Metallation and Metal-Halogen Exchange Reactions of Imidazoles [1]

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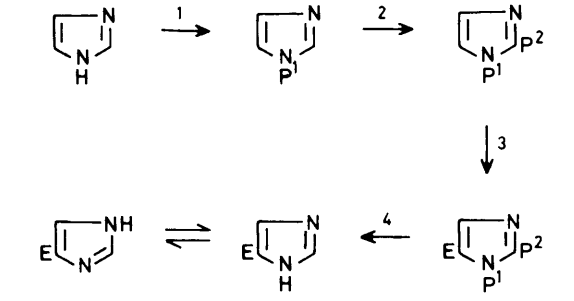
1-Ethoxymethyl-2-phenylthioimidazol-5-yl-lithium (4) has been prepared by metallation of 1-ethoxymethyl-2-phenylthioimidazole with n-butyl-lithium in ether or tetrahydrofuran and allowed to react with carbon dioxide, 4-methylbenzaldehyde, dimethyl disulphide, diphenyl disulphide, and the disulphide prepared from 2-mercaptoacetaldehyde diethyl acetal. 1-Ethoxymethyl-5-methylthio-2-phenylthioimidazol-4-yl-lithium (18) has been prepared *via* bromination of 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (9) and exchange of the bromine atom in the product (15) with n-butyl lithium. It has been treated with dimethyl disulphide, *NN*-dimethylformamide, and carbon dioxide, to give the corresponding sulphide (14), aldehyde (16), and acid (17), respectively. 2,5(4)-Bis(phenylthio)imidazole (23) prepared by treatment of its 1-ethoxymethyl derivative (10) with acid, iodinated in the 4-position to yield 4(5)-iodo-2,5(4)-bis(phenylthio)imidazole (24).

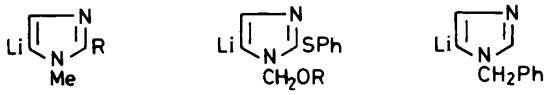
One of the aims of our current work is to make available 4(5)-mono- and 4,5-di-substituted imidazoles, which have not been readily available hitherto, along the lines suggested by Scheme 1. This involves protection of imidazole in its 1- and 2-positions followed by substitution in the 5-position and removal of the protecting groups. Ideally, the protecting groups should be available from cheap reagents and capable of being removed in a 'one-pot' reaction under reaction conditions which do not affect other functional groups. As a means of introducing the substituent into the 5-position (Scheme 1; step 3) we have studied the metallation of several 1,2-disubstituted imidazoles. Only five imidazol-5-yl-lithium compounds, (1)—(5), have been reported previously.[2] We have described already our observations on the preparation and synthetic usefulness of 1,2-dimethylimidazol-5-yl-lithium (2).[2] In continuation of this work we have studied 1-ethoxymethyl-2-phenylthioimidazol-5-yl-lithium (4), introduced recently by Breslow's group [3] as one of the first two, (3) and (4), 5-lithiated imidazoles which can be employed to give 5-substituted imidazoles with removable N-1 and C-2 protecting groups. The ethoxymethyl group is removable with concentrated hydrochloric acid in 50% aqueous ethanol whilst the phenylthio-group can be removed with aluminium amalgam.[3]

Breslow's group [3] metallated 1-ethoxymethyl-2-phenylthioimidazole with lithium di-isopropylamide (LDA); they reported that n-butyl-lithium resulted in C–S bond cleavage. In our hands, however, several attempts to metallate this compound with LDA under various reaction conditions and using various reagents to quench the reaction mixtures gave only starting material (using LDA we successfully converted 3-methylpyridine into diphenyl-3-pyridylmethylmethanol in 51% yield [4]) whereas its metallation with n-butyl-lithium (in ether or tetrahydrofuran), to give (4), caused no problems.[5]

Breslow's group [3] treated 1-ethoxymethyl-2-phenylthioimidazol-5-yl-lithium (4) only with ethyl *NN*-dimethyloxalate whilst its analogue (3) was treated with benzaldehyde, diethyl carbonate, and ethyl formate. We have converted the former lithium compound (4) into the carboxylic acid (6) (99% yield), which probably exists as a zwitterion (see Experimental section). Its addition in ether to a solution of *o*-nitrofluorobenzene in ether at −70 °C (this mode of addition was used in order to avoid oxidation of the lithium compound by the nitro-group [6]) followed by allowing the mixture to warm slowly to ambient temperature failed to give any of the *o*-nitrophenyl-derivative (7) (*cf.* ref. 7). With 4-methylbenzaldehyde, however, the lithium compound (4) (prepared in tetrahydrofuran in this case) gave a good yield of the carbinol (8).



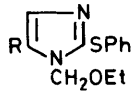
Scheme 1



(1) R = H
(2) R = Me

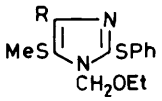
(3) R = Me
(4) R = Et

(5)

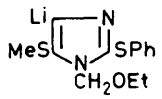


(6) R = CO_2H
(7) R = $C_6H_4NO_2$—2
(8) R = $CH(OH)C_6H_4Me$—4
(9) R = SMe
(10) R = SPh
(11) R = $SCH_2CH(OEt)_2$
(12) R = $SC_6H_4NO_2$—2
(13) R = SCH_2CO_2H

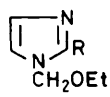
Various sulphides, (9)—(11), required for further work were prepared in moderate to high yields (see Experimental section for details) by reaction of the lithium compound (4) with dimethyl disulphide, diphenyl disulphide, and the disulphide prepared by oxidation of 2-mercaptoacetaldehyde diethyl acetal, respectively. With the disulphide derived from *o*-nitrobenzenethiol there was no reaction. The expected



(14) R = SMe
(15) R = Br
(16) R = CHO
(17) R = CO_2H



(18)



(19) R = $SiMe_3$
(20) R = $SiEt_3$
(21) R = $C(OH)Ph_2$
(22) R = Bu^t

Table. Attempts to prepare 1-ethoxymethyl-2-trimethylsilylimidazole (19)

Metallating agent	Solvent	Temperatures (°C) [a]
Bu^nLi/TMEDA	Et_2O	−15 → −15
Bu^nLi	Et_2O	−60 → R.T.
Bu^nLi	THF	−60 → −60
LDA	Et_2O	−70 → −70
PhLi	Et_2O	−15 → −20

[a] The first temperature is that at which metallation was carried out, the second is the temperature of addition of chlorotrimethylsilane (R.T. = ambient temperature).

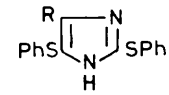
product was (12). Similarly, we failed to prepare compound (13) by successive treatment of the lithium compound (4) with sulphur and chloroacetic acid.

In order to discover whether 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (9) could be metallated in the 4-position we treated it with n-butyl-lithium in tetrahydrofuran at −70 °C, then quenched the mixture with deuterium oxide at −58 °C. There was no incorporation of deuterium. A similar reaction with *NN*-dimethylformamide as the quenching agent gave no trace of aldehyde (16). Next we attempted to metallate the imidazole (9) with LDA at −70 °C. When this mixture was quenched with dimethyl disulphide (initially at −70 °C, then warmed to ambient temperature), the expected product (14) could not be detected (starting material was recovered in 100% yield). However, use of potassium diisopropylamide–lithium t-butoxide (KDA) [8] at −78°C resulted in metallation in the 4-position. That metallation had occurred in this case was proved by addition of dimethyl disulphide, which gave an inseparable mixture of starting material and 1-ethoxymethyl-4,5-bis(methylthio)-2-phenylthioimidazole (14) (ratio 2 : 1 by ^1H n.m.r. spectroscopy) (see later).

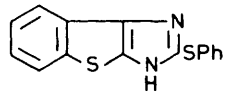
The lithium compound (18) was prepared *via* bromination of 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (in 92% yield) and metal–halogen exchange of the bromine atom in the product (15) with n-butyl-lithium in ether at −70 °C, and its treatment with dimethyl disulphide gave 1-ethoxymethyl-4,5-bis(methylthio)-2-phenylthioimidazole (14) (100% yield). With *NN*-dimethylformamide or carbon dioxide lithium compound (18) gave high yields of the corresponding aldehyde (16) (84% yield) and acid (17) (100%), respectively.

As far as we are aware, not only is this the first reproducible bromine–lithium exchange reaction of a *mono*bromoimidazole,* but 1-ethoxymethyl-5-methylthio-2-phenylthioimidazol-4-yl-lithium (18) is the first imidazol-4-yl-lithium derivative to be reported.[9,10]

Breslow's group [3] reported that attempts to prepare organometallic reagents from 1-protected 4(5)-bromoimidazoles failed, leading either to C-2 metallation or reduction. Our experiments with simple *mono*bromoimidazoles, which we shall report in detail elsewhere, have been similarly unsuccessful. Stensiö *et al.*[11] have converted 2,4,5-tribromoimidazole into 4(5)-bromoimidazole by its successive treatment with 4 molar equivalents of n-butyl-lithium and acid and claim to have prepared 4(5)-deuterioimidazole by successive treatment of the monobromo-compound with almost 5 molar equivalents of n-butyl-lithium, deuteriomethanol, and acid.



(23) R = H
(24) R = I



(25)

Attempts (see Table) to prepare an imidazole, namely 1-ethoxymethyl-2-trimethylsilylimidazole (19), possessing N-1 and C-2 protecting groups removable in a ' one-pot ' reaction failed as did similar attempts to prepare compound (20). That the first step of these reactions, *i.e.* metallation, could be accomplished was shown by quenching a similar reaction mixture with benzophenone, which gave a high yield (81%) of carbinol (21). When we employed the conditions used previously to prepare 1-methyl-2-trimethylsilylimidazole [12] we obtained an inseparable mixture of the desired product (19) and starting material (ratio 1 : 1 by ^1H n.m.r. spectroscopy). Attempts to introduce a 2-t-butyl group into 1-ethoxymethylimidazole by treating its 2-lithio-derivative with t-butyl bromide failed to give the desired product (22), presumably because this alkyl halide readily undergoes elimination in the presence of base.[13] 1-Ethoxymethylation of 2-t-butylimidazole [14] is an alternative route to this product (22) which we have not explored.

We deprotected 1-ethoxymethyl-2,5-bis(phenylthio)imidazole (10) with acid (88% yield) and iodinated the product (23) with iodine and potassium iodide in aqueous sodium hydroxide, to give a quantitative yield of 4(5)-iodo-2,5(4)-bis(phenylthio)imidazole (24). Photolysis of this iodo-compound (24) for 7 h in ether, through a Pyrex filter,[15] in an attempt to synthesise the novel heterocyclic system (25), gave only diphenyl disulphide, starting material, and the deiodinated compound (23) [ratio 1 : 6 : 6 (w/w) isolated]. Using a quartz filter and ethanol or tetrahydrofuran as the solvent similar results were obtained. Photodeiodination during reactions of this type is well known.[16]

Experimental

The instruments used to record i.r., mass, and ^1H and ^{13}C n.m.r. spectra and the general experimental conditions were the same as those described in our previous paper.[2] Photochemical reactions were carried out in a RPR-100 Rayonet reactor using either a RPR-3000 Å lamp (Pyrex filter) or a RPR-2537 Å lamp (quartz filter).

* *Note added in proof:* See the recent paper by J. P. Dirlan, R. B. James, and E. V. Shoop, *J. Org. Chem.*, 1982, **47**, 2196.

The following compounds were prepared by literature procedures: 1-ethoxymethylimidazole (80%), b.p. 50—80 °C at 0.1 mmHg (lit.,[3] 85% and b.p. 60—100 °C at 0.2 mmHg); 1-ethoxymethyl-2-phenylthioimidazole (82%), b.p. 100—120 °C at 0.1 mmHg (lit.,[3] b.p. 128—130 °C at 0.2 mmHg); and the disulphide of 2-mercaptoacetaldehyde diethyl acetal, 1,1,1',1'-tetraethoxyethyl disulphide, was prepared (29% yield) as an oil [17] using the method used previously [18] for the synthesis of the tetramethoxy-analogue. For the sake of brevity details (other than those given in the Discussion) of unsuccessful reactions have been omitted. Ether refers to diethyl ether throughout.

1-Ethoxymethyl-2-phenylthioimidazole-5-carboxylic Acid (6).—1.12M-n-Butyl-lithium in hexane (11.5 ml, 12.9 mmol) was added dropwise to a stirred solution of 1-ethoxymethyl-2-phenylthioimidazole (3.0 g, 12.9 mmol) in tetrahydrofuran (150 ml) at −78 °C. After 2 h an excess of solid carbon dioxide was added and the mixture was allowed to warm slowly to ambient temperature. The product was extracted with 2% aqueous sodium hydroxide and the extracts were combined and made acidic by addition of 4M-hydrochloric acid. The resulting precipitate was filtered off and dried to give the *acid* (6) (3.56 g, 99%), m.p. 140—141 °C (from methanol), $\nu_{max.}$ 1 690 (CO) and 2 300—2 500 cm^{-1} ($\overset{+}{N}H$); δ ($CDCl_3$—[$(CD_3)_2SO$] 9.65br (1 H, s, exchangeable, $\overset{+}{N}H$), 7.70 (1 H, s, 4-H), 7.32 (5 H, s, SPh), 5.82 (2 H, s, NCH_2), 3.46 (2 H, q, OCH_2), and 1.03 p.p.m. (3 H, t, Me); δ [$(CD_3)_2SO$] 160.66 (s, CO_2-), 145.75 (s, C-2), 137.58 (d, C-4), 132.34 (s, C-5), 130.26, 129.41, 127.81, and 125.63 * (SPh), 73.61 (t, NCH_2), 63.74 (t, OCH_2), and 14.78 p.p.m. (q, Me) (Found: C, 56.0; H, 5.2; N, 10.0%; M^+, 278. $C_{13}H_{14}N_2O_3S$ requires C, 56.1; H, 5.1; N, 10.1%; *M*, 278).

1-Ethoxymethyl-2,5-bis(phenylthio)imidazole (10).—1.76M-n-Butyl-lithium in hexane (2.2 ml, 3.87 mmol) was added dropwise to a stirred solution of 1-ethoxymethyl-2-phenylthioimidazole (0.9 g, 3.85 mmol) in tetrahydrofuran (45 ml) at −70 °C, and the reaction mixture was stirred at this temperature for a further 3 h; it was then allowed to warm to −60 °C. Diphenyl disulphide (0.85 g, 3.90 mmol) was added and the mixture was allowed to warm slowly to ambient temperature; 20% aqueous ammonium chloride (10 ml) was then added. The aqueous layer was separated and extracted with chloroform. The extracts and organic layer were combined, dried ($MgSO_4$), and distillation of the solvents gave a reddish brown oil (1.6 g) which was chromatographed on alumina. Light petroleum eluted diphenyl disulphide (0.25 g) and light petroleum–ethyl acetate (1 : 1) eluted the *product* (10) (1.31 g, 100%) as an oil, δ ($CDCl_3$) 7.50 (1 H, s, 4-H), 7.10—7.40 (10 H, m, 2- and 5-SPh), 5.39 (2 H, s, NCH_2), 3.30 (2 H, q, OCH_2), and 0.90 p.p.m. (3 H, t, Me); δ ($CDCl_3$) 143.42 (s, C-2), 138.90 (d, C-4), 135.73 (s, C-5), 132.79 (s, C-1 of 2-SPh), 129.38, 128.72, 126.96, 126.45, 125.84 * (SPh), 122.05 (s, C-1 of 5-SPh), 72.86 (t, NCH_2), 63.71 (t, OCH_2), and 14.08 p.p.m. (q, Me) (Found: C, 63.1; H, 5.4; N, 8.3%; M^+, 342. $C_{18}H_{18}N_2OS_2$ requires C, 63.1; H, 5.3; N, 8.2%; *M*, 342).

The following compounds were prepared similarly (time of metallation at −70 °C and purification techniques given in parenthesis): *1-ethoxymethyl-5-methylthio-2-phenylthioimidazole* (9) (83%) (2.5 h; alumina column, eluted with light petroleum–ethyl acetate), oil; δ ($CDCl_3$) 7.30 (1 H, s, 4-H), 7.25 (5 H, m, 2-SPh), 5.50 (2 H, s, NCH_2), 3.45 (2 H, q, OCH_2), 2.35 (3 H, s, Me), and 1.10 p.p.m. (3 H, t, Me); δ ($CDCl_3$) 140.8 (s, C-2), 135.19 (d, C-4), 133.33 (s, C-5), 128.56, 127.79, 127.48, 126.59 * (SPh), 72.70 (t, NCH_2), 63.54 (t, OCH_2), 20.07 (q, SMe), and 14.22 p.p.m. (q, Me) (Found: C, 55.6; H, 5.7; N, 9.9%; M^+, 280. $C_{13}H_{16}N_2OS_2$ requires C, 55.7; H, 5.75; N, 10.0%; *M*, 280); *1-ethoxymethyl-2-phenylthioimidazol-5-yl-4-methylphenylmethanol* (8) (62%) (2.0 h; recrystallised from light petroleum–carbon tetrachloride), m.p. 99—100 °C; $\nu_{max.}$ 3 100—3 400 cm^{-1} (OH); δ ($CDCl_3$) 7.18 (9 H, m, aromatic), 6.80 (1 H, s, 4-H), 5.89 (1 H, s, CH), 5.34 (2 H, s, NCH_2), 3.70br (1 H, s, exchangeable, OH), 3.30 (2 H, q, CH), 5.34 (2 H, s, NCH_2), 3.70br (1 H, s, exchangeable, OH), 3.30 (2 H, q, OCH_2), 2.30 (3 H, s, Me), and 1.01 p.p.m. (3 H, t, Me); δ ($CDCl_3$) 139.49 (s, C-2), 137.59 (s, C-5), 137.37 (s, C-1 of SPh), 134.29 (s, C-1 of C_6H_4Me-4), 129.92, 128.91, 128.16, 127.41, 126.95, 126.60, 126.21 * (C-4 and aromatic C's), 73.67 (t, NCH_2), 67.12 (d, CH), 64.00 (t, OCH_2), 20.85 (q, Me), and 14.39 p.p.m. (q, Me) (Found: C, 67.7; H, 6.3; N, 8.0%; M^+, 354. $C_{20}H_{22}N_2O_2S$ requires C, 67.8; H, 6.3; N, 7.9%; *M*, 354); *2-(1-ethoxymethyl-2-phenylthioimidazol-5-ylthio)acetaldehyde diethyl acetal* (11) (31%) (2.0 h; chromatographed on alumina eluted with light petroleum–ethyl acetate), oil, δ ($CDCl_3$) 7.33 (1 H, s, 4-H), 7.25 (5 H, s, SPh), 5.50 (2 H, s, NCH_2), 4.57 (1 H, t, CH), 3.30—3.70 (6 H, m, 3 × OCH_2), 2.88 (2 H, d, SCH_2), and 1.10 p.p.m. (9 H, q, 3 × Me); δ ($CDCl_3$) 141.41 (s, C-2), 137. 01 (d, C-4), 133.21 (s, C-5), 128.64 (d, C-2 and C-6 of SPh), 127.86 (d, C-4 of SPh), 126.66 (d, C-3 and C-5 of SPh), 125.21 (s, C-1 of SPh), 100.89 (d, CH), 72.67 (t, NCH_2), 63.59 (t, OCH_2), 61.22 (t, OCH_2), 39.38 (t, SCH_2), and 14.66, 14.19, and 13.90 * p.p.m. (all Me) (Found: C, 56.5; H, 6.8; N, 7.2%; M^+, 382. $C_{18}H_{26}N_2O_3S_2$ requires C, 56.5; H, 6.85; N, 7.3%; *M*, 382). An increased yield (61%) of compound (11) was obtained by adding (using a syringe) a solution of 1-ethoxymethyl-2-phenylthioimidazol-5-yl-lithium (4) in ether (prepared at −74 °C) to a solution of the disulphide prepared from 2-mercaptoacetaldehyde diethyl acetal in ether at ambient temperature (resulting mixture stirred at 28 °C for 2 h before being worked up in the manner described for the preceding experiment).

Reactions of 1-Ethoxymethyl-5-methylthio-2-phenylthioimidazole (9).—(a) *With KDA.*[8] 1.76M-n-Butyl-lithium in hexane (1.36 ml, 2.4 mmol) was added to a stirred mixture of potassium t-butoxide (0.336 g, 3.0 mmol) and di-isopropylamine (0.304 g, 3.0 mmol) in tetrahydrofuran (8.0 ml) at −78 °C; the resulting mixture was stirred at −78 °C for 10 min. A solution of 1-ethoxymethyl-5-methylthio-2-phenylthiomidazole (9) (0.560 g, 2.0 mmol) in tetrahydrofuran (3.0 ml) was added during 1 min followed by a solution of dimethyl disulphide (0.282 g, 3.0 mmol) in tetrahydrofuran (1.0 ml); the resulting mixture was stirred at −78 °C for a further 10 min. Methanol (2.0 ml) was then added followed by saturated aqueous ammonium chloride (8.0 ml); the organic solvents were then distilled off. Extraction of the residue with chloroform gave a viscous orange oil (0.53 g) which ^{1}H n.m.r. spectroscopic examination showed to be a mixture of starting material (9) and 1-ethoxymethyl-4,5-bis(methylthio)-2-phenylthioimidazole (14) (ratio 2 : 1) (prepared unambiguously as described later). T.l.c. of the mixture on alumina (elution with light petroleum–ethyl acetate) failed to separate the components (single spot under a u.v. lamp); however, when the plate was sprayed with an ethanolic solution of dodecamolybdophosphoric acid the ' single spot ' showed up as a major blue spot with an outer yellow ring. With this developing reagent pure starting material gives a yellow spot.

(b) *Bromination.* Bromine (0.4 g, 2.5 mmol) in acetic acid (1.0 ml) was added dropwise to a stirred mixture of 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (9) (0.7 g, 2.5 mmol) and anhydrous sodium acetate (0.15 g) in acetic acid

* Asterisked signals were too close together for meaningful assignments to be made.

(3.0 ml) at ambient temperature; the mixture was then stirred for a further 1 h. The acetic acid was distilled off and water (10 ml) added to the residue. The product was extracted with chloroform (3 × 10 ml) and the extracts were combined, washed successively with 20% aqueous potassium carbonate and water, and then dried ($MgSO_4$). Distillation of the solvent gave a yellow oil (0.87 g, 97%), which was chromatographed on alumina. Ethyl acetate–light petroleum eluted 4-*bromo*-1-*ethoxymethyl*-5-*methylthio*-2-*phenylthioimidazole* (15) (0.85 g, 92%), m.p. 56—57 °C (from light petroleum); δ ($CDCl_3$) 7.30 (5 H, m, SPh), 5.51 (2 H, s, NCH_2), 3.46 (2 H, q, OCH_2), 2.30 (3 H, s, SMe), and 1.10 p.p.m. (3 H, t, Me); δ ($CDCl_3$) 141.14 (s, C-2), 132.75 (s, C-5), 129.32 (d, C-2 and C-6 of SPh), 129.05 (d, C-4 of SPh), 127.29 (d, C-3 and C-5 of SPh), 126.21 (s, C-4), 125.42 (s, C-1 of SPh), 74.13 (t, NCH_2), 64.19 (t, OCH_2), 19.28 (q, SMe), and 14.59 p.p.m. (q, Me) (Found: C, 43.6; H, 4.0; N, 8.0%; M^+, 358. $C_{13}H_{15}BrN_2OS_2$ requires C, 43.5; H, 4.2; N, 7.8%; *M*, 358).

Reactions of 4-*Bromo*-1-*ethoxymethyl*-5-*methylthio*-2-*phenylthioimidazole* (15).—1.0M-n-Butyl-lithium in hexane (0.83 ml, 0.83 mmol) was added to a solution of 4-bromo-1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (15) (0.3 g, 0.83 mmol) in ether (35 ml) at such a rate that the temperature did not rise above −70 °C. After 1 h further, dimethyl disulphide (0.073 ml, 0.077 g, 0.83 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature. Saturated aqueous ammonium chloride (5.0 ml) was added, the organic layer was separated, and the aqueous layer was extracted with ether (30 ml). The organic layer and ethereal extract were combined, dried ($MgSO_4$), and distillation of the solvent gave a yellow oil which was chromatographed on alumina. Chloroform–light petroleum eluted 1-*ethoxymethyl*-4,5-*bis*(*methylthio*)-2-*phenylthioimidazole* (14) (0.27 g, 100%); δ ($CDCl_3$) 7.23 (5 H, m, SPh), 5.47 (2 H, s, NCH_2), 3.42 (2 H, q, OCH_2), 2.53 (3 H, s, 4-SMe), 2.28 (3 H, s, 5-SMe), and 1.05 p.p.m. (3 H, t, Me); δ($CDCl_3$) 143.91 (s, C-2), 140.48 (s, C-4), 133.77 (s, C-5), 128.89 (d, C-2 and C-6 of SPh), 128.50 (d, C-4 of SPh), 126.81 (d, C-3 and C-5 of SPh), 124.51 (s, C-1 of SPh), 73.57 (t, NCH_2), 63.95 (t, OCH_2), 19.40 (q, 4-SMe), 15.54 (q, 5-SMe), and 14.55 p.p.m. (q, Me) (Found: C, 51.6; H, 5.5; N, 8.5%; M^+, 326. $C_{14}H_{18}N_2OS_3$ requires C, 51.5; H, 5.6; N, 8.6%; *M*, 326).

The following compounds were prepared similarly: 1-*ethoxymethyl*-5-*methylthio*-2-*phenylthioimidazole*-4-*carbaldehyde* (16) (84%) (DMF added after 2 h; product chromatographed on a medium-pressure silica column and eluted with light petroleum–ethyl acetate), oil, $\nu_{max.}$ 1 680 cm^{-1} (CO); δ($CDCl_3$) 10.03 (1 H, s, C*H*O), 7.18—7.50 (5 H, m, SPh), 5.53 (2 H, s, NCH_2), 3.45 (2 H, q, OCH_2), 2.45 (3 H, s, SMe), and 1.07 p.p.m. (3 H, t, Me); δ($CDCl_3$) 184.19 (d,CHO), 143.30 (s, C-2), 142.56 (s, C-4), 135.37 (s, C-5), 131.48 (s, C-1 of SPh), 129.63 (d, C-2 and C-6 of SPh), 128.79 (d, C-4 of SPh), 127.31 (s, C-3 and C-5 of SPh), 73.11 (t, NCH_2), 64.08 (t, OCH_2), 19.39 (q, SMe), and 14.28 p.p.m. (q, Me) (Found: C, 54.6; H, 5.25; N, 9.0%; M^+, 308. $C_{14}H_{16}N_2O_2S_2$ requires C, 54.5; H, 5.2; N, 9.1%; *M*, 308); *semicabrazone* (70%), m.p. 166—167 °C (from carbon tetrachloride–light petroleum); $\nu_{max.}$ 1 690 (CO) and 3 150—3 425 cm^{-1} (NH and NH_2) (Found: M^+, 365.0977. $C_{15}H_{19}N_5O_2S_2$ requires *M*, 365.0979); *oxime* (29%), m.p. 120—121 °C (from carbon tetrachloride–light petroleum); $\nu_{max.}$ 970 (NO) and 3 000—3 200 cm^{-1} (OH) (Found: M^+, 323. $C_{14}H_{17}N_3O_2S_2$ requires *M*, 323) (the derivatives also had ^1H and ^{13}C n.m.r. spectra consistent with their structures): 1-*ethoxymethyl*-5-*methylthio*-2-*phenylthioimidazole*-4-*carboxylic acid* (17) (100%) (solid carbon dioxide added after 1 h; product extracted with 2% aqueous sodium hydroxide, combined extracts acidified with 4M-hydrochloric acid, then extracted with chloroform), m.p. 103—104 °C (from chloroform–light petroleum) (74% yield after recrystallisation); $\nu_{max.}$ 1 680 (CO) and 2 500—3 200 cm^{-1} (OH); δ($CDCl_3$) 8.95br (1 H, s, exchangeable, OH), 7.30 (5 H, m, SPh), 5.55 (2 H, s, NCH_2), 3.45 (2 H, q, OCH_2), 2.50 (3 H, s, SMe), and 1.10 p.p.m. (3 H, t, Me), δ($CDCl_3$) 162.45 (s, CO_2H), 141.86 (s, C-2), 135.17 (s, C-4), 131.81 (s, C-5), 130.10 (d, C-2 and C-6 of SPh), 129.25 (d, C-4 of SPh), 127.81 (d, C-3 and C-5 of SPh), 73.73 (t, NCH_2), 64.44 (t, OCH_2), 19.28 (q, SMe), and 14.64 p.p.m. (q, Me) (C-1 of SPh probably overlaid) (Found: C, 51.85; H, 5.1; N, 8.7%; M^+, 324. $C_{14}H_{16}N_2O_3S_2$ requires C, 51.8; H, 5.0; N, 8.6%; *M*, 324).

Attempts to prepare 1-*Ethoxymethyl*-2-*trimethylsilylimidazole* (19) (cf. *Conditions used in Ref.* 12).—A solution of 1-ethoxymethylimidazole (0.5 g, 4.0 mmol) in ether (2.0 ml) was added dropwise to a stirred solution of 1.12M-n-butyl-lithium in hexane (3.5 ml, 4.0 mmol) in ether (30 ml) at ambient temperature; the mixture was then heated under reflux gently for 1 h. Chlorotrimethylsilane (0.75 ml, 0.642 g, 6.0 mmol) was added using a syringe and the mixture was heated under reflux for a further 2 h. It was then filtered under nitrogen and the solvents were distilled off, to give a yellow oil (0.75 g) shown by ^1H n.m.r. spectroscopy to be a mixture of starting material and 1-ethoxymethyl-2-trimethylsilylimidazole (19) (ratio 1 : 1 by ^1H n.m.r. spectroscopy) which could not be separated either by distillation (b.p. 50—60 °C at 6 × 10^{-4} mmHg) or column chromatography.

Other attempts to prepare 1-ethoxymethyl-2-trimethylsilylimidazole (19) are summarised in the Table (see Discussion).

1-*Ethoxymethylimidazol*-2-*yldiphenylcarbinol* (21).—A mixture of 1.28M-n-butyl-lithium in hexane (6.17 ml, 7.9 mmol) and TMEDA (0.92 g, 7.9 mmol) was added dropwise to a stirred solution of 1-ethoxymethylimidazole (1.0 g, 7.9 mmol) in ether (25 ml) at −15 °C and the mixture was kept at this temperature for 25 min. A solution of benzophenone (1.44 g, 7.9 mmol) in ether (6 ml) was added dropwise, after which the mixture was allowed to warm slowly to ambient temperature; it was then stirred at this temperature for 30 min. Water (25 ml) was added and the resulting precipitate was filtered off, washed with ether, and dried to give the *product* (21) (1.95 g, 81%), m.p. 129—130 °C, m.p. 131—132 °C after sublimation at 0.1 mmHg; $\nu_{max.}$ 1 600 (Ph) and 3 050—3 400 cm^{-1} (OH); δ($CDCl_3$) 7.30 (10 H, s, Ph_2), 6.98 (2 H, d, 4-H and 5-H), 4.98 (2 H, s, N-CH_2), 4.72br (1 H, s, exchangeable, OH), 3.25 (2 H, q, OCH_2), and 1.05 p.p.m. (3 H, t, Me); δ($CDCl_3$) 151.72 (s, C-2), 145.25 (s, C-OH), 129.00, 128.52, 128.16, 127.92* (aromatic C's), 127.18 (d, C-4), 121.81 (d, C-5), 76.89 (t, N-CH_2), 64.93 (t, OCH_2), and 15.13 p.p.m. (q, Me) (Found: C, 73.9; J, 6.5; N, 8.9%; M^+, 308. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.1%; *M*, 308).

2,5(4)-*Bis*(*phenylthio*)*imidazole* (23).—A mixture of 1-ethoxymethyl-2,5-bis(phenylthio)imidazole (10) (0.5 g, 1.46 mmol), 50% aqueous ethanol (50 ml), and concentrated hydrochloric acid (25 ml) was heated gently under reflux for 6 h, after which the ethanol was distilled off and solid potassium carbonate added to the residue until gas evolution ceased. Extraction of the mixture with chloroform gave a pale yellow solid which was triturated with a small amount of methanol; chloroform was then added. The solid was filtered off, washed with ether, and air dried to give the *product* (23) (0.35 g, 88%), m.p. 150 °C (from chloroform–carbon tetrachloride); δ(CD_3OD) 7.44 (1 H, s, 4-H), 7.30 (5 H, s, 2-SPh), and 7.20 p.p.m. (5 H, s, 5-SPh); δ(CD_3OD) 141.22 (s, C-2), 138.66 (s, C-5), 135.36 (s, C-1 of SPh), 130.29 (d, C-4), 129.88 (d, C-2 and C-6 of SPh), 128.30 (d, C-4 of SPh), and 126.94

p.p.m. (d, C-3 and C-5 of SPh) (Found: C, 63.5; H, 4.4; N, 10.0%; M^+, 284. $C_{15}H_{12}N_2S_2$ requires C, 63.35; H, 4.25; N, 9.85%; *M*, 284).

4(5)-*Iodo*-2,5(4)-*bis*(*phenylthio*)*imidazole* (24).—Methanol (*ca.* 1.0 ml) was added to a suspension of 2,5(4)-bis(phenylthio)imidazole (23) (0.1 g, 0.35 mmol) in 2% aqueous sodium hydroxide (10.0 ml) until a clear solution was obtained. A solution of iodine (0.087 g, 0.35 mmol) in 20% aqueous potassium iodide (5.0 ml) was then added dropwise with stirring until a persistent cloudiness appeared. The mixture was stirred at ambient temperature until t.l.c. indicated absence of starting material. The mixture was neutralised by careful addition of 20% aqueous acetic acid and a few crystals of sodium thiosulphate were added to destroy the excess of iodine. Extraction of the mixture with chloroform (3 × 15 ml) gave the *product* (24) (0.145 g, 100%), m.p. 140 °C (from chloroform–hexane); δ(CD_3OD) 7.28 (5 H, s, 2-SPh) and 7.18 (5 H, m, 5-SPh); δ[$(CD_3)_2CO$] 143.43 (s, C-2), 136.10 (s, C-5), 133.42, 130.25, 129.62, 129.41, 127.92, 127.67, and 126.69* (2 × SPh), and 93.98 p.p.m. (s, C-4) (Found: C, 43.9; H, 2.8; N, 6.8%; M^+, 410. $C_{15}H_{11}IN_2S_2$ requires C, 43.9; H, 2.7; N, 6.8%; *M*, 410).

Photolysis of 4(5)-*Iodo*-2,5(4)-*bis*(*phenylthio*)*imidazole* (24).—A solution of the imidazole (24) (0.2 g, 0.49 mmol) in ether (100 ml) was irradiated for 7 h through a Pyrex filter, when t.l.c. indicated absence of starting material. The mixture was cooled, washed successively with 0.1M-sodium thiosulphate and water, and dried ($MgSO_4$); the ether was then distilled off to give a viscous oil (0.13 g) which was chromatographed on a medium-pressure silica column. Light petroleum–ethyl acetate eluted: (i) diphenyl disulphide (5 mg); (ii) starting material (24)(30 mg, 15%), m.p. 140—141 °C (from chloroform–hexane), identical in other respects (t.l.c. and i.r. and ^{1}H n.m.r. spectra) with an authentic sample; and (iii) 2,5(4)-bis(phenylthio)imidazole (23) (30 mg, 22%), m.p. 150 °C (from chloroform–carbon tetrachloride), identical in other respects (t.l.c. and i.r., and ^{1}H n.m.r. spectra) with an authentic sample.

Similar irradiation experiments in ethanol or tetrahydrofuran using a quartz filter gave similar results.

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