment of the mixture of isomers of **36** with aluminium oxide (Scheme 31).[92]



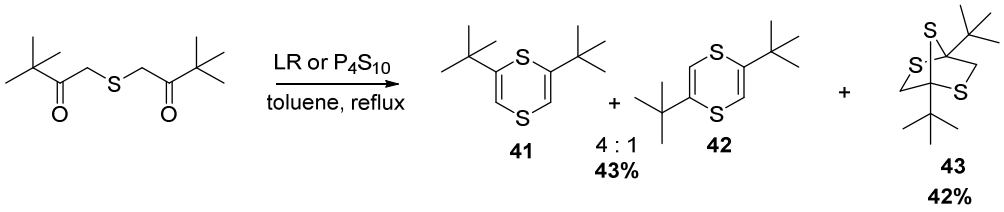
Scheme 31

Nakayama *et al.* described that treatment of 1,5-diketones **39** with Lawesson's reagent (LR) or phosphorus pentasulfide in refluxing benzene, toluene, or chlorobenzene, smoothly produced 1,4-dithiins **40** as the exclusive product (Scheme 32).[93] Sulfide precursors **39** are obtained by treatment of α-haloketones with $Na_2S.9H_2O$.



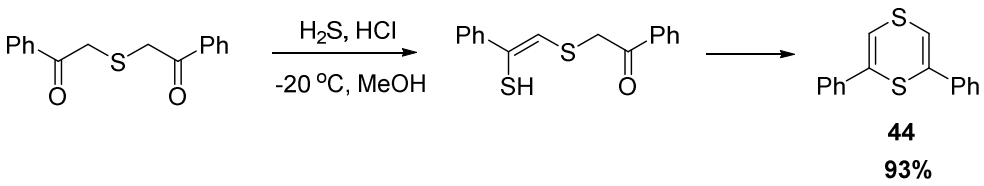
Scheme 32

However, when R = Aryl group of **39** was replaced with R = *t*-Bu, the reaction affords **43**, in 42% yield and a mixture of **41** and **42** in 43% yields in the ratio 4 : 1 respectively (Scheme 33).[93]



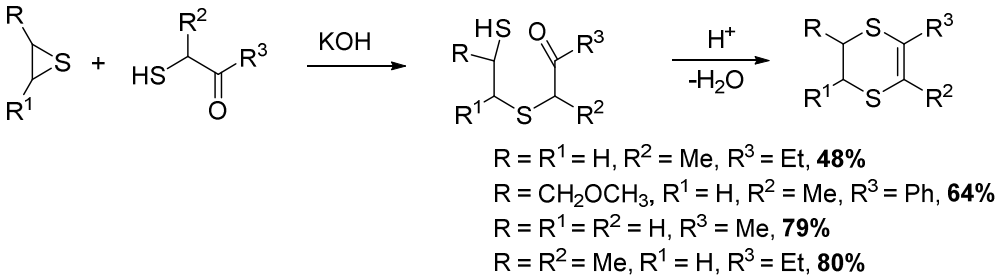
Scheme 33

Voronkov *et al.* developed a method for the isolation of 2,6-diphenyl-1,4-dithiin **44** in 93% yield by hydrothiolysis of a methanolic solution of diphenacyl sulfide in the presence of HCl at -20 °C (Scheme 34).[94] However, the attempt to obtain 2,6-dimethyl-1,4-dithiin under these conditions led to macrocyclic oligosulfides.



Scheme 34

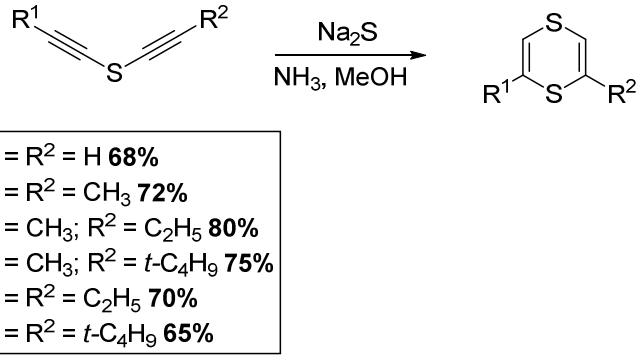
The method developed by Asinger *et al.*[17] described in *Section 2.D.* can also be employed for dithiin synthesis from episulfide precursors (Scheme 35). The regio- and/or the stereochemistry of the reaction was not discussed, and the products were afforded in moderate to good yields.



Scheme 35

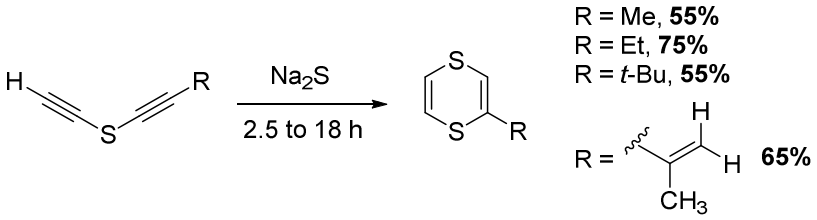
B. From alkyne precursors

Methods for the synthesis of dithiin systems from alkyne precursors are also reported in the literature. Dialkynyl sulfides in which two triple bonds are available for nucleophilic attack, are useful starting materials for the synthesis of heterocycles.[95,96] In 1973, Meijer *at al.* reported that interaction between di-(1-alkynyl)sulfides and sodium sulfide in mixture of liquid ammonia and methanol, or DMF and methanol, gives 1,4-dithiins in good yields (Scheme 36).[95] The reaction time and temperature vary depending on the substituents R^1 and R^2 of the alkyne precursor. The reaction was completed within a few minutes while employing the compound $R^1 = R^2 = H$ at about -30 °C, while complete conversion was observed for the *t*-butyl precursors after at least 24 hours at room temperature.



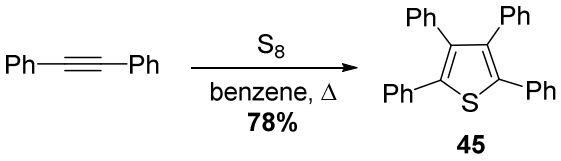
Scheme 36

Zilverschoon *et al.* extended the scope of the transformation to include mono-substituted 1,4-dithiins obtained in moderate to good yields (Scheme 37).[97]



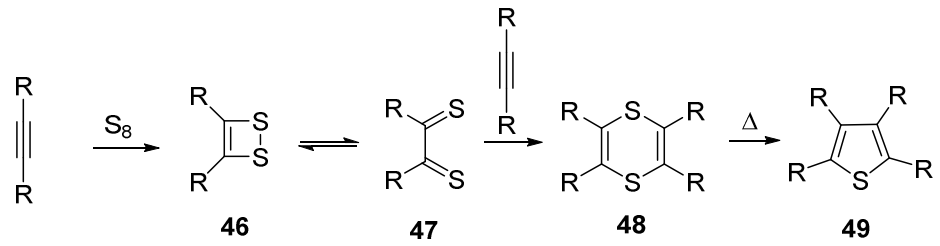
Scheme 37

The reaction of diphenylacetylene with elemental sulfur in benzene at 200-210 °C using an autoclave produces tetraphenylthiophene **45** in 78% yield (Scheme 38).[98]



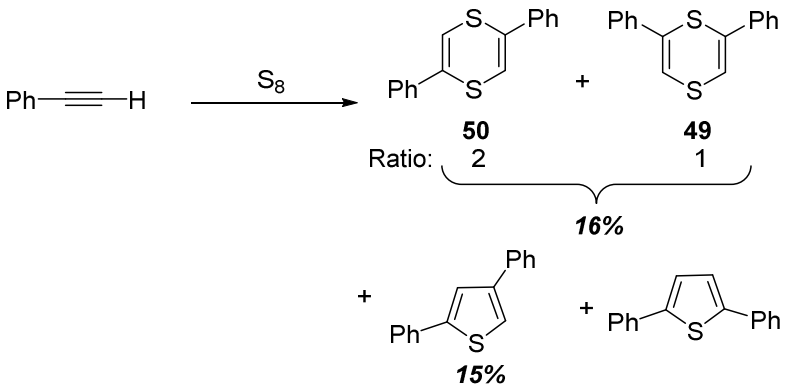
Scheme 38

A mechanism has been proposed for this transformation from the initial formation of the 1,2-dithietes **46** by electrophilic attack of the acetylene on sulfur (Scheme 39).[98] Diels-Alder reaction of **47**, the tautomeric form of **46**, with the acetylene gives 1,4-dithiins **48**. Thermal decomposition of **48** leads then to thiophene **49**.



Scheme 39

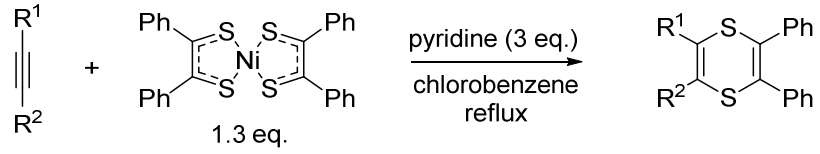
While using a mixture of sulfur and phenylacetylene (2 eq.) with progressive heating to 125 °C without solvent, the crude mixture consisted of 2,5- **50** and 2,6-diphenyl-1,4-dithiins **49** (ratio 2 : 1 respectively) in 16% yield, along with 2,4-diphenylthiophene (15%) contaminated with a trace amount of 2,5-diphenylthiophene (Scheme 40).[98]



Scheme 40

Ghosal *et al.* had synthesised 1,4-oxathiins in good yield by treatment of alkynes with nickel bisdithiolene and pyridine in refluxing chlorobenzene (Table 1).[99] The only by-product of the dithioannulation process involved thermal transformation of dithiins to produce small amounts of the corresponding thiophenes (less than 10% yield).[100]

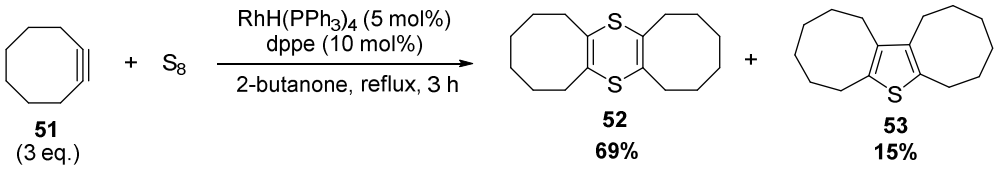
Table 1



Entry	R^1	R^2	Reaction time (h)	Yield of dithiin (%)
1	*n*-C_4H_9	H	1.0	83
2	$AcOCH_2$	H	0.5	63
3	$AcOCH_2CH_2$	H	0.5	65
4	$THPOCH_2CH_2$	H	2.5	77
5	$BnOCH_2CH_2$	H	0.75	82
6	*E*-R-$C(CH_3)$=$CHCH_2$ R = $(Me)_2C$=$CHCH_2CH_2$	*n*-C_4H_9	1.0	76
7	*E*-R-$C(CH_3)$=$CHCH_2$ R = $(Me)_2C$=$CHCH_2CH_2$	$THPOCH_2$	1.0	60
8	4-$CH_3OC_6H_4CH(OH)$	$THPOCH_2$	0.75	47
9	4-$CH_3OC_6H_4CH_2CH(OH)$	$THPOCH_2$	0.5	52

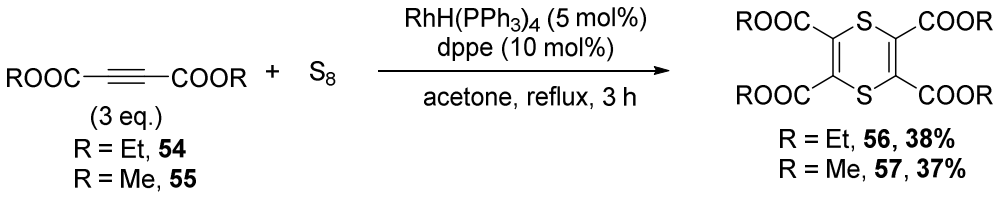
The results described in Entry 6 and 7 were of particular interest with selective dithioannulation wherein exclusive addition to the acetylenic bond occurred. Also, this method is mild enough to tolerate various heterogroups and protecting groups. For entries 8 and 9, partial dehydration of the initial dithiin adduct was observed, and this subsequently decreased the yield of the product.

The addition of sulfur to cyclooctyne **51** catalyzed by a rhodium complex in refluxing 2-butanone yields the corresponding symmetrical 1,4-dithiine **52** and the thiophene derivative **53** (Scheme 41).[101] The authors investigated the scope of the transformation with various cycloalkyne precursors affording the corresponding symmetrical dithiins in good yields. As for the synthesis of **52**, formation of the corresponding thiophenes were observed in almost all cases.



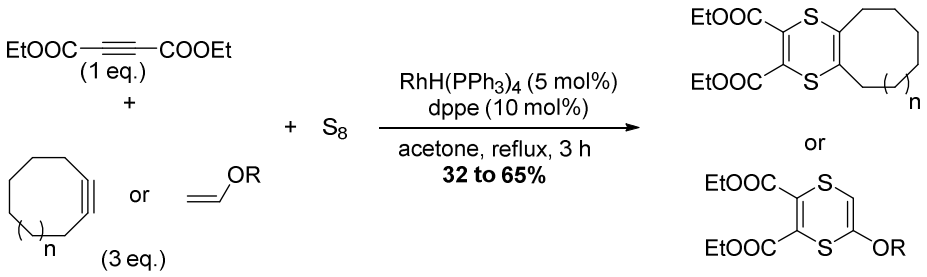
Scheme 41

Transformation using acyclic alkynes **54** and **55** was more efficient while using acetone as solvent leading to the symmetrical 1,4-dithiins **56** and **57** in moderate yields (Scheme 42).[101] In this cases, the corresponding thiophenes were not formed.



Scheme 42

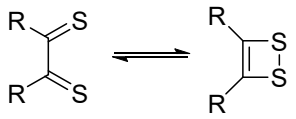
Interestingly, while employing acetylenedicarboxylate and cyclic alkynes or alkenes, the reaction afforded the unsymmetrical dithiins in moderate to good yields as the sole products (Scheme 43).[101]



Scheme 43

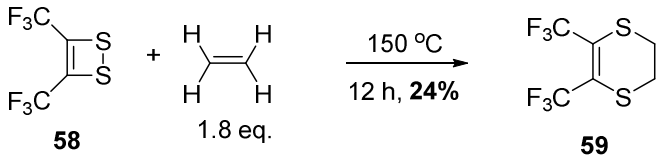
C. From 1,2-dithione and 1,2-ethanedithiol precursors

1,2-Dithiones exist in valence tautomeric equilibrium with 1,2-dithiacyclobutene (Scheme 44).[102] The synthesis of 1,4-dithiin derivatives from 1,2-dithiones has been reported in the literature.



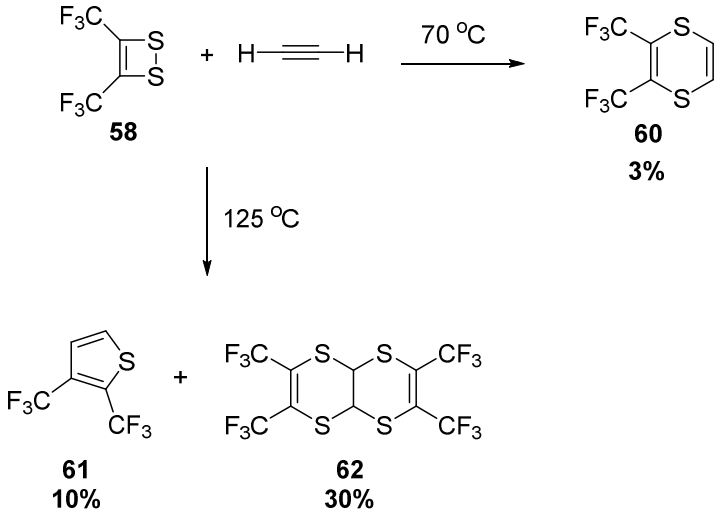
Scheme 44

In 1961, Krespan and McKusick reported that dithiones **58** reacts readily with ethylene at 150 °C to yield 5,6-dihydro-dithiin **59** in 24% yield (Scheme 45).[103] Substitution by alkyl or aryl groups of the ethylene protons results in increased reactivity of the olefin, giving the corresponding dihydro-dithiin as the sole product at 100 °C in yield ranging from 31 to 47%.



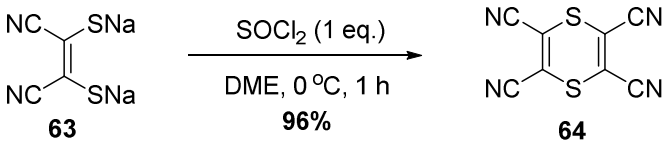
Scheme 45

Otherwise, treatment of acetylene with **58** at 125 °C generates the thiophene **61** in 10% yield due to the thermal decomposition of the initially formed dithiin **60** by sulfur elimination (Scheme 46). The unsaturated system in **60** is reactive toward further addition of **58** at 125 °C, so that a bicyclic compound **62** is also formed in 30% yield. In contrast, at 70 °C the reaction is much slower but dithiin **60** is stable and can be isolated in low yield as the sole product.



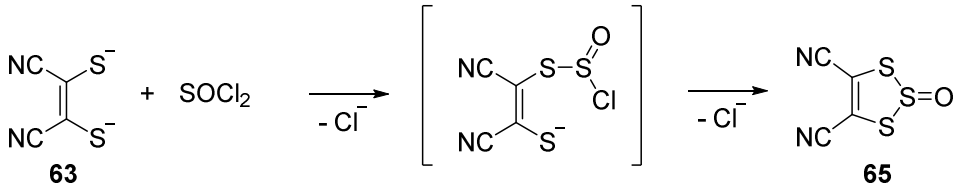
Scheme 46

Simmons *et al.* reported reaction of disodium dimercaptomaleonitrile salt **63** with thionyl chloride led to tetracyano-1,4-dithiin **64** (Scheme 47).[104]



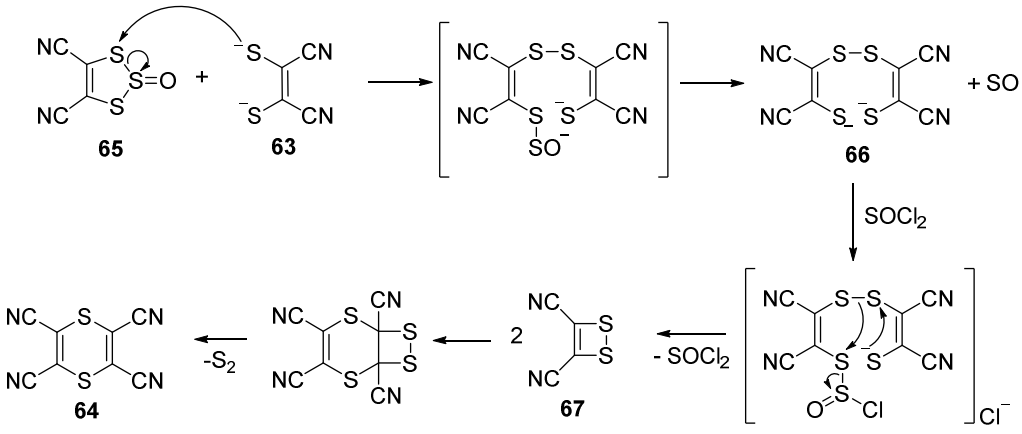
Scheme 47

A mechanism has been proposed for this transformation by the same author.[105] Nucleophile displacement by salt **63** on thionyl chloride, followed by intramolecular ring closure give trithiole oxide **65** (Scheme 48).



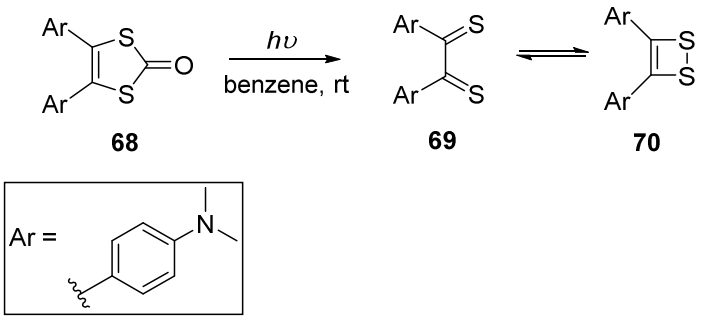
Scheme 48

Reaction of **65** with salt **63** led readily to disulfide salt **66** as *cis* isomer exclusively (Scheme 49). Subsequent transformation of **66** *via* dimerization of **67** to form dithiin **64** completes the overall process.



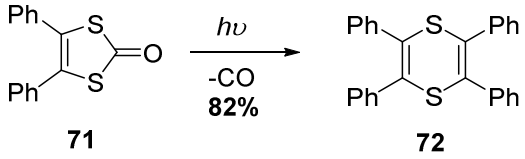
Scheme 49

Küsters and Mayo reported formation of dithione **69** and 1,2-dithiacyclobutene **70** by irradiation of a benzene solution of vinylene dithiocarbonate **68** under nitrogen at room temperature with light of wavelength λ > 350 nm (Scheme 50).[102]



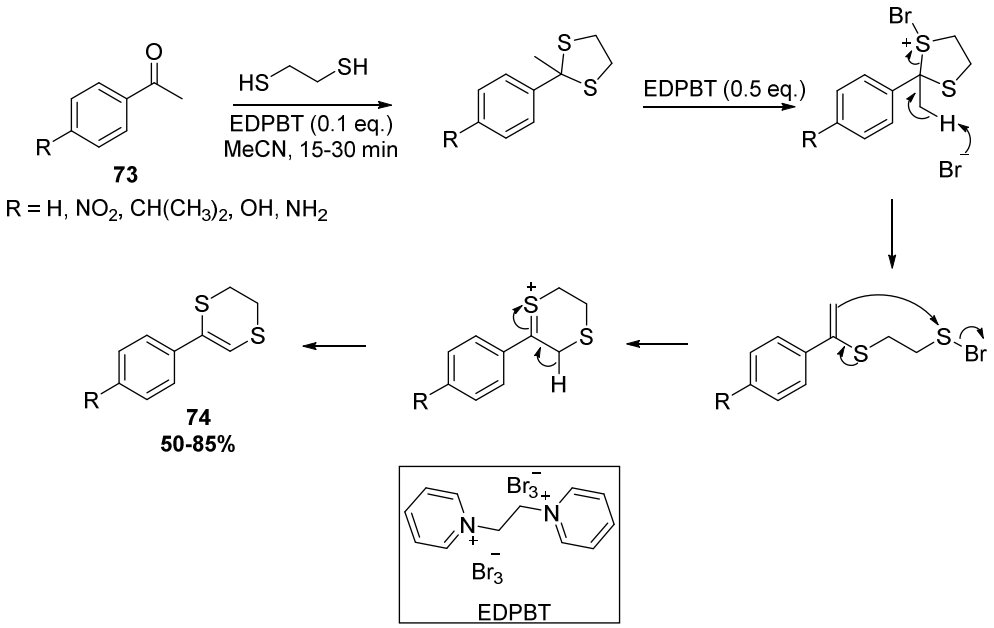
Scheme 50

Subsequently, Schroth *et al.* undertook photochemical decarbonylation of 4,5-diphenyl-1,3-dithiol-2-ones **71** leading to the corresponding tetrasubstituted 1,4-oxathiin **72**, presumably through generation of the corresponding dithione and dithiete derivatives (Scheme 51).[106]



Scheme 51

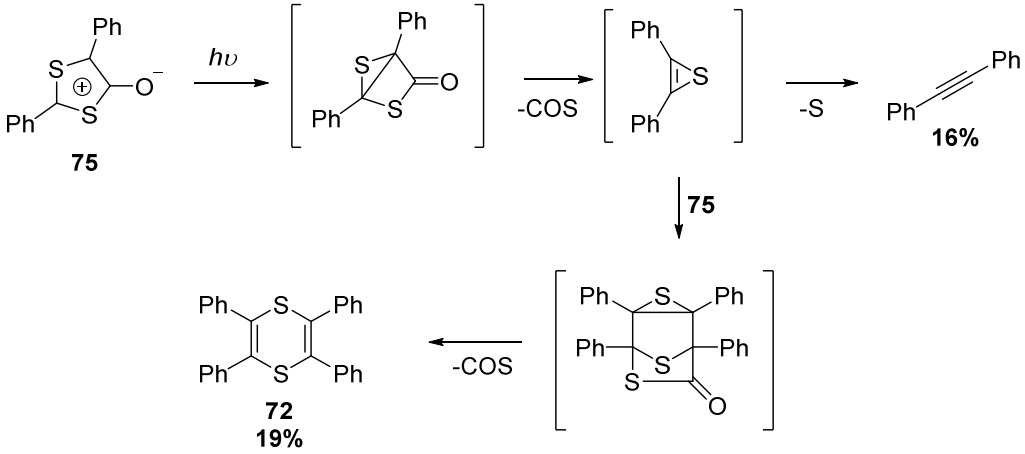
Murru *et al.* developed a one-pot transformation of aryl ketones **73** with 1,2-ethanedithiol to 1,4-dithiins **74** using the recyclable reagent 1,1'-(ethane-1,2-diyl)dipyridium bistribromide (EDPBT) in good to high yields (Scheme 52).[107] In this reaction, EDPBT acts as a promotor in the formation of 1,3-dithiolanes and as a reagent in the ring expansion to dithiins.



Scheme 52

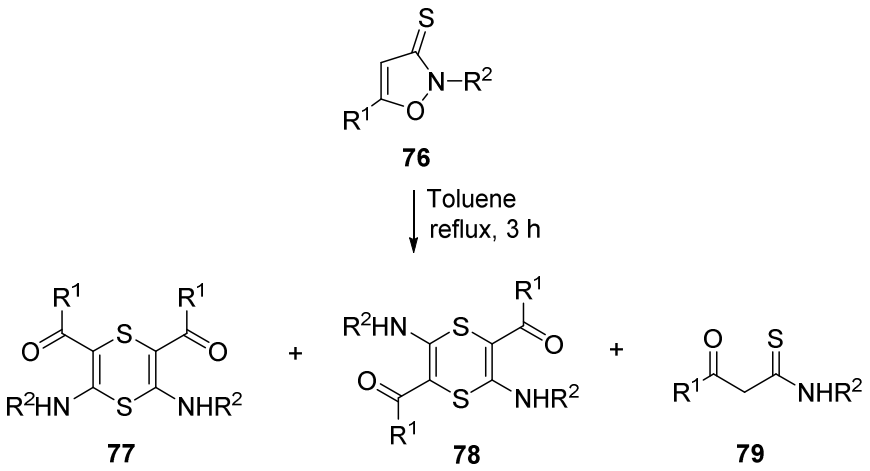
D. By ring enlargement

In 1970, Kato *et al.* described the photolysis of mesoionic 2,5-diphenyl-1,3-dithiol-4-one **75**, affording tetraphenyl 1,4-oxathiin **72** in 19% yield, along with diphenyl acetylene (16%), probably *via* a thiirene intermediate (Scheme 53).[108]



Scheme 53

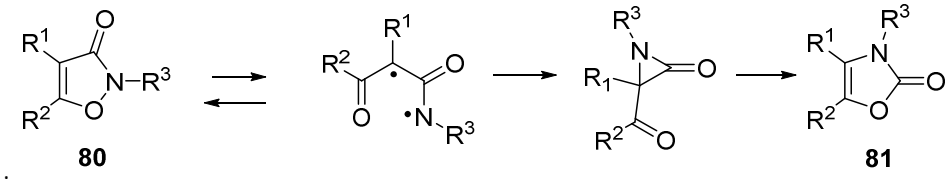
Sugai and Tomita reported pyrolysis in boiling toluene of 4-isoxazolin-3-thiones **76** affording two regioisomeric 1,4-dithiins **77** and **78** and thioacetamides **79** (Scheme 54).[109] The isolated major isomers were assigned as **77** by NMR spectroscopy.



R^1	R^2	Yield (%)		
		77	**78**	**79**
Me	Me	20.8	0.8	2.0
Me	Et	27.6	5.5	2.2
Me	Bn	20.0	5.3	0.9
Me	Ph	5.0	0	25.8
Ph	Me	9.0	4.6	2.8

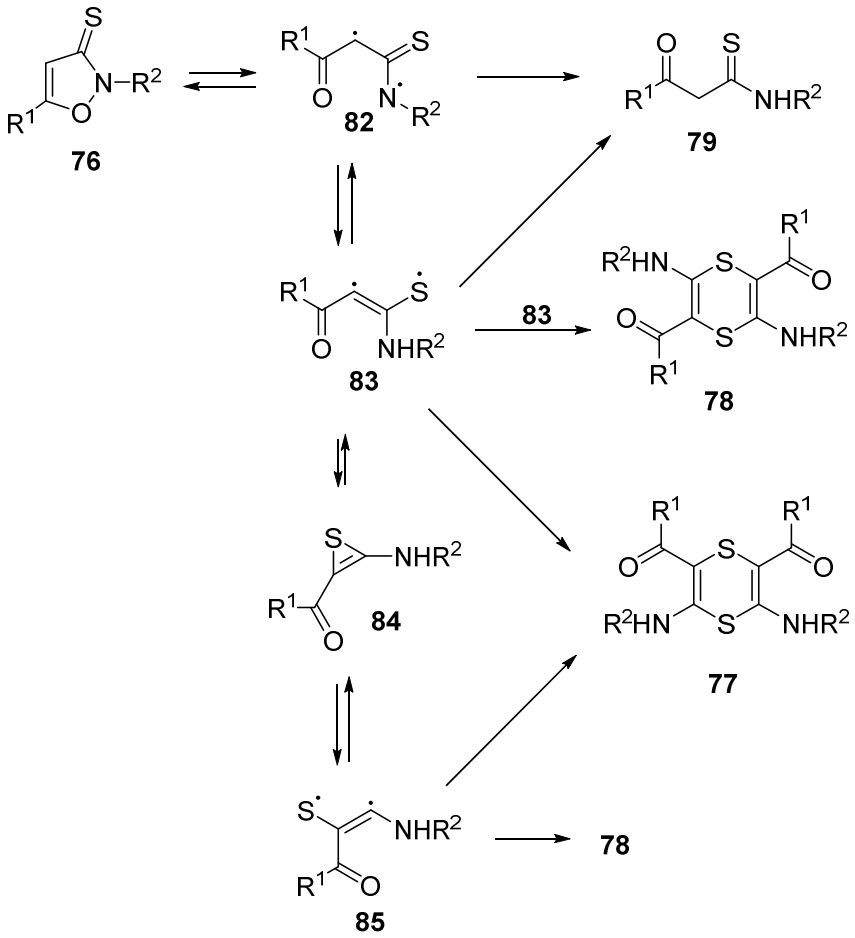
Scheme 54

By comparison with the established mechanism for the thermal rearrangement of 2-phenyl-4-isoxazolin-3-ones **80** to 3-phenyl-1,4-oxazolin-2-ones **81** (Scheme 55), in which resonance-stabilised diradicals are involved,[110] a mechanism for the conversion of **76** to **77**, **78** and **79** has been proposed (Scheme 56).[109]



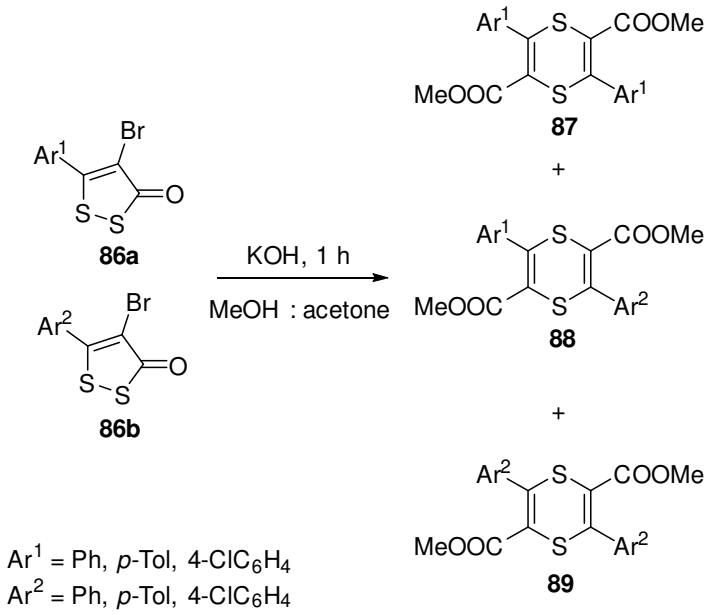
Scheme 55

Firstly, the N-O bond of **76** undergoes homolysis to afford a C,N-radical **82** which rapidly isomerizes to a C,S-radical **83**, and then to another diradical **85** *via* thiirene **84** formation. From the two radicals **83** and **85** in equilibrium, two competitive reactions affording the dithiins **77** and **78** are presumed to proceed.



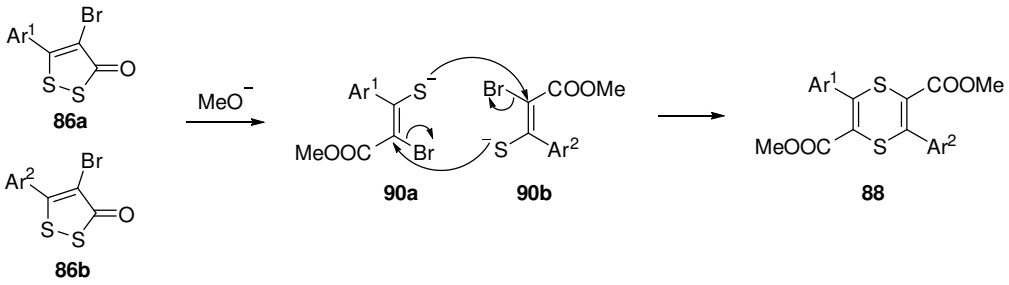
Scheme 56

Boberg reported that a mixture of 4-bromo-1,2-dithiole-3-ones **86a** and **86b** containing different aryl substituents in the 5-position react with KOH in methanol to afford dimethyl-1,4-dithiin-2,5-dicarboxylates with identical and different aryl substituents in the 3,6-position (Scheme 57).[111] Dithiins **88** were obtained as the major product in each case. The isolated yields were not reported.



Scheme 57

The same author proposed a mechanism for this transformation. Firstly, hydrolysis of the dithiole precursors **86a** and **86b** generates the thiolates **90a** and **90b** respectively (Scheme 58).[112-114] Intermolecular elimination of bromide then generates the dithiin **88**.

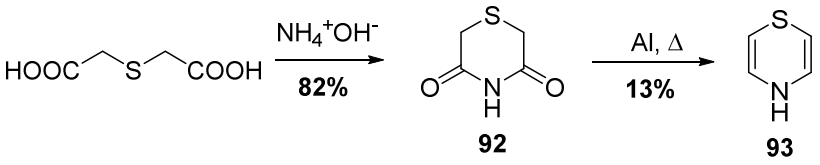


Scheme 58

4. SYNTHESIS OF 1,4-THIAZINES

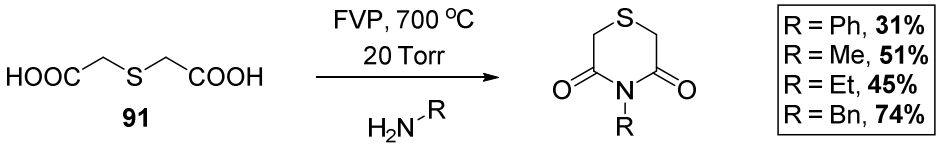
Several biologically active and naturally occurring compounds contain the 1,4-thiazine ring. Therefore, synthetic methodology for these heterocycles has been widely reported in the literature.

Barkenbus and Landis reported for the first time the preparation of 1,4-thiazine in 1948.[115] The cyclic imide **92** was prepared by heating a mixture of dry ammonium salt with thiodiglycolic acid (Scheme 59). Then, gas-phase deoxygenation of **92** over aluminium at 450 °C generates the 1,4-thiazine **93** in low yield.



Scheme 59

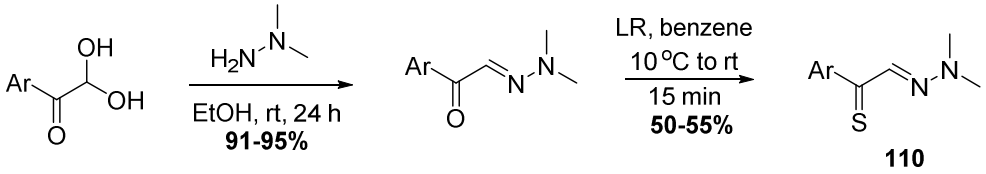
Later, Aitken *et al.* reported the synthesis of a range of *N*-substituted cyclic imide by flash vacuum pyrolysis (FVP) at 700 °C, in moderate to good yield from the appropriate amine (Scheme 60).[116]



Scheme 60

A. By Diels Alder cycloaddition

In 1991, Reliquet *et al.* described the synthesis of 1,4-thiazine by Diels-Alder cycloaddition from 2-(diallkylhydrazono)thioacetophenones **110**.[128] The precursors **110** are synthesised by reaction of 1,1-dimethylhydrazine with arylglyoxal hydrate in ethanol leading to the monohydrazones, followed by treatment with Lawesson's reagent (Scheme 70).

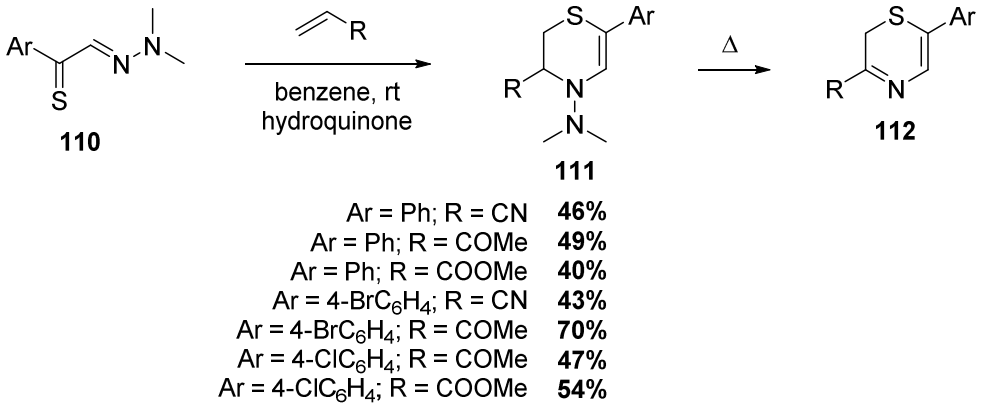


Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4

Scheme 70

Despite the lability of compounds **110**, requiring rapid purification and further reactions, NMR experiments demonstrate that only one isomer was formed.

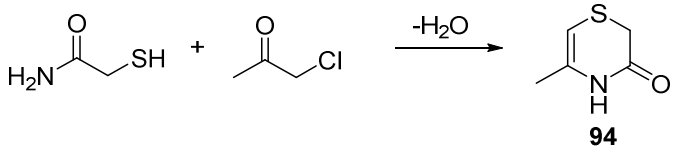
Precursors **110** are used as heterodienes in Diels-Alder cycloaddition reaction with acrylic dienophiles generating 1,4-thiazines **111** (Scheme 71). Heating the crude mixture led to the deamination of **111** giving the corresponding thiazine **112**.[129,130]



Scheme 71

A. From carbonyl precursors

In 1948, Sokol and Ritter described obtaining 1,4-thiazine **94** from the condensation of thioglycolamide with chloroacetone (Scheme 61).[117] The yield of the transformation was not reported.

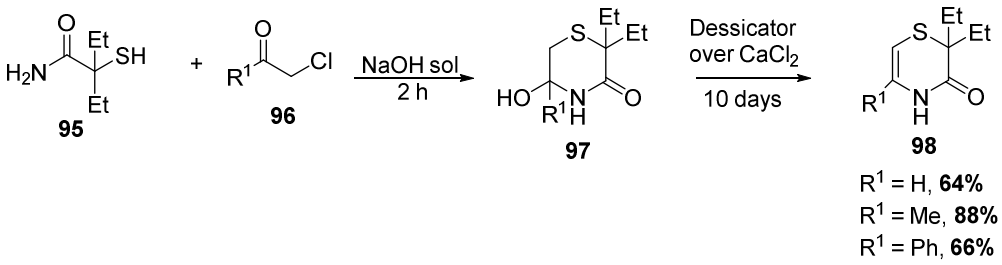


Scheme 61

Later, Johnson prepared 1,4-thiazine-3-one **94** by reaction of chloroacetone with thioglycolamide and triethylamine in 75% yield (Scheme 61).[118]

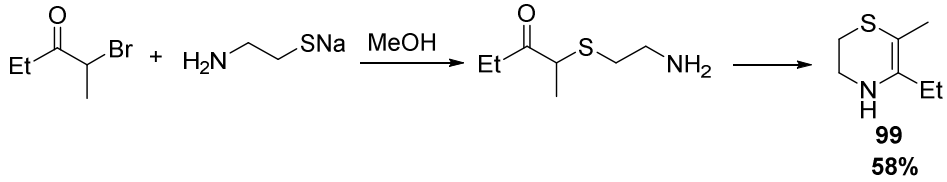
This reaction has been studied and extended to aryl substituted bromoketone precursors,[119] and secondary amide precursors.[120]

Skinner *et al.* reported that the condensation of dialkylmercaptoacetamides **95** with α-chlorocarbonyl compounds **96** gives the intermediate cyclic keto alcohols **97** which finally leads to 4H-1,4-thiazin-3-ones **98** by dehydration (Scheme 62).[121]



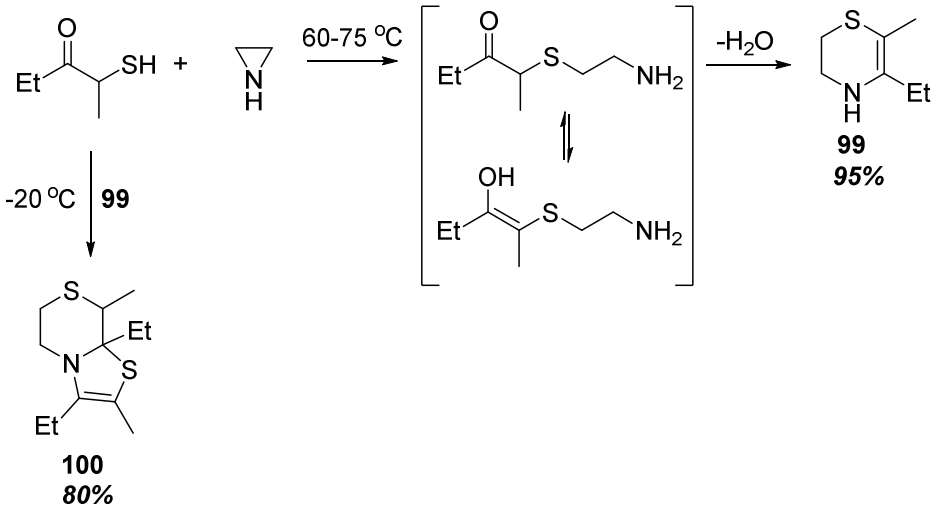
Scheme 62

In addition to the work describing the synthesis of oxathiins and dithiins from α-mercaptoketones,[17] Asinger *et al.* also performed the synthesis of 1,4-thiazine **99** from α-haloketone precursor in 58% yield (Scheme 63).[122]



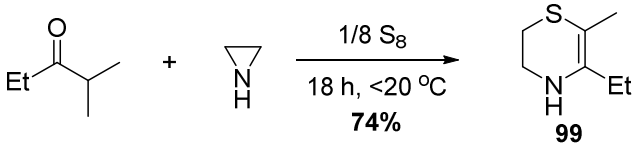
Scheme 63

Using the same methodology as described previously for the synthesis of 1,4-oxathiins (*cf. Section 2.C*) and 1,4-dithiins (*cf. Section 3.A*), Asinger *et al.* prepared 1,4-thiazine derivative **99** by the reaction of α-mercaptoketones with ethylenimine (Scheme 64).[122] When the reaction was performed at below 60 °C, formation of **100** was observed by a second addition of α-mercaptoketone precursor on the product **99**. Interestingly, formation of **100** does not depend mainly on the molar ratio of α-mercaptoketone to ethyleminine but the reaction temperature is a much more important factor for this transformation. A reaction temperature between 60 to 75 °C prevents the second addition of α-mercaptoketones, and **99** was isolated in 95% yield. On the other hand, if the reaction is carried out at -20 °C, **100** is obtained in 80% yield.



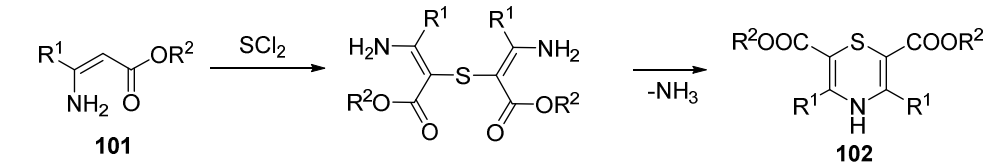
Scheme 64

Asinger *et al.* also reported the synthesis of **99** from ketones, sulfur and ethylenimide at temperature below 20 °C in 74% yield (Scheme 65).[123,124] This transformation was also extended to the synthesis of other disubstituted 1,4-thiazines in good yield.



Scheme 65

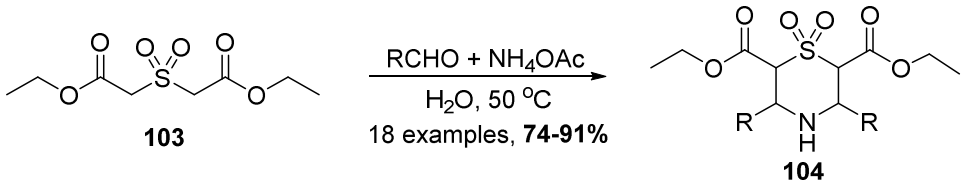
Lee and Howe prepared 1,4-thiazine **102** from aminoacrylates **101** with sulfur dichloride with good yield (Scheme 66).[125] Inverse addition of **101** to SCl_2 was essential to produce the 1,4-thiazine as the main product, otherwise, the corresponding pyrrole derivatives were instead obtained by sulfur extrusion of the thiazine. Also, an electron-withdrawing group at R^1 was found necessary to promote the cyclisation.



$R^1 = CF_3$; R^2 = Et, **78%**
$R^1 = CF_3CF_2$; R^2 = Me, **60%**
$R^1 = CF_3CF_2$; R^2 = Et, **83%**
$R^1 = CF_3CF_2CF_2$; R^2 = Et, **71%**

Scheme 66

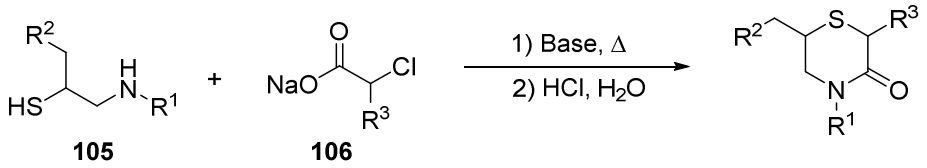
Diacetates **103** generate thiomorpholines **104** with aldehydes and ammonium acetate in water in good to excellent yield (Scheme 67).[51]



R = Ph, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, *p*-$OMeC_6H_4$, *p*-MeC_6H_4, furane, indole, thiophene, pyridine, pyrrole, quinolline

Scheme 67

Magerramov *et al.* reported efficient preparation of tetrahydro-1,4-thiazine-3-ones by the condensation of 1,2-aminopropanethiols **105** and sodium chlorocarboxylates **106** under basic conditions (Scheme 68).[126] The products were isolated in moderate to good yield by distillation and identified by elemental analysis. The reaction conditions depend on the nitrogen substituent (R^1) in the precursor with phenyl derivatives more reactive than benzylamines. Therefore, phenyl derivatives **105** react with **106** in the presence of sodium hydroxide solution at 30 °C in 1 hour, while reaction with the benzylic derivatives proceeds only at 80-90 °C with metallic sodium.

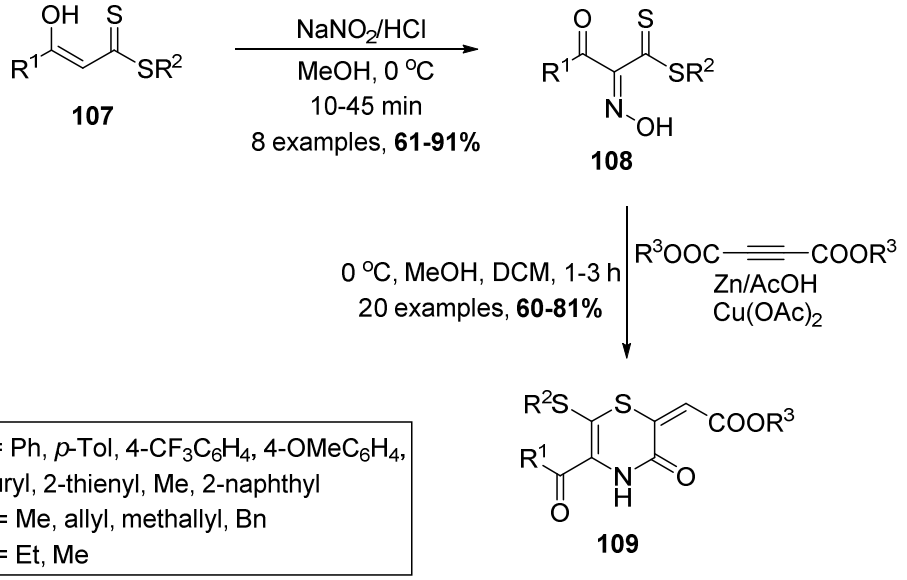


105 106

R^1 = Ph; R^2 = R^3 = H, **55%**
R^1 = Ph; R^2 = H; R^3 = Et, **70%**
R^1 = Ph; R^2 = OBu; R^3 = H, **52%**
R^1 = Ph; R^2 = OBu; R^3 = Et, **57%**
R^1 = Bn; R^2 = OBu; R^3 = H, **45%**
R^1 = Bn; R^2 = R^3 = H, **50%**

Scheme 68

Nitrosation of α-enolicdithioesters **107** and further treatment of the resulting α-hydroxyimino-β-oxodithioesters **108** with alkynes affords 1,4-thiazines **109** via domino reduction/annulation strategy under mild conditions (Scheme 69).[127]



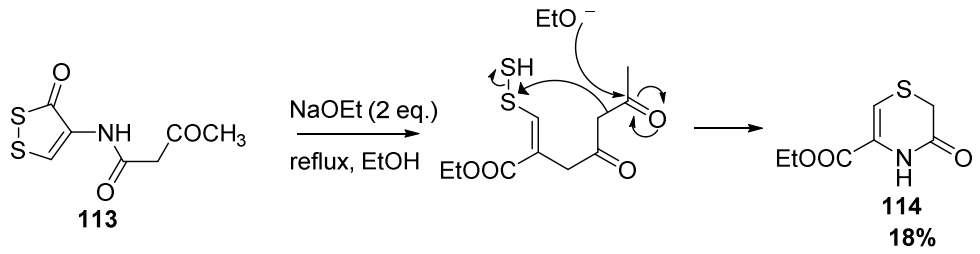
107 108 109

R^1= Ph, *p*-Tol, 4-$CF_3C_6H_4$, 4-$OMeC_6H_4$, 2-furyl, 2-thienyl, Me, 2-naphthyl
R^2 = Me, allyl, methallyl, Bn
R^3 = Et, Me

Scheme 69

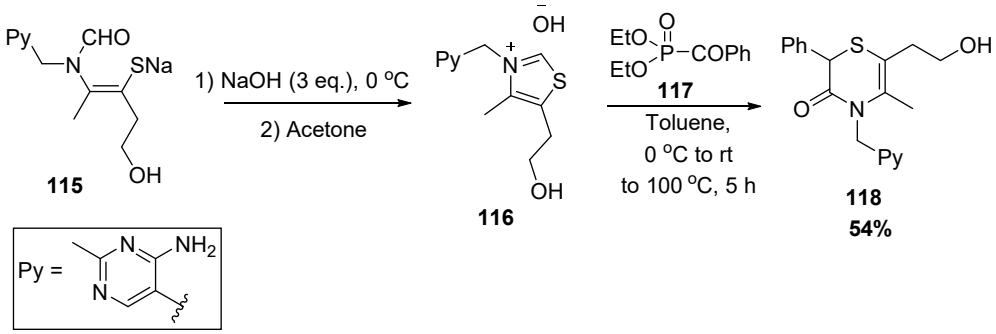
B. By ring enlargement

In 1965, Brown and Rae reported that the reaction of 1,2-dithiol-3-one **113** with sodium ethoxide in refluxing ethanol gives 1,4-thiazin-3-one **114** in low yield (Scheme 72).[131]



Scheme 72

Takamizawa *et al.* intensively explored the synthesis of 1,4-thiazines from thiazoles.[132-141] Reaction of the salt **115** with excess of sodium hydroxide gave the thiazole **116** which reacted further with diethyl benzoylphosphonate **117** giving the 1,4-thiazine **118** (Scheme 73).[140]



Scheme 73

Extension of the scope of the transformation has been explored by the same author, the yields were not always reported (Figure 5).[133,137]

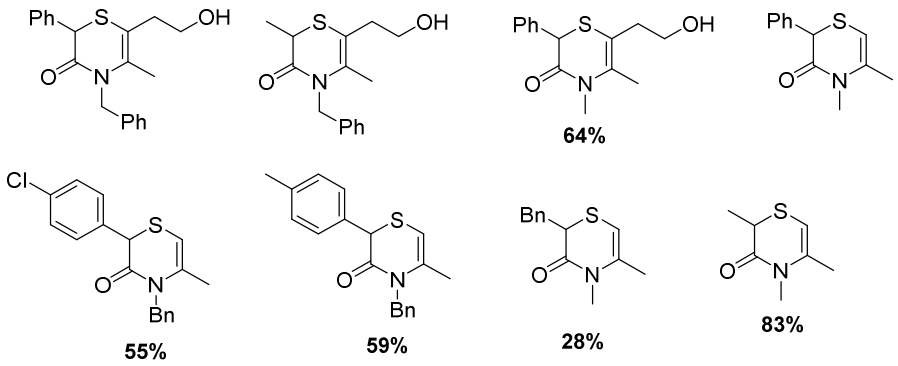
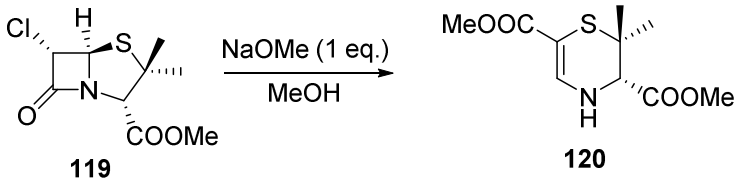


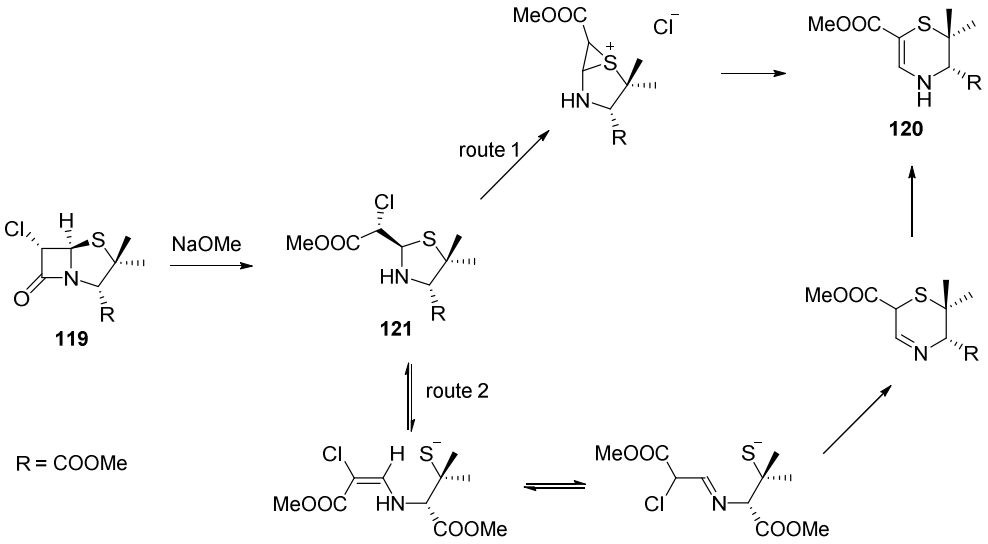
Figure 5

Stoodley and coworker stated treatment of chloropenicillanate **119** with a molar equivalent of sodium methoxide led to 1,4-thiazine **120** (Scheme 74).[142]



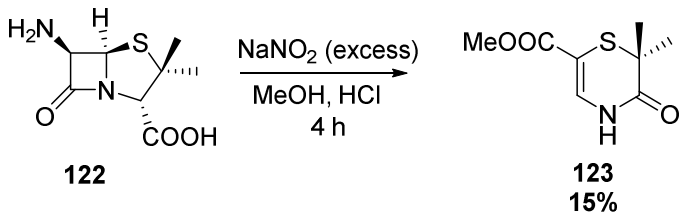
Scheme 74

The mechanism of formation of **120** from **119** involves nucleophilic opening of the β-lactam to give **121** (Scheme 75). From this intermediate, two rearrangements leading to **120** are possible; the route 1 process is through solvolysis to the episulfonium cation followed by loss of a proton. In this route, the ionization is presumably the rate limiting step and consequently the rate of formation of **120** should be independent of the sodium methoxide concentration. Successive β-elimination, tautomerisation, internal displacement and second tautomerisation appears to be a more plausible route (route 2). Indeed, in this reaction, transformation of **121** to **120** is dependent upon the sodium methoxide concentration, which discredits the first route proposed.



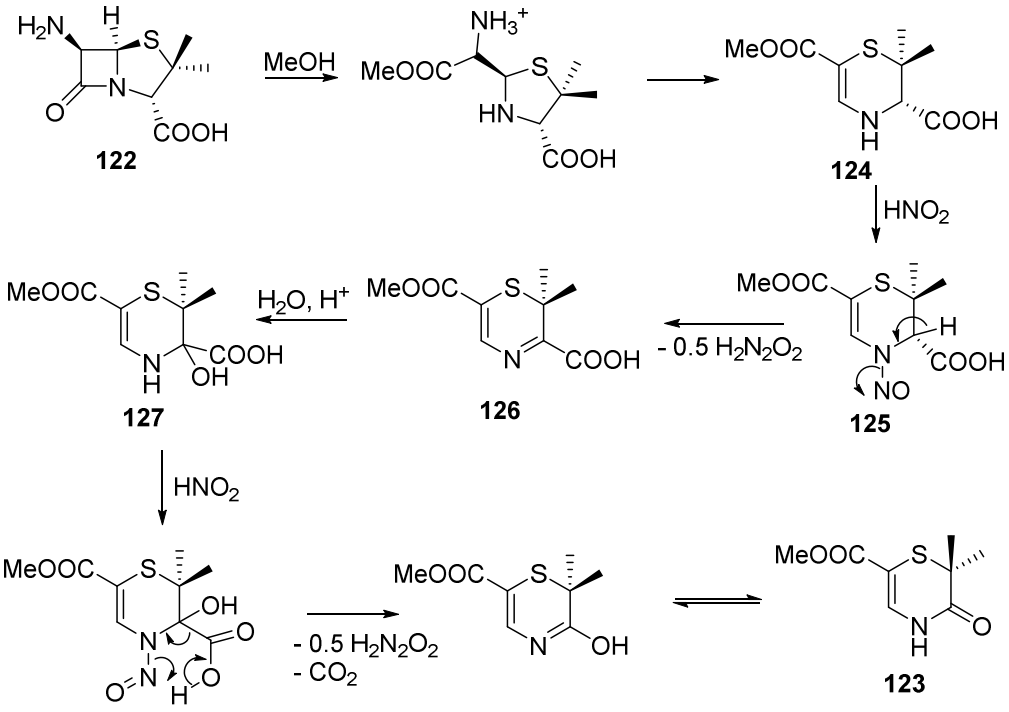
Scheme 75

Stoodley also described formation of the 1,4-thiazin-3-one **123** by treatment of 6-β-aminopenicillanic acid **122** with an excess of sodium nitrite in methanolic hydrogen chloride (Scheme 76).[143, 144]



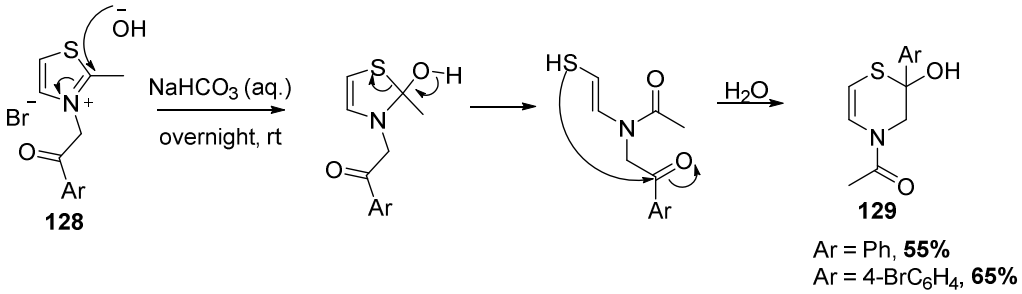
Scheme 76

Here again, the reaction outcome is directly dependent on the methanol concentration. The precise mechanism of the transformation was not established but further studies support the rearrangement described in Scheme 77.[144] Nucleophilic opening of the β-lactam followed by deaminative ring expansion would generate **124**. The thiazine **124** is then nitrosated by the nitrous acid into its nitroso-derivative, which loses the hyponitrous acid to give the imino-acid **126**. Hydration of **126** gives the hydroxy-acid **127** which is further nitrosated and undergoes an oxidative decarboxylation to yield the tautomeric form of **123**.



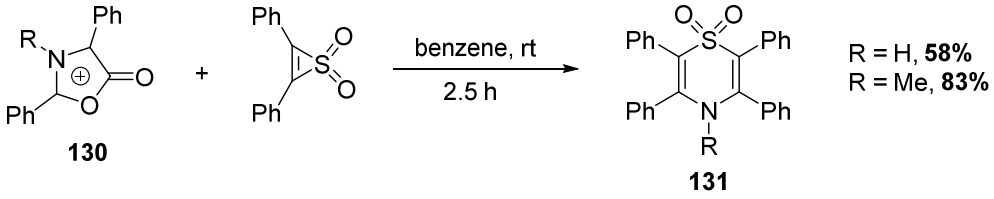
Scheme 77

Adam and Wharmby stated that treatment of phenacylthiazolium bromide **128** with aqueous base yields 1,4-thiazine **129** in good yield, and the proposed mechanism for this transformation is described Scheme 78.[145]



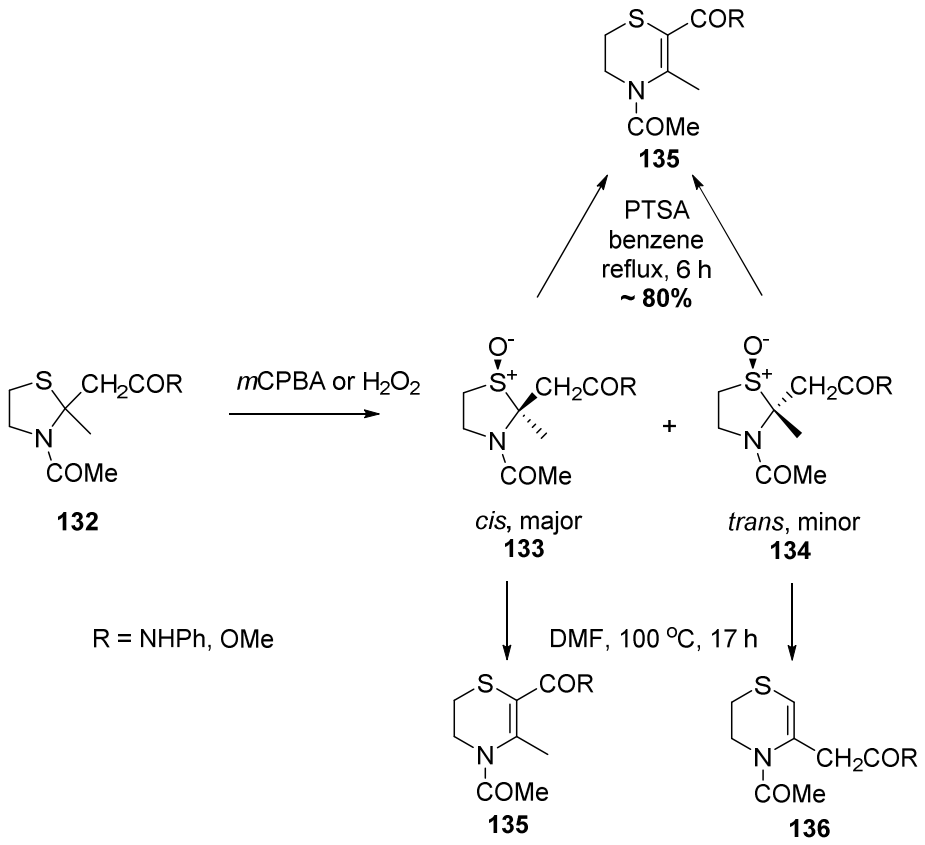
Scheme 78

Kato and coworker reported the reaction of diphenylthiirene-1,1'-dioxide with a mesoionic oxazol-5-one **130** at room temperature to give the corresponding 1,4-thiazine dioxide **131** in high yield (Scheme 79).[146] This transformation has a similar pattern to those previously described in *Section 3.D* for the synthesis of dithiin derivatives by the same author.



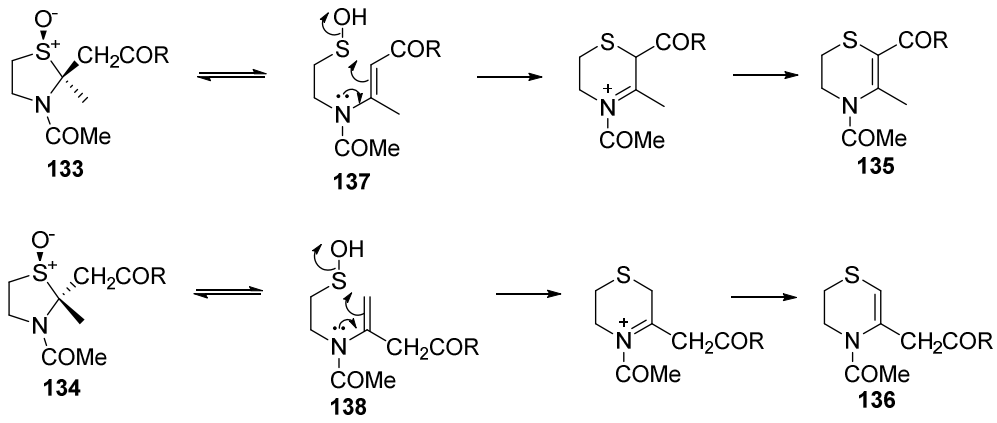
Scheme 79

Oxidation of the 1,3-thiazolidine sulfide **132** with various oxidizing agents gave a mixture of *cis*- and *trans*-sulfoxides **133** and **134** as major and minor products respectively (Scheme 80).[147] Both **133** and **134** with acid catalyst in refluxing benzene undergo ring expansion generating the 1,4-thiazine **135** with good yield. However, in dimethylformamide at 100 °C under neutral condition only the *cis*-sulfoxide **133** rearranged to **135**, while the *trans*- **134** produces thiazine **136**, with no yields reported.



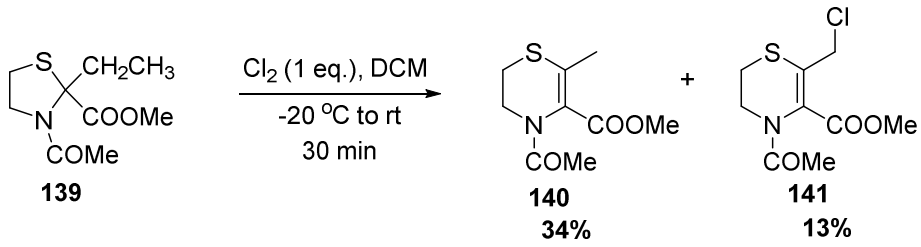
Scheme 80

A mechanism for the sulfoxide rearrangements in DMF has been proposed and may proceed *via* sulfenic acids **137** and **138**, respectively from **133** and **134**, as generated by a sigmatropic rearrangement involving the 2-methylene or 2-methyl group (Scheme 81).[147] Following nucleophilic attack at the sulfur atom by the π-electrons of the unsaturation system form the iminium ions, which finally generate the 1,4-thiazines.



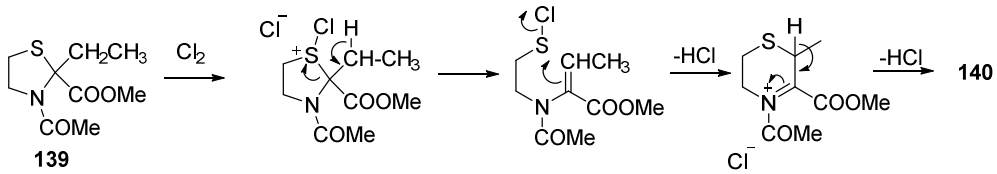
Scheme 81

Kato and coworker later investigated the rearrangement of thiazolidines.[148] Chlorinolysis of thiazolidine sulfide **139** using chlorine in DCM at -20 °C to room temperature leads to a mixture of the thiazines **140** and **141** (Scheme 82). The primary alkyl chloride **141** results from further chlorination of **140**.



Scheme 82

For this transformation, Lee *et al.* proposed a mechanism as outlined in Scheme 83. Chlorination of the sulfur atom generates the chlorosulfonium salt which further proceeds to ring opening by concerted β-elimination involving the methylene proton. As described above, nucleophilic attack of the unsaturated system on the sulfur atom gives the iminium ion which produces **140** by hydrogen chloride elimination.



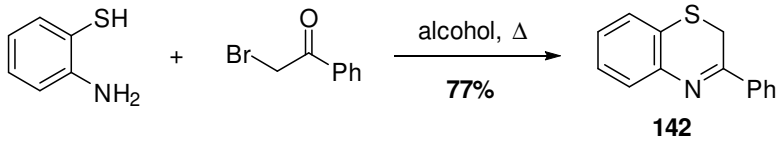
Scheme 83

5. SYNTHESIS OF 1,4-BENZOTHIAZINES

1,4-Benzothiazine derivatives are important because of their interesting biological properties and therefore have led chemists to explore diverse pathways for the synthesis of these compounds.[7]

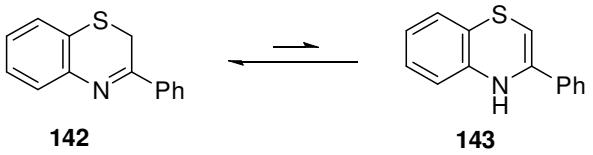
A. From 2-aminothiophenol or disulfide equivalents

In 1897, Unger reported the synthesis of 1,4-benzothiazine **142** by condensation of 2-aminothiophenol with 2-bromoacetophenone in good yield (Scheme 84).[149]



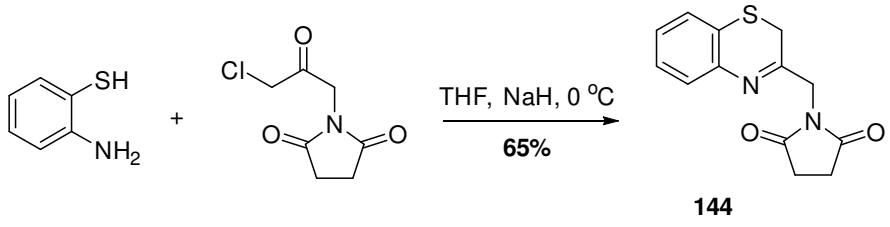
Scheme 84

Wilhelm and Schmidt investigated this transformation and stated that **142** existed in equilibrium with **143**, but that **142** was predominant (Scheme 85).[150]



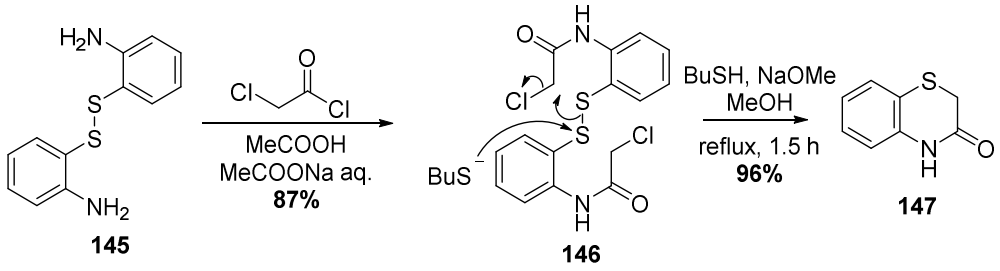
Scheme 85

In an extension of this methodology, Banzatti *et al.* reported the synthesis of **144** from 2-aminothiophenol with 1-chloro-3-(*N*-succinimido)propan-2-one in good yield (Scheme 86).[151]



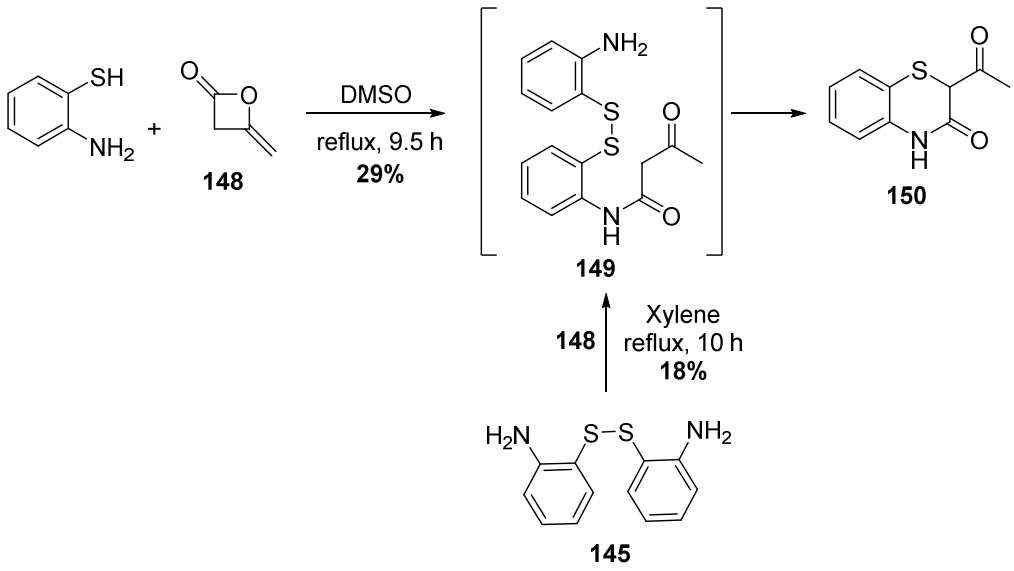
Scheme 86

In 1958, Weinstein *et al.* synthesised in high yield the bis(2-chloroacetamidophenyl) disulfide **146** by treatment of bis(2-aminophenyl) disulfide **145** with chloroacetyl chloride (Scheme 87).[152] Further attempts to replace the chlorine atoms of **146** with an *n*-butylthio substituent resulted in formation of the benzothiazine **147** in excellent yield.



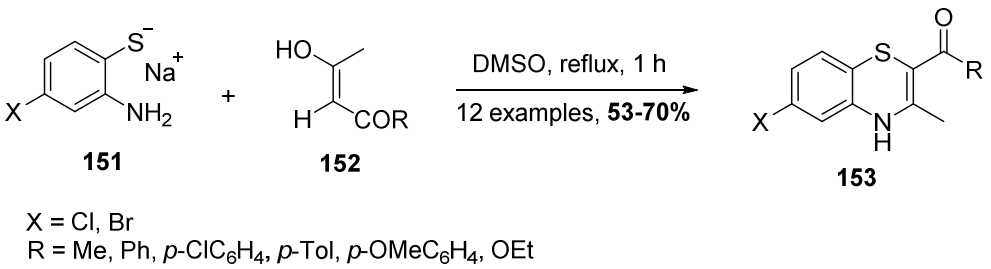
Scheme 87

Sakamoto *et al.* prepared the 1,4-benzothiazine **150** by refluxing a mixture of 2-aminothiophenol and diketene **148** in DMSO (Scheme 88).[153] The same product **150** was obtained from bis(2-aminophenyl) disulfide **145**, supporting that **149** is an intermediate in the reaction.



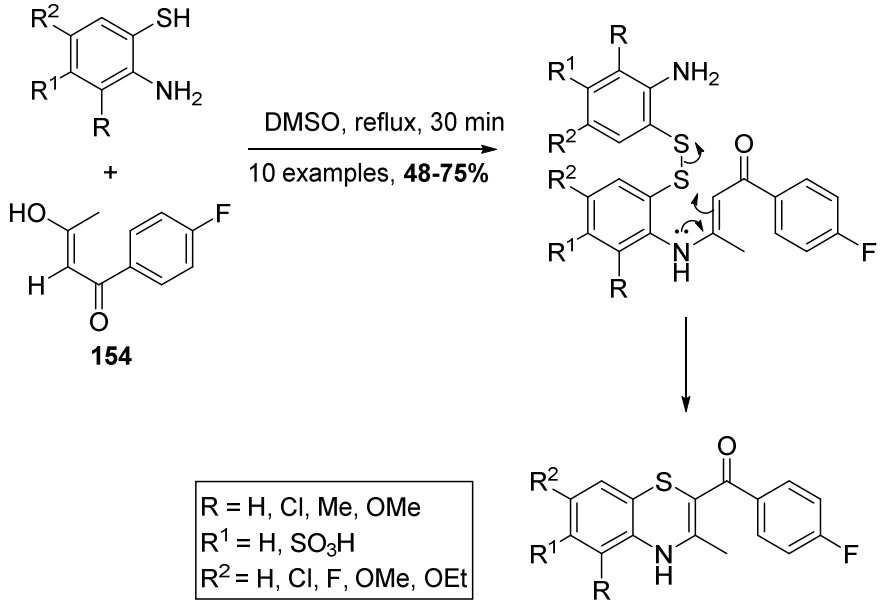
Scheme 88

Gupta *et al.* reported the synthesis of 6-halogenated 4H-1,4-benzothiazines **153** by condensation and oxidative cyclisation of 2-aminothiophenol sodium salt **151** with β-diketones **152** in refluxing DMSO (Scheme 89).[154]



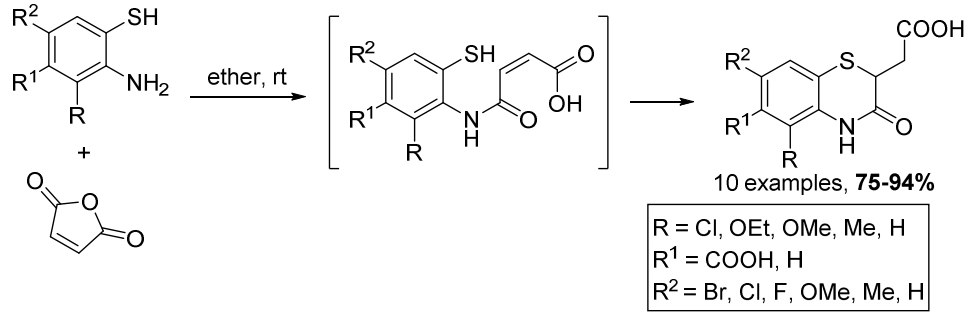
Scheme 89

Later, the same author extended the scope of the transformation with *p*-fluorobenzoylacetone **154** and proposed a mechanism for the transformation (Scheme 90).[155] 2-Aminobenzenethiol is believed to be oxidized to the corresponding disulfide which undergoes condensation followed by cyclisation yielding 1,4-benzothiazine.



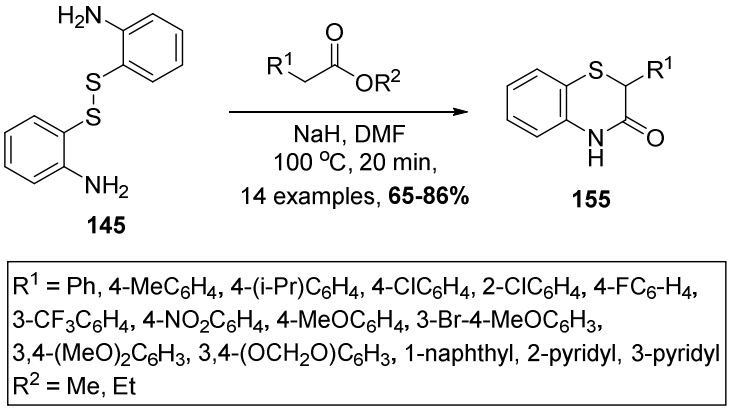
Scheme 90

Gupta *et al.* also described the synthesis of benzothiazine while employing maleic anhydride at room temperature (Scheme 91).[156] It is believed that the reaction proceeds through initial nucleophilic anhydride ring opening with the amino nitrogen.



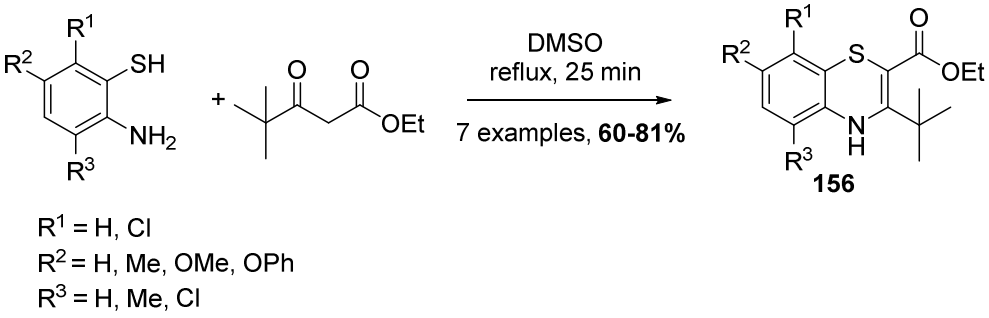
Scheme 91

Jacobsen and Andersen investigated the synthesis of benzothiazines **155** from disulfide **145** with methyl or ethyl aryl or pyridylacetates and sodium hydride (Scheme 92).[157] The method developed provides an efficient access to **155** with a large scope of substituents tolerated.



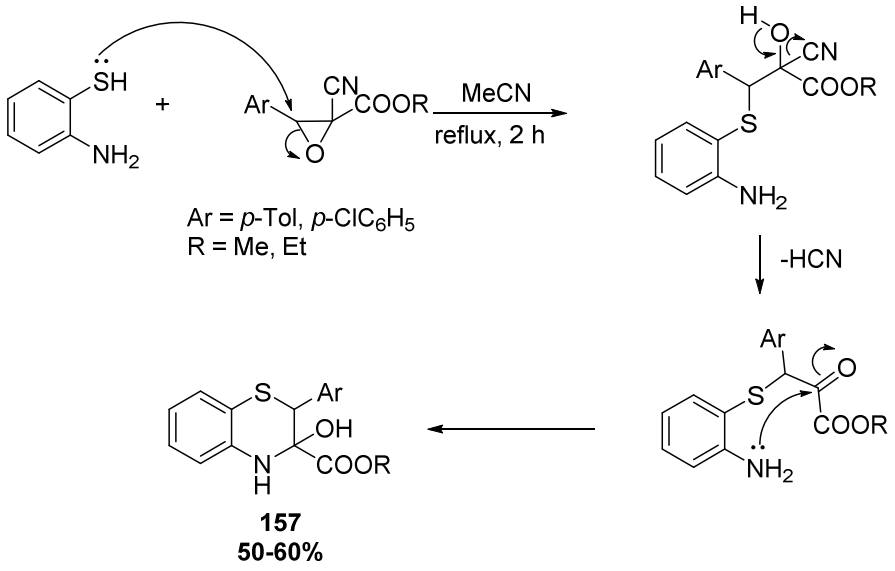
Scheme 92

Sharma *et al.* synthesised 1,4-benzothiazine **156** by heterocyclisation of β-ketoesters with substituted 2-aminothiophenols in DMSO (Scheme 93).[43]



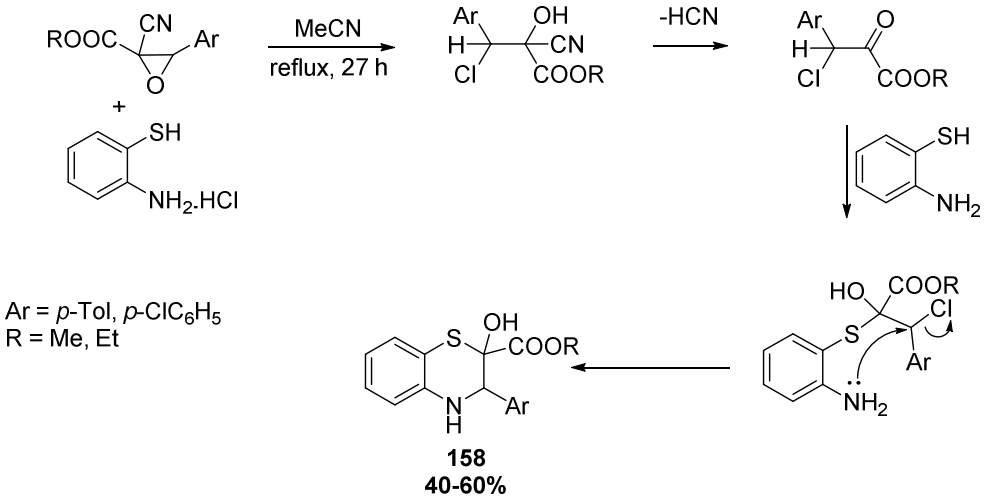
Scheme 93

Saadouni *et al.* explored the synthesis of 1,4-benzothiazines **157** from α-cyano α-alkoxy carbonyl epoxides and 2-aminothiophenol in refluxing acetonitrile (Scheme 94).[158] The sulfur atom only attacks the benzylic carbon of the epoxide and therefore the reaction is regioselective.



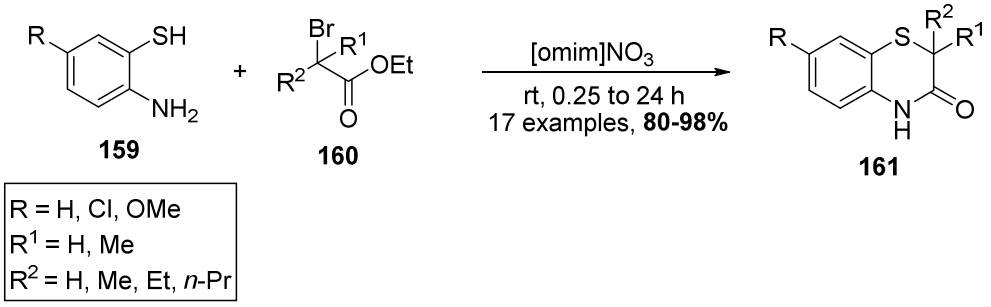
Scheme 94

However, when the reaction was performed with 2-aminothiophenol hydrochloride, attack on the epoxide is kinetically favored in the medium again at the benzylic carbon leading to **158**. The mechanism has been established and is described in Scheme 95.[159, 160]



Scheme 95

Sharifi *et al.* developed a room temperature procedure for the synthesis of benzothiazine **161** in high to excellent yield from the reaction of 2-aminothiophenols **159** with 2-bromoalkanoates **160** in ionic liquid [omim]NO_3 (Scheme 96).[161] The ionic liquid was recovered and reused in subsequent reactions. In this transformation the ionic liquid dissolves the reagents, initiates the reaction by the basicity of its anion and catalyzes the nucleophilic addition of the thiolate to the carbonyl moiety.

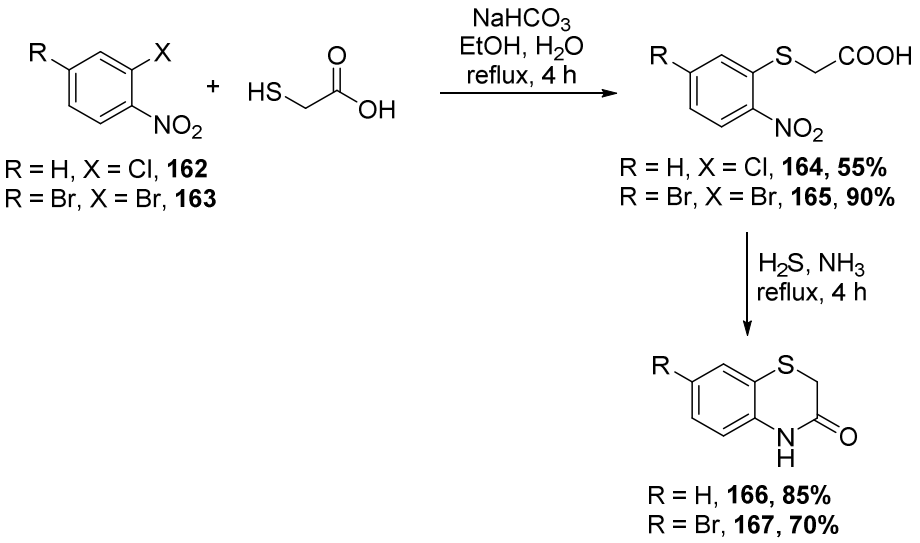


Scheme 96

Later, the same author established a procedure to access **161** in high yields from **159** and **160** using potassium fluoride on alumina (KF-Al_2O_3) at room temperature.[162] Here again, the catalyst could be recycled in further reactions while maintaining its activity.

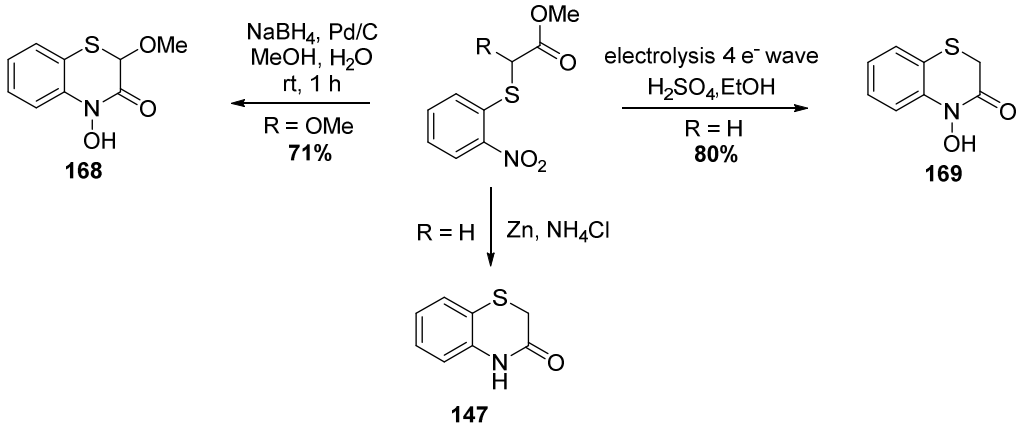
B. From halo and nitro aryl precursors

In 1957, Badger *et al.* prepared (2-nitrophenylthio)acetic acids **164** and **165** by direct interaction of nitrobenzenes **162** and **163** with mercaptoacetic acid (Scheme 97).[163] Further reduction with hydrogen sulfide and ammonia gave the benzothiazines **166** and **167** in high yields.



Scheme 97

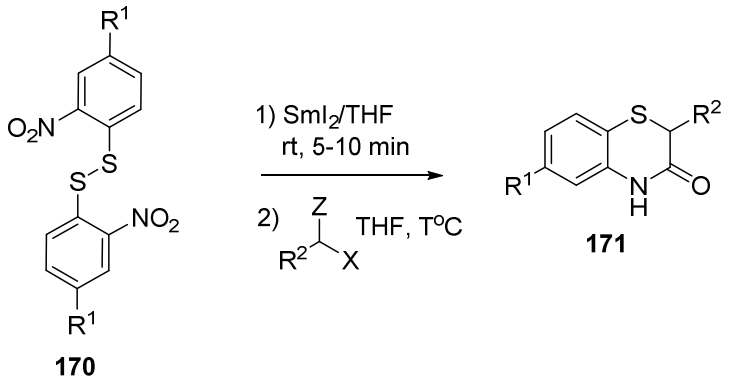
For similar precursors, Sicker *et al.*[164] performed reductive cyclisation with sodium borohydride following a slightly modified method from Coutts,[165] using Pd/C, yielding the acetal **168** (Scheme 98). While reduction with zinc dust in ammonium chloride solution yielded benzothiazine **147** as major product, electrochemical reduction in a mixture of sulfuric acid and ethanol at -0.4 V SCE (corresponding to the polarographic plateau of the 4 electron wave) gave **169**.



Scheme 98

Zhong and Zhang reported easy reduction of bis(*o*-nitrophenyl) disulfides **170** by Kargan's reagent, samarium(II) iodide, followed by treatment *in situ* of α-halocarboxylic derivatives yield the desired 1,4-benzothiazine **171** in good yield

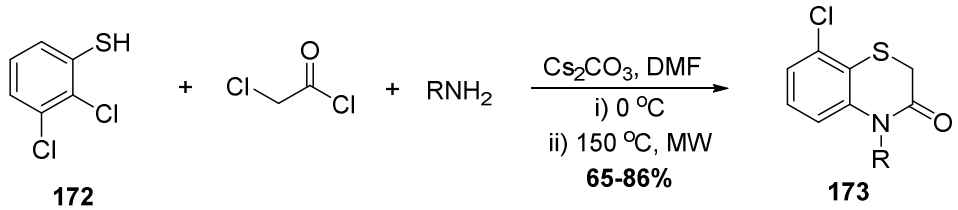
(Scheme 99).[166] The α-bromoesters was found more reactive than other α-halocarboxylic derivatives.



$R^1 = R^2 = H$, X = Br, Z = COOEt, rt, 2 h, **83%**
$R^1 = R^2 = H$, X = Cl, Z = COOEt, 60 °C, 3 h, **61%**
R^1 = Cl, R^2 = H, X = Br, Z = COOEt, rt, 2 h, **84%**
R^1 = Cl, R^2 = Me, X = Br, Z = COOH, 40 °C, 3 h, **71%**

Scheme 99

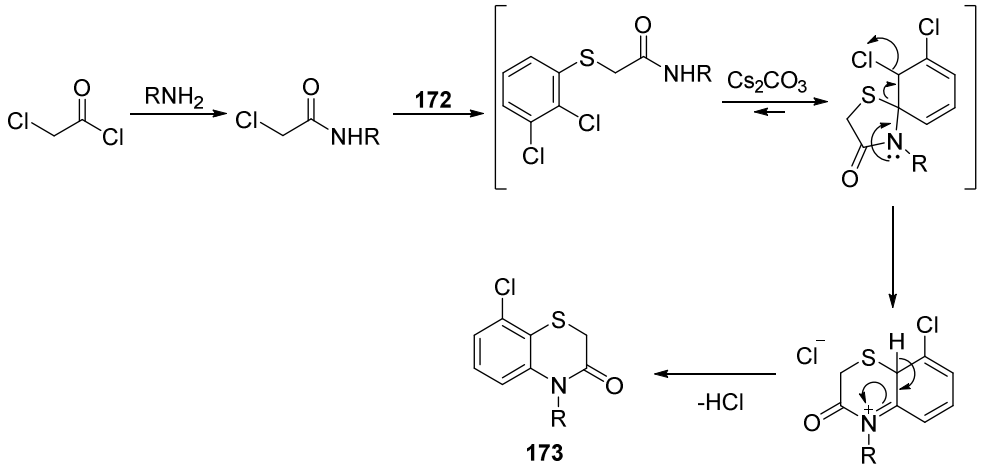
Zuo *et al.* reported the one-pot synthesis of 1,4-benzothiazine **173** under microwave irradiation *via* Smiles rearrangement in the presence of cesium carbonate from 2,3-dichlorobenzenethiol **172** (Scheme 100).[167] The desired products **173** were obtained in 65 to 86% yield.



R = Bn, hexane, cyclohexane, pyrrole

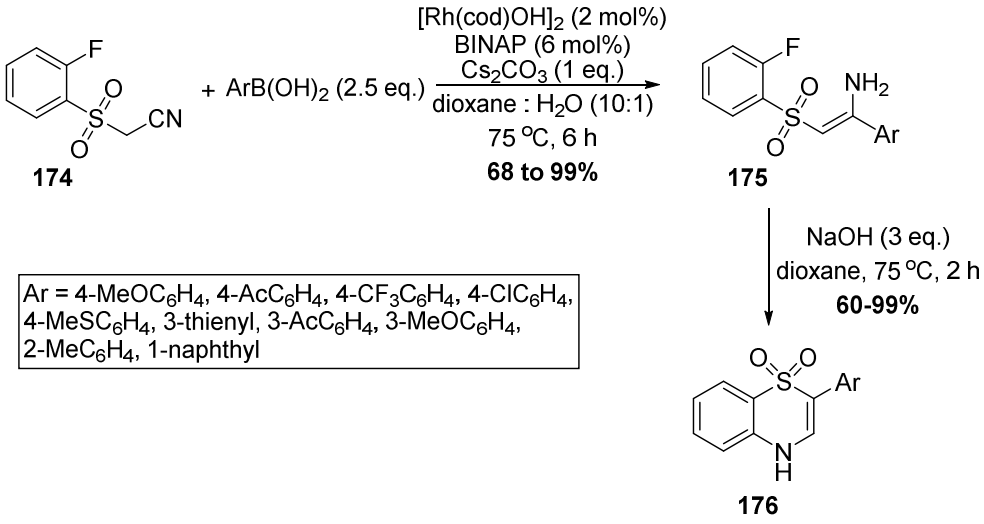
Scheme 100

A mechanism has been proposed by the authors with initial formation of the *S*-alkylated product, facilitated by the presence of cesium carbonate (Scheme 101).[167] Further cyclisation by Smiles rearrangement generates the spiro-type intermediate and underwent rearrangement with loss of hydrogen chloride.



Scheme 101

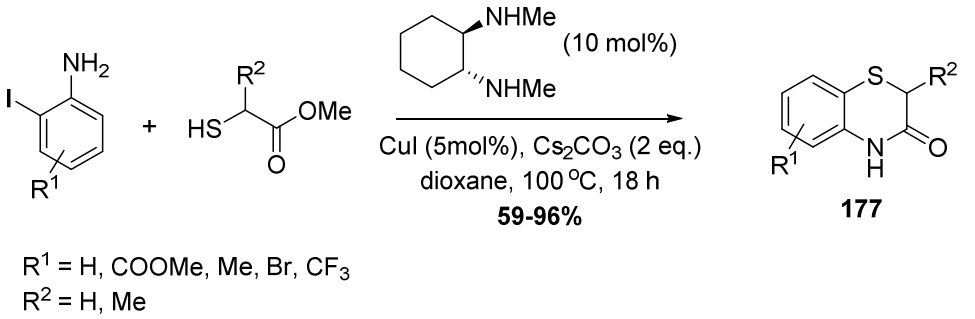
Tsui *et al.* developed a synthetic route to arylated 1,4-benzothiazines **176** utilizing *Z*-β-(2-fluorobenzenesulfonyl)vinylamines **175** (Scheme 102).[168] Arylated vinylamines **175** were formed by rhodium catalyzed reaction of **174** with arylboronic acid in good yield. Due to the wide array of commercial arylboronic acids, the scope of the substituent of the vinylamine was explored and good functional group tolerance was observed. Only formation of the *Z*-**175** was observed. Further intramolecular cyclisation *via* nucleophilic aromatic substitution yields the benzothiazines **176** in good to excellent yield.



Scheme 102

Huang *et al.* reported a one-step synthesis of benzothiazines **177** from copper catalyzed coupling of readily available 2-iodoanilines and 2-mercaptoacetates

(Scheme 103).[169] *trans-N,N'*-Dimethylcyclohexane-1,2-diamine was found as an efficient ligand in this process.

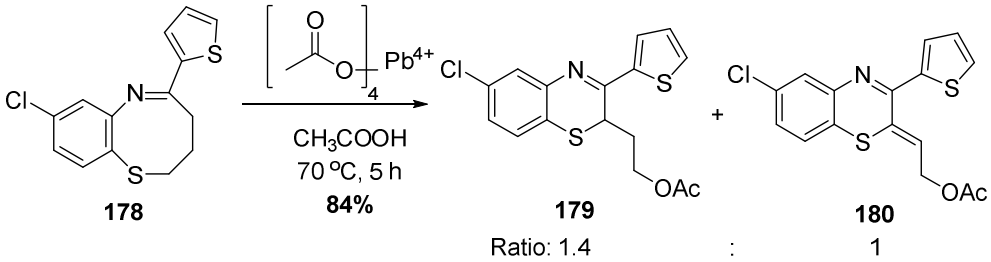


Scheme 103

C. By ring enlargement or contraction

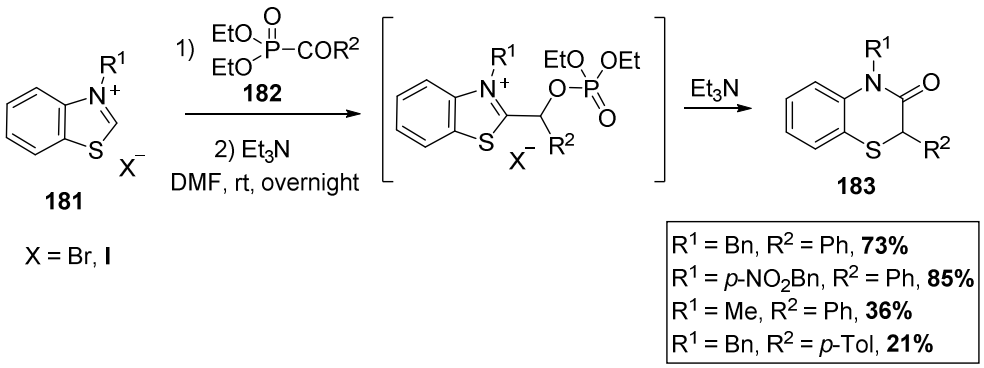
Synthesis of 1,4-benzothiazine by ring expansion from benzothiazole is extensively reported in the literature, while synthesis by ring contraction is much less common.

In 1980, Press *et al.* reported that treatment of benzothiazocine **178** with lead tetraacetate at 70 °C led to benzothiazines **179** and **180** (Scheme 104).[170] The products could be separated by chromatography but the isolated yields were not reported.



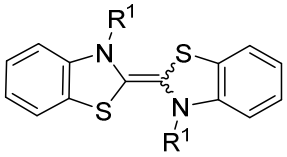
Scheme 104

Takamizawa *et al.* reported ring expansion of thiazolium salts to 1,4-thiazines with diethyl benzoylphosphonate (*Section 4.C.*).[132-141] In 1972, the same author extended the scope of the transformation to ring expansion of benzothiazolium salts.[137] Reaction of salts **181** was first treated with several diethyl acylphosphonates **182** followed by triethylamine, yielding the desired benzothiazines **183** (Scheme 105).



Scheme 105

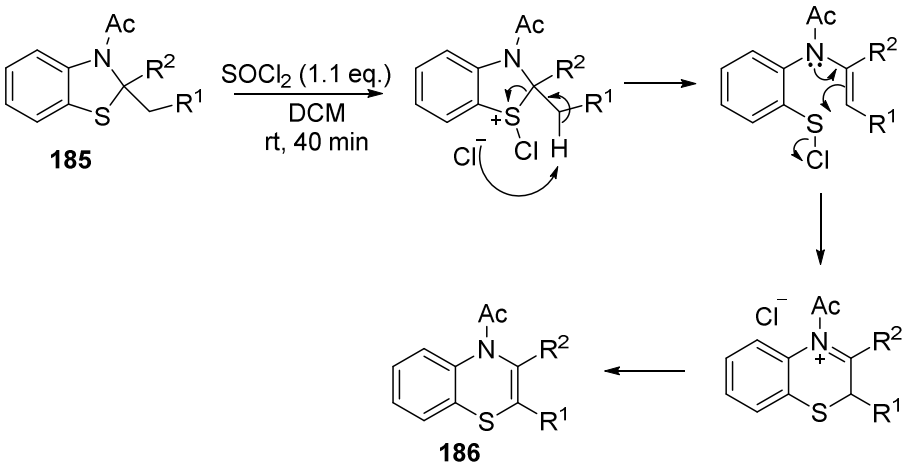
The reagent addition order is crucial as treatment of **181** with triethylamine promotes dimerisation at the C_2 position to give **184** (Figure 6). When the phosphonate is added to the reaction mixture before triethylamine, the benzothiazolium is readily consumed in the nucleophilic reaction with **182** affording the product **183**.



184

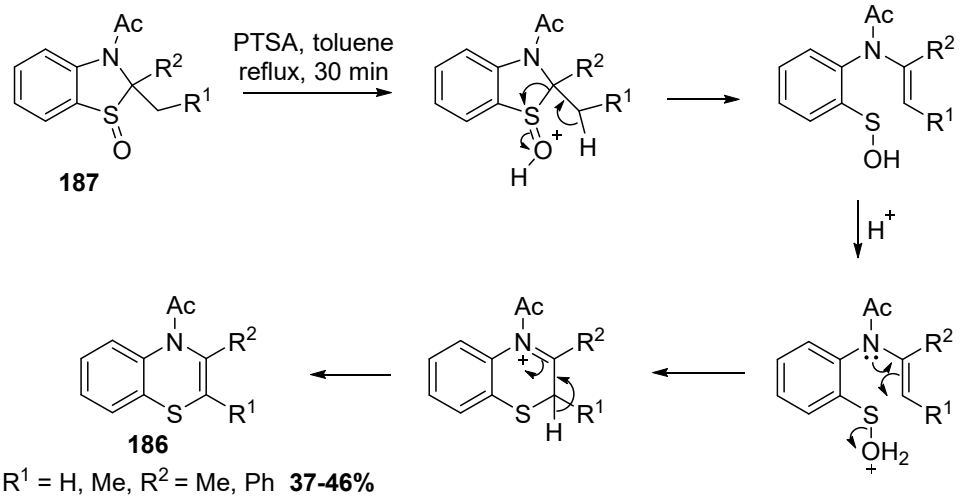
Figure 6

Ring expansion reactions of appropriately substituted cyclic sulfides *via S*-chlorosulfonium salts, formed *in situ* by chlorination in non-aqueous medium, have been reported in the literature.[77,171] In 1977, Chioccara *et al.* described ring expansion of this type from 2,3-dihydro-1,3-benzothiazoles **185** to 4H-1,4-benzothiazines **186** on treatment with sulfuryl chloride (Scheme 106).[172] The authors proposed the mechanism outlined in Scheme 106 for this transformation.



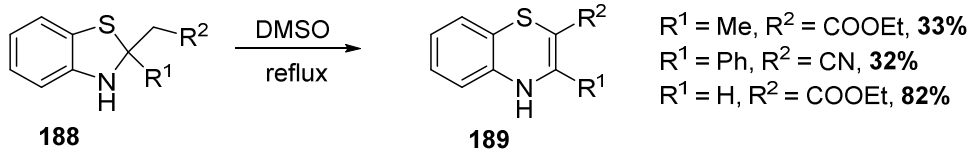
Scheme 106

Chioccara *et al.* also describes formation of **186** by acid catalyzed rearrangement of dihydrobenzothiazole 1-oxides **187** (Scheme 107).[173] The pathway proposed by the author involves an acid catalyzed ring-opening of the sulfoxide **187** with subsequent ring closure to form **186**. The reaction is applicable to both *cis* and *trans* sulfoxides.



Scheme 107

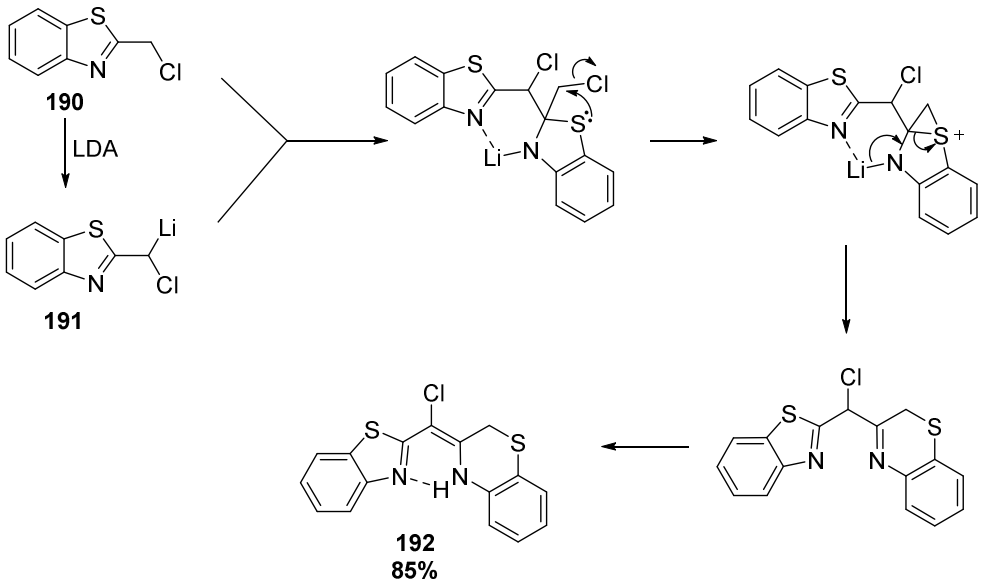
Liso *et al.* observed direct conversion of *N*-unsubstituted benzothiazoline **188** to benzothiazine **189** in refluxing DMSO (Scheme 108).[174,175]



Scheme 108

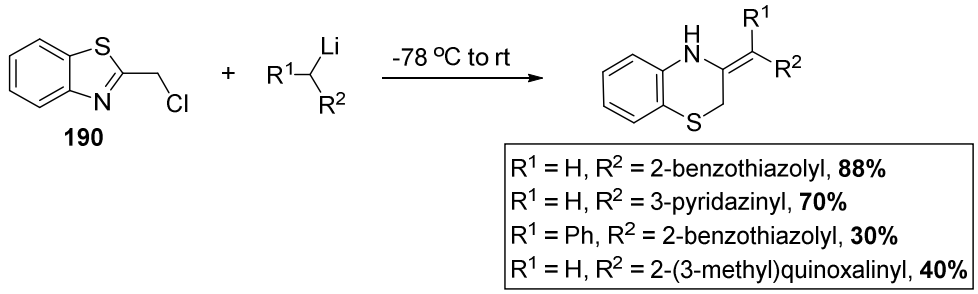
Later, the same author developed a method for synthesis of *N*-unsubstituted benzothiazine **189** from benzothiazoline in better yields and under mild conditions.[176] The procedure consists of treating **188** with potassium *t*-butoxide followed by powdered iodine at room temperature in toluene.

Florio reported lithiation of chloromethylbenzothiazole **190** with lithium diisopropylamide (LDA) at -78 °C resulting in formation of **192** when the solution was allowed to warm to room temperature (Scheme 109).[177] A mechanism has been proposed for the transformation, and is outlined in Scheme 109, starting by addition of **191** to the C-N double bond of **190** generating the thiazole-thiazoline intermediate, stabilized by intramolecular chelation of lithium.



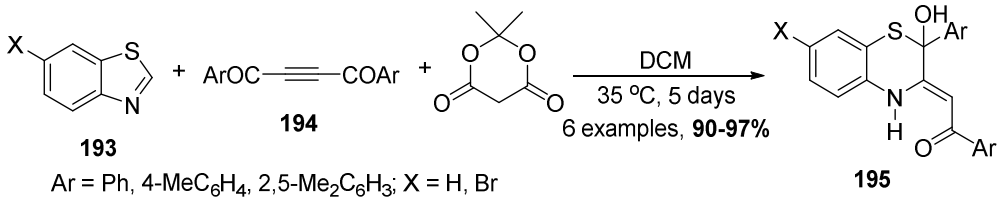
Scheme 109

Later, the same author investigated the synthetic potential of such a thiazole-thiazine ring enlargement for the preparation of heteroarylalkylidene benzothiazines (Scheme 110).[178]



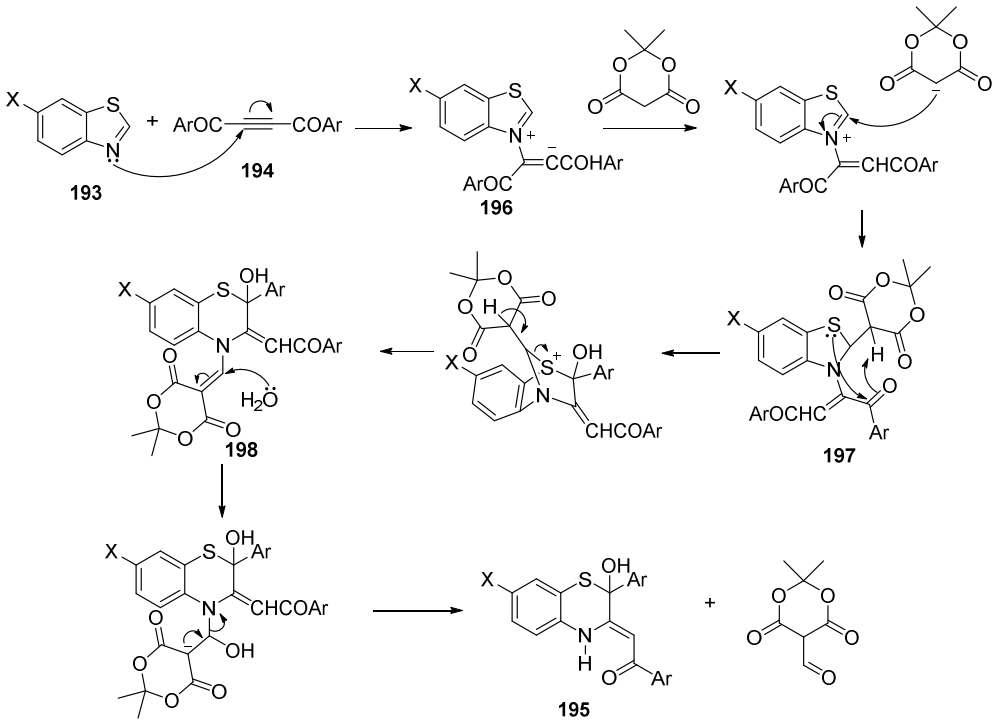
Scheme 110

Adib *et al.* developed an efficient ring expansion protocol of benzothiazoles **193** to give functionalized 1,4-benzothiazines **195** (Scheme 111).[179] The reaction proceeds via addition of benzothiazoles **193** and diaroylacetylenes **194** in the presence of Meldrum's acid under mild conditions leading to **195** in excellent yield.



Scheme 111

A mechanism for the transformation has been proposed and is outlined in Scheme 112. The first step was proposed to involve initial addition of **193** to the electron deficient acetylenic compound **194** resulting in formation of the zwitterionic intermediate **196**, which is readily protonated by Meldrum's acid. Then, the conjugate base of the Meldrum's acid attacks the positively charged intermediate produced, generating **197**. Nucleophilic attack of the sulfur atom on the carbonyl group and further ring opening forms the *N*-substituted benzothiazine intermediate **198**. Finally, hydrolysis of **198** and elimination of formyl Meldrum's acid affords **195**.



Scheme 112

In summary, diverse synthetic methods can be employed to lead to 1,4-oxathiins, 1,4-dithiins, 1,4-thiazines and 1,4-benzothiazines, many of which display interesting biological activities. These compounds continue to be of interest for pharmaceutical application today.

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"The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed."

C.G. Jung

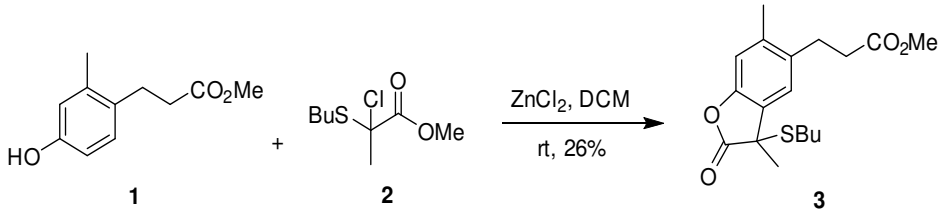
CHAPTER 2

Studies into Controlling Reactivity and Product Formation in the Oxidative Transformation of α-Thioamide to α-Thio-β-chloroacrylamide with Enhanced Control of a Cascade Transformation

Table of Contents

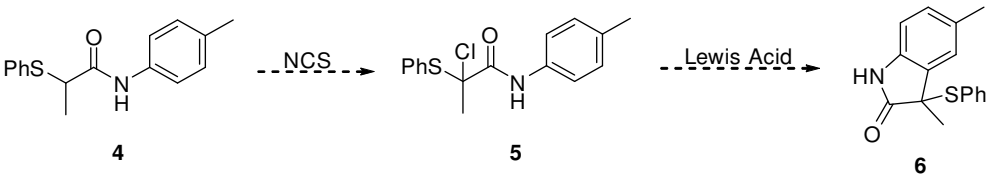
1. BACKGROUND

McKervey *et al.*[1] had previously reported that the Friedel Crafts alkylation of methyl *ρ*-hydroxy dihydrocinnamate **1** with α-chlorosulfide **2** followed by lactonisation forms **3** (Scheme 1). Indeed, the alkylthio substituent on the geminal position of the chlorine polarises the carbon–halogen bond promoting electrophilic aromatic substitution.



Scheme 1

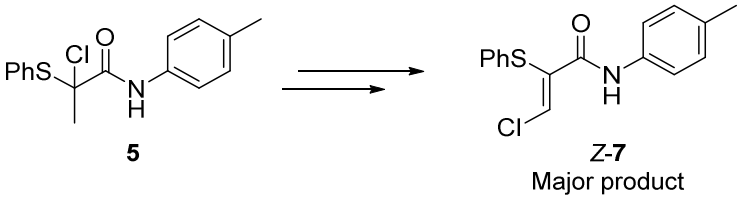
By analogy, it was envisaged that α-chlorosulfide **5**, on treatment with a Lewis acid, would undergo intramolecular electrophilic aromatic substitution leading to the desired lactam **6** (Scheme 2).[2]



Scheme 2

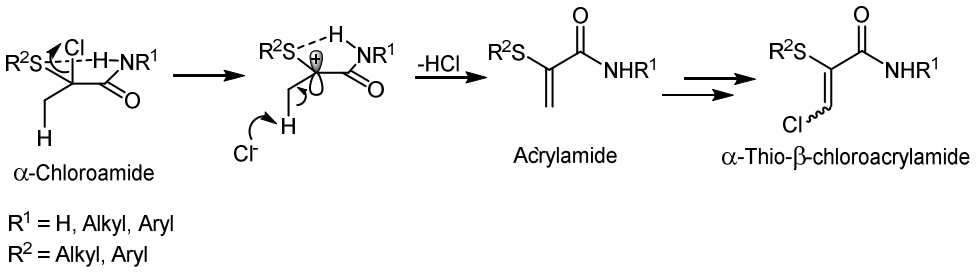
The chlorination of α-thioesters with NCS is well established[3] and consequently this methodology was initially applied to the chlorination of α-thioamide **4**.[4,5] However, the reaction pathway involved ultimately proved more complex. The desired α-chlorosulfide **5** was initially formed but, due to its lability, reacted

further to form other compounds including α-thio-β-chloroacrylamide **7** as the main product (Scheme 3).



Scheme 3

The difference in stability between the ester **2** and the amide α-chlorosulfide **5** is likely to be due to conformational factors.[4, 6, 7] Indeed, for primary and secondary amide α-chlorosulfides, the intramolecular hydrogen bond holds the compound in a conformation in which loss of the chloride from the α-carbon is favored through captodative stabilization of the resulting sulfur stabilized carbocation (Scheme 4).[8] As a result, the elimination of HCl from the amide α-chlorosulfides happens spontaneously leading to the acrylamide intermediate and further reaction affords the α-thio-β-chloroacrylamide derivative. This mechanism will be described later in this chapter.



Scheme 4

For ester, ketone and nitrile α-chlorosulfides (Figure 1), there is greater freedom of rotation due to the absence of hydrogen bonding.[9,7,1, 3] In these cases, the α-chlorosulfides presumably adopt a different conformation of the intermediate from which loss of the chloride is less favored. Therefore, the HCl elimination requires more forcing conditions to get through from the corresponding α-thio-β-chloroester/ketone/nitrile.

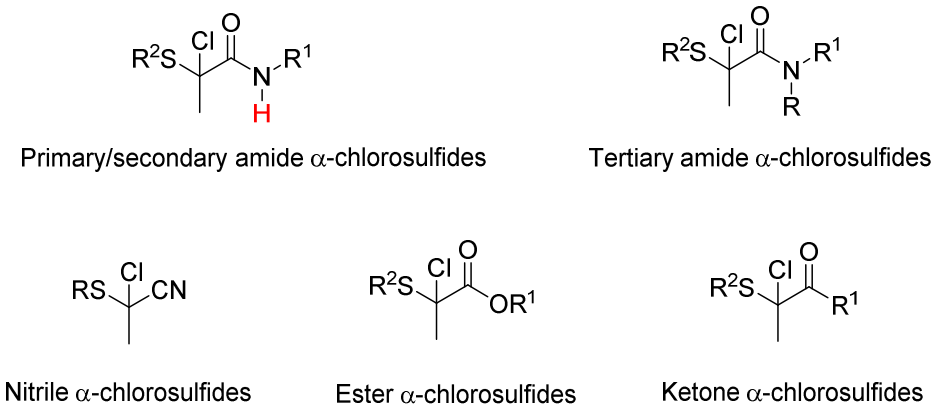


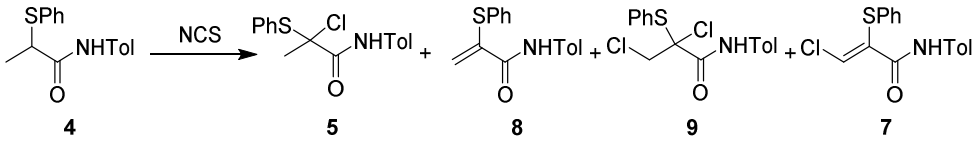
Figure 1

However, the α-chlorosulfides containing a tertiary amide (Figure 1) were reported to be unstable.[4] The fact than the α-chlorosulfides containing a tertiary amide do not display the same stability as the ester, ketone and nitrile series, discredits this theory.

Further explanation for the decreased ease of elimination in the ester/ketone and nitrile series, relative to the amide series, could be explained by the increased electron withdrawing effect of the ester, ketone and nitrile group compared to the amide. This effect would destabilize a carbonium ion at the α-carbon, therefore the chloride elimination from these α-chlorosulfides would be less favored.

Murphy *et al*[4] conducted experiments (Table 1) in order to understand the reaction observed in Scheme 3. Tetrachloromethane was used as solvent in many of these reactions due to the efficient precipitation of *N*-succinimide by-product, which could be easily filtered from the solution. Also, proficient reaction monitoring could be performed as this solvent does not bear any protons. Therefore, the reaction mixtures can be studied/monitored in real time using ^{1}H NMR spectroscopy without the need for suppression of the proton signal of the solvent. Despite the toxicity of tetrachloromethane,[10] it was useful for this study as transient by-products could be observed. The ratio of the products formed during the transformation of α-thioamide **4** to α-thio-β-chloroacrylamide **7** was observed to be dependent on the reaction conditions.[4]

Table 1 Transformation of α-thioamide **4** to α-thio-β-chloroacrylamide **7** [4]



4 **5** **8** **9** **7**

					Molar ratio of products[a]			
Entry	NCS (eq.)	Temperature (°C)	Time (h)	Solvent	**5**	**8**	**9**	**7**
1	1.1	0	3	CCl_4	only	-	-	-
2	1.1	20	24	CCl_4	1	1	-	-
3	2.2	20	48	CCl_4	-	1	2	-
4	2.1	40	22	toluene	-	-	3.3	1
5	2.2	47-50	18-24	CCl_4	-	-	1	10
6	2.2	reflux	18	CCl_4	-	-	-	only
7	2.2	reflux	2	toluene	-	-	-	only

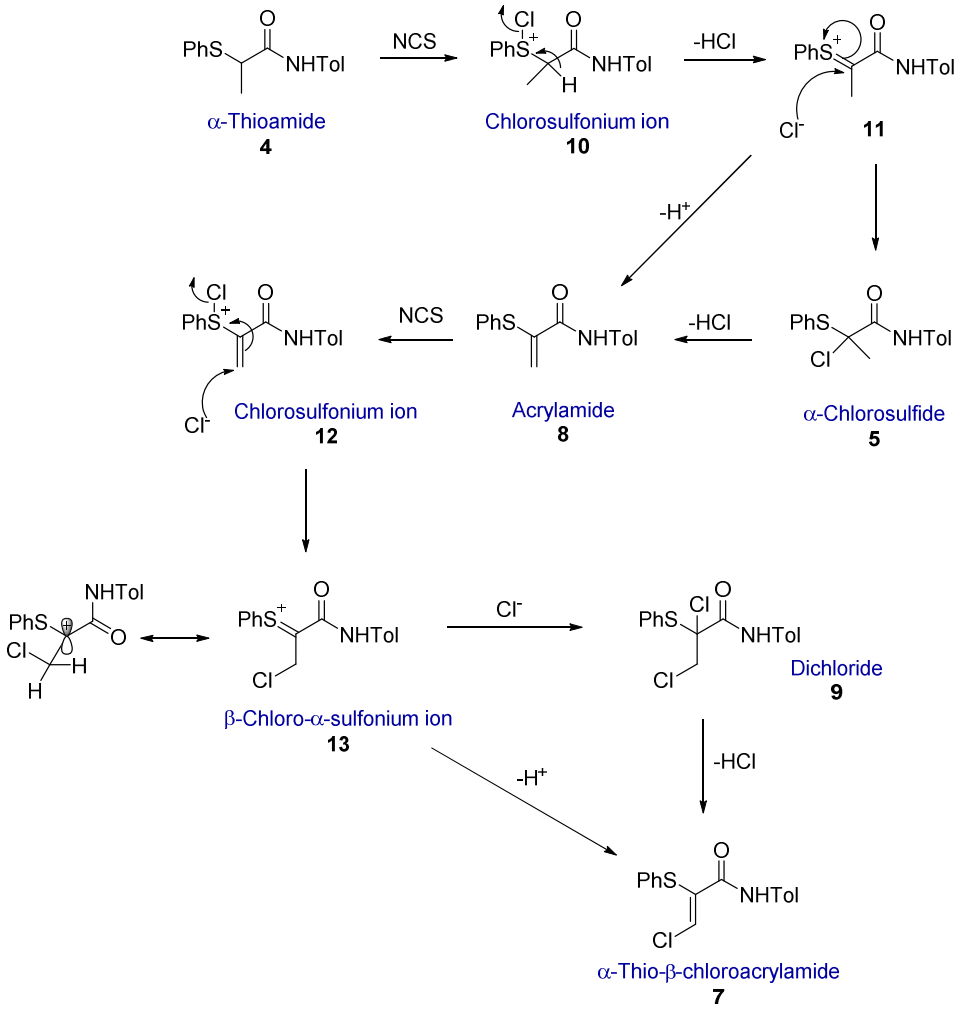
[a] Ratios of products were determined by integration of ^{1}H NMR spectra of crude reaction mixtures.

When the reaction was performed using 1.1 equivalents of NCS at 0 °C, only α-chlorosulfide **5** was formed (Entry 1, Table 1).[4] At room temperature, acrylamide **8** was also obtained as an equimolar mixture with α-chlorosulfide **5** (Entry 2, Table 1). This suggests that the acrylamide is the product resulting from the HCl elimination of α-chlorosulfide **5** mentioned previously. Consequently, it can be asserted that this elimination will not occur spontaneously at 0 °C and needs more energy to proceed.

Two equivalents of NCS were found to be necessary to form dichloride **9** and α-thio-β-chloroacrylamide **7** (Entries 3 to 7, Table 1), suggesting that a second chlorination occurs during this reaction.[4] A reaction temperature of at least 40 °C is required to form α-thio-β-chloroacrylamide **7** derivative. As dichloride **9** formation was not described by Maguire *et al.*[5] during the attempted synthesis of lactam **6** (Scheme 2), the dichloride may be a precursor of α-thio-β-chloroacrylamide **7**, probably formed *via* HCl elimination, which require at least 40 °C to proceed.

Finally, only α-thio-β-chloroacrylamide **7** was formed under reflux conditions using either tetrachloromethane or toluene as the reaction solvent (Entries 6 and 7, Table 1). However, in toluene the reaction was found to be noticeably quicker.[4, 6]

Taking this data into consideration, a mechanism was proposed by Maguire et *al.*[4] for this transformation (Scheme 5).



Scheme 5 Mechanism proposed by Maguire *et al.*[4]

The first equivalent of NCS generates α-chlorosulfonium ion **10** by chlorination of the sulfur group of α-thioamide **4**. Following, elimination of hydrogen chloride and subsequent addition of chloride, formation of α-chlorosulfide **5** occurs. Acrylamide **8** is then generated by elimination of another molecule of hydrogen chloride. A second equivalent of NCS chlorinates the sulfur of **8**, leading to chlorosulfonium ion **12**. Attack by chloride ion causes elimination of the chloride

from sulfur to generate intermediate **13**. A further chloride addition leads to formation of dichloride intermediate **9** which affords the final α-thio-β-chloroacrylamide **7**, again by elimination of hydrogen chloride.

The key intermediates involved including **8**, as well as the labile compounds **5** and **9**, were previously isolated and characterized within the group (Figure 2).[4, 6] Thus, characteristic ^{1}H NMR spectroscopic data for the starting material, intermediates and final product were obtained, permitting identification and quantification of these molecules as part of reaction mixtures.

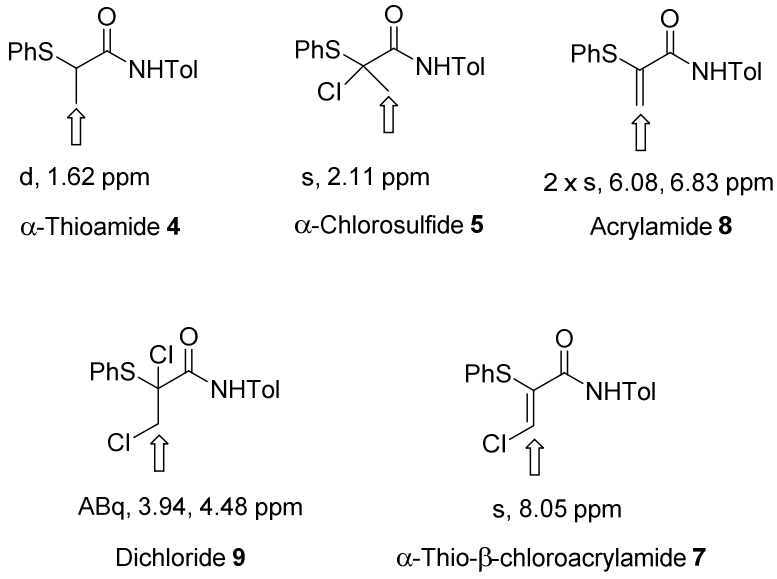


Figure 2 Characteristic ^{1}H NMR signals in $CDCl_3$.[6]

The α-thioamide starting material **4** is characterised by a doublet at δ_H 1.62 ppm corresponding to the methyl group (Figure 2).[4] A singlet at δ_H 2.11 ppm corresponds to the methyl resonance for α-chlorosulfide **5**. α-Chlorosulfide **5** was analysed as a tetrachloromethane solution using ^{1}H NMR spectroscopy, but partial decomposition occurred on storage in solution at temperatures as low as -20 °C (*ca.* 50% in 7 days), or more rapidly on concentration of the compound (*ca.* 50% in 1 h).[4]

Acrylamide **8** is identified by the characteristic terminal alkene resonances of two singlets at δ_H 6.08 and 6.83 ppm (Figure 2).[4, 6] Dichloride **9** is identified by an AB quartet system at δ_H 3.94 and 4.48 ppm which corresponds to the protons of the

β-carbon and was only isolated as a mixture with the product **7**. Partial decomposition of the dichloride occurred on storage or exposure to silica gel, which implies that it is not possible to isolate this intermediate in pure form. The decomposition product was found to be α-thio-β-chloroacrylamide **7** by ^{1}H NMR spectroscopy.[4] A singlet at δ_H 8.05 ppm is assigned to the proton of the β-carbon in the final α-thio-β-chloroacrylamide product **7**.

In order to further investigate the reaction mechanism proposed, Foley *et al.*[6] performed a study using React ^{1}H NMR *in situ* monitoring (Figure 3). The reaction profile in tetrachloromethane at 25 °C showed that the starting material **4** began to be consumed within 16 min of NCS addition (Figure 3). This delay was suggested to be due to some form of activation of the NCS involved, possibly activated by HCl that is produced as the reaction proceeds.[6]

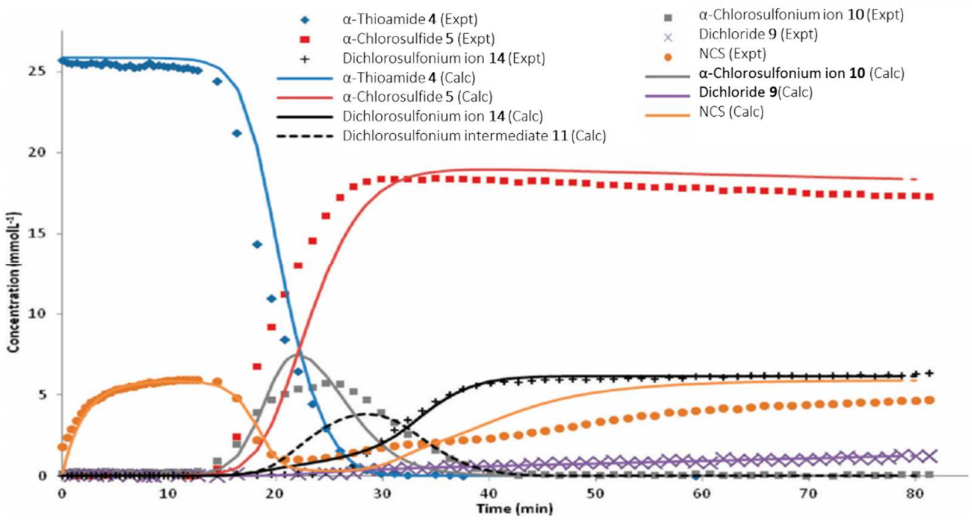


Figure 3 React NMR of α-thio-β-chloroacrylamide formation in tetrachloromethane at 25 °C.[6]

When the α-thioamide was consumed, the appearance of two separate doublets at δ_H 1.28 and 1.67 ppm was observed in the ^{1}H NMR spectra (Figure 3).[6] These have been assigned as the diastereomeric methyl signals of chlorosulfonium ion **10** resulting from the formation of a new stereogenic center by chlorination of the sulfur (Figure 4). The methine proton [C(2)H] on the α-carbon was observed at δ_H 3.33 and 3.67 ppm. This characterization was confirmed by ^{1}H-^{13}C Heteronuclear Single Quantum Correlation (HSQC) spectroscopy.[6] The proton at δ_H 3.67 ppm in particular, which correlated to a methine carbon at δ_C 61.6 ppm, and a

diastereomeric resonance at δ_H 3.33 ppm with the corresponding carbon at δ_c 62.8 ppm correlate with the values reported by Liu and Vederas, who described a downfield shift in chlorosulfonium ion methylene carbons adjacent to sulfur at δ_C ~66 ppm for a similar compound.[11, 12]

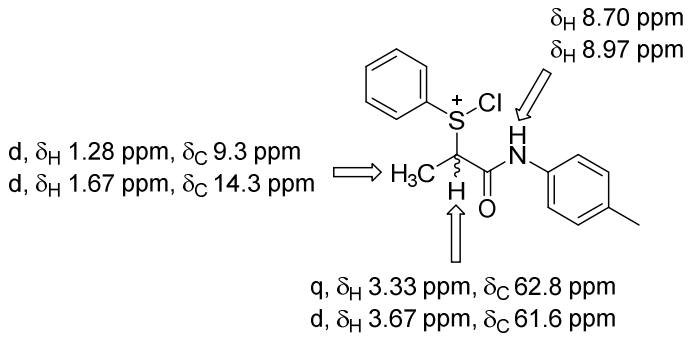


Figure 4 NMR signals of the diastereoisomers of chlorosulfonium ion **10**.[6]

Chlorosulfonium ion intermediates have been reported in the literature for the NCS mediated chlorination of sulfides.[13] Hence, it has been proposed as an intermediate in this cascade transformation based on the experimental and NMR data.

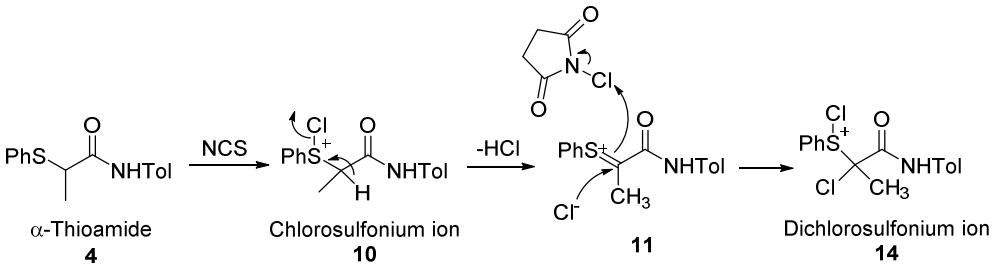
Chlorosulfonium ion intermediate **10** was quickly converted to α-chlorosulfide **5** (Figure 3).[6] The emergence of α-chlorosulfide **5** coincided with the disappearance of **10**, suggesting that chlorosulfonium ion **10** is a precursor for formation of intermediate **5**. Acrylamide **8** could only be detected at very low levels in the ^{1}H NMR spectrum. This showed that acrylamide **8** was quickly transformed to dichloride **9** *via* addition of the second NCS equivalent.[6]

The HCl liberated during the formation of **5** can protonate a second equivalent of NCS resulting in an increase in its reactivity. This activated NCS species allows the second chlorination step to occur.

An elevation of temperature to 40 °C was found to be necessary to promote hydrogen chloride elimination leading to the α-thio-β-chloroacrylamide **7** formation.[6]

The reaction monitoring study also revealed the formation of dichlorosulfonium ion **14**, which coincided with the total consumption of starting α-thioamide **4**.[6] On

examination of the experimental reaction profile (Figure 3), it appears that this dichlorosulfonium ion **14** is derived from α-chlorosulfonium ion **10** *via* dichlorosulfonium intermediate **11**, as described in Scheme 6. Once formed, dichlorosulfonium ion **14** is not further transformed through the reaction cascade. This constitutes a competitive pathway that can reduce the overall yield of α-thio-β-chloroacrylamide **7**.[6]

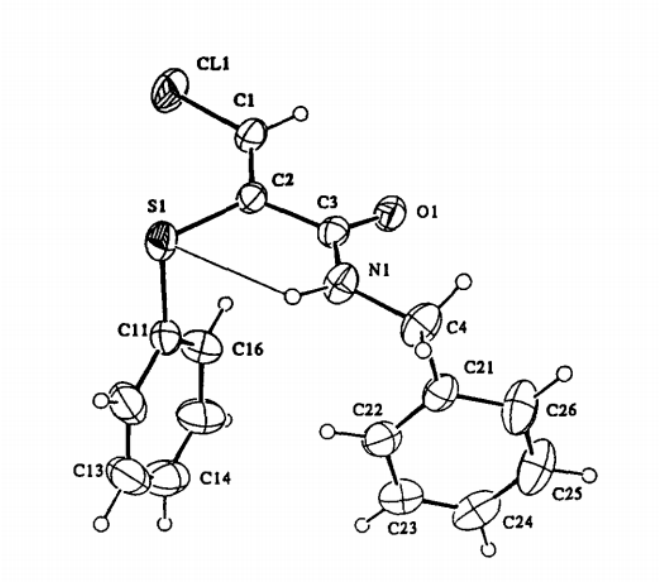


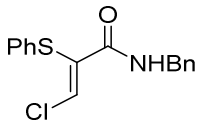
Scheme 6 Competitive pathway observed during α-thio-β-chloroacrylamide formation in CCl_4 as reaction solvent.[6]

α-Chlorosulfonium ion **10** and dichlorosulfonium ion **14** were detected when the reaction was conducted in CCl_4, but not in toluene or acetonitrile-d_3.[6] The rate of this HCl elimination and the second chlorination step is therefore solvent dependent, presumably due to differences in solvent polarity.

The transformation of α-thioamide **4** to α-thio-β-chloroacrylamide **7** was explored in detail allowing a full reaction mechanism to be proposed.[4] The React NMR study performed supported the mechanism proposed by Maguire *et al.* but also provided evidence of the formation of dichlorosulfonium ion **14** as a competitive pathway in the overall reaction cascade.[6] The characteristic ^{1}H NMR signals for the key intermediates formed were obtained, allowing easy reaction monitoring using ^{1}H NMR spectroscopy.

The stereochemistry of the transformation was established by single crystal X-ray diffraction of the *N*-benzyl derivative **15** (Figure 5); the stereochemistry of other derivatives has been assigned by analogy to α-thio-β-chloroacrylamide **15**.[4, 5, 9]



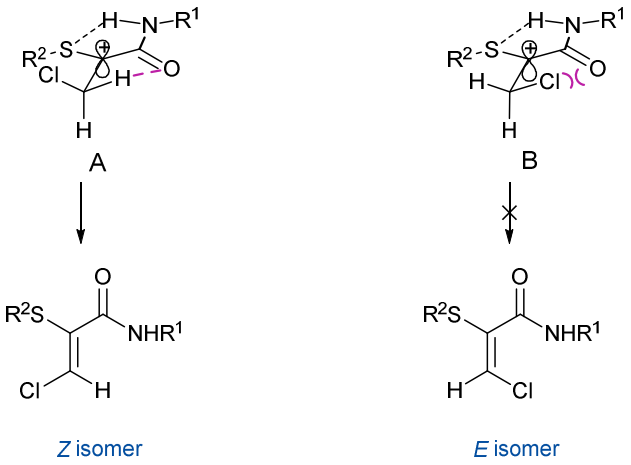


15

Figure 5 A view of **15** showing the stereochemistry and the crystallographic numbering scheme. Non-hydrogen atom ellipsoids are at the 30% level; for clarity hydrogen atoms are shown as small spheres of an arbitrary size. The intramolecular NH-S hydrogen bond 2.59 Å is also shown.[5]

During the oxidative transformation of α-thioamide **4** to α-thio-β-chloroacrylamide **7**, only the *Z*-isomer formation would have been observed at this point.

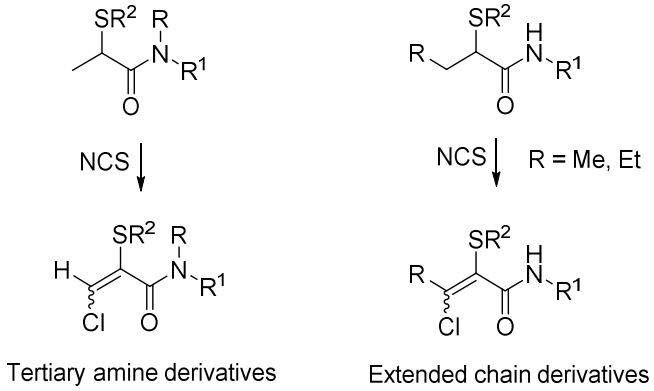
The stereochemical outcome is determined in the final deprotonation step which proceeds *via* elimination of HCl.[4] The intramolecular hydrogen bond between the amide proton and the sulfide is believed to hold the planar sulfur-stabilized carbocation intermediate in the conformation illustrated in Scheme 7. Delocalisation of the sulfur lone pair to stabilise the carbocation is envisaged to impact on hydrogen bonding capacity.



Scheme 7

As loss of the proton must occur coplanar with the vacant orbital, two conformations of the final product are possible (A and B). The hyperconjugation of the positive charge by delocalization of lone pair electrons from the sulfur decreases the carbocation reactivity promoting the most stable conformation. The hydrogen bond between the carbonyl group and the β-proton holds the intermediate in conformation A which, as a result, is more stable, leading to formation of the *Z*-stereoisomer. Steric repulsion between the carbonyl and the chloride substituent makes conformation B, leading to the *E* isomer formation, disfavored.[2]

This stereoselectivity does not occur for the transformation of tertiary amide and extended-chain derivatives illustrated in Scheme 8, where formation of both the *Z*- and *E*-stereoisomers is observed.[14, 15]



Scheme 8

For the tertiary amide, the absence of a hydrogen bond donor results in a change in conformation of the intermediate carbocation. Together with the increase in the steric demand of the amide, the deprotonation step can lead to both *E*- and *Z*-stereoisomer formation (Figure 6).[14, 15]

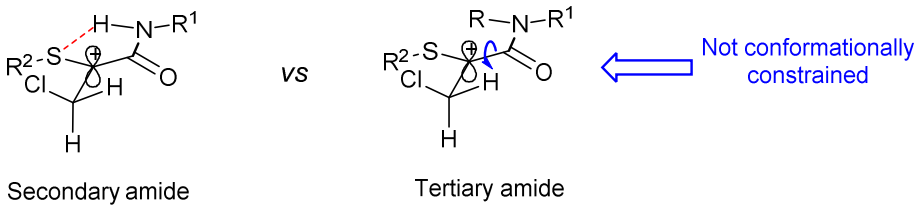
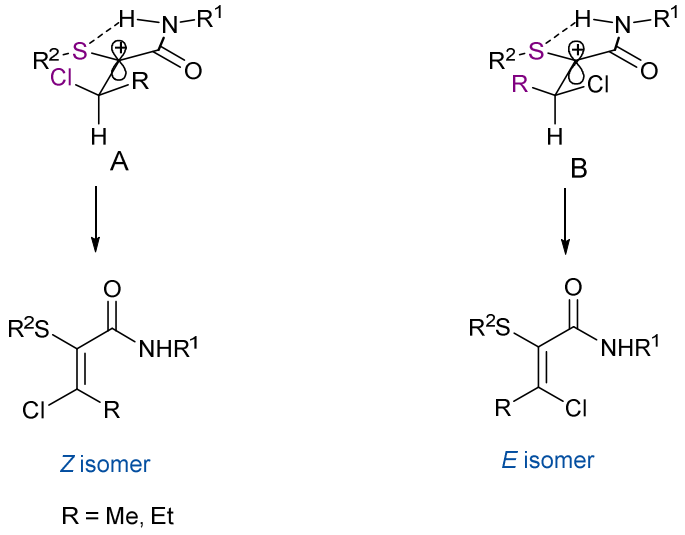


Figure 6

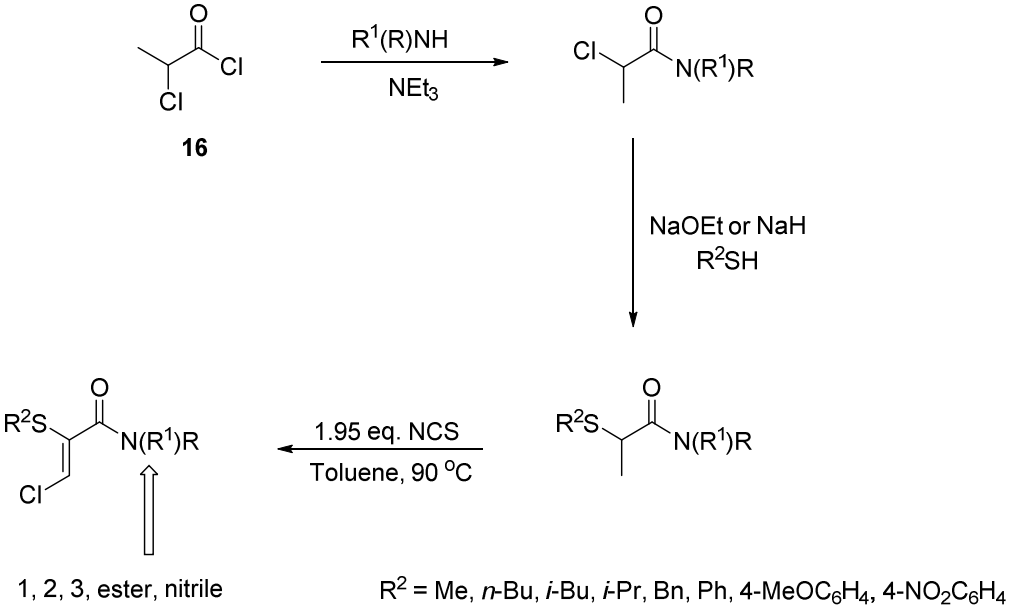
For the extended-chain derivatives, the steric demands of an alkyl group R^2 and a chlorine substituent are rather similar. Therefore, the energy difference between the two conformations A and B is not likely to be significant and thus the two isomers can also be formed (Scheme 9).[15]



Scheme 9

The cascade transformation of α-thioamides to α-thio-β-chloroacrylamides has been optimized within our group for substrates bearing a wide range of substituents, affording good yields and purities.[9, 14, 16] The scope of the transformation has been explored, including alkyl and arylthio substituents (R^2). Primary, secondary and tertiary amides can be employed, as well as esters to form

β-chloroacrylates and nitrile derivatives forming β-chloroacrylonitriles.[4] The starting materials for these transformations are formed in two steps from commercially available 2-chloropropionyl chloride **16** (Scheme 10).



Scheme 10

In each case, the unreactive sp^3 β-carbon is transformed into a highly activated sp^2 carbon in a highly stereoselective manner.

The objectives of this research are:

- To synthesise, isolate and characterise a series of α-thioamides, acrylamides, dichlorides and α-thio-β-chloroacrylamides.
- To investigate the consistency of the reaction pathway across these series to explore if similar key intermediates are formed in each case.
- To determine a HPLC method for rapid quantification and characterization of the starting material, intermediates and products formed during the α-thio-β-chloroacrylamide synthesis.
- To develop a scalable continuous flow process for the α-thio-β-chloroacrylamide synthesis.

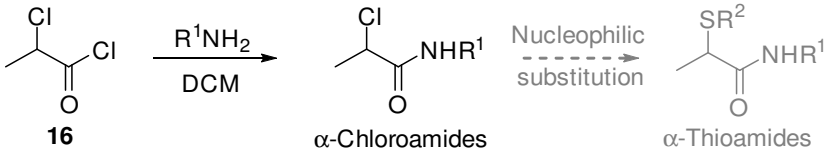
2. SYNTHESIS OF α-THIO-β-CHLOROACRYLAMIDES

The α-thio-β-chloroacrylamides can be synthesised in three steps from commercially available 2-chloropropionyl chloride **16**.

A. Synthesis of α-chloroamides

The first stage of this project involved the synthesis of a series of α-chloroamides, with various substituents, as α-thioamide precursors.

The reaction conditions for the synthesis of α-chloroamides have been previously optimised in our group,[16,17] employing the appropriate amines with 2-chloropropionyl chloride **16** in dichloromethane (Scheme 11).



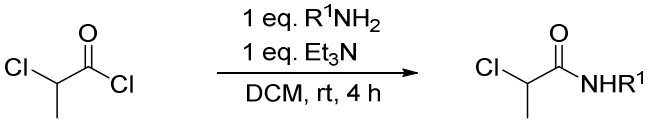
Scheme 11

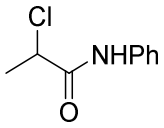
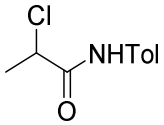
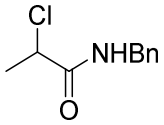
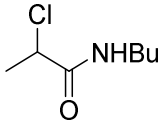
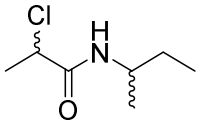
An excess of the amine (1.5 eq.) was used, in order to neutralize the hydrochloric acid liberated during the reaction, with a resulting yield of approximately 60%.[16] Increasing equivalents of amine (2 eq.) improved the yield to approximately 90%. This result showed that the neutralization of the hydrochloride acid by the amine is a competitive pathway. However, this excess of amine is not a desirable option, especially when chiral amines are used because of the cost of these reagents.[19] The introduction of a tertiary amine as base, for example triethylamine, could be used to consume this acid, without reacting with the starting material.[16]

The optimal procedure developed previously by Lynch[16] was applied to the synthesis of five α-chloroamides for this project (Table 2), using 1 equivalent of 2-chloropropionyl chloride **16**, 1 equivalent of triethylamine and 1 equivalent of the appropriate amine at room temperature in dichloromethane for 4 hours. The acid chloride is added as a solution in dichloromethane to a solution of the amine and triethylamine dropwise at 0 °C, due to the exothermic nature of the reaction. The

products were obtained cleanly after workup and could be used without further purification.

Table 2 Preparation of α-chloroamides



α-Chloroamide		R^1	Yield (%)[a]
17[4]		Ph	98
18[4]		Tol	99
19[4]		Bn	97
20[4]		Bu	95
21[b]		*sec*-Bu	48 98[c]

[a] Yield of the crude product which required no further purifications.

[b] Product was isolated as an equimolar mixture of diastereomers.

[c] The reaction mixture was stirred at room temperature overnight.

Compounds **17**, **18**, **19** and **20** were obtained in better yield than previously reported in the group (ranging from 92 to 94% yield)[4]. The novel α-chloroamide **21** was obtained as an equimolar mixture of two diastereoisomers, in a lower yield of 48%. This lower yield could be explained by the more bulkly *sec*-butylamine used which was less reactive, resulting in a slower conversion. The conversion could not be determined due to the work-up, which removed the starting materials remaining in the aqueous layer. A longer reaction time or increasing of the reaction temperature for α-chloroamide **21** synthesis may be required to

reach full completion. Consequently, the synthesis of **21** was performed at room temperature overnight and the resulting novel α-chloroamide **21** was isolated in pure form without required purification in 98% yield.

Spectral characteristics for **17**, **18**, **19** and **20** were consistent with earlier reports. The novel α-chloroamide **21** was fully characterized in this project. A pair of signals in the ^{1}H and ^{13}C NMR spectra of **21** provided clear evidence of the two diastereoisomers produced.

The α-chloroamides are identified easily by ^{1}H NMR spectroscopy due to a characteristic doublet between δ_H 1.65-1.84 ppm corresponding to the protons of the methyl group and a quartet between δ_H 4.32-4.55 ppm corresponding to the proton of the α-carbon.

A characteristic NH stretch is observed in the region 3250-3254 cm^{-1} In the IR spectra for *N*-aryl derivatives **17** and **18**. When the nitrogen lone pair is not delocalised into an α-aryl group, the NH stretch is observed at a lower frequency, with a maximum value of 3288 cm^{-1} for *N*-*sec*-butyl derivative **21**. In the ^{1}H NMR spectra, a characteristic NH signal is observed deshielded for *N*-aryl derivatives compared to the *N*-alkyl/benzyl derivatives (*N*-phenylamide **17** at 8.21 ppm *vs* *N*-*sec*-butylamide **21** at 6.37 ppm).

Interestingly, for the *N*-alkyl derivatives, the carbonyl stretching frequency shift (~ 1660 cm^{-1}) is observed approximately 10 wavenumbers lower than the *N*-aryl derivatives (~ 1650 cm^{-1}), due to a decrease of the carbonyl bond order with a more efficient delocalization of the nitrogen lone pair into the carbonyl group.

The α-chloroamides are stable compounds which could be synthesised on a 30 g scale and stored at room temperature for up to a year without any evidence of significant deterioration in the quality of the material.

The α-chloroamides synthesised were used for preparation of the corresponding α-thioamides, as α-thio-β-chloroacrylamides precursors.

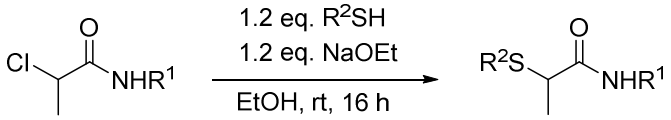
B. Synthesis of α-thioamides

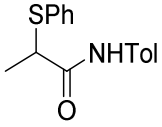
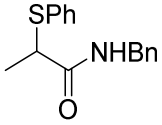
Having successfully synthesised a range of pure α-chloroamides, the next step in the reaction sequence was synthesis of the corresponding α-thioamides. The synthesis of α-thioamides from α-chloroamides was undertaken using the method employed during the work of Murphy and Lynch.[16, 17]

Firstly, the thiol (1.2 eq.) in the presence of sodium ethoxide, freshly prepared from sodium (1.2 eq.) in ethanol at 0 °C, generated the corresponding thiolate anion which reacts *via* a S_N2 mechanism to form the desired α-thioamide.

These reaction conditions were applied successfully to α-chloroamides **18** and **19** giving α-thioamides **4** and **22** respectively in an excellent yield, after purification by chromatography on silica gel (Table 3).

Table 3 Preparation of α-thioamides using thiophenol



α-Chloroamide	α-Thioamide		R^1	R^2	Yield (%)[a]
18[4]	**4**[4]		Tol	Ph	80
19[4]	**22**[4]		Bn	Ph	94

[a] Yield of the pure product after chromatography on silica gel.

Yields were comparable with those previously reported in the group.[4]

During reactions using benzyl and butyl mercaptan, the presence of dibenzyldisulfide **23** and dibutyldisulfide **24** by-products were observed in the ^1H NMR spectra of the crude reaction mixtures. Disulfides **23** and **24** were characterised by a singlet at δ_H 3.59 ppm and a triplet at 2.63 ppm respectively, corresponding to the methylene adjacent to sulfur (Figure 7). Identification of the disulfides was achieved by comparison of the ^1H and ^{13}C spectra with the literature

chemical shifts of disulfides **23**[20] and **24**[21]. In addition, the interaction between the Cα and the Hα by ^{1}H-^{13}C HMBC analysis confirmed the dimer structure (Figure 7).

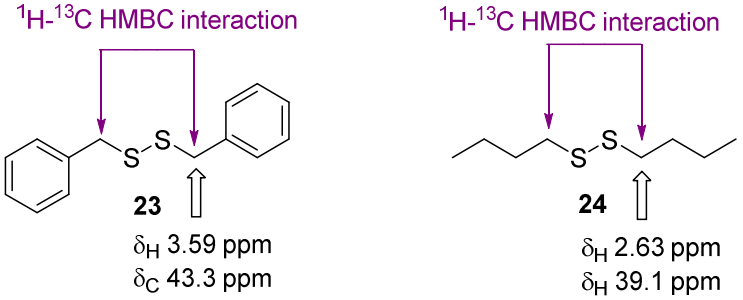
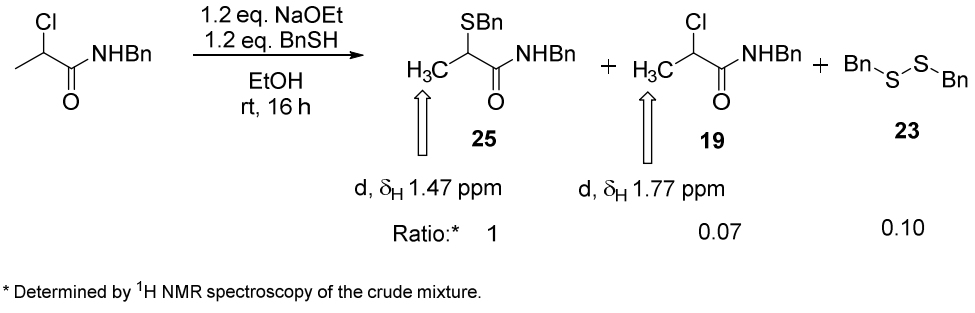


Figure 7

When the reaction was performed with thiophenol, the formation of diphenyldisulfide by-product was not observed, probably due to greater reactivity of the benzylthiolate or butylthiolate anion towards oxidation. The negative charge of the phenylthiolate is delocalised into the aromatic ring while in the alkylthiolate anion, α-methylene group does not facilitate delocalization of the sulfur lone pair. The increased electron density on the sulfur in the benzyl and butylthiolate anion consequently makes it sufficiently reactive to form the disulfide. The pKa of thiophenol (10.3), benzyl mercaptan (15.3) and *n*-butyl mercaptan (17.9) in DMSO reflect this analysis, with more reactive thiolates derived from benzyl and butyl mercaptan.[22]

This competitive pathway consumed the benzyl mercaptan and resulted in significant level of starting material **19** remaining when the synthesis of α-thioamide **25** was attempted (Scheme 12).



* Determined by ^{1}H NMR spectroscopy of the crude mixture.

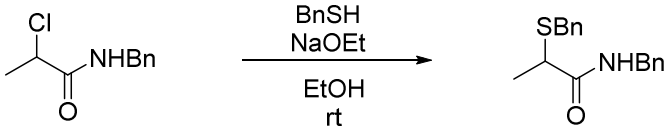
Scheme 12 Synthesis of α-thioamide **25** using the experimental procedure described by Lynch.[16]

Starting material **19** could not be removed by recrystallization or column chromatography, because it possessed the same retention factor as the product, and was carried through to the next step of the reaction sequence; the synthesis of α-thio-β-chloroacrylamide **26**, as will be discussed later in *Section 2.C.*. Unfortunately, the isolation of the pure α-thio-β-chloroacrylamide **26** in the presence of α-chloroamide **19** proved just as difficult. It was thought that full conversion is required to overcome this purification problem.

However, Kissane reported a full conversion to the desired α-thioamide **25**, with only 4 mol% of disulfide **23** formation while using freshly distilled ethanol.[14] Distillation of ethanol, in order to deoxygenate and dry the solvent, is a long process taking at least 3 hours to proceed. This had to be performed prior the synthesis and cannot be conserved for a long period.

In this project, we explored the possibility to obtain full conversion in this transformation using absolute ethanol without fresh distillation. To this end, the α-thioamide synthesis was further optimised (Table 4).

Table 4 Optimisation of preparation of α-thioamide **25**



19 **25**

Entry	BnSH (eq.)	NaOEt (eq.)	Conditions	Reaction time (hour)	Ratio[a] (sulfide : chloride)	Yield (%)[b]
1	1.2	1.2	1) Add thiol 2) Wait 20 min 3) Add chloride	16	93 : 7	-
2	1.2	2.2		16	1 : 0	46
3	1.2	1.2	1) Add thiol 2) Add chloride	16	1 : 0	63
4	1.5	1.5		22	1 : 0	84
5	1	1		22	94 : 6	-
6	1.2	1.2		22	1 : 0	88

[a] Ratio determined by ^{1}H NMR spectroscopy based on the integration of the doublet representing the C(3)H_3 of α-thioamide **25** (δ_H 1.46 ppm) and α-chloroamide **19** (δ_H 1.77 ppm).
[b] Yield of the pure product after chromatography on silica gel.

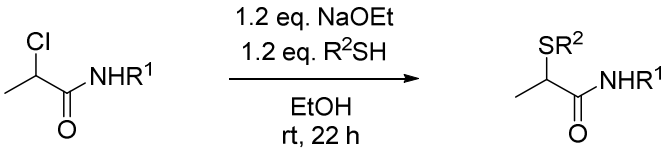
The initial protocol described by Lynch and Murphy specifies a required 20 min waiting time between the addition of thiol and α-chloroamide.[16, 17] During this time, the formation of dibenzyldisulfide **23** occurs with incomplete consumption of the α-chloroamide, in the case where the benzyl mercaptan was not in excess (Entry 1, Table 4). Removing the 20 min hold time, a new protocol developed during this work led to more effective conversion (Entry 3, Table 4).

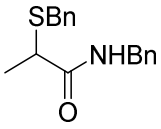
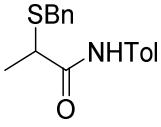
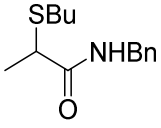
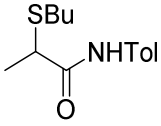
A large excess of benzyl mercaptan and sodium ethoxide (Entry 4, Table 4) was not necessary to obtain full conversion, but an equimolar addition of reagents led to a lower conversion (Entry 5, Table 4). A reaction time of 22 hours versus 16 hours improved the yield to 88% after purification by chromatography on silica gel (Entry 6, Table 4). Ultimately, 1.2 equivalents of sodium ethoxide and benzyl mercaptan with 22 hours reaction time was selected as optimum.

Interestingly, while the solution of phenyl thiolate could be held for 20 min, the more reactive benzyl thiolate could not be held without disulfide formation. The new protocol developed in this work, removing the 20 min hold time, allows the reaction to be performed with absolute ethanol.

α-Thioamides **27**, **28** and **29** were synthesised (Table 5) using this optimised protocol (Entry 6, Table 4). Products were isolated with comparable yield than previously reported in the group using the method described by Lynch.[4]

Table 5 Preparation of α-thioamides using benzyl or butyl mercaptan



α-Chloroamide	α-Thioamide		R^1	R^2	Yield (%)
19[4]	**25**[4]		Bn	Bn	88[a]
18[4]	**27**[4]		Tol	Bn	93[b]
19[4]	**28**[4]		Bn	Bu	80[a]
18[4]	**29**[4]		Tol	Bu	68[a]

[a] Yield of the pure product after chromatography on silica gel.

[b] Yield of the crude product, as a 1 : 0.07 mixture with the dibenzyldisulfide **23** by ^{1}H NMR spectroscopy (93% purity).

In all of these experiments, the only impurity observed in the ^{1}H NMR spectra of the crude product was the disulfide derivatives **23** and **24**. As an example, the ^{1}H NMR spectrum of the crude mixture for the synthesis of α-thioamides **25**, shown in Figure 8, was clean with only **23** as impurity.

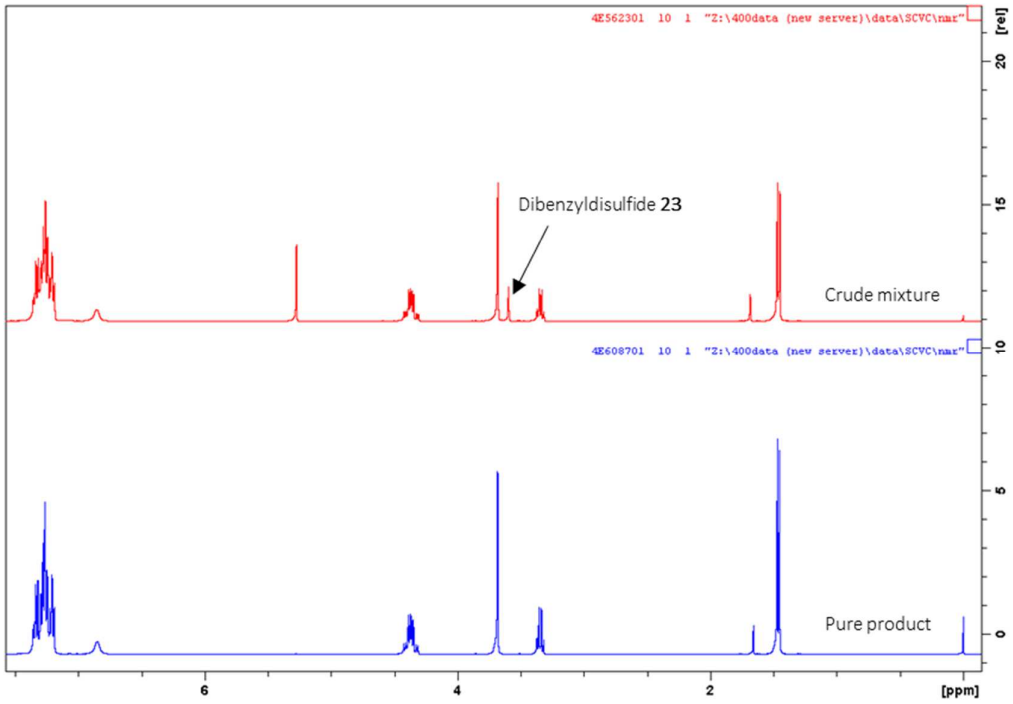


Figure 8 ^{1}H NMR spectra of crude and pure product **25**

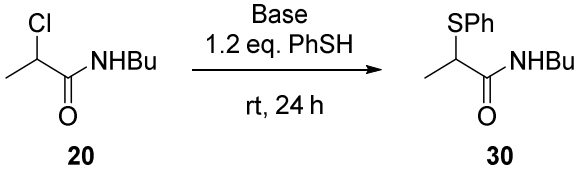
Preparation of α-thio-*N*-butylamides

The initial protocol described in Table 3 was also used for the reaction employing α-chloroalkylamides **20** and **21** with benzylmercaptan or thiophenol, which led to an inseparable mixture of the α-thioamide and the starting material in both instances. Since the starting material could not be removed, it was carried through to the synthesis of the corresponding α-thio-β-chloroacrylamides but late stage purification proved to be similarly difficult. This problem was reported by Lynch[4], who attempted to optimise the reaction conditions, including the number of equivalents of reagent, the concentration in solution, and the order of addition of reagents to obtain a conversion of 100% but this ultimately proved unsuccessful.

The incomplete conversion observed is due to the weaker reactivity of the carbon bearing the chlorine substituent for the *N*-alkyl amide derivatives, the reactivity of thiolate anion must be increased. The thiolate anion can interact with ethanol by hydrogen bonding and thus decrease its reactivity. Lynch reported that sodium hydride in DMF were ideal conditions for thiolation with alkylthiolates.[16] This was due to the aprotic and polar nature of DMF which favours S_N2 reactions.

The protocol described by Lynch[16] was attempted for the reaction of α-chloroamide **20** with thiophenol to give α-thioamide **30** (Entry 1, Table 6).

Table 6 Optimisation of preparation of α-thioamides **30**



20 **30**

Entry	Base	No. Eq. Base	Solvent	Addition conditions	Ratio[a] **20** : **30**	Yield (%)
1	NaH	1.05	DMF	1) Add Thiol 2) Wait 20 min 3) Add Chloride	26 : 74	
2	NaOEt	2.2	Ethanol	1) Add Thiol 2) Add Chloride	5 : 95	76[c]
3[b]	NaOEt	2.2	Ethanol		21 : 79	

[a] Ratio determined by ^{1}H NMR spectroscopy based on the integration of the doublet representing the C(3)H_3 of α-thioamide **30** (δ_H 1.52 ppm) and α-chloroamide **20** (δ_H 1.72 ppm).

[b] Addition of pyridine to remove HCl.

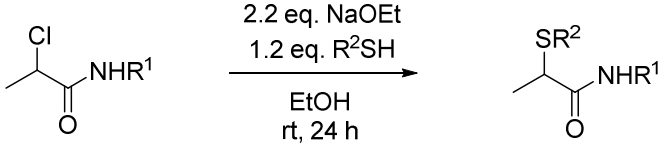
[c] Yield of the product, as a 1 : 0.05 mixture with α-chloroamide **20** by ^{1}H NMR spectroscopy (95% purity).

Lynch reported full conversion to the desired product **30** by using sodium hydride in DMF, and the product was isolated with 87% yield.[16] However, the reaction proved challenging to drive to completion when repeated in this work. After 4 hours of reaction time at room temperature, full conversion was observed in previous work.[16] In this work, with comparable scale and concentration applied, even though leaving the reaction for 24 hours at room temperature, only a 74% conversion was observed by ^{1}H NMR spectroscopy (Entry 1, Table 6). Using an excess of sodium ethoxide (2.2 eq.) in ethanol and removing the 20 min hold time, provided an improved conversion to 95% (Entry 2, Table 6). The synthesis was also carried out in the presence of pyridine (Entry 3, Table 6) with no increase of the conversion observed.

With the same observations, the novel α-thioamides **31**, **32** and **33** were synthesised and isolated as mixtures with the corresponding α-chloroamide starting material (Table 7). Whilst the novel α-thioamide **33** could be purified to remove the α-chloroamide **21**, α-thioamides **30**, **31** and **32** remained contaminated by the analogous starting material after column chromatography on silica gel.

α-Thioamides **31** and **33** were obtained as an equimolar mixture of two diastereoisomers as clearly evidenced by pairs of signals in the ^{1}H and ^{13}C NMR spectra. The α-thioamide **33** was purified by subsequent column chromatography, while **30**, **31**, **32** could not be separated from the corresponding α-chloroamides.

Table 7 Preparation of α-thio-*N*-butylamides



R^1 = Bu or *sec*-Bu

α-Chloroamide	α-Thioamide	R^1	R^2	Ratio[a] (chloride : sulfide)	Yield (%)
20[4]	**30**[16]	Bu	Ph	5 : 95	76[b]
21[4]	**31**	*sec*-Bu	Ph	37 : 63	77[b]
20[4]	**32**	Bu	Bu	23 : 77	77[b]
21[4]	**33**	*sec*-Bu	Bn	10 : 90	64[c]

[a] Ratios determined by ^{1}H NMR spectroscopy based on the integration of the doublet representing the C(3)H_3 of the α-thioamides and the α-chloroamides.

[b] Yield of the product, as a mixture with the corresponding α-chloroamide.

[c] Yield of the pure product after chromatography on silica gel, as an equimolar mixture of the two diastereoisomers.

Spectral characteristic for **30** was consistent with earlier reports and the novel α-thioamides **31, 32** and **33** were fully characterized.

In the ^{1}H NMR spectra of compounds **4**, **22**, **30** and **31**, the signal of the proton in alpha of the sulfur group is seen to be deshielded by the increase of the electron-withdrawing character of the sulfide substituent (δ_H-C(2)*H* of *S*-phenyl derivatives

appearing at 3.82 ppm for **30** and at 3.89 ppm for **4** *cf. S*-alkyl derivatives which give corresponding signals at 3.28 ppm for **32** and at 3.43 ppm for **28**) (Figure 8).

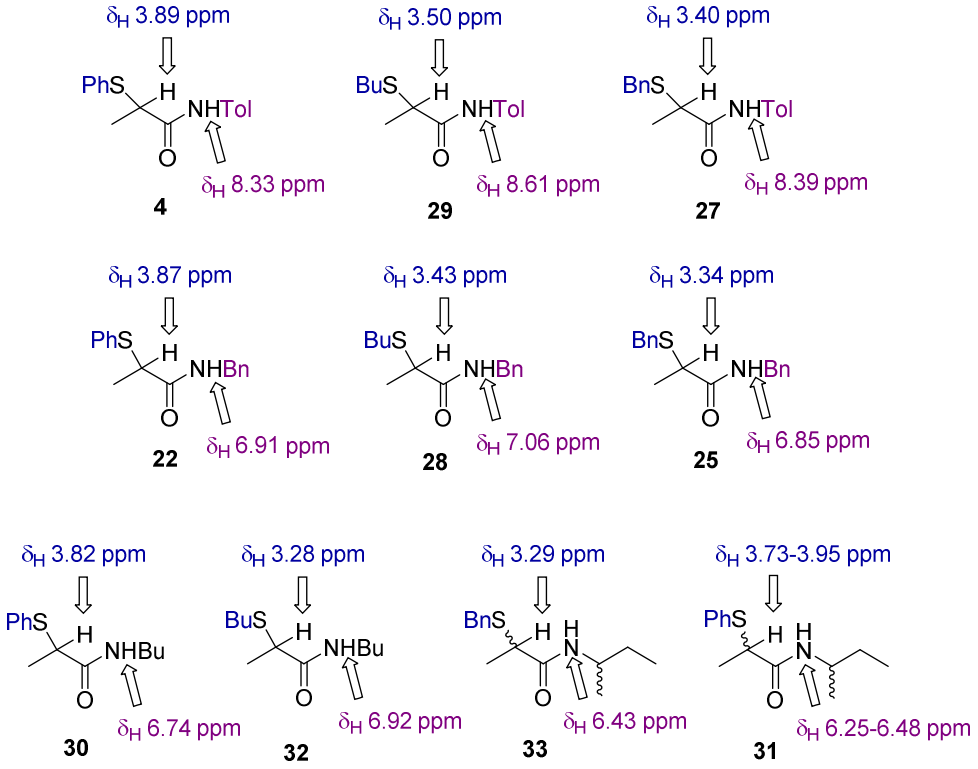


Figure 9

The delocalisation of the nitrogen lone pair into an aryl group has a deshielding effect and the observed chemical shift of the N-H signal at 8.33 ppm for the SPh/NHTol derivative **4** is downfield compared to that of the corresponding signal at 6.91 ppm, 6.74 ppm and 6.37 ppm for the SPh/NHBn **22**, SPh/NHBu **30** and SPh/NH*sec*-Bu **31** derivatives respectively.

Each of the α-thioamides showed two characteristic amide bands at approximately 1550 and 1660 cm^{-1}. An interesting feature concerning the relative intensity of the two signals was observed. For the *N*-phenyl derivatives, the band at ~ 1550 cm^{-1} was observed with higher intensity compared to the other band (Figure 10) than for the *N*-alkyl, *N*-benzyl derivatives.

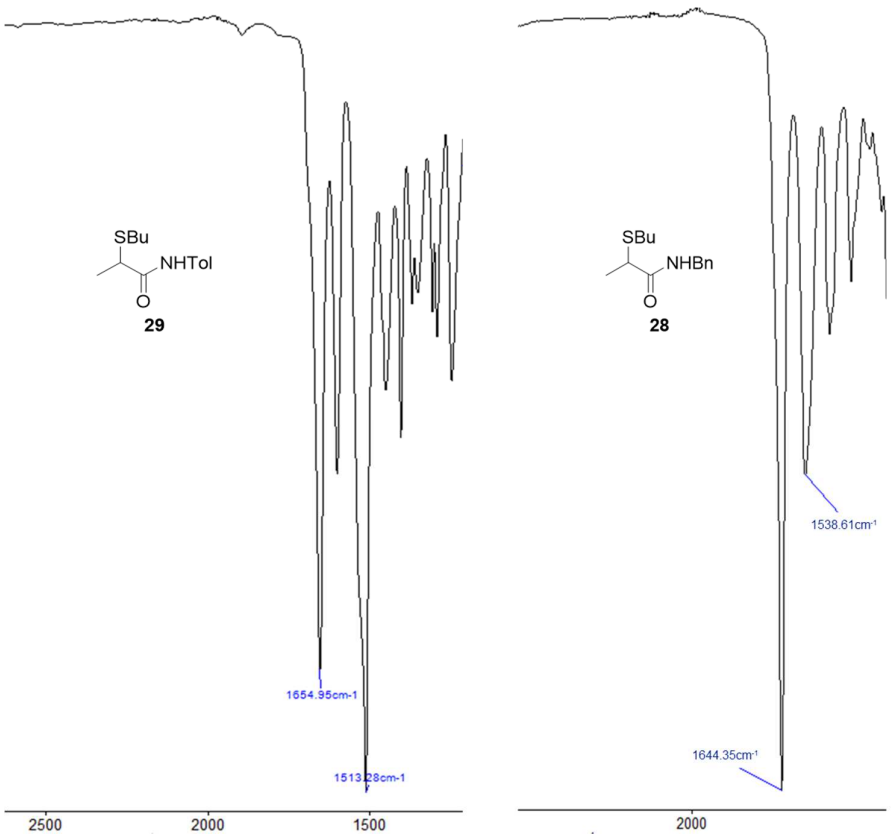


Figure 10

A new method for α-thioamide synthesis was developed in this work, allowing use of absolute ethanol for this transformation, making the distillation of ethanol prior synthesis unnecessary. The optimal conditions consisted of 1.2 equivalents of thiol and sodium ethoxide. Immediate addition of reagents, instead of the 20 min hold previously required, led to amazingly clean transformation and the desired products were isolated with high yield.

The α-thioamides are stable compounds which could be synthesised on a 10 g scale and stored at room temperature for up to a year without any evidence of significant deterioration in the quality of the material.

C. Synthesis of α-thio-β-chloroacrylamides

The six α-thioamides successfully isolated in a pure state, **4**, **22**, **25**, **27**, **28** and **29**, were taken forward to the key step of the reaction sequence to generate the corresponding α-thio-β-chloroacrylamides.

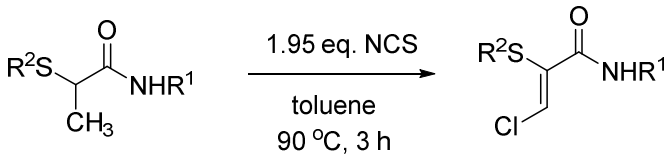
Due to the challenging isolation in a pure form of the *N*-alkyl α-thioamides **30**, **31**, **32** and **33**, the α-thio-β-chloroacrylamide synthesis from these precursors was not carried out.

The protocol for synthesis of α-thio-β-chloroacrylamides has been previously optimised within the group.[2,23,4,17,16] While the reactions were originally carried out in tetrachloromethane,[17] for safety reasons and due to shorter reaction times, toluene was substituted as the reaction solvent.[16] In addition, the succinimide by-product formed during the reaction can be easily removed as it insoluble in cold toluene and can be separated by filtration from the cold reaction mixture.[24]

While Lynch[16] reported the use of recrystallized NCS for this reaction, it was found that this was unnecessary and the reaction proceeded equally well with commercial material without the need for recrystallisation.[14] The 'hot plunge' technique consists of plunging the reaction mixture into a pre-heated bath at the required reaction temperature immediately after addition of the NCS. This method has been proven necessary to get an efficient transformation for α-thio-β-chloroacrylamide synthesis, when compared to heating the reaction solution progressively from room temperature. According to this method, immediately following NCS addition in one portion, the reaction vessel was plunged into a pre-heated oil bath at the desired reaction temperature. Rapid heating progresses the reaction cascade more efficiently from the α-thioamide, to the acrylamide, to the dichloride and finally to the α-thio-β-chloroacrylamide (*cf.* Scheme 5, *Section 1.*). The rapid heating required limited the scalability of the reaction; for reaction greater than 4 to 5 g, the results obtained were poor. Progressive heating of the reaction mixture from room temperature leads to less rapid transformation of the intermediates, which in turn leads to the recovery of intermediates and by-products, consequently reducing the yield of the transformation.

The optimised procedure developed previously in the group[4] was applied to six α-thioamides **4**, **22**, **25**, **27**, **28** and **29**, using 1.95 equivalent of NCS, at 90 °C in toluene for 3 hours (Table 8).

Table 8 Preparation of α-thio-β-chloroacrylamides



α-Thioamide	α-Thio-β-chloroacrylamide	R^1	R^2	Yield (%)[a]
4[4]	**7**[4]	Tol	Ph	82
22[4]	**15**[4]	Bn	Ph	72
25[4]	**26**[4]	Bn	Bn	62
27[4]	**34**[4]	Tol	Bn	71
28[4]	**35**[4]	Bn	Bu	69
29[4]	**36**[4]	Tol	Bu	79

[a] Yield of the pure product isolated after chromatography on silica gel.

In all cases, the *Z*-stereoisomers of the α-thio-β-chloroacrylamides were exclusively obtained, in good yields, after purification by chromatography on silica gel, with comparable result than those reported previously. α-Thio-β-chloroacrylamides **35** and **36** has been synthesised previously in the group employing 2.1 equivalents of NCS at 130 °C and isolated with 84% yield.[4] In this project, clean transformation was achieved for these compounds using 1.95 equivalent of NCS at 90 °C.

Even through the complexity of this transformation, with many intermediates and by-products implicated, the ^{1}H NMR spectra of the crude mixture from these experiments were extremely clean. As an example, the ^{1}H NMR spectra of the crude mixture for the synthesis of α-thio-β-chloroacrylamides **36** is shown in Figure 11.

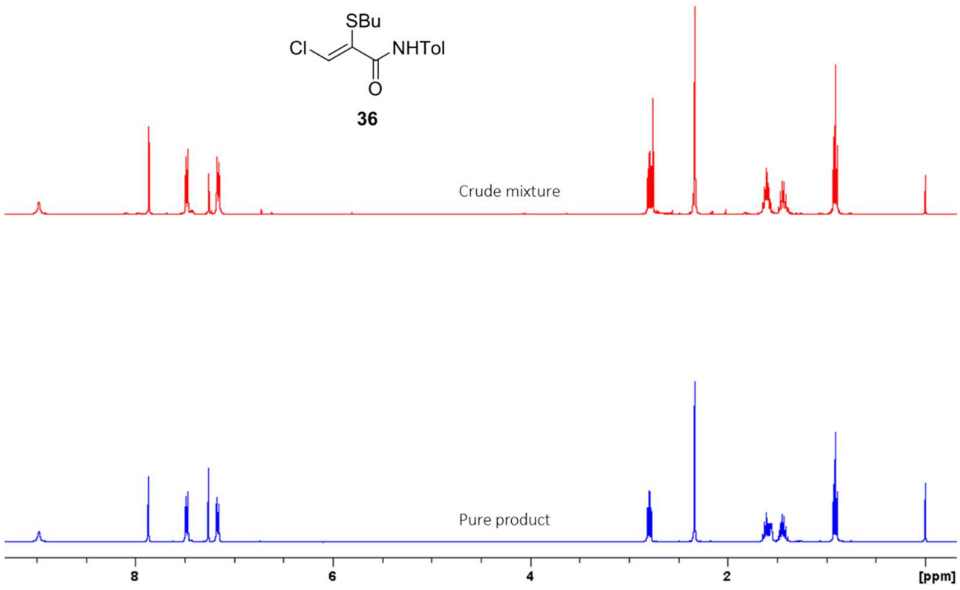


Figure 11 ^{1}H NMR spectra of the crude mixture and pure isolated product for **36** synthesis

Spectral characteristics for these α-thio-β-chloroacrylamides were consistent with earlier reports.[4]

On formation of the α,β-unsaturated systems, the delocalization of the double bond affords more single bond character to the C=O bond (Figure 12 and 13).

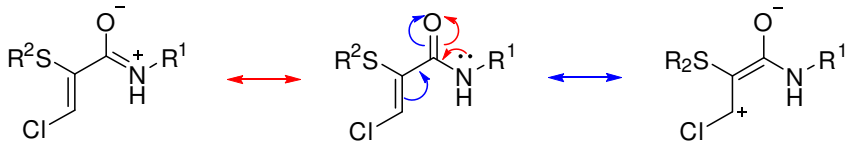


Figure 12

Due to conjugation in the α-thio-β-chloroacrylamides, δ_H N-H of the amide is significantly deshielded for the products when compared to the α-thioamides (Figure 12). Also, the carbonyl chemical shift in the corresponding ^{13}C NMR spectra is affected by this new system, resulting in a pronounced shielding effect of the δ_C C=O by *ca.* 10 ppm.

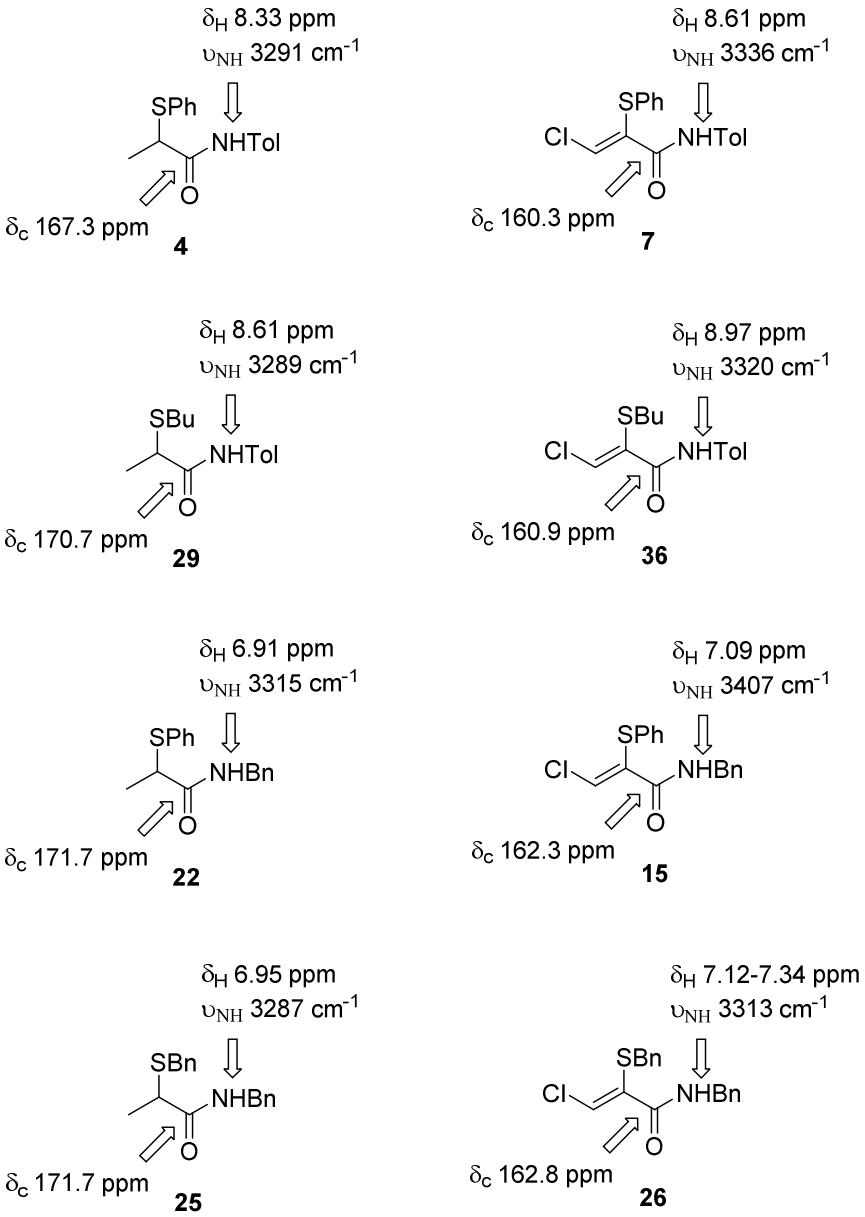


Figure 13

As discussed previously in *Section 2.B.* for the α-thioamides, the same feature concerning the intensity of the characteristic amide bands at approximately 1650 and 1515 cm^{-1} was observed (Figure 14).

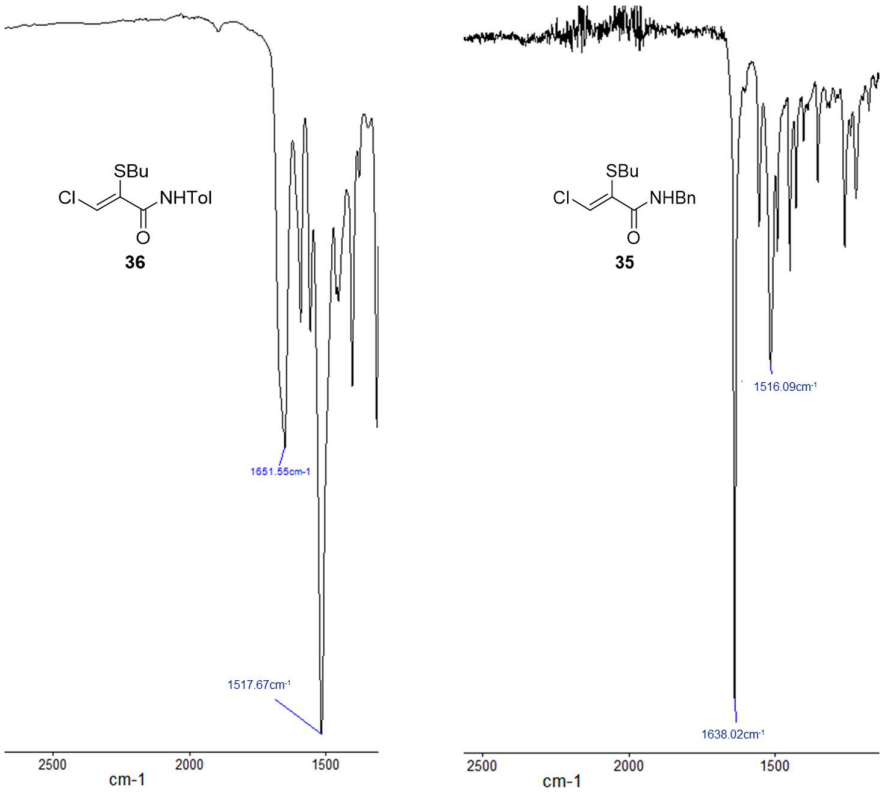
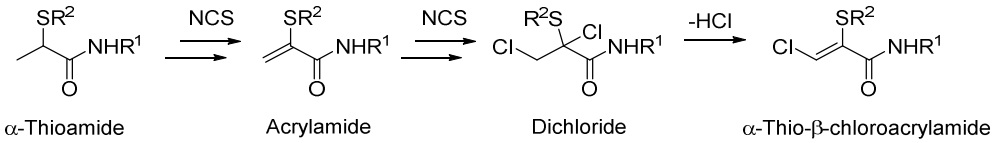


Figure 14

The synthesis of six α-thio-β-chloroacrylamides were successfully carried out, generating incredibly clean crude mixtures. We determined that a single protocol, employing 1.95 equivalents of NCS at 90 °C, could be used for a large range of substituents in the *N*-aryl or *N*-benzyl series, without impacting the reaction outcome.

3. SYNTHESIS OF OXIDATIVE CHLORINATION INTERMEDIATES

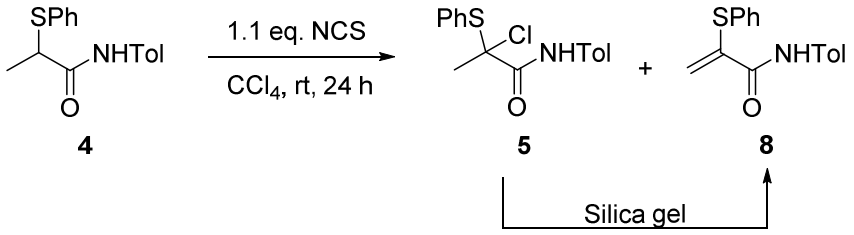
In order to investigate the consistency of the reaction pathway and to establish if the same key intermediates formed in each case during the synthesis of α-thio-β-chloroacrylamides **7**, **15**, **26**, **34**, **35** and **36**, the synthesis of the acrylamide and dichloride intermediates for these series was investigated (Scheme 13).



Scheme 13

A. Synthesis of acrylamide intermediates

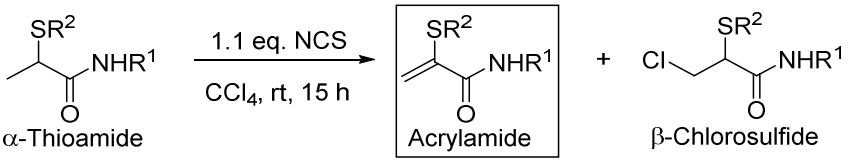
The synthesis and isolation of acrylamide **8** was described by Murphy.[4] On treatment of the corresponding α-thioamide **4** with 1.1 equivalents of NCS at room temperature in tetrachloromethane for 24 hours, an equimolar mixture of **5** and **8** was obtained (Scheme 14).[4] When the crude mixture was passed through a column of silica gel, complete conversion to **8** occured. Isolation of acrylamide **8** was performed in this manner, with 39% yield.[4]



Scheme 14[4]

In this project, extension of the scope of acrylamide synthesis was performed. The protocol described by Murphy[4] was applied to ten α-thioamides synthesised in this project (Table 9).

Table 9 Preparation of acrylamide intermediates



Entry	α-Thioamide	Acrylamide	R^1	R^2	δ_H C(3)H_2	Yield (%)
1[a]	**4**	**8**	Tol	Ph	6.11, 6.87	35[b]
2	**27**	**37**	Tol	Bn	5.78, 6.65	49[b]
3[c]	**22**	**38**	Bn	Ph	6.03, 6.78	Isolated as a mixture with the corresponding β-chlorosulfide[f]
4[d]	**25**	**39**	Bn	Bn	5.60, 6.47	
5[e]	**28**	**40**	Bn	Bu	5.57, 6.40	
6[g]	**29**	**41**	Tol	Bu	5.81, 6.61	Isolated as a mixture with an unknown compound[h]
7	**30**	**42**	Bu	Ph	5.99, 6.74	Acrylamide formation was observed but attempted isolation was unsuccessful[i]
8	**31**	**43**	*sec*-Bu	Ph	5.78, 6.58	
9	**32**	**44**	Bu	Bu	5.61, 6.44	
10	**33**	**45**	*sec*-Bu	Bn	5.61, 6.55	

[a] The crude product consists of a mixture of the acrylamide **8** and the dichloride **9** with a ratio 1 : 0.22 respectively by ^{1}H NMR spectroscopy.

[b] Yield of the pure product isolated after chromatography on silica gel.

[c] The crude product consists of a mixture of the acrylamide **38** and the β-chlorosulfide **47** with a ratio 1 : 0.40 respectively by ^{1}H NMR spectroscopy.

[d] The crude product consists of a mixture of the acrylamide **39**, the β-chlorosulfide **46** and the α-thioamide **25** with a ratio 0.35 : 1 : 0.13 respectively by ^{1}H NMR spectroscopy.

[e] The crude product consists of a mixture of the acrylamide **40**, the β-chlorosulfide **48**, the α-thioamide **28** and the tentatively assigned α-chlorosulfide with a ratio 0.80 : 1 : 0.81 : 0.10 respectively by ^{1}H NMR spectroscopy.

[f] Product isolated as a mixture with the corresponding β-chlorosulfide, after chromatography on silica gel.

[g] The crude product consists of a mixture of the acrylamide **41**, the β-chlorosulfide **49**, the α-thio-β-chloroacrylamide **36** and the tentatively assigned α-chlorosulfide and the dichloride **58** with a ratio 0.62 : 0.73 : 1 : 0.19 : 0.23 respectively by ^{1}H NMR spectroscopy.

[h] Product isolated as a mixture with an unknown compound (87% pure, 31% yield), after chromatography on silica gel.

[i] The characteristic signals corresponding to the terminal alkene of the acrylamide intermediate was observed in ^{1}H NMR spectra of the crude mixtures. The acrylamide was not the main product formed and attempted isolation using chromatography on silica gel was unsuccessful.

Whilst the previously synthesized acrylamides **8** and the derivative **37** could be purified by column chromatography on silica gel, the novel acrylamides **42**, **43**, **44**

and **45** could only be observed by ^{1}H NMR spectroscopy but could not be obtained as the primary product. Attempts at purification of these acrylamides remained unsuccessful. The overlapping of the characteristic signals in the ^{1}H NMR spectra, particularly in the aliphatic region, made challenging the identification of the other products formed.

The stability of the acrylamide derivatives depends strongly on their substituents. Acrylamide **8** and **37** could be purified and were isolated in 35 and 49% yield respectively (Entry 1 and 2, Table 9). In contrast, acrylamide **39** was labile (92% decomposed to a complex mixture of products after 48 hours at room temperature) and chromatography was not fully effective as a means of purification. Acrylamides **37** and **38** demonstrated a greater stability than compound **39**, with total degradation of acrylamide **38** (Entry 3, Table 9) and partial degradation of acrylamide **37** after 15 days at room temperature (Entry 2, Table 9), observed by ^{1}H NMR spectroscopy.

The acrylamides formed were easily observed by ^{1}H NMR spectroscopy, giving rise to terminal alkene resonances that appear as two singlets in the region of 5.5 to 7.0 ppm (Figure 15).

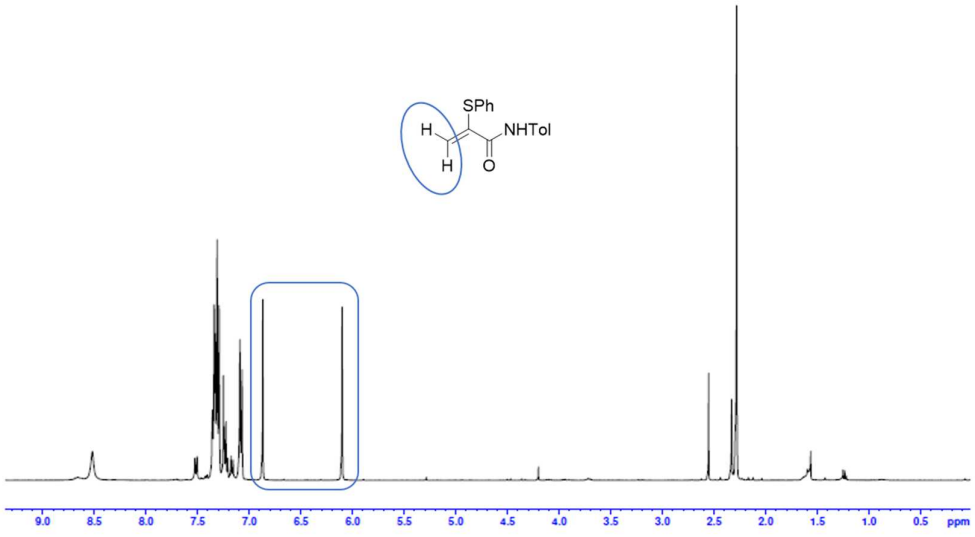


Figure 15 ^{1}H NMR spectrum of the acrylamide **8**

Comparison of the signals for the terminal methylene in the ^{1}H NMR spectra of the toluidine- **8** and benzylamide **38** and **39** derivatives proved interesting, with the position of the signals reflecting the extent of conjugation in the system (Figure 16). Substituting the *N*-aryl with *N*-benzyl substituent results in shielding of the terminal methylene protons, as the nitrogen lone pair is not delocalised into the aromatic ring. The carbonyl signals $\delta_{C=O}$ are deshielded in the ^{13}C NMR spectra, presumably due to the same effect.

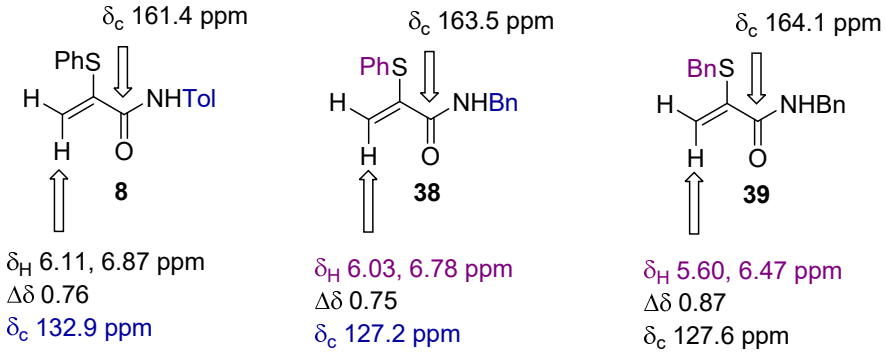


Figure 16

A similar effect is seen when the phenyl moiety replaced the benzyl moiety, where enhanced electron donation from the sulfur atom has a shielding effect on the alkene protons of the acrylamide (Figure 17).

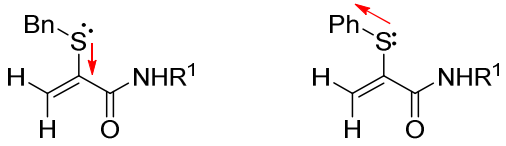


Figure 17

The difference in chemical shift between the two signals of the terminal methylene protons (Δδ) in the ^{1}H NMR spectra was dependent on the thio substituent, being larger for *S*-benzyl derivative **39** compared to the *S*-phenyl derivative **38** (Figure 16). This suggests that the β-protons interact with the sulfur lone pair, when not delocalized into the aryl ring, possibly due to through space interaction with the more electron rich sulfur atom of the *S*-benzyl derivatives (Figure 18).

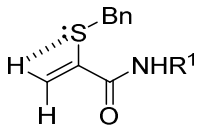
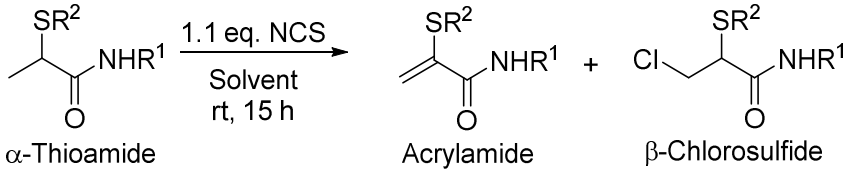


Figure 18

As discussed previously in *Section 2.B.* for the α-thioamides, and *in Section 2.C.* for the α-thio-β-chloroacrylamides, in the *N*-phenyl derivatives, the N-H bend band in the acrylamide was observed with higher intensity, compared to the C=O stretch band, than for the *N*-alkyl, *N*-benzyl derivatives.

The purification of the acrylamides **38**, **39** and **40** led to a mixture of the acrylamide and the corresponding co-eluting β-chlorosulfide (Entry 3 to 5, Table 10).

Table 10 Ratio of acrylamide : β-chlorosulfide in the ^{1}H NMR spectra of the crude material when the reaction was performed in toluene or tetrachloromethane as reaction solvent.



Entry	Acrylamide	β-chlorosulfide	R^1	R^2	Ratio[a] acrylamide : β-chlorosulfide	
					in Tol	in CCl_4
1	**8**	-	Tol	Ph	-	1 : 0[b]
2	**38**	**47**	Bn	Ph	-	1 : 40[c]
3	**39**	**46**	Bn	Bn	0.87 : 1[d]	0.35 : 1[e]
4	**40**	**48**	Bn	Bu	-	0.80 : 1[f]
5	**41**	**49**	Tol	Bu	-	0.85 : 1[g]

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

[b] The crude product consists of a mixture of the acrylamide **8** and the dichloride **9** with a ratio 1 : 0.22 respectively by ^{1}H NMR spectroscopy.

[c] The crude product consists of a mixture of the acrylamide **38** and the β-chlorosulfide **47** with a ratio 1 : 0.40 respectively by ^{1}H NMR spectroscopy.

[d] The crude product consists of a mixture of the acrylamide **39**, the β-chlorosulfide **46** and the α-thioamide **25** with a ratio 0.87 : 1 : 0.14 respectively by ^{1}H NMR spectroscopy.

[e] The crude product consists of a mixture of the acrylamide **39**, the β-chlorosulfide **46** and the α-thioamide **25** with a ratio 0.35 : 1 : 0.13 respectively by ^{1}H NMR spectroscopy.

[f] The crude product consists of a mixture of the acrylamide **40**, the β-chlorosulfide **48**, the α-thioamide **28** and the tentatively assigned α-chlorosulfide with a ratio 0.80 : 1 : 0.81 : 0.10 respectively by ^{1}H NMR spectroscopy.

[g] The crude product consists of a mixture of the acrylamide **41**, the β-chlorosulfide **49**, the α-thio-β-chloroacrylamide **36** and the tentatively assigned α-chlorosulfide and the dichloride **58** with a ratio 0.62 : 0.73 : 1 : 0.19 : 0.23 respectively by ^{1}H NMR spectroscopy.

Column chromatography of the crude acrylamide **40** resulted in an equimolar mixture of the acrylamide with β-chlorosulfide **48** (Entry 4, Table 10). The structure of the β-chlorosulfide was confirmed by 2D NMR spectroscopy and mass spectrometry. Butler *et al.* reported a closely similar pattern for the analogues alkyl acrylate-methanesulfenyl chloride derivatives, with an ABX system between 3 and 4.5 ppm, and with similar coupling to those observed for compound **48**.[25]

The characteristic signals corresponding to β-chlorosulfide **48** are a doublet of doublets at 3.5 ppm and two overlapping ABq systems between 3.8 and 4.1 ppm, corresponding to the α-CH and the β-CH_2 protons respectively. As a result, the β-chlorosulfide derivative can be easily identified as an ABX system where X is the α-CH and, A and B correspond to the diastereotopic β-CH_2 protons (Figure 19). A molecular ion of *m/z* 320.1 with a distinctive isotopic chlorine pattern for an ion containing one chlorine atom, as well as the exact mass in High Resolution Mass Spectrometry (Δppm 0.0003) were observed.

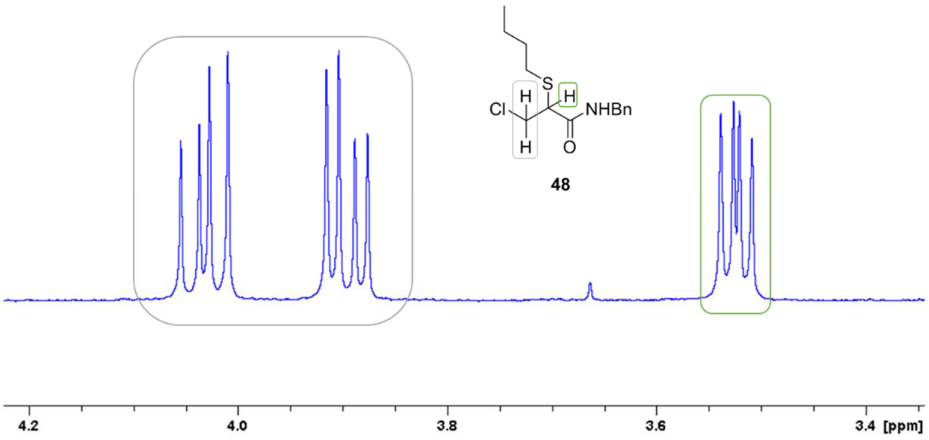


Figure 19

The crude product from the synthesis of acrylamides **39** and **41** consisted of a mixture of the acrylamide and the corresponding β-chlorosulfide by ^{1}H NMR spectroscopy, along with other products formed (Entries 3 and 5, Table 10). During these reactions, the β-chlorosulfides were formed in preference to the acrylamide. Again, the characteristic ABX system corresponding to the β-chlorosulfide was easily identified.

During the synthesis of acrylamide **8**, β-chlorosulfide formation was not observed (Entry 1, Table 10). However, for acrylamide **38**, when the reaction was performed in tetrachloromethane, β-chlorosulfide **47** could be tentatively assigned (Entry 2, Table 10). Indeed, the ABX system may be observed, with the X component of the splitting pattern overlapping with the B component (Figure 20). In addition to high resolution mass spectrometry, the ^{13}C NMR spectra, with a characteristic signal at

55 ppm, correlating with the X component of the ABX system at 3.91 ppm through HSQC, support this assignment.

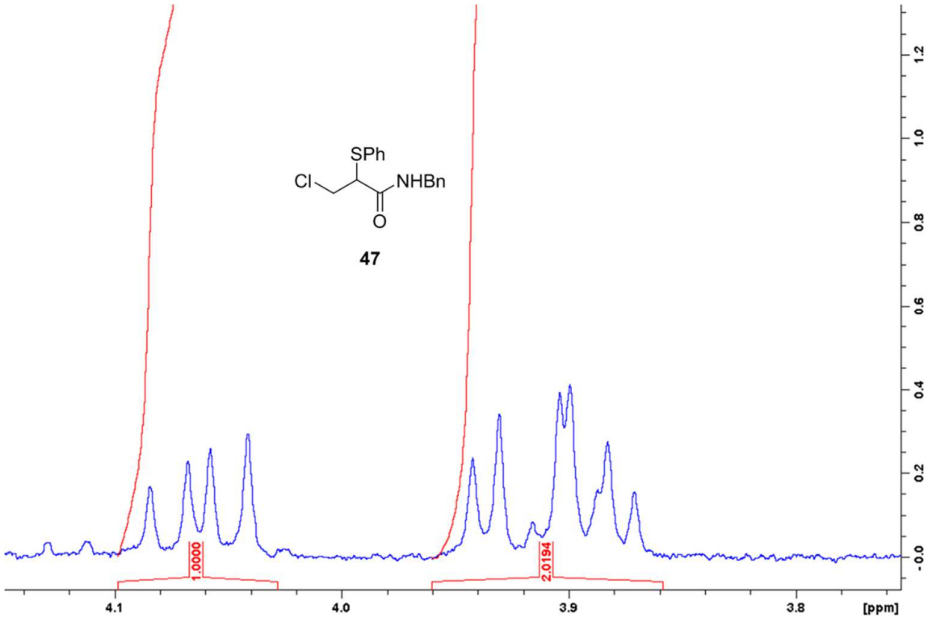


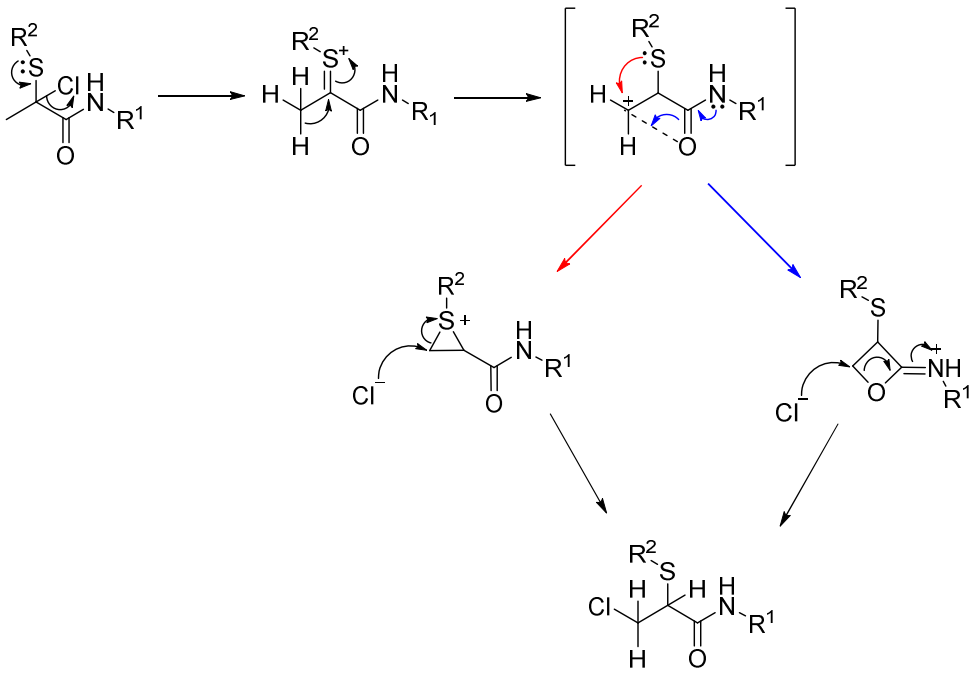
Figure 20

For acrylamide **39** synthesis, the ratio of β-chlorosulfide : acrylamide formed appears dependent on the solvent system, with more β-chlorosulfide was formed when the reaction was performed in tetrachloromethane instead of toluene. β-Chlorosulfide formation was mainly observed while employing butylthio or benzylthio derivatives, suggesting the involvement of the sulfur lone pair in the formation of this new product. A minor amount of β-chlorosulfide was formed in the case of the *S*-phenyl *N*-benzyl substituents (**47**) when the reaction was performed in tetrachloromethane, while none was formed for the *N*-aryl derivative. This suggests some involvement also of the amide substituent in the β-chlorosulfide formation.

Once formed, the β-chlorosulfides are not further transformed through the reaction cascade. The β-chlorosulfides are stable over time (no appreciable decomposition was observed by ^{1}H NMR spectroscopy after 10 months storage at room temperature) and column chromatography on silica gel.

B. Mechanism of formation and reactivity of the β-chlorosulfides

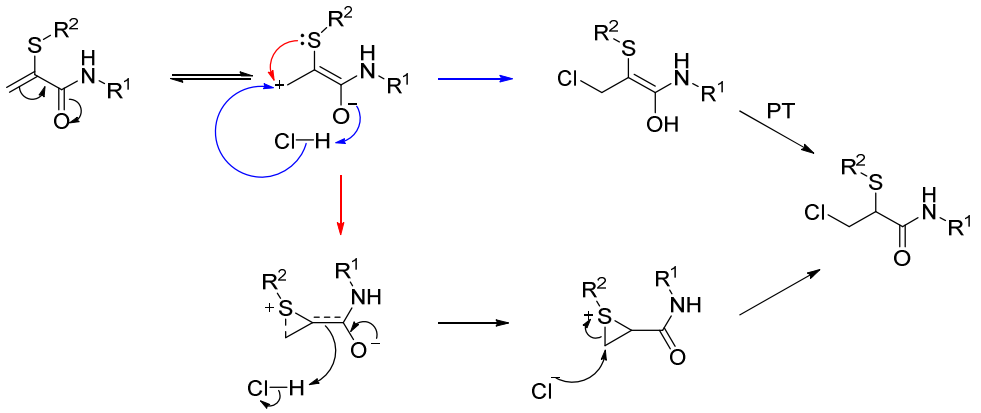
Taking the mechanism proposed by Maguire et *al.*[4, 6] for the formation of α-thio-β-chloroacrylamides in to account, two mechanisms for the formation of the β-chlorosulfides have been proposed. The first requires the α-chlorosulfide as the starting material (Scheme 15). Delocalisation of the sulfur lone pair leads to the chloride elimination. Subsequent hydride shift to form a carbocation would allow two different mechanistic pathways to proceed. Trapping of the carbocation by intramolecular nucleophilic attack at either the sulfide or carbonyl group would help stabilize this intermediate. Nucleophilic attack by chloride then proceeds as shown in Scheme 15 on either the thiirane or oxetane, giving the β-chlorosulfide. The formation of the doubtful primary carbocation makes this pathway unlikely.



Scheme 15

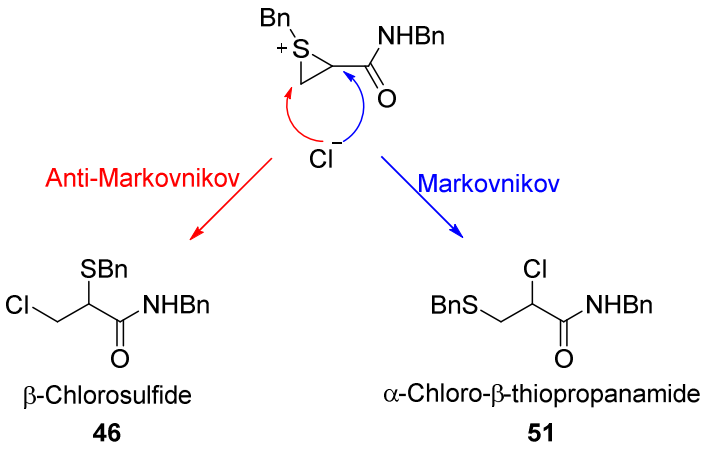
The second hypothesis would make the acrylamide intermediate the starting point for the reaction (Scheme 16). From the acrylamide, two mechanistic pathways are envisaged for the β-chlorosulfide formation. *In situ* generated hydrochloric acid addition could directly produce the β-chlorosulfide (blue arrow). The second pathway proposed proceeds through an episulfonium ion intermediate formed by attack of the electron rich sulfur atom (red arrow). The ring-opening reaction

occurs by attack at the terminal carbon giving the anti-Markovnikov product. Butler *et al*[25] reported the formation of an episulfonium ion intermediates by reaction between methanesulfenyl chloride and a diene. This would explain in our case the anti-Markovnikov orientation observed in this transformation.



Scheme 16

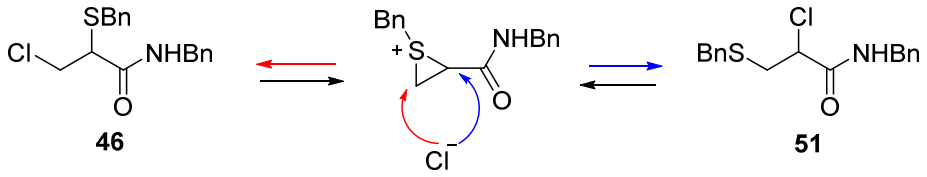
Butler *et al.*[26] reported that the steric factors appear to be important with nonconjugated olefins, since chloride ions preferentially attack at the least hindered terminal carbon, giving the primary chloride (Scheme 17). Also, Butler *et al.* described that the Markovnikov orientation was the major reaction product when precautions were taken to keep the reaction free from traces of acid.[25] In our case, the HCl liberated during the reaction may influence the ring opening, leading to the anti-Markovnikov derivative **46**.



Scheme 17

To confirm one or the other precursor for this transformation (α-chlorosulfide Scheme 15 *cf.* acrylamide Scheme 16), a large quantity of β-chlorosulfide **46** had to be isolated. For this, the synthesis of acrylamide **39** from α-thioamide **25** was undertaken in tetrachloromethane providing in the same way the desired β-chlorosulfide **46** (*cf.* Entry 4, Table 9 and Entry 3, Table 10). The crude mixture consisted of the acrylamide **39**, the β-chlorosulfide **46** and the α-thioamide **25** in a ratio 0.35 : 1 : 0.13 respectively by ^{1}H NMR spectroscopy. As, the acrylamide derivative **39** was seen co-eluting with the desired β-chlorosulfide **46**, decomposition of the acrylamide in the mixture was carried out by leaving the sample, concentrated, at room temperature for 48 hours (92% of acrylamide decomposed). The resulting mixture consisted of the α-thioamide **25**, the β-chlorosulfide **46**, the acrylamide **39**, and the α-chloro-β-thiopropanamide **51**, generated during the standing of the initial crude mixture, in a ratio 0.03 : 1 : 0.13 : 0.29. The β-chlorosulfide **46** and acrylamide **39** and the α-chloro-β-thiopropanamide **51** co-eluted upon column chromatography of the mixture on silica gel. α-Chloro-β-thiopropanamide **51** could only be partially removed by cold recrystallisation from ethyl acetate/hexane, leading to a mixture of **46** : **39** : **51** in a ratio 1 : 0.03 : 0.15 respectively by ^{1}H NMR spectroscopy.

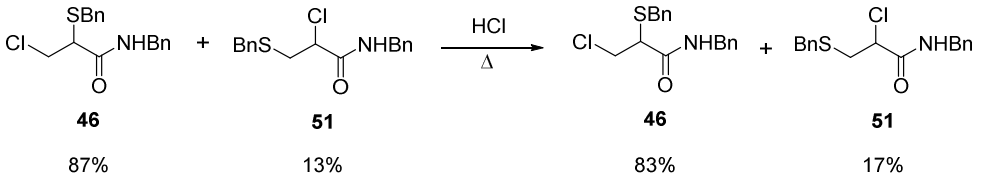
α-Chloro-β-thiopropanamide **51** was not formed initially during the reaction, but is generated later from β-chlorosulfide **46**. However, a few of the products rearranged spontaneously on standing at room temperature (Scheme 18).



Scheme 18

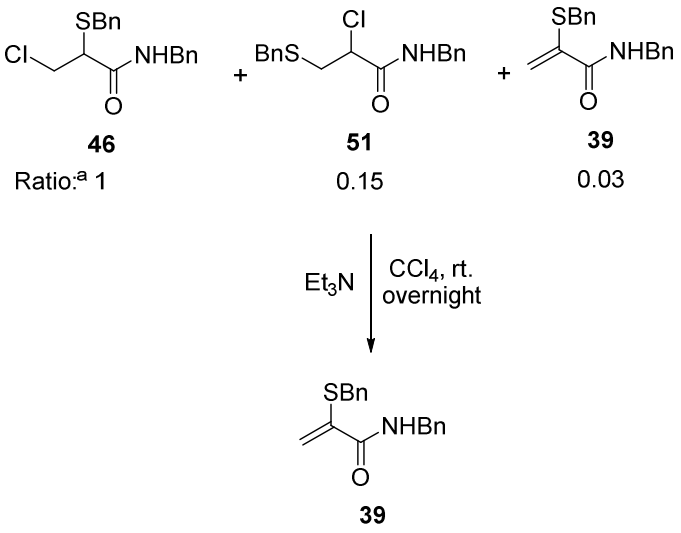
Heating of the mixture of β-chlorosulfide **46** and α-chloro-β-thiopropanamide **51** (ratio 1 : 0.15 respectively) under reflux in dichloromethane for 1 hour using catalytic HCl led to a mixture of the same compounds in a ratio of 1 : 0.23 respectively by ^{1}H NMR spectroscopy (Scheme 19, minor amount of acrylamide **39** was also present in the initial mixture and the crude product mixture). It is

reasonable to assume that the anti-Markovnikov orientation was preferred thermodynamically, although, the ratio change was not sufficiently significant to allow unequivocal conclusions.



Scheme 19

To support the hypothesis that acrylamide **39** is precursor of β-chlorosulfide **46** and chloro-β-thiopropanamide **51**, the mixture was also treated with 1 equivalent of triethylamine in tetrachloromethane at room temperature (Scheme 20). Full consumption of **46** and **51** was observed, with significant amount of acrylamide **39** observed by the ^{1}H NMR spectra of the crude material, along with minor amounts of unknown compounds formed.

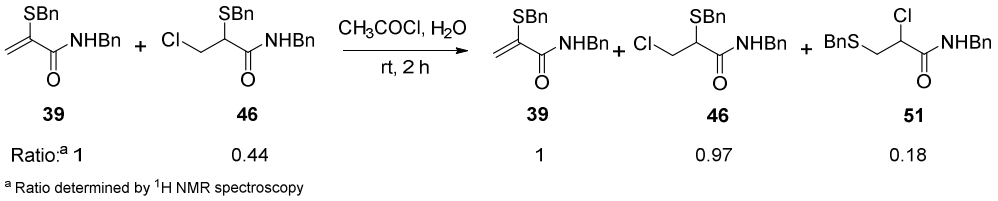


[a] Ratio by ^{1}H NMR spectroscopy of the crude mixture.

Scheme 20

Also, a mixture of acrylamide **39** and β-chlorosulfide **46** (ratio 1 : 0.44 respectively by ^{1}H NMR spectroscopy, obtained from another acrylamide **39** synthesis) treated with *in situ* generated HCl at room temperature, gave a mixture of acrylamide **39**, β-chlorosulfide **46** and α-chloro-β-thiopropanamide **51** in a ratio of 1 : 0.97 : 0.18

respectively (Scheme 21). It is important to specify that the ^{1}H NMR spectra of the crude mixture obtained was clean, with no evidence of decomposition of acrylamide **39**. The reaction was conducted in a time frame which revealed the reactivity rather than the decomposition of the acrylamide.



a Ratio determined by ^{1}H NMR spectroscopy

Scheme 21

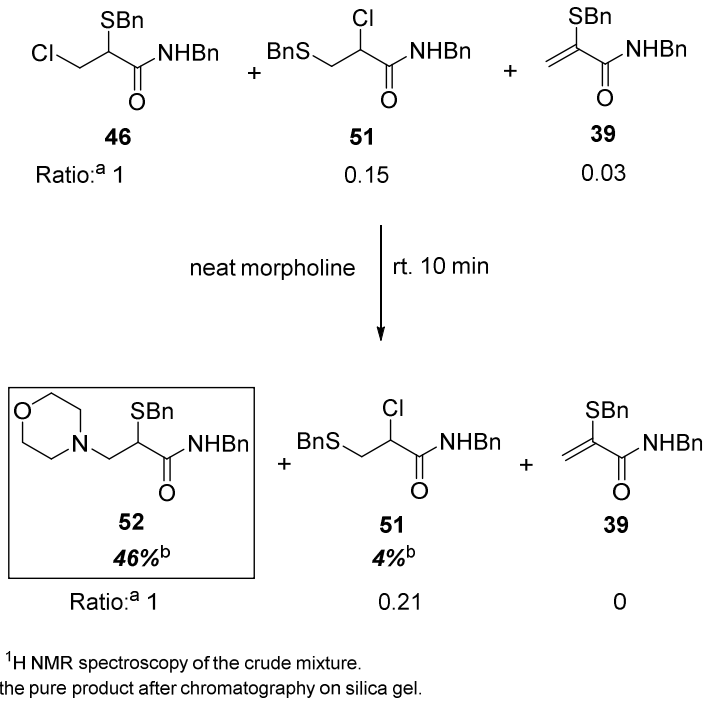
This data would suggest that acrylamide is a precursor to the β-chlorosulfide and, therefore, would support the second mechanism proposed (Scheme 16).

β-Chlorosulfide formation was not observed during the synthesis of dichloride or α-thio-β-chloroacrylamide derivatives, even when the synthesis was performed at room temperature. This would suggest that the second equivalent of NCS introduced prevents HCl attack forming the β-chlorosulfide derivative. Therefore, the HCl formed during the first chlorination step of the mechanism may directly react with the second equivalent of NCS in the reaction mixture, making it a more reactive species. Consequently, the HCl is already consumed and the alternative pathway leading to the β-chlorosulfide cannot occur. This experimental result indicates that the activation of NCS with HCl happens preferentially to the thiirane attack.

Nucleophilic substitutions, using nitrogen or oxygen nucleophiles, with the mixture of β-chlorosulfide **46** and α-chloro-β-thiopropanamide **51** (ratio 1 : 0.15 respectively) were performed in order to investigate the synthetic potential of these derivatives.

β-Chlorosulfide **46**, as a mixture with α-chloro-β-thiopropanamide **51**, and a minor amount of acrylamide **39** (ratio 1 : 0.15 : 0.03 respectively) was stirred in morpholine, as the solvent system (Scheme 22). The reaction afforded the corresponding α-thio-β-morpholinoamide **52** in 46% yield after chromatography

on silica gel. Some product may have been lost during the work-up, which would explain the low yield of the transformation.



[a] Ratio by ^{1}H NMR spectroscopy of the crude mixture.
[b] Yield of the pure product after chromatography on silica gel.

Scheme 22

Interestingly, α-chloro-β-thiopropanamide **51** did not react, probably due to the amide substituent at alpha position of the chloride, along with its sterically crowded postition. As all the β-chlorosulfide **46** was consumned, the α-chloro-β-thiopropanamide **51** was isolated in a pure form in 4% yield.

The structure was confirmed by 2D NMR experiments and mass spectrometry. A molecular ion of *m/z* 320.1 with a distinctive isotopic chlorine pattern for an ion containing one chlorine atom, as well as the exact mass in High Resolution Mass Spectrometry (Δppm 0.0004) were observed. The ^{1}H and ^{13}C NMR shifts correlate with literature values of an analogous derivative.[25, 27] The characteristic signals are a doublet of doublets at 4.37 ppm and two overlapping ABq systems at 3.03 and 3.18 ppm, corresponding to the α-CH and the β-CH_2 protons respectively. The chemical shifts of α-chloro-β-thiopropanamide **51** with those of β-chlorosulfide **46** were compared (Figure 21). For β-chlorosulfide **46**, the chlorine atom has a deshielding effect on the methylene C(3)H_2 and the observed ^{1}H and ^{13}C NMR

chemical shift is down-field. The same effect was observed for the methine C(2)H of α-chloro-β-thiopropanamide **51** derivative.

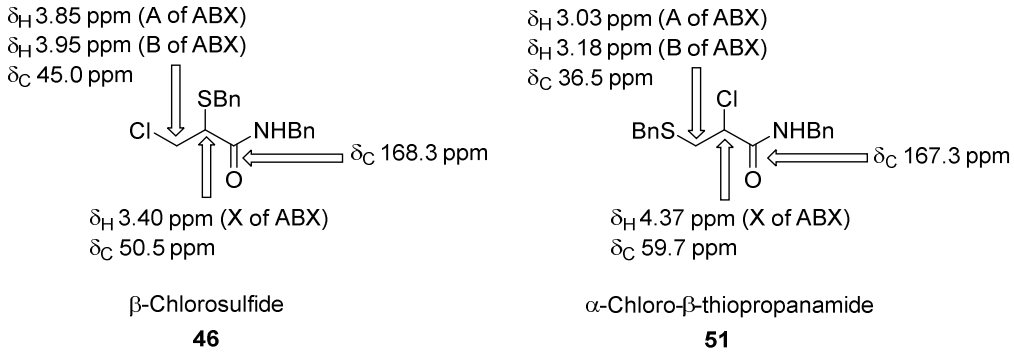
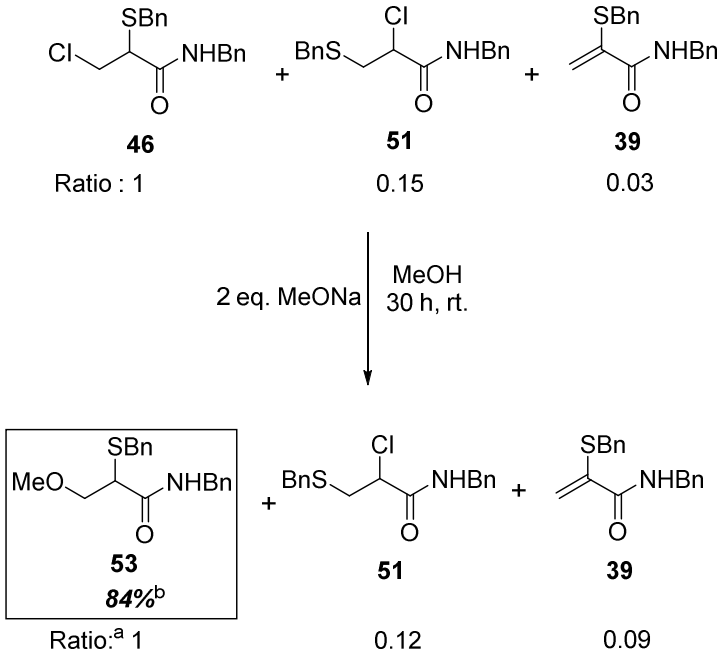


Figure 21

Reaction with sodium methoxide did not achieve full conversion, with 88% product formation based on ^{1}H NMR analysis of the crude mixture (Scheme 23). The corresponding α-thio-β-methoxyamide **53** was obtained in 84% yield after chromatography on silica gel. Here again, α-chloro-β-thiopropanamide **51** was found unreacted, showing the high stability of this derivative.



[a] Ratio by ^{1}H NMR spectroscopy of the crude mixture
[b] Yield of the pure product after chromatography on silica gel

Scheme 23

Interestingly, acrylamide **39** was found unreacted in the reaction using sodium methoxide (Scheme 23) but was fully consumed in the corresponding reaction using morpholine (Scheme 22), as indicated by ^{1}H NMR spectroscopy of the crude mixtures. It is reasonable to suggest that acrylamide **39** reacted with the morpholine leading to α-thio-β-morpholinoamide **52** (Scheme 22).

For the morpholine adducts prepared by Kissane,[28] from the *N*-phenyl, *S*-benzyl α-thio-β-chloroacrylamide, the ^{1}H NMR spectra provided evidence for the delocalization of the nitrogen lone pair of the morpholino group into the conjugated system (Figure 22). The signals for the protons alpha to the nitrogen of the morpholino group are shifted up-field compared to the morpholine derivative **52**.

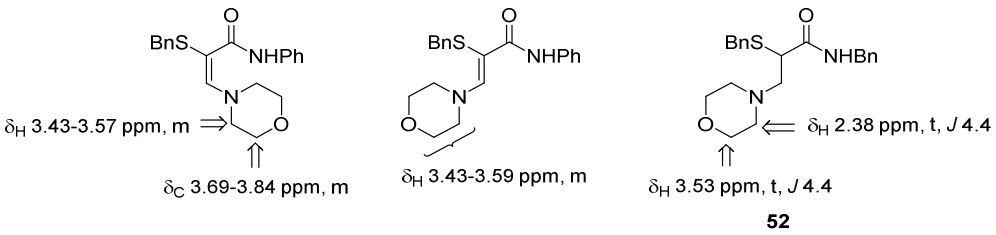
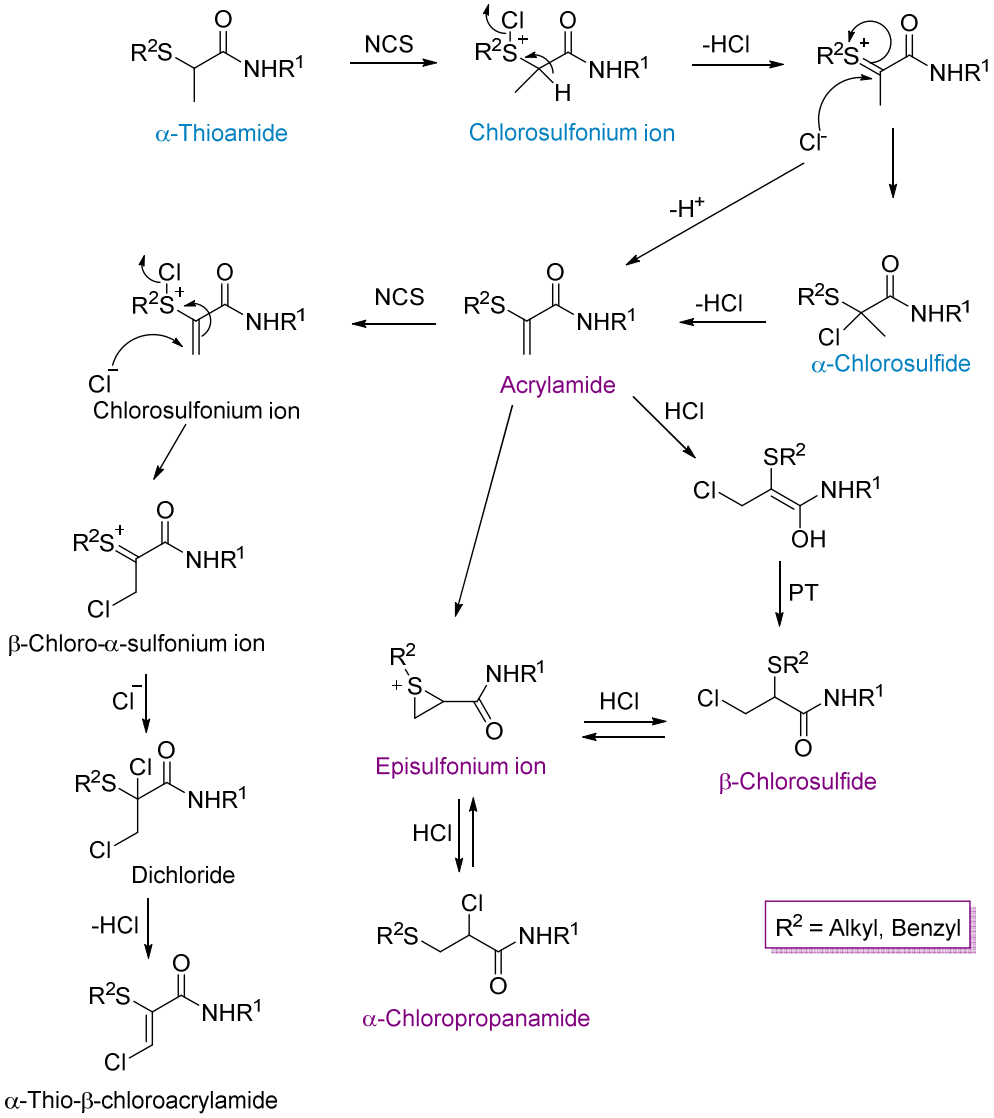


Figure 22

The multiplicity of the proton signals of the morpholino group was strongly affected by the unsaturation system in the molecule. For the morpholine adducts, the protons were observed as a multiplet, while in the morpholine derivative **52**, the methylenes of the morpholino group appeared as triplets, corresponding with the literature data of morpholine derivatives.[29]

The discovery of the β-chlorosulfide derivative highlighted a new route in the reaction pathway of the α-thio-β-chloroacrylamide formation (Scheme 24). This new route, with the acrylamide as key intermediate, occurred when 1 equivalent of NCS was employed at room temperature. Also, only the *S*-benzyl and *S*-butyl derivatives access this pathway. The resulting β-chlorosulfide was involved in an equilibrium with the α-chloro-β-thiopropanamide through the episulfonium ion

intermediate. These novel products revealed interesting access to new derivatives by nucleophilic substitution.

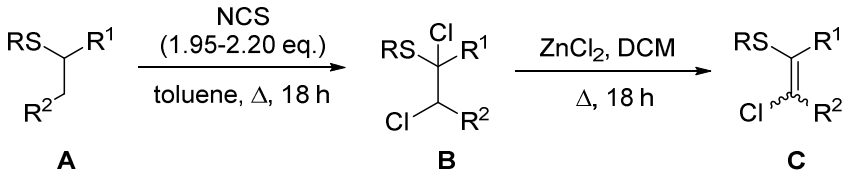


Scheme 24

The dichloride intermediate is the second key intermediate formed during the reaction pathway leading to α-thio-β-chloroacrylamide (Scheme 24) and will be discussed in the next section.

C. Synthesis of dichloride intermediates

The stability of the dichloride intermediates was found to vary across the series.[4,7,9] An increase in the stability of the ester, ketone and nitrile derivatives was seen in formation of the dichloride when the corresponding sulfide **A** were treated with NCS in toluene under reflux conditions (Scheme 25). For the amide series, the dichloride rapidly eliminates hydrogen chloride under these conditions to give the α-thio-β-chloroacrylamide.[4,7, 9] Furthermore, extended storage of the dichloride **B** was possible without apparent degradation for the ester, ketone and nitrile series. In contrast to the amide series, use of $ZnCl_2$ was required to achieve the final elimination of hydrogen chloride in the nitrile, ester and ketone series, with the corresponding dichlorides isolated from the NCS reactions.

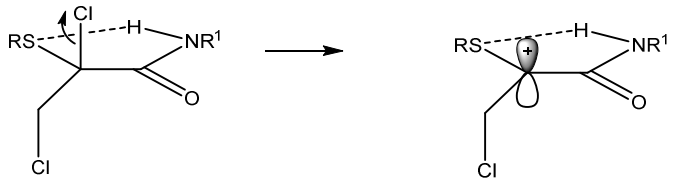


R = Ph, R^1 = CN, R^2 = H
R = Ph, R^1 = CO_2Me, R^2 = H
R = Ph, R^1 = CO_2Et, R^2 = H
R = *n*-Bu, R^1 = CO_2Me, R^2 = H
R = Ph, R^1 = CO_2Me, R^2 = Me
R = Ph, R^1 = COMe, R^2 = H
R = Ph, R^1 = COEt, R^2 = H

Scheme 25

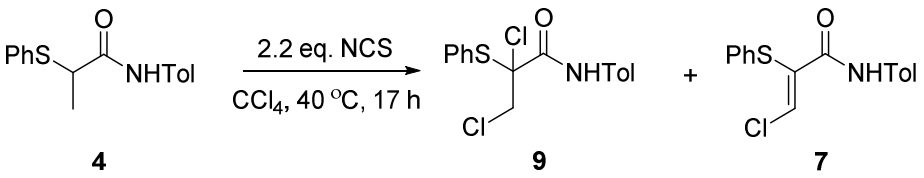
The rationale for the increased ease of elimination in the amide series relative to the ether, ester and nitrile series is presumably due to electronic effects of the substituents as discussed previously for the α-chlorosulfides (*cf*. *Section 1*.). The increased electron withdrawing effect of the ester, ketone and nitrile stabilized the dichlorides relative to the analogous amides.[4,7] Further explanation for the decreased ease of HCl elimination in these series relative to the amide could be due to conformational factors; for the amides, the intramolecular hydrogen bond holds the compound in a conformation in which loss of the chloride from the α-carbon is favoured through captodative stabilization of the resulting sulfur stabilized carbocation (Scheme 26). In the ketone, ester and nitrile derivatives

there is no restriction on the conformation and presumably the dichloride adopts a different conformation from which loss of the chloride is less favored.



Scheme 26

Therefore, milder conditions may be employed to preferentially form the dichloride instead of the α-thio-β-chloroacrylamide in the amide series. However, the isolation of the intermediate was not possible in almost all cases due to the high lability. Murphy[4] developed an optimised process for the synthesis of the dichloride intermediate **9** using 2.2 equivalents of NCS, in tetrachloromethane at 40 °C for 17 hours (Scheme 27). The dichloride could be observed as a mixture with the corresponding α-thio-β-chloroacrylamide **7** in a ratio of 1 : 0.33 respectively, however, attempted purification resulted in full conversion of the dichloride to the α-thio-β-chloroacrylamide.[4]

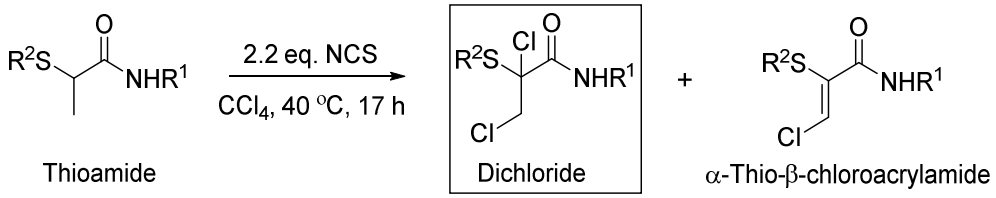


4 **9** **7**

Scheme 27

In this work, the same protocol was employed for α-thioamides **22**, **25**, **27**, **28** and **29** (Table 11). Dichloride **9** was obtained as a mixture with α-thio-β-chloroacrylamide **7**, providing similar results to those reported by Murphy (Entry 1, Table 11). It was not possible to purify dichloride **9** by column chromatography due to the degradation of the product in presence of silica gel or alumina.

Table 11 Preparation of dichlorides at 40 °C



Entry	Thioamide	Dichloride	α-Thio-β-chloroacrylamide	R^1	R^2	Ratio[a] (dichloride : α-thio-β-chloroacrylamide)
1	**4**	**9**	**7**	Tol	Ph	1 : 0.52[b]
2	**22**	**54**	**15**	Bn	Ph	1 : 0[c] 56% Yield[d] **54**
3	**25**	**55**	**26**	Bn	Bn	0 : 1[e]
4	**27**	**56**	**34**	Tol	Bn	0 : 1[e]
5	**28**	**57**	**35**	Bn	Bu	0 : 1[e]
6	**29**	**58**	**36**	Tol	Bu	0 : 1[e]

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

[b] The crude product consists of a mixture of the dichloride **9**, the α-thio-β-chloroacrylamide **7** and the trichloride **60** with a ratio 1 : 0.52 : 0.13 respectively by ^{1}H NMR spectroscopy.

[c] The crude product consists of a mixture of the dichloride **54** and the corresponding trichloride with a ratio 1 : 0.18 respectively by ^{1}H NMR spectroscopy.

[d] Yield of the pure product after chromatography on silica gel.

[e] The characteristic signals corresponding to the dichloride intermediates (ABq, δ_H ~ 4 ppm) was not observed in the ^{1}H NMR spectra of the crude mixture. The α-thio-β-chloroacrylamide was the main product formed.

Dichloride **54** was more stable and, indeed, could be purified by column chromatography on silica gel (Entry 2, Table 11). The formation of α-thio-β-chloroacrylamide **15** was not observed by ^{1}H NMR spectroscopy, consistent with the stability of this dichloride **54**, which required further heating to promote the HCl elimination leading to **15** (heating at 90 °C).[4] For the synthesis of the dichlorides **9** and **54**, a minor amount of the corresponding trichloride was observed by ^{1}H NMR spectroscopy of the crude product mixture. Interestingly, when the conditions were used with α-thioamides bearing a benzyl or butyl substituent on the sulfide group, dichloride formation was not observed at 40 °C,

as the hydrogen chloride elimination happens rapidly leading to the corresponding α-thio-β-chloroacrylamides (Entries 3 to 6, Table 11). This can be rationalized by the increased electronic density in the sulfur stabilized carbocation.

Taking into account the higher reactivity of the benzyl or butyl-thio derivatives, milder conditions to achieve the synthesis of the elusive dichlorides have to be employed.

The presence of dichloride compounds can be easily identified in ^{1}H NMR spectra by a ABq system at δ_H ~ 4 ppm corresponding to the terminal alkyl resonances (Figure 23). As a result, formation of these intermediates could easily be observed in real time when the reaction was performed in tetrachloromethane. The ^{1}H NMR spectra were generally recorded after filtration to remove the NCS and *N*-succinimide, although this was not essential. In this way, decomposition to the α-thio-β-chloroacrylamide on concentration was avoided and this enabled direct observation of the labile dichloride in reaction mixture.

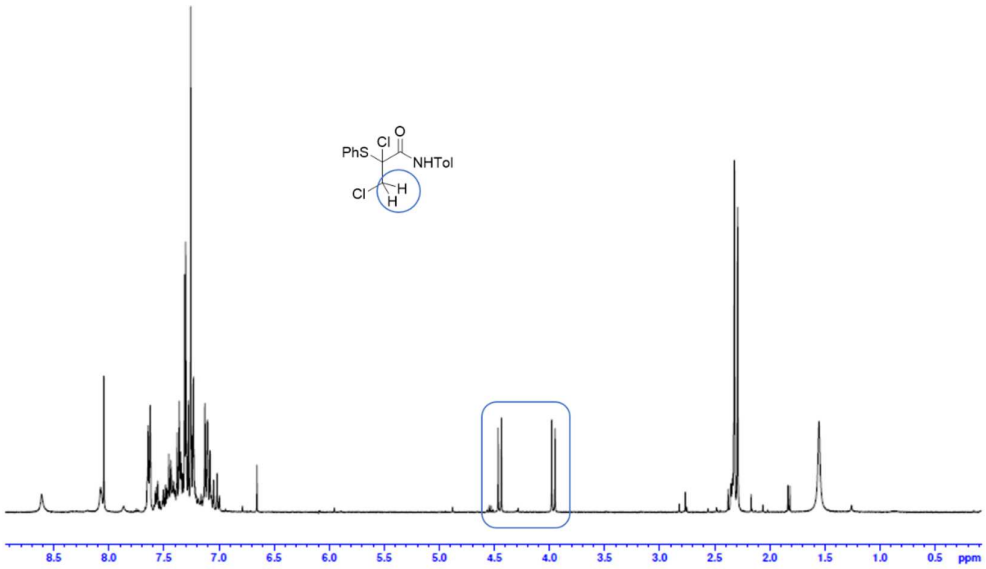


Figure 23 ^{1}H NMR spectra of the dichloride **9**

The synthesis of the SPh/NHBn dichloride **56** was then attempted under milder conditions. NCS (2.2 eq.) was added to a solution of α-thioamide **27** in tetrachloromethane at room temperature. Full consumption of the starting material (α-thioamide **27**) was observed in less than 30 minutes reaction time at

room temperature, by ^{1}H NMR spectroscopy (Figure 24). After 5.5 hours total reaction time, formation of acrylamide **37** was observed. After 7 hours of reaction time, the acrylamide **37** was fully converted to dichloride **56**. Dichloride **56** was still present after 30 hours of reaction time, with a minor amount of α-thio-β-chloroacrylamide **34** formed.

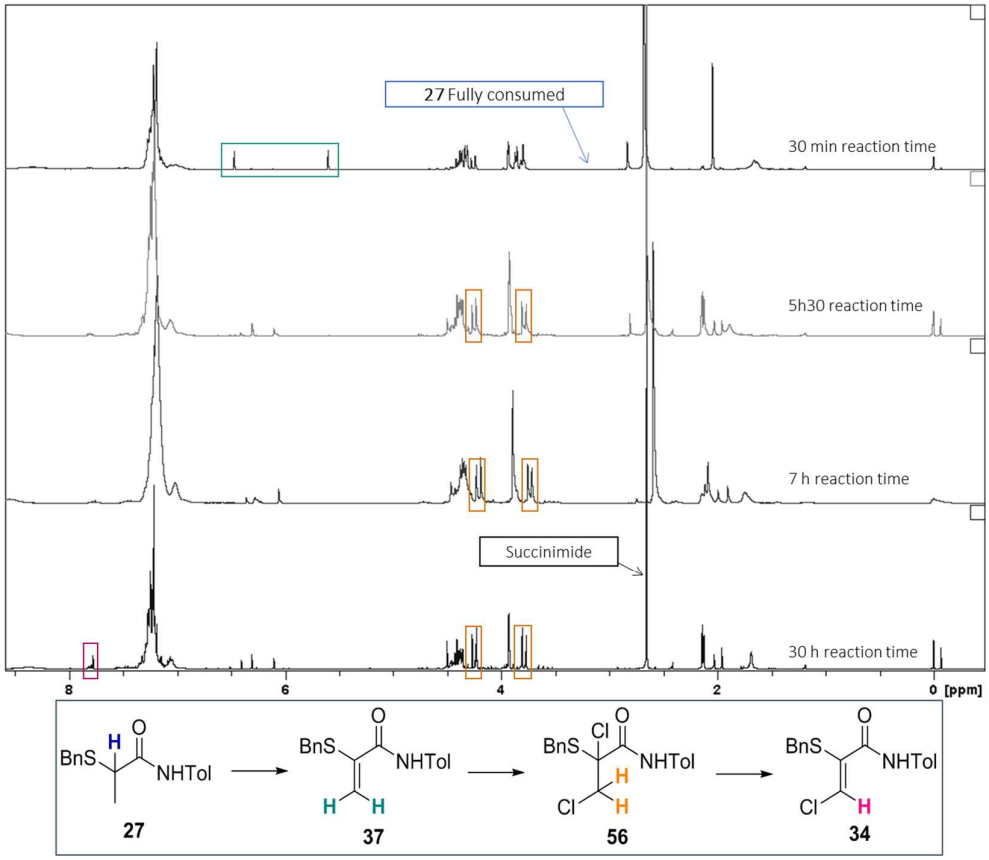
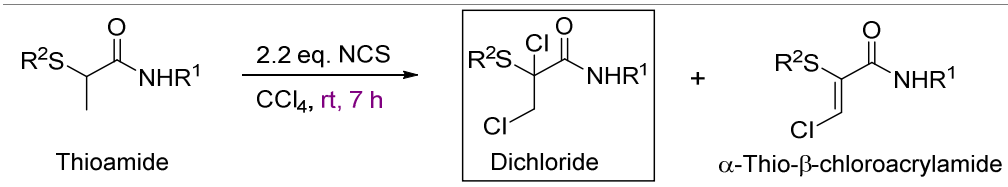


Figure 24

Therefore, the optimal conditions for the synthesis of dichlorides from α-thioamides bearing a benzyl or butyl substituent on the sulfide group (α-thioamides **25**, **27**, **28** and **29**) was found to be 2.2 equivalents of NCS at room temperature for 7 hours. Therefore, the dichlorides **55**, **56**, **57** and **58** were synthesised using this procedure (Table 12).

Table 12 Preparation of dichlorides at room temperature



Entry	Thioamide	Dichloride	α-Thio-β-chloroacrylamide	R^1	R^2	Ratio[a] (dichloride : α-thio-β-chloroacrylamide)
1	**25**	**55**	**26**	Bn	Bn	1 : 0.09[b]
2	**27**	**56**	**34**	Tol	Bn	1 : 0[c]
3	**28**	**59**[d]	**35**	Bn	Bu	1 : 0
4	**29**	**58**	**36**	Tol	Bu	1 : 0.93[e]

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

[b] The crude product consists of a mixture of the dichloride **55**, the acrylamide **39** and the α-thio-β-chloroacrylamide **26** with a ratio 1 : 0.33 : 0.09 respectively by ^{1}H NMR spectroscopy.

[c] The crude product consists of a mixture of the dichloride **56**, the corresponding trichloride with a ratio 1 : 0.18 respectively by ^{1}H NMR spectroscopy.

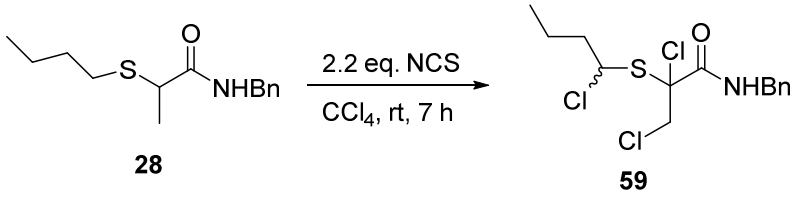
[d] The dichloride was chlorinated on the butyl chain and characterised as a mixture of diastereoisomers.

[e] The crude product consists of a mixture of the dichloride **58**, the α-thio-β-chloroacrylamide **36** and the corresponding trichloride with a ratio 1 : 0.93 : 0.42 respectively by ^{1}H NMR spectroscopy.

The yields were not determined as these dichlorides were not stable enough to be purified by column chromatography.

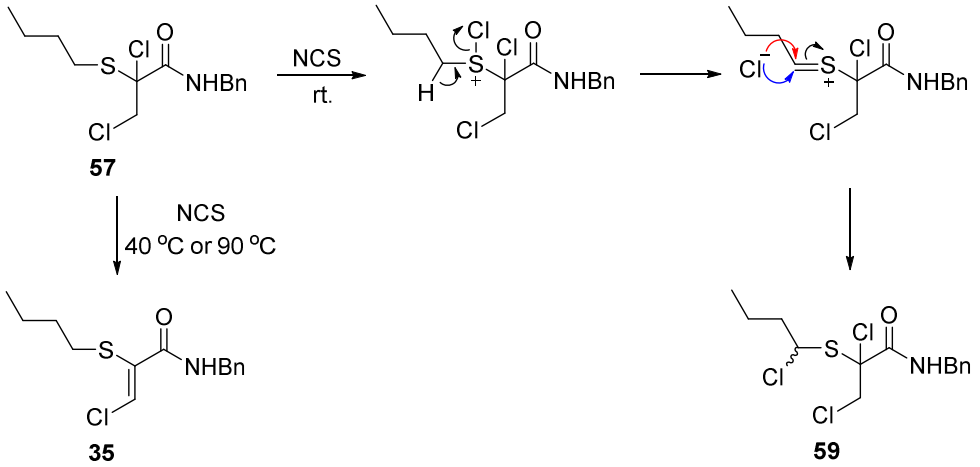
The ratio of dichloride : α-thio-β-chloroacrylamide varied with the sulfide substituent suggesting that the sulfide substituent influences the kinetic control of the reaction. Indeed, the lack of delocalization on the lone-pair of the sulfur into the aromatic ring seems to destabilize the dichloride intermediate, with greater α-thio-β-chloroacrylamide formation observed. Therefore, to access elusive *S*-alkyl and *S*-benzyl dichlorides, the optimum conditions are 2 equivalents of NCS in tetrachloromethane at room temperature for 7 hours.

α-Thioamide **28** in presence of 2.2 equivalents of NCS at room temperature led to dichloride **59** with chlorination on both sides of the sulfur atom as a mixture of diastereoisomers with ratio 1 : 0.55 by ^{1}H NMR spectroscopy (Scheme 28).



Scheme 28

No evidence of the butyl chain chlorination was observed during the corresponding acrylamide **40** synthesis (1.1 eq. NCS, room temperature). This suggest that the dichloride synthesis happens firstly and the butyl chain chlorination occurred only on dichloride **57** formed. However, dichloride **57** formation was never observed in ^{1}H NMR spectroscopy. As no evidence of the butyl chain chlorination was observed during the synthesis of the corresponding α-thio-β-chloroacrylamide **35** (40 °C or 90 °C), this chlorination presumably occurred only at room temperature, while the HCl elimination from dichloride **57** occurred preferentially above 40 °C (Scheme 29). From this, a mechanism can be proposed for this transformation.

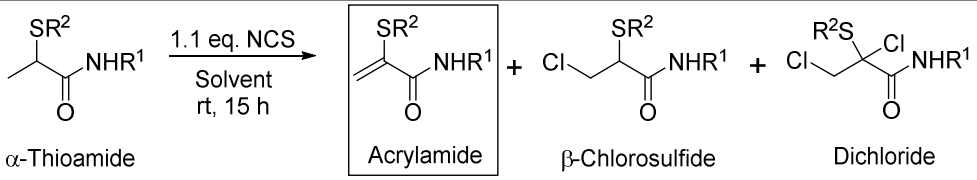


Scheme 29

D. Results reproducibility

Considering the sensitivity of these transformations to alteration in reaction condition and substituents, their reproducibility was an important factor to study. When the acrylamide synthesis was performed two times for the series of α-thioamides, the ratio of the crude mixtures components by ^{1}H NMR spectroscopy were similar, indicating the reproducibility of this transformation (Table 13)

Table 13 Study of the reproducibility of acrylamide synthesis.



α-Thioamide β-Chlorosulfide Dichloride

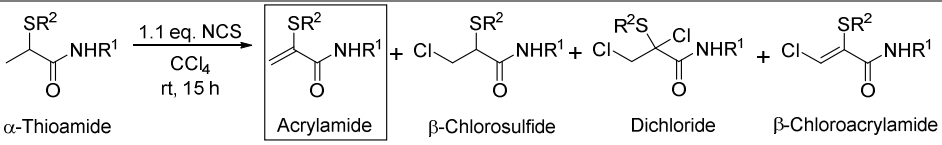
Entry	Solvent	Series		Crude ratio[a]			
				Thioamide	Acrylamide	β-Chlorosulfide	Dichloride
1	CCl_4	SPh	Exp 1	0.04	1	0	0.31
		NHTol	Exp 2	0	1	0	0.22
2	Tol	SBn	Exp 1	0.14	0.87	1	0
			Exp 2	0.12	0.79	1	0
3	CCl_4	NHBn	Exp 1	0.13	0.44	1	0
			Exp 2	0.13	0.35	1	0
4	CCl_4	SPh	Exp 1	0	1	0.40	0
		NHBn	Exp 2	0	1	0.42	
5	CCl_4	SBn	Exp 1	0	1	0	0
		NHTol	Exp 2	0	1	0	0

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

The reaction outcome was found to be strongly dependent on the substituent of the sulfur and amide groups. When both the sulfur and amide groups were not linked to an aryl substituent (Entry 2 and 6, Table 14), unconsumed starting material was observed on the ^{1}H NMR spectra of the crude mixture. Tuleen *et al.*[30] reported than the presence of electron withdrawing groups α or β to the sulfide functionality contributes significantly to the ease of chlorination step. This would

explain that the first chlorination step of the mechanism involved (*cf.* CHAPTER 2, *section 1.*) is more difficult when the sulfur and amide substituents are both alkyl or benzyl.

Table 14 Comparison between the ratio of the crude mixture components and the substituents.



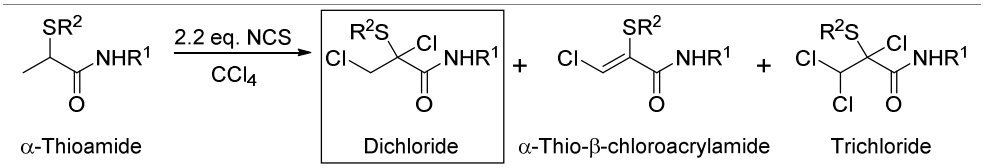
Entry	Series	Crude ratio[a]				
		Thioamide	Acrylamide	β-Chlorosulfide	Dichloride	β-Chloro acrylamide
1	SPh NHTol	0	1	0	0.22	0
2	SBn NHBn	0.13	0.35	1	0	0
3	SPh NHBn	0	1	0.40	0	0
4	SBn NHTol	0	1	0	0	0
5	SBu NHTol	0	0.62	0.73	0.23	1
6	SBu NHBn	0.81	0.80	1	0	0

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

For the SBu/NHTol series, a complex mixture of products was observed, including the corresponding α-thio-β-chloroacrylamide. No apparent pattern would explain this result, suggesting that a more complex contribution of the substituent was involved in the reaction outcome.

When the dichloride synthesis was performed two times on three series of α-thioamides, the ^{1}H NMR spectra of the resulting crude mixtures were again similar (Table 15).

Table 15 Study of the reproducibility of dichloride synthesis.



α-Thioamide | Dichloride | α-Thio-β-chloroacrylamide | Trichloride

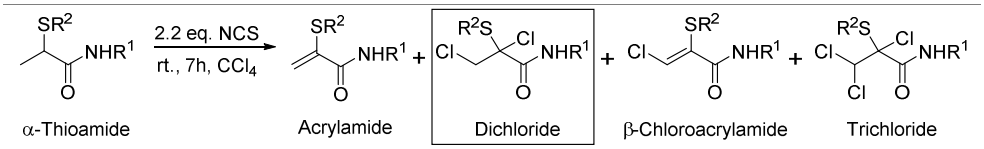
Entry	Conditions	Series		Crude ratio[a]		
				Dichloride	α-Thio-β-Chloroacrylamide	Trichloride
1	40 °C, 17 h	SPh NHTol	Exp 1	1	0.80	0.19
			Exp 2	1	0.52	0.13
2		SPh NHBn	Exp 1	1	0	0.18
			Exp 2	1	0	0.23
3	rt, 7 h	SBn NHTol	Exp 1	1	0	0.10
			Exp 2	1	0	0.18
			Exp 3	1	0	0.16

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

For SPh/NHTol series (Entry 1, Table 15), the dichloride appeared less stable than for the SPh/NHBn series (Entry 2, Table 15) leading to more α-thio-β-chloroacrylamide formed. The presence of aryl substituent on the amide group contributes significantly to the ease of HCl elimination from the dichloride. This was possibly due to enhanced acidity of the amide N-H bond leading to stronger intramolecular bond and therefore favored the conformation for chloride elimination (*cf. Section 3.C.* Scheme 24).

As previously noted, due to the high instability of the dichlorides, their synthesis for *S*-benzyl or *S*-butyl series required milder conditions than for the *S*-phenyl series. The corresponding crude mixtures obtained are summarised in Table 16. As reported above for the acrylamide synthesis, the chlorination of sulfur group in the SBn/NHBn series have more difficulty to occur fully. As a result, partial second chlorination step in the reaction mechanism, from the acrylamide intermediate to the dichloride, was observed, resulting in unreacted acrylamide remaining (Entry 1, Table 16)

Table 16 Substituent effect on the reaction outcome for the dichloride synthesis.



Entry	Series	Crude ratio[a]			
		Acrylamide	Dichloride	β-Chloroacrylamide	Trichloride
1	SBn NHBn	0.33	1	0.09	0
2	SBn NHTol	0	1	0	0.18
3	SBu NHTol	0	1	0.93	0.42
4	SBu NHBn	0	1[b]	0	0

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.
[b] The dichloride was chlorinated on the butyl chain and characterised as a mixture of diastereoisomers.

Once again, the most complex outcome for this transformation was provided by the SBu/NHTol series (Entry 3, Table 16; *cf.* Entry 5, Table 14)

The synthesis and isolation in a pure form of acrylamide **8** was performed previously within the group, and was performed in this work with comparable yield. In this project, synthesis of nine novel acrylamides was achieved and they were spectroscopically characterised. In addition, this study allowed the discovery of a new reaction pathway for the α-thio-β-chloroacrylamide transformation: the β-chlorosulfide. Full spectroscopic characterization for this new derivative was achieved, as well as a mechanism for its formation proposed. A new protocol for the dichloride synthesis was developed and 4 novel dichlorides were obtained thanks to this new method. Overall, this study has provided the key spectroscopic features of the acrylamide and dichloride enabling detail in the mechanistic process across the series.

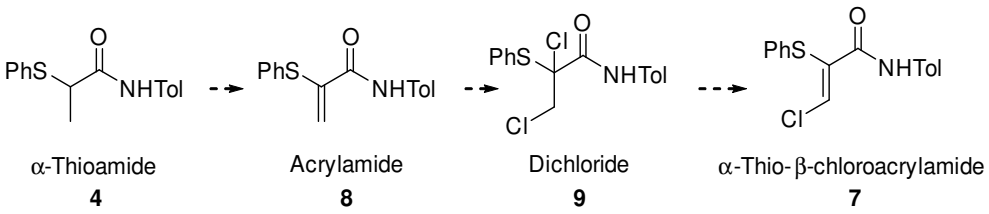
4. HPLC AS AN ALTERNATIVE MONITORING METHOD FOR THE DEVELOPMENT OF A CONTINUOUS PROCESS

The use of High Performance Liquid Chromatography (HPLC)[31] is widely employed as a process analytical chemistry tool, especially for process development and is routinely used in pharmaceutical industry.[32] With the use of well-developed and appropriate analysis methods, the chromatographic conditions provide analyte specificity with time and the components are subsequently detected.[33, 34] Detector response for quantitative measurements is an essential consideration when dealing with multicomponent reaction mixtures. It is important, therefore, to establish the relative response factor for each species being analyzed by HPLC in order to obtain quantitative data.

For future scale up of the oxidative chlorination and implementation of this process by collaborators, a robust HPLC method for rapid quantitation of reaction products, intermediates and starting materials was developed.

A. Development of the HPLC method

The synthesis of α-thio-β-chloroacrylamide **7** from α-thioamide **4** using NCS occurs *via* two chlorination steps as already discussed extensively previously (Scheme 30). One equivalent of NCS leads to the acrylamide intermediate **8**. At this stage, a second equivalent of NCS is necessary to carry through to the dichloride intermediate **9**, which leads to the stable α-thio-β-chloroacrylamide **7** by HCl elimination.



Scheme 30

Chromatography was carried out using an achiral reverse phase column with a flow rate of 0.8 mL/min. An initial method was developed using a solution of methanol (70%) in water as the mobile phase and reaction components were detected by measurement of their UV absorbance at 290 nm. Using this method, the starting material, key intermediates and α-thio-β-chloroacrylamide of the phenylthio toluidine series (**4**, **8**, **9** and **7**) could be successfully identified (Table 17). The efficient separation of each compound/intermediate allows the reaction to be followed using this HPLC technique. No evidence of decomposition of the labile dichloride **9** in aqueous methanol was observed.

Table 17 Retention times of the phenylthiol toluidine series using methanol/water using MeOH : H_2O (70 : 30) as mobile phase

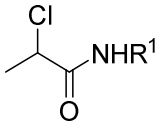
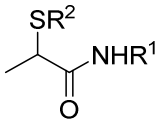
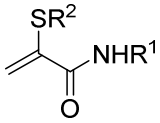
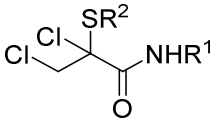
	4	**8**	**9**	**7**
Retention times	11.4 min	13.2 min	22.1 min	18.1 min

Chromatography was carried out using a YMC-Pack ODS-A reverse phase column (250 mm x 4.6 mm, 5 µm) with a flow rate of 0.8 mL/min. Samples were injected (5 µL) by the autosampler and were detected by UV absorbance at 250 nm and by a 385-ELSD evaporative light scattering detector (LC-ELSD).

In order to explore the scope of our HPLC method developed, it was used for the analysis of the benzylthio benzylamide series (**25**, **39**, **55** and **26**). Unfortunately, in this instance, using methanol (70%) in water as the mobile phase lead to the co-elution of α-thioamide **25** with acrylamide **39**.

Therefore, a new HPLC method was developed, using isocratic acetonitrile (60%) in water as mobile phase. This eluent allows a good separation of the starting material **25**, the intermediates **39** and **55**, and the final α-thio-β-chloroacrylamide **26**. Also, the same method can be used for the analysis of other series of analogous compounds: SBn/NHTol, SPh/NHBn, SBu/NHTol and SBu/NHBn series (Table 18).

Table 18 HPLC Retention times of α-chloroamides, α-thioamides, acrylamides, dichlorides and α-thio-β-chloroacrylamides using MeCN : H_2O (60 : 40) as mobile phase

	Retention time (min)[a]					
	R^1 = Tol R^2 = Ph	R^1 = Bn R^2 = Bn	R^1 = Tol R^2 = Bn	R^1 = Bn R^2 = Ph	R^1 = Tol R^2 = Bu	R^1 = Bn R^2 = Bu
	7.4 **18**	5.8 **19**	7.4 **18**	5.8 **19**	7.4 **18**	5.8 **19**
	12.2 **4**	9.9 **25**	14.2 **27**	8.8 **22**	14.6 **29**	10.1 **28**
	14.9 **8**	13.8 **39**	16.3 **37**	10.4 **38**	18.1 **41**	11.8 **40**
	26.3 **9**	25.2 **55**	28.6 **56**	18.2 **54**	27.3[b] **58**	29.6[c] **57**
	19.9 **7**	15.6 **26**	24.8 **34**	13.9 **15**	27.9[b] **36**	16.9 **35**

[a] Chromatography was carried out using a YMC-Pack ODS-A reverse phase column (250 mm x 4.6 mm, 5 µm) with a flow rate of 0.8 mL/min. Samples were injected (5 µL) by the autosampler and were detected by UV absorbance at 250 nm and by a 385-ELSD evaporative light scattering detector (LC-ELSD).

[b] Co-elution of the dichloride and the α-thio-β-chloroacrylamide.

[c] The dichloride was chlorinated on the butyl chain and characterised as a mixture of diastereoisomers which co-eluted.

The *N*-tolyl series showed longer retention times than the *N*-benzyl/*N*-butyl series, demonstrating that these series are less polar, possibly associated with the pKa of the amide N-H bond. This is explained by the delocalization of the nitrogen lone pair into the aromatic ring for the *N*-tolyl series, resulting in less delocalization into the carbonyl group. The carbonyl appears at a higher frequency in this series compared to the *N*-benzyl/*N*-alkyl series previously discussed supporting this observation.

The polarity of each of the derivatives increases across the series in the following order: the dichloride, the α-thio-β-chloroacrylamide, the acrylamide, the α-thioamide and the α-chloroamide.

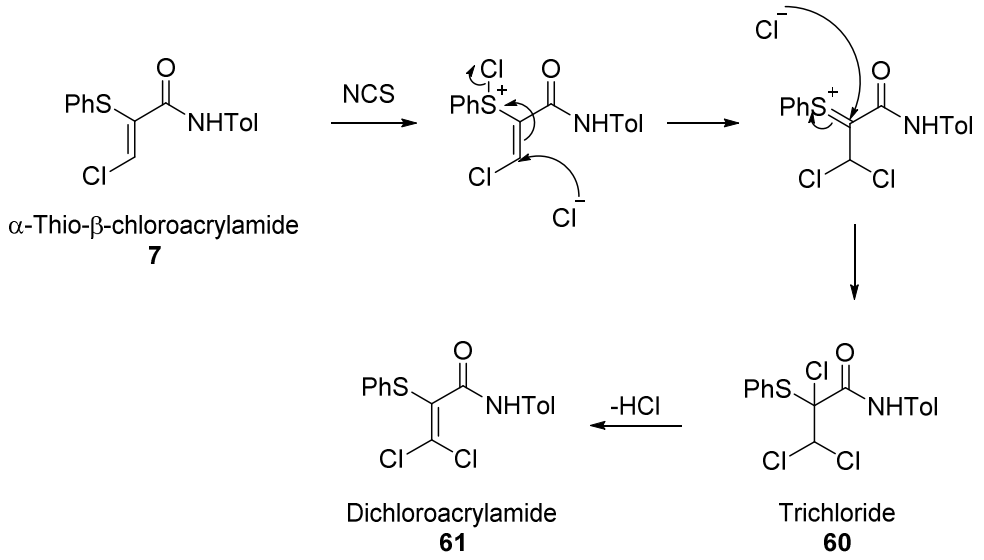
B. Calibration curve

In order to quantify the consumption of the starting material and the formation of key intermediates and final product, calibration curves were measured. For each compound, 3 standard solutions were made, with concentrations ranging from 0.03 mg/mL to 2.3 mg/mL. The peak area / response from each concentration with the standard were plotted against the concentration of analyte.

The calibration curve of α-thioamide **4**, α-thio-β-chloroacrylamide **7** and acrylamide intermediate **8** were measured. A calibration curve could not be attempted on dichloride intermediate **9** due to its high instability. The dichloride **9** concentration has been estimated with the assumption that it has the same UV response as α-thioamide **4**. Indeed, it has a UV chromaphore most similar to α-thioamide **4**, as it could not be compared with acrylamide **8** or α-thio-β-chloroacrylamide **7** because of their level of unsaturation.

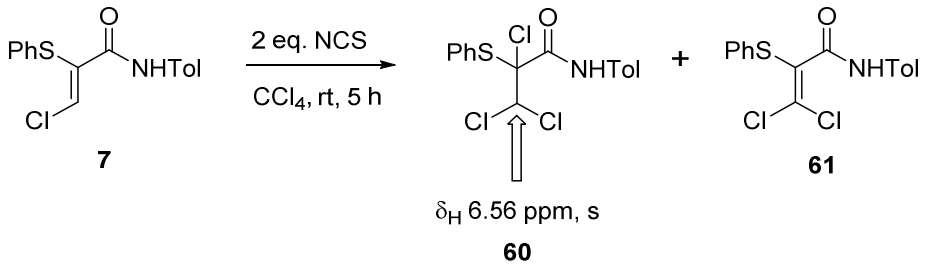
C. Retention time of over-chlorinated products

Lynch had also reported over-chlorination occurring during the synthesis of α-thio-β-chloroacrylamide leading to the formation of the trichloride **60** and finally the dichloroacrylamide **61**, by hydrogen chloride elimination (Scheme 31).[16] The formation of these derivatives is favored by using an excess of NCS (greater than two equivalents) or over-heating of the reaction (above 90 ^{o}C).



Scheme 31

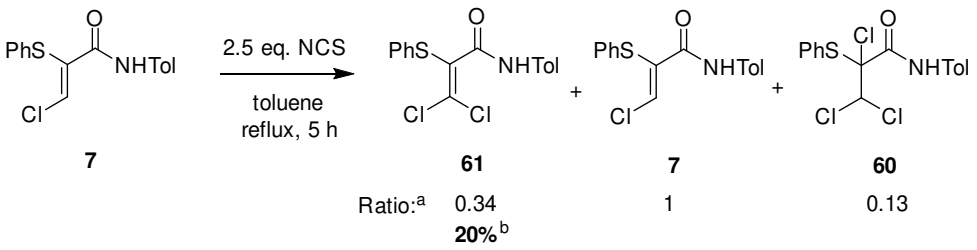
The trichloride **60** by-product can be easily detected and quantified using ^{1}H NMR spectroscopy, with a characteristic singlet at 6.56 ppm corresponding to the proton of the β-carbon. The derivative was characterized as a mixture with the dichloroacrylamide **61** and the α-thio-β-chloroacrylamide **7**, generated by reaction of **7** with two equivalents of NCS at room temperature (Scheme 32).



Scheme 32

However, the trichloride was observed to be unstable and was readily decomposed to the dichloroacrylamide **61**, making isolation as a pure compound impossible.

Synthesis of the dichloroacrylamide **61** was performed using the α-thio-β-chloroacrylamide **7** in presence of 2.5 equivalents of NCS in toluene under reflux (Scheme 33).



[a] Ratio of the crude mixture by 1H NMR spectroscopy.
[b] Yield of the pure product after chromatography on silica gel.

Scheme 33

The product was isolated pure in 20% yield, after chromatography on silica gel. The dichloroacrylamide **61** does not have characteristic signals in the ^{1}H NMR spectra because the β-carbon is fully substituted. Characteristic signal corresponding to the β-carbon could be identified in the ^{13}C NMR spectra, however, the quantification was impossible, and the acquisition time required to perform the analysis would not allow the real crude mixture composition. Therefore, it is challenging to quantify or to easily detect the formation using NMR spectroscopy.

This makes reaction process monitoring using HPLC more advantageous. For these compounds, the retention time representing each was determined using 60% acetonitrile in water as isocratic eluent system (Table 19).

Table 19 Retention time of the over-chlorinated products using MeCN : H_2O (60 : 40) as mobile phase

	60	**61**
Retention time	33.0 min	18.3 min

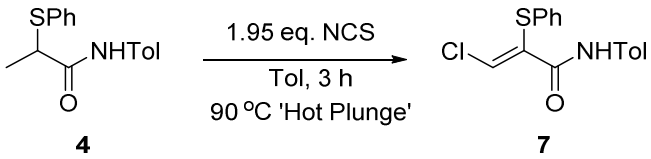
Chromatography was carried out using a YMC-Pack ODS-A reverse phase column (250 mm x 4.6 mm, 5 µm) with a flow rate of 0.8 mL/min. Samples were injected (5 µL) by the autosampler and were detected by UV absorbance at 250 nm and by a 385-ELSD evaporative light scattering detector (LC-ELSD).

5. DEVELOPMENT OF A CONTINUOUS PROCESS

Recently, continuous flow processing has become an attractive alternative to batch processing in the academic, pharmaceutical and fine chemical sectors. Numerous reviews exist in the literature on the advantages and limitations of flow

chemistry.[35-45] Some of the many advantages include the potential to increase the safety profile of a reaction due to enhanced mass and heat transfer. The task of scale up of reactions is much easier than batch processing as the reagents can be pumped for a longer period of time.[38, 46] The high surface area to volume ratio (1000x greater than a batch reactor) enables almost instantaneous heating or cooling and therefore ultimate temperature control, resulting in cleaner reactions being made possible.[47] In addition, continuous processing offers a major safety benefit as heat can be removed much more effectively and so reactions can be performed safely and easily.

As discussed previously, preparation of α-thio-β-chloroacrylamides is typically achieved in a final cascade/domino reaction[48] where a solution of α-thioamide and NCS in toluene is subjected to a 'hot plunge' by placing it into a pre-heated oil bath at 90 °C (Scheme 34).



Scheme 34

The rapid heating *via* 'hot-plunge' minimizes formation of process impurities during the initial heating phase.[4] Efficient rapid heating poses practical difficulties for scale-up using batch processing and furthermore, chromatographic separation is required to remove product impurities. Development of a continuous flow process would be an attractive alternative to batch in order to scale-up α-thio-β-chloroacrylamide synthesis. The temperature control afforded by continuous processing would be expected to provide excellent transformation conditions.

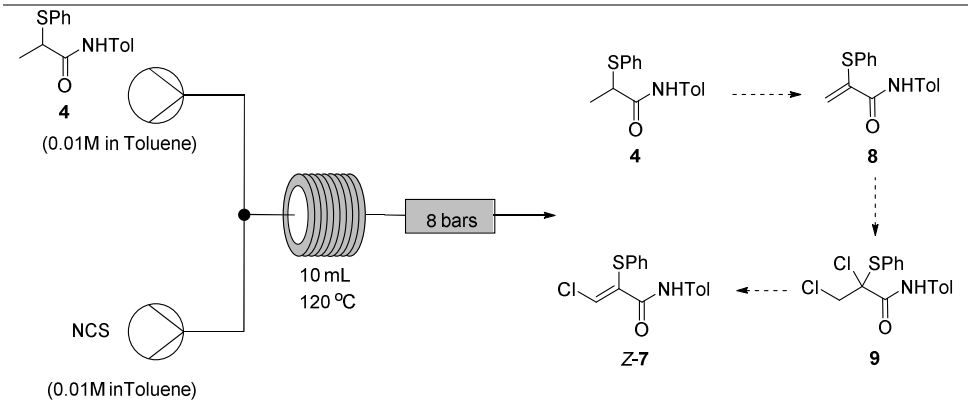
The goal of this study was to develop a scalable flow process for α-thio-β-chloroacrylamide synthesis, employing a model system with α-thio-β-chloroacrylamide **7** as the target product.[49]

For this study, it was necessary to use NCS that was freshly recrystallized or from an unopened bottle. NCS may be subject to air hydrolysis, resulting in HCl salt formation, which affects the solubility properties of the reagent.

A. Study for controlling reactivity and product formation – test of the HPLC method

The oxidative chlorination transformation of α-thioamide **4** to α-thio-β-chloroacrylamide **7** in a continuous process using NCS was investigated (Table 20). NCS and starting material **4** were both dissolved separately in toluene, each to a concentration of 0.01 M. The α-thioamide **4** : NCS ratio was changed by manipulating the flow rate ratios to get the required stoichiometry. In five experiments, a 10 mL reactor coil was used and the reaction was performed at 120 ^{o}C. Results were analysed using the HPLC method developed previously employing MeCN : H_2O (60 : 40) as the mobile phase (*cf. CHAPTER 2, section 4.*).

Table 20 Flow process for conversion of **4** to *Z*-**7** using toluene as solvent with 0.01 M concentration



Entry	Ratio SM : NCS	Residence Time (min)	Conversion by HPLC (%)			
			4	**8**	**9**[a]	*Z*-**7**
1	1 : 2	20	19	15	18	47
2	1 : 2	50	21	19	0	60
3	1 : 2.3	20	22	8	20	49
4	1 : 3	20	25	1	12	62
5	1 : 1	20	21	77	<1	2

[a] Based on the calibration curve of α-thioamide **4**.

The residence time, 20 min or 50 min, has an influence on the reaction outcome (Entry 1 and 2, Table 20). Specifically, while using a residence time of 20 min, 19% of starting material **4** was not consumed and 15% of acrylamide intermediate **8** does not get through the second chlorination step of the mechanistically defined process (Entry 1, Table 20). Meanwhile, using 50 min of residence time, 21% unconsumed α-thioamide **4** and 19% of acrylamide **8** were observed (Entry 2, Table 20). Indeed, the conversion of starting material **4** to acrylamide **8**, in addition to consumption of acrylamide to give dichloride **9** or α-thio-β-chloroacrylamide **7** were similar and show a parallel evolution. Taking into consideration that the dichloride **9** decomposes to the final product **7** due to its instability, the outcome of these two entries were similar. The outcomes of Entry 1 and 2 (Table 20) show that the course of the reaction from α-thioamide **4** to acrylamide **8**, dichloride **9**

and finally to α-thio-β-chloroacrylamide **7** was essentially identical but the longer residence time resulted in total decomposition of **9** to **7** over the additional 30 min.

Increasing the equivalents of NCS used (Entry 3 and 4, Table 20) led to a better conversion of acrylamide **8** to dichloride **9** or α-thio-β-chloroacrylamide **7**, with < 1% of acrylamide left unreacted when three equivalents of NCS were used (Entry 4, Table 20). This ratio was found to be necessary to obtain a full conversion of the acrylamide to the dichloride intermediate **9** and the α-thio-β-chloroacrylamide **7** in the second step of this reaction. However, formation of the over-chlorinated products **60** and **61** was not observed, even when using three equivalents of NCS in a flow process. Visual observation indicates that the α-thio-β-chloroacrylamide has formed by the end of the reactor coil (yellow color). Therefore, once formed, the α-thio-β-chloroacrylamide was pumped out of the reactor and over-chlorination did not occur in this system.

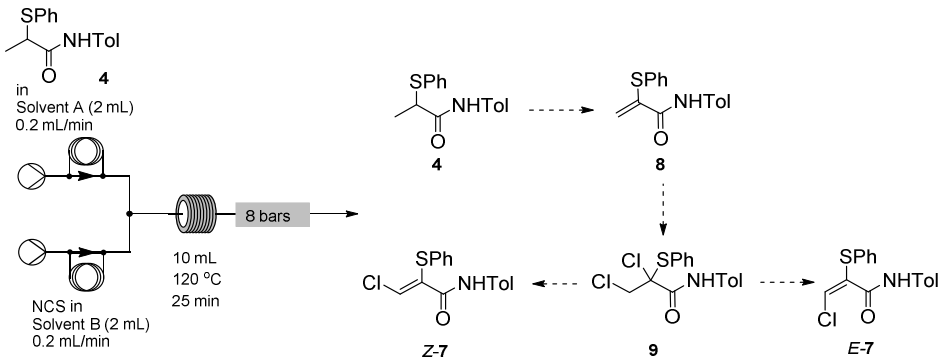
The use of a stoichiometric ratio (1:1) allowed the reaction to be stopped after the first chlorination and led to a reaction mixture with acrylamide intermediates **8** as the main product formed (Entry 5, Table 20). This experiment showed the possibility to isolate selected intermediates in the cascade reaction using a continuous process. The enhanced control of reaction stoichiometry allowed reaction progress to be selectively stopped at the acrylamide intermediate (Entry 5, Table 20) or pushed through to the α-thio-β-chloroacrylamide (Entry 4, Table 20).

B. Optimisation of the solvent system

In all the aforementioned cases, around 20% of the starting material was found to be unreacted. The key limitation to overcome was the low solubility of NCS in toluene. To offset this problem, the use of an alternative solvent was investigated for increased reactor output. Acetonitrile was found to be an interesting alternative solvent due to the high solubility of NCS it offers.[24] Hence, experiments were carried out in order to compare the two solvents and thus the concentration of NCS and the starting material (Table 21).

In this study, the conversion was determined using ^{1}H NMR spectroscopy. Indeed, it is also possible to follow the reaction using ^{1}H NMR technique as the starting material, intermediates and product are easily identifiable due to the characteristic proton signals, provided concentration of the solution undertaken at room temperature to avoid decomposition of the dichloride.

Table 21 Solvent screen for conversion of **4** to **7** in continuous mode



Entry	[**4**] (mM)	[NCS] (mM)	Solvent A/B	Product Ratio (%)[a]				
				4	**8**	**9**	*Z*-**7**	*E*-**7**
1	25	50	Tol/Tol	0	10	10	79	1
2	25	50	Tol/MeCN	0	4	0	82	14
3	25	50	MeCN/MeCN	0	0	0	87	13
4	200	400	Tol/MeCN	0	7	0	84	9
5	200	400	MeCN/MeCN	0	0	0	88	12

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture.

As the flow rates of the reagent solutions were equivalent, the reaction mixture was in a ratio 1 : 1 solvent A : solvent B.

The initial procedure using toluene as a solvent for both reagents (α-thioamide **4** and NCS) led to 10% unreacted acrylamide **8** after the first chlorination of the reaction cascade (Entry 1, Table 21).

When the starting material **4** was dissolved in toluene while NCS was dissolved in acetonitrile, the same outcome was observed, in either low or high concentration, with no significant difference in residual acrylamide intermediate **8** (Entry 2 and 4, Table 21).

When acetonitrile was used for dissolution of both reagents (α-thioamide **4** and NCS), full conversion to the final product was observed, with high or low concentration of reagents (Entry 3 and 5, Table 21). Notably, using a high concentration of reagents allows formation of more product using the same residence time. In this case, the production could be increased eight fold by using higher concentration of reagents (g/L) (Entry 5, Table 21). In addition, the use of acetonitrile as the solvent system allows a higher concentration of reagents facilitating a greener synthesis as there is less solvent being utilized. Therefore, it allows for a throughput eight times higher than the original solvent system.

Interestingly, during this development study using acetonitrile as the solvent system, the formation of the *E* isomer of the α-thio-β-chloroacrylamide **7** was observed.[49] Olga Dennehy* first identified this component by HPLC. The HPLC retention time of *E*-**7** using the method developed in this project was found to be 13.1 min *vs.* 19.9 min for *Z*-**7**, suggesting a noticeable difference in the polarity between the *E* and *Z* isomers of **7**. This isomer can be easily identified by ^{1}H NMR spectroscopy, characterized by a singlet at 6.96 ppm, corresponding to the proton of the β-carbon (*cf.* 8.04 ppm for the corresponding proton of *Z*-**7**).

* This work was performed by Olga Dennehy, PhD student in UCC.

Given the success of performing the reaction cascade in acetonitrile using continuous processing, it was decided to explore the use of this solvent in batch for comparison instead of using toluene or tetrachloromethane. When the reaction was performed in batch, using acetonitrile as solvent system with 1.95 equivalents of NCS in hot plunge at 80 °C, the crude mixture consisted of *Z*-**7**, *E*-**7** and trichloride **60** in a ratio of 1 : 0.10 : 0.22 respectively, as seen by ^{1}H NMR spectroscopy. When the process was conducted in flow compared to batch, over-chlorination is avoided as the product is removed from the heat soon after formation. The *E* isomer of **7** is formed both in batch or in flow using acetonitrile as solvent, with a slightly higher amount formed using the continuous flow system.

The primary challenge associated with conducting the reaction in acetonitrile is the competing formation of the *E* isomer, which is not attractive from a synthetic perspective, but can be overcome by selective recrystallisation of *Z*-**7** from the isomeric mixture.

In all continuous processing experiments, the formation of over-chlorinated products **60** and **61** was not observed by HPLC. In contrast, when similar conditions were employed in batch, high levels of formation of these by-products was observed.[2, 16]

6. CONCLUSIONS

α-Thio-β-chloroacrylamides and the corresponding α-thioamide starting materials were successfully synthesised in high yield for six series; SPh/NHTol, SBn/NHBn, SPh/NHBn, SBn/NHTol, SBu/NHTol and SBu/NHBn. Significant improvement in the synthetic protocol was made. Syntheses of *N*-alkyl α-thioamides SPh/NHBu, SPh/NH*sec*Bu, SBu/NHBu and SBn/NH*sec*Bu were investigated but complete conversion could not be achieved, with residual α-chloroamide remaining in each case.

Formation of the acrylamide intermediate for the ten series discussed in detail above was detected by ^{1}H NMR spectroscopy. While the SPh/NHTol and the SBn/NHTol could be isolated in pure form, the SPh/NHBn, SBn/NHBn, SBu/NHTol and SBu/NHBn were characterized as a mixture with the corresponding β-chlorosulfide. For the four other series, characteristic signals for the acrylamides were seen by ^{1}H NMR spectroscopy but the compounds were not isolated.

The identification of two newly discovered intermediates, the β-chlorosulfide and the α-chloropropanamide, in the reaction leading to the α-thio-β-chloroacrylamides, highlights a new competitive pathway for this transformation. Therefore, a mechanism leading to both the β-chlorosulfide and the α-chloropropanamide, has been proposed and supported by further studies. The characteristic signals corresponding to the β-chlorosulfide and α-chloro-β-thiopropanamide have been established as ABX systems and thus the formation can be easily identified and quantified by ^{1}H NMR spectroscopy.

Optimisation of the synthesis of labile dichloride intermediate allowed the detection of its formation by ^{1}H NMR spectroscopy for the six series studied (SPh/NHTol, SBn/NHBn, SPh/NHBn, SBn/NHTol, SBu/NHTol and SBu/NHBn). Purification of the dichloride for the SPh/NHBn substrates was successfully carried out.

A full analytical package including HPLC retention times was successfully achieved for the six series including the α-chloroamides **18** and **19**, α-thioamides **4**, **22**, **25**,

27 to 29, α-thio-β-chloroacrylamides 7, 15, 26, 34 to 36 and the corresponding acrylamides and dichlorides. For the SPh/NHTol model study series, the over-chlorinated by-products, dichloroacrylamide 61 and trichloride 60, were also fully characterised and included in the HPLC processing.

Having these analytical data in hand, a continuous flow process for the synthesis of the corresponding α-thio-β-chloroacrylamide (SPh/NHTol) was developed. The α-thio-β-chloroacrylamide formation cascade can be controlled through this continuous system, leading to selective recovery of individual components from the reaction. Optimisation of the solvent system allows full conversion into the desired product with increase of the productivity of the reaction, albeit with a decrease in stereo-control.

Despite more than two decades of research concerning the α-thio-β-chloroacrylamides, the results from this project have led to new mechanistic insight and substantial synthetic improvement, enabling the scale-up of α-thio-β-chloroacrylamide synthesis using continuous flow process for the first time.

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CHAPTER 2

Experimental

Table of Contents

1. General Procedure

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide, ethyl acetate was distilled from potassium carbonate, hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used without further purification unless otherwise stated. Organic layers were dried over magnesium sulfate and filtered through cotton bud.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. ^{1}H (600 MHz) and ^{13}C (150.9 MHz) NMR spectra were recorded on a Bruker Avance 600 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in hertz (Hz). Splitting patterns in ^{1}H spectra are designated as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), ddd (doublet of doublets of doublets), dt (doublet of triplets), tt (triplet of triplets), td (triplet of doublets), q (quartet) and m (multiplet).

The method for calculating the chemical shifts of A and B in ABq system is detailed below:[1]

$J_{AB} = (\nu_a - \nu_b) = (\nu_c - \nu_d)$

$\nu_{center} = ½ (\nu_b + \nu_c)$

$\Delta\nu_{AB} = \sqrt{(\nu_a - \nu_d)(\nu_b - \nu_c)}$

$\nu_a = \nu_{center} + ½ \Delta\delta_{AB}$

$\nu_b = \nu_{center} - ½ \Delta\delta_{AB}$

The pattern was treated as first order when the AB quartets have a large $\Delta\nu_{AB}$ / J_{AB} ratio > 4, where the error in chemical shifts caused by simply taking the middle of each doublet is small: ie. 3.95 (1H, ABq, *J* 12.0), 4.46 (1H, ABq, *J* 12.0) or 3.95, 4.46 (2H, ABq, *J* 12.0).

For closely spaced AB quartets ($\Delta\nu_{AB}$ / J_{AB} ratio < 4), the chemical shift was so reported as the center of the AB quartet: ie. 3.78 (2H, ABq, J_{AB} 13.3, $\Delta\delta_{AB}$ 0.03).

All the structures were assigned using ^{1}H and ^{13}C NMR spectroscopy including COSY, HSQC and HMBC experiments.

Infrared spectra were measured using a Perkin Elmer FTIR UATR2 spectrometer. Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV (254 nm) light absorption.

Elemental analysis was carried out by Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in electrosprayionization mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. Samples prepared for either LRMS or HRMS by employing acetonitrile as solvent. Melting points were obtained using a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

HPLC was performed on an Agilent Technologies 1120 Compact LC system (Agilent Technologies, Santa Clara, CA, USA) on Agilent Chemstation (Rev. B.04.03[52]) software for data acquisition. Chromatography was carried out using a YMC-Pack ODS-A reverse phase column (250 mm x 4.6 mm, 5 µm) with a flow rate of 0.8 mL/min. Samples were injected (5 µL) by the autosampler and were detected by UV absorbance at 250 nm and by a 385-ELSD evaporative light scattering detector (LC-ELSD) (Agilent Technologies, Santa Clara, CA, USA). Nitrogen (99.995%) was used as the evaporation gas at a flow rate of 1.6 $L.min^{-1}$. The ELSD was operated with the nebulizer and evaporator temperatures at 40 ^{o}C.

Method 1: Mobile phase consisting of 70% of methanol in water. Detection was achieved by UV absorbance at 290 nm.

Method 2: Mobile phase consisting of 60% of acetonitrile in water. Detection was achieved by UV absorbance at 250 nm.

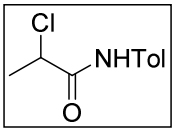
All continuous processes were performed using a Vapourtec R-Series flow reactor. The R-Series flow reactor consists of four piston pumps and up to four temperature controlled tubular reactors. To prepare the reactor for operation pumps were purged with the solvent to be used in the reaction prior to use. All reaction tubing, coils, inlets and connections were also purged thoroughly in a similar manner.

Table 22 General specifications for R-Series continuous-flow reactor

Material of tubing	PFA
Diameter of tubing	1 mm
Working flow rates	0.05 mL/min – 9.99 mL/min
Tubular reactor working volume	10 mL
Temperature range	-70 °C to 250 °C

2. SYNTHESIS OF α-CHLOROAMIDES

N-(4'-Methylphenyl)-2-chloropropanamide 18[2,3]

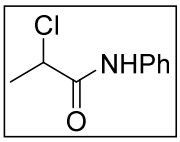


A solution of 2-chloropropionyl chloride (2.33 mL, 24.06 mmol) in dichloromethane (25 mL) was added dropwise over 20 min to a solution of *p*-toluidine (2.58 g, 24.06 mmol) and triethylamine (3.25 mL, 24.06 mmol) in dichloromethane (25 mL) at 0 °C using an ice bath, while stirring. On completion of the addition, the reaction solution was removed from the ice bath and stirred at room temperature for 4 h. Water (40 mL) was added and the layers separated. The organic layer was washed with a saturated solution of sodium bicarbonate (2 × 30 mL), water (40 mL) and brine (40 mL), dried and

concentrated under reduced pressure to give the α-*chloroamide* **18** (4.73 g, 99%) as a white solid which required no further purification; mp 113-115 °C (Lit.,[4] 108 °C); δ_H (400 MHz, $CDCl_3$) 1.82 [3H, d, *J* 7.1, C(3)*H*$_3$], 2.33 (3H, s, ArC*H*$_3$), 4.53 [1H, q, *J* 7.0, C(2)*H*], 7.15 (2H, d, *J* 8.1, Ar*H*), 7.41 (2H, d, *J* 8.3, Ar*H*), 8.21 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 20.9 (CH_3, Ar*C*H_3), 22.7 (CH_3, C(3)H_3), 56.2 [CH, *C*(2)H], 120.1 (1 x CH signal, 2 x aromatic *C*H), 129.6 (1 x CH signal, 2 x aromatic *C*H), 134.4, 134.8 (2 x Cq, 2 x aromatic *C*q), 167.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3250 (NH), 1664 (C=O), 1545, 814, 501; m/z (ES+) 198.3 {[($C_{10}H_{12}{}^{35}ClNO$)+H^+], 100%, 200.3 {[($C_{10}H_{12}{}^{37}ClNO$)+H^+], 34%}; HPLC retention time: (Method 2) 7.4 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

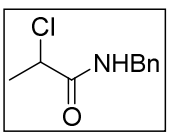
N-Phenyl-2-chloropropanamide 17[2,3]



This was synthesised using the procedure described for **18** from 2-chloropropionyl chloride (3.50 mL, 36.05 mmol), aniline (3.30 mL, 36.05 mmol) and triethylamine (5.00 mL, 36.05 mmol) in dichloromethane (25 mL) to give the α-*chloroamide* **17** (6.50 g, 98%) as a white solid which required no further purification; mp 88-90 °C (Lit.,[2] 93 °C); δ_H (400 MHz, $CDCl_3$) 1.82 [3H, d, *J* 7.1, C(3)*H*$_3$], 4.55 [1H, q, *J* 6.8, C(2)*H*)], 7.14 (1H, t, *J* 7.2, Ar*H*para), 7.35 (2H, t, *J* 8.0, Ar*H*meta), 7.53 (2H, d, *J* 8.0, Ar*H*ortho), 8.26 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 22.7 [CH_3, *C*(3)*H*$_3$], 56.3 [CH, *C*(2)*H*], 120.0 (CH, aromatic *C*H ortho), 125.1 (CH, aromatic *C*H para), 129.1 (CH, aromatic *C*H meta), 136.9 (Cq, aromatic *C*q), 167.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3254 (NH), 3065, 2931, 1667 (C=O), 1539, 1444, 752, 697; m/z (ES+) 184.3 {[($C_9H_{10}{}^{35}ClNO$)+H^+], 100%}, 186.3 {[($C_9H_{10}{}^{37}ClNO$)+H^+], 34%; (ES-) 182.3 {[($C_9H_{10}{}^{35}ClNO$)-H^+], 78%}, 184.3 {[($C_9H_{10}{}^{37}ClNO$)+H^+], 24%}.

Spectroscopic characteristics were consistent with those previously reported.[2]

N-Benzyl-2-chloropropanamide 19[2]

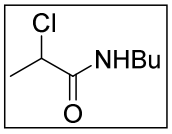


This was synthesised using the procedure described for **18** from 2-chloropropionyl chloride (2.33 mL, 24.06 mmol), benzylamine (2.63 mL, 24.06 mmol) and triethylamine (3.25 mL, 24.06 mmol)

in dichloromethane (50 mL) to give the α-*chloroamide* **19** (4.60 g, 97%) as a white solid which required no further purification; mp 78-80 °C (Lit.,[5] 80-82 °C); δ_H (400 MHz, $CDCl_3$) 1.77 [3H, d, *J* 7.1, C(3)*H*$_3$], 4.40-4.53 [3H, m, C(2)*H*, C*H*$_2$NH], 6.87 (1H, br s, N*H*), 7.23-7.42 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.8 (CH_3, *C*(3)H_3), 43.9 (CH_2, *C*H_2NH), 56.0 [CH, *C*(2)H], 127.7 (1 x CH signal, 2 x aromatic *C*H), 128.8 (1 x CH signal, 2 x aromatic *C*H), 137.5 (Cq, aromatic *C*q), 169.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3268 (NH), 1651 (C=O), 1561, 1219, 693, 506; m/z (ES+) 198.3 {[($C_{10}H_{12}{}^{35}ClNO$)+H$^+$], 100%}, 200.3 {[($C_{10}H_{12}{}^{37}ClNO$)+H$^+$], 36%}; HPLC retention time: (Method 2) 5.8 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

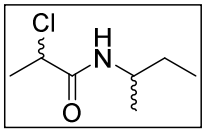
N-Butyl-2-chloropropanamide 20[2]



This was synthesised using the procedure described for **18** from 2-chloropropionyl chloride (2.33 mL, 24.06 mmol), butylamine (2.4 mL, 24.06 mmol) and triethylamine (3.25 mL, 24.06 mmol) in dichloromethane (50 mL) to give the α-*chloroamide* **20** (3.75 g, 95%) as a colourless oil which required no further purification; δ_H (100 MHz, $CDCl_3$) 0.94 [3H, t, *J* 7.6, C(4')*H*$_3$], 1.30-1.42 [2H, m, apparent sextet, *J* 7.2, C(3')*H*$_2$], 1.48-1.60 [2H, m, apparent quint, *J* 7.5, C(2')*H*$_2$], 1.72 [3H, d, *J* 7.0, C(3)*H*$_3$], 3.28 (2H, q, *J* 6.6, C*H*$_2$NH), 4.42 [1H, q, *J* 7.0, C(2)*H*), 6.71 (1H, br s, N*H*); δ_c (400 MHz, $CDCl_3$) 13.7 [CH_3, *C*(4')H_3], 19.9 [CH_3, *C*(3)H_3], 22.7 [CH_2, *C*(3')H_2], 31.3 [CH_2, *C*(2')H_2], 39.6 [CH_2, *C*(1')H_2], 56.0 [CH, *C*(2)H], 169.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3288 (NH), 1656 (C=O), 1588, 1219, 676; m/z (ES+) 164.3 {[($C_7H_{14}{}^{35}ClNO$)+H$^+$], 100%}, 166.3 {[($C_7H_{14}{}^{37}ClNO$)+H$^+$].

Spectroscopic characteristics were consistent with those previously reported.[2]

N-(*sec*-Butyl)-2-chloropropanamide 21

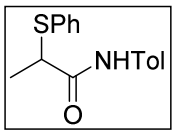


This was synthesised using the procedure described for **18** from 2-chloropropionyl chloride (2.00 mL, 20.60 mmol), *sec*-butylamine (2.08 mL, 20.60 mmol) and triethylamine (2.90 mL, 20.60 mmol) in dichloromethane (40 mL) and stirred at room temperature for 10 h to give the α-*chloroamide* **21** as an inseparable mixture of two diastereoisomers with ratio 1:1 by ^{1}H NMR spectroscopy (3.30 g, 98%) as a low melting point white

solid; δ_H (400 MHz, $CDCl_3$) 0.89 [6H, both diastereoisomers, t, *J* 7.4, C(4')*H*$_3$], 1.10-1.15 {6H, including 1.12 [3H, d, *J* 6.6, C(1')*H*$_3$ of 1 diastereoisomer] and 1.13 [3H, d, *J* 6.6, C(1')*H*$_3$ of 1 diastereoisomer]}, 1.41-1.53 [4H, both diastereoisomers, m, C(3')*H*$_2$], 1.67-1.72 {6H, including 1.69 [3H, d, *J* 7.1, C(3)*H*$_3$ of 1 diastereoisomer] and 1.70 [3H, d, *J* 7.1, C(3)*H*$_3$ of 1 diastereoisomer]}, 3.78-3.92 (2H, both diastereoisomers, m, C(2')*H*), 4.32-4.41 {2H, including 4.36 [1H, q, *J* 7.2, C(2)*H* of 1 diastereoisomer] and 4.37 [1H, q, *J* 7.2, C(2)*H* of 1 diastereoisomer]}, 6.37 (2H, both diastereoisomers, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 10.1 [CH_3, *C*(4')H_3 of 1 diastereoisomer], 10.2 [CH_3, *C*(4')H_3 of 1 diastereoisomer], 20.1 [CH_3, *C*(1')H3 of 1 diastereoisomer], 20.2 [CH_3, *C*(1')H3 of 1 diastereoisomer], 22.7 [CH_3, *C*(3)H_3 of 1 diastereoisomer], 22.8 [CH_3, *C*(3)H_3 of 1 diastereoisomer], 29.4 [CH_2, *C*(3')H_2 of 1 diastereoisomer], 29.5 [CH_2, *C*(3')H_2 of 1 diastereoisomer], 47.1 [CH, *C*(2')H of 1 diastereoisomer], 47.2 [CH, *C*(2')H of 1 diastereoisomer], 56.1 [CH, *C*(2)H of 1 diastereoisomer], 56.2 [CH, *C*(2)H of 1 diastereoisomer], 168.8 (Cq, *C*=O of both diastereoisomers); ν_{max}/cm^{-1} 3276 (NH), 1653 (C=O), 1553, 1221, 990, 671; HRMS (ES+): Exact mass calculated for $C_7H_{15}{}^{35}ClNO$ [$M+H^+$], 164.0842; Found 164.0753.

3. SYNTHESIS OF α-THIOAMIDES

N-(4'-Methylphenyl)-2-(phenylthio)propanamide 4[2,3]

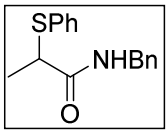


Thiophenol (2.90 mL, 23.78 mmol) was added to a solution of freshly prepared sodium ethoxide [from sodium (0.66 g, 28.53 mmol) in absolute ethanol (60 mL) at 0 °C] while stirring under nitrogen. Immediately, a solution of *N*-(4'-methylphenyl)-2-chloropropanamide **18** (4.70 g, 28.53 mmol) in absolute ethanol (40 mL) was added dropwise over 15 min to the reaction mixture. Following stirring for 17 h at room temperature, the reaction was quenched by addition of water (50 mL) and dichloromethane (40 mL). The aqueous layer was extracted with dichloromethane (2 x 40 mL). Organic layers were washed with aqueous sodium hydroxide (1M, 2 x 50 mL), water (80 mL) and brine (80 mL), dried and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane : ethyl

acetate as eluent (gradient elution 2 to 10% of ethyl acetate) gave the *α-thioamide* **4** (5.17 g, 80%) as a white solid; mp 97-99 °C (Lit.,[2] 112-113 °C); δ_H (400 MHz, $CDCl_3$) 1.63 [3H, d, *J* 7.3, C(3)*H*$_3$], 2.30 (3H, s, ArC*H*$_3$), 3.89 [1H, q, *J* 7.3, C(2)*H*], 7.10 (2H, d, *J* 8.4, Ar*H*), 7.19-7.41 (7H, m, Ar*H*), 8.34 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.2 [CH_3, *C*(3)H_3], 20.8 (CH_3, Ar*C*H_3), 47.9 [CH, *C*(2)H], 119.9, 127.6, 129.3, 129.5, 130.7 (5 x CH signals, 9 x aromatic *C*H), 133.3, 134.2, 134.9 (3 x Cq, 3 x aromatic *C*q), 169.9 (Cq, *C*=O); ν_{max}/cm^{-1} 3290 (NH), 1660 (C=O), 1511, 823, 691; m/z (ES+) 272.2 [(M+H$^+$), 100%]; HPLC retention time: (Method 1) 11.4 min; (Method 2) 12.2 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

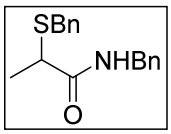
N-Benzyl-2-(phenylthio)propanamide 22[2]



This synthesis follows the procedure described for **4** using *N*-benzyl-2-chloropropanamide **19** (0.80 g, 4.05 mmol) in ethanol (4 mL), thiophenol (0.50 mL, 4.86 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.11 g, 4.86 mmol) in ethanol (5 mL) at 0 °C]. The crude *α-thioamide* was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 20 to 40% of ethyl acetate) to give the *α-thioamide* **22** (1.04 g, 94%) as a white solid; mp 62-63 °C (Lit.,[2] 62-63 °C); δ_H (400 MHz, $CDCl_3$) 1.57 [3H, d, *J* 7.3, C(3)*H*$_3$], 3.87 [1H, q, *J* 7.3, C(2)*H*], 4.32-4.47 {2H, m, can be distinguished 4.39 [1H, A of ABX, J_{AB} 14.8, J_{AX} 5.5, one of C*H*$_2$NH], 4.41 [1H, B of ABX, J_{AB} 14.8, J_{BX} 6.2, one of C*H*$_2$NH]}, 6.90 (1H, br s, N*H*), 7.03-7.11 (2H, m, Ar*H*), 7.21-7.32 (8H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 18.3 [CH_3, *C*(3)H_3], 43.7 [CH, *C*(2)H], 46.9 (CH_2, *C*H_2NH), 127.2, 127.5, 127.6, 128.6, 129.2, 130.1 (6 x CH signals, 10 x aromatic *C*H), 133.9, 137.8 (2 x Cq, 2 x aromatic *C*q), 171.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3315 (NH), 1654 (C=O), 1526, 693, 492; m/z (ES+) 272.2 [(M+H$^+$), 100%]; HPLC retention time: (Method 2) 8.8 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

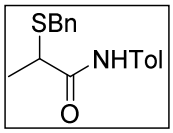
N-Benzyl-2-(benzylthio)propanamide 25[2]



This synthesis follows the procedure described for **4** using *N*-benzyl-2-chloropropanamide **19** (1.00 g, 5.06 mmol) in ethanol (3 mL), benzyl mercaptan (0.71 mL, 6.07 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.14 g, 6.07 mmol) in ethanol (4 mL) at 0 °C]. The crude *α-thioamide* was obtained as an off white solid. Following purification by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 5 to 30 % of ethyl acetate) the pure *α-thioamide* **25** (1.27 g, 88%) was obtained as a white solid; mp 69-70 °C (Lit.,[2] 66-67 °C); δ_H (400 MHz, $CDCl_3$) 1.46 [3H, d, *J* 7.3, C(3)H_3], 3.34 [1H, q, *J* 7.2, C(2)*H*], 3.68 (2H, s, CH_2S), 4.31-4.43 {2H, m, can be distinguished 4.36 [1H, A of ABX, J_{AB} 14.7, J_{AX} 5.8, one of CH_2NH], 4.37 [1H, B of ABX, J_{AB} 14.7, J_{BX} 5.8, one of CH_2NH]}, 6.85 (1H, br s, N*H*), 7.16-7.40 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 18.5 (CH_3, C(3)H_3), 36.3 (CH_2, *C*H_2S), 43.7 (CH_2, *C*H_2NH), 44.2 [CH, *C*(2)H], 127.3, 127.6, 127.8, 128.7, 128.8, 128.9 (6 x CH signals, 10 x aromatic *C*H), 137.3, 138.2 (2 x Cq, 2 x aromatic *C*q), 172.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3287 (NH), 1641 (C=O), 1552, 692; m/z (ES+) 286.2 [($M+H^+$), 100%]; HPLC retention time: (Method 2) 9.9 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

N-(4'-Methylphenyl)-2-(benzylthio)propanamide 27[2]



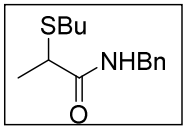
This synthesis followed the procedure described for **4** using *N*-(4'-methylphenyl)-2-chloropropanamide **18** (2.00 g, 10.12 mmol) in ethanol (8 mL), benzyl mercaptan (1.42 mL, 12.14 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.28 g, 12.14 mmol) in ethanol (10 mL) at 0 °C]. The *α-thioamide* **27** (δ_H 3.40, 1H, q, *J* 7.3) was obtained as a mixture with the dibenzyldisulfide **23** (δ_H 3.58, 4H, s) in a ratio 1 : 0.07 respectively by ^{1}H NMR spectroscopy (2.68 g, 93%*), as a white solid, mp 69-72 °C (Lit.,[2] 69-71 °C); δ_H (400 MHz, $CDCl_3$) 1.49 [3H, d, *J* 7.4, C(3)H_3], 2.30 (3H, s, ArCH_3), 3.40 [1H, q, *J* 7.3, C(2)*H*], 3.75 (2H, s, CH_2S), 7.10 (2H, d, *J* 8.4, Ar*H*), 7.14-7.33 (5H, m, Ar*H*), 7.35 (2H, d, *J* 8.4, Ar*H*), 8.39 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.5 [CH_3, C(3)H_3], 20.9 (3H, s, ArCH_3), 36.4 (CH_2, *C*H_2S), 45.1 [CH, *C*(2)H], 119.7, 127.4, 128.7,

128.8, 129.4 (5 x CH signals, 9 x aromatic *C*H), 134.0, 135.0, 137.1 (3 x Cq, 3 x aromatic *C*q), 170.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3278 (NH), 1648 (C=O), 1601, 1540, 1510, 819, 696, 509; m/z (ES+) 286.2 [($M+H^+$), 100%]; HPLC retention time: (Method 2) 14.2 min.

*The yield calculation takes in consideration the presence of the dibenzyldisulfide by-product in the product.

Spectroscopic characteristics were consistent with those previously reported.[2]

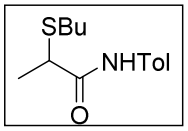
N-Benzyl-2-(butyllthio)propanamide 28[2]



This synthesis followed the procedure described for **4** using *N*-benzyl-2-chloropropanamide **19** (1.94 g, 9.81 mmol) in ethanol (7 mL), butyl mercaptan (1.30 mL, 11.78 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.27 g, 11.78 mmol) in ethanol (10 mL) at 0 °C]. The crude *α-thioamide* was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (80:20) to give the *α-thioamide* **28** (2.30 g, 80%) as a low melting point white solid; δ_H (400 MHz, $CDCl_3$) 0.87 [3H, t, *J* 7.3, C(4')H_3], 1.27-1.41 [2H, m, C(3')H_2], 1.46-1.55 [5H, m, C(3)H_3 and C(2')H_2; C(3)H_3 could be distinguished as a doublet at 1.48 ppm, *J* 7.4],, 2.48 [2H, t, J 7.1, SC(1')H_2], 3.43 [1H, q, *J* 7.3, C(2)*H*], 4.37-4.50 {2H, m, can be distinguished 4.43 [1H, A of ABX, J_{AB} 14.8, J_{AX} 6.0, one of CH_2NH], 4.45 [1H, B of ABX, J_{AB} 14.8, J_{BX} 6.1, one of CH_2NH]}, 7.06 (1H, br s, N*H*), 7.23-7.38 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.6 [CH_3, *C*(4')H_3], 18.7 [CH_3, C(3)H_3], 22.0 [CH_2, *C*(3')H_2], 31.3 [CH_2, *C*(2')H_2], 31.4 [CH_2, *C*(1')H_2], 43.6 (CH_2, *C*H_2NH), 44.6 [CH, *C*(2)H], 127.5, 128.7, 128.8 (3 x CH signals, 5 x aromatic *C*H), 138.2 (Cq, aromatic *C*q), 172.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3280 (NH), 2957, 2928, 1644 (C=O), 1538, 730, 696; HPLC retention time: (Method 2) 10.1 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

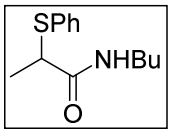
N-(4'-Methylphenyl)-2-(butyllthio)propanamide 29[2]



This synthesis followed the procedure described for **4** using *N*-(4'-methylphenyl)-2-chloropropanamide **18** (2.29 g, 11.61 mmol) in ethanol (7 mL), butyl mercaptan (1.5 mL, 13.93 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.32 g, 13.93 mmol) in ethanol (10 mL) at 0 °C]. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (90:10) to give the *α-thioamide* **29** (1.98 g, 68%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 0.89 [3H, t, *J* 7.3, C(4')H_3], 1.34-1.46 [2H, m, C(3')H_2], 1.48-1.68 [5H, m, C(3)H_3 and C(2')H_2; C(3)H_3 could be distinguished as a doublet at 1.54 ppm, *J* 7.4], 2.31 (3H, s, ArCH_3), 2.58 [2H, t, *J* 7.3, C(1')H_2], 3.50 [1H, q, *J* 7.3, C(2)*H*], 7.14 (2H, d, *J* 8.2, ArH_{meta}), 7.43 (2H, d, *J* 8.2, ArH_{ortho}), 8.60 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.5 [CH_3, *C*(4')H_3], 18.6 [CH_3, C(3)H_3], 20.8 (3H, s, ArCH_3), 21.9 [CH_2, *C*(3')H_2], 31.3 [CH_2, *C*(2')H_2], 31.4 [CH_2, *C*(1')H_2], 45.6 [CH, *C*(2)H], 119.6 (1 x CH signal, 2 x aromatic CH_{ortho}), 129.5 (1 x CH signal, 2 x aromatic CH_{meta}), 134.0, 135.1 (2 x Cq, 2 x aromatic *C*q), 170.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3289 (NH), 2958, 2927, 1655 (C=O), 1513, 814; HPLC retention time: (Method 2) 14.6 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

N-Butyl-2-(phenylthio)propanamide 30[2]



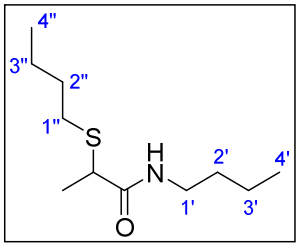
This synthesis follows the procedure described for **4** using *N*-butyl-2-chloropropanamide **20** (1.00 g, 6.11 mmol) in absolute ethanol (20 mL), thiophenol (0.75 mL, 7.33 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.32 g, 13.44 mmol) in absolute ethanol (30 mL) at 0 °C]. The product is an inseparable mixture of the *α-thioamide* **30** (δ_H 1.52, 3H, d, *J* 7.2) and the *α-chloroamide* **20** (δ_H 1.72, 3H, d, *J* 7.0) with ratio 1 : 0.05 respectively by ^{1}H NMR spectroscopy as a colourless oil (1.10 g, 76%); δ_H (400 MHz, $CDCl_3$) 0.84 [3H, t, *J* 7.3, C(4')H_3], 1.10-1.26 [2H, m, C(3')H_2], 1.29-1.43 [2H, m, C(2')H_2], 1.52 [3H, d, *J* 7.2, C(3)H_3], 3.09-3.32 (2H, m, CH_2NH), 3.82 [1H, q, *J* 7.3, C(2)*H*), 6.74 (1H, br s, N*H*), 7.15-7.38 (5H, m, Ar*H*); δ_c (400 MHz, $CDCl_3$) 13.7 [CH_3, *C*(4')H_3], 18.4 [CH_3, *C*(3)H_3], 20.0 [CH_2, *C*(3')H_2], 31.4 [CH_2,

C(2')H_2], 39.4 [CH_2, *C*(1')H_2], 46.9 [CH, *C*(2)H], 127.1 (CH, aromatic *C*H), 129.2 (1 x CH signal, 2 x aromatic *C*H), 129.8 (1 x CH signal, 2 x aromatic *C*H), 134.2 (Cq, *C*q aromatic), 171.7 (Cq, *C*=O). Characteristic signals for the *α-chloroamide* **21** were also present and overlap with the product signals in some instance; ν_{max}/cm^{-1} 3285 (NH), 1644 (C=O), 1551, 736, 689; HRMS (ES+): Exact mass calculated for $C_{13}H_{20}NOS$ $[M+H]^+$, 238.1266; Found 238.1263; m/z (ES+) 238.3 [$M+H^+$], 30%.

*The yield calculation takes in consideration the presence of the *α-chloroamide* **20** in the product (95% purity).

Spectroscopic characteristics were consistent with those previously reported.[2]

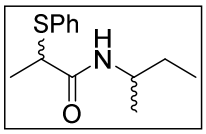
N-Butyl-2-(butylthio)propanamide 32



This synthesis follows the procedure described for **4** using *N*-butyl-2-chloropropanamide **20** (3.20 g, 19.55 mmol) in absolute ethanol (40 mL), butanethiol (2.5 mL, 23.46 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.54 g, 23.46 mmol) in absolute ethanol (60 mL) at 0 °C]. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 2 to 20% of ethyl acetate) to give an inseparable mixture of the *α-thioamide* **32** (δ_H 3.42, 1H, q, *J* 7.2) and the *α-chloroamide* **20** (δ_H 4.42, 1H, q, *J* 7.0) with ratio 1 : 0.27 respectively by ^{1}H NMR spectroscopy as a colourless oil (3.22 g, 77%); δ_H (400 MHz, $CDCl_3$) 0.76-0.86 {6H, m, which includes [0.80, 3H, t, *J* 7.3, C(4")H_3], [0.83, 3H, t, *J* 7.3, C(4')H_3]}, 1.20-1.51 {11H, m, which includes [C(2',3',2",3")H_2], 1.34 [3H, d, *J* 7.3, C(3)H_3]}, 2.52 [2H, t, *J* 7.3, SC(1")H_2], 3.20-3.37 [2H, m, NHC(1')H_2], 3.42 [1H, q, *J* 7.2, C(2)*H*), 6.92 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.5, 13.6 [2 x CH_3, *C*(4")H_3 and *C*(4')H_3], 18.7 [CH_3, *C*(3)H_3], 19.9, 21.9 [2 x CH_2, *C*(3')H_2 and *C*(3")H_2], 31.3, 31.4, 31.6 [3 x CH_2, S*C*(1")H_2 and *C*(2')H_2 and *C*(2")H_2], 39.3 (CH_2, NH*C*H_2), 44.5 [CH, *C*(2)H], 172.5 (Cq, *C*=O). Characteristic signals for the *α-chloroamide* **20** were also present and overlap with the product signals in some instance; ν_{max}/cm^{-1} 3283 (NH), 2958, 2929, 1644 (C=O), 1550;

HRMS (ES+): Exact mass calculated for $C_{11}H_{24}NOS$ $[M+H]^+$, 218.1579; Found 218.1581; m/z (ES+) 218.3 $[M+H^+]$, 5%.

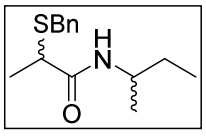
N-(*sec*-Butyl)-2-(phenylthio)propanamide 31



This synthesis follows the procedure described for **4** using *N*-(*sec*-butyl)-2-chloropropanamide **21** as a mixture of the two diastereoisomers (ratio 1 : 1) (0.80 g, 4.89 mmol) in absolute ethanol (10 mL), thiophenol (0.60 mL, 5.87 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.13 g, 5.87 mmol) in absolute ethanol (15 mL) at 0 ^oC]. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 2 to 50 % of ethyl acetate) to give an inseparable mixture of the two diastereoisomers of the *α-thioamide* **31** in a ratio 1 : 1 and the α-*chloroamide* **21** (ratio both diastereoisomers α-thioamide : α-chloroamide 1 : 0.4 respectively by ^1H NMR spectroscopy), as a low melting point white solid (0.90 g, 77%); δ_H (400 MHz, $CDCl_3$) 0.68 [3H, t, *J* 7.5, C(4')H_3 of one diastereoisomer of α-thioamide **31**], 0.82-0.99 {8.4H, m, including 0.86 [3H, t, *J* 7.5, C(4')H_3 of one diastereoisomer of α-thioamide **31**, 0.92 [2.4H, t, *J* 7.5, C(4')H_3 of both diastereoisomers of α-chloroamide **21**], 0.96 [3H, d, *J* 6.5, C(1')H_3 of one diastereoisomer of α-thioamide **31**]}, 1.07 [3H, d, *J* 6.5, C(1')H_3 of one diastereoisomer of α-thioamide **31**], 1.13-1.18 {2.4H, m, including 1.15 [d, J 6.7, C(1')H_3 of one diastereoisomer of α-chloroamide **21**] and 1.16 [d, J 6.7, C(1')H_3 of one diastereoisomer of α-chloroamide **21**]}, 1.22-1.60 {11.6H, m, C(3')H_2 of both diastereoisomers of α-thioamide **31** and C(3')H_2 of both diastereoisomers of α-chloroamide **21**, also can be distinguished 1.55 [d, *J* 7.3, C(3)H_2 of one diastereoisomer of α-thioamide **31**] and 1.56 [d, *J* 7.3, C(3)H_2 of one diastereoisomer of α-thioamide **31**]}, 1.71-1.75 {2.4H, m, including 1.73 [d, *J* 7.0, C(3)H_3 of one diastereoisomer of α-chloroamide **21**] and 1.74 [d, J 7.0, C(3)H_3 of one diastereoisomer of α-chloroamide **21**]}, 3.73-3.95 [4.8H, m, C(2')H_2 of both diastereoisomers of α-chloroamide **21**, C(2')H_2 of both diastereoisomers of α-thioamide **31**, C(2)*H* of both diastereoisomers of α-thioamide **31**], 4.35-4.44 [0.8H, m, C(2)H_2 of both diastereoisomers of α-chloroamide **21**], 6.25-6.48 [2.8H, br s, N*H* of both diastereoisomers of α-chloroamide **21** and N*H* of both

diastereoisomers of α-thioamide **31**], 7.18-7.88 [10H, m, ArH of both diastereoisomers of α-thioamide **31**]; δ_C (100 MHz, $CDCl_3$) 10.0 [CH_3, *C*(4')H_3 of one diastereoisomer of α-thioamide **31**], 10.2 [2 x CH_3, *C*(4')H_3 of one diastereoisomer of α-thioamide **31** and *C*(4')H_3 of one diastereoisomer of α-chloroamide **21**], 10.22 [CH_3, *C*(4')H_3 of one diastereoisomer of α-chloroamide **21**], 18.3 [CH_3, *C*(3)H_3 of one diastereoisomer of α-thioamide **31**], 18.4 [CH_3, *C*(3)H_3 of one diastereoisomer of α-thioamide **31**], 20.0 [CH_3, *C*(1')H_3 of one diastereoisomer of α-thioamide **31**], 20.1 [CH_3, *C*(1')H_3 of one diastereoisomer of α-chloroamide **21**], 20.2 [CH_3, *C*(1')H_3 of one diastereoisomer of α-chloroamide **21**], 20.3 [CH_3, *C*(1')H_3 of one diastereoisomer of α-thioamide **31**], 22.8 [CH_3, *C*(3)H_3 of one diastereoisomer of α-chloroamide **21**], 22.9 [CH_3, *C*(3)H_3 of one diastereoisomer of α-chloroamide **21**], 29.4, 29.5, 30.9 [4 x CH_2, *C*(3')H_2 of both diastereoisomers of α-chloroamide **21** and α-thioamide **31**], 46.7, 46.8, 46.9, 47.1, 47.2 [6 x CH, *C*(2')H of both diastereoisomers of α-chloroamide **21** and α-thioamide **31**, and *C*(2)H of both diastereoisomers of α-thioamide **31**], 56.1 [CH, *C*(2)H of one diastereoisomer of α-chloroamide **21**], 56.2 [CH, *C*(2)H of one diastereoisomer of α-chloroamide **21**], 127.0, 127.1, 129.2, 129.8, 130.0 (10 x CH, aromatic *C*H of both diastereoisomers of α-thioamide **31**), 134.1 (Cq, aromatic *C*q of one diastereoisomer of α-thioamide **31**), 134.2 (Cq, aromatic *C*q of one diastereoisomer of α-thioamide **31**), 168.8 (Cq, *C*=O of both diastereoisomers of α-chloroamide **21**), 170.9 (Cq, *C*=O of one diastereoisomer of α-thioamide **31**) 171.0 (Cq, *C*=O of one diastereoisomer of α-thioamide **31**); ν_{max}/cm^{-1} 3267 (NH), 2968; 1641 (CO), 1550, 737, 688; HRMS (ES+): Exact mass calculated for $C_{13}H_{20}NOS$ $[M+H]^+$, 238.1266; Found 238.1263; m/z (ES+) 238.3 [$M+H^+$], 100%.

N-(*sec*-Butyl)-2-(benzylthio)propanamide 33

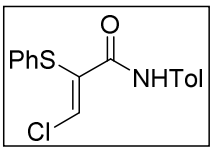


This synthesis follows the procedure described for **4** using *N*-(*sec*-butyl)-2-chloropropanamide **21** as a mixture of the two diastereoisomers (ratio 1 : 1) (0.80 g, 4.89 mmol) in ethanol (10 mL), benzyl mercaptan (0.70 mL, 5.87 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.13 g, 5.87 mmol) in ethanol (15 mL) at 0 °C]. The crude product was purified by column chromatography on silica gel using

hexane : ethyl acetate as eluent (gradient elution 1 to 50% of ethyl acetate) to give a mixture of the two diastereoisomers of the α-*thioamide* **33** with ratio 1 : 1 respectively by ^{1}H NMR spectroscopy as a white solid (0.79 g, 64%); mp 53-54 ^{o}C; δ_H (400 MHz, $CDCl_3$) 0.87-0.98 {[6H, m, 2 x t overlapped, 0.90 [3H, t, *J* 7.5, C(4')*H*$_3$ of one diastereoisomer] and 0.93 [3H, t, *J* 7.5, C(4')*H*$_3$ of one diastereoisomer]}, 1.08-1.16 [6H, m, 2 x d overlapped, *J* 6.7, C(1')*H*$_3$ of both diastereoisomers], 1.39-1.54 [10H, m, C(3')*H*$_2$ and C(3)*H*$_3$ of both diastereoisomers], 3.24-3.34 {2H, m, 2 x q overlapped; 3.28 [1H, q, *J* 7.2, C(2)*H* of one diastereoisomer] and 3.29 [1H, q, *J* 7.2, C(2)*H* of one diastereoisomer]}, 3.67-3.77 (4H, m, SC*H*$_2$ of both diastereoisomers), 3.80-3.96 [2H, m, C(2')*H* of both diastereoisomers), 6.43 (2H, br s, N*H* of both diastereoisomers), 7.23-7.33 (10H, m, Ar*H* of both diastereoisomers); δ_C (100 MHz, $CDCl_3$) 10.3 [CH_3, *C*(4')H_3 of one diastereoisomer], 10.4 [CH_3, *C*(4')H_3 of one diastereoisomer], 18.5 [CH_3, *C*(3)H_3 of one diastereoisomer], 18.7 [CH_3, *C*(3)H_3 of one diastereoisomer], 20.3 [CH_3, *C*(1')H_3 of one diastereoisomer], 20.4 [CH_3, *C*(1')H_3 of one diastereoisomer], 29.5 [CH_2, *C*(3')H_2 of one diastereoisomer], 29.6 [CH_2, *C*(3')H_2 of one diastereoisomer], 36.3 (CH_2, S*C*H_2 of one diastereoisomer), 36.4 (CH_2, S*C*H_2 of one diastereoisomer), 44.3 [CH, *C*(2)H of one diastereoisomer], 44.5 [CH, *C*(2)H of one diastereoisomer], 46.6 [CH, *C*(2')H of one diastereoisomer], 46.7 [CH, *C*(2')H of one diastereoisomer], 127.3, 128.7, 128.9 (3 x CH, 10 x aromatic *C*H of both diastereoisomers), 137.3 (Cq, aromatic *C*q of one diastereoisomer), 137.4 (Cq, aromatic *C*q of one diastereoisomer), 171.4 (Cq, *C*=O of both diastereoisomers); ν_{max}/cm^{-1} 3279 (NH), 2967, 1638 (CO), 1541, 709, 694; HRMS (ES+): Exact mass calculated for $C_{14}H_{22}NOS$ $[M+H]^+$, 252.1422 Found 252.1420; m/z (ES+) 252.3 {[$M+H^+$], 64%}, 274.2 {[M+Na] 48%}.

4. SYNTHESIS OF A-THIO-B-CHLOROACRYLAMIDES

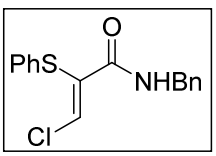
N-(4'-Methylphenyl)-*Z*-3-chloro-2-(phenylthio)propenamide 7[2,3]



N-Chlorosuccinimide (0.27 g, 2.01 mmol) was added in one portion to a solution of *N*-(4'-methylphenyl)-2-(phenylthio)propanamide **4** (0.28 g, 1.95 mmol) in toluene (6 mL). The flask was immediately immersed in an oil bath at 90 °C, while stirring, and maintained in this state for 3 h. Following this, the reaction mixture was cooled to 0 °C. The succinimide by-product precipitated and was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 2 to 10% of ethyl acetate) to give the α-*thio*-β-*chloroacrylamide* **7** (0.26 g, 82%) as a white solid, mp 106-108 °C (Lit.,[2] 110-111 °C); δ_H (300 MHz, $CDCl_3$) 2.29 (3H, s, ArC*H*$_3$), 7.09 (2H, d, *J* 8.4, Ar*H*), 7.17-7.31 (7H, m, Ar*H*), 8.04 (1H, s, C*H*Cl), 8.61 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 20.8 (CH_3, Ar*C*H_3), 120.2, 127.3, 128.2, 129.5, 129.7 (5 x CH, 9 x aromatic *C*H), 130.7, 132.5, 134.5, 134.7 (4 x Cq, 3 x aromatic *C*q and S*C*=), 140.7 (CH, *C*HCl), 160.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3336 (NH), 1650 (C=O), 1519 (NH bend), 817, 734, 641, 516; m/z (ES+) 304.1 {[($C_{16}H_{14}{}^{35}ClNOS$)+H$^+$], 100%}, 306.1 {[($C_{16}H_{14}{}^{37}ClNOS$)+H$^+$], 42%; (ES-) 302.2 {[($C_{16}H_{14}{}^{35}ClNOS$)-H$^+$], 100%}, 304.2 {[($C_{16}H_{14}{}^{37}ClNOS$)+H$^+$], 39%}; HPLC retention time: (Method 1) 18.0 min; (Method 2) 20.0 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

N-Benzyl-*Z*-3-chloro-2-(phenylthio)propenamide 15[2]

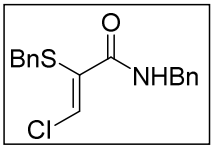


This synthesis followed the procedure described for **7** using *N*-chlorosuccinimide (0.96 g, 7.19 mmol) and *N*-benzyl-2-(phenylthio)propanamide **22** (1.00 g, 3.68 mmol) in toluene (20 mL). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 5 to 10% of ethyl acetate) to give the α-*thio*-β-*chloroacrylamide* **15** (0.80 g, 72%) as a white solid, mp 72-73

°C (Lit.,[2] 72-74 °C); δ_H (400 MHz, $CDCl_3$) 4.40 (2H, d, *J* 5.9, C*H*$_2$NH), 6.89-7.58 [11H, m, which includes 7.10 (1H, br s, NH) and 10 × Ar*H*], 8.02 (1H, s, C*H*Cl); δ_C (75 MHz, $CDCl_3$) 44.1 (CH_2, NH*C*H_2), 127.1, 127.3, 127.4, 128.1, 128.6, 129.5 (6 x CH signals, 10 x aromatic *C*H), 130.4, 132.8, 137.3 (3 x Cq, 2 × aromatic *C*q and S*C*=), 139.6 (CH, *C*HCl), 162.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3407 (NH), 3053, 2925, 1660 (C=O), 1496 (NH bend), 746, 726, 692, 453, 477; m/z (ES+) 304.2 {[($C_{16}H_{14}{}^{35}ClNOS$)+H$^+$], 100%}, 306.1 {[($C_{16}H_{14}{}^{37}ClNOS$)+H$^+$], 40%; (ES-) 302.2 {[($C_{16}H_{14}{}^{35}ClNOS$)-H$^+$], 46%}, 304.2 {[($C_{16}H_{14}{}^{37}ClNOS$)-H$^+$], 11%}; HPLC retention time: (Method 2) 13.9 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

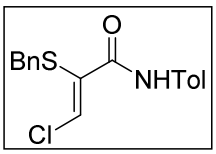
N-Benzyl-*Z*-3-chloro-2-(benzylthio)propenamide 26[2]



This synthesis followed the procedure described for **7** using *N*-chlorosuccinimide (0.46 g, 3.42 mmol) and *N*-benzyl-2-(benzylthio)propanamide **25** (0.50 g, 1.75 mmol) in toluene (10 mL). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 7 to 15% of ethyl acetate) to give the α-*thio*-β-*chloroacrylamide* **26** (0.33 g, 62%) as a white solid, mp 73-76 °C (Lit.,[2] 69-72 °C); δ_H (400 MHz, $CDCl_3$) 3.88 (2H, s, C*H*$_2$S), 4.32 (2H, d, *J* 6.0, C*H*$_2$NH), 7.02-7.34 (11H, m, 10 × Ar*H* and N*H*), 7.86 (1H, s, C*H*Cl); δ_C (100 MHz, $CDCl_3$) 38.3 (CH_2, S*C*H_2), 44.1 (CH_2, *C*H_2NH), 127.6, 127.7, 127.8, 128.6, 128.7, 128.8 (6 x CH signals, 10 x aromatic *C*H), 131.0 (Cq, S*C*=), 137.0, 137.5 (2 x Cq, 2 x aromatic *C*q), 139.4 (CH, *C*HCl), 162.8 (Cq, *C*=O); ν_{max}/cm^{-1} 3313 (NH), 3061, 1639 (C=O), 1516 (NH bend), 709, 690; m/z (ES+) 318.2 {[($C_{17}H_{16}{}^{35}ClNOS$)+H$^+$], 100%}, 320.2 {[($C_{17}H_{16}{}^{37}ClNOS$)+H$^+$], 43%; (ES-) 316.2 {[($C_{17}H_{16}{}^{35}ClNOS$)-H$^+$], 100%}, 318.3 {[($C_{17}H_{16}{}^{37}ClNOS$)+H$^+$], 40%}; HPLC retention time: (Method 2) 15.6 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

N-(4'-Methylphenyl)-*Z*-3-chloro-2-(benzylthio)propenamide 34[2]

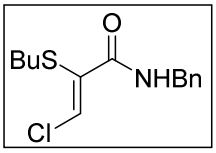


This synthesis followed the procedure described for **7** using *N*-chlorosuccinimide (0.91 g, 6.83 mmol) and *N*-(4'-methylphenyl)-2-(benzylthio)propanamide **27** (1.00 g, 3.50

mmol) in toluene (20 mL). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) to give the α-*thio*-β-*chloroacrylamide* **34** (0.79 g, 71%) as a white solid, mp 90-91 °C (Lit.,[2] 84-86 °C); δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, ArCH_3), 3.97 (2H, s, CH_2S), 7.07-7.33 (9H, m, Ar*H*), 7.91 (1H, s, C*H*Cl), 8.56 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 20.9 (CH_3, ArCH_3), 38.7 (CH_2, SCH_2), 119.9, 127.9, 128.7, 128.9, 129.4 (5 x CH, 9 x aromatic *C*H), 131.4, 134.5, 134.6, 136.9 (4 x Cq, 3 × aromatic *C*q and S*C*=), 140.3 (CH, *C*H=Cl), 160.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3277 (NH), 2982, 1645 (C=O), 1517 (NH bend), 696, 501; m/z (ES+) 318.2 {[($C_{17}H_{16}{}^{35}ClNOS$)+H^+], 100%}, 320.2 {[($C_{17}H_{16}{}^{37}ClNOS$)+H^+], 44%; (ES-) 316.2 {[($C_{17}H_{16}{}^{35}ClNOS$)-H^+], 98%}, 318.2 {[($C_{17}H_{16}{}^{37}ClNOS$)+H^+], 40%}; HPLC retention time: (Method 2) 24.8 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

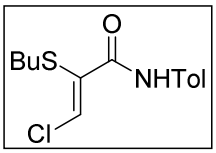
N-Benzyl-*Z*-3-chloro-2-(butylthio)propenamide 35[2]



This synthesis followed the procedure described for **7** using *N*-chlorosuccinimide (0.52 g, 3.84 mmol) and *N*-benzyl-2-(butylthio)propanamide **28** (0.50 g, 1.99 mmol) in toluene (10 mL). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (99:1) to give the α-*thio*-β-*chloroacrylamide* **35** (0.38 g, 69%) as a low melting white solid; δ_H (400 MHz, $CDCl_3$) 0.86 [3H, t, *J* 7.3, C(4')H_3], 1.18-1.81 [4H, m, C(3')H_2 and C(2')H_2], 2.69 [2H, t, *J* 7.5, C(1')H_2], 4.53 (2H, d, *J* 5.7, CH_2NH), 7.25-7.54 [6H, m, which includes 7.46 (1H, br s, NH) and 5 × Ar*H*], 7.79 (1H, s, C*H*Cl); δ_C (100 MHz, $CDCl_3$) 13.5 [CH_3, *C*(4')H_3], 21.7 [CH_3, C(3')H_3], 31.7 [CH_2, *C*(2')H_2], 34.1 [CH_2, *C*(1')H_2], 44.2 (CH_2, CH_2NH), 127.7, 128.0, 128.8 (3 x CH signals, 5 x aromatic *C*H), 131.8 (Cq, aromatic *C*q), 137.7 (CH, *C*HCl), 137.9 (Cq, S*C*=), 163.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3275 (NH), 2961, 2927, 1638 (C=O), 1516, 1281, 697; m/z (ES+) 284.2 {[($C_{14}H_{18}{}^{35}ClNOS$)+H^+], 100%}, 286.2 {[($C_{14}H_{18}{}^{37}ClNOS$)+H^+], 43%; HPLC retention time: (Method 2) 16.9 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

N-(4'-Methylphenyl)-*Z*-3-chloro-2-(butylthio)propenamide 36[2]



This synthesis followed the procedure described for **7** using *N*-chlorosuccinimide (0.52 g, 3.84 mmol) and *N*-(4'-methylphenyl)-2-(butylthio)propanamide **29** (0.50 g, 1.99 mmol) in toluene (10 mL). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 2 to 5% of ethyl acetate) to give the α-*thio*-β-*chloroacrylamide* **36** (0.44 g, 79%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 0.90 [3H, t, *J* 7.2, C(4')H_3], 1.38-1.52 [2H, m, C(3')H_2], 1.52-1.69 [2H, m, C(2')H_2], 2.33 (3H, s, ArCH_3), 2.79 [2H, t, *J* 7.5, C(1')H_2), 7.16 (2H, d, *J* 8.0, 2 × Ar*H*), 7.48 (2H, d, *J* 8.0, 2 × Ar*H*), 7.87 (1H, s, C*H*Cl), 8.98 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.5 [CH_3, *C*(4')H_3], 20.9 (3H, s, ArCH_3), 21.7 [CH_3, C(3')H_3], 31.7 [CH_2, *C*(2')H_2], 34.4 [CH_2, *C*(1')H_2], 119.9 (1 x CH signal, 2 x aromatic *C*H), 129.6 (1 x CH signal, 2 x aromatic *C*H), 132.1, 134.6, 134.8 (3 x Cq, 2 × aromatic *C*q and S*C*=), 138.9 (CH, *C*HCl), 160.9 (Cq, *C*=O); ν_{max}/cm^{-1} 3320 (NH), 2958, 2928, 1651 (C=O), 1517 (NH bend), 813, 727; m/z (ES+) 284.2 {[($C_{14}H_{18}{}^{35}ClNOS$)+H^+], 100%}, 286.2 {[($C_{14}H_{18}{}^{37}ClNOS$)+H^+], 44%; HPLC retention time: (Method 2) 27.9 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

5. SYNTHESIS OF OXIDATIVE CHLORINATION INTERMEDIATES

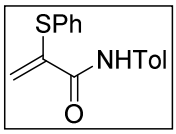
Isolation of the various reaction intermediates in analytically pure form was challenging in some instances. In many cases, samples of these compounds contained minor amount of other intermediates or the final α-thio-β-chloroacrylamide product. Due to their instability, the HPLC retention time of intermediates are determined from different batches in some instances.

The purity of the intermediates was estimated by ^{1}H NMR spectroscopy, based on the integration of the aromatic area when compared to the integration of a specified characteristic signal of each described intermediate that corresponds to a known number of protons. This method takes into consideration that impurities

formed are all derivatives of the α-thioamide starting material and, hence, all display the same number of aromatic protons as the corresponding α-thioamide starting material.

A. Acrylamides, β-chlorosulfides and analogues

N-(4'-Methylphenyl)-2-(phenylthio)propenamide 8[2,3]

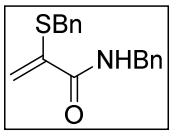


N-Chlorosuccinimide (0.18 g, 1.36 mmol) was added in one portion to a solution of *N*-(4'-methylphenyl)-2-(phenylthio)propanamide **4** (0.33 g, 1.24 mmol) in tetrachloromethane (6 mL) at room temperature. Following stirring for 15 h at room temperature, the solvent was evaporated under reduced pressure. The crude product consisted of a mixture of the *acrylamide* **8** (δ_H 6.11, 1H, s), the *dichloride* **9** (δ_H 4.46, 1H, apparent d, *J* 11.5) and succinimide with ratio 1 : 0.22 : 0.92 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (97 : 3) to give the pure *acrylamide* **8** (0.12 g, 35%) as a white solid; mp 101-102 ^{o}C; (Lit.,[1] 137-139 ^{o}C); δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s, ArC*H*$_3$), 6.11, 6.87 (2H, 2 x s, C(3)*H*$_2$=), 7.08 (2H, d, *J* 8.4, Ar*H*), 7.18-7.36 (7H, m, Ar*H*), 8.52 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 20.9 (CH_3, Ar*C*H$_3$), 120.1, 127.4, 128.9, 129.5, 129.6 (5 x CH signals, 9 x aromatic *C*H), 132.9 (CH_2, *C*(3)H$_2$=), 133.5, 134.5, 134.7, 136.1 (4 × Cq, 3 × aromatic *C*q and S*C*(2)=), 161.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3342 (NH), 3029, 2918, 1663 (C=O), 1514, 960, 816, 741, 641; HRMS (ES+): Exact mass calculated for $C_{16}H_{16}NOS$ $[M+H]^+$, 270.0953; Found 270.0954; m/z (ES+) 270.2 [M+H$^+$], 19%. HPLC retention time: (Method 1) 13.2 min; (Method 2) 14.9 min.

Spectroscopic characteristics were consistent with those previously reported.[2]

The other products formed were not isolated as the purpose of this experiment was the isolation of the acrylamide intermediate. The isolation of the *dichloride* **9**, as well as the characteristic data, are described in *section 2.B*.

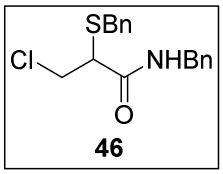
N-Benzyl-2-(benzylthio)propenamide 39



This synthesis followed the procedure described for **8** using *N*-chlorosuccinimide (0.26 g, 1.92 mmol) and *N*-benzyl-2-(benzylthio)propanamide **25** (0.50 g, 1.75 mmol) in toluene (3 mL) in place of tetrachloromethane. The crude product consisted of a mixture of the *acrylamide* **39** (δ_H 5.60, 1H, s), the β-*chlorosulfide* **46** (δ_H 3.40, 1H, X of ABX, *J* 7.2, 4.6), the α-*thioamide* **25** (δ_H 1.46, 3H, d, *J* 7.3) and succinimide with ratio 0.79 : 1 : 0.12 : 0.70 respectively by ^{1}H NMR spectroscopy. The mixture was purified by successive column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 3 to 5% of ethyl acetate) to give a mixture containing the *acrylamide* **39** and the β-*chlorosulfide* **46** with ratio 1 : 0.20 respectively by ^{1}H NMR spectroscopy (0.06 g) as a white solid; Data for a*crylamide* **39**: δ_H (400 MHz, $CDCl_3$) 3.81 (2H, s, SC*H*$_2$), 4.32-4.49 (2H, m, NHC*H*$_2$), 5.60, 6.47 (2H, 2 x s, C(3)*H*$_2$=), 6.96 (1H, br s, N*H*), 7.10-7.31 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 39.3 (CH_2, S*C*H$_2$), 44.2 (CH_2, NH*C*H$_2$), 127.6 [CH_2, *C*(3)H$_2$=], 127.5, 127.6, 127.8, 128.7, 128.8, 128.9 (6 x CH signals, 10 x aromatic *C*H), 136.5 [Cq, S*C*(2)=], 137.3, 137.8 (2 x Cq, 2 x aromatic *C*q), 164.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3301 (NH), 1652 (C=O); HRMS (ES+): Exact mass calculated for $C_{17}H_{18}NOS$ $[M+H]^+$, 284.1109; Found 284.1096; m/z (ES+) 284.3 [($M+H^+$), 100 %]; HPLC retention time: (Method 2) 13.8 min. Characteristic signals for the β-*chlorosulfide* **46** were also present.

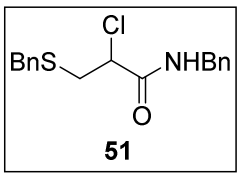
The other products formed were not isolated as the purpose of this experiment was the isolation of the acrylamide intermediate. The isolation of the β-*chlorosulfide* **46**, as well as the characteristic data, are described in this section. The isolation of the dichloride **9** and the α-*thioamide* **25**, as well as their characteristic data, are described in *section 2.B* and *section 3.* respectively.

N-Benzyl-2-(benzylthio)-3-chloropropanamide 46



46

This synthesis followed the procedure described for **8** using *N*-chlorosuccinimide (0.99 g, 7.44 mmol) and *N*-benzyl-2-(benzylthio)propanamide **25** (1.93 g, 6.76 mmol) in tetrachloromethane (16 mL). The crude product consisted of a mixture of the *acrylamide* **39** (δ_H 5.60, 1H, s), the β-*chlorosulfide* **46** (δ_H 3.40, 1H, X of ABX, *J* 7.2, 4.6) and the α-*thioamide* **25** (δ_H 1.46, 3H, d, *J* 7.3) with ratio 0.35 : 1 : 0.13 respectively by ^{1}H NMR spectroscopy. After two days at room temperature, the crude product consisted of a mixture of the *acrylamide* **39**, the β-*chlorosulfide* **46**, the α-*thioamide* **26** and the α-*chloropropanamide* **51** (δ_H 3.03, 1H, apparent dd, J_{AB} 14.1, J_{AX} 5.8) with ratio 0.03 : 1 : 0.13 : 0.29 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 5 to 10% of ethyl acetate) to give a mixture containing the β-*chlorosulfide* **46**, the *acrylamide* **39** and the α-*chloropropanamide* **51** with ratio 1 : 0.03 : 0.30 respectively by ^{1}H NMR spectroscopy (1.06 g) as a pale yellow oil. Following cold recrystallisation from ethyl acetate and hexane gave the β-*chlorosulfide* **46** (0.56 g) which contains a minor amount of the *acrylamide* **39** and the α-*chloropropanamide* **51** (ratio 1 : 0.03 : 0.15 respectively by ^{1}H NMR spectroscopy) as a white solid; mp 50-57 °C; Data for β-*chlorosulfide* **46**: δ_H (400 MHz, $CDCl_3$) 3.40 [1H, X of ABX, J_{AX} 4.8, J_{BX} 7.1, C(2)*H*], 3.71-3.89 {3H, m, can be distinguished 3.78 (2H, ABq, J_{AB} 13.4, $\Delta\delta_{AB}$ 0.03, S*CH*$_2$) and 3.85 [1H, A of ABX, J_{AB} 10.8, J_{AX} 4.9, one of C(3)*H*$_2$]}, 3.95 [1H, B of ABX, J_{AB} 10.8, J_{BX} 7.0, one of C(3)*H*$_2$], 4.30-4.52 {2H, m, can be distinguished 4.38 [1H, A of ABX, J_{AB} 14.9, J_{AX} 5.7, one of C*H*$_2$NH], 4.42 [1H, B of ABX, J_{AB} 14.8, J_{BX} 6.1, one of C*H*$_2$NH]}, (2H, m, apparent qd, NHC*H*$_2$), 6.50 (1H, br s, N*H*), 7.17-7.40 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 36.3 (CH_2, S*C*H$_2$), 44.0 (CH_2, NH*C*H$_2$), 45.0 [CH_2, C(3)H$_2$], 50.5 [CH, *C*(2)H], 127.6, 127.7, 127.8, 128.8, 128.9, 129.0 (6 x CH, 10 x aromatic *C*H), 137.0 (Cq, aromatic *C*qCH$_2$S), 137.6 (Cq, aromatic *C*qCH$_2$NH), 168.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3256 (NH), 3086, 3060, 3029, 1675 (C=O), 1641 (C=O of **46**), 1562, 730, 693; HRMS (ES+): Exact mass calculated for



51

$C_{17}H_{19}NOSCl$ $[M+H]^+$, 320.0876 Found 320.0879; m/z (ES+) 320.1 {[($C_{17}H_{19}{}^{35}ClNOS$)+H^+], 100%; 322.1 {[($C_{17}H_{19}{}^{37}ClNOS$)+H^+], 48%. Characteristic signals of the *acrylamide* **39** and the α-*chloropropanamide* **51** were also present.

The isolation of the acrylamide **39** and the α-*chloropropanamide* **51**, as well as their characteristic data, are described elsewhere in this section. The isolation of the α-*thioamide* **26**, as well as the characteristic data, are described in *section 3*.

Mechanistic studies on the β-*chlorosulfide* 46 formation

Using *in-situ* generated HCl

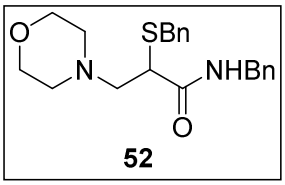
A solution of water (0.01 mL, 0.70 mmol) in tetrachloromethane (0.50 mL) was added using syringe to a solution of acetyl chloride (0.05 mL, 0.64 mmol) in tetrachloromethane (1 mL). On completion of the addition, a solution of the *acrylamide* **39** and the β-*chlorosulfide* **46** (0.18 g, ~ 0.64 mmol), with ratio 1 : 0.44 respectively by ^{1}H NMR spectroscopy, in tetrachloromethane (2 mL). The reaction mixture was stirred 2 h at room temperature and then, the reaction solvent was removed under reduced pressure at room temperature. The mixture was dissolved in dichloromethane (20 mL) and washed with water (20 mL). The layers were separated and the aqueous layer was extracted using dichloromethane (2 x 10 mL). Combined organic layers were washed with a saturated solution of sodium bicarbonate (2 x 20 mL) and brine (40 mL), dried and concentrated under reduced pressure. The crude product consisted of a mixture of the *acrylamide* **39** (δ_H 5.60, 1H, s), the β-*chlorosulfide* **46** (δ_H 3.40, 1H, X of ABX, *J* 7.2, 4.6) and the α-*chloropropanamide* **51** (δ_H 3.03, 1H, apparent dd, J_{AB} 14.1, J_{AX} 5.8) with ratio 1 : 0.97 : 0.18 respectively by ^{1}H NMR spectroscopy.

Using triethylamine

Triethylamine (0.04 mL, 0.31 mmol) was added to a solution of a mixture of the β-*chlorosulfide* **46**, the α-*chloropropanamide* **51** and the *acrylamide* **39** from the previous reaction described above (ratio 1 : 0.15 : 0.03 respectively) (0.10 g, ~0.31 mmol) in tetrachloromethane (2 mL). The reaction mixture was stirred overnight at room temperature and then, the reaction solvent was removed under reduced

pressure. The crude product consisted of the *acrylamide* **39** as the main product, along with minor amount of an unknow compound.

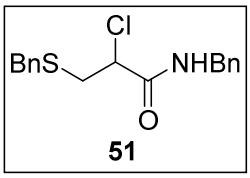
N-Benzyl-2-(benzylthio)-3-morpholinopropanamide 52 and the *N*-benzyl-3-(benzylthio)-2-chloropropanamide 51



52

Neat morpholine (5 mL, 57.8 mmol) was stirred with a mixture of the β-*chlorosulfide* **46**, the α-*chloropropanamide* **51** and the *acrylamide* **39** from the previous reaction described above (ratio 1 : 0.15 : 0.03 respectively) (0.10 g, ~0.31 mmol) at room temperature. After 10 min the reaction was seen to be complete by TLC analysis. Saturated aqueous ammonium chloride (40 mL) and dichloromethane (50 mL) were added and the layers were separated. The organic layer was washed with water (50 mL) and brine (50 mL), dried and concentrated under reduced pressure. The crude product consisted of a mixture of the α-*thio*-β-*morpholinoamide* **52** (δ_H 3.32, 1H, X of ABX, J_{AX} 5.6, J_{BX} 7.6) and the unchanged α-*chloropropanamide* **51** (δ_H 3.03, 1H, A of ABX, J_{AB} 14.1, J_{AX} 5.8) with ratio 1 : 0.21 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 80% ethyl acetate) to give the α-*thio*-β-*morpholinoamide* **52** (52 mg, 46%) as a white solid as the more polar fraction; mp 86-88 ^{o}C; (Found C, 67.64; H, 6.90; N, 7.37. $C_{21}H_{26}N_2O_2S$ requires C, 68.08; H, 7.07; N, 7.56%); δ_H (400 MHz, $CDCl_3$) 2.38 (4H, t, *J* 4.4, 2 x NC*H*$_2$), 2.65 [1H, A of ABX, J_{AB} 13.1, J_{AX} 5.7, one of NC(3)*H*$_2$], 2.76 [1H, B of ABX, J_{AB} 13.1, J_{BX} 7.6, one of NC(3)*H*$_2$], 3.32 [1H, X of ABX, J_{AX} 5.7, J_{BX} 7.6, C(2)*H*], 3.53 (4H, t, *J* 4.4, 2 x OC*H*$_2$), 3.78 (2H, ABq, J_{AB} 13.3, $\Delta\delta_{AB}$ 0.03, SC*H*$_2$), 4.32-4.51 {2H, m, can be distinguished 4.39 [1H, A of ABX, J_{AB} 14.6, J_{AX} 5.3, one of C*H*$_2$NH], 4.42 [1H, B of ABX, J_{AB} 14.6, J_{BX} 5.7, one of C*H*$_2$NH]}, 7.19-7.75 [11H, m, can be distinguished 7.19-7.43 (10H, m, Ar*H*) and 7.51 (1H, br t, *J* 5.4, N*H*)]; δ_C (100 MHz, $CDCl_3$) 36.4 (CH_2, SCH_2), 43.7 (CH_2, NHCH_2), 46.7 [CH, *C*(2)H], 53.7 (CH_2, 2 x NCH_2), 60.2 [CH_2, NC(3)H_2], 66.8 (CH_2, 2 x OCH_2), 127.3, 127.6, 127.8, 128.6, 128.7, 129.1 (6 x CH signals, 10 x aromatic *C*H), 137.4 (Cq, aromatic *C*qCH_2S), 138.2 (Cq, aromatic *C*qCH_2NH), 170.8 (Cq, *C*=O); ν_{max}/cm^{-1} 3247 (NH),

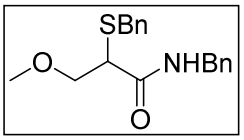
2859, 2811, 1644 (C=O), 1115, 701, 456; HRMS (ES+): Exact mass calculated for $C_{21}H_{27}N_2O_2S$ $[M+H]^+$, 371.1793 Found 371.1784.



51

The unchanged α-*chloropropanamide* **51** was also isolated as the less polar fraction (4.9 mg, 4%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 3.03 [1H, A of ABX, J_{AB} 14.1, J_{AX} 5.8, one of SCH_2], 3.18 [1H, B of ABX, J_{AB} 14.1, J_{BX} 5.7, one of SCH_2], 3.77 (2H, s, SCH_2Ph), 4.37 [1H, apparent t, X of ABX, J_{AX} 5.8, J_{BX} 5.7, C*H*Cl], 4.49 (2H, d, *J* 5.8, NHCH_2Ph), 6.68 (1H, br s, N*H*), 7.16-7.57 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 36.5 [CH_2, S*C*H_2], 37.3 (CH_2, S*C*H_2Ph), 44.1 (CH_2, NH*C*H_2Ph), 59.7 [CH, *C*HCl], 127.3, 127.8, 128.6, 128.8, 129.0, 129.9 (6 x CH, 10 x aromatic *C*H), 137.2 (Cq, aromatic *C*qCH_2NH), 137.9 (Cq, aromatic *C*qCH_2S), 167.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3291 (NH), 2920, 1649 (C=O), 1529, 1493, 1453, 1031, 694 (C-Cl), 411; HRMS (ES+): Exact mass calculated for $C_{17}H_{19}NOS^{35}Cl$ $[M+H]^+$, 320.0876 Found 320.0872; m/z (ES+) 320.1 {[($C_{17}H_{19}{}^{35}ClNOS$)+H^+], 100%; 322.1 {[($C_{17}H_{19}{}^{37}ClNOS$)+H^+], 45%.

N-Benzyl-2-(benzylthio)-3-methoxypropanamide 53

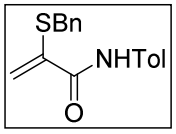


A freshly prepared sodium methoxide solution [from sodium (0.03 g, 1.25 mmol) in methanol (6 mL)] was added to a solution of the β-*chlorosulfide* **46**, the α-*chloropropanamide* **51** and the *acrylamide* **39** from the reaction described previously (ratio 1 : 0.15 : 0.03 respectively) (0.20 g, ~0.63 mmol) in methanol (4 mL) at room temperature. TLC monitoring of the reaction indicated incomplete conversion even after 30 hours reaction time. Saturated aqueous ammonium chloride (10 mL) and ether (15 mL) were added and the layers were separated. The aqueous layer was extracted with ether (2 x 5mL) and the combined organic layers were washed with brine (2 x 20 mL), dried and concentrated under reduced pressure. The crude product consisted of a mixture of the α-*thio*-β-*methoxyamide* **53** (δ_H 3.66, 1H, A of ABX, J_{AB} 9.6, J_{Ax} 4.9), the unchanged α-*chloropropanamide* **51** (δ_H 3.03, 1H, A of ABX, J_{AB} 14.1, J_{AX} 5.8) and the unchanged *acrylamide* **39** (δ_H 5.60, 1H, s) with ratio 1 : 0.12 : 0.09 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate

as eluent (gradient elution 10 to 20% ethyl acetate) to give the α-*thio*-β-*methoxyamide* **53** (0.16 g, 84%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 3.28-3.44 {4H, m, can be distinguished 3.33 (3H, s, OC*H*$_3$) and 3.36 [1H, apparent t, X of ABX, J_{AX} 4.9, J_{BX} 4.4, C(2)*H*]}, 3.66 [1H, A of ABX, J_{AB} 9.6, J_{AX} 4.9, one of OC(3)*H*$_2$], 3.73-3.94 {3H, m, can be distinguished 3.76 (2H, s, SC*H*$_2$Ph) and 3.78 [1H, B of ABX, J_{AB} 9.6, J_{BX} 4.3, one of OC(3)*H*$_2$]}, 4.34-4.52 {2H, m, can be distinguished 4.37 [1H, A of ABX, J_{AB} 15.0, J_{AX} 6.0, one of C*H*$_2$NH], 4.44 [1H, B of ABX, J_{AB} 15.0, J_{BX} 6.1, one of C*H*$_2$NH]}, 7.00 (1H, br t, *J* 5.0, N*H*), 7.18-7.46 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 36.4 (CH_2, S*C*H$_2$), 43.6 (CH_2, NH*C*H$_2$), 49.3 [CH, *C*(2)H], 59.3 (CH_3, O*C*H$_3$), 73.1 [CH_2, OC(3)H$_2$], 127.4, 127.5, 127.6, 128.7, 129.0 (5 x CH signals, 10 x aromatic *C*H), 137.4 (Cq, aromatic *C*qCH$_2$S), 138.1 (Cq, aromatic *C*qCH$_2$NH), 170.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3287 (NH), 1644 (C=O), 1531, 1453, 1115 (C-O), 695; HRMS (ES+): Exact mass calculated for $C_{18}H_{22}NO_2S$ $[M+H]^+$, 316.1371 Found 316.1364.

The isolation of the *acrylamide* **39** and the α-*chloropropanamide* **51**, as well as their characteristic data, are described elsewhere in this section.

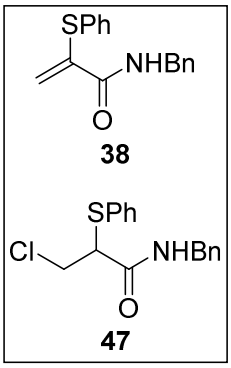
N-(4'-Methylphenyl)-2-(benzylthio)propenamide 37



This synthesis followed the procedure described for **8** using *N*-chlorosuccinimide (0.05 g, 0.37 mmol) and *N*-(4'-methylphenyl)-2-(benzylthio)propanamide **27** (0.09 g, 0.34 mmol) in tetrachloromethane (1 mL). The crude product consist of the *acrylamide* **37** as the main product formed and was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (98:2) to give the pure *acrylamide* **37** (0.05 g, 49%) as a white solid; mp 84-88 °C; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, ArC*H*$_3$), 3.94 (2H, s, SC*H*$_2$), 5.78, 6.65 [2H, 2 x s, C(3)*H*$_2$=], 7.13 (2H, d, *J* 8.2, Ar*H*), 7.19-7.33 (4H, m, Ar*H*), 7.39 (2H, d, *J* 8.2, Ar*H*), 8.57 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 20.9 (CH_3, Ar*C*H$_3$), 39.9 (CH_2, S*C*H$_2$), 119.9, 127.6, 128.8, 128.9, 129.5 (5 x CH signals, 9 x aromatic *C*H), 130.0 (CH_2, *C*(3)H$_2$=), 134.4, 134.9, 136.6 (3 x Cq, 3 x aromatic *C*q), 137.4 [Cq, S*C*q(2)=], 161.9 (Cq, *C*=O); ν_{max}/cm^{-1} 3257 (NH), 1651 (C=O), 1514, 815; HRMS (ES+): Exact mass calculated for $C_{17}H_{18}NOS$ $[M+H]^+$, 284.1109 Found

284.1111; m/z (ES+) 284.3 [(M+H$^+$), 19%]; HPLC retention time: (Method 2) 16.3 min.

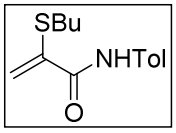
N-Benzyl-2-(phenylthio)propenamide 38 and *N*-benzyl-3-chloro-2-(phenylthio)propanamide 49



This synthesis followed the procedure described for **8** using *N*-chlorosuccinimide (0.27 g, 1.84 mmol) and *N*-benzyl-2-(phenylthio)propanamide **22** (0.50 g, 2.03 mmol) in tetrachloromethane (3 mL). The crude product consisted of a mixture of the *acrylamide* **38** (δ_H 6.03, 1H, s), the β-*chlorosulfide* **47** (tentatively assigned, δ_H 3.92-4.03, 2H, m) and succinimide with ratio 1 : 0.40 : 0.75 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 30% ethyl acetate) to give the desired *acrylamide* **38** as a mixture with the β-*chlorosulfide* **47**, with ratio 1 : 0.24 respectively by ^{1}H NMR spectroscopy, (0.18 g) as a low melting point white solid; Characteristic data for the *acrylamide* **38**: δ_H (400 MHz, $CDCl_3$) 4.41 (2H, d, *J* 5.9, NHC*H*$_2$), 6.03, 6.78 [2H, 2 x s, C(3)*H*$_2$=], 7.01 (1H, br s, N*H*), 7.14-7.40 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.0 (CH_2, NH*C*H$_2$), 127.2 [CH_2, *C*(3)H$_2$=], 127.2, 127.3, 127.4, 128.6, 128.8, 129.5 (6 x CH signals, 10 x aromatic CH), 133.7, 135.8 (2 x Cq, 2 x aromatic *C*q), 137.5 [Cq, S*C*(2)=], 163.5 (Cq, *C*=O); ν_{max}/cm^{-1} 3363 (NH), 1649 (C=O), 1515, 690; HRMS (ES+): Exact mass calculated for $C_{16}H_{16}NOS$ [M+H]$^+$; 270.0953 Found 270.0916; m/z (ES+) 270.1 [(M+H$^+$), 92%]; HPLC retention time: (Method 2) 10.2 min. Characteristic signals for the β-*chlorosulfide* **47** were also present; δ_H 3.86-3.96 {2H, m, can be distinguished 3,89 [1H, B of ABX, J_{AB} 6.7, one of C(3)*H*$_2$Cl], 3.91 [1H, X of ABX, J_{AX} 4.6, C(2)*H*]}, 4.06 [1H, A of ABX, J_{AB} 6.7, J_{AX} 4.1, one of C(3)*H*$_2$Cl]; δ_C 44.4 [CH_2, *C*(3)H$_2$Cl], 54.7 [CH, *C*(2)H]; Exact mass calculated for $C_{16}H_{17}NOS^{35}Cl$ [M+H]$^+$, 306.0719 Found 306.0706 (Δ 13ppm); m/z (ES+) 306.2 [(M+H$^+$), 48%].

Isolation of the *α-chlorosulfide* was not attempted as the purpose of this experiment was the isolation of the acrylamide intermediate.

N-(4'-Methylphenyl)-2-(butylthio)propenamide 41



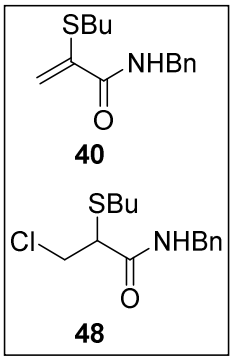
This synthesis followed the procedure described for **8** using *N*-chlorosuccinimide (0.23 g, 1.93 mmol) and *N*-(4'-methylphenyl)-2-(butylthio)propanamide **29** (0.50 g, 1.75 mmol) in tetrachloromethane (3 mL). The crude product was composed of the α-*thio*-β-*chloroacrylamide* **36** (δ_H 7.86, 1H, s), the β-*chlorosulfide* **49** (δ_H 3.64, 1H, X of ABX, *J* 4.9, 1.8), the desired *acrylamide* **41** (δ_H 5.81, 1H, s), the corresponding α-*chlorosulfide* (tentatively assigned, δ_H 2.15, 1H, s), the *dichloride* **58** (δ_H 4.40, 1H, apparent d, *J* 11.5) with ratio 1 : 0.73 : 0.62 : 0.19 : 0.23 respectively by ^{1}H NMR spectroscopy. Characteristic signal for the *s*uccinimide by-product was also present but the ratio could not be determined due to overlapping signals. The mixture was purified by successive column chromatography on silica gel using hexane : ethyl acetate as eluent (99:1) to give the desired *acrylamide* **41** (0.12 g, 87% pure, 31%) as a mixture with an unknown compound, as a yellow oil; Data for a*crylamide* **42**: δ_H (400 MHz, $CDCl_3$) 0.92 [3H, t, *J* 7.3, C(4')*H*$_3$], 1.31-1.80 [4H, m, C(3')*H*$_2$ and C(2')*H*$_2$], 2.32 (3H, s, ArC*H*$_3$), 2.75 [2H, t, *J* 7.4, C(1')*H*$_2$), 5.81, 6.61 (2H, 2 x s, C(3)*H*$_2$=), 7.09-7.21 (2H, m, Ar*H*), 7.43-7.63 (2H, m, Ar*H*), 8.66 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.6 [CH_3, *C*(4')H_3], 20.9 (CH_3, Ar*C*H_3), 21.8 [CH_2, *C*(3')H_2], 31.0 [CH_2, C(2')H_2], 34.2 [CH_2, *C*(1')H_2], 119.9 (1 x CH signals, 2 x aromatic *C*H), 127.1 [CH_2, *C*(3)H_2=], 129.7 (1 x CH signal, 2 x aromatic *C*H), 134.4 (Cq, aromatic *C*q-NH), 135.0 (Cq, aromatic *C*q-Me), 138.1 [Cq, *C*q(2)=], 162.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3322 (NH), 2957, 2928, 2867, 1652 (C=O), 1514, 814, 510; HRMS (ES+): Exact mass calculated for $C_{14}H_{20}NOS$ $[M+H]^+$, 250.1266 Found 250.1256; HPLC retention time: (Method 2) 18.1 min.

The isolation of the α-*thio*-β-*chloroacrylamide* **36** and the *dichloride* **58**, as well as their characteristic data, are described in *section 4*. and *section 5.B* respectively. Isolation of the tentatively assigned *α-chlorosulfide* and the β-*chlorosulfide* **49** were not attempted as the purpose of this experiment was the isolation of the acrylamide intermediate.

The other products formed were not isolated as this was not the main purpose of this experiment.

This batch was estimated to be 87% pure by ^{1}H NMR using the method described in the general procedure, comparing the integration of the one hydrogen signal at 5.81 ppm to the integration of the aromatic region at 7.09-7.63 ppm, which also includes the $CHCl_3$ residual signal at 7.26 ppm. The remaining material, *ca.* 13%, was **(zzx190)** but also accounted for residual $CHCl_3$ in the deuterated solvent.

N-Benzyl-2-(butylthio)propenamide 40 and *N*-benzyl-2-(butylthio)-3-chloropropanamide 48 (tentatively assigned)



This synthesis followed the procedure described for **8** using *N*-chlorosuccinimide (0.17 g, 1.31 mmol) and *N*-benzyl-2-(butylthio)propanamide **28** (0.30 g, 1.19 mmol) in tetrachloromethane (2 mL). The crude product is composed of the β-*chlorosulfide* **48** (δ_H 3.52, 1H, X of ABX, J_{AX} 7.1, J_{BX} 4.7), the desired *acrylamide* **40** (δ_H 5.66, 1H, s), the α-*thioamide* **28** (δ_H 3.43, 1H, q, *J* 7.3) and the corresponding α-*chlorosulfide* (tentatively assigned, δ_H 2.09, 3H, s), with ratio 1 : 0.80 : 0.81 : 0.10 respectively, by ^{1}H NMR spectroscopy, and was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) to give an inseparable mixture of the desired *acrylamide* **40** and the β-*chlorosulfide* **48** with ratio 0.80 : 1 respectively by ^{1}H NMR spectroscopy (0.05 g) as a colorless oil; ν_{max}/cm^{-1} 3288 (NH), 2957, 2928, 1644 (C=O), 1519, 696; Data for *acrylamide* **40**: δ_H (400 MHz, $CDCl_3$) 0.88 [3H, t, *J* 7.3, C(4')*H*$_3$], 1.29-1.45 [2H, m, C(3')*H*$_2$], 1.47-1.66 [2H, m, C(2')*H*$_2$], 2.68 [2H, t, *J* 7.5, C(1')*H*$_2$], 4.45-4.56 (2H, m, C*H*$_2$NH), 5.66, 6.50 (2H, 2 x s, C(3)*H*$_2$=), 6.90 (1H, br s, N*H*), 7.22-7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 13.6 [CH_3, *C*(4')H_3], 21.9 [CH_2, *C*(3')H_2], 30.7 [CH_2, C(2')H_2], 33.6 [CH_2, *C*(1')H_2], 44.0 (CH_2, C*H*$_2$NH), 124.5 [CH_2, *C*(3)H_2=], 127.8, 127.9, 128.8 (3 x CH, 5 x aromatic), 137.9 (Cq, aromatic *C*q), 138.0 [Cq, *C*q(2)=], 164.5 (Cq, *C*=O), 168.7 (Cq, *C*=O); HRMS (ES+): Exact mass calculated for $C_{14}H_{20}NOS$ $[M+H]^+$, 250.1266 Found

250.1260; m/z (ES+) 250.3 [(M+H$^+$), 100%]; HPLC retention time (Method 2) 11.8 min.

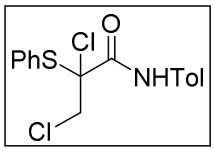
Data for β-*chlorosulfide* **48**; δ_H (400 MHz, $CDCl_3$) 0.89 [3H, t, *J* 7.3, C(4')H_3], 1.29-1.45 [2H, m, C(3')H_2], 1.47-1.66 [2H, m, C(2')H_2], 2.58 [2H, td, *J* 7.5, 2.9, C(1')H_2], 3.52 [1H, X of ABX, J_{AX} 7.1, J_{BX} 4.7, C(2)*H*], 3.90 [1H, B of ABX, J_{AB} 10.9, J_{BX} 4.7, one of C(3)H_2Cl], 4.03 [1H, A of ABX, J_{AB} 10.9, J_{AX} 7.1, one of C(3)H_2Cl], 4.45-4.56 (2H, m, CH_2NH), 7.08 (1H, br s, N*H*), 7.22-7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 13.6 [CH_3, *C*(4')H_3], 21.9 [CH_2, *C*(3')H_2], 31.4 [CH_2, C(1')H_2], 31.6 [CH_2, C(2')H_2], 44.0 (CH_2, CH_2NH), 45.0 [CH_2, *C*(3)H_2Cl], 51.2 [CH, *C*(2)H], 127.6, 127.7, 128.8 (3 x CH, 5 x aromatic *C*H), 137,8 [Cq, aromatic *C*q], 168.7 (Cq, *C*=O); m/z (ES+) 286.2 {[($C_{14}H_{21}{}^{35}ClNOS$)+H$^+$], 98%}, 288.2 {[($C_{14}H_{21}{}^{37}ClNOS$)+H$^+$], 42%.

The isolation of the α-*thio*amide **28**, as well as the characteristic data, are described in *section 3*. Isolation of the tentatively assigned *α-chlorosulfide* was not attempted as the purpose of this experiment was the isolation of the acrylamide intermediate.

B. Dichloride intermediates

In some cases, the purification of dichloride intermediates, using column chromatography or recrystallisation techniques, may result in the formation of the corresponding α-thio-β-chloroacrylamide, due to their instabilities. As a result, purification was not attempted for many of the dichlorides described below.

N-(4'-Methylphenyl)-2,3-dichloro-2-(phenylthio)propanamide 9[2,3]



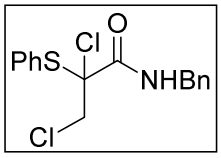
N-Chlorosuccinimide (0.32 g, 2.42 mmol) was added in one portion to a solution of *N*-(4'-methylphenyl)-2-(phenylthio)propanamide **4** (0.30 g, 1.11 mmol) in tetrachloromethane (6 mL) while stirring at room temperature under nitrogen. The mixture was stirred for 10 min at room temperature then heated to 40 ^oC and stirred at this temperature for 17 h. Evaporation of the solvent gave the crude product which is composed of the *dichloride* **9** (δ_H 3.95, 1H, apparent d, *J* 12.0), the α-*thio*-β-*chloroacrylamide* **7** (δ_H 8.04, 1H, s), the *trichloride* **60** (δ_H 6.56, 1H, s)

and the succinimide with ratio 1 : 0.52 : 0.13 : 0.80 respectively by ^{1}H NMR spectroscopy; Data for d*ichloride* **9**: δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, ArC*H*$_3$), 3.95, 4.46 (2H, ABq, *J* 12.0, C*H*$_2$Cl), 7.01-7.72 (9H, m, 9 × Ar*H*), 8.06 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 29.5 (CH_3, Ar*C*H$_3$), 50.2 (CH_2, C(3)H$_2$), 81.4 (Cq, *C*qCl), 162.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3334 (NH), 1673 (C=O), 1516, 812; HRMS (ES+): Exact mass calculated for $C_{16}H_{16}{}^{35}Cl_2NOS$ $[M+H]^+$, 340.0330; Found 340.0347; HPLC retention time: (Method 1) 22.1 min; (Method 2) 26.3 min. Characteristic signals for the α-*thio*-β-*chloroacrylamide* **7** and the *trichloride* **60** were also present.

Spectroscopic characteristics were consistent with those previously reported.[2]

The isolation of the α-*thio*-β-*chloroacrylamide* **7** and the *trichloride* **60**, as well as their characteristic data, are described in *section 4* and *section 6* respectively. Date

N-Benzyl-2,3-dichloro-2-(phenylthio)propanamide 54[2]



This synthesis followed the procedure described for **9** using *N*-chlorosuccinimide (0.32 g, 2.43 mmol) and a solution of *N*-benzyl-2-(phenylthio)propanamide **22** (0.30 g, 1.11 mmol) in tetrachloromethane (4 mL). The crude product consisted of the desired *dichloride* **54** (δ_H 3.90, 1H, apparent d, *J* 11.5), the corresponding *trichloride* (tentatively assigned, δ_H 6.56, 1H, s) and the succinimide with ratio 1 : 0.18 : 0.49 respectively, by ^{1}H NMR spectroscopy, and was purified by successive chromatography on silica gel using ethyl acetate : hexane as eluent (5:95) to give the pure *dichloride* **54** (0.21 g, 56%) as a white solid; mp 91-92 °C (Lit.,[2] 93-94 °C); (Found C, 56.24; H, 4.44; Cl, 20.82; N, 3.47; S, 9.50. $C_{16}H_{15}Cl_2NOS$ requires C, 56.48; H, 4.44; Cl, 20.84; N, 4.12; S, 9.42%); δ_H (400 MHz, $CDCl_3$) 3.90 (1H, H_A of ABq, *J* 11.5, one of C*H*$_2$Cl), 4.23-4.31 (1H, dd, $H_{A'}$ of A'B'X system, $J_{A'B'}$ 14.9, $J_{A'X}$ 5.5, one of C*H*$_2$NH), 4.39-4.49 [2H, overlapping signals, δ_B 4.42 (1H, apparent d, H_B of ABq, *J* 11.5, one of C*H*$_2$Cl), $\delta_{B'}$ 4.44 (1H, dd, $H_{B'}$ A'B'X system, $J_{A'B'}$ 14.9, $J_{B'X}$ 5.5, one of C*H*$_2$NH)], 6.84 (1H, s, N*H*), 7.15 (2H, d, *J* 7.4, Ar*H*), 7.24-7.40 (5H, m, 5 × Ar*H*), 7.47 (1H, t, *J* 7.4, Ar*H*), 7.60 (2H, d, *J* 7.5, 2 × Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.6 (CH_2, NH*C*H$_2$), 50.5 (CH_2, *C*H$_2$Cl), 81.5 [Cq, *C*(2)Cl], 127.7, 127.8 (2 x CH signal, 3 x aromatic *C*H), 128.0 (Cq, aromatic *C*q), 128.8, 129.2, 130.9 (3 x CH signals, 5 x aromatic *C*H),

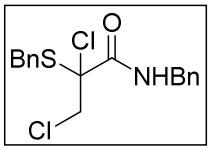
136.8 (Cq, aromatic *C*q), 137.4 (1 x CH signal, 2 x aromatic *C*H), 164.9 (Cq, *C*=O); ν_{max}/cm^{-1} 3307 (NH), 1666 (C=O), 1530, 687; HPLC retention time: (Method 2) 18.2 min; HRMS (ES+): Exact mass calculated for $C_{16}H_{16}{}^{35}Cl_2NOS$ $[M+H]^+$, 340.0330; Found 340.0258.

HPLC analysis was carried out on a separate sample of the dichloride 2 from another batch; this batch was estimated to be 95% pure by ^1H NMR using the method described in the general procedure, comparing the integration of the one hydrogen signal at 3.90 ppm to the integration of the aromatic region at 7.10-7.63 ppm, which also includes the $CHCl_3$ residual signal at 7.26 ppm. The remaining material, *ca.* 5%, was unidentified product(s) but also accounted for residual $CHCl_3$ in the deuterated solvent.

Spectroscopic characteristics were consistent with those previously reported.[2]

Isolation of the tentatively assigned *trichloride* was not attempted as the purpose of this experiment was the isolation of the dichloride intermediate.

N-Benzyl-2,3-dichloro-2-(benzylthio)propanamide 55



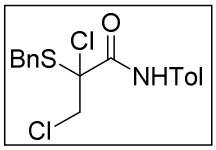
N-Chlorosuccinimide (0.15 g, 1.15 mmol) was added in one portion to a solution of *N*-(4'-methylphenyl)-2-(phenylthio)propanamide **25** (0.15 g, 0.52 mmol) in tetrachloromethane (2 mL) while stirring at room temperature under nitrogen. The mixture was stirred for 7 h at room temperature. Evaporation of the solvent gave the crude product which by ^1H NMR consisted of the *dichloride* **55** (δ_H 3.74, 1H, apparent d, *J* 11.5), the *acrylamide* **39** (δ_H 5.60, 1H, s), and the α-*thio*-β-*chloroacrylamide* **26** (δ_H 7.86, 1H, s), with ratio 1 : 0.33 : 0.09 respectively; Characteristic data for *dichloride* **55**: δ_H (400 MHz, $CDCl_3$) 3.74 (1H, H_A of ABq, *J* 11.5, one of C*H*$_2$Cl), 3.94 (2H, ABq, J_{AB} 12.3, $\Delta\delta_{AB}$ 0.03, SC*H*$_2$), 4.21 (1H, H_B of ABq, *J* 11.5, one of C*H*$_2$Cl), 4.27-4.50 (2H, m, NHC*H*$_2$), 6.89-7.59 [11H, m, can be distinguished 7.02 (1H, br s, N*H*), 7.06-7.33 (10H, m, 10 × Ar*H*)]; δ_C (75 MHz, $CDCl_3$) 36.7 (CH_2, SH*C*H$_2$), 44.7 (CH_2, NH*C*H$_2$), 50.7 (CH_2, *C*H$_2$Cl), 79.0 [Cq, *C*(2)Cl], 126.9, 128.2, 128.4, 128.5, 128.9, 129.4 (6 x CH signals, 10 x aromatic *C*H), 135.3, 137.1 (2 x Cq, 2 x aromatic *C*q), 165.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3332 (NH), 3062, 3030, 2930,

1661 (C=O), 1515, 1453, 695; HRMS (ES+): Exact mass calculated for $C_{17}H_{17}{}^{35}Cl_2NOS$ $[M+H]^+$, 354.0486 Found 354.0482; HPLC retention time: (Method 2) 25.2 min. Characteristic signals for the α-*thio*-β-*chloroacrylamide* **26** and the *acrylamide* **39** were also present.

HPLC analysis was carried out on a separate sample of the *dichloride* **55** from another batch; this batch was estimated to be 71% pure by ^{1}H NMR using the method described in the general procedure, comparing the integration of the one hydrogen signal at 4.21 ppm to the integration of the aromatic region at 7.67-7.82 ppm, which also includes the $CHCl_3$ residual signal at 7.26 ppm. The remaining material, *ca.* 29%, was unidentified product(s) but also accounted for residual $CHCl_3$ in the deuterated solvent.

The isolation of the α-*thio*-β-*chloroacrylamide* **26** and the *acrylamide* **39**, as well as their characteristic datas, are described in *section 4.* and *section 5.A* respectively.

N-(4'-Methylphenyl)-2,3-dichloro-2-(benzylthio)propanamide 56



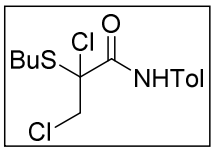
This synthesis followed the procedure described for **55** using *N*-chlorosuccinimide (0.15 g, 1.15 mmol) and *N*-(4'-methylphenyl)-2-(benzylthio)propanamide **27** (0.15 g, 0.52 mmol) in tetrachloromethane (2 mL). Evaporation of the solvent gave the crude product which contain the *dichloride* **56** (δ_H 4.28, 1H, H_B of ABq, *J* 11.5) and the corresponding *trichloride* (tentatively assigned, δ_H 6.44, s), with ratio 1 : 0.18 respectively by ^{1}H NMR spectroscopy; Characteristic data for d*ichloride* **56**: δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, C*H*$_3$), 3.85 (1H, H_A of ABq, *J* 11.5, one of C*H*$_2$Cl), 4.00 (2H, m, C*H*$_2$S), 4.28 (1H, H_B of ABq, *J* 11.5, one of C*H*$_2$Cl), 6.95-7.50 (9H, m, 9 × Ar*H*), 8.41 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3, Ar*C*H_3), 36.9 (CH_2, S*C*H_2), 50.6 (CH_2, *C*H_2Cl), 79.2 [Cq, *C*(2)Cl], 163.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3330 (NH), 2981, 2922, 1681 (C=O), 1517, 697; m/z (ES+) 376.3 [($C_{17}H_{17}{}^{35}Cl_2NOS+Na^+$), 18%]; HPLC retention time: (Method 2) 28.6 min.

HPLC analysis was carried out on a separate sample of the *dichloride* **56** from another batch; this batch was estimated to be 75% pure by ^{1}H NMR using the

method described in the general procedure, comparing the integration of the one hydrogen signal at 4.28 ppm to the integration of the aromatic region at 6.95-7.52 ppm, which also includes the $CHCl_3$ residual signal at 7.26 ppm. The remaining material, *ca.* 25%, was unidentified product(s) but also accounted for residual $CHCl_3$ in the deuterated solvent.

Isolation of the tentatively assigned *trichloride* was not attempted as the purpose of this experiment was the isolation of the dichloride intermediate.

N-(4'-Methylphenyl)-2,3-dichloro-2-(butylthio)propanamide 58

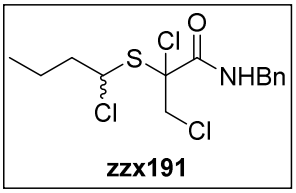


This synthesis followed the procedure described for **55** using *N*-chlorosuccinimide (0.35 g, 2.34 mmol) and *N*-(4'-methylphenyl)-2-(butyllthio)propanamide **29** (0.30 g, 1.07 mmol) in tetrachloromethane (4 mL). Filtration and evaporation of the solvent from the filtrate gave the crude product which contains the *dichloride* **58** (δ_H 4.02, 1H, apparent d, *J* 11.5), the α-*thio*-β-*chloroacrylamide* **36** (δ_H 7.87, 1H, s) and the corresponding *trichloride* (tentatively assigned, δ_H 6.52, 1H, s) with ratio 1 : 0.93 : 0.42 respectively by ^{1}H NMR spectroscopy; Characteristic data for *dichloride* **58**: δ_H (400 MHz, $CDCl_3$) 0.86-0.98 [3H, m, C(4')*H*$_3$], 1.34-1.52 [2H, m, C(3')*H*$_2$], 1.52-1.69 [2H, m, C(2')*H*$_2$], 2.33 (3H, s, ArC*H*$_3$), 2.79 [2H, t, *J* 7.6, C(1')*H*$_2$), 4.02, 4.40 (2H, ABq, *J* 11.5, C*H*$_2$Cl), 7.12-7.20 (2H, m, Ar*H*), 7.40-7.51 (2H, m, Ar*H*), 8.53 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.6 [CH_3, *C*(4')H_3], 20.9 (3H, s, ArC*H*$_3$), 21.8 [CH_2, C(3')H_2], 31.7 [CH_2, *C*(2')H_2], 34.4 [CH_2, *C*(1')H_2], 50.4 (CH_2, *C*H_2Cl), 79.8 [Cq, *C*(2)Cl], 119.7 (1 x CH signal, 2 x aromatic *C*H), 129.6 (1 x CH signal, 2 x aromatic *C*H), 134.7, 138.9 (2 x Cq, 2 × aromatic *C*q), 161.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3331 (NH), 1673 (C=O); HPLC retention time: (Method 2) 27 min; HRMS (ES+): Exact mass calculated for $C_{14}H_{20}{}^{35}Cl_2NOS$ $[M+H]^+$, 320.0643 Found 320.0648; m/z (ES-) 318.0 [(M-H$^+$), 10%]. Characteristic signals for the α-*thio*-β-*chloroacrylamide* **36** and the tentatively assigned *trichloride* were also present.

Isolation of the tentatively assigned *trichloride* was not attempted as the purpose of this experiment was the isolation of the dichloride intermediate. Isolation of

the α-*thio*-β-*chloroacrylamide* **36**, as well as the characteristic data, are described in *section 4*.

N-Benzyl-2,3-dichloro-2-((1-chlorobutyl)thio)propanamide 59

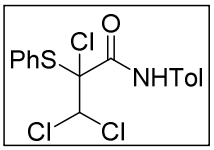


This synthesis followed the procedure described for **55** using *N*-chlorosuccinimide (0.44 g, 2.20 mmol) and *N*-benzyl-2-(butylthio)propanamide **28** (0.30 g, 1.00 mmol) in tetrachloromethane (3 ml) at room temperature. Evaporation of the solvent from the filtrate gave the crude product which by ^{1}H NMR spectroscopy consisted of a mixture of the two diastereoisomers of the *dichloride* **59** with ratio 1 : 0.55, as the main product formed; δ_H (400 MHz, $CDCl_3$) 0.86-0.99 [4.6H, m, C(4')*H*$_3$ of both diastereoisomers], 1.44-1.62 [3.1H, m, C(3')*H*$_2$ of both diastereoisomers], 1.90-2.06 [3.1H, m, C(2')*H*$_2$ of both diastereoisomers], 3.99 (1H, H_A of ABq, *J* 11.4, one of C*H*$_2$Cl of one diastereoisomer), 4.26 (0.6H, H_A of ABq, *J* 11.7, one of C*H*$_2$Cl of one diastereoisomer), 4.40-4.62 [3.7H, m, C*H*$_2$Ph of both diastereoisomers, can be distinguished 4.46 (0.6H, H_B of ABq, *J* 11.7, one of C*H*$_2$Cl of one diastereoisomer)], 4.66 (1H, H_B of ABq, *J* 11.4, one of C*H*$_2$Cl of one diastereoisomer), 5.38 [0.6H, t, *J* 6.6, ClC(1')*H* of one diastereoisomer], 5.58 [1H, t, *J* 6.9, ClC(1')*H* of one diastereoisomer], 7.70-7.48 [9.6H, m, Ar*H* of both diastereoisomers, can be distinguished 7.11 (0.6H, br s, N*H* of one diastereoisomer) and 7.17 (1H, br s, N*H* of one diastereoisomer)]; δ_C (100 MHz, $CDCl_3$) 13.2 [CH_3, *C*(4')H_3 of both diastereoisomers], 19.8 [CH_2, *C*(3')H_2 of both diastereoisomers], 41.0 [CH_2, *C*(2')H_2 of one diastereoisomer], 41.2 [CH_2, *C*(2')H_2 of one diastereoisomer], 44.8 (CH_2, NH*C*H_2 of one diastereoisomer), 45.1 (CH_2, NH*C*H_2 of one diastereoisomer), 50.8 (CH_2, *C*H_2Cl of one diastereoisomer), 51.1 (CH_2, *C*H_2Cl of one diastereoisomer), 66.3 [CH, Cl*C*(1')H of one diastereoisomer], 66.8 [CH, Cl*C*(1')H of one diastereoisomer], 76.1 [Cq, *C*(2)Cl of one diastereoisomer], 79.2 [Cq, *C*(2)Cl of one diastereoisomer], 127.7, 127.8, 127.9, 128.0, 128.8, 128.9 (6 x CH, 10 x aromatic *C*H of both diastereoisomers), 136.8 (Cq, aromatic *C*q of one diastereoisomer), 136.9 (Cq, aromatic *C*q of one diastereoisomer), 164.7 (Cq, *C*=O of one diastereoisomer), 165.3 (Cq, *C*=O of one diastereoisomer); ν_{max}/cm^{-1} 3347 (NH),

2963, 2933, 1667 (C=O), 1518, 784, 754; HRMS (ES+): Exact mass calculated for $C_{14}H_{18}{}^{35}Cl_3NOS$ $[M+H]^+$, 354.0247 Found 354.0289 (Δ 42ppm).

6. SYNTHESIS OF OVER-CHLORINATION PRODUCTS

N-(4'-Methylphenyl)-2,3,3-trichloro-2-(phenylthio)propanamide 60[3]

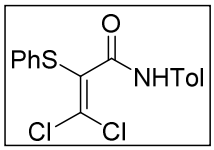


N-Chlorosuccinimide (0.34 g, 2.34 mmol) was added in one portion to a solution of *N*-(4'-methylphenyl)-*Z*-3-chloro-2-(phenylthio)propanamide **7** (0.20 g, 1.32 mmol) in tetrachloromethane (3 mL) while stirring at room temperature under nitrogen. The mixture was stirred at this temperature for 5 h. Filtration and evaporation of the solvent from the filtrate gave the crude product which consist of the *trichloride* **60** (δ_H 6.56, 1H, s), the *dichloroacrylamide* **61** (δ_H 2.26-2.34, 3H, m, overlapped 2 x s)* and the α-*thio*-β-*chloroacrylamide* **7** (δ_H 8.04, 1H, s) with ratio of 0.18 : 0.23 : 1 respectively by ^{1}H NMR spectroscopy; *Trichloride* **60** signals: δ_H (400 MHz, $CDCl_3$) 2.65 (3H, s, C*H*$_3$), 6.56 [1H, s, C(3)*H*], 6.89-7.29 (9H, m, 9 × Ar*H*), 7.79 (1H, br s, N*H*); HPLC retention time: (Method 2) 33.0 min. Characteristic signals for the *dichloroacrylamide* **61** and the α-*thio*-β-*chloroacrylamide* **7** were also present.

* The ratio of the *dichloroacrylamide* **61** was calculating from the integration of the region at 2.26-2.34 ppm, which also includes 3H/molecule of the α-*thio*-β-*chloroacrylamide* **7**. According to the integration of the s at δ_H 2.29 ppm, representing 3H/molecule of **7**, the corresponding integration attributed to the **61** can be determined.

The purification of the *trichloride* **60** resulted in the full conversion of the trichloride into the *dichloroacrylamide* **61**. The isolation of the α-*thio*-β-*chloroacrylamide* **7** and the *dichloroacrylamide* **61**, as well as the characteristic datas, are described in *section 4.* and in this section respectively.

N-(4'-Methylphenyl)-2-(phenylthio)-3,3-dichloropropenamide 61[3]



N-Chlorosuccinimide (0.22 g, 1.62 mmol) was added in one portion to a solution of *N*-(4'-methylphenyl)-*Z*-3-chloro-2-(phenylthio)propanamide **7** (0.20 g, 0.65 mmol) in toluene (6 mL). The flask was immediately immersed in an oil bath at 90 °C while stirring, under nitrogen, and stirred at this temperature for 5 h. Then the reaction mixture was cooled to 0 °C. The succinimide by-product was removed by filtration and the solvent was evaporated from the filtrate. The crude product consisted of the *trichloride* **60** (δ_H 6.56, 1H, s), the *dichloroacrylamide* **61** (δ_H 2.26-2.34, 3H, m, overlapped 2 x s)* and the α-*thio*-β-*chloroacrylamide* **7** (δ_H 8.04, 1H, s) with a ratio of 0.13 : 0.34 : 1 respectively by ^{1}H NMR spectroscopy. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (99:1) to give the pure *dichloroacrylamide* **61** (43 mg, 20%) as a white solid; mp 128-130 °C; (Found C, 56.75; H, 3.99; N, 4.00; S, 9.16; Cl; 20.63. $C_{16}H_{13}Cl_2NOS$ requires C, 56.82; H, 3.87; N, 4.14; S, 9.48; Cl, 20.96%); δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, C*H*$_3$), 7.02-7.10 (4H, m, apparent q, 4 × Ar*H*), 7.28-7.34 (3H, m, 3 × Ar*H*), 7.40-7.51 (3H, m, N*H* and 2 x Ar*H*, N*H* could be distinguished as a br. singlet at 7.44 ppm); δ_C (100 MHz, $CDCl_3$) 20.9 (CH_3, Ar*C*H$_3$), 120.4 (1 x CH signal, 2 x aromatic *C*H), 125.2 [Cq, *C*q(2)= or *C*q(3)=], 128.9, 129.5 (2 x CH, 5 x aromatic *C*H), 130.5 (Cq, aromatic *C*q), 131.0 [Cq, *C*q(2)= or *C*q(3)=], 132.2 (1 x CH signal, 2 x aromatic *C*H), 133.9, 135.0 (2 x Cq, 2 x *C*q aromatic), 160.0 (Cq, *C*=O); ν_{max}/cm^{-1} 3244 (NH), 2920, 1647 (C=O), 1508, 812, 748, 689; HRMS (ES+): Exact mass calculated for $C_{16}H_{14}{}^{35}Cl_2NOS$ $[M+H]^+$, 338.0173 Found 338.0169; m/z (ES+) 338.1 {[($C_{16}H_{15}{}^{35}Cl_2NOS$)+$H^+$], 33%}, 340.1 {[($C_{16}H_{15}{}^{37}Cl^{35}ClNOS$)+$H^+$], 22%}, 342.1 {[($C_{16}H_{15}{}^{37}Cl_2NOS$)+$H^+$], 4%}; HPLC retention time: (Method 2) 18.3 min.

* The ratio of the *dichloroacrylamide* **61** was calculating from the integration of the region at 2.26-2.34 ppm, which also includes 3H/molecule of the α-*thio*-β-*chloroacrylamide* **7**. According to the integration of the s at δ_H 2.29 ppm, representing 3H/molecule of **7**, the corresponding integration attributed to the **61** can be determined.

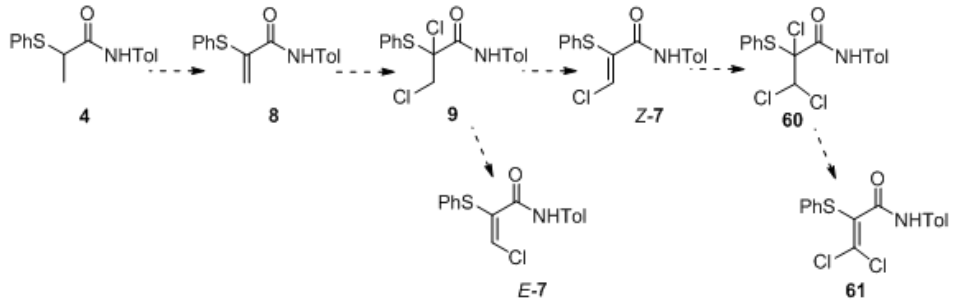
HPLC analysis were carried out on a separate sample of another batch of product which was pure by ^{1}H NMR.

7. CONTINUOUS FLOW SETUP

A. HPLC conditions

The HPLC method 2 described in General Procedure was used for optimisation of the α-thio-β-chloroacrylamide **7** cascade in flow. The retention times for key components of the α-thio-β-chloroacrylamide **7** cascade reaction by HPLC is summarised in Table 1.

Table 1 Retention times for key components of the α-thio-β-chloroacrylamide cascade reaction by HPLC method 2[a]



	4	**8**	**9**	***Z*-7**	***E*-7**	**60**[b]	**61**
Retention times (min)	12.2	14.9	26.3	20.0	13.1	33.0	18.3

[a] Chromatography was carried out using a YMC-Pack ODS-A reverse phase column (250 mm x 4.6 mm, 5 µm) with a flow rate of 0.8 mL/min. Samples were injected (5 µL) by the autosampler and were detected by UV absorbance at 250 nm and by a 385-ELSD evaporative light scattering detector (LC-ELSD).

[b] The structure of the labile compound **60** has been tentatively assigned based on comparison with related derivatives by ^{1}H NMR spectroscopy of a mixture which also contained significant amounts of **7**, **9** and **61**.

Relative response factors for key components of the α-thio-β-chloroacrylamide **7** cascade reaction were determined using calibration curves summarized in Table 2 (Details included in Annexes).

Table 2 Relative response factors at 250 nm for key components of the α-thio-β-chloroacrylamide cascade reaction by HPLC method[a].

Component	Relative Response Factor[a] at 250 nm
4	1
8	4.41
Z-**7**	5.45
9/**60**	1[b]
E-**7**[3]	5.93

[a] Determined using calibration curves.

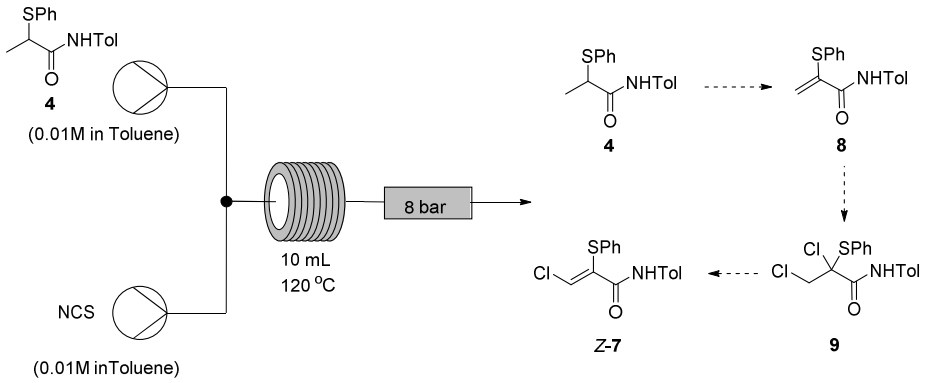
[b] As the compounds **60** and **9** could not be isolated, their relative response factors were estimated to give the same response as *α-thioamide* **4**, based on a similar level of conjugation.

B. Initial Flow Process

Preparation of α-Thio-β-chloroacrylamide *Z*-**7** in Continuous Flow

The product ratio in Table 3 was determined by weighting the peak areas generated against the relative response factors of the compounds under investigation at 250 nm.

Table 3 Initial flow process for conversion of **4** to *Z*-**7** using toluene as solvent



Entry	Ratio **4** : NCS[a]	Residence Time (min)	Product Ratio (%)[b]			
			4	**8**	**9**	*Z*-**7**
1	1 : 2	20	19	15	18	47
2	1 : 2	50	21	19	0	60
3	1 : 2.3	20	22	8	20	49
4	1 : 3	20	25	1	12	62
5	1 : 1	20	21	77	<1	2

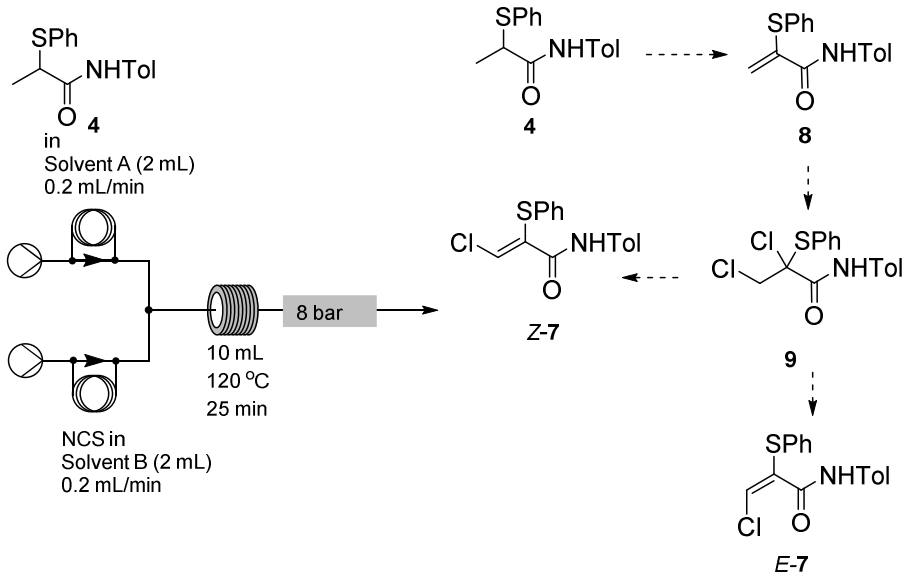
[a] Stoichiometric ratio of α-thioamide **4** : NCS controlled by manipulating the relative flow rates.
[b] Ratio determined by HPLC analysis (peak area weighted for relative response factors of each component) of samples taken directly from flow reactor as effluent solutions and diluted in MeCN prior to analysis.

α-*Thioamide* **4** solution (0.01M in toluene) was pumped into a T-piece where it met *N*-chlorosuccinimide solution (0.01M in toluene). The combined stream was then passed through a PFA coil reactor (10 mL) which was heated to 120 °C. The flow rates were adjusted to facilitate the residence time and the desired stoichiometry. The product stream passed through a back pressure regulator (8 bar) before exiting the reactor. Reactor effluents were collected in a round bottom

flask and then concentrated under reduced pressure to remove the solvent. The resulting crude mixture was diluted in MeCN prior to HPLC analysis.

C. Solvent Screen

Table 4 Solvent screen for conversion of **4** to *Z*-**7** in continuous mode



Entry	[**4**] (mM)	[NCS] (mM)	Solvent A/B	Product Ratio[a]				
				4	**8**	**9**	*Z*-**7**	*E*-**7**
1	25	50	Tol/Tol	0	10	10	79	1
2	25	50	Tol/MeCN	0	4	0	82	14
3	25	50	MeCN/MeCN	0	0	0	87	13
4	200	400	Tol/MeCN	0	7	0	84	9
5	200	400	MeCN/MeCN	0	0	0	88	12

[a]Determined by ^{1}H NMR spectroscopy.

A solution of α-*thioamide* **4** (50 or 400 mmol) in solvent A (2 mL) was prepared. A solution of NCS (100 or 800 mmol) in solvent B (2 mL) was also prepared. The reagent solutions were injected into flowing streams (0.2 mL/min each) of solvent A or B. After the reagent solutions combined, they were passed into a PFA coil reactor (10 mL) which was heated to 120 °C for 25 min before passing through a

back pressure regulator (8 bar) and exiting the reactor. A sample of the reactor output was collected and the solvent removed by evaporation under reduced pressure. The sample was subsequently dissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy. The relative proportions of α-*thioamide* **4**, *acrylamide* **8**, *dichloride* **9** and α-*thio*-β-c*hloroacrylamide*s *Z*-**7** and *E*-**7** were measured based on the integrals of their characteristic signals.

8. REFERENCES

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CHAPTER 3

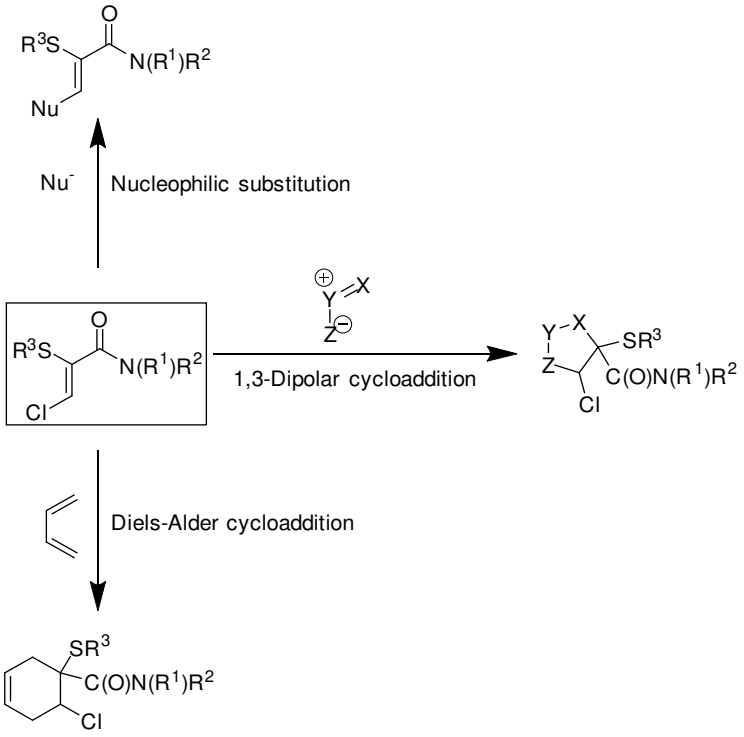
Synthesis of Functionalised α-Thio-β-chloroacrylamides and Application in Formation of Heterocyclic Derivatives

Table of Contents

1. BACKGROUND

α-Thio-β-chloroacrylamides (Scheme 1) provide a highly-functionalised class of compounds that are strongly reactive due to the electronic influence of their substituents. The β-carbon possesses an overall electrophilic character thanks to the electron withdrawing effect of the amide and chloro groups, despite the electron density donated by the sulfide group through delocalized conjugation.

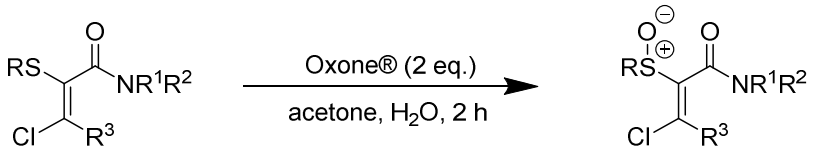
Consequently, these compounds have enormous potential in organic synthesis as dienophiles in Diels-Alder cycloadditions,[1] dipolarophiles in 1,3-dipolar cycloadditions[2-4] and Michael acceptors in nucleophilic substitutions[5] (Scheme 1).



Scheme 1

The sulfide group of α-thio-β-chloroacrylamides can be oxidized to give the sulfoxide or sulfone derivatives (Scheme 2).[6-8] The reactivity of these compounds towards nucleophiles is enhanced, due to a decrease in the extent of resonance electron donation by sulfur onto the electrophilic β-carbon through the

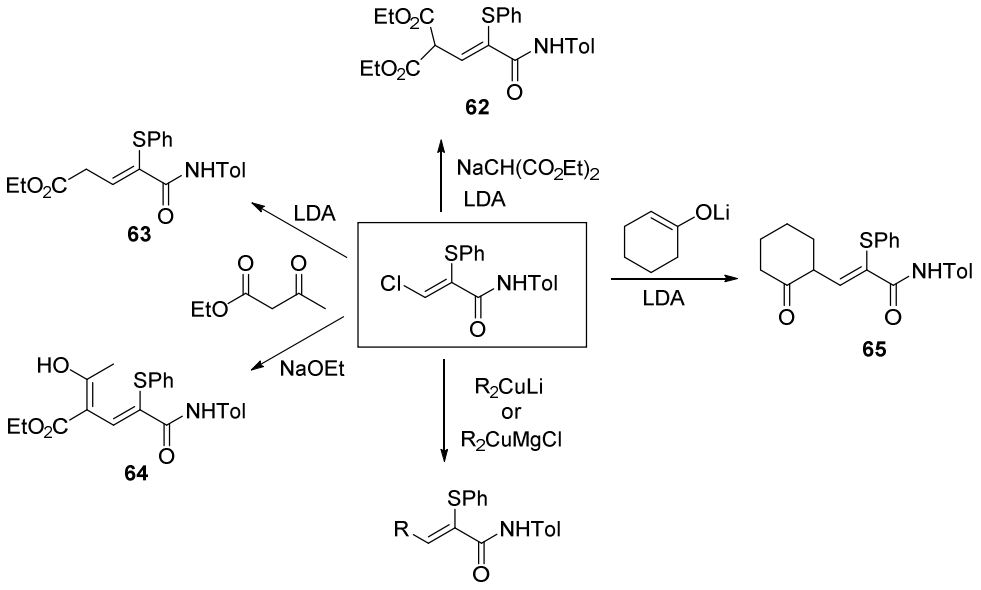
unsaturation system and to an enhanced electronegativity of the sulfoxide and sulfone moiety.



Scheme 2

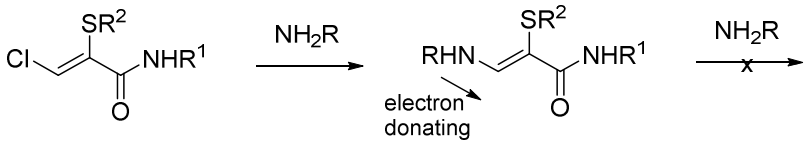
α-Thio-β-chloroacrylamides, at the sulfide, sulfoxide and sulfone oxidation levels, act as Michael acceptors and easily undergo substitution reactions with carbon-, nitrogen-, oxygen-, sulfur-, and selenium-based nucleophiles.[5, 9] This high reactivity enables simple extension of the carbon framework and introduction of different functional groups at the β-position.

Substitution at the β-position occurs using carbon nucleophiles ranging from stabilized enolates to more reactive anionic species (Scheme 3).[5] Addition of carbon nucleophiles proceeds with modest yields, in most instances, but with excellent retention of stereochemistry. Nucleophilic addition of the enolate of diethyl malonate yielded the malonate substituted product **62**, while employing the enolate of ethyl acetoacetate yielded products that were strongly dependent on the nature of the basic conditions used. When the enolate of ethyl acetoacetate was generated with sodium ethoxide, a nucleophilic reaction gave the substituted product **64**, while, using LDA, following a retro Claisen-type cleavage of the acetyl group, the deacylated product **63** was afforded. Nucleophilic addition was also observed with the less stabilized enolate of cyclohexanone as carbon nucleophile giving **65**. O'Brien has also explored nucleophilic substitution of α-thio-β-chloroacrylamides with a wide range of organocopper reagents.[5,10]



Scheme 3

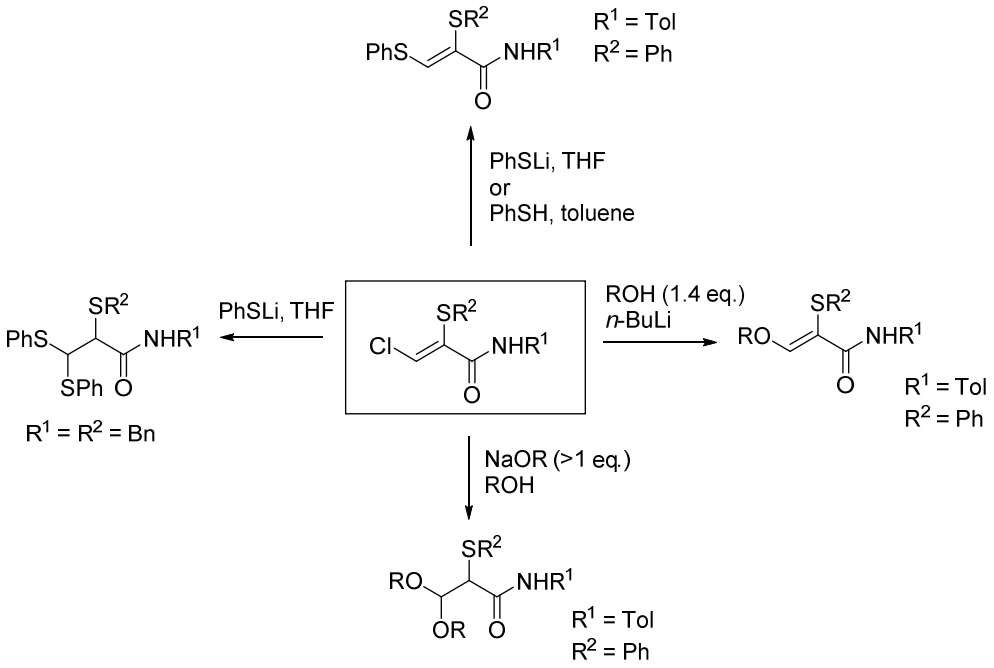
In the case of nitrogen nucleophiles, only the monosubstituted product is formed.[5] Indeed, the addition of a second equivalent of amine to the nitrogen-substituted acrylamide adducts should be disfavored as delocalization of the nitrogen lone pair significantly reduces the electrophilicity of the β-carbon (Scheme 4).



Scheme 4

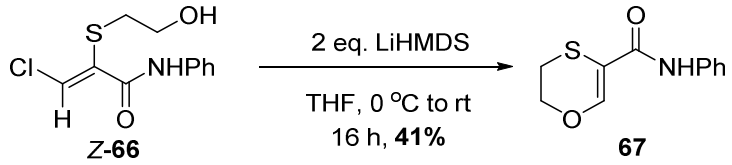
Primary and secondary amines act as very effective nucleophiles. The *E* : *Z* ratio of the product depends on the substituents and the level of sulfur oxidation, in the α-thio-β-chloroacrylamide substrate system and uniquely in this work reflects thermodynamic ratios. Chopra explored the reactivity of the sulfoxide derivatives with nitrogen-based nucleophiles, reporting that the stereochemistry of the product was strongly dependent on the nature of the amine employed as the nucleophile.[11]

In contrast, oxygen and sulfur nucleophiles can undergo a second addition since the electrophilicity of the β-carbon is enhanced by the strongly inductive electron withdrawing effect of the oxygen substituent (Scheme 5).[5]



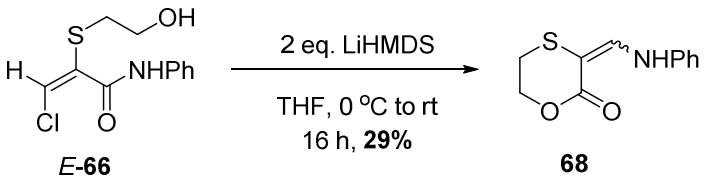
Scheme 5

A preliminary investigation by Murphy showed that α-thio-β-chloroacrylamide *Z*-**66** can also undergo intramolecular substitution by an oxygen based nucleophile, leading to the oxathiin derivative **67** (Scheme 6).[5]



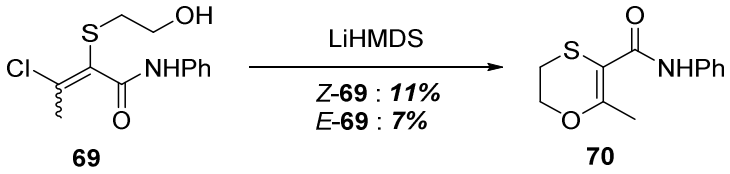
Scheme 6

Murphy[5,9] found LiHMDS to be the best choice of base for performing this reaction, with a yield of 41%. However, only the *Z*-isomer of **66** yields the oxathiin **67**. The *E*-isomer leads solely to the oxathianone **68** (Scheme 7), presumably by nucleophilic displacement of anilide by the alkoxide, followed by nucleophilic substitution of chloride by the displaced aniline, thus formation of **67** was not observed. The oxathianone **68** was isolated as a single isomer, but the stereochemistry was not determined.[9]



Scheme 7

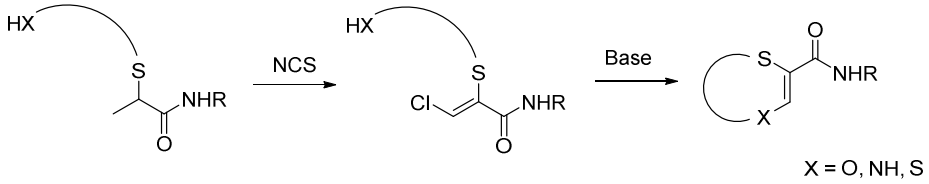
Also, the conditions developed by Murphy (LiHMDS 2 eq., THF, 0 °C to rt) transformed the α-thio-β-chlorobutenamides *E*-**69** to oxathiin **70** in just 7% yield while the *Z*-**69** gave 11% yield (Scheme 8).[5,9]



Scheme 8

Based on the information gained from intermolecular nucleophilic substitution employing various nucleophiles, investigation to include intramolecular oxygen, nitrogen and sulfur based nucleophilic substitution was targeted.

In this project, extension of the scope of the transformation was explored. Investigation of intramolecular substitution involved preparation of α-thioamides in which the sulfur substituent bears a hydroxy, amino or thiol group which can act as an internal nucleophile. This approach offers an innovative route to oxathiin, thiazine and dithiin compounds using highly functionalised α-thio-β-chloroacrylamides (Scheme 9).



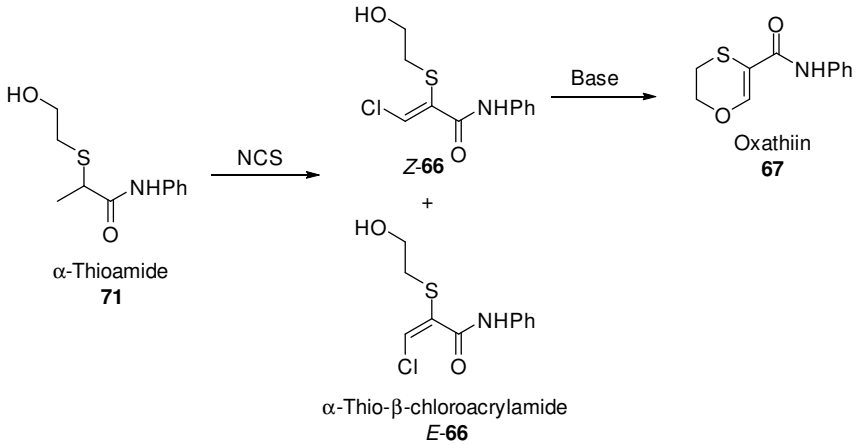
Scheme 9

The objectives of this research are:

- To optimise the synthesis of oxathiin derivatives developed by Murphy and to bring this early observation to a synthetically useful process.
- To extend the scope of the reaction to include the synthesis of thiazine, benzothiazine and dithiin derivatives from the appropriate α-thio-β-chloroacrylamides.
- To design the precursors and to develop effective routes and protecting group strategy as a key feature of this work.
- To functionalize thiazines synthesised to generate new thiomorpholine derivatives.
- To evaluate the biological activity of the heterocycles synthesised.

2. OXATHIIN SYNTHESIS

Murphy investigated the synthesis of the functionalised α-thio-β-chloroacrylamide *Z*-**66**, from α-thioamide **71**, in order to yield oxathiin **67** *via* intramolecular oxygen based nucleophilic substitution (Scheme 10).[5,9] Given the low stereoselectivity reported by Murphy during the synthesis of *Z*-**66** and the overall low yield for the oxathiin synthesis, optimisation of each steps of the reaction sequence was required.



Scheme 10

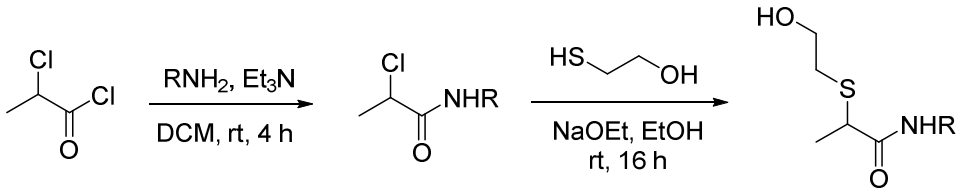
A. Synthesis of α-thio-β-chloroacrylamides

1. Synthesis of α-thioamides

The α-chloroamides **17** and **19** were prepared using the protocol described in *Chapter 2, Section 2.A.*, using 1 equivalent of the corresponding amine and 1 equivalent of triethylamine in dichloromethane (Table 1). No further purification was required before the products could be used in subsequent reactions.

Synthesis of the corresponding α-thioamides **71** and **72** was achieved using 1.2 equivalents of mercaptoethanol with 1.2 equivalents of sodium ethoxide in ethanol, as previously described in *Chapter 2, Section 2.B*. The α-thioamide **71** did not require further purification before subsequent use, leading to the pure product with a high yield, while the α-thioamide **72** was purified using chromatography on silica gel.

Table 1 Preparation of the α-thioamides **71** and **72**



	α-Chloroamide		α-Thioamide	
R	Compound	Yield (%)	Compound	Yield (%)
Ph	**17**[12]	98[a]	**71**[9]	93[a]
Bn	**19**[12]	97[a]	**72**	70[b]

[a] Yield of the isolated crude product which required no further purification.
[b] Yield of the pure product isolated after chromatography on silica gel.

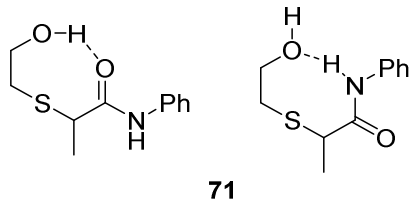
Compounds **17**, **19** were obtained in better yield than previously reported in the group (*cf. Chapter 2. Section 2.A.*).[12] Significantly increased yield was obtained for **71** compared to that previously reported (67%).[9] The novel α-thioamide **72** was isolated in good yield after chromatography on silica gel.

2. Synthesis of α-thio-β-chloroacrylamides

The synthesis of *E*- and *Z*-α-hydroxyethyl-thio-β-chloroacrylamides **66** was previously performed by Murphy (Entry 1, Table 2).[9, 13] Murphy reported the formation of both the *E*- and *Z*- isomer and that these could be separated by column chromatography, with the *Z*-isomer as the main product, though formed in 33% yield and the *E*-isomer in 12% yield.

We reported previously that extension of the main carbon chain (butanamide derivatives) or the presence of a tertiary amide are responsible for decreasing the stereoselectivity of the transformation from α-thioamide to α-thio-β-chloroacrylamide leading to formation of both isomers (*cf. Chapter 2, Section 1. Schemes 8 and 9 and Figure 6*).[14]

However, the *N*-phenyl-2-[2'-(hydroxyethyl)thio]propanamide **71** produced both the *E* and *Z* isomers without the influence of either of these features. In the case of this derivative, intramolecular hydrogen bonding between the hydroxyl and the amide group can be envisaged, thereby altering the conformation of the compound (Figure 1).



71

Figure 1

This intramolecular hydrogen bonding, between the hydroxyl and the amide group (Figure 1), would compete with the intramolecular hydrogen bonding between the sulfur and the amide group (Figure 2), which is believed to be responsible for the stereoselectivity.

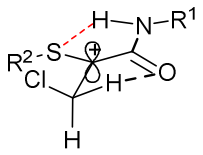
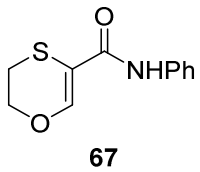


Figure 2

Therefore, this new intramolecular hydrogen bonding (Figure 1) may result in a change of conformation in the transition state of the sulfur stabilized carbocation leading to the α-thio-β-chloroacrylamide.

Considering that only *Z*-**66** was reported by Murphy[5,9] to lead to the formation of the desired oxathiin derivative **67** (Figure 3), increasing the stereoselectivity of the transformation generating the α-thio-β-chloroacrylamide was advantageous in order to increase the overall yield of the synthesis (Table 2).



67

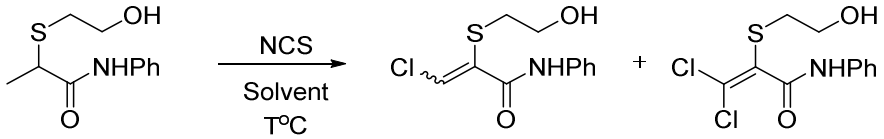
Figure 3 Target product

The optimal conditions described in *Chapter 2, Section 2.C* for the synthesis of α-thio-β-chloroacrylamides gave the product *Z*-**66** with low yield (Entry 2, Table 2), due to the large proportion of *E*-isomer formed (1 : 0.39, *Z* : *E* ratio). In addition, formation of the over-chlorinated product, dichloroacrylamide **73**, was observed in the ^{1}H NMR spectra of the partially isolated product, co-eluting with *Z*-**66** upon column chromatography.

The use of acetonitrile instead of toluene as reaction solvent (Entries 3 to 5, Table 2) significantly improved the stereoselectivity of the reaction with an increase in the ratio of *Z* : *E* isomers from 1 : 0.39 to 1 : 0.05 (Entry 3, Table 2) with a significant increase in the isolated yield of the *Z* product. This was directly in contrast with the results observed for the α-thio-β-chloroacrylamide **7** (*cf. Chapter 2, Section 5.B.*) in which the stereoselectivity decreased by the use of acetonitrile instead of toluene as solvent for the transformation. This stereoselectivity afforded by the substitution of the solvent could be explained by the high polarity of the

acetonitrile compared to toluene. By using a polar solvent, the hydrogen bonding between the hydroxyl group and the solvent compete with the hydrogen bonding between the hydroxyl and amide groups. This allows hydrogen bonding to occur between sulfur and the amide group, enhancing stereoselectivity.

Table 2 Optimisation of preparation of α-thio-β-chloroacrylamide **66**



71 **66** **73**

Entry	Solvent	NCS (eq.)	Reaction time	T (°C)	Ratio[a] *Z*-**66** : *E*-**66** : **73**	Ratio[b] *Z*-**66** : **73**	Yield (%)[c] mixture *Z*-**66**/**73**
1[d]	Tol	2.2	5 min	110	-	-	33
2	Tol	1.95	3 h	90	1 : 0.39 : 0.05	1 : 0.05	24
3	MeCN	1.95	3 h	80	1 : 0.05 : 0.10	1 : 0.10	40
4	MeCN	2.2	25 min	80	1 : 0.10 : 0.40	1 : 0.40	73[e]
5	MeCN	1.95	20 min	60	1 : 0.01 : 0.00[f]	1 : 0.00	62[g]

[a] Determined by integration of ^{1}H NMR spectra of crude mixture.

[b] Determined by integration of ^{1}H NMR spectra of product after chromatography on silica gel.

[c] The ratios were determined by the integration of the NH signals of the pure ^{1}H NMR spectra and therefore was approximate.

[d] Experiment reported by Murphy.[9, 13] The formation of **73** was not described and the crude ratio of *Z* : *E* isomer of the **66** was not determined. *E*-**66** was also isolated in 12% yield.

[e] *E*-**66** was also isolated in pure form in 4% yield.

[f] The crude product contained also 10% of an unidentifiable side product.

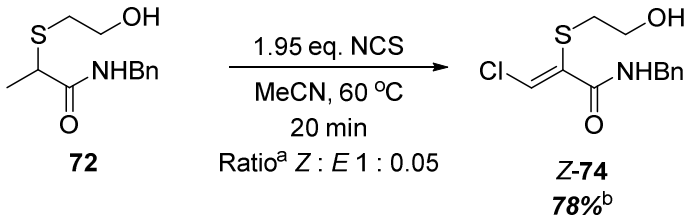
[g] Yield of the pure isolated **66** after chromatography on silica gel.

Murphy described that an excess of NCS (2.2 equivalents) increased the yield of this transformation.[9] Indeed, the use of 2.2 equivalents of NCS instead of 1.95 equivalents, in acetonitrile, with 25 minute reaction time, increased the yield of *Z*-**66** (Entry 4, Table 2). However, the resulting mixture, obtained after chromatography on silica gel, still contained around 30% of the dichloroacrylamide product **73**. The excess of NCS resulted in a large amount of over-chlorination. The presence of the over-chlorinated product was difficult to

observe using ^{1}H NMR spectroscopy, as each signal has the same chemical shift as the *Z*-isomer derivative *Z*-**66** except for the NH amide signal, which was observed at 8.5 ppm for dichloroacrylamide **73** *vs* 9.5 ppm for the *Z*-isomer. Consequently, the quantification of the dichloroacrylamide in the mixture was approximate due to the broad nature of the N-H signals. Therefore, Murphy may not have detected dichloroacrylamide **73** in the isolated mixture (Entry 1, Table 2) while employing 60 MHz NMR spectrometer.[9] In this work however, an authentic sample of **73** was isolated and fully characterized, and 400 MHz spectrometer was used, helping detection of **73** formation in the samples (Entries 2 to 5, Table 2).

A decrease in reaction temperature to 60 °C in acetonitrile, using 1.95 equivalents of NCS with 20 minutes reaction time prevented over-chlorination and, thus, pure *Z*-**66** was isolated in 62% of yield after chromatography on silica gel (Entry 5, Table 2).

Using this optimised procedure, the novel α-thio-β-chloroacrylamide *Z*-**74**, bearing a benzylamide substituent, was obtained as a mixture with *E*-**74** (ratio 1 : 0.05 respectively), and successfully isolated in pure form in 78% yield (Scheme 11).



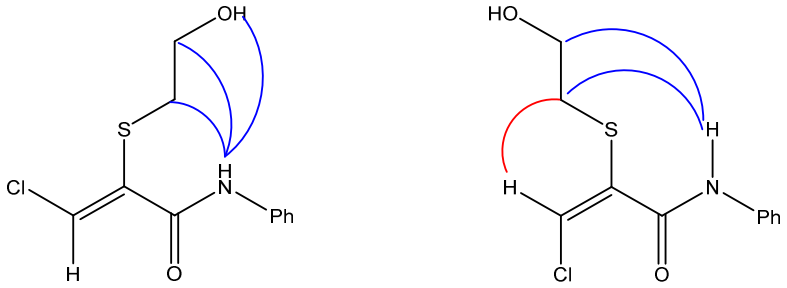
[a] Ratio by ^{1}H NMR spectroscopy of the crude mixture.
[b] Yield of *Z*-**74** after chromatography on silica gel.

Scheme 11

This represents a significant process improvement and a useful quantity of each *Z*-**66** and *Z*-**74** has been obtained with high stereoselectivity for the first time.

To confirm the assignment of the *Z* and *E* isomer of the α-hydroxyethyl-thio-β-chloroacrylamides **66**, NOESY NMR experiments were run on a pure sample of each isomer. The β-proton and the methylene proton α to the sulfur group was observed to interact for the tentatively assigned *E*-isomer, the less polar derivative

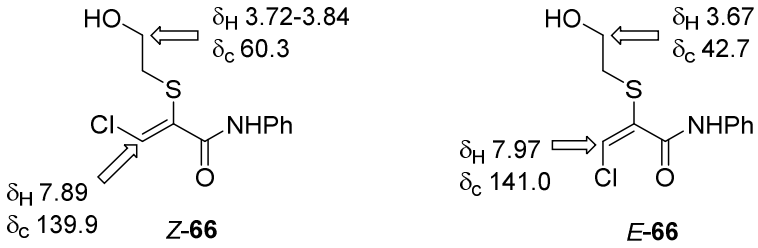
(Figure 4). This interaction was not observed for the tentatively assigned *Z*-isomer, confirming this assignment.



Z-**66** *E*-**66**

Figure 4

The chemical shift of the β-proton is commonly observed shielded of 0.5 to 1 ppm in the *E*-isomer compared to the corresponding proton in the *Z*-isomer (*cf.* 7.9 to 8.1 ppm).[9, 12, 15] Murphy suggested that the *E*-isomer would cause more strain between the chloride group and the carbonyl group and hence more out-of-plane distortion. This leads to poorer orbital overlap and, therefore, a decrease in the extent of resonance delocalization between the double bond and the carbonyl group, resulting in a shielding of the β-proton in the *E*-isomer compared to the corresponding proton in the *Z*-isomer. Interestingly, the β-proton of *E*-**66** was observed deshielded compared to its usual shift in other compounds (Figure 5).



Z-**66** *E*-**66**

Figure 5

In addition, the shift of the methylene alpha to the alcohol group was observed significantly shielded by ^{13}C NMR spectroscopy in the *E*-**66** at 42.7 ppm, compared to the *Z*-**66** with the corresponding carbon seen at 60.3 ppm. Interaction between the oxygen atom of the hydroxy group and the β-proton, through hydrogen bonding, would explain these two unusual observations (Figure 6). Indeed, this

hydrogen bonding would have a deshielding effect on the β-proton, as it is linked to an electronegative oxygen atom. As well, *via* this hydrogen bonding, the α-hydroxy carbon is brought closer to the π cloud from the unsaturated system, making it subject to an anisotropic shielding effect by 'face' interaction.

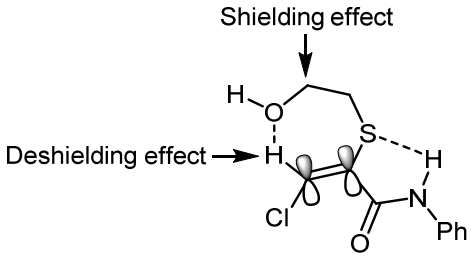


Figure 6

There is a precedent in the literature for the unusual shielded carbon shift of the α-hydroxymethylene. Bouhadir observed the α-hydroxymethylene signal in the 9-(2-hydroxyethyl)adenine at 45.6 ppm by ^{13}C NMR spectroscopy (Figure 7).[16]

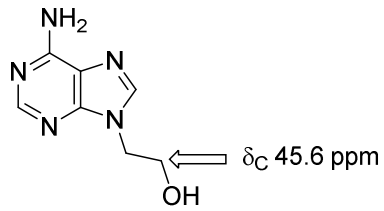


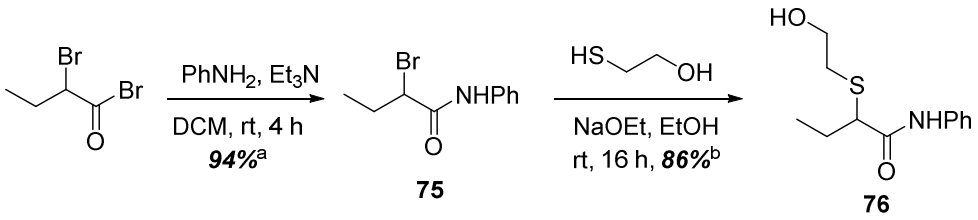
Figure 7

3. Synthesis of α-thio-β-chloroacrylamides – Extended chain

As stereocontrol was achieved in the formation of *Z*-**66** through variation of the reaction solvent, investigation to accomplish similar selectivity in the extended chain series was explored.

The synthesis of α-thio-β-chloroacrylamide **69** containing a butanamide chain was previously performed by Murphy.[5,9,13]

In this project, the precursor α-thioamide **76** was prepared from the corresponding α-haloamide **75** by reaction with the sodium salt of mercaptoethanol (Scheme 12).



[a] Yield of the crude product which required no further purification.
[b] Yield of the pure product isolated after chromatography on silica gel.

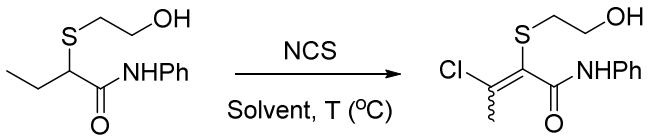
Scheme 12

Murphy previously prepared the α-haloamide **75** with a high yield of isolated product (80%) from coupling reaction of the corresponding carboxylic acid derivative, using DCC and aniline.[9] However, these experimental conditions required an additional purification step in order to remove the dicyclohexyl urea by-product. The use of an acyl bromide derivative, meanwhile, allows the isolation of the product in high yield without the requirement for further purification.

Synthesis of α-thio-β-chloroacrylamide **69** from α-thiobutanamide **76** was also performed by Murphy.[5, 9] The experiments reported by Murphy are highlighted in blue in Table 3 (Entries 1 and 2).[9] The *Z* : *E* ratios in the crude mixtures were not reported by Murphy. On a 2 mmol scale, the reaction gave a mixture of isomers in poor yield (Entry 1, Table 3). Murphy reported that on a larger scale, slow addition of NCS was required due to the exothermic character of the transformation. In this case, decomposition occurs and the desired products were isolated in very poor yields (Entry 2, Table 3).[9]

In this work, experiments were performed in order to increase the yield of the transformation (Entries 3 to 5, Table 3). At this point, the assignment of the relative stereochemistry of *Z*- and *E*-isomer was tentative, but was in agreement with those of Murphy.[9]

Table 3 Optimisation of the preparation of **69**



76 **69**

Entry	Solvent	T (°C)	Reaction time	NCS (eq.)	Ratio *Z*-**69** : *E*-**69**[a]	Yield *Z*-**69** (%)[b]	Yield *E*-**69** (%)[b]
1[c]	Tol	110	5 min	2.20	-	34	22
2[d]	Tol	110	15 min	2.20	-	17	8
3[e]	Tol	90	2 h	1.95	1 : 0.56	31	34
4[e]	MeCN	60	15 min	1.95	1 : 0.44	41	39
5[e]	MeCN	80	15 min	1.95	0.62 : 1	24	44

[a] Ratios were determined by integration of the NH signals in the crude ^{1}H NMR spectra and therefore were approximate.

[b] Yield of the pure product isolated after chromatography on silica gel.

[c] Experiment reported by Murphy,[9, 13] performed on a 2 mmol scale. Ratio of *Z*- : *E*- isomers for **69** as crude product was not reported.

[d] Experiment reported by Murphy,[9, 13] performed on a 27 mmol scale. Ratio of *Z*- : *E*- isomers for **69** as crude product was not reported.

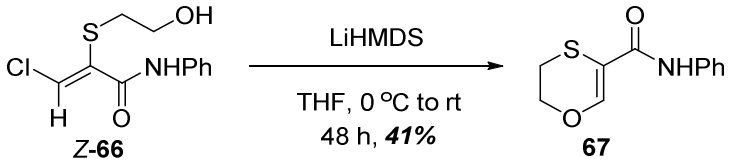
[e] Experiment performed on 1.25 mmol scale.

The ratio of the *Z* : *E* isomers in the ^{1}H NMR spectra of the crude product was determined using the integrations of the NH amide signals, observed at 8.01 ppm and 8.67 ppm respectively. Consequently, the ratio determination was approximate due to the broad nature of the signals observed. The solvent choice was not found to impact significantly on the stereoselectivity, while the increase of the reaction temperature to 80 °C in acetonitrile increased the *E*-isomer formation (Entry 5, Table 3). In contrast to the propyl chain derivative, the butyl derivative appears to hold the compound in a conformation which cannot be impacted by the polarity of the reaction solvent used. Clearly, with the extended chain derivatives, formation of both the *Z*- and *E*- isomer is seen due to the small steric difference between the methyl (or ethyl) group and the chloride (*cf. Chapter 2, Section 1. Scheme 9*).

Murphy reported that both the *Z*- and *E*- isomer of the α-thio-β-chloroacrylamide **69** can form the oxathiin derivative **70** in presence of base, with similar yields (7 - 11%).[5,9] When a crude mixture of both isomers was employed, the cyclisation was observed in the ^{1}H NMR spectra of the crude material but isolation of the desired product was not possible.[5,9]

B. Synthesis of oxathiins

The intramolecular cyclisation of the α-thio-β-chloroacrylamide *Z*-**66** had previously been optimised by Murphy. Addition of LiHMDS as base (2 equivalents) at 0 °C in THF, was found to offer the best conditions for this synthesis, yielding the oxathiin **67** in 41% yield (Scheme 13).[5, 9]

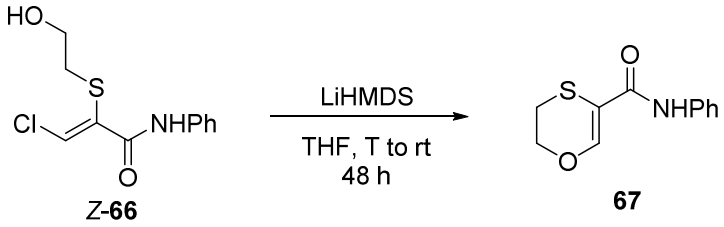


Scheme 13

Murphy has also investigated the use of LDA, with or without DMPU as additive, affording lower yields of **67** (10-14%), while use of sodium hydride did not provide any evidence for cyclised product.[9] Use of lithium triphenylmethane as base, however, also gave some cyclisation (< 30% by ^{1}H NMR spectroscopy of the crude mixture, not isolable).

For this work, optimisation of the reaction conditions for the oxathiin **67** synthesis using LiHMDS as base was first investigated (Table 4).

Table 4 Optimisation of preparation of oxathiin **67** using LiHMDS as base



Z-**66** **67**

Entry	No. eq. LiHMDS	Temperature of addition (°C)[a]	Yield **67** (%)
1	1	0 °C	-[b]
2	2	0 °C	32[c]
3	2	- 40 °C	48[c]

[a] LiHMDS was added to the reaction mixture at temperature T and the reaction flask was allowed to warm slowly to room temperature.

[b] ^{1}H NMR spectrum of the crude product corresponded to remaining starting material.

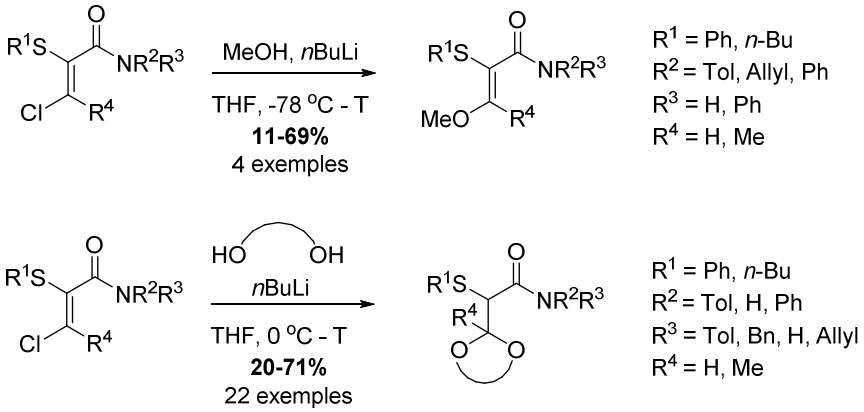
[c] Yield of the pure product isolated after chromatography on silica gel and subsequent recrystallisation.

As described by Murphy,[9] no reaction occurred when the reaction was attempted using only 1 equivalent of LiHMDS (Entry 1, Table 4). Indeed, 2 equivalents of base are required for this transformation, as the first equivalent presumably deprotonates the amide group.

When 2 equivalents of LiHMDS were added to α-thio-β-chloroacrylamide *Z*-**66** at 0 °C, formation of the oxathiin was observed (entry 2, Table 4). After chromatography on silica gel, using the purification conditions described by Murphy,[9] the product was obtained during this work in 41% yield, as described in the literature. However, a quantity of low level impurities was observed using ^{1}H NMR 400 MHz spectroscopy. These low level impurities were unlikely to have been observed employing ^{1}H NMR 60 MHz spectroscopy, as used by Murphy in 1998.[9] In this work, further cold recrystallisation using dichloromethane and hexane (as anti-solvent) led to isolation of the pure product in 32% yield.

A decrease in the temperature of the reaction mixture during the addition of LiHMDS, to -40 °C, allowed isolation of the pure oxathiin with a yield of 48%, after column chromatography and recrystallisation (Entry 3, Table 4).

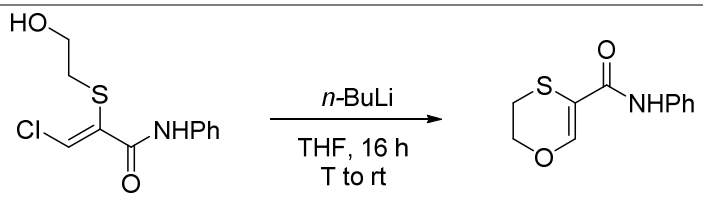
Use of another alternative base was also investigated in order to increase the yield of the transformation. Nucleophilic substitution of a range of α-thio-β-chloroacrylamides using oxygen nucleophiles using *n*-BuLi as base are described in literature and have provided the *O*-substituted product with low to high yield (Scheme 14).[5]



Scheme 14

Thus, these conditions were applied to α-thio-β-chloroacrylamide *Z*-**66** (Table 5).

Table 5 Investigation of preparation of oxathiin *Z*-**67** using *n*-BuLi as base



Z-**66** **67**

Entry	*n*-BuLi (eq.)	Temperature of addition T (°C)	Yield **67** (%)
1	1.6	0 °C	18[a]
2	2	- 40 °C	9[b]
3	1.6	- 78 °C	-[c]

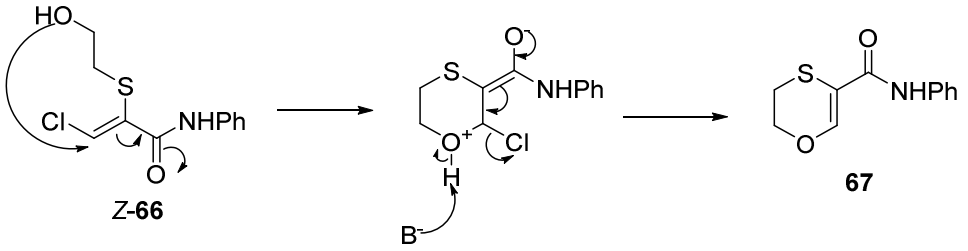
[a] Yield of the product after chromatography on silica gel, as a mixture with unidentified products with 81% purity estimated by ^{1}H NMR spectroscopy.

[b] Yield of the pure product isolated after chromatography on silica gel and recrystallisation.

[c] The ^{1}H NMR spectra of the crude material corresponded to the remaining starting material.

The use of *n*-butyl lithium as base led to the formation of the oxathiin as the major product detected in the ^{1}H NMR spectra of the crude mixture when the addition was performed at 0 °C or -40 °C (Entries 1 and 2, Table 5) but no reaction occurred when the addition was conducted at -78 °C and surprisingly the starting material was recovered unreacted (Entry 3, Table 5). However, in the two former instances, the product was obtained in a lower yield than when the reaction was conducted using LiHMDS as base. Isolation of the product proved challenging due to the formation of a large quantity of unidentified products.

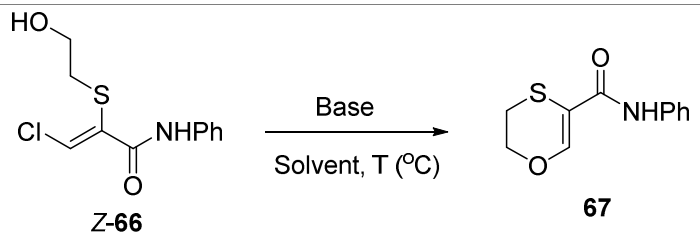
It was also envisaged that oxathiin formation could be spontaneous, with the α-thio-β-chloroacrylamide reacting to form the oxathiin (Scheme 15).



Scheme 15

Use of weaker bases was therefore investigated to trap the oxathiin formed (Table 6). However, no reactions were observed in the presence of sodium hydroxide at room temperature, or sodium hydroxide and triethylamine under reflux conditions (Entry 1, 2 and 3, Table 6). On the other hand, in the presence of NaH at 80 °C or DBU at room temperature, formation of a complex mixture of unidentifiable products was observed, with no evidence for formation of the oxathiin derivative (Entries 4 and 5, Table 6).

Table 6 Optimisation of preparation of oxathiin **67** using non-lithium bases

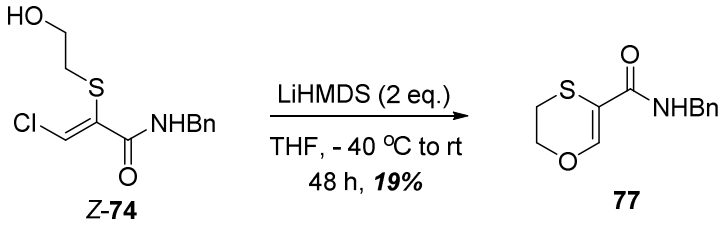


Entry	Base	Base (eq.)	Solvent	Reaction temperature (°C)	Reaction time	Observations
1	NaH	1.5	DMF	rt	24 h	SM remaining[a]
2	NaOH	1.5	Tol	90	4h	
3	Et_3N	1.1	DCM	reflux	2 h	
4	NaH	1.5	DMF	80	6 h	Complex mixture of unidentified products[b]
5	DBU	1	THF	rt	16 h	

[a] The ^{1}H NMR spectra of the crude material corresponded to the remaining starting material.

[b] The ^{1}H NMR spectra of the crude material consisted in a complex mixture of unidentified products, with no evidence for formation of **67.**

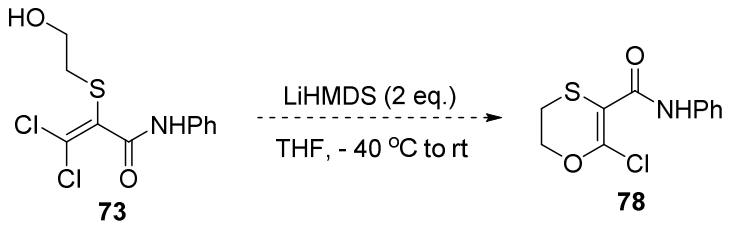
In conclusion, LiHMDS as a base (2 eq.) in THF, added at -40 °C and allowed to warm slowly to room temperature, appeared to be the best conditions for this transformation. The *N*-benzylated oxathiin **77** was also synthesised using this procedure, with a low isolated yield of 19% (Scheme 16).



Scheme 16

This decrease in yield may be explained by a decrease in the electrophilicity at the β-position when the amine is *N*-benzyl substituted, compared to the electron withdrawing phenyl substituent, reducing the efficiency of the substitution reaction.

The dichloroacrylamide derivative **73** is the main by-product formed during α-thio-β-chloroacrylamide **66** synthesis (Table 2). This compound could potentially provide a highly reactive oxathiin derivative **78** following intramolecular cyclisation (Scheme 17).



73 **78**

Scheme 17

However, the optimised protocol developed previously, using LiHMDS, led to a complex mixture of compounds with no evidence of the desired product **78** formed by either NMR spectroscopy or mass spectrometry analysis.

Chemical shift analysis

The effect of the stereochemistry and cyclisation on the extent of electron delocalization by sulfur and oxygen into the conjugated system can be easily analyzed using ^{1}H NMR spectroscopy (Figure 8). This can be observed by noting changes in chemical shift of the methylene protons adjacent to the sulfur and oxygen substituents.

The downfield shifts of the methylene alpha to the oxygen in both the ^{1}H and ^{13}C NMR spectra of the cyclised products was significant as electron-donation by the oxygen into the unsaturated system causes deshielding of the immediately adjacent CH_2-O protons and carbon.

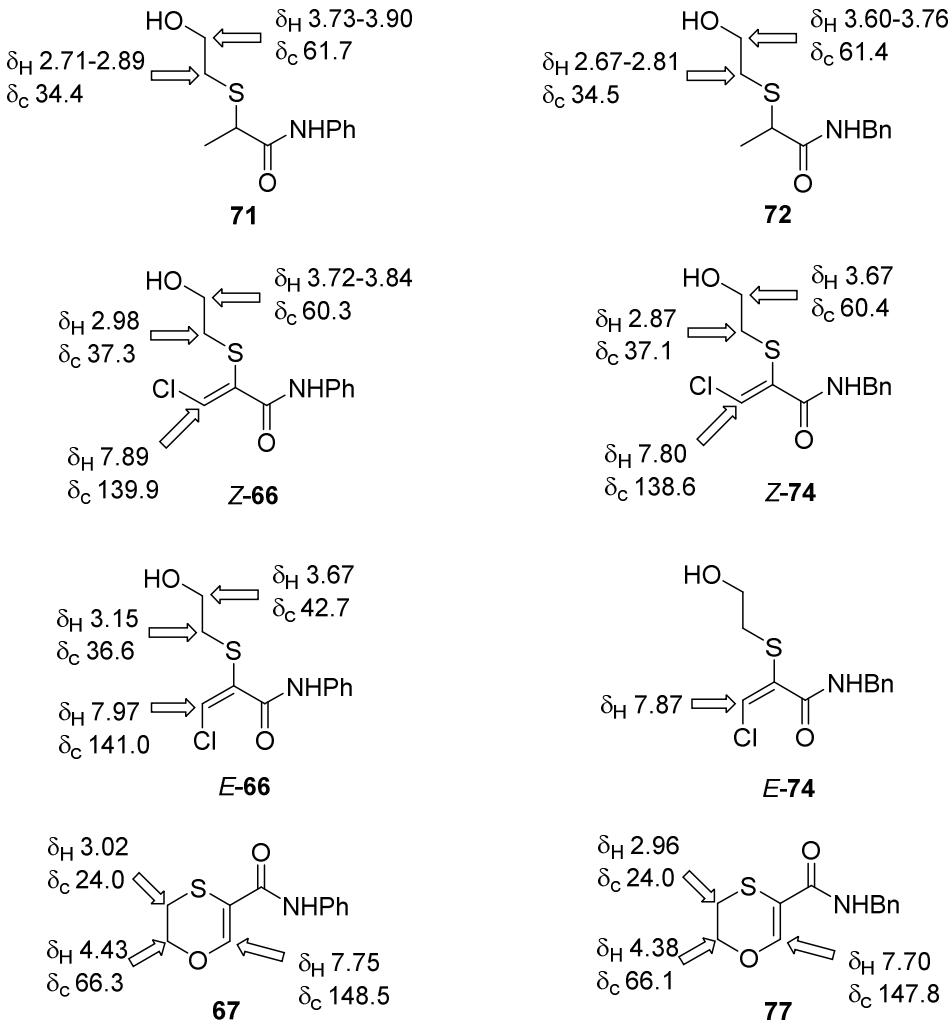
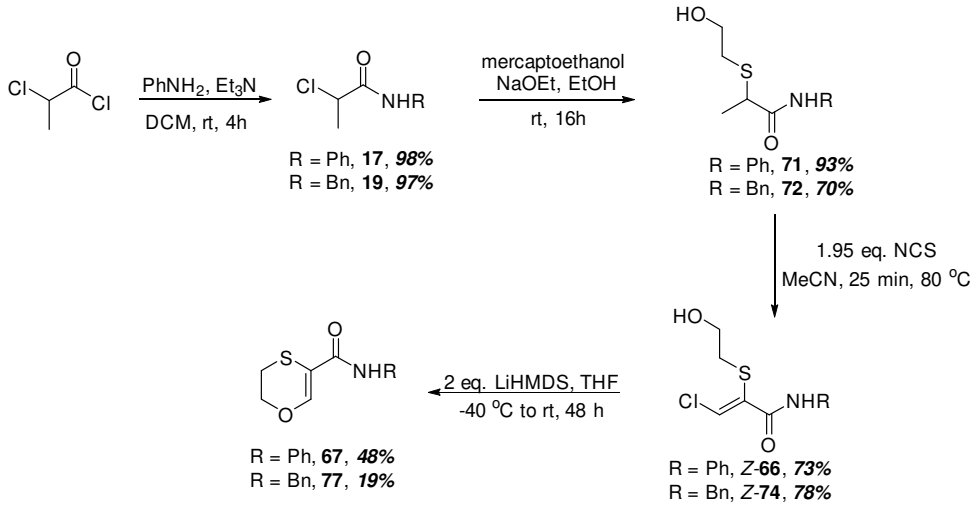


Figure 8

The synthesis of α-thio-β-chloroacrylamide *Z*-**66** from α-thioamide **71** was successfully optimised, and high stereoselectivity was achieved for this transformation, in contrast to Murphy's earlier studies. The optimal protocol developed was successfully applied for synthesis of the analogous novel α-thio-β-chloroacrylamide *Z*-**74**. Both of these derivatives were isolated in good yield. A reasonable explanation of the unusual chemical shifts in the *E*-isomer of **66** was proposed, highlighting a hydrogen bond between the hydroxy group and the β-proton within the molecule. Stereoselectivity for the α-thio-β-chloroacrylamide in the extended chain series was explored but stereocontrol could not be achieved.

Optimisation of the synthesis of the corresponding oxathiin derivative **67** was performed using LiHMDS as reagent, and the product could be isolated in

moderate yield. The novel oxathiin **77** was also synthesised and characterised in this section. Alternative reagents for this transformation were intensively investigated but better yields could not be obtained for these reactions.

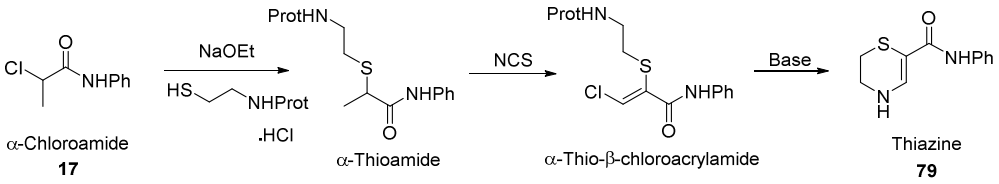


Scheme 18 Multistep synthesis of 1,4-oxathiins with optimal conditions

3. THIAZINE SYNTHESIS

Intermolecular nucleophilic substitution using nitrogen nucleophiles on a large range of α-thio-β-chloroacrylamides has previously proved highly successful.[5] Therefore, extension of the scope of this transformation in order to synthesise thiazine derivatives by intramolecular nucleophilic substitution was investigated.

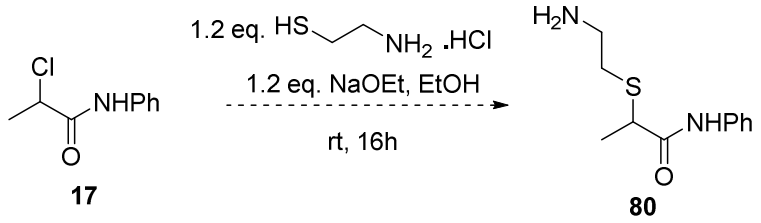
The strategy for synthesis of thiazine **79** was proposed using α-chloroamide **17**, previously synthesised (*Chapter 2, Section 2.A*), as the starting material (Scheme 19). Following synthesis of α-thioamide using commercially available cysteamine, oxidative transformation with NCS was expected to lead to α-thio-β-chloroacrylamide, which was envisaged to cyclise to the target thiazine **79** under basic conditions. It was not obvious at the outset whether protection of the amine group will be required through this reaction sequence.



Scheme 19

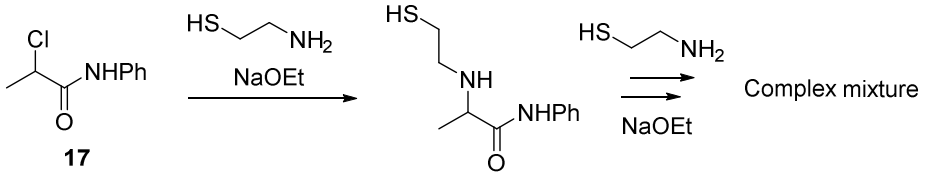
A. Synthesis of α-thioamide

The formation of α-thioamide **80** was attempted from α-chloroamide **17** using cysteamine hydrochloride (1.2 eq.) and sodium ethoxide (1.2 eq.), as described in *Chapter 2, Section 2.A.*, resulting in a complex mixture of products (Scheme 20).



Scheme 20

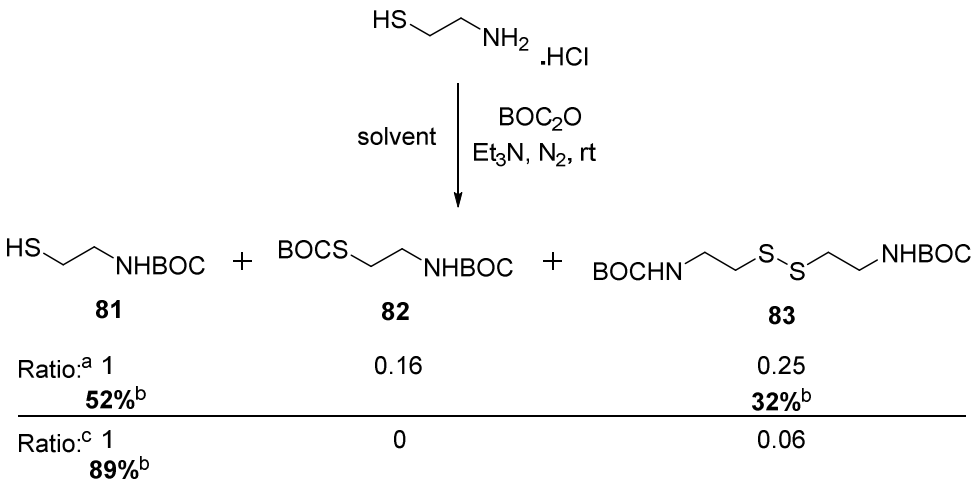
This outcome is due to the strong nucleophilicity of the amine, acting as a competitive pathway with the thiolate in the cysteamine, giving rise to a large amount of products formed, as we had anticipated (Scheme 21).



Scheme 21

To prevent this competitive pathway, the amine group of cysteamine had to be protected. The selective protection of the amine group was performed using di-*tert*-butyl dicarbonate (1.1 eq.) and triethylamine (3 eq.) at room temperature in dioxane : water (4 : 1) (Scheme 22). The crude mixture resulted in the desired mono protected cysteamine **81**, diprotected cysteamine **82** and protected disulfide **83** in a ratio of 1 : 0.16 : 0.25 respectively, by ^{1}H NMR spectroscopy. A yield of disulfide **83** of 32%, after chromatography, meant that the monoprotected

cysteamine **81** is highly sensitive to oxidation, forming **83**. Therefore, the isolated desired product was obtained in moderate yield.



[a] Ratio of the crude product mixture by ^{1}H NMR spectroscopy when the reaction was performed in **dioxane : H_2O** (8 : 2).
[b] Yield of isolated products after chromatography on silica gel.
[c] Ratio of the crude product mixture by ^{1}H NMR spectroscopy when the reaction was performed in **deoxygenated THF : H_2O** (8 : 2).

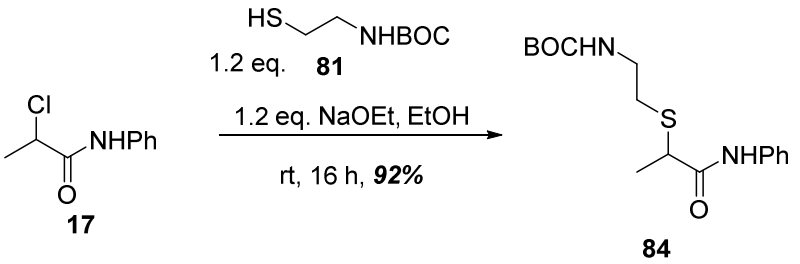
Scheme 22

As the dioxane used was potentially dissolving substantial quantities of oxygen (O_2), the solvent was substituted with freshly distilled THF, to minimise the thiol oxidation. The water, used as the second component of the solvent system was deoxygenated, by bubbling nitrogen gas through the solvent for 20 min.

Using this solvent system, THF : deoxygenated H_2O (4 : 1), diprotected cysteamine **82** formation was not observed and the crude mixture consisted of disulfide **83** and thiol **81** in a ratio 0.06 : 1 respectively, by ^{1}H NMR spectroscopy. Furthermore, ^{1}H NMR spectroscopy of the cysteamine hydrochloride starting material in D_2O revealed 5% of the corresponding disulfide present. Therefore, the disulfide **83** in the crude mixture may be formed from the starting material cysteamine, and not as a result of *in situ* oxidation.

Also, purification by chromatography was performed immediately after the reaction work-up to minimise oxidation of the thiol group to the disulfide **83**, with the product **81** isolated in 89% yield (Scheme 23).

The pure thiol **81** was also carried forward to the next step without delay to prevent formation of the corresponding disulfide. The synthesis of α-thioamide **84** was performed from α-chloroamide **17**, using the optimised protocol previously described in *Chapter 2, Section 2.B.* (Scheme 23). Again, the ethanol used for this transformation was deoxygenated prior to the start of the reaction. The product was isolated in 92% yield after chromatography on silica gel.



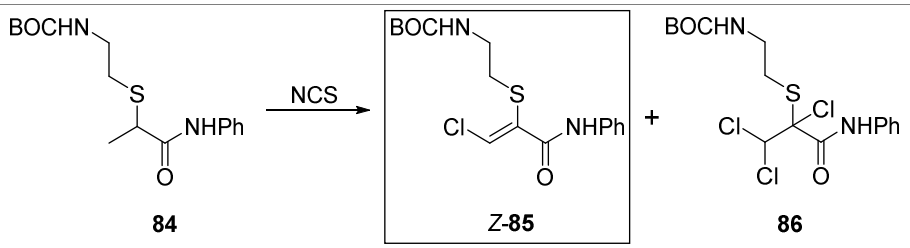
Scheme 23

Having successfully synthesised α-thioamide **84**, the next step in the reaction sequence was preparation of the corresponding α-thio-β-chloroacrylamide *Z*-**85**.

B. Synthesis of α-thio-β-chloroacrylamide

The synthesis of α-thio-β-chloroacrylamide *Z*-**85** proved a far more challenging undertaking than that of α-hydroxyethylthio-β-chloroacrylamide **66** (*cf. Chapter 2, Section 2.B.3.*). The reaction was first attempted using protected α-thioamide **84** in presence of 2.2 equivalent of NCS in acetonitrile at 80 ^{o}C (Entry 1, Table 7). The ^{1}H NMR spectra of the crude material consisted of a complex mixture of unidentified products, with no characteristic signals relevant to the dichloride, acrylamide, trichloride or α-thio-β-chloroacrylamide observed. However, after chromatography on silica gel, *Z*-**85** was isolated in 1% yield, as a single isomer.

Table 7 Investigation of the preparation of *Z*-**85**



84 *Z*-**85** **86**

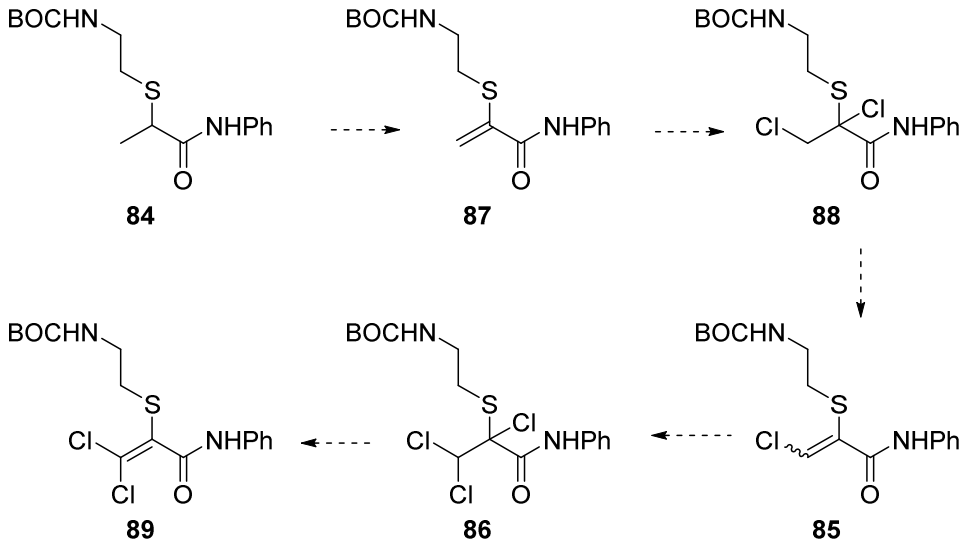
Entry	NCS (eq.)	Solvent	Temperature (°C)	Reaction time	Yield (%) *Z*-**85**
1	2.2	MeCN	80	20 min	1[a]
2	2	CCl_4	rt	(1) 6 h 30 (2) storage for 3 days[b]	32[a]
3	2	MeCN	40	20 min	31[a]
4	2	Toluene	40	3 h	53[a]
5	2	Toluene	60	20 min	62[a]
6	2	Toluene	90	20 min	*Z*-**85** : **86**[c] 1 : 0.35

[a] Yield of the pure product isolated after chromatography on silica gel.

[b] The concentrated crude mixture was stored 2 days at 0 °C, followed by 24 h at room temperature.

[c] Product partially isolated, as a mixture with the corresponding trichloride, after chromatography on silica gel and the ratio was determined by ^{1}H NMR spectroscopy.

To understand the mechanisms involved in this reaction and to investigate if the two isomers of **85** and the typical intermediates for α-thio-β-chloroacrylamide synthesis were formed (Scheme 24), the reaction was performed in tetrachloromethane, under mild conditions, for the purposes of observation by ^{1}H NMR spectroscopy (Entry 2, Table 7).



Scheme 24

After 2 hours of reaction time, formation of the corresponding dichloride intermediate **88** was observed by ^{1}H NMR spectroscopy (characteristic ABq signal: 4.02 and 4.40 ppm, *J* 11.6 Hz). After 6.5 hours, all the starting material was consumed and the reaction was stopped. After storage of the concentrated crude mixture for two days at 0 °C, 35% of the dichloride intermediate was observed to have decomposed into the α-thio-β-chloroacrylamide *Z*-**85**, as a single isomer, by ^{1}H NMR spectroscopy. At room temperature, the consumption of the dichloride was faster, with full conversion into the final product within a day. The α-thio-β-chloroacrylamide *Z*-**85** was isolated, after chromatography on silica gel, in 32% yield as a single isomer, tentatively assigned as the *Z*-isomer. No evidence of the formation of the other stereoisomer was observed.

When the reaction was performed in toluene instead of acetonitrile, the corresponding ^{1}H NMR spectrum of the crude mixture was cleaner (Entry 3 *vs* Entry 4, Table 7). The resulting yield increased up to 53% when using toluene as solvent at 40 °C.

Increasing the reaction temperature to 60 °C further revised the yield of the isolated product to 62% (Entry 5, Table 7). However, when the reaction was performed at higher temperature (90 °C), formation of the trichloride **86** by-product was observed (Entry 6, Table 7) by ^{1}H NMR spectroscopy, characterised

by a singlet at 6.53 ppm corresponding to the β-proton. The trichloride results from an over chlorination of α-thio-β-chloroacrylamide *Z*-**85**. The by-product **86** co-eluted with the corresponding α-thio-β-chloroacrylamide and, therefore, the product could not be isolated in a pure form. In contrast to earlier series studied, the trichloride **86** by-product was stable, and decomposition to the dichloroacrylamide **89** by-product was not observed.

In order to synthesise a large amount of α-thio-β-chloroacrylamide *Z*-**85**, to further study thiazine **79** formation, the reaction using the conditions described in Entry 5 (Table 7) was extensively repeated. Some of these experiments led to an equimolar mixture of the trichloride **86** by-product and the α-thio-β-chloroacrylamide *Z*-**85**. As separation of **86** and *Z*-**85** proved challenging, the formation of the over-chlorinated product needed to be limited.

With this in mind, four reactions were run to evaluate the reproducibility of the process. Each reaction was attempted using 0.6 g of α-thioamide **84** in 20 mL of toluene, with 1.95 eq. of NCS, in a pre-heated oil bath at 60 ^{o}C for 20 min. The round bottom flasks (50 mL, 1 neck), stirrer size, stirring speed (200 rev/min) used were all identical. In addition, the experiments were run in series, with the same oil bath to provide an identical reaction temperature. Three of these reactions presented the same ^{1}H NMR crude spectra, with the major product present as the α-thio-β-chloroacrylamide *Z*-**85** and no trace of the corresponding dichloride **88**, acrylamide **87** or trichloride **86** present. However, one of the experiments led to a mixture of acrylamide **87** and the final product with ratio of 1 : 0.23 respectively. No trichloride **86** formation was observed.

Synthesis of α-thio-β-chloroacrylamide *Z*-**85** was observed to be highly sensitive to reaction conditions with difficulty of reproducibility.

Investigation of a continuous flow process

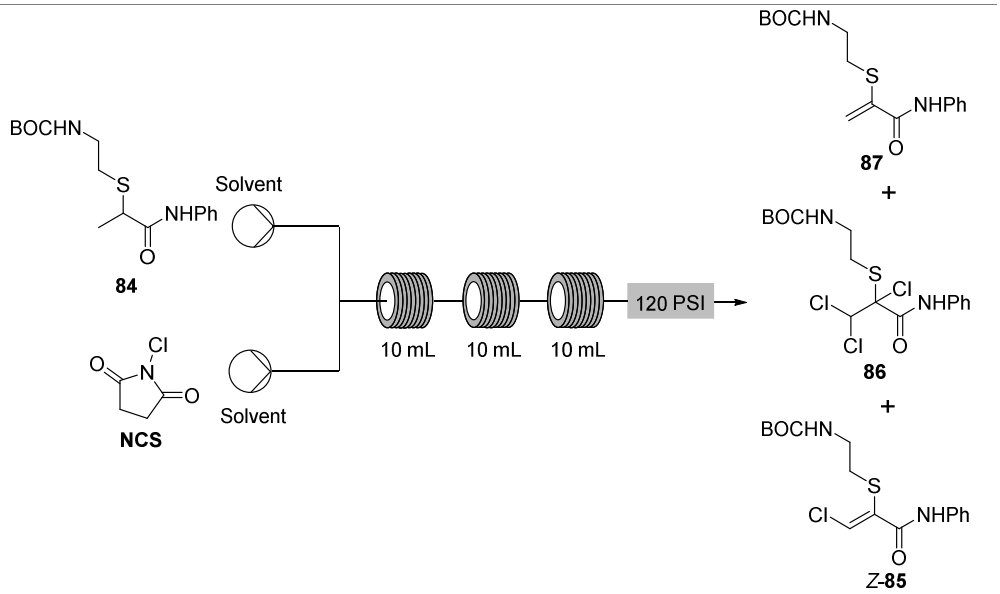
Previous work performed on the α-thio-β-chloroacrylamide **7** SPh/NHTol series demonstrates the high process control afforded by continuous flow system (*cf. Chapter 2. Section 5.*). Flow processes offers an interesting alternative to batch processing for this transformation due to the high consistency of the generated

results. The results of these experiments could be easily interpreted using ^{1}H NMR spectroscopy due to the characteristic signals seen for each of the products and intermediates. The acrylamide intermediate **87** is characterised with two singlets at 5.91 and 6.62 ppm, while the dichloride intermediate **88** has a characteristic ABq system at 4.02 and 4.40 ppm (*J* 11.6 Hz). Trichloride by-product **86** formation is especially problematic as it co-elutes with the final product, but it is easily identifiable by ^{1}H NMR spectroscopy with a singlet at 6.53 ppm. Also, α-thioamide **84** starting material is observed by the presence of a doublet at 1.53 ppm.

The experiments were undertaken using three 10 mL reactors in series, in order to achieve a fast flow rate while maintaining residence time, and thereby prevent precipitation (Table 8). In previous work, acetonitrile was found to be an interesting alternative solvent for toluene in continuous process, due to the low solubility of NCS in toluene (*cf. Chapter 2. Section 5.B*). Therefore, α-thioamide starting material and NCS were introduced in solution in toluene or acetonitrile, with different concentrations and flow rates in order to develop an optimum protocol for this transformation.

During this study, challenges with solubility of the NCS in toluene and acetonitrile were observed, suggesting that it contains an amount of a by-product, possibly succinimide. Consequently, the NCS was freshly recrystallized from water before use.

Table 8 Flow process for the transformation of **84** to *Z*-**85**



Entry	Ratio **84** : NCS	Flow rate (mL/min)		Residence time (min)	Solvent	Ratio[a]			
		84	NCS			**84**	**87**	**86**	*Z*-**85**
1[b]	1 : 2	0.2	0.8	30	Tol	1	0.9	0	0.8
2[c]	1 : 2	0.75	0.75	20	MeCN	0.2	0.2	0	1
3[c]	1 : 2.4	0.60	0.72	22	MeCN	0	0	0	1

[a] Ratio of the crude mixture determined by ^{1}H NMR spectroscopy.

[b] [**84**] = 50 mmol/L; [NCS] = 25 mmol/L. The reactors temperature was 120 °C.

[c] [**84**] = 25 mmol/L; [NCS] = 50 mmol/L. The reactors temperature was 80 °C.

When toluene was used for dilution of both reagents, with 2 equivalents of NCS, the reaction did not reach full completion (Entry 1, Table 8). Specifically, the second chlorination step did not occur fully, as acrylamide **87** was still present. The low conversion could be due to the toluene solvent system similar to the observations previously discussed in *Chapter 2. Section 5.B.*.

Once again, substitution of the toluene solvent by acetonitrile, resulted in a better conversion to *Z*-**85** (Entry 2, Table 8). Also, the concentration of NCS employed could be increased as solubility is higher in this solvent. Use of NCS (2.4 eq.) in acetonitrile led to full reaction completion (Entry 3, Table 8).

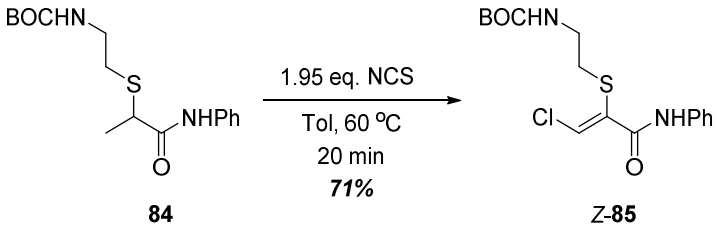
Trichloride **86** formation was not observed in any of the experiments run in flow, suggesting that the continuous process avoids the over-chlorination of the α-thio-β-chloroacrylamide (as discussed in *Chapter 2, Section 5.*).

Back to batch process

As NCS purity may be the origin of the reproducibility issues observed in batch, reactions were run using freshly recrystallized NCS in batch.

When using in batch the optimised protocol developed in continuous process (Entry 3, Table 8), ^{1}H NMR spectroscopy of the crude material consisted of a complex mixture of products, as reported previously for the batch reaction using acetonitrile and not recrystallized NCS.

When employing the optimised protocol described previously in batch (60 °C in toluene, 20 min reaction time, 1.95 eq. NCS), the isolated yield increased to 71% (Scheme 25). Acidic impurities in commercial NCS are likely to partially deprotect the BOC group of the amine, which might explain the increased efficiency while employing freshly recrystallized material. This reaction outcome was consistent over a run of ten experiments. The concentration of the starting material ranged from 5 mmol/L to 15 mmol/L without influence on the results obtained.



84 ***Z*-85**

Scheme 25

It is interesting to compare the batch and flow process for this transformation. While using toluene in flow process generated crude material with complex ^{1}H NMR spectrum, the batch process in this solvent produced a clean transformation and the resulting ^{1}H NMR spectrum of the crude mixture was extremely clean (Figure 9). However, the reverse was observed while using acetonitrile as solvent, with a clean transformation *via* flow process and a complex outcome in batch.

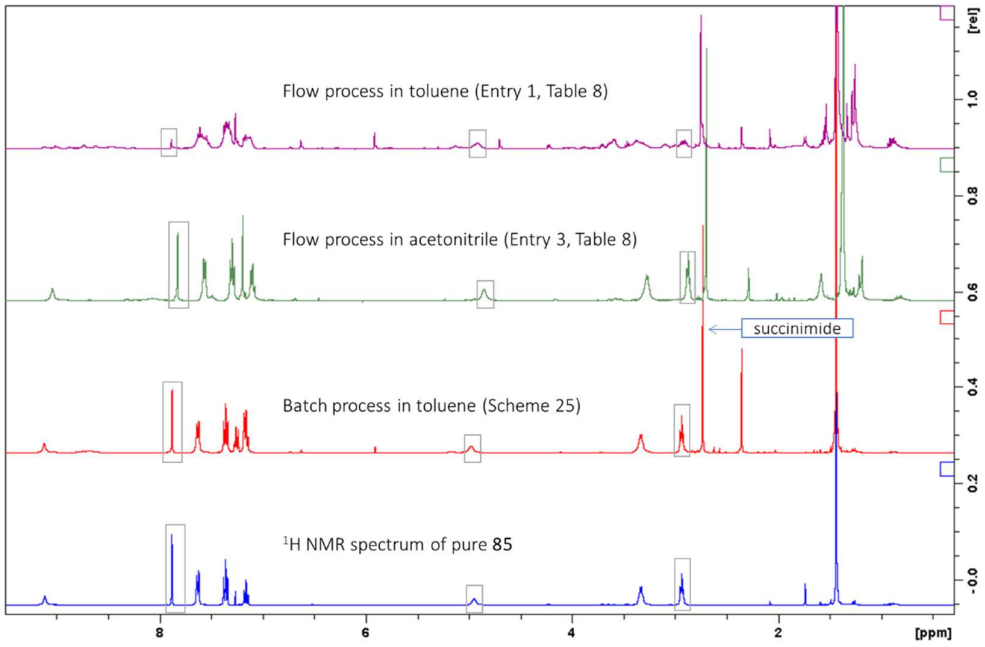
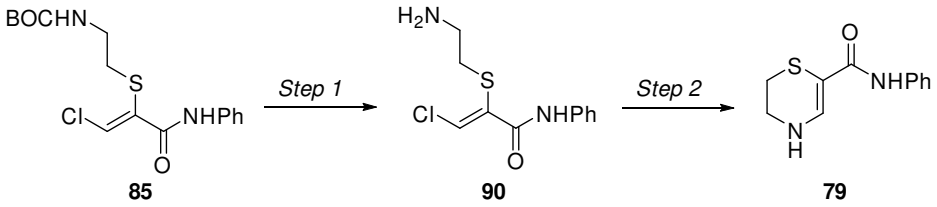


Figure 9 ^{1}H NMR spectra of the crude materials from synthesis of **85** under various conditions

The flow process using toluene was not efficient presumably due to the concentration issues, as previously observed in *Chapter 2. Section 5.B.*. For the batch process instead, the concentration employed did not impact the reaction outcome.

C. Synthesis of thiazine

The last step in the reaction sequence consists of two consecutive stages. First, deprotection of the amino group under acidic conditions, followed by cyclisation under basic conditions (Scheme 26).

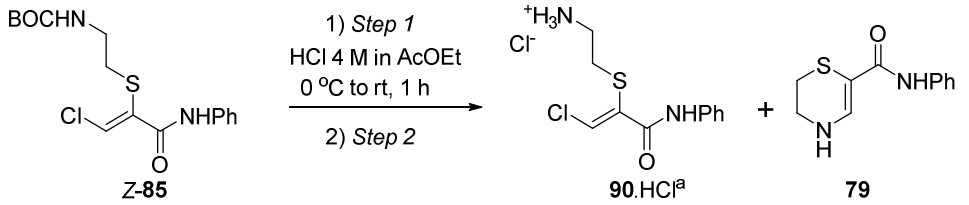


Scheme 26

Deprotection of the amine group of α-thio-β-chloroacrylamide **85**, using a hydrochloric acid solution (4 M), and resulted in formation of the deprotected α-thio-β-chloroacrylamide **90**.HCl and thiazine **79** in a ratio of 1 : 0.70 respectively

(Entry 1, Table 9). Consequently, it was proposed that the intramolecular cyclisation of α-thio-β-chloroacrylamide **90** occurred spontaneously but not with full completion. Interestingly, α-thio-β-chloroacrylamide **90** was insoluble in chlorinated solvents and isolation was performed by filtration from the thiazine **79** solution in dichloromethane. ^{1}H NMR spectroscopy was therefore performed using deuterated DMSO. Integration of the amine signal in the ^{1}H NMR spectrum (a 3H broad singlet) indicated that the α-thio-β-chloroacrylamide **90** was isolated as its chloride salt; **90**.HCl.

Table 9 Investigation of the preparation of thiazine **79**



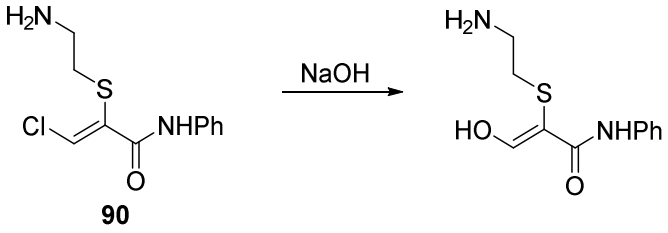
Entry	*Step 2*	Ratio[b] **90**.HCl : **79**	Yield **79** (%)[c]
1	None	1 : 0.70	-
2	NaOH 10M (pH = 14), 15 min, rt	0.45 : 1	24.8
3	NaOH 10M (pH = 14), 1 h, 50 °C	0 : 1	20.0
4	Et_3N 1 eq. in DCM, 1 h, rt	0 : 1	44.2

[a] α-Thio-β-chloroacrylamide **90** was later fully characterized as trifluoroacetate salt (**90**.CF_3COOH).
[b] The ratios were determined by integration of the =CH signals of **90**.HCl and **79** in ^{1}H NMR spectra of the crude products in deuterated DMSO.
[c] Yield of the pure product isolated after washing and filtration of the crude product.

To achieve complete conversion to the thiazine derivative, a second step under basic conditions was required to promote full cyclisation (*Step 2*).

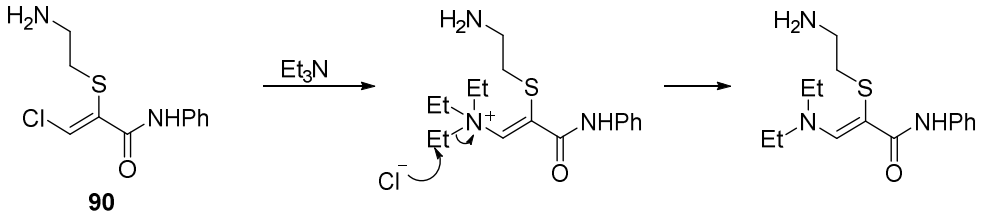
Addition of a sodium hydroxide solution, to the reaction mixture after the deprotection step, was found to increase the quantity of thiazine **79** formed (Entries 2 and 3, Table 9). Heating the reaction mixture to 50 °C was found to be necessary to observe reaction completion under these conditions (Entry 3, Table 9). The yields of the isolated product, however, were low, potentially due to formation of the corresponding hydroxyl derivate from reaction with sodium hydroxide (Scheme 27), decreasing the yield of the thiazine **79** (Entry 2 and 3,

Table 9). Saponification of the amide portion, with elimination of an anilide salt as the by-product formed, was also envisaged. However, no evidence was found by ^{1}H NMR spectroscopic analysis of the crude mixture for either of these suggestions.



Scheme 27

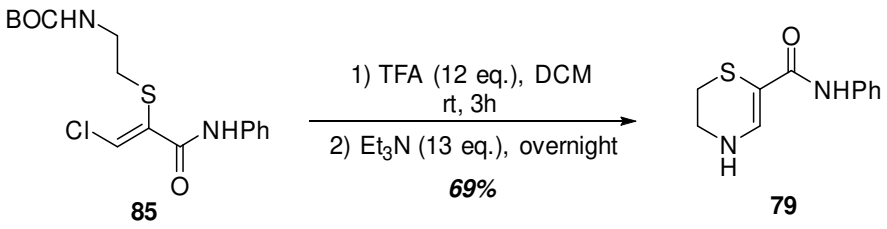
Consequently, the second step was performed by employing a milder base (Entry 4, Table 9). Full conversion was observed using triethylamine in DCM. However, the isolated yield of thiazine was still poor. Indeed, the triethylamine in the reaction mixture could also react with the α-thio-β-chloroacrylamide **90** *via* nucleophilic substitution (Scheme 28), decreasing the thiazine yield.[9] However, here again, no evidence of this side reaction was observed by ^{1}H NMR spectroscopy.



Scheme 28

Interestingly, when the deprotection step (*step 1*) was performed using TFA in DCM at room temperature, the resulting ratio of α-thio-β-chloroacrylamide **90**.CF_3COOH (as the TFA salt) and the thiazine **79** was 0.29 : 1. The cyclisation appeared to be more efficient using DCM as the solvent system.

The unreacted TFA was then neutralized with triethylamine, and an extra equivalent of triethylamine was added to the reaction mixture. Full conversion was observed under these conditions and the thiazine **79** was isolated in 69% yield after a simple washing using ethyl acetate : hexane (20:80) followed by filtration of the product (Scheme 29).



Scheme 29

The ^{1}H NMR spectra of the crude mixture was clean with **79** as the main product formed (Figure 10). The filtrate from the purification contained the thiazine as the main product, along with unknown impurities.

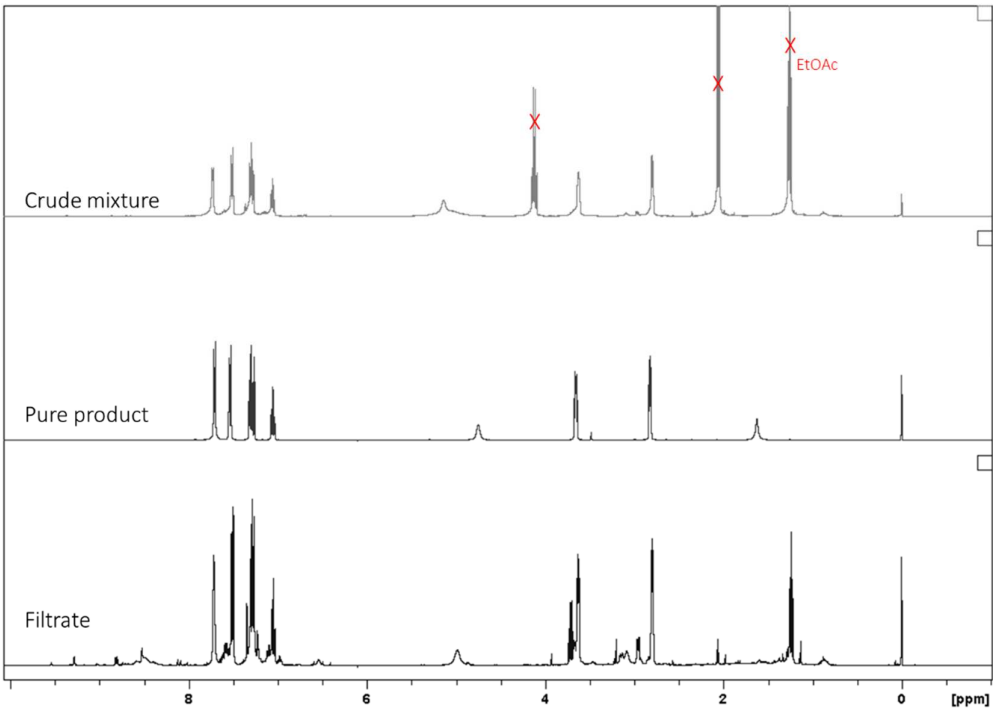


Figure 10 ^{1}H NMR spectra of **79**

Structure determination of the thiazine **79** was achieved using two dimensional NMR experiments. The signals corresponding to protons at C-3 and N-8 could be distinguished by singlets at 7.72 ppm and 7.71 ppm respectively (Figure 11).

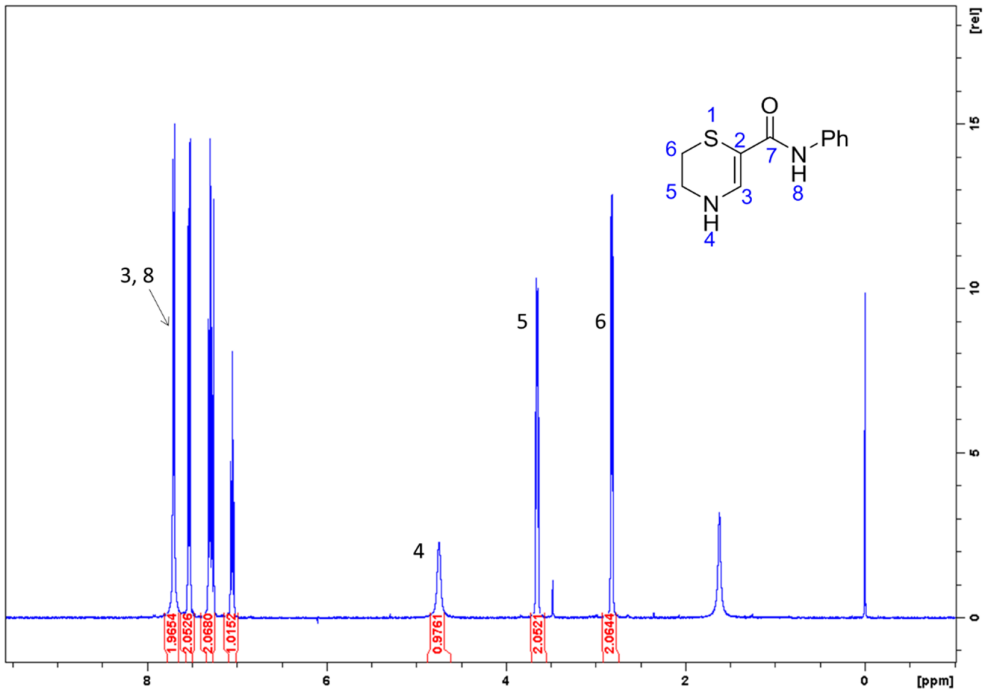


Figure 11 ^{1}H NMR Spectrum of thiazine **79** in $CDCl_3$

Due to the overlapping of these two signals, H/D exchange experiment was performed to support this assignment (Figure 12). Following addition of D_2O to the sample NMR tube, the integration of the signal in the portion 7.0-7.3 ppm was significantly decreased, in the resulting ^{1}H NMR spectra, leading to a singlet at 7.72 ppm integrating for one proton.

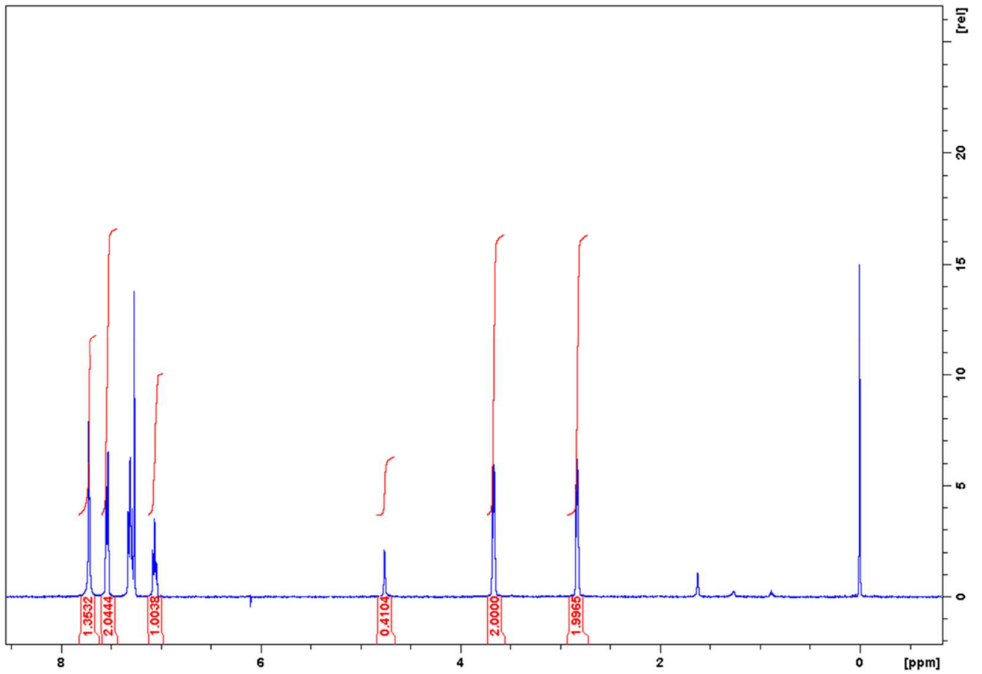


Figure 12 ^{1}H NMR Spectrum of thiazine **79** with D_2O in $CDCl_3$

In the COSY spectrum of thiazine **79**, correlation between the N-4-H of the thiazine ring and C-3-H (Figure 13) is observed. This correlation is not present for α-thio-β-chloroacrylamide **90**.

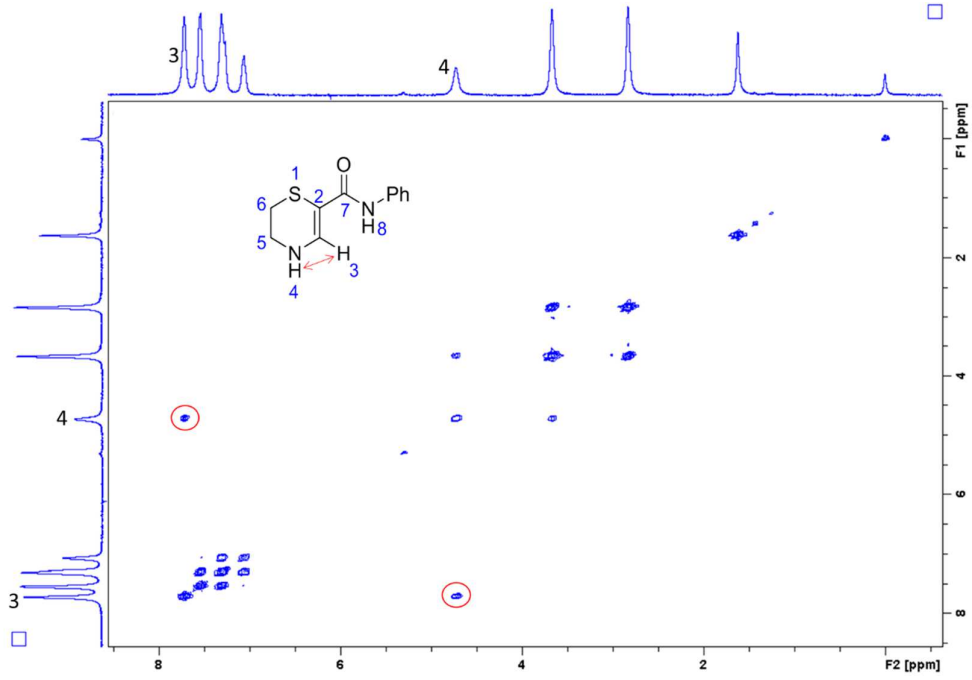


Figure 13 COSY Spectrum of thiazine **79** in $CDCl_3$

In addition, the HMBC spectrum shows a correlation between the methylene group at C-5 and C3-H demonstrating the cyclic structure (Figure 14).

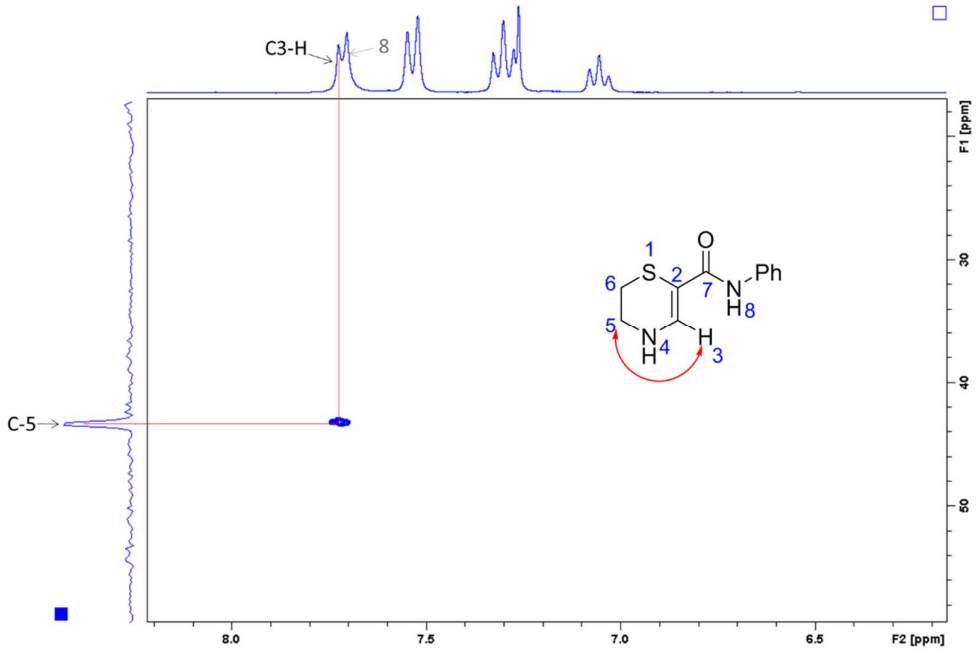


Figure 14 HMBC Spectrum of thiazine **79** in $CDCl_3$

Comparison of the signals of the amide NH proton in the ^1H NMR spectra of α-thio-β-chloroacrylamide **66** and **85** proved very interesting, with a shielding effect when replacing the alcohol group by a NH-BOC group in the molecule (Figure 15).

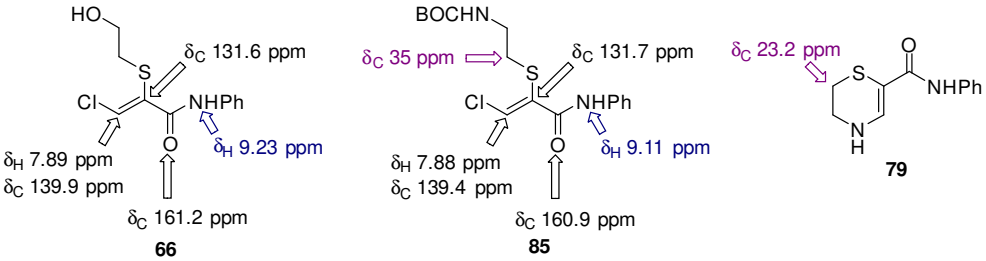
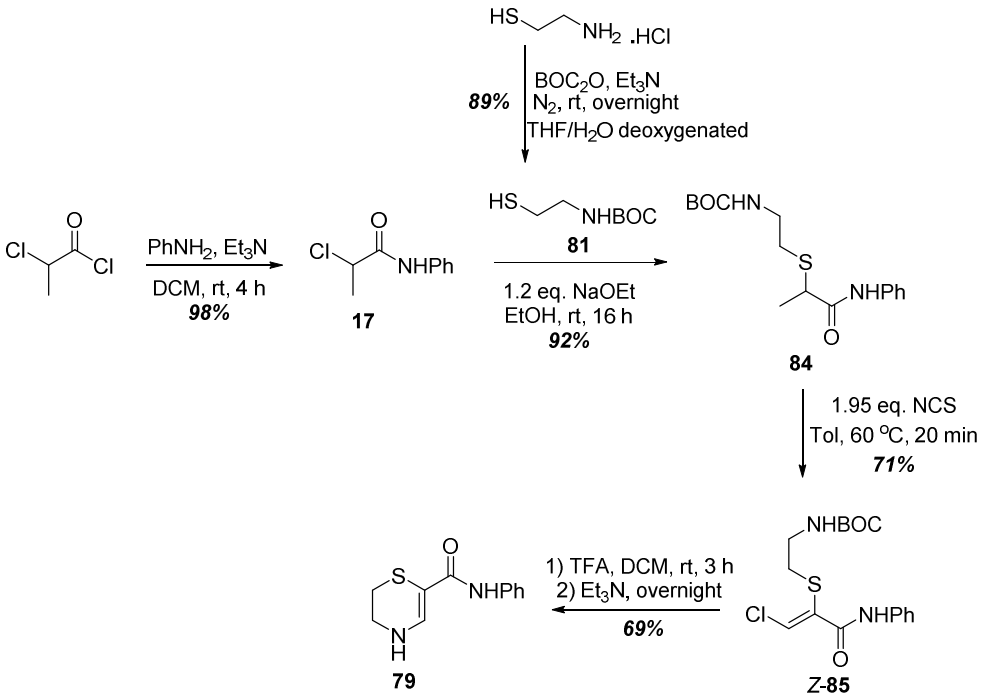


Figure 15

The intramolecular hydrogen bonding between the hydroxyl and the amide group in **66** decreases the electronic density of the amide NH proton and therefore the observed chemical shift is upfield. Other protons and carbons in these molecules are not affected by this change of functional group.

Cyclisation of α-thio-β-chloroacrylamide *Z*-**85** to thiazine **79** has a pronounced shielding effect on the methylene carbon CH_2S and the chemical shift is significantly upfield.

In conclusion, the thiazine **79** was successfully synthesised from the commercially available 2-chloropropionyl chloride, through α-thio-β-chloroacrylamide *Z*-**85** (Scheme 30). Each step was carefully optimised to improve transformation selectivity and to maximize the yield.



Scheme 30 Multistep synthesis of 1,4-thiazine with optimal conditions

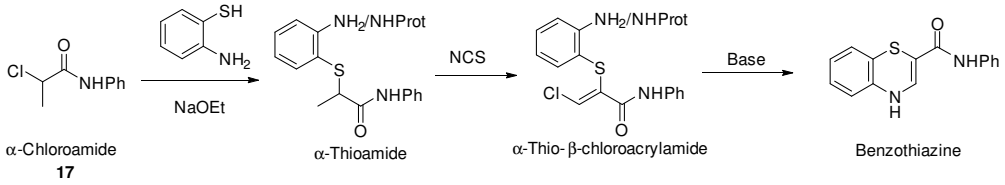
In this project, the synthesis of benzothiazine has also been performed using the same methodology *via* cyclisation of α-thio-β-chloroacrylamide derivative.

4. BENZOTHIAZINE SYNTHESIS

The synthesis of benzothiazine derivatives from α-thio-β-chloroacrylamides was also investigated. This transformation was performed by introducing a 2-amino-phenyl substituent to the sulfur group of the α-thioamide precursor.

The impact of the electronic and conformational alteration on replacing the aminoethyl chain in the 1,4-thiazine series with the aminoaryl in the 1,4-benzothiazine series was of interest. For example, it was appealing to establish whether protection would be required in this system, as seen in the series previously studied (*cf. Section 3.A.*).

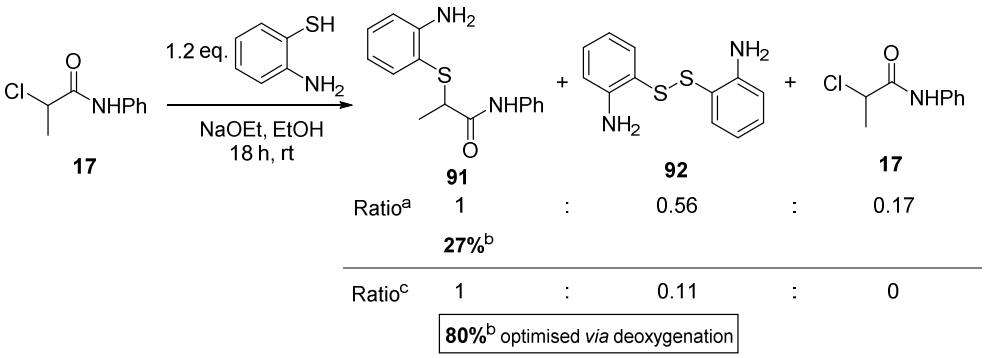
The strategy adopted was similar to that used for synthesis of thiazine **79** (*cf. Chapter 3, Section 3*) and was achieved using α-chloroamide **17** as the starting material (Scheme 31).



Scheme 31

A. Synthesis of α-thioamides

The first step in the reaction sequence was synthesis of the aryl α-thioamide precursor. The synthesis of α-thioamide **91** was first achieved using 2-aminothiophenol, employing the protocol described in *Chapter 2, Section 2.A.* (Scheme 32). Contrary to the synthesis of α-thioamide **80** (*cf. Chapter 3, Section 3.A.*), α-thioamide **91** could be prepared without prior protection of the substrate's amino group and was obtained in 27% yield after chromatography on silica gel. Indeed, by delocalization into the aromatic ring, the amine group of the 2-aminothiophenol starting material was less much nucleophilic than that of cysteamine and therefore did not initiate a competitive pathway.



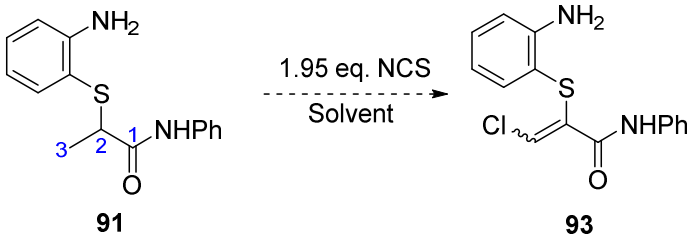
[a] Ratio of the crude product mixture by ^{1}H NMR spectroscopy when the reaction was performed in ethanol
[b] Yield of isolated product **91** after chromatography on silica gel
[c] Ratio of the crude product mixture by ^{1}H NMR spectroscopy when the reaction was performed in **deoxygenated** ethanol

Scheme 32

The low isolated yield was explained by a large amount of disulfide **92** present in the starting material[17] formed *in situ* during the reaction (crude ratio of **91** : **92** was 1 : 0.56 by ^{1}H NMR spectroscopy) and resulting in a partial conversion into the desired product.

When the reaction solvent was deoxygenated prior to the synthesis, the desired α-thioamide **91** was isolated in 80% yield following chromatography on silica gel (crude ratio of **91** : **92** was 1 : 0.11 respectively by ^{1}H NMR spectroscopy) (Scheme 32). This 10% of disulfide **92** in the crude material correspond to the excess of 2-aminothiophenol in the reaction mixture (1.2 equivalents).

Attempts of α-thio-β-chloroacrylamide synthesis from unprotected α-thioamide **91**



Scheme 33

Attempted synthesis of the corresponding α-thio-β-chloroacrylamide **93**, in toluene or acetonitrile at 70 °C (Scheme 33), provided no evidence for formation

of the corresponding dichloride, acrylamide, trichloride or α-thio-β-chloroacrylamide derivatives.

In order to facilitate further investigation, the reaction was run in tetrachloromethane while it was monitored by ^{1}H NMR spectroscopy every hour. No reaction occurred when performed at room temperature. Heating the reaction mixture under reflux conditions for 2 hours was required for consumption of the starting material to occur. However, here again, no characteristic signals corresponding to the dichloride, acrylamide, trichloride or α-thio-β-chloroacrylamide was observed by ^{1}H NMR of the crude mixture.

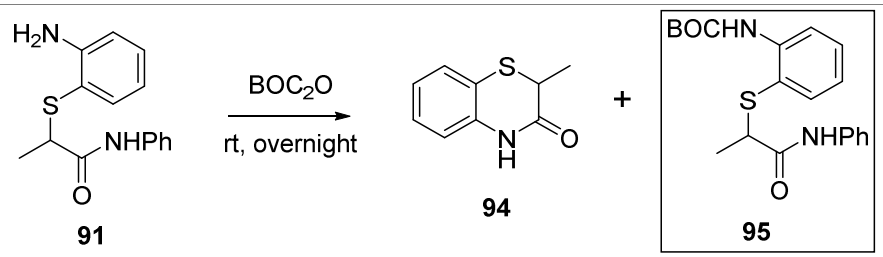
Interestingly, for these experiments, the crude product mixture shows evidence of the signals corresponding to the C(2)H and C(3)H_3 of the starting material **91**. It is possible that protonation of the primary amine group occurred during the transformation, preventing the usual oxidative chlorination cascade from occurring.

Clearly, the oxidative transformation is not compatible with the free amine group in the α-thioamide **91**. Protection of the functional group was then proposed as a potential alternative.

Protection of the α-thioamide **91**

The protection of the amine group was attempted using di-*tert*-butyl dicarbonate and triethylamine (1 equivalent each), in THF at rt overnight (Entry 1, Table 10). Unfortunately, low conversion to the novel protected α-thioamide **95** was observed, with competitive intramolecular cyclisation of the α-thioamide **91** to the benzothiazine **94**. Spectral characteristics for **94** were consistent with literature report.[18] The benzothiazine **94** is probably formed by nucleophilic displacement of anilide by the amine group, possibly with BOC activation of the leaving group. Similar transformation was observed for the formation of oxathianone **68** (*Section 1, Scheme 7*). The yield of the resulting isolated product **95** was consequently low.

Table 10 Optimisation of the preparation of **95**



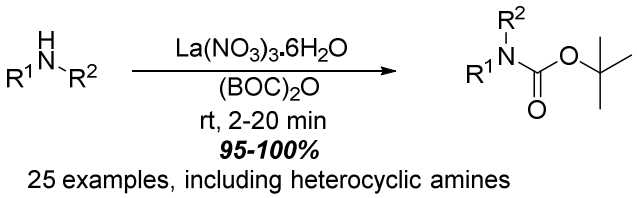
Entry	Reaction condition	BOC_2O eq.	Solvent	Ratio[a] **91** : **94** : **95**	Yield **94** (%)[b]	Yield **95** (%)[b]
1	Et_3N (1 eq.)	1	THF	1 : 0.20 : 0.74	10	31
2	-	1	THF	1 : 0 : 0	0	0
3	$La(NO_3)_3.6H_2O$ (5 mol%)	1.4	Solvent free	1 : 0 : 0	0	0
4	$La(NO_3)_3.6H_2O$ (5 mol%)	1.4	MeCN	0 : 0 : 1	0	80

[a] Crude products ratios determined by ^1H NMR spectroscopy.

[b] Yield of the pure product isolated after chromatography on silica gel.

When the transformation was attempted without triethylamine, no reaction occurred, leading to only starting material remaining demonstrating the low nucleophilic character of the amine group (Entry 2, Table 10).

Venkateswarlu *et al.*[19] had reported use of lanthanum nitrate hexahydrate [$La(NO_3)_3.6H_2O$] as a mild and efficient catalyst for *N-tert*-butoxycarbonylation of a large range of amines using di-*tert*-butyl dicarbonate under solvent free conditions (Scheme 34).



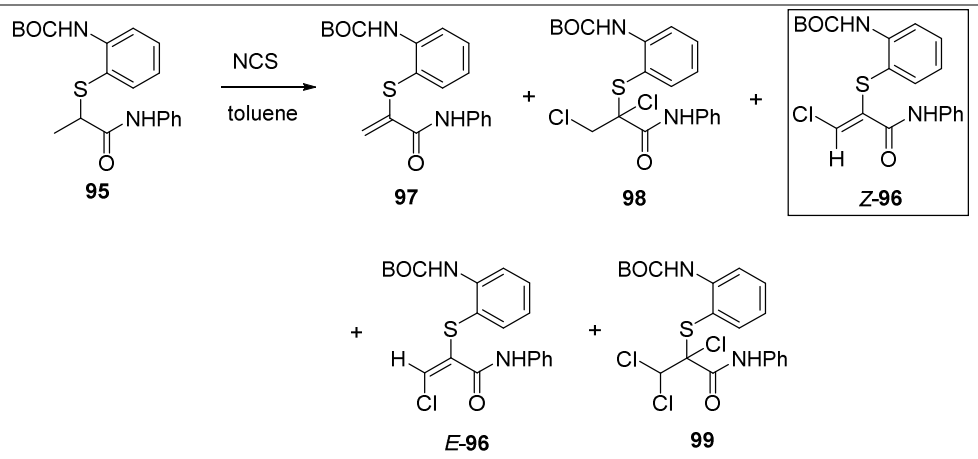
Scheme 34

It is believed that the Lewis acid coordinates with the carbonyl group of the di-*tert*-butyl dicarbonate, leading to conformation that results in a better exposure of the carbonyl groups to reaction with the substrate. In our case, the reagents are solids, therefore, the solvent free reaction (Entry 3, Table 10) led to recovery of the starting material. Acetonitrile is commonly used as the reaction solvent for *N*-tert-butoxycarbonylation of amines and high solubility of the reagents were observed in this system.[20-22] Using $La(NO_3)_3.6H_2O$ as catalyst in acetonitrile led to full conversion, with no side reaction observed by ^1H NMR spectroscopy of the crude reaction mixture (Entry 4, Table 10). The novel α-thioamide **95** was isolated in 88% yield after chromatography on silica gel.

B. Synthesis of α-thio-β-chloroacrylamides

α-Thio-β-chloroacrylamide *Z*-**96** synthesis was then attempted from the corresponding BOC protected α-thioamide **95** after it had been successfully isolated (Table 11). Due to the success previously obtained while employing acetonitrile as solvent for the synthesis of α-thio-β-chloroacrylamide *Z*-**66** (*cf. Section 2.A.2.*), the reaction was first attempted in this system. However, the transformation in acetonitrile appeared to be complex, from the crude product material recovery, presumably due to the solvent polarity. Interestingly, this result was consistent with the observations previously reported for the synthesis of α-thio-β-chloroacrylamide *Z*-**85**, also bearing a BOC protected amine (*cf. Section 3.B.*). Therefore, the optimization reactions were performed in toluene (Table 11).

Table 11 Optimisation of the preparation of *Z*-**96**



Entry	[**95**] mmol/L	T °C	Reaction time	NCS eq.	Ratio[a]					Yield *Z*-**96** (%)[b]
					97	**98**	*Z*-**96**	*E*-**96**	**99**	
1	70	60	3 h	1.95	0	2.4	1	0.2	0.4	30
2	80	100	2 h	1.95	0.2	0.3	1	0.2	0	30
3	45	90	3 h	1.95	0.3	0.1	1	0.1	0	49
4	34	90	3 h	2.30	0	0.2	1	0.1	0.1	60
5	100	90	3 h	2.05	0.1	0.5	1	0.1	0	44
6[c]	120	90 then 110	3 h 2 h	2.00	0	0	1	0	0.1	36

[a] Crude product ratios determined by ^{1}H NMR spectroscopy.

[b] Yield of the pure product isolated after chromatography on silica gel.

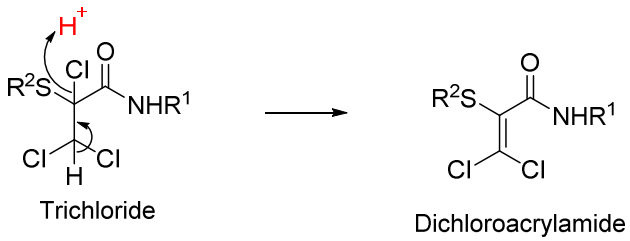
[c] The reaction was plunge into a pre-heated oil bath at 90 °C and stirred at this temperature for 3 h, then the heating was increased to 110 °C and stirred at this temperature for 2 h.

All the optimisation experiments were run by employing a 'hot plunge' technique, and the succinimide by-product was removed by filtration of the reaction mixture at 0 °C.

For some experiments, trichloride **99** formation was observed by ^{1}H NMR spectroscopy of the crude mixture (Entries 1, 4 and 6, Table 11). The trichloride of this series remained stable as no evidence of the corresponding

dichloroacrylamide forming was found using mass spectrometry of the crude mixture. Therefore, the integration of the β-proton of the trichloride derivative using ^{1}H NMR spectroscopy of the crude mixture represented the ratio of over-chlorination happening during the reaction.

In contrast to earlier series, the stability of the trichloride **99** was consistent with the result observed previously for the trichloride **86** of the 1,4-thiazine series, also bearing a BOC protected amine (*cf. Section 3.B.*). It is believed that traces of hydrochloric acid trigger loss of chloride from the trichloride derivative leading to the dichloroacrylamide (Scheme 35). It was envisaged that the BOC group present in the molecule may well consume any HCl present and thereby prevent decomposition to the corresponding dichloroacrylamide. This may also result in reducing the yield of the isolated α-thio-β-chloroacrylamide.



Scheme 35

When the reaction was performed at 60 °C, a large amount of dichloride intermediate **98** was observed in the ^{1}H NMR crude spectra (Entry 1, Table 11). Also, the over-chlorinated product **99** was formed in the mixture. This suggested that a higher reaction temperature was required for a clean transformation, with respect to the products formed.

In almost all experiments, formation of the *E*-isomer was observed, with a ratio between 0.1-0.2 relative to the *Z*-isomer. The stereoselectivity did not appear to be dependent on the reaction temperature or equivalents of NCS employed.

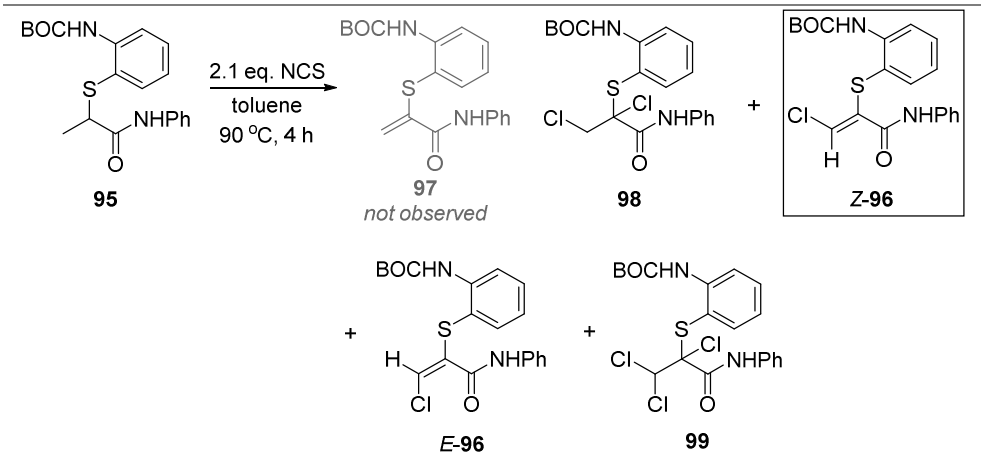
In all experiments, the corresponding isolated yield of *Z*-**96** was not necessarily reflected in the crude mixture obtained, but the concentration of the starting material seemed to be directly related to the yield of the isolated product (*ie.* Entry

6, Table 11). Therefore, further investigations were undertaken on the reaction process such as the concentration of the reaction solution and the work-up directly related to it (*i.e.* filtration) (Table 12).

^{1}H NMR spectroscopy of the crude mixtures showed that *Z*- and *E*-**96** were formed in 10 to 1 ratio respectively under each of the conditions (Table 12). Also, using these conditions, acrylamide **97** formation was not observed.

When the reaction mixture was gradually heated to 90 ^{o}C, after addition of NCS, the reaction outcome was only slightly impacted by the concentration of the reagent in solution (Entry 1 *vs* Entries 2 and 3, Table 12). When the reaction mixture was plunged into an oil bath at 90 ^{o}C instantly after addition of NCS, increase of reagent concentration significantly increased the trichloride **99** ratio in the crude mixture (Entry 4 *vs* Entries 5 and 6, Table 12). Even though mild changes were observed on the reaction outcome, interestingly in this system, the efficiency of the transformation cascade, as evidenced by the product ratio, was not significantly impacted from the standard hot plunge technique to gradual heating of the reaction mixture (Entry 1 *vs* Entry 6 and Entry 3 *vs* Entry 4, Table 12).

Table 12 Optimisation of the preparation of *Z*-**96**



Entry	Heating	Work-up	[**95**] mmol/L	Ratio[a]				Yield[b] *Z*-**96** (%)
				98	*Z*-**96**	*E*-**96**	**99**	
1[c]	Gradual	Filtration[d]	134	0	1	0.1	0.2	40
2[c]	Gradual	Filtration[d]	70	0.1	1	0.1	0	65
3[c]	Gradual	-[f]	70	0.06	1	0.1	0.1	62
4[e]	Hot Plunge	-[f]	70	0.03	1	0.1	0	73
5[e]	Hot Plunge	-[f]	134	0.1	1	0.1	0.3	36
6[e]	Hot Plunge	Filtration[d]	134	0.1	1	0.1	0.25	27

[a] Crude ratios determined by ^{1}H NMR spectroscopy.

[b] Yield of the pure product isolated after chromatography on silica gel.

[c] The reaction mixture was heated progressively from room temperature.

[d] Succinimide by-product was removed from the reaction mixture by filtration at 0 °C.

[e] The 'hot plunge' technique was used.

[f] Succinimide was not removed from the mixture, the column chromatography was performed without any previous treatment of the crude mixture.

In addition, the isolated yield of *Z*-**96** seemed to be directly related to the concentration of starting material employed (Entries 1 and 2, Table 12). When the succinimide by-product was not removed by filtration from the reaction mixture, after the transformation, the yield of *Z*-**96** was increased, by employing the same

95 concentration (Entry 5 *vs* Entry 6, Table 12). These observations suggest that the products are slightly insoluble in toluene at 0 °C, when highly concentrated. Therefore, the desired product was removed from the crude mixture when the succinimide filtration was performed, and thus, significantly decreased the yield (Entry 6, Table 12). Using a lower concentration of the starting material resulted in less precipitation of the product in the crude mixture and, consequently, more *Z*-**96** would be recovered after the filtration step (Entries 1 and 3, Table 12).

Therefore, the optimal conditions for this transformation employed a solution of starting material **95** at 70 mmol concentration in toluene, using hot plunge heating conditions at 90 °C. After heating the reaction mixture at 90 °C for 4 hours, the reaction solvent was removed under reduced pressure, without prior filtration of the succinimide by-product. *Z*-**96** was isolated in pure form after chromatography on silica gel in 73% yield.

Based on our study in *Chapter 2*, the characteristic signals corresponding to the β-proton of intermediates, products and by-product could easily be identified by ^{1}H NMR spectroscopy (Figure 16).

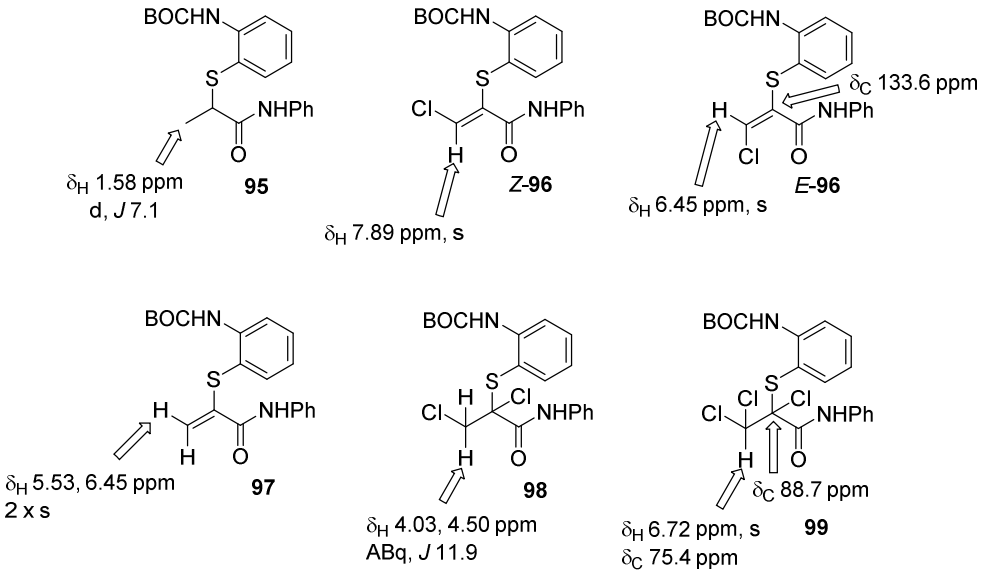


Figure 16 Characteristic signals by ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$

The main product formed for all these experiments (Tables 11 and 12) was the α-thio-β-chloroacrylamide **96**, assigned as the less polar *Z*-isomer. The derivative

was characterised and quantitated using a singlet at δ_H 7.89 ppm by ^{1}H NMR spectroscopy, corresponding to the proton of the β-carbon. The more polar *E*-isomer was characterised by a singlet at δ_H 6.45 ppm.

For previous series studied in this work, the *E*-isomers are generally less polar while the *Z*-isomers are more polar.[23] It was suggested that the *E*-isomer would cause more strain between the chloride and the carbonyl group and therefore more out-of-plane distortion, leading to poorer orbital overlap (Figure 17),[9] affecting directly the polarity.

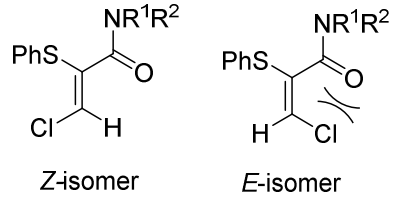


Figure 17

This leads to a decrease in the extent of resonance delocalization between the unsaturation system and the carbonyl group, resulting in a shielding of the β-proton in the *E*-isomer, compared to the corresponding β-proton in the *Z*-isomer by ^{1}H NMR spectroscopy. The upfield shift of the β-proton in the *E*-isomer, relative to that of the *Z*-isomer reflects this analysis.

In addition, previous work in the group by Murphy[9] also assigned the stereochemistry with the order of polarity, in addition to NMR analysis.

Due to the aromatic NHBOC substituent in the α-thio-β-chloroacrylamide **96**, the interactions with the surface of the silica gel and the molecule are substantially altered, resulting in a switch of the isomer relative polarity.

For the *N*,*N*-dimethyl-β-chloroacrylamides **100**, **101** and **102** synthesised by Lynch[24] and Kissane[15], the less polar isomer was the major isomer and the more polar isomer was the minor isomer in each instance (Figure 18).

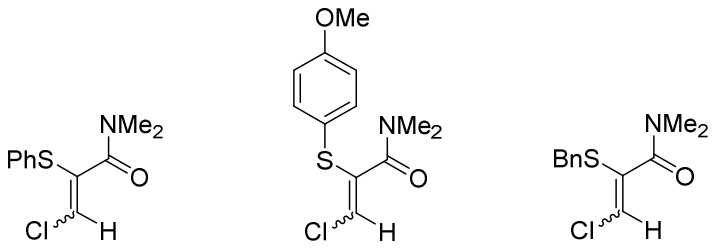


Figure 18

The signal of the β-carbon in the ^{13}C NMR spectrum of the less polar isomer appeared further downfield than the corresponding signal in the ^{13}C NMR spectrum for the more polar isomer. Accordingly, the less polar isomer was tentatively assigned as *Z*.[15] The same assignment can be made for **96** (Figure 19).

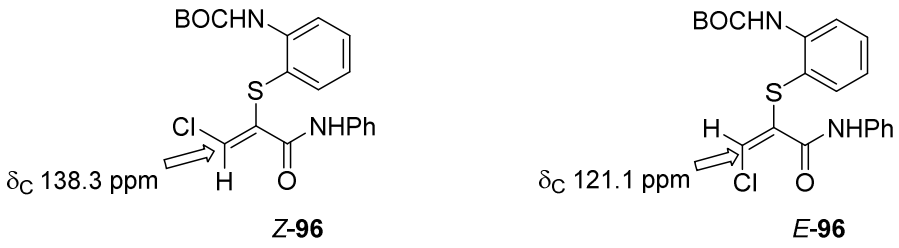


Figure 19

While the stereochemistry of **96** has not been definitely confirmed by X-ray crystal structure, the spectroscopic evidence strongly supports this assignment.

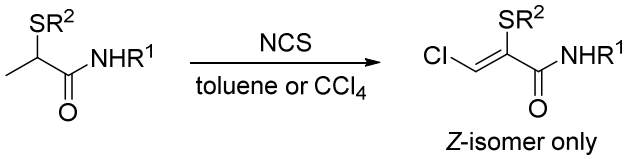
α-Thio-β-chloroacrylamide *E*-**96** can not be separated from the acrylamide **97** by chromatography on silica gel and, therefore, was isolated as a mixture with **97** (Entry 2, Table 11), while *Z*-**96** can be isolated in pure form.

The characteristic signals corresponding to *E*-**96** and acrylamide **97** overlapped in the region δ_H 6.42-6.47 ppm on the ^1H NMR spectra (Figure 16). Indeed, the acrylamide intermediate was characterised by two singlets at δ_H 5.53 and 6.45 ppm. For determination of an accurate ratio of formation of these two derivatives from the crude spectra, the ratio of the acrylamide **97** was assessed using the integration of the singlet at δ_H 5.53 ppm and the ratio of the *E*-isomer, using the integration of the signals at δ_H 6.45 ppm, taking into consideration that one proton of the acrylamide was contained within this signal.

The dichloride intermediate could be characterised by a AB quartet pattern between δ_H 4.0 and 4.6 ppm (Figure 16). The dichloride **98** was found more stable than those of the earlier series studied and can be isolated in pure form. Here again, for this series, the increase in the dichloride stability is believed to be associated with the BOC protected amine substituent as previously discussed for the trichloride **99** stability (Scheme 35).

C. Stereoselectivity insight of α-thio-β-chloroacrylamide synthesis

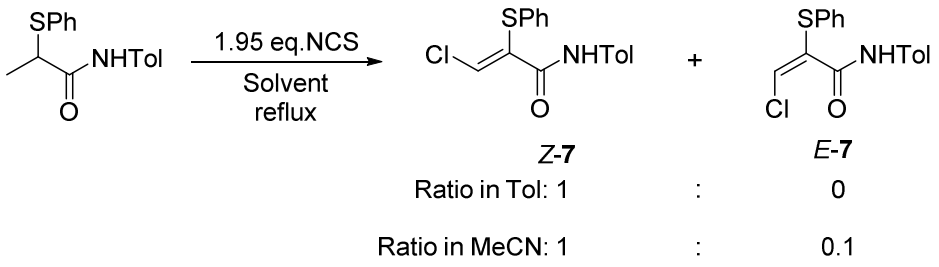
Earlier studies in the group reported that α-thio-β-chloroacrylamides, from secondary propenamides, are formed exclusively as the *Z*-isomer (Scheme 36).[9,15,23,24]



Scheme 36

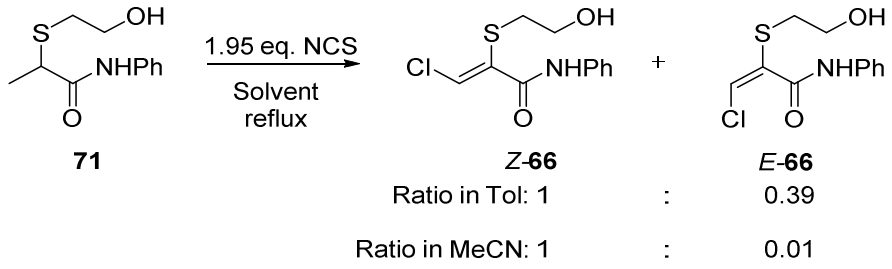
However, with butanamides, pentanamides or tertiary propenamide derivatives, a mixture of *E*- and *Z*-isomers is formed.[23] Intramolecular hydrogen bonding between sulfur atom and the amide proton, as well as steric hindrance are both responsible for this stereoselectivity, as previously discussed in *Chapter 2, Section 1*.[14]

For the first time, formation of the *E*-isomer of α-thio-β-chloroacrylamide **7** was observed, while employing acetonitrile as solvent for the transformation, instead of the commonly used toluene or tetrachloromethane (Scheme 37).[25]



Scheme 37

In contrast to these observations, synthesis of the functionalized α-thio-β-chloroacrylamide **66** in toluene generates both the *Z*- and *E*-isomer in ratio 1 : 0.39 respectively by ^{1}H NMR spectroscopy (Scheme 38), while in acetonitrile the ratio of *E*-**66** drops to 0.01 (*cf. Section 2.A.2*).



Scheme 38

It was first envisaged that intramolecular hydrogen bonding between the hydroxy group and the amide proton competes with the intramolecular hydrogen bond between the sulfur and the amide group, which is believed to be responsible for the stereoselectivity (Figure 20).

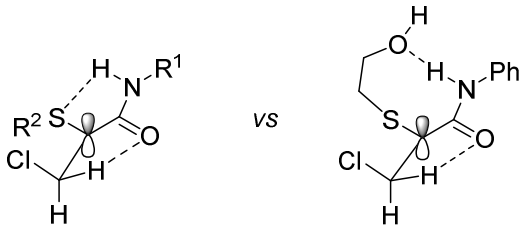
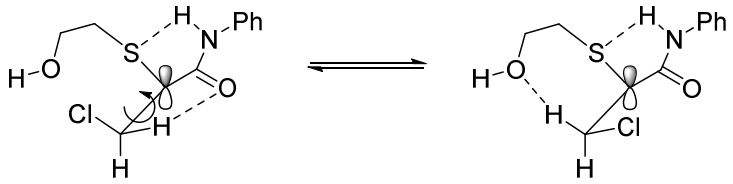


Figure 20

However, NMR experiments suggests that the hydroxy group of *E*-**66** is interacting with the β-H. Therefore, intramolecular hydrogen bonding between the hydroxy

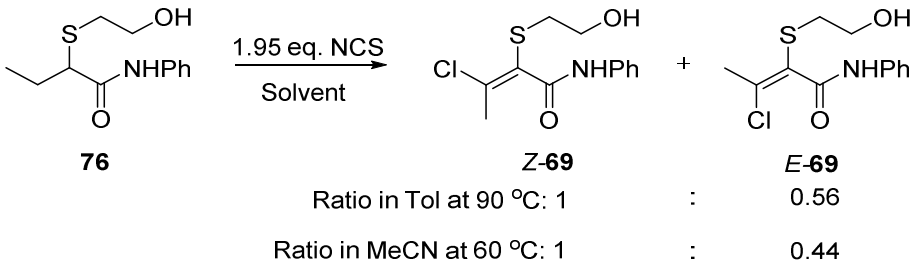
group and the β-proton may results in a change of conformation in the transition state of the sulfur carbocation leading to the *E*-isomer (Scheme 39).



Scheme 39

Stereoselectivity was increased while using the polar acetonitrile solvent, presumably due to the competing hydrogen bonding with the hydroxy group and the solvent.

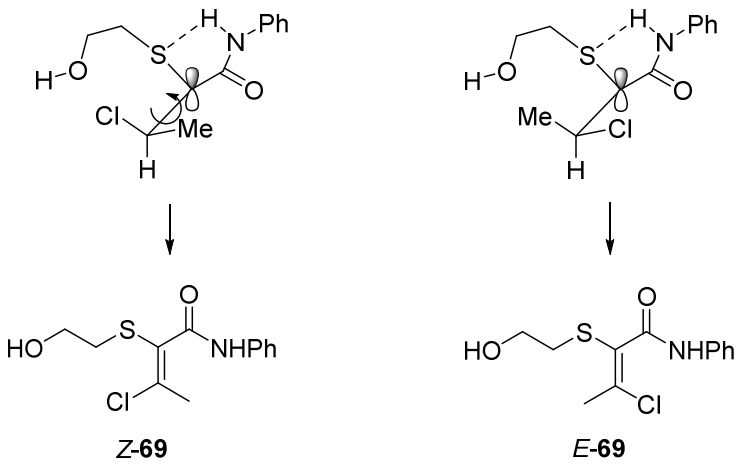
However, for the butanamide precursor **76**, using acetonitrile instead of toluene as the solvent system did not significantly increase the stereoselectivity of the transformation (Scheme 40).



76 *Z*-**69** *E*-**69**

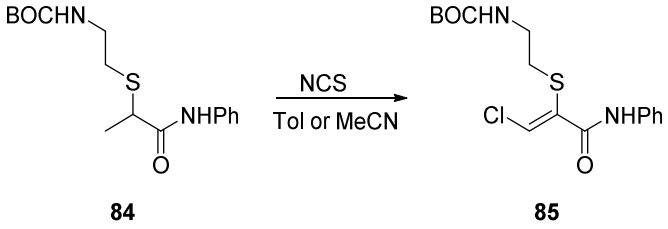
Scheme 40

This may favor the second hypothesis, as for this precursor no intramolecular hydrogen bond can happen between the hydroxy group and the β-proton (Scheme 41). Therefore, the hydroxy group can interact with the solvent system without impacting the conformation of the molecule during the last proton elimination step.



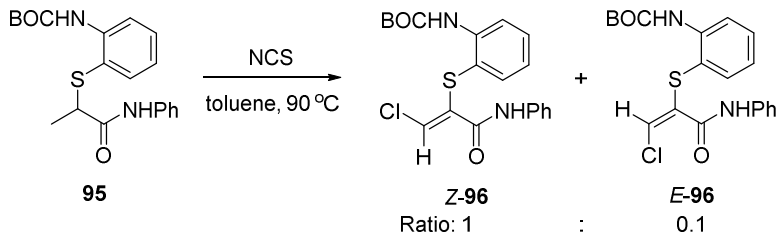
Scheme 41

Interestingly, for the alkyl BOC protected amine derivative **85**, only the *Z* isomer was formed in toluene and acetonitrile (Scheme 42). It can be envisaged that, in contrast to the hydroxy-derivative **66**, the BOC protection prevents the amine group from being involved in intramolecular hydrogen bonding.



Scheme 42

The synthesis of α-thio-β-chloroacrylamide **96** in toluene affords both the *Z*- and *E*-isomer in a ratio 1 : 0.1 respectively by ^{1}H NMR spectroscopy (Scheme 43). The bulky *o*-NHBOCphenyl substituent may influence the conformation in the transition state of the sulfur carbocation, and the elimination leading to the *E*-isomer happens in 10% of the case.



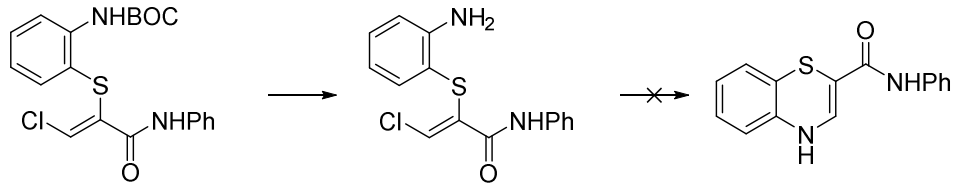
Scheme 43

For the first time, it was observed that not only employing butanamides, pentanamides or tertiary propenamide derivatives impact the stereoselectivity of the transformation, but also the sulfur substituent and the solvent system was crucial.

D. Synthesis of benzothiazine

Having successfully generated the α-thio-β-chloroacrylamide *Z*-**96**, the deprotection of the amine group of *Z*-**96** and its cyclisation were first attempted *in situ*, as successfully performed for thiazine **79** synthesis, in which the deprotection and subsequent cyclisation was achieved (*cf. Chapter 3, Section 3.C*). Interestingly, the deprotected α-thio-β-chloroacrylamide *Z*-**93** does not cyclise to the benzothiazine derivative **103** using conditions developed for thiazine **79** synthesis (Table 13). Therefore, the corresponding deprotected α-thio-β-chloroacrylamide *Z*-**93** was isolated prior to the cyclisation step, in moderate yield as the main product formed.

Table 13 Preparation of *Z*-**93**



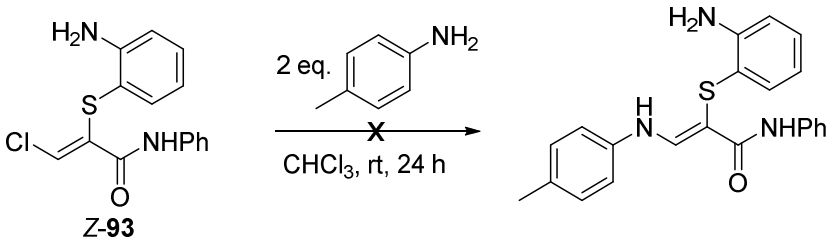
***Z*-96** ***Z*-93** **103**

Entry	Conditions	Yield[a] (%) **93**
1	1) TFA, rt in DCM 2) Et_3N, overnight	63
2	1) HCl 4M in EtOAc 2) NaOH, 60 °C, 2h	47

[a] Yield of the pure deprotected α-thio-β-chloroacrylamide *Z*-**93** after chromatography on silica gel.

The lack of spontaneous cyclisation of *Z*-**93** may be due to electronic effects or conformational constraint. To explore the electronic effect which may be involved, the electrophilicity of the β-carbon toward nitrogen nucleophiles was investigated by reaction with *para*-toluidine. Interestingly, when α-thio-β-chloroacrylamide *Z*-

93 was treated with *para*-toluidine in chloroform, no evidence for nucleophilic substitution was observed by NMR spectroscopy (Scheme 44).



Scheme 44

Interestingly, Michael addition of amines such as morpholine proceeds very quickly across the α-thio-β-chloroacrylamide series. However, when the reaction with *para*-toluidine was attempted with the *N*-benzyl-*Z*-3-chloro-2-(benzylthio)propenamide **26**, no reaction was observed demonstrating the decreased nucleophilicity of the aryl amine.

The reactivity of sulfoxide and sulfone derivatives of the α-thio-β-chloroacrylamides was envisaged to be significantly different to that of the sulfide. The decrease in the extent of resonance electron-donation by the sulfur atom and the increase in the inductive electron withdrawing effect results in a more electrophilic β-carbon for these derivative (Figure 21). Therefore, the reactivity of the α-thio-β-chloroacrylamides as Michael acceptors should be increased. Earlier work in the group has demonstrated this effect.[5]

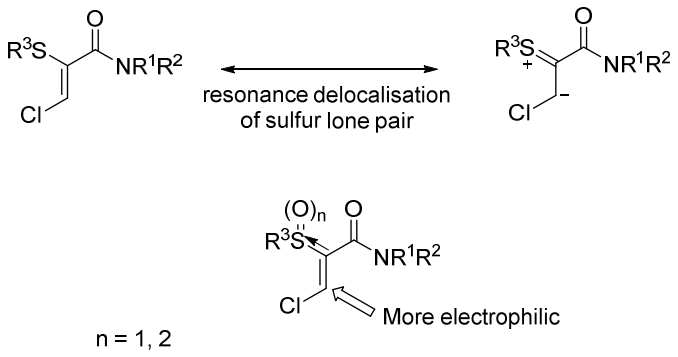
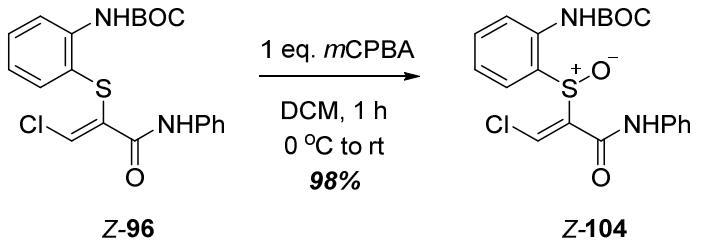


Figure 21

Accordingly, synthesis of the sulfoxide derivative of α-thio-β-chloroacrylamide *Z*-**96** was conducted by treatment with 1 equivalent of *m*CPBA (Scheme 45). After 1

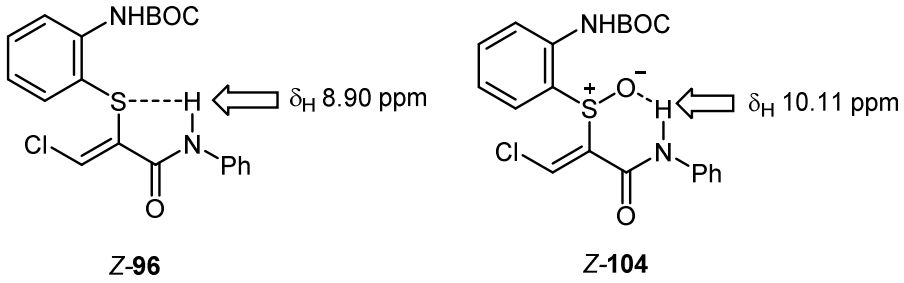
hour at room temperature, full conversion was observed by TLC analysis, and the pure novel α-thio-β-chloroacrylamide *Z*-**104** was isolated in 98% yield which required no further purification. Also, no evidence for over oxidation to the sulfone level was observed.



Z-**96** *Z*-**104**

Scheme 45

In line with earlier results described by Lynch,[24] the participation of the amide proton in strong hydrogen bonding in the sulfoxide, as reported *via* crystal structure analysis of an analogue sulfoxide derivative, is reflected in the significant downfield shift of 1.2 ppm of the NH signal in the ^{1}H NMR spectra of the sulfoxide **104** (Figure 22).



Z-**96** *Z*-**104**

Figure 22

The frequency of the carbonyl stretch in the IR spectra increased by 25 cm^{-1} on oxidation of the α-thio-β-chloroacrylamide *Z*-**96** (Figure 23). The decreased electronic delocalisation in the acrylamide system due to the inductive effect of the sulfoxide group accounts for this effect.

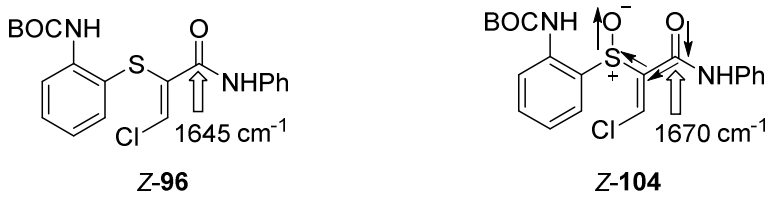
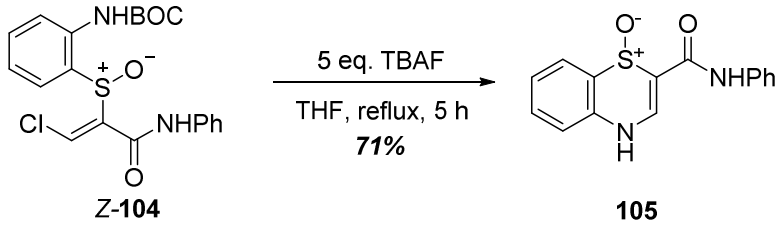


Figure 23

In contrast to the deprotection of *Z*-**96** at the sulfide level of oxidation, deprotection of the amine group of *Z*-**104** using TFA or HCl led to a complex mixture of products. Indeed, the Pummerer reaction is known to occur by the addition of a stoichiometric amount of strong acid or anhydride to an alkylsulfoxide derivatives, and so, could be leading to a complex mixture of products.[26]

Coudert *et al.*[27] had reported a mild and efficient deprotection of carbamates with tetra-*n*-butylammonium fluoride (TBAF). Using 5 equivalents of TBAF under reflux, as described in the literature, *Z*-**104** led to the benzothiazine **105** with full conversion (Scheme 46). Addition of ammonium chloride initiated the crashing out of the product and the resulting precipitate was washed with dichloromethane followed by hot methanol. The final product was successfully isolated as a high melting point white solid with 71% yield.



Scheme 46

The spontaneous intramolecular cyclisation of the deprotected α-thio-β-chloroacrylamide *Z*-**93** demonstrates the increase of the electrophilicity of the β-carbon, compared to the sulfide analogue. In addition, oxidation of the sulfide group to sulfoxide may engender a new conformation of the molecule, particularly due to the hydrogen bonding between the sulfoxide and the amide group, in which the cyclisation may occur more favorably.

In the 2000's, Neurogen Corporation© described the high biological activity of 4H-1,4-benzothiazine-2-carboxamides (Figure 24) in two patents.[28, 29] Compounds of the formula in Figure 26 bind with high selectivity and high affinity to the benzodiazepine site of human $GABA_A$ receptors and therefore are highly selective agonists or antagonists for these receptors. Consequently, these compounds are valuable for treatment of anxiety, depression, sleep disorders, psychosis, Parkinson's disease, cognitive and seizure disorders, but also in case of overdose with benzodiazepine drugs and for enhancement of alertness. Benzothiazine **105** is a new compound and the conjugated system provided by the phenyl substituent of the amide group may be interesting to further evaluate for this bioactivity.

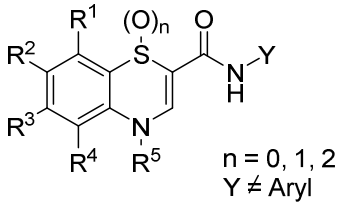


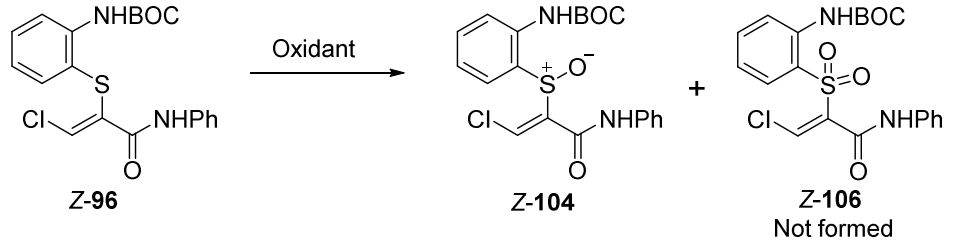
Figure 24

Attempting reduction and oxidation of the benzothiazine **105** was unsuccessful because of the low solubility of the derivative in all solvent systems. Therefore, functionalization of the scaffold proved challenging.

The sulfone analogue should have a higher solubility than the sulfoxide **105**. Synthesis, by oxidation, of the sulfone derivative of the protected α-thio-β-chloroacrylamide *Z*-**96** was attempted with many oxidizing agents (Table 14).

While, one equivalent of *m*CPBA, cumene peroxide and MMPP (2 to 5 equivalents, 40 to 83°C) led exclusively to the sulfoxide derivative *Z*-**104**, other oxidative conditions led to the starting material remaining or a complex mixture of products by decomposition.

Table 14 Oxidation of the sulfide **96**

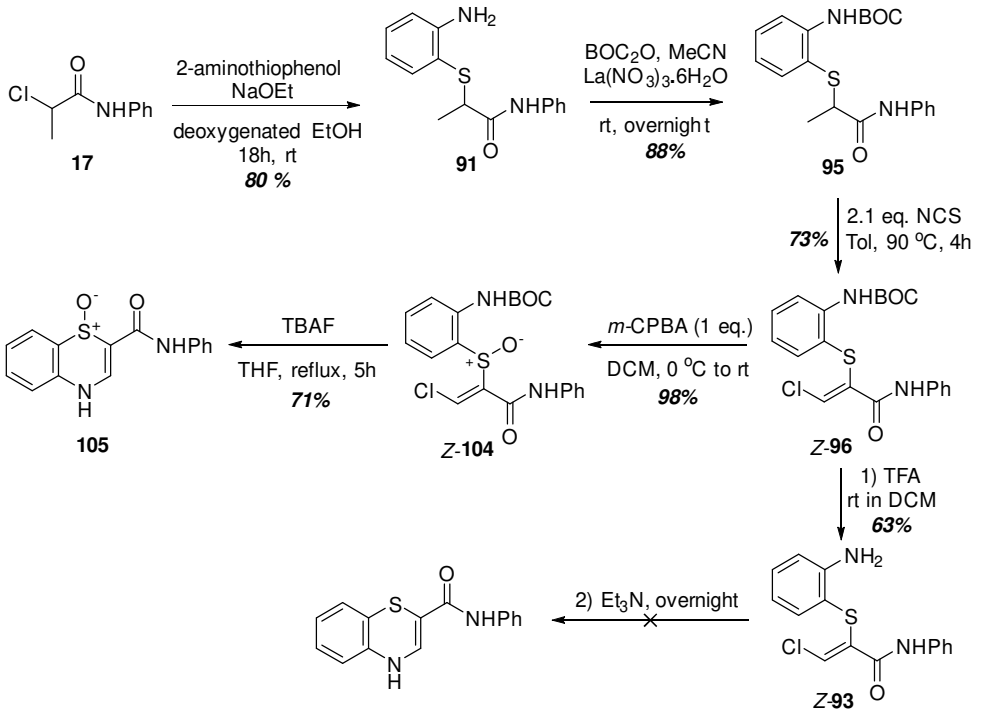


Entry	Oxidant (eq.)	Conditions	Solvent	Product	Yield[a] *Z*-**104** (%)
1	*m*CPBA (1 eq.)	0 °C to rt, 1 h	DCM	*Z*-**104**	98
2	mCPBA (4 eq.)	0 °C to rt, overnight	DCM	Complex mixture	
3	Oxone® (1.5 eq.)	60 °C, 12 h	H_2O	SM remaining	
4	Hydrogene Peroxide (3 eq.)	Reflux, 30 min	Acetic acid	Complex mixture[b]	
5	Cumene peroxide (3 eq.)	Reflux, 2 h	Acetic acid	*Z*-**104**	82
6	MMPP (2 eq.)	Reflux, 40 min	DCM	*Z*-**104**	93
7	MMPP (5 eq.)	Reflux, 2 h	DCM	*Z*-**104**	90
8	MMPP (5 eq.)	Reflux, 4 h	DCE	*Z*-**104**	95

[a] Yield of the pure product after chromatography on silica gel.
[b] *tert*-Butyloxycarbonyl signal was not observed by ^{1}H NMR spectroscopy of the crude mixture.

In all the cases, the formation of sulfone derivative *Z*-**106** was not observed. An attempt to oxidize the pure sulfoxide **104** was made using MMPP (5 eq.) under reflux in dichloroethane for 4 hours but formation of the corresponding sulfone analogue was not observed by NMR spectroscopy and mass spectrometry. Therefore, synthesis of the benzothiazine at the sulfide or sulfone oxidation level could not be attempted by this route.

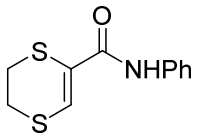
In this work, the novel amine protected α-thio-β-chloroacrylamide *Z*-**96** was successfully synthesised in good yield (Scheme 47). As the deprotected α-thio-β-chloroacrylamide *Z*-**93** was not able to process intramolecular cyclisation, due to the poor nucleophilicity of the aryl amine group, an alternative strategy was developed in order to obtain the corresponding benzothiazine. Increase of the β-carbon electrophilicity of the α-thio-β-chloroacrylamide *Z*-**96** was achieved by oxidation of the sulfur atom to the sulfoxide level. Therefore, the sulfoxide α-thio-β-chloroacrylamide *Z*-**104** spontaneously generates the benzothiazine **105** when deprotected.



Scheme 47 Multistep synthesis of benzothiazine with optimal conditions

5. DITHIIN SYNTHESIS INVESTIGATIONS

Considering the achievements reached for the 1,4-oxathiin, thiazine and benzothiazine synthesis, extension of the strategy to the synthesis of dithiin derivative **107** (Figure 25) from α-thio-β-chloroacrylamide was investigated.

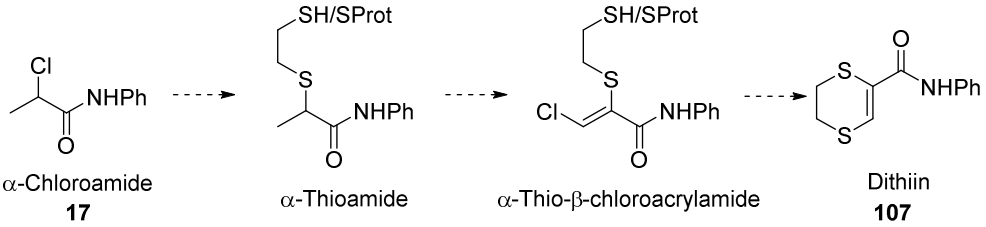


107

Figure 25

Sulfur is an excellent nucleophile because its electron cloud is polarizable. The less basic thiolate ions are less well solvated compared to alkoxide ions, so in protic solvents, the larger thiolate ions are better nucleophiles than alkoxide ions. Thus, the cyclisation could potentially be performed in protic solvents.

The reaction sequence described in Scheme 48 was investigated to synthesise dithiin **107** from α-chloroamide **17**. Following on from the experiments in earlier series, where protection of the hydroxy group was unnecessary for the oxidative chlorination (*cf. Section 2.A.*), while amine protection was essential (*cf. Section 3.B. and Section 4.B.*), it was envisaged that thiol protection was needed, especially due to the ease of disulfide formation in the oxidative conditions.

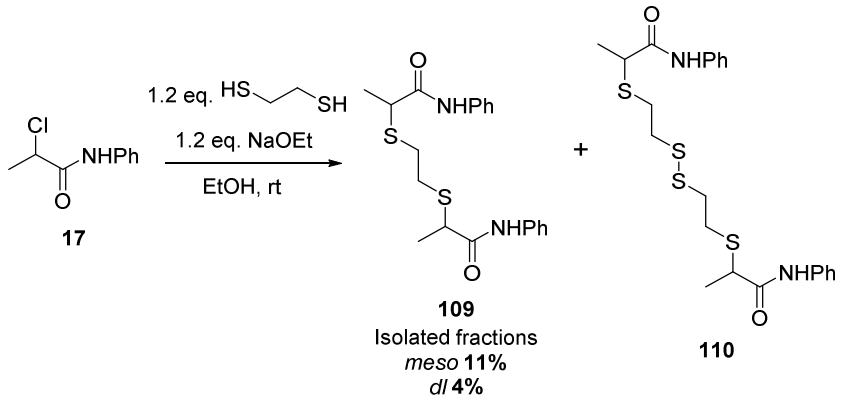


Scheme 48

A. Synthesis of α-thioamides

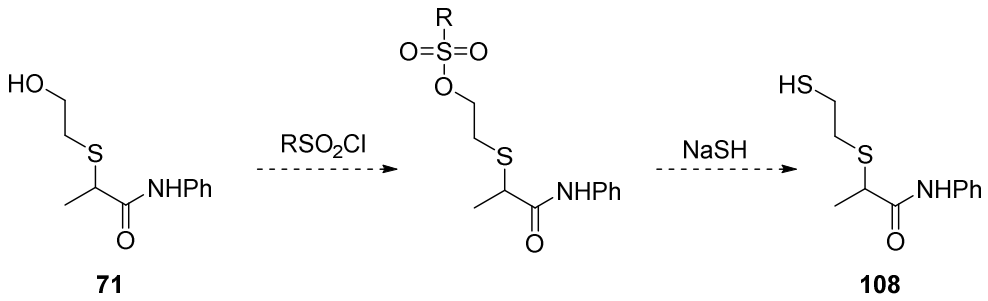
Synthesis of the unprotected α-thioamide **108** was first attempted using ethanedithiol and α-chloroamide **17** using the protocol described in *Chapter 2, Section 2.A.* (Scheme 49). The solvent was deoxygenated prior to use. The formation of the desired α-thioamide **108** was not observed by ^{1}H NMR spectroscopy of the crude mixture. The crude product consisted in a mixture of the *meso* and *dl* diastereoisomers of α-thioamide **109** and of disulfide **110**. A fraction containing the *meso* and *dl* diastereoisomers of **109** could be separated by chromatography on silica gel and are obtained in 11% and 4% yield respectively.

The major product portion was isolated as a mixture of the diastereoisomers of both **110** and **109** due to their similar polarities. The signals of the compounds overlapped on the ^{1}H NMR spectra, and therefore, the respective ratios could not be determined.



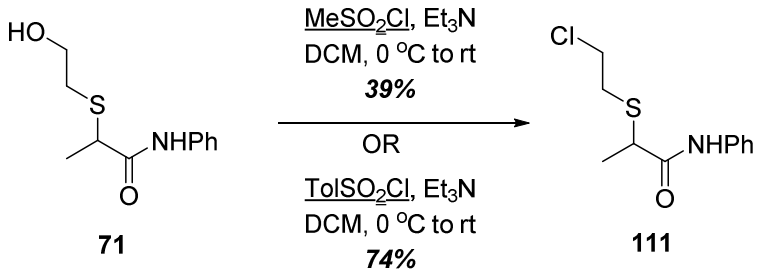
Scheme 49

An alternative approach was proposed from the previously synthesised 2-((2-hydroxyethyl)thio)-*N*-phenylpropanamide **71** (*cf. Chapter 3, Section 2.A.1.*). From the corresponding mesylated/tosylated derivatives, α-thioamide **108** could potentially be formed using sodium hydrosulfide or an alternative sulfur nucleophile (Scheme 50).



Scheme 50

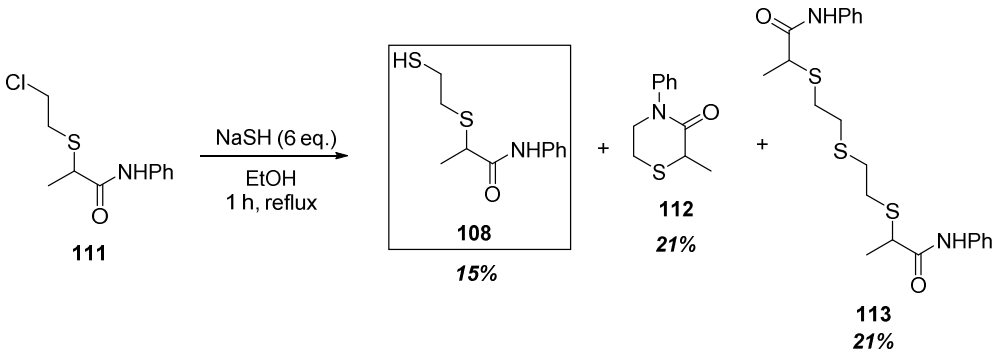
The α-thioamide **71** when reacted with mesyl or tosyl chloride led to the chlorinated α-thioamide **111** as the main product formed (Scheme 51).



Scheme 51

No evidence for the tosylated or mesylated analogue formation was observed by ^{1}H NMR spectroscopy or mass spectrometry of the crude mixture. This was consistent with Hansen *et al.*[30] earlier work, with preparation of 4,5-bis[(2'-bromoethyl)thio]-1,3-dithiole-2-thione from the hydroxy derivative through formation of the unstable tosylated derivative.

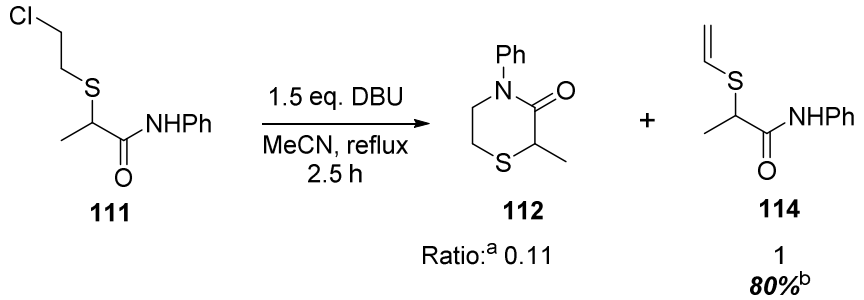
Conversion of the chloride group to a thiol group by reaction with sodium hydrogen sulfide was therefore attempted.[31,32] The reaction conditions, described employed α-thioamide **111** in ethanol, using 6 equivalents of sodium hydrosulfide under reflux (Scheme 52).



Scheme 52

The desired α-thioamide **108** was obtained as the minor product and isolated in 15% yield. Intramolecular cyclisation through chloride elimination was observed as one of the side reactions leading to thiomorpholine **112** (21% yield), along with the formation of a mixture of *meso* and *dl* diastereoisomers of sulfide **113** (21% yield).

Thiomorpholine **112** was not described in the literature and the synthesis may be of interest for further study. It was expected that α-thioamide **111** in presence of DBU might result in the cyclic derivative in high yield (Scheme 53).



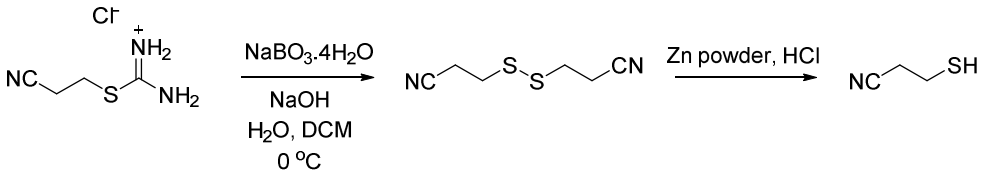
[a] Crude product ratio determined by ^{1}H NMR spectroscopy.
[b] Pure yield after chromatography on silica gel.

Scheme 53

However, the main product formed was the novel alkene **114** from HCl elimination, isolated in 80% yield, along with a minor amount of thiomorpholine **112**. This transformation is described in the literature as an easy access to vinyl sulfides, sulfoxides and sulfones.[33-35]

In a previous experiment (Scheme 49), formation of the disulfide **110** was favored and this observation was subsequently exploited to led to an efficient synthesis of α-thioamide **108**.

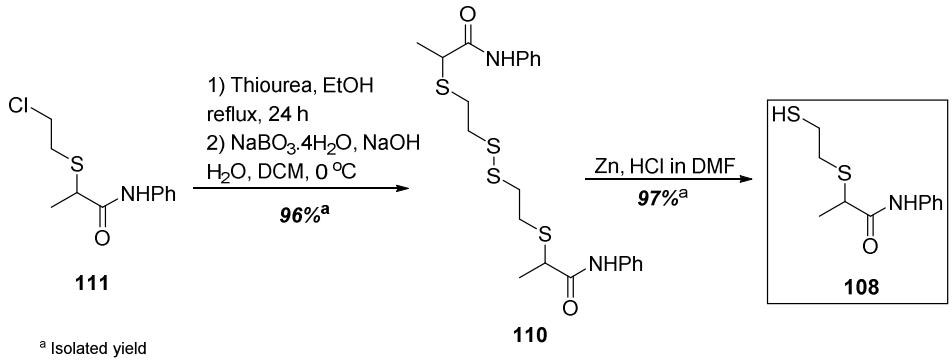
Thus, Klose *et al.*[36] had described an efficient transformation of thiouronium chloride salt, in the presence of sodium perborate, in a two phase system, through oxidative dimerization, leading to the disulfide analogue (Scheme 54). The resulting disulfide can then be easily reduced to the desired thiol.



Scheme 54

α-Thioamide **111** in the presence of two equivalents of thiourea in ethanol[37] led to full conversion of the corresponding thiouronium salt, which was reacted *in situ* with sodium perborate giving disulfide **110** (Scheme 55). The disulfide was isolated

as an equimolar mixture of the *meso* and *dl* diastereoisomers and was used in the next reduction step without further purification. Notably, thiourea is a poorly basic nucleophile which achieves clean substitution, in contrast to DBU with which 1,2-elimination happens favourably, leading therefore to the successful outcome. Reduction using zinc powder under acidic conditions led to the desired α-thioamide **108** which did not require further purification.

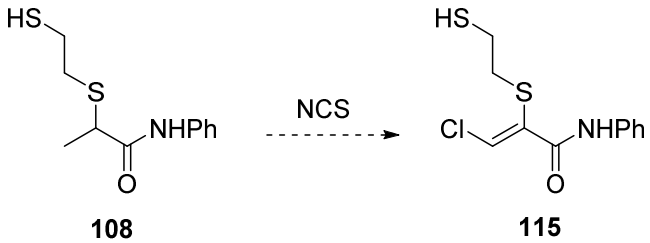


Scheme 55

Therefore, α-thioamide **108** was prepared in two steps from the chlorinated derivative **111**, in 93% overall yield. Notably, the thiol **108** was a very labile derivative which was not stored but used directly.

B. Synthesis of α-thio-β-chloroacrylamide

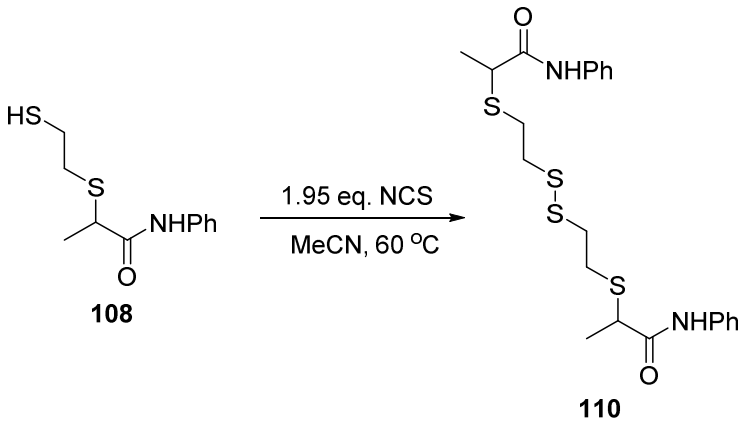
The next step of the reaction sequence was synthesis of α-thio-β-chloroacrylamide **115** (Scheme 56).



Scheme 56

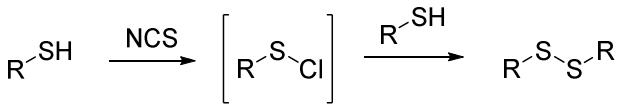
However, as anticipated, α-thioamide **108** was observed to be highly sensitive toward oxidation. α-Thioamide **108** in presence of NCS (1.95 eq.) in acetonitrile at

60 °C generated the corresponding disulfide **110** derivative with quantitative yield (Scheme 57). As for previous experiments, a mixture of diastereoisomers was seen.



Scheme 57

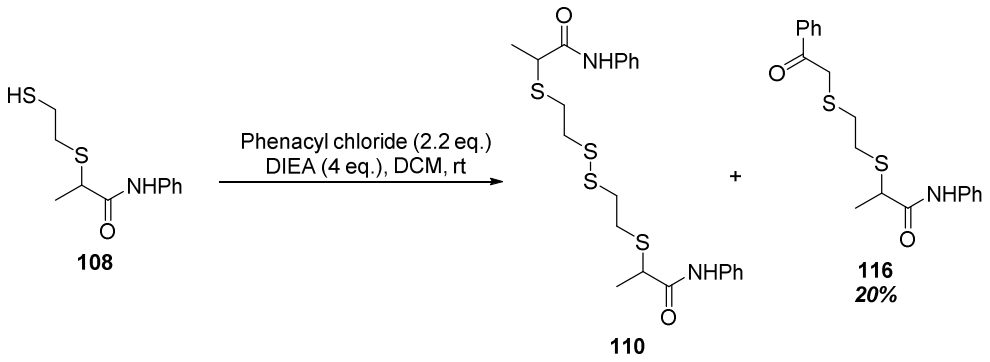
Deoxygenation of the reaction solvent did not inhibit the oxidation of the starting material. As reported in the literature, reaction between thiol and NCS generates a sulfenyl chloride, which is highly reactive toward other thiol groups, leading to the disulfide formation (Scheme 58).[38]



Scheme 58

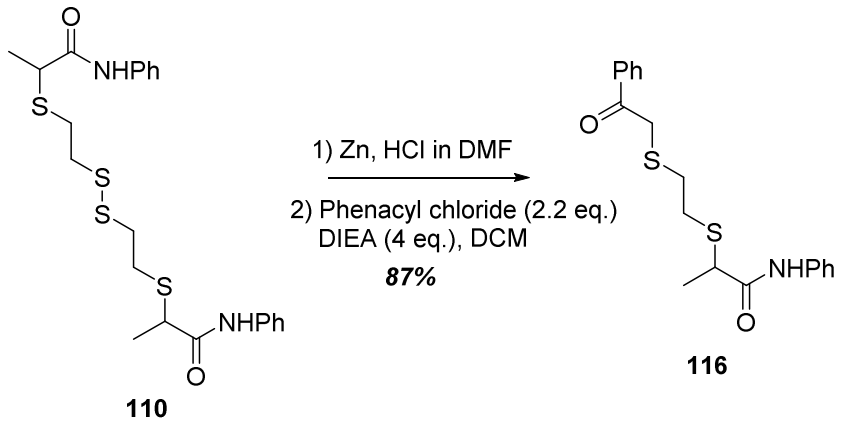
Accordingly, the oxidative transformation was next attempted with disulfide **110** using 4 equivalents of NCS at 60 °C while heating. As anticipated, the reaction performed on a symmetric derivative including two electrophilic β-carbons generated a large range of products with a complex outcome.

Protection of α-thioamide **108** looked an attractive alternative to prevent disulfide formation. Protection using *N-tert*-butoxycarbonylation was first investigated but proved unsuccessful for α-thioamide **108**. The phenacyl group is described as an efficient thiol protecting group,[39] and, therefore, protection of α-thioamide **108** using phenacyl chloride was performed. Unfortunately, the highly sensitive thiol group of the starting material was spontaneously oxidized before being protected, decreasing the yield of the transformation (Scheme 59).



Scheme 59

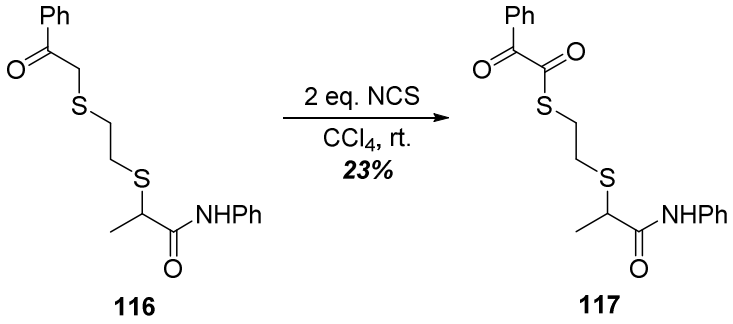
Therefore, reduction of disulfide **110** followed by thiol protection using phenacyl chloride performed *in situ* was undertaken, leading to the desired protected α-thioamide **116** in 87% isolated yield (Scheme 60). Later in the reaction sequence, the Pac group could potentially be cleaved by Zn/AcOH treatment.[39] These reductive conditions are envisaged to prevent dimerization of the corresponding deprotected α-thio-β-chloroacrylamide prior *in situ* intramolecular cyclisation.



Scheme 60

The protected α-thioamide **116** was taken forward to generate the corresponding α-thio-β-chloroacrylamide. However, using 2 equivalents of NCS in tetrachloromethane at room temperature resulted exclusively in the α-ketothioester **117** formation (Scheme 61). The ^{1}H NMR spectrym of the crude mixture was relatively clean, with no other major compounds formed. The α-ketothioester was isolated in 23% yield after chromatography on silica gel. Employing more forcing conditions (2 or 4 equivalents of NCS, in

tetrachloromethane or acetonitrile, at 40 or 80 °C) generated the same product with similar yield.



116 **117**

Scheme 61

Structure elucidation of α-ketothioester **117** proceeded by analysis of the ^{1}H, ^{13}C and two dimensional NMR spectra of the product formed. The signals corresponding to the C(2)H and C(3)H_3, as well as the amide group, were not significantly impacted on the ^{1}H and ^{13}C NMR spectra of the product, and the corresponding integrations remained intact compared to the spectra of the starting material (Figure 26). Therefore, it was reasonable to conclude that this portion of the molecule was untouched during the reaction. The main observation was the disappearance of the methylene signal of the phenacyl protecting group C(2')H_2 in both ^{1}H and ^{13}C NMR spectra. Also, a new carbonyl signal was observed on the ^{13}C NMR spectrum at δ_C 192.4 ppm. Interaction between the carbonyl and the C(2')H_2 was observed on the HMBC spectrum of **117** demonstrating the proximity of the two groups. The important deshielding of the signal corresponding to the C(2')H_2 in the product ^{1}H NMR spectrum compared to the starting material would be explained by this closeness to a carbonyl group. Lee[40] described characteristic signals at δ_C ~190 and 185 ppm corresponding to the two carbonyl groups on a large range of α-ketothioester derivatives.

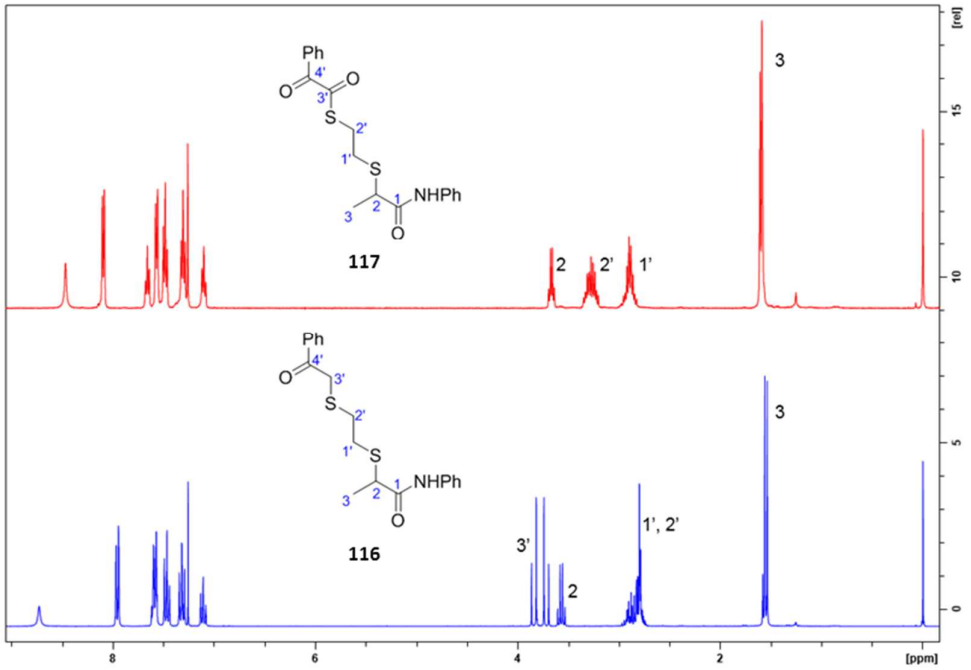
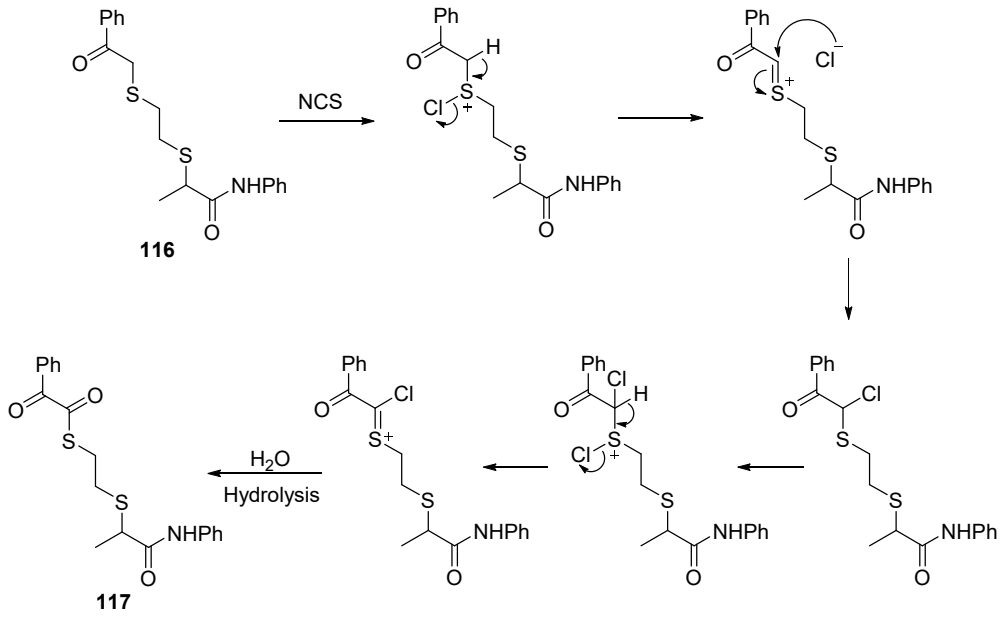


Figure 26 ^{1}H NMR spectra of pure **116** and **117**.

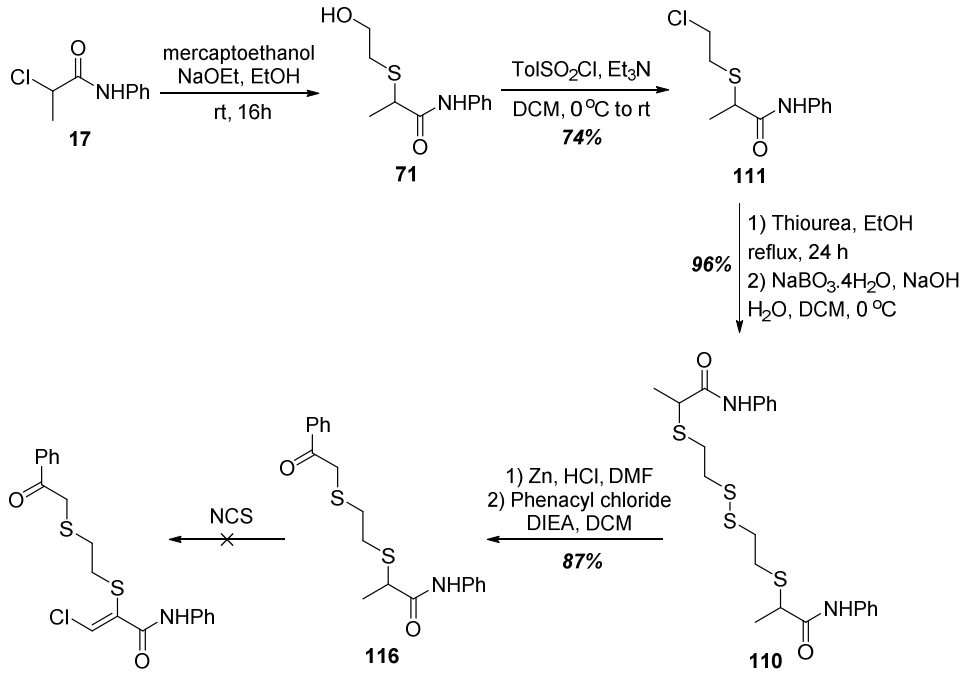
A mechanism for this transformation was proposed (Scheme 62). The initial step of the mechanism involves chlorination of the sulfur atom to give a chlorosulfonium ion. Concerted removal of HCl generates a delocalized thiocarbocation. Second chlorination of the sulfur atom *via* a second equivalent of NCS following by hydrolysis upon work-up provides α-ketothioester **117**.



Scheme 62

Clearly, chlorination occurs at the carbon bearing the more acidic hydrogen. Studies have shown that the preferred site for chlorination is consistently adjacent to the more electron withdrawing substituent.[41] Therefore, the desired chlorination on the sulfur α to the amide group in the α-thioamide **116** does not occur. Thus, synthesis of the corresponding protected α-thio-β-chloroacrylamide proved unexpectedly challenging and was not investigated further as part of this work.

However, the synthesis of the protected α-thioamide **116** was successfully performed *via* an optimised synthetic strategy (Scheme 63).



Scheme 63

The disulfide **110** and the α-thioamide **116** may prove interesting for crystallography. The sizable chain and the flexible disulfide bond of **110** enable the polymorphic nature of this compound. While the asymmetric **116**, with two different functional groups, would be useful for competitive study for ternary co-crystal, with **116** acting as a linker with two co-formers at the same time (example in Figure 27).

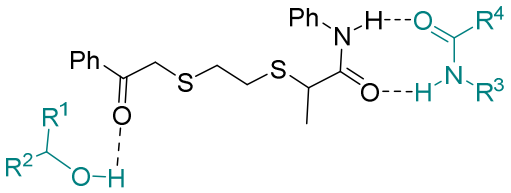
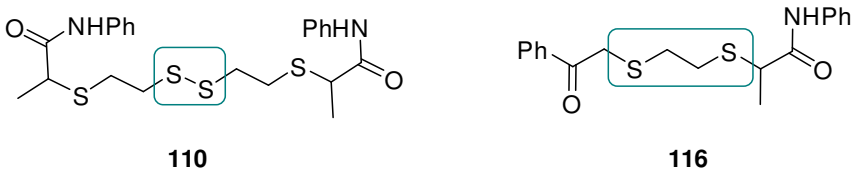


Figure 27 Example of possible ternary co-crystal envisaged

These investigations will be performed by Dr. Udaya B Rao Khandavilli. The first part of this study consists of the solid-state property study with the individual component to determine the polymorphic nature of these molecules. The comparison between the effect of the direct sulfur-sulfur bond of **110** and the ethanedisulfane of **116** will be of particular interest (Figure 29). Also, pseudo-

polymorphic behavior of these two compounds will be studied in different solvents.



110 **116**

Figure 29

The second part involves the multi-component study, including co-crystallisation behavior of these non-ionizable sulfur containing compounds with symmetric **110** and asymmetric centers **116**. In the later case, competition study between different conformers will be performed (both theoretically and experimentally), with particular interest for **116** which could be useful for preparing ternary co-crystals.

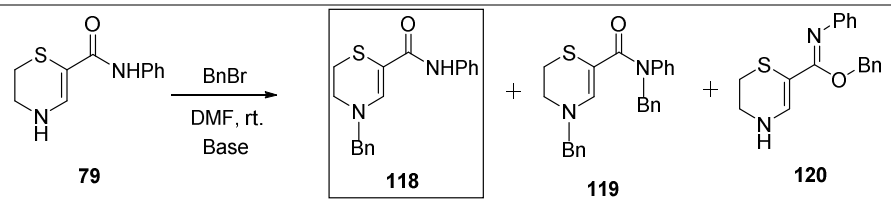
6. FUNCTIONALIZATION OF THE THIAZINE SCAFFOLD

Functionalization of the successfully synthesised 1,4-thiazine **79** was proposed to enhance the synthetic utility of this work. A structure-activity relationship study has revealed that a slight change in the substitution pattern in the thiazine scaffold, especially at the 4-position, can cause marked differences in the biological activities.[42] Therefore, substitution of the *N*-position of the thiazine scaffold was targeted to access a large range of new derivatives in a single synthetic step. In another project in the team, *N*-benzylation had positive impact on the biological activity.[43] Therefore, *N*-benzylation of **79** was first investigated in this project in order to isolate a novel *N*-benzylated thiazine. Also, reductive amination of thiazine **79**, giving access to a large range of new thiomorpholines, was extensively performed in this project.

A. *N*-Benzylation of thiazine 79

N-Benzylation of **79** was first attempted, in order to investigate the functionalization potential of this thiazine and therefore, to access a range of new thiazine derivatives (Table 15).

Table 15 Preparation of **118**



Entry	Base	BnBr Eq.	Conditions	Ratio[a] **79** : **118** : **119** : **120**	Result
1	NaH (5 eq.)	2.5	1 h, rt.	0 : 0 : 1 : 0	Yield **119** 31%[b]
2	NaH (3 eq.)	1	2 h, rt.	0.73 : 0.05 : 1 : 0	Yield **119** 37%[b]
3	K_2CO_3 (2 eq.)	1	2 h, 80 °C	0.35 : 1 : 0 : 0.44	Co-elution **118** : **120** Ratio[c] 1 : 0.44 (69%[a])

[a] Crude product ratios determined by ^{1}H NMR spectroscopy.

[b] Yield of the pure compound isolated after chromatography on silica gel.

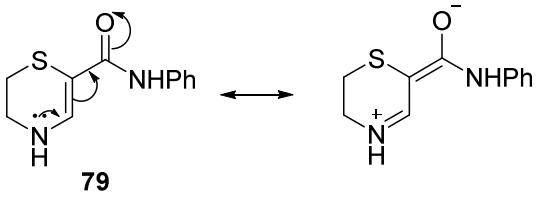
[c] Ratio determined by ^{1}H NMR spectroscopy of the mixture after chromatography on silica gel.

Using NaH (5 eq.) as base and excess of benzyl bromide in DMF at room temperature (Entry 1, Table 15) resulted in the formation of the di-benzylated thiazine **119** in 31% yield after chromatography in silica gel, with no evidence of the desired product **118** formed. The use of such a strong base with an excess of benzyl bromide was unnecessary as it deprotonated both the amine and the amide group of the starting material. Decreasing the number of equivalents of benzyl bromide employed (Entry 2, Table 15) resulted in the same product **119** being formed, along with a small amount of the desired mono-benzylated

derivative **118** in a ratio of 1 : 0.05 respectively, seen by ^{1}H NMR spectroscopy of the crude product.

Using a milder base, potassium carbonate (2 eq.), resulted in the formation of two mono-benzylated products; the desired *N*-benzylated product **118** and the *O*-benzylated derivative **120** in a ratio of 1 : 0.44 respectively, seen by ^{1}H NMR spectroscopy (Entry 3, Table 15). Isolation of **118** and **120** as pure compounds remained unsuccessful because of the similar polarity of the two components. Because of this, the structure of **120** remains tentatively assigned. The key signal for this assignment was observed at δ_C 152.8 ppm by ^{13}C NMR spectroscopy, fitting with the literature value for the imidoyl carbon of an imidate group (Figure 31).[44] Along with this, the high deshielding of the signal corresponding to the methylene of the benzyl group introduced, corroborates the structure. While two dimensional NMR spectroscopy was undertaken in an attempt to confirm the assignment of **120**, key correlations could not be observed on this sample due to the low amount of product formed.

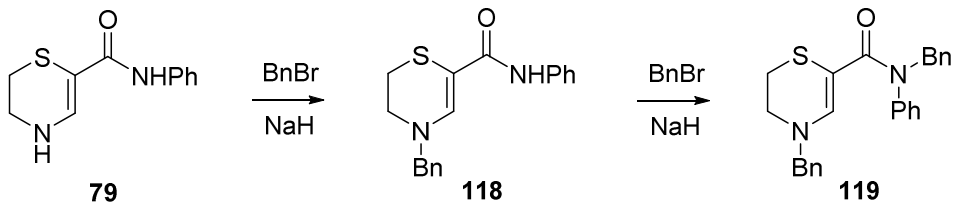
The steric hindrance in the molecule, once the 4-position of the thiazine is substituted, may account for the reaction outcomes. Indeed, in **79**, the delocalization of the nitrogen lone pair in the acrylamide system promotes *O*-alkylation (Scheme 64), leading to the imidate **120**.



79

Scheme 64

For the formation of dibenzylated **119**, it appears that the *N*-alkylation of the amine group happens first, as small amount of **118** was observed in the crude mixture of the reaction from Entry 2, Table 15 by ^{1}H NMR spectroscopy (5%) (Scheme 65).



Scheme 65

On conversion of amide to imidate, delocalization into the conjugated system is altered substantially resulting in shielding of the β-carbon which is seen at 129.6 ppm in **120** relative to the corresponding carbon in the amide derivatives **79**, **119** and **118** (Figure 29). Also, delocalization into the conjugated system is affected by the secondary or tertiary amide group in the molecule as reflected by the alteration of the carbonyl stretch in the IR spectra.

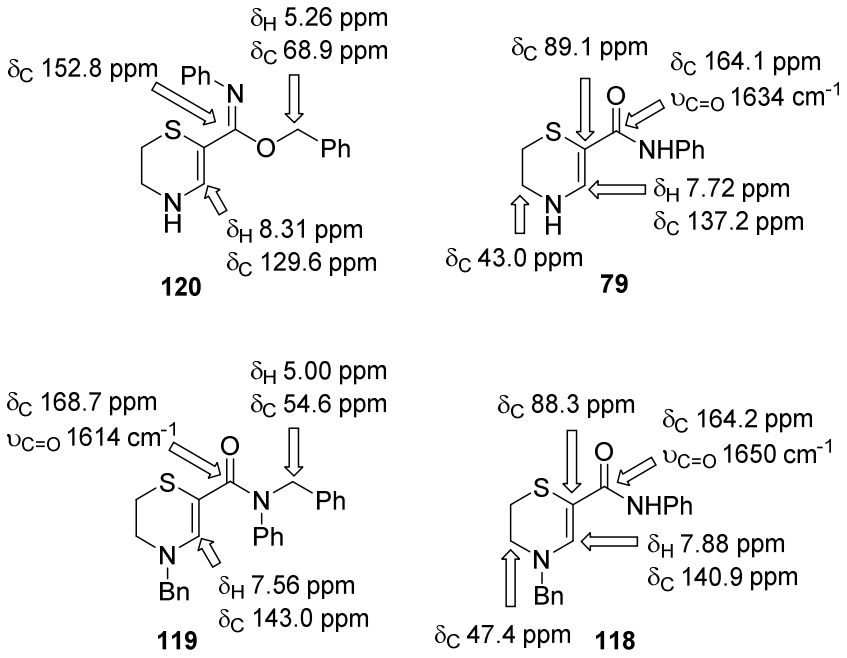


Figure 29

Interestingly, the carbonyl stretch in the tertiary amide **119** appears at 1614 cm^{-1} relative to 1650 cm^{-1} in the secondary amide **118** (Figure 29). This is consistent with the observation from Murphy for the morpholino derivatives shown in Figure 30.[5]

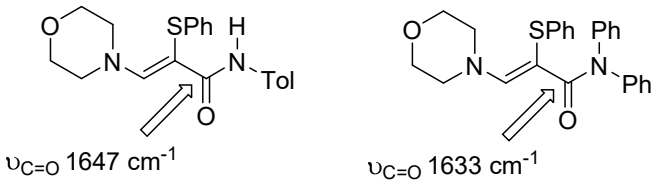
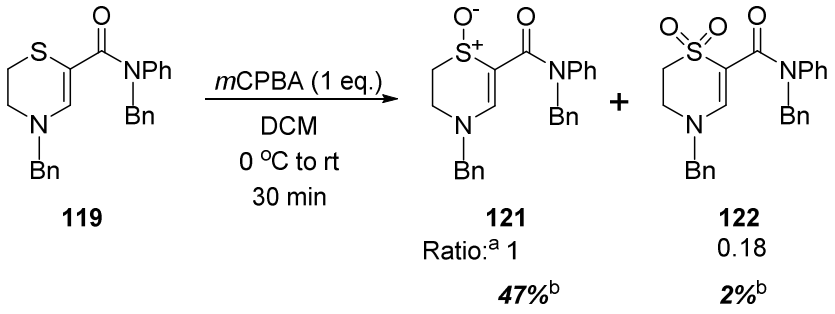


Figure 30

While the synthesis of **79** was not trivial, access to **119**, **118** and **120** in varying ratios depending on the reaction conditions for benzylation, highlights the versatility of the transformation.

According to the literature, structure-activity relationship of the thiazine scaffold revealed that the increase in oxidation state of the sulfur group caused an increase in apoptosis activity in mouse thymocytes.[45] Therefore, the oxidation of thiazine **119** was performed to provide a substrate for further biological evaluation on 60 cancer cell lines.

Thus, oxidation of the sulfur group of di-benzylated derivative **119** was investigated in this project. Using 1 equivalent of *m*CPBA, oxidation of **119** led to a mixture of sulfoxide **121** and sulfone **122** in a ratio of 1 : 0.18 respectively, by ^{1}H NMR spectroscopy of the crude product (Scheme 66).



[a] Ratio determined by ^{1}H NMR spectroscopy of the crude mixture.
[b] Yield of the pure compound isolated after chromatography on silica gel.

Scheme 66

There are interesting features in the NMR spectra of the di-benzylated thiazines (Figure 31). Upon oxidation of the sulfur group, the electron-withdrawing character increases from the sulfide to the sulfoxide to the sulfone, with a significant impact on the α-methylene and α-quaternary carbon, with a movement

downfield of the observed chemical shifts (δ_C sulfide 91.1 ppm *cf.* δ_C sulfoxide 104.1 ppm *cf.* δ_C sulfone 114.2 ppm). In addition, conversion of the sulfide to sulfoxide causes splitting of the diastereotopic protons of the α-methylene.

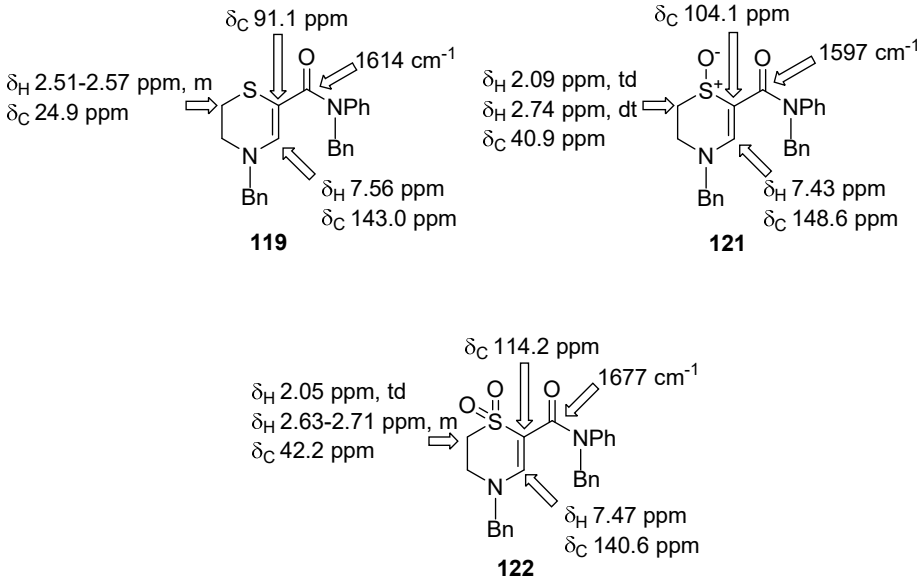


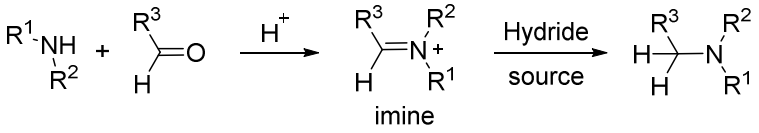
Figure 31

The carbonyl stretch signal in the IR spectra was impacted on changing the level of sulfur oxidation, presumably reflecting both conformational alteration and changes in electron delocalization across the conjugated system.

The selective *N*-benzylation of thiazine **79** proved challenging, presumably due to the conjugated system present in the molecule, conferring similar reactivity to most of the reactive sites. Reductive amination was proposed as an attractive alternative for selective *N*-alkylation of thiazine **79**.

B. Reductive amination of thiazine 79

Reductive amination of aldehydes and ketones is one of the most important ways of making primary, secondary and tertiary amines.[46] In this reaction, an amine and a carbonyl compound condense to afford an imine or iminium ion that is reduced *in situ* or subsequently to form an amine (Scheme 67).[47,48]



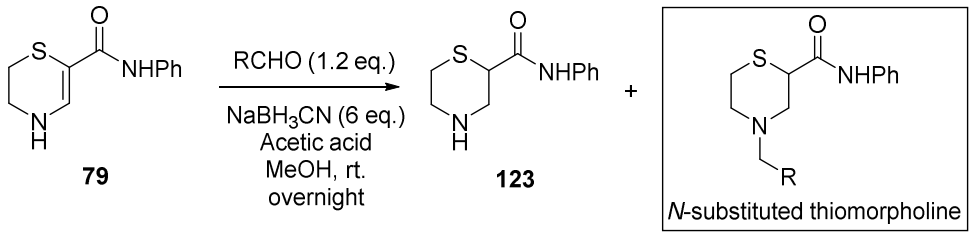
Scheme 67

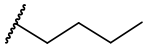
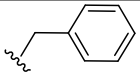
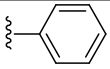
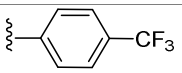
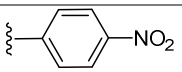
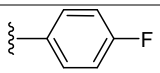
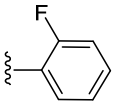
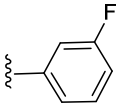
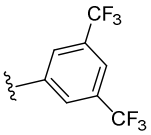
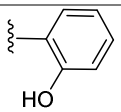
The generated imine can be reduced using formic acid (Leuckart-Wallach reaction)[49-51] or metal hydrides.[52-54] Sodium cyanoborohydride with its strong electron-withdrawing cyano group is a mild and selective reducing agent.[55,56] Borch *et al* reported that the reduction of iminium ion was much faster than the reduction of carbonyl group.[57,58] The stability of sodium cyanoborohydride in protic solvents at low pH would preserve the sodium borohydride from hydrolysis and therefore, allowed reductions to be carried out.

A general procedure for the reductive amination of heterocyclic secondary amine gave rise of a large range of derivatives with significant pharmaceutical potential.[59-64] Employing the appropriate aldehyde or ketone (1.2 eq.), sodium cyanoborohydride (6 eq.) and acetic acid in methanol at room temperature is described as an efficient way for the preparation of tertiary heterocyclic amine.

In this project, thiazine **79** was subjected to reductive amination using this protocol, with a large range of aldehydes (Table 16). Concomitant reduction of the unsaturation system within the thiazine ring was observed in all cases, leading to the corresponding thiomorpholine analogues. The thiomorpholine **123** was observed in the crude mixture in many experiments (Entries 2, 4-10, Table 16), and was easily identifiable by ^{1}H NMR spectroscopy with a characteristic amide signal at 10.25 ppm.

Table 16 Preparation of thiomorpholines using sodium cyanoborohydride



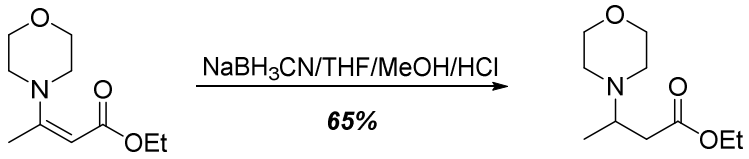
Entry	*N*-substituted thiomorpholine	R	Ratio[a] **123** : *N*-substituted thiomorpholine	Yield[b] (%) *N*-substituted thiomorpholine
1	**124**		0 : 1	80
2	**125**		0.40 : 1	50
3	**126**		0 : 1	58
4	**127**		1 : 0.42	20
5	**128**		1 : 0.17	Not isolated
6	**129**		0.39 : 1	56
7	**130**		0.79 : 1	50
8	**131**		1 : 0	-
9	**132**		1 : 0	-
10	**133**		1 : 0	-

[a] Ratio determined by ^{1}H NMR spectroscopy of the crude mixture.

[b] Yield of the pure *N*-substituted thiomorpholine isolated after chromatography on silica gel.

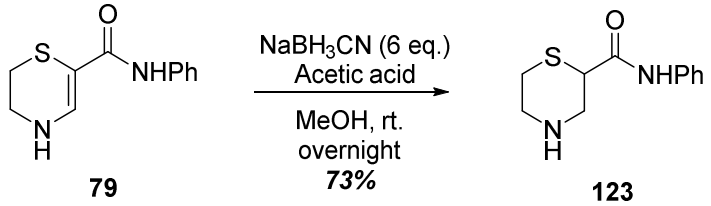
Therefore, it is believed that the enamine group of **79** was reduced by sodium cyanoborohydride prior the reductive amination. Indeed, Borch *et al.* reported

that the rapid and reversible protonation of the β-carbon of the enamine group generates a readily reducible iminium salt (Scheme 68).[57]



Scheme 68

To confirm that the enamine is reduced prior to benzylation, the thiazine **79** was treated with sodium cyanoborohydride in acetic acid and methanol solution at room temperature (Scheme 69). Full conversion to the thiomorpholine **123** was observed and the reduced product **123** was isolated in 73% yield after chromatography on silica gel.



Scheme 69

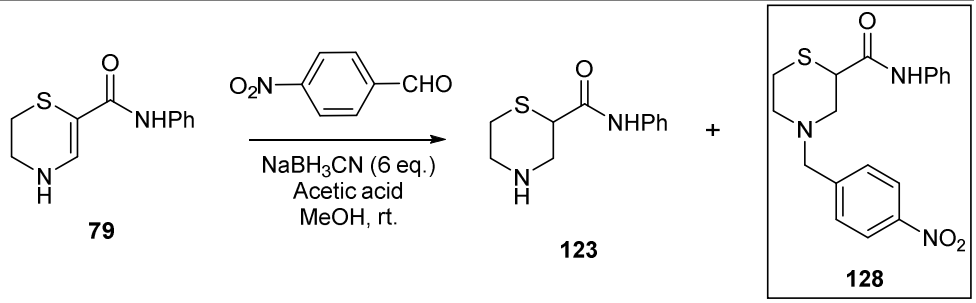
In the reductive aminations, full conversion was observed while employing benzaldehyde and valeraldehyde, and the corresponding *N*-substituted thiomorpholines were isolated in good to high yield after chromatography on silica gel (Entries 1 and 3, Table 16). In contrast, use of the readily enolisable phenylacetaldehyde led to incomplete conversion (Entry 2, Table 16).

When the benzaldehyde used was substituted, the crude mixture consisted of the reduced starting material **123** and, in some instance, the desired *N*-substituted thiomorpholine. The partial conversion into the benzylated derivatives may be due to competitive reduction of the aldehyde by sodium cyanoborohydride. With some benzaldehyde derivatives there was no evidence for formation of the *N*-substituted thiomorpholine (Entries 8 to 10, Table 16).

Interestingly, results of Entries 6 to 8 (Table 16) show the impact of the position of the fluorine substituent on the benzaldehyde precursor. In summary, the most effective transformation was obtained in Entry 1 and Entry 3 (Table 16), in which full conversion to the *N*-substituted thiomorpholine was achieved.

Investigation was performed in order to improve the conversion and the yield of the transformation. Synthesis of **128** was choosen as a model study for the optimisation of the preparation of *N*-substituted thiomorpholines from thiazine **79**. Using an increased amount of *p*-nitrobenzaldehyde improved the extending conversion into the desired product (Table 17). Using 3 equivalents of aldehyde, full completion was not observed (Entry 3, Table 17) but the conversion was sufficient to isolate the desired product **128** in 24% yield after chromatography on silica gel. This supports the hypothesis that competing reduction of the aldehyde precursor impacts on the efficiency of the transformation.

Table 17 Optimisation of preparation of **128**



Entry	*p*-Nitrobenzaldehyde (eq.)	Ratio[a] **123** : **128**	Yield[b] **128** (%)
1	1.2	1 : 0.17	
2	2.1	1 : 0.37	
3	3	1 : 0.45	24

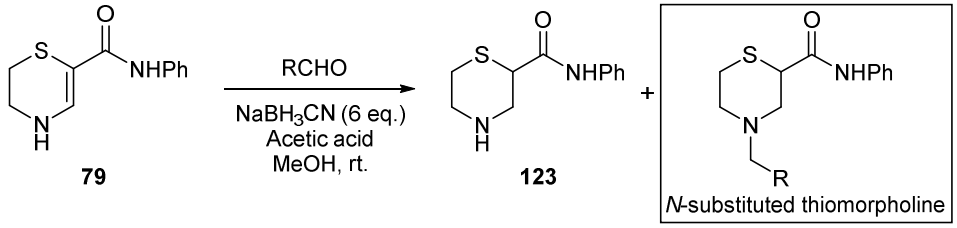
[a] Ratio determined by ^{1}H NMR spectroscopy of the crude mixture.

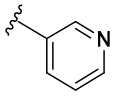
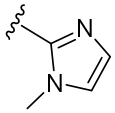
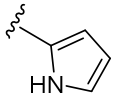
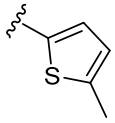
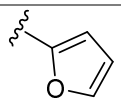
[b] Yield of the pure compound isolated after chromatography on silica gel.

Further investigation showed that reductive amination with heterocyclic aldehydes was also feasible, leading to the most efficient synthetic transformations (Table 18). Full conversion to the desired products was observed

by ^{1}H NMR spectroscopy while employing three equivalents of nicotinaldehyde, thiophenecarboxaldehyde, furaldehyde and pyrrole carboxaldehyde, and the corresponding novel *N*-substituted thiomorpholines were isolated in good to excellent yield (Entries 1, 4 and 5, Table 18). With 1-methyl-2-imidazole carboxaldehyde, full conversion to the desired substituted thiomorpholine was not achieved and product **135** was isolated with low yield (Entry 2, Table 18).

Table 18 Impact of equivalents of aldehyde on the reductive amination outcome



Entry	*N*-substituted thiomorpholine	R	Using 1.2 eq. RCHO	Using 3 eq. RCHO	
			Ratio[a] **123** : *N*-substituted thiomorpholine	Ratio[a] **123** : *N*-substituted thiomorpholine	Yield (%)[b]
1	**134**		0.41 : 1	0 : 1	73
2	**135**		1 : 0.45	1 : 0.67	20
4	**136**		0.33 : 1	0 : 1	62
3	**137**			0 : 1	95
5	**138**			0 : 1	96

[a] Ratio determined by ^{1}H NMR spectroscopy of the crude mixture.

[b] Yield of the pure compound isolated after chromatography on silica gel.

Comparison of the NMR chemical shifts for thiazine **79** and thiomorpholine **123** was interesting (Figure 32). Due to the unsaturation system, the thiazine is more

planar and therefore leads to better orbital overlap. The thiomorpholine, with more rotational freedom and reduced conjugation, results in a shielding of the methylene of the carbon C-5 and C-6 of the ring chemical shifts (SCH_2 and $NHCH_2$) in ^1H NMR spectrum.

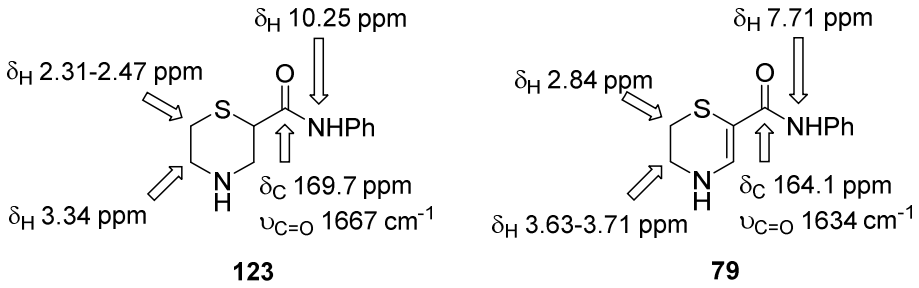


Figure 32

Due to the resonance effect in the thiazine ring, the δ_H NH of the amide is significantly shielded when compared to the thiomorpholine, due to the nitrogen lone pair delocalization into the unsaturated system. The conjugated system in the thiazine has a shielding effect on the carbonyl group and the observed chemical shift is upfield by ^{13}C NMR spectroscopy.

Substitution of the nitrogen of the thiomorpholine **123** has a deshielding effect on the α-carbons to the nitrogen and the observed chemical shifts are downfield on the ^{13}C NMR spectra (Figure 33).

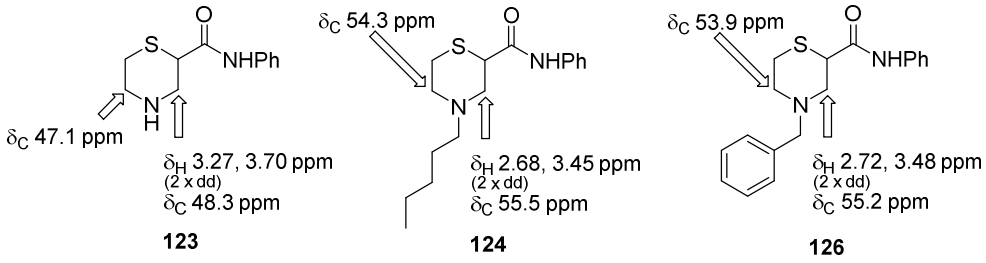
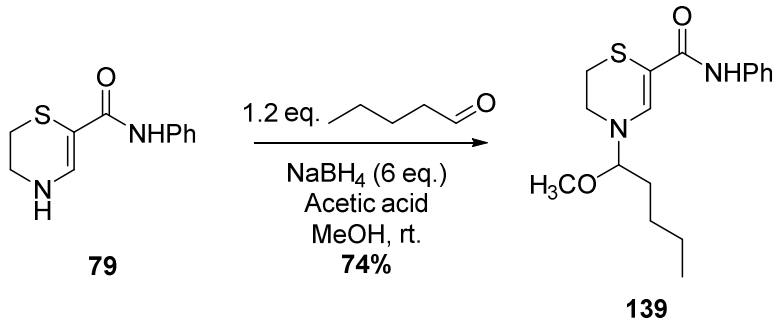


Figure 33

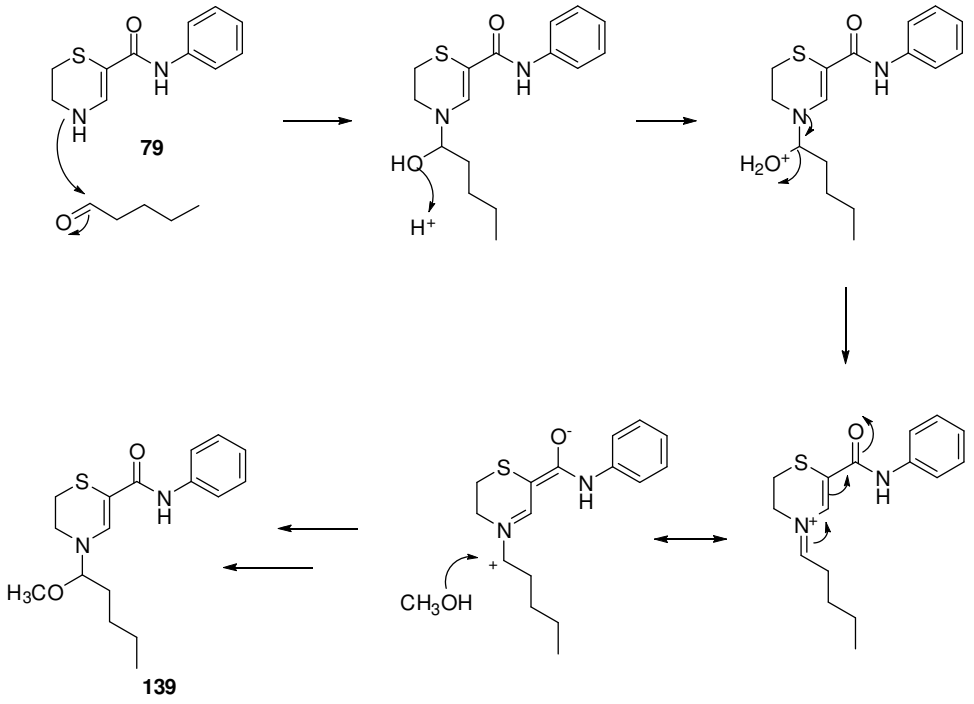
Even though sodium cyanoborohydride is the reagent of choice for reductive amination due to the high selectivity conferred, this reagent may liberate hydrogen cyanide when the reaction is quenched, which is highly toxic.[65] Sodium borohydride is a safe, green, environment-friendly and inexpensive reducing agent,[66] and therefore the reaction was attempted employing this reagent.

Thiazine **79** treated with valeraldehyde, using sodium borohydride as reducing agent generated the hemiaminal ether **139** in 74% yield after chromatography on silica gel (Scheme 70).



Scheme 70

Interestingly, the carbon-carbon double bond survived the reaction conditions in this instance. It is not clear why the reductive amination does not go to completion in this instance. It is possible that the sodium borohydride is inactivated in the medium. A mechanism for this transformation was then proposed (Scheme 71). Once the unsaturation system is conserved, the conjugated system with the imine intermediates led to the formation of the product with substitution by the methanol solvent on the alkyl chain.



Scheme 71

Interestingly, the reaction was performed using benzaldehyde and sodium borohydride leading to the starting material remaining. This observation would support that the sodium borohydride was deactivated in this medium.

In this project, twelve novel *N*-substituted thiomorpholines with aryl, benzyl and alkyl substituents were isolated by reductive amination using sodium cyanoborohydride, with full analytical data determined. Therefore, thiazine **79** can be easily functionalized in a single step *via* this transformation, giving rise to a large range of thiomorpholines.

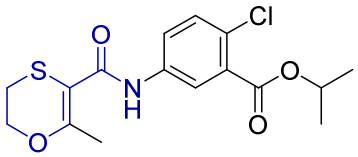
7. ANTI-CANCER ACTIVITY

Several researches have evaluated the bioactivity of oxathiin and thiazine heterocycles. Oxathiins demonstrated a wide variety of pharmacological activities such as anti-HIV and anti-cancer, and also act as carbonic anhydrase inhibitors.[67, 68]

A. Background

1. Biological activities of oxathiin derivatives

The oxathiine carboxanilide (UC84, Figure 34) has been found to be a highly active anti-HIV agent, as a non-nucleoside reverse transcriptase (RT) inhibitor.[69, 70]



UC84

Figure 34

It has recently become obvious that some other HIV drugs, which were independently developed for the specific inhibition of retroviral enzymes, represent a potential reservoir for anti-cancer drugs.[71, 72] Inhibition of tumour-cell invasion and angiogenesis were properties first ascribed to inhibition of HIV protease. Selected HIV drugs have been shown to exert tumoricidal effects (*e.g.* AZT).[73] Abacavir has shown great potential as an anticancer agent able to induce antiproliferative activity and trigger senescence in a prostate cancer cell-line.[74] Interestingly, RT is typically expressed at high levels in cancer cells. Recent studies report that RT inhibition by non-nucleoside reverse transcriptase inhibitors induces growth arrest and cell differentiation *in vitro* and antagonises growth of human tumours in animal models.[75-78]

3-(2-Haloalkyl)-1,4-oxathiin derivatives showed regression or inhibition of the growth of leukemia and tumours in mammals (Figure 35).[79]

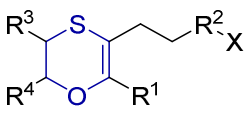


Figure 35

The compounds are cytotoxic agents, useful to induce a regression of malignancies such as lymphoid and lymphocytic leukemia, as well as to inhibit the growth of various cancers (melanocarcinoma, sarcoma, and mammary xenograft

tumors). Particularly preferred among the compounds are 3-(2-chloroethyl)-5,6-dihydro-2-methyl-1,4-oxathiin showing the more efficient activities. In this way, the 5,6-dihydro-1,4-oxathiin (R^4=R^3=H) looks to be an important feature in the structure-relationship activity.

Benzoxathiin derivatives, linked to a purine base (Figure 36), were found to possess anti-cancer activity against MCF-7 human breast cancer cell lines.[80, 81] Compounds substituted with halogens at the R^2 and/or R^6 positions have the most promising anti-proliferative activity against the MCF-7 cell line. A bromine substituent at the R^6 position gives rise to a compound which is almost equipotent to Adrucil©, a marketed drug used for colon cancer, oesophageal cancer, stomach cancer, pancreatic cancer, breast cancer and cervical cancer.[82]

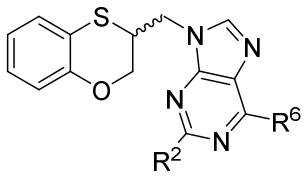


Figure 36

Most recently, the sultone derivative shown in Figure 37, containing a 1,2-oxathiin pattern, demonstrates impressive suppression of tumour weight exhibit against the murine sarcoma S180 model.[83]

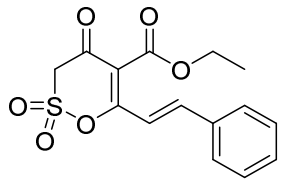


Figure 37

2. Biological activities of 1,4-thiazine and thiomorpholine derivatives

1,4-Thiazine derivatives are known as highly biological active compounds. They demonstrate a large range of biological activities such as antimalarial,[84] antibacterial,[85-88] anticonvulsant[89] and antipsychotic effects.[90] It has been reported in the literature that the 1,4-benzothiazine system demonstrates a

significant role in antitumor drug chemotherapy.[91] Some examples are described below.

A series of benzothiazine derivatives illustrated in Figure 38, displayed broad spectrum antitumor activity against HeLa, MDA-MB-231 and IMR32 cancer cell lines at the GI_{50} levels, together with a mild to moderate cytotoxic activity.[92]

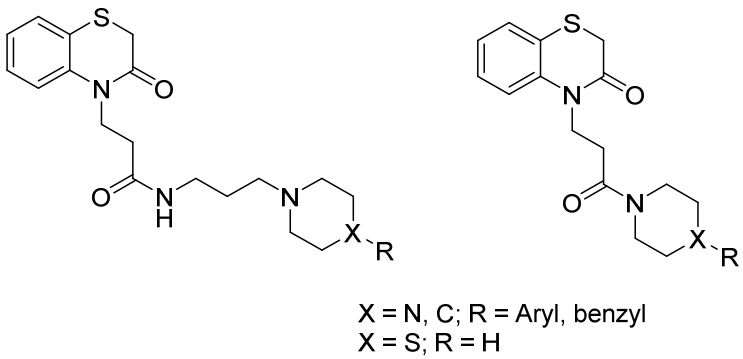


Figure 38

3-Methyl-1,4-benzothiazine derivatives represented in Figure 39 have been designed on the basis of computational drug design, showing good binding affinities with various colorectal cancer.[93] Some of them were tested *in vitro* and exhibited significant effects against the HT-29 human colon cancer cell line.

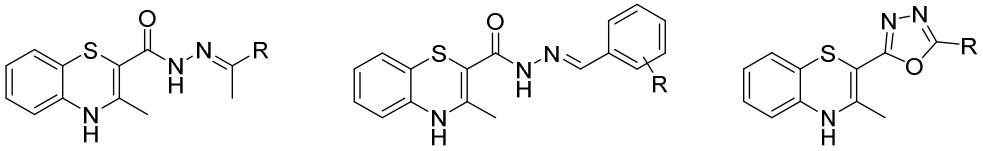


Figure 39

Benzothiazine analogues illustrated in Figure 40 induced neurotoxicity, antitumor activity and cytotoxicity on mouse thymocytes (lymphocyte arising in the thymus).[45] The oxidation of the sulfur group to sulfoxide or sulfone induced an

increase of activity. More importantly, the aryl group substituent R has been shown to have a significant effect on the apoptotic activity.

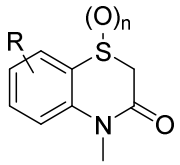


Figure 40

Some tetracyclic azaphenothiazines induce monocyclic differentiation and apoptotic cell death in human myelogenous leukemic cell lines HL-60, ML-1, U-937 and THP-1.[94, 95]

9-Fluoroquino-1,4-benzothiazine (Figure 41) shows strong suppressive actions on growth of L1210, SW948, A-431 and CX-1 tumour cell lines which were close to those of Cisplatin.[96] Also, the compound appears to be equally as effective as cyclosporine A in the inhibition of human two-way mixed lymphocyte reaction.

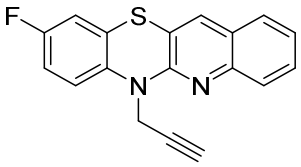


Figure 41

Thiazinoquinone derivatives (Figure 42) show potential cytotoxic and proapoptotic activity against a number of tumor cell-lines which inhibits TNF α-induced NF-κB in a human leukaemia T cell line.[97]

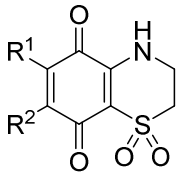
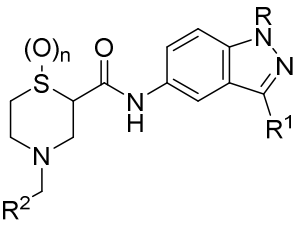


Figure 42

The thiomorpholine derivatives of general structure seen in Figure 43 inhibit ERK activity.[98] It is reported that these molecules are useful for the treating a broad

spectrum of cancer, such as melanoma, pancreatic, thyroid, colorectal, lung, breast and ovarian cancer.



n = 0, 2
R^2 = *o*-halophenyl, pyridine, thiophene, thiazole, phenacyl

Figure 43

B. National Cancer Institute 60-cell line screening

1. Introduction

The U.S. National Cancer Institute's Developmental Therapeutics Program (DTP) 60 human tumor cell line service (NCI-60) is the drug discovery and developmental arm of the NCI. This program was set up in the 1980s and allows researchers to submit novel compounds or purified natural products for testing against cell lines from nine different cancer types: leukemia, lung cancer, colon cancer, central nervous system cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer.[99] In addition to identifying novel compounds with activity against particular tumour types as an aid to drug discovery, the screen is useful in identifying modes of action of compounds by comparison of the patterns of relative drug sensitivity and resistance.[100]

Since its establishment, the DTP has been involved in the discovery or development of more than 40 U.S. licensed chemotherapeutic agents, which translates to >70% of the anticancer drugs on the market today.[101-103]

Structures are submitted online along with the justification for testing their potential activity. Screening of accepted compounds is initially conducted as a single concentration of 10 μM, also called one dose testing and the results are provided as a mean growth percent graph (the one dose results graph for 1,4-thiazine **79** is shown as an example in Figure 44). The mean percentage growth

across the 60 cell lines tested is given as 92.74%. This mean is represented by the central vertical line in the graph marked "0". The colored bars extending to the right of the central line indicate that the growth inhibition in that cell line was higher than the mean, whereas extending to the left indicate that the activity in that cell line was lower than the mean, meaning a higher growth percent was obtained. The delta is also an important piece of data, indicating the maximum growth inhibition expressed against one cell line relative to the mean growth.

Compounds which achieve a set inhibition level in a minimum number of cells lines progress to five dose testing at 0.01 μM, 0.1 μM, 1 μM, 10 μM and 100 μM, with the cell lines incubated with the compound at 37 ^{o}C for 48 hours.[99] The resulting dose response curves obtained enable determination of GI_{50} (drug concentration at which 50% of growth is inhibited), TGI (drug concentration at which total growth inhibition occurs) and LC_{50} (drug concentration at which 50% of cells are killed).

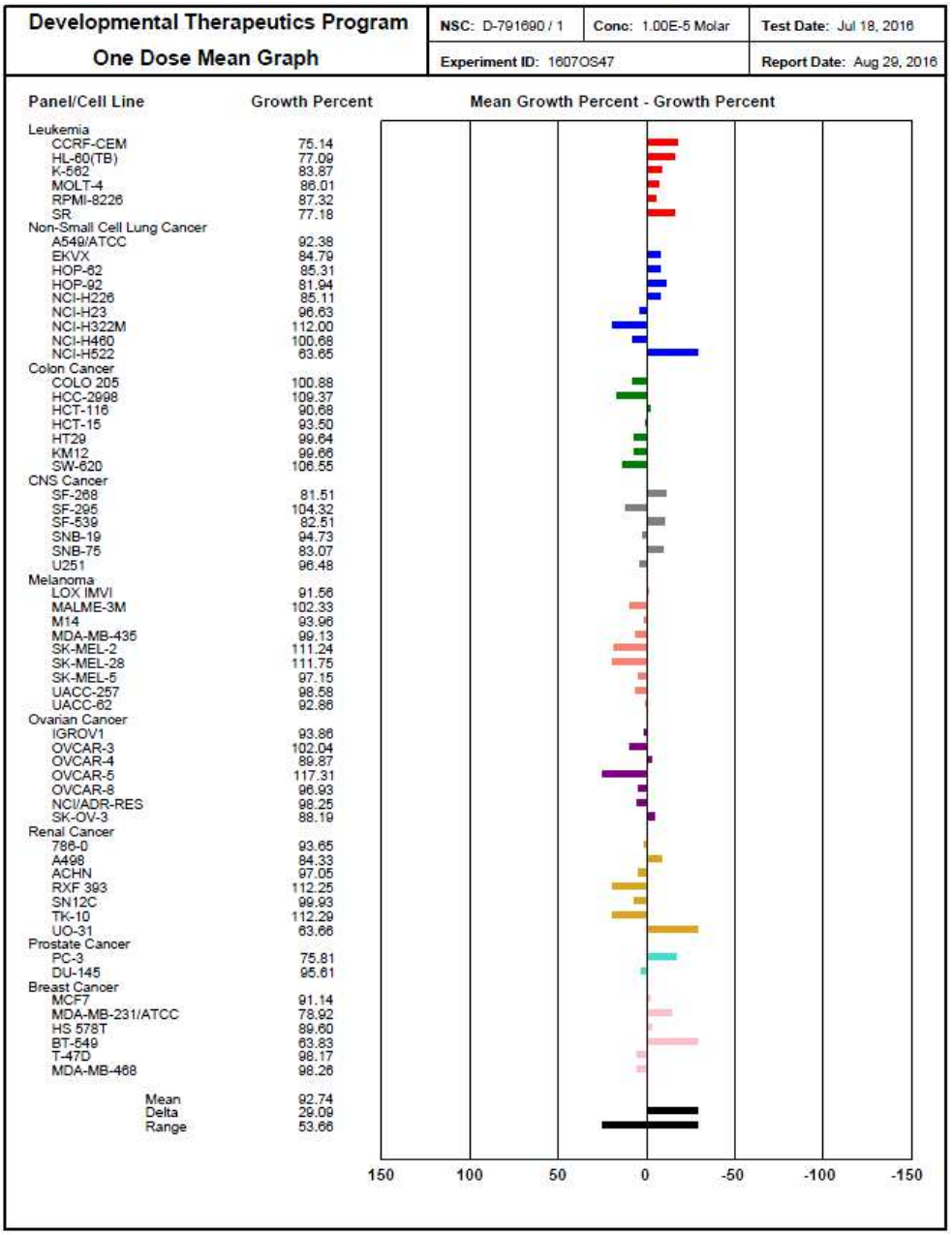


Figure 44 One dose percentage growth mean graph for thiazine **79**

2. One-dose screen results

Two novel oxathiins, two novel thiazines, one novel benzothiazine and thirteen thiomorpholines were submitted for NCI screening. The first round of compounds evaluated included an unsaturated carbon-carbon bond in the heterocycle, including 1,4-oxathiins **67** and **77**, 1,4-thiazines **79** and **119**, and 1,4-benzothiazine **105** (Figure 45). The compounds are novel 5,6-dihydro-1,4-oxathiin and 5,6-

dihydro-1,4-thiazine derivatives incorporating an amide substituent. It was envisioned that the selection of novel derivatives would provide alternative types of binding interactions that could enhance or alter the biological activity by introducing a hydrogen bond donor/acceptor group.

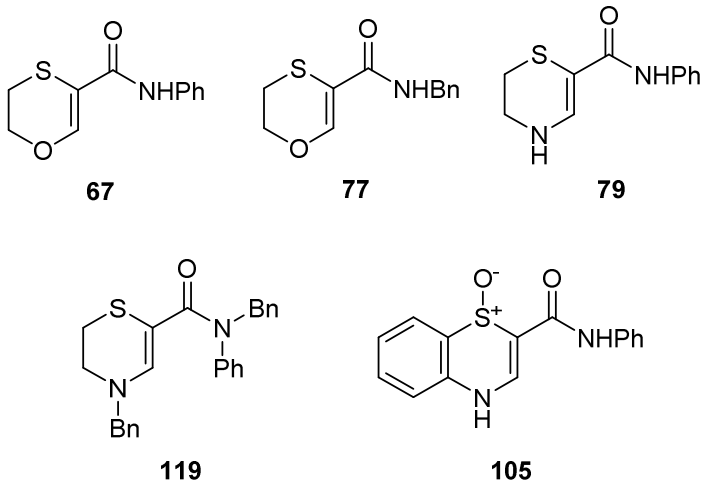


Figure 45 Initial series of oxathiins, thiazines and benzothiazine submitted to DTP for NCI-60 cell line screening

It was interesting to evaluate if the alteration of the amide substituent (phenyl *vs* benzyl), the heteroatom containing heterocycle (N *vs* O), the substitution on the heterocyclic ring and the level of sulfur oxidation, would impact the activity.

The derivatives in Figure 45 were investigated for initial NCI-60 one dose (10 μM) tumour cell line activity and the one dose graphs for each of the compounds depicted are presented in Appendix II. The pattern of quantifiable growth inhibition of these molecules on the NCI-60 human cell line panel is outlined in Figure 46.

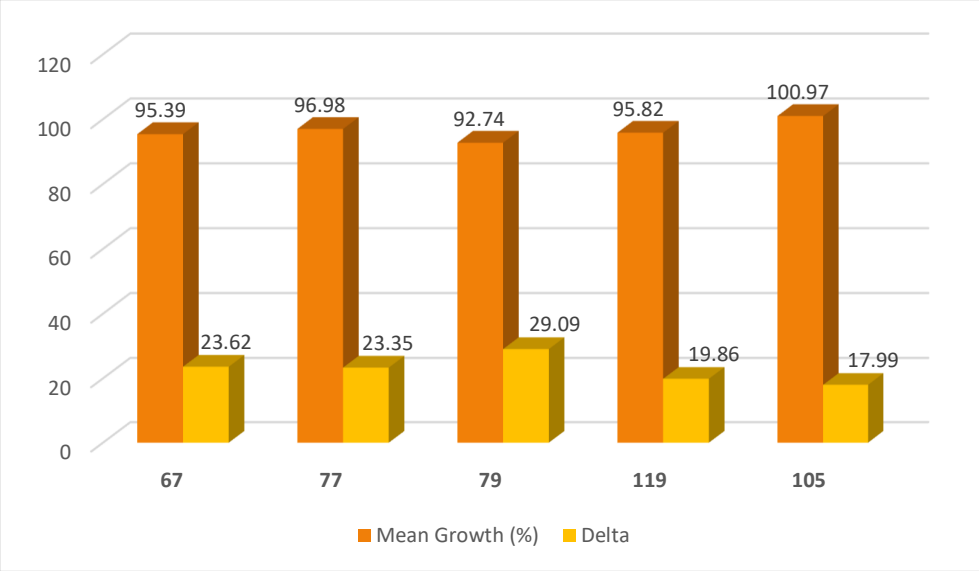


Figure 46 Results from oxathiins, thiazines and benzothiazine in NCI one dose testing

Mean growths at a 10 μM concentration across the 60 cell lines ranged from 92.74% for the most active derivative thiazine **79** to 100.97% for the least active compound benzothiazine **105**. Therefore, these compounds demonstrate low anti-cancer activities. However, a pattern can be observed for the most active derivatives **67**, **77** and **79**, with the maximum exhibit growth inhibition were against the renal cancer cell line UO-31 (Table 19), developed from female epithelial cells (carcinoma).

Table 19 Growth inhibition (%) against UO-31 cell line

Compound	Growth inhibition of UO-31 cell (%)	Delta	Mean Growth (%)
67	28.23	23.62	95.39
77	26.37	23.35	96.98
79	36.34	29.09	92.74

The oxathiin **67** exhibits up to 28% of growth inhibition in HOP-62 non-small cell lung cancer (adenocarcinoma), SK-OV-3 ovarian cancer (adenocarcinoma, female over 64 years old) and UO-31 renal cancer cell lines. Substitution of the phenyl substituent by a benzyl group in **77** decreased the overall activity of the

compound, except for the NCI-H226 non small cell lung cancer line (squamous cell carcinoma) with an increase growth inhibition (Figure 47). The amide group with phenyl substituent, leading to an extended π system may provide an interesting π-stacking effect which increases the anti-cancer activity in some tumor cell lines.

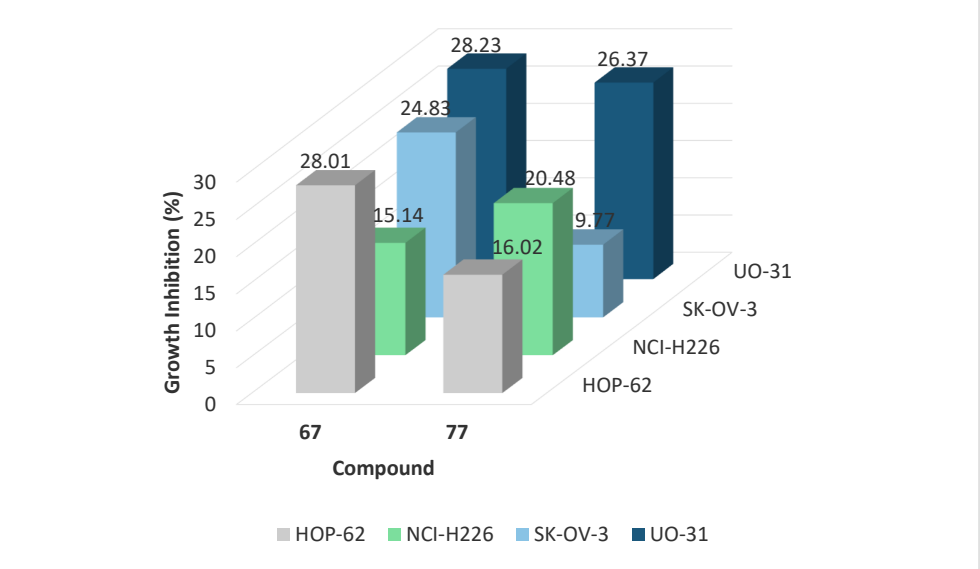
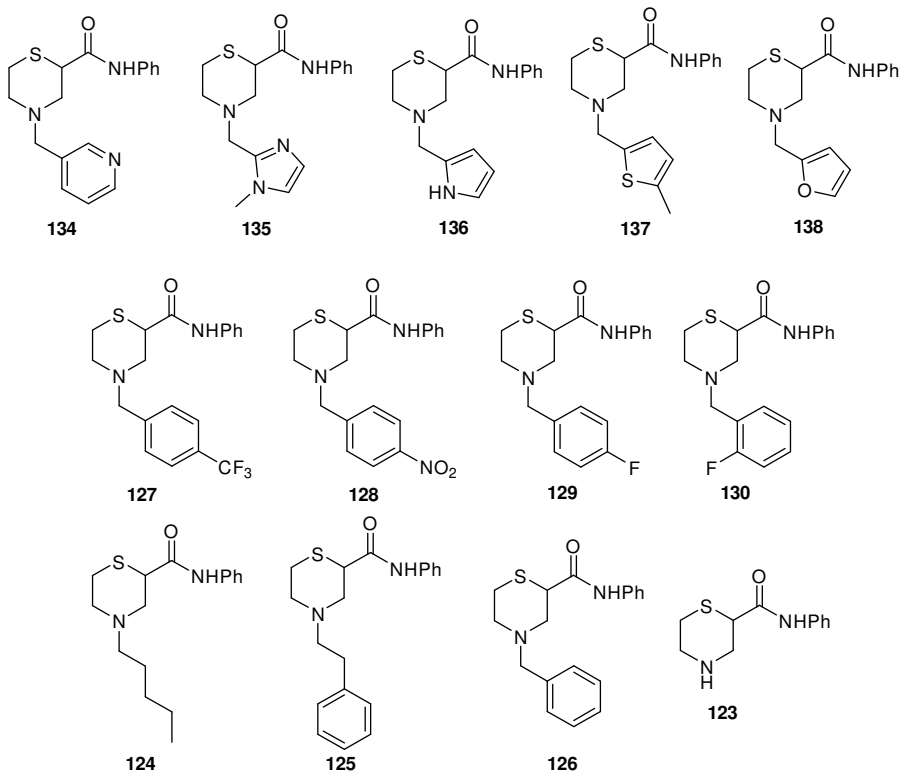


Figure 47 Activity against particular cell lines displayed by the oxathiins

The overall activity is seen increased from 1,4-oxathiin derivative **67** to 1,4-thiazine **79** from 95.39% growth inhibition to 92.74%, with maximum growth inhibition against one cell from 28.23 to 36.34% respectively (Figure 46). The benzothiazine **105** and the benzylated derivative **119** demonstrated very poor activities in all the cell lines, displaying a fairly indiscriminate profile.

Thirteen novel thiomorpholines were also submitted for one dose screening to the NCI and the results are summarized in Figure 48.



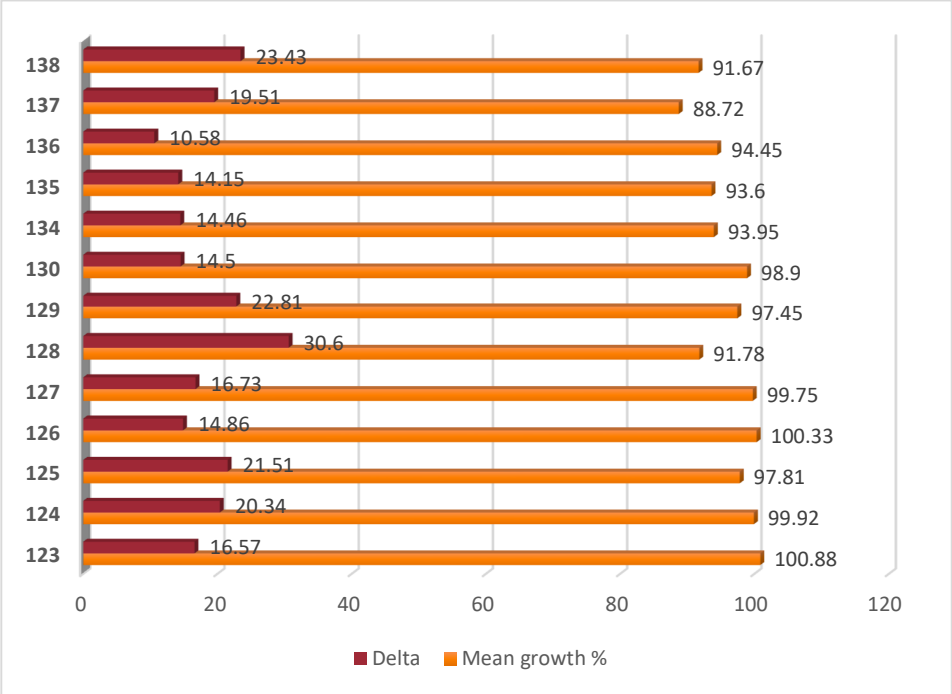


Figure 48 Results from thiomorpholines in NCI one dose testing

Comparing the results from all the compounds screened was of particular interest. For many of them, the maximum growth inhibition exhibited was against the renal

cancer cell line UO-31 (carcinoma) (Table 20), in line with the pattern observed for the derivatives **67**, **77** and **79** (Table 19).

Table 20 Growth inhibition (%) against UO-31 cell line

Compound	Growth inhibition of UO-31 cell (%)	Delta	Mean Growth (%)
124	20.42	20.34	99.92
125	23.70	21.51	97.81
129	25.36	22.81	97.45
130	15.60	14.50	98.90
128	38.82	30.60	91.78

The derivatives **129**, **79**, **137** and **128** are the most active compounds in the 17 molecules screened in this project (Figure 49). Thiomorpholine **129** with mean growth 91.67% respectively, reduced growth up to 20% in all but 4 of the cell lines, displaying a fairly indiscriminate profile.

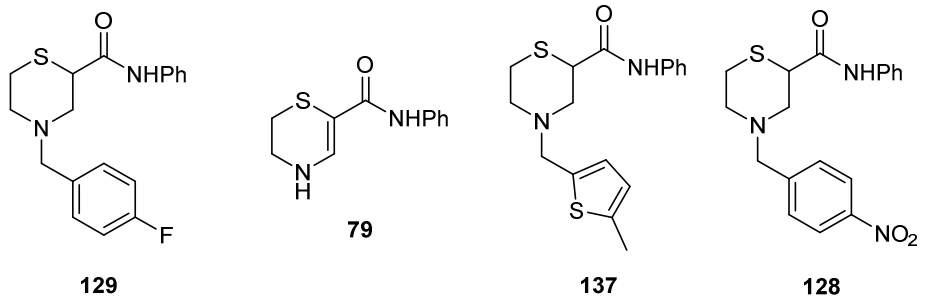


Figure 49 Most active compounds tested

Interestingly, each of the derivatives **79**, **137** and **128** demonstrate selectivity against three cancer cell lines (Figure 50). Growth inhibition against the renal cancer cell line UO-31 and the non-small cell lung cancer NCI-H522 (stage 2, adenocarcinoma for males over 58 years old) are communal to these three molecules. Growth inhibition of cell lung cancer UACC-62, corresponding to stage 2 adenocarcinoma lung cancer for males of 58 years old or more, was only observed for the thiomorpholine **137** and **128**. In contrast, only the thiazine **79**

demonstrates growth inhibition for breast cancer cell line BT-549, corresponding to ductal carcinoma for females over 72 years old.

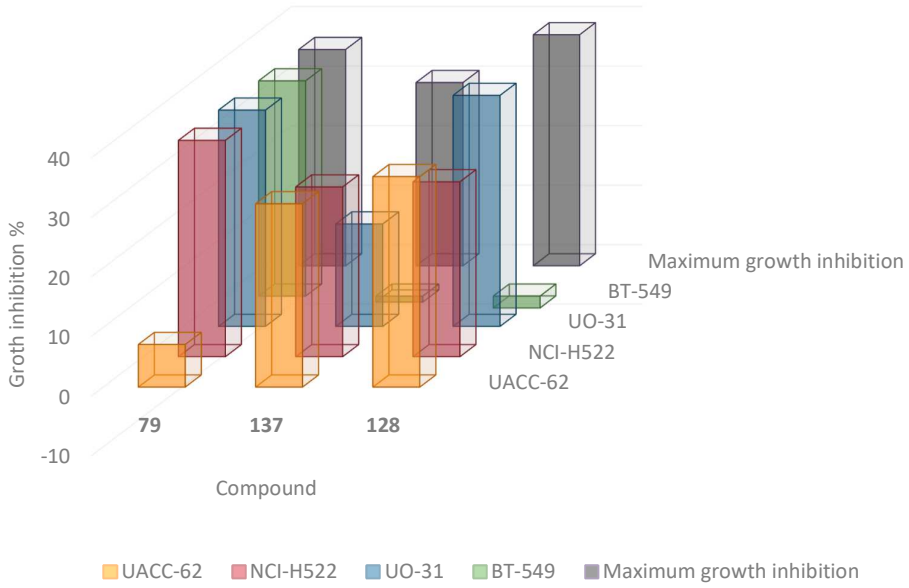


Figure 50 Activity against cell lines displayed by the most active thiomorpholines

In a general aspect, the nineteen novel compounds screened in this project do not display an active profile for anti-cancer activity. Therefore, it would be interesting to evaluate the biological activity of these derivatives in other pathology, in which the activity may be highly selective due to the relatively non-toxic profile of these compounds.

For example, the novel 1,4-oxathiins **67** and **77** may display interesting anti-HIV activity, due to similar structure with the oxathiin carboxanilide derivatives seen in Figure 51, a class of non-nucleoside HIV-1 specific reverse transcriptase inhibitors.[104]

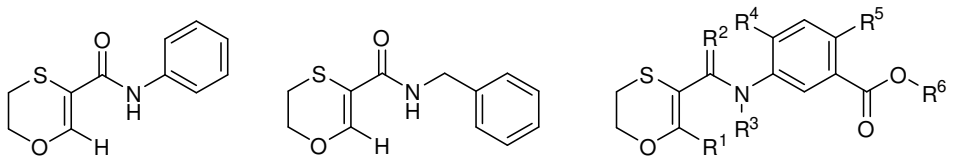


Figure 51

The novel 1,4-thiazines **79** and **119** could potentially be useful as antirheumatic agents, as the aroyl substituted dihydro-1,4-thiazines seen in Figure 52.[105]

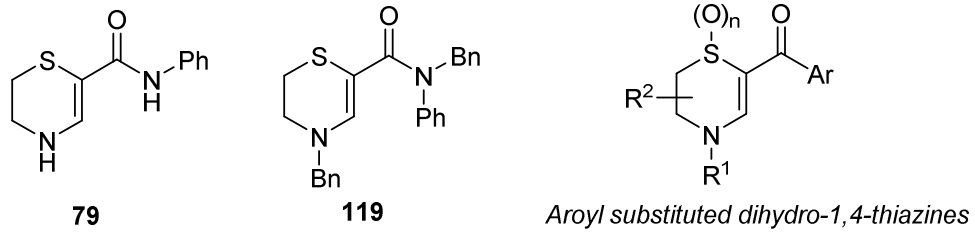


Figure 52

As described previously in *Section 4.D.*, compounds of the formula in Figure 53 are highly selective agonists or antagonists for $GABA_A$ receptors.[28, 29] The novel benzothiazine **105**, with its analogous structure could exhibit similar activity.

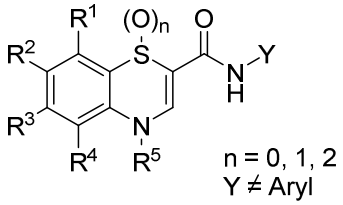


Figure 53

The *N*-substituted thiomorpholine derivatives of general structure seen in *Figure 54* possess antioxidant and hypocholesterolemic activity.[106] Therefore, it may be interesting to evaluate the novel thiomorpholines synthesised in this work for similar bioactivity.

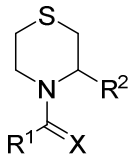


Figure 54

8. CONCLUSIONS

Substantial advances have been made in exploiting the oxidative chlorination cascade to lead to 1,4-oxathiin, 1,4-thiazine and 1,4-benzothiazine which have potential for biological interest. Extension of the strategy to dithiin synthesis has also been investigated.

The α-thio-β-chloroacrylamides *Z*-**66** and the novel *Z*-**74**, both bearing a primary alcohol on the sulfur substituent, were successfully synthesised from the corresponding α-thioamides in good yield. High stereoselectivity for these transformations was achieved by optimisation of the solvent system (toluene *vs* acetonitrile). In contrast, stereocontrol for synthesis of the α-thio-β-chloroacrylamide *Z*-**76** in the extended chain series was investigated but could not be achieved. These observations have been rationalized.

Optimisation of the reagent conditions for synthesis of the corresponding oxathiin derivative **67** and **77** was performed. Employing LiHMDS as reagent at -40 °C was found to be the optimal conditions for this transformation.

The α-thioamide precursor **84** for the 1,4-thiazine series was successfully synthesised in excellent yield but, in this case, protection was necessary. The corresponding α-thio-β-chloroacrylamide *Z*-**85** was obtained in good yield, as a single isomer. Interestingly, the synthesis in batch was found more efficient while employing toluene as solvent system, in contrast to the flow process which required acetonitrile to achieve efficient transformation. The use of freshly recrystallised NCS was key to achieve reproducible reaction outcome.

Cyclisation to the corresponding 1,4-thiazine **79** was performed in two steps *in situ*: deprotection of the amine group following by intramolecular 1,4-Michael addition. Once deprotected, it was interesting to notice partial spontaneous cyclisation of the α-thio-β-chloroacrylamide *Z*-**85**.

Synthesis of the α-thioamide precursor **91** for 1,4-benzothiazine series did not require protection of the amine group due to its less much nucleophilic character

by delocalization into the aryl ring. However, the oxidative NCS mediated transformation proved incompatible with the free amino group, which was therefore protected. Interestingly, as for the 1,4-thiazine series, the trichloride derivative **99** was found to be stable, in contrast to earlier series studied. Interestingly again, for this series, the commonly used 'hot plunge' technique was not required, with no significant impact on the efficiency of the transformation cascade while employing gradual heating. After optimisation, the novel α-thio-β-chloroacrylamide *Z*-**96** was obtained as a mixture with the *E*-isomer, and was isolated in pure form in good yield.

During the synthesis of α-thio-β-chloroacrylamides **66**, **74**, **76**, **85** and **96**, it was observed that not only employing butanamides, pentanamides or tertiary propenamide derivatives, but also alteration of the sulfur substituent and the solvent system, have significant impact on the stereoselectivity of the transformation.

Due to the poor nucleophilic character of the aryl amine, the intramolecular cyclisation did not occur from the unprotected sulfide **93**. Increasing the electrophilicity of the β-carbon through synthesis of the sulfoxide analogous **104** led to spontaneous cyclisation once deprotected. The resulting novel benzothiazine **105** was isolated in good yield. Attempts of oxidation to the sulfone level of the α-thio-β-chloroacrylamide proved unsuccessful.

For the dithiin series, synthesis of the protected thiol α-thioamide precursor **116** was performed from the hydroxy α-thioamide **71** with tosyl chloride, leading to the chlorinated analogue **111**, and subsequent disulfide **110** formation, using thiourea, and reduction. However, oxidative chlorination proved challenging due to the two sulfur atoms in the molecule and the desired α-thio-β-chloroacrylamide required for the dithiin formation could not be obtained.

N-Benzylation of the novel thiazine **79** was investigated and the reaction outcome strongly depends on the reaction conditions. Competition between benzylation of the amine and the amide groups was the main challenge for this transformation.

Reductive amination of 79 was more successful and a large scope of substituents was tolerated, including alkyl, benzyl, aryl and various heterocycles. Reduction of the heterocyclic unsaturated system was believed to first occurred, leading to crude mixtures containing essentially the thiomorpholine 123 and the desired *N*-substituted thiomorpholines. The reaction outcome was directly dependent on the aldehyde employed, and the *N*-substution did not occur with some substrates.

In this work, thirteen novel thiomorpholines were successfully isolated and were sent for biological evaluation for anticancer activity to the NCI, along with the two novel thiazines, two novel oxathiins and the new benzothiazine successfully obtained. Overall these compounds do not display an active profile for anti-cancer activity. Therefore, the non-toxic profile of these derivatives proved interesting to further investigate potential selective biological activity.

Overall, this work demonstrates the synthetic versatility of the oxidative chlorination cascade which can tolerate the presence of a range of functionalities on the α-thioamide precursor. In particular, it has been demonstrated that careful control of the reaction conditions can lead to an effective outcome even with processes that were initially inefficient.

9. REFERENCES

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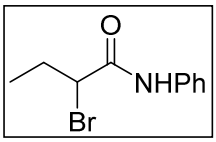
CHAPTER 3

Experimental

Table of Contents

1. SYNTHESIS OF oxathiin derivatives

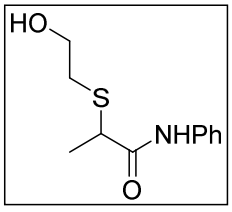
2-Bromo-*N*-phenylbutanamide 75[4]



A solution of 2-bromobutyryl bromide (1.00 mL, 8.29 mmol) in dichloromethane (10 mL) was added dropwise over 20 min to a solution of aniline (0.75 mL, 8.29 mmol) and triethylamine (1.15 mL, 8.29 mmol) in dichloromethane (10 mL) at 0 °C, while stirring. On completion of the addition, the reaction solution was removed from the ice bath and stirred at room temperature for 4 h. Water (30 mL) was added and the layers were separated. The organic layer was washed with a saturated solution of sodium bicarbonate (2 × 20 mL), distilled water (40 mL) and brine (40 mL), dried and concentrated under reduced pressure to give the α-*bromoamide* **75** (1.87 g, 94%) as a white solid which required no further purification; mp 84-87 °C; δ_H (400 MHz, $CDCl_3$) 1.11 [3H, t, *J* 7.4, C(4)H_3], 2.09-2.32 [2H, m, C(3)H_2], 4.43 [1H, dd, *J* 5.1, 2.6, C(2)*H*)], 7.16 (1H, t, *J* 7.0, ArH_{para}), 7.36 (2H, t, *J* 8.1, ArH_{meta}), 7.54 (2H, d, *J* 7.5, ArH_{ortho}), 8.09 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 11.8 [CH_3, *C*(4)H_3], 29.4 [CH_2, *C*(3)H_2], 54.1 [CH, *C*(2)*H*], 119.9 (CH, aromatic *C*H$_{ortho}$), 125.0 (CH, aromatic *C*H$_{para}$), 129.1 (CH, aromatic *C*H$_{meta}$), 137.1 (Cq, aromatic *C*q), 166.5 (Cq, *C*=O); ν_{max}/cm^{-1} 3244 (NH), 3068, 2971, 1651 (C=O), 1548, 1443, 754, 694.

Data reference incorrect.[4]

N-Phenyl-2-[2'-(hydroxyethyl)thio]propanamide 71[4]

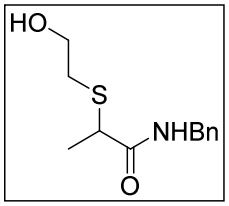


Mercaptoethanol (2.30 mL, 32.61 mmol) was added to a solution of freshly prepared sodium ethoxide [from sodium (0.75 g, 32.61 mmol) in absolute ethanol (30 mL) at 0 °C] while stirring under nitrogen. Immediately after the addition, a solution of 2-chloro-*N*-phenylpropanamide **17** (5.00 g, 27.23 mmol) in absolute ethanol (25 mL) was added dropwise over 15 min to the reaction mixture. Following stirring for 16 h at room temperature, the reaction was quenched by addition of water (60 mL) and dichloromethane (50 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2

x 40 mL). The combined organic layers were washed with aqueous sodium hydroxide (1M, 2 x 50 mL), water (100 mL) and brine (100 mL), dried and concentrated under reduced pressure to give the pure *α-thioamide* **71** (5.68 g, 93%) as a white solid which required no further purification; mp 74-77 °C (Lit.,[4] 70-72 °C); δ_H (300 MHz, $CDCl_3$) 1.55 [3H, d, *J* 7.2, C(3)*H*$_3$], 2.35 (1H, br t, *J* 5.5, O*H*), 2.71-2.89 (2H, m, C*H*$_2$S), 3.63 [1H, q, *J* 7.2, C(2)*H*], 3.73-3.90 [2H, m, C*H*$_2$OH], 7.12 (1H, t, *J* 7.3, Ar*H*$_{para}$), 7.32 (2H, t, *J* 7.6, Ar*H*$_{meta}$), 7.55 (2H, d, *J* 8.0, Ar*H*$_{ortho}$), 8.64 [1H, br s, N*H*]; δ_C (100 MHz, $CDCl_3$) 18.5 [CH_3, *C*(3)*H*$_3$], 34.4 (CH_2, *C*H_2S), 44.9 [CH, *C*(2)*H*], 61.7 (CH_2, *C*H_2OH), 119.8, 124.5, 129.0 (3 x CH signals, 5 x aromatic *C*H), 137.6 (Cq, aromatic *C*q), 170.9 (Cq, *C*=O); ν_{max}/cm^{-1} 3239 (NH, OH), 3031, 2903, 1660 (C=O), 1600, 1557, 1443, 1067, 754, 689; m/z (ES+) 226.2 [(M+H$^+$), 100%]; (ES-) 224.3 [(M-H$^+$), 100%].

Spectroscopic characteristics were consistent with those previously reported.[4]

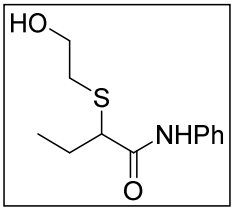
N-Benzyl-2-[2'-(hydroxyethyl)thio]propanamide 72



This synthesis follows the procedure described for **71** using *N*-benzyl-2-chloropropanamide **19** (2.00 g, 10.12 mmol) in absolute ethanol (7 mL), mercaptoethanol (0.85 mL, 12.14 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.30 g, 12.14 mmol) in absolute ethanol (10 mL) at 0 °C]. The crude product contained the α-*thioamide* **72** (δ_H 1.49, 3H, d, *J* 7.2) and the α-*chloroamide* **19** (δ_H 1.82, 3H, d, *J* 7.1) in the ratio 1 : 0.08 respectively by ^{1}H NMR spectroscopy and was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 60% ethyl acetate) to give the pure *α-thioamide* **72** (1.69 g, 70%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 1.49 [3H, d, *J* 7.2, C(3)*H*$_3$], 2.39 (1H, br t, *J* 5.7, O*H*), 2.67-2.81 (2H, m, apparent qt, C*H*$_2$S), 3.51 [1H, q, *J* 7.4, C(2)*H*], 3.60-3.76 (2H, m, C*H*$_2$OH), 4.45 (2H, d, *J* 5.8, C*H*$_2$Bn), 6.96 (1H, br s, N*H*), 7.26-7.42 (5H, m, Ar*H)*; δ_C (100 MHz, $CDCl_3$) 18.6 [CH_3, *C*(3)*H*$_3$], 34.5 (CH_2, *C*H_2S), 43.8 (CH_2, *C*H_2Ph), 44.0 [CH, *C*(2)*H*], 61.4 (CH_2, *C*H_2OH), 127.6, 127.7, 127.8 (3 x CH signals, 5 x aromatic *C*H), 138.0 (Cq, aromatic *C*q), 172.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3283 (NH), 3064, 3031, 2926 (OH), 2871, 1644 (C=O),

1531, 1557, 1443, 1044, 732, 697; HRMS (ES+): Exact mass calculated for $C_{12}H_{18}NO_2S$ $[M+H]^+$, 240.1058; Found 240.1050; m/z (ES+) 240.3 [$(M+H^+)$, 14%], (ES-) 238.3 [$(M-H^+)$, 100%].

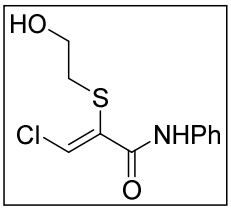
N-Phenyl-2-[2'-(hydroxyethyl)thio]butanamide 76[4]



This synthesis follows the procedure described for **71** using mercaptoethanol (0.65 mL, 9.27 mmol), a solution of freshly prepared sodium ethoxide [from sodium (0.21 g, 9.27 mmol) in absolute ethanol (12 mL) at 0 °C] and a solution of 2-bromo-*N*-phenylbutanamide **75** (0.30 g, 7.72 mmol) in absolute ethanol (10 mL). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 30 to 40% ethyl acetate) to give the pure *α-thioamide* **76** (1.58 g, 86%) as a white solid; mp 75-77 °C (Lit.,[4] 71-73 °C); δ_H (400 MHz, $CDCl_3$) 1.09 [3H, t, *J* 7.2, C(4)H_3], 1.82 [1H, sept, *J* 7.3, one of C(3)H_2], 1.95-2.20 {2H, m, which includes [1H, sept, *J* 7.3, one of C(3)H_2], (1H, br t, *J* 5.7, O*H*)}, 2.70-2.90 (2H, m, CH_2S), 3.44 [1H, t, *J* 6.8, C(2)*H*], 3.77-3.86 (2H, m, CH_2OH), 7.13 (1H, t, *J* 6.8, ArH_{para}), 7.34 (2H, t, *J* 8.0, ArH_{meta}), 7.57 (2H, d, *J* 8.0, ArH_{ortho}), 8.55 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 12.1 [CH_3, *C*(4)H_3], 26.2 [CH_2, *C*(3)H_2], 34.6 (CH_2, *C*H_2S), 52.5 [CH, *C*(2)*H*], 61.6 (CH_2, *C*H_2OH), 119.7 (CH, aromatic *C*H_{ortho}), 124.5 (CH, aromatic *C*H_{para}), 129.1 (CH, aromatic *C*H_{meta}), 137.6 (Cq, aromatic *C*q), 170.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3390 (OH), 3283 (NH), 3075, 2966, 2930, 1665 (C=O), 1600, 1546, 1444, 1068, 753; m/z (ES+) 240.3 [$(M+H^+)$, 100%], (ES-) 238.3 [$(M-H^+)$, 100%].

Spectroscopic characteristics were consistent with those previously reported.[4]

N-Phenyl-*Z*-3-chloro-2-[2'-(hydroxyethyl)thio]propenamide *Z*-66[4]

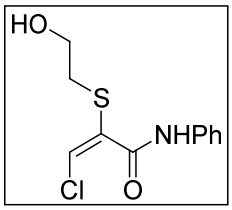


N-Chlorosuccinimide (4.30 g, 32.00 mmol) was added in one portion to a solution of *N*-phenyl-2-[2'-(hydroxyethyl)thio]propanamide **71** (3.70 g, 16.40 mmol) in acetonitrile (60 mL). The flask was immediately immersed in an oil bath at 60 °C while stirring and maintained at this temperature for 20 min. Following this, the solvent was evaporated under reduced pressure. ^{1}H NMR

analysis showed the crude product to contain a mixture of the desired α-*thio*-β-*chloroacrylamide Z*-**66** (83%, δ_H 7.89, 1H, s), the α-*thio*-β-*chloroacrylamide E*-**66** (7%, δ_H 7.97, 1H, s) and an unidentifiable side product (estimated 10%, δ_H 4.62, t). The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 15% ethyl acetate), then recrystallised from toluene to give the pure α-*thio*-β-*chloroacrylamide Z*-**66** (2.61 g, 62%) as a white solid; mp 69-72 °C; δ_H (400 MHz, $CDCl_3$) 2.15 (1H, br s, O*H*), 2.98 (2H, t, *J* 5.6, CH_2S), 3.72-3.84 (2H, m, apparent br s, CH_2OH), 7.13 (1H, t, *J* 7.3, ArH_{para}), 7.35 (2H, t, *J* 8.4, ArH_{meta}), 7.62 (2H, d, *J* 7.6, ArH_{ortho}), 7.89 (1H, s, C*H*), 9.23 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 37.3 (CH_2, *C*H_2S), 60.3 (CH_2, *C*H_2OH), 120.0 (CH, aromatic *C*H_{ortho}), 124.9 (CH, aromatic *C*H_{para}), 129.1 (CH, aromatic *C*H_{meta}), 131.6 [Cq, *C*(2)q], 137.4 (Cq, aromatic *C*q), 139.9 [CH, *C*(3)H], 161.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3286 (NH), 3133, 3059, 2929, 2876, 1650 (C=O), 1596 (C=C), 1525, 1442, 748, 689; m/z (ES+) 258.2 {[($C_{11}H_{12}{}^{35}ClNO_2S$)+$H^+$], 100%}, 260.2 {[($C_{11}H_{12}{}^{37}ClNO_2S$)+$H^+$], 34%; (ES-) 256.2 {[($C_{11}H_{12}{}^{35}ClNO_2S$)-$H^+$], 96%}, 258.2 {[($C_{11}H_{12}{}^{37}ClNO_2S$)+$H^+$], 40%}.

Spectroscopic characteristics were consistent with those previously reported.[4]

N-Phenyl-*E*-3-chloro-2-[2'-(hydroxyethyl)thio]propenamide *E*-66[4]



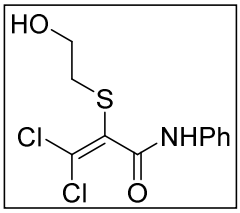
N-Chlorosuccinimide (0.52 g, 3.89 mmol) was added in one portion to a solution of *N*-phenyl-2-[2'-(hydroxyethyl)thio]propanamide **71** (0.40 g, 1.77 mmol) in acetonitrile (100 mL). The flask was immediately immersed in an oil bath at 80 °C while stirring and maintained at this temperature for 25 min. Following this, the solvent was evaporated under reduced pressure. ^{1}H NMR analysis showed the crude product to contain a mixture of α-*thio*-β-*chloroacrylamide Z*-**66** (δ_H 7.89, 1H, s), α-*thio*-β-*chloroacrylamide E*-**66** (δ_H 7.97, 1H, s) and *dichloroacrylamide* **73** (δ_H 1.49, 1H, br s) with ratio 1 : 0.10 : 0.40 respectively by ^{1}H NMR spectroscopy. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 5 to 10% ethyl acetate) to give the pure α-*thio*-β-*chloroacrylamide E*-**66** (0.02 g, 4%) as a yellow oil; δ_H (600 MHz, $CDCl_3$) 3.15 (2H, t, *J* 6.8, CH_2S), 3.67 (2H,

t, *J* 6.8, C*H*$_2$OH), 7.17 (1H, t, *J* 6.5, Ar*H*$_{para}$), 7.37 (2H, t, *J* 7.9, Ar*H*$_{meta}$), 7.62 (2H, d, *J* 7.9, Ar*H*$_{ortho}$), 7.97 (1H, s, C*H*), 9.06 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 36.6 (CH_2, *C*H_2S), 42.7 (CH_2, *C*H_2OH), 120.1 (CH, aromatic *C*H$_{ortho}$), 125.1 (CH, aromatic *C*H$_{para}$), 129.2 (CH, aromatic *C*H$_{meta}$), 130.6 [Cq, *C*(2)q], 137.2 (Cq, aromatic *C*q), 141.0 [CH, *C*(3)H], 160.6 (Cq, *C*=O); ν_{max}/cm^{-1} 3331 (NH), 3059, 2964, 1660 (C=O), 1596 (C=C), 1520, 1439, 748, 689; HRMS (ES+): Exact mass calculated for $C_{11}H_{13}NO_2SCl$ $[M+H]^+$, 258.0356; Found 258.0352.

The α-*thio*-β-*chloroacrylamide Z*-**66** (δ_H 7.89, 1H, s, CH) was also isolated as a mixture with the dichloroacrylamide **73** (δ_H 1.49, 1H, br s, NH) with ratio 1 : 0.4 respectively by ^{1}H NMR spectroscopy (0.33 g).

Spectroscopic characteristics were consistent with those previously reported.[4]

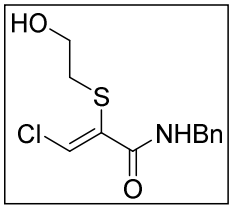
3,3-Dichloro-2-((2-hydroxyethyl)thio)-*N*-phenylacrylamide 73



Lithium *bis*(trimethylsilyl)amide (1M in THF, 1.41 mmol, 0.89 mL) was added dropwise over 30 min to a solution of *N*-phenyl-*Z*-3-chloro-2-[2'-(hydroxyethyl)thio]propanamide *Z*-**66** (0.33 g, 1.28 mmol) in THF (5 mL) at 0 °C. Then the reaction mixture was removed from the bath, allowed to warm to room temperature and stirred at this temperature for 48 h. The reaction mixture was quenched by addition of a saturated ammonium chloride solution (8 mL). Extraction with dichloromethane (3 x 10 mL) and washing of the combined organic layers with brine (3 x 20 mL) gave the crude product. ^{1}H NMR analysis showed the crude product to contain the *dichloroacrylamide* **73** as the main product formed, with a large amount of unidentifiable impurities and no evidence of the oxathiin **67** formed or α-*thio*-β-*chloroacrylamide Z*-**74** remaining. Purification by column chromatography on silica gel using hexane : ethyl acetate as eluent (2:98) gave the pure *dichloroacrylamide* **73** (55 mg, 18%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.42 (1H, t, *J* 5.4, O*H*), 3.04 (2H, t, *J* 5.5, C*H*$_2$S), 3.56-3.93 (2H, m, apparent q, C*H*$_2$OH), 7.18 (1H, t, *J* 7.3, Ar*H*$_{para}$), 7.37 (2H, t, *J* 8.0, Ar*H*$_{meta}$), 7.57 (2H, d, *J* 8.0, Ar*H*$_{ortho}$), 8.03 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 36.4 (CH_2, *C*H_2S), 62.1 (CH_2, *C*H_2OH), 120.0 (CH, aromatic *C*H$_{ortho}$), 124.4 (Cq, *C*qCl_2), 125.3 (CH,

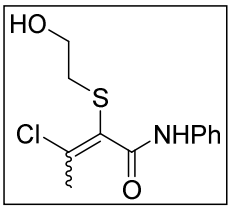
aromatic *C*H*para*), 129.2 (CH, aromatic *C*H*meta*), 130.5 [Cq, *C*(2)q], 137.0 (Cq, aromatic *C*q), 161.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3252 (NH), 3195, 3061, 2919, 1650 (C=O), 1597 (C=C), 1543, 1497, 1442, 1318, 752, 689, 506; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}{}^{35}Cl_2NO_2S$ $[M+H]^+$, 291.9958; Found 291.9966; m/z (ES+) 292.1 {[($C_{11}H_{12}{}^{35}Cl_2NO_2S$)+$H^+$], 58%}; (ES-) 290.2 {[($C_{11}H_{12}{}^{35}Cl_2NO_2S$)-$H^+$], 100%}, 292.1 {[($C_{11}H_{12}{}^{35}Cl^{37}ClNO_2S$)+$H^+$], 68%}, 294.1 {[($C_{11}H_{12}{}^{37}Cl_2NO_2S$)+$H^+$], 10%}.

N-Benzyl-*Z*-3-chloro-2-[2'-(hydroxyethyl)thio]propenamide *Z*-74



N-Chlorosuccinimide (0.61 g, 4.59 mmol) was added in one portion to a solution of *N*-benzyl-2-[2'-(hydroxyethyl)thio]propanamide **72** (0.50 g, 2.09 mmol) in acetonitrile (10 mL). The flask was immediately immersed in an oil bath at 80 °C while stirring and maintained at this temperature for 20 min. Following this, the solvent was evaporated under reduced pressure. ^{1}H NMR analysis showed the crude product to contain a mixture of α-*thio*-β-*chloroacrylamide Z*-**74** (δ_H 7.80, 1H, s), α-*thio*-β-*chloroacrylamide E*-**74** (δ_H 7.87, 1H, s) and *α-thioamide* **72** (δ_H 1.49, 3H, d, *J* 7.2) with ratio 1 : 0.05 : 0.03 respectively by ^{1}H NMR spectroscopy and was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 5 to 10% ethyl acetate) to give the pure α-*thio*-β-*chloroacrylamide Z*-**74** (0.44 g, 78%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.02 (1H, br s, O*H*), 2.87 (2H, t, *J* 5.6, CH_2S), 3.67 (2H, t, *J* 5.6, CH_2OH), 4.51 (2H, d, *J* 5.7, CH_2Ph), 7.22-7.38 (5H, m, Ar*H*), 7.65 (1H, br s, N*H*), 7.80 (1H, s, C*H*); δ_C (100 MHz, $CDCl_3$) 37.1 (CH_2, *C*H_2S), 44.3 (CH_2, *C*H_2Ph), 60.4 (CH_2, *C*H_2OH), 127.8, 128.8, 129.0 (3 x CH signals, 5 x aromatic *C*H), 131.3 [Cq, *C*(2)q], 137.6 (Cq, aromatic *C*q), 138.6 [CH, *C*(3)H], 163.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3287 (NH), 3061, 3031, 2937, 2844, 1705 (C=O), 1641 (C=C), 1516, 1033, 697; HRMS (ES+): Exact mass calculated for $C_{12}H_{15}{}^{35}ClNO_2S$ $[M+H^+]$, 272.0512; Found 272.0513; m/z (ES+) 272.2 {[($C_{12}H_{14}{}^{35}ClNO_2S$)+$H^+$], 20%}; (ES-) 270.2 {[($C_{12}H_{14}{}^{35}ClNO_2S$)-$H^+$], 100%}, 272.2 {[($C_{12}H_{14}{}^{37}ClNO_2S$)+$H^+$], 40%}.

N-Phenyl-*Z*-3-chloro-2-[2'-(hydroxyethyl)thio]butenamide 69[4]



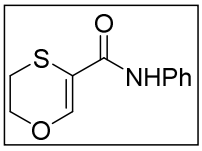
N-Chlorosuccinimide (0.33 g, 2.44 mmol) was added in one portion to a solution of *N*-phenyl-2-[2'-(hydroxyethyl)thio]butanamide **76** (0.30 g, 1.25 mmol) in acetonitrile (3 mL). The flask was immediately immersed in an oil bath at 60 °C while stirring and maintained at this temperature for 15 min. Following the solvent was evaporated at reduced pressure. The crude product contained the tentatively assigned α-*thio*-β-*chloroacrylamide Z*-**69** (δ_H 8.01, 1H, br s) and α-*thio*-β-*chloroacrylamide E*-**69** (δ_H 8.67, 1H, br s) with a ratio 1 : 0.44 respectively by ^{1}H NMR spectroscopy and was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (80:20) to give the pure less polar α-*thio*-β-*chloroacrylamide E*-**69** (0.13 g, 39%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.40 (1H, br s, O*H*), 2.48 [3H, s, C(4)H_3], 2.95 (2H, t, *J* 6.2, CH_2S), 3.80 (2H, t, *J* 5.7, CH_2OH), 7.15 (1H, t, *J* 7.6, ArH_{para}), 7.35 (2H, t, *J* 7.9, ArH_{meta}), 7.57 (2H, d, *J* 7.9, ArH_{ortho}), 8.67 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 25.6 [CH_3, *C*(4)H_3], 36.6 (CH_2, *C*H_2S), 61.1 (CH_2, *C*H_2OH), 119.9 (CH, aromatic *C*H$_{ortho}$), 124.9 (CH, aromatic *C*H$_{para}$), 126.5 [Cq, *C*(2)q], 129.2 (CH, aromatic *C*H$_{meta}$), 137.4 (Cq, aromatic *C*q), 144.7 [Cq, *C*(3)Cl], 163.5 (Cq, *C*=O); ν_{max}/cm^{-1} 3236 (OH), 3192 (NH), 3061, 2976, 2919, 2978 (CH stretch), 1645 (C=O), 1596 (C=C stretch), 1546 (NH bend), 1442 (CN stretch), 1321 (C-O), 753, 684 (CH bend); m/z (ES+) 272.2 {[($C_{12}H_{14}{}^{35}ClNO_2$)+H$^+$], 100%}, 274.2 {[($C_{12}H_{14}{}^{37}ClNO_2$)+H$^+$], 40%}; m/z (ES-) 270.2 {[($C_{12}H_{14}{}^{35}ClNO_2$)-H$^+$], 100%}, 272.2 {[($C_{12}H_{14}{}^{37}ClNO_2$)-H$^+$], 40%}.

The more polar α-*thio*-β-*chloroacrylamide Z*-**69** (0.14 g, 41%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 2.44 [3H, s, C(4)H_3], 2.92 (2H, t, *J* 5.6, CH_2S), 3.85 (2H, t, *J* 5.5, CH_2OH), 7.15 (1H, t, *J* 7.0, ArH_{para}), 7.34 (2H, t, *J* 8.2, ArH_{meta}), 7.58 (2H, d, *J* 7.9, ArH_{ortho}), 8.01 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 24.4 [CH_3, *C*(4)H_3], 37.1 (CH_2, *C*H_2S), 62.1 (CH_2, *C*H_2OH), 119.8 (CH, aromatic *C*H$_{ortho}$), 125.0 (CH, aromatic *C*H$_{para}$), 126.3 [Cq, *C*(2)q], 129.1 (CH, aromatic *C*H$_{meta}$), 136.6 [Cq, *C*(3)Cl], 137.3 (Cq, aromatic *C*q), 164.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3276 (OH), 3133 (NH), 3062, 2923, 2873, 1651 (C=O), 1597 (C=C), 1543, 1443, 1319, 728, 690; m/z (ES+) 272.2

{[($C_{12}H_{14}{}^{35}ClNO_2$)+$H^+$], 100%}, 274.2 {[($C_{12}H_{14}{}^{37}ClNO_2$)+$H^+$], 40%}; m/z (ES-) 270.2 {[($C_{12}H_{14}{}^{35}ClNO_2$)-$H^+$], 100%}, 272.2 {[($C_{12}H_{14}{}^{37}ClNO_2$)-$H^+$], 40%}.

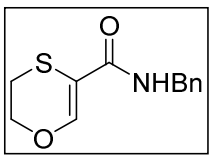
Spectroscopic characteristics were consistent with those previously reported.[4]

N-Phenyl-5,6-dihydro-1,4-oxathiine-3-carboxamide 67[4]



Lithium *bis*(trimethylsilyl)amide (1M in THF, 3.88 mmol, 3.90 mL) was added dropwise over 30 min to a solution of *N*-phenyl-*Z*-3-chloro-2-[2'-(hydroxyethyl)thio]propanamide *Z*-**66** (1.94 mmol, 0.50 g) in THF (5 mL) at -40 °C. Then the reaction mixture was removed from the bath and allowed to warm to room temperature and stirred at this temperature for 48 h. The reaction mixture was quenched by addition of a saturated ammonium chloride solution (10 mL), followed by extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (3 x 20 mL), dried and concentrated under reduced pressure. ^{1}H NMR analysis showed the crude product to be was relatively clean, with the *oxathiin* **67** as the main product formed. Purification by column chromatography on silica gel using hexane : ethyl acetate : DCM as eluent (70:25:5) following by a cold recrystallization using DCM : hexane gave the pure *oxathiin* **67** (0.20 g, 48%) as a white solid; mp 129-130 °C (Lit.,[5] 131-133 °C); δ_H (400 MHz, $CDCl_3$) 3.02 (2H, t, *J* 4.5, CH_2S), 4.43 (2H, t, *J* 4.5, CH_2O), 7.11 (1H, t, *J* 7.2, ArH_{para}), 7.33 (2H, t, *J* 7.5, ArH_{meta}), 7.49-7.70 [3H, m, which includes 7.53 (2H, d, *J* 8.1, ArH_{ortho}), 7.62 (1H, br s, N*H*)], 7.75 (1H, s, C*H*); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_2, *C*H_2S), 66.3 (CH_2, *C*H_2O), 101.6 (Cq, S*C*=), 120.1 (CH, aromatic *C*H_{ortho}), 124.4 (CH, aromatic *C*H_{para}), 129.0 (CH, aromatic *C*H_{meta}), 137.7 (Cq, aromatic *C*q), 148.5 (CH, *C*H=), 162.6 (Cq, *C*=O); HRMS (ES+): Exact mass calculated for $C_{11}H_{12}NO_2S$ $[M+H]^+$, 222.0589; Found 222.0583.

N-Benzyl-5,6-dihydro-1,4-oxathiine-3-carboxamide 77

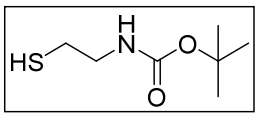


This synthesis follows the procedure described for **67** using lithium bis(trimethylsilyl)amide (1M in THF, 3.68 mmol, 3.70 mL) and a solution of *N*-benzyl-*Z*-3-chloro-2-[2'-

(hydroxyethyl)thio]propanamide *Z*-**74** (0.50 g, 1.84 mmol) in THF (5 mL). ^{1}H NMR analysis showed the crude product to contain the *oxathiin* **77** as the main product formed, with a large amount of unidentifiable impurities. Purification by column chromatography on silica gel using hexane : ethyl acetate : DCM as eluent (87:8:5) following by a recrystallization from absolute ethanol gave the pure *oxathiin* **77** (0.08 g, 19%) as a pale yellow solid; mp 116-116.5 ^{o}C; δ_H (400 MHz, $CDCl_3$) 2.96 (2H, t, *J* 4.4, C*H*$_2$S), 4.38 (2H, t, *J* 4.8, C*H*$_2$O), 4.52 (2H, d, *J* 5.8, C*H*$_2$Ph), 6.14 (1H, br s, N*H*), 7.27-7.38 (5H, m, Ar*H*), 7.70 (1H, s, C*H*); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_2, *C*H$_2$S), 43.8 (CH_2, *C*H$_2$Ph), 66.1 (CH_2, *C*H$_2$O), 101.4 (Cq, S*C*=), 127.5, 127.8, 128.7 (3 x CH signals, 5 x aromatic *C*H), 138.2 (Cq, aromatic *C*q), 147.8 (CH, *C*H=), 164.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3319 (NH), 2981, 1639 (C=O), 1591 (C=C), 1516, 1033, 731; HRMS (ES+): Exact mass calculated for $C_{12}H_{13}NO_2S$ $[M+H]^+$, 236.0745; Found 236.0740; m/z (ES+) 236 [($M+H^+$), 99%].

2. SYNTHESIS OF THIAZINE DERIVATIVE

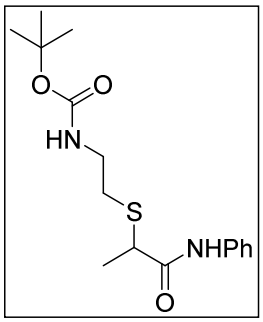
tert-Butyl (2-mercaptoethyl)carbamate 81[6]



A solution of di-*tert*-butyl dicarbonate (4.22 g, 19.36 mmol) in freshly distilled THF (5 mL) was added dropwise to a solution of cysteamine hydrochloride (2.00 g, 17.60 mmol) in THF : deoxygenated water (12 : 3 mL). Triethylamine (7.80 mL, 56.32 mmol) was added slowly by successive addition over 30 min. The reaction mixture was stirred at room temperature for 24 h and neutralised with hydrochloric acid solution (1M, 30 mL). The crude product was extracted with ethyl acetate (2 x 50 mL), dried and concentrated under reduced pressure to give a mixture of the *protected cysteamine* **81** (δ_H 2.65, 2H, apparent q) and the *protected disulfide* **83** (δ_H 2.80, 4H, t, *J* 6.4) in the ratio 1 : 0.06 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) gave the pure *protected cysteamine* **81** (2.77 g, 89%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.38 (1H, t, *J* 8.1, S*H*), 1.45 (9H, s, 3 x C*H*$_3$), 2.65 (2H, apparent q, overlapped dt, *J* 8.4, 6.4, C*H*$_2$S), 3.30 (2H, apparent q, overlapped

dt, *J* 6.2, 6.0, C*H*$_2$NH), 5.12 (1H, br s, N*H* BOC); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2, *C*H_2S), 28.3 (CH_3, 3 x *C*H_3 BOC), 43.6 (CH_2, *C*H_2NH), 79.4 [Cq, *C*-$(CH_3)_3$], 155.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3354 (NH), 2977 (SH), 1689 (C=O), 1506, 1249, 1162 ; HRMS (ES+): Exact mass calculated for $C_7H_{16}NO_2S$ $[M+H]^+$, 178.0902; Found 178.0909; m/z (ES+) 178.3 [($M+H^+$), 80%].

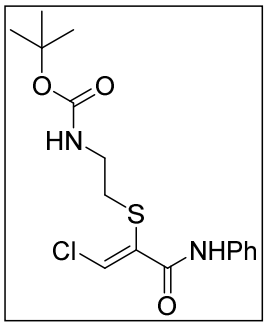
tert-Butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate 84



This synthesis follows the procedure described for **71** using *N*-phenyl-2-chloropropanamide **17** (1.40 g, 7.59 mmol) in absolute ethanol (10 mL), *tert*-butyl-(2-mercaptoethyl)carbamate **81** (1.61 g, 9.11 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.21 g, 9.11 mmol) in absolute ethanol (12 mL) at 0 ^oC]. The crude product contained the α-*thioamide* **84** (δ_H 3.57, 1H, q, *J* 7.1) and the α-*chloroamide* **17** (δ_H 4.55, 1H, q, *J* 6.8) in the ratio 1 : 0.06 respectively by ^1H NMR spectroscopy and was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (80:20) to give the pure *α-thioamide* **84** (2.25 g, 92%) as a white solid; mp 101-103 ^oC; (Found C, 59.60; H, 7.40; N, 8.45; S, 10.13. $C_{16}H_{24}N_2O_3S$ requires C, 59.23; H, 7.46; N, 8.63; S, 9.88%); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, 3 x C*H*$_3$), 1.53 [3H, d, *J* 7.2, C(3)*H*$_3$], 2.65-2.81 (2H, m, C*H*$_2$S), 3.20-3.45 (2H, m, C*H*$_2$NH), 3.57 [1H, q, *J* 7.1, C(2)*H*], 4.97 (1H, br s, N*H* BOC), 7.11 (1H, t, *J* 7.6, Ar*H*$_{para}$), 7.32 (2H, t, *J* 7.6, Ar*H*$_{meta}$), 7.59 (2H, d, *J* 7.8, Ar*H*$_{ortho}$), 8.66 (1H, br s, N*H* amide); δ_C (100 MHz, $CDCl_3$) 18.1 [CH_3, *C*(3)H_3], 28.4 (CH_3, 3 x *C*H_3 BOC), 31.7 (CH_2, *C*H_2S), 39.8 (CH_2, *C*H_2NH), 44.1 [CH, *C*(2)*H*], 79.7 [Cq, *C*-$(CH_3)_3$], 120.0 (CH, aromatic *C*H$_{ortho}$), 124.4 (CH, aromatic *C*H$_{para}$), 128.9 (CH, aromatic *C*H$_{meta}$), 137.8 (Cq, aromatic *C*q), 156.2 (Cq, *C*=O BOC), 170.8 (Cq, *C*=O amide); ν_{max}/cm^{-1} 3294 (NH), 2972, 1681 (C=O), 1661 (C=O), 1546, 1175, 757; HRMS (ES+): Exact mass calculated for $C_{16}H_{25}N_2O_3S$ $[M+H]^+$, 325.1586; Found 325.1577; m/z (ES+) 325.3 [($M+H^+$), 100%]; m/z (ES-) 323.3 [($M-H^+$), 60%].

tert-Butyl-(*Z*)-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate *Z*-85

Batch Process

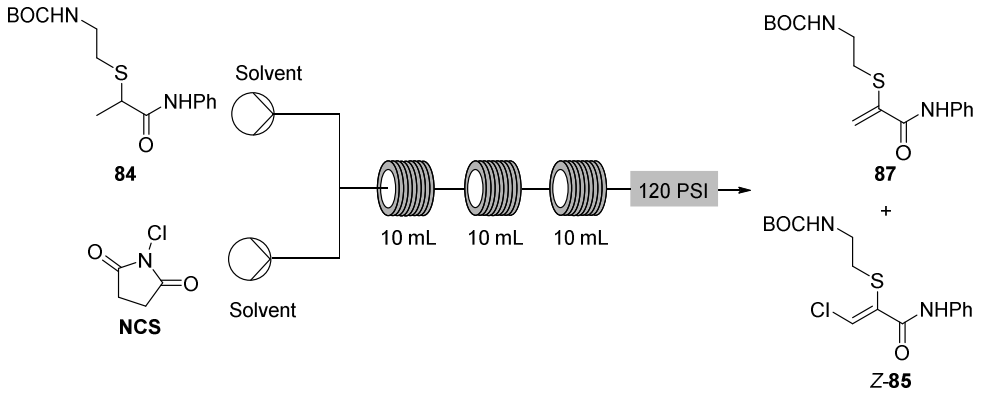


N-Chlorosuccinimide (1.48 g, 11.09 mmol) was added in one portion to a solution of *tert*-butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate **84** (1.80 g, 5.55 mmol) in toluene (60 mL). The flask was immediately immersed in an oil bath at 60 °C while stirring and maintained at this temperature for 20 min. Following this, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (92:8) to give the pure α-*thio*-β-*chloroacrylamide Z*-**85** (1.39 g, 71%) as a single isomer as a white solid; mp 78-81 °C; (Found C, 53.73; H, 5.75; Cl, 10.20; N, 7.79; S, 9.07. $C_{16}H_{21}ClN_2O_3S$ requires C, 53.85; H, 5.93; Cl, 9.93; N, 7.85; S, 8.98%); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, 3 x C*H*$_3$), 2.93 (2H, t, *J* 6.2, C*H*$_2$S), 3.25-3.38 (2H, m, apparent br q, C*H*$_2$NH), 4.95 (1H, br s, N*H* BOC), 7.16 (1H, t, *J* 7.4, Ar*H*$_{para}$), 7.36 (2H, t, *J* 8.2, Ar*H*$_{meta}$), 7.63 (2H, d, *J* 7.9, Ar*H*$_{ortho}$), 7.88 (1H, s, C*H*), 9.11 (1H, br s, N*H* amide); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_3, 3 x *C*H$_3$ BOC), 35.0 (CH_2, *C*H$_2$S), 40.0 (CH_2, *C*H$_2$NH), 79.9 [Cq, *C*-$(CH_3)_3$], 120.2 (CH, aromatic *C*H$_{ortho}$), 125.0 (CH, aromatic *C*H$_{para}$), 129.1 (CH, aromatic *C*H$_{meta}$), 131.7 [Cq, *C*(2)q], 137.3 (Cq, aromatic *C*q), 139.4 [CH, *C*(3)H], 155.9 (Cq, *C*=O BOC), 160.9 (Cq, *C*=O amide); ν_{max}/cm^{-1} 3409 (NH), 3313 (NH), 2977, 2935, 2874, 1689 (C=O), 1666 (C=O), 1509, 1440, 1158, 689; HRMS (ES+): Exact mass calculated for $C_{16}H_{22}{}^{35}ClN_2O_3S$ $[M+H]^+$, 357.1040; Found 357.1028; m/z (ES+) 379.1 {[($C_{16}H_{21}{}^{35}ClN_2O_3S$)+$Na^+$], 34%}, 381.1 {[($C_{16}H_{21}{}^{37}ClN_2O_3S$)+$Na^+$], 12%}; (ES-) 355.2 {[($C_{16}H_{21}{}^{35}ClN_2O_3S$)-$H^+$], 100%}, 357.2 {[($C_{16}H_{21}{}^{37}ClN_2O_3S$)+$H^+$], 40%}.

The outcome of the reaction was quite variable, and problems of reproducibility were encountered. In some instance, the *acrylamide* **87** (δ_H 5.91, 6.62, 2H, 2 x s), the *dichloride* **88** (δ_H 4.02, 4.40, 2H, ABq, *J* 11.6) and the *trichloride* **86** (δ_H 6.53, 1H, s) formation was observed using ^{1}H NMR spectroscopy of the crude product. The

trichloride could not be removed by recrystallization or column chromatography, because it possessed the same retention factor as the desired α-*thio*-β-*chloroacrylamide Z*-**85**. A continuous flow process for this transformation was developed in order to propose a reproducible synthetic method.

Continuous Flow Process



Entry	Ratio **84**:NCS[a]	Temp. (°C)	Residence Time (min)	Solvent	Product Ratio[b]		
					84	**87**	*Z*-**85**
1	1 : 2	120	30	Tol	1	0.9	0.8
2	1 : 2	80	20	MeCN	0.2	0.2	1
3	1 : 2.4	80	22	MeCN	0	0	1

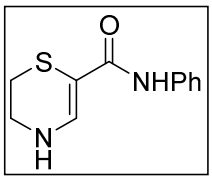
[a]Stoichiometric ratio were adjusted by manipulating the flow rates.

[b]Determined by ^{1}H NMR spectroscopy.

α-*Thioamide* **84** solution (0.025M) in solvent (acetonitrile or toluene) was pumped into a T-piece where it met *N*-chlorosuccinimide solution (0.05M) in Solvent (MeCN or toluene). The combined stream was then passed through three conventional flow coil reactor (3 x 10 mL) in series, heated to the appropriate temperature according to the solvent used (80 °C or 120 °C). The flow rate was 0.75 mL/min for both α-thioamide and NCS solutions in *entry 1* and *entry 2*, while the stoichiometric ratio of starting materials was adjusted using a flow rate of 0.72 mL/min for NCS solution and 0.60 mL/min for α-thioamide solution in *entry 3*. The product stream passed through a back pressure regulator (8 bar) before exiting the reactor. Reactor effluents were collected in a round bottom flask and then concentrated under reduced pressure to remove the solvent. The sample was

subsequently dissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy. The relative molar proportions of *α-thioamide* **84** (δ_H 1.53, 3H, d, *J* 7.2), *acrylamide* **87** (δ_H 5.91, 6.62, 2H, 2 x s) and α-*thio*-β-*chloroacrylamide Z*-**85** (δ_H 7.88, 1H, s) were measured based on the integrals of their characteristic signals. The characteristic signals corresponding to the *dichloride* **88** (δ_H 4.02, 4.40, 2H, ABq, *J* 11.6) and the *trichloride* **86** (δ_H 6.53, 1H, s) were not observed by 1H NMR spectroscopy of the crude mixtures.

N-Phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide 79

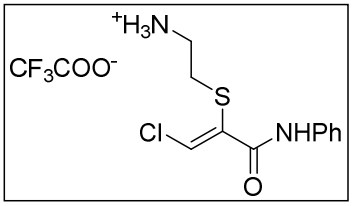


Trifluoroacetic acid (2.90 mL, 38.10 mmol) was added dropwise to a solution of *tert*-butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate **85** (1.13 g, 3.18 mmol) in DCM (12 mL) while stirring at room temperature. To achieve full reaction completion (TLC monitoring), trifluoroacetic acid (0.25 mL, 3.18 mmol) was added to the reaction mixture after 3 h of reaction time. Following 1 hour of stirring, triethylamine (6.1 mL, 44.48 mmol) was added dropwise over 30 min at 0 ^oC. Following the addition, the ice bath was removed and the reaction mixture was then allowed to warm to room temperature and stirred overnight. Water (60 mL) was added followed by successive extraction with DCM : ethyl acetate 50:50 (3 x 50 mL). The layers were separated and the combined organic layers were washed with a saturated solution of sodium bicarbonate (60 mL) and brine (100 mL), dried and concentrated under reduced pressure to give the crude product as a yellow solid. Washing using ethyl acetate : hexane (20:80) following by filtration gave the pure *thiazine* **79** (0.48 g, 69%) as a white solid; mp 161-164 ^oC; (Found C, 59.93; H, 5.59; N, 12.50. $C_{11}H_{12}N_2OS$ requires C, 59.98; H, 5.49; N, 12.72); δ_H (400 MHz, $CDCl_3$) 2.84 (2H, t, *J* 4.8, CH_2S), 3.63-3.71 (2H, m, CH_2NH), 4.68 (1H, br s, N*H* thiazine), 7.06 (1H, t, *J* 7.2, ArH_{para}), 7.30 (2H, t, *J* 8.1, ArH_{meta}), 7.54 (2H, d, *J* 8.1, ArH_{ortho}), 7.68-7.74 [2H, apparent d, which contains 7.72 (1H, s, C*H*), 7.71 (1H, br s, N*H* amide)]; δ_C (100 MHz, $CDCl_3$) 23.2 (CH_2, CH_2S), 43.0 (CH_2, CH_2NH), 89.1 (Cq, S*C*=), 119.8 (CH, aromatic CH_{ortho}), 123.5 (CH, aromatic CH_{para}), 128.9 (CH, aromatic CH_{meta}), 137.2 (CH, *C*H=), 138.6 (Cq, aromatic *C*q), 164.1 (Cq, *C*=O).

δ_H (400 MHz, DMSO) 2.76 (2H, t, *J* 4.5, C*H*$_2$S), 3.45 (2H, t, *J* 4.6, C*H*$_2$NH), 6.87-6.99 {3H [6.90 (1H, br s, N*H* thiazine)], [6.95 (1H, t, *J* 7.0, Ar*H*$_{para}$)]}, 7.23 (2H, t, *J* 7.5, Ar*H*$_{meta}$), 7.57 (2H, d, *J* 7.9, Ar*H*$_{ortho}$), 7.61 (1H, d, *J* 6.5, C*H*), 8.90 (1H, br s, N*H* amide); δ_C (100 MHz, DMSO) 22.8 (CH$_2$, *C*H$_2$S), 41.7 (CH$_2$, *C*H$_2$NH), 89.5 (Cq, S*C*=), 119.6 (CH, aromatic *C*H$_{ortho}$), 122.1 (CH, aromatic *C*H$_{para}$), 128.3 (CH, aromatic *C*H$_{meta}$), 136.6 (CH, *C*H=), 139.9 (Cq, aromatic *C*q), 164.2 (Cq, *C*=O).

ν_{max}/cm^{-1} 3267 (NH), 2962 (NH), 3047, 2962, 2867, 1634 (C=O), 1578 (C=C), 1498; HRMS (ES+): Exact mass calculated for $C_{11}H_{13}N_2OS$ $[M+H]^+$, 221.0749; Found 221.0749; m/z (ES+) 221.3 {$[(C_{11}H_{12}N_2OS)+H^+]$, 100%}.

Z-2-((1-Chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio)ethan-1-aminium 2,2,2-trifluoroacetate *Z*-90.CF_3COOH



Triflurorоacetic acid (0.70 mL, 9.14 mmol) was added dropwise to a solution of *tert*-butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate (0.30 g, 0.84 mmol) in DCM (2 mL) while stirring at room temperature. The reaction mixture was stirred at room temperature for 40 min (TLC monitoring, full consumption of starting material). Saturated sodium bicarbonate solution (5 mL) was added slowly to the reaction mixture. The crude product was extracted using ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (30 mL), dried and concentrated under reduced pressure. ^{1}H NMR analysis showed the crude product to contain the α-*thio*-β-*chloroacrylamide salt Z*-**90**.CF_3COOH (δ_H 7.13, 1H, t, *J* 7.4) and *thiazine* **79** (δ_H 7.61, 1H, d, *J* 6.5) with a ratio 0.29 : 1 respectively by ^{1}H NMR spectroscopy in DMSO. Washing using a large amount dichloromethane following by filtration gave the pure α-*thio*-β-*chloroacrylamide salt Z*-**90**.CF_3COOH (0.04 g, 13%) as a white solid; mp 185-187 ^{o}C; δ_H (400 MHz, DMSO) 2.95-3.07 (4H, m, C*H*$_2$$NH_3^+$ + C*H*$_2$S), 7.13 (1H, t, *J* 7.4, Ar*H*), 7.35 (3H, m, apparent t, Ar*H* and C*H*), 7.67 (2H, d, *J* 7.5, Ar*H*), 8.02 (3H, br s, N*H*$_3^+$), 10.63 (1H, br s, N*H*); δ_C (100 MHz, DMSO) 28.3 (CH$_2$, *C*H$_2$S), 39.4 (CH$_2$, *C*H$_2$$NH_3^+$), 120.2 (CH, aromatic *C*H$_{ortho}$), 124.3 (CH, aromatic *C*H$_{para}$), 125.2 (CH, *C*H=), 128.7 (CH, aromatic *C*H$_{meta}$), 134.9 (Cq,

S*C*=), 138.3 (Cq, aromatic *C*q), 161.3 (Cq, *C*=O); δ_H (282 MHz, DMSO) -76.0 (Cq, *C*F_3); ν_{max}/cm^{-1} 3352 (NH), 2970, 2922 (NH_2), 1669 (C=O), 1523, 1078. HRMS (ES+): Exact mass calculated for $C_{11}H_{14}ClN_2OS$ $[M+H]^+$, 257.0515; Found 257.0513; m/z (ES+) 257.3 {[($C_{11}H_{13}N_2OS^{35}Cl$)+H^+], 100%}, 259.2 {[($C_{11}H_{13}N_2OS^{37}Cl$)+H^+], 46%}.

The filtrate was concentrated and the resulting solid washed using ethyl acetate : hexane (20:80) following by filtration gave the pure *thiazine* **79** (0.14 g, 32%).

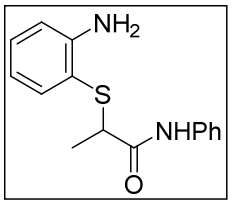
Following storage at room temperature for 14 months, the pure α-*thio*-β-*chloroacrylamide salt Z*-**90**.CF_3COOH turned red. ^{1}H NMR analysis showed the sample to contain *thiazine* **79** estimated at 95% pure, with no evidence of α-*thio*-β-*chloroacrylamide salt Z*-**90**.CF_3COOH remained.

Prove of the α-*thio*-β-*chloroacrylamide Z*-**90** structure

Triethylamine (0.12 mL, 0.86 mmol) was added dropwise to a solution of (*Z*)-2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio)ethan-1-aminium chloride *Z*-**90**.HCl in ethyl acetate (5 mL) at 0°C. Following the addition, the ice bath was removed and the reaction mixture was then allowed to warm to room temperature and stirred overnight. Water (10 mL) was added and the layers were separated. The organic layer was washed with a saturated solution of sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL), dried and concentrated under reduced pressure to give the crude product. ^{1}H NMR analysis showed the crude product to contain the *thiazine* **79** as the main product formed.

3. SYNTHESIS OF BENZOTHIAZINE DERIVATIVE

2-((2-Aminophenyl)thio)-*N*-phenylpropanamide 91

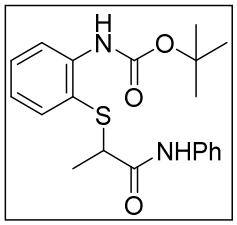


This synthesis follows the procedure described for **71** using *N*-phenyl-2-chloropropanamide **17** (0.46 g, 2.52 mmol) in absolute ethanol (2 mL), 2-aminothiophenol (0.32 mL, 3.03 mmol) and freshly prepared sodium ethoxide [prepared from sodium (0.07 g, 3.03 mmol) in absolute ethanol (3 mL) at 0 °C]. The crude

product contained α-*thioamide* **91** (δ_H 3.73, 1H, q, *J* 7.3) , α-*chloroamide* **17** (δ_H 4.55, 1H, q, *J* 6.8) and 2,2'-disulfanediyldianiline **92** (δ_H 7.97, 2H, d, *J* 8.0)[6] in the ratio 1 : 0.17 : 0.56 respectively by ^{1}H NMR spectroscopy and was washed using hexane : ethyl acetate (80:20) following by filtration to give the pure *α-thioamide* **91** (0.18 g, 27%)* as a white solid; mp 125-127 °C; (Found C, 65.80; H, 5.92; N, 10.61; S, 11.41. $C_{15}H_{16}N_2OS$ requires C, 66.15; H, 5.92; N, 10.29; S, 11.77%); δ_H (400 MHz, $CDCl_3$) 1.58 [3H, d, *J* 7.1, C(3)*H*$_3$], 3.73 [1H, q, *J* 7.3, C(2)*H*], 4.39 [2H, br s, N*H*$_2$], 6.69 (1H, t, *J* 7.6, Ar*H*), 6.74 (1H, d, *J* 8.1, Ar*H*), 7.09 (1H, t, *J* 7.2, Ar*H*), 7.16 (1H, t, *J* 7.4, Ar*H*), 7.28 (2H, t, *J* 8.8, Ar*H*), 7.34-7.41 (3H, m, Ar*H*), 7.62 (1H, br s, N*H* amide); δ_C (100 MHz, $CDCl_3$) 17.6 [CH_3, *C*(3)H_3], 47.4 [CH, *C*(2)*H*], 115.5 (CH, aromatic *C*H), 115.6 (Cq, aromatic *C*q), 119.1, 119.8, 124.4, 128.9, 131.0, 136.6 (6 x CH signals, 8 x aromatic *C*H), 137.6, 148.7 (2 x Cq, 2 x aromatic *C*q), 170.0 (Cq, *C*=O amide); ν_{max}/cm^{-1} 3422 (NH_2), 3294 (NH), 3026, 1657 (C=O), 1520, 1440, 755; HRMS (ES+): Exact mass calculated for $C_{15}H_{17}N_2OS$ $[M+H]^+$, 273.1062; Found 273.1055; m/z (ES+) 273.3 [($M+H^+$), 98%]; m/z (ES-) 271.3 [($M-H^+$), 74%].

*A yield of 80% was obtained for a batch of **91** that was later synthesised using deoxygenated absolute ethanol on a 16.3 mmol scale.

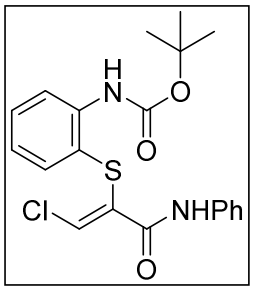
tert-Butyl-(2-((1-oxo-1-(phenylamino)propan-2-yl)thio)phenyl)carbamate 95



To a mixture of di-*tert*-butyl dicarbonate (0.30 g, 1.40 mmol) and 2-((2-aminophenyl)thio)-*N*-phenylpropanamide (0.27 g, 1.00 mmol) in acetonitrile (2 mL) was added lanthanum nitrate hexahydrate (5 mol%) and the reaction mixture was stirred at room temperature overnight. Water (20 mL) was added to the reaction mixture and the product was extracted with ethyl acetate (3 x 20 mL). The layers were separated and the combined organic layers was washed with brine (30 mL), dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) to give the pure *α-thioamide* **95** (0.30 g, 80%) as a white solid; mp 142-143 °C; (Found C, 64.24; H, 6.44; N, 8.11; S, 8.20. $C_{20}H_{24}N_2O_3S$ requires C, 64.49; H, 6.49; N, 7.52; S, 8.61%) δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, 3 x

CH_3), 1.58 [3H, d, *J* 7.1, C(3)*H*$_3$], 3.62 [1H, q, *J* 7.0, C(2)*H*], 6.95 (1H, t, *J* 7.3, Ar*H*), 6.85 (1H, t, *J* 7.4, Ar*H*), 7.23-7.42 (6H, m, ArH), 7.46 (1H, br s, N*H*Ph), 7.49 (1H, d, *J* 7.8, Ar*H*), 7.68 (1H, br s, N*H*BOC), 8.13 (1H, d, *J* 8.2, Ar*H*); δ_C (100 MHz, $CDCl_3$) 17.6 [CH_3, *C*(3)H_3], 28.3 (CH_3, 3 x *C*H_3 BOC), 48.7 [CH, *C*(2)*H*], 80.9 (Cq, *C*q BOC), 119.6 (Cq, aromatic *C*q), 119.9, 123.3, 124.6, 128.9, 130.9, 136.2 (6 x CH signals, 9 x aromatic *C*H), 137.4, 140.7 (2 x Cq, 2 x aromatic *C*q), 152.7 (Cq, *C*=O BOC), 169.4 (Cq, *C*=O amide); ν_{max}/cm^{-1} 3383 (NH), 3295 (NH), 2981, 1736 (C=O from BOC), 1659 (C=O from amide), 1499, 1427, 1151, 751; HRMS (ES+): Exact mass calculated for $C_{20}H_{25}N_2O_3S$ $[M+H]^+$, 373.1586; Found 373.1580; m/z (ES+) 372.3 [M, 20%].

tert-Butyl-(*Z*)-(2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio) phenyl)carbamate *Z*-96

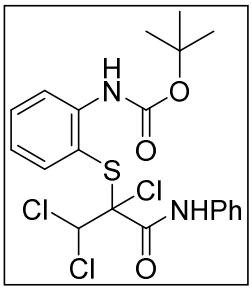


N-Chlorosuccinimide (0.16 g, 1.18 mmol) was added in one portion to a solution of *tert*-butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate **95** (0.21 g, 0.56 mmol) in toluene (8 mL). The flask was immediately immersed in an oil bath at 90 °C while stirring and maintained at this temperature for 4 hours. Following this, the solvent was evaporated at reduced pressure. ^{1}H NMR analysis showed the crude product to contain a mixture of the α-*thio*-β-*chloroacrylamide Z*-**96** (δ_H 7.89, 1H, s), the *E*-**96** (δ_H 6.46, 1H, s) and the *dichloride* **98** (δ_H 4.03, 4.50, 2H, ABq, *J* 11.9) with ratio 1 : 0.1 : 0.03 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) to give the pure tentatively assigned *Z* isomer α-*thio*-β-*chloroacrylamide Z*-**96** (0.16 g, 73%) as a pale yellow solid; mp 130-133 °C; (Found C, 58.79; H, 5.12; N, 6.90. $C_{20}H_{21}ClN_2O_3S$ requires C, 59.33; H, 5.23; N, 6.92%); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, 3 x C*H*$_3$), 6.94 (1H, br s, N*H*), 7.04-7.12 (2H, m, Ar*H*), 7.23-7.34 (4H, m, Ar*H*), 7.50 (2H, d, *J* 7.8, Ar*H*), 7.65 (1H, dd, *J* 8.1, 1.1, Ar*H*), 7.89 (1H, s, C*H*=), 8.90 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3, 3 x *C*H_3 BOC), 81.2 [Cq, *C*-$(CH_3)_3$], 120.5, 123.7 (2 x CH signals, 3 x aromatic *C*H), 124.5 (Cq, aromatic *C*q), 124.9, 125.8, 128.9 (3 x CH signals, 6 x aromatic *C*H), 129.4 (Cq, aromatic *C*q),

131.5 [Cq, C(2)q=], 137.4, 137.5 (2 x Cq, 2 x aromatic *C*q), 138.3 [CH, *C*(3)H], 153.1 (Cq, *C*=O BOC), 160.3 (Cq, *C*=O amide); ν_{max}/cm^{-1} 3374 (NH), 3363 (NH), 3057, 2929, 2972, 1736 (C=O), 1645 (C=O), 1509, 1435, 1149, 751; HRMS (ES+): Exact mass calculated for $C_{20}H_{22}{}^{35}ClN_2O_3S$ $[M+H]^+$, 405.1040; Found 405.1042; m/z (ES+) 427.1 {[($C_{20}H_{22}{}^{35}ClN_2O_3S$)+$Na^+$], 18%}, 429.1 {[($C_{20}H_{22}{}^{37}ClN_2O_3S$)+$Na^+$], 9%}.

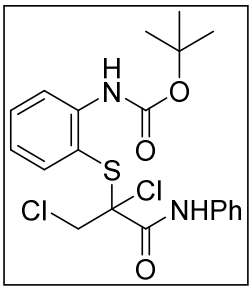
tert-Butyl-(2-((1,1,2-trichloro-3-oxo-3-(phenylamino)propan-2-yl)thio)phenyl)carbamate 99 and *tert*-butyl(2-((2,3-dichloro-1-oxo-1-(phenylamino)propan-2-yl)thio) phenyl)carbamate 98

N-Chlorosuccinimide (0.09 g, 0.67 mmol) was added in one portion to a solution of *tert*-butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate **95** (0.13 g, 0.34 mmol) in toluene (5 mL). The flask was immediately immersed in an oil bath at 60 °C while stirring and maintained at this temperature for 3 hours. Following this, the solvent was evaporated at reduced pressure. ^{1}H NMR analysis showed the crude product to contain a mixture of the α-*thio*-β-*chloroacrylamide* *Z*-**96** (δ_H 7.89, 1H, s), the *E*-**96** (δ_H 6.46, 1H, s), the *trichloride* **99** (δ_H 6.72, 1H, s) and the *dichloride* **98** (δ_H 4.03, 4.50, 2H, ABq, *J* 11.9) with ratio 1 : 0.2 : 0.4 : 2.4 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) to give the pure *Z* isomer α-*thio*-β-*chloroacrylamide* *Z*-**96** (0.04 g, 30%).



The *trichloride* **99** was also isolated as a mixture with the *dichloride* **98** with ratio 1 respectively by ^{1}H NMR spectroscopy (5 mg, 3%); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, 3 x C*H*$_3$), 6.72 (1H, s, C*H*Cl_2), 6.87 (1H, td, *J* 7.6, 1.1, Ar*H*), 7.04-7.11 (2H, m, Ar*H*), 7.16-7.22 (3H, m, Ar*H*), 7.29 (1H, td, *J* 7.8, 1.6, Ar*H*), 7.54 (1H, dd, *J* 7.8, 1.6, Ar*H*), 7.65 (1H, br s, N*H*), 7.90 (1H, br s, N*H*), 8.03 (1H, d, *J* 8.4, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3, 3 x *C*H_3 BOC), 75.4 (CH, *C*HCl_2), 80.9 [Cq, *C*-$(CH_3)_3$], 88.7 (Cq, *C*-Cl), 114.8 (Cq, aromatic *C*q), 119.7, 120.6, 122.9, 125.9, 128.9, 132.9 (6 x CH signals, 8 x aromatic *C*H), 135.6 (Cq, aromatic *C*q), 138.5 (CH, aromatic *C*H), 142.44 (Cq, aromatic *C*q), 152.4, 161.8 (2 x Cq, 2 x *C*=O); Characteristic signals from the *dichloride* **98** (ABq, *J*

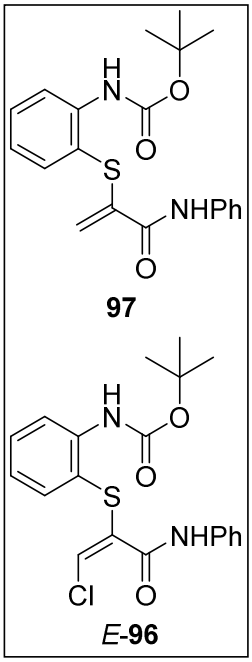
11.9, δ_H 4.03, 4.50) were also presents; HRMS (ES+): Exact mass calculated for $C_{20}H_{21}{}^{35}Cl_3N_2O_3SNa$ $[M+Na]^+$, 497.0236 Found 497.0228.



The *dichloride* **98** was also isolated in pure form (0.02 g, 14%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, 3 x C*H*$_3$), 4.03, 4.50 (2H, ABq, *J* 11.9, C*H*$_2$Cl), 6.97 (1H, td, *J* 7.5, 1.4, Ar*H*), 7.12-7.19 (1H, m, Ar*H*), 7.27-7.37 (4H, m, Ar*H*), 7.39-7.45 (1H, m, Ar*H*), 7.58 (1H, dd, *J* 7.7, 1.5, Ar*H*), 7.79 (1H, br s, N*H*), 8.07 (1H, br s, N*H*), 8.18 (1H, d, *J* 8.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3, 3 x *C*H$_3$ BOC), 50.3 (CH_2, *C*H$_2$Cl), 81.0 [Cq, *C*-$(CH_3)_3$], 81.7 (Cq, *C*-Cl), 114.5 (Cq, aromatic *C*q), 119.3, 120.4, 122.7, 125.6, 129.0, 132.9 (6 x CH signals, 8 x aromatic *C*H), 136.1 (Cq, aromatic *C*q), 138.9 (CH, aromatic *C*H), 142.6 (Cq, aromatic *C*q), 152.3 (Cq, *C*=O BOC), 162.9 (Cq, *C*=O amide); HRMS (ES+): Exact mass calculated for $C_{20}H_{22}{}^{35}Cl_2N_2O_3SNa$ $[M+Na]^+$, 463.0626; Found 463.0623; m/z (ES-) 439.2 {$[(C_{20}H_{22}{}^{35}Cl_2N_2O_3S)-H^+]$, 6%}.

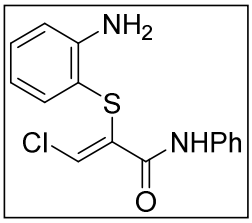
tert-butyl-(2-((3-oxo-3-(phenylamino)prop-1-en-2-yl)thio)phenyl)carbamate 97 and *tert*-butyl-(*E*)-(2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio) phenyl)carbamate *E*-96

N-Chlorosuccinimide (0.05 g, 0.42 mmol) was added in one portion to a solution of *tert*-butyl-(2-((1-(phenylamino)-1-oxopropan-2-yl)thio)ethyl)carbamate **95** (0.08 g, 0.21 mmol) in toluene (5 mL). The flask was immediately immersed in an oil bath at 100 ^oC while stirring and maintained at this temperature for 2 hours. Following this, the solvent was evaporated at reduced pressure. ^1H NMR analysis showed the crude product to contain a mixture of the α-*thio*-β-*chloroacrylamide* *Z*-**96** (δ_H 7.89, 1H, s), the *E*-**96** (δ_H 6.46, 1H, s), the *acrylamide* **97** (δ_H 5.53, 1H, s), and the *dichloride* **98** (δ_H 4.03, 4.50, 2H, ABq, *J* 11.9) with ratio 1 : 0.2 : 0.2 : 0.3 respectively by ^1H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (95:5) to give the pure *Z* isomer α-*thio*-β-*chloroacrylamide* *Z*-**96** (0.04 g, 30%).



The *acrylamide* **97** was also isolated as an equimolar mixture with the *E* isomer α-*thio*-β-*chloroacrylamide E*-**96** by ^{1}H NMR spectroscopy (24 mg); δ_H (400 MHz, $CDCl_3$) 1.53 (18H, s, 6 x C*H*$_3$), 5.53 [1H, s, one of C(2)*H*$_2$= of *acrylamide* **97**], 6.42-6.47 {2H, including 6.44 [1H, s, one of C(3)*H*$_2$= of *acrylamide* **97**] and 6.46 [1H, s, C(3)*H*= of α-*thio*-β-*chloroacrylamide E*-**96**]}, 7.10-7.13 (3H, m, ArH), 7.17-7.23 (1H, m, ArH), 7.26-7.39 (5H, m, ArH), 7.39-7.47 (4H, m, apparent t, ArH), 7.51 (1H, dd, *J* 7.8, 1.5, ArH), 7.55 (2H, d, *J* 8.4, ArH), 7.91 (1H, br s, NH), 7.97 (2H, d, *J* 8.1, ArH), 8.37 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3, 6 x *C*H$_3$ BOC), 81.2, 81.3 [2 x Cq, 2 x *C*-$(CH_3)_3$], 120.3, 121.0 (2 x CH, 6 x aromatic *C*H), 121.1 [CH, *C*(3)*H*= of α-*thio*-β-*chloroacrylamide E*-**96**], 121.9 (CH, 2 x aromatic *C*H), 124.5 (Cq, aromatic *C*q), 124.7 (CH, aromatic *C*H), 124.8 [CH_2, *C*(3)H_2= of *acrylamide* **97**], 125.1, 129.0, 130.4, 131.2 (4 x CH, 7 x aromatic *C*H), 133.6 [Cq, C(2)q= of α-*thio*-β-*chloroacrylamide E*-**96**], 134.0, 135.4 (2 x CH, 2 x aromatic *C*H), 136.9, 137.4 (2 x Cq, 2 x Cq aromatic), 138.2 (Cq, *C*(2)q= of *acrylamide* **97**], 138.9, 139.9 (2 x Cq, 2 x aromatic *C*q), 152.8, 153.1 (2 x Cq, 2 x *C*=O BOC), 160.6 (Cq, NH*C*=O of α-*thio*-β-*chloroacrylamide E*-**96**), 161.9 (Cq, NH*C*=O of *acrylamide* **97**); HRMS (ES+): Exact mass calculated for $C_{20}H_{22}N_2O_3SNa$ $[M+Na]^+$, 393.1249; Found 393.1242 and $C_{20}H_{22}{}^{35}ClN_2O_3S$ $[M+H]^+$, 405.1040; Found 405.1031; m/z (ES+) 393.2 {[($C_{20}H_{22}N_2O_3S$)+Na^+], 38%}, 427.1 {[($C_{20}H_{21}{}^{35}ClN_2O_3S$)+$Na^+$], 37%}, 429.1 {[($C_{20}H_{21}{}^{37}ClN_2O_3S$)+$Na^+$], 16%}; m/z (ES-) 369.3 {[($C_{20}H_{22}N_2O_3S$)-H^+], 8%}, 403.3 {[($C_{20}H_{21}{}^{35}ClN_2O_3S$)-$H^+$], 18%}, 405.2 {[($C_{20}H_{21}{}^{37}ClN_2O_3S$)-$H^+$], 6%}.

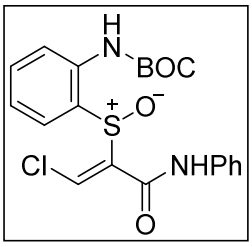
(*Z*)-2-((2-Aminophenyl)thio)-3-chloro-*N*-phenylacrylamide *Z*-93



Trifluoroacetic acid (0.17 mL, 2.22 mmol) was added dropwise to a solution of *tert*-Butyl-(*Z*)-(2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio) phenyl)carbamate *Z*-**96** (75 mg, 0.18 mmol) in DCM (2 mL) while stirring at room temperature. Following 2 hours of

stirring, triethylamine (0.38 mL, 2.77 mmol) was added at 0 °C. Following the addition, the ice bath was removed and the reaction mixture was then allowed to warm to room temperature and stirred overnight. Water (20 mL) was added followed by successive extraction with DCM : ethyl acetate 50:50 (3 x 15 mL). The layers were separated and the combined organic layers were washed with a saturated solution of sodium bicarbonate (2 x 20 mL) and brine (30 mL), dried and concentrated under reduced pressure to give the crude product. The crude ^{1}H NMR spectra was clean, with the *α-thio*-β-*chloroacrylamide Z*-**93** as the main product. Washing using ethyl acetate : hexane (10:80) following by filtration gave the pure *α-thio*-β-*chloroacrylamide Z*-**93** (35 mg, 63%) as a white solid; δ_H (400 MHz, $CDCl_3$) 4.33 (1H, br s, N*H*$_2$), 6.73 (2H, t, *J* 8.0, Ar*H*), 7.05-7.16 (2H, m, Ar*H*), 7.28 (2H, t, *J* 7.7, Ar*H*), 7.35 (1H, d, *J* 7.4, Ar*H*), 7.44 (2H, d, *J* 8.0, Ar*H*), 7.73 (1H, s, C*H*=), 8.62 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 114.1 (Cq, aromatic *C*q), 116.2, 120.0, 120.3, 124.8, 129.0, 130.9 (6 x CH signals, 8 x aromatic *C*H), 132.8 [Cq, *C*(2)q], 134.7 (CH, aromatic *C*H), 135.7 [CH, *C*(3)H], 137.3, 147.4 (2 x Cq, 2 x aromatic *C*q), 160.4 (Cq, *C*=O); HRMS (ES+): Exact mass calculated for $C_{15}H_{14}{}^{35}ClN_2OS$ $[M+H]^+$, 305.0515; Found 305.0516; m/z (ES-) 303.2 {[($C_{15}H_{14}{}^{35}ClN_2OS$)+$H^+$], 10%}.

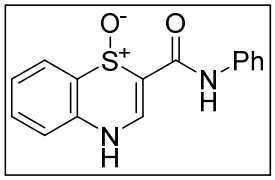
tert-Butyl-(*Z*)-(2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio)phenyl)carbamate *Z*-104



A solution of *m*CPBA (77%, 0.30 g, 1.43 mmol) in DCM (25 mL) was added dropwise to a solution of *tert*-butyl-(*Z*)-(2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio)phenyl)carbamate **96** (0.58 g, 1.43 mmol) in DCM (20 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then washed with a saturated solution of sodium bicarbonate (3 x 30 mL), water (50 mL) and brine (50 mL), dried and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using hexane : ethyl acetate as eluent (50:50) to give the pure *sulfoxide Z*-**104** (0.59 g, 98%) as a pale orange solid; mp 150-152 °C; (Found C, 56.50; H, 4.93; N, 6.34. $C_{20}H_{21}ClN_2O_4S$ requires C, 57.07; H, 5.03; N, 6.66%); δ_H (400 MHz,

$CDCl_3$) 1.37 (9H, s, 3 x C*H*$_3$), 7.10-7.20 (2H, m, apparent q, Ar*H*), 7.33 (2H, t, *J* 8.1, Ar*H*), 7.49 (1H, t, *J* 8.1, Ar*H*), 7.58 (2H, d, *J* 7.8, Ar*H*), 7.65 (1H, dd, *J* 8.1, 1.3, Ar*H*), 7.71 (1H, br s, N*H*), 7.77 (1H, s, C*H*=), 8.07 (1H, d, *J* 8.2, Ar*H*), 10.11 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (CH_3, 3 x *C*H_3 BOC), 81.5 [Cq, *C*-$(CH_3)_3$], 120.7, 125.1, 126.4, 129.1, 133.4 (5 x CH signals, 9 x aromatic *C*H), 136.9 [Cq, *C*(2)q], 137.2 (Cq, aromatic *C*q), 137.8 [CH, *C*(3)H], 138.4 (Cq, aromatic *C*q), 152.3 (Cq, *C*=O BOC), 158.6 (Cq, *C*=O amide); ν_{max}/cm^{-1} 3247 (NH), 3082, 2978, 2931, 1726 (C=O), 1670 (C=O), 1499, 1439, 1243, 1151, 738; HRMS (ES+): Exact mass calculated for $C_{20}H_{21}{}^{35}ClN_2O_4SNa$ $[M+Na]^+$, 443.0808; Found 443.0816; m/z (ES+) 443.1 {[($C_{20}H_{21}{}^{35}ClN_2O_4S$)+$Na^+$], 52%}, 445.1 {[($C_{20}H_{21}{}^{37}ClN_2O_4S$)+$Na^+$], 24%}.

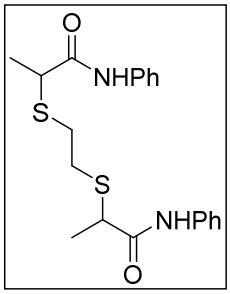
N-Phenyl-4H-benzo[b][1,4]thiazine-2-carboxamide 1-oxide 105



TBAF solution (1M, 1.2 mL, 1.19 mmol) was added to a solution of the *tert*-butyl-(*Z*)-(2-((1-chloro-3-oxo-3-(phenylamino)prop-1-en-2-yl)thio)phenyl)carbamate *Z*-**104** (0.10 g, 0.24 mmol) in freshly distilled THF (15 mL) at room temperature. The reaction mixture was heated under reflux for 5 hours and a saturated solution of ammonium chloride (10 mL) was added. The residual TBAF was extracted with DCM (10 mL) and the precipitate in suspension in both layers was filtered. The resulting pale yellow solid was washed with hot methanol and filter to give the pure *benzothiazine* **105** (0.04 g, 71%) as a white solid; mp 212-217 ^oC; δ_H (600 MHz, DMSO) 7.07 (1H, t, *J* 7.3, Ar*H*), 7.34 (2H, t, *J* 7.7, Ar*H*), 7.40 (1H, t, *J* 7.7, Ar*H*), 7.53 (1H, d, *J* 7.9, Ar*H*), 7.64-7.70 (3H, m, Ar*H*), 7.93 (1H, d, *J* 7.8, Ar*H*), 8.34 [1H, s, C(3)*H*], 9.92 (1H, br s, N*H* amide); δ_C (150 MHz, DMSO) 109.3 [Cq, C(2)q=], 117.9, 120.1, 123.2 (3 x CH signals, 4 x aromatic *C*H), 124.1 (Cq, Cq aromatic), 124.6, 128.6, 131.1, 132.1 (4 x CH signals, 5 x aromatic *C*H), 133.9 (Cq, Cq aromatic), 135.9 [CH, C(3)H], 139.4 (Cq, aromatic *C*q), 163.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3230 (NH), 3143 (NH), 3053, 2830, 2798, 1644 (C=O), 1600, 1550, 1478, 1361, 928, 748; HRMS (ES+): Exact mass calculated for $C_{15}H_{13}N_2O_2S$ $[M+H]^+$, 285.0698; Found 285.0697; m/z (ES+) 318 [($M+H^+$), 50%]; (ES-) 283.3 [($M-H^+$), 4%].

4. SYNTHESIS OF DITHIIN DERIVATIVE

2,2'-(Ethane-1,2-diylbis(sulfanediyl))bis(N-phenylpropanamide) 109

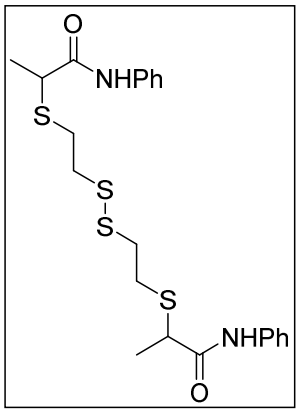


Ethanedithiol (0.30 mL, 3.27 mmol) was added to a solution of freshly prepared sodium ethoxide [from sodium (0.08 g, 3.27 mmol) in absolute ethanol (8 mL) at 0 ^{o}C] while stirring under nitrogen. Immediately after the addition, a solution of 2-chloro-*N*-phenylpropanamide **17** (0.50 g, 2.72 mmol) in absolute ethanol (3 mL) was added dropwise over 7 min to the reaction mixture. Following stirring for 16 h at room temperature, the reaction was quenched by addition of water (20 mL) and dichloromethane (20 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with aqueous sodium hydroxide (1M, 2 x 20 mL), water (40 mL) and brine (40 mL), dried and concentrated under reduced pressure to give a mixture of the disulfide **110** and the *α-thioamide* **109** in an unidentifiable ratio. The crude mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 20% ethyl acetate) to give the *dl* diastereoisomer of *α-thioamide* **109** (24 mg, 4%) as a white solid; δ_H (300 MHz, $CDCl_3$) 1.53 [6H, d, *J* 6.7, 2 x C(3)H_3], 2.71-2.99 (4H, m, 2 x CH_2S), 3.55 [2H, q, *J* 7.0, 2 x C(2)*H*], 7.14 (2H, t, *J* 7.2, 2 x ArH_{para}), 7.34 (4H, t, *J* 7.3, 4 x ArH_{meta}), 7.59 (4H, d, *J* 7.6, 4 x ArH_{ortho}), 8.57 [2H, br s, 2 x N*H*]; δ_C (100 MHz, $CDCl_3$) 18.1 [CH_3, 2 x *C*(3)H_3], 31.2 (CH_2, 2 x *C*H_2S), 44.7 [CH, 2 x *C*(2)*H*], 119.8 (CH, 4 x aromatic *C*H$_{ortho}$), 124.7 (CH, 2 x aromatic *C*H$_{para}$), 129.1 (CH, 4 x aromatic *C*H$_{meta}$), 137.6 (Cq, 2 x aromatic *C*q), 171.1 (Cq, 2 x *C*=O); Exact mass calculated for $C_{20}H_{24}N_2O_2S_2$ $[M+H]^+$, 389.1357; Found 389.1357; m/z (ES+) 389.2 [$(M+H^+)$, 12%]; (ES-) 387.2 [$(M-H^+)$, 22%]. Fraction of the *meso* diastereoisomer of *α-thioamide* **109** was also isolated (70 mg, 11%) as a white solid; δ_H (300 MHz, $CDCl_3$) 1.52 [6H, d, *J* 6.9, 2 x C(3)H_3], 2.84 (4H, dd, *J* 11.6, 2.8, 2 x CH_2S), 3.52 [2H, q, *J* 7.3, 2 x C(2)*H*], 7.12 (2H, t, *J* 7.3, 2 x ArH_{para}), 7.32 (4H, t, *J* 8.0, 4 x ArH_{meta}), 7.54 (4H, d, *J* 8.3, 4 x ArH_{ortho}), 8.43 [2H, br s, 2 x N*H*]; δ_C (100 MHz, $CDCl_3$) 18.5 [CH_3, 2 x *C*(3)H_3], 31.5 (CH_2, 2 x *C*H_2S), 45.2 [CH, 2 x *C*(2)*H*], 119.8

(CH, 4 x aromatic *C*H$_{ortho}$), 124.6 (CH, 2 x aromatic *C*H$_{para}$), 129.1 (CH, 4 x aromatic *C*H$_{meta}$), 137.5 (Cq, 2 x aromatic *C*q), 170.5 (Cq, 2 x *C*=O); Exact mass calculated for $C_{20}H_{24}N_2O_2S_2Na$ $[M+Na]^+$, 411.1177; Found 411.1165; m/z (ES+) 389.2 [$(M+H^+)$, 4%], 411.1 [$(M+Na^+)$, 20%]; (ES-) 387.2 [$(M-H^+)$, 10%]. An inseparable mixture of the *disulfide* **110** and the *α-thioamide* **109** (as a mixture of diastereoisomers) was also isolated as major fraction (0.19 g).

The *disulfide* **110** was further isolated as an equimolar mixture of diastereoisomers and data are reported in this section.

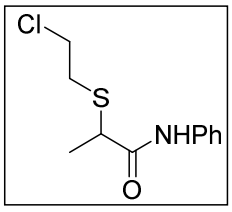
2,2'-((Disulfanediylbis(ethane-2,1-diyl))bis(sulfanediyl))bis(*N*-phenylpropanamide) 110



Thiourea (0.06 g, 0.83 mmol) was added to a solution of the α-thioamide **111** (0.10 g, 0.41 mmol) in ethanol (2 mL). The mixture was heated under reflux for 20 h and concentrated under reduced pressure to give a white solid. Dichloromethane (2 mL), followed by sodium perborate tetrahydrate (0.05 g, 0.24 mmol) were added to a stirred solution of the thiouronium chloride salt in water (2 mL) at 0 ^oC. A solution of sodium hydroxide (0.02 g, 0.60 mmol) in water (2 mL) was then added dropwise over 20 min to the cooled, stirred reaction mixture. After a further period of 5 h, water was added (10 mL), the layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were dried and concentrated under reduced pressure to give the pure *disulfide* **110** (0.09 g, 96%) as an equimolar mixture of the meso and *dl* diastereoisomers, as a white solid which required no further purification; mp 112-115 ^oC; δ_H (400 MHz, $CDCl_3$) 1.51-1.60 {12H, m, including two overlapped d, 1.55 [6H, d, *J* 7.5, C(3)*H*$_3$ of one diastereoisomer] and 1.56 [6H, d, *J* 7.5, C(3)*H*$_3$ of one diastereoisomer]}, 2.79-2.98 (16H, m, 8 x C*H*$_2$S of both diastereoisomers), 3.51-3.60 {4H, m, including two overlapped q, 3.55 [2H, q, *J* 7.3, 2 x C(2)*H* of one diastereoisomer] and 3.56 [2H, q, *J* 7.3, 2 x C(2)*H* of one diastereoisomer]}, 7.13 (4H, t, *J* 7.1, Ar*H*$_{para}$ of both

diastereoisomers), 7.29-7.37 {8H, m, including two overlapped t, 7.33 [4H, t, *J* 8.0, ArH_{meta} of one diastereoisomer] and 7.34 [4H, t, *J* 8.0, ArH_{meta} of one diastereoisomer]}, 7.51-7.59 {8H, m, including two overlapped d, 7.33 [4H, d, *J* 7.6, ArH_{ortho} of one diastereoisomer] and 7.34 [4H, d, *J* 7.6, ArH_{ortho} of one diastereoisomer]}, 8.52 (2H, br s, 2 x N*H* of one diastereoisomer), 8.58 (2H, br s, 2 x N*H* of one diastereoisomer); δ_C (100 MHz, $CDCl_3$) 18.5 [CH_3, 4 x *C*(3)H_3 of both diastereoisomers], 30.8 (CH_2, 2 x *C*H_2S of one diastereoisomer), 37.9 (CH_2, 2 x *C*H_2S of one diastereoisomer), 37.9 (CH_2, 4 x *C*H_2S of both diastereoisomers), 45.3 [CH, 2 x *C*(2)*H* of one diastereoisomer], 45.4 [CH, 2 x *C*(2)*H* of one diastereoisomer], 119.8 (signal, 8 x aromatic *C*H_{meta} of both diastereoisomers), 124.6 (CH, 4 x aromatic *C*H_{para} of both diastereoisomers), 129.1 (CH, 8 x aromatic *C*H_{ortho} of both diastereoisomers), 137.5 (Cq, 4 x aromatic *C*q of both diastereoisomers), 170.0 (Cq, 2 x *C*=O of one diastereoisomer), 170.1 (Cq, 2 x *C*=O of one diastereoisomer); ν_{max}/cm^{-1} 3252 (NH), 3074, 3036, 2975, 2921, 2860, 1651 (C=O), 1599, 1545, 1441, 1173, 748, 691, 509 (S-S); HRMS (ES+): Exact mass calculated for $C_{22}H_{29}N_2O_2S_4$ $[M+H]^+$, 481.1112; Found 481.1108; m/z (ES+) 481.0 [($M+H^+$), 6%], 503.0 [($M+Na^+$), 8%].

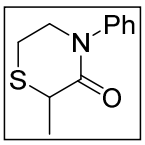
N-Phenyl-2-[2'-(chloroethyl)thio]propanamide 111



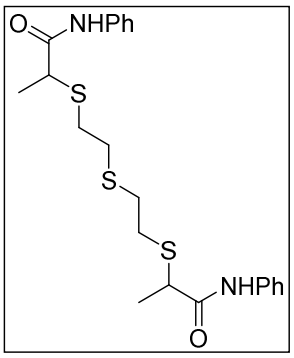
A solution of tosyl chloride (0.51 g, 2.66 mmol) in DCM (20 mL) was added dropwise to a solution of *N*-phenyl-2-[2'-(hydroxyethyl)thio]propanamide **71** (0.50 g, 2.22 mmol), triethylamine (0.37 mL, 2.66 mmol) and DMAP (0.05 g, 0.44 mmol) in DCM (30 mL) at 0 °C while stirring. Following the addition, the reaction mixture was stirred at 0 °C for 10 min and then stirred at room temperature overnight. The reaction mixture was washed with a solution of sodium hydroxide (1M, 2 x 50 mL) and brine (70 mL), dried and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 5 to 50% ethyl acetate) to give the pure *α-thioamide* **111** (0.40 g, 74%) as a white solid; mp 105-106 °C; δ_H (400 MHz, $CDCl_3$) 1.57 [3H, d, *J* 7.2, C(3)H_3], 2.90-3.04 (2H, m, CH_2S), 3.58 [1H, q, *J* 7.3, C(2)*H*], 3.65 (2H, t, *J* 7.3, CH_2Cl), 7.14 (1H, t,

J 7.4, Ar*H*$_{para}$), 7.34 (2H, t, *J* 8.5, Ar*H*$_{meta}$), 7.55 (2H, d, *J* 8.3, Ar*H*$_{ortho}$), 8.50 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.5 [CH_3, *C*(3)*H*$_3$], 33.8 (CH_2, *C*H_2S), 42.9 (CH_2, *C*H_2Cl), 45.4 [CH, *C*(2)*H*], 119.8 (CH, aromatic *C*H$_{ortho}$), 124.7 (CH, aromatic *C*H$_{para}$), 129.1 (CH, aromatic *C*H$_{meta}$), 137.4 (Cq, aromatic *C*q), 170.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3242 (NH), 3071, 3038, 2978, 2933, 1652 (C=O), 1597, 1543, 1444, 753; HRMS (ES+): Exact mass calculated for $C_{11}H_{15}NOS^{35}Cl$ $[M+H]^+$, 244.0563; Found 244.0551; m/z (ES+) 244.2 {[($C_{11}H_{15}NOS^{35}Cl$)+H^+], 18%}.

2-Methyl-4-phenylthiomorpholin-3-one 112 and 2,2'-((thiobis(ethane-2,1-diyl))bis(sulfanediyl))bis(*N*-phenylpropanamide) 113



Sodium hydrosulfide (0.07 g, 1.23 mmol) was added to a solution of *N*-phenyl-2-[2'-(chloroethyl)thio]propanamide **111** (0.05 g, 0.20 mmol) in ethanol (5 mL) at room temperature while stirring under nitrogen. Following the addition, the reaction mixture was heat to reflux and stirred under reflux for 1 hour. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 x 5 mL), dried and concentrated under reduced pressure. The crude product consisted of a mixture of the *α-thioamide* **114** (δ_H 6.34, 1H, dd, J 10.0, 6.7), the *thiomorpholine* **112** (δ_H 3.73, 1H, q, *J* 6.7), the *sulfide* **113** (δ_H 3.49-3.60, 2H, m)* and the α-*thioamide* **108** (δ_H 1.69, 1H, t, *J* 8.3), with ratio 0.3 : 0.3 : 0.8 : 1 respectively by ^{1}H NMR spectroscopy. The mixture was purified by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 20% ethyl acetate) to give the pure the *thiomorpholine* **112** (9 mg, 21%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.7, C*H*$_3$), 2.95-3.09 (2H, m, C*H*$_2$S), 3.73 (1H, q, *J* 6.7, C*H*), 3.93-3.99 [2H, m which includes 3.95 (1H, d, *J* 7.5), 3.97 (1H, d, *J* 7.5), C*H*$_2$N], 7.16-7.23 (3H, m, Ar*H*), 7.32 (2H, t, *J* 7.4, Ar*H*); δ_C (100 MHz, $CDCl_3$) 15.4 (CH_3, *C*H_3-CH), 27.3 (CH_2, *C*H_2S), 36.1 (CH, *C*H-CH_3), 51.1 (CH2, N*C*H_2), 126.0, 126.8, 129.2 (3 x CH signals, 5 x aromatic *C*H), 143.1 (Cq, aromatic *C*q), 170.8 (Cq, *C*=O); ν_{max}/cm^{-1} 2977, 2929, 1663 (C=O), 1492, 1399, 765, 695; HRMS (ES+): Exact mass calculated for $C_{11}H_{14}NOS$ $[M+H]^+$, 208.0796; Found 208.0795; m/z (ES+) 230.2 [($M+Na^+$), 12%].

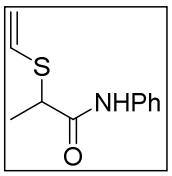


The *sulfide* **113** was also isolated as a mixture as mixture of the meso and *dl* diastereoisomers (unidentified ratio), (39 mg, 21%) as a white solid; mp 95-103 °C; δ_H (400 MHz, $CDCl_3$) 1.48-1.59 {6H, m, 2 x C(3)*H*$_3$ of both diastereoisomers}, 2.61-2.99 (8H, m, 4 x C*H*$_2$S of both diastereoisomers), 3.49-3.60 {2H, m, 2 x C(2)*H* of both diastereoisomers}, 7.08-7.18 (2H, m, apparent br t, 2 x Ar*H* of both diastereoisomers), 7.29-7.38 (4H, m, 4 x Ar*H* of both diastereoisomers], 7.50-7.62 [4H, m, 4 x Ar*H* of both diastereoisomers], 8.46-8.66 (2H, m, 2 x N*H* of both diastereoisomers); δ_C (100 MHz, $CDCl_3$) 18.6 [CH_3, 2 x *C*(3)*H*$_3$ of both diastereoisomers], 30.9, 31.7, 32.0, 37.9 (CH_2, 4 x *C*H_2S of both diastereoisomers), 45.4 [CH, 2 x *C*(2)*H* of both diastereoisomers], 119.8 (CH, 4 x aromatic *C*H of both diastereoisomers), 124.7 (CH, 2 x aromatic *C*H of both diastereoisomers), 129.1 (CH, 4 x aromatic *C*H of both diastereoisomers), 137.5 (Cq, 2 x aromatic *C*q of both diastereoisomers), 170.7, 170.9 (Cq, 2 x *C*=O of both diastereoisomers); ν_{max}/cm^{-1} 3313 (NH), 3136, 2974, 2926, 1653 (C=O), 1587, 1530, 1441, 751, 688; HRMS (ES+): Exact mass calculated for $C_{22}H_{28}N_2O_2S_3Na$ $[M+Na]^+$, 471.1213; Found 471.1125; m/z (ES+) 471.1 [($M+Na^+$), 18%]; m/z (ES-) 447.2 [($M-H^+$), 4%].

The α-*thioamide* **108** was also isolated (7 mg, 15%), data are further reported in this session.

* The ratio of the *sulfide* **113** was calculating from the integration of the region at 3.49-3.60 ppm, which also includes 1H/molecule of the α-*thioamide* **108**. According to the integration of the t at δ_H 1.69 ppm, representing 1H/molecule of **108**, the corresponding integration attributed to the **113** can be determined.

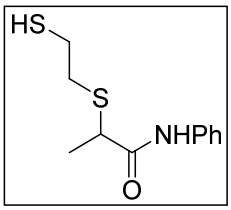
N-Phenyl-2-(vinylthio)propanamide 114



DBU (0.09 mL, 0.62 mmol) was added to a solution of the α-*thioamide* **111** (0.10 g, 0.41 mmol) in acetonitrile (20 mL) and was heated to 80 °C. After 2.5 hour in reflux condition, the reaction mixture was cooled down to room temperature and the solvent

evaporated under reduced pressure. The crude product was dissolved in dichloromethane (20 mL) and washed with copper(II) sulfate solution (10%, 2 x 20 mL), water (30 mL) and brine (30 mL), dried and concentrated under reduced pressure. The crude product contained the *α-thioamide* **114** (δ_H 1.61, 3H, d, *J* 7.3) and the *thiomorpholine* **112** (δ_H 1.42, 3H, d, *J* 6.7) in the ratio 1 : 0.11 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 20% ethyl acetate) gave the pure *α-thioamide* **114** (0.07 g, 80%) as a white solid; mp 98-99 ^{o}C; δ_H (300 MHz, $CDCl_3$) 1.61 [3H, d, *J* 7.3, C(3)H_3], 3.73 [1H, q, *J* 7.2, C(2)*H*], 5.28-5.39 (2H, m, =CH_2), 6.34 (1H, dd, *J* 10.0, 6.7, =C*H*), 7.13 (1H, tt, *J* 7.4, 1.2, ArH_{para}), 7.33 (2H, tt, *J* 7.4, 2.0, ArH_{meta}), 7.52 (2H, dd, *J* 8.3, 1.3, ArH_{ortho}), 8.35 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.0 [CH_3, *C*(3)H_3], 45.2 [CH, *C*(2)*H*], 115.8 (CH_2, =*C*H_2), 119.9 (CH, aromatic *C*H_{ortho}), 124.6 (CH, aromatic *C*H_{para}), 128.8 (CH, =*C*H), 129.0 (CH, aromatic *C*H_{meta}), 137.5 (Cq, aromatic *C*q), 169.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3235 (NH), 2980, 1655 (C=O), 1596, 1545, 1443, 1033 (=CH), 758, 695; HRMS (ES+): Exact mass calculated for $C_{11}H_{14}NOS$ $[M+H]^+$, 208.0796; Found 208.0793; m/z (ES+) 208.3 [($M+H^+$), 100%]; (ES-) 206.3 [($M-H^+$), 20%].

N-Phenyl-2-[2'-(thioethyl)thio]propanamide 108

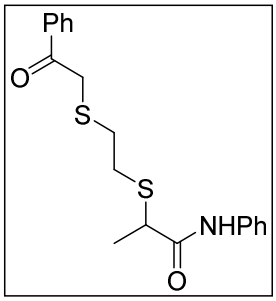


Zinc powder (0.20 g/mmol) was added gradually over 30 min to a stirred mixture of the *disulfide* **110** (0.07 g, 0.15 mmol), HCl solution (2M, 4 mL) and DMF (4 mL) at 60 ^{o}C. After a further period of 1 hour, the reaction mixture was cooled, filtered and the solid washed successively with water to remove any residual zinc powder. The product was extracted with DCM (4 x 15 mL) and the combined organic layers were washed with brine (3 x 50 mL), dried and concentrated under reduced pressure to give the pure *α-thioamide* **108** (0.02 g, 97%) as a low melting point white solid which required no further purification; δ_H (400 MHz, $CDCl_3$) 1.59 [3H, d, *J* 7.1, C(3)H_3], 1.69 (1H, t, *J* 8.3, S*H*), 2.71-2.94 (4H, m, CH_2S + CH_2SH), 3.57 [1H, q, *J* 7.5, C(2)*H*], 7.16 (1H, t, *J* 7.3, ArH_{para}), 7.37 (2H, t, *J* 8.0, ArH_{meta}), 7.59 (2H, d, *J* 8.0, ArH_{ortho}), 8.55 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.7 [CH_3, *C*(3)H_3], 24.5 (CH_2, *C*H_2SH), 35.6 (CH_2, *C*H_2S), 45.4 [CH, *C*(2)*H*], 119.7, 127.6, 129.1 (3 x CH signals,

5 x aromatic *C*H), 137.5 (Cq, aromatic *C*q), 170.4 (Cq, *C*=O); HRMS (ES+): Exact mass calculated for $C_{11}H_{16}NOS_2$ $[M+H]^+$, 242.0673; Found 242.0674; m/z (ES+) 242.3 [($M+H^+$), 20%], (ES-) 240.3 [($M-H^+$), 40%].

As this compound was highly malodorous, an IR spectrum was not recorded and the product was carried directly forward to the next step.

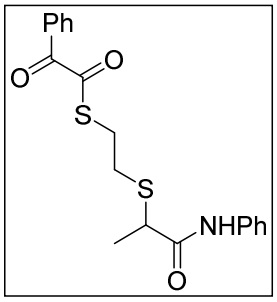
2-((2-((2-Oxo-2-phenylethyl)thio)ethyl)thio)-*N*-phenylpropanamide 116



Zinc powder (0.20 g/mmol) was added gradually over 30 min to a stirred mixture of the *disulfide* **110** (0.69 g, 1.44 mmol), HCl solution (2M, 40 mL), methanol (20 mL) and DMF (50 mL) at 80 °C. After a further period of 1 hour, the reaction mixture was cooled, filtered and the solid washed successively with water to remove any residual zinc powder. The product was extracted with DCM (4 x 50 mL) and the combined organic layers were washed with brine (3 x 100 mL), dried and concentrated under reduced pressure. The *α-thioamide* **108** produced was then dissolved in DCM (20 mL) and phenacylchloride (0.49 g, 3.16 mmol) and DIEA (1 mL, 5.76 mmol) was added to the solution at room temperature and stirred overnight. On completion, the product was concentrated under reduced pressure. The crude mixture was dissolved in ethyl acetate (100 mL) and washed with water (100 mL) and brine (120 mL), dried and concentrated under reduced pressure. Purification with column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 10 to 15% ethyl acetate) to give the pure protected *α-thioamide* **116** (0.86 g, 87%) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 1.55 [3H, d, J 7.2, C(3)H_3], 2.74-2.96 (4H, m, 2 x CH_2S), 3.56 [1H, q, *J* 7.2, C(2)*H*], 3.73, 3.84 (2H, ABq, *J* 13.9, CH_2-C=O), 7.11 (1H, t, 7.4, Ar*H*), 7.32 (2H, t, *J* 7.05, Ar*H*), 7.47 (2H, t, *J* 8.29, Ar*H*), 7.57-7.60 (2H, m, Ar*H*), 7.95 (2H, d, *J* 8.29, Ar*H*), 7.91-7.99 (2H, m, Ar*H*), 8.73 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 18.3 [CH_3, *C*(3)H_3], 30.8 (CH_2, *C*H_2S), 31.5 (CH_2, *C*H_2S), 36.4 (CH_2, *C*H_2-C=O), 44.9 [CH, C(2)H], 119.7, 124.4, 128.8, 128.9, 129.0, 133.7 (6 x CH signals, 10 x aromatic *C*H), 134.8, 137.8 (2 x Cq, 2 x aromatic *C*q), 170.6 (Cq, amide *C*=O), 194.7 (Cq, ketone *C*=O); ν_{max}/cm^{-1} 3313 (NH), 3136, 3059, 2972, 2928,

1666 (C=O), 1597, 1440, 1276, 687; HRMS (ES+): Exact mass calculated for $C_{19}H_{22}NO_2S_2$ $[M+H]^+$, 360.1092; Found 360.1087; m/z (ES+) 360.1 [$(M+H^+)$, 100%], (ES-) 358.2 [$(M-H^+)$, 100%].

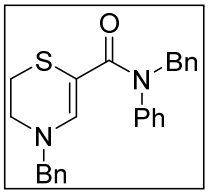
(2-((1-Oxo-1-(phenylamino)propan-2-yl)thio)ethyl)-2-oxo-2-phenylethane thioate 117



N-Chlorosuccinimide (0.08 g, 0.58 mmol) was added in one portion to a solution of 2-((2-((2-oxo-2-phenylethyl)thio)ethyl)thio)-*N*-phenylpropanamide **116** (0.10 g, 0.29 mmol) and triethylamine (0.1 mL, 0.58 mmol) in tetrachloromethane (6 mL) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the crude product was dissolved in DCM (20 mL), washed with water (30 mL), a saturated solution of sodium bicarbonate (2 x 40 mL), water (40 mL) and brine (40 mL), dried and concentrated under reduced pressure. Purification by successive column chromatography on silica gel using hexane : ethyl acetate as eluent (gradient elution 2 to 100% ethyl acetate) gave the pure protected *α-thioamide* **117** (0.02 g, 23%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 1.59 [3H, d, *J* 7.3, C(3)H_3], 2.76-3.01 [2H, m, C(2')H_2S], 3.16-3.39 [2H, m, C(1')H_2S], 3.66 [1H, q, *J* 7.2, C(2)*H*], 7.10 (1H, tt, *J* 7.3, 1.1, Ar*H*), 7.30 (2H, t, *J* 8.3, Ar*H*), 7.48 (1H, t, *J* 7.6, Ar*H*), 7.56 (2H, d, *J* 8.7, Ar*H*), 7.62 (1H, tt, *J* 7.5, 1.3, Ar*H*), 8.09 (2H, dd, *J* 8.4, 1.3, Ar*H*), 8.45 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.4 [CH_3, *C*(3)H_3], 28.6 [CH_2, C(2')H_2S], 31.1 [CH_2, C(1')H_2S], 45.2 [CH, *C*(2)*H*], 119.7, 124.6, 128.9, 129.0, 130.8 (5 x CH signals, 8 x aromatic *C*H), 131.4 (Cq, aromatic *C*q), 135.02 (1 x CH signal, 2 x aromatic *C*H), 137.5 (Cq, aromatic *C*q), 170.3 (Cq, amide *C*=O), 185.5 (Cq, Ph-*C*=O), 192.4 (Cq, S-*C*=O); ν_{max}/cm^{-1} 3312 (NH), 3136, 3060, 2972, 2928, 1667 (C=O), 1596, 1530, 1440, 688; HRMS (ES+): Exact mass calculated for $C_{19}H_{20}NO_3S_2$ $[M+H]^+$, 374.0885; Found 374.0889; m/z (ES+) 374.1 [$(M+H^+)$, 100%], (ES-) 372.1 [$(M-H^+)$, 12%].

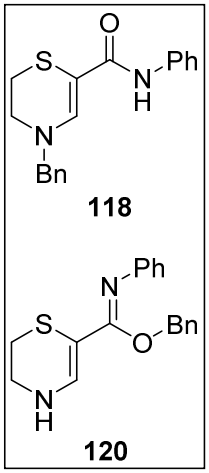
5. FUNCTIONALISATION OF THIAZINE DERIVATIVE

N,4-Dibenzyl-*N*-phenyl-3,4-dihydro-2H-1,4-thiazine-6-carboxamide 119



Sodium hydride (55% in oil, 0.13 g, 2.72 mmol) was added in one portion to a solution of the *thiazine* **79** (0.20 g, 0.91 mmol) and benzyl bromide (0.11 mL, 0.91 mmol) in DMF (30 mL) at room temperature. After stirring for 2 hours, the sodium hydride was quenched by addition dropwise of isopropyl alcohol (10 mL), followed by the addition of water (30 mL) and extraction with DCM : ethyl acetate (50:50) (3 x 40 mL). The layers were separated and the combined organic layers were washed with a solution of sodium hydroxide (1M, 50mL), water (50 mL) and brine (50 mL), dried and concentrated under reduced pressure to give the crude product. The crude product contained the *thiazine* **79**, *dibenzylated thiazine* **119** (δ_H 7.56, 1H, s) and the tentatively assigned mono *4-benzylated thazine* **118** (δ_H 7.88, 1H, s) with a ratio 0.73 : 1 : 0.05 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 2 to 40% ethyl acetate) gave the pure *dibenzylated thiazine* **119** (0.14 g, 37%) as a white solid; mp 101-104 ^{o}C; δ_H (400 MHz, $CDCl_3$) 2.51-2.57 (2H, m, C*H*$_2$S), 3.22-3.29 (2H, m, C*H*$_2$N), 4.20 (2H, s, C*H*$_2$ of N-Bn on ring), 5.00 (2H, s, C*H*$_2$ of N-Bn on amide), 7.07-7.35 (15H, m, Ar*H*), 7.56 (1H, s, C*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2, *C*H_2S), 47.8 (CH_2, *C*H_2N), 54.6 (CH_2, *C*H_2 of N-Bn on amide), 60.9 (CH_2, *C*H_2 of N-Bn on ring), 91.1 (Cq, S*C*q=), 126.1, 126.9, 127.5, 127.7, 127.9, 128.3, 128.8, 128.9 (8 x CH signals, 15 x aromatic *C*H), 136.5 (Cq, *C*q aromatic Bn on ring), 138.4 (Cq, *C*q aromatic Ph or *C*q aromatic Bn amide), 143.0 (CH, *C*H=), 143.9 (Cq, *C*q aromatic Ph or *C*q aromatic Bn amide), 168.7 (Cq, *C*=O); ν_{max}/cm^{-1} 1614 (C=O), 1548 (C=C), 1169, 694; HRMS (ES+): Exact mass calculated for $C_{25}H_{25}N_2OS$ $[M+H]^+$, 401.1688; Found 401.1671; m/z (ES+) 401.2 [($M+H^+$), 100%].

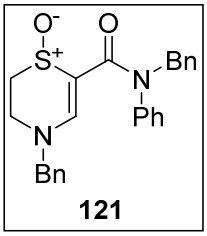
4-Benzyl-*N*-phenyl-3,4-dihydro-2H-1,4-thiazine-6-carboxamide 118 and *O*-benzyl-*N*-phenyl-3,4-dihydro-2H-1,4-thiazine-6-carbimidate 120



Potassium carbonate (0.26 g, 1.90 mmol) and benzyl bromide (0.11 mL, 0.95 mmol) was added to a solution of the *thiazine* **79** (0.21 g, 0.95 mmol) in DMF (20 mL) at room temperature under nitrogen. After stirring the solution for 2 hours, the mixture was heated to 80 °C and stirred at this temperature for an extra 2 hours. The reaction mixture was then diluted in brine (30 mL) and extracted with methyl *tert*-butyl ether (3 x 30 mL). The combined organic layers was washed with water (3 x 30 mL), dried and concentrated under reduced pressure. The crude product contained the *thiazine* **79** (δ_H 3.63-3.71, 2H, m), the tentatively assigned *imidate* **120** (δ_H 4.01, 2H, t, *J* 4.7) and the *4-benzylated thiazine* **118** (δ_H 3.44, 2H, t, *J* 4.9) with a ratio 0.35 : 0.44 : 1 respectively by ^{1}H NMR spectroscopy. Attempted purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 10 to 15% ethyl acetate) gave a mixture of the *4-benzylated thiazine* **118** and the tentatively assigned *imidate* **120** with ratio 1 : 0.44 respectively by ^{1}H NMR spectroscopy as a low melting point yellow solid (0.20 g, 69%); δ_H (400 MHz, $CDCl_3$) 2.79 (2H, t, *J* 4.9, C*H*$_2$S of *thiazine* **118**), 2.98 (2H, t, *J* 4.8, C*H*$_2$S of *imidate* **120**), 3.44 (2H, t, *J* 4.9, C*H*$_2$NH of *thiazine* **118**), 4.01 (2H, t, *J* 4.7, C*H*$_2$N of *imidate* **120**), 4.37 (2H, s, C*H*$_2$Ph *thiazine* **118**), 5.26 (2H, s, C*H*$_2$Ph of *imidate* **120**), 6.95-7.81 [21H, m, ArH, may be distinguished 7.72 (br s, NH amide of *thiazine* **118**)], 7.88 (1H, s, C*H*= of *thiazine* **118**), 8.31 (1H, s, C*H*= of *imidate* **120**); δ_C (100 MHz, $CDCl_3$) 23.8 (CH_2, *C*H_2S of *thiazine* **118**), 24.7 (CH_2, *C*H_2S of *imidate* **120**), 43.6 (CH, *C*H_2N of *imidate* **120**), 47.4 (CH_2, *C*H_2NH of *thiazine* **118**), 61.0 (CH_2, *C*H_2Ph of *thiazine* **118**), 68.9 (CH_2, *C*H_2Ph of *imidate* **120**), 88.3 (Cq, *C*q= of *thiazine* **118**), 119.7, 120.1, 123.4, 124.4, 127.5, 128.1, 128.5, 128.7, 128.8, 128.9, 129.0 (11 x CH signals, 20 x aromatic *C*H of *thiazine* **118** and *imidate* **120**), 129.6 (CH, *C*H= of *imidate* **120**), 135.2 (Cq, aromatic Cq of Bn of *imidate* **120**), 136.2 (Cq, aromatic Cq of Bn of *thiazine* **118**), 137.8 (Cq, aromatic Cq of Ph of *imidate* **120**), 138.8 (Cq, aromatic Cq of Ph of *thiazine* **118**), 140.9 (CH, *C*H= of *thiazine* **118**), 152.8 (Cq, O-

*C*q=N of *imidate* **120**), 162.3 (Cq, *C*=O of *imidate* **120**), 164.2 (Cq, *C*=O of *thiazine* **118**); ν_{max}/cm^{-1} 3300 (NH amide), 3059, 3030, 2923 (NH amine), 1714 (C=O), 1650 (C=O), 1593 (C=C), 1523, 1439, 1309, 1201 (C-O), 750, 691; HRMS (ES+): Exact mass calculated for $C_{18}H_{19}N_2OS$ $[M+H]^+$, 311.1218; Found 311.1232; m/z (ES+) 311.2 [$(M+H^+)$, 13%].

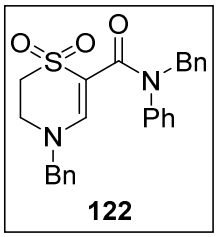
N,4-dibenzyl-*N*-phenyl-3,4-dihydro-2H-1,4-thiazine-6-carboxamide 1,1-oxide 121 and *N*,4-dibenzyl-*N*-phenyl-3,4-dihydro-2H-1,4-thiazine-6-carboxamide 1,1-dioxide 122



121

A solution of mCPBA (77%, 0.07 g, 0.34 mmol) in DCM (7 mL) was added dropwise to a solution of the *dibenzylated thiazine* **119** (0.16 g, 0.34 mmol) in DCM (7 mL) at 0 °C while stirring. Upon completion of the addition, the ice bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 30 min up to full conversion (TLC monitoring). The crude product was washed with a saturated solution of sodium bicarbonate (3 x 20 mL), water (50 mL) and brine (50 mL), dried and concentrated under reduced pressure to give the crude product, which contained the *sulfoxide* **121** (δ_H 7.43, 1H, s) and the *sulfone* **122** (δ_H 7.47, 1H, s) with a ratio 1 : 0.18 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate : dichloromethane (gradient elution 30:50:20 to 0:80:20) gave the pure *dibenzylated thiazine sulfoxide* **121** (0.08 g, 47%) as a white solid; mp 156-159 °C; δ_H (400 MHz, $CDCl_3$) 2.09 (1H, td, *J* 14.0, 3.7 one of CH_2S), 2.74 (1H, dt, *J* 13.6, 2.8, one of CH_2S), 3.17 (1H, dt, *J* 14.0, 3.6, one of CH_2N), 3.66 (1H, td, *J* 14.3, 2.6, one of CH_2N), 4.28 (2H, s, CH_2Ph thiazine), 4.98, 5.05 (2H, ABq, J_{AB} 14.7, CH_2Ph amide), 7.01 (2H, t, *J* 3.6, Ar*H*), 7.11 (2H, d, *J* 7.6, Ar*H*), 7.13-7.38 (11H, m, Ar*H*), 7.43 (1H, s, C*H*); δ_C (100 MHz, $CDCl_3$) 34.7 (CH_2, *C*H_2N), 40.9 (CH_2, *C*H_2S), 54.7 (CH_2, *C*H_2Ph amide), 61.4 (CH_2, *C*H_2Ph thiazine), 104.1 (Cq, =*C*qS), 126.8, 127.2, 127.6, 128.1, 128.3, 128.6, 129.1, 129.5 (8 x CH signals, 15 x aromatic *C*H), 134.5, 137.8, 144.2 (3 x Cq, 3 x *C*q aromatic), 148.6 (CH, *C*H=), 167.2 (Cq, *C*=O); ν_{max}/cm^{-1} 1597 (C=O), 1043 (S=O), 746; HRMS (ES+): Exact mass calculated for

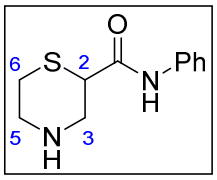
$C_{25}H_{24}N_2O_2SNa$ $[M+Na]^+$, 439.1456; Found 439.1463; m/z (ES+) 417.3 [$(M+H^+)$, 20%].



122

The pure *dibenzylated thiazine sulfone* **122** was also isolated (4 mg, 2%); δ_H (400 MHz, $CDCl_3$) 2.05 (1H, td, *J* 14.1, 3.9, one of C*H*$_2$S), 2.63-2.71 (1H, m, apparent d, one of C*H*$_2$S), 3.07 (1H, td, *J* 13.9, 1.9, one of C*H*$_2$N), 3.70 (1H, td, *J* 14.0, 3.3, one of C*H*$_2$N), 4.82 (2H, ABq, J_{AB} 14.9, $\Delta\delta_{AB}$ 0.02, C*H*$_2$Ph), 4.96, 5.04 (2H, ABq, J_{AB} 14.7, C*H*$_2$Ph amide), 6.74 (2H, d, *J* 7.6, Ar*H*), 6.98 (2H, d, *J* 7.6, Ar*H*), 7.12-7.35 (11H, m, Ar*H*), 7.47 (1H, s, C*H*); δ_C (100 MHz, $CDCl_3$) 34.2 (CH_2, *C*H_2N), 42.2 (CH_2, *C*H_2S), 54.3, 56.1 (2 x CH_2, 2 x *C*H_2Ph), 114.2 (Cq, =*C*qS), 125.8, 127.3, 127.8, 128.4, 128.5, 128.6, 129.3, 130.0, 136.4 (9 x CH signals, 15 x aromatic *C*H), 140.6 (CH, *C*H=), 142.1, 143.5, 156.4 (3 x Cq, 3 x *C*q aromatic), 166.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3062, 3031, 2924, 1678, 1632, 1592 (C=O), 1318 (S=O), 1260 (S=O), 727, 696; HRMS (ES+): Exact mass calculated for $C_{25}H_{25}N_2O_3S$ $[M+H]^+$, 433.1586; Found 433.1606.

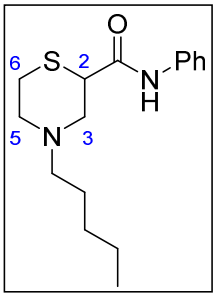
N-Phenylthiomorpholine-2-carboxamide 123



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.17 g, 2.70 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.10 g, 0.45 mmol) and acetic acid (0.20 mL) in methanol (6 mL). Purification by column chromatography on silica gel using dichloromethane : methanol (98:2) gave the pure *thiomorpholine* **123** (0.11 g, 73%) as a white solid; ; mp 70-74 ^oC; (Found C, 58.86; H, 6.22; N, 12.73. $C_{11}H_{14}N_2OS$ requires C, 59.43; H, 6.35; N, 12.60); δ_H (300 MHz, $CDCl_3$) 1.86 [1H, br s, N(4)*H*], 2.31-2.47 [1H, m, apparent qd, one of C(6)*H*$_2$S], 2.99-3.13 [2H, m, apparent q, one of C(5)*H*$_2$N and one of C(6)*H*$_2$S], 3.15-3.41 {3H, m including 3.20 [1H, t, *J* 2.9, C(2)*H*S], 3.27 [1H, dd, *J* 12.7, 3.1, one of C(3)*H*$_2$N], 3.34 [1H, dd, *J* 8.6, 3.3, one of C(5)*H*$_2$N]}, 3.70 [1H, dd, *J* 12.7, 3.0, one of C(3)*H*$_2$N], 7.10 (1H, tt, *J* 7.4, 1.1, Ar*H*$_{para}$), 7.33 (2H, t, *J* 8.6, Ar*H*$_{meta}$), 7.60 (2H, d, *J* 8.6, Ar*H*$_{ortho}$), 10.25 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.8 [CH_2, *C*(6)H_2S], 41.0 [CH, *C*(2)HS], 47.1 [CH_2, *C*(5)H_2N], 48.3 [CH_2, *C*(3)H_2N], 119.9 (CH, aromatic *C*H$_{ortho}$),

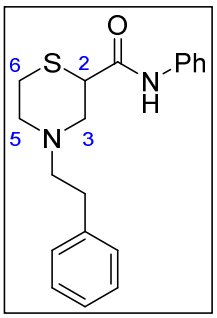
124.2 (CH, aromatic *C*H$_{para}$), 129.0 (CH, aromatic *C*H$_{meta}$), 138.1 (Cq, *C*q aromatic), 169.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3260 (NH), 2950, 2920, 1667 (C=O), 1598, 1554, 1497, 1443, 1321, 806, 751, 687, 504; HRMS (ES+): Exact mass calculated for $C_{11}H_{15}N_2OS$ $[M+H]^+$, 223.0905; Found 223.0903; m/z (ES+) 223.3 [($M+H^+$), 100%].

4-Pentyl-*N*-phenylthiomorpholine-2-carboxamide 124



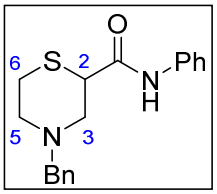
This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.17 g, 2.70 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.10 g, 0.45 mmol), valeric aldehyde (0.06 mL, 0.54 mmol) and acetic acid (0.20 mL) in methanol (6 mL). Purification by column chromatography on silica gel using hexane : ethyl acetate (90:10) gave the pure *N-alkylated thiomorpholine* **124** (0.12 g, 80%) as a colourless oil; δ_H (300 MHz, $CDCl_3$) 0.90 [3H, t, *J* 6.6, C(5')*H*$_3$], 1.20-1.45 (4H, m, 2 x alkyl C*H*$_2$), 1.45-1.67 (2H, m, alkyl C*H*$_2$), 2.36-2.56 [4H, m, C(6)*H*$_2$S, one of C(1')*H*$_2$ and one of C(5)*H*$_2$N], 2.68 [1H, dd, *J* 12.3, 3.0, one of C(3)*H*$_2$N], 3.10-3.37 [3H, m, one of C(1')*H*$_2$, one of C(5)*H*$_2$N and C(2)*H*S], 3.45 [1H, dd, *J* 12.5, 3.0, one of C(3)*H*$_2$N], 7.09 (1H, tt, *J* 7.5, 1.1, Ar*H*$_{para}$), 7.32 (2H, t, *J* 8.3, Ar*H*$_{meta}$), 7.56 (2H, d, *J* 8.5, Ar*H*$_{ortho}$), 10.69 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 14.0 [CH_3, *C*(5')H_3], 22.6 (CH_2, alkyl *C*H_2), 25.7 [CH_2, *C*(6)H_2S], 26.3 (CH_2, alkyl *C*H_2), 29.8 (CH_2, alkyl *C*H_2), 42.0 [CH, *C*(2)HS], 54.3 [CH_2, *C*(5)H_2N], 55.5 [CH_2, *C*(3)H_2N], 59.2 [CH_2, *C*(1')H_2], 119.9 (CH, aromatic *C*H$_{ortho}$), 124.0 (CH, aromatic *C*H$_{para}$), 128.9 (CH, aromatic *C*H$_{meta}$), 138.2 (Cq, *C*q aromatic), 169.9 (Cq, *C*=O); ν_{max}/cm^{-1} 2927 (NH), 1682 (C=O), 1598, 1548, 1443, 753, 691, 494; HRMS (ES+): Exact mass calculated for $C_{16}H_{25}N_2OS$ $[M+H]^+$, 293.1688; Found 293.1653; m/z (ES+) 293.3 [($M+H^+$), 100%].

4-Phenethyl-*N*-phenylthiomorpholine-2-carboxamide 125



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), phenacylacetaldehyde (0.09 mL, 0.82 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 3.70, 1H, dd, *J* 12.7, 3.0) and the *N-substituted thiomorpholine* **125** (δ_H 3.53, 1H, dd, *J* 12.6, 3.1) with ratio 0.40 : 1 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 5 to 10% ethyl acetate) gave the pure *N-substituted thiomorpholine* **125** (0.11 g, 50%) as yellow solid; mp 105-108 ^{o}C; (Found C, 69.60; H, 6.71; N, 8.03. $C_{19}H_{22}N_2OS$ requires C, 69.90; H, 6.79; N, 8.58); δ_H (300 MHz, $CDCl_3$) 2.47-2.60 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 2.70-2.75 [3H, m, one of C(3)H_2N and C(1')H_2], 2.75-2.97 [2H, m, C(2')H_2], 3.08-3.24 [1H, m, one of C(5)H_2N], 3.27-3.41 [2H, m, C(2)*H*S and one of C(6)H_2], 3.53 [1H, dd, *J* 12.6, 3.1, one of C(3)H_2], 7.07 (1H, tt, *J* 7.4, 1.3, Ar*H*), 7.14-7.41 (9H, m, Ar*H*), 10.34 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.7 [CH_2, *C*(6)H_2S], 32.9 [CH_2, *C*(2')H_2], 42.1 [CH, *C*(2)HS], 54.2 [CH_2, *C*(5)H_2N], 55.5 [CH_2, *C*(3)H_2N], 60.6 [CH_2, C(1')H_2], 119.9, 124.1, 126.5, 128.5, 128.7, 128.9 (6 x CH signals, 10 x aromatic *C*H), 137.9, 139.2 (2 x Cq, 2 x *C*q aromatic), 169.6 (Cq, *C*=O); ν_{max}/cm^{-1} 2922 (NH), 1679 (C=O), 1597, 1546, 1443, 752, 691, 494; HRMS (ES+): Exact mass calculated for $C_{19}H_{23}N_2OS$ $[M+H]^+$, 327.1531; Found 327.1532; m/z (ES+) 327.2 [($M+H^+$), 100%]; (ES-) 325.2 [($M-H^+$), 58%].

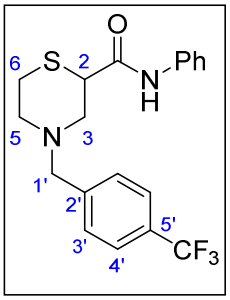
4-Benzyl-*N*-phenylthiomorpholine-2-carboxamide 126



Sodium cyanoborohydride (0.20 g, 3.67 mmol) was added slowly to a solution of *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.13 g, 0.61 mmol), benzaldehyde (0.07 mL, 0.67 mmol) and acetic acid (0.20 mL) in methanol (6 mL) at room temperature while stirring. After stirring the reaction mixture at room temperature overnight, the reaction mixture was quenched with addition of water

(20 mL) and neutralised with a solution of sodium hydroxide (10M, 4 mL). The mixture was extracted with ethyl acetate (2 x 30 mL). The layers were separated and the combined organic layers was washed with water (30 mL) and brine (30 mL), dried and concentrated under reduced pressure to give the crude product. Purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 5% to 15% ethyl acetate) gave the pure *N-substituted thiomorpholine* **126** (0.11 g, 58%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.40-2.52 [2H, m, one of C(5)H_2N and one of C(6)H_2S], 2.72 [1H, dd, *J* 12.4, 3.2, one of C(3)H_2N], 3.13 [1H, td, *J* 12.8, 3.4, one of C(6)H_2S], 3.24 [1H, dt, *J* 11.9, 3.3, one of C(5)H_2N], 3.34 [1H, t, *J* 2.9, C(2)*H*S), 3.48 [1H, dd, *J* 12.5, 3.2, one of C(3)H_2N], 3.59 (2H, ABq, J_{AB} 12.9, $\Delta\delta_{AB}$ 0.02, CH_2Ph), 7.11 (1H, t, *J* 7.4, Ar*H*), 7.24-7.38 (7H, m, Ar*H*), 7.56 (2H, d, *J* 8.2, Ar*H*), 10.39 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 25.7 [CH_2, *C*(6)H_2S], 42.1 [CH, *C*(2)HS], 53.9 [CH_2, *C*(5)H_2N], 55.2 [CH_2, *C*(3)H_2N], 63.8 (CH_2, *C*H_2Ph), 120.2, 124.2, 127.9, 128.7, 129.0, 129.5 (6 x CH signals, 10 x aromatic *C*H), 136.3 (Cq, *C*q aromatic Ph), 137.9 (Cq, *C*q aromatic Bn), 169.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3027 (NH), 1679 (C=O), 1545; HRMS (ES+): Exact mass calculated for $C_{18}H_{21}N_2OS$ $[M+H]^+$, 313.1375; Found 313.1366; m/z (ES+) 313.2 [($M+H^+$), 100%].

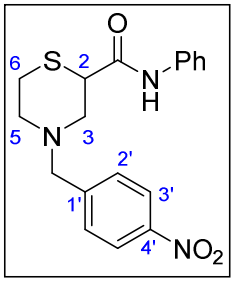
4-(Trifluoromethyl)-benzyl-*N*-phenylthiomorpholine-2-carboxamide 127



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 4-(trifluoromethyl)benzaldehyde (0.11 mL, 0.82 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 2.31-2.47, 1H, m) and the *N-benzylated thiomorpholine* **127** (δ_H 2.78, 1H, dd, *J* 12.2, 3.0) with ratio 1 : 0.42 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using dichloromethane : methanol (gradient elution 100 to 95% dichloromethane) gave the pure *N-benzylated thiomorpholine* **127** (0.05 g, 20%) as a colourless oil; δ_H (300 MHz, $CDCl_3$) 2.41-2.61 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 2.78 [1H, dd, *J* 12.2, 3.0, one of C(3)H_2N], 2.99-3.22 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 3.39

[1H, t, *J* 3.3, C(2)*H*S], 3.52 [1H, dd, *J* 12.1, 3.5, one of C(3)H_2], 3.65 [2H, ABq, J_{AB} 13.4, $\Delta\delta_{AB}$ 0.06, CH_2Ar], 7.13 (1H, tt, *J* 7.4, 1.1, ArH_{para}), 7.35 (2H, t, *J* 7.4, ArH_{meta}), 7.44 (2H, d, *J* 8.2, Ar(3')*H*), 7.49-7.65 [4H, m including at 7.58 (t, *J* 7.58, Ar*H*)], 9.92 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.9 [CH_2, *C*(6)H_2S], 42.6 [CH, *C*(2)HS], 53.9 [CH_2, *C*(5)H_2N], 55.5 [CH_2, *C*(3)H_2N], 63.1 [CH_2, *C*H_2Ph], 120.0 (CH, aromatic *C*H_{ortho}), 124.4 (CH, aromatic *C*H_{para}), 125.6 [CH, q, J_{CF} 3.6, aromatic *C*(4')H], 129.1 (CH, aromatic *C*H_{meta}), 129.4 [Cq, aromatic *C*(3')H], 137.8 (Cq, *C*q aromatic), 140.8 [Cq, *C*(2')q aromatic], 168.9 (Cq, *C*=O); Chemical ^{13}C NMR shifts of *C*(5')q and *C*F_3 were not clearly observed in the ^{13}C NMR spectra due to overlapping signals in the range 119.0-132.0 ppm; δ_H (282 MHz, DMSO) -62.5 (Cq, *C*F_3); ν_{max}/cm^{-1} 3193 (NH), 1680 (C=O), 1598, 1546, 1321, 1118, 1064, 753; HRMS (ES+): Exact mass calculated for $C_{19}H_{20}N_2OF_3S$ $[M+H]^+$, 381.1248; Found 381.1248; m/z (ES+) 381.2 [($M+H^+$), 100%]; (ES-) 379.2 [($M-H^+$), 100%].

4-(4-Nitrobenzyl)-*N*-phenylthiomorpholine-2-carboxamide 128

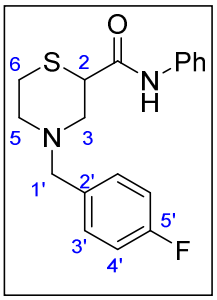


This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 4-nitrobenzaldehyde (0.31 mL, 2.04 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 3.70, 1H, dd, *J* 12.7, 3.0)* and the *N-benzylated thiomorpholine* **128** (δ_H 3.57, 1H, dd, *J* 12.1, 3.4) with ratio 1 : 0.43 respectively by ^{1}H NMR spectroscopy. Purification by successive column chromatography on silica gel using ethyl acetate : hexane (gradient elution 5 to 20% ethyl acetate) gave the pure *N-benzylated thiomorpholine* **128** (0.06 g, 24%) as a yellow solid; mp 125-127 ^{o}C; (Found C, 59.84; H, 5.31; N, 11.26. $C_{18}H_{19}N_3O_3S$ requires C, 60.49; H, 5.36; N, 11.76); δ_H (400 MHz, $CDCl_3$) 2.47-2.61 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 2.79 [1H, dd, *J* 12.0, 3.1, one of C(3)H_2N], 3.01-3.15 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 3.43 [1H, t, *J* 2.8, C(2)*H*S], 3.57 [1H, dd, *J* 12.1, 3.4, one of C(3)H_2], 3.69 [2H, ABq, J_{AB} 13.9, $\Delta\delta_{AB}$ 0.05, CH_2Ar], 7.16 (1H, t, *J* 7.2, ArH_{para}), 7.38 (2H, t, *J* 8.0, ArH_{meta}), 7.50 [2H, d, *J* 8.5, Ar(2')*H*], 7.57 (2H, d, *J* 7.8, ArH_{ortho}), 8.20 [2H, d, *J* 8.5, Ar(3')*H*],

9.69 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 26.1 [CH_2, *C*(6)H_2S], 42.9 [CH, *C*(2)HS], 54.0 [CH_2, *C*(5)H_2N], 55.5 [CH_2, *C*(3)H_2N], 62.8 [CH_2, *C*H_2Ph], 119.8 (CH, aromatic *CH*$_{ortho}$), 123.8 [CH, aromatic *C*(3')H], 124.6 (CH, aromatic *CH*$_{para}$), 129.1 (CH, aromatic *CH*$_{meta}$), 129.7 [CH, aromatic *C*(2')H], 137.7 (Cq, aromatic *C*q-Ph), 144.6 [Cq, aromatic *C*(1')q], 147.6 [Cq, aromatic *C*(4')q], 168.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3284 (NH), 1643 (C=O), 1518 (N-O), 1339 (N-O), 732; HRMS (ES+): Exact mass calculated for $C_{18}H_{20}N_3O_3S$ $[M+H]^+$, 358.1225; Found 358.1209; m/z (ES+) 358.2 [$(M+H^+)$, 100%], (ES-) 356.2 [$(M+H^+)$, 100%].

* The ratio of the *thiomorpholine* **123** was calculating from the integration of the region at 3.63-3.76 ppm, which also includes 2H/molecule of the *N-benzylated thiomorpholine* **128**. According to the integration of the ABq at δ_H 3.69 ppm, representing 2H/molecule of **128**, the corresponding integration attributed to the **123** can be determined.

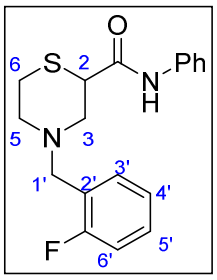
4-Fluorobenzyl-*N*-phenylthiomorpholine-2-carboxamide 129



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 4-fluorobenzaldehyde (0.09 mL, 0.82 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 3.70, 1H, dd, *J* 12.7, 3.0) and the *N-benzylated thiomorpholine* **129** (δ_H 2.72, 1H, dd, *J* 12.1, 3.4) with ratio 0.39 : 1 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 7.5 to 10% ethyl acetate) gave the pure *N-benzylated thiomorpholine* **129** (0.12 g, 56%) as a pale pink solid; mp 99-100 °C; (Found C, 65.19; H, 5.80; N, 8.34. $C_{18}H_{19}FN_2OS$ requires C, 65.43; H, 5.80; N, 8.48); δ_H (300 MHz, $CDCl_3$) 2.39-2.57 [2H, m, one of C(6)*H*$_2$S and one of C(5)*H*$_2$N], 2.72 [1H, dd, *J* 12.3, 3.2, one of C(3)*H*$_2$N], 3.04-3.24 [2H, m, one of C(6)*H*$_2$S and one of C(5)*H*$_2$N], 3.36 [1H, t, *J* 3.1, C(2)*H*S], 3.43-3.63 {3H, m, including 3.48 [1H, dd, *J* 12.1, 3.4, one of C(3)*H*$_2$], 3.57 [2H, ABq, J_{AB} 12.9, $\Delta\delta_{AB}$ 0.03, C(1')*H*$_2$Ar]}, 7.03 [2H, tt, *J* 8.6, 2.1, Ar(4')*H*], 7.12 (1H, tt, *J* 7.4, 1.1,

Ar*H*$_{para}$), 7.22-7.39 (5H, m, Ar*H*), 7.49-7.59 (2H, m, Ar*H*$_{ortho}$), 10.10 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.8 [CH_2, *C*(6)H_2S], 42.3 [CH, *C*(2)HS], 53.8 [CH_2, *C*(5)H_2N], 55.2 [CH_2, *C*(3)H_2N], 62.9 [CH_2, *C*H_2Ph], 115.5 [CH, d, J_{CF} 21.4, aromatic *C*(4')H], 120.0 (CH, aromatic *C*H$_{ortho}$), 124.3 (CH, aromatic *C*H$_{para}$), 129.0 (CH, aromatic *C*H$_{meta}$), 130.9 [CH, d, J_{CF} 8.0, aromatic *C*(3')H], 132.2 [Cq, d, J_{CF} 3.4, *C*(2')q aromatic], 137.7 (Cq, *C*q aromatic Ph), 162.4 [Cq, d, J_{CF} 246.5, *C*(5')q aromatic], 169.3 (Cq, *C*=O); ν_{max}/cm^{-1} 3236 (NH amide), 1652 (C=O), 1598, 1496, 1220, 743; HRMS (ES+): Exact mass calculated for $C_{18}H_{20}N_2OFS$ $[M+H]^+$, 331.1280; Found 331.1273; m/z (ES+) 331.2 [($M+H^+$), 100%].

2-Fluorobenzyl-*N*-phenylthiomorpholine-2-carboxamide 130

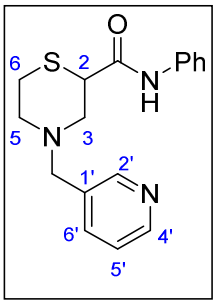


This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 2-fluorobenzaldehyde (0.09 mL, 0.82 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 3.70, 1H, dd, *J* 12.7, 3.0)* and the *N-benzylated thiomorpholine* **130** (δ_H 3.50, 1H, dd, *J* 12.4, 3.2) with ratio 0.79 : 1 respectively by ^{1}H NMR spectroscopy. Purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 5 to 7.5% ethyl acetate) gave the pure *N-benzylated thiomorpholine* **130** (0.11 g, 50%) as a brown oil; δ_H (300 MHz, $CDCl_3$) 2.41-2.58 [2H, m, one of C(6)*H*$_2$S and one of C(5)*H*$_2$N], 2.75 [1H, dd, *J* 12.6, 3.5, one of C(3)*H*$_2$N], 3.14 [1H, td, *J* 12.8, 3.5, one of C(6)*H*$_2$S], 3.26 [1H, dt, *J* 11.5, 3.0, one of C(5)*H*$_2$N], 3.34 [1H, t, *J* 3.0, C(2)*H*S], 3.50 [1H, dd, *J* 12.4, 3.2, one of C(3)*H*$_2$], 3.66 [2H, s, C*H*$_2$Ar], 7.00-7.19 (3H, m, Ar*H*), 7.22-7.39 (4H, m, Ar*H*), 7.55 (2H, d, *J* 8.6, Ar*H*$_{ortho}$), 10.21 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.6 [CH_2, *C*(6)H_2S], 42.1 [CH, *C*(2)HS], 53.9 [CH_2, *C*(5)H_2N], 55.0 [CH_2, *C*(3)H_2N], 57.0 [CH_2, d, J_{CF} 1.7, *C*H_2Ph], 115.8 [CH, d, J_{CF} 21.9, aromatic *C*(6')H], 120.2 (CH, aromatic *C*H$_{ortho}$), 123.2 [Cq, d, J_{CF} 14.6, *C*(2')q aromatic], 124.0-124.3 {2 x *C*H, m, including 124.1 (CH, aromatic *C*H$_{para}$) and 124.2 [CH, d, J_{CF} 3.7, aromatic *C*(4')H]}, 128.8 (CH, aromatic *C*H$_{meta}$), 130.0 [CH, d, J_{CF} 8.5, aromatic *C*(5')H], 132.0 [CH, d, J_{CF} 4.3, aromatic *C*(3')H], 138.0 (Cq, *C*q aromatic Ph), 161.6 (Cq, d, J_{CF} 246.9,

*C*q-F aromatic), 169.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3183 (NH), 1678 (C=O), 1597, 1543, 1490, 1443, 752; HRMS (ES+): Exact mass calculated for $C_{18}H_{20}N_2OFS$ $[M+H]^+$, 331.1280; Found 331.1270; m/z (ES+) 331.2 [($M+H^+$), 100%]; (ES-) 329.2 [($M-H^+$), 12%].

* The ratio of the *thiomorpholine* **123** was calculating from the integration of the region at 3.60-3.70 ppm, which also includes 2H/molecule of the *N-benzylated thiomorpholine* **130**. According to the integration of the dd at δ_H 3.50 ppm, representing 1H/molecule of **130**, the corresponding integration attributed to the **123** can be determined.

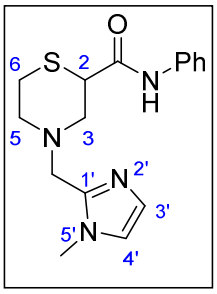
N-Phenyl-4-(pyridin-3-ylmethyl)thiomorpholine-2-carboxamide 134



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.27 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.16 g, 0.68 mmol), nicotinaldehyde (0.19 mL, 2.04 mmol) and acetic acid (0.30 mL) in methanol (9 mL). Purification by column chromatography on silica gel using methanol : dichloromethane (gradient elution 0 to 2% methanol) gave the pure *N-substituted thiomorpholine* **134** (0.16 g, 73%) as an orange oil; δ_H (300 MHz, $CDCl_3$) 2.41-2.60 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 2.77 [1H, dd, *J* 12.7, 3.2, one of C(3)H_2N], 2.97-3.21 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 3.40 [1H, t, *J* 3.2, C(2)*H*S], 3.44-3.74 {3H, m, including 3.52 [1H, dd, *J* 12.1, 3.3, one of C(3)H_2], 3.62 [2H, ABq, J_{AB} 13.3, $\Delta\delta_{AB}$ 0.06, CH_2Ar]}, 7.12 (1H, tt, *J* 7.4, 1.2, ArH_{para}), 7.21-7.42 [3H, m, Ar(5')*H* and ArH_{meta}], 7.55 (2H, d, *J* 8.3, ArH_{ortho}), 7.65 (1H, dt, *J* 7.8, 1.9, Ar(6')*H*), 8.48-8.63 [2H, m, Ar(2')*H* and Ar(4')*H*], 9.87 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.9 [CH_2, *C*(6)H_2S], 42.6 [CH, *C*(2)HS], 53.8 [CH_2, *C*(5)H_2N], 55.4 [CH_2, *C*(3)H_2N], 60.9 [CH_2, *C*H_2Ph], 120.0 (CH, aromatic *C*H Ph), 123.6 [CH, aromatic *C*(5')H], 124.4, 129.1 (1 x CH signal, 2 x aromatic *C*H Ph), 132.1 [Cq, *C*(1')q], 136.8 [CH, aromatic *C*(6')H], 137.8 (Cq, aromatic *C*q Ph), 149.3 [CH, aromatic *C*(4')H], 150.5 [CH, aromatic *C*(2')H], 168.8 (Cq, *C*=O); ν_{max}/cm^{-1} 2973, 2922, 1678 (C=O), 1597, 1546, 1442, 754, 726, 691, 491; HRMS (ES+): Exact mass calculated for

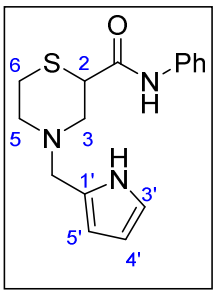
$C_{17}H_{20}N_3OS$ [M+H]$^+$, 314.1327; Found 314.1323; m/z (ES+) 314.2 [(M+H$^+$), 100%]; m/z (ES-) 312.3 [(M-H$^+$), 100%].

4-((1-Methyl-1H-imidazol-2-yl)methyl)-*N*-phenylthiomorpholine-2-carboxamide 135



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 1-methyl-2-imidazole carboxaldehyde (0.22 g, 2.04 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 2.31-2.47, 1H, m) and the *N-substituted thiomorpholine* **135** (δ_H 2.77, 1H, dd, *J* 12.1, 2.7) with ratio 1 : 0.67 respectively by ^{1}H NMR spectroscopy. Purification by successive column chromatography on silica gel using methanol : dichloromethane (gradient elution 0 to 5% methanol) gave the pure *N-substituted thiomorpholine* **135** (0.04 g, 20%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.38-2.66 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 2.77 [1H, dd, *J* 12.1, 2.7, one of C(3)H_2N], 2.91-3.21 {2H, m, including 3.00 [1H, td, *J* 12.6, 2.3, one of C(6)H_2S] and 3.10 [1H, dt, *J* 11.4, 2.9, one of C(5)H_2N]}, 3.43 [1H, br t, *J* 2.7, C(2)*H*S], 3.55-3.85 [6H, m, one of C(3)H_2, CH_2-imidazol and CH_3N, can be distinguished 3.61 (3H, s, CH_3N)], 6.84 [1H, s, Ar(4')*H*], 6.93 [1H, s, Ar(3')*H*], 7.12 (1H, t, *J* 7.7, ArH_{para}), 7.33 [2H, t, *J* 8.0, ArH_{meta}], 7.61 (2H, d, *J* 8.0, ArH_{ortho}), 9.79 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 26.2 [CH_2, *C*(6)H_2S], 33.0 [CH_3, NCH_3], 43.2 [CH, *C*(2)HS], 53.6 [CH_2, *C*(5)H_2N], 54.8 (CH_2, *C*H_2-imidazole), 55.4 [CH_2, *C*(3)H_2N], 120.0 (CH, aromatic *C*H$_{ortho}$), 121.8 [CH, aromatic C(4')*H*], 124.4 (CH, aromatic *C*H$_{para}$), 127.3 [CH, aromatic C(3')H], 129.0 (CH, aromatic *C*H$_{meta}$), 138.0 [Cq, aromatic C(1')q], 143.9 (Cq, aromatic *C*q Ph), 168.4 (Cq, *C*=O); ν_{max}/cm^{-1} 3188 (NH), 2923, 2818, 1673 (C=O), 1597, 1547, 1498, 1441, 727; HRMS (ES+): Exact mass calculated for $C_{16}H_{21}N_4OS$ [M+H]$^+$, 317.1436; Found 317.1434; m/z (ES+) 317.3 [(M+H$^+$), 100%]; m/z (ES-) 315.3 [(M-H$^+$), 100%].

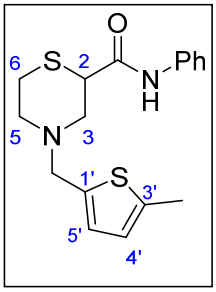
4-((1H-Pyrrol-2-yl)methyl)-*N*-phenylthiomorpholine-2-carboxamide 136



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), pyrrole-2-carboxaldehyde (0.19 g, 2.04 mmol) and acetic acid (0.30 mL) in methanol (9 mL). The crude product consisted of a mixture of the *thiomorpholine* **123** (δ_H 2.99-3.13, 2H, m)* and the *N-substituted thiomorpholine* **136** (δ_H 2.61, 1H, dd, *J* 12.0, 3.1) with ratio 0.33 : 1 respectively by ^{1}H NMR spectroscopy. Purification by successive column chromatography on silica gel using ethyl acetate : hexane (gradient elution 5 to 30% ethyl acetate) gave the pure *N-substituted thiomorpholine* **136** (0.13 g, 62%) as a brown oil; δ_H (400 MHz, $CDCl_3$) 2.40-2.68 {3H, m, including 2.40-2.56 [2H, m, one of C(6)H_2S, one of C(5)H_2N] and can be distinguished 2.61 [1H, dd, *J* 12.0, 3.1, one of C(3)H_2N]}, 2.98-3.22 {2H, m including 3.05 [1H, td, *J* 13.0, 3.3, one of C(6)H_2S], 3.16 [1H, dt, *J* 12.0, 3.1, one of C(5)H_2N]}, 3.36 [1H, t, *J* 3.0, C(2)*H*S], 3.52-3.66 [3H, m, one of C(3)H_2 and CH_2-pyrrole], 6.01-6.08 [1H, m, Ar(5')*H*], 6.15 [1H, dd, *J* 2.8, 2.7, Ar(4')*H*], 6.75 [1H, dd, *J* 2.5, 1.5, Ar(3')*H*], 7.13 (1H, t, *J* 7.2, ArH_{para}), 7.35 [2H, t, *J* 8.0, ArH_{meta}], 7.55 (2H, d, *J* 7.7, ArH_{ortho}), 8.67 (1H, br s, N(2')*H*), 9.95 (1H, br s, N*H*Ph); δ_C (100 MHz, $CDCl_3$) 26.2 [CH_2, *C*(6)H_2S], 42.8 [CH, *C*(2)HS], 54.0 [CH_2, *C*(5)H_2N], 54.7 [CH_2, *C*(3)H_2N], 56.0 [CH_2, *C*H_2-pyrrole], 107.9 [CH, aromatic *C*(5')H], 108.4 [CH, aromatic *C*(4')H], 117.9 [CH, aromatic *C*(3')H], 120.1 (CH, aromatic *C*H$_{ortho}$), 124.5 (CH, aromatic *C*H$_{para}$), 127.0 [Cq, aromatic *C*(1')q], 129.1 (CH, aromatic *C*H$_{meta}$), 137.8 (Cq, aromatic *C*q Ph), 169.2 (Cq, *C*=O); ν_{max}/cm^{-1} 3300, 2923 (NH), 1660 (C=O), 1597, 1549, 1444, 907, 722, 492; HRMS (ES+): Exact mass calculated for $C_{16}H_{20}N_3OS$ $[M+H]^+$, 302.1327; Found 302.1320; m/z (ES+) 302.3 [($M+H^+$), 100%]; m/z (ES-) 300.3 [($M-H^+$), 100%].

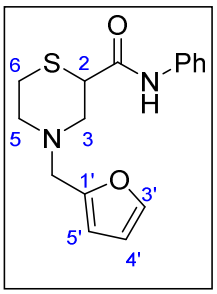
* The ratio of the *NH thiomorpholine* **123** was calculating from the integration of the region at 2.99-3.13 ppm, which also includes 2H/molecule of the *benzylated thiomorpholine* **136**. According to the integration of the td at δ_H 3.05 ppm, representing 2H/molecule of **(zzx0090)**, the corresponding integration attributed to the **123** can be determined.

4-((5-Methylthiophen-2-yl)methyl)-*N*-phenylthiomorpholine-2-carboxamide 137



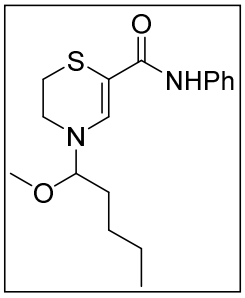
This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 3-methyl-2-thiophenecarboxaldehyde (0.22 mL, 2.04 mmol) and acetic acid (0.30 mL) in methanol (9 mL). Purification by column chromatography on silica gel using ethyl acetate : hexane (gradient elution 2 to 30% ethyl acetate) gave the pure *N-substituted thiomorpholine* **137** (0.21 g, 95%) as an orange oil; δ_H (400 MHz, $CDCl_3$) 2.37-2.56 [5H, m, one of C(6)H_2S, one of C(5)H_2N and CH_3, can be distinguished 2.45 (3H, s, CH_3)], 2.71 [1H, dd, *J* 12.4, 3.2, one of C(3)H_2N], 3.15 [1H, td, *J* 12.9, 2.7, one of C(6)H_2S], 3.25-3.38 {2H, m, including 3.30 [1H, dt, *J* 11.7, 3.0, one of C(5)H_2N] and 3.35 [1H, t, *J* 2.8, C(2)*H*S]}, 3.51 [1H, dd, *J* 12.3, 2.5, one of C(3)H_2], 3.74 [2H, s, CH_2-thiophen], 6.57-6.63 [1H, m, Ar(4')*H*], 6.73 [1H, d, *J* 3.2, Ar(5')*H*], 7.12 (1H, t, *J* 7.3, ArH_{para}), 7.35 [2H, t, *J* 8.0, ArH_{meta}], 7.65 (2H, d, *J* 7.8, ArH_{ortho}), 10.26 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 15.5 (CH_3, *C*H_3-thiophene), 25.7 [CH_2, *C*(6)H_2S], 42.1 [CH, *C*(2)HS], 53.8 [CH_2, *C*(5)H_2N], 54.9 [CH_2, *C*(3)H_2N], 58.1 [CH_2, *C*H_2-thiophene], 120.3 (CH, aromatic *C*H_{ortho}), 124.2 (CH, aromatic *C*H_{para}), 124.8 [CH, aromatic *C*(4')H], 127.5 [CH, aromatic *C*(5')H], 128.9 (CH, aromatic *C*H_{meta}), 136.5 [Cq, aromatic *C*(1')q], 138.0 (Cq, aromatic *C*q Ph), 140.6 [Cq, aromatic *C*(3')q], 169.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3185 (NH), 3028, 2919, 2822, 1676 (C=O), 1597, 1544, 1442, 1311, 726; HRMS (ES+): Exact mass calculated for $C_{17}H_{21}N_2OS_2$ $[M+H]^+$, 333.1095; Found 333.1087; m/z (ES+) 333.2 [$(M+H^+)$, 100%].

4-(Furan-2-ylmethyl)-*N*-phenylthiomorpholine-2-carboxamide 138



This synthesis follows the procedure described for **126** using sodium cyanoborohydride (0.26 g, 4.08 mmol), *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.15 g, 0.68 mmol), 2-furaldehyde (0.17 mL, 2.04 mmol) and acetic acid (0.30 mL) in methanol (9 mL). Purification by column chromatography on silica gel using ethyl acetate : hexane (gradient elution 2 to 30% ethyl acetate) gave the pure *N-substituted thiomorpholine* **138** (0.19 g, 96%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.43-2.61 [2H, m, one of C(6)H_2S and one of C(5)H_2N], 2.71 [1H, dd, *J* 12.5, 2.9, one of C(3)H_2N], 3.11-3.56 {3H, m including 3.19 [1H, td, *J* 12.9, 2.3, one of C(6)H_2S], 3.27 [1H, dt, *J* 11.7, 3.5, one of C(5)H_2N] and 3.32 [1H, t, *J* 2.8, C(2)*H*S]}, 3.44 [1H, dd, *J* 12.6, 2.6, one of C(3)H_2], 3.64 [2H, ABq, J_{AB} 14.1, $\Delta\delta_{AB}$ 0.09, CH_2-furan], 6.24-6.30 [1H, m, Ar(5')*H*], 6.30-6.37 [1H, m, Ar(4')*H*], 7.10 (1H, t, *J* 7.6, ArH_{para}), 7.29-7.40 {3H, m, including 7.33 [2H, t, *J* 8.0, ArH_{meta}] and Ar(3')*H*}, 7.65 (2H, d, *J* 7.9, ArH_{ortho}), 10.57 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 25.6 [CH_2, *C*(6)H_2S], 42.0 [CH, *C*(2)HS], 54.0 [CH_2, *C*(5)H_2N], 54.4 [CH_2, *C*(3)H_2N], 55.3 [CH_2, CH_2-furane], 109.8 [CH, aromatic *C*(5')H], 110.3 [CH, aromatic *C*(4')H], 119.9 (CH, aromatic CH_{ortho}), 124.1 (CH, aromatic CH_{para}), 128.9 (CH, aromatic CH_{meta}), 138.2 (Cq, aromatic *C*q Ph), 124.8 [CH, aromatic *C*(3')H], 149.9 [Cq, aromatic *C*(1')q], 169.7 (Cq, *C*=O); ν_{max}/cm^{-1} 3183 (NH), 2825, 1674 (C=O), 1597, 1546, 1443, 731; HRMS (ES+): Exact mass calculated for $C_{16}H_{19}N_3OS$ $[M+H]^+$, 303.1167; Found 303.1165; m/z (ES+) 303.2 [($M+H^+$), 100%]; m/z (ES-) 301.3 [($M-H^+$), 20%].

4-(1-Methoxypentyl)-*N*-phenyl-3,4-dihydro-2H-1,4-thiazine-6-carboxamide 139



Sodium borohydride (0.10 g, 2.72 mmol) was added slowly to a solution of *N*-phenyl-5,6-dihydro-1,4-thiazine-3-carboxamide **79** (0.10 g, 0.45 mmol), valeraldehyde (0.06 mL, 0.54 mmol) and acetic acid (0.20 mL) in methanol (6 mL) at room temperature while stirring. After stirring the reaction mixture at room temperature overnight, the reaction mixture was quenched with water (20 mL) and neutralised with a solution of sodium hydroxide (10M, 4 mL). The mixture was extracted with ethyl acetate (2 x 30 mL). The layers were separated and the combined organic layers was washed with water (50 mL) and brine (50 mL), dried and concentrated under reduced pressure to give the crude product. Purification by column chromatography on silica gel using hexane : ethyl acetate (gradient elution 5 to 80% ethyl acetate) gave the pure *thiazine* **139** (0.14 g, 74%) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 0.90 [3H, t, *J* 7.1, C(5')H_3], 1.15-1.44 [4H, m, C(3')H_2 and C(4')H_2], 1.56-1.82 [2H, m, C(2')H_2], 2.74-2.86 (1H, m, one of SCH_2), 2.86-2.99 (1H, m, one of SCH_2), 3.23 (3H, s, O-CH_3), 3.37-3.50 (1H, m, one of NCH_2), 3.58-3.69 (1H, m, one of NCH_2), 4.22 [1H, t, *J* 6.6, C(1')*H*], 7.05 (1H, t, *J* 7.6, ArH_{para}), 7.30 (2H, t, *J* 8.2, ArH_{meta}), 7.55 (2H, d, *J* 8.6, ArH_{ortho}), 7.63-7.76 [2H, m, which includes 7.69 (1H, br s, N*H*), 7.72 (1H, s, C*H*)]; δ_C (75 MHz, $CDCl_3$) 13.9 [CH_3, *C*(5')H_3], 22.3 [CH_2, *C*(4')H_2], 23.8 (2H, SCH_2), 27.2 [2H, *C*(3')H_2], 32.8 [CH_2, *C*(2')H_2], 41.5 (CH_2, NCH_2), 55.6 (CH_3, O-CH_3), 88.7 (Cq, S*C*q=), 97.1 [CH, *C*(1')H], 119.7 (CH, aromatic *C*H_{ortho}), 123.5 (CH, aromatic *C*H_{para}), 128.9 (CH, aromatic *C*H_{meta}), 138.6 (Cq, aromatic *C*q), 139.5 (CH, *C*H=), 164.1 (Cq, *C*=O); ν_{max}/cm^{-1} 3312 (NH), 2952, 2929, 1638 (C=O), 1591, 1498 (C=C), 1298, 1226, 750; HRMS (ES+): Exact mass calculated for $C_{17}H_{25}N_2O_2S$ $[M+H]^+$, 321.1637; Found 321.1637; m/z (ES+) 321.2 [($M+H^+$), 52%]; (ES-) 319.3 [($M-H^+$), 100%].

6. REFERENCES

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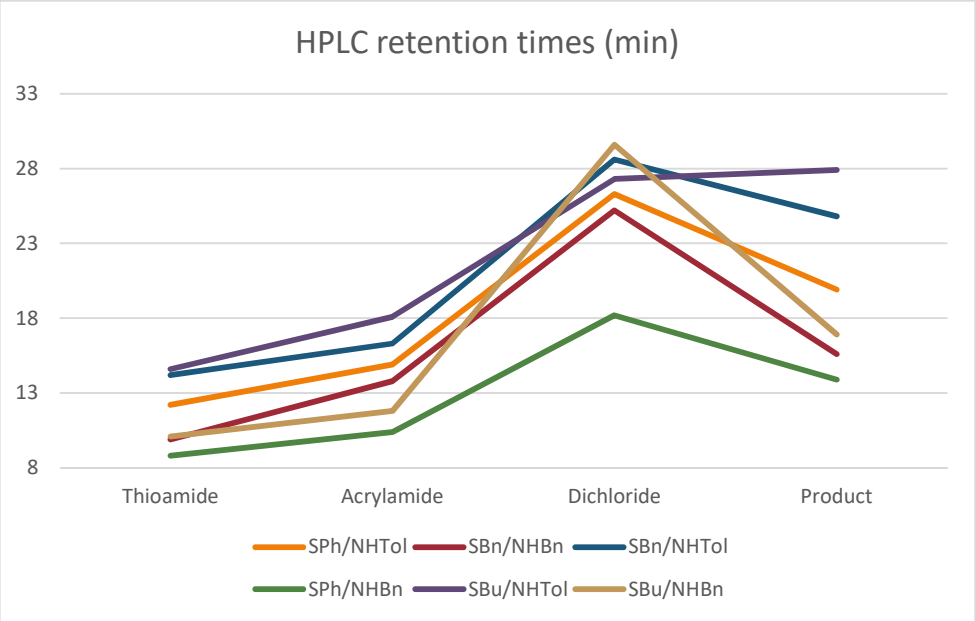
APPENDIX I

HPLC Supporting Information

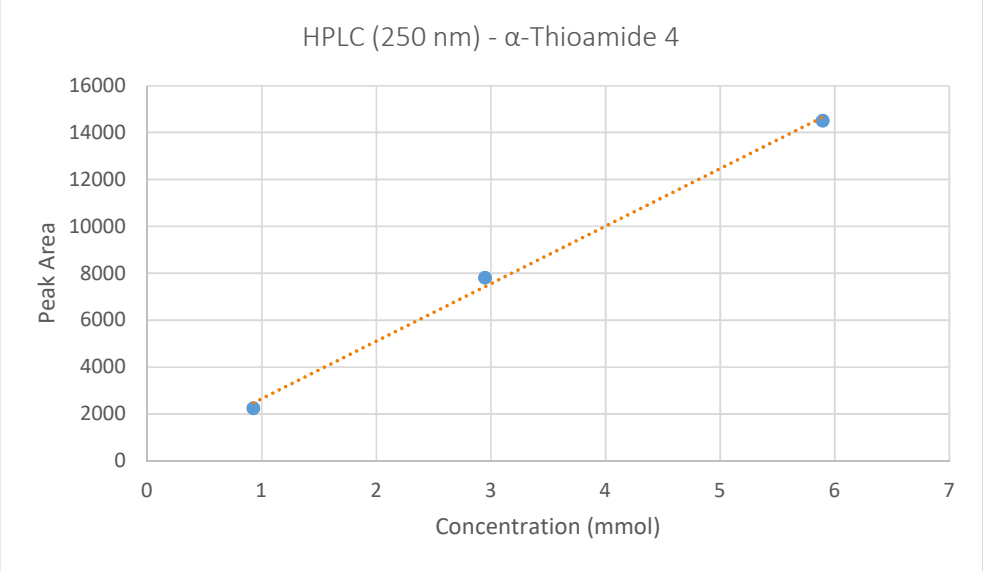
HPLC retention times slope



Calibration Curves

Calibration curve for *α-thioamide* **4** (starting material):

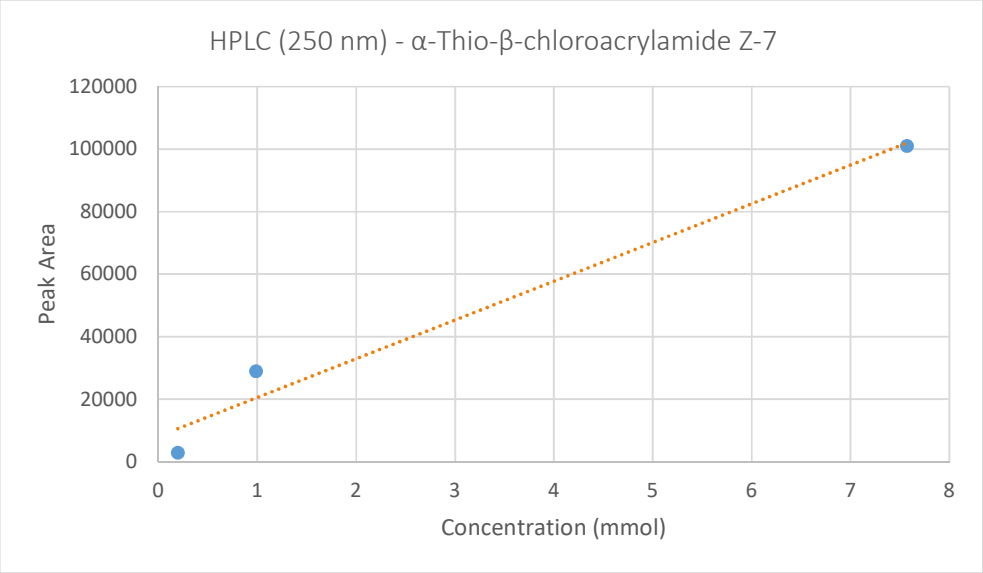
Concentration in MeOH		Peak Area
mg/mL	mmol/L	
0.252	0.929	2241.73438
0.8	2.948	7813.27588
1.6	5.896	14509.3



$$Concentration = \frac{\text{Peak Area}}{2497.2}$$

Calibration curve for *α-thio-β-chloroacrylamide* **7**:

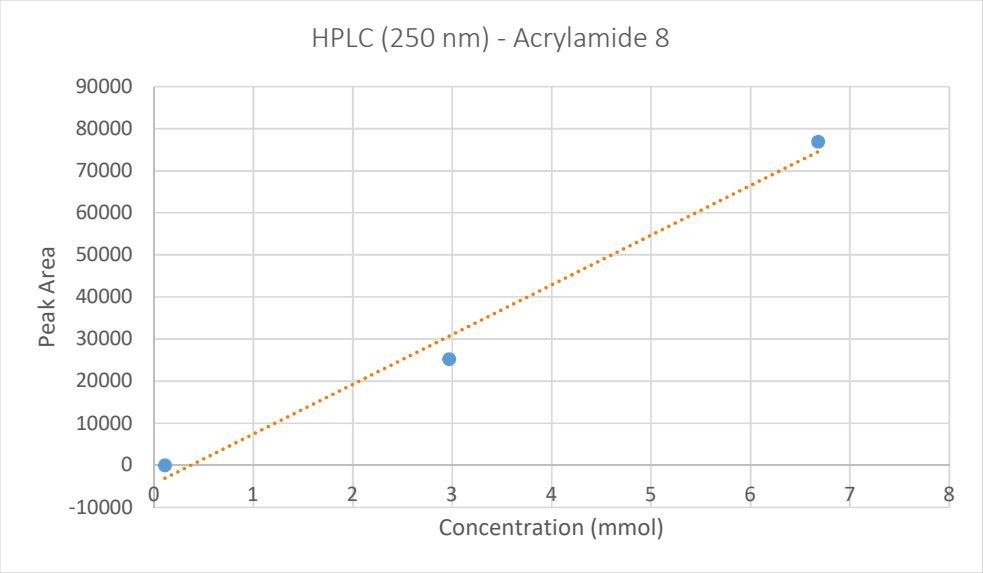
Concentration in MeOH		Peak Area
mg/mL	mmol/L	
0.06	0.197	2910.47852
0.3	0.987	28983.4
2.3	7.571	101061



$$Concentration = \frac{\text{Peak Area}}{13617}$$

Calibration curve for *acrylamide* **8**:

Concentration in MeOH		Peak Area
mg/mL	mmol/L	
0.03	0.111	1390.62817
0.8	2.970	25189.2
1.8	6.682	76900.2



$$Concentration = \frac{\text{Peak Area}}{11009}$$

APPENDIX II

NCI-60 One-Dose Mean Graphs

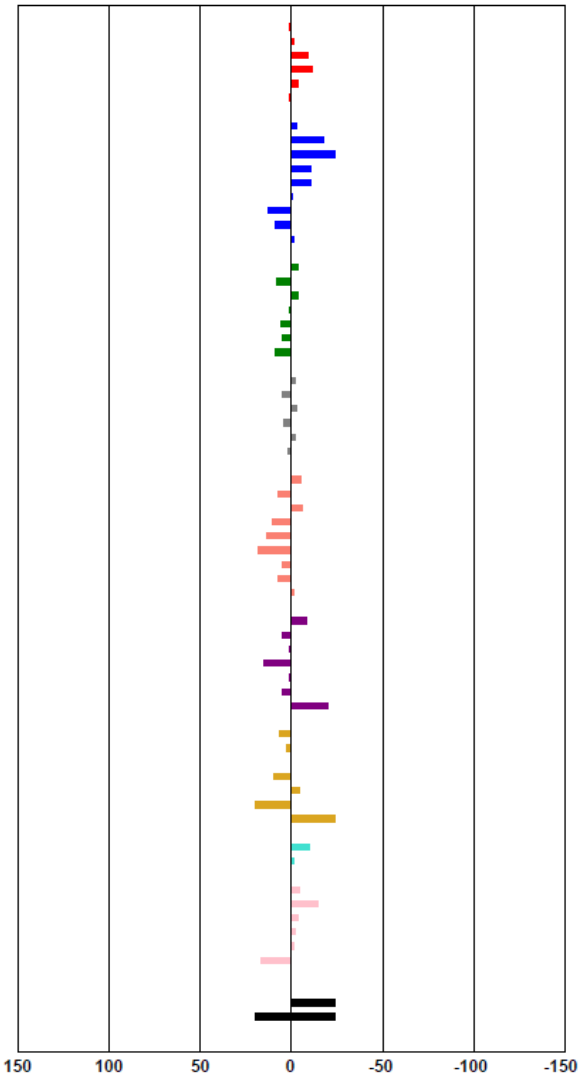
Developmental Therapeutics Program

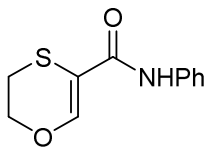
One Dose Mean Graph

NSC: D-791689 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 18, 2016
Experiment ID: 1607OS47		Report Date: Aug 29, 2016

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	96.17
HL-60(TB)	94.22
K-562	86.40
MOLT-4	84.24
RPMI-8226	91.51
SR	96.61
Non-Small Cell Lung Cancer	
A549/ATCC	92.74
EKVX	77.66
HOP-62	71.99
HOP-92	84.91
NCI-H226	84.86
NCI-H23	94.63
NCI-H322M	108.38
NCI-H460	104.03
NCI-H522	94.06
Colon Cancer	
COLO 205	91.87
HCC-2998	103.66
HCT-116	91.69
HCT-15	96.22
HT29	101.56
KM12	100.33
SW-620	104.51
CNS Cancer	
SF-268	93.21
SF-295	100.36
SF-539	92.52
SNB-19	99.42
SNB-75	93.29
U251	97.39
Melanoma	
LOX IMVI	90.66
MALME-3M	103.16
M14	89.33
MDA-MB-435	105.96
SK-MEL-2	109.38
SK-MEL-28	113.88
SK-MEL-5	100.49
UACC-257	102.55
UACC-62	93.90
Ovarian Cancer	
IGROV1	86.86
OVCAR-3	100.48
OVCAR-4	96.24
OVCAR-5	110.89
OVCAR-8	96.89
NCI/ADR-RES	100.09
SK-OV-3	75.17
Renal Cancer	
786-0	102.32
A498	97.85
ACHN	95.65
RXF 393	105.05
SN12C	91.18
TK-10	115.27
UO-31	71.77
Prostate Cancer	
PC-3	85.99
DU-145	94.58
Breast Cancer	
MCF7	90.74
MDA-MB-231/ATCC	81.23
HS 578T	92.19
BT-549	93.66
T-47D	93.91
MDA-MB-468	112.10
Mean	95.39
Delta	23.62
Range	43.50

Mean Growth Percent - Growth Percent





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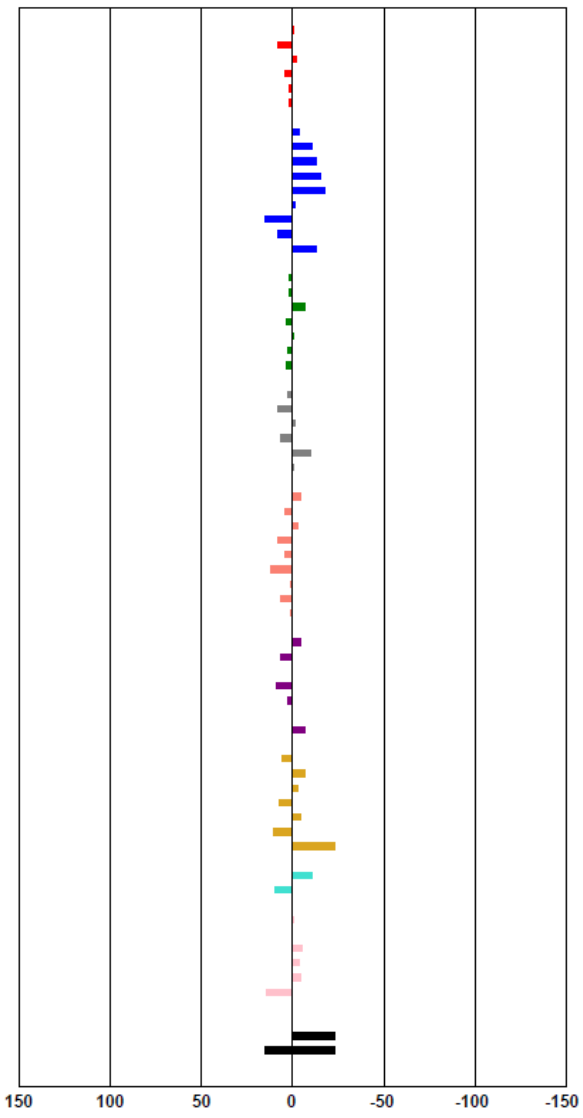
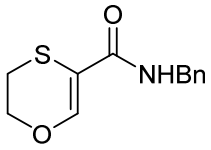
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-791688 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 18, 2016
Experiment ID: 1607OS47		Report Date: Aug 29, 2016

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	96.59
HL-60(TB)	105.15
K-562	95.18
MOLT-4	100.87
RPMI-8226	98.60
SR	98.64
Non-Small Cell Lung Cancer	
A549/ATCC	93.31
EKVX	86.30
HOP-62	83.98
HOP-92	81.50
NCI-H226	79.52
NCI-H23	95.99
NCI-H322M	111.83
NCI-H460	104.86
NCI-H522	84.05
Colon Cancer	
COLO 205	98.76
HCC-2998	99.17
HCT-116	90.56
HCT-15	100.85
HT29	96.57
KM12	99.64
SW-620	100.20
CNS Cancer	
SF-268	99.92
SF-295	105.04
SF-539	96.02
SNB-19	103.26
SNB-75	87.53
U251	96.62
Melanoma	
LOX IMVI	92.77
MALME-3M	101.50
M14	94.14
MDA-MB-435	105.29
SK-MEL-2	101.46
SK-MEL-28	109.04
SK-MEL-5	98.12
UACC-257	103.85
UACC-62	97.82
Ovarian Cancer	
IGROV1	92.50
OVCAR-3	103.58
OVCAR-4	97.75
OVCAR-5	105.57
OVCAR-8	99.66
NCI/ADR-RES	97.13
SK-OV-3	90.23
Renal Cancer	
786-0	102.65
A498	90.04
ACHN	94.55
RXF 393	104.32
SN12C	92.73
TK-10	107.27
UO-31	73.63
Prostate Cancer	
PC-3	86.52
DU-145	106.63
Breast Cancer	
MCF7	96.29
MDA-MB-231/ATCC	97.60
HS 578T	91.59
BT-549	93.56
T-47D	92.54
MDA-MB-468	111.13
Mean	96.98
Delta	23.35
Range	38.20





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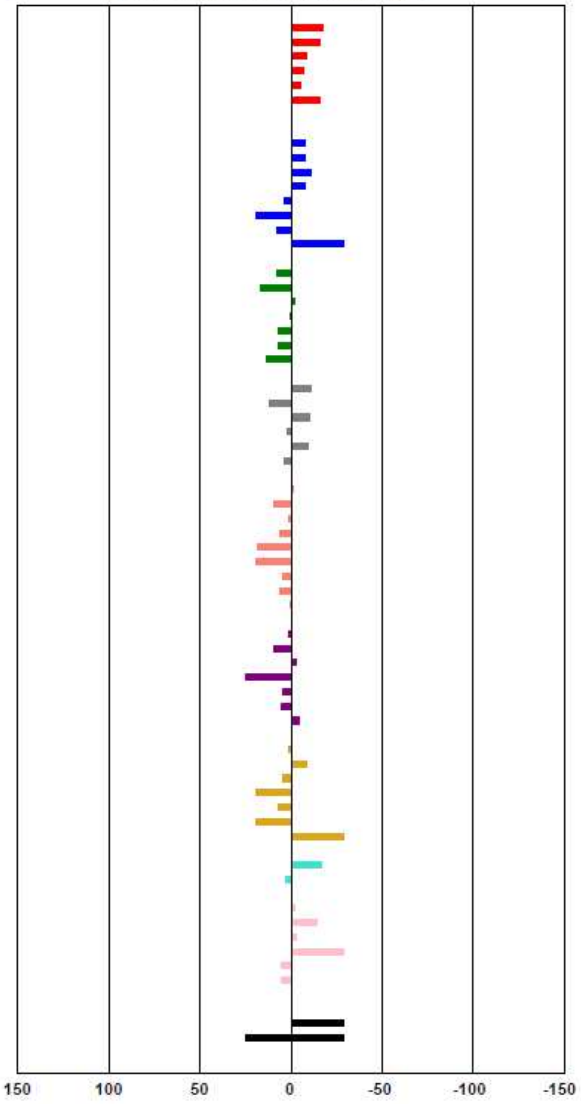
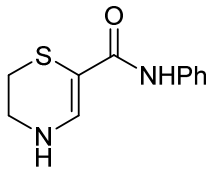
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-791690 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 18, 2016
Experiment ID: 1607OS47		Report Date: Aug 29, 2016

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	75.14
HL-60(TB)	77.09
K-562	83.87
MOLT-4	86.01
RPMI-8226	87.32
SR	77.18
Non-Small Cell Lung Cancer	
A549/ATCC	92.38
EKVX	84.79
HOP-62	85.31
HOP-92	81.94
NCI-H226	85.11
NCI-H23	96.63
NCI-H322M	112.00
NCI-H460	100.68
NCI-H522	63.65
Colon Cancer	
COLO 205	100.88
HCC-2998	109.37
HCT-116	90.68
HCT-15	93.50
HT29	99.64
KM12	99.66
SW-620	106.55
CNS Cancer	
SF-268	81.51
SF-295	104.32
SF-539	82.51
SNB-19	94.73
SNB-75	83.07
U251	96.48
Melanoma	
LOX IMVI	91.56
MALME-3M	102.33
M14	93.96
MDA-MB-435	99.13
SK-MEL-2	111.24
SK-MEL-28	111.75
SK-MEL-5	97.15
UACC-257	98.58
UACC-62	92.86
Ovarian Cancer	
IGROV1	93.86
OVCAR-3	102.04
OVCAR-4	89.87
OVCAR-5	117.31
OVCAR-8	96.93
NCI/ADR-RES	98.25
SK-OV-3	88.19
Renal Cancer	
786-0	93.65
A498	84.33
ACHN	97.05
RXF 393	112.25
SN12C	99.93
TK-10	112.29
UO-31	63.66
Prostate Cancer	
PC-3	75.81
DU-145	95.61
Breast Cancer	
MCF7	91.14
MDA-MB-231/ATCC	78.92
HS 578T	89.60
BT-549	63.83
T-47D	98.17
MDA-MB-468	98.26
Mean	92.74
Delta	29.09
Range	53.66





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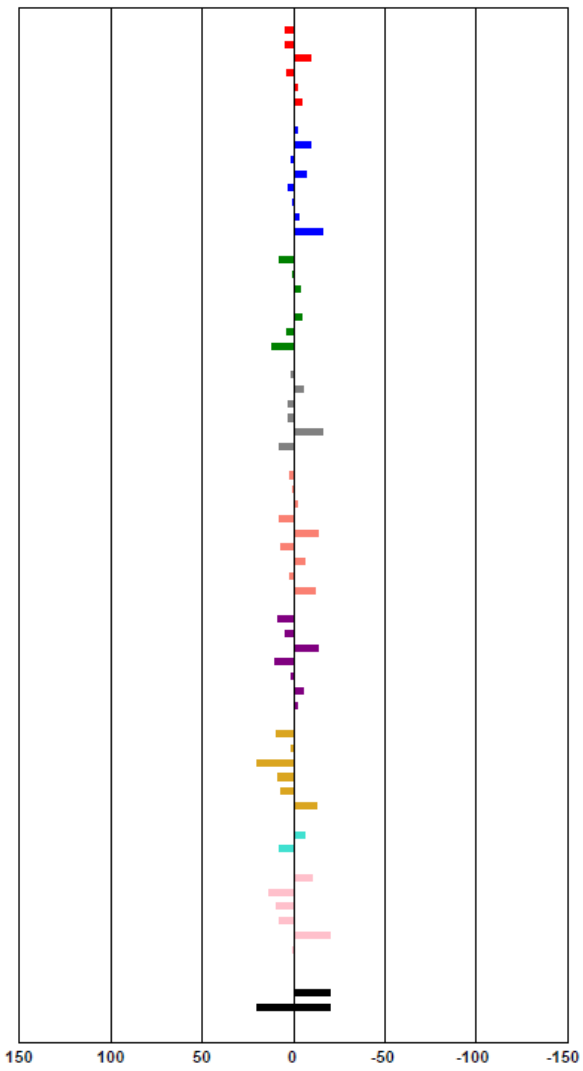
Developmental Therapeutics Program

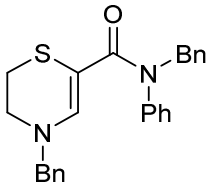
One Dose Mean Graph

NSC: D-795706 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 06, 2017
Experiment ID: 1702OS52		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	100.73
HL-60(TB)	100.06
K-562	86.55
MOLT-4	99.73
RPMI-8226	93.44
SR	91.61
Non-Small Cell Lung Cancer	
A549/ATCC	93.80
EKVX	86.83
HOP-62	97.21
HOP-92	88.88
NCI-H226	98.44
NCI-H23	96.23
NCI-H322M	93.20
NCI-H522	79.93
Colon Cancer	
COLO 205	103.44
HCC-2998	96.49
HCT-116	92.28
HCT-15	95.46
HT29	91.17
KM12	99.63
SW-620	107.78
CNS Cancer	
SF-268	96.79
SF-295	90.30
SF-539	98.90
SNB-19	98.73
SNB-75	80.19
U251	103.66
Melanoma	
LOX IMVI	97.92
MALME-3M	96.32
M14	93.98
MDA-MB-435	103.36
SK-MEL-2	82.11
SK-MEL-28	102.71
SK-MEL-5	90.11
UACC-257	97.78
UACC-62	84.25
Ovarian Cancer	
IGROV1	104.04
OVCAR-3	100.00
OVCAR-4	82.65
OVCAR-5	105.75
OVCAR-8	97.34
NCI/ADR-RES	90.39
SK-OV-3	93.62
Renal Cancer	
786-0	105.22
ACHN	97.31
RXF 393	115.64
SN12C	104.58
TK-10	102.71
UO-31	83.08
Prostate Cancer	
PC-3	89.73
DU-145	103.77
Breast Cancer	
MCF7	86.02
MDA-MB-231/ATCC	109.49
HS 578T	105.32
BT-549	103.21
T-47D	75.96
MDA-MB-468	95.94
Mean	95.82
Delta	19.86
Range	39.68

Mean Growth Percent - Growth Percent





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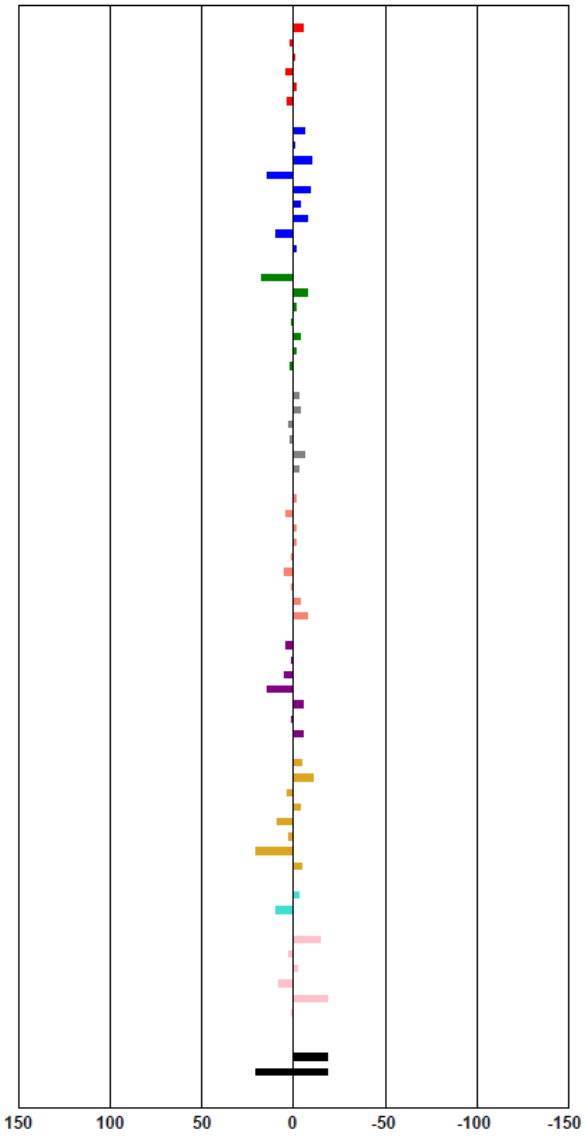
Developmental Therapeutics Program

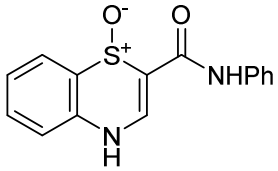
One Dose Mean Graph

NSC: D-797237 / 1	Conc: 1.00E-5 Molar	Test Date: Apr 10, 2017
Experiment ID: 1704OS85		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	95.98
HL-60(TB)	102.67
K-562	100.37
MOLT-4	104.91
RPMI-8226	99.97
SR	104.12
Non-Small Cell Lung Cancer	
A549/ATCC	95.48
EKVX	100.31
HOP-62	91.54
HOP-92	115.55
NCI-H226	92.09
NCI-H23	97.34
NCI-H322M	93.52
NCI-H460	110.75
NCI-H522	99.49
Colon Cancer	
COLO 205	118.49
HCC-2998	93.75
HCT-116	99.85
HCT-15	102.08
HT29	97.25
KM12	100.04
SW-620	103.23
CNS Cancer	
SF-268	97.96
SF-295	97.69
SF-539	104.06
SNB-19	102.69
SNB-75	95.38
U251	98.46
Melanoma	
LOX IMVI	100.05
MALME-3M	105.31
M14	99.61
MDA-MB-435	100.17
SK-MEL-2	102.01
SK-MEL-28	105.89
SK-MEL-5	101.82
UACC-257	97.43
UACC-62	93.63
Ovarian Cancer	
IGROV1	105.45
OVCAR-3	102.46
OVCAR-4	105.82
OVCAR-5	115.39
OVCAR-8	96.22
NCI/ADR-RES	102.16
SK-OV-3	95.60
Renal Cancer	
786-0	96.44
A498	90.71
ACHN	104.43
CAKI-1	97.77
RXF 393	110.00
SN12C	103.61
TK-10	121.36
UO-31	96.46
Prostate Cancer	
PC-3	98.37
DU-145	110.77
Breast Cancer	
MCF7	86.95
MDA-MB-231/ATCC	104.01
HS 578T	98.91
BT-549	109.27
T-47D	82.98
MDA-MB-468	101.94
Mean	100.97
Delta	17.99
Range	38.38

Mean Growth Percent - Growth Percent





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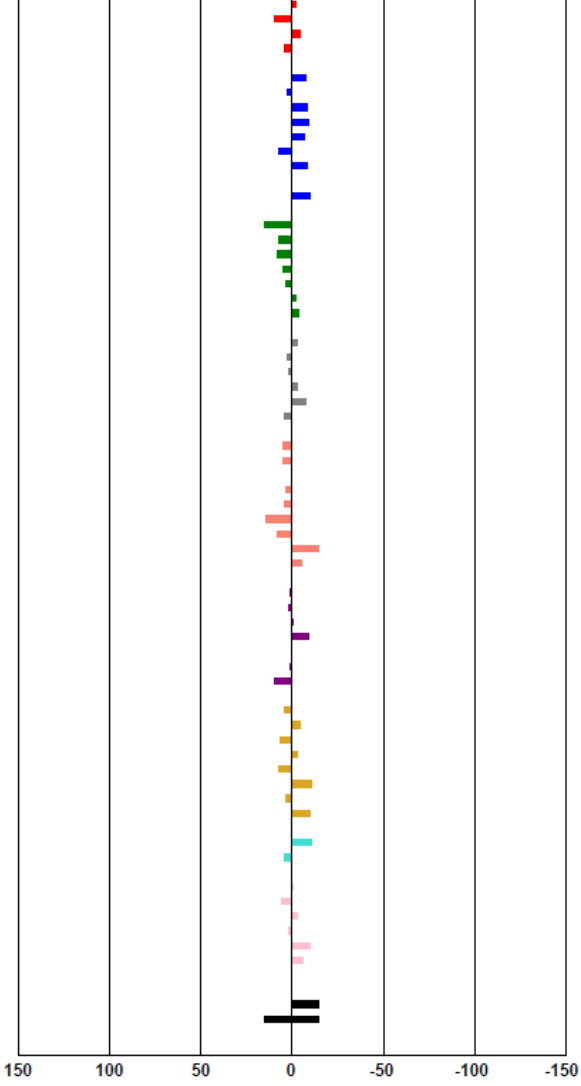
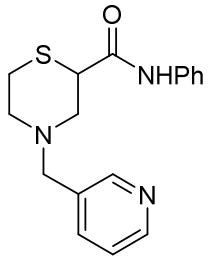
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-801070 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	87.87
HL-60(TB)	98.71
K-562	92.17
MOLT-4	103.82
RPMI-8226	89.52
SR	98.13
Non-Small Cell Lung Cancer	
A549/ATCC	86.37
EKVX	96.67
HOP-62	86.12
HOP-92	84.84
NCI-H226	87.00
NCI-H23	101.36
NCI-H322M	85.84
NCI-H460	94.63
NCI-H522	83.83
Colon Cancer	
COLO 205	109.21
HCC-2998	101.16
HCT-116	101.80
HCT-15	98.67
HT29	97.09
KM12	91.85
SW-620	90.43
CNS Cancer	
SF-268	91.04
SF-295	96.62
SF-539	95.76
SNB-19	91.28
SNB-75	86.20
U251	98.55
Melanoma	
LOX IMVI	99.27
MALME-3M	98.87
M14	94.53
MDA-MB-435	97.43
SK-MEL-2	98.58
SK-MEL-28	108.50
SK-MEL-5	101.98
UACC-257	79.49
UACC-62	88.96
Ovarian Cancer	
IGROV1	95.17
OVCAR-3	95.53
OVCAR-4	93.94
OVCAR-5	84.83
OVCAR-8	94.51
NCI/ADR-RES	95.34
SK-OV-3	103.84
Renal Cancer	
786-0	98.01
A498	89.48
ACHN	100.56
CAKI-1	91.59
RXF 393	101.27
SN12C	83.34
TK-10	97.13
UO-31	84.26
Prostate Cancer	
PC-3	83.33
DU-145	98.38
Breast Cancer	
MCF7	93.73
MDA-MB-231/ATCC	99.50
HS 578T	90.93
BT-549	95.76
T-47D	84.48
MDA-MB-468	87.97
Mean	93.95
Delta	14.46
Range	29.72





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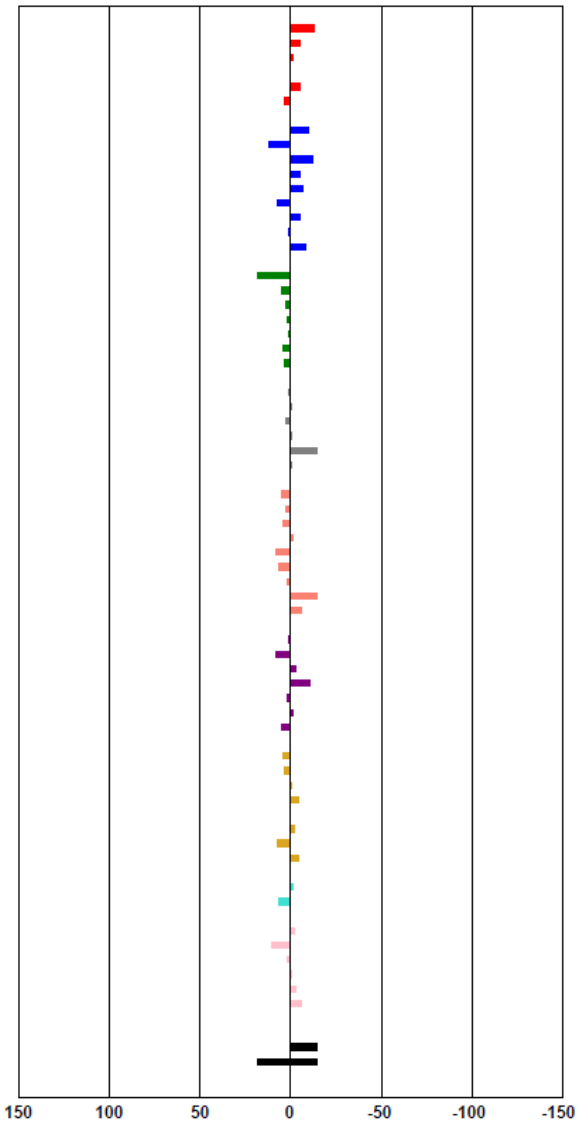
Developmental Therapeutics Program

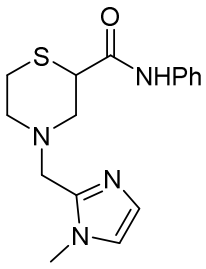
One Dose Mean Graph

NSC: D-801071 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	80.91
HL-60(TB)	88.62
K-562	92.07
MOLT-4	94.30
RPMI-8226	88.48
SR	96.83
Non-Small Cell Lung Cancer	
A549/ATCC	83.85
EKVX	105.65
HOP-62	81.55
HOP-92	88.74
NCI-H226	87.06
NCI-H23	101.09
NCI-H322M	88.68
NCI-H460	94.80
NCI-H522	85.55
Colon Cancer	
COLO 205	112.26
HCC-2998	98.59
HCT-116	96.25
HCT-15	95.42
HT29	95.10
KM12	97.68
SW-620	96.87
CNS Cancer	
SF-268	95.12
SF-295	92.90
SF-539	95.99
SNB-19	93.01
SNB-75	79.45
U251	93.13
Melanoma	
LOX IMVI	98.74
MALME-3M	96.55
M14	98.10
MDA-MB-435	92.16
SK-MEL-2	101.76
SK-MEL-28	100.09
SK-MEL-5	95.45
UACC-257	79.58
UACC-62	87.65
Ovarian Cancer	
IGROV1	94.50
OVCAR-3	101.67
OVCAR-4	90.69
OVCAR-5	83.10
OVCAR-8	95.51
NCI/ADR-RES	92.67
SK-OV-3	98.69
Renal Cancer	
786-0	97.95
A498	97.03
ACHN	93.17
CAKI-1	89.23
RXF 393	94.17
SN12C	91.41
TK-10	101.11
UO-31	89.19
Prostate Cancer	
PC-3	92.32
DU-145	100.38
Breast Cancer	
MCF7	91.56
MDA-MB-231/ATCC	104.14
HS 578T	95.91
BT-549	93.31
T-47D	90.70
MDA-MB-468	87.83
Mean	93.60
Delta	14.15
Range	32.81

Mean Growth Percent - Growth Percent





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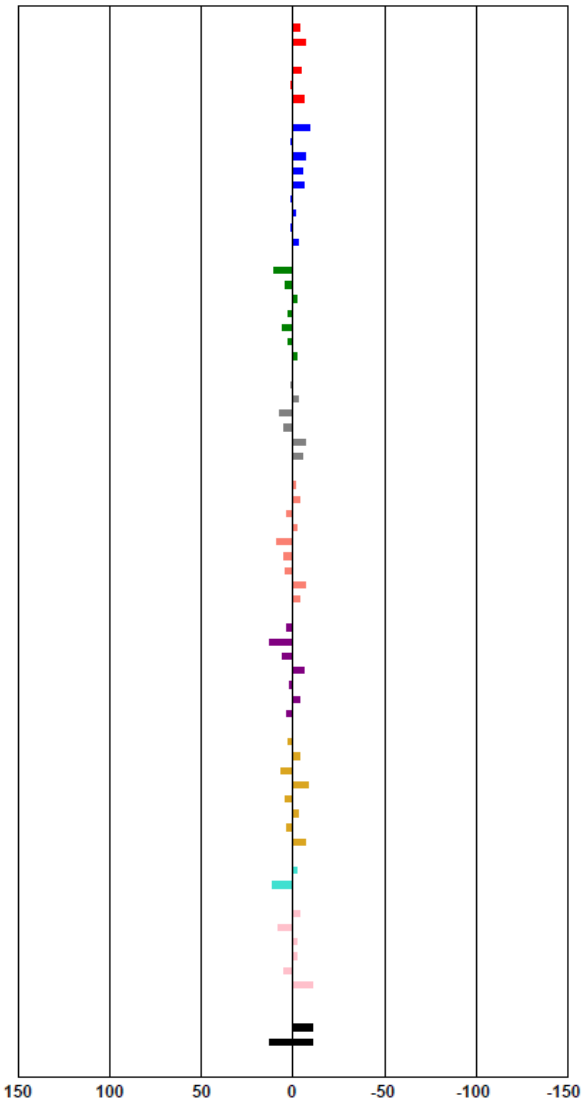
Developmental Therapeutics Program

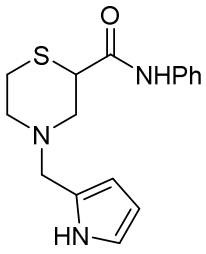
One Dose Mean Graph

NSC: D-801072 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	90.70
HL-60(TB)	88.02
K-562	94.77
MOLT-4	90.01
RPMI-8226	95.52
SR	88.64
Non-Small Cell Lung Cancer	
A549/ATCC	85.70
EKVX	95.68
HOP-62	87.74
HOP-92	89.00
NCI-H226	88.65
NCI-H23	95.85
NCI-H322M	93.29
NCI-H460	95.89
NCI-H522	91.78
Colon Cancer	
COLO 205	105.14
HCC-2998	98.37
HCT-116	92.45
HCT-15	97.16
HT29	100.54
KM12	97.01
SW-620	92.66
CNS Cancer	
SF-268	95.81
SF-295	91.46
SF-539	101.98
SNB-19	99.35
SNB-75	87.74
U251	89.57
Melanoma	
LOX IMVI	93.62
MALME-3M	91.19
M14	98.07
MDA-MB-435	92.65
SK-MEL-2	103.55
SK-MEL-28	99.40
SK-MEL-5	98.40
UACC-257	87.93
UACC-62	90.90
Ovarian Cancer	
IGROV1	97.98
OVCAR-3	107.03
OVCAR-4	100.43
OVCAR-5	88.27
OVCAR-8	96.39
NCI/ADR-RES	91.06
SK-OV-3	98.29
Renal Cancer	
786-0	96.81
A498	91.07
ACHN	100.69
CAKI-1	86.12
RXF 393	98.69
SN12C	92.04
TK-10	97.90
UO-31	87.82
Prostate Cancer	
PC-3	92.31
DU-145	106.07
Breast Cancer	
MCF7	91.25
MDA-MB-231/ATCC	102.54
HS 578T	92.28
BT-549	92.25
T-47D	99.43
MDA-MB-468	83.87
Mean	94.45
Delta	10.58
Range	23.16

Mean Growth Percent - Growth Percent





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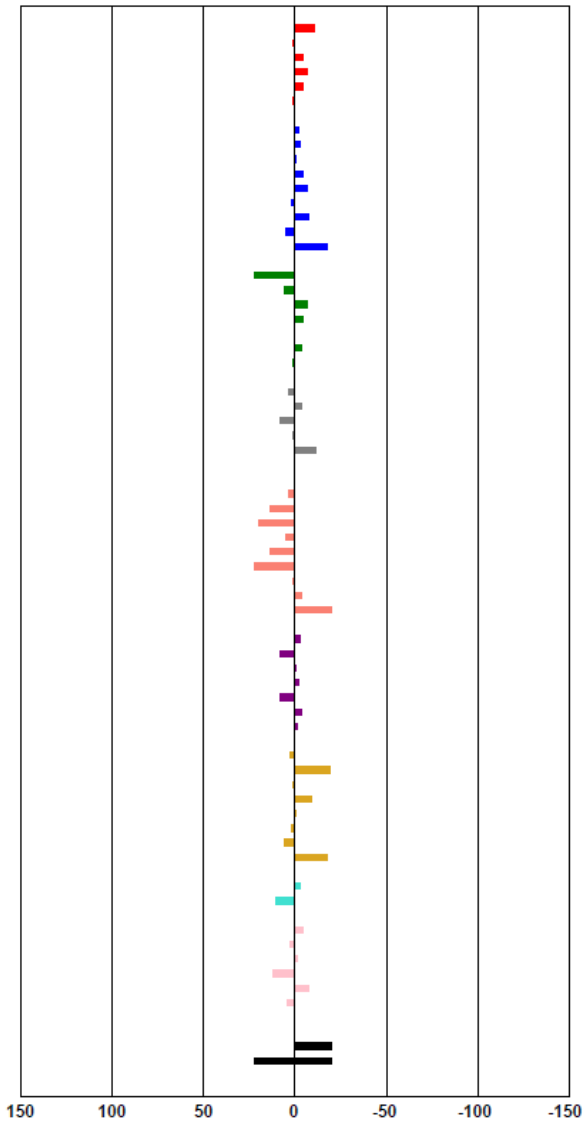
Developmental Therapeutics Program

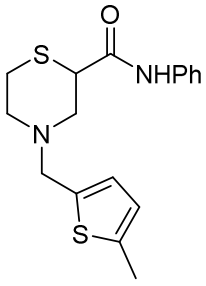
One Dose Mean Graph

NSC: D-801073 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	78.12
HL-60(TB)	89.69
K-562	84.19
MOLT-4	82.30
RPMI-8226	84.63
SR	89.93
Non-Small Cell Lung Cancer	
A549/ATCC	86.87
EKVX	85.89
HOP-62	87.96
HOP-92	84.40
NCI-H226	82.39
NCI-H23	90.51
NCI-H322M	81.63
NCI-H460	93.93
NCI-H522	71.48
Colon Cancer	
COLO 205	111.19
HCC-2998	94.18
HCT-116	82.28
HCT-15	84.46
HT29	88.98
KM12	85.05
SW-620	89.77
CNS Cancer	
SF-268	91.91
SF-295	85.04
SF-539	96.99
SNB-19	90.09
SNB-75	77.10
U251	89.37
Melanoma	
LOX IMVI	92.32
MALME-3M	102.24
M14	108.39
MDA-MB-435	93.74
SK-MEL-2	102.33
SK-MEL-28	110.88
SK-MEL-5	89.75
UACC-257	85.24
UACC-62	69.21
Ovarian Cancer	
IGROV1	86.03
OVCAR-3	97.22
OVCAR-4	88.69
OVCAR-5	87.01
OVCAR-8	97.21
NCI/ADR-RES	85.58
SK-OV-3	87.62
Renal Cancer	
786-0	91.23
A498	69.89
ACHN	89.62
CAKI-1	80.04
RXF 393	88.38
SN12C	90.66
TK-10	94.42
UO-31	71.51
Prostate Cancer	
PC-3	85.81
DU-145	99.20
Breast Cancer	
MCF7	84.62
MDA-MB-231/ATCC	91.45
HS 578T	87.66
BT-549	101.05
T-47D	80.98
MDA-MB-468	93.13
Mean	88.72
Delta	19.51
Range	41.98

Mean Growth Percent - Growth Percent





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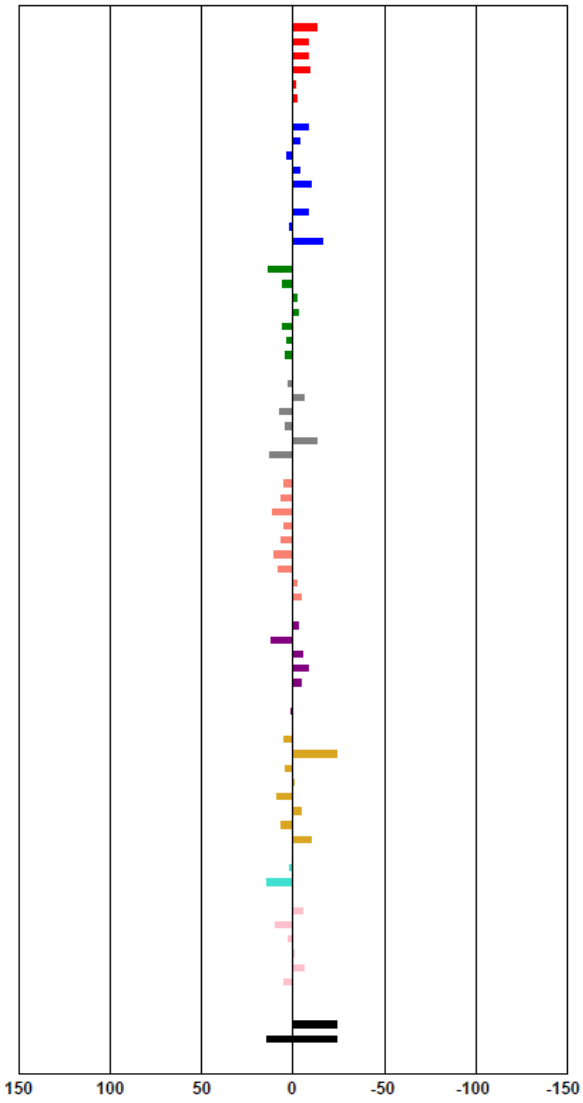
Developmental Therapeutics Program

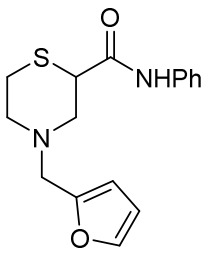
One Dose Mean Graph

NSC: D-801074 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	79.07
HL-60(TB)	83.73
K-562	83.50
MOLT-4	83.01
RPMI-8226	90.58
SR	89.87
Non-Small Cell Lung Cancer	
A549/ATCC	83.19
EKVX	87.80
HOP-62	94.91
HOP-92	87.95
NCI-H226	82.25
NCI-H23	91.76
NCI-H322M	83.33
NCI-H460	93.44
NCI-H522	75.39
Colon Cancer	
COLO 205	104.93
HCC-2998	97.62
HCT-116	89.93
HCT-15	88.73
HT29	97.28
KM12	95.16
SW-620	95.70
CNS Cancer	
SF-268	94.13
SF-295	85.99
SF-539	98.71
SNB-19	95.60
SNB-75	79.05
U251	104.17
Melanoma	
LOX IMVI	96.84
MALME-3M	98.63
M14	102.65
MDA-MB-435	96.61
SK-MEL-2	98.59
SK-MEL-28	102.03
SK-MEL-5	100.11
UACC-257	89.43
UACC-62	87.38
Ovarian Cancer	
IGROV1	88.57
OVCAR-3	103.75
OVCAR-4	86.55
OVCAR-5	83.18
OVCAR-8	87.41
NCI/ADR-RES	92.42
SK-OV-3	93.13
Renal Cancer	
786-0	96.90
A498	68.24
ACHN	96.32
CAKI-1	91.43
RXF 393	100.37
SN12C	87.39
TK-10	97.99
UO-31	82.30
Prostate Cancer	
PC-3	93.45
DU-145	105.85
Breast Cancer	
MCF7	86.39
MDA-MB-231/ATCC	101.36
HS 578T	94.56
BT-549	90.98
T-47D	86.07
MDA-MB-468	96.41
Mean	91.67
Delta	23.43
Range	37.61

Mean Growth Percent - Growth Percent





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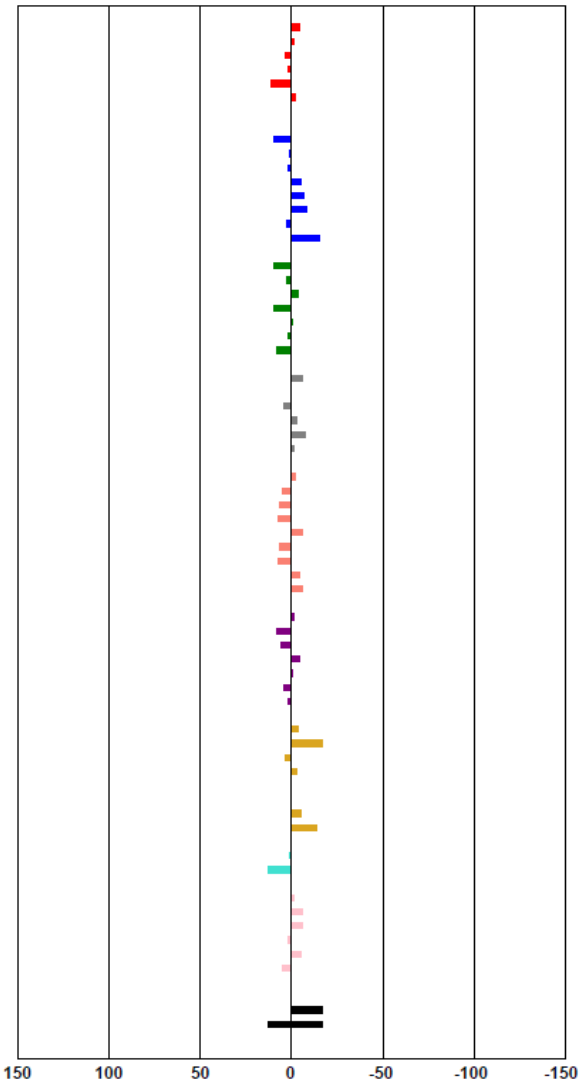
Developmental Therapeutics Program

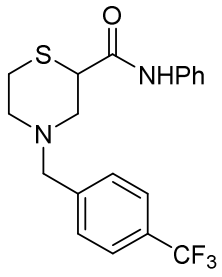
One Dose Mean Graph

NSC: D-801067 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	95.30
HL-60(TB)	98.55
K-562	103.22
MOLT-4	101.95
RPMI-8226	110.98
SR	98.16
Non-Small Cell Lung Cancer	
A549/ATCC	99.76
EKVX	109.74
HOP-62	100.67
HOP-92	101.58
NCI-H226	95.00
NCI-H23	93.14
NCI-H322M	91.20
NCI-H460	102.66
NCI-H522	84.18
Colon Cancer	
COLO 205	109.52
HCC-2998	102.35
HCT-116	96.00
HCT-15	109.15
HT29	99.43
KM12	101.80
SW-620	107.58
CNS Cancer	
SF-268	93.66
SF-295	100.01
SF-539	103.77
SNB-19	97.29
SNB-75	92.16
U251	98.80
Melanoma	
LOX IMVI	97.97
MALME-3M	104.91
M14	106.24
MDA-MB-435	107.30
SK-MEL-2	93.84
SK-MEL-28	106.66
SK-MEL-5	107.39
UACC-257	95.19
UACC-62	93.92
Ovarian Cancer	
IGROV1	98.63
OVCAR-3	107.90
OVCAR-4	105.97
OVCAR-5	95.78
OVCAR-8	99.41
NCI/ADR-RES	103.81
SK-OV-3	101.62
Renal Cancer	
786-0	96.59
A498	83.02
ACHN	103.03
CAKI-1	96.85
RXF 393	100.06
SN12C	99.87
TK-10	94.46
UO-31	86.01
Prostate Cancer	
PC-3	101.01
DU-145	112.59
Breast Cancer	
MCF7	98.89
MDA-MB-231/ATCC	93.78
HS 578T	93.62
BT-549	101.90
T-47D	94.75
MDA-MB-468	104.47
Mean	99.75
Delta	16.73
Range	29.57

Mean Growth Percent - Growth Percent





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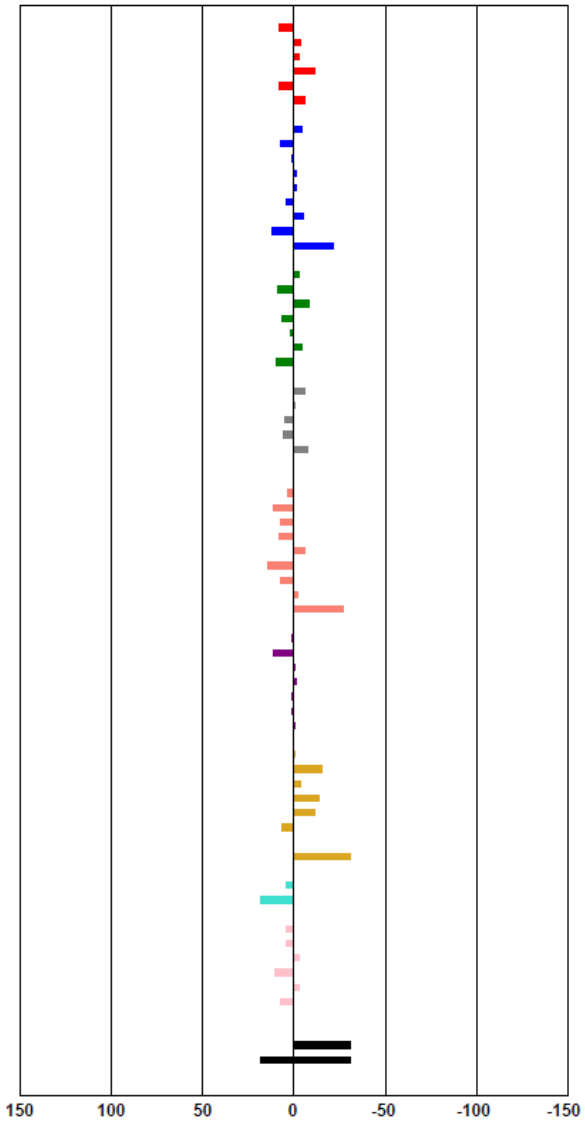
Developmental Therapeutics Program

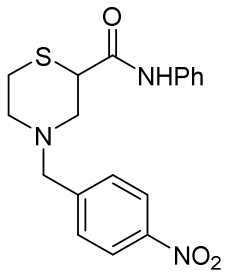
One Dose Mean Graph

NSC: D-801068 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	99.82
HL-60(TB)	88.30
K-562	89.09
MOLT-4	80.52
RPMI-8226	99.88
SR	85.97
Non-Small Cell Lung Cancer	
A549/ATCC	87.19
EKVX	99.45
HOP-62	92.83
HOP-92	90.43
NCI-H226	90.81
NCI-H23	96.33
NCI-H322M	86.80
NCI-H460	103.83
NCI-H522	70.61
Colon Cancer	
COLO 205	89.08
HCC-2998	100.55
HCT-116	83.36
HCT-15	98.70
HT29	93.68
KM12	87.44
SW-620	101.43
CNS Cancer	
SF-268	86.00
SF-295	91.36
SF-539	96.96
SNB-19	97.43
SNB-75	84.03
U251	92.32
Melanoma	
LOX IMVI	94.96
MALME-3M	103.44
M14	99.27
MDA-MB-435	99.71
SK-MEL-2	86.15
SK-MEL-28	106.53
SK-MEL-5	99.21
UACC-257	90.21
UACC-62	64.65
Ovarian Cancer	
IGROV1	93.08
OVCAR-3	102.72
OVCAR-4	91.37
OVCAR-5	90.39
OVCAR-8	92.57
NCI/ADR-RES	92.74
SK-OV-3	91.02
Renal Cancer	
786-0	91.11
A498	76.75
ACHN	88.28
CAKI-1	78.22
RXF 393	80.24
SN12C	98.55
TK-10	92.26
UO-31	61.18
Prostate Cancer	
PC-3	95.91
DU-145	110.07
Breast Cancer	
MCF7	96.33
MDA-MB-231/ATCC	96.07
HS 578T	89.29
BT-549	102.10
T-47D	89.13
MDA-MB-468	99.10
Mean	91.78
Delta	30.60
Range	48.89

Mean Growth Percent - Growth Percent





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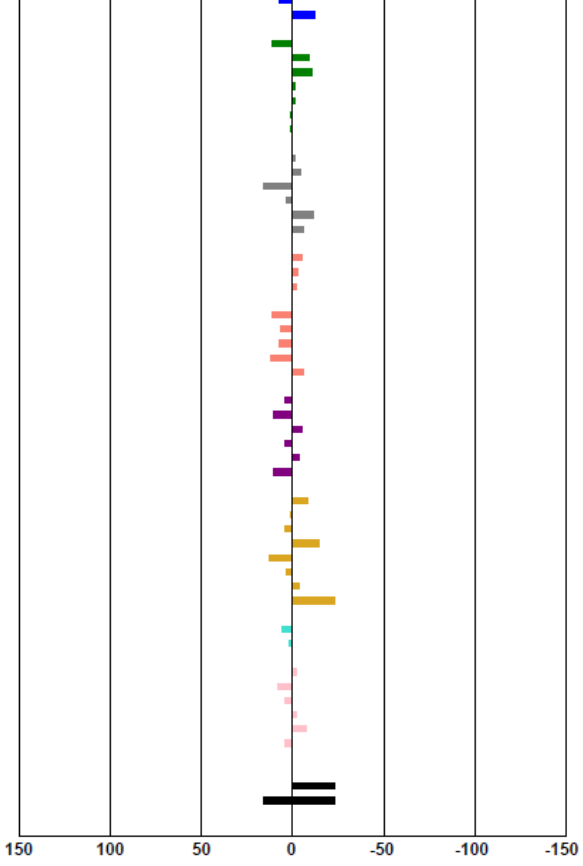
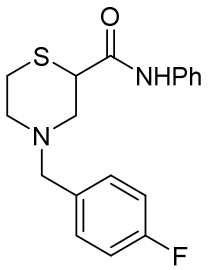
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-798970 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 26, 2017
Experiment ID: 1706OS27		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	91.48
HL-60(TB)	95.26
MOLT-4	98.06
RPMI-8226	97.90
SR	99.06
Non-Small Cell Lung Cancer	
A549/ATCC	104.16
EKVX	95.28
HOP-62	97.73
HOP-92	106.94
NCI-H226	97.12
NCI-H23	90.07
NCI-H322M	86.52
NCI-H460	104.46
NCI-H522	85.52
Colon Cancer	
COLO 205	108.37
HCC-2998	88.71
HCT-116	87.09
HCT-15	96.48
HT29	96.00
KM12	98.56
SW-620	98.71
CNS Cancer	
SF-268	96.23
SF-295	92.99
SF-539	113.45
SNB-19	101.10
SNB-75	85.86
U251	91.67
Melanoma	
LOX IMVI	92.08
MALME-3M	94.40
M14	95.27
MDA-MB-435	97.88
SK-MEL-2	108.39
SK-MEL-28	104.32
SK-MEL-5	104.73
UACC-257	109.70
UACC-62	91.31
Ovarian Cancer	
IGROV1	101.63
OVCAR-3	107.92
OVCAR-4	92.15
OVCAR-5	101.43
NCI/ADR-RES	93.69
SK-OV-3	107.97
Renal Cancer	
786-0	89.16
A498	98.52
ACHN	101.56
CAKI-1	82.81
RXF 393	110.50
SN12C	100.68
TK-10	94.06
UO-31	74.64
Prostate Cancer	
PC-3	103.19
DU-145	99.09
Breast Cancer	
MCF7	95.68
MDA-MB-231/ATCC	105.36
HS 578T	101.75
BT-549	95.25
T-47D	90.39
MDA-MB-468	101.77
Mean	97.45
Delta	22.81
Range	38.81





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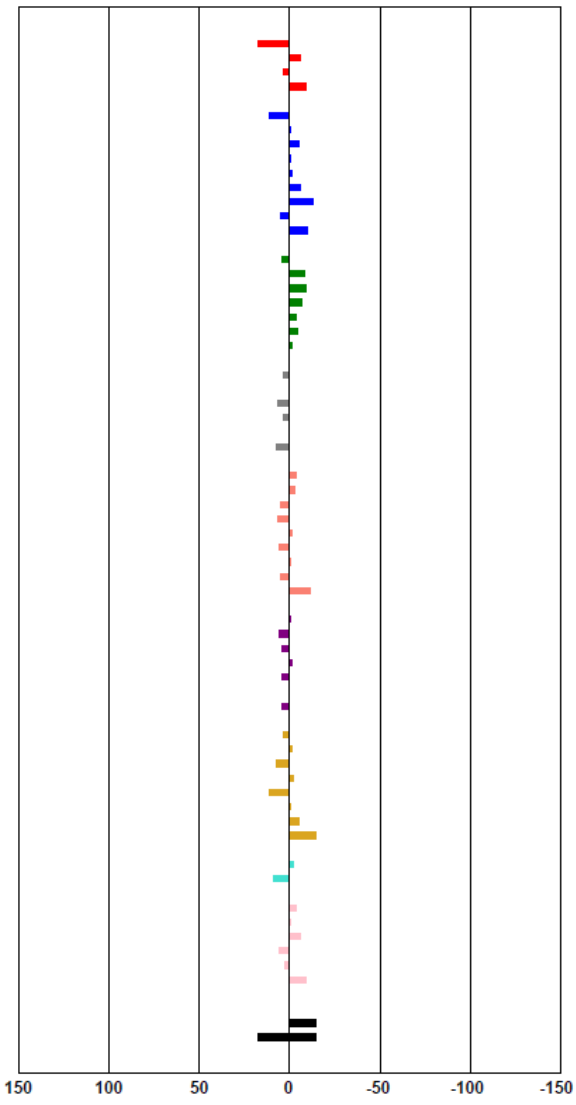
Developmental Therapeutics Program

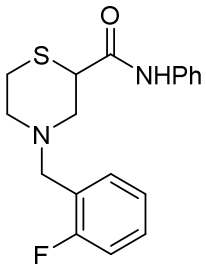
One Dose Mean Graph

NSC: D-798971 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 26, 2017
Experiment ID: 1706OS27		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	99.18
HL-60(TB)	116.44
MOLT-4	92.99
RPMI-8226	102.07
SR	89.89
Non-Small Cell Lung Cancer	
A549/ATCC	110.48
EKVX	98.32
HOP-62	94.19
HOP-92	98.40
NCI-H226	97.47
NCI-H23	92.67
NCI-H322M	86.23
NCI-H460	104.27
NCI-H522	88.99
Colon Cancer	
COLO 205	102.86
HCC-2998	90.85
HCT-116	90.10
HCT-15	92.36
HT29	95.54
KM12	94.64
SW-620	97.52
CNS Cancer	
SF-268	102.46
SF-295	99.39
SF-539	105.59
SNB-19	102.09
SNB-75	99.39
U251	106.63
Melanoma	
LOX IMVI	95.71
MALME-3M	96.54
M14	104.06
MDA-MB-435	105.54
SK-MEL-2	97.86
SK-MEL-28	104.70
SK-MEL-5	98.77
UACC-257	103.94
UACC-62	87.68
Ovarian Cancer	
IGROV1	98.67
OVCAR-3	105.07
OVCAR-4	103.36
OVCAR-5	97.37
OVCAR-8	103.20
NCI/ADR-RES	99.60
SK-OV-3	103.43
Renal Cancer	
786-0	102.61
A498	97.69
ACHN	105.97
CAKI-1	97.23
RXF 393	110.39
SN12C	98.43
TK-10	93.99
UO-31	84.40
Prostate Cancer	
PC-3	96.58
DU-145	107.64
Breast Cancer	
MCF7	95.49
MDA-MB-231/ATCC	98.62
HS 578T	93.33
BT-549	105.04
T-47D	101.45
MDA-MB-468	89.59
Mean	98.90
Delta	14.50
Range	32.04

Mean Growth Percent - Growth Percent





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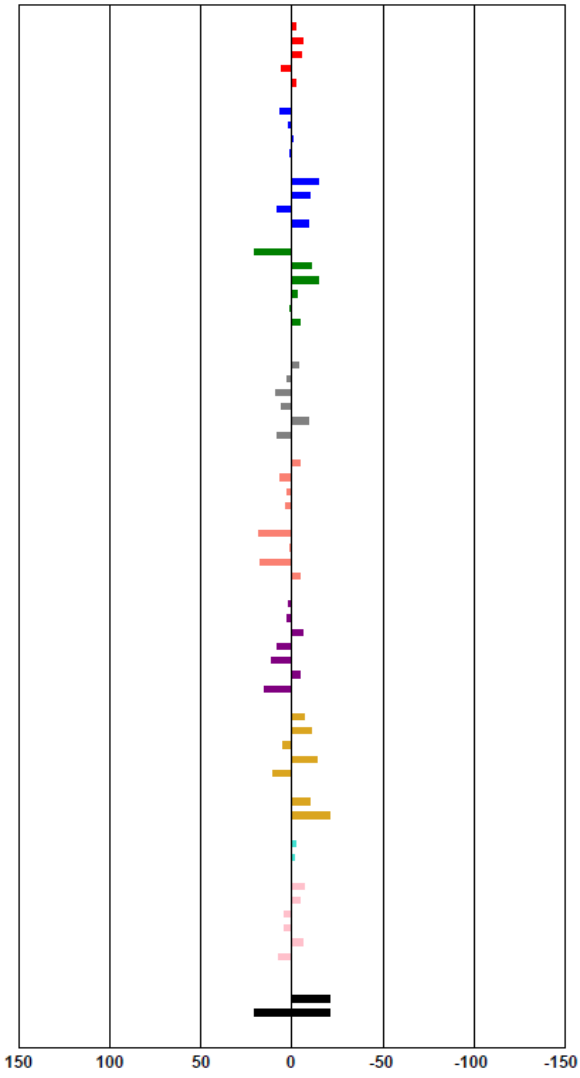
Developmental Therapeutics Program

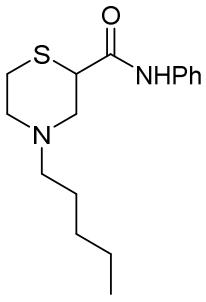
One Dose Mean Graph

NSC: D-798969 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 26, 2017
Experiment ID: 1706OS27		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	97.96
HL-60(TB)	94.34
MOLT-4	94.85
RPMI-8226	105.83
SR	98.00
Non-Small Cell Lung Cancer	
A549/ATCC	106.77
EKVX	101.67
HOP-62	99.44
HOP-92	101.16
NCI-H226	100.62
NCI-H23	85.34
NCI-H322M	89.91
NCI-H460	108.08
NCI-H522	90.76
Colon Cancer	
COLO 205	120.19
HCC-2998	89.09
HCT-116	85.34
HCT-15	97.02
HT29	101.39
KM12	95.71
SW-620	100.15
CNS Cancer	
SF-268	96.56
SF-295	102.27
SF-539	109.06
SNB-19	105.93
SNB-75	90.72
U251	108.37
Melanoma	
LOX IMVI	95.57
MALME-3M	106.78
M14	102.60
MDA-MB-435	103.22
SK-MEL-2	100.35
SK-MEL-28	117.97
SK-MEL-5	100.92
UACC-257	117.36
UACC-62	95.50
Ovarian Cancer	
IGROV1	102.08
OVCAR-3	102.36
OVCAR-4	94.02
OVCAR-5	108.07
OVCAR-8	111.07
NCI/ADR-RES	95.62
SK-OV-3	115.45
Renal Cancer	
786-0	93.41
A498	89.75
ACHN	105.34
CAKI-1	86.19
RXF 393	110.79
SN12C	100.29
TK-10	89.80
UO-31	79.58
Prostate Cancer	
PC-3	97.70
DU-145	98.80
Breast Cancer	
MCF7	93.23
MDA-MB-231/ATCC	95.72
HS 578T	104.19
BT-549	104.04
T-47D	94.10
MDA-MB-468	107.12
Mean	99.92
Delta	20.34
Range	40.61

Mean Growth Percent - Growth Percent





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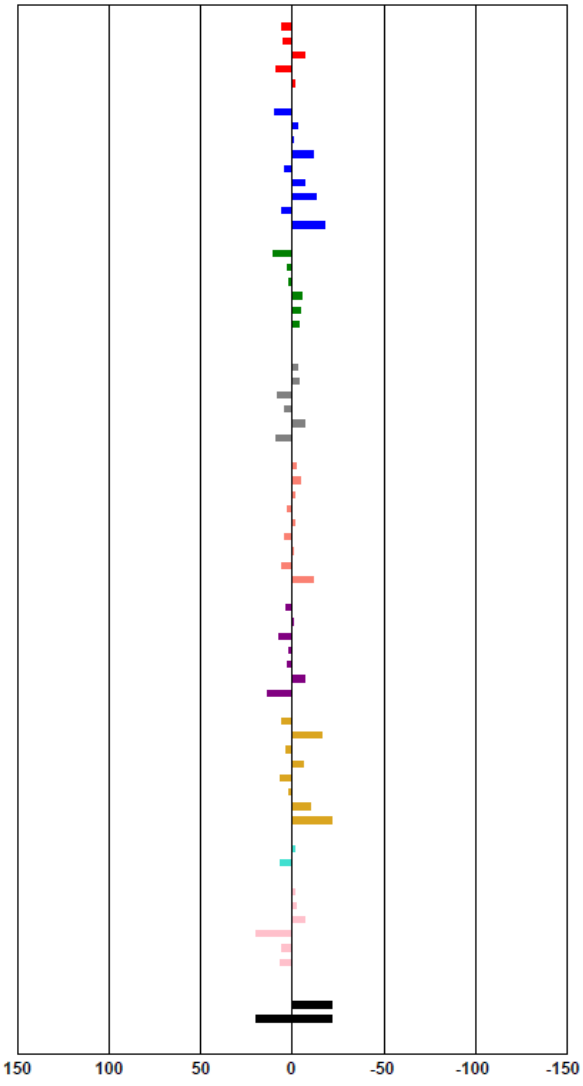
Developmental Therapeutics Program

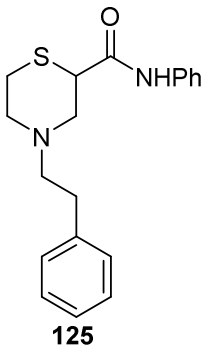
One Dose Mean Graph

NSC: D-798972 / 1	Conc: 1.00E-5 Molar	Test Date: Jun 26, 2017
Experiment ID: 1706OS27		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	103.66
HL-60(TB)	102.73
MOLT-4	91.26
RPMI-8226	106.57
SR	96.38
Non-Small Cell Lung Cancer	
A549/ATCC	107.25
EKVX	95.32
HOP-62	97.69
HOP-92	86.85
NCI-H226	102.13
NCI-H23	91.18
NCI-H322M	84.76
NCI-H460	104.03
NCI-H522	79.91
Colon Cancer	
COLO 205	108.07
HCC-2998	100.24
HCT-116	99.67
HCT-15	92.85
HT29	93.63
KM12	94.52
SW-620	98.27
CNS Cancer	
SF-268	94.74
SF-295	94.49
SF-539	106.06
SNB-19	101.86
SNB-75	91.49
U251	106.91
Melanoma	
LOX IMVI	95.90
MALME-3M	93.51
M14	96.92
MDA-MB-435	100.70
SK-MEL-2	96.79
SK-MEL-28	102.10
SK-MEL-5	97.07
UACC-257	103.71
UACC-62	86.37
Ovarian Cancer	
IGROV1	101.48
OVCAR-3	97.41
OVCAR-4	105.08
OVCAR-5	99.73
OVCAR-8	100.53
NCI/ADR-RES	91.06
SK-OV-3	111.80
Renal Cancer	
786-0	103.41
A498	81.60
ACHN	101.60
CAKI-1	92.24
RXF 393	104.29
SN12C	99.73
TK-10	88.16
UO-31	76.30
Prostate Cancer	
PC-3	96.69
DU-145	104.27
Breast Cancer	
MCF7	96.93
MDA-MB-231/ATCC	96.23
HS 578T	90.95
BT-549	117.29
T-47D	104.03
MDA-MB-468	104.53
Mean	97.81
Delta	21.51
Range	40.99

Mean Growth Percent - Growth Percent





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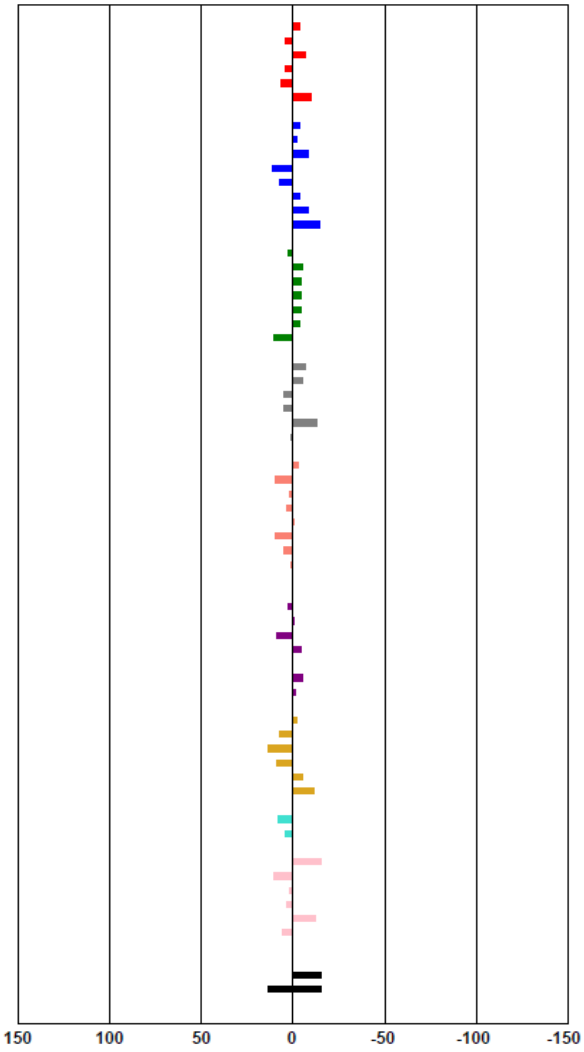
Developmental Therapeutics Program

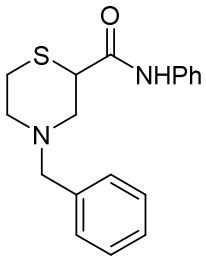
One Dose Mean Graph

NSC: D-795707 / 1	Conc: 1.00E-5 Molar	Test Date: Feb 06, 2017
Experiment ID: 1702OS52		Report Date: Jul 14, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	97.21
HL-60(TB)	104.80
K-562	93.90
MOLT-4	104.58
RPMI-8226	107.09
SR	90.59
Non-Small Cell Lung Cancer	
A549/ATCC	96.96
EKVX	98.43
HOP-62	91.95
HOP-92	111.32
NCI-H226	108.08
NCI-H23	96.87
NCI-H322M	92.38
NCI-H522	85.79
Colon Cancer	
COLO 205	102.89
HCC-2998	95.27
HCT-116	96.14
HCT-15	96.22
HT29	96.39
KM12	96.48
SW-620	111.02
CNS Cancer	
SF-268	93.85
SF-295	95.22
SF-539	105.34
SNB-19	105.07
SNB-75	87.60
U251	101.51
Melanoma	
LOX IMVI	97.34
MALME-3M	110.20
M14	102.57
MDA-MB-435	103.72
SK-MEL-2	100.00
SK-MEL-28	109.71
SK-MEL-5	105.00
UACC-257	101.43
UACC-62	100.84
Ovarian Cancer	
IGROV1	103.04
OVCAR-3	99.61
OVCAR-4	109.05
OVCAR-5	96.10
OVCAR-8	100.81
NCI/ADR-RES	95.26
SK-OV-3	99.54
Renal Cancer	
786-0	98.20
ACHN	107.98
RXF 393	113.56
SN12C	108.91
TK-10	95.24
UO-31	88.66
Prostate Cancer	
PC-3	108.15
DU-145	104.49
Breast Cancer	
MCF7	85.47
MDA-MB-231/ATCC	111.07
HS 578T	102.09
BT-549	104.02
T-47D	87.90
MDA-MB-468	106.15
Mean	100.33
Delta	14.86
Range	28.09

Mean Growth Percent - Growth Percent





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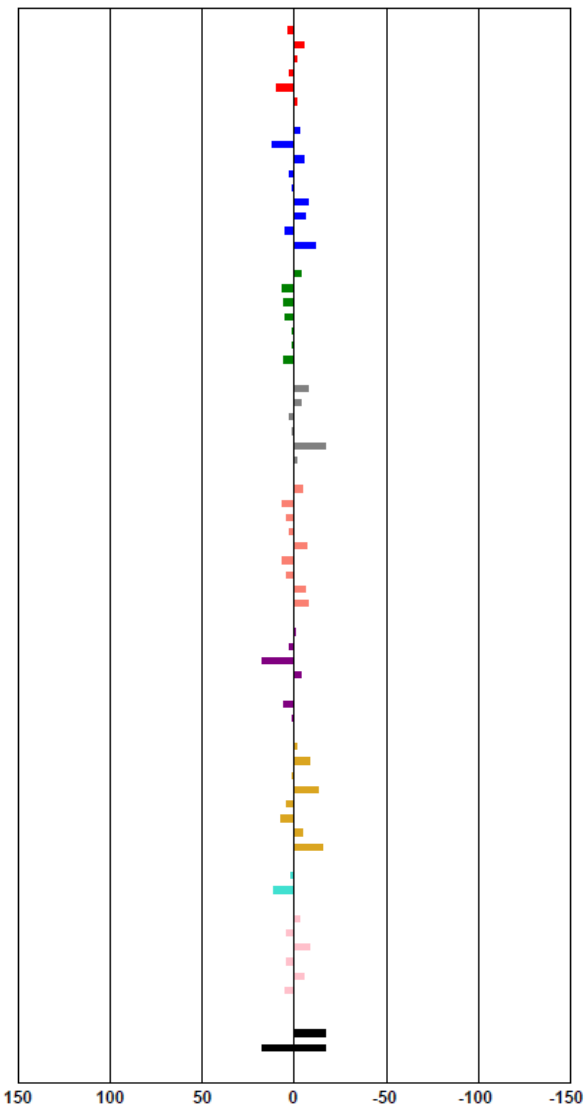
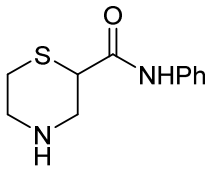
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-801069 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 10, 2017
Experiment ID: 1710OS81		Report Date: Nov 08, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	104.73
HL-60(TB)	96.20
K-562	99.72
MOLT-4	103.27
RPMI-8226	110.94
SR	99.89
Non-Small Cell Lung Cancer	
A549/ATCC	97.84
EKVX	112.98
HOP-62	96.13
HOP-92	103.41
NCI-H226	101.67
NCI-H23	93.28
NCI-H322M	94.65
NCI-H460	105.91
NCI-H522	89.34
Colon Cancer	
COLO 205	97.66
HCC-2998	107.31
HCT-116	106.87
HCT-15	106.28
HT29	102.02
KM12	101.99
SW-620	106.57
CNS Cancer	
SF-268	93.74
SF-295	97.14
SF-539	103.62
SNB-19	101.93
SNB-75	84.31
U251	100.06
Melanoma	
LOX IMVI	96.62
MALME-3M	107.70
M14	104.88
MDA-MB-435	103.23
SK-MEL-2	94.09
SK-MEL-28	107.18
SK-MEL-5	104.86
UACC-257	95.20
UACC-62	93.29
Ovarian Cancer	
IGROV1	100.48
OVCAR-3	103.22
OVCAR-4	118.15
OVCAR-5	97.57
OVCAR-8	101.44
NCI/ADR-RES	106.95
SK-OV-3	102.11
Renal Cancer	
786-0	99.90
A498	92.86
ACHN	102.04
CAKI-1	88.17
RXF 393	105.25
SN12C	108.62
TK-10	96.76
UO-31	85.89
Prostate Cancer	
PC-3	102.84
DU-145	112.11
Breast Cancer	
MCF7	97.80
MDA-MB-231/ATCC	104.91
HS 578T	92.92
BT-549	105.07
T-47D	95.54
MDA-MB-468	105.77
Mean	100.88
Delta	16.57
Range	33.84





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