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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.\textsuperscript{2} We have extended this work to include β-bromoacrylamides, β-chloroacrylates and β-chloroacrylonitriles.\textsuperscript{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.\textsuperscript{4} The β-chloroacrylamides, which can have a wide variety of substituents on the basic acrylamide framework, have synthetic potential as the $2\pi$ 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.\textsuperscript{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.\textsuperscript{8-12} The 1,3-dipolar cycloaddition of vinyl sulfides with nitrones has also been reported.\textsuperscript{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 particularly 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 benzensulfinyl substituted β-chloroacrylamide 1 involved the generation of $p$-nitrobenzonitrile oxide \textit{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 \textit{in situ} generation of the dipole was not feasible.
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.

**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**
Due to its rapid dimerisation, benzonitrile oxide has a lifetime of approximately one hour,\textsuperscript{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 \textsuperscript{1}H NMR spectroscopic analysis. Notably, cycloadditions with diazoalkanes require longer reaction times to go to completion.\textsuperscript{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

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \beta\text{-Cl} )</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( n )</th>
<th>Isoxazoline</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Bn</td>
<td>Tol</td>
<td>1</td>
<td>18</td>
<td>48\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Bn</td>
<td>Bn</td>
<td>1</td>
<td>19</td>
<td>72\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Bn</td>
<td>Me</td>
<td>1</td>
<td>20</td>
<td>43\textsuperscript{a}</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>Ph</td>
<td>Bn</td>
<td>1</td>
<td>21</td>
<td>32\textsuperscript{a}</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Ph</td>
<td>Tol</td>
<td>1</td>
<td>22</td>
<td>13\textsuperscript{b}</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Ph</td>
<td>Me</td>
<td>1</td>
<td>23</td>
<td>12\textsuperscript{b}</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>( n\text{-Bu} )</td>
<td>Tol</td>
<td>1</td>
<td>24</td>
<td>16\textsuperscript{a}</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>( n\text{-Bu} )</td>
<td>Bn</td>
<td>1</td>
<td>25</td>
<td>33\textsuperscript{c}</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>Bn</td>
<td>Tol</td>
<td>0</td>
<td>26</td>
<td>21\textsuperscript{a}</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>Bn</td>
<td>Bn</td>
<td>0</td>
<td>27</td>
<td>11\textsuperscript{d}</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>Bn</td>
<td>( n\text{-Bu} )</td>
<td>0</td>
<td>28</td>
<td>21\textsuperscript{b,c}</td>
</tr>
</tbody>
</table>

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

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).
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; 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.

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, 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 group which blocks

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

Figure 2
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), 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) in dichloromethane, with the results summarised in Table 2.

Table 2 Reaction of β-Chloroacrylamides with nitrone 30

<table>
<thead>
<tr>
<th>Entry</th>
<th>sulfoxide</th>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>product</th>
<th>% yield</th>
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<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>Ph</td>
<td>Ph</td>
<td>CH₂Cl₂, 6 d, rt</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>Ph</td>
<td>Ph</td>
<td>mw, 100 °C, 20 min</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Ph</td>
<td>Me</td>
<td>mw, 100 °C, 10 min</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>Bn</td>
<td>4-F-C₆H₄</td>
<td>mw, 100 °C, 20 min</td>
<td>33</td>
<td>34 b</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>Bn</td>
<td>Me</td>
<td>mw, 100 °C, 15 min</td>
<td>32</td>
<td>34 c</td>
</tr>
</tbody>
</table>

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\textsuperscript{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 nitrene 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 nitrene 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$^1$S(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).

\begin{center}
\textbf{Scheme 4}
\end{center}

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.
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.
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](image.png)

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 $\delta_H$ 9.61 ppm for 31 and at $\delta_H$ 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 $\delta_C$ 184 ppm are consistent with the conjugated 
aldehyde carbons.

Thus, nitrone cycloaddition is feasible with the sulfanyl substituted $\beta$-
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 $\beta$-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 ($\delta_H$ & $\delta_C$) 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.\textsuperscript{21} 2,3,4,5-Tetrahydropyridine \(N\)-oxide was prepared by oxidation of 1-hydroxypiperidine with yellow mercuric oxide.\textsuperscript{11}

Single crystal X-ray data for compound 30 was collected on a Nonius Mach 3 diffractometer using Mo-K\(\alpha\) graphite monochromated radiation and data for 63 was collected by STOE on a STOE IPDS 2T diffractometer using Cu-K\(\alpha\) 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,\textsuperscript{86} PLATON,\textsuperscript{87} Nonius,\textsuperscript{88} CrystalClear,\textsuperscript{89} X-AREA and X-RED32\textsuperscript{90} suite of programs were used. Full structural data have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference numbers 759494 and 759495.

\((E)-4\text{-Nitro-}N\text{-}[(Z)-3\text{-oxo-}2\text{-}(\text{phenylsulfinyl})\text{-}3\text{-}(\text{\textit{p}-tolylamino})\text{prop-1-enyloxy}]\text{benzimidoyl chloride 3}\)

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 (0.19 g, 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; \(\nu_{\text{max}}/\text{cm}^{-1}\) (KBr) 1642 (CO), 1556; Found C, 56.68; H, 3.98, N, 8.48, S, 6.83, Cl, 7.09; \(\text{C}_{23}\text{H}_{18}\text{N}_3\text{ClO}_5\text{S}\) requires C, 57.08; H, 3.78; N, 8.68; S, 6.63; Cl, 7.33; \(\delta_{\text{H}}\) 2.30 (3H, s, \(\text{CH}_3\) of Tol), 7.02-7.41 (13H, m, Ar\(H\)), 8.03 (1H, s, =CHO); \(\delta_{\text{C}}\) 21.3 (CH\(3\), CH\(3\) of Tol), 115.7 (C, =CS), 121.0, 124.4, 129.2, 129.9, 130.1, 131.9 (CH, ArCH), 134.7, 135.5, 136.3, 142.6, 145.2, 150.1 (C, Ar\(C\) and N=CCl), 160.1 (CH, CHO\(H\)), 160.3 (CO); MS m/z (ES+) 483 (\(M^+\), 10%).
(4R*,5R*,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 MgSO₄ 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. C₂₄H₂₁ClN₂O₃S requires C, 63.64; H, 4.67; N, 6.18; S, 7.08, Cl, 7.83%); \(\nu_{max}/cm^{-1}\) (KBr) 3266 (NH), 3014 (CH), 1665 (CO), 1601, 1536, 1079 (SO); \(\delta_H\) (400 MHz, CDCl₃) 2.34 (3H, s, ArCH₃), 4.11 (1H, d, A of AB system, \(J_{12.8}\), SC₂H₂), 4.54 (1H, d, B of AB system, \(J_{12.8}\), SC₂H₂), 6.47 (1H, s, C₄HCl), 7.17 (2H, d, \(J_{8.4}\), ArH), 7.35-7.39 (5H, m, ArH), 7.46-7.56 (5H, m, ArH), 7.82 (2H, dd, \(J_{8.4}, 1.6\), ArH), 8.50 (1H, br s, NH); \(\delta_C\) (75.5 MHz, DMSO-d₆) 20.5 (CH₃, ArCH₃), 55.1 (CH₂, SCH₂), 65.2 (CH, CHCl), 101.0 [C, (C(5))], 121.4 (CH, aromatic CH), 125.1 (C, aromatic C), 127.8, 128.4, 128.85, 128.94, 129.1, 130.5 (6 × CH, 6 × aromatic CH), 130.7 (C, aromatic C), 131.6 (CH, aromatic CH), 134.2, 134.6 (2 × C, 2 × aromatic C), 157.5 [C, (C(3)Ph)], 162.0 (C, CO); HRMS (ES+): Exact mass calculated for C₂₄H₂₂N₂O₃S³⁵Cl [M+H]+ 453.1040. Found 453.1041; m/z (ES+) 455.0 [{(C₂₄H₂₁N₂O₃S³⁷Cl)+H⁺}, 46%, 453.0 [{(C₂₄H₂₁N₂O₃S³⁵Cl)+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).

(4R*,5R*,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<sub>max</sub>/cm<sup>-1</sup> (KBr) 3299 (NH), 3001 (CH), 1677 (CO), 1527, 1075 (SO); δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 4.03 (1H, d, A of AB system, J 13.2, SCH<sub>2</sub>), 4.46 (1H, d, B of AB system, J 12.9, SCH<sub>2</sub>), 4.50 (1H, dd, A of ABX, J<sub>AB</sub> 15.0, J<sub>AX</sub> 6.0, one of NHCH<sub>2</sub>), 4.67 (1H, dd, B of ABX, J<sub>AB</sub> 15.0, J<sub>BX</sub> 6.3, one of NHCH<sub>2</sub>), 6.41 (1H, s, CH<sub>Cl</sub>), 7.20-7.58 (14H, m, ArH & NH), 7.80 (2H, dd, J 8.4, 1.6, ArH); δ<sub>C</sub> (75.5 MHz, DMSO-d<sub>6</sub>) 43.0 (CH<sub>2</sub>, NHCH<sub>3</sub>), 55.1 (CH<sub>2</sub>, SCH<sub>2</sub>), 64.5 (CH, CHCl), 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 x CH, 8 x aromatic CH), 130.7 (C, aromatic C), 131.7 (CH, aromatic CH), 138.2 (C, aromatic C), 157.6 [C, C(3)Ph], 163.1 (C, CO); HRMS (ES+): Exact mass calculated for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S<sub>3</sub>Cl [M+H]<sup>+</sup> 453.1040. Found 453.1042; m/z (ES+) 455.2 <sup>{(C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S<sub>3</sub>Cl)+H<sup>+</sup>}, 44%}, 453.2 <sup>{(C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S<sub>3</sub>Cl)+H<sup>+</sup>}, 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 1H NMR spectroscopy).

(4R*,5R*,S<sub>5</sub>* )-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-(benzylationyl)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<sub>18</sub>H<sub>17</sub>CIN<sub>2</sub>O<sub>3</sub>S requires C, 57.37; H, 4.55; N, 7.43%); ν<sub>max</sub>/cm<sup>-1</sup> (KBr) 3368 (NH), 2986 (CH), 1665 (CO), 1532, 1074 (SO); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 2.98 (3H, d, J 4.8, NHCH<sub>3</sub>), 4.10 (1H, d, A of AB system, J 12.8, SCH<sub>2</sub>), 4.53 (1H, d, B of AB system, J 12.8, SCH<sub>2</sub>), 6.36 (1H, s, CHCl), 6.81 (1H, br d, J 4.8, NH), 7.36-7.56 (8H, m, ArH), 7.79 (2H, dd, J 8.4, 1.6, ArH); δ<sub>C</sub> (75.5 MHz, DMSO-d<sub>6</sub>) 26.3 (CH<sub>3</sub>, NHCH<sub>3</sub>), 55.2 (CH<sub>2</sub>, SCH<sub>2</sub>), 64.7 (CH,
CHCl), 100.8 [C, C(5)], 125.1 (C, aromatic C), 127.7, 128.3, 128.8, 129.1, 130.4 (5 × CH, 5 × aromatic CH), 130.9 (C, aromatic C), 131.6 (CH, aromatic CH), 157.4 [C, C(3)Ph], 163.4 (C, CO); HRMS (ES+): Exact mass calculated for C₁₈H₁₈N₂O₃S₃₅Cl [M+H]⁺ 377.0727. Found 377.0720; m/z (ES+) 379.2 {[(C₁₈H₁₇N₂O₃S₃₅Cl)+H⁺], 16%}, 377.2 {[(C₁₈H₁₇N₂O₃S₃₅Cl)+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).

(4R*,5R*,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; v_max/cm⁻¹ (KBr) 3264 (NH), 3061 (CH), 1673 (CO), 1538, 1075 (SO); δ_H (300 MHz, CDCl₃) 3.96 (1H, dd, A of ABX, J_{AB} 14.7, J_{AX} 5.7, one of NHCH₂), 4.13 (1H, dd, B of ABX, J_{AB} 14.7, J_{BX} 5.4, one of NHCH₂), 6.24 (1H, s, CHCl), 6.51 (1H, br s, NH), 6.87-6.95 (2H, m, ArH), 7.22-7.29 (2H, m, ArH), 7.42-7.61 (7H, m, ArH), 7.78 (2H, dd, J 8.4, 1.8, ArH), 7.84 (2H, dd, J 8.1, 1.2, ArH); δ_C (75.5 MHz, DMSO-d₆) 42.0 (CH₂, NHCH₂), 65.8 (CH, CHCl), 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 CH), 137.8, 138.6 (2 × C, 2 × aromatic C), 156.7 [C, C(3)Ph], 164.0 (C, CO); HRMS (ES+): Exact mass calculated for C₂₃H₂₀N₂O₃S₃₅Cl [M+H]⁺ 439.0883. Found 439.0883; m/z (ES+) 441.2 {[(C₂₃H₁₉N₂O₃S₃₅Cl)+H⁺], 46%}, 439.2 {[(C₂₃H₁₉N₂O₃S₃₅Cl)+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).
(4R*,5R*,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; v\text{max}/\text{cm}^{-1} (KBr) 3391 (NH), 1672 (CO), 1597, 1526, 1090 (SO); δ\text{H} (300 MHz, CDCl\text{3}) 2.28 (3H, s, ArCH\text{3}), 6.32 (1H, s, C\text{HCl}), 6.95-7.08 (4H, m), 7.35-7.62 (6H, m), 7.74-7.91 (5H, m) (Ar\text{H} & NH); δ\text{C} (75.5 MHz, CDCl\text{3}) 20.9 (CH\text{3}, ArCH\text{3}), 63.7 (CH, CHCl), 102.3 [C, C(5)], 120.0 (CH, aromatic CH), 125.2 (C, aromatic C), 126.4, 127.8, 128.3, 129.0, 129.5, 131.8, 132.8 (7 × CH, 7 × aromatic CH), 133.0, 135.4, 138.4 (3 × C, 3 × aromatic C), 157.9 [C, C(3)Ph], 161.8 (C, CO); HRMS (ES+): Exact mass calculated for C\text{23}H\text{20}N\text{2}O\text{3}S\text{35}Cl [M+H]\text{+} 439.0883. Found 439.0862; m/z (ES+) 441.1 {[(C\text{23}H\text{19}N\text{2}O\text{3}S\text{37}Cl)+H\text{+}], 44%}, 439.2 {[(C\text{23}H\text{19}N\text{2}O\text{3}S\text{35}Cl)+H\text{+}], 100%}.

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

(4R*,5R*,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; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3350 (NH), 2995 (CH), 1667 (CO), 1518, 1086 (SO); $\delta_H$ (300 MHz, CDCl$_3$) 2.46 (3H, d, J 5.1, $N$HC$_3$H), 6.22 (2H, overlapping s and br s, $CH$Cl & $N$H$_3$), 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$H$); $\delta_C$ (75.5 MHz, CDCl$_3$) 26.1 (CH$_3$, ArCH$_3$), 63.7 (CH, CHCl), 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 CH), 138.7 (C, aromatic C), 157.6 [C, C(3)Ph], 164.6 (C, CO); HRMS (ES+): Exact mass calculated for C$_{17}$H$_{16}$N$_2$O$_3$S$_3$Cl [M+H$^+$] 363.0570. Found 363.0554; m/z (ES+) 365.2 [{C$_{17}$H$_{15}$N$_2$O$_3$S$_3$Cl$^+$}+H$^+$], 44%; 363.2 [{C$_{17}$H$_{15}$N$_2$O$_3$S$_3$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; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3348 (NH), 2919 (CH), 1664 (CO), 1599, 1528, 1078 (SO); $\delta_H$ (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, Ar$CH_3$), 3.01 (1H, ddd, J 12.8, 8.8, 5.6, one of SCH$_2$), 3.13 (1H, ddd, J 12.8, 8.8, 7.8, one of SCH$_2$), 6.38 (1H, s, $CHCl$), 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, NH); $\delta_C$ (75.5 MHz, DMSO-d$_6$) 13.5 [CH$_3$, C(4')$H$_3], 20.5 (CH$_3$, Ar$CH_3$), 21.2 [CH$_2$, C(3')$H$_2], 24.3 [CH$_2$, C(2')$H$_2], 47.5 (CH$_2$, SCH$_2$), 65.4 (CH, $CHCl$), 100.7 [C, C(5)], 121.3 (CH, aromatic CH), 125.2 (C, aromatic C), 127.8, 128.9, 129.1, 131.5 (4 × CH, 4 × aromatic CH), 134.1, 134.5 (2 × C, 2 × aromatic C), 157.4 [C, C(3)Ph], 162.2 (C, CO); HRMS
(ES+): Exact mass calculated for C_{21}H_{24}N_{2}O_{3}S^{35}Cl [M+H]^+ 419.1196. Found 419.1208; m/z (ES+) 436.0 \{[(C_{21}H_{23}N_{2}O_{3}S^{35}Cl)+H]^+, 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 ^1H NMR spectroscopy).

(4R*,5R*,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-(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\text{max}/\text{cm}^{-1} (KBr) 3338 (NH), 2956 (CH), 1661 (CO), 1533; δH (300 MHz, CDCl\text{3}) 0.97 [3H, t, J 7.2, C(4')H3], 1.41-1.93 [4H, m, C(3')H2 & C(2')H2], 2.82-3.16 (2H, m, SCH2), 4.40-4.66 (2H, m, NHCH2), 6.30 (1H, s, CHCl), 7.18 (1H, br t, NH), 7.23-8.23 (10H, m, ArH); δC (75.5 MHz, CDCl\text{3}) 13.7 [CH3, C(4')H3], 21.9 [CH2, C(3')H2], 25.2 [CH2, C(2')H2], 44.4, 50.0 (2 × CH2, SCH2 & NHCH2), 62.0 (CH, CHCl), 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 CH), 136.5 (C, aromatic C), 157.8 [C, C(3)Ph], 162.7 (C, CO); HRMS (ES+): Exact mass calculated for C_{21}H_{24}N_{2}O_{3}S^{35}Cl [M+H]^+ 419.1196. Found 419.1191; m/z (ES+) 421.1 \{[(C_{21}H_{23}N_{2}O_{3}S^{37}Cl)+H]^+, 50\%\}, 419.0 \{[(C_{21}H_{23}N_{2}O_{3}S^{35}Cl)+H]^+, 100\%\}, 300.0 \{[(C_{14}H_{18}NO_{2}S^{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 \(\times\) 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%); \(v_{\text{max}}/\text{cm}^{-1}\) (KBr) 3336 (NH), 2924 (CH), 1668 (CO), 1606, 1526; \(\delta_H\) (400 MHz, CDCl\(_3\)) 2.36 (3H, s, ArCH\(_3\)), 7.21 (2H, d, \(J\) 8.4, ArH), 7.50-7.61 (5H, m, ArH), 7.86-7.91 (2H, m, ArH); \(\delta_C\) (75.5 MHz, DMSO-\(d_6\)) 21.0 (CH\(_3\), ArCH\(_3\)), 112.7 (C, aromatic C), 126.2, 128.3, 128.9, 129.8, 130.9, 130.5 (5 \(\times\) CH, 5 \(\times\) aromatic CH), 133.9, 135.4, 152.8, 156.9 (4 \(\times\) C, 4 \(\times\) aromatic C, 4 signals for 5 carbons), 161.5 (C, CO); HRMS (ES+): Exact mass calculated for C\(_{17}\)H\(_{13}\)ClN\(_2\)O\(_2\)S\(_3\)Cl \([\text{M}+\text{H}]^+\) 313.0744. Found 313.0735; m/z (ES+) 315.0 \{[(C\(_{17}\)H\(_{13}\)N\(_2\)O\(_2\)S\(_3\)Cl)+H]\^+\}, 36\%; 313.0 \{[(C\(_{17}\)H\(_{13}\)N\(_2\)O\(_2\)S\(_3\)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\(_2\)O\(_2\), \(M = 312.74\), \(a = 6.352(2)\) Å, \(b = 12.196(4)\) Å, \(c = 18.983(8)\) Å, \(\alpha = 90.00^\circ\), \(\beta = 97.414(17)^\circ\), \(\gamma = 90.00\) \(^\circ\), \(U = 1458.3(9)\) Å\(^3\), \(F(000) = 648\), \(\mu(\text{Mo-K}\alpha) = 0.270\) mm\(^{-1}\), \(R(F_o) = 0.0781\), for 2442 observed reflections with I\(>2\sigma(I)\), wR\(_2(F^2) = 0.1738\) for all 3071 unique reflections. Data in the \(\theta\) range 2.16-27.53 \(^\circ\) were collected at 125 K on a Rigaku Saturn 724 CCD diffractometer using Mo-K\(\alpha\) graphite monochromated radiation, \(\lambda = 0.7107\) 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.
(4R*,5R*)-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_{2}O_{2}S requires C, 65.97; H, 4.84; N, 6.41%); \(c_{\text{max}}/\text{cm}^{-1}\) (KBr) 3272 (NH), 3015 (CH), 2919 (CH), 1667 (CO), 1597, 1531; \(\delta_{H}\) (300 MHz, CDCl\(_3\)) 2.32 (3H, s, ArCH\(_3\)), 4.01 (1H, d, A of AB system, J\(_{AB}\) 12.3, one of SCH\(_2\)), 4.10 (1H, d, B of AB system, J\(_{AB}\) 12.3, one of SCH\(_2\)), 6.12 (1H, s, CHCl), 7.14 (2H, d, J 8.4, ArH), 7.22-7.58 (8H, m, ArH), 7.77 (2H, dd, J 8.1, 2.1, ArH), 8.47 (1H, br s, NH); \(\delta_{C}\) (75.5 MHz, DMSO-\(d_6\)) 20.4 (CH\(_3\), ArCH\(_3\)), 34.1 (CH\(_2\), SCH\(_2\)), 66.2 (CH, CHCl), 97.5 [C, C(5)], 121.1 (CH, aromatic CH), 125.7 (C, aromatic CH), 127.6, 128.6, 128.9, 129.1, 131.5 (5 \times CH, 5 \times aromatic CH, 5 signals for 7 carbons), 133.9, 134.7, 135.6 (3 \times C, 3 \times aromatic C), 158.3 [C, C(3)Ph], 164.7 (C, CO); HRMS (ES+): Exact mass calculated for C\(_{24}\)H\(_{21}\)ClN\(_2\)O\(_2\)S\(_{35}\)Cl [M+H]\(^+\) 437.1091. Found 437.1086; m/z (ES+) 437.0 [(C\(_{24}\)H\(_{21}\)N\(_2\)O\(_2\)S\(_{35}\)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).

(4R*,5R*)-N-Benzyl-5-(benzylthio)-4-chloro-4,5-dihydro-3-phenyloisoxazole-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).
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; νmax/cm⁻¹ (of mixture) (KBr) 3310 (NH), 3029 (CH), 1664 (CO), 1518; δH (300 MHz, CDCl₃) 3.90 (1H, d, A of AB system, JAB 12.0, one of SCH₂), 4.02 (1H, d, B of AB system, JAB 11.7, one of SCH₂), 4.34 (1H, dd, A of ABX, JAB 14.7, JAX 5.7, one of NHCH₂), 4.47 (1H, dd, A of ABX, JAB 14.7, JBX 6.0, one of NHCH₂), 6.07 (1H, s, CHCl), 7.05-7.52 (14H, m, NH & ArH), 7.77 (2H, dd, J 8.1, 2.1, ArH); δC (75.5 MHz, DMSO-d₆) 35.4 (CH₂, SCH₂), 44.1 (CH₂, NHCH₂), 66.0 (CH, CHCl), 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 CH), 135.7, 137.2 (2 × C, 2 × aromatic C), 159.0 [C, C(3)Ph], 167.5 (C, CO); HRMS (ES+): Exact mass calculated for C₂₄H₂₂N₂O₂S₃Cl [M+H]+ 437.1091. Found 437.1093; m/z (ES+) 437.0 [{[(C₂₄H₂₁N₂O₂S₃Cl)+H⁺], 12%}.

(4R*,5R*)-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; νmax/cm⁻¹ (of mixture) (KBr) 3313 (NH), 3062 (CH), 2959 (CH), 1649 (CO),
1561, 1519; δH (300 MHz, CDCl3) 0.87 [3H, t, J 7.2, C(4')H3], 1.18-1.52 [4H, m, C(3')H2 & C(2')H2], 3.18-3.28 (2H, m, NHCH2), 3.96 (1H, d, A of AB system, JAB 11.7, one of SCH2), 4.07 (1H, d, B of AB system, JAB 12.0, one of SCH2), 6.04 (1H, s, CHCl), 6.86 (1H, br s, NH), 7.15-7.56 (8H, m, ArH), 7.77 (2H, dd, J 8.1, 2.1, ArH); δC (75.5 MHz, DMSO-d6) 13.6 [CH3, C(4')H3], 20.0 [CH2, C(3')H2], 31.3 [CH2, C(2')H2], 35.2 (CH2, SPh), 39.8 (CH2, NHCHO), 65.8 (CH, CHCl), 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 CH), 135.6 (C, aromatic C), 158.7 [C, C(3)Ph], 166.9 (C, CO); HRMS (ES+): Exact mass calculated for C21H24N2O2S35Cl [M+H]+ 403.1247. Found 403.1231; m/z (ES+) 403.1

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 1H 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; νmax/cm−1 (KBr) 3379 (NH), 3192 (NH), 2930, 1638, 1622, 1579, 1537; δH (400 MHz, CDCl3) 1.84-1.92 [4H, m, C(4)H2 & C(5)H2], 2.89-2.95 [2H, m, C(6)H2], 3.49-3.55 [2H, m, C(3)H2], 7.03-7.10 (1H, m, ArH), 7.28-7.35 (2H, m, ArH), 7.55-7.61 (2H, m, ArH), 9.61 [1H, s, CHO], 12.04 (1H, s, NH), 12.98 (1H, br s, NH); δC (75.5 MHz, CDCl3) 18.8, 21.0 [2 × CH2, C(4)H2 & C(5)H2], 24.8 [CH2, C(6)H2], 42.0 [CH2, C(3)H2], 100.2 (C, CCHO), 120.9, 123.2, 128.7 (3 × CH, 3 × aromatic CH), 138.7 (C, aromatic C), 168.3, 172.8 [2 × C, CO & C(2)], 184.2 [CH, CCHO]; HRMS (ES+): Exact mass calculated for C14H17N2O2 [M+H]+ 245.1290. Found 245.1291; m/z (ES+) 245.0 [{(C14H16N2O2)+H+}, 100%], 489.2 [{(C28H32N4O4)+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; 1\( \text{H} \)max/cm\(^{-1}\) (KBr) 3436 (NH), 3227 (NH), 2917 (CH), 1630 (CO), 1609, 1539; \( \delta \text{H} \) (300 MHz, CDCl\(_3\)) 1.78-1.92 \[4\text{H}, \text{m, C(4)H}_2 \& \text{C(5)H}_2\], 2.78-2.96 \[5\text{H}, \text{m, C(6)H}_2 \& \text{NHCH}_3\]; \text{NHCH}_3 could be distinguished as a doublet at 2.83 ppm, \( J \) 4.8], 3.37-3.56 \[2\text{H}, \text{m, C(3)H}_2\], 9.55 \[1\text{H}, \text{s, CHO}\], 9.77 \[1\text{H}, \text{br s, NH}\], 13.03 \[1\text{H}, \text{br s, NH}\]; \( \delta \text{C} \) (75.5 MHz, CDCl\(_3\)) 18.9, 21.1 \[2 \times \text{CH}_2, \text{C(4)H}_2 \& \text{C(5)H}_2\], 24.5 \[\text{CH}_2, \text{C(6)H}_2\], 25.0 \[\text{CH}_3, \text{NHCH}_3\], 41.8 \[\text{CH}_2, \text{C(3)H}_2\], 100.2 \[\text{C, CCHO}\], 170.6, 172.1 \[2 \times \text{C, CO} \& \text{C(2)}\], 183.9 \[\text{CH}, \text{CHO}\]; HRMS (ES+): Exact mass calculated for C\(_9\)H\(_{15}\)N\(_2\)O\(_2\) [M+H]\(^+\) 183.1134. Found 183.1137; m/z (ES+) 183.0 \{[(C\(_9\)H\(_{14}\)N\(_2\)O\(_2\))+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\(_9\)H\(_{14}\)N\(_2\)O\(_2\), \( M = 182.22, a = 6.8793(6) \ \AA, b = 8.6766(6) \ \AA, c = 15.5216(13) \ \AA, \alpha = 90.00 \ ^\circ, \beta = 96.679(12) \ ^\circ, \gamma = 90.00 \ ^\circ, \ U = 920.18(13) \ \AA^3, F(000) = 392, \mu(\text{Mo-K\( \alpha \)}) = 0.094 \text{ mm}^{-1}, R(F_o) = 0.0668, \) for 906 observed reflections with I>2\( \sigma(I)\), 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 F² 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%); \(v_{\text{max}}/\text{cm}^{-1}\) (KBr) 3434 (NH), 3308 (NH), 2924, 1721, 1665, 1635, 1602, 1578, 1552, 1506; \(\delta_H\) (400 MHz, CDCl₃) 1.81-1.95 [4H, m, C(4)H₂ & C(5)H₂], 2.88-2.98 [2H, m, C(6)H₂], 3.47-3.57 [2H, m, C(3)H₂], 6.95-7.08 (2H, m, ArH), 7.48-7.61 (2H, m, ArH), 9.60 [1H, s, CHO], 12.02 (1H, s, NH), 12.93 (1H, br s, NH); \(\delta_C\) (75.5 MHz, CDCl₃) 18.8, 21.0 [2 × CH₂, C(4)H₂ & C(5)H₂], 24.8 [CH₂, C(6)H₂], 42.0 [CH₂, C(3)H₂], 100.1 (C, CCHO), 115.3 [CH, d, \(^2J_{\text{CF}}\) 22, aromatic C(3')H], 122.5 [CH, d, \(^3J_{\text{CF}}\) 8, aromatic C(2')H], 134.6 (C, aromatic C), 159.0 [C, d, \(^1J_{\text{CF}}\) 242, aromatic C(4')], 168.2 (C, CO), 172.8 [C, C(2)], 184.3 [CH, CHO]; Exact mass calculated for C₁₄H₁₆N₂O₂ [M+H⁺] 263.1196. Found 262.1202; m/z (ES+) 263.1 \{[(C₁₄H₁₅N₂O₂)+H⁺], 100%\}.

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References


