Mechanistic aspects of the synthesis of 3-aminopyrroles from substituted 2-methyl-1,2-thiazolium salts or 3-amino-thioacrylamides

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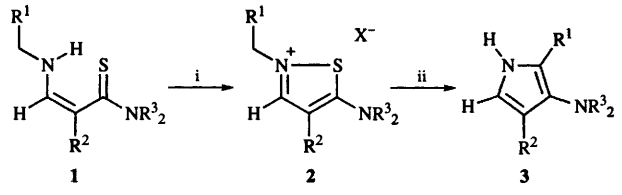
The mechanism of the synthesis of 3-aminopyrroles 3 by ring transformation–desulfurisation of substituted 2-methyl-1,2-thiazolium salts 2 has been investigated. 3-Alkylideneaminothioacrylamides 4 and 2*H*-1,3-thiazines 5 could be synthesised by base treatment of 1,2-thiazolium bromides 2 and proved to be intermediates in the ring transformation–desulfurisation. Hitherto unknown bis(2-aminothiocarbonylvinyl)amines 6 are observed as by-products. When 3-phenacylaminothioacrylamide 1c is oxidised with hydrogen peroxide a novel pyrrole formation occurs to give 2-benzoylthiopyrrole 8a, where the sulfur atom is retained in the product. An erroneously reported 1,2-thiazolium-2-methanide 7 has been reassigned as 3-(4-nitrobenzylideneamino)thioacrylamide 4a on the basis of an X-ray crystal structure determination.

Recently we reported a novel and versatile synthesis of 3-aminopyrroles **3** by base-catalysed ring transformation–desulfurisation of substituted 5-amino-2-methyl-1,2-thiazolium salts **2**, which were generated by oxidative ring closure of 3-aminothioacrylamides **1** (Scheme 1).[1,2] Powerful novel



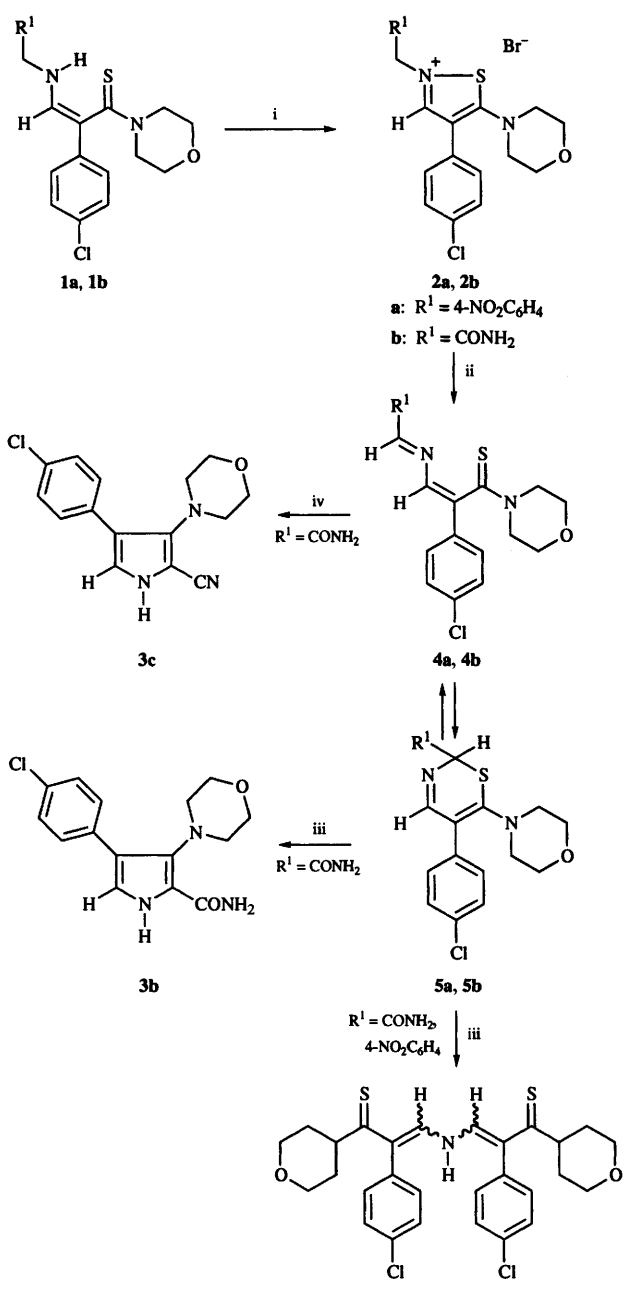
Scheme 1 *Conditions:* i, oxidation; ii, base

anticonvulsive compounds have been found in this family of pyrroles **3**.[3] The transformation of **2** to **3** was extremely facile and no intermediates could be isolated, especially if the electron-withdrawing group R^1 was CO_2Alkyl or CN. The transformation of **2** to **3** was assumed[1] to start with deprotonation of the acidic R^1CH_2-position affording zwitterionic 1,2-thiazolium-2-methanides, followed by ring opening to give 3-alkylideneaminothioacrylamides **4**. Subsequent electrocyclic ring closure to 2*H*-1,3-thiazines **5**, extrusion of sulfur and finally protonation gives the pyrroles **3**. Although with other substituent patterns, ring contractions of aryl-substituted 1,3-thiazine anions to pyrroles[4,5] and of 2-phenacyl-1,2-thiazolium salts to 2-benzoyl-1,3-thiazines as final products[6] were reported in the literature, the mechanism of the transformation of 1,2-thiazolium salts **2** to pyrroles **3** was speculative because none of the assumed intermediates could be isolated and further reacted to give the corresponding final product **3**. One product with a 4-nitrophenyl group as the electron-withdrawing substituent R^1 was obtained, which resisted desulfurisation and was preliminarily assigned as the betaine **7** (Fig. 1).

We now report results of further investigations leading to the isolation of a number of intermediates and to the hitherto unknown formation of a 3-amino-2-benzoylthiopyrrole **8a**. These results further reveal a more detailed insight into the mechanism of the formation of pyrroles **3** from 1,2-thiazolium salts **2** or 3-aminothioacrylamides **1** and indicate a revision of the reported structure **7**.

Reaction of the corresponding 3-(4-nitrobenzylamino)- or 3-aminocarbonylmethylamino-substituted thioacrylamide **1a** or **1b** with bromine afforded 5-morpholino-1,2-thiazolium salts **2a** and **2b** in high yields (Scheme 2). Treatment of these compounds **2** with triethylamine in methanol did not result in desulfurisation but in simple deprotonation. The products, however, do not have a betaine structure (*e.g.* **7**, Fig. 1) as assumed previously for the product derived from **2a**[1] but have now been determined as isomeric 3-alkylideneaminothioacrylamides **4** or 6-morpholino-2*H*-1,3-thiazines **5**, depending on the medium (Scheme 2). The X-ray crystal structure analysis of the nitrophenyl derivative proved the structure to be the open-chain 3-alkylideneaminothioacrylamide **4a** in the solid state (Fig. 2). The same structure **4a** was observed in dimethylformamide (DMF) solution, confirmed by ^{13}C NMR spectroscopy and compared with a corresponding solid state spectrum (see Experimental section). Surprisingly, in CF_3COOD solution the product adopts an isomeric 6-morpholino-2*H*-1,3-thiazine structure **5a**. The 3-alkylideneaminothioacrylamide **4a** was reformed from **5a** if the the trifluoroacetic acid was evaporated and the remaining material was treated with methanol. The same remarkable ring–chain tautomerism was found with the aminocarbonylmethyl derivative (R^1 = $CONH_2$), which exists as **4b** in DMF solution and as **5b** in CF_3COOD. The two ring–chain isomers **4** and **5** can easily be differentiated by typical ^{13}C NMR signals for CH=N (**4a**: δ 161.0, **4b**: δ 157.0) *versus* NCHS (**5a**: δ 61.3, **5b**: δ 56.9) respectively, or C=S (**4a**: δ 195.6, **4b**: δ 193.2) *versus* C=*C*–S (**5a**: δ 170.7, **5b**: δ 171.4). After keeping compound **5b** in CF_3COOD solution for a longer time (several days) a H/D-exchange at position 2 was observed by NMR spectroscopy (see experimental details).

Further ring transformation of compounds **5** was approached by treatment of CF_3COOH solutions with aqueous NaOH. In the case of the 4-nitrophenyl-substituted compound, however, the bis(2-aminothiocarbonylvinyl)amine **6** and 4-nitrobenzaldehyde were obtained rather than the expected pyrrole **3** (Scheme 2). Obviously a hydrolytic cleavage of the S,N-acetal unit of the thiazine **5** must have occurred. Under the same conditions the aminocarbonyl-substituted 1,3-thiazine **5b** afforded the pyrrole



Scheme 2 *Reagents and conditions:* i, Br_2, $CHCl_3$–MeOH; ii, $(C_2H_5)_3N$, CH_3OH; iii, NaOH; iv, $(CF_3CO)_2O$, C_5H_5N, DME

3b in low yield together with **6**, thus establishing thiazines **5** as intermediates in the transformation of 1,2-thiazolium salts **2** to pyrroles **3**.

Further proof for the intermediacy of 3-alkylideneaminothioacrylamides **4** in the formation of pyrroles **3** was obtained when the aminocarbonyl-substituted compound **4b** was dehydrated with trifluoroacetic anhydride, resulting in the pyrrole-2-carbonitrile **3c**. Obviously the dehydration of the aminothiocarbonyl group (R^1 = $CONH_2$) to the corresponding nitrile (R^1 = CN) affords a more strongly acidic 1,3-thiazine **5** (R^1 = CN), enabling easier deprotonation and further ring transformation–sulfur extrusion to the corresponding pyrrole **3c**. Alternatively, the latter product **3c** could be obtained in 62% yield by oxidising the corresponding 3-(cyanomethylamino)-thioacrylamide **1** (R^1 = CN) with iodine,[1] whereby no intermediates could be isolated (Scheme 2).

Finally, we investigated the hydrogen peroxide oxidation of 3-benzoylmethylaminothioacrylamide **1c** in order to access the corresponding 2-benzoyl-1,3-thiazine **5** (R^1 = COC_6H_5) analogous to a case reported[6] in the diaryl-series. Surprisingly, the 2-benzoylthiopyrrole **8a** was obtained rather than any product analogous to those already observed (Scheme 3). The formation of 2-mercaptopyrroles has not been reported in reactions of 1,3-thiazine anions either;[4,5] only 3-mercaptopyrroles could be obtained by reaction of thiazinium anions generated in situ from 6*H*-1,3-thiazines.[5] The structure of the 2-benzoylthio-3-morpholinopyrrole **8a** was confirmed by spectroscopic data and the saponification of the benzoylthio group. The resulting extremely electron-rich 2-mercaptopyrrole was air-sensitive. It was *S*-methylated to the corresponding 2-methylthiopyrrole **9**, which was somewhat more stable.

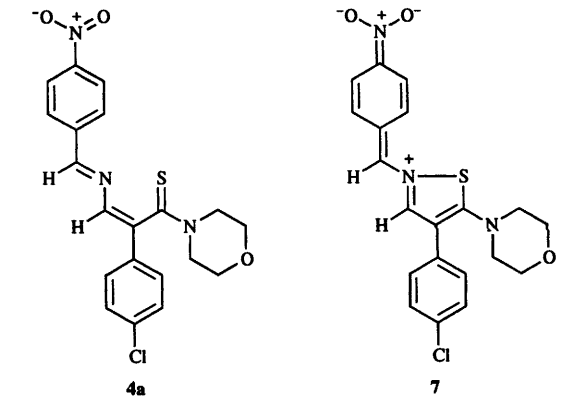


Fig. 1 Correct structure **4a** and previously assumed isomeric structure **7**

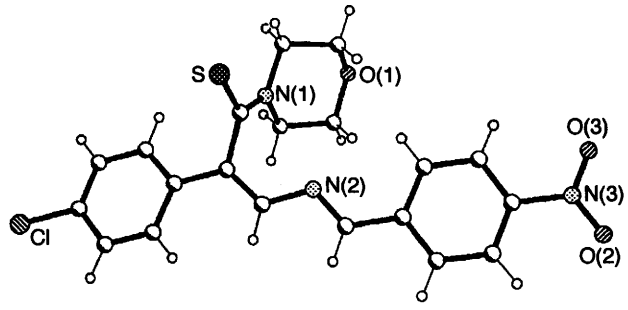
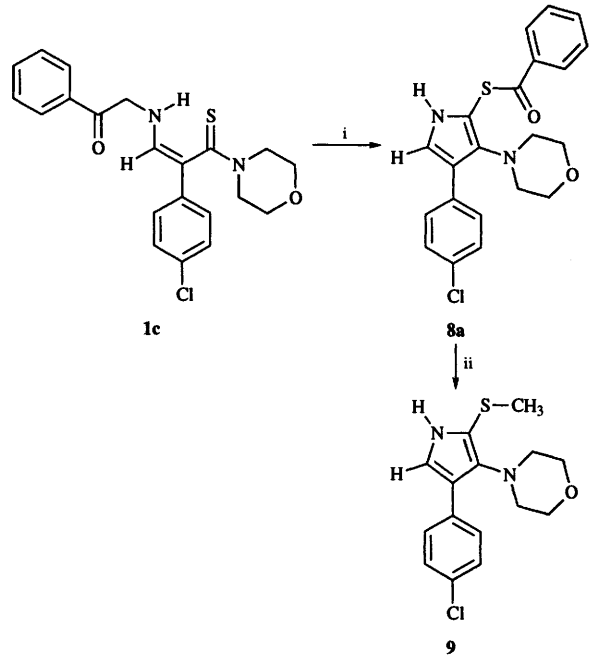
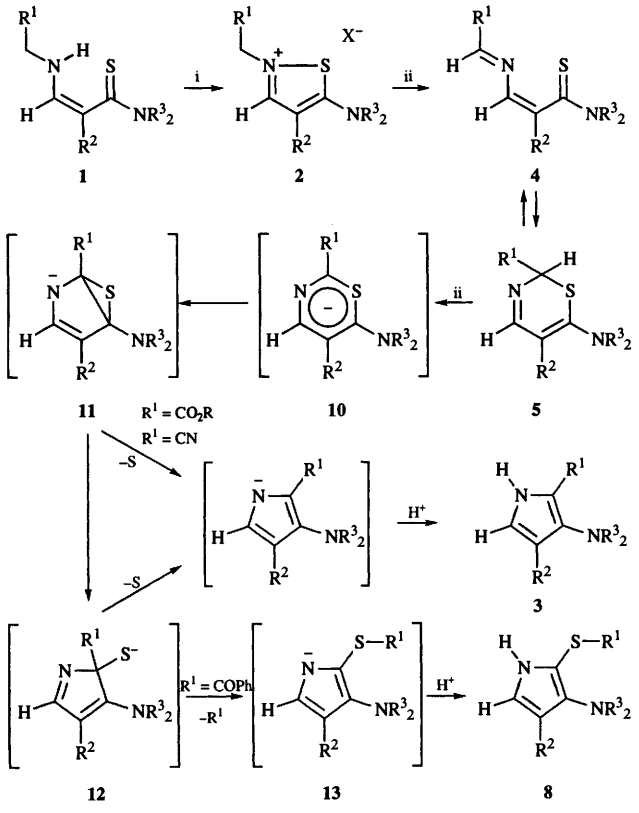


Fig. 2 X-Ray crystal structure of **4a**



Scheme 3 *Reagents and conditions:* i, H_2O_2, CH_3OH; ii, (*a*) NaOH (*b*) CH_3I, CH_3OH

The aforementioned results confirm the intermediates originally proposed[1] for the transformation of 1,2-thiazolium salts **2** to pyrroles **3** and indicate the following more detailed mechanism (Scheme 4). The reaction sequence starts with



Scheme 4 *Conditions:* i, oxidation; ii, base

primary ring opening by deprotonation to give 3-alkylideneaminothioacrylamides **4** with subsequent electrocyclic ring closure to 1,3-thiazines **5** followed by deprotonation (indirectly confirmed by H/D-exchange at **5b**) to give 8π-1,3-thiazine systems **10**. The latter extrude sulfur *via* thiiranes **11** or 2-mercaptopyrrole anions **12** as reported in the literature[4,5] for 2,4-diaryl-1,3-thiazine anions derived from the corresponding 1,3-thiazinium salts or 1,3-thiazines. As a remarkable extension of the known reaction behaviour of 8π-1,3-thiazine anions, the thiiranes **11** or 2-mercaptopyrrole anions **12** can not only undergo sulfur extrusion giving **3** but also can retain the sulfur atom giving 2-benzoylthiopyrroles **8** (R^1 = PhCO) by 1,2-acyl shift and final protonation of **13**.

Experimental

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise stated. The reactions and the purity of compounds were monitored by TLC performed on pre-coated silica gel plates with a fluorescent indicator (Merck 60 F_{254}). Column chromatography was carried out on Merck Kieselgel 60 (0.040–0.063). The ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts are given in δ values relative to residual proton or carbon resonances of the solvents. *J* Values are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal; Cq, quaternary C. Elemental analyses were performed in a Leco CHNS-932 apparatus. The IR spectra were recorded in KBr. Mass spectra were obtained with a VARIAN MAT 711 (70 eV).

4-[3-Amino-2-(4-chlorophenyl)thioacryloyl]morpholines 1

Starting materials **1** were obtained by reaction of 4-[2-(4-chlorophenyl)-3-dimethylaminothioacryloyl]morpholine hydroperchlorate with the corresponding $R^1CH_2NH_2$·HCl, adopting the reported procedure.[7]

4-[2-(4-Chlorophenyl)-3-(4-nitrobenzylamino)thioacryloyl]-morpholine 1a. Red crystals, mp 171–172 °C (from CH_3CN) (Found: C, 57.44; H, 4.73; N, 10.31; S, 7.75; Cl, 8.50. $C_{20}H_{20}ClN_3O_3S$ requires C, 57.48; H, 4.82; N, 10.06; S, 7.67; Cl, 8.48%); *E*/*Z* isomeric mixture (8:92) major isomer: δ_H(300 MHz; $CDCl_3$) 3.56 (4 H, m, CH_2), 3.88 (4 H, m, CH_2), 4.44 (2 H, d, *J* 6.3, NHCH_2), 6.08 (1 H, m, NH), 6.52 (1 H, d, *J* 12.6, 3-H), 7.02 (2 H, d, *J* 8.7), 7.18 (2 H, d, *J* 8.7), 7.49 (2 H, d, *J* 8.8) and 8.17 (2 H, d, *J* 8.8); δ_C(75 MHz; $CDCl_3$) 50.4 (CH_2NH), 51.4, 66.4 (CH_2), 111.6 (C-2), 124.0, 125.4, 127.6, 129.1 (*C*H-ClC_6H_4, $NO_2C_6H_4$), 130.8, 137.6, 139.8, 146.7 (Cq), 139.8 (C-3) and 196.8 (CS); *m*/*z* 419 (M^+ + 2, 11.5%), 417 (M^+, 27.9), 386 (11.5), 384 (32.6), 268 (19.2), 266 (46.4), 233 (14.2), 136 (17.2), 106 (22.4), 89 (32.1), 78 (33.1), 45 (20.3), 30 (100), 28 (42.2) and 18 (38.1).

4-[3-(Aminocarbonylmethylamino)-2-(4-chlorophenyl)thioacryloyl]morpholine 1b. Pale yellow crystals, mp 168–169 °C (from CH_3OH) (Found: C, 52.91; H, 5.50; N, 12.29; S, 9.21; Cl, 10.43. $C_{15}H_{18}ClN_3O_2S$ requires C, 53.01; H, 5.34; N, 12.37; S, 9.43; Cl, 10.43%); *E*/*Z* isomeric mixture (10:90) major isomer: δ_H(300 MHz; [$^2H_6$]DMSO) 3.62 (4 H, m, CH_2), 3.65 (2 H, d, *J* 6.1, CH_2), 3.95 (4 H, m, CH_2), 5.73 (1 H, m, NH), 6.63 (1 H, d, *J* 12.7, 3-H), 7.08 (2 H, d, *J* 8.5), 7.16 (1 H, s, NH), 7.18 (1 H, s, NH) and 7.22 (2 H, d, *J* 8.5); δ_C(75 MHz, [$^2H_6$]DMSO) 49.9 (CH_2), 50.0, 65.9 (CH_2), 109.2 (C-2), 124.6, 128.3 (*C*H-ClC_6H_4), 127.8, 137.6 (Cq-ClC_6H_4), 134.9 (C-3), 172.5 (CO) and 196.4 (CS); *m*/*z* 341 (M^+ + 2, 5.9%), 339 (M^+, 15.1), 266 (16.8), 265 (27.3), 264 (36.2), 235 (16.4), 233 (19.8), 181 (20.4), 173 (12.8), 100 (16.3), 86 (21.9), 45 (22.0), 32 (45.8), 31 (100), 29 (40.9) and 18 (75.9).

4-[3-(Benzoylmethylamino)-2-(4-chlorophenyl)thioacryloyl]-morpholine 1c. Pale yellow crystals, mp 142–144 °C (from $CHCl_3$–CH_3OH) (Found C, 62.35; H, 4.98; N, 7.06; S, 7.96. $C_{21}H_{21}ClN_2O_2S$ requires C, 62.91; H, 5.28; N, 6.99; S, 8.00%); *E*/*Z* isomeric mixture (25:75) major isomer: δ_H(300 MHz; $CDCl_3$) 3.63 (4 H, m, CH_2), 3.96 (4 H, m, CH_2), 4.65 (2 H, d, *J* 5.7, CH_2), 5.64 (1 H, m, NH), 6.49 (1 H, d, *J* 12.7, 3-H), 7.06 (2 H, d, *J* 8.7), 7.17 (2 H, d, *J* 8.7) and 7.46–7.90 (5 H, arom. H); δ_C(75 MHz; $CDCl_3$) 50.3 (CH_2), 53.7, 66.5 (CH_2), 111.9 (C-2), 125.2, 127.7 (*C*H-ClC_6H_4), 128.9 (*C*H-C_6H_5), 129.0, 130.5 (Cq-ClC_6H_4), 134.0 (*C*H-C_6H_5), 136.3 (C-3), 137.1 (Cq-C_6H_5), 195.0 (CO) and 197.2 (CS); *m*/*z* 402 (M^+ + 2, 22.4%), 400 (M^+, 54.4), 367 (14.6), 295 (16.9), 280 (38.6), 268 (38.6), 266 (100), 265 (41), 233 (31.7), 181 (41.4), 105 (80.1), 100 (89.6), 77 (69.1), 51 (23.5) and 28 (29.2).

Substituted 4-(4-chlorophenyl)-2-methyl-5-morpholino-1,2-thiazol-2-ium bromides 2

A solution of triethylamine (0.76 g, 7.5 mmol) in 10 cm^3 methanol was combined with a solution of 7.5 mmol 4-(3-aminothioacryloyl)morpholine **1** in 100 cm^3 chloroform–methanol (1:1). A solution of bromine (1.2 g, 7.5 mmol) in 10 cm^3 of chloroform was added. After the oxidation was complete (TLC) the resulting solution was evaporated with a rotatory evaporator and combined with 30 cm^3 of methanol. The precipitated crystals were filtered off, washed with a small amount of methanol and dried.

4-(4-Chlorophenyl)-5-morpholino-2-(4-nitrobenzyl)-1,2-thiazol-2-ium bromide 2a. Colourless crystals (2.67 g, 71.8%), mp 171–75 °C (decomp.) [from CH_3OH–$(C_2H_5)_2O$] (Found: C, 48.01; H, 3.89; N, 8.36; S, 6.44. $C_{20}H_{19}BrClN_3O_3S$ requires C, 48.35; H, 3.86; N, 8.46; S, 6.45%); δ_H(300 MHz; $CDCl_3$) 3.22 (4 H, m, CH_2), 3.71 (4 H, m, CH_2), 6.18 (2 H, s, CH_2), 7.33 (2 H, d, *J* 8.5), 7.43 (2 H, d, *J* 8.5), 7.91 (2 H, d, *J* 8.7), 8.14 (2 H, d, *J* 8.7) and 9.64 (1 H, s, 3-H); δ_C(75 MHz; $CDCl_3$) 51.5, 65.0 (CH_2), 55.4 (CH_2), 116.0 (C-4), 124.2, 129.6, 130.5, 130.6 (*C*H-ClC_6H_4, $NO_2C_6H_4$), 127.6, 135.6

(Cq-ClC_6H_4), 140.6, 148.3 (Cq-$NO_2C_6H_4$), 158.8 (C-3) and 172.8 (C-5).

2-(Aminocarbonylmethyl)-4-(4-chlorophenyl)-5-morpholino-1,2-thiazol-2-ium bromide 2b. Colourless solid (2.70 g, 86.1%), mp 205–210 °C (decomp.) (from CH_3OH) (Found: C, 42.65; H, 4.08; N, 10.23; S, 7.78. $C_{15}H_{17}BrClN_3O_2S$ requires C, 43.02; H, 4.09; N, 10.04; S, 7.66%); δ_H(300 MHz; [$^2H_6$]DMSO) 3.29 (4 H, m, CH_2), 3.68 (4 H, m, CH_2), 5.07 (2 H, s, CH_2), 7.51 (2 H, d, *J* 8.7), 7.57 (2 H, d, *J* 8.7), 7.70 (1 H, s, NH), 8.05 (1 H, s, NH) and 8.85 (1 H, s, 3-H); δ_C(75 MHz; [$^2H_6$]DMSO) 51.2, 64.6 (CH_2), 53.7 (CH_2), 114.0 (C-4), 133.6, 133.6 (Cq-ClC_6H_4), 129.2, 131.0 (CH-ClC_6H_4), 159.3 (C-3), 167.2 (C-5) and 173.5 (CO).

4-[3-Alkylideneamino-2-(4-chlorophenyl)thioacryloyl]morpholines 4 or 5-(4-chlorophenyl)-6-morpholino-2*H*-1,3-thiazines 5

A solution of triethylamine (0.51 g, 5 mmol) in 10 cm^3 of methanol was added to a stirred solution of 5 mmol of the 1,2-thiazolium bromide **2** in 50 cm^3 hot methanol. After cooling to room temperature the resulting crystals were filtered off, washed with a small portion of methanol and dried.

4-[2-(4-Chlorophenyl)-3-(4-nitrobenzylideneamino)thioacryloyl]morpholine 4a. Yellow crystals (1.95 g, 93.6%), mp 248–250 °C (decomp.) (from CH_3CN) (lit.,[1] 254–255 °C); δ_H(300 MHz; [$^2H_7$]DMF) 3.65 (2 H, m, CH_2), 3.80 (1 H, m, CH_2), 3.86 (1 H, m, CH_2), 3.95 (2 H, m, CH_2), 4.35 (1 H, m, CH_2), 4.72 (1 H, m, CH_2), 7.50 (2 H, d, *J* 8.6), 7.59 (1 H, s, 3-H), 7.73 (2 H, d, *J* 8.6), 8.17 (2 H, d, *J* 8.8), 8.41 (2 H, d, *J* 8.8) and 8.69 (1 H, s, 5-H); δ_C(75 MHz; [$^2H_7$]DMF) 48.7, 52.6, 66.9, 67.1 (CH_2), 124.8, 128.9, 129.6, 130.3 (*C*H-ClC_6H_4, $NO_2C_6H_4$), 134.3, 135.2 (Cq), 136.0 (C-3), 141.1, 149.8 (Cq-ClC_6H_4, $NO_2C_6H_4$), 142.6 (C-2), 161.0 (C-5) and 195.6 (CS); δ_C(100 MHz; solid) 49.3, 52.9, 66.4, 124.8, 128.2, 129.7, 131.4, 132.2, 137.7, 121.5, 134.4, 141.6, 147.9, 163.5 and 194.0; *m/z* 417 (M^+ + 2, 24.0%), 415 (M^+, 60.7), 382 (11.9), 332 (35.7), 330 (89.6), 295 (42.7), 266 (35.0), 249 (30.8), 89 (27.6), 86 (100), 63 (21.4), 45 (35.6), 30 (28.9) and 28 (35.8).

5-(4-Chlorophenyl)-6-morpholino-2-(4-nitrophenyl)-2*H*-1,3-thiazine 5a. δ_H(300 MHz; CF_3CO_2D) 4.11 (4 H, s br, CH_2), 4.22 (4 H, s br, CH_2), 6.72 (1 H, s, 2-H), 7.57 (2 H, d, *J* 8.3), 7.81 (2 H, d, *J* 8.3), 8.22 (2 H, d, *J* 8.7), 8.28 (1 H, s, 4-H) and 8.75 (2 H, d, *J* 8.7); δ_C(75 MHz; CF_3CO_2D) 55.8, 68.3 (CH_2), 61.3 (C-2), 112.0 (C-5), 131.3, 131.4, 133.0, 138.3 (*C*H-ClC_6H_4, $NO_2C_6H_4$), 127.2, 135.8, 141.5, 151.6 (Cq-ClC_6H_4, $NO_2C_6H_4$), 165.0 (C-4) and 170.7 (C-6).

4-[3-Aminocarbonylmethyleneamino-2-(4-chlorophenyl)thioacryloyl]morpholine 4b. Pale yellow solid (1.40 g, 83.0%), mp 180–183 °C (from CH_3OH) (Found: C, 52.97; H, 4.85; N, 12.54; S, 9.53. $C_{15}H_{16}ClN_3O_2S$ requires C, 53.33; H, 4.77; N, 12.44; S, 9.49%); ν_{max}/cm^{-1} 3484 and 3323 (NH), 1682 (CO); δ_H(300 MHz; [$^2H_6$]DMSO) 3.58 (4 H, m, CH_2), 3.78 (2 H, m, CH_2), 4.31 (1 H, m, CH_2), 4.40 (1 H, m, CH_2), 7.30 (1 H, s, NH), 7.41 (1 H, s, 3-H), 7.46 (2 H, d, *J* 8.7), 7.57 (2 H, d, *J* 8.7), 7.63 (1 H, s, NH) and 7.65 (1 H, s, 5-H); δ_C(75 MHz; [$^2H_6$]DMSO) 47.7, 51.6, 65.9, 66.0 (CH_2), 128.4, 128.9 (*C*H-ClC_6H_4), 133.3 (C-3), 133.7, 133.8 (Cq-ClC_6H_4), 141.3 (C-2), 157.0 (C-5), 165.1 (CO) and 193.2 (CS); *m/z* 339 (M^+ + 2, 4.2%), 337 (M^+, 10.4), 294 (37.1), 293 (17.9), 292 (100), 209 (13.1), 173 (27.7), 173 (14), 136 (13.6), 86 (40.7), 45 (25.6), 44 (32.6) and 28 (33.1).

2-Aminocarbonyl-5-(4-chlorophenyl)-6-morpholino-2*H*-1,3-thiazine 5b. δ_H(300 MHz; CF_3CO_2D) 3.70 (4 H, s br, CH_2), 3.78 (4 H, s br, CH_2), 5.84 (1 H, s, 2-H, gradually vanishing), 7.10 (2 H, arom. H), 7.34 (2 H, arom. H) and 7.80 (1 H, s, 4-H); δ_C(75 MHz; CF_3CO_2D) 55.5, 67.8 (CH_2), 56.9 (C-2), 111.5 (C-5), 130.9, 132.3 (*C*H-ClC_6H_4), 135.3, 137.6 (Cq-ClC_6H_4), 160.2 (C4), 168.5 (CO) and 171.4 (C-6); δ_C(75 MHz; CF_3CO_2D; 40 °C), 55.7, 67.9 (CH_2), 57.0 (t, J_{CD} 22.8, *C*-2-D), 111.8 (C-5), 131.1, 132.6 (*C*H-ClC_6H_4), 135.4, 138.1 (Cq-ClC_6H_4), 160.3 (C-4), 168.8 (CO) and 171.5 (C-6).

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carbonitrile 3c

Trifluoroacetic anhydride (0.63 g, 3 mmol) was added dropwise to a suspension of the 4-[3-aminocarbonylmethyleneamino-2-(4-chlorophenyl)thioacryloyl]morpholine **4b** (1.01 g, 3 mmol) in 50 cm^3 of dry dimethoxyethane. A solution of dry pyridine (0.48 g, 6 mmol) in 10 cm^3 of dimethoxyethane was added dropwise to the resulting mixture. After stirring for 15 min at room temperature the reaction mixture was poured into water. The product was separated by threefold extraction with about 100 cm^3 of ethyl acetate. The combined organic phases were washed with water and dried with sodium sulfate. The solvent was evaporated with a rotatory evaporator. The residue was purified by column chromatography (silica gel; ethyl acetate–hexane 4:6) to give **3c** as colourless crystals (0.38 g, 44.1%), mp 222–223.5 °C [from (C_2H_5)$_2$O–C_6H_{14}] (Found: C, 62.40; H, 4.98; N, 14.68. $C_{15}H_{14}ClN_3O$ requires C, 62.61; H, 4.90; N, 14.61%); ν_{max}/cm^{-1} 2203 (C≡N); δ_H(300 MHz; [^2H]$_6$DMSO) 2.96 (4 H, m, CH_2), 3.65 (4 H, m, CH_2), 7.33 (1 H, d, *J* 3.3, 5-H), 7.39 (2 H, d, *J* 8.6), 7.69 (2 H, d, *J* 8.6) and 12.0 (1 H, s br, NH); δ_C(75 MHz; [$^2H_6$]DMSO) 51.7, 66.2 (CH_2), 90.8 (C-2), 115.5 (CN), 116.0 (C-4), 123.7 (C-5), 128.0, 128.5 (*C*H-ClC_6H_4), 130.5, 133.0 (Cq-ClC_6H_4) and 143.7 (C-3); *m/z* 289 (M^+ + 2, 34.7%), 287 (M^+, 100), 286 (18.9), 230 (35.7), 229 (49.8), 228 (86.1), 194 (47.1), 166 (11.6), 140 (16.1), 97 (15.7), 83 (12.1), 28 (25.1) and 18 (21.7).

Synthesis of 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxamide 3b and bis[2-(4-chlorophenyl)-2-(morpholinothiocarbonyl)vinyl]amine 6

A solution of **4** (5 mmol) in 30 cm^3 trifluoroacetic acid was stirred at room temperature. After 24 h the solution was neutralised with aqueous sodium hydroxide. The solution was extracted five times with *ca.* 70 cm^3 $CHCl_3$. The organic phases were combined, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; $CHCl_3$–CH_3OH) and afforded **6** (1.05 g, 76.6%) and 4-nitrobenzaldehyde (starting from **4a**) or **6** (0.81 g, 59.1%) and pyrrole **3b** (0.45 g, 29.4%) (starting from **4b**).

Amine 6. Yellow crystals, mp 249–251 °C (from $CHCl_3$–CH_3OH) (Found: C, 56.77; H, 4.88; N, 7.89; S, 11.76. $C_{26}H_{27}Cl_2N_3O_2S_2$ requires C, 56.93; H, 4.96; N, 7.66; S, 11.69%); δ_C(75 MHz; $CDCl_3$) (major isomer) 50.0, 52.4, 66.6, 67.0 (CH_2), 117.4 (C-2), 125.7, 132.4 (*C*H-ClC_6H_4), 129.6 (C-3), 132.4, 134.4 (Cq-ClC_6H_4) and 195.9 (CS); *m/z* 549 (M^+ + 2, 14.9%), 547 (M^+, 20.2), 429 (11.2), 282 (27.7), 281 (19.5), 280 (29.4), 268 (42.9), 266 (100), 254 (22.5), 233 (34.6), 222 (20.2), 196 (26.6), 181 (21.7), 155 (20.2), 130 (38.8), 86 (74.9), 45 (59.7) and 28 (62.0).

Amide 3b. Colourless crystals, mp 273–276 °C (decomp.) (from CH_3OH) (Found: C, 58.70; H, 5.12; N, 13.60. $C_{15}H_{16}ClN_3O_2$ requires C, 58.92; H, 5.27; N, 13.75%); δ_H(300 MHz; [$^2H_7$]DMF) 2.96 (4 H, m, CH_2), 3.67 (4 H, m, CH_2), 6.88 (1 H, d, *J* 3.35, 5-H), 7.13 (1 H, br, NH_2), 7.47 (4 H, s, arom. H), 8.31 (1 H, br, NH_2) and 11.49 (1 H, br, NH); δ_C(75 MHz; [$^2H_7$]DMF) 53.9, 67.9 (CH_2), 120.3 (C-5), 120.9 (C-2), 122.3 (C-4), 128.7, 132.5 (*C*H-ClC_6H_4), 132.6, 136.3 (Cq-ClC_6H_4), 136.4 (C-3) and 162.9 (CO); *m/z* 307 (M^+ + 2, 2.3%), 305 (M^+, 6.6), 287 (11.3), 246 (11.3), 145 (12.0), 231 (13.3), 229 (13.7), 195 (13.9), 168 (11.0), 167 (13.8), 140 (31.5), 127 (10.3), 113 (11.7), 75 (14.4), 44 (67.5), 30 (47.4), 28 (100) and 27 (55).

2-Benzoylthio-4-(4-chlorophenyl)-3-morpholinopyrrole 8a

30% Aqueous hydrogen peroxide (2 cm^3) was added to a stirred suspension of 4-[3-benzoylmethylamino-2-(4-chlorophenyl)-thioacryloyl]morpholine **1c** (2.0 g, 5 mmol) in 80 cm^3 ethanol. After heating to boiling the mixture was further stirred at room temperature for 2 h. The crystals formed were filtered, washed with a small amount of methanol and dried. Further purification was possible by dissolving the compound in 50 cm^3 hot chloroform and adding 50 cm^3 methanol.

Compound **8a** was obtained as a colourless solid (1.4 g, 70.4%), mp 201–203 °C (decomp.) (from C_2H_5OH) (Found: C, 62.93; H, 4.72; N, 7.27; S, 8.29. $C_{21}H_{19}ClN_2O_2S$ requires C, 63.23; H, 4.80; N, 7.02; S, 8.04%); ν/cm^{-1} 3323, 1661 (CO), 1209, 1115, 905; δ_H(300 MHz; [$^2H_6$]DMSO) 2.96 (4 H, m, CH_2), 3.58 (4 H, m, CH_2), 7.29 (1 H, d, *J* 3.3, 5-H), 7.37 (2 H, d, *J* 8.5, arom. H), 7.60 (2 H, arom. H), 7.74 (1 H, arom. H), 7.81 (2 H, d, *J* 8.5, arom. H), 7.99 (2 H, arom. H) and 11.27 (1 H, br, NH); δ_C(75 MHz; [$^2H_6$]DMSO) 52.0, 66.9 (CH_2), 102.8 (C-2), 118.4 (C-4), 120.6 (C-5), 127.3, 128.0 (*C*H-ClC_6H_4), 128.2, 129.4, 134.5 (*C*H-C_6H_5), 129.8 (Cq-C_6H_5), 134.3, 135.5 (Cq-ClC_6H_4), 140.4 (C-3) and 190.8 (CO); *m*/*z* 400 (M^+ + 2, 12.4%), 398 (M^+, 30.9), 293 (49.6), 295 (18.9), 200 (4.8), 203 (3.9), 105 (100), 77 (34.4), 51 (13.1) and 28 (5.9).

4-(4-Chlorophenyl)-2-methylthio-3-morpholinopyrrole 9

A solution of NaOH (0.12 g, 3 mmol) in 10 cm^3 of water was added to a suspension of the 2-benzoylthiopyrrole **8a** (1 g, 2.5 mmol). After 15 min at reflux, methyl iodide (0.43 g, 3 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and was then diluted with water. The mixture was extracted with chloroform. After drying the organic phase with Na_2SO_4 and evaporation of the solvent with a rotatory evaporator the remainder was purified by column chromatography (silica gel; hexane–ethyl acetate 3:1) to give a colourless solid (0.44 g, 57.0%), mp 185–186 °C (from CH_3OH) (Found: C, 58.25; H, 5.46; N, 9.08; S, 10.39. $C_{15}H_{17}ClN_2OS$ requires C, 58.34; H, 5.55; N, 9.07; S, 10.38%); δ_H(300 MHz; $CDCl_3$) 2.31 (3 H, s, SCH_3), 3.17 (4 H, m, CH_2), 3.73 (4 H, m, CH_2), 6.81 (1 H, d, *J* 3.2, 5-H), 7.27 (2 H, d, *J* 8.6, arom. H), 7.63 (2 H, d, *J* 8.6, arom. H) and 7.92 (1 H, br, NH); δ_C(75 MHz; $CDCl_3$) 22.6 (CH_3), 52.3, 67.8 (CH_2), 114.1 (C-2), 117.2 (C-5), 120.0 (C-4), 128.2, 128.3 (*C*H-ClC_6H_4), 131.4, 133.7 (Cq-ClC_6H_4) and 138.6 (C-3); *m*/*z* 310 (M^+ + 2, 38.1%), 308 (M^+, 100), 295 (34.0), 294 (16.6), 293 (90.7), 235 (19.8), 200 (15.4), 114 (9.0), 140 (7.4), 100 (16.7), 45 (12.8), 28 (18.3) and 27 (10.9).

Crystal data for compound 4a

$C_{20}H_{18}ClN_3O_3S$, M_r = 415.88, monoclinic, space group $P2_1$, a = 10.4761(14), b = 7.1666(10), c = 13.114(2) Å, β = 93.826(14)°, V = 982.4 Å^3, Z = 2, D_x = 1.406 Mg m^{-3}, λ(Mo-Kα) = 0.710 73 Å, μ = 0.33 mm^{-1}, T = −100 °C. Data collection and reduction: a yellow needle 0.8 × 0.15 × 0.15 mm was mounted in inert oil. Data were collected to $2\theta_{max}$ 55° on a Siemens P4 diffractometer. Of 4740 measured data, 4339 were unique (R_{int} 0.021). Structure solution and refinement: the structure was solved by direct methods and refined anisotropically on F^2 as a racemic twin [components 0.52, 0.48(7)] using all reflections (program SHELXL-93, G. M. Sheldrick, University of Göttingen). Hydrogen atoms were included with a riding model. The final wR (F^2) was 0.095 for 254 parameters, conventional $R(F)$ 0.042. S = 1.03; max. $\Delta\rho$ 0.22 e Å^{-3}.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/46.

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