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<td><strong>Author(s)</strong></td>
<td>Kissane, Marie; Lawrence, Simon E.; Maguire, Anita R.</td>
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<td><strong>Publication date</strong></td>
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1,3-Dipolar Cycloadditions of 2-Thio-3-Chloroacrylamides with Diazoalkanes.

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

Introduction

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

We have recently reported the highly efficient and stereoselective transformation of α-thioamides to the corresponding α-thio-β-chloroacrylamide derivatives on treatment with NCS. 2 We have extended this work to include β-bromoacrylamides, β-chloroacrylates and β-chloroacrylonitriles. 3 The α-thio-β-chloroacrylamides can be chemoselectively oxidised to either the racemic sulfoxide or sulfone very efficiently, and furthermore enantioselective oxidation to the sulfoxide derivatives of the α-thio-β-chloroacrylamides has been achieved. 4 The β-chloroacrylamides, which can have a wide variety of substituents on the basic...
acrylamide framework, have synthetic potential as the 2π component in 1,3-dipolar cycloadditions.

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

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

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

![Scheme 1](image_url)

The pyrazoline and pyrazole systems are present in a number of pharmaceutically active compounds.13 While the carboxamide adducts synthesised during this work are novel, 5-methyl-pyrazole-3-carboxylic acid 1, the acid analogue of the pyrazoles synthesised during this work, has a history of applications in the pharmaceutical and agricultural industry.14
In recent years, 1 has been developed as an alternative to nicotinic acid as an agonist of the GPR109a receptor. A key feature of the potency of 1 at the receptor was the presence of the hydrogen bond acceptor in the 3-position of the heterocycle relative to the carboxylate function. More currently, Adage and co-workers have communicated that 1 has the potential for anti-psychotic action toward both cognitive and positive symptoms of schizophrenia. \(^{20}\) \(N\)-Aryl derivatives of 1 such as the \(N\)-substituted benzyl derivative 2 and the pyrazole organotin(IV) ester 3 also display desirable physicochemical properties. \(^{21,22}\) Like the 3-methyl analogues, 3(\(H\))-5-substituted pyrazoles have also found applications in the pharmaceutical industry. For example, researchers at Abbott laboratories in Illinois have found the pyrazole amido-derivative 4 to be a potent inhibitor of dipeptidyl peptidase IV (DPPIV); \(^{23}\) inhibition of DPPIV has been reported as a potential treatment of diabetes and obesity. \(^{24}\)

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

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

Cycloadditions with diazoethane

The dipolarophilic reactivity of the β-chloroacrylamides towards diazoethane as the 1,3-dipole was explored first as summarised in Table 1. A solution of the β-chloroacrylamide (sulfoxide or sulfide) in ether was added dropwise to an excess of an ethereal solution of diazoethane at –20 °C. The reaction solution was allowed to return slowly to room temperature and was stirred at room temperature for 4 hours. The product was isolated either by concentration at reduced pressure or, in instances where the product precipitated out of solution as the reaction progressed, by filtration of the reaction mixture. The effect of varying the amide group was investigated by employment of a range of N-aryl and N-alkyl moieties.

Table 1 Reaction of β-Chloroacrylamides with Diazoethane

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<td>R3</td>
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<td>47&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 : 0.10&lt;sup&gt;i&lt;/sup&gt;</td>
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</table>

a) *endo*/*exo* ratio of the pyrazoliones as determined by <sup>1</sup>H NMR spectroscopy.

b) Yield after filtration of the reaction mixture.

c) Isolated yield after chromatography.

d) Isolated yield after recrystallisation.

e) Crude ratio was 1 : 0.16.

f) Crude ratio was approximately 1 : 0.28.

g) Crude ratio was 1 : 0.27.

h) Crude ratio was 1 : 0.27.

i) Crude ratio was 1 : 0.30.

In cycloadditions of α-benzylsulfinyl-β-chloroacrylamides (entries 1-6, Table 1), α-benzylthio-β-chloroacrylamides (entries 13-15, Table 1) and α-benzenethio-β-chloroacrylamides with diazoethane (entries 16-19,
Table 1), a mixture of two diastereomeric pyrazoline cycloadducts was isolated in each instance, while pyrazoles were obtained from the reaction of α-benzenesulfynil-β-chloroacrylamides with diazoethane (entries 7-12.

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

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

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

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

Table 1).

While the N-aryl pyrazolines derived from α-benzensulfynil-β-chloroacrylamides proved stable and were stored in the freezer for long periods without apparent deterioration, decomposition occurred readily over a period of approximately 2 hours at room temperature
for the \( N \)-alkyl and \( N \)-benzyl substituted pyrazolines 34, 35 and 36. The \( N \)-methyl substituted
cycloadducts 34a and 34b decomposed to a complex mixture which contained the pyrazole
40 (Scheme 3), confirmed by the agreement of the \(^1\)H NMR spectroscopic data with that of a
pure sample of 40 which was independently synthesised. The mechanism of this
decomposition will be discussed later. The \( N \)-benzyl and \( N \)-\( n \)-butyl substituted pyrazolines
were also found to undergo decomposition at room temperature over approximately 2 hours
to a mixture of unidentifiable products.

![Scheme 3](image_url)

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

![Figure 2](image_url)

The \( \alpha \)-benzylsulfinyl-\( \beta \)-chloroacrylamides are conformationally constrained due to
the intramolecular hydrogen-bond between the amide proton and sulfoxide, adopting the \( s \)-\( cis \)
conformation. In each of the reactions, just two diastereomers of each of the cycloadducts are
observed. Complete diastereofacial control from the sulfoxide is envisaged, with the favoured
approach of diazoethane to the β-chloroacrylamides avoiding steric interactions with the benzyl group which blocks the approach of the dipole from above (Figure 3).

![Figure 3](image)

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

In instances where the pyrazole is isolated directly from the cycloaddition (entries 7–12, Table 1), the proposed mechanism involves the initial formation of the pyrazoline cycloadducts, which are unstable and readily eliminate the elements of PhSOCl to yield the pyrazoline lacking the sulfur moiety (Scheme 4).
X-Ray crystallographic analysis on the trimethylsilyldiazomethane derived pyrazole 51 confirmed its regiochemistry in the solid state as the 3-carboxamido substituted pyrazole (see later). The regiochemistry of the pyrazoles 40–43 was assigned by analogy.

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

The pyrazole 43 prepared during this work was conveniently transformed to 52 by a simple methylation reaction (Scheme 6). The melting point and 1H NMR spectroscopic data was in agreement with the reported data, specifically supporting the tautomeric assignment (mp this work, 135–137 °C; mp 3-carboxamido pyrazole, 142–144 °C; mp 5-carboxamido pyrazole, 98–99 °C). 28
Reaction of β-chloroacrylate 54 with diazoethane.

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

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

Decomposition of pyrazoline cycloadducts.

The decomposition of pyrazolines by photochemical or thermal means has been reported as a very efficient method for the preparation of cyclopropanes.\textsuperscript{7,29,30} The decomposition is usually achieved photochemically as the thermally-induced process leads to lower stereoselectivity and smaller amounts of cyclopropanes.\textsuperscript{31-33} Although the thermal extrusion of nitrogen mainly gives alkenes, there have been a few examples reported in the
literature in which cyclopropanes are the main products from the thermal process. As there was literature precedent for the thermolysis of pyrazolines to afford cyclopropanes, it was decided to explore the thermal decomposition of a pyrazoline synthesised during the current work to determine if the cyclopropane would be the major product isolated.

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

Scheme 8

Cycloadditions with trimethylsilyldiazomethane and diazomethane.

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

Table 2 Reaction of β-Chloroacrylamides with Trimethylsilyldiazomethane and Diazomethane
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<th>R²</th>
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Cycloaddition of the β-chloroacrylamides at the sulfoxide level of oxidation with trimethylsilyldiazomethane employing method A led to the isolation of the desulfinylated pyrazoles 51, 58–61 (entries 1–9, Table 2) following concentration of the reaction mixture and chromatographic purification. The pyrazoles which were synthesised from the α-benzylsulfinyl-β-chloroacrylamides were isolated in higher yields (52–66%) than the pyrazoles which were isolated from the reaction of trimethylsilyldiazomethane with the α-benzenesulfinyl-β-chloroacrylamides (16–31%). This is in contrast to the diazoethane case, and possibly indicates competing decomposition pathways for the benzenesulfinyl derivatives.

In contrast, cycloadditions between trimethylsilyldiazomethane and the β-chloroacrylamides at the sulfide level of oxidation provided a series of rearranged pyrazoles 62–65 (entries 10–13, Table 2), where the thio substituent underwent a 1,2-migration, the first time that this was observed. The sulfide derivatives were found to be much less reactive than the corresponding sulfoxides in cycloadditions with trimethylsilyldiazomethane, with much longer reaction times (48 h vs. 6 h) and greater amounts of trimethylsilyldiazomethane (15 eq. vs. 5 eq.) required. The reaction solution was concentrated to give the crude rearranged pyrazoles (which were relatively clean by 1H NMR spectroscopy compared to the pyrazoles 51, 58–61 produced from the reaction of the sulfoxide derivatives with trimethylsilyldiazomethane). Following purification by chromatography on silica gel, 62, 63–65 were isolated as white solids in moderate yields of 50–63%. The 4-phenylthio pyrazoles 64 and 65 were found to be much more polar and less soluble than the 4-benzylthio pyrazoles 62 and 63, with use of DMSO-d6 required to record the 13C NMR spectra of 64 and 65.

Meanwhile, cycloadditions of the α-sulfinyl-β-chloroacrylamides with diazomethane using Method C afforded the pyrazolines 66–69 as single diastereomers in yields of 55–77% for the S-alkyl derivatives (entries 14–17, Table 2), whilst the desulfinylated pyrazoles 51 and
were isolated from the cycloadditions with the $S$-phenyl derivatives (entries 18 & 19, Table 2). The $^1$H NMR spectra of the crude products were very complex and the isolated yields were poor (16–40%); some decomposition may have occurred during chromatography on the silica gel. While the $^{13}$C NMR spectra of the pyrazolines 66 and 67 could be recorded in CDCl$_3$, with the less stable pyrazolines 68 and 69 the $^{13}$C NMR spectra were recorded in DMSO-$d_6$, and analysis of the spectra indicated that the pyrazolines had decomposed to the corresponding pyrazoles 61 and 58 on dissolution in DMSO-$d_6$ (Scheme 9). Once the $^{13}$C NMR spectra had indicated decomposition, the $^1$H NMR spectra were re-recorded and comparison of both the $^1$H and $^{13}$C NMR spectroscopic data with those of pure samples of 61 and 58 (which had been previously synthesised independently) confirmed the identity of these decomposition products. Thus, while the sulfinyl pyrazolines were stable as solids and in CDCl$_3$, they undergo spontaneous elimination in DMSO-$d_6$.

\[
\begin{align*}
\text{R}^1 &= \text{Bn}, \text{R}^2 = \text{Me} & \text{68} & \text{61} \\
\text{R}^1 &= \text{n-Bu}, \text{R}^2 = \text{Bn} & \text{69} & \text{58}
\end{align*}
\]

Scheme 9

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

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

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

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

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

\[
\text{Scheme 10}
\]

The regiochemistry of the cycloaddition and the tautomer of the pyrazole 51 was determined by single crystal X-ray diffraction following recrystallisation from ethyl acetate
Figure 4. Examination of the crystal structure reveals a number of interesting features. In the solid state, the pyrazole \textbf{51} exists as the tautomer with the carboxamide group at the 3-position of the heterocycle rather than the 5-substituted pyrazole. The 5-substituted tautomer may be present in the solution state, although usually the tautomer in solution coincides with that found in the solid state.\textsuperscript{41-43} The principal tautomer of the diazoethane derived pyrazoles was assigned by analogy.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Anisotropic displacement parameters are drawn at the 30\% probability level}
\end{figure}

The hydrogen-bonding network present in the pyrazole \textbf{51} is depicted in Figure 5; an intramolecular hydrogen bond exists from the amide NH to the nitrogen at the 2-position of the heterocycle with a bond length of 2.30 Å to form a 5-membered ring system, and an intermolecular hydrogen bond is present between the NH of the pyrazole and the carbonyl group with a bond length of 1.96 Å. The presence of the intramolecular hydrogen bond confers rigidity to the structure and is presumably the driving force for the formation of the 3-substituted tautomer.
The mechanism of the formation of the rearranged pyrazoles 62, 63–65 is not fully understood, but the following is postulated: regioselective cycloaddition of trimethylsilyldiazomethane with the sulfides leads to the pyrazoline cycloadducts initially, and loss of chloride generates a carbocation, stabilised by the adjacent sulfur and silicon groups. Subsequent trimethylsilyl migration in the resulting sulfonium ion intermediate with concomitant aromatisation affords the N-trimethylsilyl rearranged pyrazole; hydrolytic cleavage of the N-Si bond would yield the final rearranged pyrazole product (Scheme 11). The observation that the same reaction pathway does not occur in the sulfoxide derivatives supports the proposed mechanism as the sulfinyl group would be much less nucleophilic than the sulfide. Furthermore, the efficiency of the analogous process in the diazomethane cycloadditions is much lower, presumably due to the absence of the stabilising trimethylsilyl group in the key carbocationic intermediate.
An alternative pathway, involving loss of trimethylsilylchloride followed by sigmatropic rearrangement, is illustrated in Scheme 12.

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

*Figure 6 (Anisotropic displacement parameters are drawn at the 30% probability level)*
The mechanism for the formation of the pyrazoles 51 and 58 is believed to be similar to that outlined in Scheme 4 for the preparation of the 5-methyl pyrazoles from the cycloaddition of the phenylsulfinyl derivatives and diazoethane. Thus, the pyrazoline cycloadduct is formed regioselectively but is unstable and elimination of PhSOCl yields the pyrazoline intermediate lacking the sulfur function. Subsequent tautomerisation yields the pyrazole.

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

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

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

**Cycloadditions with phenyldiazomethane.**

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

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Cycloaddition of the benzylsulfinyl derivatives with phenyldiazomethane yielded the pyrazoline cycloadducts 76–78 as single diastereomers (entries 1–3, Table 3) in yields of 31–64%. A number of factors may have contributed to the low yield; to avoid the risk of explosion during its distillation, phenyldiazomethane was used in its crude form which may have impacted the yield. Also, in some instances some of the product was lost to the mother liquor after filtration (confirmed by 1H NMR spectroscopy in a number of samples following concentration with caution). On dissolution of the pyrazolines in DMSO-d6, decomposition to the desulfinylated pyrazoles readily occurred. In contrast to the isolation of the pyrazolines with the benzylsulfinyl derivatives, on reaction of a range of benzenesulfinyl and n-butylsulfinyl derived β-chloroacrylamides with phenyldiazomethane, desulfinylation occurred to afford the pyrazoles 79, 80 and 82 as solids (entries 4–8, Table 3), with yields of 38–79%. The N-methyl substituted pyrazole 82 isolated from the cycloaddition of the S-benzenesulfinyl-β-chloroacrylamide 15 also contained the pyrazoline 81, evident by the appearance of two doublets in the 1H NMR spectrum at δH 4.68 and 5.53 ppm when recorded in CDCl3 (approximately 10%) and at δH 5.04 and 5.55 ppm when recorded in DMSO-d6.
(approximately 25%), indicating that elimination to form the pyrazole 82 is not as facile as the corresponding N-tolyl and N-benzyl derivatives 79 and 80.

On reaction of a range of phenylthio and benzylthio β-chloroacrylamides with phenyldiazomethane, either the rearranged pyrazole (entries 9–11, Table 3) or the pyrazoline cycloadduct as a single diastereomer (entry 12, Table 3) was isolated. Following reaction of the sulfides 28, 20 and 24 with phenyldiazomethane at room temperature for 16 hours, the reaction mixtures were concentrated to yield the crude products. The presence of the pyrazolines 87, 88 and 89 was evident in the complex ¹H NMR spectra of the crude products in each instance by the appearance of a doublet at δ_H 5.53–5.63 ppm, characteristic of the proton attached to the carbon at the 5-position of the ring. After purification by chromatography on silica gel, the rearranged pyrazoles 83, 84, and 85 were obtained as clean compounds (entries 9–11, Table 3). For the cycloaddition of the phenylthio derivative 25 with phenyldiazomethane (entry 12, Table 3), the pyrazoline 86 was isolated in 25% yield (in a pure state by ¹H NMR spectroscopy); the presence of 86 in the mother liquor contributed to the low isolated yield. When the ¹H and ¹³C NMR spectra of 86 were recorded in DMSO-d₆, decomposition to the pyrazole 82 [confirmed by the appearance of a CH signal in the ¹³C NMR spectrum at δ_C 102.2 ppm, characteristic of C(4)H] and the rearranged pyrazole 90 [confirmed by the appearance of a C signal in the ¹³C NMR spectrum at δ_C 102.1 ppm, characteristic of C(4)] was observed (Scheme 14). The cycloadditions of the sulfides with phenyldiazomethane displayed similar reactivity patterns to those observed previously for the reaction of the sulfide derivatives with diazomethane. Analogous to what was seen in the previously for the reaction of the N-methyl benzenesulfinyl derivative with phenyldiazomethane, the ease of elimination is again less facile for the N-methyl phenylthio derivative, while this trend was not seen with the other diazoalkanes.

![Scheme 14](image)

While the relative stereochemistry of the pyrazolines 76–78 has not been definitively confirmed, it is believed that they have the relative stereochemistry illustrated in Table 3. The
formation of a single diastereomer of the pyrazolines can be readily rationalised; as before, complete diastereofacial control is effected by the sulfinyl group, and in contrast to diazoethane, the energy differences between the transition state for the endo and exo approaches is sufficient to result in exclusive formation of the endo-cycloadduct, whereas with the smaller methyl group in diazoethane, both diastereomers result (Figure 3).

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

**Overview of cycloadditions with diazoalkanes.**

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

The cycloadducts derived from the diazoethane cycloadditions proved to be the most stable; the eliminated pyrazoles were only isolated from the cycloadditions with the benzenesulfinyl-β-chloroacrylamides, and the pyrazolines were obtained from the cycloadditions of the benzylsulfinyl-, benzyldithio- and phenylthio-β-chloroacrylamides as a mixture of two diastereomers. The cycloadditions with diazomethane led to slightly less stable products – at the sulfoxide level of oxidation, the pyrazolines were isolated for the benzylsulfinyl and n-butyldisulfanyl derivatives as single diastereomers, while the eliminated pyrazoles were obtained from the reaction with the benzenesulfinyl derivatives, in agreement with the diazoethane cycloadditions. However, in contrast to the diazoethane cycloadditions, the pyrazoline cycloadducts with diazomethane were not isolated in all instances for the thio-substituted β-chloroacrylamides (Figure 7); in some cases the rearranged pyrazole was obtained. Reaction of the β-chloroacrylamides with phenyldiazomethane led to even less stable cycloadducts, and even in instances where the pyrazoline cycloadducts were isolated from the cycloaddition, rapid decomposition was observed in DMSO-d₆. The pyrazoline cycloadducts derived from the cycloadditions with phenyldiazomethane were isolated as single diastereomers, signifying that the energy differences between the transition states for the endo and exo approaches is sufficient to result in exclusive formation of one cycloadduct, tentatively assigned as the endo. When trimethylsilyldiazomethane was employed as the dipole, the pyrazoline cycloadduct was not isolated in any case, with elimination of the sulfoxide group observed for the sulfinyl derivatives and migration of the sulfur group observed for the thio derivatives.

The main mechanistic difference between the sulfide and sulfoxide derivatives is that in instances where the pyrazoline cycloadducts are too unstable to isolate, the sulfinyl group eliminates while the sulfide group migrates. In the mechanism outlined in Scheme 11, the loss of chloride to form a carbocation is unlikely for the sulfoxide derivatives, as the sulfinyl group is much less nucleophilic than the sulfide group. Furthermore, the sulfide migration is cleaner in the trimethylsilyl cycloadducts, presumably facilitated by the presence of the trimethylsilyl group, than in the diazomethane and phenyldiazomethane cycloadducts in
which the rearranged pyrazoles are isolated.
Figure 7
Conclusion

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

Experimental

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

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

$^1$H (300 MHz) and $^{13}$C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. $^1$H (400 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform (CDCl$_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal standard. $^1$H NMR spectra that were recorded in deuterated dimethylsulfoxide (DMSO-$d_6$) were assigned using the DMSO peak as the reference peak. Chemical shifts ($\delta_H$ & $\delta_C$) 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 PF254). Visualisation was achieved by UV (254nm) light detection, iodine staining, vanillin staining and ceric sulfate staining.

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

Diazomethane was generated from Diazald® in glassware containing clear glass joints.45 Diazoethane was generated from N-ethyl-N-nitrosourea46,47 and phenyldiazomethane from the vacuum pyrolysis of benzaldehyde tosylhydrazone.48

Single crystal X-ray data for compound 30 was collected on a Nonius Mach 3 diffractometer using Mo-Kα graphite monochromated radiation and data for 63 was collected by STOE on a STOE IPDS 2T diffractometer using Cu-Kα graphite monochromated radiation. The data was corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full-matrix least-squares
using all F² data. The SHELXL-97,¹⁹ PLATON,²⁰ Nonius,²¹ X-AREA and X-RED32²² suite of programs were used.

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

(3R*,4R*,5R*,S₅*)-3-(Benzylsulfinyl)-4-chloro-N-(4-fluorophenyl)-4,5-dihydro-5-methyl-3H-pyrazole-3-carboxamide 32a and (3R*,4R*,5S*,S₅*)-3-(benzylsulfinyl)-4-chloro-N-(4-fluorophenyl)-4,5-dihydro-5-methyl-3H-pyrazole-3-carboxamide 32b

An excess of an ethereal solution of diazoethane [prepared from N-ethyl-N-nitrosoourea 91 (0.45 g, 3.8 mmol)] was added to a solution of N-(4-fluorophenyl)-Z-3-chloro-2-(benzylsulfinyl)propenamide 7 (0.19 g, 0.55 mmol) in ether (20 mL) and acetone (5 mL) cooled in an ice-salt bath while stirring. The solution was allowed to return slowly to room temperature while stirring for 4 h. A precipitate formed as the reaction progressed. The products were collected by filtration through a sintered glass funnel (grade 3) to give 32a and 32b (32a:32b 1:0.21 by ¹H NMR spectroscopy) as a white solid (0.20 g, 94%), mp 98-100 °C; (Found C, 54.77; H, 4.30; N, 10.66. C₁₈H₁₇ClN₃O₂SF requires C, 54.89; H, 4.35; N, 10.67%); v_max/cm⁻¹ (KBr) 3298 (NH), 3029 (CH), 1668 (CO), 1552 (N=N), 1514, 1407, 1226, 1038 (SO);

Major diastereomer 32a: δ_H (300 MHz, CDCl₃) 1.52 [3H, d, J 7.5, C(5)CH₃], 4.07 (1H, d, A of AB system, J_AB 12.8, SCH₂), 4.45 (1H, d, B of AB system, J_AB 12.8, SCH₂), 4.75 [1H, d, J 3.6, C(4)H], 5.25 [1H, dq, J 3.6, 7.5, C(5)H], 7.04-7.13 (2H, m, ArH)*, 7.31-7.40 (5H, m, ArH)*, 7.49-7.64 (2H, m, ArH)*, 8.90 (1H, br s, NH).

δ_C (75.5 MHz, DMSO-d₆) (signals for major diastereomer 32a only detected) 15.8 [CH₃, C(5)CH₃], 54.1, (CH₂, SCH₂), 61.3 [CH, C(5)H], 90.0 [CH, C(4)H], 107.1 [C, C(3)], 115.6 [CH, d, ²J_CF 22, aromatic C(3')H], 124.1 [CH, d, ³J_CF 8, aromatic C(2')H], 128.7, 129.1, 130.9 (3 × CH, 3 × aromatic CH), 131.2, 134.0 (2 × C, 2 × aromatic C), 159.4 [C, d, ¹J_CF 244, aromatic C(4')], 162.4 (C, CO).
Minor diastereomer 32b: δ 
H (300 MHz, CDCl3) 1.87 [3H, d, J 7.3, C(5)CH3], 4.05 (1H, d, A of AB system, JAB 12.8, SCCH2), 4.48 (1H, d, B of AB system, JAB 12.8, SCCH2), 4.78-4.82 [1H, m, C(5)H], 5.32 [1H, d, J 5.5, C(4)H], 7.04-7.13 (2H, m, ArH)*, 7.31-7.40 (5H, m, ArH)*, 7.49-7.64 (2H, m, ArH)*, 9.14 (1H, br s, NH).

*The aromatic signals were indistinguishable for the two diastereomers.

HRMS (ES+): Exact mass calculated for C18H18NO2S35ClF [(M+H)+ – N2], 366.0731. Found 366.0727; m/z (ES+) 396.2 [(C18H17N3O2S37ClF)+H+], 2%; 394.2 [(C18H17N3O2S35ClF)+H+], 8%; 368.2 [(C18H17NO2S35ClF)+H+], 18%; 366.2 [(C18H17NO2S37ClF)+H+], 40%; 220.2 (100%).

N-(4-Fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamide 38

An excess of an ethereal solution of diazoethane [prepared from N-ethyl-N-nitroso urea 91 (0.77 g, 6.6 mmol)] was added to a solution of N-(4-fluorophenyl)-Z-3-chloro-2-(benzenesulfinyl)propenamide 13 (0.30 g, 0.9 mmol) in ether (30 mL) cooled in an icesalt bath while stirring. The reaction solution was allowed to return slowly to room temperature while stirring for 4 h. The solvent was removed by evaporation at reduced pressure to give 38 as a yellow oil. Following purification by column chromatography using hexane-ethyl acetate (gradient elution 5-40% ethyl acetate) as eluent, the pyrazole 38 was obtained as an off-white solid (0.10 g, 49%), mp 196-197 °C; (Found C, 60.18; H, 4.67; F, 8.91. C11H10FN3O requires C, 60.27; H, 4.60; F, 8.67%); νmax/cm−1 (KBr) 3380 (NH), 3193 (NH), 3121, 2986 (CH), 1662 (CO), 1555, 1509, 1412, 1218; δH (300 MHz, DMSO-d6) 2.34 [3H, s, C(5)CH3], 6.54 [1H, s, C(4)H], 7.13-7.27 (2H, m, ArH), 7.81-7.93 (2H, m, ArH), 10.09 (1H, br s, NH of carboxamide), 13.12 [1H, br s, N(1)H]; δC (75.5 MHz, DMSO-d6) 10.7 [CH3, C(5)CH3], 105.0 [CH, C(4)H], 115.4 [CH, d, 2JCF 22, aromatic C(3′)H], 122.2 [CH, d, 3JCF 8, aromatic C(2′)H], 135.6 (C, aromatic C), 140.6, 147.2 [2 × C, C(3) & C(5)], 158.4 [C, d, 1JCF 239, aromatic C(4′)], 160.9 (C, CO); HRMS (ES+): Exact mass calculated for C11H10N3OF [M+H]+, 220.0886. Found 220.0897; m/z (ES+) 220.2 [(C11H10N3OF)+H+], 100%; 272.1.
(1R*, 2R*, 3R*/S*)-1-(Benzylthio)-2-chloro-N-(4-fluorophenyl)-3-
methylcyclopropanecarboxamide 56a, (1R*, 2R*, 3S*/R*)-1-(benzylthio)-2-chloro-N-
(4-fluorophenyl)-3-methylcyclopropanecarboxamide 56b & 2-(benzylthio)-3-chloro-
N-(4-fluorophenyl)pent-2-enamide 57

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

Major diastereomer 56a: \(\delta_{H}\) (300 MHz, CDCl\(_3\)) 1.36 [3H, d, \(J 6.6\), C(3)CH\(_3\)], 2.14 [1H, 
dq, \(J 8.1, 6.3\), C(3)H], 3.91 (1H, d, A of AB system, \(J_{AB} 12.6\), one of SCH\(_2\)], 3.97 (1H, d, 
B of AB system, \(J_{AB} 12.6\), one of SCH\(_2\)], 4.22 [1H, d, \(J 8.1\), C(2)H], 6.90-7.34 (9H, m, 
ArH*)*, 9.05 (1H, br s, NH); \(\delta_{C}\) (75.5 MHz, CDCl\(_3\)) 7.9 [CH\(_3\), C(3)CH\(_3\)], 26.8 [CH, 
C(3)H], 34.8 (CH\(_2\), SCH\(_2\)), 36.6 [C, C(1)], 44.2 [CH, C(2)H], 166.5 (C, CO).

Minor diastereomer 56b: \(\delta_{H}\) (300 MHz, CDCl\(_3\)) 1.20 [3H, d, \(J 6.3\), C(3)CH\(_3\)], 1.88 [1H, 
dq, \(J 9.9, 6.6\), C(3)H], 3.96 (2H, s, SCH\(_2\)], 4.22 [1H, d, \(J 6.0\), C(2)H], 6.90-7.34 (9H, m, 
ArH*)*, 8.91 (1H, br s, NH); \(\delta_{C}\) (75.5 MHz, CDCl\(_3\)) 9.2 [CH\(_3\), C(3)CH\(_3\)], 33.8 [CH, 
C(3)H], 35.9 (CH\(_2\), SCH\(_2\)), 38.2 [C, C(1)], 43.5 [CH, C(2)H], 163.7 (C, CO).

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

The aromatic signals were not distinguished in the \(^{13}\)C NMR spectrum for the two 
diastereomers and were seen at \(\delta_{C}\) 113.7 [CH, d, \(^{2}J_{CF} 21\), aromatic C(3’)H], 119.5 [CH, d,
3\(J_{\text{CF}}\) 8, aromatic C(2')H], 125.8, 125.9, 127.0, 127.1, 127.3 (5\( \times \) CH, 5\( \times \) aromatic CH), 131.7, 135.3, 135.5 (3\( \times \) C, 3\( \times \) aromatic C), 157.6 [C, d, \(J_{\text{CF}}\) 243, aromatic C(4')].

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

57 was also isolated from this reaction as a white solid (0.02g, 5\%) as a single stereoisomer; \(v_{\text{max}}/\text{cm}^{-1}\) (KBr) 3245 (NH), 3068 (CH), 2972 (CH), 1641 (CO), 1507; \(\delta_H\) (300 MHz, CDCl\(_3\)) 1.20 [3H, t, \(J_{\text{CF}}\) 7.3, C(5)H\(_3\)], 2.80 [2H, q, \(J_{\text{CF}}\) 7.3, C(4)H\(_2\)], 3.97 (2H, s, S\(\text{C}H\)_2), 6.93-7.06 (2H, m, ArH), 7.20-7.40 (7H, m, ArH), 7.83 (1H, br s, NH); \(\delta_C\) (75.5 MHz, CDCl\(_3\)) 13.4 [CH\(_3\)], 32.3 [CH\(_2\)], 116.0 [CH, d, \(J_{\text{CF}}\) 22, aromatic C(3')H], 121.9 [CH, d, \(J_{\text{CF}}\) 8, aromatic C(2')H], 126.1 [C, C(2)], 128.0, 129.2, 129.3 (3\( \times \) CH, 3\( \times \) aromatic CH), 133.8, 137.5 (2\( \times \) C, 2\( \times \) aromatic C), 153.6 [C, C(3)], 159.9 [C, d, \(J_{\text{CF}}\) 244, aromatic C(4')], 163.3 (C, CO); HRMS (ES+): Exact mass calculated for \(\text{C}_{18}\text{H}_{18}\text{NOS}_{35}\text{ClF} (\text{M}+\text{H})^+\), 350.0782. Found 350.0796; m/z (ES+) 352.0 \(\{[(\text{C}_{18}\text{H}_{17}\text{NOS}_{37}\text{ClF})+\text{H}]^+, 38\%\}\), 350.0 \(\{[(\text{C}_{18}\text{H}_{17}\text{NOS}_{35}\text{ClF})+\text{H}]^+, 100\%\}\).

\(N\)-(4-Methylphenyl)-1\(H\)-pyrazole-3-carboxamide 51

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

An ethereal solution of trimethylsilyldiazomethane (1.62 mL of a 2M solution, 3.3 mmol) was added to a stirring solution of \(N\)-(4-methylphenyl)-Z-3-chloro-2-(benzylsulfinyl)propenamide 8 (0.22 g, 0.7 mmol) in ether (25 mL) and acetone (2 mL) under nitrogen at room temperature in the dark. The reaction solution was then stirred for 6 h. The solvent and excess trimethylsilyldiazomethane were removed by evaporation at reduced pressure to give the crude product as a yellow solid. Purification by column chromatography using hexane-ethyl acetate (gradient elution 10-40\% ethyl acetate) gave 51 as a white solid (0.07 g, 54\%), mp 190-191 °C; (Found C, 65.21, H, 5.50, N, 20.19; \(\text{C}_{11}\text{H}_{11}\text{N}_{3}\text{O}\) requires C, 65.66, H, 5.51, N, 20.88\%); \(v_{\text{max}}/\text{cm}^{-1}\) (KBr) 3378 (NH), 3134
(CH), 2950 (CH), 1643 (CO), 1596, 1541, 1320; δ \text{H}(300 MHz, DMSO-d\text{6}) 2.28 (3H, s, ArC\text{H}3), 6.78 [1H, br s, C(4)H], 7.14 (2H, d, J 8.1, ArH), 7.69 (2H, d, J 8.1, ArH), 7.88 [1H, br s, C(5)H], 9.91 (1H, br s, NH of carboxamide), 13.38 [1H, br s, N(1)H]; δ \text{C}(75.5 MHz, DMSO-d\text{6}) 20.8 (CH\text{3}, ArC\text{H}3), 105.9 [CH, C(4)H], 120.5, 129.3 (2 × CH, 2 × aromatic CH), 130.7 [CH, C(5)H], 132.6, 136.7 (2 × C, 2 × aromatic C), 147.1 [C, C(3)], 160.7 (C, CO); HRMS (ES+): Exact mass calculated for C\text{11}H\text{12}N\text{3}O [M+H]+, 202.0980. Found 202.0987; m/z (ES+) 202.2 {[(C\text{11}H\text{11}N\text{3}O)+H]+}, 100%).

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

Crystals of \textbf{51} are monoclinic, space group \textit{P} 2\textit{1}/c, formula C\text{11}H\text{11}N\text{3}O, M = 201.23, a = 15.936(5) Å, b = 6.1614(10) Å, c = 10.962(3) Å, α = 90.00 °, β = 108.19(3) °, γ = 90.00 °, U = 1022.5(5) Å\textsuperscript{3}, F(000) = 424, μ(Mo-Kα) = 0.088 mm\textsuperscript{-1}, R(F\text{o}) = 0.0448, for 979 observed reflections with I>2σ(I), wR\text{2}(F\text{2}) = 0.1287 for all 1788 unique reflections. Data in the θ range 2.69-24.92 ° were collected at 293 K on a Nonius MACH3 diffractometer using Mo-Kα graphite monochromated radiation, λ = 0.7107 Å, and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F\text{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.

\textit{b) Prepared from N-(4-methylphenyl)-Z-3-chloro-2-(benzenesulfinyl)propenamide 16 and trimethylsilyldiazomethane}

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

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

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

A solution of N-(4-fluorophenyl)-Z-3-chloro-2-(benzylsulfinyl)propenamide 7 (0.16 g, 0.5 mmol) in ether (15 mL) and acetone (3.5 mL) was added to an excess of an ethereal solution of diazomethane [prepared from Diazald® (0.84 g, 3.9 mmol)] cooled in an ice-salt bath while stirring. The solution was allowed to return slowly to room temperature while stirring for 4 h. A precipitate formed as the reaction progressed. The product was collected by filtration through a sintered glass funnel (grade 3) to give 66 as a white solid (0.12 g, 69%) as a single diastereomer, mp 89-90 °C; (Found C, 54.02; H, 3.90; N, 11.36; F, 4.85; Cl, 9.11; S, 8.78. C_{17}H_{15}ClN_{3}O_{2}SF requires C, 53.76; H, 3.98; N, 11.06; F, 4.98; Cl, 9.33; S, 8.46 %); ν_{max}/cm^{-1} (KBr) 3306 (NH), 3036 (CH), 2920 (CH), 1676 (CO), 1542 (N=O), 1510, 1408, 1220, 1040 (SO); δ_{H} (300 MHz, CDCl_{3}) 4.07 [1H, d, A of AB system, J_{AB} 12.9, S(CH)], 4.44 (1H, d, B of AB system, J_{AB} 12.9, S(CH)], 4.97 [1H, dd, A of ABC system, J_{AB} 18.9, J_{AC} 5.7, one of C(5)H], 5.25 [1H, dd, C of ABC, J_{AC} 5.7, J_{BC} 1.5, C(4)H], 5.31 [1H, dd, B of ABX, J_{AB} 18.9, J_{BC} 1.5, one of C(5)H], 6.99-7.09 (2H, m, ArH), 7.30-7.38 (5H, m, ArH of benzyl), 7.47-7.56 (2H, m, ArH), 9.21 (1H, br s, NH); δ_{C} (75.5 MHz, CDCl_{3}) 51.5 [CH, C(4)H], 57.1 (CH_{2}, S(CH)), 88.0 [CH_{2}, C(5)H], 108.8 [C,
C(3)], 115.9 [CH, d, \(^2J_{CF} 23\), aromatic C(3')H], 122.4 [CH, d, \(^3J_{CF} 8\), aromatic C(2')H], 129.1, 129.2, 130.4 (3 × CH, 3 × aromatic CH), 132.6, 132.7 (2 × C, 2 × aromatic C), 157.8 (C, CO), 160.0 [C, d, \(^1J_{CF} 245\), aromatic C(4')]; HRMS (ES+): Exact mass calculated for C\(_{17}\)H\(_{16}\)NO\(_2\)S\(_{35}\)ClF \([(M+H)\]^+ – N\(_2\)]. 352.0574. Found 352.0574; m/z (ES+) 352.1 \([(C\(_{17}\)H\(_{16}\)NO\(_2\)S\(_{35}\)ClF)+H\(^+\)] \(4\%), 87.9 (100%).

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

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

An ethereal solution of trimethylsilyldiazomethane (2.40 mL of a 2M solution, 4.8 mmol) was added to a stirring solution of N-methyl-Z-3-chloro-2-(benzylthio)propenamide 26 (0.23 g, 1.0 mmol) in ether (25 mL) under nitrogen at room temperature in the dark. The reaction solution was then stirred at room temperature and the reaction progress was monitored by TLC analysis. After stirring for 5 h, TLC analysis showed that a lot of starting material still remained and a further 2.40 mL of trimethylsilyldiazomethane solution was added. Following stirring for 24 h, a further 2.40 mL of trimethylsilyldiazomethane solution was added to the reaction mixture. After stirring for 48 h, TLC analysis indicated complete consumption of the starting material and the solvent and excess trimethylsilyldiazomethane were removed by evaporation at reduced pressure to give the crude product as an off-white solid. Purification by column chromatography using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) gave 63 as a white solid (0.14 g, 59%), mp 145-147 °C; (Found C, 58.17; H, 5.12; N, 16.89; S, 13.12. C\(_{12}\)H\(_{13}\)N\(_3\)OS requires C, 58.28; H, 5.30; N, 16.99; S, 12.97%); \(\nu_{max}/\text{cm}^{-1}\) (KBr) 3310 (NH), 3099 (NH), 2922 (CH), 1646 (CO), 1566, 1492, 1352; \(\delta_H\) (300 MHz, CDCl\(_3\)) 2.79 (3H, d, \(J 4.8\), NHCH\(_3\)), 3.85 (2H, s, SCH\(_2\)), 6.93-7.13 (2H, m, ArH), 7.17-7.36 (3H, m, ArH), 7.55 [2H, br s, NH of carboxamide & C(5)H], 12.50 [1H, br s, N(1)H]; \(\delta_C\) (75.5 MHz, CDCl\(_3\)) 25.9 (CH\(_3\), NHCH\(_3\)), 42.5 (CH\(_2\), SCH\(_2\)), 107.7 [C, C(4)], 127.6, 128.7 (1 signal for 2 × CH) (2 × CH, aromatic CH), 137.4 [C, aromatic C & C(3)], 143.6 [CH, br, C(5)H], 159.9 (C, CO); \(\delta_C\) (75.5 MHz, DMSO-\(d_6\)) 25.5 (CH\(_3\), NHCH\(_3\)), 37.8 (CH\(_2\), br,
SCH2), 112.7 [C, C(4)], 126.9, 128.2, 128.8, (3 × CH, 3 × aromatic CH), 130.1 [C, br, C(3)], 137.9 (C, aromatic C), 143.8 [CH, br, C(5)H], 160.1 (C, br, CO); HRMS (ES+): Exact mass calculated for C12H14N3OS [M+H]+, 248.0858. Found 248.0851; m/z (ES+) 248.1 {[(C12H13N3OS)+H]+, 100%}, 495.2 {[(C24H26N6O2S2)+H]+, 28%}.

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

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

Crystals of 63 are centric monoclinic, space group C 2/c, formula C12H13N3OS, M = 247.31, a = 22.4891(18) Å, b = 10.3523(6) Å, c = 12.2712(10) Å, α = 90.00 °, β = 119.882(6) °, γ = 90.00 °, U = 2477.1(3) Å³, F(000) = 1040, μ(Cu-Kα) = 2.222 mm⁻¹, R(Fo) = 0.0531, for 1836 observed reflections with I>2σ(I), wR2(F2) = 0.1516 for all 2003 unique reflections. Data in the θ range 4.54-64.15 ° were collected at 150 K on a STOE IPDS 2T diffractometer using Cu-Kα graphite monochromated radiation, λ = 1.54186 Å, and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

(3R*,4R*,5R*,S5*)-3-(Benzylsulfinyl)-4-chloro-4,5-dihydro-5-phenyl-N-(4-methylphenyl)-3H-pyrazole-3-carboxamide 76 & N-(4-methylphenyl)-5-phenyl-1H-pyrazole-3-carboxamide 79
A solution of N-(4-methylphenyl)-Z-3-chloro-2-(benzylsulfinyl)propenamide 8 (0.21 g, 0.6 mmol) in ether (15 mL) and acetone (4 mL) was added dropwise to an excess of phenyldiazomethane [generated from benzaldehyde tosylhydrazone (1.68 g, 6.0 mmol)] cooled to −50 °C using a cryocooler. The solution was allowed to return slowly to room temperature while stirring for 16 h. A precipitate formed as the reaction progressed. The product was collected by filtration through a sintered glass funnel (grade 3) to give 76 as a white solid (0.09 g, 31%) and as a single diastereomer, mp 72–74 °C; (Found C, 63.75; H, 4.88; N, 8.92; S, 6.79; Cl, 7.59. C24H22ClN3O2S requires C, 63.78; H, 4.91; N, 9.30; S, 7.09, Cl, 7.84%); νmax/cm−1 (KBr) 3271 (NH), 2919 (CH), 1679 (CO), 1609, 1595, 1525 (N=N), 1076 (SO); δH (300 MHz, CDCl3) 2.36 (3H, s, ArCH3), 4.25 (1H, d, A of AB system, J12.6, one of SCH2), 4.46 (1H, d, B of AB system, J12.9, one of SCH2), 4.83 [1H, d, J 6.6, C(4)Cl], 6.03 [1H, d, J 6.3, C(5)HPh], 7.17-7.47 (12H, m, ArH), 7.52 (2H, d, J 8.4, ArCH), 8.78 (1H, br s, NH); δH (300 MHz, DMSO-d6) 2.31 (3H, s, ArCH3), 4.47 (1H, d, A of AB system, J12.9, one of SCH2), 4.52 (1H, d, B of AB system, J12.9, one of SCH2), 5.12, 5.57 [2 × 1H, 2 × d, J 8.7, 9.0, C(5)HPh & C(4)HCl], 7.20 (2H, d, J 8.1, ArH), 7.31-7.58 (10H, m, ArH), 7.64 (2H, d, J 8.4, ArCH), 10.45 (1H, br s, NH). There was some evidence of decomposition to the pyrazole 79 in the 1H NMR spectrum in DMSO-d6, with characteristic signals at δH 7.70 (2H, d, J 8.4, ArH), 7.86 (2H, d, J 6.6, ArH), 10.06 (1H, br s, NH); When the 13C NMR spectrum was recorded in DMSO-d6, total decomposition to the pyrazole 79 occurred, with characteristic signals at δC (75.5 MHz, DMSO-d6) 20.5 (CH3, ArCH3), 103.0 [CH, C(4)H], 120.2, 125.3, 128.3 129.0 (4 × CH, 4 × aromatic CH, 4 signals for 5 carbons), 132.5, 136.2 (2 × C, 2 × aromatic C), 159.1 (C, CO). The signals for C(3), C(5) and one aromatic C were not detected in the 13C NMR spectrum. Spectroscopic details agreed with a genuine sample of 79; HRMS (ES+): Exact mass calculated for C24H22NO2S35Cl [(M+H)+ – N2], 424.1138. Found 424.1130; m/z (ES+) 426.2 {[(C24H22NO2S37Cl)+H]+, 4%}, 424.2 {[(C24H22NO2S35Cl)+H]+, 14%}, 278.2 {[(C17H15N3O)+H]+, 6%}, 87.9 (100%).

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References


25. See supplementary information.


