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Authors	McCaw, Patrick G.;Buckley, Naomi M.;Eccles, Kevin S.;Lawrence, Simon E.;Maguire, Anita R.;Collins, Stuart G.
Publication date	2017-03-08
Original Citation	McCaw, P. G., Buckley, N. M., Eccles, K. S., Lawrence, S. E., Maguire, A. R. and Collins, S. G. (2017) 'Synthesis of cyclic alpha-diazo-beta-keto sulfoxides in batch and continuous flow', Journal of Organic Chemistry, 82(7), pp. 3666-3679. doi:10.1021/acs.joc.7b00172
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1021/acs.joc.7b00172
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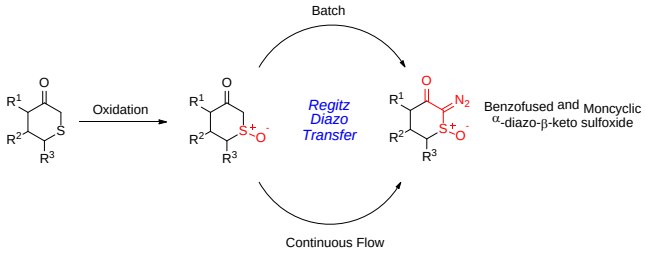
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Synthesis of cyclic α-diazo-β-keto sulfoxides in batch and continuous flow.

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Abstract

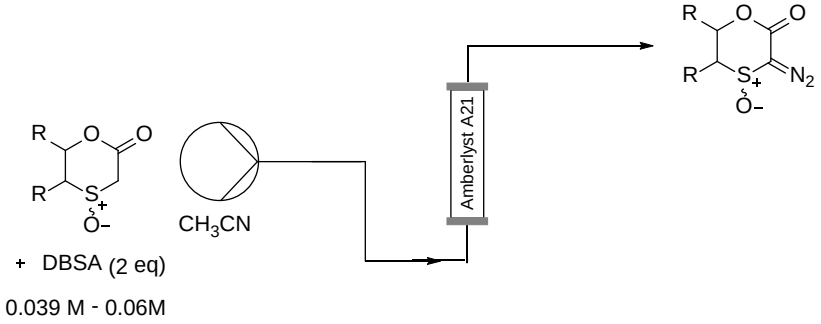
Diazo transfer to β–keto sulfoxides to form stable isolable α-diazo-β-keto sulfoxides has been achieved for the first time. Both monocyclic and benzofused ketone derived β-keto sulfoxides were successfully explored as substrates for diazo transfer. Use of continuous flow leads to isolation of the desired compounds in enhanced yields relative to standard batch conditions, with short reaction times, increased safety profile and potential to scale up.

Keywords: α-diazo-β-keto-sulfoxide, diazo transfer, continuous flow, Amberlyst A21.

1. Introduction

α-Diazocarbonyl compounds, first reported in 1883 by Curtius[1] are a highly reactive class of compounds with a wide ranging spectrum of reactivity and broad uses in synthesis. Many reviews on the versatility and reactivity of these diazo compounds in organic synthesis exist, detailing among other transformations, C-H insertions, cyclopropanations, X-H insertions, dimerization and ylide formation.[2-6] Successful generation of α-diazocarbonyl compounds *via* the Regitz methodology requires the use of a diazo transfer reagent. These reagents are renowned for their shock sensitivity, explosive nature and thermal decomposition properties [3,7,8] limiting potential use of diazo chemistry in large batch applications. Currently there is great interest in continuous flow processing for handling diazo compounds and the associated increased safety profile. [9-11] Our research group has recently reported the ability to generate, use, and subsequently quench the explosive diazo transfer reagent tosyl azide *in situ* using continuous flow processing.[12] This approach limits the amounts of hazardous compounds formed at any point in time, and is extremely advantageous to making diazo chemistry more acceptable for broader use.[12-15] Additionally, by taking advantage of the process control enabled in continuous flow we have established a high yielding diazo transfer methodology for the synthesis of lactone derived α-diazosulfoxides using the Regitz diazo transfer methodology and the relatively safe diazo transfer reagent dodecylbenzenesulfonyl azide (DBSA) **(Scheme 1**). [16-19]

Scheme 1: Solid supported base for the synthesis of α-diazosulfoxides in continuous flow.[15]



Stable, isolable α-diazo-β-oxo sulfoxides have considerable synthetic potential, especially providing a mild and effective route to α-oxo sulfines. For α-diazocarbonyl compounds an intermediate carbene or carbenoid ylide has multiple possible reaction pathways, including dimerization, aromatic addition and Wolff rearrangement.[2] The first attempts at generating α-diazosulfoxides were reported by Hodson and Holt in 1968 and did not lead to isolable compounds.[20] This was followed by the successful generation of a series of cephalosporins containing α-diazosulfoxides by Rosati[21] based on an earlier report by Campbell.[22,23] The Maguire group rationalized that the unprecedented stability of these α-diazosulfoxides was the decreased availability of the sulfinyl lone pair for donation, facilitated by reduced conformational mobility in the

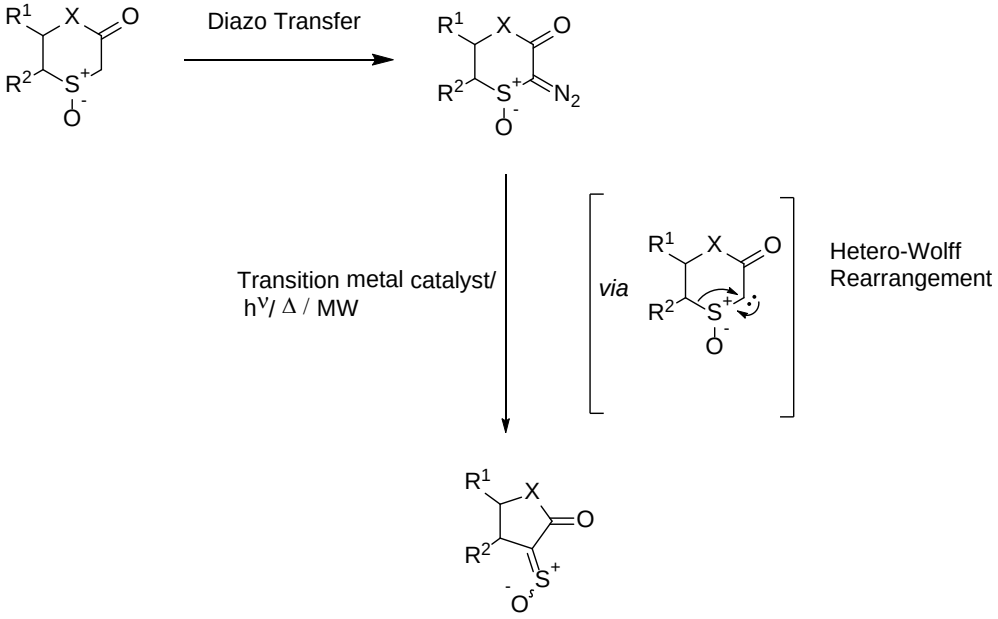
system. This led to a report on the design and synthesis of a range of stable lactone and lactam derived α-diazosulfoxides for the first time (**Figure 1**).[17]



Figure 1: Structure of stable, isolable lactone and lactam derived α-diazosulfoxides. [17]

On generation of the carbene from the α-diazosulfoxide, the predominant transformation observed is the hetero-Wolff rearrangement to an α-oxo sulfine (**Scheme 2**).[17,24,25] The synthesis and synthetic versatility of sulfines has been recently reviewed in the literature. [26,27]

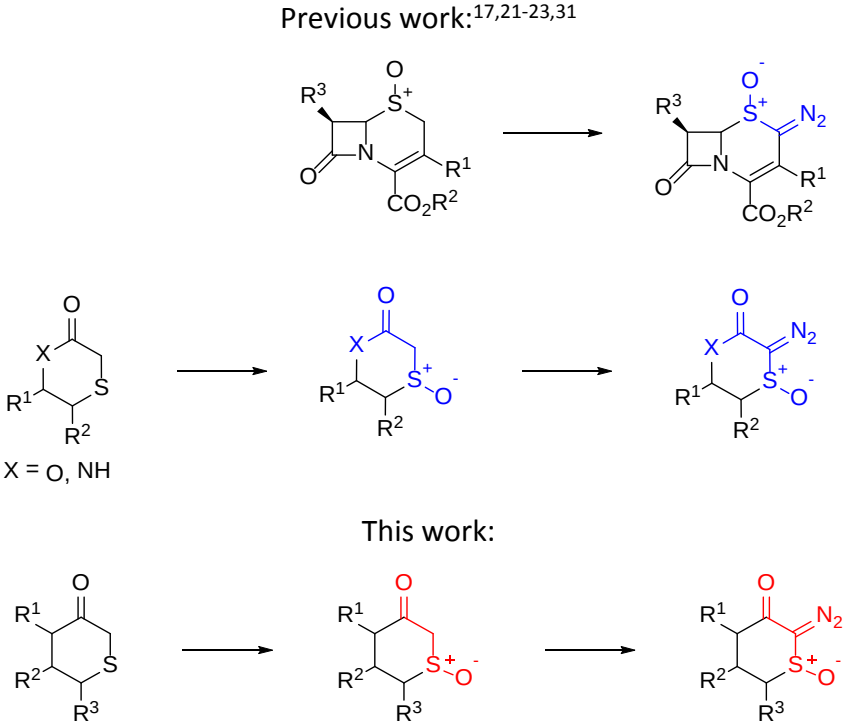
Scheme 2: Generation of α-oxo sulfine from α-diazo-β-oxo sulfoxide *via* hetero-Wolff rearrangement**.**



The targets in this work were a newly designed class of novel α-diazosulfoxide derivatives containing α-diazoketone functionality as opposed to the diazolactone and diazolactam derivatives previously described (**Scheme 3**).[17] The properties, stability and reactivity of α-diazoketones are distinctly different to those of α-diazoesters and diazo compounds derived from carboxylic acids in general. Typically, α-diazoketones are more labile than α-diazoesters, therefore opening the possibility of different reactivity and more diverse synthetic applications.[4] Some recent examples of this complex reactivity of α-diazoketones include their highly regioselective cross-coupling with allylboronic acids under copper catalyzed conditions,[28] and the rhodium catalyzed annulation of benzamides[29] and benzylamine[30] with diazoketones to form highly functionalized isoquinolinones and isoquinolines respectively.

Herein, we report the successful design, synthesis and isolation of novel α-diazo-β-keto sulfoxides – both benzofused and monocyclic, and how the synthesis of this novel class of compounds is suited exceptionally well to generation in a continuous flow manner utilizing the Regitz diazo transfer methodology.

Scheme 3: Comparison of previous work and this work.



2. Results and Discussion.

A preliminary investigation of diazo transfer to acyclic β-keto sulfoxides did not lead to stable isolable diazo derivatives; accordingly use of a cyclic system is necessary to reduce the conformational mobility around the sulfinyl lone pair and provide stability to the α-diazosulfoxide moiety. [19] Based on our previous experiences with the lactone and lactam derivatives a set of benzofused bicyclic (**1** - **4**) and monocyclic α-diazo-β-keto sulfoxides (**5** - **7**) were designed as novel synthetic targets (**Figure 2**), which have the potential to possess interesting reactivity. We envisaged the benzofused bicyclic compounds to be more rigid, and therefore more stable than the monocyclic systems.

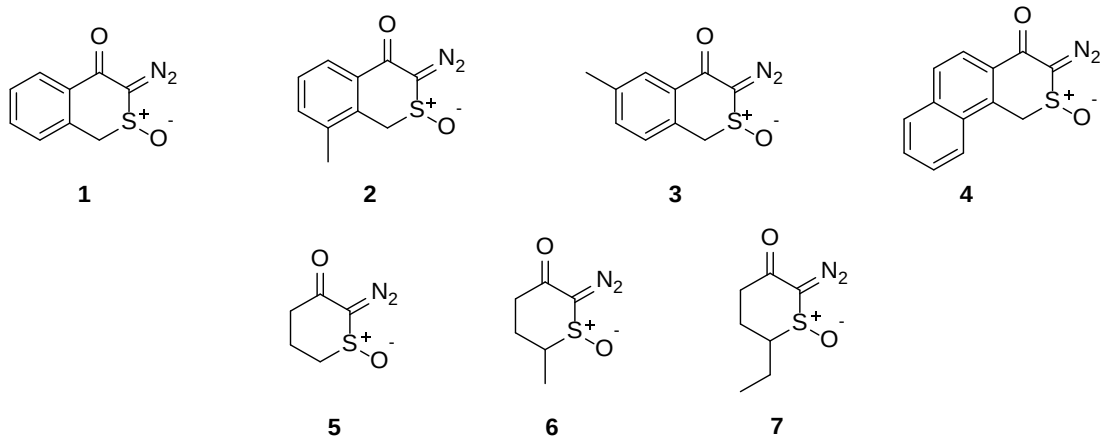
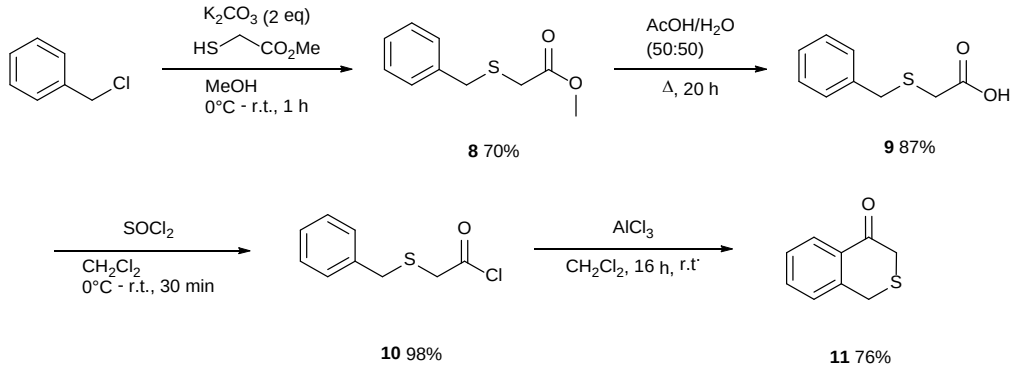


Figure 2 : The novel α-diazo-β-keto-sulfoxides designed as target molecules.

2.1 Synthesis of sulfides.

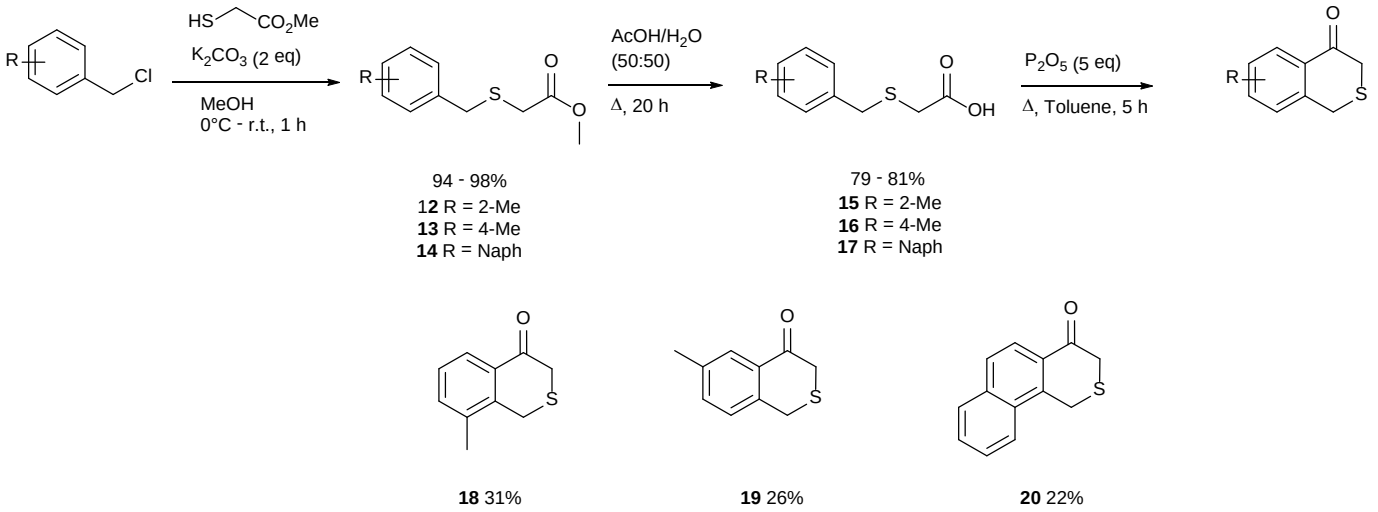
The first step towards these novel α-diazosulfoxides is the synthesis of the cyclic sulfides. The β-keto sulfide **11** was prepared using a modified procedure from the literature, as described by Akkurt (**Scheme 4**).[32]

Scheme 4: Synthesis of the unsubstituted benzofused β-keto sulfide **11**.



A similar cyclodehydration procedure has recently been described by Aitken for the synthesis of the cyclic sulfide **11** where a combination of phosphorus pentoxide and celite® are used to induce the transformation from the carboxylic acid **9**.[33] The other benzofused sulfides **18-20** were synthesized using a procedure described in the literature by Ramadas .[34] The final step in the synthesis of the sulfides **18-20** is a direct cyclization in a cyclodehydration step, which involved an intramolecular Friedel-Crafts reaction of the acid directly to the sulfide (**Scheme 5).**

Scheme 5: Cyclisation to the sulfides **18** - **20.**



94 - 98%
12 R = 2-Me
13 R = 4-Me
14 R = Naph

79 - 81%
15 R = 2-Me
16 R = 4-Me
17 R = Naph

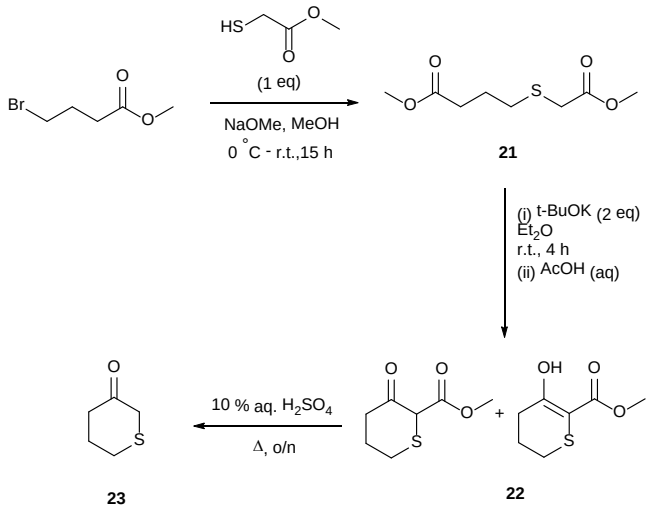
18 31% **19** 26% **20** 22%

The yields of these sulfides are not optimized; despite the harsh reaction conditions required for the transformation, the cyclisation step provided us with sufficient material for this synthetic study. These sulfides **18 - 20** were found to be relatively unstable and short lived at room temperature and were stored in the dark, in the freezer to successfully prevent decomposition to unidentified, highly coloured, intractable material. The sulfides were typically used within 24 hours of purification.

Synthesis of monocyclic β-keto-sulfides

Moving on to the monocyclic sulfides, as monocyclic lactone derived α-diazosulfoxides have been successfully prepared,[17] we aimed to investigate whether the monocyclic α-diazo-β-keto sulfoxides would also be stable and isolable. The first target was the monocyclic sulfide **23** which was synthesized using a modification of a procedure previously reported by Kamenka (**Scheme 6**).[35]

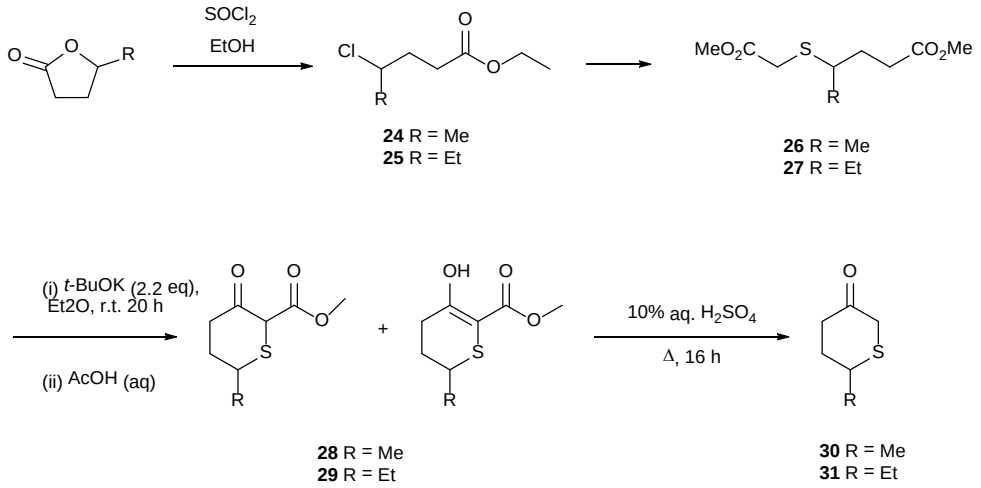
Scheme 6 : Generation of the monocyclic sulfide **23** through cyclisation of the diester **21** followed by hydrolysis and decarboxylation of keto enol mixture **22**



The first step towards the sulfide **23** is generation of the diester **21**, followed by treatment with potassium *t*-butoxide in a Dieckmann condensation. Following hydrolysis of the keto enol mixture **22**, and thermal decarboxylation, the sulfide **23** was obtained as a yellow oil in 50% yield after chromatography.

With success in preparing the unsubstituted monocyclic sulfide **23**, the next targets were alkyl substituted analogues **30** and **31**, to investigate the impact of steric and electronic effects on both sulfoxidation and diazo transfer. The methyl substituted sulfide **30** is mentioned in the literature but the synthesis and characterization is not fully described.[36] The same procedure, used for the synthesis of diester **21** above, is used for the synthesis of the substituted diesters **26** and **27** and cyclisation to the sulfides **30** and **31**. The starting secondary alkyl chlorides **24** and **25** that were needed were not commercially available but were obtained through ring opening γ-lactones with thionyl chloride (**Scheme 7**).

Scheme 7: Synthesis of the monocyclic sulfides **30** and **31**.



2.2 Synthesis of sulfoxides.

Having successfully obtained the sulfides using the procedures detailed above, exploration of the optimum conditions for oxidation to the corresponding novel β-keto sulfoxides was investigated. Using two oxidation methods, Oxone® in acetone or sodium periodate in methanol a range of novel monocyclic and benzofused β-keto sulfoxides were synthesized. The novel sulfoxides **32**, **36** - **38** were each synthesized using sodium periodate as the oxidant following a standard procedure while sulfides **18** - **20** were oxidized to the corresponding sulfoxides **33** - **35** using Oxone® as oxidant (**Figure 3**). The exceptionally polar compounds **32** - **38** were obtained in good yield as white crystalline solids and did not require further purification after aqueous work up; interestingly there was no evidence for the formation of the sulfones at any point in this study. As with the lactone derived sulfoxides,[17] the oxidant can approach the monocyclic sulfides **30** and **31** from either face with essentially equal ease, and in practise for sulfoxides **37** and **38**, two diastereomers

were formed with no diastereoselectivity observed. The novel sulfoxide series **32 - 38** possess a similar stability profile as the sulfides and to prevent thermal or photochemical decomposition, they are kept in the freezer after preparation and used within 24 hours.

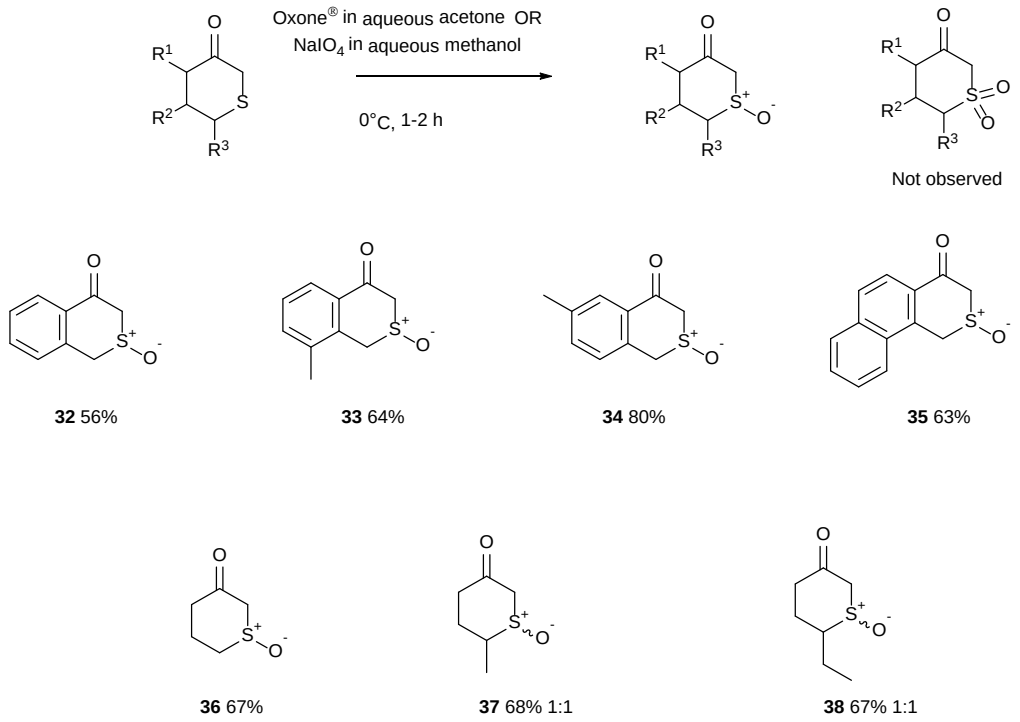


Figure 3: Oxidation of β-keto sulfides to novel β-keto sulfoxides.

2.3 Synthesis of α-diazosulfoxides in batch.

Diazo transfer to the sulfoxides was carried out using the Regitz diazo transfer methodology.[37] Previously, the optimum conditions for diazo transfer to sulfoxides have been reported in the literature with tosyl azide being the preferred diazo transfer reagent, triethylamine as base and acetonitrile as solvent.[17] Multiple reports exist in the literature on the safe generation and use of diazo transfer reagents,[3,7,8,18,38,39] and although tosyl azide is known to be shock sensitive and highly explosive it can be used effectively when proper precautions are taken - such as the addition of the diazo transfer to the reaction at 0°C. Diazo transfer to the sulfoxide substrates **32 - 38** is generally complete in 9 hours or less, and the ^{1}H NMR spectrum of the crude material shows the disappearance of the SOC*H*$_2$ signal and is accompanied by the appearance of the diazo stretch between 2111 cm $^{-1}$ and 2120 cm^{-1} in the infrared spectrum. The novel α-diazosulfoxide products **1 – 4** were isolated in moderate yields after purification by column chromatography (**Figure 4**). Interestingly, the naphthalene derived α-diazosulfoxide **4** was not successfully isolated as a pure compound after chromatography due to the presence of inseparable impurities caused by product decomposition, however the indicative signals were present in the ^{1}H NMR spectrum of the crude material. Additionally the monocyclic α-diazosulfoxides **5-7** were challenging to isolate as pure compounds but were present in low

yields (<12%). With the synthetic routes to these α-diazosulfoxides established in batch, and their syntheses achieved in moderate yields, in line with the dramatically enhanced yields from the lactone and lactam series utilizing continuous flow, this approach was next explored for the synthesis of the β-keto sulfoxide derivatives.[15]

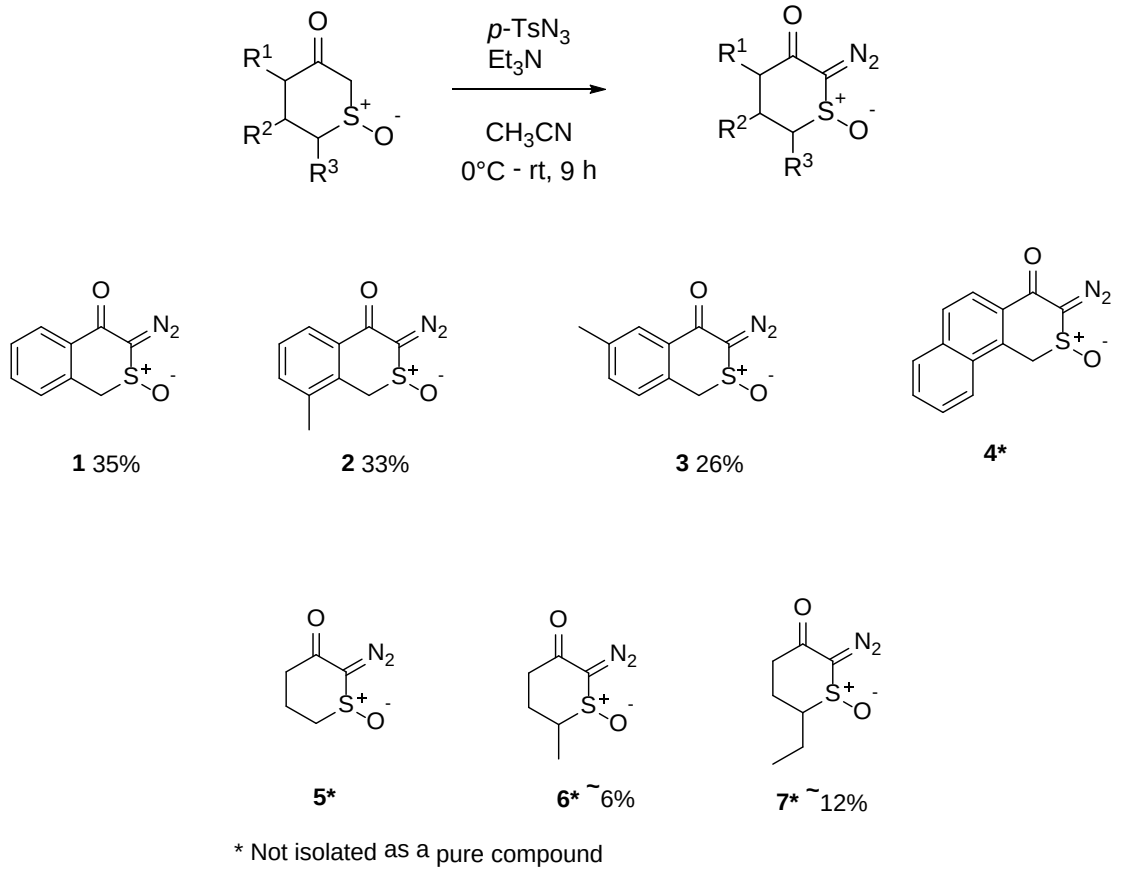


Figure 4: Synthesis of novel α-diazo-β-keto sulfoxides in standard batch conditions.

At the outset of this work we anticipated that the ketone derivatives of the α-diazosulfoxides would be much more reactive than our earlier lactone and lactam derivatives, based on general literature precedent across α-diazocarbonyl compounds.[4] While each of the α-diazosulfoxides was stored in a freezer, they proved to be remarkably stable compounds. Additionally, a thermogravimetric analysis of compound **1** shows the loss of molecular nitrogen and subsequent decomposition, which begins at the temperature of approximately 108°C (**Figure 5**).

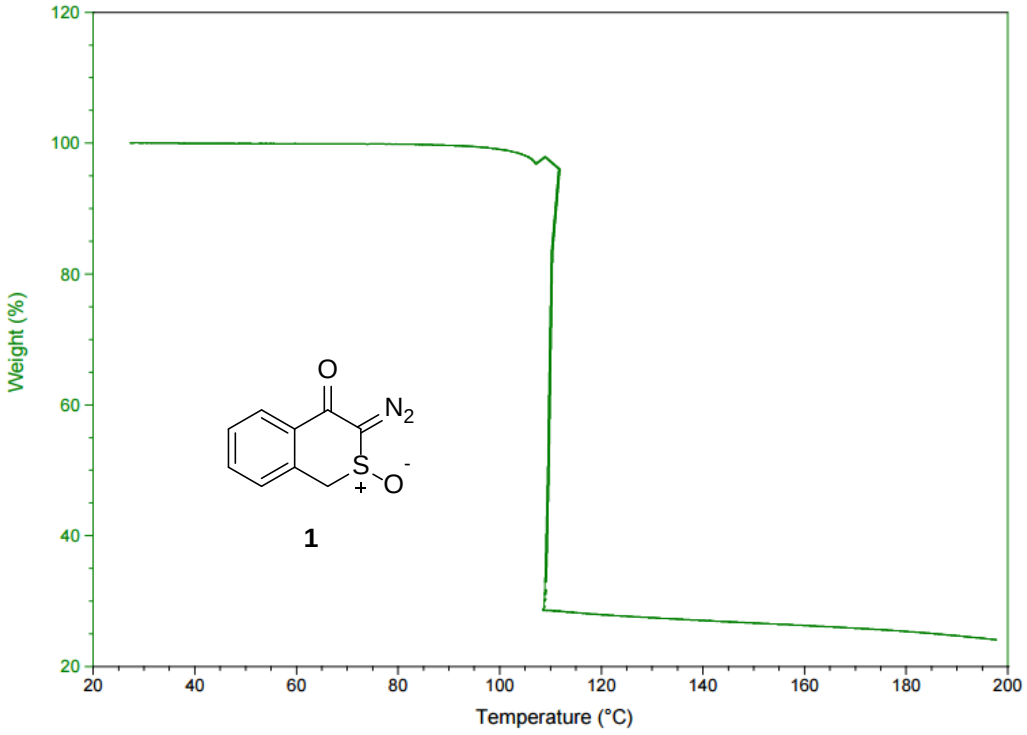


Figure 5

Indeed, a crystal structure of **3** was obtained demonstrating the stability of this compound; with its structure and stereochemistry unambiguously defined. Interestingly, the solid state structure demonstrates that the puckered conformation of the sulfoxide group results in the lone pair of electrons lying essentially in plane with the unsaturated diazo moiety and orthogonal to the π-orbitals of the diazo group (**Figure 6**). This prevents overlap with the π-orbitals which would facilitate loss of the diazo group. This provides further evidence for the suggested explanation for the stability of these cyclic α-diazosulfoxides.[19]

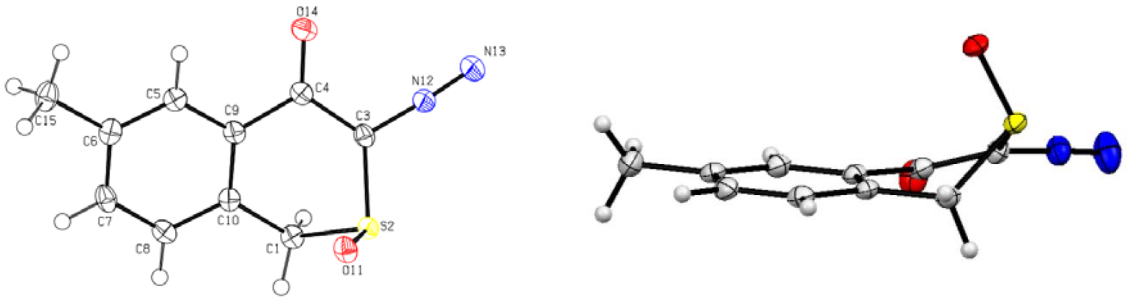


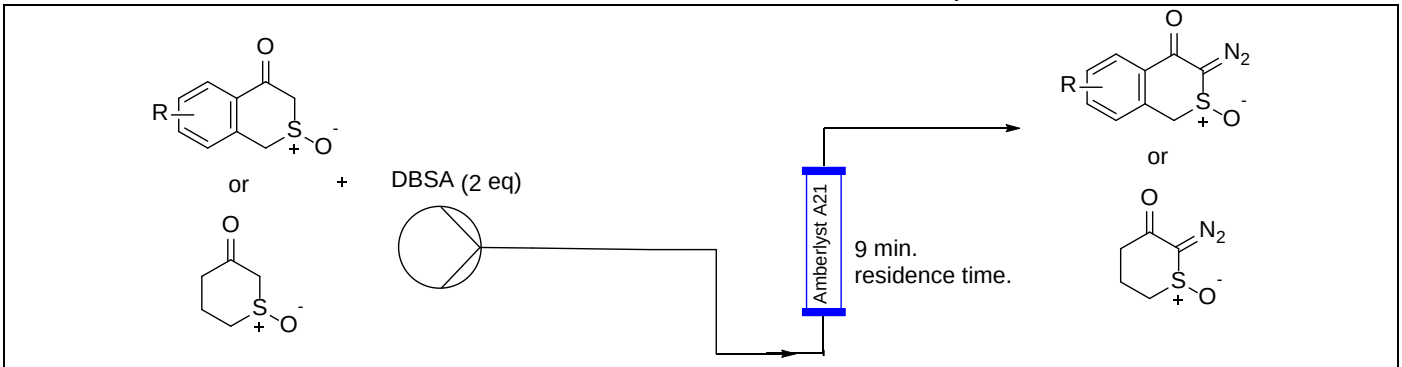
Figure 6: A front face view and a side view of **3** showing the structure and relative stereochemistry. Anisotropic displacement parameters are drawn at the 40% probability level.

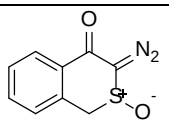
2.4 Continuous flow synthesis of α-diazo-β-keto sulfoxides.

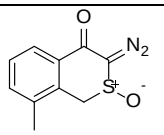
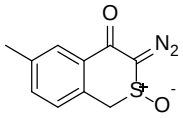
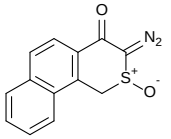
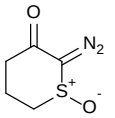
The generation of α-diazocarbonyl compounds utilizing continuous flow protocols has recently been reported by our group, and others, highlighting its applicability to continuous flow.[12-14] Having previously demonstrated a very useful, high yielding, synthetic method for the synthesis of lactone derived α-diazosulfoxides in continuous flow[15] we applied this protocol to the synthesis of the novel ketone derived α-

diazosulfoxides. Notably, this continuous flow protocol led to a 2 – 3 fold increase in the isolated yields of the lactone derived α-diazosulfoxides, has an enhanced safety profile through the use of dodecylbenzenesulfonyl azide (DBSA), is carried out at room temperature and has greater potential for scale-up, relative to the batch process. These conditions, optimised for the lactones derivatives, consist of flowing a solution of a mixture of the sulfoxide substrate and 2 equivalents of the diazo transfer reagent (DBSA) over solid supported base. This methodology using Amberlyst A21/solid supported dimethylamine is effective at promoting the transformation, with high conversions and high yields in short residence times (9 minutes). We are pleased to report, that application of this methodology to the synthesis of the novel, ketone derived α-diazosulfoxides proved successful also (**Table 1**). For effective conversion, two equivalents of the diazo transfer reagent were employed, and accordingly DBSA was chosen for its enhanced safety profile, relative to other diazo transfer agents.[8] The advantage of using DBSA in this instance, is that the crude reaction mixture can be safely concentrated under reduced pressure, and using column chromatography on silica gel, the residual sulfonyl azide can be separated from the sulfonyl amide and α-diazosulfoxide products; the extra equivalent of the sulfonyl azide to be efficiently recovered and reused.

Table 1: Diazo transfer to ketone derived sulfoxide in a continuous flow system.



Entry	Product	Conversion[c]	Flow Yield	Batch Yield
1	 **1**	96%	80%	35%

2	 **2**	89%	84%	33%
3	 **3**	95%	71%[a]	26%
4	 **4**	65%	39%[b]	Not isolated
5	 **5**	72%	19%	Not isolated

[a] On purification of the crude reaction mixture *via* column chromatography the starting sulfoxide **34** was recovered (15%) and the diazo was recovered in a yield of 60% (71% corrected for recovered SM).
[b] After purification of the crude reaction mixture by column chromatography on silica gel, new peaks of unidentified decomposition products appeared in the ^{1}H NMR spectrum of the diazosulfoxide product. The product was about 90% pure. A pure sample of the α-diazosulfoxide was isolated by slow recrystallization from DCM/Hexane.
[c] Conversions were calculated using ^{1}H NMR spectra of the product relative to starting material.

By balancing the efficiency of diazo transfer and the extent of base mediated side reactions, yields are significantly increased compared to the yields from the standard batch reactions. The process control which is enabled in flow reduces decomposition by limiting exposure to strongly basic conditions. For diazo transfer in the batch conditions a deep red colour is observed; this coloration is not seen in the crude product of the continuous flow reactions, however the solid supported base does undergo a colour change from yellow to a red/purple colour. For Table 1, entries 1–3 the diazosulfoxide targets **1**-**3**, are efficiently separated from the dodecylbenzene sulfonamide byproduct and the residual sulfoxide starting material by column chromatography. Interestingly, both the naphthalene derived diazosulfoxide **4** and the monocyclic diazosulfoxide **5** were isolated albeit in modest yield (Table 1 entries 4-5). In comparison to the batch process this methodology is a significant enhancement enabling for the first time isolation of these novel labile targets **4** and **5.**

The diazo transfer to these β-keto-sulfoxides in a continuous flow manner has proven to be much more effective than the corresponding batch reaction. Most importantly, careful control of the reaction conditions limits the loss of product through side reaction or decomposition. Currently, work is ongoing within our lab

to investigate the reactivity of this novel class of α-diazocarbonyl compounds which will be reported in due course.

Conclusion

Building on our earlier work we have successfully designed and isolated a series of novel α-diazo-β-keto sulfoxides leading to ketone derivatives for the first time. The adaption of the diazo transfer to a continuous flow process led to the formation of the desired products in higher yields and shorter reaction times than the respective batch conditions. Significantly, by limiting decomposition of more sensitive substrates these flow conditions allowed the synthesis of two of the targeted α-diazosulfoxides which could not be isolated from the analogous batch reaction, highlighting the utility of continuous flow in the synthesis of α-diazosulfoxides.

Experimental

General Procedures

All commercial reagents were used without further purification unless otherwise stated. ^{1}H NMR (400.13 Hz) and ^{13}C (100 MHz) NMR spectra were recorded on a 400 NMR spectrometer, ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a 300 MHz, All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm) and coupling constants in Hertz (Hz). Elemental analyses were performed using an elemental analyzer. Melting points were carried out on a capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a double focusing high resolution mass spectrometer (EI), a time of flight spectrometer (ESI) and a triple quadrupole spectrometer (ESI). Infrared (IR) spectra were recorded on the neat compound using an instrument with a UATR single reflection diamond, and only the characteristic peaks are reported. Thin layer chromatography (TLC) was carried out on precoated silica gel plates. Column chromatography was performed using silica gel 60. Visualisation was achieved by UV (254 nm) light detection, iodine staining, vanillin staining and ceric sulfate staining.

Sulfides

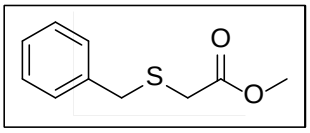
General procedure A for the synthesis of synthesis of sulfide esters

All reactions were carried out in an inert nitrogen atmosphere in a round bottomed flask equipped with a magnetic stirrer. Potassium carbonate (2 eq) was slowly added to a solution of methyl thioglycolate (1 eq) in methanol over 5 min at 0 °C. The mixture was allowed to reach room temperature and a solution of the alkyl halide (1 eq) in methanol was added. The reaction mixture was stirred for 1 h and filtered to remove the inorganic salts which had precipitated. The filtrate was concentrated *in vacuo* and the residue partitioned between water and diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The combined ethereal layers were washed with sat. sodium bicarbonate solution, water, brine and dried with anhydrous $MgSO_4$.

General Procedure B for the synthesis of sulfide esters.

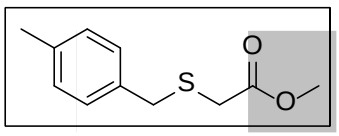
Potassium carbonate (1.5 eq) was directly added to a solution of the alkyl halide (1 eq) in acetone. Methyl thioglycolate (1 eq) in acetone was added over 5 mins at 0 °C, followed by a catalytic amount of sodium iodide (5 mol%). The mixture was heated under reflux for 14 h, cooled to room temperature and concentrated *in vacuo*. The white solid was partitioned between water and ethyl acetate and the aqueous layer washed with ethyl acetate. The combined organic layers were washed with water, brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo.*

Methyl 2-(benzylthio)acetate **8**



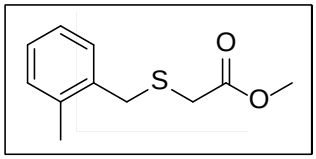
Known product synthesized according to general procedure A. Clear oil (4.58 g, 70%); ν_{max} (neat)/cm^{-1} 1736 (C=O); δ_H (400 MHz) 3.08 (2H, s), 3.71 (3H, s), 3.82 (2H, s), 7.18-7.47 (5H, m); δ_C (75.5 MHz) 32.1, 36.4, 52.3, 127.3, 128.6, 129.2, 137.2, 170.8; HRMS (ESI+): Exact mass calculated for $C_{10}H_{13}O_2S$ $[M+H]^+$, 197.0636. Found 197.0632; m/z (ESI+) 197 [$(M+H)^+$, 8%)]. Spectral details are in agreement with those reported in the literature.[40]

Methyl 2-(4-methylbenzylthio)acetate **12**[41]



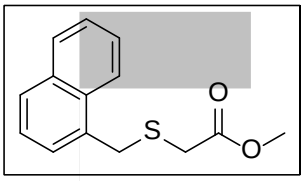
Known product synthesized according to general procedure B. Clear oil (11.29 g, 96 %); ν_{max} (film)/cm^{-1} 1737 (C=O).δ_H (400 MHz) 2.32 (3H, s), 3.07 (2H, s), 3.70 (3H, s), 3.78 (2H, s), 7.09-7.16 (2H, m), 7.18-7.23 (2H, m); δ_C (75.5 MHz) 21.1, 32.1, 36.1, 52.3, 129.1, 129.2, 134.1, 136.9, 170.9; HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_2S$ $[M+H]^+$, 211.0793. Found 211.0784; m/z (ESI+) 211 [$(M+H)^+$, 17%)].

Methyl 2-(2-methylbenzylthio)acetate **13**[42]



Known product according to general procedure B. Pale yellow oil (7.37 g, 98 %); ν_{max} (film)/cm^{-1} 1736 (C=O); δ_H (400 MHz) 2.41 (3H, s), 3.11 (2H, s), 3.74 (3H, s), 3.82 (2H, s), 7.07-7.23 (4H, m); δ_C (75.5 MHz) 19.1, 32.4, 34.5, 52.4, 125.8, 127.6, 130.0, 130.8, 134.8, 137.0, 171.0; Exact mass calculated for $C_{11}H_{15}O_2S$ $[M+H]^+$, 211.0793. Found 211.0780; m/z (ESI+) 211 [$(M+H)^+$, 18%)].

Methyl 2-(naphthalen-1-ylmethylthio)acetate **14**

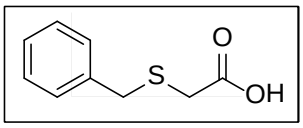


Known product synthesized according to general procedure B. Clear viscous oil (6.55 g, 94 %); ν_{max} (neat)/cm^{-1} 1732 (C=O); δ_H (400 MHz) 3.12 (2H, s), 3.71 (3H, s), 4.29 (2H, s), 7.35-7.57 (4H, m), 7.72-7.87 (2H, m), 8.13 (1H, d, *J* 8.4); δ_C (75.5 MHz) 32.6, 34.1, 52.4, 124.0, 125.1, 125.9, 126.3, 127.8, 128.5, 128.8, 131.4, 132.4, 134.2, 171.0; HRMS (ESI+): Exact mass calculated for $C_{14}H_{15}O_2S$ [M+H]$^+$, 247.0793. Found 247.0788; m/z (ESI+) 247 [(M+H)$^+$, 5%)]. Spectral details are in agreement with those reported in the literature.[34]

General procedure for the synthesis of sulfide acids.

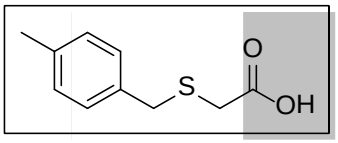
The sulfide ester precursor was added to a solution of acetic acid and water (50:50). The reaction mixture was heated under reflux for 20 h and cooled to room temperature. The mixture was extracted with diethyl ether (2 × 40 mL). The combined ethereal layers were washed with water (6 × 150 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo.*

2-(Benzylthio)acetic acid **9**



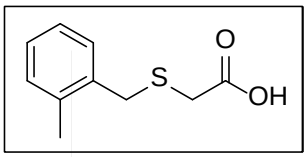
Known product, according to general procedure. White crystalline solid (3.63 g, 87 %); m.p. 62-63 °C (lit.,[32] 64 °C); ν_{max} (neat)/cm^{-1} 3431 (O-H) 1708 (C=O); δ_H (400 MHz) 3.10 (2H, s), 3.86 (2H, s), 7.21-7.48 (5H, m), 10.25 (1H, br s); δ_C (75.5 MHz) 31.9, 36.4, 127.4, 128.6, 129.2 136.9, 176.7; HRMS (ESI+): Exact mass calculated for $C_9H_{11}O_3S$ [M+O+H]$^+$, 199.0429. Found 199.0430; m/z (ESI$^-$) 181 [(M-H)$^-$, 90%]. Spectral details are in agreement with those provided in the literature. [32]

2-(4-Methylbenzylthio)acetic acid **16**



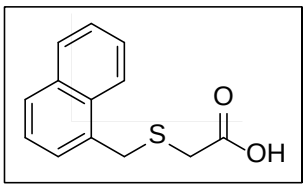
Clear oil (8.42 g, 80 %); m.p. 66-68 °C ν_{max} (neat)/cm^{-1} 3431 (O-H), 1642 (C=O). δ_H (400 MHz) 2.33 (3H, s), 3.09 (2H, s), 3.82 (2H, s), 7.13 (2H, d, *J* 7.9), 7.22 (2H, d, *J* 8.0), 10.56 (1H, br s); δ_C (75.5 MHz) 21.1, 32.0, 36.1, 129.1, 129.3, 133.8, 137.1, 177.1. Spectral details are in agreement with those provided in the literature.[43]

2-(2-Methylbenzylthio)acetic acid **15** [42]



Known product, synthesized according to the general procedure. Off-white solid (5.45 g, 79 %); m.p. 42-44 °C (lit.,[45] 43.5°C); ν_{max} (neat)/cm^{-1} 3019 (O-H), 1706 (C=O). δ_H (400 MHz) 2.41 (3H, s), 3.14 (2H, s), 3.88 (2H, s), 7.12-7.26 (4H, m), 9.50 (1H, br s); δ_C (75.5 MHz) 19.1, 32.3, 34.5 , 125.9, 127.8, 130.1, 130.9, 134.5, 137.0, 176.9.

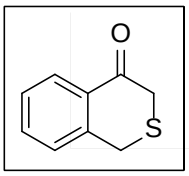
2-(Naphthalen-1-ylmethylthio)acetic acid **17** [34]



Off-white crystalline solid (1.16 g, 81 %); m.p. 110-112 °C (lit.,[34] 112 °C); ν_{max} (neat)/cm^{-1} 3049 (O-H), 1704 (C=O). δ_H (400 MHz) 3.16 (2H, s), 4.35 (2H, s), 7.36-7.62 (4H, m), 7.75-7.85 (1H, d, *J* 7.9), 7.85-7.92 (1H, d, *J* 8.2), 8.12 (1H, d, *J* 8.4), 11.20 (1H, br s); δ_C (75.5 MHz) 32.5, 34.1, 123.9, 125.1, 126.0, 126.3, 127.9, 128.6, 128.9, 131.3, 132.1, 134.2, 176.3; m/z (ESI$^-$) 231 [(M-H)$^-$, 100%]. Spectral details are in agreement with those reported in the literature.[34]

Cyclisation to sulfides.

Isothiochroman-4-one **11**[32]



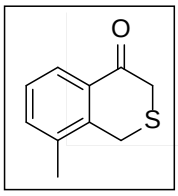
(i)Thionyl chloride (2 eq) in dichloromethane (10 mL) was added dropwise to 2-(benzylthio)acetic acid (1 eq) in dichloromethane (40 mL) over 10 min at 0 °C. The reaction mixture was allowed to slowly reach room temperature while stirring for 20 min. The solvent and excess thionyl chloride were removed *in vacuo* to leave 2-(benzylthio)acetyl chloride as a yellow oil which was used without further purification (2.45 g, 98 %); ν_{max} (neat)/cm^{-1} 1791 (C=O); δ_H (400 MHz) 3.51 (2H, s), 3.82 (2H, s), 7.21-7.49 (5H, m); δ_C (75.5 MHz) 36.2, 43.6, 127.7, 128.8, 129.2, 136.1, 170.1. Spectral details in agreement with those reported in the literature.[32]

(ii) Anhydrous aluminium chloride (1.2 eq) in dichloromethane (10 mL) was added to a solution of 2-(benzylthio)acetyl chloride (1 eq) in dichloromethane (40 mL). The reaction mixture was stirred overnight at room temperature. A solution of conc. hydrochloric acid in water (50:50, 40 mL) was added and the two layers were partitioned. The organic layer was washed with sat. sodium bicarbonate solution (2 × 10 mL), water (10 mL), brine (10 mL) and dried with anhydrous $MgSO_4$. The solution was concentrated *in vacuo* to give isothiochroman-4-one as a brown solid which was used without further purification (1.53 g, 76 %); m.p. 61-62 °C (lit.,[32] 60 °C); ν_{max} (neat)/cm^{-1} 1673 (C=O); δ_H (400 MHz) 3.53 (2H, s), 3.90 (2H, s), 7.17 (1H, d, *J* 7.9), 7.34-7.40 (1H, m), 7.43-7.49 (1H, m), 8.09 (1H, d, *J* 7.9); δ_C (75.5 MHz) 30.6, 37.1 127.7, 127.8, 129.0, 131.9, 133.0, 141.8, 191.0. Spectral details in agreement with those reported in the literature.[32]

General procedure for the cyclisation from the carboxylic acid to the cyclic sulfides.

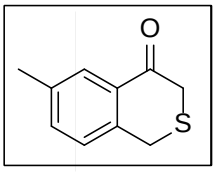
Phosphorous pentoxide (3 eq) was directly added to a stirring solution of the sulfide acid (1 eq) in hot toluene (60 °C). The mixture was stirred vigorously under reflux for 3 h, and a further 2 eq phosphorous pentoxide were then added. The mixture was stirred for an additional 2 h under reflux and cooled to room temperature. The organic solution was decanted from the brown insoluble mass, which was extracted twice with hot toluene (60 °C) The combined organic layers were washed with water, brine and dried with anhydrous $MgSO_4$. Concentration *in vacuo* gave the crude product, which can be recrystallized from 95% ethanol or purified by column chromatography on silica gel.

8-Methylisothiochroman-4-one **18**[42]



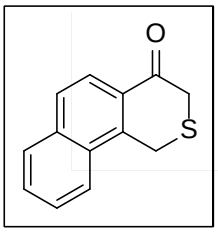
The title compound was prepared following the general procedure for the cyclisation to the sulfides. After purification of the crude reaction mixture by column chromatography on silica gel the product was isolated as a bright yellow solid (0.67 g, 31 %); m.p. 56-57 °C; ν_{max} (neat)/cm^{-1} 1681 (C=O).δ_H (400 MHz) 2.26 (3H, s), 3.41 (2H, s), 3.77 (2H, s), 7.18-7.27 (1H, m), 7.33 (1H, d, *J* 6.9 *H*), 7.94 (1H, d, *J* 7.8); δ_C (75.5 MHz) 19.6 , 27.5, 35.9, 127.6, 127.7, 132.6, 134.3, 135.4, 139.8, 191.1; HRMS (ESI+): Exact mass calculated for $C_{11}H_{11}OS$ $[M+H]^+$, 179.0531. Found 179.0526, m/z (ESI-) 178 $[(M)^-]$.

6-Methylisothiochroman-4-one **19**[44]



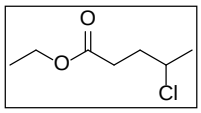
The title compound was prepared following the general procedure for the cyclisation to the sulfides. Following work-up, the crude product was isolated as a viscous yellow oil (0.85 g). ^{1}H NMR analysis indicated the presence of the desired product 6-methylisothiochroman-4-one along with a small quantity of unidentifiable impurities (~60% pure). Purification by flash chromatography (90:10 hexane:ethyl acetate) gave 6-methylisothiochroman-4-one as a bright yellow crystalline solid (0.53 g, 26%); m.p. 53-54 °C (lit.,[44] 52-53 °C); ν_{max} (neat)/cm^{-1} 1678 (C=O); δ_H (400 MHz) 2.22 (3H, s), 3.36 (2H, s), 3.70 (2H, s), 6.92 (1H, d, *J* 7.8), 7.10 (1H, m), 7.73 (1H, s); δ_C (75.5 MHz) 21.0, 30.3, 37.1, 127.7, 129.2, 131.6, 133.9, 137.5, 138.9 , 191.5. Spectral details in agreement with those reported in the literature.[44]

1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **20**[34]



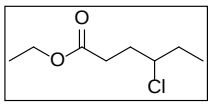
The title compound was prepared following the general procedure for the cyclisation to the sulfides giving the crude product as a light brown solid (2.33 g) which was purified by recrystallization from 95% ethanol to give 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene and a small amount of 2-(naphthalen-1-ylmethylthio)acetic acid (~4%) as a bright yellow solid (1.20 g, 22%). Found: C, 72.15; H, 4.69; S, 15.30. $C_{13}H_{10}OS$ requires C, 72.87; H, 4.69; S, 14.96%; m.p. 120-122°C (lit.,[34] 123-124 °C); ν_{max} (neat)/cm^{-1} 1678 C=O). δ_H (400 MHz) 3.58 (2H, s), 4.37 (2H, s), 7.58-7.65 (2H, m), 7.81 (1H, d, *J* 8.0), 7.84-7.91 (1H, m), 8.00-8.11 (1H, m), 8.15 (1H, d, *J* 7.9); δ_C (75.5 MHz) 26.9, 35.6, 124.0, 124.1, 127.3, 127.8, 128.5, 129.0, 129.8, 130.5, 135.3, 139.4, 191.2. Spectral details in agreement with those reported in the literature.[34]

Ethyl 4-chloropentanoate **24**



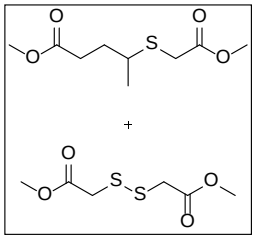
γ-Valerolactone (2.04 g, 20.35 mmol, 1 eq) was added directly to thionyl chloride (1.55 mL, 21.36 mmol, 1.05 eq) at room temperature. The mixture was stirred at 80 °C for 3 h and cooled to room temperature. Ethanol (1.31 mL, 22.38 mmol, 1.1 eq) was added dropwise over 5 min at 0 °C. The solution was then stirred for 16 h under reflux, cooled to room temperature, and concentrated *in vacuo* to give a brown oil (2.15 g). ^{1}H NMR analysis indicated the presence of γ-valerolactone and the product (1.6:1). The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (90:10) as eluent to give ethyl 4-chloropentanoate **24** as a pale yellow oil (1.77 g, 53%); ν_{max}(film)/cm^{-1} 1731 (C=O), 1334 (C-O), 1187 (C-O); δ_H (400 MHz) 1.24 (3H, t, *J* 7.0, C*H*$_3$), 1.51 (3H, d, *J* 6.1, C*H*$_3$), 1.88-1.99 (1H, m, one of C*H*$_2$), 2.02-2.16 (1H, m, one of C*H*$_2$), 2.41-2.60 (2H, m, C*H*$_2$), 4.01-4.20 (3H, m, contains 1H m of C*H*, and 2H q, *J* 7.2, of C*H*$_2$ at 4.10); δ_C (75.5 MHz) 14.2 (*C*H$_3$), 25.3 (*C*H$_3$), 31.3 (*C*H$_2$), 35.1 (*C*H$_2$), 57.7 (*C*H), 60.5 (*C*H$_2$), 172.9 (*C*=O). Spectral details in agreement with those reported in the literature.[45]

Ethyl 4-chlorohexanoate **25**



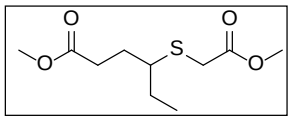
The title compound was prepared following the procedure described in for ethyl ester **24** using thionyl chloride (11.01 mmol, 0.80 mL, 1.05 eq), γ-caprolactone (10.49 mmol, 1.20 g, 1 eq) and ethanol (11.54 mmol, 0.66 mL, 1.1 eq). Following work up, the crude product was isolated as a yellow oil (0.99 g). ^{1}H NMR analysis indicated the presence of ethyl 4-chlorohexanoate and γ-caprolactone (1:2). The crude material was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent to give the ester **25** as the major component of a fraction which was a pale yellow oil (0.60 g, 33%); ν_{max}(film)/cm^{-1} 1736 (C=O), 1179 (C-O); δ_H (400 MHz) 1.04 (3H, t, J 7.3, CH$_3$), 1.26 (3H, t, J 7.1, CH$_3$), 1.67-1.86 (2H, m, CH$_2$), 1.87-1.99 (1H, m, one of CH$_2$), 2.07-2.18 (1H, m, one of CH$_2$), 2.44-2.61 (2H, m, CH$_2$), 3.84-3.93 (1H, m, CH), 4.14 (2H, q, *J* 7.1, CH$_2$); A signal for a minor impurity was observed at 1.32 – 1.39 ppm as a triplet. δ_C (75.5 MHz) 10.9 (CH$_3$), 14.2 (CH$_3$), 31.3, 31.6, 33.0, (3 × CH$_2$), 60.5 (OCH$_2$), 64.6 (CH), 173.0 (C=O); m/z (ESI+)179 {[(C$_8$H$_{15}$^{35}ClO$_2$)H+], 30%, 181 {[(C$_8$H$_{15}$^{37}ClO$_2$)+H+], 15%}, [(M-HCl)+, 100%]. Spectral details in agreement with those reported in the literature. [36]

Methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **26**



Methyl thioglycolate (5.82 mL, 65.15 mmol, 1 eq) in methanol (10 mL) was added to a solution of sodium methoxide (1.50 g sodium, 65.15 mmol, 1 eq) in methanol (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 10 min and then ethyl 4-chloropentanoate **24** (9.81 g, 65.15 mmol, 1 eq) in methanol (10 mL) was added slowly. The reaction mixture was stirred for 72 h under reflux. The filtrate was concentrated *in vacuo* to give a yellow oil. Water (80 mL) was added to the oil and extracted with diethyl ether (3 × 30 mL). The combined ethereal layers were washed with water (20 mL), brine (20 mL), dried with anhydrous MgSO$_4$ and concentrated *in vacuo* to give the crude product as a pale yellow oil (10.32 g). ^{1}H NMR analysis indicated the presence of a complex mixture of compounds, including the product methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **26.** The mixture was purified by Kugelrohr distillation. The product methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **26** and a small quantity of remaining disulfide, methyl bis(thioacetate) (4:1, 3.97 g, ~22%) were isolated at 175-180 °C, 15 Torr. Attempts to further purify the mixture by distillation and base extraction were unsuccessful however the disulfide is removed during the Dieckmann condensation in the presence of potassium *t*-butoxide; ν_{max}(film)/cm^{-1} 1733 (C=O). Methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **26**: δ_H (400 MHz) 1.31 (3H, d, *J* 6.8, CH$_3$), 1.87 (2H, dt appears as q, *J* 7.7, CH$_2$), 2.47 (2H, m, CH$_2$), 2.95 (1H, sextet, *J* 6.7, CH), 3.26 (2H, fine ABq appears as s, CH$_2$), 3.68 (3H, s, OCH$_3$), 3.73 (3H, s, OCH$_3$); δ_C (75.5 MHz) 20.9 (CH$_3$), 31.1, 31.2, 32.0 (3 × CH$_2$), 40.2 (CH), 51.6 (OCH$_3$), 52.4 (OCH$_3$), 171.1 (C=O), 173.6 (C=O); m/z (ESI+) HRMS (ESI+): Exact mass calculated for C$_9$H$_{17}$O$_4$S [M+H]+, 221.0848. Found 221.0844; m/z (ESI+) 221 [(M+H)+, 40 %)], 243 [(M+Na)+, 62%].Characteristic signals of the methyl bis(thioacetate); δ_H (400 MHz) 3.60(4H, s, 2 x CH$_2$), 3.78 (6H, s, 2 x OCH$_3$); δ_C (75.5 MHz) 41.2 (2 x CH$_2$,), 52.6 (2 x CH$_3$), 169.8 (2 x C=O).

Methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate ***27***



The title compound was prepared following the procedure described for methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **26** using ethyl 4-chlorohexanoate **25** (10.25 g, 62.29 mmol, 1 eq), methyl thioglycolate (5.57 mL, 62.29 mmol, 1 eq), sodium (1.143 g sodium, 62.29 mmol, 1 eq) and methanol (80 mL). Following work up, the crude product was isolated as a yellow oil (12.76 g). ^{1}H NMR analysis of the crude material indicated the presence of a mixture of a complex mixture of compounds, including the product methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **27** and methyl bis(thioacetate). The crude product was purified by Kugelrohr distillation. Methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **27** and remaining disulfide, methyl bis(thioacetate) were isolated at 180-185 °C, 15 Torr (1.8:1, 4.60 g). ν_{max}(film)/cm^{-1} 1736 (C=O). Methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **27** δ_H (400 MHz) 1.00 (3H, t, *J* 7.4, CH$_3$), 1.52-1.69 (2H, m, CH$_2$), 1.73-1.84 (1H, m, one of CH$_2$), 1.90-2.01 (1H, m, one of CH$_2$), 2.50 (2H, t, *J* 7.6, CH$_2$), 2.68-2.77 (1H, m, CH), 3.22 (2H, fine ABq appears as s, SCH$_2$), 3.68 (3H, s, OCH$_3$), 3.73 (3H, s, OCH$_3$); δ_C (75.5 MHz) 11.0 (CH$_3$), 27.7, 29.1,

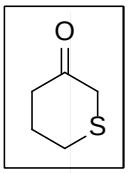
31.5, 32.3 (4 × CH_2), 47.6 (CH), 51.8, 52.5 (2 × OCH_3), 171.0, 173.7 (2 × C=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_{19}O_4S$ $[M+H]^+$, 235.1004. Found 235.1004; m/z (ESI+) 234 [(M+H)+, tentative]. Characteristic signals of the methyl bis(thioacetate); δ_H (400 MHz) 3.60(4H, s, 2 x CH_2), 3.78 (6H, s, 2 x OCH_3); δ_C (75.5 MHz) 41.2 (2 x CH_2,), 52.6 (2 x CH_3), 169.8 (2 x C=O).

General procedure for the synthesis of monocyclic sulfides.

a) Potassium *t*-butoxide (2 eq) was added directly to a solution of methyl 4-[(2-methoxy-2-oxomethyl)thio]butanoate **21** (1 eq) in diethyl ether (150 mL) at 0 °C. The solution was allowed to slowly reach room temperature while stirring for 4 h. The mixture was hydrolysed with water/acetic acid (80:20, 60 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 30 mL). The combined ethereal layers were washed with water (5 × 60 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the cyclised β-keto ester and enol mixture (1:4, 6.96 g) as a yellow oil which was used directly in the next step.

b) The crude β-keto ester and enol mixture 22 (1:4) was stirred under reflux in aqueous sulfuric acid (10%, 100 mL) overnight and then cooled to room temperature. Aqueous sodium hydroxide solution (10%) was added dropwise to pH 7. The mixture was extracted with diethyl ether (3 × 40 mL). The combined ethereal layers were washed with water (20 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product **23**. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using ethyl acetate/hexane as eluent (50:50).

Dihydro-2H-thiopyran-3(4H)-one **23**[46]

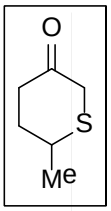


(a)The keto enol mixture was prepared following the general procedure outlined above. The product (1:4, 6.96 g) was isolated as a yellow oil which was used directly in the next step.

β-Keto ester **22**: δ_H (400 MHz) 2.41-2.53 (2H, m), 2.60-2.69 (2H, m), 3.05-3.3.14 (2H, m), 3.80 (3H, s), 4.00 (1H, s). Enol: δ_H (400 MHz) 2.08-2.17 (2H, m), 2.38-2.45 (2H, m), 2.77-2.83 (2H, m), 3.81 (3H, s), 12.17 (1H, br s).

(b)Known product **23**, isolated as a yellow oil (3.97 g, 50% over the two steps); ν_{max} (neat)/cm^{-1} 1708 (C=O); δ_H (400 MHz) 2.43-2.44 (4H, m), 2.77-2.80 (2H, m), 3.21 (2H, s); δ_C (75.5 MHz) 28.6, 33.4, 38.6, 41.9, 203.9; HRMS (ESI+): Exact mass calculated for C_5H_9OS $[M+H]^+$, 117.0374. Found 117.0371; m/z (ESI+) 117 $[(M+H)^+$, 8%]. Spectral details in agreement with those reported in the literature. [46]

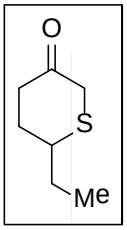
6-Methyl-dihydro-2H-thiopyran-3(4H)-one **30**[47]



(a)The keto enol mixture **28** was prepared following the general procedure outlined above. *β*-keto ester and enol mixture (1:9, 1.87 g) as an orange oil which was used directly in the next step. Characteristic signals for β-keto ester: δ_H (400 MHz) 1.22 (3H, d, *J* 6.0), 3.78 (3H, s), 3.85 (1H, s). Characteristic signals for enol: δ_H (400 MHz) 1.31 (3H, d, *J* 6.0), 3.80 (3H, s), 12.16 (1H, br s).

(b) The crude reaction mixture was concentrated *in vacuo* to give 6-methyldihydro-2*H*-thiopyran-3(4*H*)-one **30** as a dark orange oil which was used without further purification (0.56 g, 64% over the two steps); ν_{max} (neat)/cm^{-1} 1713 (C=O); δ_H (400 MHz) 1.29 (3H, d, *J* 6.1), 2.09-2.20 (1H, m), 2.35-2.52 (3H, m), 3.00 (1H, d, *J* 12.0, A of AB_q), 3.10-3.19 (1H, m), 3.44 (1H, d, *J* 12.0, B of AB_q); δ_C (75.5 MHz) 20.0 , 37.3, 37.7, 40.7, 40.9, 204.4 ; m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_6H_{11}OS$ $[M+H]^+$, 131.0531. Found 131.0525; m/z (ESI+) 129 $[(M-H)^-$, tentative].

6-Ethyl-dihydro-2H-thiopyran-3(4H)-one **31** [35]



(a) The keto enol mixture was prepared following the general procedure outlined above. The β-keto ester and enol mixture **29** (1:5, 1.97 g) as an orange oil which was used directly in the next step. Characteristic signals for β-keto ester: δ_H (400 MHz) 1.20 (3H, t, *J* 7.4), 3.76 (3H, s), 3.90 (1H, s). Characteristic signals for enol: δ_H (400 MHz) 1.12 (3H, t, *J* 7.4), 3.81 (3H, s), 12.20 (1H, br s).

(b) The crude reaction mixture was concentrated *in vacuo* to give 6-ethyldihydro-2*H*-thiopyran-3(4*H*)-one (1.04 g, 71% over the two steps) and a trace amount of impurities as a viscous yellow oil which was used without further purification; ν_{max} (neat)/cm^{-1} 1714 (C=O); δ_H (400 MHz) 1.04 (3H, t, *J* 7.4), 1.57-1.68 (2H, m), 2.06-2.19 (1H, m), 2.36-2.53 (2H, m), 2.95-3.04 (1H, m), 3.05 (1H, d, *J* 13.3, A of AB_q), 3.36 (1H, d, *J* 13.3, B of AB_q); δ_C (75.5 MHz) 12.1, 27.6, 37.3, 38.0, 40.4, 44.2, 204.7; m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_7H_{13}OS$ $[M+H]^+$, 145.0687. Found 145.0682; m/z (ESI+) 145 $[(M+H)^+$, 43%)].

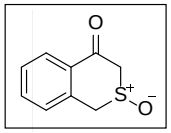
General Procedure A for the preparation of sulfoxides – $NaIO_4$

A solution of sodium metaperiodate (1 eq) in water was added slowly to a solution of the sulfide (1 eq) in methanol while stirring at 0 °C. After 5 min, a white precipitate had formed. The reaction was monitored by TLC and stirred for 2.5 h while returning to room temperature. The precipitate was filtered and the filtrate concentrated *in vacuo* to leave the sulfoxide and remaining salt mixture as a solid. Dichloromethane was added and the mixture stirred for 10 min. The remaining solid was removed by filtration and the filtrate concentrated *in vacuo* to give the pure sulfoxide as a light brown solid which was pure by ^{1}H NMR spectroscopy.

General Procedure B for the preparation of sulfoxides – Oxone®.

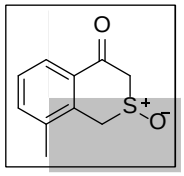
Oxone® (0.5 eq) in water was added dropwise to a stirring solution the sulfide (1 eq) in acetone at 0 °C. The mixture was allowed to slowly reach room temperature while stirring over 2 h. Water was then added to the flask to dissolve the inorganic salts. The resulting solution was extracted with dichloromethane (2 × 20 ml) and the combined organic layers washed with water, brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude sulfoxide.

Isothiochroman-4-one 2-oxide ***32***[48]



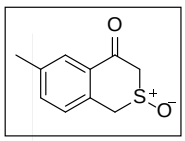
The sulfoxide was prepared using general procedure A for the preparation of sulfoxides. Light brown crystals (0.17 g, 56%); m.p. 169-171 °C (lit.,[48] 170-171 °C); ν_{max} (neat)/cm^{-1} 1681 (C=O), 1024 (S-O); δ_H (300 MHz) 3.94 (1H, d, *J* 15.4, A of AB_q), 3.98 (1H, d, *J* 15.4, B of AB_q), 4.32 (1H, d, *J* 15.3, A of AB_q), 4.36 (1H, d, *J* 15.3, B of AB_q), 7.36 (1H, d, *J* 7.6), 7.46-7.53 (1H, m), 7.61-7.67 (1H, m), 8.13 (1H, d, *J* 7.9); δ_C (75.5 MHz) 52.4, 59.0, 128.3, 129.2, 131.1, 131.4, 131.6, 135.4, 187.9; HRMS (ESI+): Exact mass calculated for $C_9H_9O_2S$ [M+H]$^+$, 181.0323. Found 181.0317, m/z (ESI$^-$) 179 [(M-H)$^-$, 10%)]. Spectral details in agreement with those reported in the literature.[48]

8-Methylisothiochroman-4-one S-oxide ***33***



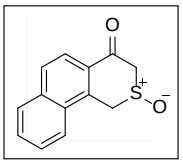
The sulfoxide was prepared using general procedure B for the preparation of sulfoxides. Bright white crystalline solid (208 mg, 64%); found: C, 62.20; H, 5.13; S, 16.48. $C_{10}H_{10}O_2S$ requires C, 61.83; H, 5.19; S, 16.51%; m.p. 148-149 °C; ν_{max} (neat)/cm^{-1} 1680 (C=O), 1047 (S-O); δ_H (400 MHz) 2.42 (3H, s), 3.96 (1H, d, *J* 14.7, A of AB_q), 4.02 (1H, d, *J* 14.7, B of AB_q), 4.23 (1H, d, *J* 16.0, A of AB_q), 4.30 (1H, d, *J* 16.0, B of AB_q), 7.33-7.39 (1H, m), 7.52 (1H, d, *J* 18.2), 7.98 (1H, d, *J* 18.2) δ_C (75.5 MHz) 20.0, 48.8, 58.6, 126.2, 128.4, 129.9, 131.8, 137.1, 138.1, 188.5; HRMS (ESI+): Exact mass calculated for $C_{10}H_{11}O_2S$ [M+H]$^+$, 195.0480. Found 195.0471, m/z (ESI+) 195 [(M+H)$^+$, 10%)].

6-Methylisothiochroman-4-one 2-oxide ***34***



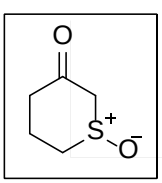
The sulfoxide was prepared using general procedure B for the preparation of sulfoxides. Bright white crystalline solid (220 mg, 80%). Found: C, 62.10; H, 5.24; S, 16.35. $C_{10}H_{10}O_2S$ requires C, 61.83; H, 5.19; S, 16.51%; m.p. 140-142 °C; ν_{max} (neat)/cm^{-1} 1679 (C=O), 1048 (S-O); δ_H (400 MHz) 2.41 (3H, s), 3.94 (1H, d, *J* 15.6, A of AB_q), 4.02 (1H, d, *J* 15.6, B of AB_q), 4.25 (1H, d, *J* 14.9, A of AB_q), 4.32 (1H, d, *J* 14.9, B of AB_q), 7.26 (1H, d, *J* 15.6), 7.46 (1H, d, *J* 15.6), 7.93 (1H, s); δ_C (75.5 MHz) 21.1, 52.4, 59.3, 128.4, 128.6, 129.2, 131.1, 131.4 136.4, 139.5 188.1; HRMS (ESI+): Exact mass calculated for $C_{10}H_{11}O_2S$ [M+H]$^+$, 195.0480. Found 195.0472, m/z (ESI+) 195 [(M+H)$^+$, 95%)].

1H-Benzo[h]isothiochromen-4(3H)-one 2-oxide ***35***



The sulfoxide was prepared using general procedure B for the preparation of sulfoxides. White crystalline solid (81 mg, 63%). Found: C, 67.80; H, 4.34; S, 13.61. $C_{13}H_{10}O_2S$ requires C, 67.80; H, 4.38; S, 13.92%; m.p. 189-191 °C; ν_{max} (neat)/cm^{-1} 1681 (C=O), 1045 (S-O); δ_H (400 MHz) 4.10 (1H, d, *J* 14.9, A of AB_q), 4.19 (1H, d, *J* 14.9, B of AB_q), 4.64 (1H, d, *J* 15.2, A of AB_q), 4.86 (1H, d, *J* 15.2, B of AB_q), 7.64-7.78 (2H, m), 7.83-8.00 (2H, m), 8.05-8.20 (2H, m); δ_C (75.5 MHz) 48.1, 58.7, 122.8, 124.3, 128.0, 129.3, 129.3, 129.4, 129.7, 129.9, 131.3, 136.7 , 188.4 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{11}O_2S$ [M+H]$^+$, 231.0480. Found 231.0477, m/z (ESI$^+$) 231 [(M+H)$^+$, 15%)].

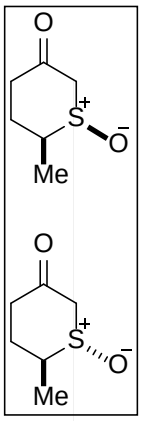
Dihydro-2H-thiopyran-3(4H)-one S-oxide ***36***[49]



The sulfoxide was prepared using general procedure A for the synthesis of sulfoxides. Pale yellow solid (0.38 g, 67 %), which was used without further purification; Found: C, 45.06; H, 6.14; S, 23.94. $C_5H_8SO_2$ requires C, 45.43; H, 6.10; S, 24.26%; m.p. 84-85 °C (lit.,[49] 85-88 °C); ν_{max} (neat)/cm^{-1} 1715 (C=O); δ_H (400 MHz) 2.26-2.36 (1H, m, one of CH_2), 2.51-2.64 (2H, m, CH_2), 2.78-2.94 (1H, m, one of CH_2), 2.95-3.05 (1H, m, one of CH_2), 3.08-3.16 (1H, m, one of CH_2), 3.63 (1H, A of AB_q, *J* 13.3, one of CH_2), 3.69 (1H, B of AB_q, *J* 13.3, one of CH_2); δ_C (75.5 MHz) 19.3,

41.4, 46.7, 59.8, 199.7 ; m/z (ESI+) 133 [$(M+H)^+$, 30%)]. Spectral details in agreement with those reported in the literature.[49]

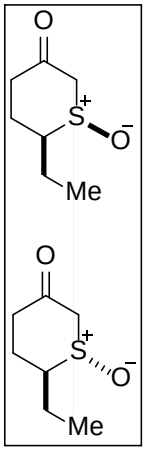
(1R, 6S*)-6-Methyl-dihydro-2H-thiopyran-3(4H)-one S-oxide and (1R*, 6R*)-6-methyl-dihydro-2H-thiopyran-3(4H)-one S-oxide* ***37***[36]



The sulfoxides were prepared using general procedure A for the synthesis of both sulfoxides. Isolated as a pale yellow crystalline solid (1:1 by ^{1}H NMR, 0.11 g, 68 %). ν_{max} (neat)/cm^{-1} 1718 (C=O), 1011 (S-O); δ_H (300 MHz) 1.44 (3H, d, *J* 7.0, C*H*$_3$ of one diastereomer), 1.54 (3H, d, *J* 7.0, C*H*$_3$ of one diastereomer), 1.79-1.91, (1H, m, one of C*H*$_2$ of one diastereomer), 2.11-2.21 (1H, m, one of C*H*$_2$ of one diastereomer), 2.46-2.78 (6H, m, 3 × C*H*$_2$ of two diastereomers), 3.02-3.16 (2H, m, C*H* of two diastereomers), 3.61-3.70 (3H, m, containing 2H AB_q of one diastereomer and 1H A of AB_q of other diastereomer), 3.89 (1H, dd, *J* 12.6, 0.8, B of AB_q of one diastereomer); δ_C (75.5 MHz) 14.3*, 15.5 (2 × *C*H$_3$ of two diastereomers), 25.5*, 27.5 (2 × *C*H$_2$ of two diastereomers), 39.1*, 40.9 (2 × C*H*$_2$ of two diastereomers), 51.1, 55.0* (2 × C*H* of two diastereomers), 58.1, 60.0* (2 × C*H*$_2$ of two diastereomers), 199.6*, 200.6 (2 × *C*=O of two diastereomers); m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_6H_{11}O_2S$ $[M+H]^+$, 147.0480. Found 147.0475; m/z (ESI+) 147 [$(M+H)^+$, tentative].

* Signals relating to one diastereomer as evident in ^{13}C NMR spectrum of a sample when the ratio was not identical.

(1R, 6S*)-6-Ethyl-dihydro-2H-thiopyran-3(4H)-one S-oxide and (1R*, 6R*)-6-ethyl-dihydro-2H-thiopyran-3(4H)-one S-oxide* ***38***



The sulfoxides were prepared using general procedure A for the synthesis of sulfoxides. Sulfoxides (major:minor 1: 0.9*, 0.11 g, 67%) were isolated as a pale yellow crystalline solid; ν_{max} (KBr)/cm^{-1} 1718 (C=O), 1018 (S-O); δ_H (300 MHz) 1.11-1.20 (5.8H, m, contains 2 × overlapping C*H*$_3$, t of two diastereomers), 1.59-2.25 (7.7H, m, 2 × C*H*$_2$ of two diastereomers), 2.47-2.97 (5.9H, m, contains C*H*$_2$ and C*H* of two diastereomers), 3.54-3.70 (2.8H, m, contains A of AB_q of major diastereomer and AB_q of minor diastereomer), 3.86 (1H, B of AB_q, *J* 12.8, 0.8, major diastereomer); δ_C (75.5 MHz) 11.1 (*C*H$_3$ of major diastereomer), 11.8 (*C*H$_3$ of minor diastereomer), 21.5, 22.7, 23.1, 25.7 (4 × *C*H$_2$ of two diastereomers), 38.9 (*C*H$_2$ of major diastereomer), 41.1 (*C*H$_2$ of minor diastereomer), 58.0 (*C*H$_2$ of minor diastereomer), 58.2 (*C*H of minor diastereomer), 59.7 (*C*H$_2$ of major diastereomer), 61.4 (*C*H of major diastereomer), 199.7 (*C*=O of major diastereomer), 200.8 (*C*=O of minor diastereomer); HRMS (ESI+): Exact mass calculated for $C_7H_{13}O_2S$ $[M+H]^+$, 161.0636. Found 161.0634; m/z (ESI+) 161 [$(M+H)^+$, 18 %)].

Unidentifiable signal observed, presumably due to small amount of impurities: δ_H (300 MHz) 3.71-3.84 (m).

* For the diastereomeric sulfoxides, it is not known which is the major diastereomer and which is the minor diastereomer.

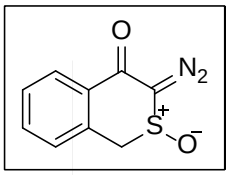
Synthesis of α-diazosulfoxides in batch.

General procedure A for the synthesis of α-diazosulfoxides in batch.

A solution of triethylamine (1 eq) in acetonitrile was added dropwise to a solution of the sulfoxide (1 eq) in acetonitrile while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and a solution of tosyl azide* (1 eq) in acetonitrile was then added slowly while stirring at 0 °C under a nitrogen atmosphere. The solution was allowed to slowly reach room temperature while stirring under the inert atmosphere over 9 h. The solvent was removed under reduced pressure to yield the crude product. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent to give α-diazosulfoxides.

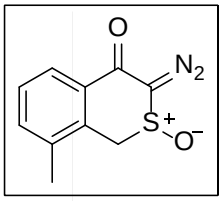
*Tosyl azide is a reactive sulfonyl azide and should always be handled with care. Precautions taken include storage in a freezer at -4°C. The sulfonyl azide is melted before use in a bath of luke warm water and weighed out as a liquid. Sulfonyl azides should never be handled with metal spatulas, sharp glass pipettes, heated or dropped, due to their heat and shock sensitivity. Care should be taken while handling diazo compounds to limit personal exposure. While no explosion or detonation occurred during these studies it is prudent to handle diazo compounds behind a blast shield.

3-Diazoisothiochroman-4-one S-oxide ***1***



The α-diazosulfoxide was synthesized using the batch procedure, and following purification isolated as pale brown solid (0.31 g, 35%). Decolourisation of a dichloromethane solution with activated charcoal gave yellow crystals; found: C, 52.13; H, 2.67; N, 13.22. $C_9H_6N_2O_2S$ requires C, 52.42; H, 2.93; N, 13.58%; m.p. 78-79 °C (decomp.); ν_{max} (neat)/cm^{-1} 2120 (C=N_2), 1632 (C=O), 1054 (S-O); δ_H (400 MHz) 4.32 (2H, fine AB_q appears as s), 7.39 (1H, d, *J* 7.1), 7.52-7.65 (2H, m), 8.14 (1H, dd, *J* 7.6, 1.5); δ_C (75.5 MHz) 52.9, 79.2, 127.6, 129.4, 130.3, 131.2, 131.7, 133.9, 176.0; HRMS (ESI+): Exact mass calculated for $C_9H_7N_2O_2S$ $[M+H]^+$, 207.0228. Found 207.0228.

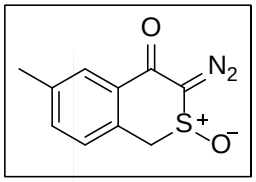
3-Diazo-8-methylisothiochroman-4-one S-oxide ***2***



The α-diazosulfoxide was synthesized using the batch procedure, and following purification isolated as a pale brown solid (602 mg, 33%). Decolourisation of a dichloromethane solution with activated charcoal gave yellow crystals; m.p. 72-74 °C (decomp.); ν_{max} (neat)/cm^{-1} 2114 (C=N_2), 1624 (C=O); δ_H (400 MHz) 2.44 (3H, s), 4.07 (1H, d, *J* 15.5, A of ABq), 4.58 (1H, d, *J* 15.5, B of ABq), 7.42 (1H, t, *J* 7.7), 7.49 (1H, d, *J* 7.0,), 8.01 (1H, d, *J* 6.9); δ_C (75.5 MHz) 19.9, 48.8, 78.7, 125.6, 128.6, 131.6, 135.9, 138.5), 176.5 (*C*=O)*. HRMS (ESI+): Exact mass calculated for $C_{10}H_9N_2O_2S$ $[M+H]^+$, 221.0385. Found 221.0384, m/z (ESI+) 221 $[(M+H)^+$, 18%], 193 $[(C_{10}H_9O_2S)^+$, sulfine 80%].

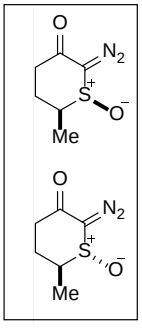
Note: One C_q signal was not observed in the ^{13}C NMR spectrum.

3-Diazo-6-methylisothiochroman-4-one S-oxide ***3***



The α-diazosulfoxide was synthesized using the batch procedure, and following purification isolated as pale brown crystals (0.38 mg, 26%). Decolourisation of a dichloromethane solution with activated charcoal gave yellow crystals; m.p. 64-65 °C (decomp.); ν_{max} (KBr)/cm^{-1} 2111 (C=N_2), 1680 (C=O), 1084 (S-O); δ_H (400 MHz) 2.43 (3H, s), 4.27 (2H, fine AB_q appears as s), 7.27 (1H, d, *J* 6.4), 7.41 (1H, dd, *J* 7.7, 1.3), 7.94 (1H, unresolved d, *J* 1.1); δ_C (75.5 MHz) 21.2, 52.7, 79.2, 127.2, 127.9, 130.9, 131.6, 134.6, 139.6 176.2. HRMS (ESI+): Exact mass calculated for $C_{10}H_9N_2O_2S$ $[M+H]^+$, 221.0385. Found 221.0378, m/z (ESI+) 221 $[(M+H)^+$, 64%], 193 $[(C_{10}H_9O_2S)^+$ 100%]. *Note*: the quaternary *C*=N_2 was not detected in the ^{13}C spectrum. The structure was confirmed by single crystal X-ray diffraction on a crystalline sample recrystallised from dichloromethane/hexane. Crystals are triclinic, space group $P\bar{1}$ with a = 4.5638(10) Å, b = 7.0494(16) Å, c = 15.476(4) Å, α = 95.825(5)°, β = 95.748(5)°, γ = 99.306(6)°.

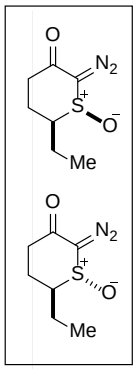
(1R, 6R*)-2-Diazo-6-methyl-dihydro-2H-thiopyran-3(4H)-one S-oxide and (1R*, 6S*)-2-diazo-6-methyl-dihydro-2H-thiopyran-3(4H)-one S-oxide* **6**



The α-diazosulfoxide was synthesized using the batch procedure, and following purification a fraction was isolated containing an inseparable mixture of diazosulfoxides (major:minor 1: 0.6*, 22 mg, 6%) together with small quantities of unidentifiable impurities as a yellow residue. Characteristic spectroscopic signals were seen at: ; ν_{max} (film)/cm^{-1} 2129 (C=N_2), 1718 (C=O); δ_H (400 MHz) 1.38 (1.8H, d, *J* 7.2, CH_3 of minor diastereomer), 1.47 (3H, d, *J* 6.9, CH_3 of major diastereomer), 1.88-1.95 (1H, sym m, one of CH_2 of major diastereomer), 1.97-2.06 (0.6H, sym m, one of CH_2 of minor diastereomer), 2.38-2.86 (4.8H, m, CH_2 of both diastereomers), 2.96-3.12 (1H, m, C*H* of major diastereomer), 3.23-3.31 (0.6H, m, C*H* of minor diastereomer); *Note:* Although some decomposition was evident for both diazosulfoxides in $CDCl_3$ overnight some signals in the ^{13}C spectrum of the mixture were distinguished δ_C (75.5 MHz) 11.9, 16.4, 20.16, 22.1, 32.2, 37.4, 53.2, 186.5 (*C*=O of one diastereomer), 186.6 (*C*=O of one diastereomer).

* It is not known which is the major diastereomer and which is the minor diastereomer.

(1R, 6R*)-2-Diazo-6-ethyl-dihydro-2H-thiopyran-3(4H)-one S-oxide and (1R*, 6S*)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4H)-one S-oxide* **7**



The α-diazosulfoxide was synthesized using the batch procedure, and following purification a fraction was isolated containing a mixture of compounds including the inseparable diazosulfoxides, sulfonamide (1: 1: 0.8) and a small quantity of the sulfoxide starting materials (~5%) as a yellow oil (154 mg, ~12%). Characteristic spectroscopic signals were seen at: ν_{max} (film)/cm^{-1} 2113 (C=N_2), 1630 (C=O); Exact mass calculated for sulfine decomposition product $C_7H_{10}O_2S$ $[M+H]^+$, 159.0480. Found 159.0481. δ_H (400 MHz) 1.16 (6H, m, overlapping 2 × CH_3 of two diastereomers), 1.54-2.14 (6H, m, CH_2 of two diastereomers), 2.43-2.80 (6H, m, CH_2 of two diastereomers), 2.96-3.09 (2H, m, C*H* of two diastereomers); δ_C (75.5 MHz) 11.4, 11.7 (2 × *C*H_3 of two diastereomers), 18.3, 19.7, 20.6, 24.0, 32.5, 37.5 (6 × *C*H_2 of two diastereomers), 60.4, 60.5 (2 × *C*H of two diastereomers), 186.7, 187.1 (2 × *C*=O of two diastereomers); HRMS (ESI+): Exact mass calculated for $C_7H_{11}O_2S$ $[M+H-N_2]^+$, 159.0480. Found 159.0469, m/z (ESI+) 186 $[(M+H)^+$, 15%].

* It is not known which is the major diastereomer and which is the minor diastereomer.

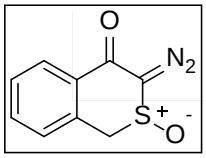
Synthesis of α-diazosulfoxides in flow.

General diazo transfer Procedure for the Synthesis α-diazo-β-keto sulfoxides in continuous Flow.[15]

A 10 mm ID Omnifit® glass column was packed with Amberlyst A21 (5 eq, dispersed in acid washed sand approximately 4x mass of A21). Acetonitrile was pumped through the column at a flow rate of 0.2 mL min^{-1} for 10 min to prepare the system by means of a peristaltic pump. Solutions of the sulfoxide substrate (1 eq) and dbsa* (2 eq) in acetonitrile were fed into the column reactor (18°C, 9 min residence time) at a flow rate of 0.2 mL min^{-1}. The product was collected after passing through an 8 bar back pressure regulator and collected in a round bottomed flask. The collected product was then concentrated under reduced pressure to give the crude product as a pale yellow oil, at which point conversion was determined by ^{1}H NMR spectroscopy. Purification of the crude reaction mixture was carried out by column chromatography on silica gel using hexane/ethyl acetate (70/30) increasing to 100 % ethyl acetate to elute the pure α-diazosulfoxides as crystalline solids.

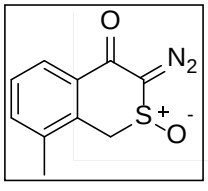
*Although DBSA is regarded as a relatively safe diazo transfer reagent it is a sulfonyl azide and should be handled with the appropriate care as detailed above for tosyl azide.

3-Diazoisothiochroman-4-one S-oxide ***1***



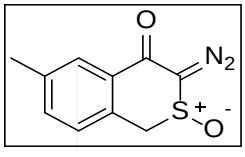
The diazosulfoxide was synthesized using the general procedure. Isolated as a pale brown solid (0.101 g, 80%). Spectral characteristics are in agreement with those reported above.

3-Diazo-8-methylisothiochroman-4-one 2-oxide ***2***



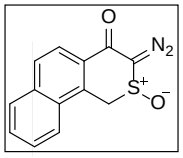
The α-diazosulfoxide was synthesized using the general procedure. Pale brown solid (0.096 g, 84%). Spectral characteristics are in agreement with those reported above.

3-Diazo-6-methylisothiochroman-4-one 2-oxide ***3***



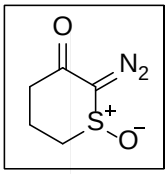
The diazosulfoxide was synthesized according to the general procedure. Pale brown crystalline solid (0.067 g, 60%). Spectral characteristics are in agreement with those reported above.

3-Diazo-1H-benzo[h]isothiochromen-4(3H)-one 2-oxide ***4***



The diazosulfoxide was synthesized according to the general procedure. Crystalline bright yellow solid. R_f 0.5 in 100% EtOAc – streaking is seen on the silica TLC plates as decomposition occurs. The product stains red in vanillin in heating. Isolated as an off-yellow crystalline solid (0.045 g, 39%) An analytical sample was obtained by slow recrystallization from dichloromethane and ether. mp 118 – 120°C ν_{max}(neat)/cm^{-1} 2126 (C=N_2), 1681 (C=O); δ_H (400 MHz) 4.35 (1H, d, *J* 15.8), 5.20 (1H, d, *J* 15.9), 7.64 – 7.66 (2H, m), 7.92 – 7.97 (2H, m), 8.08 – 8.10 (1H,m) 8.18 – 8.20 (1H, d). δ_C 48.1, 122.8, 124.3, 128.1, 128.2, 128.3, 129.1, 129.4, 129.6, 129.7, 132.2, 136.3, 176.5. *Note*: the quaternary *C*=N_2 was not detected in the ^{13}C spectrum; HRMS (ESI+): Exact mass calculated for $C_{13}H_9N_2O_2S$ m/z (ESI+) 257 [(M+H)+, 10%] [M+H]+, 257.0385. Found 257.0378

2-Diazo-dihydro-2H-thiopyran-3(4H)-one S-oxide ***5***



The α-diazosulfoxide was synthesized according to the general procedure following purification of the crude reaction mixture by column chromatography on silica gel using (EtOAc-MeOH 90-10) as eluent, the diazosulfoxide was isolated as a crystalline bright yellow solid (0.027 g, 19%). υ_{max} (neat)/cm^{-1}, 2118 (C=N_2), 1641 (C=O), 1161 (S-O). δ_H (400 MHz) 2.19-2.28 (1H, m), 2.41-2.55 (1H, m), 2.70-2.80 (1H, sym m), 2.86-3.06 (2H, m), 3.05-3.21 (1H, m)] 3 × CH_2; δ_C (75.5 MHz) 14.5 (CH_2), 37.3 (CH_2), 48.1 (CH_2), 186.5 (*C*=O). *Note*: the quaternary *C*=N_2 was not detected in the ^{13}C spectrum; HRMS (ESI+): Exact mass calculated for $C_5H_7N_2O_2S$ $[M+H]^+$, 159.0228. Found 159.0231; m/z (ESI+) 159 $[(M+H)^+$, 22 %]. Signals corresponding to the hetero-Wolff rearrangement product, the α-oxosulfine are present in the ^{13}C NMR spectrum at 19.5, 31.1, 39.3 and 185.6 ppm.

Supporting Information

The supporting information is available free of charge at DOI containing:

^{1}H and ^{13}C NMR spectra for sulfides, sulfoxides and α-diazosulfoxides.

Thermal ellipsoid plot of compound **3**.

Acknowledgements

We thank The Irish Research Council (IRC) for financial support (PGM Project ID GOIPG/2013/244, NMB). We also thank the Synthesis and Solid State Pharmaceutical Centre supported by the Science Foundation Ireland (grant: SFI SSPC2 12/RC/2275) and for equipment grant 05/PICA/B802/EC07. Michael Cronin is acknowledged for undertaking thermogravimetric analysis of **1**.

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