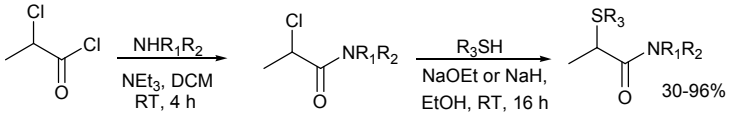
Synthesis of α–thioamide precursors

The α-thioamides were prepared in two steps: formation of the α-chloroamides followed by nucleophilic substitution of the chloride to yield the α-thioamides as summarised in Table 1.

Table 1. Synthesis of α–thioamides



1, 9-41, 132-134

R^1	R^2	R^3	Method	Sulfide	% Yield[†]
p-Tol	H	Ph	A	**1**	86
Bn	H	Ph	A	**9**	85
Et	H	Ph	B	**10**	87
i-Pr	H	Ph	B	**11**	72
n-Bu	H	Ph	B	**12**	88
Me	H	Ph	B	**13**	42
Allyl	H	Ph	B	**14**	83
Cinnamyl	H	Ph	C	**15**	52[‡]
4-F-C_6H_4	H	Ph	A	**16**	96
H	H	Ph	A	**17**	58[§]
Ph	Ph	Ph	C	**18**	34¶
Me	Me	Ph	A	**19**	60
(R/S)-$CH(CH_3)$Ph	H	Ph	C	**20**	36
(S)-$CH(CH_3)$Ph	H	Ph	C	**21**	58
Bn	H	*n*-Bu	D	**22**	90
p-Tol	H	*n*-Bu	D	**23**	84
4-F-C_6H_4	H	*n*-Bu	D	**24**	96
p-Tol	H	4-MeO-C_6H_4	C	**25**	75
Bn	H	4-MeO-C_6H_4	C	**26**	84
Et	H	4-MeO-C_6H_4	C	**27**	88
H	H	4-MeO-C_6H_4	C	**132**	75
Me	Me	4-MeO-C_6H_4	C	**28**	59
Ph	Ph	4-MeO-C_6H_4	C	**133**	75
p-Tol	H	4-NO_2-C_6H_4	E	**29**	68
p-Tol	H	*i*-Bu	A	**30**	77
4-F-C_6H_4	H	*i*-Bu	A	**31**	84
Et	H	*i*-Bu	B	**32**	68
i-Pr	H	*i*-Bu	B	**134**	68
4-F-C_6H_4	H	*i*-Pr	A	**33**	86
Bn	H	Bn	A	**34**	74
4-F-C_6H_4	H	Bn	A	**35**	83
n-Bu	H	Bn	B	**36**	60
Me	Me	Bn	A	**37**	65
p-Tol	H	Bn	A	**38**	52
Me	H	Bn	A	**39**	51

Ph	H	Bn	A	**40**	64
H	H	Bn	A	**41**	30[§]

Method A: 1.2 eq Na, 1.2 eq RSH, Ethanol, RT, 16 hr
Method B: 1.05 eq NaH, 1.1 eq RSH, DMF, RT, 16 hr
Method C: 2.2 eq Na, 1.1 eq RSH, Ethanol, RT 16 hr
Method D: 1.5 eq Na, 1.5 eq RSH, Ethanol, RT, 16 hr
Method E: 1.5 eq NaH, 1.5 eq RSH, DMF, RT, 16 hr
† Overall yield over two steps
‡ 1.5 equivalents of the amine was used with no added NEt_3 in preparing the α-chloroamide.
§ 4 equivalents of the amine was used with no added NEt_3 in preparing the α-chloroamide
¶ Reaction conducted in THF

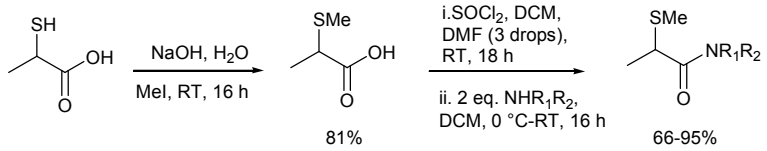
The α-chloroamides were synthesized from commercially available 2-chloropropionyl chloride. Earlier experiments were conducted by treatment of the 2-chloropropionyl chloride (in DCM at room temperature) with a solution of the amine (1.5 equivalents) in DCM to give the corresponding α-chloroamide. Later, an improved procedure was developed involving just 1 equivalent of the amine to effect amide formation and 1 equivalent of triethylamine (added first to the stirred solution of 2-chloropropionyl chloride in DCM) to neutralize the HCl released. A range of simple amines was employed: *p*-toluidine, aniline, ethylamine, *i*-propylamine, benzylamine, allylamine, diphenylamine, dimethylamine, methylamine, 4-fluoroaniline, *n*-butylamine. For studies with chiral amides, both the racemic α-methylbenzylamine and the enantiopure (S)-α-methylbenzylamine were employed. The treatment of the chiral amine with 2-chloropropionyl chloride resulted in a diastereomeric mixture (1:1) of α-chloroamides. The crude α-chloroamides were usually sufficiently pure by ^{1}H NMR, ^{13}C NMR and IR spectroscopy to use in subsequent reactions without further purification.

Two methods were employed for the synthesis of α-thioamides from α-chloroamides. α-Chloroamides with *N*-aryl, *N*-benzyl, primary or tertiary amides can be sulfenylated in ethanol by reaction with the freshly prepared sodium salt of the thiol generated using sodium ethoxide. Initially, this reaction was conducted using 2.2 equivalents of sodium ethoxide and 1.1 equivalents of the thiol (Method C). Later experiments indicated that use of just 1.2 equivalents of sodium ethoxide was sufficient (Method A). The *N*-alkyl α-thioamides were more efficiently obtained using sodium hydride in DMF (method B). The sodium hydride was initially washed with hexane, dried and then suspended in DMF followed by slow addition of the thiol as the deprotonation

proved exothermic. Addition of the appropriate *N*-alkyl α-chloroamide as a solution in DMF provided the α-thioamide in essentially quantitative yield. Use of sodium hydride in DMF to form the sulfide **29** derived from 4-nitrobenzenethiol (Method E) similarly proved more efficient than use of sodium ethoxide in ethanol, presumably due to the decreased reactivity of this thiolate.

Preparation of the α-methylthioamides

Table 2. Synthesis of α-methylthioamides



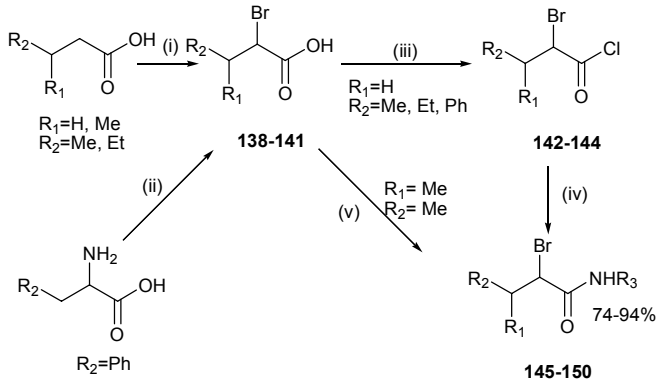
R^1	R^2	Sulfide	% Yield †
4-F-C_6H_4	H	**42**	95
Bn	H	**43**	90
n-Bu	H	**44**	73
i-Pr	H	**45**	84
Me	H	**135**	68
p-Tol	H	**46**	80‡
H	H	**136**	76§
Et	Et	**137**	66

†Yield calculated over two steps from the α-methylthio acid
‡Amide prepared using DCC coupling reaction
§Primary amide synthesised in acetone

To avoid the use of methanethiol, the α-methylthioamides were prepared from the corresponding acid, which in turn was prepared by methylation of thiolactic acid using dimethyl sulfate in aqueous base as reported by Bernardi *et al*[1], to provide the acid as a clear oil in 46% yield. Replacement of dimethyl sulfate with methyl iodide led to an improved yield (81%).

The amides were originally prepared using a DCC promoted coupling reaction. It was subsequently found that the route outlined in Table 2 *via* the acid chloride afforded a cleaner product. Preparation of the primary amide using concentrated ammonia proceeded very inefficiently in DCM but was successful in acetone.

Extended chain α-thioamides



Scheme 1 Reagents and Conditions: (i) Br_2, PCl_3, Δ, 4.5 h (ii) HBr, $NaNO_2$, 0 °C, 1 h (iii) 1.1 eq. $(COCl)_2$, DMF (5 drops), DCM, 0 °C-RT, 5h (method F) or 5.5 eq. $SOCl_2$, Δ, 1h (method G) (iv) 1.5 eq. amine, RT, 25h or 1.1 eq amine, 1.1 eq NEt_3, RT, 16h (v) 1.1 eq. amine, 1.1 eq. DCC, 0°C-RT, 2h

Table 3 Synthesis of α-bromoamides

R^1	**R^2**	**α-Bromo acid**	**% Yield**	**Acid chloride**	**% Yield**	**R^3**	**Amide**	**% Yield**
H	Me	**138**	78	**142**†	73	*p*-Tol	**145**	91
H	Et	**139**	91	**143**†	Quant	*p*-Tol or (S)-$CHCH_3Ph$	**146** **147**	85 94
H	Ph	**140**	88	**144**‡	83	*p*-Tol	**148**	85
Me	Me	**141**	97	-	-	*p*-Tol	**149**	74§
H	Me	**138**	78	-	-	Ph	**150**	80§

†Prepared by Method F
‡Prepared by Method G
§ Product contains approx. 10% DCU as estimated by ^{1}H NMR integration.

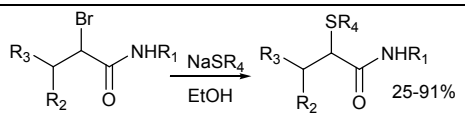
The extended chain α-thioamides were prepared from the analogous carboxylic acids or α-amino acid as summarised in Table 3. α-Bromination using bromine and phosphorous trichloride gave the α-brominated acids **138**, **139** and **141**. As the α-bromination of β-phenylpropanoic acid proved complex, α-bromo-β-phenylpropanoic acid **140** was prepared instead by treatment of (L)-phenylalanine with hydrogen bromide and sodium nitrite.[2] Although this bromination proceeds with retention of configuration, no effort was made to determine the enantiopurity of the α-bromo-β-phenylpropanoic acid **140.** The acid chlorides of α-bromobutanoic and pentanoic acids were generated using oxalyl or thionyl chloride. Use of oxalyl chloride in DCM with catalytic DMF (Method E) gave the α-bromobutanoyl and pentanoyl chlorides **142, 143** in good yield (73% and quantitative respectively). However, complete removal of DMF was difficult. Alternatively, thionyl chloride (method F) was used to

generate the α-bromobutanoyl chloride **142** (obtained in 64% yield). The volatility of the α-bromobutanoyl chloride **142** rendered purification difficult as the work up involved removal of excess thionyl chloride by azeotropic distillation with toluene.

The α-bromobutanamides and pentanamides **145-147** were then prepared using the corresponding acid chloride and *p*-toluidine or (S)-α-methylbenzylamine (again a 1:1 mixture of diastereomers formed). An alternative method of amide synthesis was employed to form isovalerylamide **149** and the butanamide **150**, involving direct coupling of the α-bromoacid and the amine using DCC, although at least 9% DCU remains in each product mixture even after chromatography.

Each of the α-bromoamides were then sulfenylated in ethanol by reaction with the freshly-prepared sodium thiolate as summarised in Table 4.

Table 4. Synthesis of extended chain α-thioamides



76-80 **82-86**

α-bromoamide	**R^1**	**R^2**	**R^3**	**R^4**	**Method**	**α-thioamide**	**Yield**
145	*p*-Tol	H	Me	Ph	A	**47**	91
146	*p*-Tol	H	Et	Ph	C	**48**	91
147	(S)-CH(CH$_3$)Ph	H	Et	Ph	H	**49**	80
148	*p*-Tol	H	Ph	Ph	C	**50**	57
149	*p*-Tol	Me	Me	Ph	C	**151**	48

Method A: 1.2 eq Na, 1.2 eq RSH, Ethanol, RT, 16 hr

Method C: 2.2 eq Na, 1.1 eq RSH, Ethanol, RT, 16 hr

Method H: 1.6 eq Na, 1.1 eq RSH, Ethanol, RT, 16 hr

Experimental

The 2-bromoacids **138, 139 & 141**[3] and **140**[2] were prepared using established procedures.

Synthesis of the α-Haloamides

_N_-4'-Methylphenyl-2-chloropropanamide S1

2-Chloropropionyl chloride (20.00 g, 157 mmol) in dichloromethane (100 ml), was added dropwise over 20 min to a solution of *p*-toluidine (16.59 g, 155 mmol) and triethylamine (15.86 g, 157 mmol) in dichloromethane (300 ml) at 0^{o}C, while stirring under nitrogen. On completion of the addition, the reaction solution was allowed to warm to room temperature. After stirring for 4 hours, distilled 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 and evaporated at reduced pressure to give the amide **S1** as a white solid (29.10 g, 92%) which required no further purification, mp 118-120 °C (Lit.,[4] 108^{o}C); ν_{max}/cm^{-1} (KBr) 3253 (NH), 3188 (CH), 1664 (CO), 1598, 1514 (NH bend), 1369 (CN stretch); δ_H (270 MHz) 1.81 [3H, d, *J* 7, C(3)*H*$_3$], 2.32 (3H, s, ArC*H*$_3$), 4.53 [1H, q, *J* 7, C(2)*H*], 7.12-7.16 (2H, A of ABq, *J* 8, Ar*H*), 7.40-7.44 (2H, B of ABq, *J* 8, Ar*H*), 8.28 (1H, b s, N*H*); δ_C (67.8 MHz) 20.9 (Ar*C*H$_3$), 22.6 [*C*(3)H$_3$], 56.2 [*C*(2)H], 120.2, 129.6 (aromatic *C*H), 134.4, 134.8 (quaternary aromatic *C*), 167.4 (*C*O).

_N_-Benzyl-2-chloropropanamide S2

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (2.50 g, 20 mmol), benzylamine (2.14 g, 20 mmol) and triethylamine (1.98 g, 20 mmol) in dichloromethane (25 ml) to give the amide **S2** as a white solid (3.64 g, 93%) which required no further purification, mp 74-76^{o}C (Lit.,[5] 80-82^{o}C); ν_{max}/cm^{-1} (KBr) 3289 (NH), 3090 (CH), 3033 (CH), 1650 (CO), 1556 (NH bend), 1497, 1455 (CN stretch); δ_H (270 MHz) 1.72 [3H, d, *J* 7, C(3)*H*$_3$], 4.37-4.49 [3H, m, C(2)*H*Cl, NC*H*$_2$], 6.95 (1H, b s, N*H*), 7.24-7.40 (5H, m, Ar*H*); δ_C (67.8 MHz) 22.7 [*C*(3)H$_3$], 43.9 (N*C*H$_2$), 55.9 [*C*(2)H], 127.7, 127.8, 128.9 (aromatic *C*H), 137.6 (quaternary aromatic *C*), 169.5 (*C*O).

_N_-Ethyl-2-chloropropanamide S3[6]

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (2.50 g, 20 mmol), ethylamine (60% soln. in ethanol; 1.50 ml, 20 mmol) and triethylamine (1.98 g, 20 mmol) in dichloromethane (25 ml) to give the amide **S3** as a white solid (2.43 g, 91%) which required no further purification; δ_H (270 MHz) 1.18

(3H, t, *J* 7, CH_2CH_3), 1.73 [3H, d, *J* 7, C(3)H_3], 3.28-3.42 (2H, m, NCH_2), 4.41 [1H, q, *J* 7, C(2)*H*], 6.67 (1H, b s, N*H*); δ_C (67.8 MHz) 14.5 (CH_2CH_3), 22.6 [*C*(3)H_3], 34.7 (NCH_2), 55.8 [*C*(2)H], 169.3 (*C*O).

_N_-Isopropyl-2-chloropropanamide S4[7]

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (25.40 g, 0.20 mol), isopropylamine (11.80 g, 0.20 mol) and triethylamine (20.20 g, 0.20 mol) in dichloromethane (250ml) to give the amide **S4** as a white solid (23.09 g, 77%) which required no further purification; δ_H (270 MHz) 1.18 [6H, d, *J* 7, $CH(CH_3)_2$], 1.72 [3H, d, *J* 7, C(3)H_3], 3.96-4.14 (1H, m, NC*H*), 4.38 [1H, q, *J* 7, C(2)*H*], 6.44 (1H, b s, N*H*); δ_C (67.8 MHz) 22.5 [$CH(CH_3)_2$], 22.7 [*C*(3)H_3], 42.0 (NCH), 56.0 [*C*(2)H], 168.6 (*C*O).

_N_-n-Butyl-2-chloropropanamide S5

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (3.52 g, 27.70 mmol), n-butylamine (2.00 g, 27.40 mmol) and triethylamine (2.80 g, 27.70 mmol) in dichloromethane (30 ml) to give the amide **S5** as a white solid (4.20 g, 94%) which required no further purification; ν_{max}/cm^{-1} (film) 3295 (NH), 3090 (CH), 1661 (CO), 1560 (NH bend), 1447 (CN stretch); δ_H (300 MHz) 0.95 [3H, d, *J* 7.2, C(4′)H_3], 1.28-1.45 [2H, m, C(3′)H_2], 1.46-1.61 [2H, m, C(2′)H_2], 1.74 [3H, d, *J* 7.1, C(3)H_3], 3.27 (2H, q, *J* 5.8, CH_2NH), 4.44 [1H, q, *J* 7.1, C(2)*H*], 6.61 (1H, b s, N*H*).

_N_-Methyl-2-chloropropanamide S6[7]

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (10.1 ml, 102 mmol), methylamine (12.6 ml, 25% solution, 100 mmol) and triethylamine (14.3 ml, 102 mmol) in dichloromethane (80 ml) to give the amide **S6** as a colourless oil (9.11 g, 74%) which required no further purification; ν_{max}/cm^{-1} (film) 3306 (NH), 3098 (CH), 1668 (CO), 1539 (NH bend), 1413 (CN stretch); δ_H (300 MHz) 1.75 [3H, d, *J* 7.1, C(3)H_3], 2.88 (3H, d, *J* 4.9, CH_3NH), 4.41 [1H, q, *J* 7.1, C(2)*H*], 6.51 (1H, b s, N*H*); δ_C (75.5 MHz) 22.7 [*C*(3)H_3], 26.7 (NCH_3), 55.8 [*C*(2)H], 170.4 (*C*O); *m/z* 121 (M^+ , 6%), 86 (96, M-Cl^{35}), 63 (52, $[CH_3CHCl]^+$), 58 (100, $[CONHCH_3]^+$).

_N_-2′-Propenyl-2-chloropropenamide S7[7]

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (3.00 g, 23.62 mmol), 2'-propenylamine (1.28 g, 22.5 mmol) and triethylamine (2.39 g, 23.62 mmol) in dichloromethane (28 ml) to give the amide **S7** as a clear oil (3.02 g, 91%) which required no further purification; δ_H (60 MHz) 1.70 [3H, d, *J* 8, C(3)H_3], 3.77-4.10 (2H, m, NCH_2), 4.48 [1H, q, *J* 8, C(2)*H*], 5.00-5.43 (2H, m, =CH_2), 5.57-6.25 (1H, m, C*H*=), 7.08 (1H, b s, N*H*).

_N_-3′-Phenylpropenyl-2-chloropropanamide S8

A solution of 2-chloropropanoyl chloride (1.03 g, 8.1 mmol) in DCM (30 ml) was stirred at room temperature. Cinnamyl amine (1.62 g, 12.2 mmol) was added slowly. Stirring was continued for 16 h then water (30 ml) was added, the layers were separated, the aqueous layer was extracted with DCM (2 x 10 ml) and the combined organic layers washed with saturated sodium bicarbonate (2 x 20 ml), water (2 x 20 ml) and brine (2 x 20 ml), dried and concentrated to give **S8** as a pale yellow solid (1.32 g, 73 %) which was used without further purification; mp 65-66 °C; ν_{max}/cm^{-1} (KBr) 3054 (br NH), 1675 (CO amide); δ_H (60 MHz) 1.75 [3 H, d, *J* 7, C(3)H_3], 4.07 [(2 H, m, C(3′)H_2], 4.43 [1 H, q, *J* 7, C(2)*H*], 6.07-6.50 (2 H, m, C*H*=C*H*), 7.02-7.51 (5 H, m, Ar*H*).

_N_-4'-Fluorophenyl-2-chloropropanamide S9

The title compound was prepared following the procedure described for **S1** from 4-fluoroaniline (6.66 g, 60.00 mmol), 2-chloropropionyl chloride (7.75 g, 61.00 mmol) and triethylamine (6.16 g, 61.00 mmol) in DCM (140 ml) to give the amide **S9** as a pink solid (11.98 g, 99%) which required no further purification, mp 79-81^{o}C (Lit.,[8] 106-108^{o}C); ν_{max}/cm^{-1} (KBr) 3254 (NH), 1661 (CO), 1542 (NH bend), 1509, 1374 (CN stretch); δ_H (300 MHz) 1.83 [3H, d, *J* 7.1, C(3)H_3], 4.53 [1H, q, *J* 7.1, C(2)*H*], 7.06 {2H, overlapping dd [appears as a triplet], *J* 7.8, 7.8, C(3′)*H*}, 7.48-7.56 [2H, m, C(2′)*H*], 8.41 (1H, b s, N*H*); δ_C (75.5 MHz) 22.8 [*C*(3)H_3], 56.3 [*C*(2)H], 116.3 [d, $^2J_{CF}$ 24, ArC(3′)], 122.5 [ArC(2′)], 133.4 [ArC(1′)], 160.3 [d, $^1J_{CF}$ 245, ArC(4′)], 168.1 (*C*O).

***N*-Phenyl-2-chloropropanamide S10**

This was synthesized using the procedure described for **S1** from 2-chloropropionyl chloride (7.00 ml, 0.07 mol), aniline (6.41 ml, 0.07 mol) and triethylamine (9.86 ml, 0.07 mol) in dichloromethane (150 ml) to give the amide **S10** (11.85 g, 93%) as a yellow solid which was carried forward without further purification, mp 83-84^{o}C (Lit.,[9] 93^{o}C); ν_{max}/cm^{-1} (KBr) 3260 (NH), 3135 (CH), 1669 (CO), 1599, 1544 (NH bend), 1371 (CN stretch); δ_H (300 MHz) 1.83 [3H, d, *J* 7.1, C(3)*H*$_3$], 4.55 [1H, q, *J* 7.1, C(2)*H*], 7.12-7.59 (5H, m, Ar*H*), 8.28 (1H, b s, N*H*).

2-Chloropropanamide S11

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (6.88 g, 55 mmol) and aqueous ammonia (35% soln; 10mls, 182 mmol) in dichloromethane to give the amide **S11** as a white solid (17.14g, 88%) which required no further purification, mp 83-84^{o}C (Lit.,[10] 75-77^{o}C); ν_{max}/cm^{-1} (KBr) 3379 (NH), 3199 (NH), 2998 (CH), 1664 (CO), 1412 (CN stretch); δ_H (300 MHz) 1.76 [3H, d, *J* 7.1, C(3)*H*$_3$], 4.44 [1H, q, *J* 7.1, C(2)*H*], 5.60 (1H, b s, N*H*), 6.53 (1H, b s, N*H*); δ_C (75.5 MHz) 22.7 [*C*(3)H$_3$], 55.3 [*C*(2)H], 173.0 (*C*O).

***N,N*-Diphenyl-2-chloropropanamide S12**

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (2.50 g, 20 mmol), diphenylamine (3.38 g, 20 mmol) and triethylamine (1.98 g, 20 mmol) in dichloromethane (250ml) to give the amide **S12** as a grey solid (4.48 g, 92%) which required no further purification; ν_{max}/cm^{-1} (film) 1678 (CO); δ_H (60MHz) 1.67 [3H, d, *J* 7, C(3)*H*$_3$], 4.52 [1H, q, *J* 7, C(2)*H*], 7.23-7.40 (10H, m, Ar*H*).

***N,N*-Dimethyl-2-chloropropanamide S13**

This was obtained following the procedure described for **S1** from 2-chloropropionyl chloride (2.50 g, 20 mmol), dimethylamine (2.50 g, 20 mmol) and triethylamine (1.98 g, 20 mmol) in dichloromethane (25 ml) to give the amide **S13** as a yellow oil (1.96 g, 72%) which required no further purification; ν_{max}/cm^{-1} (film) 1659 (CO); δ_H (60MHz) 1.58 [3H, d, *J* 7, C(3)*H*$_3$], 2.98 [3H, s, one of N(C*H*$_3$)$_2$], 3.10 [3H, s, one of N(C*H*$_3$)$_2$], 4.63 [1H, q, *J* 7, C(2)*H*].

(±)-*N*-1′-Phenylethyl-2-chloropropanamide S14

This was prepared following the procedure described for amide **S1** using 2-chloropropanoyl chloride (3.00 g, 23.6 mmol), (±)-1-phenylethylamine (4.6 ml, 35.4 mmol), DCM (30 ml) to give (±)-*N*-1′-phenylethyl-2-chloropropanamide **S14** (3.56 g, 72%, an equimolar mixture of two diastereomers) as a white, crystalline solid, which was used without further purification; ν_{max}/cm^{-1} (KBr) 1656 (CO); δ_H (60 MHz) 1.55 [3H, d, *J* 7, C(2′)H_3], 1.71, 1.73 [3H, 2 x d, *J* 7, 7, C(3)H_3], 4.39, 4.41 [1H, 2 x q, *J* 7, 7, C(2)*H*], 4.83-5.38 (1H, dq, *J* 7, NC*H*), 6.87 (1H, br s, N*H*), 7.34 (5H, s, aromatic C*H*).

(S)-*N*-1′-Phenylethyl-2-chloropropanamide S15

This was prepared following the procedure described for amide **S1** using 2-chloropropanoyl chloride (3.00 g, 23.8 mmol), (S)-(-)-1-phenylethyl amine (4.6 ml, 35.7 mmol) in DCM (60 ml) gave (2R/S, 1′S)-*N*-1′-phenylethyl-2-chloropropanamide **S15** (3.65 g, 73 % as an equimolar mixture of diastereomers) as a white, crystalline solid which was used without further purification (spectral data as observed for amide **S14).**

Synthesis of the α-thioamides

***N*-4'-Methylphenyl-2-(phenylthio)propanamide 1**

Method A

Thiophenol (5.00 ml, 48.6 mmol) was added to a solution of freshly prepared sodium ethoxide [made from sodium (1.12 g, 48.6 mmol) in dry ethanol (90 ml) at 0°C] while stirring under nitrogen. The resulting solution was stirred for 20 minutes when *N*-4'-methylphenyl-2-chloropropanamide **S1** (8.00 g, 40.5 mmol) was added gradually over 15 minutes. The reaction solution was typically seen to become cloudy 30 minutes after the final addition of the α-chloroamide. Following stirring for 16 hours, the reaction was quenched by addition of water (100 ml) and DCM (70 ml). The phases were separated and the aqueous layer was extracted with DCM (2 x 50 ml). The combined organic layers were washed with NaOH (1M, 2 x 100 ml), water (200 ml) and brine (200 ml), dried and concentrated at reduced pressure to give **1** as an off-

white solid. Purification by column chromatography using ethyl acetate-hexane (40:60) as eluent gave the sulfide **1** (10.17 g, 93%) as a white, crystalline solid, mp 112-113 °C; (Found C, 70.87; H, 6.51; N, 5.33; S, 11.74. $C_{16}H_{17}NOS$ requires C, 70.81; H, 6.31; N, 5.16; S,11.82%); ν_{max}/cm^{-1} (KBr) 3292 (br, NH), 1661 (CO), 1537, 1514, 824; δ_H (270 MHz) 1.63 [3H, d, *J* 7, C(3)*H*$_3$], 2.29 (3H, s, ArC*H*$_3$), 3.90 [1 H, q, *J* 7 , C(2)*H*], 7.04-7.44 (9H, m, Ar*H*), 8.40 (1H, br s, N*H*); δ_C (67.8 MHz) 19.7 [*C*(3)H$_3$], 22.1 (Ar*C*H$_3$), 49.1 [C(2)H], 121.2, 128.9, 130.6, 131.1, 132.0 (aromatic *C*H), 134.6, 135.4, 136.1 (quaternary aromatic *C*), 171.1 (*C*O); *m/z* 271 (M^+, 18%), 163 (11, M^+ - PhS), 137 (21, $[PhS{=}CHCH_3]^+$), 110 (100).

_N_-Benzyl-2-(phenylthio)propanamide 9

The title compound was prepared using the procedure (Method A) described for 1 using *N*-benzyl-2-chloropropanamide **S2** (8.00 g, 40.5 mmol), thiophenol (5.00 ml, 48.6 mmol) and sodium (1.12 g, 48.6 mmol) in dry ethanol (90 ml). The reaction solution was stirred for 16 hours before work-up as described for **1** to give **9** (9.95 g, 91%) as a colourless solid which was used without further purification, mp 62-63 °C; (Found C, 70.42; H, 6.35; N, 5.01; S, 12.15. $C_{16}H_{17}NOS$ requires C, 70.81; H, 6.31; N, 5.16; S, 11.82%); ν_{max}/cm^{-1} 3283 (br NH), 1653 (CO); δ_H (300 MHz) 1.58 [3H, d, *J* 7.3, C(3)*H*$_3$], 3.88 [1H, q, *J* 7.3, C(2)*H*], 4.38 (1H, dd, A of ABX, J_{AB} 14.9, J_{AX} 5.9, NHC*H*$_2$), 4.40 (1H, dd, B of ABX, J_{AB} 14.9, J_{BX} 5.5, NHC*H*$_2$), 6.91 (1H, b s, N*H*), 7.01-7.13 (2H, m, Ar*H*), 7.16-7.39 (8H, m, Ar*H*); δ_C (75.5 MHz) 18.3 [*C*(3)H$_3$], 43.7 (N*C*H$_2$), 46. 9 [*C*(2)H], 127.0, 127.2, 127.4, 128.6, 129.2, 130.2 (aromatic *C*H), 133.9, 137.8 (quaternary aromatic *C*), 171.7 (*C*O).

_N_-Ethyl-2-(phenylthio)propanamide 10

Method B

Sodium hydride (1.55 g of 60% dispersion in mineral oil, 38.90 mmol) was placed in a 3-necked round bottomed flask under a flow of nitrogen. Following washing with hexane (3 x 20 ml), dry DMF (150 ml) was added *via* cannula and the resulting suspension stirred for 10 minutes. The reaction mixture was cooled to 0°C and thiophenol (4.19 ml, 40.70 mmol) was added slowly *via* syringe. After stirring for 20 minutes, a solution of *N*-ethyl-2-chloropropanamide **S3** (5.00 g, 37.00 mmol) in DMF

(5 ml) was added. On completion of the addition, the ice bath was removed and the reaction mixture stirred at room temperature for 4 hours when water (200 ml) and DCM (150 ml) were added and the phases separated. The aqueous layer was extracted with DCM (2 x 100 ml) and the combined organic layers washed with NaOH (1M, 200 ml), water (2 x 200 ml) and brine (100 ml), dried and concentrated at reduced pressure to give the crude sulfide **10**. ^{1}H NMR analysis (60 MHz) of the crude product showed it to contain up to 20% DMF. Following chromatography on silica gel using ethyl acetate-hexane as eluent (gradient elution 2-20% ethyl acetate), the sulfide **10** was isolated (7.40 g, 96%) as a colourless solid, mp 49-51 °C; (Found C, 63.07; H, 7.35; N, 6.79. $C_{11}H_{15}NOS$ requires C, 63.12; H, 7.22; N, 6.69%); ν_{max}/cm^{-1} (KBr) 3270 (br NH), 1637(CO), 1560 (C=C); δ_H (270 MHz) 1.06 (3H, t, *J* 7, CH_2CH_3), 1.54 [3H, d, *J* 7, C(3)H_3], 3.15-3.37 (2H, m, NCH_2), 3.79 [1H, q, *J* 7, C(2)*H*], 6.61 (1H, b s, N*H*), 7.19-7.40 (5H, m, Ar*H*); δ_C (67.8 MHz) 14.6 (NCH_2CH_3), 18.3 [*C*(3)H_3], 34.6 (NCH_2), 46.7 [*C*(2)H], 127.0, 129.1, 129.4 (aromatic *C*H), 134.1 (quaternary aromatic *C*), 171.6 (*C*O).

_N_-Isopropyl-2-(phenylthio)propanamide 11

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N-i*-propyl-2-chloro-propanamide **S4** (5.00 g, 33.45 mmol) in DMF (15 ml) added to a solution of sodium hydride (1.41 g of 60% dispersion in mineral oil, 35.12 mmol) and thiophenol (3.80 ml, 36.80 mmol) in DMF (150 ml). After chromatography on silica gel using ethyl acetate-hexane (gradient elution 5-30% ethyl acetate) as eluent, the sulfide **11** was isolated (6.89 g, 93%) as a colourless solid, mp 42-44 °C; (Found C, 64.70; H, 7.92; N, 6.30; S, 14.03. $C_{12}H_{17}NOS$ requires C, 64.54; H, 7.67; N, 6.27; S, 14.36%); ν_{max}/cm^{-1} (KBr) 3289 (br NH), 1662, 1638 (CO); δ_H (270 MHz) 0.99 [3H, d, *J* 7, one of $CH(CH_3)_2$], 1.09 [3H, d, *J* 7, one of $CH(CH_3)_2$], 1.56 [3H, d, *J* 7, C(3)H_3], 3.78 [1H, q, *J* 7, C(2)*H*], 3.91-4.06 (1H, m, NC*H*), 6.37 (1H, b s, N*H*), 7.18-7.37 (5H, m, Ar*H*); δ_C (67.8 MHz) 18.2 [*C*(3)H_3], 21.9, 22.3 [$CH(CH_3)_2$], 41.5 [$CH(CH_3)_2$], 47.0 [*C*(2)H], 127.2, 129.1, 130.3 (aromatic *C*H), 134.1 (quaternary aromatic *C*), 170.71 (*C*O).

_N-n_-Butyl-2-(phenylthio)propanamide 12

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N*-*n*-butyl-2-chloro-propanamide **S5** (3.22 g, 19.70 mmol) in DMF (5 ml) added to a solution of sodium hydride (0.83 g of 60% dispersion in mineral oil, 20.69 mmol) and thiophenol (2.38 g, 21.67 mmol) in DMF (97 ml). After chromatography on silica gel using ethyl acetate-hexane (gradient elution 5-30% ethyl acetate) as eluent, the sulfide **12** was isolated (3.41 g, 94%) as a clear oil; ; ν_{max}/cm^{-1} (film) 3293 (NH), 3064 (CH), 1647 (CO), 1603 (NH bend), 1495, 1452 (CN stretch); δ_H (270 MHz) 0.85 [3H, t, *J* 7, C(4′)*H*$_3$], 1.11-1.28 [2H, m, C(3′)*H*$_2$], 1.30-1.45 [2H, m, C(2′)*H*$_2$], 1.55 [3H, d, *J* 7, C(3)*H*$_3$], 3.09-3.31 (2H, m, NC*H*$_2$), 3.82 [1H, q, *J* 7, C(2)*H*], 6.62 (1H, b s, N*H*), 7.16-7.36 (5H, m, Ar*H*); δ_c (67.8 MHz) 14.2 [CH_3, *C*(4′)H_3], 19.0 [CH_3, *C*(3)H_3], 20.5 [CH_2, *C*(3′)H_2], 32.0 [CH_2, *C*(2′)H_2], 36.8 (CH_2, *C*H_2S), 39.8 (CH_2, *C*H_2N), 44.8 [CH, *C*(2)H], 127.7 (CH, aromatic *C*H), 129.1 (CH, aromatic *C*H), 129.2 (CH, aromatic *C*H), 137.8 (C, quaternary aromatic *C*), 172.5 (C, *C*O).

_N_-Methyl-2-(phenylthio)propanamide 13

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N*-methyl-2-chloro-propanamide **S6** (5.00 g, 41 mmol) in DMF (15 ml) added to a solution of sodium hydride (1.04 g of 60% dispersion in mineral oil, 43 mmol) and thiophenol (4.7 ml, 45 mmol) in DMF (150 ml). After chromatography on silica gel using ethyl acetate-hexane (25:75) as eluent, the sulfide **13** was isolated (4.56 g, 57%) as a white solid; mp 48-49 °C; (Found C, 61.83; H, 6.99; N, 6.98; S, 16.77; $C_{10}H_{13}NOS$ requires C, 61.50; H, 6.71; N, 7.17; S, 16.42%); ν_{max}/cm^{-1} (KBr) 3289 (NH), 1650 (CO), 1560 (C=C); δ_H (270 MHz) 1.54 [3H, d, *J* 7, C(3)*H*$_3$], 2.78 (3H, d, *J* 4.9, NC*H*$_3$), 3.73-3.85 [1H, q, *J* 7, C(2)*H*], 6.72 (1H, b s, N*H*), 7.13-7.40 (5H, m, Ar*H*); δ_C (67.8 MHz) 18.8 [*C*(3)H_3], 27.0 (N*C*H_3), 47.3 [*C*(2)H], 127.5, 129.6, 130.4 (aromatic *C*H), 134.5 (quaternary aromatic *C*), 172.9 (*C*O); *m/z* 195 (M^+, 68%), 137 (100, $[CH_3CHSPh]^+$), 109 (71, $[PhS]^+$), 86 (17, M-$[PhS]^+$), 58 (87, $[CONHCH_3]^+$).

_N_-2′-Propenyl-2-(phenylthio)propanamide 14

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N*-2'-propenyl-2-chloropropanamide **S7** (3.00 g, 20.34

mmol) in DMF (5 ml) added to a solution of sodium hydride (0.86 g of 60% dispersion in mineral oil, 21.36 mmol) and thiophenol (2.30 ml, 22.37 mmol) in DMF (90 ml). After chromatography on silica gel using ethyl acetate-hexane (gradient elution 5-30% ethyl acetate) as eluent, the sulfide **14** was isolated (4.10 g, 91%) as a colourless solid, mp 64-66 °C; (Found C, 64.95; H, 7.07; N, 6.46; S, 14.71. $C_{12}H_{15}NOS$ requires C, 65.12; H, 6.83; N, 6.33; S, 14.49%); ν_{max}/cm^{-1} (KBr) 3253 (br NH), 1653, 1638 (CO); δ_H (270 MHz) 1.58 [3 H, d, *J* 7, C(3)*H*$_3$], 3.83 [3 H, m, C(2)*H* and C*H*$_2$CH=], 4.84-5.24 (2 H, m, *CH*$_2$=), 5.52-5.92 (1 H, m, *CH*=CH2), 6.75 (1 H, br s, N*H*), 7.19- 7.40 (5 H, m, Ar*H*); δ_C (67.8 MHz) 18.4 [*C*(3)H$_3$], 42.0 (*C*H$_2$CH=), 47.00 [*C*(2)H], 116.3 (*C*H=CH$_2$), 127.3, 129.2, 130.3 (aromatic *C*H), 133.8 (CH=*C*H$_2$), 134.0 (quaternary *C*), 171.7 (*C*O).

***N*-3′-Phenylpropenyl-2-(phenylthio)propanamide 15**

Method C

Sodium thiophenoxide was freshly prepared by addition over 30 min of thiophenol (0.6 ml, 5.6 mmol) to a freshly prepared sodium ethoxide solution [made from sodium (0.26 g, 11.1 mmol) in dry ethanol (25 ml)] while stirring under nitrogen. *N*-3′-Phenylpropenyl-2-chloropropanamide **S8** (1.14 g, 5.1 mmol) was added slowly and stirring was continued at room temperature under nitrogen for 24 h. The ethanol was then evaporated at reduced pressure and the residue partitioned between DCM (20 ml) and water (15 ml). The organic layer was washed with NaOH (5M, 2 x 10 ml), water (2 x 10 ml), dried and concentrated under reduced pressure. Trituration using cold hexane gave the sulfide **15** (1.07 g, 71 %) as a pink, crystalline solid, mp 69-70 °C; (Found C, 72.43; H, 6.33; N, 4.68; S, 10.55. $C_{18}H_{19}NOS$ requires C, 72.69; H, 6.44; N, 4.71; S, 10.78%); ν_{max}/cm^{-1} (KBr) 3269 (br NH), 1670, 1646 (CO); δ_H (270 MHz) 1.58 [3H, d, *J* 7, C(3)*H*$_3$], 3.87 [1H, q, *J* 7, C(2)*H*], 3.97-4.10 [2H, m, C(1′)*H*$_2$], 5.97-6.07 [1H, dt, *J* 16, 6, C(3′)*H*], 6.37 [1H, d, *J* 16, C(2′)*H*], 6.78 (1H , br s, N*H*), 7.19-7.36 (10H, m, Ar*H*); δ_C (67.8 MHz) 18.3 [*C*(3)H$_3$], 41.6 [*C*(1′)H$_2$], 47.0 [*C*(2)H], 125.1, 126.4, 127.3, 127.9, 128.5, 129.0, 129.7, 132.1 (aromatic *C*H and *C*H=*C*H), 134.0, 136.5 (quaternary aromatic *C*), 171.7 (*C*O); *m/z* 297 (M^+, 3 %), 188 (100, M^+ - PhS), 137 (32, $[PhSCHCH_3]^+$), 117 (33).

_N_-4'-Fluorophenyl-2-(phenylthio)propanamide 16

The title compound was prepared using the procedure (Method A) described for **1** using *N*-4'-fluorophenyl-2-chloropropanamide **S9** (5.00 g, 24.80 mmol), thiophenol (3.85 ml, 37.20 mmol) and sodium (0.86 g, 37.20 mmol) in dry ethanol (70 ml). The reaction solution was stirred for 16 hours before work-up as described for **1** to give the sulfide **16** (6.63 g, 97%) as a pink solid which was used without further purification, mp 90-91 ^{o}C; (Found C, 65.76; H, 4.95; N, 5.04. $C_{15}H_{14}NFOS$ requires C, 65.43; H, 5.13; N, 5.09%); ν_{max}/cm^{-1} (KBr) 3500-2800 (NH), 1655 (CO), 1552, 1509, 1213, 834; δ_H (270 MHz) 1.60 [3H, d, *J* 7, C(3)H_3], 3.88 [1H, q, *J* 7, C(2)*H*], 6.90 [2H, overlapping dd, *J* 8, 8, C(3′)H], 7.03-7.42 (7H, m, Ar*H*), 8.45 (1H, b s, N*H*); δ_C (67.8 MHz) 17.9 [*C*(3)H_3], 47.7 [*C*(2)H], 115.5 [d, $^2J_{CF}$ 22, Ar*C*(3′)], 121.8 [d, $^3J_{CF}$ 9, Ar*C*(2′)], 128.0, 129.3, 131.1 (aromatic *C*H), 133.1, 133.5 (quaternary aromatic *C*), 159.5 [d, $^1J_{CF}$ 244, Ar*C*(4′)], 170.1 (*C*O); *m/z* 275 (M^+, 16), 137 (100, M^+- CONHAr), 109 (42, $[SPh]^+$).

2-(Phenylthio)propanamide 17

The title compound was prepared using the procedure (Method A) described for **1** using 2-chloropropanamide **S10** (4.00 g, 37.20 mmol), thiophenol (4.60 ml, 44.64 mmol) and sodium (1.03 g, 44.64 mmol) in dry ethanol (80 ml). The reaction solution was stirred for 16 hours before work-up as described for **1** to give **17**. Purification of the crude sulfide by chromatography using ethyl acetate-hexane (20:80) as eluent gave **17** (4.41 g, 66%) as a white, crystalline solid; mp 121-122 °C; (Found C, 60.00; H, 6.00; N, 8.11; S, 17.65. $C_9H_{11}NOS$ requires C, 59.64; H, 6.12; N, 7.73; S, 17.69%); ν_{max}/cm^{-1} (KBr) 3375 (br NH), 1652 (CO); δ_H (270 MHz) 1.50 [3 H, d, *J* 8, C(3)H_3], 3.75 [1 H, q, *J* 8, C(2)*H*], 6.03 (1 H, br s, N*H*), 6.28 (1 H, br s, N*H*), 7.23-7.41 (5 H, m, Ar*H*); δ_C (67.8 MHz) 18.3 [*C*(3)H_3], 47.0 [*C*(2)H], 128.9, 129.5, 131.4 (aromatic *C*H), 134.3 (quaternary aromatic *C*), 174.8 (*C*O); *m/z* 181 (M^+, 37 %), 137 (100, $[PhSCHCH_3]^+$), 109 (37, $[PhS]^+$), 77 (13).

_N,N_-Diphenyl-2-phenylthiopropanamide 18

Sodium (2.48 g, 21.2 mmol) was added to a solution of thiophenol (4.3 ml, 42.4 mmol) in THF (80 ml) followed by heating at 70 °C for 2 h to generate sodium thiophenoxide (21.18 mmol). *N,N*-Diphenyl-2-chloropropanamide **S12** (5 g, 19.25

mmol) was added to the cooled solution with stirring and the reaction was complete after 17 h (by TLC analysis). The THF was evaporated under reduced pressure and DCM (80 ml) was added. The organic phase was washed with saturated sodium bicarbonate (2 x 30 ml) and brine (3 x 30 ml), dried, and concentrated to give the sulfide in quantitative yield (6.4 g). Recrystallisation from dry ethanol-hexane (10:90) gave the sulfide **18** (3.26 g, 51 %) as a white, crystalline solid, mp 85-87 °C; (Found C, 75.38; H, 5.79; N, 4.03; S, 9.67. $C_{21}H_{19}NOS$ requires C, 75.64; H, 5.74; N, 4.20; S, 9.62%); ν_{max}/cm^{-1} (KBr) 1671, 1591 (CO); δ_H (270 MHz) 1.50 [3 H, d, *J* 7, C(3)H_3], 3.93 [1 H, q, *J* 7, C(2)*H*], 7.10-7.37 (15 H, m, Ar*H*); δ_C (67.8 MHz) 18.2 [*C*(3)H_3], 44.6 [*C*(2)H], 126.4-133.3 (signals could not be distinguished except for signals at 127.8 and 129.2, aromatic *C*H), 134.0 (aromatic *C*H), 133.3, 142.6 (quaternary aromatic *C*), 172.3 (*C*O); *m/z* 333 (M^+, 70%), 224 (8, M^+ - PhSH), 196 (20), 169 (100), 137 (45, $[PhSCHCH_3]^+$).

***N, N*-Dimethyl-2-(phenylthio)propanamide 19**

The title compound was prepared using the procedure (Method A) described for **1** using *N, N*-dimethyl-2-chloropropanamide **S13** (5.00 g, 36.90 mmol), thiophenol (4.56 ml, 44.28 mmol) and sodium (1.02 g, 44.28 mmol) in dry ethanol (85 ml). The reaction solution was stirred for 16 hours before work-up as described for **1** to give the crude product which was purified by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent to give **19** (6.49 g, 84%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 1648 (CO); δ_H (270 MHz) 1.46 [3H, d, *J* 7, C(3)H_3], 2.95, 3.00 [2 x 3H, 2 x s, N(CH_3)$_2$], 4.02 [1H, q, *J* 7, C(2)*H*], 7.27-7.48 (5H, m, Ar*H*); δ_C (67.8 MHz) 18.7 [*C*(3)H_3], 36.3, 37.4 (N*C*H_3), 42.7 [*C*(2)H], 128.2, 129.4 (aromatic *C*H), 133.8 (quaternary aromatic *C*), 134.5 (aromatic *C*H), 171.3 (*C*O); *m/z* 209.08658 (M^+, $C_{11}H_{15}NOS$ requires 209.08744209), (209, 84 %), 137 (97, M^+ - CON$(CH_3)_2$), 109 (56, $[PhS]^+$), 100 (50, M^+ - PhS).

(2R*, 1′R*)-*N*-1′-Phenylethyl-2-(phenylthio)propanamide and (2R*, 1′S*)-*N*-1′-phenylethyl-2-(phenylthio)propanamide 20

This was prepared following the procedure (Method C) described for sulfide **15** using (1′R/S)-*N*-1′-phenylethyl-2-chloropropanamide **S14** (3.00 g, 14.2 mmol), thiophenol (1.6 ml, 15.6 mmol), sodium (0.72 g, 31.3mmol) and dry ethanol (60 ml) to give the

crude product {3.56 g, 88% as 1:2 [(2R*, 1′R*): (2R*, 1′S*)] mixture of diastereomers}. Purification by radial chromatography using ethyl acetate-hexane (10:90) gave 2 diastereomers; (2R*, 1′R*)-*N*-1′-Phenylethyl-2-(phenylthio)propanamide **20-(2R*,1′R*)** (0.63 g, 16 %) as a white, crystalline solid [Rf 0.35 using ether-hexane (50:50) as eluent], mp 97-98 °°C; (Found C, 71.78; H, 6.66; N, 4.88. $C_{17}H_{19}NOS$ requires C, 71.54; H, 6.71; N, 4.91%); ν_{max}/cm^{-1} (KBr) 3276 (br NH), 1643 (CO); δ_H (270 MHz) 1.33 [3H, d, *J* 7, C(2′)H_3], 1.56 [3H, d, *J* 7, C(3)H_3], 3.85 [1H, q, *J* 7, C(2)*H*], 4.98-5.11 (1H, dq, *J* 7, 8, NC*H*), 6.85 (1 H, br s, N*H*), 7.15-7.40 (10 H, m, Ar*H*); δ_C (67.8 MHz) 18.1 [*C*(3)H_3], 21.4 [*C*(2′)H_3], 46.9 [*C*(2)H], 48.8 (N*C*H), 126.0, 127.2, 127.3, 128.6, 129.1, 130.3 (aromatic *C*H), 133.8, 142.8 (quaternary aromatic *C*), 170.7 (*C*O) ; *m/z* 285 (M^+, 18 %), 176 (92, M^+ - PhS), 137 (100, $[PhSCHCH_3]^+$), 105 (100), 91 (12), 77 (32), and (2R*, 1′S*)-*N*-1′-phenylethyl-2-(phenylthio)propanamide **20-(2R*,1′S*)** (1.36 g, 34 %) as a white, crystalline solid (Rf 0.4); mp 123-124 °C; (Found C, 71.92; H, 6.92; N, 5.20; S, 11.34. $C_{17}H_{19}NOS$ requires C, 71.54; H, 6.71; N,4.91; S, 11.23%); ν_{max}/cm^{-1} (KBr) 3314 (br NH), 1648 (CO); δ_H (270 MHz) 1.29 [3H, d, *J* 7, C(2′)H_3], 1.55 [3H, d, *J* 7, C(3)H_3], 3.84 [1H, q, *J* 7, C(2)*H*], 4.95-5.08 (1H, dq, *J* 7, 8, NC*H*), 6.83 (1H, br s, N*H*), 6.95-7.35 (10H, m, Ar*H*); δ_C (67.8 MHz) 18.1 [*C*(3)H_3], 21.5 [*C*(2′)H_3], 46.5 [*C*(2)H], 48.0 (N*C*H), 125.9, 127.1, 128.5, 129.1, 129.9 (aromatic *C*H), 133.9, 142.7 (quaternary aromatic *C*), 170.8 (*C*O); *m/z* 285 (M^+, 12 %), 176 (98, M^+ -PhS), 137 (100, $[PhSCHCH_3]^+$), 105 (73), 77 (22).

(2R/S, 1′S) *N*-1′-Phenylethyl-2-(phenylthio)propanamide 21

This was prepared following the procedure described for (2R*, 1′R*)(2R*, 1′S*) sulfides **20** using (2R/S, 1′S)-*N*-1′-phenylethyl-2-chloropropanamide **S15** (3.60 g, 17.06 mmol), thiophenol (1.7 ml, 18.8 mmol), sodium (0.86 g, 37.5 mmol) and dry ethanol (60 ml) to give the sulfide **21** as a light yellow solid (4.30 g, 88 %). Purification by chromatography using ethyl acetate-hexane (10:90) as eluent gave the sulfide **21** (3.90 g, 80 % as an equimolar mixture of diastereomers) as a white, crystalline solid.

***N*-4'-Methylphenyl-2-(*n*-butylthio)propanamide 23**

Method D

n-Butanethiol (3.43 g, 37.98 mmol) was added to a solution of freshly prepared sodium ethoxide [made from sodium (0.87 g, 37.98 mmol) in dry ethanol (70 ml) at 0^oC] while stirring under nitrogen. The resulting solution was stirred for 20 minutes when *N*-4'-methylphenyl-2-chloropropanamide **S1** (5.00 g, 25.32 mmol) was added gradually over 15 minutes. The reaction solution was typically seen to become cloudy 30 minutes after the final addition of the α-chloroamide. Following stirring for 16 hours, the reaction was quenched by addition of water (100 ml) and DCM (70 ml). The phases were separated and the aqueous layer was extracted with DCM (2 x 50 ml). The combined organic layers were washed with NaOH (1M, 2 x 100 ml), water (200 ml) and brine (200 ml), dried and concentrated at reduced pressure to give the crude sulfide **23**. This was purified by chromatography on silica gel using ethyl acetate-hexane as eluent (gradient elution 5-20% ethyl acetate) to give the sulfide **23** (6.08 g, 96%) as a clear oil; (Found C, 66.44; H , 8.30; N, 5.57; S, 12.75. $C_{14}H_{21}NOS$ requires C, 66.89; H, 8.42; N, 5.57; S, 12.76%); ν_{max}/cm^{-1} (film) 3296 (br NH), 1656 (CO); δ_H (270 MHz) 0.91 [3H, t, *J* 7, C(4′)H_3], 1.31-1.48 [2H, m, C(3′)H_2], 1.49-1.65 [5H, m, C(3)H_3, C(2′)H_2; C(3)H_3 could be distinguished as a doublet at approximately 1.54 ppm], 2.31 (3H, s, ArCH_3), 2.58 (2H, t, *J* 8, SCH_2), 3.51 [1H, q, *J* 7, C(2)*H*], 7.12 (2H, A of ABq, *J* 8, Ar*H*), 7.43 (2H, B of ABq, *J* 8, Ar*H*), 8.66 (1H, b s, N*H*); δ_C (67.8 MHz) 13.4 [*C*(4′)H_3], 18.5 [*C*(3)H_3], 20.7 [Ar*C*H_3], 21.9 [*C*(3′)H_2], 31.3 [*C*(2′)H_2], 31.3 (S*C*H_2), 45.4 [*C*(2)H], 120.0, 129.6 (aromatic *C*H), 133.9, 135.2 (quaternary aromatic *C*), 170.7 (*C*O); *m/z* 251 (M^+, 18 %), 163 (100), 134 (11, $[CONHTol]^+$), 117 (12, M^+ - CONHTol).

_N_-Benzyl-2-(_n_-butylthio)propanamide 22

The title compound was prepared according to the procedure (Method D) described for **23** using *N*-benzyl-2-chloropropanamide **S2** (5.00 g, 25.32 mmol), *n*-butanethiol (3.43 g, 37.98 mmol) and sodium (0.87 g, 37.98 mmol) in dry ethanol (70 ml) to give the crude sulfide **22** which was purified by chromatography on silica gel using ethyl acetate-hexane as eluent (gradient elution 5-20% ethyl acetate) to give the sulfide **22** (6.18 g, 97%) as an off-white low melting solid; ν_{max}/cm^{-1} (film) 3294 (br NH), 1648 (CO); δ_H (270 MHz) 0.87 [3H, t, *J* 7, C(4′)H_3], 1.22-1.41 [2H, m, C(3′)H_2], 1.43-1.59 [5H, m, C(3)H_3, C(2′)H_2; C(3)H_3 could be distinguished as a doublet at approximately

1.50 ppm], 2.51 (2H, t, *J* 8, SC*H*$_2$), 3.42 [1H, q, *J* 7, C(2)*H*], 4.36-4.53 (2H, m, NC*H*$_2$), 7.14 (1H, b s, N*H*), 7.22-7.36 (5H, m, Ar*H*); δ_C (67.8 MHz) 13.4 [*C*(4′)H$_3$], 18.3 [*C*(3)H$_3$], 21.8 [*C*(3′)H$_2$], 31.2 [*C*(2′)H$_2$], 31.3 (S*C*H$_2$), 43.6 (N*C*H$_2$), 44.9 [*C*(2)H], 127.4, 127.8, 128.6 (aromatic *C*H), 138.2 (quaternary aromatic *C*), 172.5 (*C*O).

_N_-4'-Fluorophenyl-2-(*n*-butylthio)propanamide 24

The title compound was prepared using the procedure (Method D) described for **23** using *N*-4'-fluorophenyl-2-chloropropanamide **S9** (5.00 g, 24.80 mmol), *n*-butanethiol (3.36 g, 37.20 mmol) and sodium (0.86 g, 37.20 mmol) in dry ethanol (70 ml). The reaction solution was stirred for 16 h before work-up as described for **23** to give the crude sulfide **24** (6.63 g, 97%) as a pale pink solid which was purified by chromatography on silica gel using ethyl acetate-hexane (gradient elution 5-20% ethyl acetate) as eluent to give **24** as a colourless solid, mp 43-46^{o}C; (Found C, 61.37; H, 7.10; N, 5.51; F, 7.62; S, 12.56. $C_{13}H_{18}NFOS$ requires C, 61.50; H, 7.11; N, 5.49; F, 7.44; S, 12.66%); ν_{max}/cm^{-1} (KBr) 1658 (CO), 1509 (vs), 1211; δ_H (270 MHz) 0.89 [3H, t, *J* 7, C(4')*H*$_3$], 1.31-1.66 [7H, m, C(3)*H*$_3$, C(3')*H*$_2$, C(2')*H*$_2$], 2.58 (2H, t, *J* 8, SC*H*$_2$), 3.52 [1H, q, *J* 7, C(2)*H*], 7.02 {2H, overlapping dd [appears as a triplet], *J* 8, 8, C(3′)*H*}, 7.49-7.58 [2H, m, C(2′)*H*], 8.78 (1H, b s, N*H*); δ_C (67.8 MHz) 13.4 [*C*(4')H$_3$], 18.3 [*C*(3)H$_3$], 21.8 [*C*(3')H$_2$], 31.1 [*C*(2')H$_2$ and S*C*H$_2$], 44.9 [*C*(2)H], 115.5 (d, $^2J_{CF}$ 24, aromatic CH, Ar*C*(3′)], 121.5 (aromatic CH, Ar*C*(2′)], 133.7 (quaternary aromatic, Ar*C*(1′)], 159.3 [d, $^1J_{CF}$ 244, quaternary aromatic, ArC(4′)], 170.9 (CO); *m/z* 255.1098 (M$^+$, $C_{13}H_{18}NFOS$ requires 255.1093). 255 (M$^+$, 2%), 167 (100), 138 (22, [CONHAr]$^+$), 117 (26, M$^+$ - CONHAr), 111 (40), 75 (45).

_N_-4'-Methylphenyl-2-(4-methoxybenzenethio)propanamide 25

The title compound was prepared according to the procedure (Method C) described for **15** using *N*-4'-methylphenyl-2-chloropropanamide **S1** (3.80 g, 19.25 mmol), 4-methoxybenzenethiol (2.75 ml, 22.25 mmol) and sodium (1.03 g, 44.8 mmol) in dry ethanol (80 ml) to give the sulfide **25** as a brown solid (4.70 g, 81%). Trituration with hexane gave **25** (4.36 g, 75%) as a white solid, mp 101-102 ^{o}C; (Found C, 67.95; H, 6.45; N, 4.76; S, 10.40. $C_{17}H_{19}NO_2S$ requires C, 67.74; H, 6.35; N, 4.65; S, 10.64%); ν_{max}/cm^{-1} (KBr) 3314, 1661 (CO), 1600, 1534, 1493; δ_H (270 MHz) 1.55 [3H, d, *J* 7,

C(3)H_3], 2.30 (3H, s, Ar CH_3), 3.72 [1H, q, *J* 7, C(2)*H*], 3.76 (3H, s, OCH_3), 6.79-6.84 (2H, m, Ar*H*), 7.09-7.15 (2H, m, Ar*H*), 7.35-7.44 (4H, m, Ar*H*), 8.26 (1H, b s, N*H*); δ_C (67.8 MHz) 17.8 [*C*(3)H_3], 20.8 (Ar*C*H_3), 49.0 [*C*(2)H], 55.2 (O*C*H_3), 114.9, 119.8 (aromatic *C*H), 123.0 (quaternary aromatic *C*), 129.4 (aromatic *C*H), 134.0 (quaternary aromatic *C*), 134.7 (aromatic *C*H), 135.0 (quaternary aromatic *C*), 160.0 (*C*-OMe), 170.0 (*C*O); *m/z* 301 (M^+, 82%), 167 (100, M^+ - CONHTol), 139 (41, $[SAr]^+$), 134 (76, $[CONHTol]^+$), 107 (56), 91(47).

_N_-Benzyl-2-(4-methoxybenzenethio)propanamide 26

The title compound was prepared according to the procedure (Method C) described for **15** using *N*-benzyl-2-chloropropanamide **S2** (2.00 g, 10.13 mmol), 4-methoxybenzenethiol (1.50 ml, 12.16 mmol) and sodium (0.51 g, 22.29 mmol) in dry ethanol (22 ml) to give the crude sulfide which was purified by chromatography on silica gel using ethyl acetate-hexane (30:70) as eluent to give the sulfide **26** (2.74 g, 90%) as a colourless solid, mp 88-90^{o}C; (Found C, 67.89; H, 6.25; N, 4.90; S, 10.66. $C_{17}H_{19}NO_2S$ requires C, 67.74; H, 6.35; N, 4.65; S, 10.645); ν_{max}/cm^{-1} (KBr) 3268, 1652 (CO), 1246; δ_H (270 MHz) 1.51 [3H, d, *J* 7, C(3)H_3], 3.69 [1H, q, *J* 7, C(2)*H*], 3.78 (3H, s, OCH_3), 4.30-4.48 (2H, symmetrical m, NCH_2), 6.73-6.81 (3H, m, N*H*, Ar*H*), 7.10-7.17 (2H, m, Ar*H*), 7.20-7.34 (5H, m, Ar*H*); δ_C (67.8 MHz) 18.1 [*C*(3)H_3], 43.8 (N*C*H_2), 48.3 [*C*(2)H], 55.3 (O*C*H_3), 114.8 (aromatic *C*H), 123.7 (quaternary aromatic *C*), 127.5, 127.8, 128.7, 134.2 (aromatic *C*H), 138.0 (quaternary aromatic *C*), 159.8 (*C*-OMe), 171.8 (*C*O); *m/z* 301.1144 (M^+, $C_{17}H_{19}NO_2S$ requires 301.1137). 301 (M^+, 12%), 162 (40, M^+ - SAr), 91 (40), 69 (100).

_N_-Ethyl-2-(4-methoxybenzenethio)propanamide 27

The title compound was prepared according to the procedure (Method C) described for **15** using *N*-ethyl-2-chloropropanamide **S3** (2.00 g, 14.80 mmol), 4-methoxybenzenethiol (2.00 ml, 16.30 mmol) and sodium (0.75 g, 32.60 mmol) in dry ethanol (60 ml) to give the sulfide **27** (3.44 g, 97%) as a golden oil which solidified on standing to a low melting solid. A sample of the crude product was purified by chromatography on silica gel using ethyl acetate-hexane as eluent for analysis; ν_{max}/cm^{-1} (KBr) 1664 (CO), 1494, 1247, 745; δ_H (270 MHz) 1.07 (3H, t, *J* 7, CH_2CH_3), 1.44 [3H, d, *J* 7, C(3)H_3], 3.22-3.38 (2H, m, NCH_2), 3.61 [1H, q, *J* 7,

C(2)*H*], 3.84 (3H, s, OCH_3), 6.48 (1H, b s, N*H*), 6.83 (2H, A of ABq, *J* 9, Ar*H*), 7.33 (2H, B of ABq, *J* 9, Ar*H*); δ_C (67.8 MHz) 14.6 (CH_2CH_3), 18.0 [*C*(3)H_3], 34.5 (NCH_2), 48.2 [*C*(2)H], 55.2 (OCH_3), 114.7 (aromatic *C*H), 123.8 (quaternary aromatic *C*), 134.2 (aromatic *C*H), 159.7 (*C*-OMe), 171.7 (O); *m/z* 239.0979 (M^+, $C_{12}H_{17}NO_2S$ requires 239.0980). 239 (M^+, 60%), 167 (100, M^+ - CONHEt), 139 (40, $[SAr]^+$), 44 (25).

Note: This compound has also been prepared using Method B to give the sulfide **27** in 76% yield.

2-(4-Methoxybenzenethio)propanamide 132

The title compound was prepared according to the procedure (Method C) described for **15** using 2-chloropropanamide **S11** (1.80 g, 16.70 mmol), 4-methoxybenzenethiol (2.30 ml, 18.40 mmol) and sodium (0.85 g, 36.80 mmol) in dry ethanol (60 ml) to give the crude sulfide **132** which was purified by trituration with ether-hexane to give the sulfide **132** (3.01 g, 85%) as a colourless solid; (Found C, 56.85; H, 6.31; N, 6.59; S, 15.22. $C_{10}H_{13}NO_2S$ requires C, 56.85; H, 6.20; N, 6.63; S, 15.17%); ν_{max}/cm^{-1} (KBr) 1630 (CO), 1459, 1248, 1027; δ_H (270 MHz) 1.48 [3H, d, *J* 7, C(3)H_3], 3.61 [1H, q, *J* 7, C(2)*H*], 3.79 (3H, s, OCH_3), 6.07 (1H, b s, N*H*), 6.33 (1H, b s, N*H*), 6.84 (2H, Aof ABq, *J* 9, Ar*H*), 7.38 (2H, B of ABq, *J* 9, Ar*H*); δ_C (67.8 MHz) 17.9 [*C*(3)H_3], 47.8 [*C*(2)H], 55.4 (OCH_3), 114.8 (aromatic *C*H), 123.5 (quaternary aromatic *C*), 134.7 (aromatic *C*H), 160.0 (*C*-OMe), 175.0 (*C*O); *m/z* 211.0663 (M^+, $C_{10}H_{13}NO_2S$ requires 211.0667), 211 (M^+, 90), 167 (100, M^+-$CONH_2$), 139 (60), 77 (28).

***N,N*-Dimethyl-2-(4-methoxybenzenethio)propanamide 28**

The title compound was prepared according to the procedure (Method C) described for **15** using *N, N*-dimethyl-2-chloropropanamide **S13** (2.00 g, 14.80 mmol), 4-methoxybenzenethiol (2.00 ml, 16.30 mmol) and sodium (0.75 g, 32.60 mmol) in dry ethanol (60 ml) to give the sulfide **28** (3.44 g, 97%) as a golden oil which solidified on recrystallisation from cyclohexane/ether to give **28** (2.91 g, 82%) as a colourless solid, (Found C, 60.22; H, 7.26; N, 5.85; S, 13.28. $C_{12}H_{17}NO_2S$ requires C, 60.22; H, 7.16; N, 5.85; S, 13.40%); ν_{max}/cm^{-1} (KBr) 1634 (CO), 1492, 1246, 1022; δ_H (270 MHz) 1.41 [3H, d, *J* 7, C(3)H_3], 2.94 [3H, s, one of N(CH_3)$_2$], 2.98 [3H, s, one of

N(C*H*$_3$)$_2$], 3.83 (3H, s, OC*H*$_3$), 3.91 [1H, q, C(2)*H*], 6.84 (2H, A of ABq, *J* 9, Ar*H*), 7.40 (2H, B of ABq, *J* 9, Ar*H*); δ_C (67.8 MHz) 17.6 [*C*(3)H$_3$], 35.9 [one of N(*C*H$_3$)$_2$], 37.0 [one of N(*C*H$_3$)$_2$], 42.8 [*C*(2)H], 55.2 (O*C*H$_3$), 114.3 (aromatic *C*H), 122.8 (quaternary aromatic *C*), 136.4 (aromatic *C*H), 160.2 (*C*-OMe), 171.3 (*C*O); *m/z* (EI) 239.0983, (M^+, $C_{12}H_{17}NO_2S$ requires 239.0980), 239 (M^+, 65), 167 (100, M^+ - CONMe$_2$), 139 (33, $[SAr]^+$), 72 (35).

***N, N*-Diphenyl-2-(4-methoxybenzenethio)propanamide 133**

The title compound was prepared according to the procedure (Method C) described for **15** using *N, N*-diphenyl-2-chloropropanamide **S12** (2.00 g, 7.70 mmol), 4-methoxybenzenethiol (1.05 ml, 8.50 mmol) and sodium (0.39 g, 17.00 mmol) in dry ethanol (40 ml) to give the crude sulfide **133** which was purified by trituration from ether-hexane to give the sulfide **133** (2.26 g, 81%) as a colourless solid, (Found C, 72.58; H, 5.86; N, 3.89; S, 9.00. $C_{22}H_{21}NO_2S$ requires C, 72.70; H, 5.82; N, 3.85; S, 8.82%); ν_{max}/cm^{-1} (KBr) 1654 (CO), 1589, 1491, 1450, 1245, 1026, 831; δ_H (270 MHz) 1.43 [3H, d, *J* 7, C(3)*H*$_3$], 3.76-3.87 (4H, m, C*H*S, OC*H*$_3$; OC*H*$_3$ could be distinguished as a singlet at 3.79 ppm), 6.77-6.83 (2H, m, Ar*H*), 7.01-7.39 (12H, broad m, Ar*H*); δ_C (67.8 MHz) 17.8 [*C*(3)H$_3$], 44.7 [*C*(2)H], 55.3 (O*C*H$_3$), 114.7 (aromatic *C*H), 123.3 (quaternary aromatic *C*), 124.5-131.0 (aromatic *C* of Ph$_2$-broad signal), 137.1 (aromatic *C*H), 142.6 (quaternary aromatic *C*), 160.3 (*C*-OMe), 172.3 (*C*O); *m/z* 363.1269, (M^+, $C_{22}H_{21}NO_2S$ requires 363.1293), 363 (M^+, 48%), 223 (18), 169 (100), 167 (65, M^+ - CONPh$_2$), 32 (43).

***N*-4′-Methylphenyl-2-(4-nitrobenzenethio)propanamide 29**

Method E

Sodium hydride (0.91 g of 60% dispersion in mineral oil, 22.8 mmol) was placed in a 3-necked round bottom flask under a flow of nitrogen. Following washing with hexane (3 x 10 ml), dry DMF (90 ml) was added *via* cannula and the resulting suspension stirred for 10 minutes. 4-Nitrobenzenethiol (4.43 g of 80% pure material, 22.8 mmol) was added as a solid from a tipper and the red solution which formed was stirred for 1 h. The amide **S1** (3.00 g, 15.2 mmol) in DMF (10 ml) was added over 10 minutes and stirring was continued for 18 h at which time a sample (3 ml) of the reaction mixture was removed for NMR analysis (60 MHz) which showed the

reaction to be 92% complete. After stirring for a further 24 hours, water (200 ml) and DCM (100 ml) were added and the phases split. The aqueous layer was extracted with DCM (2 x 50 ml) and the combined organic layers were washed with water (2 x 200ml) and brine (100 ml), dried and evaporated at reduced pressure to give the sulfide **29** as a sticky yellow solid. NMR showed the reaction to be complete and, following purification by chromatography on silica gel using ethyl acetate-hexane (gradient elution 10-30% ethyl acetate) as eluent, the sulfide **29** (3.7 g, 77%) was isolated as a yellow solid, mp 135-136 ^{o}C; (Found C, 60.67; H, 5.10; N, 8.57; S, 9.80. $C_{16}H_{16}N_2O_3S$ requires C, 60.74; H, 5.10; N, 8.86; S, 10.13%); ν_{max}/cm^{-1} (KBr) 1656 (CO), 1513, 1339; δ_H (270 MHz) 1.71 [3H, d, *J* 7, C(3)*H*$_3$], 2.29 (3H, s, ArC*H*$_3$), 4.08 [1H, q, *J* 7, C(2)*H*], 7.10 (2H, d, *J* 8, Ar*H*), 7.35 (2H, d, *J* 8, Ar*H*), 7.42 (2H, d, *J* 11, Ar*H*), 8.12 (2H, d, *J* 11, Ar*H*), 8.28 (1H, b s, N*H*); δ_C (67.8 MHz) 18.0 [*C*(3)H$_3$], 20.8 (Ar*C*H$_3$), 46.5 [*C*(2)H], 120.2, 124.2, 128.2, 129.6 (aromatic *C*H), 134.5, 134.8, 143.6, 146.3 (quaternary aromatic *C*), 168.9 (*C*O).

_N_-4′-Methylphenyl-2-(*iso*-butylthio)propanamide 30

The title compound was prepared according to the procedure (Method A) described for **1** using *N*-4′-methylphenyl-2-chloropropanamide **S1** (5.00 g, 25.32 mmol), 2-methylpropanethiol (3.00 ml, 27.85 mmol) and sodium (0.64 g, 27.85 mmol) in dry ethanol (50 ml) to give the crude sulfide **30** which was purified by chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-30% EtOAc) to give the sulfide **30** (5.40 g, 85%) as an off-white solid, mp 72-74 °C; (Found C, 66.77; H, 8.36; N, 5.63; S, 13.05. $C_{14}H_{21}NOS$ requires C, 67.04; H, 8.42; N, 5.37; S, 12.86%); ν_{max}/cm^{-1} (KBr) 3286, 1657 (CO), 1249, 817; δ_H 0.98 [3H, d, *J* 6.6, one of CH(C*H*$_3$)$_2$], 0.99 [3H, d, *J* 6.6, one of CH(C*H*$_3$)$_2$], 1.54 [3H, d, *J* 7.4, C(3)*H*$_3$], 1.69-1.91 [1H, sym m, C*H*(CH$_3$)$_2$], 2.32 (3H, s, ArC*H*$_3$), 2.36-2.54 (2H, m, SC*H*$_2$), 3.49 [1H, q, *J* 7.4, C(2)*H*], 7.12 (2H, A of ABq, *J* 6.8, Ar*H*), 7.35 (2H, B of ABq, *J* 6.8, Ar*H*), 8.63 (1H, bs, N*H*); δ_c 19.1 [*C*(3)H$_3$], 21.3 (Ar*C*H$_3$), 22.3 [one of CH(*C*H$_3$)$_2$], 22.5 [one of CH(*C*H$_3$)$_2$], 28.8 [*C*H(CH$_3$)$_2$], 41.0 (S*C*H$_2$), 46.3 [*C*(2)H], 120.0, 129.9 (aromatic *C*H), 134.4, 135.6 (quaternary aromatic *C*), 171.2 (*C*O); *m/z* 251.13439, (M$^+$, $C_{14}H_{21}NOS$ requires 251.13440). (M$^+$, 83%), 163 (100, M$^+$- SR), 134 (81), 117 (71).

_N_-4′-Fluorophenyl-2-(*iso*-butylthio)propanamide 31

The title compound was prepared according to the procedure (Method A) described for **1** using *N*-4′-fluorophenyl-2-chloropropanamide **S9** (5.00 g, 24.80 mmol), 2-methylpropanethiol (3.00 ml, 27.30 mmol) and sodium (0.63 g, 27.30 mmol) in dry ethanol (50 ml) to give the crude sulfide **31** which was purified by chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-30% EtOAc) to give the sulfide **31** (3.83 g, 87%) as an off-white solid, mp 72-74 °C; (Found C, 61.33; H, 7.11; N, 5.49; S, 12.80, F, 7.63. $C_{13}H_{18}NOSF$ requires C, 61.15; H, 7.10; N, 5.48; S, 12.56%); ν_{max}/cm^{-1} (KBr) 2957, 1660 (CO), 1509; δ_H (300 MHz) 0.99 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 1.00 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 1.54 [3H, d, *J* 7.8, C(3)H_3], 1.71-1.92 [1H, m, C*H*(CH$_3$)$_2$], 2.32-2.52 (2H, m, SCH_2), 3.49 [1H, q, *J* 7.4, C(2)*H*], 6.97-7.13 [2H, m, ArC(3′)*H*], 7.42-7.59 [2H, m, ArC(2′)*H*], 8.68 (1H, bs, N*H*); δ_c (75.5 MHz) 18.7 [*C*(3)H$_3$], 21.9 [one of CH(*C*H$_3$)$_2$], 22.1 [one of CH(*C*H$_3$)$_2$], 28.4 [*C*H(CH$_3$)$_2$], 40.7 (S*C*H$_2$), 45.9 [*C*(2)H], 115.7 [d, $^2J_{CF}$ 23, Ar*C*(3′)], 121.3 [d, $^3J_{CF}$ 8, Ar*C*(2′)], 133.5 [d, $^4J_{CF}$ 3, quaternary Ar*C*(1′)], 159.4 [d, $^1J_{CF}$ 245, Ar*C*(4′)], 170.9 (*C*O); *m/z* 255.10950, (M$^+$, $C_{13}H_{18}NFOS$ requires 255.10930), 255 (M$^+$, 53%), 138 (67, M$^+$-CONHAr), 101 (28, M$^+$-Cl-CONHAr), 88 (21, SAr$^+$) 57 (100).

_N_-Ethyl-2-(*iso*-butylthio)propanamide 32

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N*-ethyl-2-chloropropanamide **S3** (5.00 g, 36.90 mmol) in DMF (5 ml) added to a solution of sodium hydride (1.49 g of 60% dispersion in mineral oil, 38.74 mmol) and 2-methylpropanethiol (4.41 ml, 40.60 mmol) in DMF (150 ml). After chromatography on silica gel using ethyl acetate-hexane (gradient elution 0-20% ethyl acetate), the sulfide **32** was isolated (5.60 g, 80%) as a low melting solid, (Found C, 56.84; H, 10.32; N, 7.39; S, 16.69. $C_9H_{19}NOS$ requires C, 57.09; H, 10.12; N, 7.40; S, 16.94%); ν_{max}/cm^{-1} (film) 1644 (CO), 1555, 1073; δ_H (300 MHz) 0.96 [6H, d, *J* 7.0, CH(CH_3)$_2$), 1.17 (3H, t, *J* 7.2, CH$_2$CH_3), 1.45 [3H, d, *J* 7.4, C(3)H_3], 1.61-1.91 [1H, m, C*H*(CH$_3$)$_2$], 2.31-2.44 (2H, m, SCH_2), 3.31-3.42 [4H, m, CH_2CH$_3$, C(2)*H*], 6.83 (1H, bs, N*H*); δ_c (75.5 MHz) 14.8 (CH$_2$*C*H$_3$), 18.8 [*C*(3)H$_3$], 21.9 [one of CH(*C*H$_3$)$_2$], 22.1 [one of CH(*C*H$_3$)$_2$], 28.4 [*C*H(CH$_3$)$_2$], 34.5 (N*C*H$_2$), 40.7 (S*C*H$_2$), 45.1 [*C*(2)H], 172.6 (*C*O); *m/z* 189.11874, (M$^+$, $C_9H_{19}NOS$ requires 189.11893), 189 (M$^+$, 53%), 190 (M$^+$ + 1), 101 (67, M$^+$- SR), 57 (50).

_N_-Isopropyl-2-(*iso*-butylthio)propanamide 134

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N*-isopropyl-2-chloropropanamide **S4** (5.00 g, 33.40 mmol) in DMF (5 ml) added to a solution of sodium hydride (1.40 g of 60% dispersion in mineral oil, 35.07 mmol) and 2-methylpropanethiol (4.00 ml, 36.74 mmol) in DMF (150 ml). After chromatography on silica gel using ethyl acetate-hexane (gradient elution 0-20% ethyl acetate), the sulfide **134** was isolated (6.10 g, 87%) as a low melting solid, (Found C, 58.84; H, 10.42; N, 6.74; S, 15.47. $C_{10}H_{21}NOS$ requires C, 59.07; H, 10.41; N, 6.89; S, 15.77%); ν_{max}/cm^{-1} (film) 1638 (CO), 1212, 908; δ_H (300 MHz) 1.01 [6H, d, *J* 6.6, $SCH_2CH(CH_3)_2$], 1.17 [3H, t, *J* 6.6, one of $NHCH(CH_3)_2$], 1.18 [3H, t, *J* 6.6, one of $NHCH(CH_3)_2$], 1.43 [3H, d, *J* 7.3, C(3)H_3], 1.69-1.89 [1H, m, $SCH_2CH(CH_3)_2$], 2.28-2.46 (2H, m, SCH_2), 3.33 [1H, q, *J* 7.3, C(2)*H*], 3.98-4.15 [1H, m, $NCH(CH_3)_2$], 6.89 (1H, bd, *J* 7.3, N*H*); δ_c (75.5 MHz) 18.7 [*C*(3)H_3], 21.9 [one of $SCH_2CH(CH_3)_2$], 22.1 [one of $SCH_2CH(CH_3)_2$], 22.6 [2 x $NCH(CH_3)_2$], 28.4 [$SCH_2CH(CH_3)_2$], 40.5 (SCH_2), 41.4 [$NCH(CH_3)_2$], 44.9 (SCH), 171.7 (*C*O); *m/z* 204 ($M^+ + 1$, 53%), 115 (100, M^+ - SR), 57 (45).

_N_-4′-Fluorophenyl-2-(*iso*-propylthio)propanamide 33

The title compound was prepared according to the procedure (Method A) described for **1** using *N*-4′-fluorophenyl-2-chloropropanamide **S9** (9.61 g, 47.69 mmol), *iso*-propylthiol (6.11 ml, 52.17 mmol) and sodium (1.20 g, 52.17 mmol) in dry ethanol (96 ml) to give the crude sulfide **33** which was purified by chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-30% EtOAc) to give the sulfide **33** (10.34 g, 90%) as an off-white solid, mp 84-85 °C; (Found C, 59.63; H, 6.78; N, 5.75; S, 13.60, F, 7.61. $C_{12}H_{16}NOSF$ requires C, 59.72; H, 6.68; N, 5.80; S, 13.29, F, 7.87%); ν_{max}/cm^{-1} (KBr) 3264, 1660 (CO), 1509; δ_H (300 MHz) 1.29 [3H, d, *J* 6.7, one of $CH(CH_3)_2$], 1.32 [3H, d, *J* 6.7, one of $CH(CH_3)_2$], 1.55 [3H, d, *J* 7.8, C(3)H_3], 3.01 [1H, m, $CH(CH_3)_2$], 3.54 (1H, q, *J* 6.8, SCH_2), 6.91-7.08 [2H, m, ArC(3′)*H*], 7.41-7.56 [2H, m, ArC(2′)*H*], 8.72 (1H, bs, N*H*); δ_c (75.5 MHz) 19.2 [*C*(3)H_3], 23.5 [one of $CH(CH_3)_2$], 23.5 [one of $CH(CH_3)_2$], 36.2 [$CH(CH_3)_2$], 44.8 [*C*(2)H], 115.7 [d, $^2J_{CF}$ 23, ArC(3′)], 121.4 [d, $^3J_{CF}$ 8, ArC(2′)], 133.7 [d, $^4J_{CF}$ 3,

quaternary ArC(1′)], 159.4 [d, $^{1}J_{CF}$ 245, ArC(4′)], 171.4 (*C*O); *m/z* 241.09322, (M^{+}, $C_{12}H_{16}NFOS$ requires 241.09367), 241 (M^{+}, 15%), 167 (100), 138 (45), 111 (75).

_N_-Benzyl-2-(benzylthio)propanamide 34

The title compound was prepared according to the procedure (Method A) described for **1** using *N*-benzyl-2-chloropropanamide **S2** (4.00g, 20 mmol), benzylmercaptan (2.85 ml, 24 mmol) and sodium (0.55g, 24 mmol) in dry ethanol (85 ml) to give the crude sulfide **34** and dibenzyl disulfide in the ratio 1:0.22. This was purified by chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 2-40% EtOAc) to give the sulfide **34** (4.58 g, 80 %) as a white solid, mp 66-67 ^{o}C; (Found C, 71.23; H, 6.63; N, 5.05; S, 11.12. $C_{17}H_{19}NOS$ requires C, 71.54; H, 6.71; N, 4.91%; S, 11.24); ν_{max}/cm^{-1} (KBr) 3289 (NH), 3029 (CH), 1648 (CO), 1555 (NH bend), 1495, 1453 (CN stretch); δ_H (300 MHz) 1.39 [3H, d, *J* 7.3, C(3)*H*$_3$], 3.28 [1H, q, *J* 7.3, C(2)*H*], 3.70 (2H, s, C*H*$_2$S), 4.26 (1H, A of ABX, J_{AB} 14.7, J_{AX} 5.9, one of C*H*$_2$NH), 4.34 (1H, B of ABX, J_{AB} 14.7, J_{BX} 5.9, one of C*H*$_2$NH), 6.94 (1H, b s, N*H*), 7.10-7.32 (10H, m, Ar*H*); δ_c (75.5 MHz) 17.5 [*C*(3)H$_3$], 35.3 (S*C*H$_2$), 42.7 (*C*H$_2$NH), 43.2 [*C*(2)H], 126.3, 126.6, 126.7, 127.7, 127.7, 127.8 (aromatic *C*H), 136.3, 137.1 (quaternary aromatic *C*), 171.1 (*C*O); *m/z* 286 [$(M+H)^{+}$, 100%].

_N_-4′-Fluorophenyl-2-(benzylthio)propanamide 35

The title compound was prepared following the procedure (Method A) described for **1** using *N*-4′-fluorophenyl-2-chloropropanamide **S9** (2.80 g, 16 mmol), benzylmercaptan (2.28 ml, 19 mmol) and sodium (0.44 g, 19 mmol) in dry ethanol (70 ml). The reaction solution was stirred for 16 hours before work-up as described for **1** gave the crude sulfide and dibenzyl disulfide in the ratio 1:0.22. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 5-40% ethyl acetate) to give **35** (1.62 g, 35%)* as a pale pink solid, mp 99-101^{o}C; (Found C, 66.40; H, 5.59; N, 4.44; S, 11.16; F, 6.83. $C_{16}H_{16}FNOS$ requires C, 66.41; H, 5.57; N, 4.84; S, 11.08; F, 6.57%); ν_{max}/cm^{-1} (KBr) 3297 (NH), 2928 (CH), 1654 (CO), 1558 (NH bend), 1507, 1378 (CN stretch); δ_H (300 MHz) 1.53 [3H, d, *J* 7.4, C(3)*H*$_3$], 3.43 [1H, q, *J* 7.4, C(2)*H*], 3.78 (2H, s, C*H*$_2$S), 7.00 {2H, overlapping dd [appears as a triplet], *J* 8.8, 8.8, C(3′)*H*}, 7.16-7.45 (7H, m, Ar*H*), 8.43 (1H, b s, N*H*); δ_c (75.5 MHz) 18.9 [*C*(3)H$_3$], 36.9 (*C*H$_2$S), 45.6 [*C*(2)H], 116.0

[d, $^2J_{CF}$ 23, aromatic CH, Ar*C*(3′)], 121.8 [d, $^3J_{CF}$ 8, aromatic CH, Ar*C*(2′)], 127.9, 129.2, (aromatic *C*H), 134.0, 137.6 (quaternary aromatic *C*), 159.8 [d, $^1J_{CF}$ 244, quaternary aromatic, Ar*C*(4′)], 170.8 (*C*O); *m/z* 290 [$(M+H)^+$, 8%], 189 [$(M - NHAr)^+$, 17%], 91 [$(C_7H_7)^+$, 100%].

*A yield of 84% was obtained for a batch that was later synthesised.

_N_-_n_-Butyl-2-(benzylthio)propanamide 36

The title compound was prepared according to the procedure (Method B) described for **10** using a solution of *N*-*n*-butyl-2-chloropropanamide **S5** (1.60 g, 9.8 mmol) in DMF (3 ml) added to a solution of sodium hydride (0.49 g of 50% dispersion in mineral oil, 10.3 mmol) and benzylmercaptan (1.22 ml, 10.3 mmol) in DMF (50 ml). After chromatography on silica gel using ethyl acetate-hexane (gradient elution 5-40% ethyl acetate), the sulfide **36** (1.50g, 61%) was isolated as a pale yellow oil; ν_{max}/cm^{-1} (film) 3293 (NH), 3064 (CH), 1647 (CO), 1603 (NH bend), 1495, 1452 (CN stretch); δ_H (300 MHz) 0.93 [3H, t, *J* 7.2, C(4′)H_3], 1.23-1.49 [7H, m, includes C(3′)H_2, C(2′)H_2 and C(3)H_3; C(3)H_3 could be distinguished as a doublet at 1.43 ppm, *J* 7.4], 3.14-3.26 (2H, m, CH_2NH), 3.29 [1H, q, *J* 7.4, C(2)*H*], 3.72 (2H, s, SCH_2), 6.60 (1H, b s, N*H*), 7.22-7.36 (5H, m, Ar*H*); δ_c (75.5 MHz) 14.2 [*C*(4′)H_3], 19.0 [*C*(3)H_3], 20.5 [*C*(3′)H_2], 32.0 [*C*(2′)H_2], 36.8 (*C*H_2S), 39.8 (*C*H_2N), 44.8 [*C*(2)H], 127.7, 129.1, 129.2 (aromatic *C*H), 137.8 (quaternary aromatic *C*), 172.5 (*C*O); *m/z* 274.1240, ([M+Na]$^+$, $C_{14}H_{21}NOSNa$ requires 274.1242), 274 [$(M+Na)^+$, 14%], 91 ($C_7H_7^+$, 100%).

_N,N_-Dimethyl-2-(benzylthio)propanamide 37[11]

This was prepared following the procedure (Method A) described for **1** using *N,N*-dimethyl-2-chloropropanamide **S13** (7.86 g, 60 mmol), benzylmercaptan (8.25 ml, 70 mmol) and sodium (1.60 g, 70 mmol) in dry ethanol (130 ml). The reaction solution was stirred for 16 hours before work-up as described for **1** to give the crude sulfide and dibenzyl disulfide in the ratio 1:0.02. Purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 5-15% ethyl acetate) gave **37** (10.41 g, 78%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2928 (CH), 1644 (CO), 1494, 1454 (CN stretch); δ_H (300 MHz) 1.49 [3H, d, *J* 6.8, C(3)H_3], 2.86 [3H, s, one of N(CH_3)$_2$], 2.90 [3H, s, one of N(CH_3)$_2$], 3.53 [1H,q, *J* 6.8, C(2)*H*], 3.74 (1H, A of

ABq, J_{AB} 13.3, one of SCH_2), 3.80 (1H, B of ABq, J_{AB} 13.3, one of SCH_2), 7.18-7.35 (5H, m, Ar*H*); δ_c (75.5 MHz) 18.3 [*C*(3)H_3], 34.3 (S*C*H_2), 36.41 [one of N(*C*H_3)$_2$], 37.5 [one of N(*C*H_3)$_2$], 38.2 [*C*(2)H], 127.5, 128.8, 129.4 (aromatic *C*H), 138.3 (aromatic *C*), 171.5 (*C*O); *m/z* 224.1114, ([M+H]$^+$, $C_{12}H_{18}NOS$ requires 224.1109), 224 [(M+H)$^+$, 100%], 91 ($C_7H_7^+$, 15%).

_N_-4′-Methylphenyl-2-(benzylthio)propanamide 38

This was synthesized following the procedure (Method A) described for **1** using *N*-4′-methylphenyl-2-chloropropanamide **S1** (4.00 g, 20 mmol), benzylmercaptan (2.85 ml, 24 mmol) and sodium (0.55 g, 24 mmol) in dry ethanol (80 ml). The crude sulfide **38** and dibenzyl disulfide were obtained in the ratio 1:0.02. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 2-10% ethyl acetate), the pure sulfide **38** (2.45 g, 43%)* was isolated as a white solid, mp 69-71^{o}C; (Found C, 71.20; H, 6.72; N, 4.90; S, 11.68. $C_{17}H_{19}NOS$ requires C, 71.54; H, 6.71: N, 4.91; S, 11.23%); ν_{max}/cm^{-1} (KBr) 3298 (NH), 2924 (CH), 1656 (CO), 1602, 1515 (NH bend), 1495, 1372 (CN stretch); δ_H (300 MHz) 1.51 [3H, d, *J* 7.4, C(3)*H*$_3$], 2.32 (3H, s, Ar-C*H*$_3$), 3.42 [1H, q, *J* 7.4, C(2)*H*], 3.77 (2H, s, SC*H*$_2$), 7.09-7.50 (9H, m, Ar*H*), 8.38 (1H, b s, N*H*); δ_c (75.5 MHz) 18.9 [*C*(3)H$_3$], 21.3 (Ar-*C*H$_3$), 36.8 (S*C*H$_2$), 45.5 [*C*(2)H], 120.9, 127.8, 129.2, 129.3, 129.9 (aromatic *C*H), 133.1, 134.0, 136.1 (aromatic *C*), 169.2 (*C*O); *m/z* 308.1090 ([M+Na]$^+$, $C_{17}H_{19}NOSNa$ requires 308.1085), 286 [(M+H)$^+$, 40%], 189 (2%), 130 (18%), 124 (20%), 108 (22%), 91 (2%), 82 (100%).

* A yield of 57% was obtained on a batch that was prepared later.

_N_-4′-Methyl-2-(benzylthio)propanamide 39[9]

This was synthesized following the procedure (Method A) described for **1** using *N*-methyl-2-chloropropanamide **S6** (2.96 g, 24 mmol), benzylmercaptan (3.44 ml, 29 mmol) and sodium (0.67 g, 29 mmol) in dry ethanol (70 ml) to give the crude sulfide **39** and dibenzyl disulfide in the ratio 1:0.12. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 20-50% ethyl acetate), the pure sulfide **39** (4.28 g, 85%) was isolated as a white solid, mp 60-61^{o}C; ν_{max}/cm^{-1} (KBr) 3291 (NH), 2928 (NH), 1648 (CO) 1557 (NH bend), 1495, 1400 (CN stretch); δ_H (300 MHz) 1.43 [3H, d, *J* 7.4, C(3)*H*$_3$], 2.74 (3H, d, *J*

4.9, C*H*$_3$NH), 3.31 [1H, q, *J* 7.4, C(2)*H*], 3.72 (1H, s, SC*H*$_2$), 6.56 (1H, b s, N*H*), 7.21-7.37 (5H, m, Ar*H*).

_N_-Phenyl-2-(benzylthio)propanamide 40

The title compound was synthesized according to the procedure (Method A) described for **1** using *N*-phenyl-2-chloropropanamide **S10** (4.00 g, 20 mmol), benzylmercaptan (3.07 ml, 26 mmol), and sodium (0.60 g, 26 mmol) in dry ethanol (70 ml) to give the crude sulfide **40** and dibenzyl disulfide in the ratio 1:0.07. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 5-40% ethyl acetate), the pure sulfide (3.72 g, 69%) was isolated as a white solid, mp 116-117^{o}C; (Found C, 71.00; H, 6.38; N, 5.38; S, 11.98. $C_{16}H_{17}NOS$ requires C, 70.81; H, 6.31; N, 5.16; S, 11.82%); ν_{max}/cm^{-1} (KBr) 3301 (NH), 3061 (CH), 2973 (CH), 1660 (CO), 1600, 1532 (NH bend), 1499, 1372 (CN stretch); δ_H (300 MHz) 1.53 [3H, d, *J* 7.4, C(3)*H*$_3$], 3.44 [1H, q, *J* 7.4, C(2)*H*], 3.78 (2H, s, SC*H*$_2$), 7.12-7.36 (8H, m, Ar*H*), 7.47-7.54 (2H, m, Ar*H*), 8.42 (1H, b s, N*H*); δ_c (75.5 MHz) 18.9 [*C*(3)H$_3$], 36.8 (S*C*H$_2$), 45.6 [*C*(2)H], 120.0, 124.8, 127.8, 129.2, 129.3, 129.4 (aromatic *C*H), 137.5, 138.0 (aromatic *C*), 170.8 (*C*O); *m/z* (ESI) 272 [(M+H)$^+$, 100%].

2-(Benzylthio)propanamide 41[10]

This was prepared following the procedure (Method A) described for **1** using 2-chloropropanamide **S11** (1.07 g, 9.9 mmol), benzylmercaptan (1.40 ml, 11.9 mmol) and sodium (0.27 g, 11.9 mmol) in dry ethanol (20 ml). The crude reaction mixture contained the crude sulfide **41** and dibenzyl disulfide in the ratio 1:0.03. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 20-40% ethyl acetate), the pure sulfide **41** (0.80 g, 41%) was isolated as a white solid, mp 93-94^{o}C (Lit.,[10] 85-86^{o}C); (Found C, 61.43; H, 6.58; N, 7.20; S, 16.55. $C_{10}H_{13}NOS$ requires C, 61.50; H, 6.71; N, 7.17; S, 16.42%); ν_{max}/cm^{-1} (KBr) 3370 (NH), 3192 (NH), 3030 (CH), 2974 (CH), 1635 (CO), 1600 (NH bend), 1494, 1403 (CN stretch); δ_H (300 MHz) 1.46 [3H, d, *J* 7.3, C(3)*H*$_3$], 3.29 [1H, q, *J* 7.3, C(2)*H*], 3.77 (2H, s, SC*H*$_2$), 5.38 (1H, b s, one of N*H*$_2$), 6.45 (1H, b s, one of N*H*$_2$), 7.19-7.41 (5H, m, Ar*H*); δ_c (75.5 MHz) 18.7 [*C*(3)H$_3$], 36.6 (S*C*H$_2$), 43.9

[*C*(2)H], 127.8, 129.1, 129.3 (aromatic *C*H), 137.7 (aromatic *C*), 175.7 (*C*O); *m/z* 196 [$(M+H)^+$, 100%], 91 ($C_7H_7^+$, 32%).

Synthesis of the α-methylthioamides

2-(Methylthio)-propionic acid S16[12]

Thiolactic acid (89.0 ml, 106.0 g, 1 mol) was added slowly to a solution of NaOH (80 g, 2 mol) in water (250 ml). The resulting mixture was treated dropwise during 10 min with methyl iodide (63.0 ml, 1 mol) and stirring was continued for 16 h at room temperature. The mixture was diluted with water (200 ml) and dichloromethane (200 ml), the layers were separated and the aqueous phase was extracted with dichloromethane (3 x 75 ml). The combined organic layers were washed with brine (200 ml) and dried to afford a colourless liquid **S16** (96.12 g, 81%), which required no further purification; δ_H (300 MHz) 1.46 [3H, d, *J* 7.1, C(3)H_3], 2.22 (3H, s, SCH_3), 3.37 [1H, q, *J* 7.1, C(2)*H*].

***N*-4′-Fluorophenyl-2-(methylthio)propionamide 42**

A solution of 2-(methylthio)propionic acid **S16** (15.00 g, 125 mmol) in dichloromethane (120 ml) was treated dropwise with thionyl chloride (18.2 ml, 250 mmol) followed by DMF (5 drops). Gas evolution began immediately and the mixture was stirred at ambient temperature for 18 h, after which the volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane (200 ml) and cooled to 0 °C whereupon 4-fluoroaniline (24.00 ml, 250 mmol) was added with vigorous stirring. After 10 min the cooling bath was removed and stirring was continued for 16 h at room temperature. The mixture was diluted with water (200 ml), separated, and the aqueous phase extracted with dichloromethane (2 x 200 ml). The combined organic layers were extracted with HCl (2M, 200 ml) and brine (200 ml) and dried to give the sulfide **42** (25.20 g, 95%) as a pink solid, which was used without further purification, mp 84-86 °C; (Found C, 56.28; H, 5.72; N, 6.54; S, 14.60; F, 8.78. $C_{10}H_{12}FNOS$ requires C, 56.32; H, 5.67; N, 6.57; S, 15.03; F, 8.91%); ν_{max}/cm^{-1} (KBr) 3258 (NH), 1658 (CO), 1509, 882; δ_H (300 MHz) 1.54 [3H, d, *J* 6.0, C(3)H_3], 2.10 (3H, s, SCH_3), 3.43 [1H, q, *J* 7.4, C(2)*H*], 6.95-7.09 [2H, m, C(3′)*H*], 7.48-7.61 [2H, m, C(2′)*H*], 8.61 (1H, b s, N*H*); δ_c (75.5 MHz) 14.1 (S*C*H_3), 17.8 [*C*(3)H_3], 46.2 [*C*(2)H], 115.7 [d, $^2J_{CF}$ 23, Ar*C*(3′)], 121.5 [d, $^3J_{CF}$ 8, Ar*C*(2′)], 133.7

[d, $^4J_{CF}$ 3, Ar*C*(1′)], 159.4 [d, $^1J_{CF}$ 244, Ar*C*(4′)], 170.4 (*C*O); *m/z* 213 (M^+, 25%), 167 (60), 75 (M^+ - CONHAr).

_N_-Benzyl-2-(methylthio)propionamide 43

The title compound was prepared using the procedure described for **42** using 2-(methylthio)propionic acid **S16** (4.80 g, 40.0 mmol), thionyl chloride (5.78 ml, 80.0 mmol) and DMF (5 drops) in dichloromethane (100 ml). The crude acid chloride was then treated with benzylamine (9.00 g, 80.0 mmol) in dichloromethane (180 ml). The reaction mixture was stirred for 16 h before work-up as described for **42** gave the amide **43** as a white solid (7.50 g, 90%), which was used without further purification, mp 58-61 °C; (Found C, 63.17; H, 7.14; N, 6.64; S, 15.36. $C_{11}H_{15}NOS$ requires C, 63.12; H, 7.22; N, 6.69; S, 15.32%); ν_{max}/cm^{-1} (KBr) 3290 (NH), 1651 (CO), 1548, 1213, 1028; δ_H (300 MHz) 1.57 [3H, d, *J* 7.3, C(3)*H*$_3$], 2.07 (3H, s, SC*H*$_3$), 3.37 [1H, q, *J* 7.3, C(2)*H*], 4.41 (2H, d, *J* 6.8, NC*H*$_2$), 6.90 (1H, b s, N*H*), 7.21-7.41 (10H, m, Ar*H*); δ_c (75.5 MHz) 14.6 (S*C*H$_3$), 18.4 [*C*(3)H$_3$], 44.1 (*C*H$_2$NH), 45.9 [*C*(2)H], 128.0, 128.1, 129.2 (aromatic *C*H), 138.6 (quaternary aromatic *C*), 172.5 (*C*O); *m/z* 209.08841 (M^+, $C_{11}H_{15}NOS$ requires 209.08744). 209 (M^+, 25%), 163 (80), 91 (95), 75 (100).

_N-n_-Butyl-2-(methylthio)propionamide 44

The title compound was prepared using the procedure described for **42** using 2-(methylthio)propionic acid **S16** (8.00 g, 66.7 mmol), thionyl chloride (9.69 ml, 133.3 mmol) and DMF (5 drops) in dichloromethane (180 ml). The crude acid chloride was then treated with butylamine (7.31 g, 133.3 mmol) in dichloromethane (160 ml). The reaction mixture was stirred for 16 h before work-up as described for **42** gave the amide **63** as a yellow oil. Purification by column chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent gave the amide **44** as a clear oil (8.63 g, 73%), (Found C, 54.32; H, 9.74; N, 7.90; S, 18.20. $C_8H_{17}NOS$ requires C, 54.80; H, 9.78; N, 7.99; S, 18.29%); ν_{max}/cm^{-1} (film) 1646 (CO), 1533, 1210, 1073; δ_H (300 MHz) 0.93 [3H, t, *J* 7.3, C(4′)*H*$_3$], 1.22-1.59 [7H, m, includes C(3′)*H*$_2$, C(2′)*H*$_2$ and C(3)*H*$_3$], 2.08 (3H, s, SC*H*$_3$), 3.21-3.39 [3H, m, C*H*$_2$NH and C(2)*H*], 6.95 (1H, b s, N*H*); δ_c (75.5 MHz) 14.0 [*C*(4′)H$_3$], 14.2 (S*C*H$_3$), 18.0 [*C*(3)H$_3$], 20.3 [*C*(3′)H$_2$], 31.9 [*C*(2′)H$_2$],

39.6 (*C*H_2N), 45.1 [*C*(2)H], 172.5 (*C*O); *m/z* 175.10321 (M^+, $C_8H_{17}NOS$ requires 175.10308). 175 (M^+, 2%), 100 (20), 75 (100).

_N_-Isopropyl-2-(methylthio)propionamide 45

The title compound was prepared using the procedure described for **42** using 2-(methylthio)propionic acid **S16** (5.06 g, 42.16 mmol), thionyl chloride (6.10 ml, 84.33 mmol) and DMF (5 drops) in dichloromethane (100 ml). The crude acid chloride was then treated with isopropylamine (7.30 ml, 84.33 mmol) in dichloromethane (180 ml). The reaction mixture was stirred for 16 h before work-up as described for **421** gave the amide **45** as a yellow oil. Purification by column chromatography on silica gel using ethyl acetate-hexane (20:80) as eluant gave the amide **45** as a white solid (5.60 g, 84%), mp 89-91 °C; (Found C, 52.10; H, 9.09; N, 8.42; S, 20.19. $C_7H_{15}NOS$ requires C, 52.13; H, 9.38; N, 8.62; S, 19.88%); ν_{max}/cm^{-1} (KBr) 3777 (NH), 1639 (CO), 1260, 764; δ_H (300 MHz) 1.17 [3H, t, *J* 6.6, one of CH(C*H*$_3$)$_2$], 1.18 [3H, t, *J* 6.6, one of CH(C*H*$_3$)$_2$], 1.45 [3H, d, *J* 7.3, C(3)*H*$_3$], 2.08 (3H, s, SC*H*$_3$), 3.29 [1H, q, *J* 7.3, C(2)*H*], 3.98-4.16 [1H, m, NC*H*(CH$_3$)$_2$], 6.67 (1H, bs, N*H*); δ_c (75.5 MHz) 14.2 (S*C*H$_3$), 18.0 [*C*(3)H$_3$], 22.6 [one of CH(*C*H$_3$)$_2$], 22.7 [one of CH(*C*H$_3$)$_2$], 41.5 [*C*(2)H], 45.6 [*C*H(CH$_3$)$_2$], 171.1 (*C*O); *m/z* 161 (M^+, 5%), 115 (78), 75 (100).

_N_-Methyl-2-(methylthio)propionamide 135[11]

The title compound was prepared using the procedure described for **42** using 2-(methylthio)propionic acid **S16** (5.00 g, 41.60 mmol), thionyl chloride (5.96 ml, 83.20 mmol) and DMF (5 drops) in dichloromethane (100 ml). The crude acid chloride was then treated with aqueous methylamine (40 ml, 83.20 mmol) in dichloromethane (60 ml). The reaction mixture was stirred for 16 h before work-up as described for **42** gave the amide **135** as a colourless solid (3.77 g, 68%), which was used without further purification, mp 44-46 °C; ν_{max}/cm^{-1} (KBr) 3089, 2972, 1651 (CO), 1562, 1449, 1372; δ_H (300 MHz) 1.47 [3H, d, *J* 7.3, C(3)*H*$_3$], 2.09 (3H, s, SC*H*$_3$), 2.81 (3H, d, *J* 4.3, NC*H*$_3$), 3.33 [1H, q, *J* 7.3, C(2)*H*], 6.82 (1H, bs, N*H*).

Spectral characteristics were consistent with previously reported data.[11]

_N_-4'-Methylphenyl-2-(methylthio)propionamide 46

A solution of DCC (1.89 g, 9.16 mmol) and DMAP (catalytic amount) in DCM (20 ml) was slowly added to a solution of *p*-toludine (0.98 g, 9.16 mmol) in DCM (20 ml) at 0°C. A solution of 2-(methylthio)-propionic acid **S16** (1.00 g, 8.33 mmol) in DCM (20 ml) was added dropwise. The resulting solution was stirred for 10 minutes at 0°C before the ice bath was removed. The reaction was stirred at room temperature for 16 hours when most of the DCU by-product was removed by filtration of the reaction mixture through celite. The filtrate was washed with HCl (1N, 100 ml), saturated $NaHCO_3$ (100 ml) and brine (100 ml), dried and concentrated at reduced pressure to give **46** which was purified by chromatography on silica gel using ethyl acetate-hexane (gradient elution: 10 to 20% ethyl acetate) as eluent to give the amide **46** as a colourless solid (1.77 g, 102%) containing *ca*. 5% DCU (as estimated by ^{1}H NMR); δ_H (270 MHz) 1.51 [3H, d, *J* 7, C(3)*H*$_3$], 2.14 (3H, s, ArC*H*$_3$ or SC*H*$_3$), 2.33 (3H, s, ArC*H*$_3$ or SC*H*$_3$), 3.45 [1H, q, *J* 7, C(2)*H*], 7.10-7.48 (4H, ABq, *J* 7, Ar*H*), 8.55 (1H, b s, N*H*); δ_C (67.8 MHz) 14.0 [*C*(3)H$_3$ or S*C*H$_3$], 17.7 [*C*(3)H$_3$ or S*C*H$_3$], 20.8 (Ar*C*H$_3$), 46.2 [*C*(2)H], 119.7, 129.4 (aromatic *C*H), 134.0, 135.1 (quaternary aromatic *C*), 170.1 (*C*O); *m/z* 209.0885 (M^+, $C_{11}H_{15}NOS$ requires 209.0874). 209 (M^+, 9%), 163 (16), 134 (4, [CONHTol]$^+$), 84 (77), 75 (22, M^+-CONHTol), 49 (100).

2-(Methylthio)propionamide 136

A solution of 2-(methylthio)propionic acid **S16** (0.52g, 4.16 mmol) in dichloromethane (10ml) was treated dropwise with thionyl chloride (0.45ml, 6.24 mmol) followed by DMF (2 drops). Gas evolution began immediately and the mixture was stirred at ambient temperature for 18 h, after which the volatiles were removed under reduced pressure. The residue was dissolved in acetone (10ml) and cooled to 0°C whereupon ammonia (35%, 0.45 ml, 8.32 mmol) was added with vigorous stirring. After 10 min the cooling bath was removed and stirring was continued for 16 h at room temperature. The acetone and excess ammonia were removed by distillation at reduced pressure. The resulting residue was taken up in DCM (20 ml) and water (20 ml) was added. The phases were separated, and the aqueous phase extracted with dichloromethane (2 x 20ml). The combined organic layers were extracted with HCl (2M, 20ml) and then brine (20ml), dried and concentrated to give the sulfide **136** (0.38g, 76%) as a white solid; δ_H (300 MHz) 1.49 (3H, d, *J* 6.0, C(3)*H*$_3$), 2.14 (3H, s,

SC*H*$_3$), 3.32 (1H, q, *J* 7.3, C(2)*H*), 6.86 (1H, bs, N*H*), 7.04 (1H, bs, N*H*), 8.61 (1H, bs, N*H*);

Despite repeated attempts it was not possible to completely remove the DMF from this sulfide.

***N*,*N*-Diethyl-2-(methylthio)propionamide 137**

The title compound was prepared using the procedure described for **42** using 2-(methylthio)propionic acid **S16** (8.00 g, 66.66 mmol), thionyl chloride (9.54 ml, 133.33 mmol) and DMF (5 drops) in dichloromethane (100 ml). The crude acid chloride was then treated with diethylamine (13.71 ml, 133.33 mmol) in dichloromethane (80 ml). The reaction mixture was stirred for 16 h before work-up as described for **42** gave the amide **137** as a yellow oil. Purification by column chromatography on silica gel using ethyl acetate-hexane (10:90) as eluant gave the amide **137** as a clear oil (7.60 g, 66%); ν_{max}/cm^{-1} (film) 2927 (NH), 1640 (CO), 1221, 1017; δ_H (300 MHz) 1.15 (3H, t, *J* 7.1, one of CH$_2$C*H*$_3$), 1.23 (3H, t, *J* 7.1, one of CH$_2$C*H*$_3$), 1.44 [3H, d, *J* 7.3, C(3)*H*$_3$], 2.08 (3H, s, SC*H*$_3$), 3.18-3.41 (2H, m, one of C*H*$_2$CH$_3$), 3.49-3.71 [3H, m, contains one of C*H*$_2$CH$_3$ and C(2)*H*]; δ_c (75.5 MHz) 11.5 (one of CH$_2$*C*H$_3$), 13.0 (one of CH$_2$*C*H$_3$), 14.8 (S*C*H$_3$), 17.3 [*C*(3)H$_3$], 37.3 [*C*(2)H], 40.5 (one of *C*H$_2$CH$_3$), 42.0 (one of *C*H$_2$CH$_3$), 170.2 (*C*O); *m/z* (EI) 176.11120 (M$^+$, $C_8H_{18}SNO$ requires 176.11108). 176 (M$^+$ + 1, 100%), 129 (40), 100 (50).

Synthesis of extended chain α-thioamides

2-Bromobutanoyl chloride 142

Method F

A solution of 2-bromobutanoic acid **138**[3] (3.02 g, 18.1 mmol) in DCM (20 ml) was stirred at 0 °C. Oxalyl chloride (2.53 g, 19.9 mmol) was added dropwise. DMF (5 drops) was added as a catalyst. The reaction mixture was allowed to warm to RT and stirred for a further 5 h until gas evolution had ceased. The DCM was concentrated to give 2-bromobutanoyl chloride **142** (2.46 g, 73 % crude) as a white solid which was used without further purification; ν_{max}/cm^{-1} (film) 1795 (CO acid chloride).

Method G

Thionyl chloride (25.29 g, 0.22 mol) was stirred with 2-bromobutanoic acid **138**[3]

(7.10 g, 0.04 mol) while heating at reflux for 1 h until evolution of SO_2 and HCl gases had ceased. The product mixture was cooled to RT, toluene (4 x 20 ml) was added and evaporated portionwise to azeotropically remove the excess thionyl chloride. *Note:* It is important not to heat the product mixture above 40 °C as the acid chloride will evaporate. 2-Bromobutanoyl chloride **142** (5.02 g, 64 %) was obtained as a colourless oil due to the presence of < 5 % thionyl chloride) which was used without further purification;

ν_{max}/cm^{-1} (film) 1795 (acid chloride).

2-Bromopentanoyl chloride 143

This was prepared following the procedure (Method F) described for α-bromobutanoyl chloride **142** using 2-bromopentanoic acid **139**[3] (5.00 g, 27.6 mmol), oxalyl chloride (3.86 g, 30.4 mmol), DCM (35 ml) and DMF (3 drops) to give the acid chloride **143** as a brown solid in quantitative yield, which was used without further purification; ν_{max}/cm^{-1} (film) 1783 (CO acid chloride).

2-Bromo-3-phenylpropanoyl chloride 144

This was prepared following the procedure described for α-bromobutanoyl chloride (method G) using 2-bromo-3-phenylpropanoic acid **140**[2] (1.00 g, 4.4 mmol), thionyl chloride (1.3 ml, 17.5 mmol), carbon tetrachloride (2 ml) to give 2-bromo-3-phenylpropanoyl chloride **144** (0.95 g, 83 %) as a pale yellow oil which was used without further purification; ν_{max}/cm^{-1} (film) 1783 (CO acid chloride).

***N*-4′-Methylphenyl-2-bromobutanamide 145**

2-Bromobutanoyl chloride **142** (2.46 g, 18.1 mmol) was dissolved in DCM (25 ml) and stirred at RT. *p*-Toluidine (2.90 g, 27.1 mmol) was added portionwise over 15 mins as the reaction was exothermic. The reaction mixture was stirred for 25 h, then quenched with water (40 ml), the layers were separated and the organic layer washed with sodium bicarbonate (2 x 20ml). The aqueous layer was extracted with DCM (2 x 10 ml) and the combined organic layers were washed with water (2 x 20ml) and brine (2 x 20 ml), dried and concentrated to give the α-bromoamide **145** as a brown solid (4.20 g, 91 % crude) which was used without further purification; δ_H (60 MHz) 1.01 [3H, t, *J* 7, C(4)H_3], 1.76-2.40 [2H, m, C(3)H_2], 2.25 (3H, s, ArCH_3), 4.13-4.43 (1H,

dd, *J* 6, 7, C*H*Br), 6.82-7.45 (4H, m, Ar*H*), 8.05 (1H, br s, N*H*).

_N_-4′-Methylphenyl-2-bromopentanamide 146

This was prepared following the procedure described for amide **S8** using 2-bromopentanoylchloride **143** (7.45 g, 27.6 mmol), *p*-toluidine (4.43 g, 41.4 mmol) and DCM (50 ml) to give *N*-4′-methylphenyl-2-bromopentanamide **146** (6.32 g, 85 %) as a light brown solid; δ_H (60 MHz) 0.90 [3H, t, *J* 7, C(5)H_3], 1.43 [2H, q, *J* 7, C(4)H_2], 1.82-2.24 [2H, m, C(3)H_2], 2.25 (3H, s, ArCH_3), 4.43 (1H, dd, *J* 6, 7, C*H*Br), 6.87-7.50 (4H, m, Ar*H*), 8.63 (1H, br s, N*H*).

(S)-_N_-1′-Phenylmethyl-2-bromopentanamide 147

This was prepared following the procedure described for amide **S1** using 2-bromopentanoyl chloride **143** (4.40 g, 20.7 mmol), (S)-1-phenylethylamine (2.76 g, 22.8 mmol), triethylamine (3.2 ml, 22.8 mmol) in DCM (100 ml) to give the amide **147** (5.31 g, 94 % an equimolar mixture of diastereomers) as an off-white solid which was used without further purification; ν_{max}/cm^{-1} (KBr) 3276 (br NH), 1643 (CO amide); δ_H (60 MHz) 0.86-0.97 [3H, m, C(5)H_3], 1.41-1.49 [5H, m, C(4)H_2 and C(2′)H_3], 1.91-1.99 [2H, m, C(3)H_2], 4.20 (1H, m, C*H*Br), 4.85-5.10 [1H, m, C(1′)*H*], 6.50 (1H, br s, N*H*), 7.03-7.40 (5H, m, Ar*H*).

_N_-4′-Methylphenyl-2-bromo-3-phenylpropanamide 148

This was prepared following the procedure described for amide **S8** using 2-bromo-3-phenylpropanoyl chloride **144** (6.00 g, 24.3 mmol), *p*-toluidine (3.66 g, 34.2 mmol) and DCM (50 ml) to give *N*-4′-methylphenyl-2-bromo-3-phenylpropanamide **148** (6.60 g, 85 %) as a light brown solid which was used without further purification; δ_H (60 MHz) 2.40 (3H, s, ArCH_3), 3.49, 3.53 [2H, d, *J* 6, 8, C(3)H_2], 4.63, 4.65 (1H, d, *J* 6, 8, C*H*Br), 7.00- 7.37 (9H, m, Ar*H*), 7.87 (1H, br s, N*H*).

_N_-4′-Methylphenyl-2-bromo-3-methylbutanamide 149

A solution of DCC (1.00 g, 4.9 mmol) in DCM (10 ml) at 0 °C was added slowly to a stirred solution of *p*-toluidine (0.52 g, 4.9 mmol) in DCM (10 ml) also at 0 °C. A solution of 3-methyl-2-bromobutanoic acid **141** (0.81 g, 4.4 mmol) in DCM (10 ml) at

0 °C was added dropwise over 10 min. The reaction mixture was removed from the ice bath and allowed to warm slowly to room temperature, stirring was continued for 2 h. Most of the DCU by-product was removed by filtration of the reaction mixture through celite. The filtrate was washed with aqueous HCl (1 N, 10 ml), aqueous sodium bicarbonate (20 ml), brine (2 x 10 ml), dried and evaporated to give *N*-4′-methylphenyl-2-bromo-3-methylbutanamide **149** (0.88 g, 74 %) containing *ca.* 9 % DCU (as estimated by ^{1}H NMR) as a light yellow solid which was used without further purification; δ_H (60 MHz) 1.08, 1.10 [2 x 3H, 2 x d, *J* 7, 7, CH(*CH*$_3$)$_2$], 2.17-2.56 [1H, m, C(3)*H*], 2.25 (3H, s, ArC*H*$_3$), 4.34 (1H, d, *J* 6, C*H*Br), 6.97-7.45 (5H, ABq, *J* 8, Ar*H*), 8.30 (1H, br s, N*H*).

_N_-4′-Methylphenyl-2-bromo-3-methylbutanamide 150

A solution of DCC (1.00 g, 4.9 mmol) in DCM (10 ml) at 0 °C was added slowly to a stirred solution of *p*-toluidine (0.52 g, 4.9 mmol) in DCM (10 ml) also at 0 °C. A solution of 3-methyl-2-bromobutanoic acid **141** (0.81 g, 4.4 mmol) in DCM (10 ml) at 0 °C was added dropwise over 10 min. The reaction mixture was removed from the ice bath and allowed to warm slowly to room temperature, stirring was continued for 2 h. Most of the DCU by-product was removed by filtration of the reaction mixture through celite. The filtrate was washed with aqueous HCl (1 N, 10 ml), aqueous sodium bicarbonate (20 ml), brine (2 x 10 ml), dried and evaporated to give *N*-4′-methylphenyl-2-bromo-3-methylbutanamide **150** (0.88 g, 74 %) containing *ca.* 9 % DCU (as estimated by ^{1}H NMR) as a light yellow solid which was used without further purification; δ_H (60 MHz) 1.08, 1.10 [2 x 3H, 2 x d, *J* 7, 7, CH(*CH*$_3$)$_2$], 2.17-2.56 [1H, m, C(3)*H*], 2.25 (3H, s, ArC*H*$_3$), 4.34 (1H, d, *J* 6, C*H*Br), 6.97-7.45 (5H, ABq, *J* 8, Ar*H*), 8.30 (1H, br s, N*H*).

_N_-4′-Methylphenyl-2-(phenylthio)butanamide 47

This was prepared following the procedure (Method A) described for sulfide **1** using *N*-4′-methylphenyl-2-bromobutanamide **145** (2.11 g, 8.20 mmol), thiophenol (1.00 ml, 9.84 mmol), sodium (0.27 g, 9.84 mmol) and dry ethanol (20 ml) to give the product **47** (2.13 g, 91 %) as a colourless solid which was used without further purification, mp 81-83 °C; (Found C, 71.43; H, 6.64; N, 4.95; S, 10.92. $C_{17}H_{19}NOS$

requires C, 71.43; H, 6.71; N, 4.91; S, 11.23%); ν_{max}/cm^{-1} 3286 (br NH), 1676, 1656 (CO amide); δ_H (270 MHz) 1.14 (3H, t, *J* 7, C(4)H_3), 1.80-2.04 (1H, m, one of C(3)H_2), 2.05-2.28 (1H, m, one of C(3)H_2), 2.29 (3H, s, ArCH_3), 3.75 (1H, dd, *J* 7, 7, C(2)*H*), 7.04-7.45 (9H, m, ArH), 8.75 (1H, b s, NH); δ_C (67.8 MHz) 12.0 [*C*(4)H_3], 20.8 (Ar*C*H_3), 25.9 [*C*(3)H_2], 55.5 [*C*(2)H], 120.0, 127.4, 129.3, 129.4, 130.9 (aromatic *C*H), 133.7, 134.2, 134.9 (quaternary aromatic *C*), 169.4 (*C*O).

_N_-4′-Methylphenyl-2-(phenylthio)pentanamide 48

This was prepared following the procedure (Method C) described for sulfide **15** using *N*-4′-methylphenyl-2-bromopentanamide **146** (2.98 g, 11.1 mmol), thiophenol (1.3 ml, 12.2 mmol), sodium (0.56 g, 24.4 mmol) and dry ethanol (70 ml). The sulfide **48,** formed quantitatively, was purified by chromatography using ethyl acetate-hexane (7:93) as eluent to give *N*-4′-methylphenyl-2-(phenylthio)pentanamide **48** (3.01 g, 91 %) as a white, crystalline solid, mp 82-3 °C; (Found C, 72.36; H, 7.11; N, 4.74, S, 10.56. $C_{18}H_{21}NOS$ requires C, 72.20; H, 7.07; N, 4.68; S, 10.71%); ν_{max}/cm^{-1} 3281 (br NH), 1652, 1602 (CO amide); δ_H (300 MHz) 0.98 [3H, t, *J* 7, C(5)H_3], 1.50-1.69 [2H, m, C(4)H_2], 1.65-1.95 [1H, m, C(3)H_AH_B], 1.98-2.15 [1H, m, C(3)H_AH_B], 2.30 (3H, s, ArCH_3), 3.70-3.80 [1H, m, C(2)*H*], 7.05-7.44 (9H, m, Ar*H*), 8.38 (1H, br s, N*H*); δ_C (270 MHz) 13.7 [*C*(5)H_3], 20.7 [*C*(4)H_2], 20.8 (Ar*C*H_3), 34.6 [*C*(3)H_2], 53.7 [*C*(2)H], 120.0, 127.4, 129.3, 129.4, 130.5 (aromatic *C*H), 133.8, 134.2, 134.9 (quaternary aromatic *C*), 169.5 (*C*O).

(1′S)-_N_-1′-Phenylethyl-2-phenylthiopentanamide 49

This was prepared using (1′S)-*N*-1′-phenylmethyl-2-bromopentanamide **147** (4.00 g, 14.7 mmol), thiophenol (1.7 ml, 16.2 mmol), sodium (1.03 g, 23.0 mmol), and dry ethanol (65 ml) (Method H) to give the crude sulfide (4.29 g, 99 %) as an off-white solid. Purification by trituration using hexane gave the sulfide **49** (3.51 g, 80 % as an equimolar mixture of diastereomers) as a white, crystalline solid, mp 70-73 °C; -5.46 (c 8.0 in ethanol); (Found C, 72.46; H, 7.31; N, 4.46; S, 10.16. $C_{19}H_{23}NOS$ requires C, 72.80; H, 7.40; N, 4.47; S, 10.23%); ν_{max}/cm^{-1} (KBr) 3277 (br NH), 1642 (CO amide); δ_H (as a mixture of diastereomers) (270 MHz) 0.93, 0.96 [3H, t, *J* 8, 7, C(5)H_3], 1.31, 1.42 [3H, d, *J* 7, 7, C(2′)H_3], 1.39-1.47 [2H, m, C(4)H_2], 1.67-1.92

[1H, m, one of C(3)H_2], 1.95-1.99 [1H, m, one of C(3)H_2], 3.75 [1H, t, *J* 6, C(2)*H*], 4.97-5.10 [1H, m, C(1′)*H*], 7.01-7.32 (10H, m, Ar*H*); δ_C (67.8 MHz) 13.7 [*C*(5)H_3], 20.7, 20.9 [*C*(4)H_2], 21.5, 21.6 [*C*(2′)H_3], 34.6, 34.8 [*C*(3)H_2], 48.9 [*C*(1′)H], 52.7, 52.8 [*C*(2)H], 126.0, 126.1, 127.0, 127.1, 127.2, 127.4, 128.5, 128.7, 129.7, 130.1, 130.2 (aromatic *C*H), 142.8, 143.0 (quaternary aromatic *C*), 170.4 (*C*O); *m/z* 313 (M^+, 17 %), 271 (10), 204 (79, M^+ -PhS), 165 (40, M^+- CONHR), 105 (100, $[CHCH_3Ph]^+$).

***N*-4′-Methylphenyl-2-(phenylthio)-3-phenylpropanamide 50**

This was prepared following the procedure (Method C) described for sulfide **15** using amide **148** (6.50 g, 20.4 mmol), thiophenol (2.31 ml, 22.5 mmol), sodium (1.03 g, 45.0 mmol) and dry ethanol (120 ml) to give the crude sulfide **50** (5.98 g, 85 %). Purification by chromatography of a 1.00 g portion using ethyl acetate-hexane (5:95) as eluent gave pure *N*-4′-methylphenyl-2-(phenylthio)-3-phenylpropanamide **50** (0.67 g, 57 %) as an off-white, crystalline solid, mp 157-158 °C; (Found C, 75.99; H, 6.18; N, 3.99; S, 9.25. $C_{22}H_{21}NOS$ requires C, 76.05; H, 6.09; N, 4.03; S, 9.23%); ν_{max}/cm^{-1} (KBr) 3228 (br NH), 1645, 1593 (CO amide); δ_H (270 MHz) 2.30 (3H, s, ArCH_3), 3.18 [1H, dd, *J* 7, 7, C(3)H_AH_B], 3.45 [1H, dd, *J* 7, 7, C(3)H_AH_B], 4.04 (1H, dd, *J* 7, 7, C(2)*H*], 7.04-7.39 (14H, m, Ar*H*), 8.14 (1H, br s, N*H*); δ_C (67.8 MHz) 20.95 (Ar*C*H_3), 38.5 [*C*(3)H_2], 55.5 [*C*(2)H], 120.2, 127.0, 127.9, 128.5, 129.5, 131.3 (aromatic *C*H), 133.5, 134.4, 134.1, 137.6 (quaternary aromatic *C*), 168.0 (*C*O).

***N*-4′-Methylphenyl-3-methyl-2-(phenylthio)butanamide 151**

This was prepared following the procedure (Method C) described for sulfide **15** using *N*-4′-methylphenyl-2-bromo-3-methylbutanamide **149** (2.65 g, 9.8 mmol), sodium (0.46 g, 20.1 mmol), thiophenol (1.1 ml, 10.8 mmol) and ethanol (50 ml). Purification by trituration from ether gave *N*-4′-methylphenyl-3-methyl-2-(phenylthio)butanamide **151** (0.73 g, 25 %) as a white solid. On a larger scale (37 mmol of amide **147**) preparation the yield of sulfide **151** was 48 %; mp 120-123 °C; (Found C, 71.98; H, 6.90; N, 4.83; S, 10.22. $C_{18}H_{21}NOS$ requires C, 72.20; H, 7.07; N, 4.68; S, 10.71%); ν_{max}/cm^{-1} (KBr) 3246 (br NH), 1655 (CO amide); δ_H (270 MHz) 1.13, 1.19 [2 x 3H, 2 x d, *J* 7, 7, *(CH₃)₂*C(3)H], 2.30 (3H, s, ArCH_3), 2.42-2.54 [1H, m, C(3)*H*], 3.70 [1H, d, *J* 6, C(2)*H*], 7.09-7.19 (9H, m, Ar*H*), 8.60 (1H, br s, N*H*); δ_C

(67.8 MHz) 19.6 [one of $(CH_3)_2C(3)H$], 20.8 ($ArCH_3$), 21.2 [one of $(CH_3)_2C(3)H$], 31.6 [*C*(3)H], 61.9 [*C*(2)H], 120.1, 127.2, 129.5, 129.9, 130.2 (aromatic *C*H), 134.8, 134.3, 134.2 (quaternary aromatic *C*), 169.1 (*C*O); *m/z* 299 (M^+, 30%), 165 (40, $[(CH_3)_2CHCHSPh)]^+$, 134 (12, $[CONHTol]^+$).

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 ($ArCH_3$), 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*-Benzyl-*Z*-3-chloro-2-(phenylthio)propenamide 51**

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-benzyl-2-(phenylthio)propanamide **9** (10.6 g, 39.11 mmol), NCS (10.18 g, 76.26 mmol) and toluene (212 ml). The reaction solution was heated for 4 h at 90°C. Purification by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent gave the β-chloroacrylamide **51** (9.52 g, 81%) as a colourless solid, mp 78-79 °C; (Found C, 63.33; H, 4.63; N, 4.61; S, 10.98; Cl, 11.93. $C_{16}H_{14}ClNOS$ requires C, 63.26; H, 4.65; N, 4.61; S, 10.55; Cl, 11.67%); ν_{max}/cm^{-1} (KBr) 3406 (b, NH), 1654 (CO), 1519; δ_H (270 MHz) 4.40 (2H, d, *J* 6, CH_2NH),

6.82-7.35 (11H, m, Ar*H*, N*H*), 7.96 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 44.1 (*C*H_2NH), 127.1, 127.3, 127.5, 128.2, 128.6, 129.6 (aromatic *C*H), 130.5, 132.9, 137.3 [quaternary aromatic *C* and *C*(2)S], 139.6 [*C*(3)HCl=], 162.3 (*C*O); *m/z* 303 (M^+, 21 %), 268 (37, M^+- Cl), 158 (100), 134 (40, $[PhS{=}C{=}CH]^+$), 91 (50, $[PhCH_2]^+$), 77 (12).

***N*-Ethyl-*Z*-3-chloro-2-(phenylthio)propenamide 52**

This was prepared following the optimised procedure (Method A) described for β-chloroacrylamide **3** using *N*-ethyl-2-(phenylthio)propanamide **10** (6.50 g, 31.10 mmol), NCS (8.10 g, 60.65 mmol) and toluene (130 ml). The reaction mixture was heated for 2 h at 90°C. Following filtration and evaporation of the toluene, the β-chloroacrylamide **52** was isolated (6.23 g, 81%) as an off-white solid which required no further purification, mp 59-61 °C; (Found C, 54.23; H, 5.27; N, 5.66; Cl, 14.23; S, 13.68. $C_{11}H_{12}ClNOS$ requires C, 54.65; H, 5.00; N, 5.79; Cl, 14.67; S, 13.26%); ν_{max}/cm^{-1} (KBr) 3431 (b NH), 1647 (CO); δ_H (270 MHz) 0.96 [3H, t, *J* 7, C(2′)H_3], 3.19-3.35 (2H, m, NCH_2), 6.82 (1H, b s, N*H*), 7.18-7.44 (5H, m, Ar*H*), 7.91 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 14.4 [*C*(2′)H_3], 35.0 (NCH_2), 127.1 ,128.1, 129.2 (aromatic *C*H), 130.7, 133.0 [quaternary aromatic C and *C*(2)S], 138.9, [*C*(3)HCl=], 162.2 (*C*O); *m/z* 241 (M^+, 84%), 134 (100, $[PhSC{=}CH]^+$), 109 (17), 77 (12).

***N-i*-Propyl-*Z*-3-chloro-2-(phenylthio)propenamide 53**

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-isopropyl-2-(phenylthio)propanamide **11** (4.88 g, 21.88 mmol), NCS (5.70 g, 42.67 mmol) and toluene (98 ml). The reaction mixture was heated for 3 h at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **53** was isolated. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (15:85) as eluent to give the β-chloroacrylamide **53** as an off-white solid (5.00 g, 89 %), mp 74-76 °C; (Found C, 56.62; H, 5.56; N, 5.68; Cl, 14.10; S, 12.71. $C_{12}H_{14}ClNOS$ requires C, 56.35; H, 5.52; N, 5.48; Cl, 13.86; S, 12.54%); ν_{max}/cm^{-1} (KBr) 3255 (b NH), 1638 (CO), 1540, 742; δ_H (270 MHz) 0.98 [6H, d, *J* 8, CH(CH_3)$_2$], 3.90-4.08 (1H, m, NC*H*), 6.47-6.61 (1H, b d, N*H*), 7.18-7.39 (5H, m, Ar*H*), 7.83 [1H, s, C(3)*H*Cl=]; δ_C

(67.8 MHz) 22.2 [CH(*C*H_3)$_2$], 42.0 (N*C*H), 127.1, 128.4, 129.4 (aromatic *C*H), 131.1, 133.0 (quaternary aromatic *C* and *C*(2)S], 137.9 [*C*(3)HCl=], 161.3 (*C*O); *m/z* 255 (M^+, 22%), 220 (8, M^+ - Cl), 134 (39, [PhS=C=CH]$^+$), 110 (100), 91 (8), 77 (22).

***N*-*n*-Butyl-*Z*-3-chloro-2-(phenylthio)propenamide 54**

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-*n*-butyl-2-(phenylthio)propanamide **12** (3.37 g, 14.22 mmol), NCS (3.70 g, 27.73 mmol) and toluene (68 ml). The reaction mixture was heated for 3 h at 90^{o}C. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **54** was isolated. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (15:85) as eluent to give the β-chloroacrylamide **54** as clear oil (3.10 g, 81 %); (Found C, 57.77; H, 6.12; N, 5.21; Cl, 13.00; S, 12.00. $C_{13}H_{16}NClOS$ requires C, 57.87; H, 5.98; N, 5.19; Cl, 13.14; S, 11.88%); ν_{max}/cm^{-1} (film) 3314 (br, NH), 1651 (CO), 1519, 739; δ_H (270 MHz) 0.79 [3H, t, *J* 7, C(4′)*H*$_3$], 1.02-1.19 [2H, m, C(3′)*H*$_2$], 1.24-1.41 [2H, m, C(2′)*H*$_2$], 3.21 (2H, q, *J* 7, NC*H*$_2$), 6.82 (1H, b s, N*H*), 7.18-7.38 (5H, m, Ar*H*), 7.93 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 13.6 [*C*(4′)H$_3$], 20.0 [*C*(3′)H$_2$], 31.3 [*C*(2′)H$_2$], 39.8 (N*C*H$_2$), 127.1, 128.2, 129.5 (aromatic *C*H), 130.8, 133.1 [quaternary aromatic *C* and *C*(2)S], 139.0 [*C*(3)HCl=], 162.2 (*C*O); *m/z* 269.0511 (M^+, $C_{13}H_{16}N^{35}ClOS$ requires 269.0641). 269 (34, M^+), 234 (12, M^+- Cl), 197 (19, M^+- NHR), 169 (17, M^+-CONHR), 150 (12, M^+- SPh), 134 (100, [PhS=C=CH]$^+$), 109 (25, [SPh]$^+$), 57 (34).

***N*-Methyl-*Z*-3-chloro-2-(phenylthio)propenamide 55**

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-methyl-2-(phenylthio)propanamide **13** (2.84 g, 15 mmol), NCS (3.79 g, 28 mmol) and toluene (50 ml). The reaction mixture was heated for 3.5 h at 90^{o}C. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **55** was isolated. The crude product was purified by chromatography on silica gel using ethyl acetate-dichloromethane-hexane (4:1:5) as eluent to give the β-chloroacrylamide **55** as a white solid (2.28 g, 69 %); ν_{max}/cm^{-1} (KBr) 3373 (br, NH), 1648 (CO), 1518; δ_H (300 MHz) 2.79 (3H, d, *J* 5.0, NC*H*$_3$), 6.97 (1H, b s, N*H*), 7.19-7.29 (5H, m, Ar*H*), 7.98 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 26.9 (N*C*H$_3$), 126.9, 127.6, 129.5 (aromatic *C*H), 130.0, 132.9 [quaternary aromatic *C*

and *C*(2)S], 140.1 [*C*(3)HCl=], 163.1 (*C*O); *m/z* 227 (M^+, 75%), 192 (32, [M - $^{35}Cl]^+$), 134 (100, $[PhSC{=}CH]^+$), 58 (97, $[CONHCH_3]^-$).

_N_-2'-Propenyl-_Z_-3-chloro-2-(phenylthio)propenamide 56

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-2'-propenyl-2-(phenylthio)propanamide **14** (2.80 g, 12.67 mmol), NCS (3.30 g, 24.71 mmol) and toluene (60 ml). The reaction mixture was heated for 3.5 h at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **56** was isolated. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (15:85) as eluent to give the β-chloroacrylamide **56** as a clear oil (2.71 g, 84 %); (Found C, 56.45; H, 4.84; N, 5.25; S, 12.75; Cl, 14.34. $C_{12}H_{12}ClNOS$ requires C, 56.80; H, 4.77; N, 5.52; S, 12.64; Cl, 13.97%); ν_{max}/cm^{-1} (film) 3314 (br, NH), 1655 (CO), 1560, 1515, 740; δ_H (270 MHz) 3.80-3.91 (2H, m, NCH_2), 4.81-5.02 (2H, m, =CH_2), 5.56-5.73 (1H, m, C*H*=), 6.96 (1H, b s, N*H*), 7.18-7.29 (5H, m, Ar*H*), 7.96 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 42.2 (NCH_2), 116.3 (=CH_2), 127.0, 128.4, 129.4 (aromatic *C*H), 130.4, 132.95 (quaternary aromatic *C* and *C*(2)S), 133.2 (*C*H=), 139.66 [*C*(3)HCl=], 162.1 (*C*O); *m/z* 253 (M^+, 25%), 218 (52, M^+ - Cl), 144 (12), 134 (100, $[PhSC{=}C{=}CH]^+$), 108 (56), 77 (19).

_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_-4'-Fluorophenyl-_Z_-3-chloro-2-(phenylthio)propenamide 58

The title compound was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-4'-fluorophenyl-2-(phenylthio)propanamide **16** (5.00 g, 18.20 mmol), NCS (4.74 g, 35.50 mmol) and toluene (100 ml). The reaction mixture was heated at 90°C for 2.5 h. Purification by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent gave the β-chloroacrylamide **58** (5.32 g, 95%) as a colourless solid; mp 96-97°C; (Found C, 58.46; H, 3.64; N, 4.50; Cl, 11.55; F, 5.70; S, 10.23. $C_{15}H_{11}NClFOS$ requires C, 58.54; H, 3.60; N, 4.55; Cl, 11.52; F, 6.17; S, 10.42%); ν_{max}/cm^{-1} (KBr) 1658 (CO), 1608, 1523, 1406, 1214, 832; δ_H (270 MHz) 6.96 [2H, overlapping dd, *J* 9, 9, C(3′)*H*], 7.17-7.38 (7H, m, Ar*H*), 8.03 [1H, s, C(3)*H*Cl=], 8.65 (1H, b s, N*H*); δ_C (67.8 MHz) 116.1 [d, $^2J_{CF}$ 22, aromatic CH, Ar*C*(3′)], 122.5 [d, $^3J_{CF}$ 9, aromatic CH, ArC(2′)], 127.9, 128.7, 130.2 (aromatic *C*H), 131.2, 132.9, 133.6 [quaternary aromatic *C* or *C*(2)S], 141.1 [*C*(3)HCl=], 160.3 [d, $^1J_{CF}$ 245, quaternary aromatic, ArC(4′)], 160.9 (*C*O); *m/z* 307.0243 (M^+, $C_{15}H_{11}N^{35}ClFOS$ requires 307.0234). 307 (M^+, 75%), 272 (45, M^+- Cl), 271 (46, M^+- HCl), 197 (52), 169 (78, M^+- CONHAr), 134 (100, M^+- Cl - CONHAr).

_Z_-3-Chloro-2-(phenylthio)propenamide 59

This was prepared following the optimised procedure (Method A) described for β-chloroacrylamide **3** using 2-(phenylthio)propanamide **17** (2.48 g, 13.7 mmol), NCS (3.57 g, 26.72 mmol) and toluene (60 ml). The reaction solution was heated for 2.5 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **59** was isolated as a colourless solid with evidence of some impurities; integration of the crude NMR spectrum of this product suggests it contains up to 44% of the dichloroacrylamide. The succinimide cake was reslurried in CCl_4 and following filtration a further 0.14 g of clean product was recovered (total of 1.36 g, 46%). The crude product can also be purified by chromatography on silica gel using hexane ethyl acetate (75:25) as eluent, mp 128-130 °C; (Found C, 50.80; H, 3.72; N, 6.30; S, 14.65; Cl, 16.90. C_9H_8ClNOS requires C, 50.59; H, 3.77; N, 6.56; S, 15.01; Cl, 16.59%); ν_{max}/cm^{-1} (KBr) 3447 (sharp NH),

1685, 1659 (CO α,β-unsaturated amide); δ_H (270 MHz) 6.07 (1H, br s, N*H*), 6.71 (1H, br s, N*H*), 7.20-7.33 (5H, m, Ar*H*), 7.96 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 127.1, 128.1, 129.5 (aromatic *C*H), 130.0, 132.9 (quaternary aromatic *C* and *C*(2)S], 140.9 [*C*(3)HCl=], 164.7 (*C*O); *m/z* 213 (M^+, 16%), 178 (10, M^+- Cl), 134 (18, $[PhSC=CH]^+$), 110 (18).

_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) (Rf 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) (Rf 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, N_-Dimethyl-_Z_-3-chloro-2-(phenylthio)propenamide 62 and _N, N_-Dimethyl-_E_-3-chloro-2-(phenylthio)propenamide 63 and _N, N_-Dimethyl-3,3-dichloro-2-(phenyl-thio)propenamide 103 and _N, N_-Dimethyl-2,3,3-trichloro-2-(phenylthio)propenamide 104

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*, *N*-dimethyl-2-(phenylthio)-propanamide **19** (5.00 g, 23.92 mmol), NCS (6.71 g, 50.23 mmol) and toluene (100 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. NMR of the crude showed approximately 20% minor β-chloroacrylamide **63**, 40% major β-chloroacrylamide **62** and 40% of the dichloroacrylamide **103**. Following chromatography on silica using DCM-hexane (70:30), the major β-chloroacrylamide **62** eluted as a mixture with the dichloroacrylamide **103** (3.12g, 77% of isolated mass) as the less polar fraction in a ratio of 1:1. β-Chloroacrylamide **62**: ν_{max}/cm^{-1} (film) 1650 (CO), 1574; δ_H (270 MHz) 2.84 [3H, s, one of N(C*H*$_3$)$_2$], 2.89 [3H, s, one of N(C*H*$_3$)$_2$], 6.25 [1H, s, C(3)*H*Cl=], 7.31-7.42 (3H, m, Ar*H*), 7.50-7.61 (2H, m, Ar*H*). δ_C (67.8 MHz) 34.6, 38.3 (N*C*H$_3$), 116.9 [*C*(3)HCl=], 117.3 [*C*(2)S], 128.8, 129.3, 134.1 (aromatic *C*H), 136.6 (quaternary aromatic *C*), 164.3 (*C*O); *m/z* (EI) 241 (M^+, 45%), 206 (25, M^+-Cl), 134 (70, $[PHS=C=CH]^+$), 72 (100, $[CON(CH_3)_2]^+$). Dichloroacrylamide **103**: δ_H (270 MHz) 2.60 [3H, s, one of N(C*H*$_3$)$_2$], 2.81 [3H, s, one of N(C*H*$_3$)$_2$], 7.31-7.42 (3H, m, Ar*H*), 7.50-7.61 (2H, m, Ar*H*); δ_C (67.8 MHz) 34.1, 37.2 [N(*C*H$_3$)$_2$], 128.6 [quaternary aromatic *C*, *C*Cl$_2$ or *C*(2)S], 128.9, 129.1 (aromatic *C*H), 132.2, 134.1 [quaternary aromatic *C*, *C*Cl$_2$ or *C*(2)S], 162.6 (*C*O); *m/z* (EI) 275 (M^+, 10%). The minor β-chloroacrylamide **63** was isolated (0.80g, 20% of isolated mass) as a clear oil; ν_{max}/cm^{-1} (neat) 1651 (CO amide); δ_H (270 MHz) 2.56 [3H, s, one of N(C*H*$_3$)$_2$], 2.89 [3H, s, one of N(C*H*$_3$)$_2$], 6.35 [1H, s, C(3)*H*Cl=], 7.26-7.41 (3H, m, ArH), 7.46-7.59 (2H, m, ArH). δ_C (67.8 MHz) 34.4, 37.3 [N(*C*H$_3$)$_2$], 117.5 [*C*(3)HCl=], 129.3 (aromatic *C*H), 129.9, 130.2 [quaternary aromatic *C* and *C*(2)S], 133.2, 135.1 (aromatic *C*H), 164.6 (*C*O); *m/z* (EI) 206.06342 (M^+, $C_{11}H_{12}ClNOS$ requires M^+ 206.06396). 241 (M^+, 15%), 206 (9, M^+ - Cl), 134 (31, $[PhS=C=CH]^+$), 72 (100).

A further 150 mg (3% of isolated mass) of what is believed to be the trichloride **104** was also isolated: δ_H (270 MHz) 2.91 [3H, b s, one of N(C*H*$_3$)$_2$], 3.41 [3H, b s, one of N(C*H*$_3$)$_2$], 6.28 [1H, s, C*H*Cl$_2$], 7.31-7.60 (5H, m, Ar*H*); δ_C (67.8 MHz) 38.0-40.5 [2 broad signals, both of N(*C*H$_3$)$_2$], 76.8 (*C*HCl$_2$), 79.91 (S*C*Cl), 128.3 (quaternary aromatic *C*), 129.4 (aromatic *C*H), 131.2 (aromatic *C*H), 136.6 (aromatic *C*H), 163.1 (*C*O).

(±)-*N*-1′-Phenylethyl-*Z*-3-chloro-2-(phenythio)propenamide 64 and (±)-*N*-1′-phenylethyl-2-(phenylthio)propenamide 124

This was prepared following the procedure (method B) described for β-chloroacrylamide **57** using (1′R*, 2R*)-*N*-1′-phenylethyl-2-(phenylthio)propanamide **20** (156 mg, 0.55 mmol), NCS (161 mg, 1.20 mmol) and carbon tetrachloride (3 ml). Purification by chromatography using ethyl acetate-hexane (5:95) gave (±)-*N*-1′-phenylethyl-*Z*-3-chloro-2-(phenylthio)propenamide **64** (113 mg, 65%) (Rf 0.5 using ethyl acetate-hexane (25:75) as eluent) as a white, crystalline solid; mp 51-53 °C; ν_{max}/cm^{-1} 3304 (br NH), 1641 (CO), 1560; δ_H (270 MHz) 1.30 [3H, d, *J* 7, C(2′)*H*$_3$], 4.83-5.10 (1H, dq, *J* 8, 7, NC*H*), 6.95-7.34 (11H, m, Ar*H* and N*H*), 7.88 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 21.4 [*C*(2′)H$_3$], 49.4 (N*C*H), 125.8, 127.2, 128.6, 128.8, 129.6 (aromatic *C*H, 5 signals for 6 carbons), 130.8, 133.0 [quaternary aromatic *C* and *C*(2)S], 138.5 [*C*(3)HCl=], 142.3 (quaternary aromatic *C*), 161.3 (*C*O) and (1′R/ S)-N-1′-phenylethyl-2-(phenylthio)propenamide **124** (37 mg, 24%) (Rf 0.45) as an off-white solid; δ_H (60 MHz) 1.27 [3H, d, *J* 7, C(2′)*H*$_3$], 3.88-5.02 (1H, dq, *J* 7, 7, NC*H*), 5.9 (1H, d, *J* < 2, C*H*$_A$H$_B$=), 6.63 (1H, d, *J* < 2, CH$_A$*H*$_B$=), 6.77-7.34 (11H, m, Ar*H* and N*H*).

64 & **124** were also prepared using (1′R*, 2S*)-*N*-1′-phenylethyl-2-(phenylthio)propanamide **20**, NCS and carbon tetrachloride, to give **64** in 19% yield and **124** in 20% yield, with spectral characteristics identical to above.

(1′S)-*N*-1′-Phenylethyl-*Z*-3-chloro-2-(phenylthio)propenamide 65

This was prepared following the procedure (method B) described for β-chloroacrylamide **57** using (1′S)-*N*-1′-phenylethyl-2-(phenylthio)propanamide **21** (1.36 g, 4.77 mmol) as a mixture of diastereomers, NCS (1.34 g, 10.02 mmol) and

carbon tetrachloride (30 ml). Purification by chromatography using ethyl acetate-hexane (10:90) gave (1′S)-*N*-1′-phenylethyl-*Z*-3-chloro-2-(phenylthio)propenamide **65** (1.07 g, 67 %) as a white, crystalline solid; mp 53-55 °C; $[\alpha]_D^{20}$ 0.98 (c 8.0 in ethanol). and (1′S)-*N*-1′-phenylethyl-2-(phenylthio)propenamide **125** (0.23 g, 15 %). Spectral characteristics and other analyses were identical to those observed for β-chloroacrylamide **64** and acrylamide **124**.

_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, C*H*$_3$), 1.28-1.62 [4H, m, C(3′)*H*$_2$, C(2′)*H*$_2$], 2.67 (2H, d, *J* 7, SC*H*$_2$), 4.54 (2H, d, *J* 6, NC*H*$_2$), 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_-4'-Methylphenyl-_Z_-3-chloro-2-(_n_-butylthio)propenamide 67

This was prepared following the optimised procedure (Method D) described for β-chloroacrylamide **66** using *N*-4'-methylphenyl-2-(*n*-butylthio)propanamide **23** (4.00 g, 15.94 mmol), NCS (4.15 g, 31.08 mmol) and toluene (80 ml). The reaction mixture

was heated at 120°C for 2.5 hours. Following filtration and evaporation of the toluene, the crude β-chloroacrylamide **67** was isolated. The NMR spectrum of the crude product from this reaction was very clean. Purification by chromatography on silica gel using ethyl acetate-hexane (gradient elution 10-30% ethyl acetate) as eluent gave the analytically pure β-chloroacrylamide **67** as a clear oil (3.76 g, 84 %) which solidified on storing in the freezer overnight, (Found C, 59.04; H, 6.39; N, 4.72; S, 11.55. $C_{14}H_{18}ClNOS$ requires C, 59.25; H, 6.39; N, 4.94; S, 11.30%); ν_{max}/cm^{-1} (film) 3301 (br NH), 1655 (CO), 1595; δ_H (270 MHz) 0.89 (3H, t, *J* 7, C(4′)H_3), 1.38-1.69 [4H, m, C(3′)H_2, C(2′)H_2], 2.33 (3H, s, ArCH_3), 2.78 (2H, d, *J* 7, NCH_2), 7.14-7.46 (4H, ABq, *J* 8, Ar*H*), 7.84 [1H, s, C(3)*H*Cl=], 8.99 (1H, b s, N*H*); δ_C (67.8 MHz) 13.4 [*C*(4′)H_3], 20.8 (Ar*C*H_3), 21.7 [*C*(3′)H_2], 31.6 [*C*(2′)H_2], 34.3 (S*C*H_2), 120.1 (aromatic C*H*), 129.6 (aromatic C*H*), 132.4 (quaternary aromatic *C*), 134.6, 134.8 [quaternary aromatic *C* and *C*(2)S], 138.4 [*C*(3)HCl=], 160.9 (*C*O); *m/z* 283 (M^+, 47%), 248 (38, M^+- Cl), 194 (17, M^+- SBu^n), 107 (100), 91 (23).

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 6.68

***N*-4'-Fluorophenyl-*Z*-3-chloro-2-(*n*-butylthio)propenamide 68**

The title compound was prepared following the procedure (Method D) described for β-chloroacrylamide **66** using *N*-4'-fluorophenyl-2-(*n*-butylthio)propanamide **24** (5.00 g, 19.61 mmol), NCS (5.37 g, 40.20 mmol) and toluene (100 ml) at 120°C. The reaction solution was heated for 2.5 hours. Purification by chromatography on silica gel using ethyl acetate-hexane (15:85) as eluent gave the β-chloroacrylamide **68** (5.43 g, 96%) as a low melting colourless solid (oil at room temperature); (Found C, 54.68; H, 5.48; N, 4.89; Cl, 12.40; F, 6.25; S, 11.18. $C_{13}H_{15}NClFOS$ requires C, 54.25; H, 5.25; N, 4.87; Cl, 12.32; F, 6.60; S, 11.14%); ν_{max}/cm^{-1} (film) 1655 (CO, w, br), 1510 (vs); δ_H (270 MHz) 0.91 [3H, t, *J* 7, C(4′)H_3], 1.37-1.51 [2H, m, C(3′)H_2], 1.56-1.68 [2H, m, C(2′)H_2], 2.79 (2H, t, *J* 8, SCH_2), 7.06 (2H, overlapping dd, *J* 8, 8, ArC(3′′)*H*), 7.53-7.61 (2H, m, Ar*H*), 7.86 [1H, s, C(3)*H*Cl=], 9.06 (1H, b s, N*H*); δ_C (67.8 MHz) 13.7 [*C*(4′)H_3], 21.6 [*C*(3′)H_2], 31.6 [C(2′)H_2], 34.3 (S*C*H_2), 115.8 (d, $^2J_{CF}$ 22, aromatic *C*H, Ar*C*(3′′)], 121.9 [aromatic CH, Ar*C*(2′′)], 131.0, 133.4 [quaternary aromatic *C* or *C*(2)S], 138.9 [*C*(3)HCl=], 159.7 [d, $^1J_{CF}$ 245, quaternary aromatic C, Ar*C*(4′′)], 161.1 (*C*O); *m/z* 287.0561 (M^+, $C_{13}H_{15}N^{35}ClFOS$ requires

287.0547). 287 (M^+, 18%), 252 (12, M^+- Cl), 198 (10, M^+- SBu), 164 (25), 111 (100), 41 (92).

_N_-4'-Methylphenyl-_Z_-3-chloro-2-(4'-methoxybenzenethio)propenamide 69

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-4'-methylphenyl-2-(4'-methoxy-benzenethio)propanamide **25** (430 mg, 1.42 mmol), NCS (370 mg, 2.77 mmol) and toluene (9 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **69** was isolated as a colourless solid. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent to give the β-chloroacrylamide **69** as a colourless solid (416 mg, 88%), mp 119-120°C; (Found C, 61.36; H, 4.95; N, 4.61; Cl, 10.77; S, 9.54. $C_{17}H_{16}NClO_2S$ requires C, 61.16; H, 4.83; N, 4.20; Cl, 10.62; S, 9.60%); ν_{max}/cm^{-1} (KBr) 3328 (br, NH), 1657 (CO), 1522, 1249, 823; δ_H (270 MHz) 2.30 (3H, s, ArC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 6.80-6.88 (2H, m, Ar*H*), 7.08-7.13 (2H, m, Ar*H*), 7.24-7.34 (4H, m, Ar*H*), 7.90 [1H, s, C(3)*H*Cl=], 8.65 (1H, b s, N*H*); δ_C (67.8 MHz) 20.9 (Ar*C*H$_3$), 55.4 (O*C*H$_3$), 115.4, 120.2, (aromatic *C*H), 122.8 [quaternary aromatic *C*, *C*(2)S], 129.6, 131.4 (aromatic *C*H), 132.3, 134.6 [quaternary aromatic *C* or *C*(2)S], 138.8 [*C*(3)HCl=], 159.7 (*C*OMe), 160.4 (*C*O); *m/z* (EI) 333.0585 (M^+, $C_{17}H_{16}N^{35}ClO_2S$ requires 333.0590). 333 (M^+, 70%), 164 (100, M^+- CONHTol - Cl), 139 (74, $[SAr]^+$), 106 (61).

_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'-methoxy-benzenethio)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, OC*H*$_3$), 4.42 (2H, d, *J* 6, C*H*$_2$Ar), 6.80-7.46 (10H, m, Ar*H*, N*H* seen as b s at δ_H 7.09), 7.81 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 44.1 (*C*H$_2$Ar), 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_-Ethyl-_Z_-3-chloro-2-(4'methoxybenzenethio)propenamide 71

This was prepared following the optimised procedure (Method A) described for β-chloroacrylamide **3** using *N*-ethyl-2-(4'-methoxybenzenethio)propanamide **27** (1.58 g, 6.61 mmol), NCS (1.70 g, 12.89 mmol) and toluene (32 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the toluene, and purification by chromatography on silica gel using ethyl acetate-hexane (30:70) as eluent **71** (1.06g, 59%) **w**as isolated as a colourless solid, mp 90-92°C; (Found C, 52.80; H, 5.20; N, 5.26; Cl, 13.55; S, 11.76. $C_{12}H_{14}NClO_2S$ requires C, 53.03; H, 5.19; N, 5.16; Cl, 13.04; S, 11.80%). ν_{max}/cm^{-1} (KBr) 3254 (b NH), 1644 (CO), 1496, 1248, 1027; δ_H (270 MHz) 0.99 [3H, t, *J* 7, C(2′)*H*$_3$], 3.18-3.31 (2H, m, NC*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 6.73-6.91 (3H, m, Ar*H*, N*H*), 7.19-7.28 (2H, m, Ar*H*), 7.75 [1H, s, C(3)*H*Cl=]; δ_C (67.8 MHz) 14.9 [*C*(2′)H$_3$], 35.4 (N*C*H$_2$), 55.8 (O*C*H$_3$), 115.4 (aromatic *C*H), 123.6 (quaternary aromatic *C*), 131.7 (aromatic *C*H), 132.6 (quaternary aromatic *C* or *C*(2)S], 137.4 [*C*(3)HCl=], 159.9 (*C*OMe), 162.7 (*C*O); *m/z* (EI) 271.0438 (M^+, $C_{12}H_{14}N^{35}ClO_2S$ requires 271.0434). 271 (M^+, 100%), 236 (13, M^+- Cl), 164 (78, M^+- CONHEt), 140 (80), 121 (25).

_N, N_-Dimethyl-_Z_-3-chloro-2-(4'-methoxybenzenethio)propenamide 72 and _N, N_-Dimethyl-_E_-3-chloro-2-(4'-methoxybenzenethio)propenamide 73 and _N, N_-Dimethyl-3, 3-dichloro-2-(4'methoxybenzenethio)propenamide 105

This was prepared following the optimised procedure (Method A) described for β-chloroacrylamide **3** using *N*, *N*-dimethyl-2-(4'-methoxybenzenethio)propanamide **28**

(2.45 g, 11.72 mmol), NCS (3.05 g, 22.85 mmol) and toluene (49 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. NMR showed a mixture of the two β-chloroacrylamides in a ratio of 3:1 and approximately 8% of the dichloroacrylamide **105**. The crude product was chromatographed on silica gel using dichloromethane-hexane (70:30) as eluent to give a mixture of the major β-chloroacrylamide **72** and the dichloroacrylamide **105** eluting first (less polar) as a clear oil (1.66 g). Major β-chloroacrylamide **72** (73%): ν_{max}/cm^{-1} (film) 1650 (CO), 1590, 1493, 1397, 1028; δ_H (270 MHz) 2.83 [3H, s, one of N(C*H*$_3$)$_2$], 2.92 [3H, s, one of N(C*H*$_3$)$_2$], 3.81 (3H, s, OC*H*$_3$), 6.03 [1H, s, C(3)*H*Cl=], 6.88-7.50 (4H, ABq, *J* 11, Ar*H*); δ_C (67.8 MHz) 34.3 [one of N(*C*H$_3$)$_2$], 37.1 [one of N(*C*H$_3$)$_2$], 55.3 (O*C*H$_3$), 114.6 [*C*(3)HCl=], 114.9 (aromatic *C*H), 119.9 (quaternary aromatic *C*), 135.0 [*C*(2)S], 136.3 (aromatic *C*H), 160.7 (*C*OMe), 164.5 (*C*O); *m/z* (EI) 271.0413 (M^+, $C_{12}H_{14}N^{35}ClO_2S$ requires 271.0434). 271 (M^+, 100), 236 (18, M^+- Cl), 164 (50, M^+ - $CONMe_2$ - Cl), 139 (17, $[SAr]^+$). Dichloroacrylamide **105** (6%) characteristic signals: δ_H 2.62 [3H, s, one of N(C*H*$_3$)$_2$], 2.80 [3H, s, one of N(C*H*$_3$)$_2$]. Minor β-chloroacrylamide **73** eluting second (more polar) as a colourless solid (0.44 g, 21 %), mp 67-68°C; (Found C, 53.34; H, 5.29; N, 5.11; Cl, 12.70; S, 11.40. $C_{12}H_{14}NClO_2S$ requires C, 53.03; H, 5.19; N, 5.15; Cl, 13.04; S, 11.80%); ν_{max}/cm^{-1} (KBr) 1634 (CO), 1487, 1251, 1027; δ_H (270 MHz) 2.57 [3H, s, one of N(C*H*$_3$)$_2$], 2.91 [3H, s, one of N(C*H*$_3$)$_2$], 3.80 (3H, s, OC*H*$_3$), 6.23 [1H, s, C(3)*H*Cl=], 6.81-7.49 (4H, ABq, *J* 11, Ar*H*); δ_C (67.8 MHz) 34.5 [one of N(*C*H$_3$)$_2$], 38.3 [one of N(*C*H$_3$)$_2$], 55.3 (O*C*H$_3$), 114.3 [*C*(3)HCl=], 114.4 (aromatic *C*H), 119.2 (quaternary aromatic *C*), 136.6 (aromatic *C*H), 137.6 (S*C*-), 160.7 (*C*-OMe), 164.1 (*C*O); *m/z* (EI) 271.0439 (M^+, $C_{12}H_{14}N^{35}ClO_2S$ requires 271.0434). 271 (M^+, 100), 236 (20, M^+ - Cl), 164 (65, M^+- $CONMe_2$ - Cl), 139 (20, $[SAr]^+$), 72 (73).

***N*-4′-Methylphenyl-*Z*-3-chloro-2-(4-nitrobenzenethio)propenamide 74**

NCS (0.89 g, 6.65 mmol) was added in one portion to a solution of sulfide **29** (1.00 g, 3.17 mmol) in toluene (20 ml) at room temperature. The flask was immediately immersed in an oil bath at 130°C and heating at reflux was maintained for 2.5 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

crude β–chloroacrylamide **74**. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (gradient elution 15-30% ethyl acetate) to give **74** (0.57 g, 51%) or by trituration from 5% diethyl ether-hexane (71%) as a pale yellow solid, mp 122-124^{o}C; (Found C, 54.68; H, 3.74; N, 8.07; Cl, 10.28; S, 9.61. $C_{16}H_{13}N_2ClO_3S$ requires C, 55.09; H, 3.76; N, 8.03; Cl, 10.16; S, 9.19%); ν_{max}/cm^{-1} (KBr) 1674 (CO), 1512, 1334, 740; δ_H (270 MHz) 2.29 (3H, s, ArC*H*$_3$), 7.08-7.14 (2H, m, Ar*H*), 7.30-7.41 (4H, m, Ar*H*), 8.13-8.20 (2H, m, Ar*H*), 8.23 [1H, s, C(3)*H*Cl=], 8.54 (1H, b s, N*H*); δ_C (67.8 MHz) 20.8 (Ar*C*H$_3$), 120.3, 124.9, 127.0 (aromatic *C*H), 128.6 (quaternary aromatic *C*), 129.6 (aromatic *C*H), 134.2, 135.2, 141.8 [quaternary aromatic *C* or *C*(2)S], 143.4 [*C*(3)HCl=], 146.6 (*C*-NO$_2$), 159.6 (*C*O); *m/z* (EI) 348.0343 (M$^+$, $C_{16}H_{13}N_2{}^{35}ClO_3S$ requires 348.0335). 348 (M$^+$, 90%), 312 (70), 214 (20, M$^+$- CONHTol), 194 (50, M$^+$- SAr), 168 (100), 160 (90), 106 (95).

_N_-4′-Methylphenyl-_Z_-3-chloro-2-(*iso*-butylthio)propenamide 75

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-4′-methylphenyl-2-(*iso*-butylthio)-propanamide **30** (2.00 g, 7.94 mmol), NCS (2.07 g, 15.48 mmol) and toluene (40 ml). The reaction solution was heated for 2 hours at 90^{o}C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. Following purification by column chromatography on silica gel using ethyl acetate-hexane (5:95) as eluant, **75** was obtained as a white solid (1.46 g, 65%), mp 54-56^{o}C; (Found C, 59.20; H, 6.35; N, 5.00; Cl, 12.76; S, 11.08. $C_{14}H_{18}NClOS$ requires C, 59.25; H, 6.39; N, 4.94; Cl, 12.49; S, 11.30%); ν_{max}/cm^{-1} (KBr) 3303, 1658 (CO), 1533, 1246, 821; δ_H (300 MHz) 1.03 (6H, d, *J* 6.6, 2 x C*H*$_3$), 1.71-1.91 [1H, m, C*H*(CH$_3$)$_2$], 2.34 (3H, s, ArC*H*$_3$), 2.66 (2H, d, *J* 6.8, SC*H*$_2$), 7.14 (2H, A of ABq, *J* 8.4, Ar*H*), 7.49 (2H, B of ABq, *J* 8.4, Ar*H*), 7.83 [1H, s, C(3)*H*Cl=], 8.98 (1H, b s, N*H*); δ_C (75.5 MHz) 21.3 (Ar*C*H$_3$), 22.2 [CH(*C*H$_3$)$_2$], 29.2 [*C*H(CH$_3$)$_2$], 44.0 (S*C*H$_2$), 120.3, 130.1 (aromatic *C*H), 133.2, 135.0, 135.2 [quaternary aromatic *C* or *C*(2)S], 138.7 [*C*(3)HCl=], 161.3 (*C*O); *m/z* (EI) 283.07976 (M$^+$, $C_{14}H_{18}NClOS$ requires 283.08068). 283 (M$^+$, 50), 248 (40), 149 (22), 107 (95)

_N_-4′-Fluorophenyl-_Z_-3-chloro-2-(*iso*-butylthio)propenamide 76

This was prepared following the procedure (Method A) described for β-

chloroacrylamide **3** using *N*-4′-fluorophenyl-2-(*iso*-butylthio)-propanamide **31** (2.00 g, 7.84 mmol), NCS (2.04 g, 15.28 mmol) and toluene (40 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. Following purification by column chromatography on silica gel using ethyl acetate-hexane (5:95) as eluant, **76** was obtained as a white solid (1.44 g, 64%), mp 60-62 °C; (Found C, 54.05; H, 5.17; N, 4.82; Cl, 12.78; S, 11.48, F, 7.01. $C_{13}H_{15}NClFOS$ requires C, 54.26; H, 5.25; N, 4.87; Cl, 12.32; F, 6.60; S, 11.14%); ν_{max}/cm^{-1} (KBr) 3279, 1654 (CO), 1510, 1209, 833; δ_H (300 MHz) 1.05 (6H, d, *J* 6.6, 2 x C*H*$_3$), 1.75-1.92 [1H, m, C*H*(CH$_3$)$_2$], 2.67 (2H, d, *J* 6.8, SC*H*$_2$), 7.02-7.10 [2H, m, ArC(3′)*H*], 7.53-7.59 [2H, m, ArC(2′)*H*], 7.85 [1H, s, C(3)*H*Cl=], 9.04 (1H, b s, N*H*); δ_C (75.5 MHz) 21.8 [2 x CH(*C*H$_3$)$_2$], 28.9 [*C*H(CH$_3$)$_2$], 43.7 (S*C*H$_2$), 115.9 [d, $^2J_{CF}$ 23, aromatic CH, Ar*C*(3′)], 121.7 [d, *J* 8, aromatic CH, Ar*C*(2′)], 132.4, 133.4 [quaternary aromatic *C* or *C*(2)S], 139.1 [*C*(3)HCl=], 159.5 [d, $^1J_{CF}$ 212, quaternary aromatic C, Ar*C*(4′)], 161.1 (*C*O); *m/z* (EI) 287 (M^+, 38), 252 (12), 198 (22), 111 (100).

***N*-4′-Ethyl-Z-3-chloro-2-(*iso*-butylthio)propenamide 77**

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-ethyl-2-(*iso*-butylthio)-propanamide **32** (2.00 g, 10.60 mmol), NCS (2.75 g, 20.63 mmol) and toluene (40 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. Following purification by column chromatography on silica gel using ethyl acetate-hexane (5:95) as eluant, **77** was obtained as a low melting solid (1.64 g, 70%), (Found C, 48.50; H, 7.24; N, 6.23; S, 14.63. $C_9H_{16}NClOS$ requires C, 48.75; H, 7.27; N, 6.32; S, 14.46%); ν_{max}/cm^{-1} (film) 3299, 2960, 1645 (CO), 1515, 1286; δ_H (300 MHz) 1.01 (6H, d, *J* 6.6, 2 x C*H*$_3$), 1.21 (3H, t, *J* 4.8, C*H*$_3$CH$_2$), 1.69-1.89 [1H, m, C*H*(CH$_3$)$_2$], 2.59 (2H, d, *J* 6.8, SC*H*$_2$), 3.36-3.43 (2H, m, CH$_3$C*H*$_2$), 7.12 (1H, b s, N*H*), 7.62 [1H, s, C(3)*H*Cl=]; δ_C (75.5 MHz) 14.7 (CH$_2$*C*H$_3$), 21.8 [2 x CH(*C*H$_3$)$_2$], 28.9 [*C*H(CH$_3$)$_2$], 35.0 (N*C*H$_2$), 43.3 (S*C*H$_2$), 132.7 [*C*(2)S], 136.5 [*C*(3)HCl=], 162.9 (*C*O); *m/z* (EI) 221 (M^+, 6), 186 (20), 170 (22), 98 (100).

***N*-4′-Fluorophenyl-Z-3-chloro-2-(*iso*-propylthio)propenamide 78**

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-fluorophenyl-2-(*iso*-propylthio)-propanamide **33** (1.42 g, 5.89 mmol), NCS (1.73 g, 11.49 mmol) and toluene (30 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. After purification by column chromatography on silica gel using ethyl acetate-hexane (5:95) as eluant, **78** was obtained as a white solid (1.13 g, 70%), mp 45-47 °C; (Found C, 52.28; H, 4.79; N, 5.12; Cl, 13.26; F, 6.60; S, 12.08. $C_{12}H_{13}NClOFS$ requires C, 52.65; H, 4.79; N, 5.12; Cl, 12.95; F, 6.94; S, 11.71%); ν_{max}/cm^{-1} (KBr) 3326, 1672 (CO), 1509, 1212, 832; δ_H (300 MHz) 1.34 [6H, d, *J* 6.7, CH(C*H*$_3$)], 3.31-3.49 [1H, m, C*H*(CH$_3$)$_2$], 7.02-7.08 [2H, m, ArC(3′)*H*], 7.53-7.57 [2H, m, ArC(2′)*H*], 7.89 [1H, s, C(3)*H*Cl=], 9.01 (1H, b s, N*H*); δ_C (75.5 MHz) 23.3 [2 x CH(*C*H$_3$)$_2$], 39.6 [*C*H(CH$_3$)$_2$], 115.8 [d, $^2J_{CF}$ 23, aromatic CH, Ar*C*(3′)], 121.7 [d, $^3J_{CF}$ 8, aromatic CH, Ar*C*(2′)], 131.3 [*C*(2)S], 133.3 [d, $^4J_{CF}$ 3, quaternary aromatic C, Ar*C*(1′)], 141.0 [*C*(3)HCl=], 159.8 [d, $^1J_{CF}$ 248, quaternary aromatic C, Ar*C*(4′)], 161.4 (*C*O); *m/z* (EI) 273 (M^+, 10), 164 (22), 135 (18), 111 (80).

While the impurities in the SBn series have not been isolated and identified, minor signals in the NMR spectra consistent with trichloride or dichloroacrylamide impurities analogous to those described above can be seen in less than 10%. Typically, the crude products are 80-85% β-chloroacrylamide by ^1H NMR .

N-4′-Benzyl-*Z*-3-chloro-2-(benzylthio)propenamide 79

This was prepared following the procedure (Method A) described for β-chloroacrylamide **3** using *N*-benzyl-2-(benzylthio)propanamide **34** (4.45 g, 15.6 mmol), NCS (4.06 g, 30.4 mmol) and toluene (80 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-40% ethyl acetate), the pure β-chloroacrylamide **79** (3.94 g, 79%) was isolated as a white solid, mp 69-72°C; ν_{max}/cm^{-1} (KBr) 3343 (NH), 3030 (CH), 1645 (CO), 1556 (NH bend), 1518, 1421 (CN stretch); δ_H (300 MHz) 3.90 (2H, s, SC*H*$_2$), 4.32 (2H, d, *J* 5.9, C*H*$_2$NH), 7.09-7.38 (11H, m, Ar*H*, N*H*), 7.87 [1H, s, C(3)*H*Cl=]; δ_c (75.5 MHz) 38.7 (S*C*H$_2$), 44.5 (*C*H$_2$NH), 128.0, 128.1, 128.2, 129.2, 129.2, 129.4

(aromatic *C*H), 131.0, 137.4, 137.9 [aromatic *C* or *C*(2)S], 139.9 [*C*(3)HCl=], 163.2 (*C*O); *m/z* (ESI) 340.0544 ($[M+Na]^+$, $C_{17}H_{16}NOSClNa$ requires 340.0539). 318 ($[M+H]^+$, 100%), 91 ($C_7H_7^+$, 40).

***N*-4′-Fluorophenyl-*Z*-3-chloro-2-(benzylthio)propenamide 80**

The title compound was synthesized following the procedure described above for **3** using *N*-4′-fluorophenyl-2-(benzylthio)propanamide **35** (1.00 g, 3.5 mmol), *N*-chlorosuccinimide (0.90 g, 6.8 mmol) and toluene (50 ml). The reaction mixture was heated at 90°C for 2 hours. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **80** was obtained as a brown solid. This was purified by column chromatography on silica gel using hexane-ethyl acetate (98:2) as eluent to give the pure product **80** (0.94 g, 84%) as a white solid, mp 81-82°C; (Found C, 59.31; H, 3.83; N, 4.06; S, 9.98; Cl, 10.79; F, 5.68. $C_{16}H_{13}ClFNOS$ requires C, 59.72; H, 4.07; N, 4.37; S, 9.96; Cl, 11.02; F, 5.90%); ν_{max}/cm^{-1} (KBr) 3317 (NH), 3054 (CH), 1647 (CO), 1605, 1519 (NH bend), 1508, 1406 (CN stretch); δ_H (300 MHz) 3.97 (2H, s, SCH_2), 6.96-7.01 (2H, m, Ar*H*), 7.16-7.33 (8H, m, Ar*H*), 7.97 [1H, s, C(3)*H*Cl=], 8.55 (1H, b s, N*H*), ; δ_c (75.5 MHz) 39.2 (S*C*H_2), 116.0 [d, $^2J_{CF}$ 23, aromatic CH, Ar*C*(3′)], 122.1 [d, $^3J_{CF}$ 8, aromatic CH, Ar*C*(2′)], 128.3, 129.1, 129.3 (aromatic *C*H), 131.5 [*C*(2)S], 133.5, 137.4 (aromatic *C*), 141.5 [*C*(3)HCl=], 160.0 [d, $^1J_{CF}$ 244, aromatic C, Ar*C*(4′)], 161.2 (*C*O); *m/z* (ESI) 322 ($[M+H]^+$, 10%), 91 ($C_7H_7^+$, 30).

***N*-*n*-Butyl-*Z*-3-chloro-2-(benzylthio)propenamide 81**

This was prepared following the procedure described above for **3** using *N*-*n*-butyl-2-(benzylthio)propanamide **36** (1.00 g, 4.0 mmol), NCS (1.06 g, 7.8 mmol) and toluene (50 ml). The reaction mixture was heated at 90°C for 2 hours. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **81** was obtained as a pale brown oil. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 2-10% ethyl acetate) to give the pure product **81** (0.66 g, 58%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 3309 (NH), 2951 (CH), 1648 (CO), 1560 (NH bend), 1518, 1454 (CN stretch); δ_H (300 MHz) 0.90 [3H, t, *J* 7.1, C(4′)H_3], 1.18-1.41 [4H, m, C(3′)H_2 and C(2′)H_2], 3.12 (2H, q, *J* 6.8, CH_2NH), 3.91 (2H, s, SCH_2), 6.81 (1H, b s, N*H*), 7.18-7.34 (5H, m, Ar*H*),

7.82 [1H, s, C(3)*H*Cl=]; δ_C (75.5 MHz) 13.7 [*C*(4′)H_3], 20.0 [*C*(3′)H_2], 31.3 [*C*(2′)H_2], 38.4, 39.7 (N*C*H_2 & S *C*H_2), 127.7, 128.7, 128.8 (aromatic *C*H), 131.4, 137.2 [quaternary aromatic *C* and *C*(2)S], 139.0 [*C*(3)HCl=], 162.7 (*C*O); *m/z* (ESI) 306.0681 ($[M+Na]^+$, $C_{14}H_{18}NOSClNa$ requires 306.0695). 306 ($[M+Na]^+$, 11%), 91 ($C_7H_7^+$, 100%).

The ^{1}H NMR spectra of the crude and pure product also contained a compound assigned as the *E* isomer although this has not been isolated and fully characterised (~20%); δ_H (300 MHz) 0.90 [3H, t, *J* 7.1, C(4′)*H*$_3$]*, 1.18-1.41 [4H, m, C(3′)*H*$_2$ and C(2′)*H*$_2$]*, 3.32 (2H, q, *J* 6.8, C*H*$_2$NH), 3.91 (2H, s, SC*H*$_2$), 6.15 (1H, bs, N*H*), 6.46 [1H, s, C(3)*H*Cl=], 7.18-7.34 (5H, m, Ar*H*)*; δ_C (75.5 MHz) 14.2 [*C*(4′)H_3], 21.1 [*C*(3′)H_2], 31.5 [*C*(2′)H_2], 38.9, 39.5 (N*C*H_2 & S *C*H_2), 124.1, 127.6, 129.1 (aromatic *C*H), 131.6, 136.6 [quaternary aromatic *C* and *C*(2)S], 139.0 [*C*(3)HCl=], 163.4 (*C*O). *These signals were indistinguishable for the two isomers.

_N,N_-Dimethyl-_Z_-3-chloro-2-(benzylthio)propenamide 82 & _N,N_-Dimethyl-_E_-3-chloro-2-(benzylthio)propenamide 83

This was synthesized according to the procedure described for **3** using *N,N*-dimethyl-2-(benzylthio)propanamide **37** (1.95 g, 9 mmol), *N*-chlorosuccinimide (2.32 g, 17 mmol) and toluene (50 ml). The reaction mixture was heated at 90 °C for 2 h. Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide was obtained as a brown oil and as a mixture of the *Z*- and *E*-isomers in 1:0.35 ratio, as well as 10% of the dichloroacrylamide **106**. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-10% ethyl acetate) to give the sulfide **82** as the less polar fraction (1.04 g, 47%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 3062 (CH), 1647 (CO), 1572, 1495, 1454 (CN stretch); δ_H (300 MHz) 2.91 [3H, s, one of N(C*H*$_3$)$_2$], 3.00 [3H, s, one of N(C*H*$_3$)$_2$], 3.99 (2H, s, SC*H*$_2$), 6.15 [1H, s, C(3)*H*Cl=], 7.21-7.38 (5H, m, Ar*H*), δ_c (75.5 MHz) 34.8 [one of N(*C*H$_3$)$_2$], 37.6 [one of N(*C*H$_3$)$_2$], 38.2 (S*C*H$_2$), 119.0 [*C*(2)HCl=], 127.8, 128.9, 129.5 (aromatic *C*H), 131.6, 137.2 [aromatic *C* or *C*(2)S], 165.5 (*C*O); *m/z* (ESI) 256.0563 ($[M+H]^+$, $C_{12}H_{15}NOSCl$ requires 256.0550). 256 ($[M+H]^+$, 100%), 91 (C_7H_7, 30) {**82** containied ~12% of the dichloroacrylamide **106** seen at δ_H 2.69, 2.87 [2 x s, N(C*H*$_3$)$_2$]}. The second isomer **83** (0.38 g, 17%) was obtained as a pale yellow oil; δ_H (300 MHz) 2.60 [3H, s, one of N(C*H*$_3$)$_2$], 2.83 [3H, s,

one of N(C*H*$_3$)$_2$], 3.99 (2H, s, SC*H*$_2$), 6.17 [1H, s, C(3)*H*Cl=], 7.21-7.38 (5H, m, Ar*H*).

_N_-4′-Methylphenyl-_Z_-3-chloro-2-(benzylthio)propenamide 84

The title compound was prepared following the procedure described for **3** using *N*-4′-methylphenyl-2-(benzylthio)propanamide **38** (2.28 g, 8.0 mmol), *N*-chlorosuccinimide (2.08 g, 15.6 mmol) and toluene (40 ml). The reaction mixture was heated at 90 °C for 2 h. The crude β-chloroacrylamide **84** was obtained as a brown solid following filtration and evaporation of the solvent at reduced pressure. This was purified by column chromatography on silica gel using hexane-ethyl acetate (98:2) as eluent to give the pure product **84** (1.00 g, 39%*) as a white solid, mp 84-86^{o}C; (Found C, 63.92; H, 5.023; N, 4.27; S, 10.23; Cl, 11.70. $C_{176}H_{16}ClNOS$ requires C, 64.24; H, 5.07; N, 4.41; S, 10.09; Cl, 11.15%); ν_{max}/cm^{-1} (KBr) 3277 (NH), 3052 (CH), 1647 (CO), 1594, 1521 (NH bend), 1403 (CN stretch); δ_H (300 MHz) 2.31 (3H, s, Ar-C*H*$_3$), 3.97 (2H, s, SC*H*$_2$), 7.04-7.41 (9H, m, Ar*H*), 7.92 [1H, s, C(3)*H*Cl=], 8.56 (1H, b s, N*H*); δ_c (75.5 MHz) 21.3 (Ar*C*H$_3$), 39.1 (S*C*H$_2$), 120.4, 128.2, 129.1, 129.3, 129.8 (aromatic *C*H), 131.8, 134.9, 137.3 [aromatic *C* or *C*(2)S], 140.8 [*C*(3)HCl=], 161.1 (*C*O); *m/z* (ESI) 340.0555 ([M+Na]$^+$, $C_{17}H_{16}NOS^{35}ClNa$ requires 340.0539). 317 ([M+H]$^+$, 100%), 91 ($C_7H_7^+$, 20).

* A yield of 70% was obtained on a batch that was later processed.

_N_-Methyl-_Z_-3-chloro-2-(benzylthio)propenamide 85

This was synthesized following the procedure described for **3** using *N*-4′-methyl-2-(benzylthio)propanamide **39** (4.00 g, 19 mmol), *N*-chlorosuccinimide (5.08 g, 37 mmol) and toluene (80 ml). The crude β-chloroacrylamide **85** was obtained as a brown oil following filtration and evaporation of the solvent at reduced pressure. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 20-60% ethyl acetate) to yield the pure product **85** (3.83 g, 83%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 3398 (NH), 2928 (CH), 1649 (CO), 1557 (NH bend), 1495, 1409 (CN stretch); δ_H (300 MHz) 2.68 (3H, d, *J* 5.0, C*H*$_3$NH), 3.97 (2H, s, SC*H*$_2$), 6.77 (1H, b s, N*H*), 7.19-7.37 (5H, m, Ar*H*), 7.82 [1H, s, C(3)*H*Cl=]; δ_c (75.5 MHz) 27.1 (*C*H$_3$NH), 39.0 (S*C*H$_2$), 128.1, 129.1, 129.2 (aromatic *C*H), 131.5, 137.5 [aromatic *C* or *C*(2)S], 139.5 [*C*(3)HCl=], 163.9 (*C*O).

The ^{1}H NMR spectra of the crude and pure product also contained a compound assigned as the *E* isomer although this has not been isolated and fully characterised (~15%); δ_H (300 MHz) 2.91 (3H, d, *J* 4.9, C*H*$_3$NH), 3.90 (2H, s, SC*H*$_2$), 6.15 (1H, bs, N*H*), 6.48 [1H, s, C(3)*H*Cl=].

_N_-Phenyl-_Z_-3-chloro-2-(benzylthio)propenamide 86

The title compound was synthesized following the procedure outlined for **3** using *N*-phenyl-2-(benzylthio)propanamide **40** (3.00 g, 11 mmol), *N*-chlorosuccinimide (2.94 g, 21.6 mmol) and toluene (120 ml). The reaction mixture was heated at 90 °C for 2 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product **86** was obtained as a brown oil. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-5% ethyl acetate) to yield the pure β-chloroacrylamide **86** (2.61 g, 78%) as a white solid, mp 81-82^{o}C; (Found C, 62.95; H, 4.65; Cl, 11.80; N, 4.34; S, 10.32. $C_{16}H_{14}ClNOS$ requires C, 63.25; H, 4.64; Cl, 11.67; N, 4.61; S, 10.55%); ν_{max}/cm^{-1} (KBr) 3343 (NH), 1655 (CO), 1599, 1525 (NH bend), 1494, 1441 (CN stretch); δ_H (300 MHz) 3.98 (2H, s, SC*H*$_2$), 7.06-7.43 (10H, m, Ar*H*), 7.95 [1H, s, C(3)*H*Cl=], 8.61 (1H, b s, N*H*); δ_c (75.5 MHz) 39.1 (S*C*H$_2$), 120.3, 125.2, 128.3, 129.1, 129.3, 129.4 (aromatic *C*H), 131.8, 137.3, 137.5 [aromatic *C* or *C*(2)S], 141.1 [*C*(3)HCl=], 161.2 (*C*O); *m/z* (ESI) 304 ([M+H]$^+$, 100%), 91 ($C_7H_7^+$, 70).

_Z_-3-Chloro-2-(benzylthio)propenamide 87

This was prepared following the procedure described for **3** using 2-(benzylthio)propanamide **41** (0.50 g, 2.6 mmol), *N*-chlorosuccinimide (0.68 g, 5 mmol) and toluene (20 ml). Following filtration and evaporation of the solvent at reduced pressure, the crude product **87** was obtained as a yellow oil. This was purified by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 0-40% ethyl acetate) to yield the pure β-chloroacrylamide **87** (0.30 g, 51%) as a white solid, mp 72-74^{o}C; (Found C, 52.62; H, 4.52; Cl, 15.82; N, 6.31; S, 13.85. $C_{10}H_{10}ClNOS$ requires C, 52.75; H, 4.43; Cl, 15.57; N, 6.15; S, 14.08%); ν_{max}/cm^{-1} (KBr) 3391 (NH), 3298 (NH), 1650 (CO), 1618 (NH bend), 1495, 1417 (CN stretch); δ_H (300 MHz) 3.96 (2H, s, SC*H*$_2$), 5.38 (1H, b s, N*H*), 6.72 (1H, b s, N*H*), 7.19-7.41 (5H, m, Ar*H*), 7.82 [1H, s, C(3)*H*Cl=]; δ_c (75.5 MHz) 38.8 (S*C*H$_2$),

128.1, 129.2, 129.3 (aromatic *C*H), 131.1, 137.2 [aromatic *C* or *C*(2)S], 140.4 [*C*(3)HCl=], 165.8 (*C*O); *m/z* (ESI) 228 ([M+H]$^+$, 100%), 91 ($C_7H_7^+$, 56).

_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 ^{1}H 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, C*H*$_2$Cl). 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 (3.50 g, 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, SC*H*$_3$), 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 C*H*$_2$=) and 5.58 (s, one of C*H*$_2$=).

_N_-Benzyl-_Z_-3-chloro-2-(methylthio)propenamide 89

This was prepared following the procedure (Method F) described for β-chloroacrylamide **88** using sulfide **43** (2.00 g, 9.57 mmol), NCS (2.30 g, 17.22 mmol) and toluene (40 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. The ^{1}H NMR of the crude product showed the composition of

the mixture to be 75% **89**, 15% dichloroacrylamide **107** (δ_H 2.28) and 5% acrylamide **108** (δ_H 5.41 and 6.31). Following purification by column chromatography on silica gel using hexane-ethyl acetate (80:20) as eluent, the pure β-chloroacrylamide **89** (1.57 g, 68%) was isolated as a colourless oil, (Found C, 54.54; H, 4.98; N, 5.72; Cl, 14.31; S, 13.55. $C_{11}H_{12}NClOS$ requires C, 54.65; H, 5.00; N, 5.79; Cl, 14.67; S, 13.26%); ν_{max}/cm^{-1} (film) 3302 (NH), 1651 (CO), 1515, 1278; δ_H (300 MHz) 2.31 (3H, s, SC*H*$_3$), 4.52 (2H, d, *J* 5.9, C*H*$_2$NH), 7.19-7.51 (6H, m, Ar*H*, N*H*), 7.75 [1H, s, C(3)*H*Cl=]; δ_c (75.5 MHz) 17.5 (S*C*H$_3$), 44.6 (*C*H$_2$NH), 128.1, 128.2, 129.2, (aromatic *C*H), 133.7 [*C*(2)S], 137.2 [*C*(3)HCl=], 138.0 (quaternary aromatic *C*), 163.1 (*C*O); *m/z* (EI) 241 (M^+, 2), 206 (60), 158 (90), 91 (100).

_N_-_n_-Butyl-_Z_-3-chloro-2-(methylthio)propenamide 90

This was prepared following the procedure (Method F) described for β-chloroacrylamide **88** using sulfide **44 (**5.0 g, 28.5 mmol), NCS (7.4 g, 55.6 mmol) and toluene (100 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. The ^{1}H NMR spectrum of the crude product showed the composition of the mixture to be 76% **90**, 23% dichloroacrylamide **109** and 1% acrylamide **110** (δ_H 5.38 and 6.26). Following purification by column chromatography on silica gel using hexane-ethyl acetate (80:20) as eluent, the pure β-chloroacrylamide **90** (3.9 g, 65%) was isolated as a colourless oil; (Found C, 46.43; H, 6.67; N, 6.48; Cl, 17.36; S, 15.36. $C_8H_{14}NClOS$ requires C, 46.26; H, 6.79; N, 6.74; Cl, 17.07; S, 15.44%); ν_{max}/cm^{-1} (film) 3307 (NH), 1644 (CO), 1519; δ_H (300 MHz) 0.98 [3H, t, *J* 7.3, C(4′)*H*$_3$], 1.29-1.48 [2H, m, C(3′)*H*$_2$], 1.51-1.69 [2H, m, C(2′)*H*$_2$], 2.28 (3H, s, SC*H*$_3$), 3.41 (2H, q, *J* 6.0, NC*H*$_2$), 7.12 (1H, bs, N*H*), 7.68 [1H, s, C(3)*H*Cl=]; δ_c (75.5 MHz) 14.1 [*C*(4′)H$_3$], 17.4 (S*C*H$_3$), 20.5 [*C*(3′)H$_2$], 31.9 [*C*(2′)H$_2$], 40.3 (*N*CH$_2$), 133.9 [*C*(2)S], 136.1 [*C*(3)HCl=], 163.0 (*C*O); *m/z* (ESI) 207.04828 ([M]$^+$, $C_8H_{14}NOSCl$ requires 207.048246. 207 (M^+, 15%), 172 (55%), 135 (56%), 107 (81%).

***N*-Isopropyl-*Z*-3-chloro-2-(methylthio)propenamide 91**

This was prepared following the procedure (Method F) described for β-chloroacrylamide **88** using sulfide **45** (2.30 g, 15.86 mmol), NCS (3.81 g, 28.55

mmol) and toluene (60 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. Following purification by column chromatography on silica gel using hexane-ethyl acetate (80:20) as eluent, the pure β-chloroacrylamide **91** (1.80 g, 60%) was isolated as a white solid, mp 52-54 °C; (Found C, 43.11; H, 6.15; N, 7.11; S, 16.90. $C_7H_{12}NClOS$ requires C, 43.41; H, 6.24; N, 7.23; S, 16.55%); ν_{max}/cm^{-1} (KBr) 3396 (NH), 1656 (CO), 1613, 1211; δ_H (300 MHz) 1.25 [6H, d, *J* 6.5, $CH(CH_3)_2$], 2.29 (3H, s, SCH_3), 4.12-4.19 [1H, m, $CH(CH_3)_2$], 6.89 (1H, bs, N*H*), 7.61 [1H, s, C(3)*H*Cl=]; δ_c (75.5 MHz) 17.0 (SCH_3), 22.6 [$CH(CH_3)_2$], 42.2 [$CH(CH_3)_2$], 133.6 [*C*(2)S], 135.5 [*C*(3)HCl=], 162.3 (*C*O).

_N_-4'-Methylphenyl -_Z_-3-chloro-2-(methylthio)propenamide 92

This was prepared following the procedure (Method F) described for β-chloroacrylamide **88** using sulfide **46** (2.00 g, 9.58 mmol), NCS (2.59 g, 18.68 mmol) and toluene (40 ml). The reaction solution was heated for 2 hours at 90°C. Following filtration and evaporation of the solvent at reduced pressure, the crude product mixture was isolated. Following purification by column chromatography on silica gel using hexane-ethyl acetate (80:20) as eluent, the pure β-chloroacrylamide **92** (1.45 g, 60%) was isolated as a white solid, mp 103-104 °C; (Found C, 55.50; H, 4.84; N, 5.59. $C_{11}H_{12}NClOS$ requires C, 55.10; H, 4.62; N, 5.84%); ν_{max}/cm^{-1} (KBr) 3020 (NH), 1645 (CO), 1600, 1512, 1405, 1263, 822; δ_H (300 MHz) 2.36 (3H, s, C*H*$_3$), 2.43 (3H, s, SCH_3), 7.15-7.18 (2H, m, Ar*H*), 7.47-7.50 (2H, m, Ar*H*), 7.79 [1H, s, C(3)*H*Cl=], 8.93 (1H, bs, N*H*); δ_c (75.5 MHz) 17.6 (SCH_3), 21.3 ($ArCH_3$), 120.4, 130.0 (aromatic CH), 130.1, 133.9, 135.1 (S*C*= and quaternary aromatic *C*), 138.1 [*C*(3)HCl=], 161.0 (*C*O); *m/z* (EI) 241/243 (M^+).

_N_-4'-Methylphenyl-_Z_-3-chloro-2-(phenylthio)-2-butenamide 93, _N_-4'-Methylphenyl-E-3-chloro-2-(phenylthio)-2-butenamide 94, _N_-4′-Methylphenyl-2-(phenylthio)-2-butenamide 111 and _N_-4'-Methylphenyl-2,3,3-trichloro-2-(phenylthio)-2-butanamide 112.

A) Using carbon tetrachloride as solvent

This reaction was conducted following the procedure described for β-chloroacrylamide **57** using sulfide **47** (170 mg, 0.6 mmol), NCS (167 mg, 1.25 mmol)

and carbon tetrachloride (4 ml) to give a mixture of acrylamides (165 mg, 87 %). Separation of the mixture by chromatography using ethyl acetate-hexane (3:97) as eluent gave *N*-4′-methylphenyl-*E*-3-chloro-2-(phenylthio)-2-butenamide **94** (tentatively assigned) (36.9 mg, 19 %) (Rf 0.5 using ethyl acetate-hexane (25:75) as eluent) as a white, crystalline solid, mp 128-129 °C; (Found C, 64.89; H, 5.13; N, 4.20. $C_{17}H_{16}ClNOS$ requires C, 64.24; H, 5.07; N, 4.41%); ν_{max}/cm^{-1} (KBr) 3234 (br NH), 1654, 1600 (CO α,β-unsaturated amide); δ_H (270 MHz) 2.28 (3H, s, ArC*H*$_3$), 2.55 [3H, s, C(4)*H*$_3$], 7.00-7.43 (9H, m, Ar*H*), 7.56 (1H, br s, N*H*); δ_C (67.8 MHz) 20.8 (Ar*C*H$_3$), 25.3 (*C*(4)H$_3$), 120.2 (aromatic *C*H), 126.1 [*C*(2)S], 127.7, 129.4, 129.8, 130.0 (aromatic *C*H), 133.0, 134.4, 134.6 (quaternary aromatic *C*), 139.9 (*C*Cl=), 162.4 (*C*O); *m/z* (EI) 317 (M^+, 95%), 282 (20, M^+- Cl), 211 (29), 183 (79), 147 (100, $[PhS=C=C=CH_2]^+$), 107 (80), 91 (17), 77 (29) and *N*-4'-Methylphenyl-*Z*-3-chloro-2-(phenylthio)-2-butenamide **93** (51.4 mg, 27 %, more polar, colourless solid), mp 124-126 °C; (Found C, 64.37; H, 5.01, N, 4.47. $C_{17}H_{16}ClNOS$ requires C, 64.24; H, 5.07; N, 4.41%); ν_{max}/cm^{-1} (KBr) 3272 (br NH), 1656 (CO α,β-unsaturated amide); δ_H (270 MHz) 2.31 (3H, s, ArC*H*$_3$), 2.65 [3H, s, C(4)*H*$_3$], 7.03-7.45 (9H, m, Ar*H*), 8.14 (1H, br s, N*H*); δ_C (67.8 MHz) 20.8 (Ar*C*H$_3$), 25.8 [*C*(4)H$_3$], 120.3 (aromatic *C*H), 126.5 [*C*(2)S], 127.5 (aromatic *C*H), 129.4 (aromatic *C*H), 132.9, 134.5 (quaternary aromatic *C*), 147.2 (*C*Cl=), 162.0 (*C*O); *m/z* (EI) 317 (M^+, 95%), 282 (28, M^+- Cl), 183 (75), 147 (100, $[PhS=C=C=CH_2]^+$), 107 (88), 91 (22), 77 (56); and *N*-4′-methylphenyl-2-(phenylthio)-*Z*-2-butenamide **111** (as a single isomer) (34 mg, 20%) (Rf 0.45), mp 104- 106 °C; ν_{max}/cm^{-1} (KBr) 3232 (br NH), 1653, 1599 (CO α,β-unsaturated amide); δ_H (270 MHz) 2.14 (3H, d, *J* 7, C*H*$_3$CH=), 2.28 (3H, s, ArC*H*$_3$), 7.00-7.44 (9H, m, Ar*H*), 7.85 (1H, q, *J* 7, C*H*=), 8.83 (1H, br s, N*H*); δ_C (67.8 MHz) 16.9 [*C*(4)H$_3$], 20.0 (Ar*C*H$_3$), 120.1, 126.4, 126.3 (aromatic *C*H), 127.4 (PhS*C*=), 129.4 (aromatic *C*H), 134.1, 134.5, 135.1 (quaternary aromatic *C*), 148.9 (*C*H=), 162.2 (*C*O); *m/z* (ESI) 283.10239 ($[M]^+$, $C_{17}H_{17}NOS$ requires 283.10309. 283 (M^+, 17%), 262 (37), 183 (28), 149 (17), 134 (78).

B) Using toluene as solvent

This was prepared following the procedure (method A) described for β-chloroacrylamide **3** using sulfide **47** (2.75 g, 9.7 mmol), NCS (2.71 g, 20.3 mmol) and toluene (80 ml) to give crude mixture of acrylamides **93** & **94** and trichloride **112**

(3.70 g). Purification by chromatography using ethyl acetate-hexane (10:90) as eluent gave the *E*-ß-chloroacrylamide **94** (1.13 g, 41 %), *Z*-β-chloroacrylamide **93** (0.70 g, 23 %) and *N*-4'-methylphenyl-2-(phenylthio)-2,3,3-trichlorobutanamide **112** (0.34 g, 9 %) as a viscous oil; ν_{max}/cm^{-1} (film) 3405 (br NH), 1691, 1594 (CO amide); δ_H (270 MHz) 2.30 (3H, s, ArCH_3), 2.77 [3H, s, C(4)H_3], 7.07-7.69 (9H, m, Ar*H*), 8.40 (1H, br s, N*H*); δ_C (67.8 MHz) 21.2 (Ar*C*H_3), 36.4 [*C*(4)H_3], 93.4, 94.5 (*C*Cl_2 and *C*ClS), 120.9 (aromatic *C*H), 128.8 (quaternary aromatic *C*), 129.4, 129.8, 131.1 (aromatic *C*H), 134.0, 135.7 (quaternary aromatic *C* and PhS*C*=), 137.7 (aromatic *C*H), 161.t (*C*O); *m/z* (ESI) 387.00201 ($[M]^+$, $C_{17}H_{16}NOSCl_3$ requires 387.00182. 387 (M^+, 33%), 317 (18, M^+-2Cl), 282 (5, M^+-3Cl), 218 (100, $[PhS{=}CCl{=}CClCH_3]^+$), 148 (47), 106 (59).

_N_-4′-Methylphenyl-_Z_-3-chloro-2-(phenylthio)-2-pentenamide 95, _N_-4′-methylphenyl-_E_-3-chloro-2-(phenylthio)-2-pentenamide 96, _N_-4′-methylphenyl-2-(phenylthio)-2-pentenamide 122 and _N_-4′-methylphenyl-2-(phenylthio)-2,3,3-trichloropentanamide 121

A) Using carbon tetrachloride as solvent

This was conducted following the procedure (method E) described for β-chloroacrylamide **57** using *N*-4′-methylphenyl-2-(phenylthio)pentanamide **48** (100 mg, 0.33 mmol), NCS (98 mg, 0.74 mmol) and carbon tetrachloride (2 ml) with a reaction time of 20 h, to give a mixture of acrylamides. Purification by chromatography using ethyl acetate-hexane (10:90) to (25:75) as eluent gave *N*-4′-methylphenyl-*E*-3-chloro-2-(phenylthio)-2-pentenamide **96** (tentatively assigned) (13.8 mg, 17 %) (Rf 0.6 using ethyl acetate-hexane (25:75) as eluent) as a white, crystalline solid, mp 146-147 °C; (Found C, 65.09; H, 5.47; N, 4.18. $C_{18}H_{18}ClNOS$ requires C, 65.15; H, 5.47; N, 4.22%); ν_{max}/cm^{-1} (KBr) 3270 (br NH), 1657 (CO), 1603; δ_H (270 MHz) 1.23 [3H, t, *J* 7, C(5)H_3], 2.29 (3H, s, ArCH_3), 2.93 [2H, q, *J* 7, C(4)H_2], 6.97-7.43 (9H, m, Ar*H*), 7.57 (1H,br s, N*H*); δ_C (67.8 MHz) 12.3 [*C*(5)H_3], 20.8 (Ar*C*H_3), 31.4 [*C*(4)H_2], 120.2 (aromatic *C*H), 125.3 (quaternary aromatic *C*), 127.7, 129.4, 129.6, 129.7 (aromatic *C*H), 133.1, 134.4, 134.6 [quaternary aromatic *C* and *C*(2)S], 145.7 [*C*(3)Cl=], 162.4 (*C*O); *m/z* (EI) 331 (M^+, 100 %), 296 (15, M^+-Cl), 225 (27), 197 (68), 161 (58, $[PhS{=}C{=}C{=}CHCH_3]^+$), 107 (58), 91 (33), 77 (28); *N*-

4'-methylphenyl-*Z*-3-chloro-2-(phenylthio)-2-pentenamide **95** (tentatively assigned) (contains trace acrylamide **122**) (11 mg, 13 %) (Rf 0.4) as a white, crystalline solid. *Note: This compound formed a gel in some test tubes as it was eluted; 86 mg were held in 9.5 ml eluent (ethyl acetate-hexane (25:75))*, mp 114-6 °C; ν_{max}/cm^{-1} (KBr) 3293 (br NH), 1646 (CO), 1607; δ_H (270 MHz) 1.30 [3H, t, *J* 7, C(5)H_3], 2.27 (3H, s, ArCH_3), 2.93 [2H, q, *J* 7, C(4)H_2], 7.02-7.45 (9H, m, Ar*H*), 8.03 (1H, br s, N*H*); δ_C (67.8 MHz) 13.1 [*C*(5)H_3], 20.8 (Ar*C*H_3), 31.9 [*C*(4)H_2], 120.3 (aromatic *C*H), 126.3 (PhS*C*=), 127.5, 129.4, 129.7, 129.6 (aromatic *C*H), 132.8, 134.5, (quaternary aromatic *C*), 152.3 (*C*Cl=), 162.0 (*C*O); *m/z* (EI) 331 (M^+, 22%), 296 (2, M^+- Cl), 161 (17, $[PhS=C=C=CHCH_3]^+$), 134 (28), 91 (25), 77 (33); *N*-4′-methylphenyl-2-(phenylthio)-*Z*-2-pentenamide **122** (tentatively assigned) (44 mg, 54 %) (Rf 0.5) as a white, crystalline solid, mp 66-68 °C; (Found C, 72.31; H, 6.38; N, 4.77; S, 11.25. $C_{18}H_{19}NOS$ requires C, 72.69; H, 6.44; N, 4.71; S, 10.78%); ν_{max}/cm^{-1} (KBr) 3339 (br NH), 1657 (CO), 1610; δ_H (270 MHz) 1.11 [3H, t, *J* 7, C(5)H_3], 2.29 (3H, s, ArCH_3), 2.42-2.60 [2H, dq , *J* 8,7, C(4)H_2], 7.07-7.35 (9H, m, Ar*H*), 7.74 (1H, t, *J* 8, C*H*=), 8.80 (1H, br s, N*H*); δ_C (67.8 MHz) 12.8 [*C*(5)H_3], 20.8 (Ar*C*H_3), 24.5 [*C*(4)H_2], 120.1 (aromatic *C*H), 125.7 (PhS*C*=), 126.3, 126.9, 129.4, (aromatic *C*H), 134.1, 134.7, 135.1 (quaternary aromatic *C* and PhS*C*=), 155.1 (*C*H=), 162.2 (*C*O); *m/z* (EI) 297 (M^+, 100%), 163 (62), 148 (52), 121 (66), 107 (58), 91 (30), 77 (29).

B) Using toluene as solvent

This was conducted following the procedure described for β-chloroacrylamide **3** by method A using *N*-4′-methylphenyl-2-(phenylthio)pentanamide **48** (300 mg, 1.0 mmol), NCS (280 mg, 2.1 mmol) and toluene (7 ml) to give the crude product as a low melting solid (420 mg). Purification by chromatography using ethyl acetate-hexane (10:90) as eluent gave *N*-4′-methylphenyl-*E*-3-chloro-2-(phenylthio)-2-pentenamide **96** (with trace acrylamide **122**) (65 mg, 20 %), *N*-4′-methylphenyl-2-(phenylthio)-*Z*-2-pentenamide **122** (30 mg, 10 %), *N*-4′-methylphenyl-*Z*-3-chloro-2-(phenylthio)-2-pentenamide **95** (154 mg, 47 %), and *N*-4′-methylphenyl-2-(phenylthio)-2,3,3-trichloropentanamide **121** (38 mg, 10 %) as an off-white solid, mp 108-110 °C; (Found C, 53.68; H, 4.70; N, 3.38; S, 7.85; Cl, 26.40. $C_{18}H_{18}Cl_3OS$ requires C, 53.69; H, 4.51; N, 3.48; S, 7.96; Cl, 26.41%); ν_{max}/cm^{-1} (neat) 3404 (br NH), 1690, 1594 (CO amide); δ_H (270 MHz) 1.38 [3H, t , *J* 7, C(5)H_3], 2.33 (3H, s,

ArC*H*$_3$), 2.70-2.80 [1H, m, C(4)*H*$_2$], 7.08-7.69 (9H, m, Ar*H*), 8.48 (1H, br s, N*H*); δ_C (67.8 MHz) 10.7 [*C*(5)H$_3$], 20.9 (Ar*C*H$_3$), 37.8 [*C*(4)H$_2$], 95.6, 99.3 (*C*Cl$_2$ and *C*ClSPh), 120.7 (aromatic *C*H), 128.5 (quaternary aromatic *C*), 129.0, 129.4, 130.7 (aromatic *C*H), 133.8, 135.3 (quaternary aromatic *C*), 137.4 (aromatic *C*H), 161.4 (*C*O); MS *m/z* 401 (M$^+$, 1 %), 331 (2, M$^+$-2 Cl), 242 (23), 197 (10), 155 (100), 91 (20).

(1′S)-*N*-1′-Phenylethyl-*Z*-3-chloro-2-(phenylthio)-2-pentenamide 97 and (S)-*N*-1′-phenylethyl-*E*-3-chloro-2-(phenylthio)-2-pentenamide 98

This was prepared following the procedure (method B) described for β-chloroacrylamide **57** using (1′S)-*N*-1′-phenylethyl-2-(phenylthio)pentanamide **49** (1:1 mixture of diastereomers) (2.01 g, 6.4 mmol), NCS (1.71 g, 12.8 mmol) and carbon tetrachloride (40 ml) to give mixture of acrylamides (2.09 g, 89 % crude). Purification by chromatography using ethyl acetate-hexane (10:90) as eluent gave (1′S)-*N*-1′-phenylethyl-*E*-3-chloro-2-(phenylthio)-2-pentenamide **98** (tentatively assigned) (Rf 0.4 using ethyl acetate-hexane (25:75) as eluent) (0.29 g, 13 %) as a white, crystalline solid, mp 80-83 °C; $[\alpha]_D^{20}$ 4.74 (c 0.08 in EtOH); (Found C, 66.35; H, 5.68; N, 4.22; S, 9.40. $C_{19}H_{20}ClNOS$ requires C,65.98; H, 5.83; N, 4.05; S 9.27%); ν_{max}/cm^{-1} (KBr) 3254 (br NH), 1635 (CO α,β-unsaturated amide); δ_H (270 MHz, CD_2Cl_2) 1.11-1.35 [6H, m, C(5)*H*$_3$, C(2′)*H*$_3$], 2.77 [2H, q, *J* 7, C(4)*H*$_2$], 4.78 [1H, m, C(1′)*H*], 6.46 (1H, br s, N*H*), 7.20-7.29 (10H, m, Ar*H*); δ_c (67.8 MHz, CD_2Cl_2) 13.04 [*C*(5)H$_3$], 22.2 [*C*(2′)H$_3$], 32.0 [*C*(4)H$_2$], 50.0 [*C*(1′)H], 126.2, 128.1, 128.2, 128.7, 129.5, 130.7 (aromatic *C*H), 133.5, 140.0, 143.3, 149.2 (quaternary aromatic *C*, PhS*C*= and *C*Cl=), 163.5 (*C*O); *m/z* (EI) 345 (M$^+$, 37%), 310 (13, M$^+$- Cl), 161 (18, [PhS=C=C=CHCH$_3$]$^+$), 105 (100, [CHCH$_3$Ph]$^+$); (1′S)-*N*-1′-phenylethyl-*Z*-3-chloro-2-(phenylthio)-2-pentenamide **97** (tentatively assigned) (Rf 0.3) (0.54 g, 27 %), mp 95-98 °C; $[\alpha]_D^{20}$ 52.6 (c 0.08 in EtOH), ν_{max}/cm^{-1} (KBr) 3264 (br NH), 1638 (CO α,β-unsaturated amide); δ_H (270 MHz) 1.19 [3H, d, *J* 7, C(2′)*H*$_3$], 1.26 [3H, t, *J* 7, C(5)*H*$_3$], 2.83 [2H, q, *J* 7 , C(4)*H*$_2$], 4.88-5.01 [1H, dq, *J* 7, 7, C(1′)*H*], 6.05 (1H, br s, N*H*), 7.03-7.38 (10H, m, Ar*H*); δ_C (67.8 MHz) 12.4 [*C*(5)H$_3$], 21.5 [*C*(2′)H$_3$], 31.3 [*C*(4)H$_2$], 49.4 (N*C*H), 126.4, 128.1, 128.5, 128.8, 129.9, 131.1 (aromatic *C*H) 133.6,

143.2, 143.7, 143.7 (quaternary aromatic *C* and PhS*C*= and *C*Cl=), 163.9 (*C*O); *m/z* (EI) 345 (M^+, 18%), 310 (8, M^+- Cl), 208 (29), 117 (35), 105 (100, $[PhCHCH_s]^+$).

Treatment of *N*-4′-methylphenyl-2-(phenylthio)-3-phenylpropanamide 85 with NCS

This was conducted following the procedure described for β-chloroacrylamide **57** using sulfide **50** (186 mg, 0.54 mmol), NCS (156 mg, 1.18 mmol) in carbon tetrachloride (3.5 ml) under reflux conditions for 18 hours to give a reaction mixture with 3 spots by TLC analysis (168 mg). Chromatographic purification using ethyl acetate-hexane (5:95) gave *Z*- and *E*- *N*-4′-methylphenyl-3-chloro-2-(phenylthio)-3-phenylpropenamide **99 & 100** which were characterised as a mixture of isomers (essentially equimolar) (29 mg, 14 %) (Rf 0.2 using ethyl acetate-hexane (25:75) as eluent) as a white, crystalline solid, mp 183-186 °C; (Found C, 69.22; H, 4.85; N, 3.76; Cl, 9.74. $C_{22}H_{18}ClNOS$ requires C, 69.55; H, 4.78; N, 3.69; Cl, 9.33%); ν_{max}/cm^{-1} (KBr) 3274 (br NH), 1648, 1598 (CO α,β-unsaturated amide); δ_H (270 MHz) 2.23, 2.29 (3H, s, ArCH_3), 6.71-7.60 (14H aromatic; distinctive ABq seen at 6.71-6.93 for *o*- hydrogens in one isomer), 7.75 (1H, br s, N*H*); δ_C (67.8 MHz) 20.9 (Ar*C*H_3), 120.4, 120.6 (aromatic *C*H), 128.1-134.8 (overlapping signals, aromatic *C*H, quaternary aromatic *C* and PS*C*=), 136.7, 137.2 (*C*Cl=), 161.5, 162.2 (*C*O); MS *m/z* 379 (M^+, 26 %), 344 (8, M^+-Cl), 273 (21), 210 (100, $[PhS{=}C{=}CPh]^+$), 91(5), 77 (11), *N*-4′-methylphenyl-3-phenyl-*Z*-2-(phenylthio)propenamide **123** (tentatively assigned) (71 mg, 49 %) (Rf 0.3) as a colourless, low-melting solid; δ_H (270 MHz) 2.28 (3H, s, ArCH_3), 7.07-7.85 (14H, m, Ar*H*), 8.51 (1H, s, C*H*Cl=), 8.94 (1H, br s, N*H*); δ_C (67.8 MHz) 20.9 (Ar*C*H_3), 120.2 (aromatic *C*H), 124.5 (quaternary aromatic *C*), 126.7, 127.1, 128.4, 129.0, 129.9, 130.7 (aromatic *C*H), 134.3, 134.7, 135.1, 137.3 (quaternary aromatic *C* or PhS*C*=), 147.2 (=*C*HPh), 162.9 (*C*O); a third compound tentatively identified as *N*-4′-methylphenyl-3-chloro-2-phenylpropenamide **113** was isolated (12 mg, 8 %) (Rf 0.2) as a light yellow, low-melting solid, mp 35-37 °C; ν_{max}/cm^{-1} (neat) 3403 (br NH), 1694, 1594 (CO α,β-unsaturated amide); δ_H (270 MHz) 2.35 (3H, s, ArCH_3), 7.08-7.82 (9H, m, Ar*H*), 8.13 (1H, s, C*H*Cl=), 8.48 (1H, br s, N*H*); δ_C as a mixture with acrylamide **123** 171.0 (*C*O); MS *m/z* 271.07575 $C_{16}H_{14}ClNO$ requires M^+ 271.07639; 271(M^+, 75 %), 236 (90,M^+-Cl), 211 (24), 165

(100), 137 (70), 102 (70), 91(12), 77 (28).

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