Design, synthesis and antioxidant properties of ovothiol-derived 4-mercaptoimidazoles

Vincent Zoete, Fabrice Bailly,* Jean-Pierre Catteau and Jean-Luc Bernier

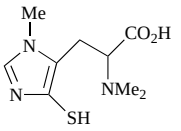
Laboratoire de Chimie Organique Physique, URA CNRS 351, Bât C3, UST Lille I, 59655 Villeneuve d'Ascq, France

Fourteen 4-mercaptoimidazoles derived from the naturally occurring family of antioxidants, the ovothiols, have been synthesized by cyclization of thioamides with trimethylsilyl trifluoromethanesulfonate (triflate). These compounds have been assayed for their radical-scavenging activity.

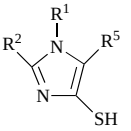
Introduction

Oxidative stress[1–5] has been implicated in the initiation, maintenance and aggravation of diverse biological processes such as ischemia, cataract, atherosclerosis, inflammation, ageing, carcinogenesis and even AIDS.[6–8] These observations have led to the design and evaluation of antioxidant agents.[9–14] Of the chemical structural features responsible for antioxidant activity, phenol and thiol functions are frequently encountered.[15–19]

Our attention has recently turned to a new structure, ovothiol,[20,21] found in a family of 4-mercaptohistidines which protect sea urchin eggs against hydrogen peroxide-induced oxidation during fertilization.[22,23] These compounds are believed to mimic the glutathione peroxidase system (GPx).[21–24] Such a GPx-like activity was verified *in vitro* and could be attributed to the large predominance of the thiolate form at physiological pH, this form being active in a manner similar to that of the selenolate form of the glutathione peroxidase enzyme (GPx). Differences in protonation state, nucleophilicity, one-electron donating ability and redox properties between 4-mercaptoimidazoles and glutathione were also evaluated. This led to the conclusion that the thiol groups of ovothiols and glutathione are chemically distinct.[25,26] The most striking difference resides in the thiol acidity since the 1,5-dimethyl-4-mercaptoimidazole and glutathione have pK_a values of 2.3 and 8.6, respectively.[25]



Ovothiol C



4-Mercaptoimidazoles

Given the current interest in the design of antioxidant molecules, we have developed a series of ovothiol derivatives having various substituents on the imidazole ring. The zwitterionic side-chain at position 5, which is not essential for the antioxidant activity, was omitted to give us the possibility of functionalizing this position. Phenyl rings with electron-withdrawing groups were introduced at position 2, to favour the stabilization of the thiolate negative charge and, as a consequence, to potentiate the GPx-like activity. In contrast, phenyl rings with electron-donating groups were used as substituents of the aromatic nitrogen atom at position 1 to stabilize the thiyl form of the SH function.

It is believed indeed that the radical scavenging activity of the 4-mercaptoimidazoles results in the formation of thiyl radicals which could be delocalized on the opposite N-1 nitrogen atom.[25] Moreover, the combined action of an electron-releasing (donor) substituent R^1 and electron-withdrawing (captor) groups R^2 and R^5 could enhance the radical stabilization according to a possible captodative effect.[27,28]

Here we report the synthesis of a series of 4-mercaptoimidazole derivatives providing a large range of substitution patterns. The radical scavenging properties of the newly synthesized compounds were evaluated by using 2,2-diphenyl-1-picrylhydrazyl and Fremy's salt radicals.

Results and discussion

Synthesis

Fourteen imidazole-4-thiols were synthesized (Table 1). Except for entry **4a**, *i.e.* 1,5-dimethyl-4-mercaptoimidazole (reported as DMI),[26] each compound includes a phenyl ring which is electron-donating when introduced on the N-1 atom (entries **4b**–**d**) and electron-withdrawing when introduced on the C-2 atom (entries **4e**–**i** and **4n**). The C-5 atom is substituted either with an electron-withdrawing phenyl group (entries **4j**–**l**) or with electron-donating phenyl groups (entries **4m** and **4n**). For compounds **4e**–**n**, N-1 was methyl substituted, as found in the original ovothiol structure.

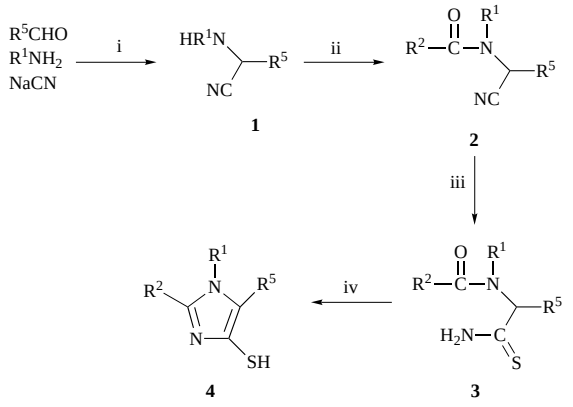
Several synthetic schemes are available for the preparation of 4-mercaptoimidazoles. The thiol function can be selectively introduced at position 4 of a pre-formed imidazole ring by nucleophilic displacement of a halogen atom with a sulfur compound (sodium thiophosphate for example);[29] nevertheless, bromination of imidazoles is non-selective and renders this scheme inadequate. An alternative method consists of condensing appropriate synthons to obtain the 4-mercaptoimidazole ring after a final cyclization. In this approach, imines can be condensed with α-oxo thioamides,[30,31] ethyl valeramidocyanoacetate with alkyl (aryl) thiols[32] and cyano amines with chloride acids.[33] Although 4-mercaptoimidazoles can also be obtained by intramolecular addition to an isothiocyanate function,[34] this scheme does not allow easy and complete substitution of the imidazole ring.

For our purposes, we have adopted the method developed by Spaltenstein *et al.*[33] (Scheme 1) since it has few steps, uses simple starting materials and allows for a wide variety of substitution patterns of the imidazole ring. The initial three steps gave the intermediates **1**–**3** in high yield but the final key cyclization was much more difficult. Spaltenstein *et al.* performed the cyclization by treating the thioamides **3** at −78 °C with an excess of triethylamine and trimethylsilyl trifluoromethanesulfonate and then with a mixture of methanol and sodium fluoride.[33] Attempts to repeat the cyclization under these conditions failed. Several points are worth making. The cyclization substrate must be extremely pure to avoid the formation of by-products, with a 0.1 M solution in dichloromethane providing the best yields. The silane reagent efficiency was markedly dependent on the experimental conditions. In each case trimethylsilyl

Table 1 Yields for the synthesis of 4-mercaptoimidazoles from the thioamides **3** and their radical scavenging activities

Entry	R^1	R^2	R^5	Yield[a] (%)	IC_{50}[b]/μM	k[c]/l mol^{-1} s^{-1}
4a	Me	H	Me	45	2900	0.065
4b	3,4-di-$MeOC_6H_3$	H	H	22	775	0.025
4c	4-$MeOC_6H_4$	H	H	39	1345	0.020
4d	2-$MeOC_6H_4$	H	H	25	2090	—
4e	Me	4-ClC_6H_4	H	35	505	—
4f	Me	3-ClC_6H_4	H	40	33	19.2
4g	Me	2-ClC_6H_4	H	25	19	12.5
4h	Me	2-$CF_3C_6H_4$	H	20	39	54.0
4i	Me	3-$CF_3C_6H_4$	H	40	19	52.5
4j	Me	H	2-$CF_3C_6H_4$	21	23	2.63
4k	Me	H	2-ClC_6H_4	25	19	2.82
4l	Me	H	4-ClC_6H_4	30	20	2.68
4m	Me	H	4-$MeOC_6H_4$	63	1310	—
4n	Me	CF_3	2-$MeOC_6H_4$	13	23	15.2

[a] Yields are evaluated after recrystallization. [b] Concentration of radical scavengers necessary to decrease by 50% the absorbance at 517 nm of a solution in alcohol of 2,2-diphenyl-1-picrylhydrazyl radical (50 μM). [c] Second-order rate constants for the reaction of radical scavengers (300 μM) with Fremy's salt (300 μM) in a pH = 7.0 phosphate buffer (50 mM). The disappearance of the nitroxide radical was followed by UV spectroscopy at 248 nm. **4d**, **4e** and **4m** are unreactive.



Scheme 1 *Reagents and conditions*: i, H_2O–MeOH, HCl; ii, HCO_2H–Ac_2O or R^2COCl–Et_3N; iii, H_2S, EtOH–Et_3N; iv, Me_3SiOTf, CH_2Cl_2, Et_3N, −5 °C to −10 °C

triflate (MeSiOTf) was used because chlorotrimethylsilane was completely unreactive. *tert*-Butyl(dimethyl)silyl triflate was not used because it failed to improve the cyclization yield. The reaction temperature had to be rigorously controlled: whilst Spaltenstein *et al.* reported reactions at −78 to 25 °C depending on the substrates,[33] we found that the cyclization is hindered at very low temperatures whereas at temperatures >30 °C hydrogen sulfide was evolved with formation of the nitrile intermediates **1** as well as several by-products. The silane was, therefore, slowly added to the reaction mixture for 30 min at −10 °C to −5 °C after which it was continued for 2 h at −10 °C to 0 °C. The optimal reactivity of the silane around −10 °C is likely due to the particular structures of the substrates containing aromatic rings.[33] Since for entries **4b**, **4g**, **4h** and **4i**, 4-mercaptoimidazoles and oxidized disulfide compounds form simultaneously, cyclizations must be complete in 1 h to limit the proportion of disulfides. To optimize the reaction rates 6 and 4 equiv. of triethylamine and Me_3SiOTf, respectively, compared to the thioamide **3** concentration, were required. If the reactivity of the silane was too low, 3 and 2 equiv. of NEt_3 and Me_3SiOTf could be further added after the reaction had run for 1 h.

Spaltenstein *et al*. used sodium fluoride after treatment with the silane.[33] This nucleophilic reagent, which easily cleaves silyl ethers, failed to improve the cyclization rate. Table 1 gives the yields for the conversion of the intermediate compounds **3** into final 4-mercaptoimidazoles **4** and shows that the cyclization is the limiting step of the synthetic scheme with yields in the range 13–63% after recrystallization. The identity of the products as the thiol tautomers was unambiguously demonstrated by NMR spectroscopy which revealed the presence of the thiol proton at 2–2.5 ppm.

Radical scavenging activity

Two stable radicals, potassium nitrodisulfonate (Fremy's salt)[35] and the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH)[36] were used to assess the one-electron-donating abilities of the 4-mercaptoimidazoles. The reduction of these free radicals was followed spectrophotometrically at 248 and 517 nm for Fremy's salt and DPPH, respectively. Glutathione and vitamin C were also tested as reference antioxidants.

Reaction with the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH)

The reaction results are presented in Table 1. Compounds **4f**–**l** and **4n** show the highest reducing effects, their activity being similar to that of glutathione (IC_{50} = 26 μM). Compounds **4g**, **4i** and **4k** (IC_{50} = 19 μM) are nearly as potent as vitamin C (IC_{50} = 13 μM).

Reaction with Fremy's salt (Table 1)

Eight molecules exhibit activity higher than glutathione (k = 0.23 l mol^{-1} s^{-1}): vitamin C (k = 1650 l mol^{-1} s^{-1}), compounds **4f**–**i** and **4n** and compounds **4j**–**l** with slower kinetics. All other compounds are far less reactive than glutathione.

In both tests, compounds **4f**–**i** and **4n** are the most active imidazole derivatives. Thus, compounds bearing a strong electron-withdrawing group at C-2 appear as the most promising ones in the antioxidant family of 4-mercaptoimidazoles. Their reactivity towards oxygen-derived species is currently being investigated.

Experimental

General

All starting materials were purchased from Aldrich. Kieselgel 60 (70–230 mesh) and (40–63 mesh) of Merck were used for column chromatography and flash column chromatography, respectively. Mass spectral analyses were performed on a Ribermag R 10-10 mass spectrometer (EI) with a kinetic energy of 70 eV or a Finnigan MAT Vision 2000 mass spectrometer (MALDI-TOF). High-resolution mass spectra were recorded on a Kratos MS80 instrument. ^{1}H NMR spectra were recorded on a Bruker AM 300 WB (300 MHz). Chemical shifts were reported from tetramethylsilane as an internal reference and are given in δ/ppm units; coupling constants are given in Hz. UV measurements were made on a UVIKON 932 spectrophotometer. Elemental analyses were determined by the CNRS microanalysis center.

Synthesis of the cyano amines 1

For entries **4e**–**i**, the cyanoamine **1e**–**i** *i.e.* (cyanomethyl)methylamine was commercially available as the hydrochloride salt.

Otherwise the intermediate compounds **1** were easily obtained on a multigram scale (1–5 g) by the condensation of appropriate aldehydes, amines and sodium cyanide. Compounds **1c**–**d** and **1j**–**n** were prepared by the method described for **1b** and **1a** respectively.

2-Methylamino-2-methylacetonitrile 1a. Acetaldehyde (3.35 cm^3, 59.9 mmol) was added dropwise to a solution of sodium cyanide (2.94 g, 59.9 mmol) and methylamine hydrochloride (4.04 g, 59.9 mmol) in water (20 cm^3) at 0 °C. The solution was stirred for 3 h at 0 °C and for 30 min at room temperature. After extraction with CH_2Cl_2, drying (Na_2SO_4) and concentration *in vacuo* of the extract gave **1a** as a yellow oil (4.53 g, 90%) (Found: M^+, 84.0683. $C_4H_8N_2$ requires *M*, 84.0687); ν_{max}(KBr)/cm^{-1} 3340, 3000–2800, 2230, 1450 and 1140; δ_H($CDCl_3$) 1.20 (1 H, br, s, NH), 1.42 (3 H, d, *J* 7.0, CH_3CH), 2.43 (3 H, s, CH_3NH) and 3.40 (1 H, q, *J* 7.0, CH).

2-(3,4-Dimethoxyphenylamino)acetonitrile 1b. Formaldehyde (37% solution; 2.40 cm^3, 32.0 mmol) was added to a mixture of 3,4-dimethoxyaniline (4.90 g, 32.0 mmol) in methanol (40 cm^3) and sodium cyanide (1.57 g, 32.0 mmol) in water (20 cm^3) at 0 °C in presence of 1 equiv. of hydrochloric acid (6 M solution; 5.4 cm^3). The mixture was stirred for 3 h at 0 °C and then overnight at room temperature. Extraction of the solution with CH_2Cl_2, followed by drying (Na_2SO_4) and concentration *in vacuo* of the extract afforded **1b** as a brown solid (5.9 g, 96%), mp 110 °C (Found: M^+, 192.0899. $C_{10}H_{12}N_2O_2$ requires *M*, 192.0899); ν_{max}(KBr)/cm^{-1} 3300, 3080–2800, 2240, 1620, 1500, 1450 and 1230; δ_H($CDCl_3$) 3.60 (1 H, s, NH), 3.81 (6 H, 2 s, 2 OCH_3), 3.98 and 4.07 (2 H, 2 s, CH_2), 6.23–6.31 (2 H, m, ArH) and 6.70 and 6.79 (1 H, 2 s, ArH).

2-(4-Methoxyphenylamino)acetonitrile 1c. This compound was prepared in a similar manner to that reported for the synthesis of **1b** except that an excess of each reactant (1.2 equiv.) relative to *p*-anisidine was used. It was a brown solid (61%), mp 72 °C (Found: M^+, 162.0797. $C_9H_{10}N_2O$ requires *M*, 162.0793); ν_{max}(KBr)/cm^{-1} 3360, 3080–2810, 2250, 1600, 1510 and 1250; δ_H($CDCl_3$) 3.69 (1 H, t, *J* 7.2, NH), 3.75 (3 H, s, OCH_3), 4.05 (2 H, d, *J* 7.2), 6.67 (2 H, d, *J* 4.3, ArH) and 6.85 (2 H, d, *J* 4.3, ArH).

2-(2-Methoxyphenylamino)acetonitrile 1d. Pink solid (94%), mp 68 °C (lit.,[37] no mp given) (Found: M^+, 162.0790. $C_9H_{10}N_2O$ requires *M*, 162.0793); ν_{max}(KBr)/cm^{-1} 3400, 3080–2840, 2240, 1600, 1510 and 1220; δ_H($CDCl_3$) 3.75 (3 H, s, OCH_3), 4.10 (2 H, d, *J* 7.0, CH_2), 4.55 (1 H, t, *J* 7.0, NH) and 6.68–6.98 (4 H, m, ArH).

2-(Methylamino)-2-(2-trifluoromethylphenyl)acetonitrile 1j. Yellow oil (77%) (Found: M^+, 214.0724. $C_{10}H_9F_3N_2$ requires *M*, 214.0718); ν_{max}(KBr)/cm^{-1} 3340, 3060–2800, 2240, 1605, 1450, 1310 and 1240; δ_H($CDCl_3$) 1.71 (1 H, br s, NH), 2.52 (3 H, s, CH_3), 4.95 (1 H, s, CH) and 7.39–7.82 (4 H, m, ArH).

2-(Methylamino)-2-(2-chlorophenyl)acetonitrile 1k. Yellow oil (91%) (Found: M^+, 180.0451. $C_9H_9ClN_2$ requires *M*, 180.0454); ν_{max}(KBr)/cm^{-1} 3320, 3080–2720, 2190, 1600, 1450 and 1280; δ_H($CDCl_3$) 1.62 (1 H, br s, NH), 2.59 (3 H, s, CH_3), 5.05 (1 H, s, CH), 7.29–7.47 (3 H, m, ArH) and 7.60 (1 H, m, ArH).

2-(Methylamino)-2-(4-chlorophenyl)acetonitrile 11. Yellow oil (89%) (Found: M^+, 180.0455. $C_9H_9ClN_2$ requires *M*, 180.0454); ν_{max}(KBr)/cm^{-1} 3340, 3100–2800, 2240, 1600, 1590 and 1250; δ_H($CDCl_3$) 1.58 (1 H, br s, NH), 2.55 (3 H, s, CH_3), 4.73 (1 H, s, CH), 7.38 (2 H, d, *J* 5.3, ArH) and 7.45 (2 H, d, *J* 5.3, ArH).

2-(Methylamino)-2-(4-methoxyphenyl)acetonitrile 1m. Yellow oil (91%) (Found: M^+, 176.0954. $C_{10}H_{12}N_2O$ requires *M*, 176.0949); ν_{max}(KBr)/cm^{-1} 3340, 3100–2800, 2230, 1600, 1460 and 1260; δ_H($CDCl_3$) 1.58 (1 H, br s, NH), 2.57 (3 H, s, NCH_3), 3.82 (3 H, s, OCH_3), 4.74 (1 H, s, CH), 7.37 (2 H, d, *J* 4.7, ArH) and 7.47 (2 H, d, *J* 4.7, ArH).

2-(Methylamino)-2-(2-methoxyphenyl)acetonitrile 1n. Yellow oil (95%) (Found: M^+, 176.0958. $C_{10}H_{12}N_2O$ requires *M*, 176.0950); ν_{max}(KBr)/cm^{-1} 3340, 3060–2800, 2230, 1600, 1460 and 1250; δ_H($CDCl_3$) 1.82 (1 H, br s, NH), 2.59 (3 H, s, CH_3), 3.89 (3 H, s, OCH_3), 4.84 (1 H, d, *J* 9.0, CH), 6.87–7.05 (2 H, m, ArH) and 7.28–7.48 (2 H, m, ArH).

Synthesis of the cyano amides 2

The cyano amides **2** were easily obtained on a multigram scale (1–5 g). The intermediate compounds **2a**–**d** and **2j**–**m** (R^2 = H) were prepared from the corresponding precursor molecules **1a**–**d** and **1j**–**m** by formylation with acetic formic anhydride; **2e**–**i** (R^2 = Ar) were prepared by condensation of **1e**–**i** with appropriate chloride acids whilst **2n** was prepared by condensation of **1n** with trifluoroacetic anhydride.

***N*-(2-Cyanoethyl)-*N*-methylformamide 2a.** Acetic anhydride (5.35 g, 52.4 mmol) was added dropwise to a 96% formic acid solution (9.87 cm^3, 251 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C and then 1 h at room temperature. The mixed anhydride was then treated dropwise with the cyano amine **1a** (1.10 g, 13.1 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C. Stirring was stopped when TLC analysis showed the reaction to be complete (1 h). After several washings with 1 M aq. NaOH and water, drying of the organic layer (Na_2SO_4) and removal of the volatiles *in vacuo* gave **2a** (1.08 g, 74%) as a brown oil (Found: M^+, 112.0648. $C_5H_8N_2O$ requires *M*, 112.0637); ν_{max}(KBr)/cm^{-1} 3160–2840, 2260 and 1680; δ_H(D_2O) 1.25 and 1.40 (3 H, 2 d, ratio 2:1, *J* 7.0, CH_3CH), 2.68 and 2.80 (3 H, 2 s, ratio 1:2, NCH_3), 4.57 and 5.22 (1 H, 2 q, ratio 1:2, *J* 7.0, CH) and 7.72 and 7.88 (1 H, 2 s, ratio 2:1, HCO).

***N*-(Cyanomethyl)-*N*-(3,4-dimethoxyphenyl)formamide 2b.** Brown solid (86%), mp 100–102 °C (Found: M^+, 220.0844. $C_{11}H_{12}N_2O_3$ requires *M*, 220.0848); ν_{max}(KBr)/cm^{-1} 3100–2810, 2240 and 1680; δ_H($CDCl_3$) 3.90 (6 H, 1 s, 2 OCH_3), 4.59 (2 H, s, CH_2), 6.59–6.92 (3 H, m, ArH) and 8.29 (1 H, s, HCO).

***N*-(Cyanomethyl)-*N*-(4-methoxyphenyl)formamide 2c.** Brown oil (83%) (Found: M^+, 190.0744. $C_{10}H_{10}N_2O_2$ requires *M*, 190.0742); ν_{max}(KBr)/cm^{-1} 3140–2800, 2250 and 1680; δ_H($CDCl_3$) 3.80 (3 H, s, OCH_3), 4.60 (2 H, s, NCH_2), 6.95 (2 H, d, *J* 9.0, ArH), 7.15 (2 H, d, *J* 9.0, ArH) and 8.25 (1 H, s, HCO).

***N*-(Cyanomethyl)-*N*-(2-methoxyphenyl)formamide 2d.** The reaction was slow and the mixture needed to be stirred for 3 h at 0 °C and 24 h at room temperature. Pink solid (70%), mp 62–64 °C (Found: M^+, 190.0747. $C_{10}H_{10}N_2O_2$ requires *M*, 190.0742); ν_{max}(KBr)/cm^{-1} 3120–2840, 2250 and 1685; δ_H($CDCl_3$) 3.88 (3 H, s, OCH_3), 4.57 (2 H, s, NCH_2), 7.05 (2 H, m, ArH), 7.18 (1 H, m, ArH), 7.40 (1 H, m, ArH) and 8.15 (1 H, s, HCO).

***N*-(Cyanomethyl)-*N*-methyl-4-chlorobenzamide 2e.** 4-Chlorobenzoyl chloride (1.00 g, 5.7 mmol) and triethylamine (0.79 cm^3, 5.7 mmol) in dichloromethane (5 cm^3) were added dropwise at 0 °C to a solution of (methylamino)acetonitrile hydrochloride (0.61 g, 5.7 mmol) and triethylamine (0.79 cm^3, 5.7 mmol) in CH_2Cl_2 (5 cm^3). After 2 h at 0 °C and 2 h a room temperature, the mixture was washed successively with 0.1 M aq. HCl, 0.1 M aq. NaOH and water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford **2e** as a white solid (1.02 g, 85%), mp 49 °C (lit.,[38] mp 42–44 °C) (Found: M^+, 208.0405. $C_{10}H_9ClN_2O$ requires *M*, 208.0403); ν_{max}(KBr)/cm^{-1} 3140–2840, 2240 and 1640; δ_H($CDCl_3$) 3.09 (3 H, s, NCH_3), 4.38 (2 H, br s, NCH_2) and 7.38 (4 H, m, ArH).

***N*-(Cyanomethyl-*N*-methyl-3-chlorobenzamide 2f.** White solid (91%), mp 54 °C (Found: M^+, 208.0407. $C_{10}H_9ClN_2O$ requires *M*, 208.0403); ν_{max}(KBr)/cm^{-1} 3120–2820, 2250 and 1650; δ_H($CDCl_3$) 3.19 (3 H, s, NCH_3), 4.43 (2 H, s, NCH_2) and 7.29–7.48 (4 H, m, ArH).

***N*-(Cyanomethyl)-*N*-methyl-2-chlorobenzamide 2g.** Yellow oil (93%) (Found: M^+, 208.0404. $C_{10}H_9ClN_2O$ requires *M*, 208.0403); ν_{max}(KBr)/cm^{-1} 3140–2810, 2230 and 1650; δ_H($CDCl_3$) 2.95 and 3.19 (3 H, 2 s, ratio 4:1, NCH_3), 4.05 and 4.52 (2 H, 2 s, ratio 1:4, NCH_2) and 7.25–7.45 (4 H, m, ArH).

***N*-(Cyanomethyl)-*N*-methyl-2-trifluoromethylbenzamide 2h.** Yellow oil (90%) (Found: M^+, 242.0674. $C_{11}H_9F_3N_2O$ requires *M*, 242.0667); ν_{max}(KBr)/cm^{-1} 3130–2820, 2240 and 1650; δ_H($CDCl_3$) 2.90 (3 H, s, NCH_3), 4.32–4.75 (2 H, m, NCH_2) and 7.25–7.72 (4 H, m, ArH).

***N*-(Cyanomethyl)-*N*-methyl-3-trifluoromethylbenzamide 2i.** Yellow oil (95%) (Found: M^+, 242.0665. $C_{11}H_9F_3N_2O$ requires *M*, 242.0667); ν_{max}(KBr)/cm^{-1} 3120–2840, 2250 and 1650; δ_H($CDCl_3$) 3.10 (3 H, s, NCH_3), 4.45 (2 H, 2 br s, NCH_2) and 7.50–7.65 (4 H, m, ArH).

***N*-[1-Cyano-1-(2-trifluoromethylphenyl)methyl]-*N*-methylformamide 2j.** Brown oil (92%) (Found: M^+, 242.0668. $C_{11}H_9F_3N_2O$ requires *M*, 242.0667); ν_{max}(KBr)/cm^{-1} 3140–2770, 2250 and 1680; δ_H($CDCl_3$) 2.71 (3 H, s, NCH_3), 5.50, 6.15 (1 H, 2 s, ratio 1:2, CH), 7.52–7.77 (3 H, m, ArH), 7.90 (1 H, m, ArH) and 8.06 and 8.30 (1 H, 2 s, ratio 2:1, HCO).

***N*-[1-Cyano-1-(2-chlorophenyl)methyl]-*N*-methylformamide 2k.** Brown oil (66%) (Found: M^+, 208.0403. $C_{10}H_9ClN_2O$ requires *M*, 208.0403); ν_{max}(KBr)/cm^{-1} 3150–2790, 2245 and 1680; δ_H($CDCl_3$) 2.75 (3 H, s, NCH_3), 6.05, 6.89 (1 H, 2 s, ratio 2:3, CH), 7.39–7.49 (3 H, m, ArH), 7.77 (1 H, m, ArH) and 8.11 and 8.42 (1 H, 2 s, ratio 3:2, HCO).

***N*-[Cyano-(4-chlorophenyl)methyl]-*N*-methylformamide 2l.** Brown oil (95%) (Found: M^+, 208.0409. $C_{10}H_9ClN_2O$ requires *M*, 208.0403); ν_{max}(KBr)/cm^{-1} 3160–2800, 2245 and 1680; δ_H($CDCl_3$) 2.75 (3 H, s, NCH_3), 6.05 and 6.86 (1 H, 2 s, ratio 2:3, CH), 7.38–7.49 (3 H, m, ArH), 7.77 (1 H, m, ArH) and 8.09 and 8.41 (1 H, 2 s, ratio 3:2, HCO).

***N*-[Cyano-(4-methoxyphenyl)methyl]-*N*-methylformamide 2m.** Brown oil (84%) (Found: M^+, 204.0896. $C_{11}H_{12}N_2O_2$ requires *M*, 204.0899); ν_{max}(KBr)/cm^{-1} 3080–2800, 2240 and 1680; δ_H($CDCl_3$) 2.75 and 2.81 (3 H, 2 s, ratio 1:3, NCH_3), 3.80 (3 H, 1 s, OCH_3), 5.74 and 6.73 (1 H, 2 s, ratio 1:3, CH), 6.91 (2 H, d, *J* 5.1, ArH), 7.31 (2 H, d, *J* 5.1, ArH) and 8.10 and 8.35 (1 H, 2 s, ratio 3:1, HCO).

***N*-[Cyano-(2-methoxyphenyl)methyl]-*N*-methyltrifluoroacetamide 2n.** Trifluoroacetic anhydride (1.072 g, 5.10 mmol) was added dropwise at 0 °C to a solution of the amine **1n** (0.768 g, 4.26 mmol) and triethylamine (1.80 cm^3, 12.76 mmol) in dichloromethane (60 cm^3). The mixture was stirred for 4 h at 0 °C and then overnight at room temperature. After this it was washed successively with 1 M aq. HCl and water, dried (Na_2SO_4) and concentrated *in vacuo* to afford **2n** as a brown oil (0.868 g, 69%) (Found: M^+, 272.0775. $C_{12}H_{11}F_3N_2O_2$ requires *M*, 272.0772); ν_{max}(KBr)/cm^{-1} 3100–2800, 2240 and 1680; δ_H($CDCl_3$) 2.89 (3 H, s, NCH_3), 3.83 (3 H, s, OCH_3), 6.90 (1 H, s, CH), 6.92–7.10 (2 H, m, ArH), 7.40–7.50 (1 H, m, ArH) and 7.61 (1 H, m, ArH).

Synthesis of the thioamides 3

The thioamides **3** were obtained on a multigram scale by the method described for **3a**.

2-(*N*-Formyl-*N*-methylamino)-2-methylthioacetamide 3a. Hydrogen sulfide was bubbled into a solution of the cyano amide **2a** (2.32 g, 20.7 mmol) and triethylamine (28.9 cm^3, 20.7 mmol) in ethanol (20 cm^3) until TLC analysis confirmed the absence of cyanide (20 min). Removal of the volatile components of the mixture *in vacuo* gave **3a** as a dark brown solid (2.57 g, 85%), mp 80–82 °C (Found: M^+, 146.0515. $C_5H_{10}N_2OS$ requires *M*, 146.0514); ν_{max}(KBr)/cm^{-1} 3400–3200, 1660 and 1225; δ_H(D_2O) 1.53, 1.63 (3 H, 2 d, ratio 1:1.5, *J* 7.2, C*H*$_3$CH), 2.79 and 3.05 (3 H, 2 s, ratio 1.5:1, CH_3N), 4.56 and 4.98 (1 H, 2 q, ratio 1.5:1, CH) and 8.07 and 8.21 (1 H, 2 s, ratio 1:1.5, HCO); *m*/*z* (EI) 146 (M^+, 68), 86 (87) and 58 (100).

2-[*N*-Formyl-*N*-(3,4-dimethoxyphenylamino)]thioacetamide 3b. Brown crystals from $CHCl_3$–MeOH 95:5 (82%), mp 142 °C (Found: M^+, 254.0731. $C_{11}H_{14}N_2O_3S$ requires *M*, 254.0725); ν_{max}(KBr)/cm^{-1} 3340, 3150, 1635, 1510 and 1360; δ_H($CDCl_3$) 3.89 (6 H, s, 2 OCH_3), 4.74 (2 H, s, NCH_2), 6.67–6.96 (3 H, m, ArH), 7.60 (1 H, br s, $CSNH_2$), 8.24 (1 H, br s, $CSNH_2$) and 8.47 (1 H, s, HCO); *m*/*z* (EI) 254 (M^+, 30), 191 (33), 160 (35), 129 (39), 83 (100) and 64 (70).

2-[*N*-Formyl-*N*-(4-methoxyphenyl)amino]thioacetamide 3c. H_2S was bubbled through the reaction mixture after which the crude product was purified by column chromatography on silica gel (solvent system: $CHCl_3$–MeOH, 95:5) to give **3c** as a brown solid (60%), mp 104 °C (Found: M^+, 224.0622. $C_{10}H_{12}N_2O_2S$ requires *M*, 224.0619); ν_{max}(KBr)/cm^{-1} 3320, 3170, 1640, 1510 and 1450; δ_H($CDCl_3$) 3.80 (3 H, s, OCH_3), 4.75 (2 H, s, NCH_2), 6.95 (2 H, d, *J* 9.0, ArH), 7.15 (2 H, d, *J* 9.0, ArH), 7.55 (1 H, br s, $CSNH_2$), 8.05 (1 H, br s, $CSNH_2$) and 8.45 (1 H, s, HCO); *m*/*z* (EI) 224 (M^+, 40), 161 (35) and 130 (100).

2-[*N*-Formyl-*N*-(2-methoxyphenyl)amino]thioacetamide 3d. Brown crystals from $CHCl_3$–MeOH (95:5) (94%); mp 152–154 °C (Found: M^+, 224.0614. $C_{10}H_{12}N_2O_2S$ requires *M*, 224.0619); ν_{max}(KBr)/cm^{-1} 3340, 3150, 1680, 1500 and 1350; δ_H($CDCl_3$) 3.87 (3 H, s, OCH_3), 4.75 (2 H, s, NCH_2), 7.00–7.40 (4 H, m, ArH), 7.55 (1 H, br s, $CSNH_2$), 8.20 (1 H, s, HCO) and 8.27 (1 H, br s, $CSNH_2$); *m*/*z* (EI) 224 (M^+, 61), 161 (45) and 130 (100).

2-[*N*-(4-Chlorobenzoyl)-*N*-methylamino]thioacetamide 3e. White solid (90%), mp 146–148 °C (Found: M^+, 242.0281. $C_{10}H_{11}ClN_2OS$ requires *M*, 242.0280); ν_{max}(KBr)/cm^{-1} 3440, 3290, 3190, 1600, 1490 and 1405; δ_H($CDCl_3$) 3.10 (3 H, s, N-CH_3), 4.50 (2 H, s, NCH_2), 7.41 (4 H, s, ArH), 7.70 (1 H, s, $CSNH_2$) and 8.47 (1 H, s, $CSNH_2$); *m*/*z* (EI), 242 (M^+, 100), 208 (98), 182 (99), 168 (42), 156 (34), 141 (74), 111 (81), 103 (53), 87 (50), 75 (87) and 42 (90).

2-[*N*-(3-Chlorobenzoyl)-*N*-methylamino]thioacetamide 3f. White solid (90%), mp 109 °C (Found: M^+, 242.0285. $C_{10}H_{11}ClN_2OS$ requires *M*, 242.0280); ν_{max}(KBr)/cm^{-1} 3360, 3300, 3180, 1610 and 1420; δ_H($CDCl_3$) 3.12 (3 H, s, NCH_3), 4.50 (2 H, s, NCH_2), 7.30–7.48 (4 H, m, ArH), 7.53 (1 H, br s, $CSNH_2$) and 8.48 (1 H, br s, $CSNH_2$).

2-[*N*-(2-Chlorobenzoyl)-*N*-methylamino]thioacetamide 3g. Beige solid (95%), mp 115–117 °C (Found: M^+, 242.0277. $C_{10}H_{11}ClN_2OS$ requires *M*, 242.0280); ν_{max}(KBr)/cm^{-1} 3280, 3120, 1615, 1450 and 1400; δ_H($CDCl_3$) 3.00 (3 H, s, NCH_3), 4.30–4.75 (2 H, m, NCH_2), 7.30–7.45 (4 H, m, ArH), 7.55 (1 H, br s, $CSNH_2$) and 8.15 (1 H, br s, $CSNH_2$); *m*/*z* (EI) 242 (100), 208 (95), 156 (42), 141 (82), 103 (60), 75 (90) and 42 (85).

2-[*N*-(2-Trifluoromethylbenzoyl)-*N*-methylamino]thioacetamide 3h. Beige solid (91%), mp 118–120 °C (Found: M^+, 276.0548. $C_{11}H_{11}F_3N_2OS$ requires *M*, 276.0544); ν_{max}(KBr)/cm^{-1} 3380, 3280, 3200, 1610 and 1395; δ_H([$^2H_6$]-DMSO) 2.89 and 2.95 (3 H, 2 s, ratio 1:1, NCH_3), 4.05 and 4.35 (2 H, 2 s, ratio 1:1, NCH_2), 7.60–7.75 (4 H, m, ArH), 9.25 (1 H, br s, $CSNH_2$) and 9.80 (1 H, br s, $CSNH_2$); *m*/*z* (EI) 276 (100) and 242 (98).

2-[*N*-(3-Trifluoromethylbenzoyl)-*N*-methylamino]thioacetamide 3i. Beige solid (85%), mp 145 °C (Found: M^+, 276.0541. $C_{11}H_{11}F_3N_2OS$ requires *M*, 276.0544); ν_{max}(KBr)/cm^{-1} 3350, 3300, 3180, 1610 and 1340; δ_H($CDCl_3$) 3.10 (3 H, s, NCH_3), 4.50 (2 H, s, NCH_2), 7.42–7.60 (4 H, m, ArH), 7.65 (1 H, br s, $CSNH_2$) and 8.30 (1 H, br s, $CSNH_2$); *m*/*z* (EI) 276 (M^+, 13), 173 (100), 145 (39) and 75 (21).

2-(*N*-Formyl-*N*-methylamino)-2-(2-trifluoromethylphenyl)-thioacetamide 3j. Brown crystals from $CHCl_3$ (50%), mp 156–158 °C (Found: M^+, 276.0550. $C_{11}H_{11}F_3N_2OS$ requires *M*, 276.0544); ν_{max}(KBr)/cm^{-1} 3240, 3100, 1670, 1380 and 1310; δ_H([$^2H_6$]-DMSO) 2.62 (3 H, s, NCH_3), 5.80 and 6.30 (1 H, 2 s, ratio 1:2, CH), 7.57–7.83 (4 H, m, ArH), 7.99 and 8.15 (1 H, 2 s, ratio 2:1, HCO), 9.30 and 9.45 (1 H, 2 s, ratio 2:1, $CSNH_2$) and 10.03 and 10.15 (1 H, 2 s, ratio 2:1, $CSNH_2$).

2-(*N*-Formyl-*N*-methylamino)-2-(2-chlorophenyl)thioacetamide 3k. White solid (83%), mp 132–134 °C (Found: M^+, 242.0283. $C_{10}H_{11}ClN_2OS$ requires *M*, 242.0280); ν_{max}(KBr)/cm^{-1} 3280, 3120, 1680 and 1400; δ_H($CDCl_3$) 2.84 (3 H, s, NCH_3), 5.85 and 6.47 (1 H, 2 s, ratio 2:3, CH), 7.28–7.55

(4 H, m, ArH), 7.70 (1 H, br s, $CSNH_2$), 7.87 (1 H, br s, $CSNH_2$) and 8.13 and 8.20 (1 H, 2 s, ratio 2:3, HCO).

2-(*N*-Formyl-*N*-methylamino)-2-(4-chlorophenyl)thioacetamide 3l. White solid (83%), mp 144 °C (Found: M^+, 242.0288. $C_{10}H_{11}ClN_2OS$ requires *M*, 242.0280); ν_{max}(KBr)/cm^{-1} 3300, 3120, 1680 and 1400; δ_H($CDCl_3$) 2.83 (3 H, s, NCH_3), 5.85 and 6.47 (1 H, 2 s, ratio 2:3, CH), 7.30–7.70 (4 H, m, ArH), 7.75 (1 H, br s, $CSNH_2$), 7.90 (1 H, br s, $CSNH_2$) and 8.13 and 8.18 (1 H, 2 s, ratio 2:3, CHO).

2-(*N*-Formyl-*N*-methylamino)-2-(4-methoxyphenyl)thioacetamide 3m. White solid (89%), mp 123 °C (Found: M^+, 238.0772. $C_{11}H_{14}N_2O_2S$ requires *M*, 238.0776); ν_{max}(KBr)/cm^{-1} 3320, 3160, 1640, 1505 and 1400; δ_H($CDCl_3$) 2.84 and 2.90 (3 H, 2 s, ratio 1:3, NCH_3), 3.83 (3 H, s, OCH_3), 5.48, 6.24 (1 H, 2 s, ratio 1:3, CH), 6.92 (2 H, d, *J* 8.6, ArH), 7.34 (2 H, d, *J* 8.6, ArH), 7.77 (1 H, br s, $CSNH_2$), 7.92 (1 H, br s, $CSNH_2$) and 8.18 (1 H, s, HCO).

2-(*N*-Trifluoroacetyl-*N*-methylamino)-2-(2-methoxyphenyl)thioacetamide 3n. Yellow solid (45%), mp 117–119 °C (Found: M^+, 306.0652. $C_{12}H_{13}F_3N_2O_2S$ requires *M*, 306.0650); ν_{max}(KBr)/cm^{-1} 3300, 3160, 1670 and 1465; δ_H($CDCl_3$) 2.89 (3 H, s, NCH_3), 3.83 (3 H, s, OCH_3), 6.49 (1 H, s, CH), 6.85–7.05 (2 H, m, ArH), 7.06 (1 H, br s, $CSNH_2$), 7.34–7.50 (2 H, m, ArH) and 7.74 (1 H, br s, $CSNH_2$).

Synthesis of the 4-mercaptoimidazoles

For the very moisture-sensitive cyclization steps, dry glassware was obtained by oven-drying and assembly under Ar; an inert atmosphere was obtained with a stream of dry Ar. Calcium chloride cartridges were placed at the inlet and outlet of the reaction apparatus. Dichloromethane and triethylamine were distilled from calcium hydride. Compounds **4b**–**n** were prepared by the method described for **4a**. Except for **4a**, the best yields were obtained with small-scale experiments [thioamides (1–2 g)].

1,5-Dimethyl-4-mercaptoimidazole 4a. Trimethylsilyl trifluoromethanesulfonate (12.2 g, 54.8 mmol) was added dropwise over 30 min to a solution of the thioamide **3a** (2.0 g, 13.7 mmol) and triethylamine (8.32 g, 82.3 mmol) in CH_2Cl_2 (140 cm^3) at (−10 °C to −5 °C). After 2 h at (−5 °C to 0 °C) the mixture was washed with water, dried and evaporated *in vacuo*. The residue was flash-chromatographed on silica gel (solvent system: CH_2Cl_2–MeOH, 80:20) to yield **4a** as a brown oil. Recrystallization of this from ethyl acetate afforded the pure imidazole as a yellow oil (0.79 g, 45%) (Found: C, 46.9; H, 6.3; N, 21.8; S, 25.1. $C_5H_8N_2S$ requires C, 46.8; H, 6.3; N, 21.8; S, 25.0%); ν_{max}(KBr)/cm^{-1} 3120, 1260, 1150 and 1030; λ_{max}(H_2O)/nm 196 and 264; δ_H($CDCl_3$) 2.31 (3 H, s, 1-CH_3), 3.68 (3 H, s, 5-CH_3) and 8.45 (1 H, s, 2-H); *m*/*z* (EI), 128 (M^+, 100), 100 (15), 68 (18), 56 (91) and 42 (22).

1-(3,4-Dimethoxyphenyl)-4-mercaptoimidazole 4b. The thioamide **3b** was treated in the same way as **3a**. Flash chromatography of the residue (solvent system: CH_2Cl_2–MeOH, 95:5) and recrystallization from CH_2Cl_2–MeOH, 97:3, gave **4b** as a brown solid (22%), mp 148–150 °C (Found: C, 55.9; H, 5.2; N, 11.8; S, 13.4. $C_{11}H_{12}N_2O_2S$ requires C, 55.9; H, 5.1; N, 11.9; S, 13.6%); ν_{max}(KBr)/cm^{-1} 3100, 3000–2820, 1600 and 1500; λ_{max}(H_2O)/nm 199 and 244; δ_H($CDCl_3$) 1.95 (1 H, br s, SH), 3.90, 3.95 (6 H, 2 s, 2 OCH_3), 6.80–6.95 (3 H, m, ArH), 7.47 (1 H, s, 2-H) and 7.75 (1 H, s, 5-H); *m*/*z* (EI) 236 (M^+, 100), 208 (13), 164 (22), 79 (12) and 51 (15).

Flash chromatography allowed isolation of the disulfide which differs in its NMR spectrum from the reduced form by the absence of the SH proton together with an important shift of the 5-H signal from 7.75 to 9.00 ppm.

1-(4-Methoxyphenyl)-4-mercaptoimidazole 4c. This compound was obtained by recrystallization of the crude product from ethyl acetate as a beige solid (39%), mp 144–145 °C (Found: C, 58.3; H, 4.8; N, 13.7; S, 15.6. $C_{10}H_{10}N_2OS$ requires C, 58.2; H, 4.9; N, 13.6; S, 15.6%); ν_{max}(KBr)/cm^{-1} 3110, 2980–2830, 1605 and 1510; λ_{max}(H_2O)/nm 198 and 246; δ_H([$^2H_6$]-DMSO) 3.05 (1 H, br s, SH), 3.70 (3 H, s, OCH_3), 7.07 (2 H, d, *J* 8.8, ArH), 7.69 (2 H, d, *J* 8.8, ArH), 8.15 (1 H, s, 2-H) and 8.75 (1 H, s, 5-H); *m*/*z* (EI) 206 (M^+, 93), 179 (10), 134 (51), 77 (36) and 64 (100).

1-(2-Methoxyphenyl)-4-mercaptoimidazole 4d. Flash chromatography (solvent system: ethyl acetate) gave **4d** as a beige solid (25%), mp 137–138 °C (Found: C, 58.3; H, 4.8; N, 13.5; S, 15.5. $C_{10}H_{10}N_2OS$ requires C, 58.2; H, 4.9; N, 13.6; S, 15.6%); ν_{max}(KBr)/cm^{-1} 3100, 3030–2840, 1600 and 1515; λ_{max}(H_2O)/nm 197 and 275; δ_H($CDCl_3$) 2.10 (1 H, br s, SH), 3.75 (3 H, s, OCH_3), 6.90–7.34 (4 H, m, ArH), 7.35 (1 H, s, 2-H) and 7.75 (1 H, s, 5-H); *m*/*z* (EI), 206 (M^+, 100) and 134 (65).

1-Methyl-2-(4-chlorophenyl)-4-mercaptoimidazole 4e. Flash chromatography (solvent system: CH_2Cl_2–MeOH, 95:5) gave an orange solid (35%), mp 196–198 °C (Found: C, 53.3; H, 4.1; N, 12.5; S, 14.3. $C_{10}H_9ClN_2S$ requires C, 53.5; H, 4.0; N, 12.5; S, 14.3%); ν_{max}(KBr)/cm^{-1} 3100, 2920, 2820, 2690, 1605 and 1495; λ_{max}(H_2O)/nm 195 and 258; δ_H($CDCl_3$) 2.03 (1 H, br s, SH), 3.69 (3 H, s, 1-CH_3), 7.12 (1 H, s, 5-H), 7.30–7.39 (2 H, d, *J* 7.5, ArH) and 7.45–7.52 (2 H, d, *J* 7.5, ArH); *m*/*z* (EI), 224 (M^+, 100), 86 (98) and 42 (95).

1-Methyl-2-(3-chlorophenyl)-4-mercaptoimidazole 4f. This compound was obtained by recrystallization of the crude product from ethyl acetate as a beige solid (40%), mp 182–184 °C (Found: C, 53.2; H, 4.2; N, 12.4; S, 14.1. $C_{10}H_9ClN_2S$ requires C, 53.5; H, 4.0; N, 12.5; S, 14.3%); ν_{max}(KBr)/cm^{-1} 3120, 2900, 2800, 2690, 1592 and 1490; λ_{max}(H_2O)/nm 198 and 276; δ_H($CDCl_3$) 1.91 (1 H, br s, SH), 3.73 (3 H, s, 1-CH_3), 7.13 (1 H, s, 5-H) and 7.29–7.50 (4 H, m, ArH); *m*/*z* (MALDI-TOF) 225 (M^+, 45).

1-Methyl-2-(2-chlorophenyl)-4-mercaptoimidazole 4g. Flash chromatography (solvent system: CH_2Cl_2–MeOH, 95:5) and recrystallization from AcOEt–CH_2Cl_2, 70:30) gave a beige solid (25%), mp 175–176 °C (Found: C, 53.5; H, 4.1; N, 12.4; S, 14.2. $C_{10}H_9ClN_2S$ requires C, 53.4; H, 4.0; N, 12.5; S, 14.3%); ν_{max}(KBr)/cm^{-1} 3140, 2890, 2790, 2650, 1610 and 1480; λ_{max}(H_2O)/nm 199 and 276; δ_H($CDCl_3$) 2.00 (1 H, br s, SH), 3.50 (3 H, s, 1-CH_3), 6.88 (1 H, s, 5-H) and 7.35–7.50 (4 H, m, ArH); *m*/*z* (EI) 224 (M^+, 80) and 86 (100).

Oxidized form: disappearance of the SH proton at 2.00 ppm and shift of the 5-H signal from 6.88 to 7.30 ppm.

1-Methyl-2-(2-trifluoromethylphenyl)-4-mercaptoimidazole 4h. Flash chromatography (solvent system: CH_2Cl_2–MeOH, 90:10) and recrystallization from AcOEt gave a red solid (20%), mp 176–178 °C (Found: C, 51.4; H, 3.5; N, 11.0; S, 12.5. $C_{11}H_9F_3N_2S$ requires C, 51.2; H, 3.5; N, 10.9; S, 12.4%); ν_{max}(KBr)/cm^{-1} 3110, 2910–2720, 1590 and 1480; λ_{max}(H_2O)/nm 197 and 280; δ_H($CDCl_3$) 2.10 (1 H, br s, SH), 3.75 (3 H, s, 1-CH_3), 6.98 (1 H, s, 5-H) and 7.55–7.90 (4 H, m, ArH); *m*/*z* (EI) 258 (M^+, 100), 86 (60) and 45 (9).

Oxidized form: disappearance of the SH proton at 2.10 ppm and shift of the 5-H signal from 6.98 to 7.30 ppm.

1-Methyl-2-(3-trifluoromethylphenyl)-4-mercaptoimidazole 4i. Flash chromatography (solvent system: CH_2Cl_2–MeOH, 95:5) gave an orange solid (40%), mp 190–192 °C (Found: C, 51.3; H, 3.6; N, 10.9; S, 12.4. $C_{11}H_9F_3N_2S$ requires C, 51.2; H, 3.4; N, 10.8; S, 12.4%); ν_{max}(KBr)/cm^{-1} 3090, 2900–2710, 1585 and 1490; λ_{max}(H_2O)/nm 197 and 269; δ_H($CDCl_3$) 2.10 (1 H, br s, SH), 3.75 (3 H, s, 1-CH_3), 7.32 (1 H, s, 5-H) and 7.53–7.94 (4 H, m, ArH); *m*/*z* (EI) 258 (M^+, 100), 173 (33), 145 (17), 86 (98) and 45 (25).

1-Methyl-5-(2-trifluoromethylphenyl)-4-mercaptoimidazole 4j. The crude product was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to afford **4j** as a white solid (21%); mp 174–176 °C (Found: C, 51.4; H, 3.4; N, 11.0; S, 12.3. $C_{11}H_9G_3N_2S$ requires C, 51.2; H, 3.5; N, 10.9; S, 12.4%); ν_{max}(KBr)/cm^{-1} 3150–2600, 1540 and 1315; λ_{max}(H_2O)/nm 200; δ_H($CDCl_3$) 2.08 (1 H, br s, SH), 3.35 (3 H, s, 1-CH_3), 7.34 (1 H,

s, 2-H), 7.52–7.68 (3 H, m, ArH) and 7.82 (1 H, m, ArH); *m*/*z* (MALDI-TOF) 258.9 (MH^+, 75).

1-Methyl-5-(2-chlorophenyl)-4-mercaptoimidazole 4k. The crude product was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to afford **4k** as a white solid (21%), mp 170–171 °C (Found: C, 53.7; H, 3.8; N, 12.5; S, 14.5. $C_{10}H_9ClN_2S$ requires C, 53.5; H, 4.0; N, 12.5; S, 14.3%); ν_{max}(KBr)/cm^{-1} 3155–2600, 1540 and 1485; λ_{max}(H_2O)/nm 201 and 255; δ_H($CDCl_3$) 2.07 (1 H, br s, SH), 3.49 (3 H, s, 1-CH_3), 7.34 (1 H, s, 2-H) and 7.38–7.60 (4 H, m, ArH); *m*/*z* (MALDI-TOF) 225 (M^+, 56).

1-Methyl-5-(4-chlorophenyl)-4-mercaptoimidazole 4l. The crude product was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to afford **4l** as a white solid (30%), mp 179–182 °C (Found: C, 53.6; H, 4.1; N, 12.7; S, 14.1. $C_{10}H_9ClN_2S$ requires C, 53.5; H, 4.0; N, 12.5; S, 14.3%); ν_{max}(KBr)/cm^{-1} 3160–2600, 1540 and 1495; λ_{max}(H_2O)/nm 198 and 260; δ_H($CDCl_3$) 3.46 (3 H, s, 1-CH_3), 7.35 (1 H, s, 2-H), 7.37–7.43 (2 H, d, *J* 7.0, ArH) and 7.51–7.56 (2 H, d, *J* 7.0, ArH); *m*/*z* (MALDI-TOF) 225.2 (M^+, 40).

1-Methyl-5-(4-methoxyphenyl)-4-mercaptoimidazole 4m. The crude product was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to afford **4m** as a white solid (63%), mp 141–144 °C (Found: C, 60.2; H, 5.5; N, 12.8; S, 14.4. $C_{11}H_{12}N_2OS$ requires C, 60.0; H, 5.5; N, 12.7; S, 14.6%); ν_{max}(KBr)/cm^{-1} 3120, 2950, 1610 and 1580; λ_{max}(H_2O)/nm 199 and 245; δ_H($CDCl_3$) 1.80 (1 H, br s, SH), 3.50 (3 H, s, 1-CH_3), 3.83 (3 H, s, OCH_3), 6.90 (2 H, d, *J* 8.7, ArH), 7.15 (2 H, d, *J* 8.7, ArH) and 7.43 (1 H, s, 2-H); *m*/*z* (MALDI-TOF) 221 (MH^+, 31).

1-Methyl-2-trifluoromethyl-5-(2-methoxyphenyl)-4-mercaptoimidazole 4n. Flash chromatography (solvent system: CH_2Cl_2–MeOH, 95:5) and recrystallization from ethyl acetate gave **4n** as a yellow solid (13%), mp 85–87 °C (Found: C, 50.1; H, 4.0; N, 9.7; S, 11.3. $C_{12}H_{11}F_3N_2OS$ requires C, 50.0; H, 3.9; N, 9.7; S, 11.1%); ν_{max}(KBr)/cm^{-1} 3100–2810, 1610 and 1480; λ_{max}(H_2O)/nm 200; δ_H($CDCl_3$) 1.65 (1 H, br s, SH), 3.50 (3 H, s, 1-CH_3), 3.80 (3 H, s, OCH_3), 7.00–7.13 (2 H, m, ArH), 7.23 (1 H, s, ArH) and 7.42–7.56 (1 H, m, ArH); *m*/*z* (MALDI-TOF) 289 (M^+, 34).

References

1 H. Sies, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1058.
2 C. A. Rice-Evans and A. T. Diplock, *Free Rad. Biol. Med.*, 1993, **15**, 77.
3 B. Halliwell and J. M. C. Gutteridge, in *Free radicals in biology and medicine*, Oxford University Press, Oxford, 1989.
4 M. Fontecave and J. L. Pierre, *Bull. Soc. Chim. Fr.*, 1991, **128**, 505.
5 R. H. Schirmer, J. G. Müller and R. L. Krauth-Siegel, *Agnew. Chem., Int. Ed. Engl.*, 1995, **34**, 141.
6 R. Schreck, K. Albermann and P. A. Baeuerle, *Free Rad. Res. Commun.*, 1992, **17**, 221.
7 M. B. Toledano and W. J. Leonard, *Proc. Natl. Acad. Sci. USA*, 1991, **88**, 4328.
8 F. Müller, *Free Rad. Biol. Med.*, 1992, **13**, 651.
9 M. Roederer, S. W. Ela, F. J. Staal and L. A. Herzenberg, *AIDS Res. Hum. Retrovir.*, 1992, **8**, 209.
10 Y. J. Suzuki and L. Packer, *Biochem. Biophys. Res. Commun.*, 1993, **193**, 277.
11 N. I. Krinsky, *Free Rad. Biol. Med.*, 1993, **7**, 617.
12 R. A. Axford-Gutley and G. J. Wilson, *Cardiovasc. Res*, 1991, **25**, 89.
13 B. Hennig, C. Enoch and C. K. Chew, *Nutr. Res.*, 1987, **7**, 1242.
14 S. Partharanthy, S. G. Young. J. L. Witzum, R. G. Pittman and D. Steinberg, *J. Clin. Invest.*, 1986, **7**, 641.
15 S. V. Jovanovic, S. Steeken, M. Tosic, B. Marjanovic and M. G. Simic, *J. Am. Chem. Soc.*, 1994, **116**, 4846.
16 N. Cotelle, J. L. Bernier, J. P. Hénichart, J. P. Catteau, E. Gaydou and J. C. Wallet, *Free Rad. Biol. Med.*, 1992, **13**, 211.
17 P. M. Mehta, K. Przyklenk and R. A. Kloner, *Eur. Heart J.*, 1990, **11**, 94.
18 I. A. Cotgreave and P. Moldeus, *Bull. Eur. Physiopathol. Respir.*, 1987, **23**, 275.
19 B. Amor, C. Mercy and A. Degery, *Arthritis*, 1982, **25**, 698.
20 E. Turner, R. Klevit, L. J. Hager and B. M. Shapiro, *Biochemistry*, 1987, **26**, 4028.
21 E. Turner, L. J. Hager and B. M. Shapiro, *Science*, 1988, **252**, 939.
22 B. M. Shapiro, *Science*, 1991, **252**, 533.
23 J. W. Heinecke and B. M. Shapiro, *J. Biol. Chem.*, 1992, **267**, 7959.
24 K. H. Weaver and D. L. Rabenstein, *J. Org. Chem.*, 1995, **60**, 1904.
25 T. P. Holler and P. B. Hopkins, *J. Am. Chem. Soc.*, 1988, **110**, 4837.
26 T. P. Holler and P. B. Hopkins, *Biochemistry*, 1990, **29**, 1953.
27 H. G. Viehe, R. Merenyi, L. Stella and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 917.
28 H. G. Viehe, Z. Janousek, R. Merenyi and L. Stella, *Acc. Chem. Res.*, 1985, **18**, 148.
29 C. Bienarz and M. J. Cornwell, *Tetrahedron Lett.*, 1993, **34**, 939.
30 F. Asinger, A. Sans, H. Offermanns, P. Krings and H. Andree, *Justus Liebigs Ann. Chem.*, 1971, **744**, 51.
31 F. Asinger, A. Sans and H. D. Hahn, *Justus Liebigs Ann. Chem.*, 1966, **691**, 92.
32 J. C. Caille, S. Didierlaurent, D. Lefrançois, M. H. Lelièvre, C. Sury and J. Aszodi, *Synthesis*, 1995, **6**, 635.
33 A. Spaltenstein, T. P. Holler and P. B. Hopkins, *J. Org. Chem.*, 1987, **52**, 2977.
34 V. S. Zyabrev, V. V. Kiselev, E. O. Romanenko and B. S. Drach, *Zh. Org. Khim.*, 1994, **5**, 715.
35 H. Zimmer, D. C. Lankin and S. W. Morgan, *Chem. Rev.*, 1971, **71**, 229.
36 M. S. Blois, *Nature*, 1958, **181**, 1199.
37 H. J. Ha, G. S. Nam and K. P. Park, *Synth. Commun.*, 1991, **21**, 155.
38 K. Takahashi, T. Masuda, K. Ogura and H. Iida, *Synthesis*, 1983, **12**, 1043.

Paper 7/03741D
Received 29*th May* 1997
Accepted 21*st July* 1997