Azoles. Part 4.[1] Nucleophilic Substitution Reactions of Halogenoimidazoles

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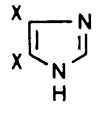
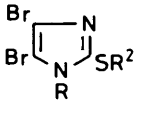
A number of *N*-protected derivatives of 2,4,5-tribromoimidazole, 4(5)-bromo-5(4)-nitroimidazole, and 2,4(5)-dibromo-5(4)-nitroimidazole have been prepared by standard procedures and treated with various nucleophiles. Whereas 2,4,5-tribromo (and tri-iodo)imidazole reacted with sodium benzenethiolate to give the corresponding 4,5-dihalogenoimidazole and diphenyl disulphide, 1-protected derivatives of 2,4,5-tribromoimidazole reacted with various sodium alkane (or arene)thiolates and with sodium isopropoxide, in isopropyl alcohol, by displacement of the 2-bromine atom. 1-Benzyl-5-bromo-4-nitroimidazole (**14**), 2-(5-bromo-4-nitroimidazol-1-yl)acetate (**25**), and 5-bromo-4-nitro-1-phenacylimidazole (**26**) reacted by displacement of the 5-bromine atom. The product arising from reaction of the last compound with ethyl 2-mercaptoacetate in ethanol in the presence of base, cyclised to give ethyl 3-hydroxy-7-nitro-3-phenylimidazolo[5,1-*b*]thiazine-2-carboxylate (**35**).

Although 2,4,5-tribromo-(and tri-iodo-)imidazole[4] have been known in the literature for a long time their nucleophilic substitution and other reactions have not been exploited.[5] Hydrogen chloride or lithium chloride convert the tribromo compound into 2,4,5-trichloroimidazole,[6] both compounds are converted by sodium hydrogensulphite into the corresponding 4(5)-monohalogenoimidazole,[7,8] whilst triphenylphosphine is claimed[9] to convert 2,4,5-tribromoimidazole into 4,5-dibromoimidazole in 63% yield (see also penultimate paragraph of Discussion).

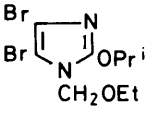
When we treated either 2,4,5-tribromoimidazole[7] or 2,4,5-triiodoimidazole[4,10] with sodium benzenethiolate in hot isopropyl alcohol we obtained in each case only the corresponding 4,5-dihalogeno-compound (**1**; 68%) and (**2**; 90%), respectively, together with some starting material and diphenyl disulphide. The tri-iodo compound behaved similarly with sodium benzenethiolate in hexamethylphosphoramide (hexamethylphosphoric triamide) (HMPA) at 82 °C. Such dehalogenations are not without precedent in the literature.[11]



(**1**) X = Br
(**2**) X = I



(**3**) $R^1 = CH_2Ph, R^2 = Ph$
(**4**) $R^1 = R^2 = CH_2Ph$
(**5**) $R^1 = CH_2OMe, R^2 = Et$
(**6**) $R^1 = CH_2OMe, R^2 = Pr^n$
(**7**) $R^1 = CH_2OMe, R^2 = CH_2Ph$
(**8**) $R^1 = CH_2OMe, R^2 = Ph$
(**9**) $R^1 = CH_2OEt, R^2 = Me$
(**10**) $R^1 = CH_2CO_2Et, R^2 = Ph$
(**11**) $R^1 = CH_2CO_2H, R^2 = Ph$
(**12**) $R^1 = CH_2COPh, R^2 = CH_2Ph$

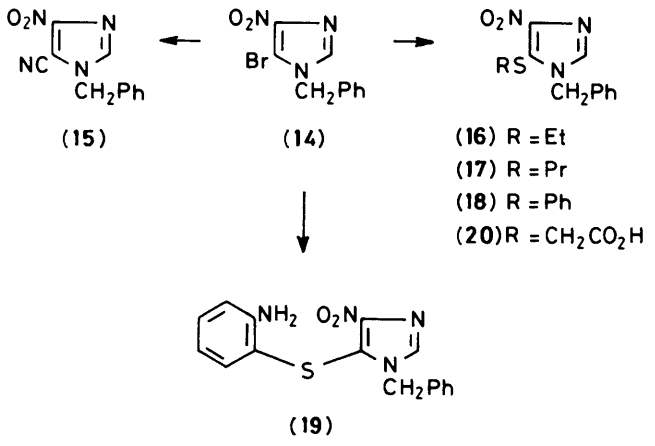


(**13**)

Next we turned our attention to 1-protected mono- and polyhalogenoimidazoles. 5-Bromo- (and chloro-)1-methylimidazole are reported[12] to react with lithium piperidide in piperidine by an addition-elimination process, to give 1-methyl-5-piperidinoimidazole by transhalogenation (*cf.* ref. 13), to give the corresponding 4-halogeno-1-methylimidazole, and by a *meta*-substitution pathway, to give 1-methyl-2-piperidinoimidazole. Encouraged by the work of an Italian group,[14] who have studied the nucleophilic displacement reactions of unactivated halogen atoms in aromatic systems, we treated 1-benzyl- and 1-methoxymethyl-2,4,5-tribromoimidazole with various sodium alkane- (or arene-)thiolates, which gave moderate yields (54—64%) of the corresponding 4,5-dibromo-2-alkyl- (or aryl-) thioimidazole (**3**)—(**8**) with isopropyl alcohol as the reaction solvent. Whilst 2,4,5-tribromo-1-ethoxymethylimidazole reacted with 1 mol equiv. of sodium methanethiolate in HMPA at 82 °C to give the 2-methylthio derivative (**9**) (44% yield), the yield of (**9**) in *N*,*N*-dimethylformamide (DMF) dropped to *ca.* 3%. 2,4,5-Tribromo-1-ethoxymethylimidazole also reacted with sodium isopropoxide in isopropyl alcohol to give the 2-isopropoxy derivative (**13**) (63%). 5-Bromo-1-methyl-imidazole[4] and 1-ethoxymethyl-4,5-di-iodoimidazole[4] failed to react with sodium benzenethiolate either in dioxane at 82 °C or in dimethyl sulphoxide at 100 °C. DMF was the preferred solvent for the conversions of ethyl 2-(2,4,5-tribromoimidazol-1-yl)-acetate and 2,4,5-tribromo-1-phenacylimidazole into the 2-substituted derivatives (**10**) (56%) and (**12**) (61%), respectively. Alkaline hydrolysis of ester (**10**) gave acid (**11**).

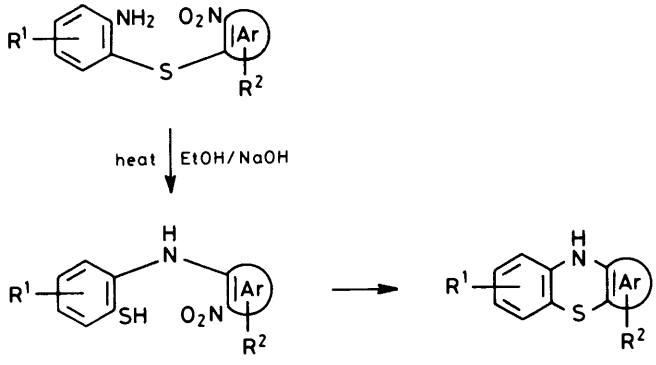
When a 4(5)-halogenoimidazole is activated by the presence of an adjacent electron-withdrawing group the halogen atom becomes much more reactive to nucleophiles.[5] Nucleophilic displacements of formyl or nitro group activated halogen atoms from imidazole substrates have been reported for oxygen,[15-19] sulphur,[18,19-28] and nitrogen[15,16,19,22,29-33] nucleophiles. A chlorine-atom in *o*-chloronitroimidazoles can be displaced also by iodide[16] or by the sodium salt derived from diethyl malonate.[34] Leonard's group[35] treated 1-benzyl-5-bromo-4-nitroimidazole (**14**) (Scheme 1) with cyanide ion in refluxing methanol and obtained a 56% yield of the nitrile (**15**) and we have confirmed this result. The isomeric 1-benzyl-4-bromo-5-nitroimidazole is surprisingly unreactive under these conditions.[35] Others[15,36] have successfully replaced halogen by cyanide ion from 5-halogeno-4-nitroimidazoles but failed[15] or succeeded only with difficulty[37,38] with the corresponding 4-halogeno-5-nitro isomers. Displacement of both the 4- and 5-substituents from 5-bromo-4-sulphonamidoimidazoles can occur with ethanolic ammonia, depending on the pressure,[39] and both halogen and nitro substituents can be displaced from 4,5-disubstituted imidazoles by secondary amines.[16]

We treated 1-benzyl-5-bromo-4-nitroimidazole (**14**) with ethanethiol, propanethiol, benzenethiol, 2-aminobenzenethiol,



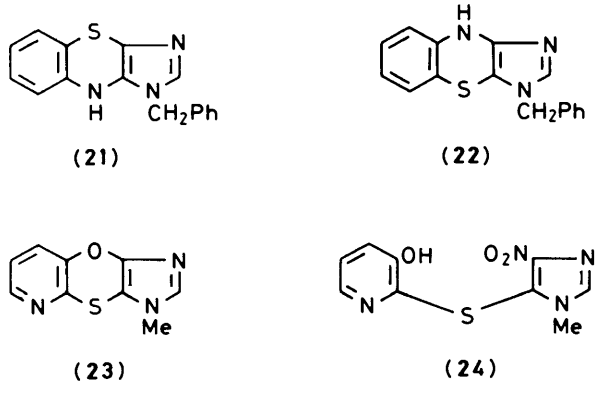
Scheme 1.

and ethyl 2-mercaptoacetate (ethyl thioglycollate) in aqueous ethanol in the presence of base and obtained compounds (**16**) (74%), (**17**) (70%), (**18**) (30%), (**19**) (93%), and (**20**) (59%) (in this case the intermediate ester underwent hydrolysis), respectively, in the yields indicated (Scheme 1).



Scheme 2.

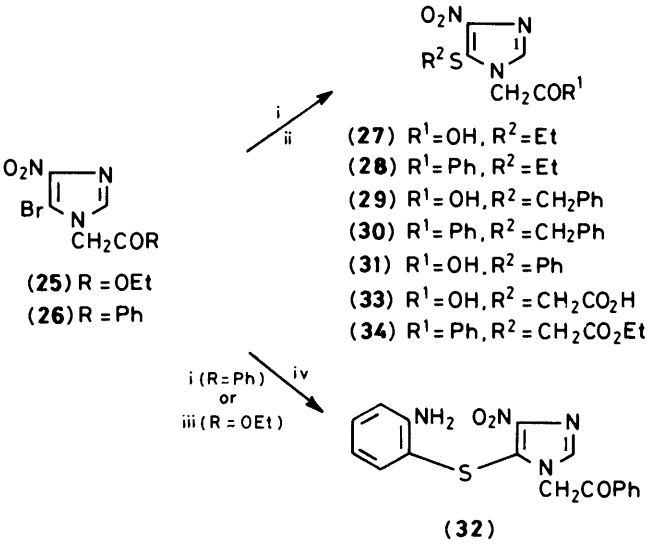
In the hope that the phenothiazine analogue (**21**) could be prepared by the Smiles rearrangement procedure[40] depicted in Scheme 2 we heated compound (**19**) in ethanolic potassium hydroxide. This failed to give the desired compound (**21**), possibly due to a reluctance of the nitro group to undergo nucleophilic displacement in the final step (*cf.* Scheme 2). An attempt to prepare compound (**23**) from 5-chloro-1-methyl-4-nitroimidazole and 3-hydroxypyridine-2(1*H*)-thione has been reported[28] to fail for similar reasons; compound (**24**) was isolated instead. We attempted also to prepare the isomeric phenothiazine analogue (**22**) *via* reductive deoxygenation of



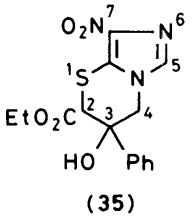
1-benzyl-4-nitro-5-phenylthioimidazole (**18**) with an excess of triethyl phosphite.[41] This reaction gave only an intractable black tar, together with some starting material.

2,4(5)-Dibromo-5(4)-nitroimidazole, 4(5)-bromo-5(4)-nitroimidazole, and 2,5-dibromo-1-methoxymethyl-4-nitroimidazole all failed in our hands to react with potassium cyanide in ethanol in the presence of potassium iodide (*cf.* refs. 15, 35—38). Starting material was recovered in each case.

Several nucleophilic displacement reactions of the nitro group activated bromine atoms in ethyl 2-(5-bromo-4-nitroimidazol-1-yl)acetate (**25**) and 5-bromo-4-nitro-1-phenacylimidazole (**26**) were carried out also and these are summarised in Scheme 3. In the reaction of the latter substrate (**26**) with ethyl 2-mercaptoacetate (ethyl thioglycollate) in ethanol in the presence of base, the intermediate product (**34**) cyclised to give the bicyclic product (**35**) whose structure was assigned on the basis of spectroscopic and other evidence (see the Experimental Section).



Scheme 3. *Reagents:* i, 10% aq. NaOH–EtOH; ii, R^2SH; iii, Na_2CO_3–EtOH; iv, $2\text{-}H_2NC_6H_4SH$



The 1-protected imidazoles required for this work and that described in the following paper, together with 2,4,5-tribromo-1-(2-phenylsulphonylethyl)imidazole, 2-(2,4,5-tribromoimidazol-1-yl)ethyl bromide, and 2,4,5-tribromo-1-vinylimidazole were prepared by treatment of 2,4,5-tribromoimidazole (**CAUTION**: this compound and its 1-protected derivatives that are deprotected *in vivo*, to give 2,4,5-tribromoimidazole, are reported to be neurotoxic[42]), 4(5)-bromo-5(4)-nitroimidazole, or 2,4(5)-dibromo-5(4)-nitroimidazole with either chloromethyl ethyl (or methyl) ether (**CAUTION**: these ethers are considered to be carcinogenic), benzyl chloride, 4-methoxybenzyl chloride, 3,4-dimethoxybenzyl chloride, 2-bromoacetate, phenacyl bromide, 2-phenylsulphonylethyl chloride, or 1,2-dibromoethane (in this case elimination of hydrogen bromide may occur from the initial alkylation product, depending on the reaction

conditions, resulting in the introduction of a vinyl group), respectively, in the presence of base. Interestingly, when 4,5-dibromoimidazole was treated successively with sodium hydride and 1,2-dibromoethane (an excess) in DMF, the product was 2-(2,4,5-tribromoimidazol-1-yl)ethyl bromide. Isolated reports exist in the literature on the capture of bromine from 1,2-dibromoethane.[43]

Previously, 2,4,5-tribromoimidazole has been *N*-alkylated with dialkyl sulphates in acetone in the presence of potassium carbonate.[44] Its treatment with an alkyl chloroacetate under these conditions yields the corresponding alkyl 2,4,5-tribromoimidazole-1-carboxylate.[45] Methyl 2,4,5-tribromoimidazole-1-carboxylate can be prepared also by successive treatment of 2,4,5-tribromoimidazole with sodium hydride and methyl formate.[45] With ethylmagnesium bromide, 2,4,5-tribromoimidazole forms a Grignard compound which reacts with 2,4-dichlorobenzoyl chloride to yield the corresponding *N*-aroylated product.[46] We[1] have alkylated 2,4,5-tribromoimidazole previously through its successive treatment with butyl-lithium and methyl iodide.

The structure of 1-benzyl-5-bromo-4-nitroimidazole (**14**) has been assigned by others[35] and those of 2,5-dibromo-1-methoxymethyl-4-nitroimidazole, ethyl 2-(5-bromo-4-nitroimidazol-1-yl)acetate (**25**), and 5-bromo-4-nitro-1-phenacylimidazole (**26**) are assigned by analogy and through formation of the bicyclic product (**35**) by reaction of the phenacyl compound (**26**) with ethyl 2-mercaptoacetate in the presence of base (see before). To support our assignments 4(5)-nitroimidazole and its *ortho*-substituted derivatives, on alkylation under similar conditions to those used in this work, are known to give either the 1-alkyl-4-nitro isomer exclusively or a mixture of the 1-alkyl-4-nitro and 1-alkyl-5-nitro isomers in which the former predominate.[16,35,37,38,47–53] The relative ease of nucleophilic displacement of halogen from compounds (**25**) and (**26**) (*cf.* refs. 15, 37, 38) is also indicative that they have the structures shown.

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 reported in an earlier paper.[2] All the mass spectra recorded for polyhalogenoimidazoles exhibited the correct isotopic abundance ratios for the type and number of halogens contained in them and the reported molecular weights are for isotopes ^{35}Cl and ^{79}Br unless stated otherwise. Coupling constants that agree with common standard values (*e.g.* for Et groups) are not given unless thought important for structural proofs. Chemical shifts for exchangeable protons are given only when the signals were clearly observable. Reactions at 82 °C were carried out in apparatus surrounded by a heating jacket containing boiling isopropyl alcohol.

2,4,5-Tribromo (and tri-iodo)imidazole, 2,4,5-tribromo-1-ethoxymethylimidazole, 1-ethoxymethyl-4,5-di-iodoimidazole, and 5-bromo-1-methylimidazole were prepared as described by us previously.[4] 1-Benzyl-5-bromo-4-nitroimidazole was prepared by the method of Leonard *et al.*[35] and 2,4(5)-dibromo-5(4)-nitroimidazole and 4(5)-bromo-5(4)-nitroimidazole were prepared by the method of Balaban and Pyman.[54]

2,4,5-*Tribromo*-1-*methoxymethylimidazole* (78%), m.p. 88—90 °C (from ethanol) (lit.,[55] m.p. 92—94 °C); $\delta_H(CDCl_3)$ 3.40 (3 H, s, OMe) and 5.35 (2 H, s, NCH_2); $\delta_C(CDCl_3)$ 56.61 (q, Me), 77.12 (t, CH_2), 105.42 (s, C-5), 117.12 (s, C-4), and 118.82 p.p.m. (s, C-2) (Found: C, 17.3; H, 1.5; N, 7.8%; M^+, 349. $C_5H_5Br_3N_2O$ requires C, 17.2; H, 1.4; N, 8.0%; *M*, 349) and 2,5-*dibromo*-1-*methoxymethyl*-4-*nitroimidazole* (67%), m.p. 95—97 °C (from ethanol); $\delta_H(CDCl_3)$ 3.35 (3 H, s, Me) and 5.53 (2 H, s, NCH_2); $\delta_C(CDCl_3)$ 57.10 (q, Me), 77.64 (t, CH_2), 106.33 (s, C-5), 120.59 (s, C-4), and 120.59 p.p.m.(s, C-2) (Found: C, 19.3; H, 1.7; N, 13.3%; M^+, 313. $C_5H_5Br_2N_3O_3$ requires C, 19.1; H, 1.6; N, 13.3%; *M*, 313) were prepared in a manner similar to that used[4] for the synthesis of 2,4,5-tribromo-1-ethoxymethylimidazole with the exception that column chromatography was not necessary in these cases.

1-*Benzyl*-2,4,5-*tribromoimidazole*.—A stirred mixture of 2,4,5-tribromoimidazole (50.0 g, 0.16 mol), benzyl chloride (20.74 g, 0.16 mol), sodium carbonate (17.37 g, 0.16 mol), and DMF (100 ml) was heated under reflux overnight. The cooled mixture was filtered and the solvent distilled off under reduced pressure. To the residue, water (50 ml) was added and the oil was triturated until solidification occurred. The water was decanted and recrystallisation of the residue from ethanol gave the product (57.0 g, 90%), m.p. 67—68 °C (this compound is reported in a patent,[56] m.p. 68—69 °C); $\delta(CDCl_3)$ 5.28 (2 H, s, NCH_2) and 7.36 (5 H, m, ArH) (Found: C, 30.2; H, 1.7; N, 7.1%; M^+, 392. $C_{10}H_7Br_3N_2$ requires C, 30.4; H, 1.8; N, 7.1%; *M*, 392).

The following compounds were prepared similarly using either 4-methoxybenzyl chloride, 3,4-dimethoxybenzyl chloride, ethyl 2-bromoacetate, or phenacyl chloride as the reagent and either 2,4,5-tribromoimidazole or 4(5)-bromo-5(4)-nitroimidazole as the substrate: 2,4,5-*tribromo*-1-(4-*methoxybenzyl*)-*imidazole* (90%), m.p. 69—70 °C (from ethanol); $\delta(CDCl_3)$ 3.80 (3 H, s, OMe), 5.14 (2 H, s, NCH_2), 6.85 (2 H, d, *J* 8.0 Hz, ArH), and 7.18 (2 H, d, *J* 8.0 Hz, ArH) (Found: C, 30.75; H, 2.1; N, 6.6%; M^+, 422. $C_{11}H_9Br_3N_2O$ requires C, 31.1; H, 2.1; N, 6.6%; *M*, 422): 2,4,5-*tribromo*-1-(3,4-*dimethoxybenzyl*)*imidazole* (60%), m.p. 122—124 °C (from ethyl acetate); $\delta(CDCl_3)$ 3.90 (6 H, s, 2 × OMe), 5.15 (2 H, s, NCH_2), and 6.78 (3 H, s, ArH) (Found: C, 31.5; H, 2.45; N, 6.2%; M^+, 452. $C_{12}H_{11}Br_3N_2O_2$ requires C, 31.7; H, 2.4; N, 6.2%; *M*, 452) (after distillation of the DMF, water was added to the residue and the product was extracted with chloroform prior to its trituration with ethanol): *ethyl* 2-(2,4,5-*tribromoimidazol*-1-*yl*)*acetate* (90%), m.p. 93—94 °C (from ethanol); $\nu_{max.}$ 1 740 cm^{-1} (CO); $\delta(CDCl_3)$ 1.36 (3 H, t, Me), 4.42 (2 H, q, OCH_2), and 4.92 (2 H, s, NCH_2) (Found: C, 21.7; H, 1.8; N, 7.25%; M^+, 388. $C_7H_7Br_3N_2O_2$ requires C, 21.5; H, 1.8; N, 7.2%; *M*, 388): *ethyl* 2-(5-*bromo*-4-*nitroimidazol*-1-*yl*)*acetate* (**25**) (70%), m.p. 104—106 °C (from ethanol); $\nu_{max.}$ 1 740 cm^{-1} (CO); $\delta(CDCl_3)$ 1.34 (3 H, t, Me), 4.30 (2 H, q, CH_2), 4.88 (2 H, s, NCH_2), and 7.72 (1 H, s, 2-H) (Found: C, 30.3; H, 3.0; N, 15.2%; M^+, 277. $C_7H_8BrN_3O_4$ requires C, 30.2; H, 2.9; N, 15.1%; *M*, 277): 2,4,5-*tribromo*-1-*phenacylimidazole* (92%), m.p. 157—158 °C (from dioxane); $\nu_{max.}$ 1 690 cm^{-1} (CO); $\delta(CDCl_3)$ 5.48 (2 H, s, NCH_2) and 7.60—8.10 (5 H, m, ArH) (Found: C, 31.3; H, 1.7; N, 6.7%; M^+, 420. $C_{11}H_7Br_3N_2O$ requires C, 31.2; H, 1.7; N, 6.6%; *M*, 420): and 5-*bromo*-4-*nitro*-1-*phenacylimidazole* (**26**) (72%), m.p. 158—160 °C (from ethanol); $\nu_{max.}$ 1 680 cm^{-1} (CO): $\delta[CDCl_3$-$(CD_3)_2SO]$ 5.75 (2 H, s, NCH_2) and 7.45—8.16 (6 H, m, ArH) (Found: C, 42.9: H, 2.7; N, 13.3%; M^+, 309. $C_{11}H_8BrN_3O_3$ requires C, 42.6; H, 2.6; N, 13.55%; *M*, 309).

2,4,5-*Tribromo*-1-(2-*phenylsulphonylethyl*)*imidazole*.—2,4,5-Tribromoimidazole (10.0 g, 32.78 mmol) was added portionwise to a stirred suspension of 60% sodium hydride in mineral oil (1.31 g, 32.78 mmol) in anhydrous DMF (50 ml) under nitrogen at ambient temperature. 1 Hour after the addition, 2-phenylsulphonylethyl chloride (6.70 g, 32.78 mmol) was added and the mixture was heated under reflux overnight. The solvent was distilled off under reduced pressure, water (50 ml) was added to the residue, and extraction of the product with ethyl acetate gave a light brown oil which solidified on trituration with ether. Recrystallisation of the solid from ethanol gave the *product* (5.82 g, 37.5%), m.p. 139—140 °C; $\delta(CDCl_3)$ 3.45—3.70 (2 H, m, CH_2), 4.30—4.50 (2 H, m, CH_2), and 7.45—8.00 (5 H,

m, ArH) (Found: C, 28.1; H, 1.9; N, 6.1%; M^+, 470. $C_{11}H_9Br_3N_2O_2S$ requires C, 27.9; H, 1.9; N, 5.9%; M, 470).

2-(2,4,5-*Tribromoimidazol*-1-*yl*)*ethyl bromide*. This was prepared similarly both from 4,5-dibromoimidazole [66% yield; 2 mol equiv. of $Br(CH_2)_2Br$ used; mixture stirred 30 min at ambient temperature, then at 100 °C for 2 h prior to work-up as described in the preceding experiment; addition of water gave a precipitate which was filtered off] and 2,4,5-tribromoimidazole (84.5% yield), m.p. 146—148 °C (from ethanol); δ($CDCl_3$) 3.60 (2 H, t, CH_2) and 4.48 (2 H, t, NCH_2) (Found: C, 14.85; H, 1.0; N, 6.8%; M^+, 408. $C_5H_4Br_4N_2$ requires C, 14.6; H, 1.0; N, 6.8%; M, 408).

2,4,5-*Tribromo*-1-*vinylimidazole*.—50% Aqueous sodium hydroxide (30 ml) was added to a stirred solution of 2,4,5-tribromoimidazole (10.0 g, 32.78 mmol) and tetrabutylammonium bromide (10.5 g, 32.78 mmol) in 1,2-dibromoethane (30 ml) at 0 °C and the mixture heated under reflux with vigorous stirring for 2—3 h. The cooled mixture was diluted with water (50 ml) and extracted with methylene dichloride. The extracts were combined, washed successively with 10% hydrochloric acid and water, dried ($MgSO_4$), and evaporated under reduced pressure to give the *product* (9.1 g, 84%), b.p. 108—110 °C at 0.5 mmHg (Kugelrohr single path distillation), m.p. 34—35 °C; $\nu_{max.}$ 1 640 cm^{-1} (C=C); δ($CDCl_3$) 5.56 (1 H, dd, J 8 Hz), 5.76 (1 H, dd, J 20 Hz), and 6.75 (1 H, dd, J 8 Hz, 20 Hz) (vinylic H) (Found: C, 18.2; H, 0.95; N, 8.74%; M^+, 328. $C_5H_3Br_3N_2$ requires C, 18.15; H, 0.9; N, 8.7%; M, 328).

Reaction of 2,4,5-*Tribromo* (*and tri-iodo*)*imidazole with Sodium Benzenethiolate*.—(*a*) A mixture of 2,4,5-tribromoimidazole (1.5 g, 4.9 mmol) and sodium benzenethiolate (0.7 g, 5.3 mmol) in isopropyl alcohol (30 ml) was heated under reflux under nitrogen for 4 h after which it was cooled, the solvent removed, and water (15 ml) added. Extraction with chloroform (4 × 20 ml) gave a solid (1.0 g) which was chromatographed on alumina. Light petroleum eluted diphenyl disulphide (0.2 g) and ethyl acetate eluted 4,5-dibromoimidazole (**1**) (0.75 g, 68%), m.p. 224 °C (from aqueous methanol) (lit., m.p. 225 °C[54] and 228 °C[57]). Ethanol eluted starting material.

(*b*) A similar reaction of 2,4,5-tri-iodoimidazole (1.0 g, 2.2 mmol) gave 4,5-di-iodoimidazole (**2**) (90%) (isolated without chromatography), m.p. 190—191 °C (from acetone) (lit., m.p. 197—198 °C[58] and 180 °C[59]); δ[$(CD_3)_2SO$] 7.30 (1 H, br s, exchangeable, NH) and 7.80 (1 H, s, 2-H).

1-*Benzyl*-4,5-*dibromo*-2-*phenylthioimidazole* (**3**).—Benzenethiol (1.4 g, 12.6 mmol) was added to a stirred solution of sodium isopropoxide (1.03 g, 12.6 mmol) in dry isopropyl alcohol (50 ml) at ambient temperature. After 30 min 1-benzyl-2,4,5-tribromoimidazole (5.0 g, 12.6 mmol) was added and the mixture was heated under reflux for 4—5 h. The solvent was removed under reduced pressure, water (50 ml) was added to the residue, and the product was extracted with chloroform. The extracts were combined, washed successively with 10% aqueous sodium hydroxide and water, then dried ($MgSO_4$), and evaporated to give a pale-yellow oil, which was chromatographed on alumina. Light petroleum–ethyl acetate eluted the title compound (**3**) (2.9 g, 54%); δ($CDCl_3$) 5.16 (2 H, s, NCH_2) and 6.90—7.40 (10 H, m, ArH) (Found: M, 422. $C_{16}H_{12}Br_2N_2S$ requires M^+, 422).*

The following compounds were prepared similarly: 1-*benzyl*-2-*benzylthio*-4,5-*dibromoimidazole* (**4**) (58%), a colourless oil; δ($CDCl_3$) 4.18 (2 H, s, SCH_2), 4.90 (s, 2 H, NCH_2), and 6.80—7.50 (10 H, m, ArH) (Found: C, 46.5; H, 3.2; N, 6.4%; M^+, 436. $C_{17}H_{14}Br_2N_2S$ requires C, 46.6; H, 3.2; N, 6.4%; M, 436): 4,5-*dibromo*-2-*ethylthio*-1-*methoxymethylimidazole* (**5**) (59%), colourless oil; δ($CDCl_3$) 1.33 (3 H, t, Me), 3.16 (2 H, q, SCH_2), 3.33 (3 H, s, OMe), and 5.25 (2 H, s, NCH_2) (Found: M^+, 328. $C_7H_{10}Br_2N_2OS$ requires M, 328): 4,5-*dibromo*-1-*methoxymethyl*-2-*propylthioimidazole* (**6**) (60%), pale-yellow oil; δ($CDCl_3$) 1.00 (3 H, t, Me), 1.66 (2 H, m, CH_2), 3.10 (2 H, t, CH_2), 3.31 (3 H, s, OMe), and 5.25 (2 H, s, NCH_2) (M^+, 345.9105. $C_8H_{12}Br_2N_2OS$ requires M, 345.8999):† 2-*benzylthio*-4,5-*dibromo*-1-*methoxymethylimidazole* (**7**) (62%), an oil; δ($CDCl_3$) 3.20 (3 H, s, OMe), 4.26 (2 H, s, SCH_2), 5.00 (2 H, s, NCH_2), and 7.26 (5 H, m, ArH) (Found: C, 36.85; H, 3.2; N, 7.2%; M^+, 390. $C_{12}H_{12}Br_2N_2OS$ requires C, 37.65; H, 3.1; N, 7.1%; M, 390): and 4,5-*dibromo*-1-*methoxymethyl*-2-*phenylthioimidazole* (**8**) (64%), a pale-yellow oil; δ($CDCl_3$) 3.22 (3 H, s, OMe), 5.30 (2 H, s, CH_2), and 7.26 (5 H, m, ArH) (Found: M^+, 376. $C_{11}H_{10}Br_2N_2OS$ requires M, 376).*

4,5-*Dibromo*-1-*ethoxymethyl*-2-*methylthioimidazole* (**9**).—A stirred mixture of 2,4,5-tribromo-1-ethoxymethylimidazole (0.5 g, 1.38 mmol) and sodium methanethiolate (0.1 g, 1.40 mmol) in HMPA (25 ml) was heated at 82 °C for 16 h and then cooled and poured into saturated brine. Extraction of the product with chloroform (3 × 20 ml) gave an oil which was chromatographed on alumina. Light petroleum–ethyl acetate (ratio 9:1) eluted the *product* (**9**) (0.2 g, 44%) as an oil; δ($CDCl_3$) 1.20 (3 H, t, Me), 2.60 (3 H, s, SMe), 3.53 (2 H, q, OCH_2), and 5.30 (2 H, s, NCH_2) (Found: C, 25.5; H, 3.0; N, 8.5%; M^+, 328. $C_7H_{10}Br_2N_2OS$ requires C, 25.5; H, 3.05; N, 8.5%; M, 328).

4,5-*Dibromo*-1-*ethoxymethyl*-2-*isopropoxyimidazole* (**13**).—2,4,5-Tribromo-1-ethoxymethylimidazole (0.5 g, 1.38 mmol) was added to a stirred solution of sodium isopropoxide (0.113 g, 1.38 mmol) in isopropyl alcohol (20 ml) and the mixture was heated under reflux for 3 days. Work-up as described before gave a bright yellow oil which was chromatographed on alumina. Light petroleum eluted the *product* (**13**) (0.23 g, 63% based on starting material consumed) as a clear, colourless oil; δ_H($CDCl_3$) 1.19 (3 H, t, $CH_2OCH_2CH_3$), 1.33 (3 H, s, Me), 1.40 (3 H, s, Me), 3.52 (2 H, q, OCH_2), and 5.12 (3 H, m, NCH_2 and OCH together); δ_C($CDCl_3$) 151.39 (s, C-2), 111.78 (s, C-4), 96.88 (s, C-5), 74.06 (d, CH), 72.12 (t, NCH_2), 64.29 (t, OCH_2), 21.76 (q, Me), and 14.60 p.p.m. (q, $CH_2OCH_2CH_3$) (Found: M^+, 341.9403. $C_9H_{14}Br_2N_2O_2$ requires M, 341.9399)† and starting material (0.11 g, 22% recovery).

Ethyl 2-(4,5-*Dibromo*-2-*phenylthioimidazol*-1-*yl*)*acetate* (**10**).—Benzenethiol (1.96 g, 17.9 mmol) in dry DMF (10 ml) was added dropwise to a stirred suspension of 60% sodium hydride in mineral oil (0.72 g, 17.9 mmol) in dry DMF (30 ml) under nitrogen and the mixture was stirred for 30 min at ambient temperature. Then ethyl 2-(2,4,5-tribromoimidazol-1-yl)acetate (7.0 g, 17.9 mmol) was added portionwise and the mixture was heated under reflux for 4 h following the addition. The solvent was removed under reduced pressure, water (30 ml) was added to the residue, and the product was extracted with chloroform. The extracts were combined, washed successsively with 10% aqueous sodium hydroxide and water, dried ($MgSO_4$), and evaporated to leave a pale-yellow oil which solidified to give the *product* (**10**) (4.25 g, 56%), m.p. 73—74 °C (from ethanol); $\nu_{max.}$ 1 735 cm^{-1} (CO); δ($CDCl_3$) 1.20 (3 H, t, Me), 4.15 (2 H, q, CH_2), 5.00 (2 H, s, NCH_2), and 7.50 (5 H, m, ArH) (Found: C, 37.6; H, 3.0; N, 6.7%; M^+, 418. $C_{13}H_{12}Br_2N_2O_2S$ requires C, 37.2; H, 2.9; N, 6.7%; M, 418).

* These compounds produced one spot on t.l.c.; they were converted into 4-bromoimidazole-5-carbaldehydes, which were fully characterised, as described in the following paper.

† M^+ for ^{81}Br measured in this case.

2-(4,5-*Dibromo*-2-*phenylthioimidazol*-1-*yl*)*acetic Acid* (**11**).—A mixture of the ester (**10**) (1.5 g, 3.57 mmol) and 10% aqueous sodium hydroxide (3 5. g NaOH in 25 ml of water) was heated under reflux for 30 min. It was then cooled and acidified with 10% hydrochloric acid, to give a precipitate which was filtered off, washed with water, and recrystallised from ethanol to give the *acid* (**11**)(1.15 g, 83%), m.p. 187—188 °C; $\nu_{max.}$ 1 710 cm^{-1} (CO) (Found: C, 33.6; H, 2.1; N, 7.1%; M^+, 390. $C_{11}H_8Br_2N_2O_2S$ requires C, 33.7; H, 2.05; N, 7.1%; *M*, 390).

2-*Benzylthio*-4,5-*dibromo*-1-*phenylacylimidazole* (**12**).—Benzenethiol (3.90 g, 35.46 mmol) in dry DMF (15 ml) was added dropwise to a stirred suspension of 60% sodium hydride in mineral oil (1.42 g, 35.46 mmol) in dry DMF (50 ml) at ambient temperature and the resulting mixture was stirred for 30 min. 2,4,5-Tribromo-1-phenacylimidazole (15.0 g, 35.46 mmol) was added portionwise after which the mixture was heated under reflux for 3—4 h. The solvent was distilled off under reduced pressure, water (100 ml) was added to the residue, and the product was extracted with chloroform. The extracts were combined, washed successively with 10% aqueous sodium hydroxide and water, dried ($MgSO_4$), and evaporated to give an oil which solidified on trituration with light petroleum, to give the *product* (**12**) (10.1 g, 61%), m.p. 100—102 °C (from methanol); $\nu_{max.}$ 1 685 cm^{-1} (CO); δ($CDCl_3$) 4.12 (2 H, s, SCH_2), 5.10 (s, 2 H, NCH_2), and 7.10—8.00 (10 H, m, ArH) (Found: C, 46.2; H, 3.0; N, 6.15%; M^+, 464. $C_{18}H_{14}Br_2N_2OS$ requires C, 46.4; H, 3.0; N, 6.0%; *M*, 464).

1-*Benzyl*-5-*ethylthio*-4-*nitroimidazole*(**16**).—Ethanethiol(1.54 g, 24.82 mmol) in ethanol (10 ml) was added dropwise at ambient temperature to a stirred suspension of 1-benzyl-5-bromo-4-nitroimidazole (**14**) (7.0 g, 24.82 mmol) in ethanol (50 ml) containing 10% aqueous sodium hydroxide (10 ml). The clear solution was stirred for a further 15 min, after which the precipitate that had formed was filtered off and recrystallised from ethanol, to give the *product* (**16**) (4.83 g, 74%), m.p. 123—124 °C; δ($CDCl_3$) 1.40 (3 H, t, Me), 3.20 (2 H, q, CH_2), 5.45 (2 H, s, NCH_2), 7.25 (5 H, m, ArH), and 7.60 (1 H, s, 2-H) (Found: M^+, 263.0720. $C_{12}H_{13}N_3O_2S$ requires *M*, 263.0728) (CHN analysis difficult because of poor combustibility).

The following compounds were prepared similarly (time of stirring after addition for precipitate to appear given in parentheses): 1-*benzyl*-4-*nitro*-5-*propylthioimidazole* (**17**) (70%) (30 min), m.p. 73—74 °C (from ethanol); δ($CDCl_3$) 0.95 (3 H, t, Me), 1.50 (2 H, m, CH_2), 2.90 (2 H, t, SCH_2), 5.45 (2 H, s, NCH_2), 7.20—7.70 (5 H, m, ArH), and 7.75 (1 H, s, 2-H) (Found: C, 56.1; H, 5.5; N, 15.2%; M^+, 277. $C_{13}H_{15}N_3O_2S$ requires C, 56.3; H, 5.45; N, 15.15%; *M*, 277): 1-*benzyl*-4-*nitro*-5-*phenylthioimidazole* (**18**) (30%) (instant precipitation), m.p. 127—128 °C (from methanol); δ($CDCl_3$) 5.40 (2 H, s, NCH_2) and 6.90—7.80 (11 H, m, ArH) (Found: C, 61.8; H, 4.0; N, 13.5%; M^+, 311.0728. $C_{16}H_{13}N_3O_2S$ requires C, 61.7; H, 4.2; N, 13.5%; *M*, 311.0723): 5-(2-*aminophenylthio*)-1-*benzyl*-4-*nitroimidazole* (**19**) (95%) (instant precipitation), m.p. 132—133 °C (from ethanol); $\nu_{max.}$ 3 350 and 3 450 cm^{-1} (NH_2); δ($CDCl_3$) 4.45 (2 H, s, exchangeable, NH_2), 5.25 (2 H, s, NCH_2) and 6.60—7.60 (10 H, m, ArH) (Found: C, 58.7; H, 4.2; N, 17.2%; M^+, 326. $C_{16}H_{14}N_4O_2S$ requires C, 58.9; H, 4.3; N, 17.2%; *M*, 326): and 2-(1-*benzyl*-4-*nitroimidazol*-5-*ylthio*)*acetic acid* (**20**) (59%) (30 min; the mixture was acidified by addition of 10% hydrochloric acid prior to work-up in the standard way), m.p. 153.5—154.5 °C (from ethanol); $\nu_{max.}$ 1 725 cm^{-1} (CO); δ[$(CD_3)_2SO$] 3.50 (1 H, br s, exchangeable, OH), 4.00 (2 H, s, SCH_2), 5.80 (2 H, s, NCH_2), 7.50—7.90 (5 H, m, ArH), and 8.60 (1 H, s, 2-H) (Found: C, 49.0; H, 3.9: N, 14.5%; M^+, 293. $C_{12}H_{11}N_3O_4S$ requires C, 49.1; H, 3.8; N, 14.3%; *M*, 293): 2-(5-*ethylthio*-4-*nitroimidazol*-1-*yl*)*acetic acid* (**27**) (71%) (1 h; after the precipitate appeared it was dissolved in water and the solution was acidified with 10% hydrochloric acid to give the product), m.p. 166—168 °C (from ethanol–light petroleum); $\nu_{max.}$ 1 710 (CO) and 3 450 cm^{-1} (OH); δ[$CDCl_3$–$(CD_3)_2SO$] 1.25 (3 H, t, Me), 3.00 (2 H, q, SCH_2), 5.15 (2 H, s, NCH_2), 6.30 (1 H, s, exchangeable, OH), and 8.20 (1 H, s, 2-H) (Found: C, 36.3; H, 3.85; N, 18.2%; M^+, 231. $C_7H_9N_3O_4$ requires C, 36.4; H, 3.9; N, 18.2%; *M*, 231): 2-(5-*benzylthio*-4-*nitroimidazol*-1-*yl*)*acetic acid* (**29**) (82%) (15 min; the precipitate was filtered off and dissolved in water whereupon acidification of this solution with 10% hydrochloric acid, gave the product), m.p. 215—216 °C (from ethanol); $\nu_{max.}$ 1 725 cm^{-1} (CO); δ[$(CD_3)_2SO$] 4.30 (2 H, s, SCH_2), 4.80 (2 H, s, NCH_2), 7.20—7.60 (5 H, m, ArH), and 8.20 (1 H, s, 2-H) (Found: C, 49.1; H, 3.7; N, 14.4%; M^+, 293. $C_{12}H_{11}N_3O_4S$ requires C, 49.1; H, 3.8; N, 14.3%; *M*, 293): 2-(4-*nitro*-5-*phenylthioimidazol*-1-*yl*)*acetic acid* (**31**) (70%) (30 min; the precipitate was dissolved in water and acidification of this solution with 10% hydrochloric acid gave the product), m.p. 173—174 °C (from ethanol); $\nu_{max.}$ 1 690 (CO) and 3 425 cm^{-1} (OH); δ[$CDCl_3$–$(CD_3)_2SO$] 4.85 (2 H, s, NCH_2), 6.25 (1 H, s, exchangeable, OH), 7.25 (5 H, s, ArH), and 7.80 (1 H, s, 2-H) (Found: C, 44.4; H, 3.7; N, 14.5%; M^+. 279. $C_{11}H_9N_3O_4S{\cdot}H_2O$ requires C, 44.4; H, 3.75; N, 14.1%; *M*, 279): 2-(1-*carboxymethyl*-4-*nitroimidazol*-5-*ylthio*)*acetic acid* (**33**) (70%) [1 h; the solvent was removed under reduced pressure, water (30 ml) was added to the residue followed by 10% hydrochloric acid, and the acidified solution was left overnight whereupon the product crystallised out as a white solid], m.p. >238 °C (with decomp.) (from water); $\nu_{max.}$ 1 660 and 1 740 cm^{-1} (CO); δ[$(CD_3)_2SO$] 3.75 (2 H, s, SCH_2), 5.10 (2 H, s, NCH_2), and 8.00 (1 H, s, 2-H) (Found: C, 32.7; H, 2.8; N, 15.8%; $[M + 1]^+$, 262.0130. $C_7H_7N_3O_6S$ requires C, 32.2; H, 2.7; N, 16.1%; $[M + 1]$, 262.0134): 5-*ethylthio*-4-*nitro*-1-*phenacylimidazole* (**28**) (79%) [1 h; the solvent was distilled off under reduced pressure, water (30 ml) was added to the residue, and the resulting solid was filtered off], m.p. 106.5—107.5 °C (from aqueous ethanol); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ($CDCl_3$) 1.15 (3 H, t, Me), 2.98 (2 H, q, CH_2), 5.60 (2 H, s, NCH_2), and 7.50—8.20 p.p.m. (6 H, m, ArH) (Found: C, 53.6; H, 4.5; N, 14.6%; M^+, 291. $C_{13}H_{13}N_3O_3S$ requires C, 53.6; H, 4.5; N, 14.4%; *M*, 291): 5-*benzylthio*-4-*nitro*-1-*phenacylimidazole* (**30**) (81%) (30 min), m.p. 151—152 °C (from ethanol); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ($CDCl_3$) 4.10 (2 H, s, SCH_2), 5.05 (2 H, s, NCH_2), and 7.00—7.80 (11 H, m, ArH) (Found: C, 61.0; H, 4.3; N, 12.2%; M^+, 353. $C_{18}H_{15}N_3O_3S$ requires C, 61.2; H, 4.3; N, 11.9%; *M*, 353): and 5-(2-*aminophenylthio*)-4-*nitro*-1-*phenacylimidazole* (**32**) (94%) (instant precipitate), m.p. >177 °C (with decomp.) (from ethyl acetate); $\nu_{max.}$ 3 340 and 3 445 (NH_2) and 1 690 cm^{-1} (CO); δ[$(CD_3)_2SO$] 5.36 (2 H, s, exchangeable, NH_2), 5.75 (2 H, s, NCH_2), and 6.30—8.00 (10 H, m, ArH) (Found: C, 57.4; H, 3.9; N, 16.05%; M^+, 354. $C_{17}H_{14}N_4O_3S$ requires C, 57.6; H, 3.9; N, 15.8%; *M*, 354).

Reaction of 5-*Bromo*-4-*nitro*-1-*phenacylimidazole* (**26**) *with Ethyl* 2-*Mercaptoacetate*.—Ethyl 2-mercaptoactate (ethyl thioglycollate) (0.8 g, 6.70 mmol) in ethanol (10 ml) was added dropwise at ambient temperature to a stirred suspension of 5-bromo-4-nitro-1-phenacylimidazole (**26**) (2.0 g, 6.45 mmol) in ethanol (30 ml) containing 10% aqueous sodium hydroxide (2.7 ml, 6.75 mmol), and the resulting mixture was stirred at this temperature for 1 h. The solvent was then removed under reduced pressure, water (30 ml), was added to the residue, and the resulting solution was acidified with 10% hydrochloric acid to give a precipitate which was filtered off and recrystallised from dioxane, to give *ethyl* 3-*hydroxy*-7-*nitro*-3-*phenylimidazo*[5,1-b]*thiazine*-2-*carboxylate* (**35**) (1.35 g, 60%), m.p. 202—204 °C; $\nu_{max.}$ 1 720 (CO) and 3 250 cm^{-1} (OH); δ[$(CD_3)_2SO$] 0.88 (3 H, t, Me), 3.95 (2 H, q, CH_2), 4.34 (1 H, s, 2-H), 4.50 (1 H, d, 4-H), 5.05 (1 H, d, 4-H), 6.60 (1 H, br s,

exchangeable, OH), 7.34—7.70 (5 H, m, ArH), and 8.05 (1 H, s, 5-H) (Found: C, 51.2; H, 4.2; N, 12.2%; M^+, 349. $C_{15}H_{15}N_3O_5S$ requires C, 51.6; H, 4.3; N, 12.0%; M, 349).

Attempted Smiles Rearrangement and Cyclisation of 5-(2-*Aminophenylthio*)-1-*benzyl*-4-*nitroimidazole* (**19**).—To a stirred suspension of the title compound (2.0 g, 6.13 mmol) in ethanol (30 ml) was added sodium hydroxide (0.25 g, 6.25 mmol) in ethanol (15 ml) and the resulting mixture was heated under reflux for 6 h. The solvent was distilled off under reduced pressure and water (30 ml) was added to the residue. The residual solid was identified as starting material (1.6 g, 80% recovery).

Attempted Cyclisation of 1-*Benzyl*-4-*nitro*-5-*phenylthioimidazole* (**18**).—A mixture of the title compound (3.0 g, 9.64 mmol) and triethyl phosphite (4.8 g, 28.94 mmol) was heated under reflux for 8 h. The excess of the reagent was removed under reduced pressure and the residue chromatographed on alumina. Chloroform eluted starting material (0.4 g, 13% recovery) and ethyl acetate eluted an intractable tar.

Attempted Nucleophilic Substitution of Bromine in 2,5-*Dibromo*-1-*methoxymethyl*-4-*nitroimidazole with Cyanide Ion.*—To a stirred suspension of the title compound (4.0 g, 12.69 mmol) in methanol (100 ml) potassium cyanide (3.3 g, 50.79 mmol) and potassium iodide (1.0 g) were added and the resulting mixture was heated under reflux for 6 h. Work-up by standard procedures gave only starting material (100% recovery).

4(5)-Bromo-5(4)-nitroimidazole and 2,4(5)-dibromo-5(4)-nitroimidazole similarly failed to react with cyanide under these conditions; a high yield of starting material was recovered in each case.

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