1,3-Dipolar Cycloadditions of 2-Thio-3-Chloroacrylamides with Diazoalkanes.

Marie Kissane,[a] Simon E. Lawrence[a] and Anita R. Maguire[b*]

[a] *Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

[b]*Department of Chemistry & School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

**Corresponding author. Tel.: +353 21 4901693; fax: +353 21 4274097. E-mail: a.maguire@ucc.ie.*

Abstract: 2-Thio-3-chloroacrylamides undergo 1,3-dipolar cycloadditions with diazoalkanes leading to a series of novel pyrazolines and pyrazoles. The mechanistic and synthetic features of the cycloadditions to the 2-thio-3-chloroacrylamides at both the sulfide and sulfoxide levels of oxidation are rationalised on the basis of the nature of the substituents.

Introduction

The 1,3-dipolar cycloaddition is a powerful synthetic tool in organic synthesis due to the high degree of regio- and stereocontrol which accompanies the reaction.[1] The versatility of the cycloaddition is evident in the structural variety of the 4π and 2π components, including functionality such as C≡C, C=C, C≡N, C=N, C=O, and C=S with both isolated or conjugated systems.

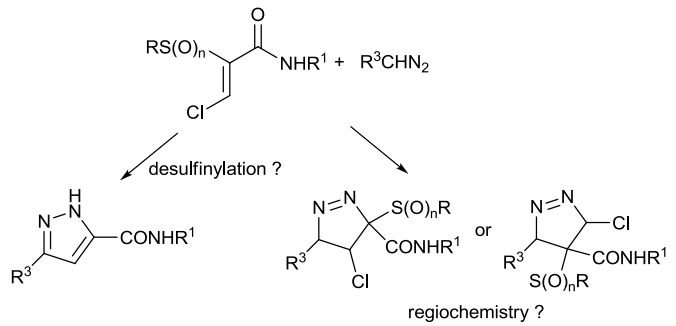
We have recently reported the highly efficient and stereoselective transformation of α-thioamides to the corresponding α-thio-β-chloroacrylamide derivatives on treatment with NCS.[2] We have extended this work to include β-bromoacrylamides, β-chloroacrylates and β-chloroacrylonitriles.[3] The α-thio-β-chloroacrylamides can be chemoselectively oxidised to either the racemic sulfoxide or sulfone very efficiently, and furthermore enantioselective oxidation to the sulfoxide derivatives of the α-thio-β-chloroacrylamides has been achieved.[4] The β-chloroacrylamides, which can have a wide variety of substituents on the basic

acrylamide framework, have synthetic potential as the 2π component in 1,3-dipolar cycloadditions.

The dipolarophilic behaviour of vinyl sulfides and in particular vinyl sulfoxides in cycloadditions with diazoalkanes has been reported, with desulfinylation of the resulting cycloadducts to afford aromatic compounds commonly observed.[5,6]

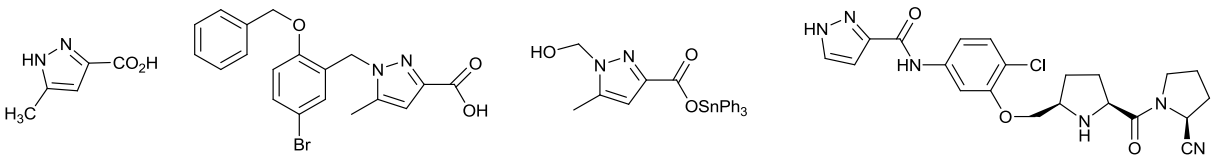
A series of reports over the past 15 years from Garcia Ruano's group discuss in detail 1,3-dipolar cycloadditions of diazomethane and diazoethane to vinyl sulfoxides of direct relevance to this work.[7-12] However, the presence of the 3-chloro substituent in the dipolarophiles in the current work potentially has a significant electronic effect on their reactivity, and more importantly, leads to chloro-substituted heterocycles, where the presence of the chloride substituent offers considerable synthetic potential and diversity *via* substitution and coupling processes.

Herein, the reactivity of a range of β-chloroacrylamides with diazoalkanes leading to a series of novel of pyrazolines and pyrazoles is discussed. While the cycloadditions have been attempted at the sulfide and sulfoxide levels of oxidation, use of the sulfoxide derivatives is clearly beneficial for stereoselective construction of dipolar cycloadducts. We were particularly interested to establish the regio- and stereochemical features of the cycloadditions, and also if the pyrazoline cycloadducts would be isolated, or if desulfinylation would occur to yield the corresponding pyrazoles (Scheme 1).



Scheme 1

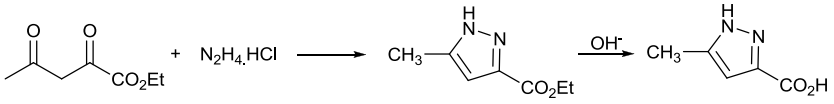
The pyrazoline and pyrazole systems are present in a number of pharmaceutically active compounds.[13] While the carboxamide adducts synthesised during this work are novel, 5-methyl-pyrazole-3-carboxylic acid **1**, the acid analogue of the pyrazoles synthesised during this work, has a history of applications in the pharmaceutical and agricultural industry.[14]



1 **2** **3** **4**

In recent years, **1** has been developed as an alternative to nicotinic acid as an agonist of the GPR109a receptor.[15-19] A key feature of the potency of **1** at the receptor was the presence of the hydrogen bond acceptor in the 3-position of the heterocycle relative to the carboxylate function. More currently, Adage and co-workers have communicated that **1** has the potential for anti-psychotic action toward both cognitive and positive symptoms of schizophrenia.[20] *N*-Aryl derivatives of **1** such as the *N*-substituted benzyl derivative **2** and the pyrazole organotin(IV) ester **3** also display desirable physicochemical properties.[21,22] Like the 3-methyl analogues, 3(*H*)-5-substituted pyrazoles have also found applications in the pharmaceutical industry. For example, researchers at Abbott laboratories in Illinois have found the pyrazole amido-derivative **4** to be a potent inhibitor of dipeptidyl peptidase IV (DPPIV);[23] inhibition of DPPIV has been reported as a potential treatment of diabetes and obesity.[24]

The pyrazole system in **1**-**3** is synthesised by cyclisation of the 1,3-diketo ester **5** with hydrazine hydrochloride to afford the 5-methyl-pyrazole-3-carboxylic ester **6**, which upon hydrolysis yields the desired acid **1** (Scheme 2).



5 **6** **1**

Scheme 2

Thus, the conventional approach involves construction of two C-N bonds (shown in red in Figure 1), whereas the current method involves construction of one C-N bond and one C-C bond (shown in blue in Figure 1) and therefore potentially allows access to a different range of pyrazole derivatives.

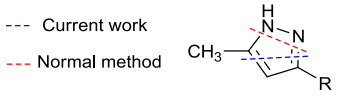


Figure 1

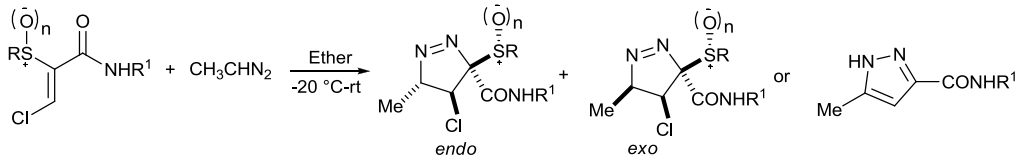
Results and Discussion

Cycloadditions with diazoethane

The dipolarophilic reactivity of the β-chloroacrylamides towards diazoethane as the 1,3-dipole was explored first as summarised in

Table 1. A solution of the β-chloroacrylamide (sulfoxide or sulfide) in ether was added dropwise to an excess of an ethereal solution of diazoethane at –20 °C. The reaction solution was allowed to return slowly to room temperature and was stirred at room temperature for 4 hours. The product was isolated either by concentration at reduced pressure or, in instances where the product precipitated out of solution as the reaction progressed, by filtration of the reaction mixture. The effect of varying the amide group was investigated by employment of a range of *N*-aryl and *N*-alkyl moieties.

Table 1 Reaction of β-Chloroacrylamides with Diazoethane



Entry	β-Cl	R	R^1	n	Product		% Yield	*endo*:*exo*[a]
					Pyrazoline	Pyrazole		
1	**7**	Bn	4-F-C_6H_4	1	**32**		94[b]	1 : 0.21
2	**8**	Bn	Tol	1	**33**		84[b]	1 : 0.27
3	**9**	Bn	Me	1	**34**		43[b]	1 : 0.22
4	**10**	Bn	Bn	1	**35**		77[b]	1 : 0.33
5	**11**	Bn	*n*-Bu	1	**36**		33[b]	1 : 0.11

6	**12**	Bn	H	1	**37**		75[b]	1 : 0.20
7	**13**	Ph	4-F-C_6H_4	1		**38**	49[c]	-
8	**14**	Ph	Bn	1		**39**	58[b]	-
9	**15**	Ph	Me	1		**40**	71[d]	-
10	**16**	Ph	Tol	1		**41**	67[b]	-
11	**17**	Ph	*n*-Bu	1		**42**	27[c]	-
12	**18**	Ph	Ph	1		**43**	64[c]	-
13	**19**	Bn	4-F-C_6H_4	0	**44**		74[b]	1 : 0.08
14	**20**	Bn	Tol	0	**45**		68[b]	1 : 0.04
15	**21**	Bn	n-Bu	0	**46**		42[d]	1 : 0.10[e]
16	**22**	Ph	4-F-C_6H_4	0	**47**		75[d]	1 : 0.20[f]
17	**23**	Ph	Bn	0	**48**		80[d]	1 : 0.22[g]
18	**24**	Ph	Tol	0	**49**		46[c]	1 : 0[h]
19	**25**	Ph	Me	0	**50**		47[d]	1 : 0.10[i]

a) *endo*/*exo* ratio of the pyrazoliones as determined by ^{1}H NMR spectroscopy.

b) Yield after filtration of the reaction mixture.

c) Isolated yield after chromatography.

d) Isolated yield after recrystallisation.

e) Crude ratio was 1 : 0.16.

f) Crude ratio was approximately 1 : 0.28.

g) Crude ratio was 1 : 0.27.

h) Crude ratio was 1 : 0.27.

i) Crude ratio was 1 : 0.30.

In cycloadditions of α-benzylsulfinyl-β-chloroacrylamides (entries 1-6, Table 1), α-benzylthio-β-chloroacrylamides (entries 13-15, Table 1) and α-benzenethio-β-chloroacrylamides with diazoethane (entries 16-19,

Table 1), a mixture of two diastereomeric pyrazoline cycloadducts was isolated in each instance, while pyrazoles were obtained from the reaction of α-benzenesulfinyl-β-chloroacrylamides with diazoethane (entries 7-12,

Table 1). The diastereomeric pyrazolines **32–37** isolated from the cycloadditions with α-benzylsulfinyl-β-chloroacrylamides were isolated by filtration of the reaction mixture as white solids in moderate to excellent yields (33–94%), and were found to be pure by ^{1}H and ^{13}C NMR spectroscopy in all cases. The lower yields were attributed to the greater solubility of some of the adducts; this was confirmed by NMR analysis of the mother liquors. Although the diastereomeric mixture of the cycloadducts **32a** and **32b** was almost identical when the reaction mixture was concentrated at reduced pressure (1 : 0.22) and when the reaction mixture was filtered (1 : 0.21),[25] the ratio may not reflect the kinetic ratio in some cases, as one of the two diastereomers may be more soluble in ether and remain in solution. In cycloadditions with the thio-β-chloroacrylamides, pyrazolines **44** and **45** (entries 13 & 14,

Table 1) were isolated by filtration of the reaction mixture in 68-74% yield, while pyrazolines **46–50** (entries 15–19,

Table 1) were isolated by concentration of the reaction mixture at reduced pressure, and further purification by recrystallisation or chromatography on neutral alumina was necessary to afford the pure pyrazolines in yields of 42–80%. The amount of the minor diastereomer present in the mixture decreased after purification by crystallisation for the pyrazolines **46**, **48** and **50**, while in the purification of the pyrazoline **49** by chromatography on alumina, the minor diastereomer was not recovered from the column. In reactions of diazoethane with α-benzenesulfinyl-β-chloroacrylamides, the pyrazole **39** (entry 8,

Table 1) was isolated in 58% yield by filtration of the reaction mixture and no further purification was necessary, while all other pyrazoles were isolated by concentration of the reaction mixture and were purified by chromatography on silica gel or recrystallisation to yield the pyrazoles **38, 40–43** in oderate to good yields (27–71%) (entries 7, 9–12,

Table 1).

While the *N*-aryl pyrazolines derived from α-benzylsulfinyl-β-chloroacrylamides proved stable and were stored in the freezer for long periods without apparent deterioration, decomposition occurred readily over a period of approximately 2 hours at room temperature

for the *N*-alkyl and *N*-benzyl substituted pyrazolines **34**, **35** and **36**. The *N*-methyl substituted cycloadducts **34a** and **34b** decomposed to a complex mixture which contained the pyrazole **40** (Scheme 3), confirmed by the agreement of the ^{1}H NMR spectroscopic data with that of a pure sample of **40** which was independently synthesised. The mechanism of this decomposition will be discussed later. The *N*-benzyl and *N*-*n*-butyl substituted pyrazolines were also found to undergo decomposition at room temperature over approximately 2 hours to a mixture of unidentifiable products.

34 **40**

Scheme 3

The cycloadditions were found to proceed with complete regiocontrol, with the carbon atom of diazoethane attacking the β-carbon of the β-chloroacrylamide. Cycloadditions of diazoalkanes to alkenes with electron-withdrawing conjugating groups attached are dipole-HOMO controlled, and the most favourable direction of combination is then that in which the two atoms with the largest orbital coefficients interact, leading to the observed regiochemistry (Figure 2).[26,27]

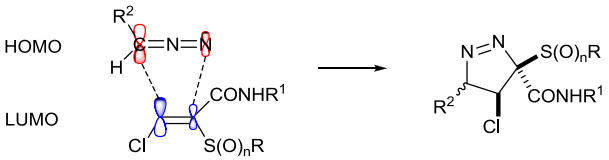


Figure 2

The α-benzylsulfinyl-β-chloroacrylamides are conformationally constrained due to the intramolecular hydrogen-bond between the amide proton and sulfoxide, adopting the s-*cis* conformation. In each of the reactions, just two diastereomers of each of the cycloadducts are observed. Complete diastereofacial control from the sulfoxide is envisaged, with the favoured

approach of diazoethane to the β-chloroacrylamides avoiding steric interactions with the benzyl group which blocks the approach of the dipole from above (Figure 3).

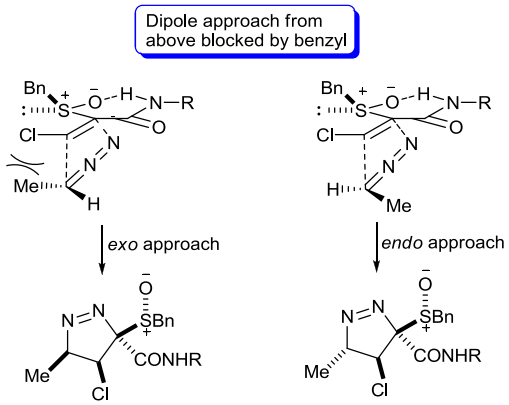
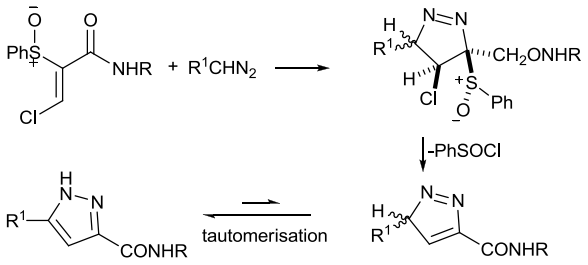


Figure 3

When approaching from the lower face, two modes of diazoethane attack (*endo* and *exo*) are possible as depicted in Figure 3, both with very different steric requirements; *endo* attack leads to the *cis*-arrangement of the methyl group of diazoethane with respect to the carbonyl of the β-chloroacrylamide, while the analogous *trans*-arrangement results from *exo* attack.[11] The *endo* approach is envisaged to be preferred due to the less favourable steric interaction between the methyl and chloro substituents in the transition state for the *exo* cycloaddition, and this was supported by NOE experiments on the diastereomers **33a** and **33b**. The formation of two diastereomers at the sulfide level of oxidation derived from *endo* and *exo* approach of diazoethane supports the proposal of complete diastereofacial control in the sulfoxide derivatives, again with *endo* and *exo* approach.

In instances where the pyrazole is isolated directly from the cycloaddition (entries 7–12,

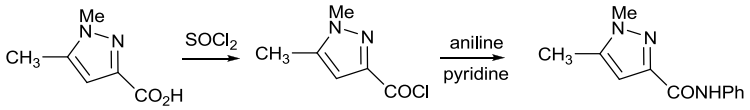
Table 1), the proposed mechanism involves the initial formation of the pyrazoline cycloadducts, which are unstable and readily eliminate the elements of PhSOCl to yield the pyrazoline lacking the sulfur moiety (Scheme 4).



Scheme 4

X-Ray crystallographic analysis on the trimethylsilyldiazomethane derived pyrazole **51** confirmed its regiochemistry in the solid state as the 3-carboxamido substituted pyrazole (see later). The regiochemistry of the pyrazoles **40–43** was assigned by analogy.

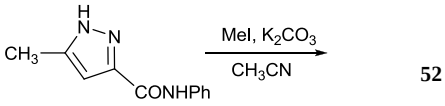
The effectiveness of the *N*-methyl pyrazole **52** in inhibiting the growth of *Rhizoctonia solani* and for the control of root rot disease caused by that organism in cotton seedlings has been assessed previously.[28] The reported synthesis of **52** involved treatment of 1,5-dimethylpyrazole-3-carboxylic acid **53** with thionyl chloride to afford the corresponding acid chloride, and subsequent reaction with aniline in pyridine yielded **52** (Scheme 5).



53 **52**

Scheme 5

The pyrazole **43** prepared during this work was conveniently transformed to **52** by a simple methylation reaction (Scheme 6). The melting point and ^{1}H NMR spectroscopic data was in agreement with the reported data, specificially supporting the tautomeric assignment (mp this work, 135–137 °C; mp 3-carboxamido pyrazole, 142–144 °C; mp 5-carboxamido pyrazole, 98–99 °C).[28]

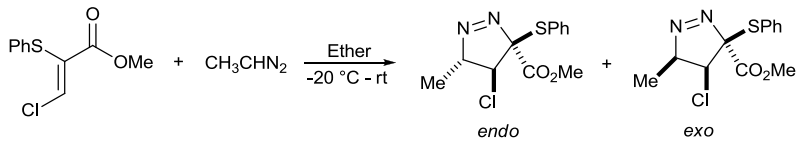


43 **52**

Scheme 6

Reaction of β-chloroacrylate 54 with diazoethane.

The effect of replacing the amide moiety of the β-chloroacrylamides with the ester functionality on the 1,3-dipolar cycloaddition with diazoethane was also investigated. The β-chloroacrylate **54** was treated with an excess of an ethereal solution of diazoethane under identical conditions to those used for the β-chloroacrylamides, and following stirring at room temperature for 6 hours the reaction mixture was concentrated to give a 1 : 0.23 mixture of the pyrazoline diastereomers **55a** and **55b** (Scheme 7). After purification by chromatography on a short column (10 cm) of neutral alumina, only the major diastereomer **55a** was recovered in 48% yield. Even on neutral alumina, decomposition of the pyrazoline diastereomer **55b** appears to have occurred, in contrast to the results for the amide series above.



54 crude ratio 1 : 0.23

55a **55b**

(isolated yield 48%)

Scheme 7

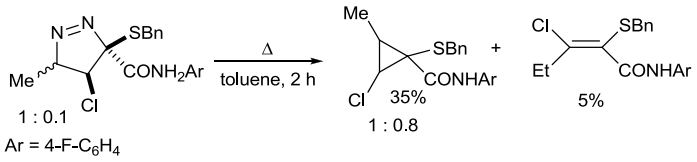
Thus, the reactivity of the β-chloroacrylates with diazoethane is very similar to that of the β-chloroacrylamides.

Decomposition of pyrazoline cycloadducts.

The decomposition of pyrazolines by photochemical or thermal means has been reported as a very efficient method for the preparation of cyclopropanes.[7,29,30] The decomposition is usually achieved photochemically as the thermally-induced process leads to lower stereoselectivity and smaller amounts of cyclopropanes.[31-33] Although the thermal extrusion of nitrogen mainly gives alkenes, there have been a few examples reported in the

literature in which cyclopropanes are the main products from the thermal process.[7,34,35] As there was literature precedent for the thermolysis of pyrazolines to afford cyclopropanes, it was decided to explore the thermal decomposition of a pyrazoline synthesised during the current work to determine if the cyclopropane would be the major product isolated.

As the benzylsulfinyl substituted pyrazolines were envisaged to readily undergo desulfinylation (although this was not attempted),[7] the thermally-induced decomposition of the benzylthio substituted cycloadduct **44** (1 : 0.1 mixture of diastereomers) was attempted by heating at reflux in toluene. The disappearance of the pyrazoline **44** was monitored by TLC analysis, with no evidence for the presence of **44** after heating for 2 hours. Following concentration of the reaction mixture and purification by chromatography on silica gel, the cyclopropane **56** was the major product, isolated in 35% yield and as a 1 : 0.8 mixture of diastereomers. A minor amount of the olefinic product **57** also formed (Scheme 8).



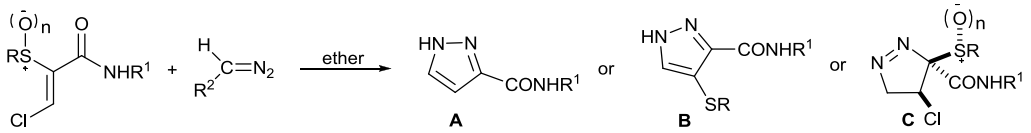
44 **56** **57**

Scheme 8

Cycloadditions with trimethylsilyldiazomethane and diazomethane.

The dipolarophilic behaviour of a range of the β-chloroacrylamides towards trimethylsilyldiazomethane and diazomethane was explored next, with the results summarised in Table 2.

Table 2 Reaction of β-Chloroacrylamides with Trimethylsilyldiazomethane and Diazomethane



Entry	β-Cl	R	R^1	R^2	n	Method[a]	Product			% Yield[b]
							A	B	C	
1	**8**	Bn	Tol	$SiMe_3$	1	A	**51**			54
2	**10**	Bn	Bn	$SiMe_3$	1	A	**58**			66
3	**7**	Bn	4-F-C_6H_4	$SiMe_3$	1	A	**59**			58
4	**11**	Bn	*n*-Bu	$SiMe_3$	1	A	**60**			52
5	**9**	Bn	Me	$SiMe_3$	1	A	**61**			73
6	**16**	Ph	Tol	$SiMe_3$	1	A	**51**			31
7	**14**	Ph	Bn	$SiMe_3$	1	A	**58**			25
8	**13**	Ph	4-F-C_6H_4	$SiMe_3$	1	A	**59**			16
9	**17**	Ph	*n*-Bu	$SiMe_3$	1	A	**60**			28
10	**20**	Bn	Tol	$SiMe_3$	0	B		**62**		63
11	**26**	Bn	Me	$SiMe_3$	0	B		**63**		59
12	**24**	Ph	Tol	$SiMe_3$	0	B		**64**		50
13	**25**	Ph	Me	$SiMe_3$	0	B		**65**		62
14	**7**	Bn	4-F-C_6H_4	H	1	C			**66**	69[c]
15	**9**	Bn	Bn	H	1	C			**67**	62[c]
16	**10**	Bn	Me	H	1	C			**68**	55[c]
17	**27**	*n*-Bu	Bn	H	1	C			**69**	77[c]
18	**16**	Ph	Tol	H	1	C	**51**			16
19	**14**	Ph	Bn	H	1	C	**58**			40
20	**19**	Bn	4-F-C_6H_4	H	0	C			**70**	79[d]
21	**28**	Bn	Bn	H	0	C		**71**	**72**	84[e]
22	**26**	Bn	Me	H	0	C		**63**		23[c]
23	**23**	Ph	Bn	H	0	C			**73**	91
24	**25**	Ph	Me	H	0	C		**65**		10[c]

25	**29**	*n*-Bu	Bn	H	0	C	**74**	38[c]
26	**30**	*n*-Bu	Tol	H	0	C	**75**	20[c]

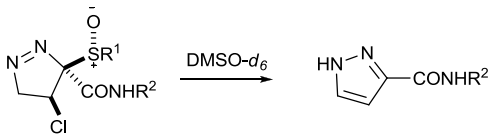
a) Method A: 5 eq. Me_3SiHN_2, ether, rt, 6h; Method B: 15 eq. Me_3SiHN_2, ether, 48h; Method C: 7 eq. CH_2N_2, –20 °C – rt, 4-6h.
b) Unless otherwise stated, isolated yield after chromatography on silica gel.
c) Isolated yield after filtration of reaction mixture.
d) Isolated yield after concentration of the reaction mixture.
e) Isolated yield of **72** following concentration of the reaction mixture. Following purification by chromatography, **71** was isolated in 18% yield.

Cycloaddition of the β-chloroacrylamides at the sulfoxide level of oxidation with trimethylsilyldiazomethane employing method A led to the isolation of the desulfinylated pyrazoles **51, 58–61** (entries 1–9, Table 2) following concentration of the reaction mixture and chromatographic purification. The pyrazoles which were synthesised from the α-benzylsulfinyl-β-chloroacrylamides were isolated in higher yields (52–66%) than the pyrazoles which were isolated from the reaction of trimethylsilyldiazomethane with the α-benzenesulfinyl-β-chloroacrylamides (16–31%). This is in contrast to the diazoethane case, and possibly indicates competing decomposition pathways for the benzenesulfinyl derivatives.

In contrast, cycloadditions between trimethylsilyldiazomethane and the β-chloroacrylamides at the sulfide level of oxidation provided a series of rearranged pyrazoles **62–65** (entries 10–13, Table 2), where the thio substituent underwent a 1,2-migration, the first time that this was observed. The sulfide derivatives were found to be much less reactive than the corresponding sulfoxides in cycloadditions with trimethylsilyldiazomethane, with much longer reaction times (48 h *vs.* 6 h) and greater amounts of trimethylsilyldiazomethane (15 eq. *vs.* 5 eq.) required. The reaction solution was concentrated to give the crude rearranged pyrazoles (which were relatively clean by ^{1}H NMR spectroscopy compared to the pyrazoles **51, 58–61** produced from the reaction of the sulfoxide derivatives with trimethylsilyldiazomethane). Following purification by chromatography on silica gel, **62, 63–65** were isolated as white solids in moderate yields of 50–63%. The 4-phenylthio pyrazoles **64** and **65** were found to be much more polar and less soluble than the 4-benzylthio pyrazoles **62** and **63**, with use of DMSO-d_6 required to record the ^{13}C NMR spectra of **64** and **65**.

Meanwhile, cycloadditions of the α-sulfinyl-β-chloroacrylamides with diazomethane using Method C afforded the pyrazolines **66–69** as single diastereomers in yields of 55–77% for the *S*-alkyl derivatives (entries 14–17, Table 2), whilst the desulfinylated pyrazoles **51** and

58 were isolated from the cycloadditions with the *S*-phenyl derivatives (entries 18 & 19, Table 2). The ^{1}H NMR spectra of the crude products were very complex and the isolated yields were poor (16–40%); some decomposition may have occurred during chromatography on the silica gel. While the ^{13}C NMR spectra of the pyrazolines **66** and **67** could be recorded in $CDCl_3$, with the less stable pyrazolines **68** and **69** the ^{13}C NMR spectra were recorded in DMSO-d_6, and analysis of the spectra indicated that the pyrazolines had decomposed to the corresponding pyrazoles **61** and **58** on dissolution in DMSO-d_6 (Scheme 9). Once the ^{13}C NMR spectra had indicated decomposition, the ^{1}H NMR spectra were re-recorded and comparison of both the ^{1}H and ^{13}C NMR spectroscopic data with those of pure samples of **61** and **58** (which had been previously synthesised independently) confirmed the identity of these decomposition products. Thus, while the sulfinyl pyrazolines were stable as solids and in $CDCl_3$, they undergo spontaneous elimination in DMSO-d_6.



R^1 = Bn, R^2 = Me	**68**	**61**
R^1 = *n*-Bu, R^2 = Bn	**69**	**58**

Scheme 9

On examining the dipolarophilic behaviour of the β-chloroacrylamides at the sulfide level of oxidation towards diazomethane, either the pyrazoline cycloadduct (as a single diastereomer) or the rearranged pyrazole were isolated as white solids depending on the nature of the substituents on the sulfide and the amide (entries 20–26, Table 2).

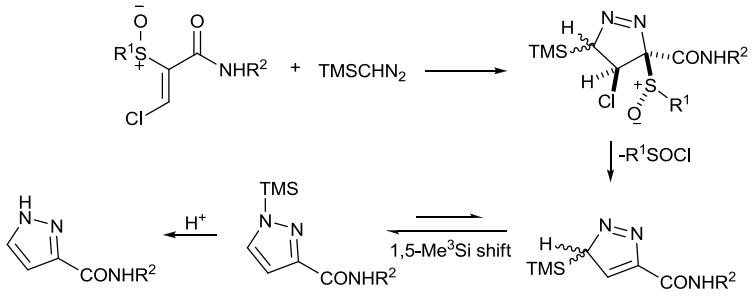
The pyrazoline cycloadducts **70** and **72** were isolated from the cycloaddition of the *N*-4-fluorophenyl- and *N*-benzyl-benzylthio derivatives **19** and **28** with diazomethane following concentration of the reaction mixture. The ^{1}H NMR spectra of the crude products were very clean. However, the *N*-benzyl substituted cycloadduct **72** proved very labile and while it could be detected in the ^{1}H NMR spectrum of the crude product, following purification by chromatography on silica gel the rearranged pyrazole **71** was isolated in just 18% yield. The rearranged pyrazole **63** was also the product isolated from the cycloaddition of the *N*-methyl-benzylthio derivative **26** with diazomethane, albeit in much lower yield than from the cycloaddition of **26** with trimethylsilyldiazomethane (23% *vs.* 59%). The ^{1}H NMR spectrum

of the crude product isolated from the diazomethane cycloaddition was much more complex than that of the crude product from the trimethylsilyldiazomethane reaction.

Reaction of the *N*-benzyl-phenylthio substituted β-chloroacrylamide **23** afforded the pyrazoline **73**, which was isolated in 91% yield (entry 23, Table 2). When the *N*-methyl-phenylthio derivative **25** was reacted with diazomethane, the rearranged pyrazole **65** was obtained (entry 24, Table 2), again in much lower yield than when **65** was isolated from the trimethylsilyldiazomethane cycloaddition (10% *cf.* 62%).

The rearranged pyrazoles **74** and **75** were isolated from the cycloaddition of the *n*-butylthio derived β-chloroacrylamides **29** and **30**, with no evidence for the presence of the pyrazoline cycloadducts in the complex ^{1}H NMR spectra of the crude products (entries 25 and 26, Table 2).

In all instances, the cycloaddition proceeds in a highly regioselective manner, with the carbon atom of the dipole attacking the β-carbon of the β-chloroacrylamide, as seen previously with diazoethane (see Figure 2). The mechanism of the desulfinylated pyrazole formation is believed to be similar to that outlined in Scheme 4 for the formation of the 5-methyl pyrazoles from the reaction of the benzenesulfinyl derivatives and diazoethane. Thus, the pyrazoline cycloadducts are initially formed, but these are unstable and spontaneous elimination of $R^1S(O)Cl$ gives the pyrazoline intermediate, which on 1,5-trimethylsilyl shift affords the *N*-trimethylsilyl pyrazole. Hydrolytic cleavage of the N-Si bond[36-40] (presumably when the crude product is purified by chromatography on silica gel) yields the final pyrazole product (Scheme 10).



Scheme 10

The regiochemistry of the cycloaddition and the tautomer of the pyrazole **51** was determined by single crystal X-ray diffraction following recrystallisation from ethyl acetate

(Figure 4). Examination of the crystal structure reveals a number of interesting features. In the solid state, the pyrazole **51** exists as the tautomer with the carboxamide group at the 3-position of the heterocycle rather than the 5-substituted pyrazole. The 5-substituted tautomer may be present in the solution state, although usually the tautomer in solution coincides with that found in the solid state.[41-43] The principal tautomer of the diazoethane derived pyrazoles was assigned by analogy.

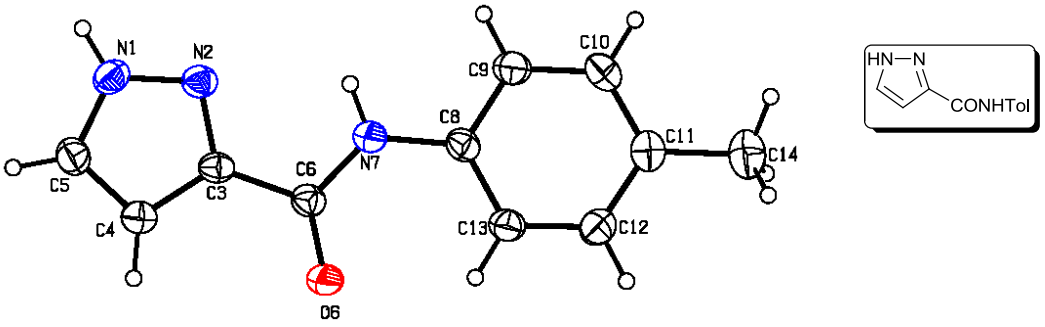


Figure 4 (Anisotropic displacement parameters are drawn at the 30% probability level)

The hydrogen-bonding network present in the pyrazole **51** is depicted in Figure 5; an intramolecular hydrogen bond exists from the amide NH to the nitrogen at the 2-position of the heterocycle with a bond length of 2.30 Å to form a 5-membered ring system, and an intermolecular hydrogen bond is present between the NH of the pyrazole and the carbonyl group with a bond length of 1.96 Å. The presence of the intramolecular hydrogen bond confers rigidity to the structure and is presumably the driving force for the formation of the 3-substituted tautomer.

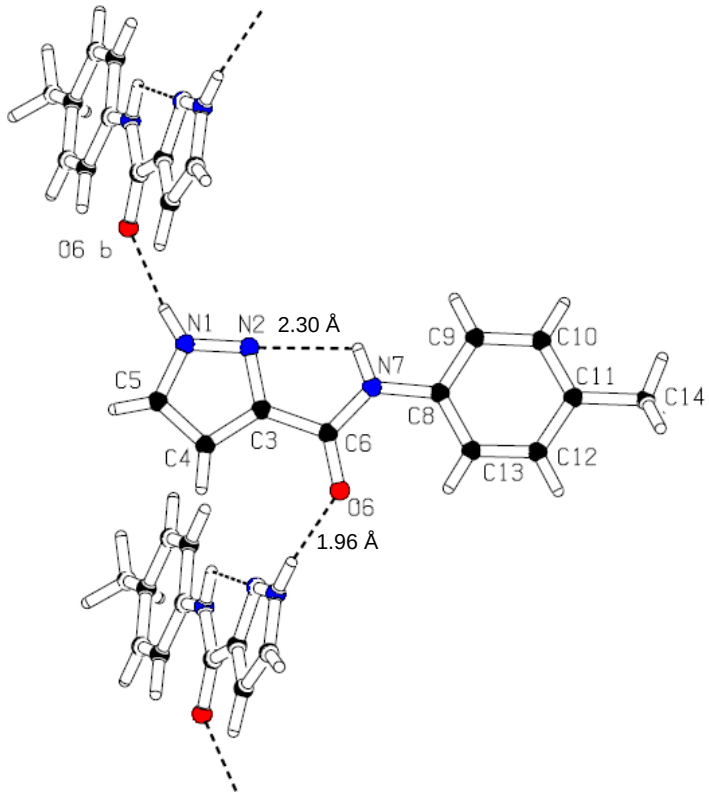
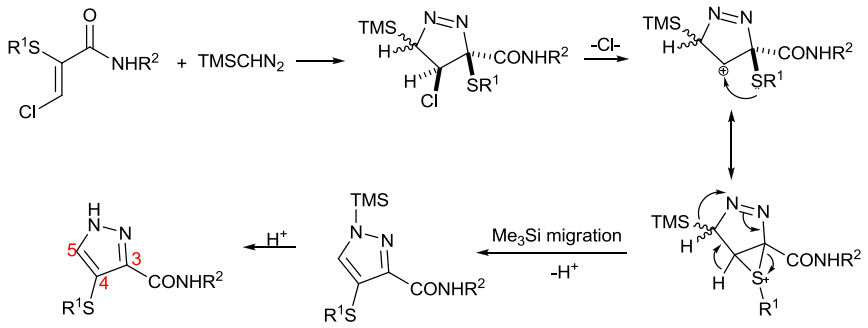


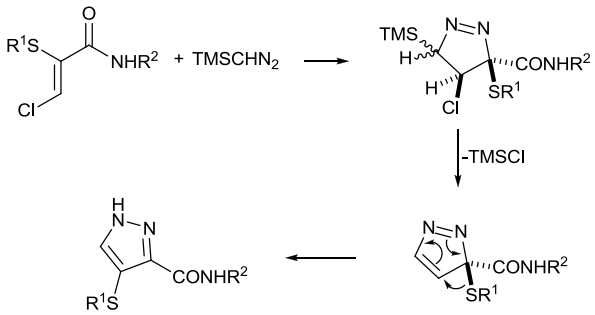
Figure 5

The mechanism of the formation of the rearranged pyrazoles **62, 63**–**65** is not fully understood, but the following is postulated: regioselective cycloaddition of trimethylsilyldiazomethane with the sulfides leads to the pyrazoline cycloadducts initially, and loss of chloride generates a carbocation, stabilised by the adjacent sulfur and silicon groups. Subsequent trimethylsilyl migration in the resulting sulfonium ion intermediate with concomitant aromatisation affords the *N*-trimethylsilyl rearranged pyrazole; hydrolytic cleavage of the N-Si bond would yield the final rearranged pyrazole product (Scheme 11). The observation that the same reaction pathway does not occur in the sulfoxide derivatives supports the proposed mechanism as the sulfinyl group would be much less nucleophilic than the sulfide. Furthermore, the efficiency of the analogous process in the diazomethane cycloadditions is much lower, presumably due to the absence of the stabilising trimethylsilyl group in the key carbocationic intermediate.



Scheme 11

An alternative pathway, involving loss of trimethylsilylchloride followed by sigmatropic rearrangement, is illustrated in Scheme 12.



Scheme 12

The regiochemistry of the cycloaddition and the principal tautomer was determined by single crystal X-ray diffraction of **63** after recrystallisation from ethyl acetate (Figure 6).

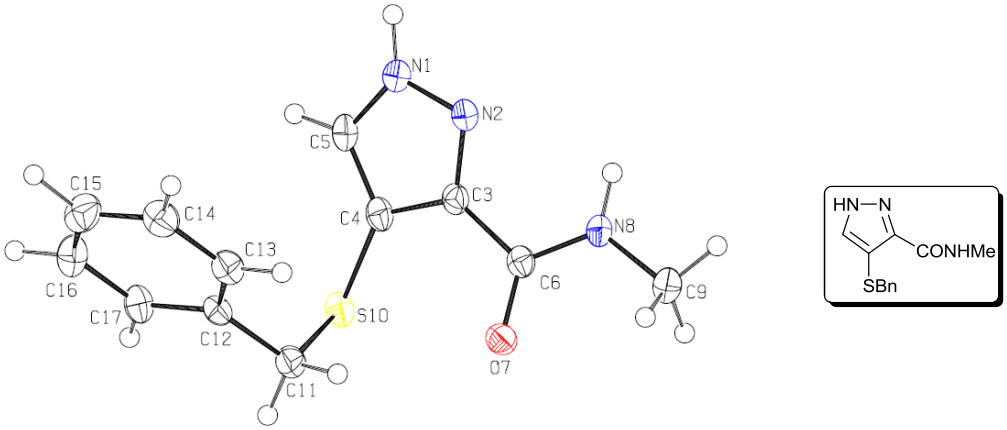
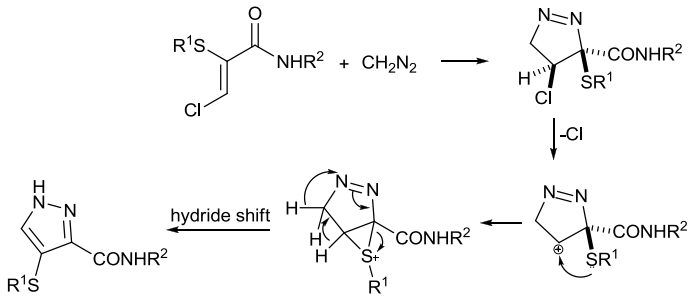


Figure 6 (Anisotropic displacement parameters are drawn at the 30% probability level)

The mechanism for the formation of the pyrazoles **51** and **58** is believed to be similar to that outlined in Scheme 4 for the preparation of the 5-methyl pyrazoles from the cycloaddition of the phenylsulfinyl derivatives and diazoethane. Thus, the pyrazoline cycloadduct is formed regioselectively but is unstable and elimination of PhSOCl yields the pyrazoline intermediate lacking the sulfur function. Subsequent tautomerisation yields the pyrazole.

The proposed mechanism for the formation of the rearranged pyrazoles from cycloadditions with diazomethane is similar to that outlined earlier for the trimethylsilyldiazomethane cycloadditions. Thus, cycloaddition of diazomethane with the sulfide derivatives leads initially to the pyrazoline cycloadducts, and this is followed by chloride elimination. Subsequent hydride shift in the resulting sulfonium ion intermediate along with concomitant aromatisation yields the rearranged pyrazole (Scheme 13).



Scheme 13

Contrasting the cycloadditions of the β-chloroacrylamides at the sulfide level of oxidation with trimethylsilyldiazomethane and diazomethane in which the rearranged pyrazoles B are formed, shows that the latter leads to much more complex reaction products. There are two possible interpretations for this; firstly, the presence of the trimethylsilyl group would stabilise the carbocation formed on loss of chloride in the first step of the rearrangement process illustrated in Scheme 11, thereby enabling a cleaner process. Alternatively, as the silyl migration is envisaged to be easier than hydride migration, this may result in a cleaner product.

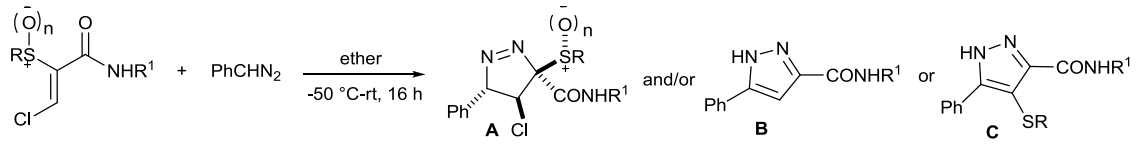
While many aspects of the reactivity of the β-chloroacrylamides with diazomethane and diazoethane are similar, there are a number of interesting differences. At the sulfoxide level of oxidation, with diazoethane the pyrazoline cycloadducts are isolated from the benzylsulfinyl derivatives, while the eliminated pyrazoles are obtained from the

benzenesulfinyl derivatives, and this pattern is retained with diazomethane. At the sulfide level of oxidation with diazoethane, the pyrazoline cycloadduct is isolated in all instances. With diazomethane, facile decomposition of these pyrazolines to the rearranged 4-thio pyrazoles is observed in most, but not all derivatives, albeit at low yields and in a complex mixture. Presumably the conformational impact of having a 5-methyl substituent slows down the analogous rearrangement process for the diazoethane derived cycloadducts. With trimethylsilyldiazomethane, the rearranged 4-thio pyrazoles were observed at the sulfide level only, but in these instances their formation was much more efficient and the reactions were cleaner. Thus, the presence of the trimethylsilyl group facilitates the rearrangement process. At the sulfoxide level of oxidation, the eliminated pyrazole was obtained for the benzylsulfinyl and benzenesulfinyl derivatives, indicating that the presence of the trimethylsilyl group also facilitates this elimination process.

Cycloadditions with phenyldiazomethane.

The dipolarophilic reactivity of the β-chloroacrylamides towards phenyldiazomethane was also investigated. Table 3 summarises the results of these experiments.

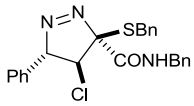
Table 3 Reaction of β-Chloroacrylamides with Phenyldiazomethane



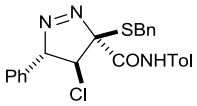
Entry	β-Cl	R	R^1	n	Product			% Yield
					A	B	C	
1	**8**	Bn	Tol	1	**76**[a]			31[d]
2	**9**	Bn	Me	1	**77**[b]			37[d]
3	**10**	Bn	Bn	1	**78**[c]			64[d]
4	**16**	Ph	Tol	1		**79**		56[e]
5	**14**	Ph	Bn	1		**80**		79[e]

6	**15**	Ph	Me	1	**81**	**82**		64[d,f]
7	**31**	*n*-Bu	Tol	1		**79**		38[d]
8	**27**	*n*-Bu	Bn	1		**80**		36[d]
9	**28**	Bn	Bn	0			**83**[g]	19[e]
10	**20**	Bn	Tol	0			**84**[h]	24[e]
11	**24**	Ph	Tol	0			**85**[i]	20[e]
12	**25**	Ph	Me	0	**86**[j]			25[d]

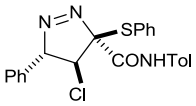
a) Decomposed to the pyrazole **79** in DMSO-d_6.
b) Decomposed to the pyrazole **82** in DMSO-d_6.
c) Decomposed to the pyrazole **80** in DMSO-d_6.
d) Isolated yield after filtration of the reaction mixture.
e) Isolated yield after chromatography on silica gel.
f) In $CDCl_3$, contained ~10% of the pyrazoline **81** and 90% of the pyrazole **82**.
g) There was evidence for the pyrazoline **87** in the ^{1}H NMR spectrum of the crude product.
h) There was evidence for the pyrazoline **88** in the ^{1}H NMR spectrum of the crude product.
i) There was evidence for the pyrazoline **89** in the ^{1}H NMR spectrum of the crude product.
j) Decomposed to the pyrazole **82** and the rearranged pyrazole **90** in DMSO-d_6 (see Scheme 14).



87



88

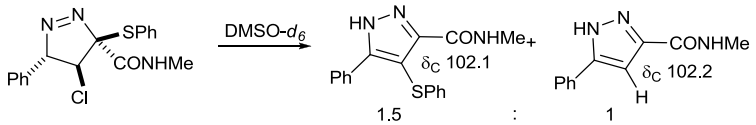


89

Cycloaddition of the benzylsulfinyl derivatives with phenyldiazomethane yielded the pyrazoline cycloadducts **76**–**78** as single diastereomers (entries 1–3, Table 3) in yields of 31–64%. A number of factors may have contributed to the low yield; to avoid the risk of explosion during its distillation,[44] phenyldiazomethane was used in its crude form which may have impacted the yield. Also, in some instances some of the product was lost to the mother liquor after filtration (confirmed by ^{1}H NMR spectroscopy in a number of samples following concentration with caution). On dissolution of the pyrazolines in DMSO-d_6, decomposition to the desulfinylated pyrazoles readily occurred. In contrast to the isolation of the pyrazolines with the benzylsulfinyl derivatives, on reaction of a range of benzenesulfinyl and *n*-butylsulfinyl derived β-chloroacrylamides with phenyldiazomethane, desulfinylation occurred to afford the pyrazoles **79**, **80** and **82** as solids (entries 4–8, Table 3), with yields of 38–79%. The *N*-methyl substituted pyrazole **82** isolated from the cycloaddition of the *S*-benzenesulfinyl-β-chloroacrylamide **15** also contained the pyrazoline **81**, evident by the appearance of two doublets in the ^{1}H NMR spectrum at δ_H 4.68 and 5.53 ppm when recorded in $CDCl_3$ (approximately 10%) and at δ_H 5.04 and 5.55 ppm when recorded in DMSO-d_6

(approximately 25%), indicating that elimination to form the pyrazole **82** is not as facile as the corresponding *N*-tolyl and *N*-benzyl derivatives **79** and **80**.

On reaction of a range of phenylthio and benzylthio β-chloroacrylamides with phenyldiazomethane, either the rearranged pyrazole (entries 9–11, Table 3) or the pyrazoline cycloadduct as a single diastereomer (entry 12, Table 3) was isolated. Following reaction of the sulfides **28**, **20** and **24** with phenyldiazomethane at room temperature for 16 hours, the reaction mixtures were concentrated to yield the crude products. The presence of the pyrazolines **87**, **88** and **89** was evident in the complex ^{1}H NMR spectra of the crude products in each instance by the appearance of a doublet at δ_H 5.53–5.63 ppm, characteristic of the proton attached to the carbon at the 5-position of the ring. After purification by chromatography on silica gel, the rearranged pyrazoles **83**, **84**, and **85** were obtained as clean compounds (entries 9–11, Table 3). For the cycloaddition of the phenylthio derivative **25** with phenyldiazomethane (entry 12, Table 3), the pyrazoline **86** was isolated in 25% yield (in a pure state by ^{1}H NMR spectroscopy); the presence of **86** in the mother liquor contributed to the low isolated yield. When the ^{1}H and ^{13}C NMR spectra of **86** were recorded in DMSO-d_6, decomposition to the pyrazole **82** [confirmed by the appearance of a CH signal in the ^{13}C NMR spectrum at δ_C 102.2 ppm, characteristic of C(4)H] and the rearranged pyrazole **90** [confirmed by the appearance of a C signal in the ^{13}C NMR spectrum at δ_C 102.1 ppm, characteristic of C(4)] was observed (Scheme 14). The cycloadditions of the sulfides with phenyldiazomethane displayed similar reactivity patterns to those observed previously for the reaction of the sulfide derivatives with diazomethane. Analogous to what was seen in the previously for the reaction of the *N*-methyl benzenesulfinyl derivative with phenyldiazomethane, the ease of elimination is again less facile for the *N*-methyl phenylthio derivative, while this trend was not seen with the other diazoalkanes.



86 **90** **82**

Scheme 14

While the relative stereochemistry of the pyrazolines **76**–**78** has not been definitively confirmed, it is believed that they have the relative stereochemistry illustrated in Table 3. The

formation of a single diastereomer of the pyrazolines can be readily rationalised; as before, complete diastereofacial control is effected by the sulfinyl group, and in contrast to diazoethane, the energy differences between the transition state for the *endo* and *exo* approaches is sufficient to result in exclusive formation of the *endo*-cycloadduct, whereas with the smaller methyl group in diazoethane, both diastereomers result (Figure 3).

Spontaneous elimination of the benzenesulfinyl derivatives to yield the pyrazoles is consistent across the diazoethane, diazomethane, trimethylsilyldiazomethane and phenyldiazomethane cycloadditions, while the ease of elimination of the benzylsulfinyl group is slightly less, allowing isolation of the intermediate pyrazoline in the diazoethane, diazomethane and phenyldiazomethane cycloadditions, albeit as labile compounds in the phenyldiazomethane cycloadducts (which readily eliminated to the pyrazoles). The proposed mechanism of this reaction is similar to that proposed earlier for the diazoethane and diazomethane derived pyrazoles (Scheme 4); initial formation of the pyrazoline cycloadduct is followed by elimination of PhSOCl, and subsequent tautomerisation yields the pyrazole. The formation of the conjugated phenyl pyrazole is evidently favourable.

Overview of cycloadditions with diazoalkanes.

Figure 7 summarises the dipolarophilic behaviour of the β-chloroacrylamides at the sulfide and sulfoxide level of oxidation towards diazoethane, diazomethane, trimethylsilyldiazomethane and phenyldiazomethane. In all instances, the cycloadditions proceeded in a highly regioselective manner, with the carbon terminus of the diazoalkane adding to the β-carbon of the β-chloroacrylamide. For the sulfoxide derived β-chloroacrylamides, the stereochemistry of the cycloaddition was controlled by the R group on the sulfoxide, which blocked the approach of the diazoalkane to one face of the β-chloroacrylamide, leading to complete diastereofacial control. The reactivity of the β-chloroacrylamides was dependent upon the level of oxidation at sulfur, with the sulfoxide derivatives proving to be much more reactive than the sulfide analogues. This was particularly evident for the trimethylsilyldiazomethane cycloadditions; the reaction with the sulfoxide substituted β-chloroacrylamides was complete after 6 hours, whereas the corresponding sulfides required reaction times of 48 hours. The products isolated from the cycloadditions were dependant on the dipole, the level of oxidation and nature of the

substitution at the sulfur centre and the nature of the amide group of the β-chloroacrylamide, with either the pyrazolines (as a mixture of two diastereomers for the diazoethane derived pyrazolines and as a single diastereomer in all other cases), the desulfinylated pyrazoles or the rearranged pyrazoles obtained.

The cycloadducts derived from the diazoethane cycloadditions proved to be the most stable; the eliminated pyrazoles were only isolated from the cycloadditions with the benzenesulfinyl-β-chloroacrylamides, and the pyrazolines were obtained from the cycloadditions of the benzylsulfinyl-, benzylthio- and phenylthio-β-chloroacrylamides as a mixture of two diastereomers. The cycloadditions with diazomethane led to slightly less stable products – at the sulfoxide level of oxidation, the pyrazolines were isolated for the benzylsulfinyl and *n*-butylsulfinyl derivatives as single diastereomers, while the eliminated pyrazoles were obtained from the reaction with the benzenesulfinyl derivatives, in agreement with the diazoethane cycloadditions. However, in contrast to the diazoethane cycloadditions, the pyrazoline cycloadducts with diazomethane were not isolated in all instances for the thio-substituted β-chloroacrylamides (Figure 7); in some cases the rearranged pyrazole was obtained. Reaction of the β-chloroacrylamides with phenyldiazomethane led to even less stable cycloadducts, and even in instances where the pyrazoline cycloadducts were isolated from the cycloaddition, rapid decomposition was observed in DMSO-d_6. The pyrazoline cycloadducts derived from the cycloadditions with phenyldiazomethane were isolated as single diastereomers, signifying that the energy differences between the transition states for the *endo* and *exo* approaches is sufficient to result in exclusive formation of one cycloadduct, tentatively assigned as the *endo*. When trimethylsilyldiazomethane was employed as the dipole, the pyrazoline cycloadduct was not isolated in any case, with elimination of the sulfoxide group observed for the sulfinyl derivatives and migration of the sulfur group observed for the thio derivatives.

The main mechanistic difference between the sulfide and sulfoxide derivatives is that in instances where the pyrazoline cycloadducts are too unstable to isolate, the sulfinyl group eliminates while the sulfide group migrates. In the mechanism outlined in Scheme 11, the loss of chloride to form a carbocation is unlikely for the sulfoxide derivatives, as the sulfinyl group is much less nucleophilic than the sulfide group. Furthermore, the sulfide migration is cleaner in the trimethylsilyl cycloadducts, presumably facilitated by the presence of the trimethylsilyl group, than in the diazomethane and phenyldiazomethane cycloadducts in

which the rearranged pyrazoles are isolated.

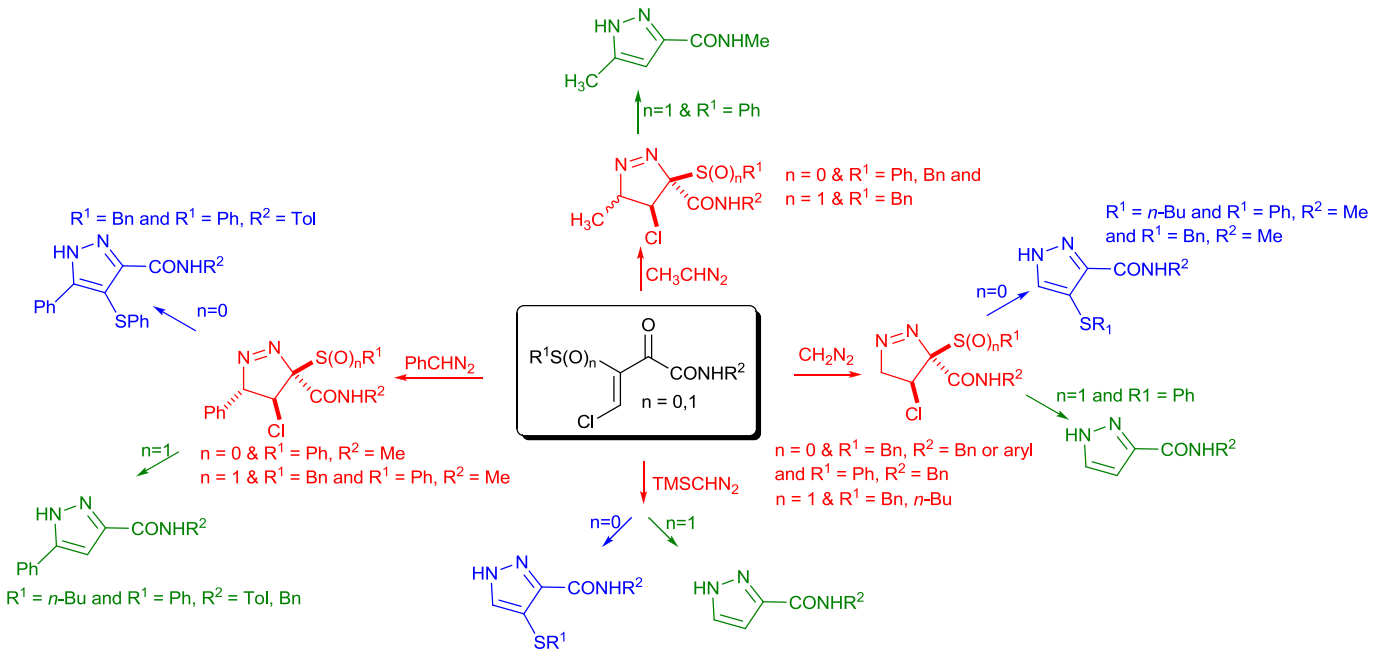

HN
N
CONHMe
H3C
n=1 & R1 = Ph
S(O)nR1
CONHR2
n = 0 & R1 = Ph, Bn and
n = 1 & R1 = Bn
H3C
Cl
CH3CHN2
R1 = Bn and R1 = Ph, R2 = Tol
HN
N
CONHR2
Ph
SPh
n=0
S(O)nR1
PhCHN2
Ph
CONHR2
Cl
n=1
n = 0 & R1 = Ph, R2 = Me
n = 1 & R1 = Bn and R1 = Ph, R2 = Me
HN
N
CONHR2
Ph
R1 = n-Bu and R1 = Ph, R2 = Tol, Bn
R1S(O)n
O
CONHR2
n = 0,1
Cl
CH2N2
S(O)nR1
CONHR2
Cl
n = 0 & R1 = Bn, R2 = Bn or aryl
and R1 = Ph, R2 = Bn
n = 1 & R1 = Bn, n-Bu
n=0
HN
N
CONHR2
SR1
R1 = n-Bu and R1 = Ph, R2 = Me
and R1 = Bn, R2 = Me
n=1 and R1 = Ph
HN
N
CONHR2
TMSCHN2
n=0
n=1
HN
N
CONHR2
SR1
HN
N
CONHR2

Figure 7

Conclusion

1,3-Dipolar cycloadditions of diazoalkanes to β-chloroacrylamides leads to a range of novel pyrazoline and pyrazole cycloadducts. The mechanistic and synthetic features of the cycloadditions to the β-chloroacrylamides at the sulfide and sulfoxide level of oxidation can be readily rationalised on the basis of the nature of the substituents, and the resulting cycloadducts have considerable synthetic potential. In the case of the sulfoxide derivatives, complete diastereofacial control is achieved.

Experimental

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorous pentoxide and ethyl acetate was distilled from potassium carbonate. Hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulphate. Diethyl ether is referred to as ether throughout.

Infrared spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids on a Perkin Elmer Paragon 1000 FT-IR spectrometer.

^{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) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. ^{1}H NMR spectra that were recorded in deuterated dimethylsulfoxide (DMSO-d_6) were assigned using the DMSO peak as the reference peak. Chemical shifts (δ_H & δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz).

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionization (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionization (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

Elemental analyses were performed by the Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

Wet flash chromatography was performed using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV (254nm) light detection, iodine staining, vanillin staining and ceric sulfate staining.

Microwave assisted synthesis was achieved using the CEM Discover Labmate Synthesiser in conjunction with ChemDriver software (Version 3.5.0) and the CEM Discover S-Class Synthesiser in conjunction with Synergy software.

Diazomethane was generated from Diazald® in glassware containing clear glass joints.[45] Diazoethane was generated from *N*-ethyl-*N*-nitrosourea[46,47] and phenyldiazomethane from the vacuum pyrolysis of benzaldehyde tosylhydrazone.[48]

Single crystal X-ray data for compound **30** was collected on a Nonius Mach 3 diffractometer using Mo-Kα graphite monochromated radiation and data for **63** was collected by STOE on a STOE IPDS 2T diffractometer using Cu-Kα graphite monochromated radiation. The data was corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full-matrix least-squares

using all F^2 data. The SHELXL-97,[49] PLATON,[50] Nonius,[51] X-AREA and X-RED32[52] suite of programs were used.

Selected experimental data, including representatives of each of the synthetic methods, are given below – full experimental procedures and spectroscopic data for all compounds described in the paper are given in the supporting information.

(3*R*,4R*,5R*,S*$_S$*)-3-(Benzylsulfinyl)-4-chloro-*N*-(4-fluorophenyl)-4,5-dihydro-5-methyl-3*H*-pyrazole-3-carboxamide 32a and (3*R*,4R*,5S*,S*$_S$*)-3-(benzylsulfinyl)-4-chloro-*N*-(4-fluorophenyl)-4,5-dihydro-5-methyl-3*H*-pyrazole-3-carboxamide 32b

An excess of an ethereal solution of diazoethane [prepared from *N*-ethyl-*N*-nitrosourea **91** (0.45 g, 3.8 mmol)] was added to a solution of *N*-(4-fluorophenyl)-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **7** (0.19 g, 0.55 mmol) in ether (20 mL) and acetone (5 mL) cooled in an ice-salt bath while stirring. The solution was allowed to return slowly to room temperature while stirring for 4 h. A precipitate formed as the reaction progressed. The products were collected by filtration through a sintered glass funnel (grade 3) to give **32a** and **32b** (**32a**:**32b** 1:0.21 by ^{1}H NMR spectroscopy) as a white solid (0.20 g, 94%), mp 98-100 °C; (Found C, 54.77; H, 4.30; N, 10.66. $C_{18}H_{17}ClN_3O_2SF$ requires C, 54.89; H, 4.35; N, 10.67%); ν_{max}/cm^{-1} (KBr) 3298 (NH), 3029 (CH), 1668 (CO), 1552 (N=N), 1514, 1407, 1226, 1038 (SO);

Major diastereomer **32a**: δ_H (300 MHz, $CDCl_3$) 1.52 [3H, d, *J* 7.5, C(5)C*H*$_3$], 4.07 (1H, d, A of AB system, J_{AB} 12.8, SC*H*$_2$), 4.45 (1H, d, B of AB system, J_{AB} 12.8, SC*H*$_2$), 4.75 [1H, d, *J* 3.6, C(4)*H*], 5.25 [1H, dq, *J* 3.6, 7.5, C(5)*H*], 7.04-7.13 (2H, m, Ar*H*)*, 7.31-7.40 (5H, m, Ar*H*)*, 7.49-7.64 (2H, m, Ar*H*)*, 8.90 (1H, br s, N*H*).

δ_C (75.5 MHz, DMSO-d_6) (signals for major diastereomer **32a** only detected) 15.8 [CH_3, C(5)*C*H$_3$], 54.1, (CH_2, S*C*H$_2$), 61.3 [CH, *C*(5)H], 90.0 [CH, *C*(4)H], 107.1 [C, *C*(3)], 115.6 [CH, d, $^2J_{CF}$ 22, aromatic *C*(3′)H], 124.1 [CH, d, $^3J_{CF}$ 8, aromatic *C*(2′)H], 128.7, 129.1, 130.9 (3 × CH, 3 × aromatic *C*H), 131.2, 134.0 (2 × C, 2 × aromatic *C*), 159.4 [C, d, $^1J_{CF}$ 244, aromatic *C*(4′)], 162.4 (C, *C*O).

Minor diastereomer **32b**: δ_H (300 MHz, $CDCl_3$) 1.87 [3H, d, *J* 7.3, C(5)C*H*$_3$], 4.05 (1H, d, A of AB system, J_{AB} 12.8, SC*H*$_2$), 4.48 (1H, d, B of AB system, J_{AB} 12.8, SC*H*$_2$), 4.78-4.82 [1H, m, C(5)*H*], 5.32 [1H, d, *J* 5.5, C(4)*H*], 7.04-7.13 (2H, m, Ar*H*)*, 7.31-7.40 (5H, m, Ar*H*)*, 7.49-7.64 (2H, m, Ar*H*)*, 9.14 (1H, br s, N*H*).

*The aromatic signals were indistinguishable for the two diastereomers.

HRMS (ES+): Exact mass calculated for $C_{18}H_{18}NO_2S^{35}ClF$ [$(M+H)^+ - N_2$], 366.0731. Found 366.0727; m/z (ES+) 396.2 {[($C_{18}H_{17}N_3O_2S^{37}ClF$)+$H^+$], 2%}, 394.2 {[($C_{18}H_{17}N_3O_2S^{35}ClF$)+$H^+$], 8%}, 368.2 {[($C_{18}H_{17}NO_2S^{37}ClF$)+$H^+$], 18%}, 366.2 {[($C_{18}H_{17}NO_2S^{35}ClF$)+$H^+$], 40%}, 220.2 (100%).

_N_-(4-Fluorophenyl)-5-methyl-1_H_-pyrazole-3-carboxamide 38

An excess of an ethereal solution of diazoethane [prepared from *N*-ethyl-*N*-nitrosourea **91** (0.77 g, 6.6 mmol)] was added to a solution of *N*-(4-fluorophenyl)-*Z*-3-chloro-2-(benzenesulfinyl)propenamide **13** (0.30 g, 0.9 mmol) in ether (30 mL) cooled in an ice-salt bath while stirring. The reaction solution was allowed to return slowly to room temperature while stirring for 4 h. The solvent was removed by evaporation at reduced pressure to give **38** as a yellow oil. Following purification by column chromatography using hexane-ethyl acetate (gradient elution 5-40% ethyl acetate) as eluent, the *pyrazole* **38** was obtained as an off-white solid (0.10 g, 49%), mp 196-197 °C; (Found C, 60.18; H, 4.67; F, 8.91. $C_{11}H_{10}FN_3O$ requires C, 60.27; H, 4.60; F, 8.67%); ν_{max}/cm^{-1} (KBr) 3380 (NH), 3193 (NH), 3121, 2986 (CH), 1662 (CO), 1555, 1509, 1412, 1218; δ_H (300 MHz, DMSO-d_6) 2.34 [3H, s, C(5)C*H*$_3$], 6.54 [1H, s, C(4)*H*], 7.13-7.27 (2H, m, Ar*H*), 7.81-7.93 (2H, m, Ar*H*), 10.09 (1H, br s, N*H* of carboxamide), 13.12 [1H, br s, N(1)*H*]; δ_C (75.5 MHz, DMSO-d_6) 10.7 [CH_3, C(5)*C*H$_3$], 105.0 [CH, *C*(4)H], 115.4 [CH, d, $^2J_{CF}$ 22, aromatic *C*(3′)H], 122.2 [CH, d, $^3J_{CF}$ 8, aromatic *C*(2′)H], 135.6 (C, aromatic *C*), 140.6, 147.2 [2 × C, *C*(3) & *C*(5)], 158.4 [C, d, $^1J_{CF}$ 239, aromatic *C*(4′)], 160.9 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{11}H_{11}N_3OF$ $[M+H]^+$, 220.0886. Found 220.0897; m/z (ES+) 220.2 {[($C_{11}H_{10}N_3OF$)+H^+], 100%}, 272.1.

(1*R,2*R**,3*R**/*S**)-1-(Benzylthio)-2-chloro-*N*-(4-fluorophenyl)-3-methylcyclopropanecarboxamide 56a, (1*R**,2*R**,3*S**/*R**)-1-(benzylthio)-2-chloro-*N*-(4-fluorophenyl)-3-methylcyclopropanecarboxamide 56b & 2-(benzylthio)-3-chloro-*N*-(4-fluorophenyl)pent-2-enamide 57**

(3*R**,4*R**,5*R**)-3-(Benzylthio)-4-chloro-*N*-(4-fluorophenyl)-4,5-dihydro-5-methyl-3*H*-pyrazole-3-carboxamide **44a** and (3*R**,4*R**,5*S**)-3-(benzylthio)-4-chloro-*N*-(4-fluorophenyl)-4,5-dihydro-5-methyl-3*H*-pyrazole-3-carboxamide **44b** (1:0.1 mixture of diastereomers) (0.37 g, 1.0 mmol) was heated at reflux in toluene (30 mL) for 2 h. Following removal of the solvent by evaporation under reduced pressure, the crude product was obtained as a pale brown oil (**56a:56b:57** 1:0.8:0.6 by ^{1}H NMR spectroscopy). Purification by column chromatography using hexane-ether (gradient elution 0-2% ether) as eluent gave **56a** and **56b** as a clear oil and a 1:0.8 mixture (by ^{1}H NMR spectroscopy) of diastereomers (0.12g, 35%); ν_{max}/cm^{-1} (KBr) 3281 (NH), 3067 (CH), 2930 (CH), 1652 (CO), 1510;

Major diastereomer **56a**: δ_H (300 MHz, $CDCl_3$) 1.36 [3H, d, *J* 6.6, C(3)C*H*$_3$], 2.14 [1H, dq, *J* 8.1, 6.3, C(3)*H*], 3.91 (1H, d, A of AB system, J_{AB} 12.6, one of SC*H*$_2$), 3.97 (1H, d, B of AB system, J_{AB} 12.6, one of SC*H*$_2$), 4.22 [1H, d, *J* 8.1, C(2)*H*], 6.90-7.34 (9H, m, Ar*H*)*, 9.05 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 7.9 [CH_3, C(3)*C*H$_3$], 26.8 [CH, *C*(3)H], 34.8 (CH_2, S*C*H$_2$), 36.6 [C, *C*(1)], 44.2 [CH, *C*(2)H], 166.5 (C, *C*O).

Minor diastereomer **56b**: δ_H (300 MHz, $CDCl_3$) 1.20 [3H, d, *J* 6.3, C(3)C*H*$_3$], 1.88 [1H, dq, *J* 9.9, 6.6, C(3)*H*], 3.96 (2H, s, SC*H*$_2$), 4.22 [1H, d, *J* 6.0, C(2)*H*], 6.90-7.34 (9H, m, Ar*H*)*, 8.91 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 9.2 [CH_3, C(3)*C*H$_3$], 33.8 [CH, *C*(3)H], 35.9 (CH_2, S*C*H$_2$), 38.2 [C, *C*(1)], 43.5 [CH, *C*(2)H], 163.7 (C, *C*O).

*The aromatic signals were indistinguishable for the two diastereomers in the ^{1}H NMR spectrum.

The aromatic signals were not distinguished in the ^{13}C NMR spectrum for the two diastereomers and were seen at δ_C 113.7 [CH, d, $^{2}J_{CF}$ 21, aromatic *C*(3′)H], 119.5 [CH, d,

$^{3}J_{CF}$ 8, aromatic *C*(2′)H], 125.8, 125.9, 127.0, 127.1, 127.3 (5 × CH, 5 × aromatic *C*H), 131.7, 135.3, 135.5 (3 × C, 3 × aromatic *C*), 157.6 [C, d, $^{1}J_{CF}$ 243, aromatic *C*(4′)].

HRMS (ES+): Exact mass calculated for $C_{18}H_{18}NOS^{35}ClF$ $(M+H)^{+}$, 350.0782. Found 350.0777; m/z (ES+) 352.1 {[($C_{18}H_{17}NOS^{37}ClF$)+H^{+}], 38%}, 350.1 {[($C_{18}H_{17}NOS^{35}ClF$)+H^{+}], 100%}, 90.9 (14%).

57 was also isolated from this reaction as a white solid (0.02g, 5%) as a single stereoisomer; ν_{max}/cm^{-1} (KBr) 3245 (NH), 3068 (CH), 2972 (CH), 1641 (CO), 1507; δ_H (300 MHz, $CDCl_3$) 1.20 [3H, t, *J* 7.3, C(5)*H*$_3$], 2.80 [2H, q, *J* 7.3, C(4)*H*$_2$], 3.97 (2H, s, SC*H*$_2$), 6.93-7.06 (2H, m, Ar*H*), 7.20-7.40 (7H, m, Ar*H*), 7.83 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 13.4 [CH_3, *C*(5)H_3], 32.3 [CH_2, *C*(4)H_2], 38.4 (CH_2, S*C*H_2), 116.0 [CH, d, $^{2}J_{CF}$ 22, aromatic *C*(3′)H], 121.9 [CH, d, $^{3}J_{CF}$ 8, aromatic *C*(2′)H], 126.1 [C, *C*(2)], 128.0, 129.2, 129.3 (3 × CH, 3 × aromatic *C*H), 133.8, 137.5 (2 × C, 2 × aromatic *C*), 153.6 [C, *C*(3)], 159.9 [C, d, $^{1}J_{CF}$ 244, aromatic *C*(4′)], 163.3 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{18}NOS^{35}ClF$ $(M+H)^{+}$, 350.0782. Found 350.0796; m/z (ES+) 352.0 {[($C_{18}H_{17}NOS^{37}ClF$)+H^{+}], 38%}, 350.0 {[($C_{18}H_{17}NOS^{35}ClF$)+H^{+}], 100%}.

_N_-(4-Methylphenyl)-1_H_-pyrazole-3-carboxamide 51

a) Prepared from N-(4-methylphenyl)-Z-3-chloro-2-(benzylsulfinyl)propenamide **8** *and trimethylsilyldiazomethane*

An ethereal solution of trimethylsilyldiazomethane (1.62 mL of a 2M solution, 3.3 mmol) was added to a stirring solution of *N*-(4-methylphenyl)-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **8** (0.22 g, 0.7 mmol) in ether (25 mL) and acetone (2 mL) under nitrogen at room temperature in the dark. The reaction solution was then stirred for 6 h. The solvent and excess trimethylsilyldiazomethane were removed by evaporation at reduced pressure to give the crude product as a yellow solid. Purification by column chromatography using hexane-ethyl acetate (gradient elution 10-40% ethyl acetate) gave **51** as a white solid (0.07 g, 54%), mp 190-191 °C; (Found C, 65.21, H, 5.50, N, 20.19; $C_{11}H_{11}N_3O$ requires C, 65.66, H, 5.51, N, 20.88%); ν_{max}/cm^{-1} (KBr) 3378 (NH), 3134

(CH), 2950 (CH), 1643 (CO), 1596, 1541, 1320; δ_H (300 MHz, DMSO-d_6) 2.28 (3H, s, ArCH_3), 6.78 [1H, br s, C(4)*H*], 7.14 (2H, d, *J* 8.1, Ar*H*), 7.69 (2H, d, *J* 8.1, Ar*H*), 7.88 [1H, br s, C(5)*H*], 9.91 (1H, br s, N*H* of carboxamide), 13.38 [1H, br s, N(1)*H*]; δ_C (75.5 MHz, DMSO-d_6) 20.8 (CH_3, Ar*C*H_3), 105.9 [CH, *C*(4)H], 120.5, 129.3 (2 × CH, 2 × aromatic *C*H), 130.7 [CH, *C*(5)H], 132.6, 136.7 (2 × C, 2 × aromatic *C*), 147.1 [C, *C*(3)], 160.7 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{11}H_{12}N_3O$ $[M+H]^+$, 202.0980. Found 202.0987; m/z (ES+) 202.2 {[($C_{11}H_{11}N_3O$)+H^+], 100%}.

The regiochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **51** recrystallised from ethyl acetate.

Crystals of **51** are monoclinic, space group *P* $2_1/c$, formula $C_{11}H_{11}N_3O$, M = 201.23, a = 15.936(5) Å, b = 6.1614(10) Å, c = 10.962(3) Å, α = 90.00 °, β = 108.19(3) °, γ = 90.00 °, U = 1022.5(5) $Å^3$, F(000) = 424, μ(Mo-Kα) = 0.088 mm^{-1}, $R(F_o)$ = 0.0448, for 979 observed reflections with I>2σ(I), $wR_2(F^2)$ = 0.1287 for all 1788 unique reflections. Data in the θ range 2.69-24.92 ° were collected at 293 K on a Nonius MACH3 diffractometer using Mo-Kα graphite monochromated radiation, λ = 0.7107 Å, and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The methyl hydrogen atoms were found from a Fourier difference map and allowed to ride on the parent atom; all other hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

b) Prepared from N-(4-methylphenyl)-Z-3-chloro-2-(benzenesulfinyl)propenamide **16** *and trimethylsilyldiazomethane*

The title compound was also prepared from an ethereal solution of trimethylsilyldiazomethane (2.27 mL of a 2M solution, 4.5 mmol) and *N*-(4-methylphenyl)-*Z*-3-chloro-2-(benzenesulfinyl)propenamide **16** (0.29 g, 0.9 mmol) in ether (25 mL) and acetone (4 mL). Following stirring at room temperature for 6 h and removal of the solvent and excess trimethylsilyldiazomethane, the crude product was obtained as a yellow solid. Following purification by column chromatography using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate), **51** was obtained as a white solid (0.06 g, 31%), with IR and ^{1}H NMR spectroscopic details identical to above.

c) Prepared from N-(4-methylphenyl)-Z-3-chloro-2-(benzenesulfinyl)propenamide **16** *and diazomethane*

The title compound was also prepared by addition of a solution of *N*-(4-methylphenyl)-*Z*-3-chloro-2-(benzenesulfinyl)propenamide **16** (0.20 g, 0.6 mmol) in ether (15 mL) and acetone (4 mL) to an ethereal solution of diazomethane [prepared from Diazald® (0.84 g, 3.9 mmol)] cooled in an ice-salt bath while stirring. The reaction solution was allowed to return slowly to room temperature, and following stirring for 6 h and removal of the solvent and excess diazomethane, the crude product was obtained as a brown oil. Following purification by column chromatography using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate), **51** was obtained as a white solid (0.02 g, 16%), with IR and ^{1}H NMR spectroscopic details identical to above.

(3*R,4*R**,*S*$_S$*)-3-(Benzylsulfinyl)-4-chloro-*N*-(4-fluorophenyl)-4,5-dihydro-3*H*-pyrazole-3-carboxamide 66**

A solution of *N*-(4-fluorophenyl)-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **7** (0.16 g, 0.5 mmol) in ether (15 mL) and acetone (3.5 mL) was added to an excess of an ethereal solution of diazomethane [prepared from Diazald® (0.84 g, 3.9 mmol)] cooled in an ice-salt bath while stirring. The solution was allowed to return slowly to room temperature while stirring for 4 h. A precipitate formed as the reaction progressed. The product was collected by filtration through a sintered glass funnel (grade 3) to give **66** as a white solid (0.12 g, 69%) as a single diastereomer, mp 89-90 °C; (Found C, 54.02; H, 3.90; N, 11.36; F, 4.85; Cl, 9.11; S, 8.78. $C_{17}H_{15}ClN_3O_2SF$ requires C, 53.76; H, 3.98; N, 11.06; F, 5.00; Cl, 9.33; S, 8.46 %); ν_{max}/cm^{-1} (KBr) 3306 (NH), 3036 (CH), 2920 (CH), 1676 (CO), 1542 (N=N), 1510, 1408, 1220, 1040 (SO); δ_H (300 MHz, $CDCl_3$) 4.07 (1H, d, A of AB system, *J* 12.9, SC*H*$_2$), 4.44 (1H, d, B of AB system, *J* 12.9, SC*H*$_2$), 4.97 [1H, dd, A of ABC, J_{AB} 18.9, J_{AC} 5.7, one of C(5)*H*$_2$], 5.25 [1H, dd, C of ABC, J_{AC} 5.7, J_{BC} 1.5, C(4)*H*], 5.31 [1H, dd, B of ABX, J_{AB} 18.9, J_{BC} 1.5, one of C(5)*H*$_2$], 6.99-7.09 (2H, m, Ar*H*), 7.30-7.38 (5H, m, Ar*H* of benzyl), 7.47-7.56 (2H, m, Ar*H*), 9.21 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 51.5 [CH, *C*(4)H], 57.1 (CH_2, S*C*H$_2$), 88.0 [CH_2, *C*(5)H$_2$], 108.8 [C,

C(3)], 115.9 [CH, d, $^{2}J_{CF}$ 23, aromatic *C*(3′)H], 122.4 [CH, d, $^{3}J_{CF}$ 8, aromatic *C*(2′)H], 129.1, 129.2, 130.4 (3 × CH, 3 × aromatic *C*H), 132.6, 132.7 (2 × C, 2 × aromatic *C*), 157.8 (C, *C*O), 160.0 [C, d, $^{1}J_{CF}$ 245, aromatic *C*(4′)]; HRMS (ES+): Exact mass calculated for $C_{17}H_{16}NO_2S^{35}ClF$ [$(M+H)^+ - N_2$], 352.0574. Found 352.0574; m/z (ES+) 352.1 {[$(C_{17}H_{15}NO_2S^{35}ClF)+H^+$], 4%}, 87.9 (100%).

4-(Benzylthio)-*N*-methyl-1*H*-pyrazole-3-carboxamide 63

a) Prepared from N-methyl-Z-3-chloro-2-(benzylthio)propenamide **26** *and trimethylsilyldiazomethane*

An ethereal solution of trimethylsilyldiazomethane (2.40 mL of a 2M solution, 4.8 mmol) was added to a stirring solution of *N*-methyl-*Z*-3-chloro-2-(benzylthio)propenamide **26** (0.23 g, 1.0 mmol) in ether (25 mL) under nitrogen at room temperature in the dark. The reaction solution was then stirred at room temperature and the reaction progress was monitored by TLC analysis. After stirring for 5 h, TLC analysis showed that a lot of starting material still remained and a further 2.40 mL of trimethylsilyldiazomethane solution was added. Following stirring for 24 h, a further 2.40 mL of trimethylsilyldiazomethane solution was added to the reaction mixture. After stirring for 48 h, TLC analysis indicated complete consumption of the starting material and the solvent and excess trimethylsilyldiazomethane were removed by evaporation at reduced pressure to give the crude product as an off-white solid. Purification by column chromatography using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) gave **63** as a white solid (0.14 g, 59%), mp 145-147 °C; (Found C, 58.17; H, 5.12; N, 16.89; S, 13.12. $C_{12}H_{13}N_3OS$ requires C, 58.28; H, 5.30; N, 16.99; S, 12.97%); ν_{max}/cm^{-1} (KBr) 3310 (NH), 3099 (NH), 2922 (CH), 1646 (CO), 1566, 1492, 1352; δ_H (300 MHz, $CDCl_3$) 2.79 (3H, d, *J* 4.8, NHCH_3), 3.85 (2H, s, SCH_2), 6.93-7.13 (2H, m, Ar*H*), 7.17-7.36 (3H, m, Ar*H*), 7.55 [2H, br s, N*H* of carboxamide & C(5)*H*], 12.50 [1H, br s, N(1)*H*]; δ_C (75.5 MHz, $CDCl_3$) 25.9 (CH_3, NH*C*H_3), 42.5 (CH_2, S*C*H_2), 107.7 [C, *C*(4)], 127.6, 128.7 (1 signal for 2 × CH) (2 × CH, aromatic *C*H), 137.4 [C, aromatic *C* & *C*(3)], 143.6 [CH, br, *C*(5)H], 159.9 (C, *C*O); δ_C (75.5 MHz, DMSO-d_6) 25.5 (CH_3, NH*C*H_3), 37.8 (CH_2, br,

S*C*H$_2$), 112.7 [C, *C*(4)], 126.9, 128.2, 128.8, (3 × CH, 3 × aromatic *C*H), 130.1 [C, br, *C*(3)], 137.9 (C, aromatic *C*), 143.8 [CH, br, *C*(5)H], 160.1 (C, br, *C*O); HRMS (ES+): Exact mass calculated for $C_{12}H_{14}N_3OS$ $[M+H]^+$, 248.0858. Found 248.0851; m/z (ES+) 248.1 {[($C_{12}H_{13}N_3OS$)+H^+], 100%}, 495.2 {[($C_{24}H_{26}N_6O_2S_2$)+H^+], 28%}.

b) Prepared from N-methyl-Z-3-chloro-2-(benzylthio)propenamide **26** *and diazomethane*

This was also prepared by addition of a solution of *N*-methyl-*Z*-3-chloro-2-(benzylthio)propenamide **26** (0.21 g, 0.9 mmol) in ether (15 mL) to an excess of an ethereal solution of diazomethane [prepared from Diazald® (0.84 g, 3.9 mmol)] cooled in an ice-salt bath while stirring. The solution was allowed to return slowly to room temperature and the reaction mixture was then stirred for 4 h. Following removal of the solvent and excess diene by evaporation under reduced pressure, the crude product was obtained as a pale yellow oil. After purification by column chromatography using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate), **63** was obtained as a white solid (0.05 g, 23%), with IR and ^{1}H NMR spectroscopic details identical to above.

The regiochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **63** recrystallised from ethyl acetate.

Crystals of **63** are centric monoclinic, space group *C* 2/*c*, formula $C_{12}H_{13}N_3OS$, M = 247.31, a = 22.4891(18) Å, b = 10.3523(6) Å, c = 12.2712(10) Å, α = 90.00 °, β = 119.882(6) °, γ = 90.00 °, U = 2477.1(3) Å^3, F(000) = 1040, μ(Cu-Kα) = 2.222 mm^{-1}, R(F_o) = 0.0531, for 1836 observed reflections with I>2σ(I), wR_2(F^2) = 0.1516 for all 2003 unique reflections. Data in the θ range 4.54-64.15 ° were collected at 150 K on a STOE IPDS 2T diffractometer using Cu-Kα graphite monochromated radiation, λ = 1.54186 Å, and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

(3*R,4*R**,5*R**,*S*$_S$*)-3-(Benzylsulfinyl)-4-chloro-4,5-dihydro-5-phenyl-*N*-(4-methylphenyl)-3*H*-pyrazole-3-carboxamide 76 & *N*-(4-methylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide 79**

A solution of *N*-(4-methylphenyl)-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **8** (0.21 g, 0.6 mmol) in ether (15 mL) and acetone (4 mL) was added dropwise to an excess of phenyldiazomethane [generated from benzaldehyde tosylhydrazone (1.68 g, 6.0 mmol)] cooled to −50 °C using a cryocooler. The solution was allowed to return slowly to room temperature while stirring for 16 h. A precipitate formed as the reaction progressed. The product was collected by filtration through a sintered glass funnel (grade 3) to give **76** as a white solid (0.09 g, 31%) and as a single diastereomer, mp 72-74 °C; (Found C, 63.75; H, 4.88; N, 8.92; S, 6.73, Cl, 7.59. $C_{24}H_{22}ClN_3O_2S$ requires C, 63.78; H, 4.91; N, 9.30; S, 7.09, Cl, 7.84%); ν_{max}/cm^{-1} (KBr) 3271 (NH), 2919 (CH), 1679 (CO), 1609, 1595, 1525 (N=N), 1076 (SO); δ_H (300 MHz, $CDCl_3$) 2.36 (3H, s, ArC*H*$_3$), 4.25 (1H, d, A of AB system, *J* 12.6, one of SC*H*$_2$), 4.46 (1H, d, B of AB system, *J* 12.9, one of SC*H*$_2$), 4.83 [1H, d, *J* 6.6, C(4)*H*Cl], 6.03 [1H, d, *J* 6.3, C(5)*H*Ph], 7.17-7.47 (12H, m, Ar*H*), 7.52 (2H, d, *J* 8.4, ArC*H*), 8.78 (1H, br s, N*H*); δ_H (300 MHz, DMSO-d_6) 2.31 (3H, s, ArC*H*$_3$), 4.47 (1H, d, A of AB system, *J* 12.9, one of SC*H*$_2$), 4.52 (1H, d, B of AB system, *J* 12.9, one of SC*H*$_2$), 5.12, 5.57 [2 × 1H, 2 × d, *J* 8.7, 9.0, C(5)*H*Ph & C(4)*H*Cl], 7.20 (2H, d, *J* 8.1, Ar*H*), 7.31-7.58 (10H, m, Ar*H*), 7.64 (2H, d, *J* 8.4, ArC*H*), 10.45 (1H, br s, N*H*). There was some evidence of decomposition to the pyrazole **79** in the ^{1}H NMR spectrum in DMSO-d_6, with characteristic signals at δ_H 7.70 (2H, d, *J* 8.4, Ar*H*), 7.86 (2H, d, *J* 6.6, Ar*H*), 10.06 (1H, br s, N*H*); When the ^{13}C NMR spectrum was recorded in DMSO-d_6, total decomposition to the pyrazole **79** occurred, with characteristic signals at δ_C (75.5 MHz, DMSO-d_6) 20.5 (CH_3, Ar*C*H$_3$), 103.0 [CH, *C*(4)H], 120.2, 125.3, 128.3 129.0 (4 × CH, 4 × aromatic *C*H, 4 signals for 5 carbons), 132.5, 136.2 (2 × C, 2 × aromatic *C*), 159.1 (C, *C*O). The signals for C(3), C(5) and one aromatic C were not detected in the ^{13}C NMR spectrum. Spectroscopic details agreed with a genuine sample of **79**; HRMS (ES+): Exact mass calculated for $C_{24}H_{23}NO_2S^{35}Cl$ [$(M+H)^+ - N_2$], 424.1138. Found 424.1130; m/z (ES+) 426.2 {[$(C_{24}H_{22}NO_2S^{37}Cl)+H^+$], 4%}, 424.2 {[$(C_{24}H_{22}NO_2S^{35}Cl)+H^+$], 14%}, 278.2 {[$(C_{17}H_{15}N_3O)+H^+$], 6%}, 87.9 (100%).

Acknowledgements

IRCSET are gratefully acknowledged for funding of this work. We thank STOE for data collection and structural analysis of compound **63**.

References

1. Kissane, M.; Maguire, A. R. *Chem.Soc.Rev.* **2010**, *39*, 845-883.
2. Murphy, M.; Lynch, D.; Schaeffer, M.; Kissane, M.; Chopra, J.; O'Brien, E.; Ford, A.; Ferguson, G.; Maguire, A. R. *Organic & Biomolecular Chemistry* **2007**, *5*, 1228-1241.
3. Kissane, M.; Murphy, M.; Lynch, D.; Ford, A.; Maguire, A. R. *Tetrahedron* **2008**, *64*, 7639-7649.
4. Kissane, M.; Lynch, D.; Chopra, J.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron: Asymmetry* **2008**, *19*, 1256-1273.
5. Ruano, J. L. G.; de la Plata, B. C. *Organosulfur Chemistry I* **1999**, *204*, 1-126.
6. Plancquaert, M. A.; Redon, M.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1996**, *52*, 4383-4396.
7. Garcia Ruano, J. L.; Alonso de Diego, S. A.; Martin, M. R.; Torrente, E.; Martin Castro, A. M. *Organic Letters* **2004**, *6*, 4945-4948.
8. Garcia Ruano, J. L.; Alonso de Diego, S. A.; Blanco, D.; Martin Castro, A. M.; Martin, M. R.; Rodriguez Ramos, J. H. *Organic Letters* **2001**, *3*, 3173-3176.
9. Ruano, J. L. G.; Fraile, A.; Martin, M. R. *Tetrahedron-Asymmetry* **1996**, *7*, 1943-1950.
10. Garcia Ruano, J. L.; Bercial, F.; Gonzalez, G.; Martin Castro, A. M.; Martin, M. R. *Tetrahedron: Asymmetry* **2002**, *13*, 1993-2002.
11. Ruano, J. L. G.; Fraile, A.; Gonzalez, G.; Martin, M. R.; Clemente, F. R.; Gordillo, R. *J.Org.Chem.* **2003**, *68*, 6522-6534.
12. Ruano, J. L. G.; Peromingo, M. T.; Alonso, M.; Fraile, A.; Martin, M. R.; Tito, A. *J.Org.Chem.* **2005**, *70*, 8942-8947.
13. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley-Interscience: 2003.
14. Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Edited by Katritzky, A. R.; Rees, Charles W.; Scriven, E. F. V., Eds.; Permagon-Elsevier Science: Oxford, 1996; pp 1-75.

15. Richman, J. G.; Kanemitsu-Parks, M.; Gaidarov, I.; Cameron, J. S.; Griffin, P.; Zheng, H.; Guerra, N. C.; Cham, L.; Maciejewski-Lenoir, D.; Behan, D. P.; Boatman, D.; Chen, R.; Skinner, P.; Ornelas, P.; Waters, M. G.; Wright, S. D.; Semple, G.; Connolly, D. T. *J.Biol.Chem.* **2007**, *282*, 18028-18036.

16. Skinner, P. J.; Cherrier, M. C.; Webb, P. J.; Shin, Y. J.; Gharbaoui, T.; Lindstrom, A.; Hong, V.; Tamura, S. Y.; Dang, H. T.; Pride, C. C.; Chen, R.; Richman, J. G.; Connolly, D. T.; Semple, G. *Bioorg.Med.Chem.Lett.* **2007**, *17*, 5620-5623.

17. Gharbaoui, T.; Skinner, P. J.; Shin, Y. J.; Averbuj, C.; Jung, J. K.; Johnson, B. R.; Duong, T.; Decaire, M.; Uy, J.; Cherrier, M. C.; Webb, P. J.; Tamura, S. Y.; Zou, N.; Rodriguez, N.; Boatman, P. D.; Sage, C. R.; Lindstrom, A.; Xu, J.; Schrader, T. O.; Smith, B. M.; Chen, R.; Richman, J. G.; Connolly, D. T.; Colletti, S. L.; Tata, J. R.; Semple, G. *Bioorg.Med.Chem.Lett.* **2007**, *17*, 4914-4919.

18. Wise, A.; Foord, S. M.; Fraser, N. J.; Barnes, A. A.; Elshourbagy, N.; Eilert, M.; Ignar, D. M.; Murdock, P. R.; Steplewski, K.; Green, A.; Brown, A. J.; Dowell, S. J.; Szekeres, P. G.; Hassall, D. G.; Marshall, F. H.; Wilson, S.; Pike, N. B. *J.Biol.Chem.* **2003**, *278*, 9869-9874.

19. Tavintharan, S.; Kashyap, M. L. *Curr.Atheroscler Rep.* **2001**, *3*, 74-82.

20. Adage, T.; Trillat, A. C.; Quattropani, A.; Perrin, D.; Cavarec, L.; Shaw, J.; Guerassimenko, O.; Giachetti, C.; Greco, B.; Chumakov, I.; Halazy, S.; Roach, A.; Zaratin, P. *Eur.Neuropsychopharmacol.* **2008**, *18*, 200-214.

21. McKeown, S. C.; Hall, A.; Giblin, G. M. P.; Lorthioir, O.; Blunt, R.; Lewell, X. Q.; Wilson, R. J.; Brown, S. H.; Chowdhury, A.; Coleman, T.; Watson, S. P.; Chessell, I. P.; Pipe, A.; Clayton, N.; Goldsmith, P. *Bioorg.Med.Chem.Lett.* **2006**, *16*, 4767-4771.

22. Yahyi, A.; Ettouhami, A.; Radi, S.; Zidane, I.; Hakkou, A.; Bouakka, M. *Lett.Drug Des.Discovery* **2007**, *4*, 382-385.

23. Pei, Z.; Li, X.; Longenecker, K.; Von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M. *J.Med.Chem.* **2006**, *49*, 3520-3535.

24. Pospisilik, J. A.; Martin, J.; Doty, T.; Ehses, J. A.; Pamir, N.; Lynn, F. C.; Piteau, S.; Demuth, H. U.; McIntosh, C. H. S.; Pederson, R. A. *Diabetes* **2003**, *52*, 741-750.

25. See supplementary information.

26. Gilchrist, T. L.; Storr, R. C. *Organic Reactions and Orbital Symmetry*; 2nd ed.; Cambridge University Press: 1979.

27. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: London, 1976.

28. Huppatz, J. L.; Phillips, J. N.; Witrzens, B. *Agric.Biol.Chem.* **1984**, *48*, 45-50.

29. Engel, P. S. *Chem.Rev.* **1980**, *80*, 99-150.

30. Martin-Vila, M.; Hanafi, N.; Jimenez, J. M.; Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Oliva, A.; Ortuno, R. M. *J.Org.Chem.* **1998**, *63*, 3581-3589.

31. Otto, A.; Ziemer, B.; Liebscher, J. *Synthesis* **1999**, 965-972.

32. Bartels, A.; Jones, P. G.; Liebscher, J. *Synthesis* **1998**, 1645-1654.

33. De Lange, B.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 5317-5320.

34. Vasquez, P. C.; Bennett, D. C.; Towns, K. K.; Kennedy, G. D.; Baumstark, A. L. *Heteroat.Chem.* **2000**, *11*, 299-302.

35. Begley, M. J.; Dean, F. M.; Houghton, L. E.; Johnson, R. S.; Park, B. K. *J.Chem.Soc., Chem.Commun.* **1978**, 461-462.

36. Sasmal, P. K.; Sridhar, S.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 8661-8665.

37. Kauch, M.; Snieckus, V.; Hoppe, D. *J.Org.Chem.* **2005**, *70*, 7149-7158.

38. Thomas, E. J.; Williams, A. C. *J.Chem.Soc., Chem.Commun.* **1987**, 992-994.

39. Vorbrueggen, H.; Ruh-Pohlenz, C. *Org.React.* **2000**, *55*, 1-630.

40. Wentrup, C.; Fischer, S.; Maquestiau, A.; Flammang, R. *Angew.Chem.* **1985**, *97*, 74-75.

41. Trofimenko, S.; Yap, G. P. A.; Jove, F. A.; Claramunt, R. M.; Garcia, M. A.; Santa Maria, M. D.; Alkorta, I.; Elguero, J. *Tetrahedron* **2007**, *63*, 8104-8111.

42. Trofimenko, S.; Rheingold, A. L.; Liable-Sands, L. M.; Maria Claramunt, R.; Lopez, C.; Dolores Santa Maria, M.; Elguero, J. *New J.Chem.* **2001**, *25*, 819-823.

43. Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv.Heterocycl.Chem.* **2000**, *76*, 157-323.

44. Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew.Chem., Int.Ed.* **2001**, *40*, 1430-1433.

45. deBoer, T. J.; Backer, B. J. *Org.Synth.* **1956**, *36*, 16.

46. Marshall, J. A.; Partridge, J. J. *J.Org.Chem.* **1968**, *33*, 4090-4097.

47. Arndt, F. *Org.Synth.,Coll.Vol.2* **1943**, 461.

48. Creary, X. *Org.Synth., Coll.Vol.7* **1990**, 438.

49. Sheldrick, G.M. *Acta Cryst. A*, 2008, **64**, 112-122.

50. Spek, A.L. *Acta Cryst. D.*, 2009, **65**, 148-155.

51. Nonius (1998). CAD-4 Data Collection Software. Nonius BV, Delft, The Netherlands.

52. Stoe & Cie (2002). X-AREA (Version 1.18) and X-RED32 (Version 1.04). Stoe & Cie, Darmstadt, Germany.