Investigation of the synthetic and mechanistic aspects of the highly stereoselective transformation of α-thioamides to α-thio-β-chloroacrylamides†

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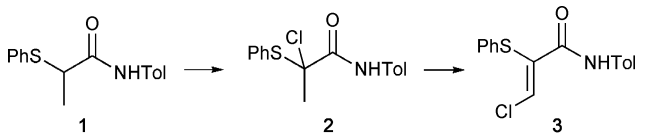
Treatment of a series of α-thioamides with *N*-chlorosuccinimide results in efficient transformation to the analogous α-thio-β-chloroacrylamides. The mechanistic pathway has been established through isolation and characterisation of intermediate compounds. The scope of the transformation has been explored—aryl and alkylthio substituents, primary, secondary and tertiary amides can be employed. In most instances, the chloroacrylamides are formed exclusively as the *Z*-stereoisomer; however, with tertiary propanamides or with amides derived from butanoic or pentanoic acid a mixture of *E*- and *Z*-stereoisomers is formed.

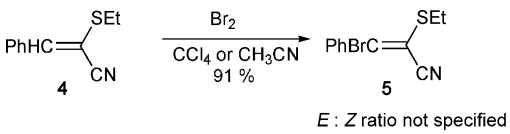
Introduction

α-Chlorination of sulfides on treatment with a range of chlorinating agents such as *N*-chlorosuccinimide (NCS) is well established.[1] As part of an ongoing synthetic programme in our laboratory, the preparation of the α-chlorosulfide **2** derived from *N*-tolyl-α-(phenylthio)propanamide (**1**) was required. Chlorination of α-thioesters on treatment with NCS is well precedented[2] and, therefore, this method was attempted with α-thioamide **1**. However, when **1** was treated with NCS, the reaction pathway was found to be more complex. The expected α-chlorosufide **2** was formed initially but, as this was not stable, it was transformed to further products, notably the α-thio-β-chloroacrylamide **3** (Scheme 1).[3] In this paper, the detailed investigation of the mechanistic pathway by which this product is formed is described. Furthermore, the investigation of the scope of this transformation is described, thereby providing an efficient and stereoselective synthetic route to α-thio-β-chloroacrylamides.



Scheme 1

Some reports of structurally-similar compounds have appeared, for example Viehe *et al.* [4] mention α-thio-β-halo-α, β-unsaturated esters/amides and β-haloacrylonitriles in a patent. No spectroscopic details for the amide derivative or details of a synthetic method for the formation of esters and amides were reported in this patent. However, Viehe employed a procedure described by Pochat[5] for the preparation of β-bromo-α-(ethylthio)acrylonitrile **5** whereby α-(ethylthio)acrylonitrile **4**was treated with bromine in carbon tetrachloride or acetonitrile as illustrated in Scheme 2.



Scheme 2

Results and discussion

Preliminary observations

Generation of the α-chlorosulfide **2** was observed by NMR when α-(phenylthio)propanamide **1** was treated with 1 equivalent of NCS in carbon tetrachloride at 0 °C for 3 h and following removal of the succinimide by filtration (Scheme 3). Further investigations led to the observation that at room temperature, after 24 h, the same amount of NCS gave an essentially equimolar mixture of α-chlorosulfide **2** and acrylamide **6**. When the number of equivalents of NCS was increased to two, under otherwise identical reaction conditions, the major compound formed was a dichloride **7**, although minor amounts of acrylamide **6** were also present. Treatment of this crude reaction mixture with 1.5 equivalents of zinc chloride in nitromethane and DCM gave a reaction mixture containing two major products, which were isolated and identified as *N*-4′-methylphenyl-*Z*-3-chloro-2-(phenylthio)propenamide (**3**) and *N*-4′-methylphenyl-*Z*-2,3-(phenylthio)propenamide (**8**).

The unexpected highly stereoselective formation of the β-chloro-α-thioacrylamide **3** caught our attention, providing a potentially valuable series of highly-functionalised acrylamides which could be envisioned to act as dienophiles or Michael acceptors, for example. To explore the scope of this transformation, the synthesis of a series of thioamides and treatment of each with NCS was undertaken.

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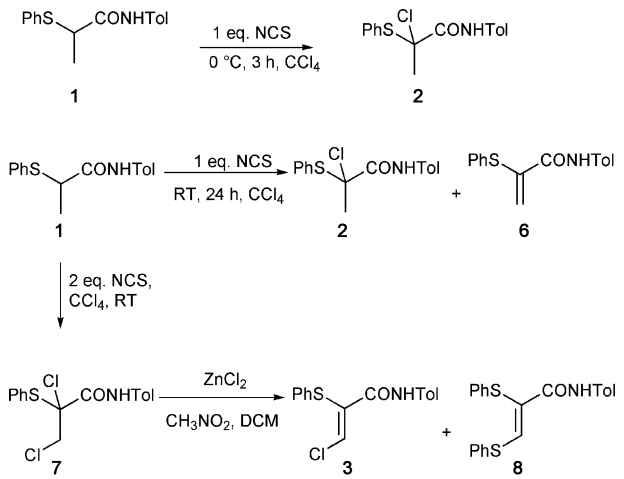


Scheme 3

Determination of the reaction pathway and mechanism

To determine the reaction pathway, the transformation of the α-thioamide **1** to the β-chloroacrylamide **3** was explored in detail. Each intermediate was isolated and identified, and the conditions for the formation of each of the intermediates were determined. The results of these experiments are outlined in Table 1, below.

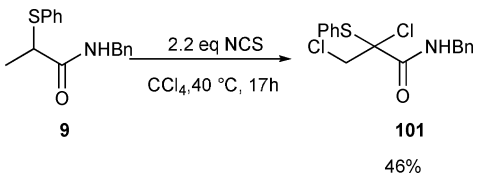
It is evident from these results that as the number of equivalents of NCS, reaction time and temperature increased, the major products changed from the α-chlorosulfide **2** and acrylamide **6** under mild conditions to the dichloride **7** and β-chloroacrylamide **3** under more forcing conditions.

The α-chlorosulfide **2** was the only product formed when **1** was treated with 1.1 equivalents of NCS at 0 °C for 3 h. Filtration of the succinimide by-product allowed ^{1}H NMR analysis of the carbon tetrachloride solution of **2**, but partial decomposition occurred rapidly (*ca.* 50% in 1 h) on concentration of the compound, or more slowly (*ca.* 50% in 7 days) on storage in solution at temperatures as low as −20 °C.

Decomposition of **2** leads to **6** by elimination of HCl. The α-chlorosulfides studied in this work were found to vary considerably in stability compared to the α-chloro-α-thioesters studied by McKervey *et al.*,[6] which were found to be stable, as a solution in carbon tetrachloride at 0 °C, for several years. The enhanced reactivity of **2** relative to the ester derivative is presumably due to increased sulfide stabilization of the carbocation generated on loss of chloride, facilitated through conformational factors as a result of the intramolecular hydrogen bond from the amide hydrogen to the sulfide group.

On treatment of **1** with 1.1 equivalents of NCS at room temperature for 24 hours, a 1 : 1 mixture of **2** and **6** was obtained. When this mixture was passed through a column of silica gel, complete conversion to **6** occurred. A pure sample of the acrylamide was readily obtained in this manner.

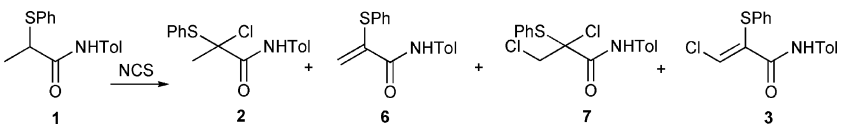
A second equivalent of NCS was necessary for chlorination of the acrylamide to occur. At temperatures of 20–45 °C in carbon tetrachloride as solvent, the products resulting from treatment of **1** with 2.2 equivalents of NCS were **6** and **7**. Variation of reaction times (16–24 h) and temperatures (20–45 °C) gave various ratios of the two products. Despite many attempts at chromatographic purification, it was not possible to obtain a pure sample of **7**: partial decomposition of **7** on storage or exposure to silica gel to form the β-chloroacrylamide **3** was observed. However, when *N*-benzyl-α-(phenylthio)propanamide (**9**) was treated with 2.2 equivalents of NCS at 40 °C for 17 h, the *N*-benzyl dichloride **101** formed, which proved considerably more stable than the *N*-tolyl analogue (Scheme 4). Purification by chromatography gave a pure sample of the *N*-benzyl dichloride **101**, which was fully characterized.



Scheme 4

When **1** was treated with 2.1 equivalents of NCS at 40 °C, using toluene as solvent in place of carbon tetrachloride, a mixture of **7**

Table 1 Transformation of α-thioamide **1** to β-chloroacrylamide **3**

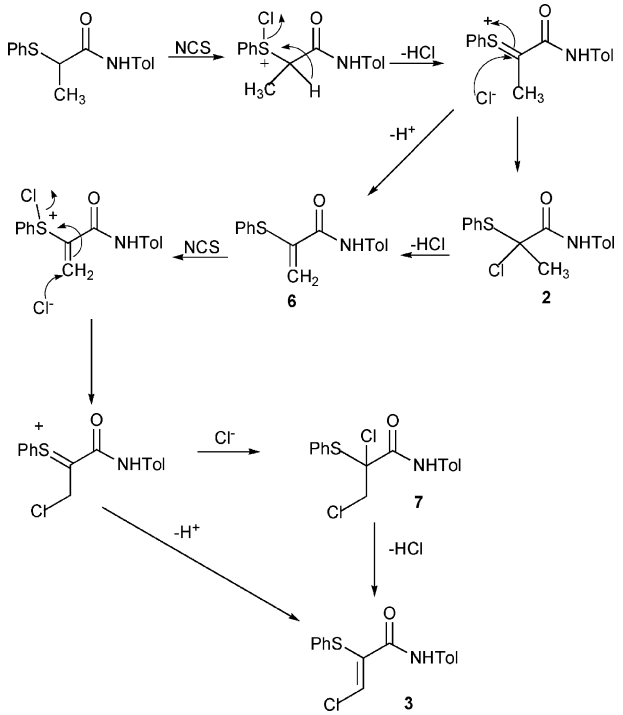


NCS/eq.	Temperature/°C	Time/h	Molar ratio of products[b] 2	6	7	3
1.1	0	3	Only	—	—	—
1.1	20	24	1	1	—	—
2.2	20	48	—	1	2	—
2.2	40–45	16–24	Mixtures of **6** and **3**, ratio dependant on time & temperature			
2.1	40[a]	22	—	—	3.3	1
2.2	47–50	18–24	—	—	1	10
2.2	Reflux	18	—	—	—	Only
2.2	Reflux[a]	2	—	—	—	Only

[a] Reaction was conducted in toluene, each of the other reactions was conducted in carbon tetrachloride. [b] Ratios of products were determined by integration of ^{1}H NMR spectrum of crude reaction mixture.

and **3** was isolated in a ratio of 3.3 : 1. However, when reactions were conducted in carbon tetrachloride above 45 °C the major product isolated was **3**. When **1** was treated with 2.2 equivalents of NCS at reflux in either carbon tetrachloride or toluene, **3** was the only product detected. The difference in reaction time when the higher boiling solvent, toluene, is used (2 h) in place of carbon tetrachloride (18 h) is significant.

Based on these observations, the reaction mechanism in Scheme 5 can be proposed.



Scheme 5

Thus, chlorination of the α-thioamide **1** using the first equivalent of NCS generates the α-chlorosulfide **2**. The mechanism of α-chlorosulfide **2** formation is believed to involve the formation of a chlorosulfonium ion. On elimination of HCl, the acrylamide **6** is formed. A second equivalent of NCS again chlorinates the sulfur substituent on the acrylamide to generate a chlorosulfonium ion. This is followed by addition of chloride ion at the β-carbon to introduce the β-chlorine. Further chloride addition to the resulting sulfur-stabilized carbonium ion gives the dichloride **7**. Subsequent elimination of HCl, presumably *via* the carbocation, produces the β-chloroacrylamide **3**. The sulfur-stabilized carbocation generated by conjugate addition of chloride to the acrylamide **6** may also be deprotonated to form the β-chloroacrylamide **3** directly.

In order to determine that the proposed mechanism was correct, the following series of experiments were performed:

(a) The decomposition of **2** to **6** on standing or on passing through a column of silica gel (as mentioned earlier) confirms the first step.

(b) When a sample of **6** was heated at 47 °C with 1.1 equivalents of NCS in carbon tetrachloride, no evidence for formation of **7** or **3** was observed. However, when a sample of **6** was treated with 1.1 equivalents of NCS in carbon tetrachloride at reflux for 18 h, the crude product mixture contained **6** and **3** in a ratio of 1 : 3. This confirmed that **6** is transformed to **3** under the reaction conditions (carbon tetrachloride, reflux, 18 h) and is an intermediate in the reaction pathway. The fact that no dichloride **7** was isolated may have been due to its lability in refluxing carbon tetrachloride. Interestingly, transformation of **6** to **3** was less efficient than transformation of **1** to **3** under the same reaction conditions.

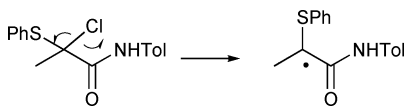
(c) When a mixture of **6** and **1** (3 : 1) was stirred with 3 equivalents of NCS in CCl_4 at room temperature for 24 h, **1** was completely transformed to the dichloride, and it appeared that some transformation of **6** had occurred as the ratio of **6** to **7** was 2 : 1 (estimated by integration of ^{1}H NMR).

(d) A sample containing a mixture of **7** and **3** (*ca.* 3 : 1) was heated at 47 °C in CCl_4 under nitrogen for 48 h. Partial thermal decomposition of **7** to **3** was observed. ^{1}H NMR integration data showed that 50% of the dichloride **7** had decomposed to **3**. Also, a sample of **7** (containing minor amounts of **6** and **3**), heated neat at 80 °C under nitrogen, was completely converted to **3** in 2 h.

(e) When a sample of **7** was treated with anhydrous zinc chloride in DCM and nitromethane at 20 °C, **3** was obtained.

Thus, experimental evidence for each step of the proposed mechanism was secured.

Despite the convincing evidence for the polar reaction mechanism, it does not rule out another possible reaction pathway involving captodative radical intermediates formed by homolytic cleavage of the C=Cl bond (Scheme 6).[7]



Scheme 6

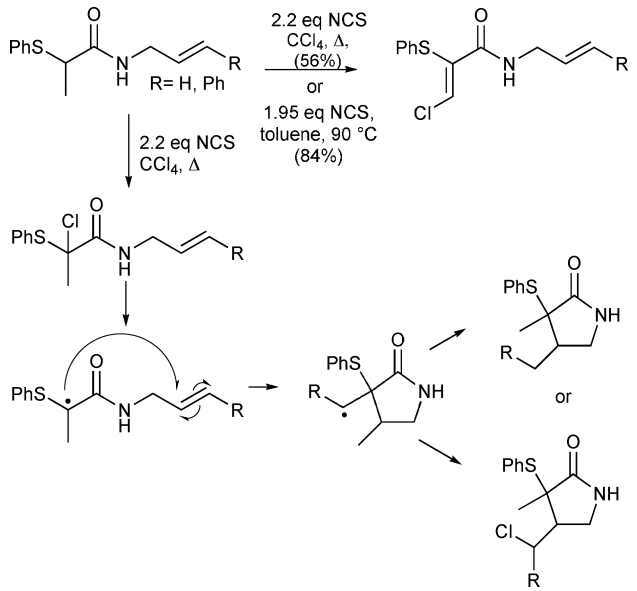
To establish if the captodative radical compound is a reaction intermediate, a number of experiments were conducted to trap this radical if it was formed.

Sato, Ishibashi and Ikeda[8–12] have shown that *N*-allyl-α-chloroamide derivatives undergo efficient 5-*exo*-*trig*-cyclisation. Based on their work, *N*-allyl-α-(phenylthio)propanamide (**14**) was prepared and treated with 2.2 equivalents of NCS in CCl_4 at reflux or 1.95 equivalents of NCS in toluene at 90 °C (Scheme 7). If the captodative radical **102** was formed, cyclisation as illustrated would be expected to form the γ-lactam. However, no evidence for cyclisation was observed. The major product was the *N*-allyl-β-chloroacrylamide **56** isolated by chromatography in 84% yield from reaction in toluene and 56% yield from reaction in CCl_4.

Since the *N*-allyl derivative did not cyclise, the *N*-cinnamyl-α-(phenylthio)propanamide (**15**) was prepared, as the cinnamyl substituent would be expected to act as a more efficient radical trap. Again, on treatment of the α-thioamide **15** with 2.2 equivalents of NCS in CCl_4 under reflux conditions, no cyclisation was observed and the corresponding β-chloroacrylamide **57** was formed in 67% yield as a white, crystalline solid. These experimental results suggest that the elimination of HCl from the α-chlorosulfide occurred by a polar mechanism rather than a radical pathway.

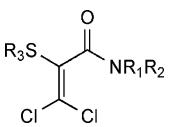
Synthesis of β-chloroacrylamides

Based on the serendipitous observation of the formation of the β-chloroacrylamide **3**, investigation of the transformation of the series of α-thioamides **1**, **9**–**50** (see the ESI for synthesis of

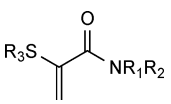


Scheme 7

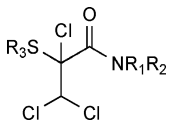
α-thioamides†) to the analogous β-chloroacrylamides **3**, **51**–**100** was undertaken[3]—the optimised results are summarized in Table 2, indicating the broad scope of this synthetic transformation. In most instances, the crude products of the reactions were sufficiently pure for use in further reactions, but could be readily obtained in an analytically pure form through chromatography, trituration or recrystallisation. The efficiency of the transformation and the purity of the crude products are readily determined by integration of the ^{1}H NMR signal for the vinylic β–H, typically at 7–8 ppm. The synthesis of the β-chloroacrylamides has been optimised so that synthetically useful amounts of these materials can be easily prepared from the corresponding sulfides, for example, the β-chloroacrylamide **51** has been successfully synthesised on a 39 mmol scale resulting in isolation of over 9.5 g of material after chromatography, with no evidence of side products detected. The β-chloroacrylamides proved quite stable and easily stored, and in many instances are crystalline solids.



Side products. Dichloroacrylamide
103 R^1 = Me, R^2 = Me, R^3 = Ph
105 R^1 = Me, R^2 = Me, R^3 = 4-MeOC$_6$H$_4$
106 R^1 = Me, R^2 = Me, R^3 = Bn
107 R^1 = Bn, R^2 = H, R^3 = Me
109 R^1 = Bu, R^2 = H, R^3 = Me



Acrylamide
108 R^1 = Bn, R^2 = H, R^3 = Me
110 R^1 = Bu, R^2 = H, R^3 = Me



Trichloride
104 R^1 = Me, R^2 = Me, R^3 = Ph

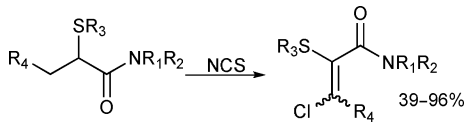
Process optimisation. Since the initial discovery of α-thio-β-chloroacrylamides, a considerable amount of research has been carried out to optimize their formation. Toluene has replaced carbon tetrachloride as the reaction solvent due to significantly shorter reaction times and for safety reasons. While the succinimide by-product is soluble in hot toluene, it was found that, as the reaction cooled, the by-product precipitated. Hence, almost all of the succinimide can be removed by cooling the reaction solution at 0 °C for 30 minutes followed by filtration. Originally, recrystallised *N*-chlorosuccinimide was employed but it was later demonstrated that there was no significant advantage in using this compared to unrecrystallised NCS, and commercial NCS is now routinely used without recrystallisation. The 'hot plunge' method has also proven more beneficial than heating the reaction solution from room temperature. Using this method, following NCS addition the reaction vessel is lowered into an oil bath which has been pre-heated to the desired temperature. The more rapid heating causes the reaction to cascade more efficiently through from the α-chlorosulfide to the acrylamide to the dichloride and ultimately to the β-chloroacrylamide. Heating the reaction solution from room temperature leads to slower transformation of the intermediates, which in turn leads to the formation of impurities.

The transformation from α-thioamide to β-chloroacrylamide was carried out using a range of amide and thiol groups. Initially, these transformations were carried out using 2.1–2.2 equivalents of NCS at 130 °C for 2 hours. On closer examination, it was found that impurities resulting from overchlorination were present in many of the reaction mixtures under these reaction conditions. These were identified as the trichloride (*e.g.*, **113**) and the dichloroacrylamide (*e.g.*, **114**) presumably formed by elimination of HCl from the trichloride. Having identified these impurities, prevention of their formation was attempted in two ways: decrease of the reaction temperature and reduction in the amount of NCS used in the reaction (Table 3). These optimization experiments were carried out using *N*-ethyl-2-(phenylthio)propanamide (**10**).

By reducing the reaction temperature, it was hoped that the rate of over-chlorination would be decreased. Reducing the reaction temperature from 130 to 90 °C (approximately the temperature to which an oil bath would have been heated in order to reflux carbon tetrachloride in the original experiments described above) gave promising results. The trichloride **113** comprised 55% of the product mixture, but it was not being transformed to the dichloroacrylamide **114**. The reaction time was next reduced from 13.5 to 4 hours. While this did not result in an improvement in product purity, it demonstrated that the reaction could be conducted over a shorter time period, whilst maintaining 100% conversion of the starting sulfide.

To date, all of the optimization studies had been conducted using 2.1–2.2 equivalents of NCS. The reaction mechanism indicates that just 2 equivalents of NCS are required for complete transformation. It was decided to reduce the quantity of NCS employed to a figure closer to this theoretically-required amount.

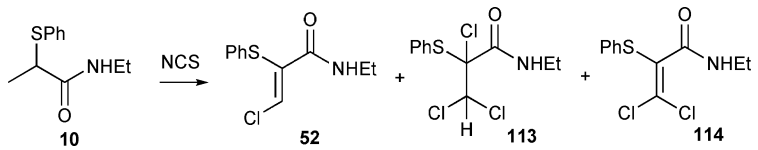
Table 2 Synthesis of the β-chloroacrylamides



Entry	Sulfide	R^1	R^2	R^3	R^4	*E*/*Z*	Method[a]	Product	Yield (%)[b]
1	**1**	*p*-Tol	H	Ph	H	*Z*	A	**3**	91
2	**9**	Bn	H	Ph	H	*Z*	A	**51**	81
3	**10**	Et	H	Ph	H	*Z*	A	**52**	81
4	**11**	*i*-Pr	H	Ph	H	*Z*	A	**53**	89
5	**12**	*n*-Bu	H	Ph	H	*Z*	A	**54**	81
6	**13**	Me	H	Ph	H	*Z*	A	**55**	69
7	**14**	Allyl	H	Ph	H	*Z*	A	**56**	84[c]
8	**15**	Cinnamyl	H	Ph	H	*Z*	B	**57**	67
9	**16**	4-FC_6H_4	H	Ph	H	*Z*	A	**58**	95
10	**17**	H	H	Ph	H	*Z*	A	**59**	46
11	**18**	Ph	Ph	Ph	H	*Z*	C	**60**	41[d]
						E		**61**	36[e]
12	**19**	Me	Me	Ph	H	*Z*	A	**62**	40[f]
						E		**63**	20
13	**20**	(±)-$CH(CH_3)Ph$	H	Ph	H	*Z*	B	**64**	65
14	**21**	(*S*)-$CH(CH_3)Ph$	H	Ph	H	*Z*	B	**65**	67
15	**22**	Bn	H	*n*-Bu	H	*Z*	D	**66**	84
16	**23**	*p*-Tol	H	*n*-Bu	H	*Z*	D	**67**	84
17	**24**	4-FC_6H_4	H	*n*-Bu	H	*Z*	D	**68**	96
18	**25**	*p*-Tol	H	4-$MeOC_6H_4$	H	*Z*	A	**69**	88
19	**26**	Bn	H	4-$MeOC_6H_4$	H	*Z*	E	**70**	64
20	**27**	Et	H	4-$MeOC_6H_4$	H	*Z*	A	**71**	59
21	**28**	Me	Me	4-$MeOC_6H_4$	H	*Z*	A	**72**	73[g]
						E		**73**	21
22	**29**	*p*-Tol	H	4-$NO_2C_6H_4$	H	*Z*	E	**74**	71[h]
23	**30**	*p*-Tol	H	*i*-Bu	H	*Z*	A	**75**	65
24	**31**	4-FC_6H_4	H	*i*-Bu	H	*Z*	A	**76**	64
25	**32**	Et	H	*i*-Bu	H	*Z*	A	**77**	70
26	**33**	4-FC_6H_4	H	*i*-Pr	H	*Z*	A	**78**	70
27	**34**	Bn	H	Bn	H	*Z*	A	**79**	79
28	**35**	4-FC_6H_4	H	Bn	H	*Z*	A	**80**	84
29	**36**	*n*-Bu	H	Bn	H	*Z*	A	**81**	58[n]
30	**37**	Me	Me	Bn	H	*Z*	A	**82**	42[i]
							E	**83**	17
31	**38**	*p*-Tol	H	Bn	H	*Z*	A	**84**	70
32	**39**	Me	H	Bn	H	*Z*	A	**85**	83[n]
33	**40**	Ph	H	Bn	H	*Z*	A	**86**	78
34	**41**	H	H	Bn	H	*Z*	A	**87**	51
35	**42**	4-FC_6H_4	H	Me	H	*Z*	F	**88**	61
36	**43**	Bn	H	Me	H	*Z*	F	**89**	68[j]
37	**44**	*n*-Bu	H	Me	H	*Z*	F	**90**	63[k]
38	**45**	*i*-Pr	H	Me	H	*Z*	F	**91**	60
39	**46**	*p*-Tol	H	Me	H	*Z*	F	**92**	60
40	**47**	*p*-Tol	H	Ph	Me	*Z*	B	**93**	27[l]
							E	**94**	19
41	**48**	*p*-Tol	H	Ph	Et	*Z*	B	**95**	13
							E	**96**	17
42	**49**	(*S*)-$CHCH_3Ph$	H	Ph	Et	*Z*	B	**97**	**27**
							E	**98**	13
43	**50**	*p*-Tol	H	Ph	Ph	*Z*	B	**99**	14[m]
							E	**100**	

[a] Method A: 1.95 equivalents NCS, toluene, 90 °C, 2–4 hours. Method B: 2.20 equivalents NCS, CCl_4, reflux, 18 hours. Method C: 2.10 equivalents NCS, toluene, 130 °C, 1.5 hours. Method D: 2.10 equivalents NCS, toluene, 120 °C, 2–3 hours. Method E: 2.20 equivalents NCS, toluene, reflux, 2.5 hours. Method F: 1.80 equivalents NCS, toluene, 90 °C, 2 hours. [b] Unless indicated otherwise, the yields quoted are after chromatography on silica gel. [c] A yield of 56% was obtained when the reaction was conducted in CCl_4. [d] The crude product was isolated as an equimolar mixture. The Z isomer contained ~10% of the *E*-isomer. [e] The *E*-isomer was isolated as a mixture (3 : 2) with the *Z*-isomer. [f] The *Z*-β-chloroacrylamide **62** was isolated as a 50 : 50 mixture with the dichloroacrylamide **103**. A sample of the trichloride **104** was also isolated from this reaction. This was also conducted in CCl_4—see Scheme 8. [g] The *Z*-β-chloroacrylamide **72** was contaminated with the chloroacrylamide **105** (6%). [h] **74** was purified by trituration with 5% diethyl ether in hexane. [i] The *Z*-β-chloroacrylamide **82** was contaminated with the dichloroacrylamide **106** (10%). [j] The crude product was composed of 75% **89**, 15% dichloroacrylamide **107** and 5% acrylamide **108**. [k] The crude product contained 76% **90**, 23% dichloroacrylamide **109** and 1% acrylamide **110**. [l] The acrylamide **111** and the trichloride **112** were also isolated from this reaction—see Table 7. [m] **99** and **100** were isolated as an equimolar mixture—see Scheme 10. [n] For the two benzylthio *N*-alkyl derivatives **81** and **85** ~20% of the *E*-isomer was detected in the product.

Table 3 Optimisation of transformation of α-thioamide **10** to β-chloroacrylamide **52**



10 **52** **113** **114**

				Crude product ratios[a]		
NCS/eq.	Solvent	Temperature/°C	Time/h	**52** (%)	**113** (%)	**114** (%)
2.2	CCl_4	Δ	16	53	27	7
2.2	Toluene	90	13.5	45	55	N.d.[b]
2.2	Toluene	90	4	59	35	6
2.05	Toluene	90	2	81	19	N.d.
1.95	Toluene	90	2	>98	N.d.	N.d.

[a] Crude product ratios as determined by ^{1}H NMR spectroscopy. [b] N.d. = not detected by ^{1}H NMR spectroscopy.

Based on the previous temperature optimization experiments, the reaction was attempted using 2.05 equivalents of NCS at 90 °C for 2 hours. At this stage the β-chloroacrylamide **52** was formed in a 4 : 1 ratio with the trichloride **113**, the best result obtained at this stage.

Although lowering the reaction temperature had improved the selectivity, it now seemed that the selective formation of the β-chloroacrylamide was more dependant on the amount of NCS used in the reaction than on any other factor. It was therefore decided to attempt the reaction using a slightly lower amount of NCS than is theoretically required. The transformation was thus attempted using 1.95 equivalents of NCS at 90 °C for 2 hours. When these reaction conditions were employed, the ^{1}H NMR spectrum of the crude product showed no evidence of any impurities.

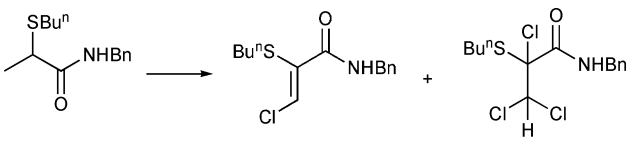
It has since been demonstrated that, for the transformation of phenylthioamides, isobutylthioamides, 4-methoxybenzenethioamides and benzylthioamides to their corresponding β-chloroacrylamides, 1.95 equivalents of NCS in toluene at 90 °C for 2 hours results in the most efficient conversion. Table 2 summarises these results.

α-Butanethio-derived β-chloroacrylamides. When the preparation of the β-chloroacrylamides of the *n*-butanethiol-derived sulfides was attempted using the conditions described above, a small, but appreciable, amount of the corresponding trichlorides formed in each case, and therefore these transformations required further optimization (Table 4).

Four reactions were conducted in toluene with the *N*-benzyl derivative **22**, two using 1.95 equivalents of NCS and two using 2.1 equivalents of NCS. One of each was lowered into an oil bath at 90 °C and one into an oil bath at 120 °C, and each reaction was heated for 2 hours. It was found that the harsher conditions gave the better results. Increasing the reaction temperature to 120 °C resulted in a decrease in the amount of trichloride **115** formed only when 2.1 equivalents of NCS were employed. Thus, 2.1 equivalents of NCS in toluene at 120 °C for 2 hours are the conditions routinely employed for conversion of the butylthioamides to the corresponding β-chloroacrylamide.

α-Methanethio-derived- β-chloroacrylamides. The transformation of the methylthioamide derivatives **42** and **46** to their corresponding β-chloroacrylamides using 1.95 equivalents of NCS in toluene at 90 °C for 2 hours led to the formation of a significant amount of the dichloroacrylamide (Table 5).

Table 4 Optimisation of transformation of α-thioamide **22** to β-chloroacrylamide **66**



22 **66** **115**

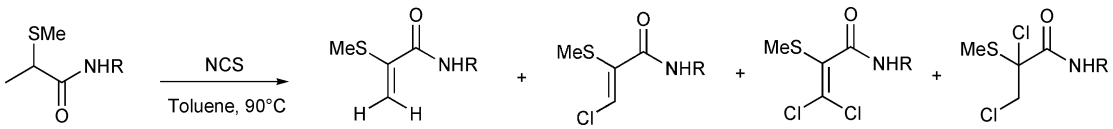
		Crude product ratios[a]	
NCS/eq.	Temperature/°C	**106** (%)	**150** (%)
1.95	90	95	5
2.1	90	93	7
1.95	120	94	6
2.1	120	97	3

[a] Crude product ratios as determined by ^{1}H NMR spectroscopy.

As the dichloroacrylamide is a product which results from overchlorination, the optimization of this transformation was attempted by reducing the number of equivalents of NCS. For the *N*-4-FC_6H_4 derivative **42**, reducing the amount of NCS to 1.8 equivalents produced 74% of the β-chloroacrylamide **88**, 20% of the dichloroacrylamide **117** and 5% of the acrylamide **116**, an under-chlorination product. On decreasing the amount of NCS further to 1.7 equivalents, 20% of the acrylamide **116** as well as 13% of the dichloroacrylamide **117** were produced. The dichloride **118** was not detected in these experiments. On the basis of these results, the optimum conditions for the formation of the β-chloroacrylamides of the *S*-methyl derivatives are the use of 1.8 equivalents of NCS in toluene at 90 °C for 2 hours.

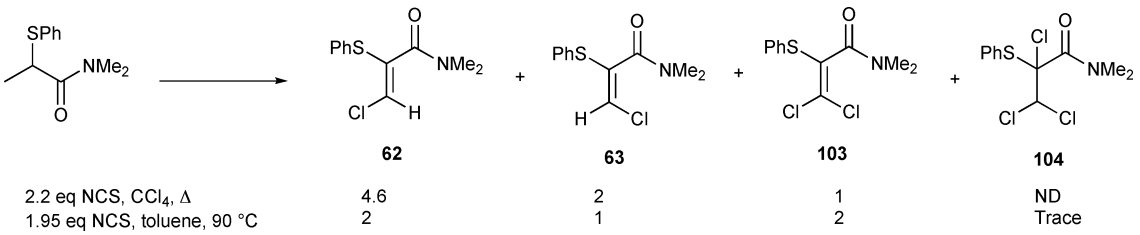
Tertiary β-chloroacrylamides. In earlier work, the preparation of the β-chloroacrylamides of the tertiary amides, in which 2.1 equivalents of NCS in CCl_4 at reflux were the conditions employed, generally resulted in the formation of both the *E*- and *Z*- β-chloroacrylamides and the dichloroacrylamide. For example, for the *N*,*N*-dimethylphenylthio derivative (entry 12, Table 2), typical

Table 5 Transformation of methylthioamides **42** and **46** to β-chloroacrylamides **88** and **92**



		Crude product ratios[b]		
R[a]	NCS/eq.	Acrylamide (%)	β-Chloroacrylamide (%)	Dichloroacrylamide (%)
Tol	1.95	0	71	29
4-FC_6H_4	1.95	0	52	48
4-FC_6H_4	1.8	5	74	20
4-FC_6H_4	1.7	20	67	13

[a] R = Tol for **46**, **92** and **119**. R = 4-FC_6H_4 for **42**, **88**, **116**, **117** and **118**. [b] Crude product ratios as determined by ^{1}H NMR spectroscopy.



Scheme 8

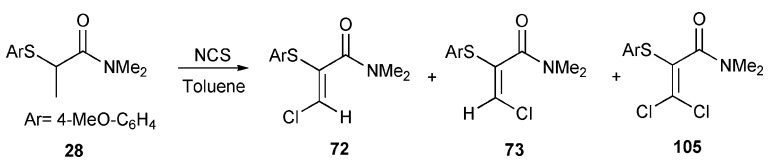
ratios of **62** : **63** : **103** were on the order of 4.6 : 2 : 1 (Scheme 8). While separation of the β-chloroacrylamides is possible by chromatography on silica gel, the dichloroacrylamide **103** elutes with the major *Z*-β-chloroacrylamide **62**. In view of the results of the optimization experiments on the other β-chloroacrylamides, the possibility of reducing the amount of dichloroacrylamide contaminant by adjusting the reaction parameters was explored.

The transformation of *N*,*N*-dimethyl-2-(4′-methoxybenzenethio)propanamide **28** to the corresponding *Z*- and *E*-β-chloroacrylamides **72** and **73** (entry 21, Table 2) was conducted under a variety of conditions as shown in Table 6. The reactions were carried out in toluene for 2 hours, the amount of NCS was varied from 1.95 to 2.2 equivalents and the temperature varied from 90 to 120 °C.

The best results were obtained using 1.95 equivalents of NCS at 90 °C. On repeating this experiment on a 12 mmol scale, a small amount (6%) of the dichloroacrylamide **105** was present in the *Z*-chloroacrylamide **72** following chromatography. Regardless of the conditions employed, the minor *E*-β-chloroacrylamide formed in approximately 20% yield, suggesting that the dichloroacrylamide is formed selectively from the *Z*-chloroacrylamide **72**.

Extended chain β-chloroacrylamides. Treatment of the butanamide **47** and the pentamide **48** with 2.1 equivalents of NCS in carbon tetrachloride at reflux resulted in the formation of the *E*- and *Z*-isomers of the β-chloroacrylamides and their corresponding acrylamides (Table 7 & entries 40 and 41, Table 2). On replacing carbon tetrachloride with toluene at reflux, the β-chloroacrylamides were formed in elevated yields and transformation

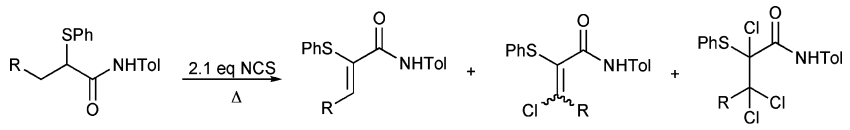
Table 6 Optimisation of transformation of α-thioamide **28** to β-chloroacrylamides **72** and **73**



			Crude product ratios[a]			
NCS/eq.	Temperature/°C	Time/h	**72** (%)	**73** (%)	**105** (%)	Ratio of β-Cls[a]
2.2	90	2	60	20	20	3.0 : 1
1.95	90	2	78	22	N.d.	3.5 : 1
2.2	120	2	61	21	18	2.6 : 1
1.95	120	2	74	18	8	4.0 : 1

[a] As estimated from the ^{1}H NMR spectra of the crude reaction products.

Table 7 Treatment of **47** and **48** with NCS



R=Me **47**
R=Et **48**

111 **122** **Z-93, E-94** **Z-95, E-96** **112** **121**

		Crude product ratios[a]		
R	Solvent[b]	Acrylamide (%)	β-Chloroacrylamides *E* : *Z* (%)	Trichloride (%)
Me	CCl_4	20	19 : 27	—
Me	Toluene	—	41 : 23	9
Et	CCl_4	54	17 : 13	—
Et	Toluene	10	20 : 47	10

[a] Crude product ratios as determined by ^{1}H NMR spectroscopy. [b] All reactions were conducted under reflux conditions.

of the acrylamides was improved—for the butanamide **47** no butenamide was detected in the product mixture and for the pentamide **48** the amount of pentenamide in the product mixture decreased significantly from 54 to 10%. However, products resulting from overchlorination, trichlorobutanamide **112** and trichloropentanamide **121** were isolated from both reactions in toluene. It is interesting to note that the major isomer isolated changed when carbon tetrachloride or toluene was used as solvent.

During the chromatographic purification of a reaction mixture, obtained from the treatment of pentanamide **48** with 2.1 equivalents of NCS in carbon tetrachloride, interesting gelation properties were observed with the *Z*-isomer **95**—the test tubes in which **95** was collected from the column in ethyl acetate–hexane contained gels, so that the test tubes could be turned upside down without loss, and indeed, DCM had to be added to get the gels out of the test tubes as they were not mobile. To illustrate this, the amount of **95** in one test tube was quantified—a sample of just 86 mg of **95** in 9.5 ml of ethyl acetate–hexane formed a firm gel. There has been considerable interest in the literature in gelation of organic solvents by small molecules.[13,14]

Treatment of (*S*)-pentanamide **49** (as an equimolar mixture of diastereomers) with NCS for 18 hours in carbon tetrachloride led to isolation of the *Z*- and *E*-β-chloroacrylamides **97** and **98** in yields of 27 and 13%, respectively (Scheme 9 and entry 42, Table 2). There was no evidence by ^{1}H NMR spectroscopy of the acrylamide derivative in the crude product mixture.

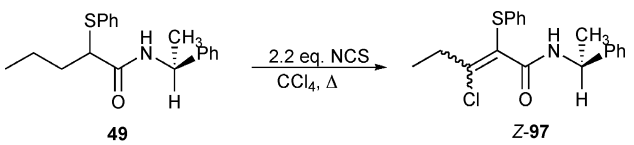
Treatment of **50** with 2.1 equivalents of NCS in carbon tetrachloride at reflux led to a mixture of four products (Scheme 10 and entry 43, Table 2).

Complete separation of the four products by chromatographic purification was not possible, **99** and **100** were isolated as an inseparable mixture in a combined yield of 14%. The intermediate acrylamide **123** formed as a single (*Z*)-isomer in 49% yield. A fourth compound tentatively assigned as *N*-tolyl-α-chloro-β-phenylpropenamide **113** was isolated as a low melting solid in 8% yield. The formation of this acrylamide is believed to occur by elimination of thiophenol from the intermediate α-chlorosulfide.

The diastereomeric propanamides **20-R*R*/R*S*** were separated chromatographically and treated individually with 2.2 equivalents of NCS in carbon tetrachloride under reflux conditions, in both cases the same β-chloroacrylamide **64** formed in addition to the acrylamide **124**. The reaction with **20-R*R*** gave **64** in higher yield (65%) than the corresponding reaction with **20-R*S***, which produced **64** in 19% yield (Table 8).

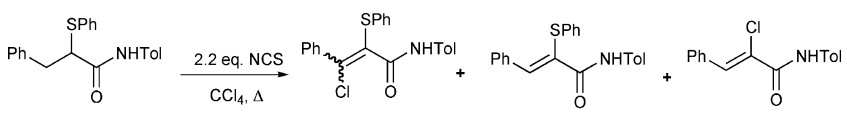
The reaction of **21**, which was an equimolar mixture of diastereomers, with 2.2 equivalents of NCS in carbon tetrachloride under reflux conditions was also carried out. The enantioenriched β-chloroacrylamide **65** and acrylamide **125** were isolated in yields of 67 and 15%, respectively (Table 8). As racemisation was not envisaged, no attempt was made to establish the enantiopurity.

The relative stereochemistry of the diastereomeric propanamides **20-R*R*/R*S***, as observed from the X-ray crystal structure (Fig. 1), allows some insight into the differences in efficiency of transformation of the diastereomeric sulfides. In **20-R*R***, the aromatic rings of the sulfide and amide groups are staggered and therefore the initial chlorination of the sulfur is



49 *Z*-**97** *E*-**98**

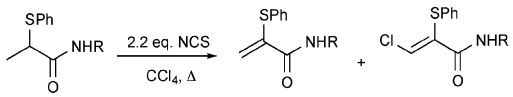
Scheme 9



50 *Z*-**99** *E*-**100** **14%** **123** **49%** **113** **8%**

Scheme 10

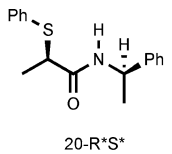
Table 8 Treatment of **20** and **21** with NCS



R= (±)-CH(CH3)Ph **20** **124** **64**
R= (S)-CH(CH3)Ph **21** **125** **65**

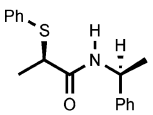
α-Thioamide	R	Acrylamide (%)[a]	β-Chloroacrylamide (%)[a]
20-R*R*	(±)-CH(CH$_3$)Ph	24	65
20-R*S*	(±)-CH(CH$_3$)Ph	20	19
21[b]	(*S*)-CH(CH$_3$)Ph	15	67

[a] Isolated yields following purification by column chromatography. [b] This compound exists as a mixture of diasteromers at C-2; the enantiopure amine was employed.



20-R*S*

Crystal structure 1



20-R*R*

Crystal structure 2

Fig. 1

easier than in the case of **20-R*S*** where the substituents are closer together.

Stereochemistry

The β-chloroacrylamides are formed, in most cases exclusively, as the *Z*-stereoisomers (Table 2). Single crystal X-ray crystallography confirmed the *Z*-stereochemistry of the *N*-benzyl derivative **51**[3] and the stereochemistry of the other derivatives is assigned by comparison. Notably, the signal for the β-H in the NMR spectra of the chloroacrylamides is very distinctive; in cases where both the *E*- and *Z*- isomers are formed this signal differs significantly as illustrated in Fig. 2. Exceptionally, for the two benzylthio *N*-alkyl derivatives **81** and **85** ~20% of the *E*-isomer was detected in the product.

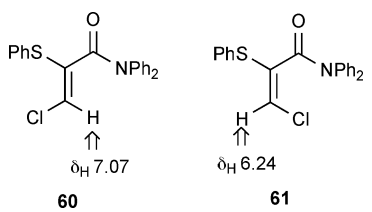
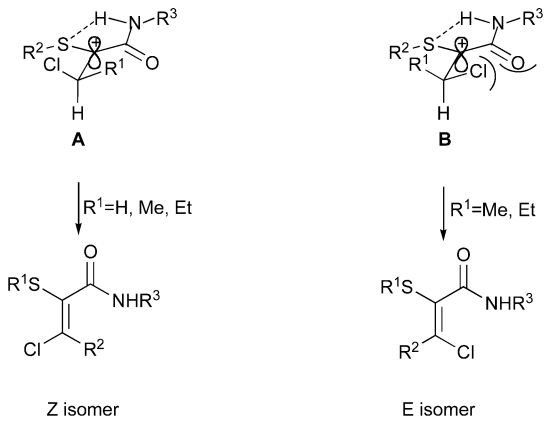


Fig. 2

The stereochemical outcome of the transformation is determined in the final deprotonation step. The planar sulfur-stabilised carbocation intermediate is held in the conformation illustrated in Scheme 11 by the intramolecular hydrogen bond between the amide and the sulfide. Loss of the β-proton must occur coplanar with the vacant orbital, *i.e.*, through either of the two conformations **A** and **B**, shown in Scheme 11. Steric repulsion between the amide carbonyl and the chloro substituent disfavour conformation **B** and, therefore, elimination occurs exclusively through conformation **A**, providing the *Z*-stereoisomer of the β-chloroacrylamides.



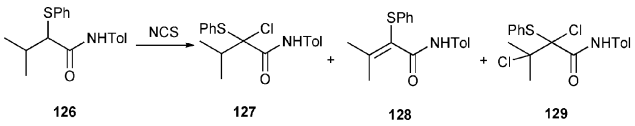
Scheme 11

With the tertiary amides and the extended chain derivatives, formation of both *E*- and *Z*-stereoisomers (**60**–**63**, **72**–**73**, **82**–**83**, **93**–**94**, **95**–**96**, **97**–**100**) is observed. For the tertiary amides, the conformation of the intermediate carbocation is different, as intramolecular hydrogen bonding is not possible and, therefore, deprotonation to form either the *E*- or *Z*-isomer is possible. In the case of the extended-chain derivatives, the energetic difference between the two conformations **A** and **B** is less, as the steric demands of an alkyl group and a chloro substitutent are rather similar, and therefore elimination through both conformations can occur.

Treatment of a β-disubstituted propanamide with NCS

Having investigated the reaction of α-thio-*n*-alkanamides with NCS in detail, we were interested to determine the effect of β-branching on the transformation. The reaction of the β-methylbutanamide **126** with NCS was thus conducted under a variety of conditions. The reactions were carried out using either toluene

Table 9 Treatment of **126** with NCS



NCS/eq.	Solvent	Temperature/°C	Time/h	Crude ratio of products[a] 156	157	158
1	CCl_4	0	4	—	—	—
1	CCl_4	20	4	2	1	1
1	Toluene	20	4	4	3	2
2.1	Toluene	20	24	Trace	2	1
2.1	CCl_4	20	24	—	—	1
2.1	Toluene	130	1	—	—	1

[a] Crude product ratios as determined by ^{1}H NMR spectroscopy.

or carbon tetrachloride as solvent, the temperature varied from 0 to 130 °C, the reaction time from 1 to 24 hours and the number of equivalents of NCS from 1 to 2.1. The results are summarised in Table 9. Evidently, elimination to form a β-chloroacrylamide is not possible in this instance due to the β-branching.

Analysis of these results show interesting comparisons to those obtained on treatment of *N*-tolyl-α-(phenylthio)propenamide **1** with NCS as illustrated in Table 1.

At 0 °C using 1 equivalent of NCS, chlorination of **1** to form **2** readily occurred whereas chlorination of sulfide **126** occurred at room temperature only. In contrast to the reaction of **1** with 1 equivalent of NCS at 20 °C, where only acrylamide **6** and α-chlorosulfide **2** were formed, some dichloride **129** was also detected in addition to **127** and **128** in the reaction of **126** under the same conditions.

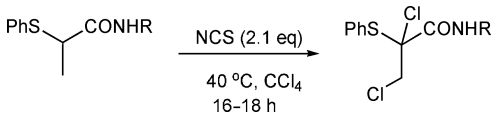
It can be seen from the results in Table 9 that the use of carbon tetrachloride results in more efficient transformation of **126** than the use of toluene. Under identical conditions, with the exception of solvent, incomplete transformation to the dichloride **129** was observed in toluene at room temperature in 24 h, while use of carbon tetrachloride led to **129**, essentially exclusively. Furthermore, use of 1 equivalent of NCS in toluene gave a lower ratio of dichloride **129** to acrylamide **128**. However, in refluxing toluene and at room temperature in carbon tetrachloride, the transformation to **129** was essentially quantitative, 80% (following purification by chromatography) in toluene and 90% in carbon tetrachloride as estimated by ^{1}H NMR spectroscopy.

Zinc chloride catalysed transformation of dichlorides

As mentioned earlier, during studies to establish the reaction mechanism, the dichloride **7** was treated with anhydrous zinc chloride in DCM and nitromethane at 20 °C. Two products resulted: the β-chloroacrylamide **3** and *N*-tolyl-2,3-di(phenylthio)propenamide **8** (which is presumably formed by nucleophilic substitution of the chloride of **3** by thiophenol formed by decomposition of the dichloride, Scheme 3).

A brief study on the formation of a number of dichlorides was conducted. This involved the preparation of dichlorides **130** and **131** by treatment of **11** and **14** with 2.2 equivalents of NCS

Table 10 Synthesis of dichlorides

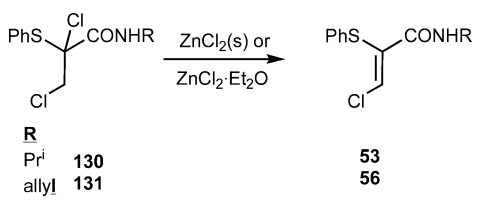


R	Dichloride	Yield (%)
Tol	**7**	75
Bn	**101**	46[a]
i-Pr	**130**	50
Allyl	**131**	45

[a] Isolated yield following purification by column chromatography.

at 40 °C for 16 hours (Table 10). These dichlorides were each formed as mixtures with the respective β-chloroacrylamide and/or acrylamide, and purification by column chromatography was not possible as decomposition to the β-chloroacrylamide occurred on exposure to silica gel. As mentioned earlier, the *N*-benzyl derivative **101** could be purified chromatographically, but this was an exception. The dichlorides were very easily characterised due to a distinctive AB quartet in the ^{1}H NMR spectra at 3.5–4.5 ppm for the methylene protons.

Investigation of Lewis acid-catalysed decomposition of **130** & **131** was undertaken. In particular, we wished to establish if elimination of HCl would be highly stereoselective producing only the *Z*-isomer or, if a mixture of *E*/*Z*-β-chloroacrylamides would be obtained. Treatment of **130** & **131** (crude products containing *ca.* 50% of **130** or **131** in addition to the respective β-chloroacrylamide and/or acrylamide) with zinc chloride, either anhydrous or as a dichloromethane solution of the etherate, led to elimination to the analogous β-chloroacrylamide **53**, **56**—in each case stereospecifically *Z* (Scheme 12). 1.5 Equivalents of either solid zinc chloride or zinc chloride etherate were used. However, in practice, use of the zinc chloride etherate was more convenient.



Scheme 12

Treatment of the dichloride **7** with a range of reagents was briefly explored: **7** (~90% pure) was treated with 1.5 equivalents triethylamine, methylaluminium chloride, *p*-toluenesulfonic acid and 1 equivalent hydrochloric acid (0.1 M) individually at room temperature for 20–24 h in DCM (Table 11). None of these reagents brought about any significant transformation of the dichloride **7** which was recovered in 70–80% yield as estimated by ^{1}H NMR integration.

Conclusion

The β-chloro-α-thioacrylamides (**3**, **51**–**100**) prepared in this work are novel compounds and offer interesting synthetic potential,

Table 11

Reagents	Equivalents	**7** (% yield)	**6** (% yield)
$ZnCl_2$ (s)	1.5	28	5
$ZnCl_2 \cdot Et_2O$	1.5	22	4
$MeAlCl_2$	1.5	No reaction	
TsOH	1.5	No reaction	
HCl	1.0	No reaction	

for example as Michael acceptors or dienophiles. The ease and stereoselectivity of the transformation on exposure to NCS, broad scope in terms of the nature of the substituents, and amenability to production of multigram quantities of the highly-functionalised β-chloro-α-thioacrylamides are particularly significant.

Experimental

All solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide and ethyl acetate was distilled from potassium carbonate, ethanol and methanol were distilled from magnesium in the presence of iodine. Acetone was distilled from potassium permanganate and toluene was distilled from sodium and stored over 4 Å molecular sieves. Dimethylformamide was stored overnight over calcium hydride, then distilled and stored over 4 Å molecular sieves. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents, including *N*-chlorosuccinimide, were used without further purification.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker (300 MHz) NMR spectrometer. ^{1}H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a Jeol GSX (270 MHz) NMR spectrometer. ^{1}H (60 MHz) NMR spectra were recorded on a Jeol PMX-60SI 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. Chemical shifts were expressed in parts per million (ppm) and coupling constants in Hertz (Hz).

Elemental analyses were performed by the Microanalysis Laboratory, National University of Ireland, Cork, using a Perkin-Elmer 240 elemental analyzer. Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus. Mass spectra were recorded on a Kratos Profile HV-4 double focusing high resolution mass spectrometer (EI), a Waters/Micromass LCT Premier Time of Flight spectrometer (ESI) and a Waters/Micromass Quattro Micro triple quadrupole spectrometer (ESI). Infrared spectra were recorded as potassium bromide (KBr) discs for solids or thin films on sodium chloride plates for oils on a Perkin-Elmer Paragon 1000 FT-IR spectrometer.

Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Column chromatography was performed using Merck silica gel 60. Visualisation was achieved by UV (254 nm) light detection, iodine staining, vanillin staining and ceric sulfate staining.

Selected experimental data, including representatives of each of the synthetic methods, are given below—full experimental procedures and spectral data for all compounds described in the paper are given in the ESI.†

X-Ray crystal determination of 20-R*R* and 20-R*S*

The structures were determined using data collected with an Enraf Nonius CAD4 diffractometer (graphite monochromator, Mo Kα radiation $\lambda = 0.71073$ Å). Crystal data for **20-R*R***: $C_{17}H_{19}NOS$, crystal dimensions 0.40 × 0.15 × 0.15 mm, orthorhombic, space group $Pca2_1$ chosen and confirmed by the successful refinement, $a = 8.1168(11)$, $b = 18.618(5)$, $c = 10.168(2)$ Å, $V = 1536.5(6)$ Å^3, $M_r = 285.40$, $Z = 4$, $D_c = 1.234$ g cm^{-3}, μ (Mo Kα) = 0.20 mm^{-1}, $F(000) = 608$, $S = 1.009$, $R_1 = 0.0827$ (for 973 observed reflections), $wR2 = 0.2278$ for all 1771 unique reflections. Crystal data for **20-R*S***: $C_{17}H_{19}NOS$, crystal dimension 0.40 × 0.40 × 0.20 mm, monoclinic, space group Cc chosen and confirmed by the successful refinement, $a = 12.848(3)$, $b = 13.3462(13)$, $c = 18.932(4)$ Å, $\beta = 103.94(2)°$, $V = 3175.5(11)$ Å^3, $M_r = 285.40$, $Z = 4$, $D_c = 1.194$ g cm^{-3}, μ (Mo Kα) = 0.19 mm^{-1}, $F(000) = 1216$, $S = 1.004$, $R_1 = 0.0399$ (for 1969 observed reflections), $wR_2 = 0.0891$ for all 3597 unique reflections.‡

The crystals were of rather poor quality and, although some diffraction peaks were not well defined, the reflection/parameter ratios were still greater than 9 and the analyses established the relative stereochemistries unequivocally.

Intermediates in the synthesis of *N*-4′-methylphenyl-3-chloro-2-phenylthiopropenamide (6)

***N*-4′-Methylphenyl-2-chloro-2-(phenylthio)propanamide (2).** A solution of *N*-4′-methylphenyl-2-(phenylthio)propanamide **1** (100 mg, 0.37 mmol) in carbon tetrachloride (2 ml) at 0 °C was stirred. NCS (54 mg, 0.41 mmol) was added and the stirring was continued for a further 3 h at 0 °C. Filtration to remove the succinimide by-product gave a solution of α-chlorosulfide **2** in carbon tetrachloride. The transformation was quantitative, δ_H (CCl_4) (60 MHz) 2.11 [3 H, s, C(3)H_3], 2.37 (3 H, s, ArCH_3), 6.83–7.83 (9 H, m, ArH). This compound is very labile (see below).

***N*-4′-Methylphenyl-2-(phenylthio)propenamide (6).** A solution of the α-thioamide **1** (100 mg, 0.37 mmol) in carbon tetrachloride (2 ml) was stirred at room temperature, NCS (54 mg, 0.41 mmol) was added in one portion and stirring was continued for 24 h. Filtration and evaporation of the solvent gave the crude product which was an equimolar mixture of **2** and **6**. After 24 h standing neat at room temperature the α-chlorosulfide **2** had almost entirely decomposed to **6**. Purification by chromatography using ethyl acetate–hexane (5 : 95) as eluent gave the acrylamide **6** (39 mg, 39%) as a white, crystalline solid, mp 137–139 °C; (found C, 71.02; H, 5.66; N, 5.27. $C_{16}H_{15}NOS$ requires C, 71.34; H, 5.61; N, 5.20%); ν_{max}/cm^{-1} (KBr) 3344 (br, NH), 1665 (CO), 1592; δ_H (270 MHz) 2.28 (3 H, s, ArCH_3), 6.08, 6.83 (2 × 1 H, 2 × br s, CH_2=), 7.02–7.61 (9 H, m, ArH), 8.52 (1 H, br s, NH); δ_C (67.8 MHz) 20.87 (ArCH$_3$), 119.92, 127.60, 129.19, 129.63 (aromatic CH), 132.6 (CH$_2$=), 133.52, 134.81, 135.06, 136.25 (quaternary aromatic C and [C(2)S], 161.49 (CO); m/z 269 (M$^+$, 100%), 160 (37), 135 (68), 120 (51), 91(56).

***N*-4′-Methylphenyl-2,3-dichloro-2-(phenylthio)propanamide (7).** A solution of the sulfide **1** (0.40 g, 1.46 mmol) in carbon tetrachloride was stirred under nitrogen at room temperature. NCS

‡ CCDC reference numbers 630666 and 630667. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b618540a

(0.43 g, 3.2 mmol) was added in one portion and the mixture was stirred for 10 min at room temperature then heated to 40 °C and stirred at this temperature for 17 h. Filtration and evaporation of the solvent from the filtrate gave the crude product which by ^{1}H NMR was at least 75% dichloride **7** containing a minor amount of **3**. Slow decomposition to **3** was observed on standing (35% of **7** had been transformed to **3** after 10 days at −20 °C) or on stirring in DCM with silica (36% of **7** had been transformed to **3** after 22 h). The dichloride **7** was characterised as a mixture with **3**: δ_H (270 MHz) 2.32 (3 H, s, ArCH_3), 3.94–4.48 (2 H, ABq, *J* 11, CH_2), 7.03–7.69 (9H, m, Ar*H*), 8.08 (1 H, br s, N*H*). Characteristic signals for the β-chloroacrylamide **3** were also present.

***N*-Benzyl-2,3-dichloro-2-phenylthiopropanamide (101).** This was prepared following the procedure described for the preparation of dichloride **7** using *N*-benzyl-2-(phenylthio)-propanamide **9** (0.15 g, 0.55 mmol), NCS (0.16 g, 1.22 mmol) and carbon tetrachloride (4 ml) and a reaction time of 16 h to give a reaction mixture containing dichloride **101** (0.12 g) as an off-white solid. Purification by chromatography using ethyl acetate–hexane (5 : 95) as eluent gave the dichloride **101** (86 mg, 46%) as a white, crystalline solid, mp 93–94 °C; (found C, 56.32; H, 4.39; N, 4.50; S, 9.71. $C_{16}H_{15}Cl_2NOS$ requires C, 56.48; H, 4.44; N, 4.12; S, 9.42%); ν_{max}/cm^{-1} (KBr) 3368 (br NH), 1667 (CO amide); δ_H (270 MHz) 3.88–4.45 (2 H, ABq, *J* 12, CH_2Cl), 7.13–7.63 (11 H, m, Ar*H* and N*H*); δ_C (67.8 MHz) 44.63 (N*C*H$_2$), 50.52 (*C*H$_2$Cl), 81.50 [*C*(2)Cl], 127.76, 128.02, 128.64, 129.18, 130.85 (aromatic *C*H), 136.84 (quaternary aromatic *C*), 137.39 (aromatic *C*H), 139.63 (quaternary aromatic *C*), 164.88 (*C*O); *m*/*z* 339 (M$^+$, 18%), 269 (100, M$^+$-2Cl).

Lewis acid mediated decomposition of dichloride 7

$ZnCl_2$ treatment of *N*-4′-methylphenyl-2,3-dichloro-2-(phenylthio)propanamide (7). A sample of dichloride **7** (2.70 g, 8.0 mmol) was freshly prepared by stirring *N*-4′-methylphenyl-2-(phenylthio)propanamide **1** (1.89 g, 7.0 mmol) with NCS (1.95 g, 14.6 mmol) in toluene (40 ml) at 40 °C for 22 h followed by filtration of the succinimide by-product and evaporation of the filtrate. This sample, which was 90% pure by ^{1}H NMR, was dissolved in DCM (13 ml) and nitromethane (9 ml). Zinc chloride (oven dried) (3.25 g, 23.9 mmol) was added and the solution was stirred at RT for 20 h. Water (20 ml) and DCM (20 ml) were added and the phases were separated. The aqueous phase was extracted with DCM (2 × 10 ml) and the combined organic layers were washed with brine (3 × 10 ml), dried and evaporated. Purification by chromatography using ethyl acetate–hexane (5 : 95) as eluent gave the *Z*-β-chloroacrylamide **3** (0.59 g, 28%) as a white, crystalline solid (spectral characteristics were identical to those described earlier) and *N*-4′-methylphenyl-2,3-di(phenylthio)propenamide (**8**, 138 mg, 5%) as a white, crystalline solid, mp 109–110 °C; (found C, 70.03; H, 5.06; N, 3.78; S, 16.54. $C_{22}H_{19}NOS_2$ requires C, 70.00; H, 5.07; N, 3.76; S, 16.99%); ν_{max}/cm^{-1} (KBr) 3255 (br NH), 1640 (CO), 1592; δ_H (270 MHz) 2.28 (3H, s, ArCH_3), 7.07–7.55 (14H, m, Ar*H*), 8.69 [1H, s, C(3)*H*=], 8.74 (1H, br s, N*H*); δ_C (67.8 MHz) 20.85 (Ar*C*H$_3$), 115.00 [*C*(2)S], 119.94, 126.55, 127.25, 129.05, 129.45, 131.05 (aromatic *C*H), 133.28, 133.30, 134.13, 135.17 (quaternary aromatic *C*), 156.00 [*C*(3)H=], 160.86 (*C*O); *m*/*z* 378 (M$^+$, 100%), 268 (45, M$^+$-PhSH), 165 (75), 134 (84, [PhS=C=CH]$^+$.

Preparation of β-chloroacrylamides

***N*-4′-Methylphenyl-*Z*-3-chloro-2-(phenylthio)propenamide (3).**

Method A. Unrecrystallised NCS (5.57 g, 41.73 mmol) was added in one portion to a solution of the sulfide **1** (5.80 g, 21.40 mmol) in toluene (116 ml). The flask was immediately immersed in an oil bath at 90 °C and heating was maintained for 3.5 h with stirring. The reaction mixture was cooled to 0 °C and the succinimide by-product removed by filtration. The solvent was evaporated at reduced pressure to give the β-chloroacrylamide **3** as an off-white solid. The crude product was purified by chromatography on silica gel using ethyl acetate–hexane (20 : 80) as eluent to give the β-chloroacrylamide **3** as a colourless solid (5.93 g, 91%), mp 110–111 °C; (found C, 63.34, H, 4.69; Cl, 11.98; N, 4.34; S, 10.24. $C_{16}H_{14}ClNOS$ requires C, 63.26; H, 4.64; Cl, 11.67; N, 4.61; S, 10.55%); ν_{max}/cm^{-1} (KBr) 3336 (b, NH), 1653 (CO), 1523, 817; δ_H (270 MHz) 2.28 (3H, s, ArCH_3), 7.04–7.45 (9 H, m, Ar*H*), 8.05 [1H, s, C(3)*H*Cl=], 8.63 (1H, b s, N*H*); δ_C (67.8 MHz) 20.8 (Ar*C*H$_3$), 120.3, 127.4, 128.3, 129.5, 129.6 (aromatic *C*H), 130.9, 132.6, 134.5, 134.7 [quaternary aromatic *C* or *C*(2)S], 140.3 [*C*(3)HCl=], 160.3 (*C*O). *m*/*z* 303 (M$^+$, 42%), 267 (30, M$^+$ −Cl), 159 (23), 134 (100, [PhS=C=CH]$^+$), 106 (21), 77 (18, Ph).

***N*-3′-Phenylpropenyl-*Z*-3-chloro-2-(phenylthio)propanamide (57).**

Method B. A solution of the sulfide **15** (0.51 g, 1.7 mmol) in carbon tetrachloride (10 ml) was stirred at room temperature under nitrogen, NCS (0.50 g, 3.7 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 10 min then heated to reflux for 18 h. The reaction mixture was cooled, filtered and concentrated to give the β-chloroacrylamide **57**. Purification by chromatography using ethyl acetate–hexane (10 : 90) as eluent gave **57** (0.37 g, 67%) as a colourless oil, ν_{max}/cm^{-1} (neat) 3384 (br NH), 1651 (CO α, β-unsaturated amide); δ_H (270 MHz) 3.97–4.03 [2H, m, C(1′)H_2], 5.86–5.97 [1H, dt, *J* 16, 6, C(2′)*H*], 6.27 [1H, dd, *J* 16, < 1, C(3′)*H*], 6.98 (1H, br s, N*H*), 7.18–7.42 (10H, m, Ar*H*), 7.96 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 41.9 [*C*(1′)H$_2$], 124.6, 126.46, 127.1, 127.4, 128.18, 128.5, 129.5 (aromatic *C*H or *C*H=*C*H), 130.4 [quaternary aromatic *C* or *C*(2)S], 132.1 (aromatic *C*H or *C*H=*C*H), 132.9, 136.4 [quaternary aromatic *C* or *C*(2)S], 139.6 [C(3)HCl=], 162.2 (*C*O); *m*/*z* 329 (M$^+$, 28%), 294 (52, M$^+$−Cl), 184 (69), 134 (100, [PhS=C=CH]$^+$).

***N*,*N*-Diphenyl-*Z*-3-chloro-2-(phenylthio)propenamide (60) and *N*,*N*-diphenyl-*E*-3-chloro-2-(phenylthio)propenamide (61).**

Method C. NCS (1.69 g, 12.0 mmol) was added in one portion to a solution of sulfide **18** (2.00 g, 6 mmol) in toluene (40 ml). The flask was immediately immersed in an oil bath at 130 °C and heating at reflux was maintained for 1.5 h while stirring. The reaction mixture was cooled to 0 °C, the succinimide by-product was removed by filtration and the solvent was evaporated under reduced pressure to give a crude reaction mixture (close to quantitative) of *E*- and *Z*-β-chloroacrylamides (equimolar mixture). Purification by repeated chromatography was possible using DCM–hexane (50 : 50) to elute the less-polar *N*,*N*-diphenyl-*E*-3-chloro-2-(phenylthio)propenamide (**61**, tentatively assigned) (R_f 0.4 ethyl acetate–hexane (25 : 75) as eluent) (0.77 g, 36% characterised as a mixture (3 : 2) with the *Z*-isomer) as a low-melting solid, (found 69.29; H, 4.56; N, 3.53; S, 9.00; Cl, 9.69.

$C_{21}H_{16}ClNOS$ requires C, 68.94; H, 4.41; N, 3.83; S, 8.76; Cl, 9.69%); δ_H (270 MHz) 6.24 [1H, s, C(3)*H*Cl=], 6.94–7.63 (15H, m, Ar*H*); δ_C (67.8 MHz) signal seen in ^{13}C NMR of mixture at 122.6 [quaternary aromatic *C* or *C*(2)S], other signals present in complex series of peaks between 127 and 143 ppm), 165.3 (*C*O); *m*/*z* 365 (M^+, 22%), 330 (25, M^+–Cl), 167 (55), 134 (95, $[PhS{=}C{=}CH]^+$); and ethyl acetate–DCM–hexane (20 : 40 : 40) to elute the more polar *N*,*N*-diphenyl-*Z*-3-chloro-2-(phenylthio)propenamide (**60**, tentatively assigned) (R_f 0.35) (0.89 g, 41% contains < 10% of *E*-isomer) as a light green, crystalline solid, mp 125–130 °C; (found 68.60; H, 4.50; N, 3.59; Cl, 9.80; S, 8.42. $C_{21}H_{16}ClNOS$ requires C, 68.94; H, 4.41; N, 3.83; Cl, 9.69; S, 8.76%); ν_{max}/cm^{-1} (KBr) 1644, 1586 (CO α, β-unsaturated amide); δ_H (270 MHz) 6.76 (3H, br m, Ar*H*), 7.07 [1H, s, C(3)*H*Cl=], 7.23–9.67 (12H, m, Ar*H*); δ_C (67.8 MHz) 127.2, 127.6 (aromatic *C*H), 128.6, 128.7 [quaternary aromatic *C* or *C*(2)S], 129.0, 129.2, 129.3, 131.7 (aromatic *C*H), 133.9, 136.8 [quaternary aromatic *C* or *C*(2)S], 142.5 (*C*(3)HCl=), 165.4 (*C*O); *m*/*z* 365 (M^+, 13%), 330 (22, M^+- Cl), 169 (45, $[NPh_2 + H]^+$), 134 (100, $[PhS{=}C{=}CH]^+$).

***N*-Benzyl-*Z*-3-chloro-2-(*n*-butylthio)propenamide (66).**

Method D. Unrecrystallised NCS (4.47 g, 33.47 mmol) was added in one portion to a solution of the sulfide **22** (4.00 g, 15.94 mmol) in toluene (80 ml). The flask was immediately immersed in an oil bath at 120 °C and heating was maintained for 3 hours with stirring. The reaction mixture was cooled to 0 °C and the succinimide by-product removed by filtration. The solvent was evaporated at reduced pressure to give the crude β-chloroacrylamide **66** (4.42 g, 98%) as an oil which was purified by chromatography on silica gel using ethyl acetate–hexane (gradient elution 5 to 30% ethyl acetate) as eluent to give the β-chloroacrylamide **66** as a clear oil (3.76 g, 84%) which solidified on storing in the freezer overnight, (found C, 58.75; H, 6.31; N, 5.06; S, 11.70. $C_{14}H_{18}ClNOS$ requires C, 59.25; H, 6.39; N, 4.94; S, 11.30%); ν_{max}/cm^{-1} (film) 3304 (br NH), 1648 (CO), 1560; δ_H (270 MHz) 0.87 (3H, t, *J* 7, CH_3), 1.28–1.62 [4H, m, C(3′)H_2, C(2′)H_2], 2.67 (2H, d, *J* 7, SCH_2), 4.54 (2H, d, *J* 6, NCH_2), 7.24–7.39 (5H, m, Ar*H*), 7.50 (1H, b s, N*H*), 7.78 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 13.9 [*C*(4′)H_3], 22.1 [*C*(3′)H_2], 32.2 [*C*(2′)H_2], 34.5 (S*C*H_2), 44.5 (N*C*H_2), 128.1, 128.2, 129.2 (aromatic *C*H), 132.2 (quaternary aromatic *C*), 137.9 [*C*(3)HCl=], 138.2 [*C*(2)S], 163.5 (*C*O); *m*/*z* (EI) 283 (M^+, 8%), 248 (12, M^+–Cl), 158 (22), 106 (11), 91 (68).

A trace amount (2%) of the corresponding trichloride was evident in the NMR spectra of both the crude and the purified material as a singlet at δ_H 6.56.

***N*-Benzyl-*Z*-3-chloro-2-(4′-methoxybenzenethio)propenamide (70).**

Method E. Unrecrystallised NCS (0.96 g, 7.14 mmol) was added in one portion to a solution of the *N*-benzyl-2-(4′-methoxybenzenethio)propanamide (**26**, 1.04 g, 3.40 mmol) in toluene (21 ml). The flask was immediately immersed in an oil bath at 130 °C and heating was maintained for 2 hours with stirring. The reaction mixture was cooled to 0 °C and the succinimide by-product removed by filtration. The solvent was evaporated at reduced pressure to give the crude β-chloroacrylamide **70**. The crude product was purified by chromatography on silica gel using ethyl acetate–hexane (20 : 80) as eluent to give the β-chloroacrylamide **70** as a colourless solid (720 mg, 64%), mp 76–77 °C; (found C, 61.03; H, 5.11; N, 4.19; Cl, 10.94; S, 9.51. $C_{17}H_{16}NClO_2S$ requires C, 61.16; H, 4.83; N, 4.20; Cl, 10.62; S, 9.60%); ν_{max}/cm^{-1} (KBr) 3323 (br, NH), 1636 (CO), 1494, 1029, 820; δ_H (270 MHz) 3.83 (3H, s, OCH_3), 4.42 (2H, d, *J* 6, CH_2Ar), 6.80–7.46 (10H, m, Ar*H*, N*H* seen as bs at δ_H 7.09), 7.81 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 44.1 (*C*H_2Ar), 55.4 (O*C*H_3), 115.0, 115.3 (aromatic *C*H), 123.1 (S-*C*), 127.7, 128.3, 131.3 (aromatic *C*H), 133.7, 135.6 [quaternary aromatic *C* or *C*(2)S], 137.5 [*C*(3)HCl=], 159.6 (*C*OMe), 162.5 (*C*O); *m*/*z* (EI) 333.0584 (M^+, $C_{17}H_{16}N^{35}ClO_2S$ requires 333.0590). 333 (M^+, 50%), 298 (7, M^+–Cl), 164 (25, M^+–CONHBn–Cl), 158 (75, M^+–SAr–HCl), 149 (23, $[SAr]^+$), 91 (100).

A signal corresponding to the analogous dichloroacrylamide was also seen at δ_H 4.21.

***N*-4′-Fluorophenyl-*Z*-3-chloro-2-(methylthio)propenamide (88).**

Method F. Unrecrystallised NCS (5.64 g, 42.50 mmol) was added in one portion to a solution of the sulfide **42** (5.00 g, 23.50 mmol) in toluene (100 ml). The flask was immediately immersed in an oil bath at 90 °C and heating was maintained for 2 hours with stirring. The reaction mixture was cooled to 0 °C and the succinimide by-product removed by filtration. The solvent was evaporated at reduced pressure to give the β-chloroacrylamide **88** as a brown solid. The ^1H NMR of the crude product showed the composition of the mixture to be 70% **88**, 20% dichloroacrylamide **117** (evidence for presence at δ_H 2.34) and 10% dichloride **118** (δ_H 4.07, 4.12, ABq, *J* 11, CH_2Cl). The product was purified by chromatography on silica gel using ethyl acetate–hexane (5 : 95) as eluent to give the β-chloroacrylamide **88** as a white solid (61%), mp 89–91 °C; (found C, 48.55; H, 3.69; N, 5.84; Cl, 14.04; F, 7.73; S, 13.28. $C_{10}H_9NClFOS$ requires C, 48.88; H, 3.69; N, 5.70; Cl, 14.43; F, 7.73; S, 13.05%); ν_{max}/cm^{-1} (KBr) 3339, 1652 (CO), 1507, 1211; δ_H (300 MHz) 2.31 (3H, s, SCH_3), 7.02–7.09 [2H, m, ArC(3′)*H*], 7.54–7.60 [2H, m, ArC(2′)*H*], 7.84 [1H, s, C(3)*H*Cl=], 9.01 (1H, b s, N*H*); δ_C (75.5 MHz) 17.35 (S*C*H$_3$), 115.9 [d, $^2J_{CF}$ 22, aromatic CH, Ar*C*(3′)], 121.8 [d, $^3J_{CF}$ 8, aromatic CH, Ar*C*(2′)], 133.2 [d, $^4J_{CF}$ 3, quaternary aromatic C, Ar*C*(1′)], 134.0 [*C*(2)S], 139.1 [*C*(3)HCl=], 159.7 [d, $^1J_{CF}$ 245, quaternary aromatic C, Ar*C*(4′)], 160.7 (*C*O); *m*/*z* (EI) 245 (M^+, 20%), 210 (30), 135 (22), 107 (100).

During optimization studies, characteristic signals for the acrylamide **116** were seen at δ_H 6.45 (s, one of CH_2=) and 5.58 (s, one of CH_2=).

Products obtained from treatment of *N*-4′-methylphenyl-3-methyl-2-(phenylthio)butanamide (126) with NCS

***N*-4′-Methylphenyl-2,3-dichloro-3-methyl-2-(phenylthio)butanamide (129).** *N*-4′-Methylphenyl-3-methyl-2-(phenylthio)butanamide (**126**, 0.99 g, 3.3 mmol) and NCS (1.05 g, 7.0 mmol) were heated in toluene (30 ml) at 130 °C. After 1 h TLC analysis indicated that the reaction was complete. Purification by chromatography using ethyl acetate–hexane (7 : 93) as eluent gave **129** (0.94 g, 80%) as a yellow, crystalline solid, mp 75–80 °C; (found C, 58.82; H, 5.14; N, 3.74; S, 19.31. $C_{18}H_{19}Cl_2OS$ requires C, 58.68; H, 5.20; N, 3.80; S, 19.26%); ν_{max}/cm^{-1} (KBr) 3405 (br NH), 1688 (CO amide); δ_H (270 MHz) 2.08 [3H, s, C(3)H_3], 2.14 [3H, s, C(3)H_3], 2.33 (3H, s, ArCH_3), 7.08–7.65 (9H, m, Ar*H*), 8.45 (1H, br s, N*H*); δ_C (67.8 MHz) 20.9 (Ar*C*H$_3$), 30.8,

31.5 {[*C*(3)H_3]$_2$}, 74.6 [*C*(3)Cl], 94.1 (*C*ClS), 119.9, 128.1, 129.1 (aromatic *C*H), 129.5 (quaternary aromatic *C*), 130.4 (aromatic *C*H), 134.1, 135.0 (quaternary aromatic *C*), 137.1 (aromatic *C*H), 162.9 (*C*O); MS *m*/*z* 367 (M^+, 28%), 297 (16, M^+-2Cl), 198 (98), 163 (29, [PhS=C=C$(CH_3)_2$]$^+$).

***N*-4′-Methylphenyl-3-methyl-2-(phenylthio)-2-butenamide (128) and *N*-4′-methylphenyl-2-chloro-3-methyl-2-(phenylthio)butanamide (127).** NCS (44 mg, 0.33 mmol) was added to a stirred solution of *N*-4′-methylphenyl-3-methyl-2-(phenylthio)-butanamide **126** (100 mg, 0.33 mmol) in carbon tetrachloride (2 ml) at RT. An aliquot was removed which contained **127** δ_H (60 MHz, CCl_4) 1.10 (3H, d, *J* 8), 1.35 (3H, d, *J* 8), 2.28 (3H, s, ArCH_3), 2.90–3.12 [1H, m, C(3)*H*], 6.89–7.67 (9H, m, Ar*H*). After stirring at RT for 4 h the reaction mixture was cooled to 0 °C, the succinimide by-product was removed by filtration and the filtrate was evaporated to dryness. The product mixture containing acrylamide **128** was allowed to stand, neat at RT, for 48 h to promote elimination of HCl from the α-chlorosulfide **127**, and purified by column chromatography using ethyl acetate–hexane (10 : 90) as eluent to give **128** (49 mg, 50%) as an off-white solid, mp 88–90 °C; (found C, 72.34; H, 6.19; N, 4.82; S, 10.43. $C_{18}H_{19}NOS$ requires C, 72.69; H, 6.44; N, 4.71; S, 10.78%); ν_{max}/cm^{-1} (KBr) 3281 (br NH), 1648, 1597 (CO α, β-unsaturated amide); δ_H (270 MHz) 2.14, 2.17 [2 × 3H, 2 × s, (CH_3)$_2$], 2.30 (3H, s, ArCH_3), 7.04–7.38 (9H, m, Ar*H*), 8.33 (1H, br s, N*H*); δ_C (67.8 MHz) 20.8 (Ar*C*H$_3$), 23.8, 25.4 [(*C*H$_3$)$_2$], 120.1, 126.3, 127.5, 129.3, 129.5 (aromatic *C*H), 133.9, 135.2, 135.2 (quaternary aromatic *C*), 155.6 (*C*O); MS *m*/*z* 297 (M^+, 40%), 163 (50, [(CH$_3$)$_2$C=CHSPh]$^+$).

Formation of dichlorides for decomposition using Lewis acids

***N*-*i*-Propyl-2,3-dichloro-2-(phenylthio)propanamide (130).** This was prepared following the procedure described for dichloride **7** using sulfide **11** (0.26 g, 1.17 mmol), NCS (0.33 g, 2.45 mmol) in carbon tetrachloride (5 ml) at 40 °C with a reaction time of 16 h. The dichloride **130** was present in *ca.* 45% with the β-chloroacrylamide **53**. The ^{1}H NMR spectrum was complex, however a signal was observed at δ_H (270 MHz) 3.70–4.50 [2H, ABq, *J* 11, C(3)H_2] for the β-hydrogens.

***N*-2′-Propenyl-2,3-dichloro-2-(phenylthio)propanamide (131).** This was prepared following the procedure described for dichloride **7** using sulfide **14** (0.30 g, 1.36 mmol), NCS (0.38 g, 2.86 mmol) in carbon tetrachloride (6 ml) at 40 °C with a reaction time of 16 h. The dichloride **131** was characterised as a *ca.* 1 : 1 mixture with the β-chloroacrylamide **56**: δ_H (270 MHz) 3.60–3.95 [2H, m, C(1′)H_2], 3.72–4.30 [2H, ABq, *J* 11, C(3)H_2], 4.72–5.98 (3H, m, C*H*=CH_2), 6.57 (1H, br s, N*H*), 7.10–7.83 (5H, m, Ar*H*). (Characteristic signals for the β-chloroacrylamide **56** were also present.)

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