Regioselective Thermal [3+2]-Dipolar Cycloadditions of α-Diazoacetates with *α*-Sulfenyl/Sulfinyl/Sulfonyl-*β*-Chloroacrylamide Derivatives to form Densely Functionalised Pyrazoles.

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Abstract: Highly regioselective synthetic methodology leading to densely functionalised C(3), C(4) and C(5) substituted pyrazoles **10a-q, 14a-i and 16a-g** via thermal [3+2]-dipolar cycloaddition, of α-diazoacetates and α-thio-β-chloroacrylamides, at the sulfide, sulfoxide and sulfone levels of oxidation, is described. This method allows access to C(4)-sulfenyl or sulfonyl pyrazoles, through migration of the sulfur substituent at the sulfide and sulfone oxidation levels, while elimination of the sulfinyl group leading to 3,5-disubstituted pyrazoles, is observed. While the sulfide migration is readily rationalised, the carbon to carbon 1,2-sulfonyl migration is unprecedented and mechanistically intriguing. The synthetically versatile generation of densely functionalised pyrazoles containing substituents amenable to further modification offers advantages over alternative synthetic routes. Isolation of the *N*-alkylated pyrazoles **11a** and **12a** as by-products from the cycloaddition through further reaction of the pyrazoles **10** with excess α-diazoacetate, proved useful in rationalising the tautomeric behaviour evident in the NMR spectra of the pyrazoles, with the position of tautomeric equilibrium influenced by solvent and substituents.

Introduction

Heterocycles are an indispensable and ubiquitous class of compounds; notably they make up more than half of all known organic compounds and have a broad range of biological, chemical and physical properties spanning an expansive spectrum of reactivity and stability.[1] Among heterocycles, the pyrazole moiety and its derivatives are an important class of nitrogen containing five-membered heterocyclic compounds that have garnered significant interest in recent times predominantly due to their usefulness as targets in drug discovery.[2] Notably, several commercialised synthetic pyrazoles have come to prominence in recent decades highlighting the diverse biological effects associated with this critical scaffold. Celecoxib **(1)**, a COX-2 inhibitor is widely used as a non-steroidal anti-inflammatory drug,[3] rimonabant **(2)** was used in the treatment of obesity by acting as an inverse agonist of the cannabinoid receptor CB1 prior to its withdrawal from market,[4] fipronil **(3)** is a broad spectrum insecticide that acts on GABA-gated and glutamate-gated chloride channels in the insect nervous system,[5] sildenafil **(4)** is used for the treatment of erectile dysfunction and pulmonary hypertension,[6] and tartrazine **(5)** is a synthetic lemon azo dye primarily used as a food colouring (Figure 1).[7] Of significant interest is the presence of highly functionalised diversified substituents bonded to the pyrazole nucleus, many of which are electron withdrawing groups, that are critical to the compound's activity.

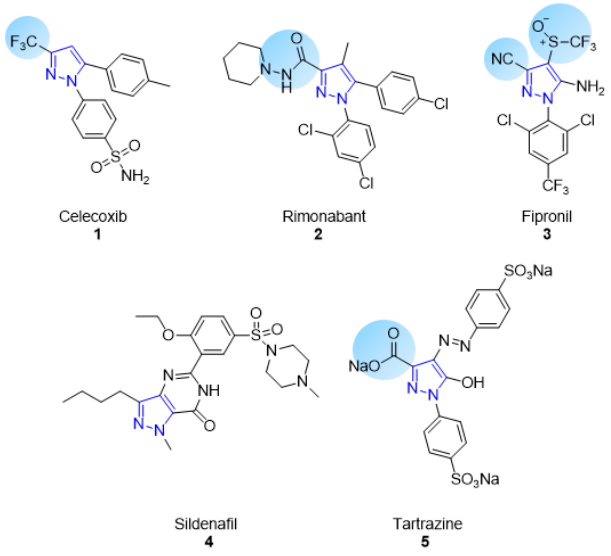

Figure 1. Commercialised substances containing the pyrazole moiety.

Markedly, the condensation of 1,3-dicarbonyl compounds with hydrazine derivatives remains the prevailing synthetic route towards formation of the pyrazole scaffold despite its associated limitations, namely the multistep sequences (in

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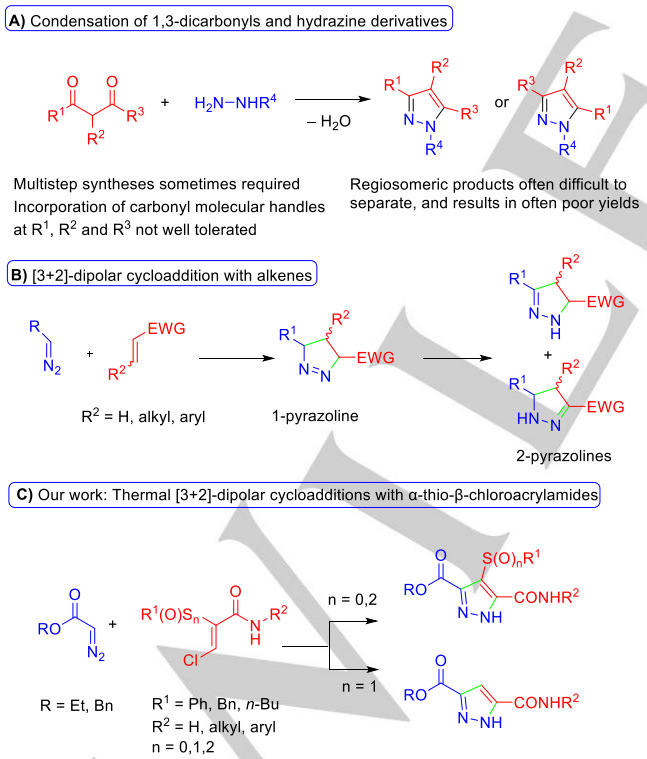
many instances) required to generate the desired starting materials, limited functional group tolerance, harsh reaction conditions and poor regioselectivities (Scheme 1, A).[2e, 8] The safety aspects of using hydrazines and its derivatives must also be considered.[9]

The [3+2]-dipolar cycloaddition offers a unique atom-economical solution to many of the aforementioned problems with excellent regioselectivities and tolerance of functional group diversity characteristic of the reaction.[10] The [3+2]-dipolar cycloaddition of alkenes with diazoalkanes is well-documented generally forming the 1-pyrazoline that readily isomerises to the more thermodynamically stable 2-pyrazoline, however a further oxidative step is usually required to form the pyrazole (Scheme 1, B).[11]

This problem can be circumvented by employing diazo compounds with an in-built synthetic handle that is retained through the cycloaddition, that can much more readily undergo further synthetic transformations. While the use of inexpensive commercially available ethyl diazoacetate as a 1,3-dipole is well-known, and the ester moiety is an excellent synthetic handle, its use is not without challenges. High temperatures,[12] Lewis acid catalysis,[13] prolonged reaction times[14] and structurally simple dipolarophiles are typical in its use in [3+2]-dipolar cycloadditions, several of which actively contribute to its known degradation pathways and side reactions.

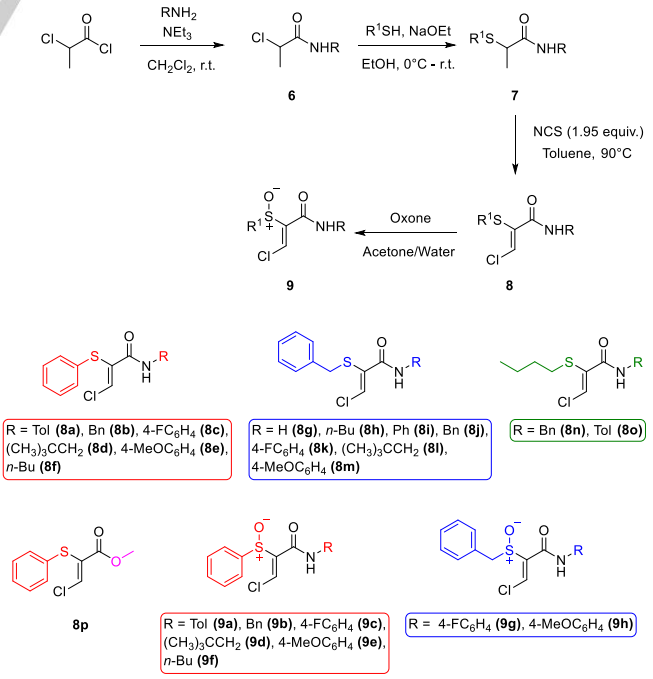


Scheme 1. Synthetic routes toward functionalised 3,4,5-substituted pyrazoles.

A major advantage of the [3+2]-dipolar cycloaddition is that the dipolarophile can be tuned to incorporate a comprehensive range of functionality that would otherwise be a difficult task using other methods. We have previously reported comprehensively on the synthesis and reactivity of *α*-thio-*β*-chloroacrylamides,[15] a family of sulfur-containing compounds that undergo a large range of reactions such as oxidation,[16] addition-substitution,[17] Diels-Alder cycloaddition[18] and [3+2] dipolar cycloaddition.[19] Significantly, while the [3+2] dipolar cycloaddition of ethyl diazoacetate with a diverse range of functionalised dipolarophiles is well explored, dipolarophiles bearing halides capable of acting as a leaving group and as a potential source of functional group migrations remains substantially less studied. In this work, we present the use of *α*-thio-*β*-chloroacrylamides as a unique dipolarophile scaffold at each of the sulfide, sulfoxide and sulfone level of oxidation with the electron deficient α-diazoacetates to generate a series of novel highly functionalised pyrazoles at the C(3), C(4) and C(5) positions (Scheme 1, C).

Results and Discussion

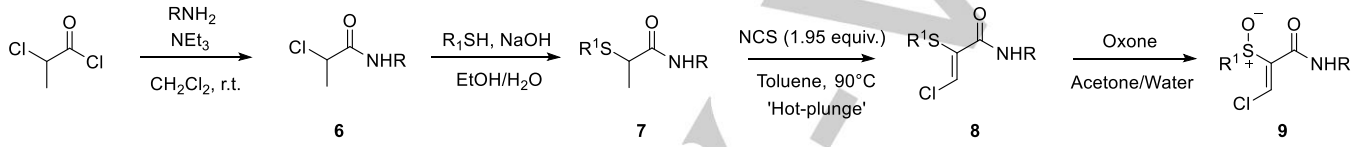
Fifteen *α*-thio-*β*-chloroacrylamides **8a-o** were chosen for investigation in this study, some of which were described in our earlier work and others which are novel **(8d, 8e, 8l, 8m)**. Each of the known substrates were synthesised following our optimised procedures as summarised in Scheme 2, affording multi-gram quantities of these compounds, the majority of which were amenable to storage at room temperature for several months without any appreciable degradation. An exception to this included the *N*-alkyl amide **8f** and alkyl sulfides **8h-o** used in this study which required storage in the freezer to avoid degradation.



Scheme 2. Synthetic route towards dipolarophile precursors (See Supporting Information for more details).

The α-chloroamides were generated in almost quantitative yields from commercially available 2-chloropropionyl chloride and the requisite aromatic or aliphatic amine source and were sufficiently pure to not require further purification. While previously described α-thioamides were generated using either thiophenol, benzyl mercaptan or 1-butanethiol in the presence of freshly prepared sodium ethoxide, each of the novel α-thioamides **7d, 7e, 7l, 7m** were generated using aqueous sodium hydroxide as base, obviating the requirement for chromatographic purification. While the generation of *α*-thio-*β*-chloroacrylamides in continuous flow is amenable to scale up,[20] all substrates used in this study were formed using optimised batch conditions described previously.[21] The novel *α*-thio-*β*-chloroacrylamides **8d, 8e, 8l, 8m** are fully characterised in this work. Notably, the signal for the *β*-H is very distinctive, and as a result, all novel *α*-thio-*β*-chloroacrylamides generated in this work were assigned as the *Z*-stereoisomer, in line with our earlier work. The *α*-thio-*β*-chloroacrylamides underwent oxidation to their sulfoxide derivatives by treatment with Oxone® overnight, without evidence for over oxidation to the sulfone. The sulfoxides in most instances were much more labile than the sulfide derivatives and required storage in the freezer to avoid degradation. In order to investigate the effect of replacing the amide functionality with an ester moiety, with greater synthetic potential, the *α*-thio-*β*-chloroacrylate **8p** was also generated.[15] The synthesis of the novel precursors is summarised in Table 1.

Table 1. Synthesis of novel dipolarophile precursors **8** and **9**



Entry	R	*α*-Chloroamide **6**	Yield[a] (%) **6**	R^1	*α*-Thioamide **7**	Yield[a,b] (%) **8**	*α*-Thio-*β*-chloroacrylamide **8**	Yield[c] (%) **8**	*α*-Sulfinyl-*β*-chloroacrylamide **9**	Yield[c,d] (%) **9**
1	$(CH_3)_3CCH_2$	**6d**	98	Ph	**7d**	98[b]	**8d**	77	**9d**	96[d]
2				Bn	**7l**	86[a]	**8l**	65	-	-
3	4-$MeOC_6H_4$	**6e**	97	Ph	**7e**	89[b]	**8e**[e]	34	**9e**	79[c]
4				Bn	**7m**	94[b]	**8m**[e]	40	**9h**	92[c]

[a] Isolated % yield post basic work up; column chromatography not required. [b] Isolated % yield post filtration; column chromatography not required. [c] Isolated % yield after chromatography on silica gel. [d] Isolated % yield post aqueous work up; column chromatography not required. [e] Low yields of *α*-thio-*β*-chloroacrylamide **8e** and **8m** due to the solubility issues encountered during chromatography.

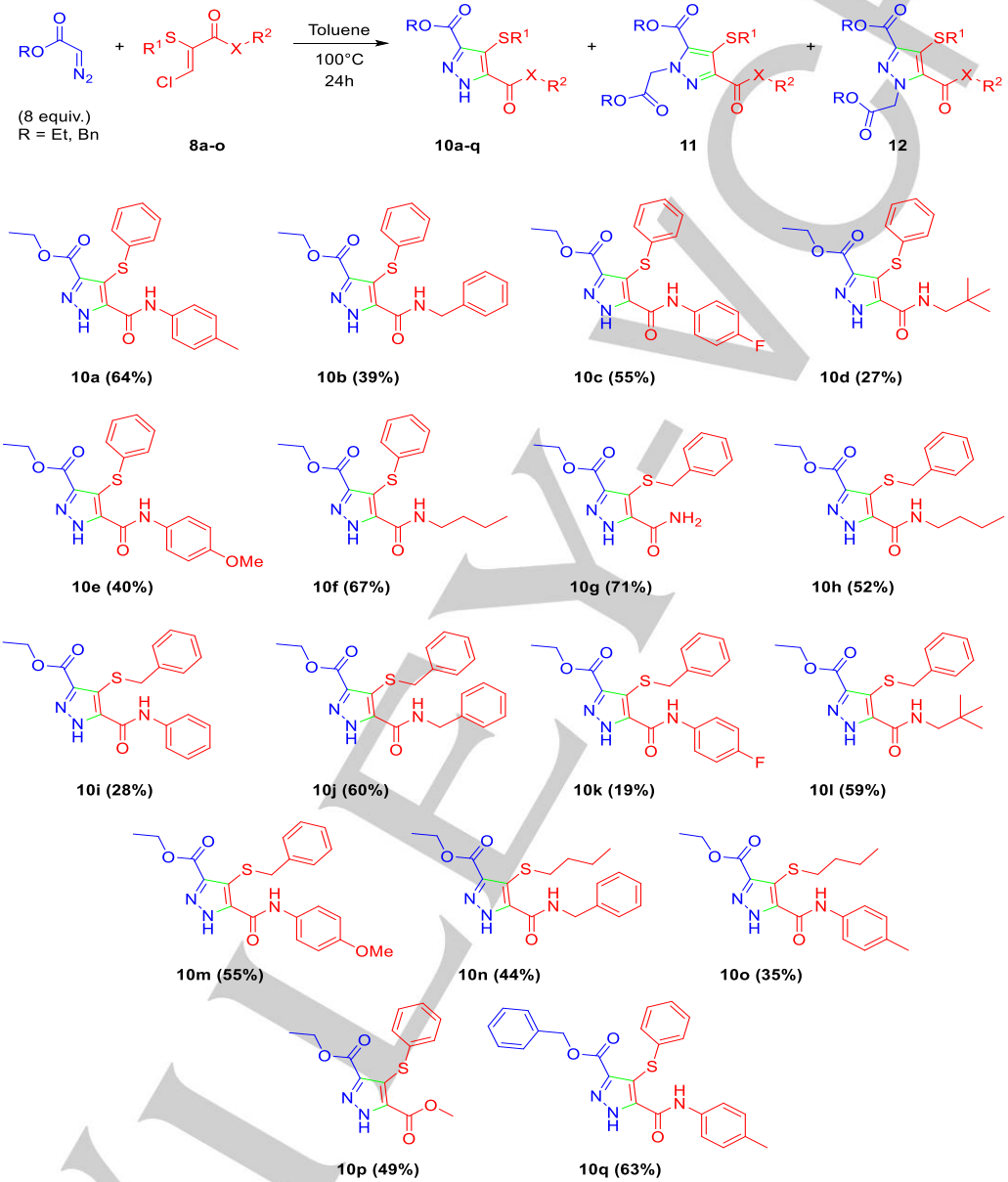
[3+2]-Dipolar Cycloadditions of *α*-thio-*β*-chloroacrylamides with ethyl diazoacetate

The dipolarophilic reactivity of the *α*-thio-*β*-chloroacrylamides towards ethyl diazoacetate (EDA) as the 1,3-dipole was first explored as shown in Table 2. An excess (8 equivalents) of ethyl diazoacetate was added in one portion to a stirring solution of the *α*-thio-*β*-chloroacrylamide in toluene (0.2 M) at room temperature. The reaction solution was heated gradually to 100˚C and the temperature was maintained at this temperature for 24 h. After 24 h the reaction mixture was cooled to room temperature and an aliquot was concentrated under reduced pressure and analysed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra indicated incomplete consumption of α-thio-β-chloroacrylamide in all instances except for pyrazole **10c**, however characteristic methylene NCH_2 signals for the two regioisomeric N–H insertion **11** and **12** was observed in most instances. As a result, despite evidence for residual α-thio-β-chloroacrylamide **8** remaining after 24 hours, further ethyl diazoacetate was not added to avoid increased formation of the N–H insertion byproducts **11** and **12**.

The pyrazoles **10a-q** were isolated in moderate to good yields across the *α*-thio-*β*-chloroacrylamides **8a-o** substrate range, predominantly as solids that proved stable on storage. Interestingly, variation of the steric and electronic properties on either the sulfur or amide substituent did not have a noticeable impact on the outcome of the cycloaddition, highlighting the generality of the method. In some instances (entries 2,4 and 11, Table 2) the formation of the N–H insertion products **11** and **12**, through further reaction of the rearranged pyrazoles with ethyl diazoacetate was significant; extensive optimization of the reaction conditions was not attempted. In addition to variation of the amide and sulfide substituents across **10a-o**, the [3+2]-

dipolar cycloaddition between benzyl diazoacetate and *α*-thio-*β*-chloroacrylamide **8a** afforded the pyrazole **10q** in 63% yield, while the *α*-thio-*β*-chloroacrylate ester **8p** also underwent cycloaddition with ethyl diazoactetate to give the C(3) and C(5) substituted dicarboxylate **10p** in 49% yield.

Table 2. [3+2]-dipolar cycloaddition using *α*-thio-*β*-chloroacrylamides **8a-p.**

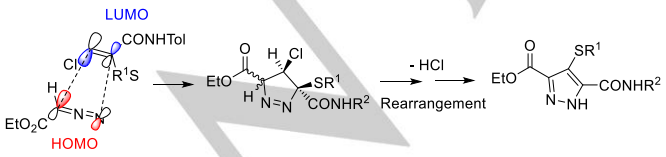


Entry	R	*α*-thio-*β*-chloro-acrylamide **8**	R^1	X	R^2	Conversion[a,b,c,d] **8** : **10**: **11**+**12**	Pyrazole **10**	Yield[e,f,g,h] **10** (%)	Pyrazole Recovery[i] **10** (%)
1	Et	**8a**	Ph	NH	Tol	[b]	**10a**	64[e]	-
2	Et	**8b**	Ph	NH	Bn	2 : 66 : 32	**10b**	39[e]	60
3	Et	**8c**	Ph	NH	4-FC_6H_4	0 : 82 : 18	**10c**	55[e]	67
4	Et	**8d**	Ph	NH	$(CH_3)_3CCH_2$	6 : 44 : 50	**10d**	27[f]	62

5	Et	**8e**	Ph	NH	4-MeOC$_6$H$_4$	12 : 66 : 22	**10e**	40[e]	60
6	Et	**8f**	Ph	NH	*n*-Bu	7 : 78 : 15	**10f**	67[f]	85
7	Et	**8g**	Bn	NH$_2$	-	8 : 86 : 5	**10g**	71[g,h]	83
8	Et	**8h**	Bn	NH	*n*-Bu	17 : 70 : 13	**10h**	52[f]	74
9	Et	**8i**	Bn	NH	Ph	5 : 74 : 21	**10i**	28[f]	38
10	Et	**8j**	Bn	NH	Bn	12 : 79 : 9	**10j**	60[e]	76
11	Et	**8k**	Bn	NH	4-FC$_6$H$_4$	3 : 38 : 58	**10k**	19[f]	49
12	Et	**8l**	Bn	NH	(CH$_3$)$_3$CCH$_2$	24 : 68 : 8	**10l**	59[f]	87
13	Et	**8m**	Bn	NH	4-MeOC$_6$H$_4$	39 : 61 : 0	**10m**	55[e]	90
14	Et	**8n**	*n*-Bu	NH	Bn	9 : 77 : 14	**10n**	44[f]	57
15	Et	**8o**	*n*-Bu	NH	Tol	2 : 84 : 14	**10o**	35[e]	42
16	Et	**8p**	Ph	O	Me	15 : 77 : 8	**10p**	49[f]	64
17	Bn	**8a**	Ph	NH	Tol	[d]	**10q**	63[e,h]	-

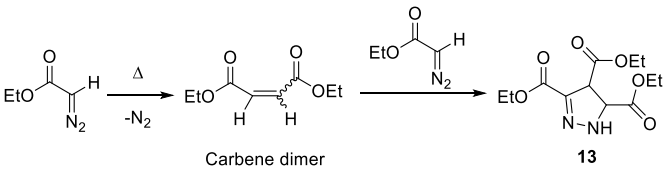
[a] Estimated % conversion of *α*-thio-*β*-chloroacrylamide **8** to pyrazole **10** and combined N–H insertion products **11**+**12** were calculated from the ^{1}H NMR spectra of the crude product in $CDCl_3$ taken after 24 h. Estimated by integration of the β-H signal of **8,** the pyrazole **10** NH signal, and the 2H, methylene NCH_2CO signals of the NH insertion products **11** and **12**. [b] ^{1}H NMR analysis of the crude reaction mixture for the generation of pyrazole **10a** was not recorded. [c] NH insertion products **11** and **12** not isolated except for **11a** and **11b**; assignment of the NH insertion products **11** and **12** in the crude ^{1}H NMR was made tentatively by analogy using the methylene NCH_2CO signals. [d] Estimated % conversion for [3+2]-dipolar cycloaddition of *α*-thio-*β*-chloroacrylamide **8a** with benzyl diazoacetate not recorded as NH insertion products **11p and 12p** (not isolated) could not readily be identified from the ^{1}H NMR of the crude reaction mixture. [e] Isolated % yield after column chromatography on silica gel using hexane: ethyl acetate as eluent followed by trituration using diethyl ether. [f] Isolated % yield after column chromatography (twice) on silica gel, first using hexane: ethyl acetate as eluent then dichloromethane: ethyl acetate. [g] Isolated % yield by filtration of the reaction mixture. [h] As the NMR spectra of pyrazoles **10g** and **10q** were recorded in DMSO-d_6 both the 3-, and 5-carboxylate tautomers were observed (see Supplementary Information for more details). [i] Calculated % recovery of pyrazole **10** based on ratio of pyrazole **10** in the ^{1}H NMR spectrum of the crude product mixture.

In line with the [3+2]-dipolar cycloadditions of α-diazoalkanes with *α*-thio-*β*-chloroacrylamides,[19] the reactions of **8a-o** and *α*-thio-*β*-chloroacrylate **8p** were found to proceed with complete regiocontrol, the carbon atom of ethyl diazoacetate adding to the electrophilic β-carbon of the *α*-thio-*β*-chloroacrylamide, followed by rearrangement to form pyrazoles **10a-q**. From literature precedent, [3+2]-dipolar cycloadditions of *α*-diazoacetates to alkenes bearing electron withdrawing groups in direct conjugation with the dipolarophilic component are generally dipole-HOMO controlled, hence the predominant interaction involves the two atoms with the largest orbital coefficients in the dipole and dipolarophile respectively, which accounts for the regiocontrol observed (Scheme 3).[11a, 22]



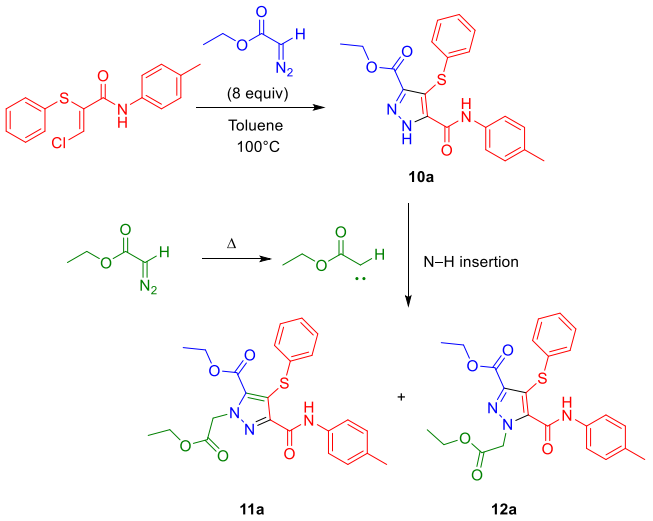
Scheme 3. Regiochemistry of the [3+2]-dipolar cycloaddition of ethyl diazoacetate with *α*-thio-*β*-chloroacrylamide.

The lower yields of pyrazoles **10d**, **10i**, **10k, 10l** and **10n** are attributable in part to their co-elution during column chromatography with the pyrazoline byproduct **13** derived from the thermal decomposition of ethyl diazoacetate (Scheme 4).[23]



Scheme 4. Thermal decomposition of ethyl diazoacetate and subsequent formation of pyrazoline **13**.

The N–H insertion byproducts **11a** and **12a** were isolated to facilitate structural assignment, however, the other derivatives **11b-q** and **12b-q** were not isolated and characterised (Scheme 5). In all instances the pyrazole **11** is observed in the ^{1}H NMR spectrum of the crude product in greater amounts than **12** indicating that N–H insertion preferentially occurs to give the 5-carboxylate **11**.



Scheme 5. Formation of the 5-carboxylate **11a** and 3-carboxylate **12a** by N–H insertion.

^{1}H-^{13}C Heteronuclear multiple bond correlation spectroscopy (HMBC) was used to determine the regiochemistry of the two N–H insertion products **11a** and **12a**. The NMR experiment revealed that the methylene protons at 5.58 ppm and the amide NH at 10.01 ppm in pyrazole **12a** both correlated to the same C(5) ring carbon at 138.8 ppm. In pyrazole **11a** the methylene protons at 5.38 ppm correlated to the C(5) ring carbon at 137.2 ppm, however there was no correlation between the amide NH at 9.07 ppm and C(5). Therefore, the pyrazole **12a** was assigned as the 3-carboxylate and pyrazole **11a** as the 5-carboxylate (Figure 2). As illustrated in Figure 2, the ^{13}C NMR chemical shifts of the C(3), C(4) and C(5) carbons of the pyrazole ring are predominantly influenced by the regiochemistry of the pyrazole, with limited impact of alteration of the substituent. Finally, X-ray crystallography of pyrazole **11a** following recrystallisation from dichloromethane unambiguously confirmed the assignment of pyrazole **11a** as the 5-carboxylate (Figure 3).

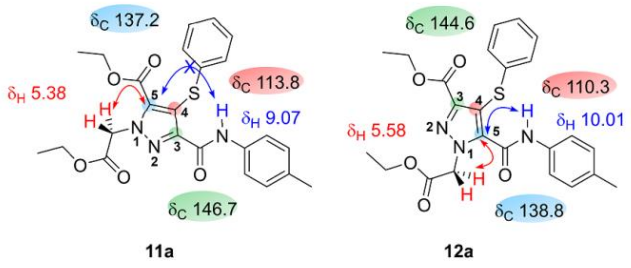


Figure 2. ^{1}H-^{13}C HMBC 3 bond correlations indicating the assignments of NH-insertion products **11a** and **12a** including relevant ^{1}H and ^{13}C NMR chemical shifts (in ppm).

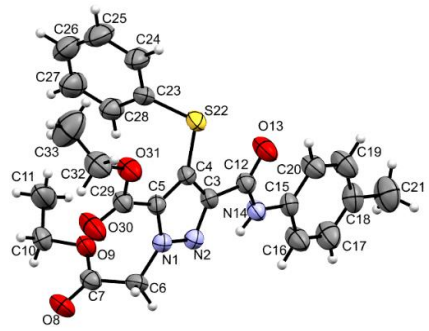
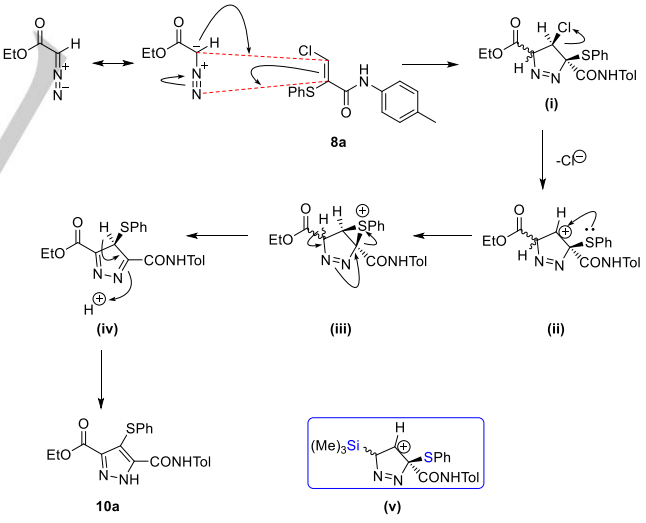


Figure 3. X-ray structure of pyrazole **11a** (anisotropic displacement parameters drawn at the 50% probability level).

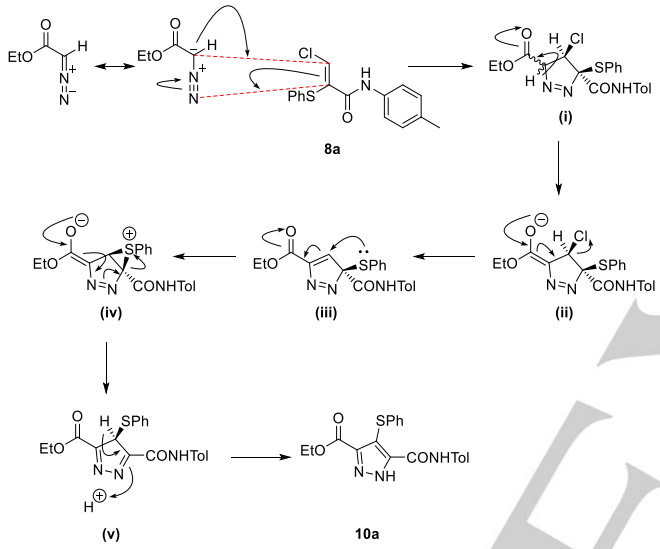
Two potential mechanisms can be envisaged for the formation of the rearranged pyrazoles **10a-q**. Firstly, thermally induced regiospecific [3+2]-dipolar cycloaddition of ethyl diazoacetate with the *α*-thio-*β*-chloroacrylamides leads to the initial pyrazoline cycloadduct **(i)**. In the first instance an E_1 elimination can be considered, with loss of chloride to form a sulfur stabilised carbocation [Scheme 6, Mechanism A, **(ii)**]. Subsequent generation of an episulfonium ion intermediate **(iii)**, followed by deprotonation of the acidic *α*-carbon leads to ring opening of the episulfonium ion and completes the sulfur migration to form **(iv)**. Finally, tautomerisation leads to aromatisation and the rearranged pyrazoles.



Scheme 6. (Mechanism A). E_1 elimination.

Alternatively, the following $E_{1C}B$-like mechanism is postulated to be more likely (Scheme 7, Mechanism B). Deprotonation of the acidic *α*-carbon, adjacent to the ester moiety, in the initial pyrazoline cycloadduct **(i)** generates an enolate **(ii)** that is stabilised through extended conjugation. Subsequent elimination of chloride generates the anti-aromatic pyrazole **(iii)**. The sulfur

migration can be envisaged to occur through an intramolecular conjugate addition to generate the episulfonium ion intermediate **(iv)**, that subsequently ring opens to complete the sulfur migration to form **(v)**. Tautomerisation affords the aromatic pyrazole **10a**. It is believed that the driving force for the sulfur migration in both mechanistic pathways is the restoration of the pyrazole aromaticity. In our earlier work with trimethylsilyldiazomethane, formation of the carbocation **(v)** analogous to **(ii)** (Scheme 6) was readily envisaged due to the β-silicon effect, however in the ester derivative the formation of the carbocation **(ii)** is less likely and as a result, the mechanistic details may be altered by the different substituents on the 1,3-dipole.[19] Studies into the nature of the mechanistic pathway are currently underway.



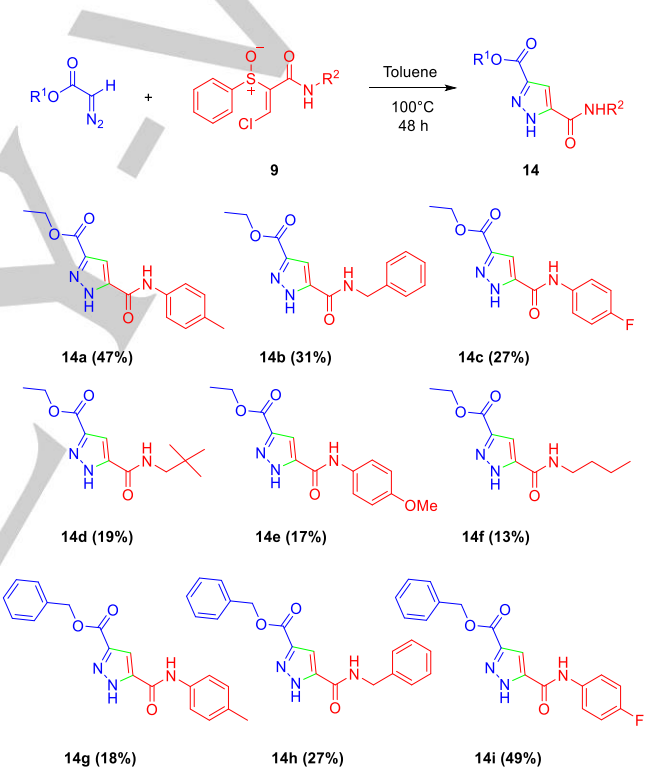
Scheme 7. (Mechanism B). $E_{1C}B$-like elimination.

[3+2]-Dipolar Cycloadditions of *α*-sulfinyl-*β*-chloroacrylamides

Initial attempts to achieve [3+2]-dipolar cycloaddition of ethyl diazoacetate (8 equivalents) and α-sulfinyl-β-chloroacrylamide **9a** at room temperature or at reflux in dichloromethane did not result in cycloaddition. Reverting to toluene at 100˚C resulted in full consumption of the sulfoxide dipolarophile after 48 h. The ^{1}H NMR spectra of the crude product mixtures were complex, hindering accurate determination of product ratios. Under these conditions a series of α-benzenesulfinyl-β-chloroacrylamides were reacted with ethyl diazoacetate and benzyl diazoacetate to afford the novel pyrazoles **14a-i** in yields of 13-47% (Table 3). However, in most instances the 3,5-substituted pyrazoles generated proved to be insoluble in toluene allowing isolation by filtration from the reaction mixture on cooling (Table 3). Analysis of the mother liquors demonstrated some loss of product through the filtration process. In cases in which no precipitate formed the pyrazoles were purified by column chromatography **(14d**, **14f)**. The low yields of the desulfinylated pyrazoles may be attributable to the generation of benzenesulfinyl chloride which could result in side reactions, or to the enhanced reactivity of the α-sulfinyl-β-chloroacrylamides relative to the α-thio-β-chloroacrylamides.

In all instances complete regiocontrol was observed, with the α-carbon of the α-diazoacetate adding to the β-carbon of the dipolarophile, with concomitant desulfinylation and aromatisation to the 3,5-disubstituted pyrazoles observed. The regiochemistry of the pyrazoles **14a-i** was assigned by comparison of the characteristic C(4) ring carbon of the ^{13}C NMR spectra to literature values for related compounds.[19] For these reactions, the outcome was comparable to our group's earlier work using trimethylsilyldiazomethane, both in terms of yield and desulfinylation, albeit the α-diazoacetates requiring more forcing conditions.

Table 3. [3+2]-Dipolar cycloadditions using α-sulfinyl-β-chloroacrylamides **9a-f**

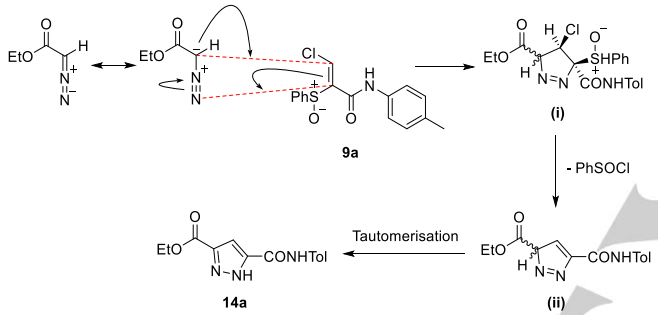


Entry	R^1	α-Sulfinyl-β-chloro-acrylamide **9**	R^2	Pyrazole **14**	Yield[a,b,c,d] (%) **14**
1	Et	**9a**	Tol	**14a**	47
2	Et	**9b**	Bn	**14b**	31
3	Et	**9c**	4-FC_6H_4	**14c**	27
4	Et	**9d**	$(CH_3)_3CCH_2$	**14d**	19[b]
5	Et	**9e**	4-$MeOC_6H_4$	**14e**	17

6	Et	**9f**	*n*-Bu	**14f**	13[b,d]
7	Bn	**9a**	Tol	**14g**	18
8	Bn	**9b**	Bn	**14h**	27
9	Bn	**9c**	4-FC_6H_4	**14i**	49

[a] Isolated % yield collected by filtration of the reaction mixture unless otherwise stated. [b] Isolated % yield after column chromatography. [c] As the NMR spectra were recorded in DMSO-d_6 (unless otherwise stated) the 3-, and 5-carboxylate tautomers were observed (see Supplementary Information for more details).

[3+2]-Dipolar cycloaddition to form the initial pyrazoline cycloadduct **(i)** is envisaged, followed by spontaneous *syn*-elimination of benzenesulfinyl chloride from the pyrazoline intermediate, leading to the desulfinylated cycloadduct **(ii)**. Subsequent tautomerisation affords the aromatic pyrazole **14** (Scheme 8).

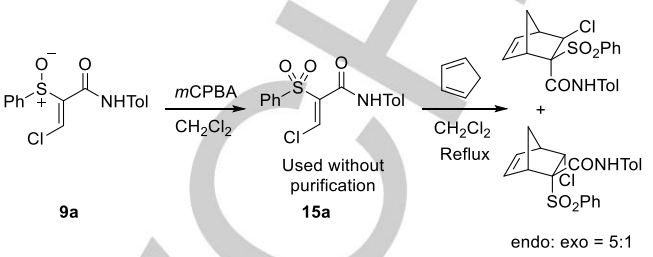


Scheme 8. Mechanistic route toward desulfinylated 3,5-substituted pyrazoles through 1,2-elimination of benzenesulfinyl chloride.

[3+2]-Dipolar Cycloadditions of α-sulfonyl-β-chloroacrylamides

Vinyl sulfones are among the most reactive and versatile dipolarophiles,[24] owing to the strongly electron withdrawing character of the sulfone moiety. Namboothiri *et al*. have reported extensively on the base-mediated [3+2]-dipolar cycloaddition of phosphorylated and sulfonylated dipoles with various dipolarophiles, including vinyl sulfones, to generate functionalised C(3)-substituted sulfonylpyrazoles.[25] However, in light of our methodology forming the C(4)-substituted sulfenylpyrazoles (Table 2) we were keen to explore whether α-sulfonyl-β-chloroacrylamides would undergo cycloaddition with α-diazoacetates, and if so, would sulfur migration be observed at this level of oxidation.

Previous work in our group demonstrated that the α-sulfonyl-β-chloroacrylamides are extremely labile compounds, for example as potent Michael acceptors, that can be generated and used directly without isolation, for example in the successful Diels–Alder cycloaddition between cyclopentadiene and sulfone **15a** (Scheme 9).[18] Notably, an extensive oxidant screen including H_2O_2, peracetic acid, $KMnO_4$, Oxone®, and MMPP determined that *m*CPBA was the only oxidant that could actuate oxidation.



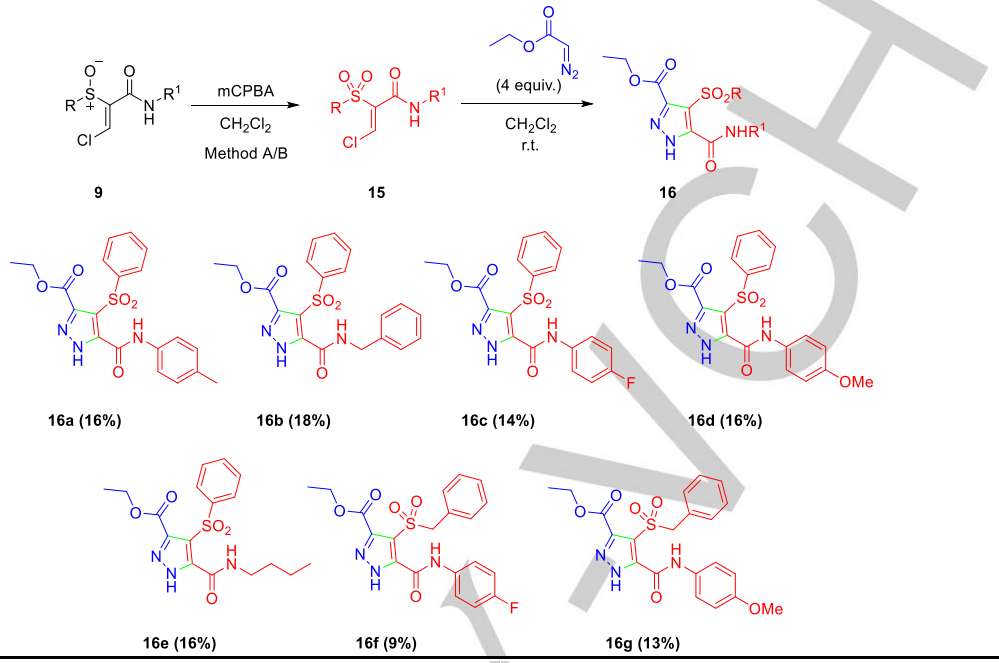
Scheme 9. Diels–Alder cycloaddition with crude α-sulfonyl-β-chloroacrylamides **15a** and cyclopentadiene.

With this is mind, the sulfoxide **9a** was treated with *m*-CPBA (2 equiv.) in dichloromethane at room temperature for 43 h. Reaction monitoring by ^{1}H NMR spectroscopy over several time increments indicated that the oxidation did not go to completion, and that over time the impurity profile deteriorated. For this reason, addition of ethyl diazoacetate was made once the level of impurities was observed to significantly increase relative to the increase of sulfone **15a**. After the addition the reaction mixture was stirred overnight at room temperature. The loading of ethyl diazoacetate was decreased to 4 equivalents relative to the 8 equivalents used at the sulfide and sulfoxide levels of cycloaddition due to the anticipated increased reactivity of the dipolarophile. The ^{1}H NMR spectrum of the crude reaction mixture was very complex, however no evidence for residual sulfone **15a** was apparent. Repeated column chromatography afforded the pure rearranged 4-sulfonylpyrazole **16a** in 16% yield over two steps.

As the oxidation to form the sulfone is a limiting factor in the overall transformation, optimisation was undertaken including variation of time and/or increasing the reaction temperature to reflux in dichloromethane. While it is clear that the sulfone is sensitive to prolonged heating at reflux in dichloromethane, with close monitoring of the reaction mixture by ^{1}H NMR spectroscopy, optimal conversions can be achieved within 10-14 hours, leading to comparable results to when the oxidation was conducted for 48 hours at room temperature.

Due to the unusual nature of the observed sulfone migration, extension of this methodology to a range of α-sulfonyl-β-chloroacrylamides with varying electronic and steric properties at both the sulfone and amide was undertaken leading to a series of 4-sulfonylpyrazoles **16a-g**, albeit in low yields of 14-18%, confirming that the sulfone migration was consistent across a series of compounds (Table 4).

Table 4. [3+2]-Dipolar cycloadditions with α-sulfonyl-β-chloroacrylamides **15**.



Entry	R	R^1	α-sulfinyl-β-chloroacrylamide **9**	Method[a]	% α-sulfonyl-β-chloroacrylamide[b] **15**	Pyrazole **16**	Yield[c] **16** (%)
1	Ph	Tol	**9a**	A	78	**16a**	16
2	Ph	Bn	**9b**	A	71	**16b**	18
3	Ph	4-FC_6H_4	**9c**	B	63	**16c**	14
4	Ph	4-$MeOC_6H_4$	**9e**	B	30	**16d**	16
5	Ph	*n*-Bu	**9f**	B	[d]	**16e**	16
6	Bn	4-FC_6H_4	**9g**	B	[d]	**16f**	9
7	Bn	4-$MeOC_6H_4$	**9h**	B	[d]	**16g**	13

[a] Method A: 2 equiv. *m*CPBA in dichloromethane (15 ml) was added dropwise to a stirring solution of α-sulfinyl-β-chloroacrylamide **9** in dichloromethane (5ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for up to 48 h. Method B: 2 equiv. *m*CPBA in dichloromethane (15 ml) was added dropwise to a stirring solution of α-sulfinyl-β-chloroacrylamide **9** in dichloromethane (5ml) at room temperature under nitrogen. The reaction mixture was heated to gentle efflux and stirred at this temperature for 10-14 h. Both methods were monitored by ^{1}H NMR spectroscopy at regular time intervals. [b] Estimated % of α-sulfonyl-β-chloroacrylamide **15** present in the reaction mixture prior to the addition of ethyl diazoacetate. Determined from the ^{1}H NMR spectra of the crude reaction mixture. [c] Isolated % yield calculated over two steps after purification by repeated column chromatography. [d] % conversion could not be accurately determined due to complexity of the ^{1}H NMR spectrum of the crude reaction mixture.

The regiochemistry of the [3+2]-dipolar cycloaddition and subsequent rearrangement of pyrazole **16a** was determined by single X-ray crystallography following recrystallisation from dichloromethane (Figure 4). Furthermore, the X-ray crystal structure confirms that migration of the sulfone moiety has occurred, with the sulfone at the C(4) position analogous to that of the sulfide migration. The regiochemistry of the 4-sulfenylpyrazole **10a** was further confirmed by independently oxidising **10a** to the 4-sulfonylpyrazole **16a** using *m*CPBA in refluxing dichloromethane (see Table S2, supplementary information).

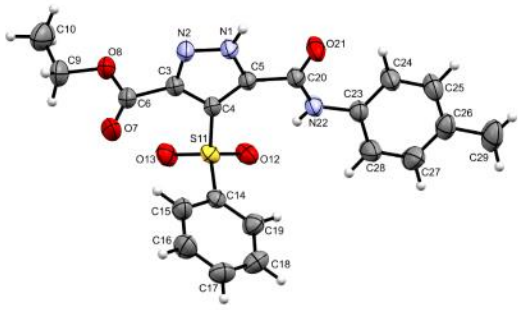
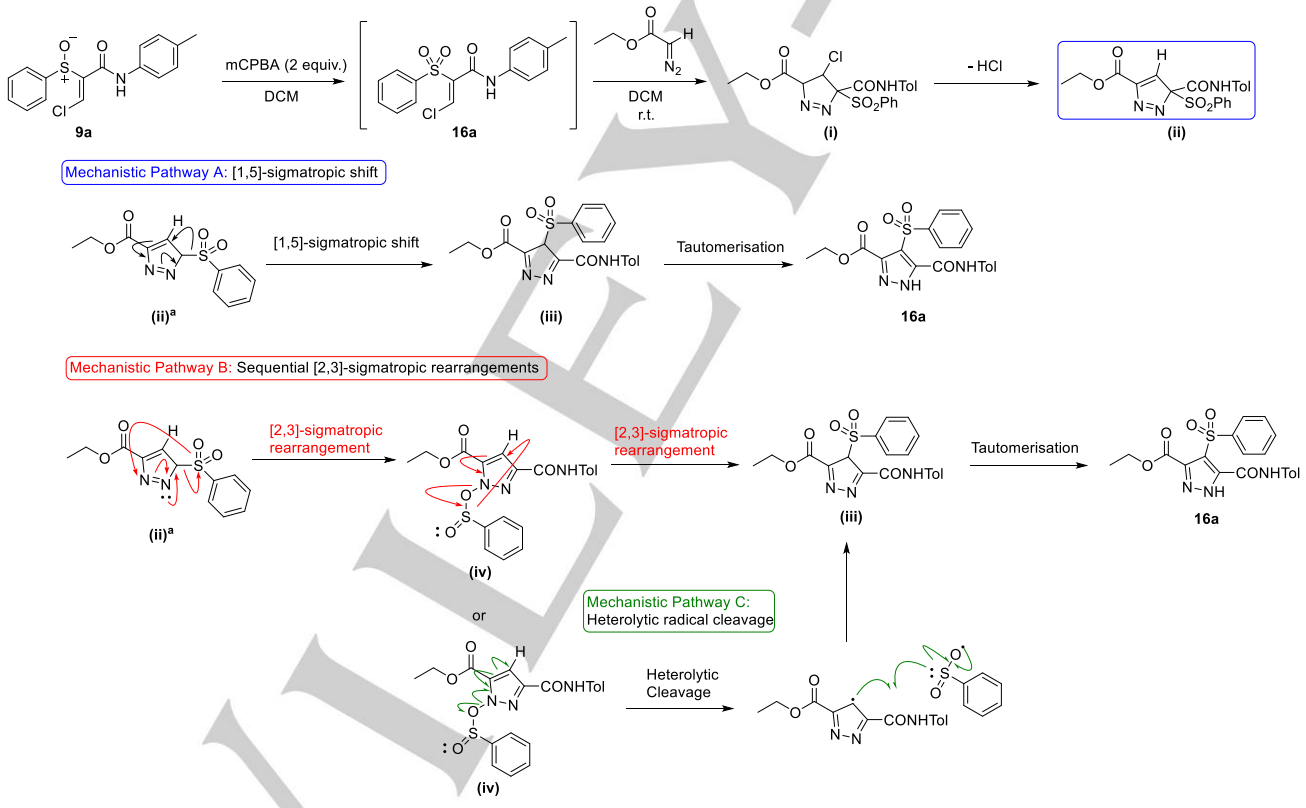


Figure 4. X-ray structure of pyrazole **16a** (anisotropic displacement parameters drawn at the 50% probability level).

Comparison of the ^{1}H, ^{13}C and IR spectroscopic data confirmed that the regiochemistry of the 4-sulfenylpyrazole **10a** and 4-sulfonylpyrazole **16a** cycloadducts were identical.

To the best of our knowledge, at the time of writing, carbon to carbon 1,2-sulfonyl migration is unprecedented, thus the rearrangement leading to **16** involving a 1,2-sulfonyl shift is highly unusual. The mechanism for the formation of the rearranged 4-sulfonylpyrazoles **16a-g** is not well understood, but several mechanistic routes can be considered based on the confirmed regiochemistry of the products. In all instances, regioselective [3+2]-dipolar cycloaddition of the crude α-sulfonyl-β-chloroacrylamide leads to the initial pyrazoline cycloadduct **(i)**, which readily undergoes elimination of HCl to give the intermediate cycloadduct **(ii)** (Scheme 10). While the sulfur migration at the sulfide level can be readily understood due to the nucleophilic character of the sulfide, extending this to rationalise the unprecedented 1,2-sulfonyl shift is not feasible

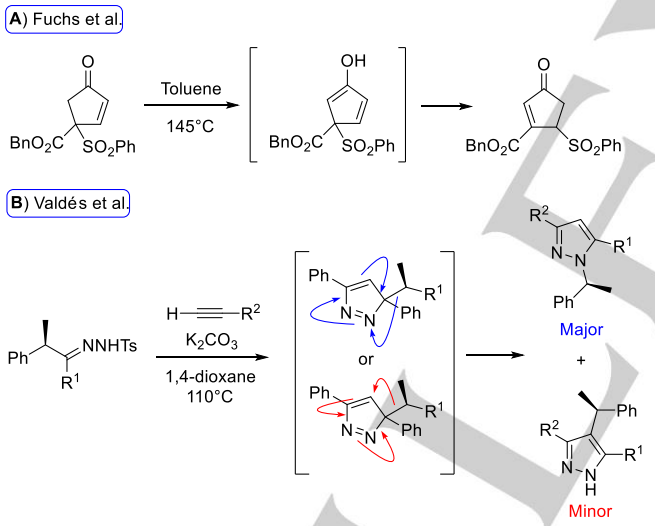


Scheme 10. Proposed mechanistic routes for sulfone migration [**(a)** CONHTol substituent not shown in intermediate **(ii)**].

In light of the following two reports a [1,5]-sigmatropic shift can be considered to rationalise the sulfonyl migration. Fuchs *et al*. reported the thermally induced rearrangement of a γ-sulfonyl enone to the rearranged sulfone in almost quantitative yields (Scheme 11, A).[26] The authors rationalised the transformation through the formation of the enol intermediate which undergoes a [1,5]-sigmatropic rearrangement. Notably, however this reaction was carried out in toluene at 145˚C in a sealed tube. Recently, Valdés *et al*. reported the synthesis of chiral pyrazoles through the [3+2]-dipolar cycloaddition of α-chiral tosylhydrazones with alkynes (Scheme 11, B).[27] Interestingly, they observed that the initial cycloadduct underwent [1,5]-

sigmatropic rearrangement with migration of the alkyl group. Significantly in their study, they observed that the [1,5]-sigmatropic rearrangement, which has two regioisomeric outcomes, preferentially, but not exclusively, migrates to nitrogen rather than the C(4) carbon. Forcing reaction conditions (110˚C in 1,4-dioxane) were also required in this instance. Considering these reports, we note that the pyrazoles **16** could be generated through a [1,5]-sigmatropic shift of the sulfonyl moiety (Scheme 10, Mechanistic Pathway A). However, the [3+2]-dipolar cycloadditions in this work were carried out at room temperature, while [1,5]-sigmatropic shifts generally require much higher temperatures as can be seen above. While the *N*(1)-substituted sulfone was not isolated or observed, since the recoveries were very low it is impossible to exclude its formation.

An alternative mechanistic pathway can be envisaged with two sequential [2,3]-sigmatropic rearrangements of the sulfonyl moiety as illustrated in Scheme 10 (Mechanistic Pathway B) followed by re-aromatisation via tautomerisation at the end of the sequence to afford the C(3) carboxylate pyrazole **17a**. The second [2,3]-sigmatropic rearrangement is somewhat akin to an allylic sulfinate-sulfone rearrangement.[28] Alternatively, from the intermediate **(iv)**, homolytic cleavage of the weak N-O bond could be envisaged generating a radical pair which on recombination forms the more stable C–S bond (Scheme 10, Mechanistic Pathway C).



Scheme 11. Literature examples of **1)** [1,5]-sigmatropic shift of sulfone moiety; **2)** [1,5]-sigmatropic shift of alkyl group in pyrazole system.

Spectroscopic Determination of the Tautomeric Composition of 3,4,5-substituted pyrazoles

Definitive spectroscopic analysis of unsubstituted NH pyrazole scaffolds is complicated by the dynamic tautomeric nature of these compounds. For this reason, significant attention has been paid in the literature to the spectroscopic analysis of these compounds particularly using ^{1}H-^{13}C HMBC and NOE experiments, often in conjunction with each other.[29]

Unambiguous assignment of the ^{13}C NMR signals for the C(3), C(4) and C(5) carbons is particularly challenging, especially in the absence of an adjoining proton (Figure 5). In order to conclusively characterise our novel pyrazoles an in-depth ^{13}C NMR study was performed.

Figure 5. Tautomeric forms of pyrazole **10a** in solution.

The elucidation of the C(3), C(4) and C(5) pyrazole ring carbon chemical shifts by ^{13}C NMR at 75.5 MHz for pyrazoles **10** in $CDCl_3$ proved to be challenging, with the C(3) and C(5) carbons not observed at this field strength, believed to be due to dynamic tautomerism in conjunction with the absence of either direct or indirect coupling to hydrogen. In most instances, however, a weak signal was observed for the C(4) carbon as the chemical shift of this carbon remains largely unaffected by tautomerism. In contrast, at 150.9 MHz broad signals were observed for C(3), C(4) and C(5). Interestingly when the spectra of the pyrazoles **10a-f** and **10h-p** were recorded at 150.9 MHz in the noninteracting solvent $CDCl_3$ only a single set of carbon signals are seen indicating one of the following possibilities:

- **A)** one exclusive tautomer in solution, *or*
- **B)** tautomers rapidly interconverting on the NMR timescale, *or*
- **C)** two tautomers in dynamic equilibrium with the equilibrium highly favouring one tautomer with the concentration of the minor tautomer so negligble that it is not detectable by ^{13}C NMR.

Due to the broadening of the signals for the C(3), C(4) and C(5), it is unlikely that one tautomer exists exclusively in solution, although the signal broadening could be due in part to the quadrupolar moment of ^{14}N rather than tautomerism only. Furthermore, the ^{13}C NMR spectra of the pyrazoles **11a** and **12a** could readily be obtained at 75.5 MHz with each of the C(3), C(4) and C(5) ring carbons observed as sharp signals, consistent with the pyrazoles **11a** and **12a** being unable to undergo prototropic tautomerism due to the alkylation of the respective N(1) positions (Figure 2). This strongly suggests that the signal broadening observed in pyrazole **10a** is not due to the ^{14}N quadrupolar moment. Direct comparison of the sp^2 region of the ^{13}C NMR spectra of the pyrazole **10a** and the two N–H insertion products **11a** and **12a** demonstrated that the chemical shifts in pyrazole **10a** and **12a** were remarkably similar, and substantially different to those of pyrazole **11a** (Figure 6). This observation allowed assignment of the major tautomer of **10a** in $CDCl_3$ to be identified as the 3-carboxylate, however, it is not the exclusive tautomer as both *N*-alkylated pyrazoles **11a** and **12a** are formed through the N–H insertion reaction. This allows us to conclude that for pyrazoles of the type **10** in the non-interacting solvent $CDCl_3$ that the tautomers exist in dynamic equilibrium

albeit with the 5-carboxylate form present in undetectable concentrations. An alternative possible explanation for the signal broadening could be due to the presence of amide rotamers; comparison of the ^{13}C NMR spectra of pyrazole **10a** with the two NH insertion products **11a** and **12a**, however, highlights that the signal broadening is due to tautomers, with no dynamic effects observed in the ^{13}C NMR spectra of **11a** and **12a**.

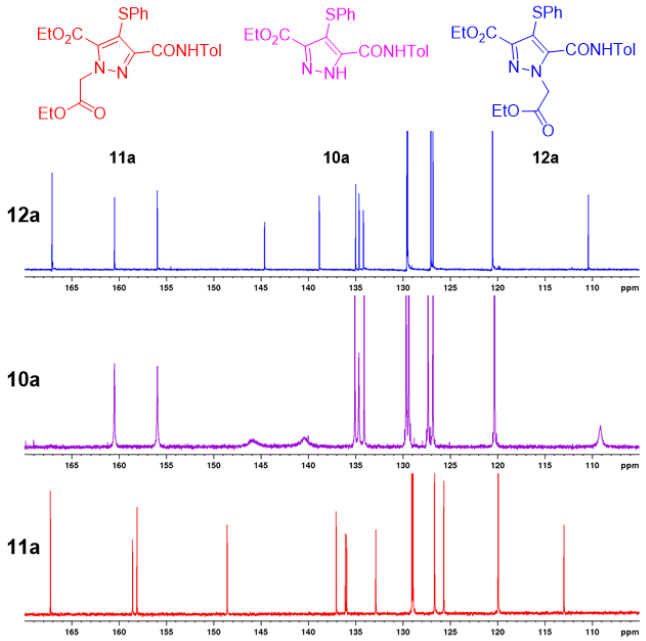
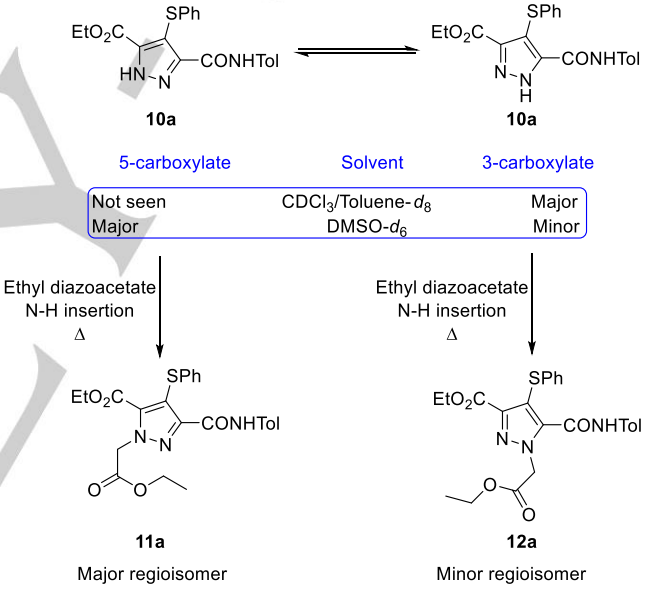


Figure 6. ^{13}C NMR (150.9 MHz) spectra of pyrazole 10a and N–H insertion products 11a and 12a illustrating that the major and minor tautomer of pyrazole 10a in $CDCl_3$ is the 3-carboxylate.

While it appears that the dynamic equilibrium in $CDCl_3$ favours the 3-carboxylate tautomeric form it is interesting that it is, in fact, the minor tautomer that undergoes N–H insertion more readily to give the pyrazole **11a** as the major regioisomer. To test whether this was due to the minor tautomer being more reactive or whether the dynamic equilibrium tended towards the 5-carboxylate in the reaction solution, ^{13}C NMR spectra for the pyrazole **10a** and the NH insertion products **11a** and **12a** were recorded in toluene-d_8, the solvent used for the cycloaddition, at 150.9 MHz (see Figure S16, supplementary information). As was observed in $CDCl_3$, substantial overlap of the signals was observed with those for N–H insertion product **12a**, indicating that the major tautomer present in toluene-d_8, and presumably the reaction medium, is the 3-carboxylate. Therefore, despite the observation that the equilibrium between the 3-carboxylate and 5-carboxylate tautomers in non-interacting solvents strongly favours the 3-carboxylate tautomer, isolation of the 5-carboxylate as the major NH insertion product **11a** suggests that the minor tautomer is significantly more reactive.

As pyrazoles **10g** and **10q** were insoluble in $CDCl_3$ their NMR spectra were recorded in DMSO-d_6 with broad signals for both tautomers observed in each instance. Considering this, the solvent dependency on the position of equilibrium was studied by comparing the ^{13}C NMR spectra for pyrazoles **10a**, **11a** and **12a** in DMSO-d_6 with those in $CDCl_3$. Notably in DMSO-d_6, two distinct sets of broad signals were observed for pyrazole **10a** at 150.9 MHz (see Figure S17, supplementary information), characteristic of both the 3-carboxylate and 5-carboxylate tautomer, with the 5-carboxylate predominating as the major tautomer in solution as evidenced by comparison of carbon signals with that of pyrazole **11a**. For tautomer assignment one of the characteristic features is that the C(4) chemical shift for the 5-carboxylate tautomer is always more deshielded than that for the 3-carboxylate. Accordingly, in the experimental section, the pyrazoles **10g** and **10q** are characterised as a mixture of the 3-, and 5-carboxylate tautomers while pyrazoles **10a-f** and **10h-p** were characterised as the major 3-carboxylate tautomer as their spectra were recorded in $CDCl_3$ (Figure 7). The impact of solvent on the dynamic equilibrium between the 3- and 5-carboxylate tautomers for pyrazole **10a** is summarised in Scheme 12.



Scheme 12. Summary of solvent effects on the dynamic equilibrium between the 3, and 5-carboxylate tautomers for pyrazole **10a**.

Pyrazoles **14a-i** were significantly less soluble than their 3,4,5,-substituted counterparts, and DMSO-d_6 was required to solubilise these compounds for NMR spectroscopy. The NMR spectra of **14f** could be recorded in $CDCl_3$. Pyrazole **14f** exhibited one set of broad signals in the ^{13}C NMR spectrum at 150.9 MHz in $CDCl_3$, while splitting of both the NH pyrazole and NH amide signals, into major and minor components, was observed in the ^{1}H NMR spectrum at 600 MHz. Two sets of broad signals were observed in the ^{13}C NMR spectra for pyrazoles **14a-e** and **14g-i** recorded in DMSO-d_6, indicative of the 3-carboxylate and 5-carboxylate, however, comparison of the ^{13}C NMR spectra of pyrazoles **10** and **14** in DMSO-d_6 strongly suggests that the dynamic equilibrium shifts towards the 3-carboxylate on removal of the sulfur moiety at the C(4)

position (see supplementary information for further details). Therefore, similar solvent effects on the dynamic equilibrium are observed for both the 3,5-substituted and 3,4,5-substituted pyrazoles **10** and **14** respectively, however, with the 5-carboxylate predominating for the 3,4,5-substuted pyrazoles **10** and the 3-carboxylate predominating for the 3,5-substituted pyrazoles **14** in DMSO-d_6. Accordingly, the pyrazoles **14a-i** are characterised as the 3-carboxylate in this work (Figure 7).

In the solid state, the 4-sulfonylpyrazole **16a** exists as the tautomer with the carboxylate at the C(3) position (Figure 4). As is the case for the pyrazoles formed at sulfide oxidation level, one set of ^{13}C NMR signals is observed for the 4-sulfonylpyrazoles **16** in the non-interacting solvent $CDCl_3$, however the C(4) carbon is considerably sharper and more deshielded for this set of compounds than for the sulfide analogues. The C(3) and C(5) carbons remain very broad, suggesting that the pyrazoles **17** are also in dynamic equilibrium, with the 3-carboxylate the favoured tautomer, and the 5-carboxylate tautomer undetectable in the ^{13}C NMR spectra as seen at the sulfide level of cycloaddition. The 4-sulfonylpyrazoles **17** are assigned as the major 3-carboxylate tautomer in this work (Figure 7).

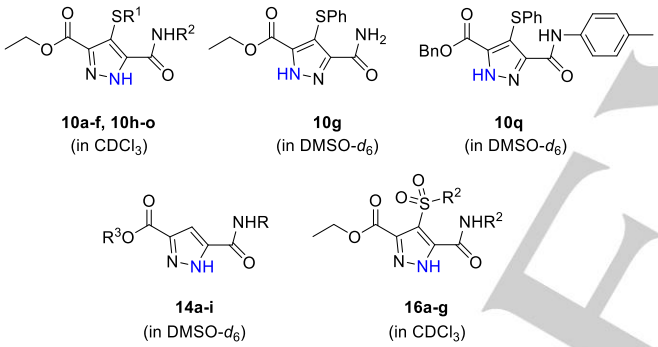
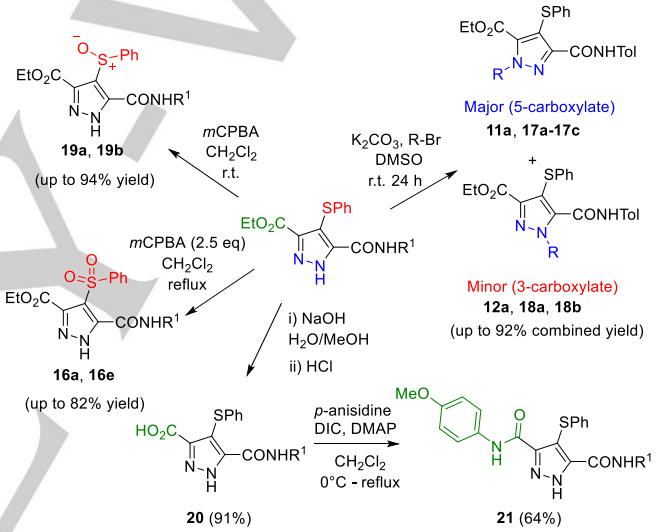


Figure 7. Principal tautomers of 3,4,5 substituted pyrazoles **10a-q** and **16a-g**, and 3,5-substituted pyrazoles **14a-i** illustrating the importance of solvent on the dynamic equilibrium. Structures are named and numbered accordingly in the experimental section/supplementary information.

Further Derivatisation of the Pyrazole Scaffold

The [3+2]-dipolar cycloaddition of α-diazoacetates is a powerful synthetic methodology that has the advantage that it allows incorporation of highly functionalised substituents at each the C(3), C(4) and C(5) positions of the pyrazole core. As there are very few examples of 3,4,5-trisubstituted pyrazoles (particularly bearing a sulfur moiety), with each substituent bearing functionalisable groups investigation of the synthetic potential of these compounds was briefly undertaken utilising pyrazole **10a** as a standard substrate.

Notably, selective oxidation of sulfides **10** to either sulfoxides **19** or sulfones **16** can readily be achieved in high yields using *m*CPBA. Therefore, despite the limitations associated with the [3+2]-dipolar cycloadditions at both the sulfoxide and sulfone levels, C(4) substituted sulfoxide and sulfone pyrazole derivatives can be accessed readily in synthetically useful quantities in the same overall number of synthetic steps. Regioselective *N*-alkylation using alkyl bromides and K_2CO_3 in DMSO[30] afforded the alkylated products in high combined yields, with the 5-carboxylate formed preferentially in all instances, consistent with selective alkylation of the major tautomer present in DMSO (Scheme 12). Hydrolysis of the ester moiety to the carboxylic acid **20** and subsequent amide coupling gave pyrazole **21** illustrating that the use of α-diazoacetates as dipoles and α-sulfenyl-β-chloroacrylamides as dipolarophiles allows access not only to the generation of highly functionalised pyrazoles but importantly functionalised pyrazoles amenable to significant further synthetic transformations. An overview of these synthetic transformations is outlined in Scheme 13, with the tabulated results included in the supplementary information (Table S1-S2 and Scheme S1).



Scheme 13. Overview of the synthetic potential of the densely functionalised 3,4,5-substituted pyrazoles **10**; facile selective sulfur oxidation, regioselective *N*-alkylation, ester hydrolysis and sequential amide coupling.

Conclusions

In summary, we have presented herein highly regioselective synthetic methodology leading to densely functionalised C(3), C(4) and C(5) substituted pyrazoles **10a-q** and **16a-g** via thermal [3+2]-dipolar cycloaddition, of α-diazoacetates and α-thio-β-chloroacrylamides, at the sulfide, sulfoxide and sulfone levels of oxidation. Significantly, this work allows access to C(4)-sulfenyl or sulfonyl pyrazoles, through migration of the sulfur substituent at the sulfide and sulfone oxidation levels, while elimination of the sulfinyl group is observed, leading to 3,5-disubstituted pyrazoles **14a-i**. Notably, use of highly functionalised dipolarophiles, and in particular a chlorine which can act as a leaving group, enables the key rearrangement following cycloaddition to provide the synthetically versatile pyrazoles, where each of the three substituents has the potential for orthogonal functional group interconversion. While the sulfide

migration to the electron deficient carbon is readily rationalised, the analogous carbon-carbon 1,2-sulfonyl migration is unprecedented and mechanistically intriguing. Notably, we have found that the [3+2]-dipolar cycloaddition is remarkably insensitive to the nature of the substituent present on both the amide and sulfide, with extension to esters also possible. While moderate to good yields are obtained using the dipolarophiles at the sulfide level of oxidation, efficiencies are decreased when conducted using the sulfoxide or sulfone, reflecting the labile nature of the reactants and products under the reaction conditions.

In contrast to alternative synthetic methods leading to pyrazoles, such as hydrazine condensation, this methodology offers distinct synthetic advantage enabling access to highly substituted and structurally diverse pyrazoles with functionality amenable to further selective synthetic transformations.

Isolation of the *N*-alkylated pyrazoles **11a** and **12a** as by-products from the cycloaddition through further reaction of the pyrazoles **10** with excess α-diazoacetate, proved useful in rationalising the tautomeric behaviour evident in the NMR spectra of the pyrazoles, with the position of tautomeric equilibrium influenced by solvent and substituents.

Experimental Section

General Procedures: Solvents were distilled prior to use as follows: Dichloromethane was distilled from phosphorus pentoxide, ethyl acetate was distilled from potassium carbonate; and hexane was distilled prior to use. For [3+2]-dipolar cycloadditions HPLC grade toluene was used. All commercial reagents were used without further purification unless otherwise stated.

^{1}H NMR spectra were run at either 300, 400 or 600 MHz and ^{13}C NMR spectra were recorded at either 75.5, 100 or 150.9 MHz. All spectra were recorded at room temperature (300K) in deuterated chloroform ($CDCl_3$), unless otherwise stated using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS, and coupling constants are expressed in hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet). ^{13}C NMR spectra were calibrated using the solvent signal, i.e., $CDCl_3$ δ_C 77.0 ppm, DMSO-d_6 39.5 ppm, toluene-d_8 20.4 ppm. Assignments were made with the aid of DEPT experiments and 2D NMR experiments including COSY, HSQC and HMBC.

Infrared spectra were measured using a FTIR UATR2 spectrometer or were recorded as films on sodium chloride plates on a PerkinElmer Paragon 1000 FT-IR spectrometer. Flash column chromatography was carried out using Kieselgel silica gel 60, 0.035−0.075 mm (Merck).
Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualization was achieved by UV (254 nm) light absorption.

The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using a PerkinElmer 240 and Exeter Analytical CE440 elemental analyser. Low-resolution mass spectra (LRMS) was recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC−MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent. High-resolution (precise) mass spectra (HRMS) were also recorded on an Agilent 6530B Accurate Mass Q-TOF LC/MS instrument in electrosprayionisation mode using 50% acetonitrile− water containing 0.1% formic acid as eluent. Samples were prepared for either LRMS or HRMS by employing acetonitrile as solvent.

Melting points were obtained using a Unimelt Thomas−Hoover capillary melting point apparatus and are uncorrected.

Single-crystal X-ray analysis was performed on a Bruker APEX II DUO diffractometer at room temperature using graphite monochromatic Mo Kα (λ = 0.7107 Å) radiation. All calculations and refinement were made using the APEX software,[31] containing the SHELX suite of programs[32] and diagrams prepared with Mercury 3.10.[33] All nonhydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or were located and refined with isotropic thermal parameters.

General procedure for the preparation for the formation of α-chloroamides. 2-Chloro-*N*-(2′,2′-dimethylpropyl)propanamide (6d)

2-Chloropropionyl chloride (7.61 g, 59.94 mmol) in dichloromethane (50 ml) was added dropwise over 20 min to a solution of 2,2-dimethylpropylamine (5.17 g, 59.35 mmol) and triethylamine (6.07 g, 59.94 mmol) in dichloromethane (100 ml) at 0°C, while stirring under nitrogen. On completion of the addition, the reaction solution was removed from the ice bath and stirred at room temperature for 4 h. Water (200 ml) was added and the layers separated. The organic layer was washed with a saturated solution of sodium bicarbonate (2 x 150 ml), water (200 ml), and brine (200 ml), dried, filtered and concentrated under reduced pressure to give the α-chloroamide **6d** as a white solid (15.38 g, 97 %) which required no further purification; mp 79-81˚C; ν_{max}/cm^{-1} (ATR) 3255 (NH), 3093 (CH), 2957 (CH), 1652 (CO), 1574, 1374 (CN stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.94 [s, 9H, $C(CH_3)_3$], 1.75 [d, J = 7.1 Hz, 3H, C(3)H$_3$], 3.06 [dd, A of ABX system, J_{AB} = 13.3 Hz, J_{AX} = 6.3 Hz, 1H, one of C$\underline{H}_2$NH], 3.13 [dd, B of ABX system, J_{BA} = 13.3 Hz, J_{BX} = 6.4 Hz, 1H, one of C$\underline{H}_2$NH], 4.45 [q, J = 7.1 Hz, 1H, C(2)H], 6.70 (br s, 1H, NH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 22.8 [CH_3, C(3)H$_3$], 27.0 [C($\underline{C}H_3$)$_3$], 31.9 [C, $\underline{C}(CH_3)_3$], 50.8 (CH_2NH), 56.3 [CH, C(2)H], 169.4 (C=O) ppm; HRMS (ES+): Exact mass calculated for $C_8H_{16}NO^{35}Cl$ $[M+H]^+$ 178.0993. Found 178.0995; m/z (ES+) 180.3 {[($C_8H_{16}NO^{37}Cl$)+H$^+$], 30%}, 178.3 {[($C_8H_{16}NO^{35}Cl$)+H$^+$], 100%}.

General procedure for the preparation for the formation of α-thioamides. *N*-(2′,2′-Dimethylpropyl)-2-(phenylthio)propanamide (7d)

Thiophenol (2.89 ml, 28.2 mmol) in ethanol (22 ml) was added to a solution of aqueous sodium hydroxide (0.8 M, 78 ml, 54.20 mmol). Immediately, a solution of 2-chloro-*N*-(2′,2′-dimethylpropyl)propenamide **6d** (4.80 g, 27.10 mmol) in ethanol (60 ml) was added gradually over 15 minutes to the reaction mixture. Following heating under reflux for 1 h, the reaction was cooled in an ice bath and was quenched by the addition of water (70 ml). The solid precipitate was isolated by suction filtration to give pure *N*-(2′,2′-dimethylpropyl)-2-(phenylthio)propenamide **7d** as a white solid (6.67 g, 98 %); mp 87-89˚C; ν_{max}/cm^{-1} (ATR) 3272 (NH), 2964 (CH), 2953 (CH), 1640 (C=O amide), 1564, 1203; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.78 [s, 9H, $C(CH_3)_3$], 1.56 [d, J = 7.3 Hz, 3H, C(2)H$_3$], 2.95 [dd, A of ABX system, J_{AB} = 13.3 Hz, J_{AX} = 6.0 Hz, 1H, one of CH_2NH], 3.06 [dd, B of ABX system, J_{BA} = 13.3 Hz, J_{BX} = 6.7, 1H, one of CH_2NH], 3.91 [q, J = 7.4 Hz, 1H, C(2)H], 6.79 (br s, 1H, NH), 7.15-7.36 (m, 5H, ArH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 18.3 [CH_3, C(3)H$_3$], 26.9 [CH_3, $C(CH_3)_3$] 31.6 [C, $C(CH_3)_3$], 46.6 [CH, C(2)H], 50.6 (CH_2, CH_2NH), 126.7 (CH, CH_{Ar}), 129.0 (CH, CH_{Ar}), 129.1 (CH, CH_{Ar}), 134.1 [C, $C_{Ar(q)}$], 171.5 (C=O) ppm; HRMS (ES+): Exact mass calculated for $C_{14}H_{21}NOS$ $[M+H]^+$ 252.1422. Found 252.1428; m/z (ES+) 252.4 {[($C_{14}H_{21}NOS$)+H$^+$], 100%}.

Novel compounds **7e** and **7l-m** were similarly prepared, see supplementary information for characterisation data.

General procedure for the preparation for the formation of α-thio-β-chloroacrylamides.
***N*-(2′,2′-Dimethylpropyl)-*Z*-3-chloro-2-(phenylthio)propenamide (8d)**

Unrecrystallised *N*-chlorosuccinimide (5.19 g, 38.90 mmol) was added in one portion to a solution of *N*-(2′,2′-dimethylpropyl)-2-(phenylthio)propenamide **7d** (5.01 g, 19.95 mmol) in toluene (110 ml). The flask was immediately immersed in an oil bath at 90 °C and heating was maintained with stirring for 3 h. The reaction mixture was cooled to 0 °C and the succinimide by-product was removed by filtration. The solvent was removed at reduced pressure to give the crude product as a brown solid. This was purified by column chromatography on silica gel using hexane: ethyl acetate (95:5) as eluent to give the pure α-thio-β-chloroacrylamide **8d** as a white solid (4.13 g, 77%); mp 79-82°C; Found C, 59.39; H, 6.35; N, 4.96. $C_{14}H_{18}NOSCl$ requires C, 59.25; H, 6.39; N, 4.94; ν_{max}/cm^{-1} (ATR) 3382 NH), 2955 (CH), 1646 (C=O amide), 1519, 1232; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.68 [s, 9H, $C(CH_3)_3$], 3.02 (d, J = 6.4

Hz, 2H, CH_2NH), 6.92 (br s, 1H, NH), 7.16-7.33 (m, 5H, ArH), 7.97 [s, 1H, ClHC(3)=] ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 26.8 [CH_3, $C(CH_3)_3$], 31.7 [C, $C(CH_3)_3$], 51.1 (CH_2, CH_2NH), 127.0 (CH, CH_{Ar}), 127.8 (CH, CH_{Ar}), 129.5 (CH, CH_{Ar}), 130.4 [C, SC(2)=], 133.0 (C, $C_{Ar(q)}$), 139.7 [CH, C(3)HCl=], 162.1 (C=O) ppm; HRMS (ES+): Exact mass calculated for $C_{14}H_{18}NOS^{35}Cl$ $[M+H]^+$ 284.0858. Found 284.0866; m/z (ES+) 286.3 {[($C_{14}H_{18}NOS^{37}Cl$)+H^+], 40%}, 284.3 {[($C_{14}H_{18}NOS^{35}Cl$)+H^+], 100%}.

Novel compounds **8e** and **7l-m** were similarly prepared, see supplementary information for characterisation data.

General procedure for the preparation for the formation of α-sulfinyl-β-chloroacrylamides.
***N*-(2′,2′-Dimethylpropyl)-*Z*-3-chloro-2-(benzenesulfinyl)propenamide (9d)**

A solution of Oxone® (6.69 g, 21.76 mmol) in water (40 ml) was added dropwise to a stirring solution of *N*-(2′,2′-dimethylpropyl)-Z-3-chloro-2-(phenylthio)propenamide **8d** (3.08 g, 10.88 mmol) in acetone (120 ml) at room temperature. A colourless precipitate formed immediately. The reaction mixture was stirred overnight at which point water (200 ml) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 70 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried, filtered and concentrated to give the pure sulfoxide **9d** as a clear oil (3.13 g, 96 %); ν_{max}/cm^{-1} (ATR) 3267 (NH stretch), 3059 (CH stretch), 2957 (CH), 1668 (C=O amide), 1556 (NH bend), 1030 (SO); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.82 [s, 9H, $C(CH_3)_3$], 2.91-3.00 [dd, A of ABX system, J_{AB} = 13.3 Hz, J_{AX} = 5.5 Hz, 1H one of CH_2NH], 3.10-3.19 [dd, B of ABX system, J_{BA} = 13.3 Hz, J_{BX} = 6.5 Hz, 1H, one of CH_2NH], 7.47-7.70 (m, 5H, ArH), 7.80 (s, 1H, ClHC(3)=), 8.34 (C=O) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.2 [CH_3, $C(CH_3)_3$], 31.7 [C, $C(CH_3)_3$], 50.8 (CH_2, CH_2NH), 124.2 (CH, CH_{Ar}), 129.6 (CH, CH_{Ar}), 131.6 (CH, CH_{Ar}), 137.5 [CH, C(3)HCl=], 138.7 [C, SC(2)=], 141.2 (C, $C_{Ar(q)}$), 160.8 (C=O) ppm; HRMS (ES+): Exact mass calculated $C_{14}H_{18}NO_2S^{35}Cl$ $[M+H]^+$ 300.0820. Found 300.0827; m/z (ES+) 302.2 {[($C_{14}H_{18}NO_2S^{37}Cl$)+H^+], 40%} 300.2 {[($C_{14}H_{18}NO_2S^{35}Cl$)+H^+], 100%}.

Novel compounds **9e** and **9h** were similarly prepared, see supplementary information for characterisation data.

General procedure for the [3+2]-dipolar cycloaddition of α-diazoacetetes and α-sulfenyl-β-chloroacrylamides.
Ethyl 4-(phenylthio)-5-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate (major tautomer) and **ethyl 4-(phenylthio)-3-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-5-carboxylate** (minor tautomer) **(10a)**

Ethyl diazoacetate (0.97 ml, 8 mmol, 87% in dichloromethane) was added in one portion to a solution of *N*-(4′-methylphenyl)-*Z*-3-chloro-2-(phenylthio)propenamide **8a** (303 mg, 1 mmol) in toluene (5 ml) at room temperature. The solution was heated gradually to 100 °C and stirred under nitrogen for 24h. The cooled reaction mixture in toluene was transferred directly onto a silica gel column to prevent any potential degradation of unreacted EDA if concentrated. Purification by column chromatography using hexane-ethyl acetate (gradient elution 20-30% ethyl acetate) as eluent, followed by trituration with diethyl ether gave the pyrazole **10a** as a white solid (245 mg, 64 %); mp 155-158 °C; ν_{max}/cm^{-1} (ATR) 3188 (NH), 1717 (C=O ester), 1661 (C=O amide), 1235, 817, 737; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.28 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.32 (s, 3H, $ArCH_3$), 4.35 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 7.15 (d, *J* = 8.3 Hz, 2H, ArH), 7.17-7.30 (m, 5H, ArH), 7.49 (d, *J* = 8.3 Hz, 2H, ArH), 9.95 (br s, 1H, NH amide), 13.08 (br s, 1H, NH pyrazole) ppm; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 1.13 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.25 (s, 3H, $ArCH_3$), 4.20 (q, *J* = 7.0 Hz, 2H, $OC\underline{H_2}CH_3$), 7.11 (app. t, unresolved coupling, 5H, ArH), 7.23 (app. t, unresolved coupling, 2H, ArH), 7.51-7.61 (m, 2H, ArH), 10.27 (br s, 1H, NH amide), 14.80 (br s, 1H, NH pyrazole) ppm; ^{1}H NMR (600 MHz, Toluene-d_8) δ = 1.01 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.04 (s, 3H, $ArCH_3$), 4.07 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 6.74-6.92 (m, 5H, ArH), 7.12-7.17 (m, 2H, ArH), 7.55-7.60 (m, 2H, ArH), 9.83 (s, 1H, NH amide), 12.63 (br s, 1H, NH pyrazole) ppm; ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 14.0 (CH_3, $OCH_2\underline{CH_3}$), 20.9 (CH_3, $ArCH_3$), 61.5 (CH_2, $O\underline{CH_2}CH_3$), 109.1 [C, br, C(4)], 120.3 (CH, CH_{Ar}), 126.8 (CH, CH_{Ar}), 127.4 (CH, CH_{Ar}), 129.3 (CH, CH_{Ar}), 129.6 (CH, CH_{Ar}), 134.1 (C, $C_{Ar(q)}$), 134.7 (C, $C_{Ar(q)}$), 135.0 (C, $C_{Ar(q)}$), 140.4 [C, br, one of C(3) or C(5)], 145.8 [C, br, one of C(3) or C(5)], 156.0 (C, C=O amide), 160.5 (C, C=O ester) ppm; ^{13}C NMR (150.9 MHz, DMSO-d_6) δ = 13.8 (CH_3, $OCH_2\underline{CH_3}$), 20.5 (CH_3, $ArCH_3$), 60.5 (CH_2, minor tautomer, $O\underline{CH_2}CH_3$), 61.3 (CH_2, major tautomer, $O\underline{CH_2}CH_3$), 108.5 [C, minor tautomer, C(4)], 111.4 [C, major tautomer, C(4)], 120.0 (CH, CH_{Ar}), 125.5 (CH, CH_{Ar}), 125.9 (CH, CH_{Ar}), 126.7 (CH, CH_{Ar}), 128.9, 129.0 129.3 (CH, overlapping broad signals, major and minor tautomers, CH_{Ar}), 132.7 (C, major tautomer, $C_{Ar(q)}$), 133.6 (C, minor tautomer, $C_{Ar(q)}$), 135.3 (C, minor tautomer, $C_{Ar(q)}$), 136.2 (C, major tautomer, $C_{Ar(q)}$),136.3 (C, major tautomer, $C_{Ar(q)}$), 136.8 (C, minor tautomer, $C_{Ar(q)}$), 137.5 [C, major tautomer, one of C(3) or C(5)],142.1 [C, minor tautomer, one of C(3) or C(5)], 144.8 [C, minor tautomer, one of C(3) or C(5)], 149.9 [C, major tautomer, one of C(3) or C(5)], 156.2 (C, minor tautomer, C=O amide), 158.0 (C, major tautomer, C=O amide), 159.2 (C, major tautomer, C=O ester), 160.8 (C, minor tautomer, C=O ester) ppm; ^{13}C NMR (150.9 MHz, Toluene-d_8) δ = 14.1 (CH_3, $OCH_2\underline{CH_3}$), 20.8 (CH_3, $ArCH_3$), 61.0 (CH_2, $O\underline{CH_2}CH_3$), 109.6 [C, br, C(4)], 120.2 (CH, CH_{Ar}), 126.8 (CH, CH_{Ar}), 129.4 (CH, CH_{Ar}), 129.9 (CH, CH_{Ar}), 134.4 (C, $C_{Ar(q)}$), 135.4 (C, $C_{Ar(q)}$), 135.8 (C, $C_{Ar(q)}$), 140.9 [C, br, one of C(3) or C(5)], 146.0 [C, br, one of C(3) or C(5)], 156.0 (C, C=O amide), 160.5 (C, C=O ester) ppm; HRMS (ES+): Exact mass calculated for $C_{20}H_{19}N_3O_3S$ $[M+H]^+$ 382.1208. Found 382.1215; m/z (ES+) 382.2 {[($C_{20}H_{19}N_3O_3S$)+H^+], 48%}, 782.7 (100%).

Note: *4 x CH_{Ar} signals observed for 5 x CH_{Ar} signals in ^{13}C NMR spectrum of pyrazole **10a** in toluene-d_8. 1 CH_{Ar} signal overlapping with toluene-d_8 residual solvent peaks.*

Compounds **10b-q** were similarly prepared, see supplementary information for characterisation data.

General procedure for the [3+2]-dipolar cycloaddition of α-diazoacetetes and α-sulfinyl-β-chloroacrylamides.
Ethyl 5-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate (14a)

Ethyl diazoacetate (0.97 ml, >87% in dichloromethane, 8 mmol) was added in one portion to a stirring solution of *N*-(4′-methylphenyl)-Z-3-chloro-2-(benzenesulfinyl)propenamide **9a** (319 mg, 1 mmol) in toluene (2 ml) at room temperature. The reaction mixture was heated gradually to 100˚C and was stirred at this temperature under nitrogen for 48 h. Upon completion, the reaction mixture was cooled to room temperature during which a precipitate formed. The reaction mixture was further cooled in an ice bath for 1 h. The precipitate was collected by filtration through a sintered glass funnel (grade 4), and was washed thoroughly with diethyl ether until all the yellow impurity had been removed to give the pyrazole **14a** as a white solid (128 mg, 47%); mp 216-218°C; ν_{max}/cm^{-1} (ATR) 3341 (NH stretch), 3213 (NH) 3000 (CH), 1692 (C=O ester), 1667 (C=O amide), 1509, 826; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.41 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.34 (s, 3H, ArH), 4.43 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 7.17 (d, *J* = 8.2 Hz, 2H, ArH), 7.42 [s, 1H, C(4)H], 7.56 (d, *J* = 8.3 Hz, 2H, ArH), 8.61 (br s, 1H, NH amide), 11.33 (br s, 1H, NH pyrazole) ppm; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 1.32 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.27 (s, 3H, $ArCH_3$), 4.32 (q, J = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 7.15 (d, *J* = 8.2 Hz, 2H, ArH), 7.48 [br s, 1H, C(4)H], 7.65 (d, *J* = 8.3 Hz, 2H ArH), 10.18 (br s, 1H, NH amide), 14.47 (br s, 1H, NH pyrazole) ppm; ^{13}C NMR (150.9 MHz, DMSO-d_6) 14.2 (CH_3, $ArCH_3$), 20.5 (CH_3, $OCH_2\underline{CH_3}$), 60.7 (CH_2, $O\underline{CH_2}CH_3$), 108.6 [CH, C(3)H], 120.3 (CH, CH_{Ar}), 129.1 (CH, CH_{Ar}), 133.0 (C, $C_{Ar(q)}$), 135.9 (C, $C_{Ar(q)}$), 157.6 (C, br, C=O amide), 160.3 (C, br, C=O ester) ppm; HRMS (ES+): Exact mass calculated for $C_{14}H_{15}N_3O_3$ $[M+H]^+$ 274.1196. Found 274.1196.

Note: *In the ^{13}C NMR spectrum of pyrazole **14a** at 150.9 MHz the C(3) and C(5) carbons were not readiliy observed (10s delay time). Signals for the minor tautomer, ethyl 3-(4′-methylphenylcarbamoyl)-1H-pyrazole-5-carboxylate were not observed.*

Compounds **14b-i** were similarly prepared, see supplementary information for characterisation data.

Purification of commercial *m*CPBA[34]

In a 1L volumetric flask sodium hydroxide (0.1 M, 410 ml) and potassium phosphate monobasic (0.2 M, 250 ml) were mixed. The flask was filled up to 1 L with deionised water and the solution was stirred vigorously for 2 min to generate the buffer solution (pH 7.5). Commercial *m*CPBA (10 g, 65-77 %) was dissolved in diethyl ether (150 ml), and washed three times with buffer solution (pH 7.5, 150 ml). The ether layer was dried with $MgSO_4$, filtered and carefully evaporated under reduced pressure to give 6.88 g pure *m*CPBA as a white solid. The peracid was transferred to a plastic container and stored in the refridgerator for 3 months without decomposition. The purity was determined by ^{1}H NMR spectroscopy.

Caution: *It has been determined that 95-100% mCPBA can be detonated by shock or sparks, whereas commercial 70-85 % mCPBA is not shock sensitive. It should be stored in a refridgerator in tightly closed containers.*

General procedure for the [3+2]-dipolar cycloaddition of α-diazoacetetes and α-sulfonyl-β-chloroacrylamides.
Ethyl 4-(phenylsulfonyl)-5-(4′-methylphenylcarbamoyl)-1H-pyrazole-3-carboxylate (16a)

m-CPBA (77%, 448 mg, 2 mmol) in dichloromethane (15 ml) was added dropwise over 2 minutes to a stirring solution of *N*-(4′-methylphenyl)-*Z*-3-chloro-2-(benzenesulfinyl)propenamide **9a** (319 mg, 1 mmol) in dichloromethane (5 ml) at room temperature. The reaction progress was monitored by ^{1}H NMR spectroscopy. Once the impurity profile of the reaction was observed to increase relative to the increase in sulfoxide **9a** to sulfone **15a** oxidation the reaction mixture was concentrated under reduced pressure to an approximate volume of 10 ml in dichloromethane. Ethyl diazoacetate (0.49 ml, 4 mmol, >87% in dichloromethane) was added in one portion to the crude sulfone and the reaction mixture was stirred overnight at room temperature under nitrogen. Repeated purification by column chromatography on silica gel using hexane: ethyl acetate (60:40) as eluent, followed by dichloromethane: ethyl acetate (80:20) gave the pure pyrazole **16a** as a white solid (67 mg, 16 % over 2 steps); mp 179-181˚C; ν_{max}/cm^{-1} (ATR) 3193 (NH), 1736 (C=O ester), 1659 (C=O amide), 1311 (asymmetric SO_2), 1241, 1148 (symmetric SO_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.37 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.35 (s, 3H, $ArCH_3$), 4.41 (q, *J* = 7.1 Hz, 2H $OC\underline{H}_2CH_3$), 7.20 (d, *J* = 8.1 Hz, 2H, ArH), 7.53 (d, *J* = 7.8 Hz, 2H, ArH), 7.59-7.70 (m, 3H, ArH), 8.07 (d, *J* = 7.8 Hz, 2H, ArH), 11.20 (br s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 14.0 (CH_3, $OCH_2C\underline{H}_3$), 21.0 (CH_3, $ArCH_3$), 62.5 (CH_2, $O\underline{C}H_2CH_3$), 120.0 [C, C(4)], 120.3 (CH, CH_{Ar}), 127.5 (CH, CH_{Ar}), 129.2 (CH, CH_{Ar}), 129.8 (CH, CH_{Ar}), 134.0 (CH, CH_{Ar}), 134.3 (C, $C_{Ar(q)}$), 135.5 (C, $C_{Ar(q)}$), 138.6 [C, one of C(3) or C(5)], 140.7 (C, $C_{Ar(q)}$), 145.2 [C, one of C(3) or C(5)], 154.0 (C, C=O amide), 160.3 (C, C=O ester) ppm; HRMS (ES+): Exact mass calculated for $C_{20}H_{19}N_3O_5S$ [M+H]$^+$ 414.1118. Found 414.1123; m/z (ES-) 412.2 {[($C_{20}H_{19}N_3O_5S$)-H$^+$], 100%}. The regiochemistry was determined by single X-ray diffraction on a crystalline sample of **16a** recrystallised from dichloromethane. Crystals of **16a** are triclinic, space group *P*, formula $C_{20}H_{19}N_3O_3S$, MW = 413.44 g mol^{-1}, a = 7.6015(5) Å, b = 8.4522(6) Å, c = 15.5976(11) Å, α = 81.209(2)°, β = 81.359(2)°, γ = 70.921(2)°, U = 930.55(11) Å3 , F(000) = 432, μ(Mo Kα) = 0.214 mm-1 , R_1(F) = 0.0560 and S = 1.019 for 4588 observed reflections with I > 2σ(I), wR_2(F^2) = 0.1698 for all 7982 unique reflections.

CCDC 1906490 (for pyrazole **16a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crstallographic Data Centre.

Compounds **16b-g** were similarly prepared, see supplementary information for characterisation data.

The title compound **16a** was also prepared by addition of *m*-CPBA (113 mg, 0.655 mmol, 100%) to a stirring solution of 4-(phenylthio)-5-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate **10a** (100 mg, 0.262 mmol) in dichloromethane (5 ml) at room temperature. The reaction solution was heated to reflux and stirred overnight. Sodium thiosulfate (10 ml, 10% w/v) was added to the cooled reaction mixture and the layers were separated. The organic layer was washed with sodium thiosulfate (2 x 10 ml, 10% w/v), sat. sodium bicarbonate (3 x 10 ml), brine (10 ml), dried, filtered and concentrated under reduced pressure to give the pure pyrazole **16a** as a white solid (89 mg, 82%). Spectroscopic characteristics were consistent with those outlined previously.

General procedure for the *N*-alkylation of pyrazole 10a.
Ethyl 1-(2-ethoxy-2-oxoethyl)-4-(phenylthio)-3-(*4′*-methylphenylcarbamoyl)-1*H*-pyrazole-5-carboxylate (11a) and **ethyl 1-(2-ethoxy-2-oxoethyl)-4-(phenylthio)-5-(*4′*-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate (12a)**

Ethyl 4-(phenylthio)-5-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate **10a** (150 mg, 0.393 mmol), potassium carbonate (71 mg, 0.512 mmol) and a stirrer bar were placed in a vial. Anhydrous dimethylsulfoxide (3 ml) was added and the resultant mixture was stirred at room temperature under nitrogen. Ethyl bromoacetate (0.06 ml, 0.472 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with iced water (10 ml). The resulting mixture was extracted with ethyl acetate (2 x 15 ml). The combined organic layers were washed with brine (20 ml), dried over magnesium sulfate, and concentrated under reduced pressure to give the crude product as a yellow oil which contained a mixture of *N*-alkylated pyrazoles **11a**:**12a** in a ratio of 72:28. Purification by column chromatography on silica gel using hexane: ethyl acetate (80:20) as eluent gave pure pyrazole **11a** as a clear oil which solidified overnight to give a white solid (112 mg, 61 %), pure pyrazole **12a** as a white solid (46 mg, 25 %), and a mixed fraction of **11a** and **12a** as a clear oil which solidified overnight to give a white solid (11 mg, 6 %) to give a combined yield of 92 %.

Pyrazole **11a**; more polar; mp 107-109°C; ν_{max}/cm^{-1} (ATR) 3340 (NH stretch), 2993 (CH stretch), 1736 (C=O ester), 1708 (C=O ester), 1682 (C=O amide), 1531 (NH bend), 1270; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.15 [t, *J* = 7.1 Hz, 3H, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 1.28 [t, *J* = 7.2 Hz, 3H, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 2.29 (s, 3H, $ArCH_3$), 4.21 and 4.24 [overlapping quartets, 4H, *J* = 7.1 Hz, C(5)$CO_2C\underline{H}_2$ or $NCH_2CO_2C\underline{H}_2$], 5.38 (s, 2H, NCH_2CO), 7.03-7.26 (m, 7H, ArH), 7.49 (d, *J* = 8.5 Hz, 2H, ArH), 9.09 (s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 13.6 [CH_3, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 13.9 [$CH_3$, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 20.7 ($CH_3$, $ArCH_3$), 55.0 (CH_2, $N\underline{C}H_2CO$], 62.0 (CH_2, overlapping C(5)$CO_2\underline{C}H_2$ or $NCH_2CO_2\underline{C}H_2$], 113.7 [C, C(4)], 119.8 (CH, CH_{Ar}), 125.9 (CH, CH_{Ar}), 126.8 (CH, CH_{Ar}), 128.9 (CH, CH_{Ar}), 129.3 (CH, CH_{Ar}), 133.9 (C, $C_{Ar(q)}$), 134.9 (C, $C_{Ar(q)}$), 136.4 (C, $C_{Ar(q)}$), 137.1 [C, C(5)], 146.6 [C, C(3)], 157.6 (C, C=O amide), 158.8 [C, C(5)$\underline{C}$=O], 166.7 [C, $NCH_2\underline{C}$=O] ppm; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 1.06 [t, *J* = 7.1 Hz, 3H, C(5)$CO_2CH_2C\underline{H}_3$], 1.21 [t, *J* = 7.1 Hz, 3H, $NCH_2CO_2CH_2C\underline{H}_3$], 2.25 (s, 3H, $ArCH_3$), 4.14 [q, *J* = 7.1 Hz, 2H, C(5)$CO_2C\underline{H}_2$], 4.19 [q, *J* = 7.1 Hz, 2H, $NCH_2CO_2C\underline{H}_2$], 5.44 (s, 2H, NCH_2CO), 7.06-7.15 (m, 5H, ArH), 7.21-7.28 (m, 2H, ArH), 7.56 (d, *J* = 8.5 Hz, 2H, ArH), 10.34 (s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, DMSO-d_6) δ = 13.5 [CH_3, C(5)$CO_2CH_2\underline{C}H_3$], 14.0 [CH_3, $NCH_2CO_2CH_2\underline{C}H_3$], 20.5 ($CH_3$, $ArCH_3$), 54.8 (CH_2, $N\underline{C}H_2CO$), 61.5 [CH_2, C(5)$CO_2\underline{C}H_2$], 61.7 [$NCH_2CO_2\underline{C}H_2$], 111.3 [C, C(4)], 119.9 (CH, CH_{Ar}), 125.7 (CH, CH_{Ar}), 126.6 (CH, CH_{Ar}), 128.9 (CH, CH_{Ar}), 129.0 (CH, CH_{Ar}), 132.9 (C, $C_{Ar(q)}$), 135.9 (C, $C_{Ar(q)}$), 136.1 (C, $C_{Ar(q)}$), 137.0 [C, C(5)], 148.6 [C, C(3)], 158.1 [C, C(5)$\underline{C}$=O], 158.6 (C, C=O amide), 167.3 [C, $NCH_2\underline{C}$=O] ppm; ^{1}H NMR (600 MHz, Toluene-d_8) δ = 0.83 [t, *J* = 7.1 Hz, 3H, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 0.89 [t, *J* = 7.1 Hz, 3H, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 2.06 (s, 3H, $ArCH_3$), 3.86 [q, *J* = 7.1 Hz, 2H, C(5)$CO_2C\underline{H}_2$], 3.88 [q, *J* = 7.1 Hz, 2H, $NCH_2CO_2C\underline{H}_2$], 5.03 (s, 2H, NCH_2CO), 6.80 (t, unresolved coupling, 1H, ArH), 6.87 (d, *J* = 8.3 Hz, 2H, ArH), 6.92 (t, *J* = 7.8 Hz, 2H, ArH), 7.27 (d, *J* = 7.5 Hz, 2H, ArH), 7.49 (d, *J* = 8.3 Hz, 2H, ArH), 8.60 (s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, Toluene-d_8) δ = 13.6 [CH_3, one of C(5)$CO_2CH_2C\underline{H}_3$] or $NCH_2CO_2CH_2C\underline{H}_3$], 13.9 [$CH_3$, one of C(5)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$], 20.7 ($CH_3$, overlapping with residual toluene-d_8 signal, $ArCH_3$), 54.9 (CH_2, $N\underline{C}H_2CO$), 61.7 [CH_2, C(5)$CO_2\underline{C}H_2$], 61.8 [$NCH_2CO_2\underline{C}H_2$], 115.9 [C, C(4)], 119.7 (CH, CH_{Ar})*, 125.8 (CH, CH_{Ar}), 127.8 (CH, CH_{Ar}), 129.6 (CH, CH_{Ar}), 133.2 (C, $C_{Ar(q)}$), 136.3 (C, $C_{Ar(q)}$), 137.2 (C, $C_{Ar(q)}$), 138.3 [C, C(5)], 147.5 [C, C(3)], 157.4 (C, C=O amide), 159.5 [C, C(5)$\underline{C}$=O], 166.8 [C, $NCH_2\underline{C}$=O] ppm; * 1 x CH_{Ar} signal in toluene-d_8 spectrum overlapping with residual solvent signal; HRMS (ES+): Exact mass calculated for $C_{24}H_{25}N_3O_5S$ [M+H]$^+$ 468.1588. Found 468.1587; m/z (ES+) 468.2 {[($C_{24}H_{25}N_3O_5S$)+H$^+$], 100%}. The regiochemistry was determined by single X-ray diffraction on a crystalline sample of **11a** recrystallised from dichloromethane. Crystals of pyrazole **11a** are triclinic, space group $P\bar{1}$, formula $C_{24}H_{25}N_3O_5S$, MW = 467.53 g mol^{-1}, *a* = 9.456(2) Å, *b* = 11.142(3) Å, *c* = 12.695(3) Å, *α* = 70.288(8)°, *β* = 81.753(8)°, *γ* = 70.999(8)°, *U* = 1189.7(5) Å^3, F(000) = 492, *m*(Mo Ka) = 0.176 mm^{-1}, R_1(F) = 0.0546 and *S* = 1.031 for 2701 observed reflections with I > 2σ(I), wR_2(F^2) = 0.1564 for all 4552 unique reflections.

CCDC 1906489 (for pyrazole **11a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crstallographic Data Centre.

Pyrazole **12a**; less polar; mp 124-127°C; ν_{max}/cm^{-1} (ATR) 3301 (NH stretch), 1741 (C=O ester), 1732 (C=O ester), 1650 (C=O amide), 1539 (NH bend), 1216, 1057; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.27 [t, *J* = 7.2 Hz, 3H, $NCH_2CO_2CH_2C\underline{H}_3$], 1.29 [t, *J* = 7.2 Hz, 3H, C(3)$CO_2CH_2C\underline{H}_3$], 2.31 (s, 3H, $ArCH_3$), 4.24 [q, *J* = 7.1 Hz, 2H, $NCH_2CO_2C\underline{H}_2$], 4.36 [q, *J* = 7.1 Hz, 2H, C(3)$CO_2C\underline{H}_2$], 5.58 (s, 2H, NCH_2CO), 7.11 (d. J = 8.4 Hz, 2H, ArH), 7.16-7.23 (m, 3H, ArH), 7.24-7.30 (m, 2H, ArH), 7.35 (d, *J* = 8.4 Hz, ArH), 10.04 (br s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 14.0 (CH_3, one of C(3)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$), 14.1 ($CH_3$, one of C(3)$CO_2CH_2C\underline{H}_3$ or $NCH_2CO_2CH_2C\underline{H}_3$), 20.8 ($CH_3$, $ArCH_3$), 55.8 (CH_2, $N\underline{C}H_2CO$), 61.5 [CH_2, C(3)$CO_2\underline{C}H_2$], 61.9 [CH_2, $NCH_2CO_2\underline{C}H_2$], 110.3 [C, C(4)], 120.5 (CH, CH_{Ar}), 126.8 (CH, CH_{Ar}), 127.0 (CH, CH_{Ar}), 129.4 (CH, CH_{Ar}), 129.5 (CH, CH_{Ar}), 134.2 (C, $C_{Ar(q)}$), 134.6 (C, $C_{Ar(q)}$), 134.9 (C, $C_{Ar(q)}$), 138.8 [C, C(5)], 144.6 [C, C(3)], 155.9 (C, C=O amide), 160.4 [C, C(3)$\underline{C}$=O], 167.0 [C, $NCH_2\underline{C}$=O] ppm; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 1.14 [t, *J* = 7.1 Hz, 3H, $NCH_2CO_2CH_2C\underline{H}_3$], 1.17 [t, *J* = 7.1 Hz, 3H, C(3)$CO_2CH_2C\underline{H}_3$], 2.26 (s, 3H, $ArCH_3$), 4.15 [q, *J* = 7.1 Hz, 2H, $NCH_2CO_2C\underline{H}_2$], 4.19 [q, *J* = 7.1 Hz, 2H, C(3)$CO_2C\underline{H}_2$], 5.40 (s, 2H, NCH_2CO), 6.96-7.27 (m, 7H, ArH), 7.47-7.50 (m, 2H, ArH), 10.56 (s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, DMSO-d_6) δ = 13.88 [CH_3, $NCH_2CO_2CH_2\underline{C}H_3$], 13.90 [t, *J* = 7.1 Hz, 3H, C(3)$CO_2CH_2\underline{C}H_3$], 20.5 (CH_3, $ArCH_3$), 53.6 (CH_2, $N\underline{C}H_2CO$), 60.8 [CH_2, C(3)$CO_2\underline{C}H_2$], 61.5 [CH_2, $NCH_2CO_2C\underline{H}_2$], 110.7 [C, C(4)], 119.9 (CH, CH_{Ar}), 125.9 (CH, CH_{Ar}), 126.6 (CH, CH_{Ar}), 129.1 (CH, CH_{Ar}), 129.2 (CH, CH_{Ar}), 133.7 (C, $C_{Ar(q)}$), 135.3 (C, $C_{Ar(q)}$), 136.9 (C, $C_{Ar(q)}$), 142.4 (C, C(5)], 143.2 (C, C(3)], 156.1 (C, C=O amide), 160.2 [C, C(3)$\underline{C}$=O], 167.0 [C, $NCH_2\underline{C}$=O] ppm; ^{1}H NMR (600 MHz, Toluene-d_8) δ = 0.87 [t, *J* = 7.1 Hz, 3H, $NCH_2CO_2CH_2C\underline{H}_3$], 0.97 [t, *J* = 7.1 Hz, 3H, C(3)$CO_2CH_2C\underline{H}_3$], 2.02 (s, 3H, $ArCH_3$), 3.86 [q, *J* = 7.1 Hz, 2H, $NCH_2CO_2C\underline{H}_2$], 4.05 [q, *J* = 7.1 Hz, 2H, C(3)$CO_2C\underline{H}_2$], 5.31 (s, 2H, NCH_2CO), 6.72-6.77 (m,

1H, ArH), 6.79-6.86 (m, 4H, ArH), 7.15-7.19 (m, 2H, ArH), 7.44-7.49 (m, 2H, ArH), 10.09 (s, 1H, NH amide) ppm; ^{13}C NMR (150.9 MHz, Toluene-d_8) δ = 13.9 [CH_3, $NCH_2CO_2CH_2\underline{C}H_3$], 14.1 [$CH_3$, $C(3)CO_2CH_2\underline{C}H_3$], 20.7 ($CH_3$, overlapping with residual toluene-d_8 signal, $ArCH_3$), 55.9 (CH_2, $N\underline{C}H_2CO$), 60.9 [CH_2, $C(3)CO_2\underline{C}H_2$], 61.5 [CH_2, $NCH_2CO_2C\underline{H}_2$], 110.6 [C, C(4)], 120.2 (CH, CH_{Ar}), 126.8 (CH, CH_{Ar}), 127.6 (CH, CH_{Ar}), 129.5 (CH, CH_{Ar}), 129.8 (CH, CH_{Ar}), 134.3 (C, $C_{Ar(q)}$), 135.5 (C, $C_{Ar(q)}$), 135.7 (C, $C_{Ar(q)}$), 138.8 [C, C(5)], 145.2 [C, C(3)], 156.2 (C, C=O amide), 160.6 [C, $C(3)\underline{C}$=O], 167.0 [C, $NCH_2\underline{C}$=O] ppm; HRMS (ES+): Exact mass calculated for $C_{24}H_{25}N_3O_5S$ $[M+H]^+$ 468.1588. Found 468.1583; m/z (ES+) 468.2 {$[(C_{24}H_{25}N_3O_5S)+H^+]$, 68%}, 721.1 (100%).

Note: *The title compounds **11a** and **12a** were also isolated as byproducts in the [3+2]-dipolar cycloaddition of α-thio-β-chloroacrylamide **8a** and ethyl diazoacetate, through competing N–H insertion. Spectroscopic data are consistent with that outlined previously.*

Compounds **17a-c and 18a-b** were similarly prepared, see supplementary information for characterisation data.

General procedure for the selective oxidation of pyrazoles 10.
Ethyl 4-(phenylsulfinyl)-5-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate (19a)

*m*CPBA (35 mg, 0.2 mmol, 100%) was added in one portion to a stirring solution of 4-(phenylthio)-5-(4′-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate **10a** (40 mg, 0.1 mmol) in dichloromethane (10 ml) at room temperature. After stirring overnight sodium thiosulfate (10 ml, 10% w/v) was added and the layers were separated. The organic layer was washed with sodium thiosulfate (2 x 10 ml, 10% w/v), sat. sodium bicarbonate (3 x 10 ml) and brine, dried with magnesium sulfate and concentrated under reduced pressure to give the crude product as a white solid. ^{1}H NMR analysis of the crude product indicated complete consumption of the starting material with evidence for both the sulfoxide **19a** and sulfone **16a** present (approx. 85:15). Purification by column chromatography using hexane: ethyl acetate as eluent (gradient elution 20-30% ethyl acetate) gave sulfoxide **19a** as a white solid (26 mg, 66 %); mp 187-189°C; ν_{max}/cm^{-1} (ATR) 3096 (NH stretch), 2994 (CH), 2918 (CH), 1699 (C=O ester), 1669 (C=O amide), 1235, 1029 (S=O), 980; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{C}H_3$), 2.34 (s, 3H, $ArCH_3$), 4.36-4.57 (m, 2H, $O\underline{C}H_2CH_3$), 7.18 (d, *J* = 8.1 Hz, 2H, ArH), 7.37-7.51 (m, 3H, ArH), 7.63-7.83 (m, 4H, ArH), 12.36 (br s, 1H, NH amide), 12.79 (br s, 1H, NH pyrazole) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 14.2 (CH_3, $OCH_2\underline{C}H_3$), 21.0 (CH_3, $ArCH_3$), 62.3 (CH_2, $O\underline{C}H_2CH_3$), 120.3 (CH, CH_{Ar}), 124.1 [C, C(4)], 125.1 (CH, CH_{Ar}), 129.6 (CH, 2 overlapping CH_{Ar} signals), 131.7 (CH, CH_{Ar}), 134.8 (C, $C_{Ar(q)}$) 135.1 (C, $C_{Ar(q)}$), 139.6 [C, one of C(3) or C(5)], 142.8 [C, one of C(3) or C(5)], 143.4 (C, $C_{Ar(q)}$), 154.8 (C, C=O amide), 161.2 (C, C=O ester) ppm; HRMS (ES+): Exact mass calculated for $C_{20}H_{19}N_3O_4S$ $[M+H]^+$ 398.1169. Found 398.1183.

Compounds **16a**, **16e** and **19b** were similarly prepared, see supplementary information for characterisation data.

4-(Phenylthio)-5-(4-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylic acid (20)

Sodium hydroxide (97 mg, 2.43 mmol) in water (15 ml) was added in one portion to a stirring solution of ethyl 4-(phenylthio)-5-(4'-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylate **10a** (232 mg, 0.61 mmol) in methanol (5 ml) at room temperature. The heterogenous reaction mixture was heated to reflux at which point the reaction mixture became homogenous, and was stirred at this temperature overnight. The reaction mixture was concentrated under reduced pressure to dryness. Water (15 ml) and ethyl acetate (15 ml) was added, and the layers separated. Concentrated HCl was added until a pH of 2 was achieved, which caused the carboxylic acid **20** to precipitate out of solution. Ethyl acetate (15 ml) was added and the layers separated. The aqueous layer was further extracted with ethyl acetate (2 x 15 ml). The combined organic layers were washed with brine (15 ml), dried, and concentrated under reduced pressure to give the pure pyrazole **20** (195 mg, 91 %) as a white solid; mp 226-229°C; ν_{max}/cm^{-1} (ATR) 3126 (OH stretch), 3025 (NH), 2953 (CH), 1690 (C=O carboxylic acid), 1648 (C=O amide), 1606, 1474, 1235; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.26 (s, 3H, $ArCH_3$), 3.40 (br s, 1H, COOH), 7.04-7.30 (m, 7H, ArH), 7.55 (d, *J* = 8.1 Hz, 2H, ArH), 10.18 (s, 1H, NH amide), 14.64 (br s, 1H, NH pyrazole) ppm; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 2.25 (s, 3H, $ArCH_3$), 3.38 (br s, 1H, COOH), 7.02-7.28 (m, 7H, ArH), 7.46-7.64 (d, *J* = 8.1 Hz, 2H, ArH), 10.20 (s, 1H, NH amide), 14.67 (br s, 1H, NH pyrazole) ppm; ^{13}C NMR (600 MHz, DMSO-d_6) δ = 20.9 (CH_3, $ArCH_3$), 110.8 [C, C(4)], 120.3 (CH, CH_{Ar}), 125.7 (CH, CH_{Ar}), 126.9 (CH, CH_{Ar}), 129.3 (CH, CH_{Ar}), 129.5 (CH, CH_{Ar}), 133.1 (C, $C_{Ar(q)}$), 136.5 (C, $C_{Ar(q)}$), 138.0 (C, $C_{Ar(q)}$), 150.2 (C, C=O carboxylic acid), 159.7 (C, C=O amide) ppm; HRMS (ES+): Exact mass calculated for $C_{18}H_{15}N_3O_3S$ $[M+H]^+$ 354.0907. Found 354.0901.

Note: *C(3) and C(5) not observed at 600 MHz*

***N*^{3}-(4′-Methoxyphenyl)-4-(phenylthio)-*N*^{5}-(4′-methylphenyl)-1*H*-pyrazole-3,5-dicarboxamide (21)**

4-Dimethylaminopyridine (7 mg, 0.06 mmol) and *p*-anisidine (150 mg, 1.22 mmol) were added to a stirring solution of 4-(phenylthio)-5-(4-methylphenylcarbamoyl)-1*H*-pyrazole-3-carboxylic acid **20** (195 mg, 0.55 mmol) in dichloromethane (25 ml) at 0˚C. The solution was stirred at this temperature for 2 minutes at which point *N*′,*N*′-diisopropylcarbodiimide (105 mg, 0.83 mmol) was added in dichloromethane (5 ml). The reaction mixture was immediately heated to reflux and was stirred at this temperature for 12 h. The cooled reaction mixture was washed with water (30 ml) and the layers separated. The organic layer was washed with 2M hydrochloric acid (2 x 30 ml) and brine (30 ml), dried, and concentrated under reduced pressure to give the crude product as a grey/brown solid. Purification by recrystallistation using ethyl acetate: heptane gave the pure product as a grey solid (162 mg, 64 %); mp 237-239°C; ν_{max}/cm^{-1} (ATR) 3211 (NH stretch), 2917 (CH), 1682, (C=O amide), 1666 (C=O amide), 1320, 1161; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.26 (s, 3H, $ArCH_3$), 3.73 (s, 3H, $ArOCH_3$), 6.58-7.87 (m, 13H, ArH), 10.18 (s, 1H, NH amide), 10.22 (s, 1H, NH amide),14.67 (br s, NH pyrazole) ppm; ^{1}H NMR (600 MHz, DMSO-d_6) δ = 2.27 (s, 3H, $ArCH_3$), 3.73 (s, 3H, $ArOCH_3$), 6.62-7.90 (m, 13H, ArH), 10.22 (s, 1H, NH amide), 10.26 (s, 1H, NH amide), 14.70 (br s, 1H, NH pyrazole) ppm; ^{13}C NMR (150.9 MHz, DMSO-d_6) δ = 20.5 (CH_3, $ArCH_3$), 55.2 (CH_3, $ArOCH_3$), 106.5 [C, C(4)], 113.9 (CH, CH_{Ar}), 119.9 (CH, CH_{Ar}), 121.4 (CH, CH_{Ar}), 125.8 (CH, CH_{Ar}), 126.7 (CH, CH_{Ar}), 129.1 (CH, CH_{Ar}), 129.2 (CH, CH_{Ar}), 131.3 (C, br, $C_{Ar(q)}$), 133.1 (C, br, $C_{Ar(q)}$), 135.7 (C, br, $C_{Ar(q)}$), 136.9 (C, $C_{Ar(q)}$), 142.2 [C, br, one of C(3) or C(5)], 148.0 [C, br, one of C(3) or C(5)], 155.8 (C, $C_{Ar(q)}OMe$), 157.6 (C, br, overlapping C=O amides) ppm; HRMS (ES+): Exact mass calculated for $C_{25}H_{22}N_4O_3S$ $[M+H]^+$ 459.1485. Found 459.1486.

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Keywords: [3+2]-dipolar cycloaddition • sulfonyl migration • pyrazole • tautomers• α-thio-β-chloroacrylamide

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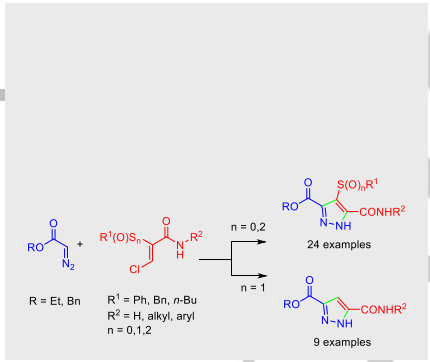
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Highly regioselective synthetic methodology leading to densely functionalised C(3), C(4) and C(5) substituted pyrazoles via thermal [3+2]-dipolar cycloaddition, of α-diazoacetates and α-thio-β-chloroacrylamides, at the sulfide, sulfoxide and sulfone levels of oxidation, is described. This method allows access to C(4)-sulfenyl or sulfonyl pyrazoles, through migration of the sulfur substituent at the sulfide and sulfone oxidation levels, while elimination of the sulfinyl group leading to 3,5-disubstituted pyrazoles, is observed.



Key Topic*

*Aaran J. Flynn, Alan Ford, U. B. Rao Khandavilli, Simon E. Lawrence, Anita R. Maguire**

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Regioselective Thermal [3+2]-Dipolar Cycloadditions of α-Diazoacetates with α-Sulfenyl/Sulfinyl/Sulfonyl-β-Chloracrylamide Derivatives to form Densely Functionalised Pyrazoles.

*[3+2]-dipolar cycloaddition, pyrazoles, tautomers, α-thio-β-chloroacylamides, sulfonyl shift