1,3-Dipolar Cycloadditions of 2-Thio-3-Chloroacrylamides with Nitrile Oxides and Nitrones.

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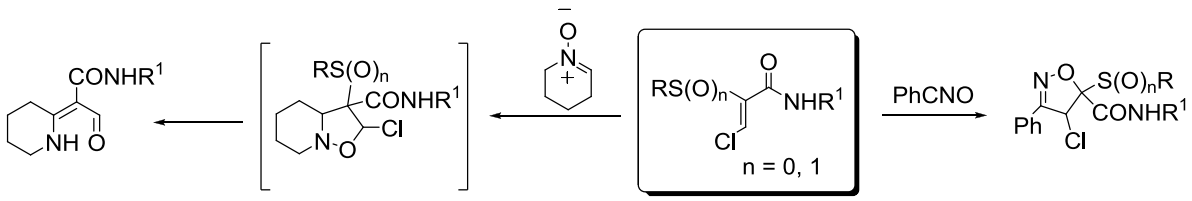


Abstract: 1,3-Dipolar cycloadditions of 2-thio-3-chloroacrylamides with nitrile oxides and nitrones is described. A series of novel isoxazolines are isolated from the nitrile oxide cycloadditions, whilst the isoxazolines generated from the nitrone cycloadditions undergo further ring opening to yield piperidines.

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.

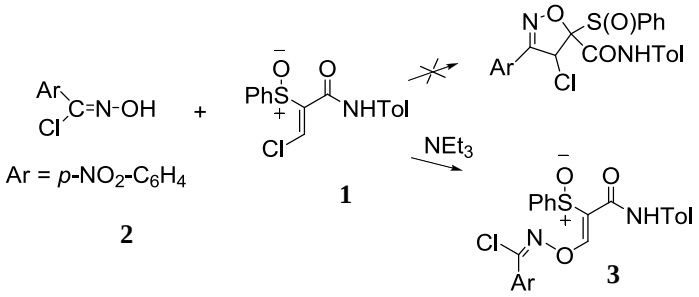
The dipolarophilic behaviour of vinyl sulfides and in particular vinyl sulfoxides in cycloadditions with nitrile oxides has been reported, with desulfinylation of the resulting cycloadducts to afford aromatic compounds commonly observed.[5-7] Reports on 1,3-dipolar cycloadditions of nitrones with vinyl sulfoxides are more limited, but in general the reactions proceed with a high degree of regio- and stereoselectivity. [8-12] The 1,3-dipolar cycloaddition of vinyl sulfides with nitrones has also been reported.[13]

Herein, the reactivity of a range of β-chloroacrylamides with benzonitrile oxide and 2,3,4,5-tetrahydropyridine *N*-oxide leading to a novel series of isoxazolines and piperidines 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 particulary interested to establish the regio- and stereochemical aspects of the cycloadditions, and also to investigate if desulfinylation of the cycloadducts would occur.

Results and Discussion

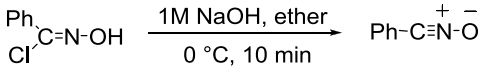
1,3-Dipolar cycloadditions with nitrile oxides

Preliminary investigations of the 1,3-dipolar cycloaddition of *p*-nitrobenzonitrile oxide with the benzenesulfinyl substituted β-chloroacrylamide **1** involved the generation of *p*-nitrobenzonitrile oxide *in situ* from *p*-nitrobenzohydroximoyl chloride **2** in the presence of triethylamine. However, the expected isoxazoline cycloadduct was not formed; instead, nucleophilic addition of **2** or its oxyanion to the β-carbon of **1** occurred to afford **3** (Scheme 1). Nucleophilic attack of **2** was much faster than dehydrohalogenation with triethylamine, therefore *in situ* generation of the dipole was not feasible.



Scheme 1

To eliminate the possibility of nucleophilic addition, benzonitrile oxide **4** was pre-formed by reaction of benzohydroximoyl chloride **5** with a 1 M solution of sodium hydroxide in ether (Scheme 2). Following stirring at 0 °C for 10 minutes, the ether layer was quickly dried and added to a solution of the β-chloroacrylamide in ether. Under these conditions, by minimising the time involved, dimerisation of the nitrile oxide did not prove to be a significant issue.



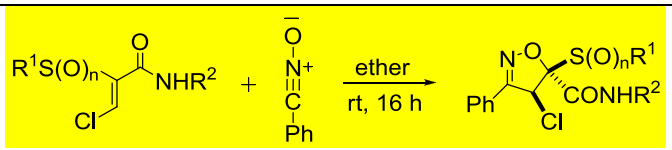
5 **4**

Scheme 2

Cycloadditions with benzonitrile oxide

The dipolarophilic behaviour of the β-chloroacrylamides towards benzonitrile oxide was explored first as summarised in Table 1. A solution of pre-formed benzonitrile oxide in ether was added to a solution of the β-chloroacrylamide (sulfoxide or sulfide) in ether and the reaction mixture was then stirred overnight at room temperature. The product was isolated either by concentration at reduced pressure followed by chromatographic purification or, in cases where the product precipitated out of solution as the reaction progressed, by filtration of the reaction mixture. In each instance the isoxazoline cycloadduct was isolated as a single regioisomer and diastereoisomer. Formation of a single regioisomer of these cycloadducts, in contrast to the literature precedent,[6,7] is particularly significant.

Table 1 Reaction of β-Chloroacrylamides with Benzonitrile Oxide



Entry	β-Cl	R^1	R^2	n	Isoxazoline	% Yield
1	**6**	Bn	Tol	1	**18**	48[a]
2	**7**	Bn	Bn	1	**19**	72[a]
3	**8**	Bn	Me	1	**20**	43[a]
4	**9**	Ph	Bn	1	**21**	32[a]
5	**1**	Ph	Tol	1	**22**	13[b]
6	**10**	Ph	Me	1	**23**	12[b]
7	**11**	*n*-Bu	Tol	1	**24**	16[a]
8	**12**	*n*-Bu	Bn	1	**25**	33[c]
9	**15**	Bn	Tol	0	**26**	21[a]
10	**16**	Bn	Bn	0	**27**	11[d]
11	**17**	Bn	*n*-Bu	0	**28**	21[b,e]

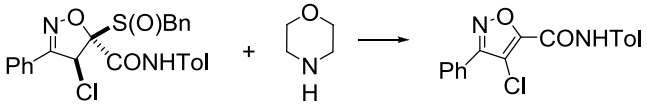
a) Isolated yield after filtration of reaction mixture.
b) Isolated yield after chromatography.
c) Calculated yield. Isolated in 48% yield as a mixture with the precursor **12** (pure ratio 0.47 : 1 **12 : 25**).
d) Calculated yield. Isolated in 63% yield as a mixture with the precursor **16** (pure ratio 1 : 0.51 **16 : 27**).
e) Calculated yield. Isolated in 79% yield as a mixture with the precursor **17** (pure ratio 1 : 0.50 **17: 28**).

Due to its rapid dimerisation, benzonitrile oxide has a lifetime of approximately one hour,[14,15] and thus even though the reactions were left overnight, in reality the cycloaddition probably took place within the first hour. None of the reactions went to completion, with unreacted dipolarophiles clearly visible by TLC and ^{1}H NMR spectroscopic analysis. Notably, cycloadditions with diazoalkanes require longer reaction times to go to completion.[16] On reaction of the sulfoxides **6**–**9** (entries 1–4, Table 1) and **11** (entry 7, Table 1) and the sulfide **15** (entry 9, Table 1) with benzonitrile oxide **4**, a precipitate formed as the reaction progressed and the isoxazoline cycloadducts **18**–**21, 24** and **26** were isolated by filtration of the reaction mixture. The filtrate was concentrated and was found to contain unreacted starting material and small amounts of the isoxazoline cycloadduct. For the reaction of the sulfoxides **1**, **10** (entries 6 and 7, Table 1) and **12** (entry 8, Table 1) and the sulfides **16** and **17** (entries 10 and 11, Table 1) with **4** the product did not precipitate from the reaction mixture and accordingly, the reaction mixture was concentrated to give a mixture of unreacted starting material and the isoxazoline cycloadduct. Purification by chromatography on silica gel afforded the

isoxazoline cycloadducts **22**, **23, 25, 27** and **28**. For the isoxazolines **25**, **27** and **28**, the isolated products also contained unreacted β-chloroacrylamides **12, 16** and **17** respectively. Modest yields of the isoxazolines were obtained in most cases. For the cycloaddition of **12** with **4**, a fresh portion of **4** in ether was added after 16 h; however, this did not succeed in driving the reaction to completion.

There is a characteristic singlet in the ^{1}H NMR spectra of the isoxazoline cycloadducts **18–25** at δ_H 6.22–6.51 ppm due to the proton of the heterocycle geminal to the chloride. A distinctive doublet of doublets is also seen in the region δ_H 7.78–7.85 ppm, assigned to the *ortho*-protons on the phenyl ring attached to the 3-position of the heterocycle. This is presumably attributed to the magnetic anisotropy of the C=N of the isoxazoline ring. In no instance were signals for regioisomeric isoxazoline cycloadducts identified.

All attempts to grow a single crystal of one of the isoxazolines for X-ray crystallographic analysis to confirm the regiochemistry of the cycloaddition were unsuccessful and therefore the isoxazoline **18** was transformed to the isoxazole **29** on treatment with morpholine to effect base-induced elimination of the sulfoxide (Scheme 3). [17-19]



Scheme 3

It was possible to grow a single crystal of **29** from acetone, and X-ray diffraction established the structure of **29** and hence the regiochemistry of the cycloaddition to be that with the amide group at the 5-position of the isoxazole ring (Figure 1).

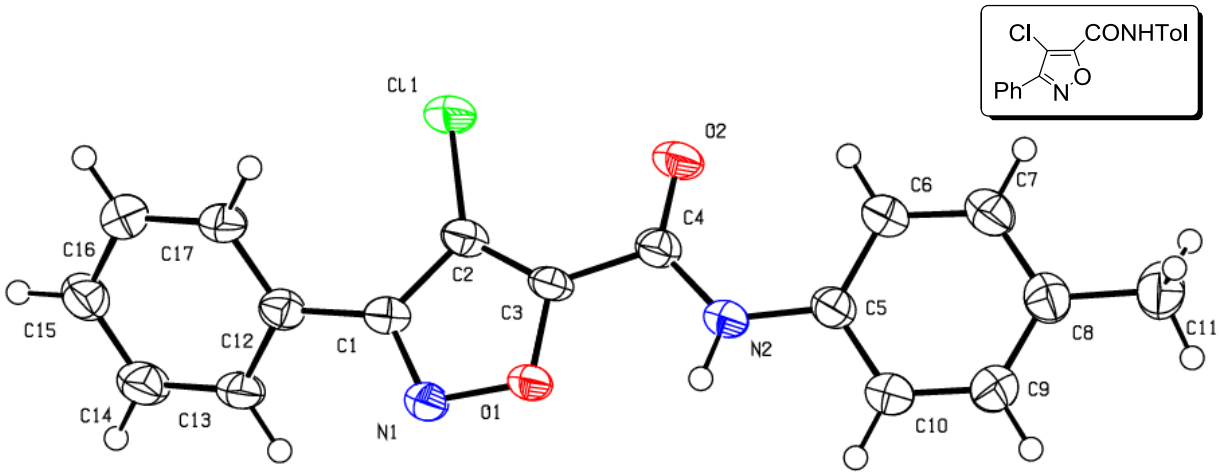


*Figure 1 Crystal Structure of **29** (Anisotropic displacement parameters are drawn at the 50% probability level)*

The regiochemistry of the isoxazoline cycloadducts was thus assigned by analogy, with the sulfoxide and amide groups at the 5-position of the isoxazoline ring. The observed regiochemistry agrees with theoretical predictions;[20] nitrile oxide cycloadditions are dipole-LUMO controlled for conjugated dipolarophiles, and the most favorable direction of combination is that in which the carbon atom of the nitrile oxide adds to the β-carbon of the β-chloroacrylamide (Figure 2). This combination is also very favourable on steric grounds, as the less crowded end of the dipole adds to the more substituted end of the dipolarophile.

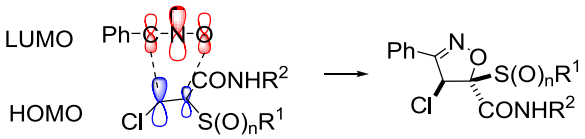


Figure 2

As well as being highly regioselective, the cycloaddition proceeds with excellent stereoselectivity, with the isoxazoline cycloadduct isolated as a single diastereomer. As described earlier based on crystallographic data,[2,4] the β-chloroacrylamides are conformationally constrained due to the intramolecular hydrogen bond between the amide proton and sulfoxide, adopting the s-*cis* conformation. Complete diastereofacial control from the sulfoxide is envisaged, with the favoured approach of benzonitrile oxide to the β-chloroacrylamides avoiding steric interactions with the R^1 group which blocks

the approach of the dipole from above (Figure 3). It is reasonable to assume that the stereochemistry of the dipolarophile is preserved in the cycloaddition.

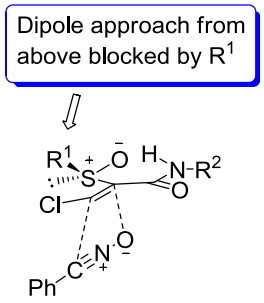


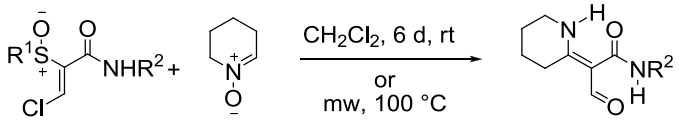
Figure 3

1,3-Dipolar cycloadditions with nitrones.

As it is not always possible to predict the stereochemical outcome on employment of acyclic nitrones (*E*/*Z* isomerisation is possible),[21] the cyclic nitrone 2,3,4,5-tetrahydropyridine *N*-oxide **30** was employed for the investigation of the dipolarophilic reactivity of the β-chloroacrylamides with nitrones to simplify the stereochemical outcome in the product mixture.

The β-chloroacrylamide was added to a solution of 2,3,4,5-tetrahydropyridine *N*-oxide **30** (freshly prepared quantitatively each time before use following the procedure described by Hootelé and Louis)[11] in dichloromethane, with the results summarised in Table 2.

Table 2 Reaction of β-Chloroacrylamides with nitrone **30**



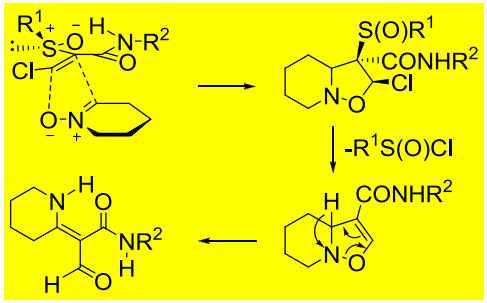
Entry	sulfoxide	R^1	R^2	Conditions	product	% yield[a]
1	**13**	Ph	Ph	CH_2Cl_2, 6 d, rt	**31**	19
2	**13**	Ph	Ph	mw, 100 °C, 20 min	**31**	19
3	**10**	Ph	Me	mw, 100 °C, 10 min	**32**	18
4	**14**	Bn	4-F-C_6H_4	mw, 100 °C, 20 min	**33**	34[b]
5	**8**	Bn	Me	mw, 100 °C, 15 min	**32**	-[c]

a) Isolated yield after chromatography.

b) In the ^{1}H NMR spectrum of **33** there was also evidence for another unidentified product.
c) Detected as the minor product by ^{1}H NMR spectroscopy.

The cycloaddition was explored under microwave[22-26] and conventional conditions; although similar yields were achieved under both sets of conditions, conducting the cycloadditions in the microwave was more advantageous due to the significantly shorter reaction times (entries 1 and 2, Table 2). The cycloaddition of the sulfoxides **13**, **10** and **14** with the nitrone **30** yielded the unexpected novel substituted piperidines **31**−**33** (entries 1−4, Table 2) as the major product. When the β-chloroacrylamide **8** was subjected to 1,3-dipolar cycloaddition with the nitrone **30** in dichloromethane under microwave conditions for 15 minutes, the substituted piperidine **32** was detected as the minor product from the reaction (entry 5, Table 2).

The mechanism of the formation of the substituted piperidines **31**−**33** is believed to involve the initial formation of the isoxazolidine cycloadduct, which subsequently eliminates the elements of $R^1S(O)Cl$ to yield the isoxazoline. Hydride transfer from the bridgehead carbon to the bridgehead nitrogen coupled with the generation of the extensively conjugated orange product leads to ring opening of the isoxazoline to yield the substituted piperidine (Scheme 4).



Scheme 4

The structure of the novel substituted piperidine products, and thus the regioselectivity of the cycloaddition, was confirmed by X-ray crystallographic analysis of a single crystal of **32** recrystallised from chloroform (Figure 4). The crystal structure confirms the *Z*-stereochemistry of the β-aminoacrylamides; presumably this is the thermodynamic isomer of these compounds, at least in the solid state. NMR studies also indicated the presence of just a single isomer in solution, presumably with the *Z*-stereochemistry.

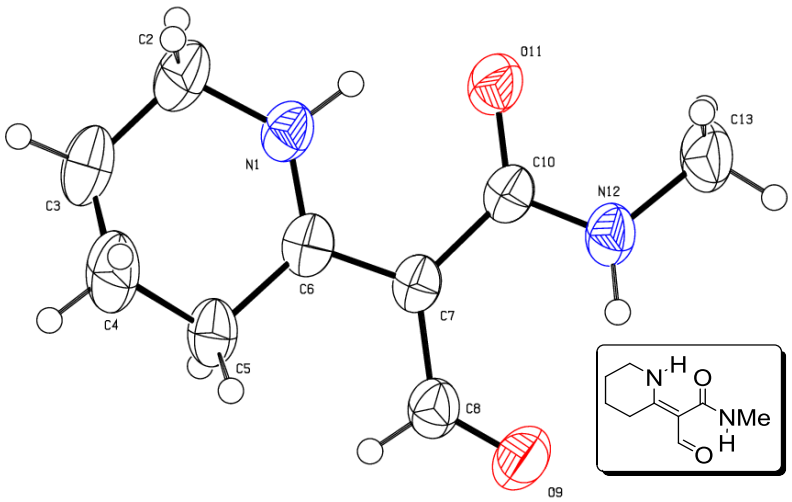


*Figure 4 Crystal Structure of **32** (Anisotropic displacement parameters are drawn at the 50% probability level)*

The hydrogen bonding network present in **32** is highlighted in Figure 5; there are intramolecular hydrogen bonds from the piperidine N-H to the oxygen of the amide group (bond length 1.75 Å) and from the amide N-H to the oxygen of the aldehyde (bond length 2.15 Å), making this a very rigid structure. An intermolecular hydrogen bond also exists from the amide N-H to the aldehyde group with a bond length of 2.56 Å.

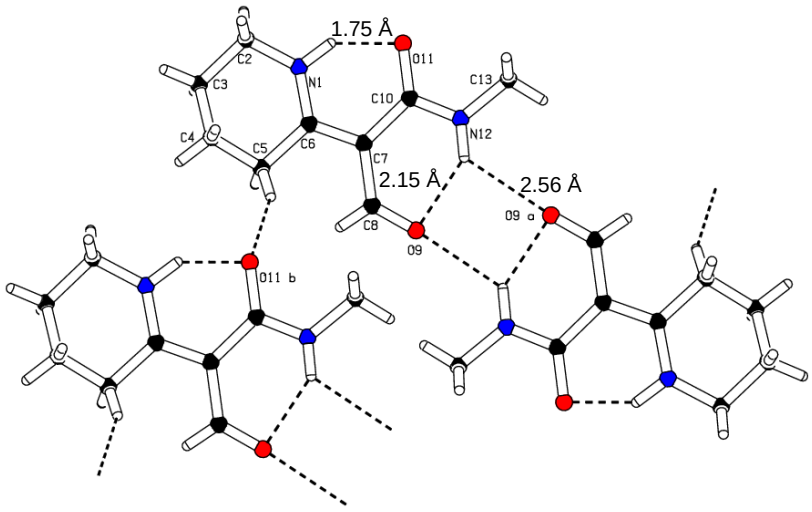


*Figure 5 Hydrogen Bonding Network in **32***

The observed regioselectivity is consistent with theoretical predications for the cycloaddition of nitrones with conjugating and electron-withdrawing dipolarophiles which are dipole-HOMO controlled, leading to the 4,4-disubstituted regioisomer (Figure 6),[27,28] and even though the isoxazolidine cycloadduct was not isolated, the piperidines **31**–**33** confirm the regiochemistry of the cycloaddition.

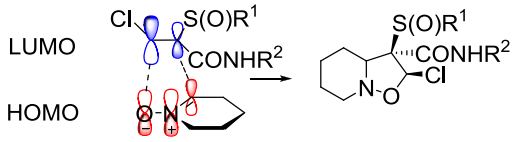


Figure 6

The ^{1}H NMR and ^{13}C NMR spectra of **31** and **32** also aided in confirming the structure. In the ^{1}H NMR spectra, a singlet is evident at δ_H 9.61 ppm for **31** and at δ_H 9.55 ppm for **32**, characteristic of an aldehyde proton. Two broad signals for the two NH protons are also present, which is further evidence that the isoxazoline ring has opened. In the ^{13}C NMR spectra, signals at δ_C 184 ppm are consistent with the conjugated aldehyde carbons.

Thus, nitrone cycloaddition is feasible with the sulfinyl substituted β-chloroacrylamides, albeit to form labile cycloadducts which undergo further reaction to generate unexpected products. While the N-O bond of the isoxazolidines is known to be cleaved under reducing conditions, the spontaneous cleavage in these reactions is rather unusual and presumably is driven by the high degree of conjugation in the products. While the isolated yields are low, there was no evidence for the formation of products derived from the regioisomeric cycloadducts.

Conclusion

1,3-Dipolar cycloadditions of nitrile oxides and nitrones to β-chloroacrylamides leads to a range of novel isoxazolines and piperidines. The cycloadditions proceed in a highly regioselective and diastereoselective manner in all instances.

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.

Benzohydroximoyl chloride was prepared by chlorination of the commercially available benzaldoxime in chloroform.[21] 2,3,4,5-Tetrahydropyridine *N*-oxide was prepared by oxidation of 1-hydroxypiperidine with yellow mercuric oxide.[11]

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,[86] PLATON,[87] Nonius,[88] CrystalClear,[89] X-AREA and X-RED32[90] suite of programs were used. Full structural data have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference numbers 759494 and 759495.

(*E*)-4-Nitro-*N*-[(*Z*)-3-oxo-2-(phenylsulfinyl)-3-(*p*-tolylamino)prop-1-enyloxy]benzimidoyl chloride 3

Triethylamine (0.14 mL, 1.03 mmol) was added to a solution of **1** (0.30 g, 0.94 mmol) in dichloromethane (10 mL). The resulting solution was cooled to 0 °C and compound **2** (0.19g, 0.94 mmol) was added. After 0.5 h a precipitate was seen to form in the reaction flask. The reaction was allowed to warm to room temperature and was stirred at this temperature for 13 h. The precipitate was removed by filtration through a bed of celite. Following removal of the solvent the crude product **3** was isolated as an off-white solid. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (20:80) to give **3** as an off-white solid (0.24 g, 52%); mp 206-208 °C; ν_{max}/cm^{-1}(KBr) 1642 (CO), 1556; Found C, 56.68; H, 3.98, N, 8.48, S, 6.83, Cl, 7.09; $C_{23}H_{18}N_3ClO_5S$ requires C, 57.08; H, 3.78; N, 8.68; S, 6.63; Cl; 7.33; δ_H 2.30 (3H, s, C*H*$_3$ of Tol), 7.02-7.41 (13H, m, Ar*H*), 8.03 (1H, s, =C*H*O); δ_C 21.3 (CH_3, *C*H$_3$ of Tol), 115.7 (C, =*C*S), 121.0, 124.4, 129.2, 129.9, 130.1, 131.9 (CH, Ar*C*H), 134.7, 135.5, 136.3, 142.6, 145.2, 150.1 (C, Ar*C* and N=*C*Cl), 160.1 (CH, *C*HOH), 160.3 (*C*O); MS m/z (ES+) 483 (M^+, 10%).

(4*R,5*R**,S_S*)-5-(Benzylsulfinyl)-4-chloro-4,5-dihydro-3-phenyl-*N*-(4-methylphenyl)isoxazole-5-carboxamide 18**

Benzohydroximoyl chloride (0.38 g, 2.4 mmol) was added portionwise over 10 min to a stirring solution of sodium hydroxide (1M, 3.64 mL) and ether (7 mL) cooled to 0 °C with an ice-bath. The ether layer was separated, quickly dried over $MgSO_4$ and added to a solution of *N*-(4-methylphenyl)-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **6** (0.17 g, 0.5 mmol) in ether (7 mL) and acetone (2 mL). After stirring at room temperature for 3 h, a precipitate formed. The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 48 h. It was decided to stop the reaction at this stage and the product was collected by filtration through a sintered glass funnel (grade 4) to give **18** as a white solid (0.12 g, 48%), mp 179-180 °C; (Found C, 63.30; H, 4.47; N, 6.19; S, 7.86, Cl, 7.84. $C_{24}H_{21}ClN_2O_3S$ requires C, 63.64; H, 4.67; N, 6.18; S, 7.08, Cl, 7.83%); ν_{max}/cm^{-1} (KBr) 3266 (NH), 3014 (CH), 1665 (CO), 1601, 1536, 1079 (SO); δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, ArC*H*$_3$), 4.11 (1H, d, A of AB system, *J* 12.8, SC*H*$_2$), 4.54 (1H, d, B of AB system, *J* 12.8, SC*H*$_2$), 6.47 (1H, s, C*H*Cl), 7.17 (2H, d, *J* 8.4, Ar*H*), 7.35-7.39 (5H, m, Ar*H*), 7.46-7.56 (5H, m, Ar*H*), 7.82 (2H, dd, *J* 8.4, 1.6, Ar*H*), 8.50 (1H, br s, N*H*); δ_C (75.5 MHz, DMSO-d_6) 20.5 (CH_3, Ar*C*H$_3$), 55.1 (CH_2, S*C*H$_2$), 65.2 (CH, *C*HCl), 101.0 [C, *C*(5)], 121.4 (CH, aromatic *C*H), 125.1 (C, aromatic *C*), 127.8, 128.4, 128.85, 128.94, 129.1, 130.5 (6 × CH, 6 × aromatic *C*H), 130.7 (C, aromatic *C*), 131.6 (CH, aromatic *C*H), 134.2, 134.6 (2 × C, 2 × aromatic *C*), 157.5 [C, *C*(3)Ph], 162.0 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{24}H_{22}N_2O_3S^{35}Cl$ $[M+H]^+$ 453.1040. Found 453.1041; m/z (ES+) 455.0 {[($C_{24}H_{21}N_2O_3S^{37}Cl$)+$H^+$], 46%}, 453.0 {[($C_{24}H_{21}N_2O_3S^{35}Cl$)+$H^+$], 100%}. The filtrate was concentrated to give a yellow solid (0.14 g), containing the β-chloroacrylamide **6** and the product **18** (ratio **6: 18** 1:0.10 by ^{1}H NMR spectroscopy).

(4*R,5*R**,S_S*)-*N*-Benzyl-5-(benzylsulfinyl)-4-chloro-4,5-dihydro-3-phenylisoxazole-5-carboxamide 19**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.32 g, 2.2 mmol) and sodium hydroxide (1M, 4.00 mL) in ether (8 mL) and benzyl-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **7** (0.19 g, 0. 6 mmol) in ether (8 mL).

A precipitate formed as the reaction progressed. After stirring at room temperature for 16 h, the product was collected by filtration through a sintered glass funnel (grade 4) to give **19** as a white solid (0.18 g, 72%), mp 151-152 °C; ν_{max}/cm^{-1} (KBr) 3299 (NH), 3001 (CH), 1677 (CO), 1527, 1075 (SO); δ_H (300 MHz, $CDCl_3$) 4.03 (1H, d, A of AB system, *J* 13.2, SC*H*$_2$), 4.46 (1H, d, B of AB system, *J* 12.9, SC*H*$_2$), 4.50 (1H, dd, A of ABX, J_{AB} 15.0, J_{AX} 6.0, one of NHC*H*$_2$), 4.67 (1H, dd, B of ABX, J_{AB} 15.0, J_{BX} 6.3, one of NHC*H*$_2$), 6.41 (1H, s, C*H*Cl), 7.20-7.58 (14H, m, Ar*H* & N*H*), 7.80 (2H, dd, *J* 8.4, 1.6, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 43.0 (CH_2, NH*C*H$_2$), 55.1 (CH_2, S*C*H$_2$), 64.5 (CH, *C*HCl), 100.8 [C, *C*(5)], 125.0 (C, aromatic *C*), 126.9, 127.4, 127.7, 128.2, 128.4, 128.9, 129.2, 130.3 (8 × CH, 8 × aromatic *C*H), 130.7 (C, aromatic *C*), 131.7 (CH, aromatic *C*H), 138.2 (C, aromatic *C*), 157.6 [C, *C*(3)Ph], 163.1 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{24}H_{22}N_2O_3S^{35}Cl$ $[M+H]^+$ 453.1040. Found 453.1042; m/z (ES+) 455.2 {[($C_{24}H_{21}N_2O_3S^{37}Cl$)+$H^+$], 44%}, 453.2 {[($C_{24}H_{21}N_2O_3S^{35}Cl$)+$H^+$], 100%}.

The filtrate was concentrated to give a yellow oil (0.18 g), containing the β-chloroacrylamide **7** and the product **19** (ratio of **7:19** 1:0.14 by ^{1}H NMR spectroscopy).

(4*R,5*R**,*S*$_S$*)-5-(Benzylsulfinyl)-4-chloro-4,5-dihydro-*N*-methyl-3-phenylisoxazole-5-carboxamide 20**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.36 g, 2.5 mmol) and sodium hydroxide (1M, 4.48 mL) in ether (9 mL) and *N*-methyl-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **8** (0.16 g, 0.6 mmol) in ether (6 mL). A precipitate formed as the reaction progressed. The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h but it was decided to work up the reaction at this stage. The product was collected by filtration through a sintered glass funnel (grade 4) to give **20** as a white solid (0.10 g, 43%), mp 144-145 °C; (Found C, 56.75; H, 4.28; N, 7.07. $C_{18}H_{17}ClN_2O_3S$ requires C, 57.37; H, 4.55; N, 7.43%); ν_{max}/cm^{-1} (KBr) 3368 (NH), 2986 (CH), 1665 (CO), 1532, 1074 (SO); δ_H (400 MHz, $CDCl_3$) 2.98 (3H, d, *J* 4.8, NHC*H*$_3$), 4.10 (1H, d, A of AB system, *J* 12.8, SC*H*$_2$), 4.53 (1H, d, B of AB system, *J* 12.8, SC*H*$_2$), 6.36 (1H, s, C*H*Cl), 6.89 (1H, br d, *J* 4.8, N*H*), 7.36-7.56 (8H, m, Ar*H*), 7.79 (2H, dd, *J* 8.4, 1.6, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 26.3 (CH_3, NH*C*H$_3$), 55.2 (CH_2, S*C*H$_2$), 64.7 (CH,

*C*HCl), 100.8 [C, *C*(5)], 125.1 (C, aromatic *C*), 127.7, 128.3, 128.8, 129.1, 130.4 (5 × CH, 5 × aromatic *C*H), 130.9 (C, aromatic *C*), 131.6 (CH, aromatic *C*H), 157.4 [C, *C*(3)Ph], 163.4 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{18}N_2O_3S^{35}Cl$ $[M+H]^+$ 377.0727. Found 377.0720; m/z (ES+) 379.2 {[($C_{18}H_{17}N_2O_3S^{37}Cl$)+$H^+$], 16%}, 377.2 {[($C_{18}H_{17}N_2O_3S^{35}Cl$)+$H^+$], 42%}, 73.9 (100%).

The filtrate was concentrated to give a yellow oil (0.18 g), containing the β-chloroacrylamide **8** and the product **20** (ratio of **8**:**20** 1:0.66).

(4*R,5*R**,S_S*)-*N*-Benzyl-5-(phenylsulfinyl)-4-chloro-4,5-dihydro-3-phenylisoxazole-5-carboxamide 21**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.33 g, 2.3 mmol) and sodium hydroxide (1M, 4.14 mL) in ether (8 mL) cooled and *N*-benzyl-*Z*-3-chloro-2-(phenylsulfinyl)propenamide **9** (0.18 g, 0.6 mmol) in ether (10 mL). A white solid was observed to precipitate out of solution as the reaction progressed. After stirring at room temperature for 16 h, the product was collected by filtration through a sintered glass funnel (grade 4) to give **21** as a white solid (0.08 g, 32%), mp 129-131 °C; ν_{max}/cm^{-1} (KBr) 3264 (NH), 3061 (CH), 1673 (CO), 1538, 1075 (SO); δ_H (300 MHz, $CDCl_3$) 3.96 (1H, dd, A of ABX, J_{AB} 14.7, J_{AX} 5.7, one of NHCH_2), 4.13 (1H, dd, B of ABX, J_{AB} 14.7, J_{BX} 5.4, one of NHCH_2), 6.24 (1H, s, C*H*Cl), 6.51 (1H, br s, N*H*), 6.87-6.95 (2H, m, Ar*H*), 7.22-7.29 (2H, m, Ar*H*), 7.42-7.61 (7H, m, Ar*H*), 7.78 (2H, dd, *J* 8.4, 1.8, Ar*H*), 7.84 (2H, dd, *J* 8.1, 1.2, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 42.0 (CH_2, NH*C*H_2), 65.8 (CH, *C*HCl), 102.5 [C, *C*(5)], 125.5 (C, aromatic *C*), 126.7, 127.0, 127.2, 127.8, 128.0, 128.8, 129.0, 131.4, 132.3 (9 × CH, 9 × aromatic *C*H), 137.8, 138.6 (2 × C, 2 × aromatic *C*), 156.7 [C, *C*(3)Ph], 164.0 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{23}H_{20}N_2O_3S^{35}Cl$ $[M+H]^+$ 439.0883. Found 439.0883; m/z (ES+) 441.2 {[($C_{23}H_{19}N_2O_3S^{37}Cl$)+$H^+$], 46%}, 439.2 {[($C_{23}H_{19}N_2O_3S^{35}Cl$)+$H^+$], 100%}.

The filtrate was concentrated to give a yellow oil (0.23 g), containing the β-chloroacrylamide **9** and the product **21** (ratio of **9**:**21** 1:0.06).

(4*R,5*R**,S_S*)-4-Chloro-4,5-dihydro-3-phenyl-5-(phenylsulfinyl)-*N*-(4-methylphenyl)isoxazole-5-carboxamide 22**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.33 g, 2.3 mmol) and sodium hydroxide (1M, 4.12 mL) in ether (10 mL) cooled and *N*-(4-methylphenyl)-*Z*-3-chloro-2-(phenylsulfinyl)propenamide **1** (0.18 g, 0.6 mmol) in ether (8 mL) and acetone (3 mL). The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h but it was decided to work up the reaction at this stage. The solvent was removed by concentration at reduced pressure to give the crude product as an orange oil. Following purification by column chromatography in silica gel using hexane-ethyl acetate (gradient elution 10-80% ethyl acetate), **22** was obtained as a white solid (0.03 g, 13%), mp 94-96 °C; ν_{max}/cm^{-1} (KBr) 3391 (NH), 1672 (CO), 1597, 1526, 1090 (SO); δ_H (300 MHz, $CDCl_3$) 2.28 (3H, s, ArC*H*$_3$), 6.32 (1H, s, C*H*Cl), 6.95-7.08 (4H, m), 7.35-7.62 (6H, m), 7.74-7.91 (5H, m) (Ar*H* & N*H*); δ_C (75.5 MHz, $CDCl_3$) 20.9 (CH_3, Ar*C*H_3), 63.7 (CH, *C*HCl), 102.3 [C, *C*(5)], 120.0 (CH, aromatic *C*H), 125.2 (C, aromatic *C*), 126.4, 127.8, 128.3, 129.0, 129.5, 131.8, 132.8 (7 × CH, 7 × aromatic *C*H), 133.0, 135.4, 138.4 (3 × C, 3 × aromatic *C*), 157.9 [C, *C*(3)Ph], 161.8 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{23}H_{20}N_2O_3S^{35}Cl$ $[M+H]^+$ 439.0883. Found 439.0862; m/z (ES+) 441.1 {[($C_{23}H_{19}N_2O_3S^{37}Cl$)+$H^+$], 44%}, 439.2 {[($C_{23}H_{19}N_2O_3S^{35}Cl$)+$H^+$], 100%}.

A fraction containing the β-chloroacrylamide **1** was also recovered as a white solid (0.09 g).

(4*R,5*R**,S_S*)-4-Chloro-4,5-dihydro-*N*-methyl-3-phenyl-5-(phenylsulfinyl)isoxazole-5-carboxamide 23**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.45 g, 3.1 mmol) and sodium hydroxide (1M, 5.56 mL) in ether (11 mL) and *N*-methyl-*Z*-3-chloro-2-(phenylsulfinyl)propenamide **10** (0.19 g, 0.8 mmol) in ether (10 mL) and acetone (1 mL). The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h but it was decided to work up the reaction at this stage. Following concentration of the reaction mixture, the crude product was obtained as a yellow oil (0.37 g), containing **10** and **23** in

a ratio of 1:0.38 by ^{1}H NMR spectroscopy. After purification by column chromatography using hexane-ethyl acetate (gradient elution 10-80% ethyl acetate) as eluent, **23** was obtained as a white solid (0.04 g, 12%), mp 139-140 °C; ν_{max}/cm^{-1} (KBr) 3350 (NH), 2995 (CH), 1667 (CO), 1518, 1086 (SO); δ_H (300 MHz, $CDCl_3$) 2.46 (3H, d, *J* 5.1, NHC*H*$_3$), 6.22 (2H, overlapping s and br s, C*H*Cl & N*H*), 7.41-7.63 (6H, m, Ar*H*), 7.77 (2H, dd, *J* 8.4, 1.2, Ar*H*), 7.85 (2H, dd, *J* 8.1, 1.5, Ar*H*); δ_C (75.5 MHz, $CDCl_3$) 26.1 (CH_3, Ar*C*H$_3$), 63.7 (CH, *C*HCl), 102.4 [C, *C*(5)], 125.3 (C, aromatic *C*), 126.6, 127.8, 128.9, 129.1, 131.7, 132.6 (6 × CH, 6 × aromatic *C*H), 138.7 (C, aromatic *C*), 157.6 [C, *C*(3)Ph], 164.6 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{17}H_{16}N_2O_3S^{35}Cl$ $[M+H]^+$ 363.0570. Found 363.0554; m/z (ES+) 365.2 {[($C_{17}H_{15}N_2O_3S^{37}Cl$)+$H^+$], 44%}, 363.2 {[($C_{17}H_{15}N_2O_3S^{35}Cl$)+$H^+$], 100%}.

(4*R,5*R**,*S*$_S$*)-5-(*n*-Butylsulfinyl)-4-chloro-4,5-dihydro-3-phenyl-*N*-(4-methylphenyl)isoxazole-5-carboxamide 24**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.42 g, 2.9 mmol) and sodium hydroxide (1M, 5.20 mL) in ether (10 mL) and *N*-(4-methylphenyl)-*Z*-3-chloro-2-(*n*-butylsulfinyl)propenamide **11** (0.22 g, 0.7 mmol) in ether (10 mL). A precipitate formed as the reaction progressed. The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h. At this stage, the product was collected by filtration through a sintered glass funnel (grade 4) to give **24** as a white solid (0.05 g, 16%), mp 157-158 °C; ν_{max}/cm^{-1} (KBr) 3348 (NH), 2919 (CH), 1664 (CO), 1599, 1528, 1078 (SO); δ_H (400 MHz, $CDCl_3$) 0.98 [3H, t, *J* 7.6, C(4′)*H*$_3$], 1.44-1.65 [2H, m, C(3′)*H*$_2$], 1.78-1.95 [2H, m, C(2′)*H*$_2$], 2.32 (3H, s, ArC*H*$_3$), 3.01 (1H, ddd, *J* 12.8, 8.8, 5.6, one of SC*H*$_2$), 3.13 (1H, ddd, *J* 12.8, 8.8, 7.8, one of SC*H*$_2$), 6.38 (1H, s, C*H*Cl), 7.14 (2H, d, *J* 8.4, Ar*H*), 7.41-7.56 (5H, m, Ar*H*), 7.79 (2H, dd, *J* 8.0, 1.6, Ar*H*), 8.43 (1H, br s, N*H*); δ_C (75.5 MHz, DMSO-d_6) 13.5 [CH_3, *C*(4′)H$_3$], 20.5 (CH_3, Ar*C*H$_3$), 21.2 [CH_2, *C*(3′)H$_2$], 24.3 [CH_2, *C*(2′)H$_2$], 47.5 (CH_2, S*C*H$_2$), 65.4 (CH, *C*HCl), 100.7 [C, *C*(5)], 121.3 (CH, aromatic *C*H), 125.2 (C, aromatic *C*), 127.8, 128.9, 129.1, 131.5 (4 × CH, 4 × aromatic *C*H), 134.1, 134.5 (2 × C, 2 × aromatic *C*), 157.4 [C, *C*(3)Ph], 162.2 (C, *C*O); HRMS

(ES+): Exact mass calculated for $C_{21}H_{24}N_2O_3S^{35}Cl$ $[M+H]^+$ 419.1196. Found 419.1208; m/z (ES+) 436.0 {[($C_{21}H_{23}N_2O_3S^{35}Cl$)+$H_2O^+$], 14%}, 109.9 (100%).

The filtrate was concentrated to give as a yellow solid (0.34 g), containing the β-chloroacrylamide **11** and the product **24** (ratio of **11**:**24** 1:0.9 by ^{1}H NMR spectroscopy).

(4*R,5*R**,S_S*)-*N*-Benzyl-5-(*n*-butylsulfinyl)-4-chloro-4,5-dihydro-3-phenylisoxazole-5-carboxamide 25**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.32 g, 2.2 mmol) and sodium hydroxide (1M, 4.00 mL) in ether (10 mL) and *N*-benzyl-*Z*-3-chloro-2-(*n*-butylsulfinyl)propanamide **12** (0.17 g, 0.6 mmol) in ether (8 mL). The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h and a further 4 equivalents of benzonitrile oxide [freshly prepared as outlined above from benzohydroximoyl chloride (0.32 g, 2.2 mmol)] was added to the reaction solution. Following stirring for a further 16 h, TLC analysis indicated that some starting material still remained and it was decided to work-up the reaction. Following concentration of the reaction mixture at reduced pressure, the product was isolated as a yellow oil, containing **25** and **12** in a ratio of 1:0.6. After purification by column chromatography using hexane-ethyl acetate (gradient elution 5-40% ethyl acetate) as eluent, **25** was obtained as a pale yellow oil (0.16 g, 48%), containing ~ 32 mol% **12**; ν_{max}/cm^{-1} (KBr) 3338 (NH), 2956 (CH), 1661 (CO), 1533; δ_H (300 MHz, $CDCl_3$) 0.97 [3H, t, *J* 7.2, C(4′)H_3], 1.41-1.93 [4H, m, C(3′)H_2 & C(2′)H_2], 2.82-3.16 (2H, m, SCH_2), 4.40-4.66 (2H, m, NHCH_2), 6.30 (1H, s, C*H*Cl), 7.18 (1H, br t, N*H*), 7.23-8.23 (10H, m, Ar*H*); δ_C (75.5 MHz, $CDCl_3$)13.7 [CH_3, *C*(4′)H_3], 21.9 [CH_2, *C*(3′)H_2], 25.2 [CH_2, *C*(2′)H_2], 44.4, 50.0 (2 × CH_2, S*C*H_2 & NH*C*H_2), 62.0 (CH, *C*HCl), 100.3 [C, *C*(5)], 125.1 (C, aromatic *C*), 127.7, 127.8, 128.8, 129.2, 130.1, 131.8 (6 × CH, 6 × aromatic *C*H), 136.5 (C, aromatic *C*), 157.8 [C, *C*(3)Ph], 162.7 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{21}H_{24}N_2O_3S^{35}Cl$ $[M+H]^+$ 419.1196. Found 419.1191; m/z (ES+) 421.1 {[($C_{21}H_{23}N_2O_3S^{37}Cl$)+$H^+$], 50%}, 419.0 {[($C_{21}H_{23}N_2O_3S^{35}Cl$)+$H^+$], 100%}, 300.0 {[($C_{14}H_{18}NO_2S^{35}Cl$)+$H^+$], 58%}.

4-Chloro-3-phenyl-*N*-(4-methylphenyl)isoxazole-5-carboxamide 29

Morpholine (0.05 mL, 0.6 mmol) was added to a solution of 5-(benzylsulfinyl)-4-chloro-4,5-dihydro-3-phenyl-*N*-(4-methylphenyl)isoxazole-5-carboxamide **18** (0.10 g, 0.2 mmol) in dichloromethane (20 mL). Following stirring at room temperature for 16 h, TLC analysis indicated that some starting material remained and a further 2.5 equivalents of morpholine (0.05 mL, 0.6 mmol) was added. Following stirring at room temperature for a further 24 h, saturated ammonium chloride (20 mL) was added. The layers were separated and the aqueous layer was washed with dichloromethane (2 × 20 mL). The combined organic layers were washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried and concentrated to give **29** as a white solid. Following purification by column chromatography using hexane-ethyl acetate 95:5, **29** was obtained as a white solid (0.06 g, 84%); ν_{max}/cm^{-1} (KBr) 3336 (NH), 2924 (CH), 1668 (CO), 1606, 1526; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, ArC*H*$_3$), 7.21 (2H, d, *J* 8.4, Ar*H*), 7.50-7.61 (5H, m, Ar*H*), 7.86-7.91 (2H, m, Ar*H*), 8.18 (1H, br s, N*H*); δ_C (75.5 MHz, DMSO-d_6) 21.0 (CH_3, Ar*C*H$_3$), 112.7 (C, aromatic *C*), 126.2, 128.3, 128.9, 129.8, 130.9, 130.5 (5 × CH, 5 × aromatic *C*H), 133.9, 135.4, 152.8, 156.9 (4 × C, 4 × aromatic *C*, 4 signals for 5 carbons), 161.5 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{17}H_{14}N_2O_2S^{35}Cl$ $[M+H]^+$ 313.0744. Found 313.0735; m/z (ES+) 315.0 {[($C_{17}H_{13}N_2O_2S^{37}Cl$)+$H^+$], 36%}, 313.0 {[($C_{17}H_{13}N_2O_2S^{35}Cl$)+$H^+$], 100%}.

The regiochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **29** recrystallised from acetone.

Crystals of **29** are monoclinic, space group *P* $2_1/n$, formula $C_{17}H_{13}ClN_2O_2$, M = 312.74, a = 6.352(2) Å, b = 12.196(4) Å, c = 18.983(8) Å, α = 90.00 °, β = 97.414(17) °, γ = 90.00 °, U = 1458.3(9) $Å^3$, F(000) = 648, μ(Mo-Kα) = 0.270 mm^{-1}, R(F_o) = 0.0781, for 2442 observed reflections with I>2σ(I), wR_2(F^2) = 0.1738 for all 3071 unique reflections. Data in the θ range 2.16-27.53 ° were collected at 125 K on a Rigaku Saturn 724 CCD 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.

(4*R,5*R**)-5-(Benzylthio)-4-chloro-4,5-dihydro-3-phenyl-*N*-(4-methylphenyl)isoxazole-5-carboxamide 26**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.27 g, 1.9 mmol) and sodium hydroxide (1M, 3.40 mL) in ether (7 mL) and *N*-(4-methylphenyl)-*Z*-3-chloro-2-(benzylthio)propenamide **15** (0.15 g, 0.5 mmol) in ether (8 mL). The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h and a further 2 equivalents of benzonitrile oxide [prepared as described above from benzohydroximoyl chloride (0.14 g, 1.0 mmol)] was added. Following stirring at room temperature for a further 24 h, a white solid precipitated out of solution. The product was collected by filtration through a sintered glass funnel (grade 4) to give **26** as a white solid (0.04 g, 21%), mp 177-178 °C; (Found C, 65.10; H, 4.54; N, 6.30. $C_{24}H_{21}ClN_2O_2S$ requires C, 65.97; H, 4.84; N, 6.41%); ν_{max}/cm^{-1} (KBr) 3272 (NH), 3015 (CH), 2919 (CH), 1667 (CO), 1597, 1531; δ_H (300 MHz, $CDCl_3$) 2.32 (3H, s, ArC*H*$_3$), 4.01 (1H, d, A of AB system, J_{AB} 12.3, one of SC*H*$_2$), 4.10 (1H, d, B of AB system, J_{AB} 12.3, one of SC*H*$_2$), 6.12 (1H, s, C*H*Cl), 7.14 (2H, d, *J* 8.4, Ar*H*), 7.22-7.58 (8H, m, Ar*H*), 7.77 (2H, dd, *J* 8.1, 2.1, Ar*H*), 8.47 (1H, br s, N*H*); δ_C (75.5 MHz, DMSO-d_6) 20.4 (CH_3, Ar*C*H$_3$), 34.1 (CH_2, S*C*H$_2$), 66.2 (CH, *C*HCl), 97.5 [C, *C*(5)], 121.1 (CH, aromatic *C*H), 125.7 (C, aromatic *C*), 127.6, 128.6, 128.9, 129.1, 131.5 (5 × CH, 5 × aromatic *C*H, 5 signals for 7 carbons), 133.9, 134.7, 135.6 (3 × C, 3 × aromatic *C*), 158.3 [C, *C*(3)Ph], 164.7 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{24}H_{22}N_2O_2S^{35}Cl$ $[M+H]^+$ 437.1091. Found 437.1086; m/z (ES+) 437.0 {[($C_{24}H_{21}N_2O_2S^{35}Cl$)+$H^+$], 78%}.

The filtrate was concentrated to give an orange oil (0.24 g), containing the β-chloroacrylamide **15** and the product **26** (ratio of **15**:**26** 1:0.16 by ^{1}H NMR spectroscopy).

(4*R,5*R**)-*N*-Benzyl-5-(benzylthio)-4-chloro-4,5-dihydro-3-phenylisoxazole-5-carboxamide 27**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.27 g, 1.9 mmol) and sodium hydroxide (1M, 3.40 mL) in ether (7 mL) and *N*-benzyl-*Z*-3-chloro-2-(benzylthio)propenamide **16** (0.15 g, 0.5 mmol) in ether (8 mL). The

reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h and a further 2 equivalents of benzonitrile oxide [prepared as described above from benzohydroximoyl chloride (0.14 g, 1.0 mmol)] was added. Following stirring at room temperature for a further 24 h, the reaction mixture was concentrated to give the product as a yellow oil (0.32 g), containing **16** and **27** in the ratio 1:0.38. Following purification using hexane-ethyl acetate (gradient elution 5-10% ethyl acetate), **27** was obtained as a white solid, (0.11 g), containing ~66 mol% **16**; ν_{max}/cm^{-1} (of mixture) (KBr) 3310 (NH), 3029 (CH), 1664 (CO), 1518; δ_H (300 MHz, $CDCl_3$) 3.90 (1H, d, A of AB system, J_{AB} 12.0, one of SCH_2), 4.02 (1H, d, B of AB system, J_{AB} 11.7, one of SCH_2), 4.34 (1H, dd, A of ABX, J_{AB} 14.7, J_{AX} 5.7, one of NHCH_2), 4.47 (1H, dd, A of ABX, J_{AB} 14.7, J_{BX} 6.0, one of NHCH_2), 6.07 (1H, s, C*H*Cl), 7.05-7.52 (14H, m, N*H* & Ar*H*), 7.77 (2H, dd, *J* 8.1, 2.1, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 35.4 (CH_2, S*C*H_2), 44.1 (CH_2, NH*C*H_2), 66.0 (CH, *C*HCl), 98.2 [C, *C*(5)], 126.4 (C, aromatic *C*), 127.8, 127.9, 128.15, 128.20, 128.9, 129.1, 129.3, 129.5, 131.8 (9 × CH, 9 × aromatic *C*H), 135.7, 137.2 (2 × C, 2 × aromatic *C*), 159.0 [C, *C*(3)Ph], 167.5 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{24}H_{22}N_2O_2S^{35}Cl$ $[M+H]^+$ 437.1091. Found 437.1093; m/z (ES+) 437.0 {[($C_{24}H_{21}N_2O_2S^{35}Cl$)+$H^+$], 12%}.

(4*R,5*R**)-5-(Benzylthio)-*N*-*n*-butyl-4-chloro-4,5-dihydro-3-phenylisoxazole-5-carboxamide 28**

This was prepared following the procedure outlined for **18** using benzohydroximoyl chloride (0.35 g, 2.4 mmol) and sodium hydroxide (1M, 3.40 mL) in ether (7 mL) and *N*-*n*-butyl-*Z*-3-chloro-2-(benzylthio)propenamide **17** (0.16 g, 0.6 mmol) in ether (8 mL). The reaction progress was monitored by TLC, which indicated that some starting material still remained after stirring at room temperature for 16 h and a further 2 equivalents of benzonitrile oxide [prepared as described above from benzohydroximoyl chloride (0.14 g, 1.0 mmol)] was added. Following stirring at room temperature for a further 24 h, the reaction mixture was concentrated to give the product as a yellow oil (0.32 g) containing **17** and **28** in the ratio 1:0.29. Following purification using hexane-ethyl acetate (gradient elution 5-10% ethyl acetate), **28** was isolated as a yellow oil (0.15 g), containing ~66 mol% **17**; ν_{max}/cm^{-1} (of mixture) (KBr) 3313 (NH), 3062 (CH), 2959 (CH), 1649 (CO),

1561, 1519; δ_H (300 MHz, $CDCl_3$) 0.87 [3H, t, *J* 7.2, C(4′)H_3], 1.18-1.52 [4H, m, C(3′)H_2 & C(2′)H_2], 3.18-3.28 (2H, m, NHCH_2), 3.96 (1H, d, A of AB system, J_{AB} 11.7, one of SCH_2), 4.07 (1H, d, B of AB system, J_{AB} 12.0, one of SCH_2), 6.04 (1H, s, C*H*Cl), 6.86 (1H, br s, N*H*), 7.15-7.56 (8H, m, Ar*H*), 7.77 (2H, dd, *J* 8.1, 2.1, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 13.6 [CH_3, *C*(4′)H_3], 20.0 [CH_2, *C*(3′)H_2], 31.3 [CH_2, *C*(2′)H_2], 35.2 (CH_2, S*C*H_2), 39.8 (CH_2, NH*C*H_2), 65.8 (CH, *C*HCl), 98.1 [C, *C*(5)], 126.2 (C, aromatic *C*), 127.5, 127.6, 128.7, 129.0, 129.2, 131.4 (6 × CH, 6 × aromatic *C*H), 135.6 (C, aromatic *C*), 158.7 [C, *C*(3)Ph], 166.9 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{21}H_{24}N_2O_2S^{35}Cl$ $[M+H]^+$ 403.1247. Found 403.1231; m/z (ES+) 403.1 {[($C_{21}H_{23}N_2O_2S^{35}Cl$)+$H^+$], 8%}.

2-Formyl-*N*-phenyl-2-(piperidin-2-ylidene)acetamide 31

Method A:

N-Phenyl-*Z*-3-chloro-2-(phenylsulfinyl)propenamide **13** (0.40 g, 1.3 mmol) was added to a solution of 2,3,4,5-tetrahydropyridine *N*-oxide **30** (0.16 g, 1.6 mmol) in dichloromethane (10 mL) and the reaction solution was stirred at room temperature for 6 days. The reaction solution was then concentrated at reduced pressure to give the crude product as an orange solid. The ^{1}H NMR spectrum of the crude product was very complex. Following purification by column chromatography using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate), **31** was obtained as a yellow solid (0.06 g, 19%), mp 140-141 °C; ν_{max}/cm^{-1} (KBr) 3379 (NH), 3192 (NH), 2930, 1638, 1622, 1579, 1537; δ_H (400 MHz, $CDCl_3$) 1.84-1.92 [4H, m, C(4)H_2 & C(5)H_2], 2.89-2.95 [2H, m, C(6)H_2], 3.49-3.55 [2H, m, C(3)H_2], 7.03-7.10 (1H, m, Ar*H*), 7.28-7.35 (2H, m, Ar*H*), 7.55-7.61 (2H, m, Ar*H*), 9.61 [1H, s, C*H*O], 12.04 (1H, s, N*H*), 12.98 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 18.8, 21.0 [2 × CH_2, *C*(4)H_2 & *C*(5)H_2], 24.8 [CH_2, *C*(6)H_2], 42.0 [CH_2, *C*(3)H_2], 100.2 (C, *C*CHO), 120.9, 123.2, 128.7 (3 × CH, 3 × aromatic *C*H), 138.7 (C, aromatic *C*), 168.3, 172.8 [2 × C, *C*O & *C*(2)], 184.2 [CH, *C*HO]; HRMS (ES+): Exact mass calculated for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290. Found 245.1291; m/z (ES+) 245.0 {[($C_{14}H_{16}N_2O_2$)+H^+], 100%}, 489.2 {[($C_{28}H_{32}N_4O_4$)+H^+], 4%}.

Method B:

This was also synthesised by addition of *N*-phenyl-*Z*-3-chloro-2-(phenylthio)propenamide **34** (0.12 g, 0.4 mmol) to a solution of 2,3,4,5-tetrahydropyridine *N*-oxide **30** (0.09 g, 0.9 mmol) in dichloromethane (1 mL) in a sealed microwave reaction vessel with stirring and subsequent heating for 20 min at 300 W at 100 °C. Following concentration at reduced pressure, the crude product was obtained as a brown oil. After purification by column chromatography using hexane-ethyl acetate (gradient elution 40-60% ethyl acetate) as eluent, **31** was isolated as a yellow oil, (0.02 g, 19%), with spectroscopic characteristics identical to those outlined above.

2-Formyl-*N*-methyl-2-(piperidin-2-ylidene)acetamide 32

N-Methyl-*Z*-3-chloro-2-(phenylsulfinyl)propenamide **10** (0.13 g, 0.5 mmol) was added to a solution of 2,3,4,5-tetrahydropyridine *N*-oxide **30** (0.06 g, 0.6 mmol) in dichloromethane (1 mL) in a sealed microwave reaction vessel with stirring and the reaction solution was subsequently heated in the microwave for 10 min at 300 W at 100 °C. The reaction mixture was directly applied to a silica column and the product was eluted with hexane-ethyl acetate (gradient elution 40-80% ethyl acetate), to give **32** as an off-white solid (0.02 g, 18%), mp 146-147 °C; ν_{max}/cm^{-1} (KBr) 3436 (NH), 3227 (NH), 2917 (CH), 1630 (CO), 1609, 1539; δ_H (300 MHz, $CDCl_3$) 1.78-1.92 [4H, m, C(4)H_2 & C(5)H_2], 2.78-2.96 [5H, m, C(6)H_2 & NHCH_3; NHCH_3 could be distinguished as a doublet at 2.83 ppm, *J* 4.8], 3.37-3.56 [2H, m, C(3)H_2], 9.55 [1H, s, C*H*O], 9.77 (1H, br s, N*H*), 13.03 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 18.9, 21.1 [2 × CH_2, *C*(4)H_2 & *C*(5)H_2], 24.5 [CH_2, *C*(6)H_2], 25.0 (CH_3, NH*C*H_3), 41.8 [CH_2, *C*(3)H_2], 100.2 (C, *C*CHO), 170.6, 172.1 [2 × C, *C*O & *C*(2)], 183.9 [CH, *C*HO]; HRMS (ES+): Exact mass calculated for $C_9H_{15}N_2O_2$ $[M+H]^+$ 183.1134. Found 183.1137; m/z (ES+) 183.0 {[($C_9H_{14}N_2O_2$)+H^+], 100%}.

The structure of **32** was determined by single crystal X-ray diffraction on a crystalline sample of **32** recrystallised from chloroform.

Crystals of **32** are monoclinic, space group *P* $2_1/c$, formula $C_9H_{14}N_2O_2$, M = 182.22, a = 6.8793(6) Å, b = 8.6766(6) Å, c = 15.5216(13) Å, α = 90.00 °, β = 96.679(12) °, γ = 90.00 °, U = 920.18(13) $Å^3$, F(000) = 392, μ(Mo-Kα) = 0.094 mm^{-1}, R(F_o) = 0.0668, for 906 observed reflections with I>2σ(I), wR_2(F^2) = 0.2180 for all 1720 unique reflections.

Data in the θ range 2.64-28.28 ° 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 hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

_N_-(4-Fluorophenyl)-2-formyl-2-(piperidin-2-ylidene)acetamide 33

N-(4-Fluorophenyl)-*Z*-3-chloro-2-(benzylsulfinyl)propenamide **14** (0.15 g, 0.4 mmol) was added to a solution of 2,3,4,5-tetrahydropyridine *N*-oxide **30** (0.05 g, 0.6 mmol) in dichloromethane (1.2 mL) in a sealed microwave reaction vessel and the reaction solution was subsequently heated in the microwave for 20 min at 300 W at 100 °C. The reaction mixture was directly applied to a silica column and the product was eluted with hexane-ethyl acetate (gradient elution 40-60% ethyl acetate), to give **33** as an off-white solid (0.04 g, 34%); ν_{max}/cm^{-1} (KBr) 3434 (NH), 3308 (NH), 2924, 1721, 1665, 1635, 1602, 1578, 1552, 1506; δ_H (400 MHz, $CDCl_3$) 1.81-1.95 [4H, m, C(4)H_2 & C(5)H_2], 2.88-2.98 [2H, m, C(6)H_2], 3.47-3.57 [2H, m, C(3)H_2], 6.95-7.08 (2H, m, Ar*H*), 7.48-7.61 (2H, m, Ar*H*), 9.60 [1H, s, C*H*O], 12.02 (1H, s, N*H*), 12.93 (1H, br s, N*H*); δ_C (75.5 MHz, $CDCl_3$) 18.8, 21.0 [2 × CH_2, *C*(4)H_2 & *C*(5)H_2], 24.8 [CH_2, *C*(6)H_2], 42.0 [CH_2, *C*(3)H_2], 100.1 (C, *C*CHO), 115.3 [CH, d, $^2J_{CF}$ 22, aromatic *C*(3′)H], 122.5 [CH, d, $^3J_{CF}$ 8, aromatic *C*(2′)H], 134.6 (C, aromatic *C*), 159.0 [C, d, $^1J_{CF}$ 242, aromatic *C*(4′)], 168.2 (C, *C*O), 172.8 [C, *C*(2)], 184.3 [CH, *C*HO]; Exact mass calculated for $C_{14}H_{16}N_2O_2$ $[M+H]^+$ 263.1196. Found 262.1202; m/z (ES+) 263.1 {[($C_{14}H_{15}N_2O_2$)+H^+], 100%}.

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