Azoles. Part 5.[1,2] Metal-Halogen Exchange Reactions of Polybromoimidazoles

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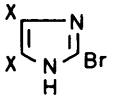
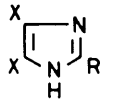
1,2-Dilithiated imidazoles were prepared by treating 2-bromo-4,5-dichloro- and 2,4,5-tribromoimidazole with 2 equivalents of butyl-lithium and trapped with various electrophiles to give moderate yields of the 2-substituted 4,5-dihalogeno compounds (**4**)—(**10**). The 4,5-dibromoimidazole (**4**), prepared in this way, was converted into the 1-protected derivatives (**18**)—(**22**) (protecting group = $CH_2CH_2SO_2Ph$, CH_2CO_2Et, CPh_3, SO_2Ph, $SO_2C_6H_4Me$-4). 4-Bromo-5-chloro-1-tritylimidazole was prepared similarly. Successive treatment of 4,5-dibromoimidazole with 2 equivalents of butyl-lithium, benzophenone, and acid gave a low yield of 4(5)-bromoimidazol-5(4)-yldiphenylmethanol (**11**). Whereas 1-protected 2,4,5-tribromoimidazoles [P = CH_2OMe, CH_2OEt, CH_2Ph, $CH_2C_6H_4OMe$-4, $CH_2C_6H_3(OMe)_2$-3,4] reacted at both the 2- and 5-bromine atoms with 1 equivalent of butyl-lithium, they reacted with 1 equivalent of other organometallic reagents (EtMgBr, MeLi, s-BuLi, PhLi) regioselectively at the 2-position and the intermediate organometallic compounds were either hydrolysed or quenched with benzophenone, to give the corresponding 1-protected 4,5-dibromoimidazoles (**13**)—(**17**) and compound (**25**), respectively, in good yields. Compounds (**13**)—(**17**) were treated with a further equivalent of butyl-lithium and the resulting imidazol-5-yl-lithium derivatives were either quenched with an electrophile or hydrolysed with water; *e.g.* 1-benzyl-4-bromoimidazol-5-yl-lithium was treated with dimethylformamide (DMF), carbon dioxide, methyl chloroformate, and elemental sulphur to give compounds (**33**)—(**36**), respectively. Other 1-protected 4-bromoimidazole-5-carbaldehydes, (**31**), (**32**), and (**37**)—(**40**) were prepared similarly from the corresponding 4,5-dibromoimidazole.

A decade (1928—1938) elapsed between the first report[3] on lithiation and the first reports[4,5] on halogen-metal exchange reactions involving organolithium reagents. Halogen-metal exchange only became important as a useful synthetic technique following a report[6] in 1970 which showed the importance of extremely low temperatures, thus enabling reactions to be carried out on bromoaromatic compounds carrying functional groups (*e.g.* NO_2, CN, *etc.*) that are reactive towards organolithium reagents at higher temperatures. However, despite considerable interest during the last decade in lithiation reactions, halogen-metal exchange reactions have been neglected by comparison.[7] This is probably due to the fact that the latter reactions involve an extra step, namely bromination of the parent system. We have embarked on a study of the halogen-metal exchange reactions of poly- and per-bromoaromatic compounds which are readily available by elemental bromination of commercially available starting materials, and we have shown that considerable advantages can be gained by employing our strategies which far outweigh this disadvantageous extra step. The first system which we have studied is 2,4,5-tribromoimidazole (**1**) (**CAUTION**: this compound and its 1-protected derivatives that can be deprotected *in vivo* to give 2,4,5-tribromoimidazole are reported to be neurotoxic[8]) on which we have reported some preliminary observations previously.[2,9]

From a review[10] of the literature our attention was drawn to the synthesis[11] of several methanols (**3**) *via* treatment of 2-bromo-4,5-dichloroimidazole (**2**) with 2 mol equiv. of butyl-lithium [in tetrahydrofuran (THF) at −78 °C] followed by addition of the appropriate aromatic aldehyde. We have extended this approach to the synthesis of compounds (**6**) (52%), (**8**) (48%), and (**10**) (42%). The butyl group is introduced into compound (**10**) *via* reaction of the intermediate thiolate anion with the butyl bromide produced by the initial halogen-metal exchange reaction. Having established, partially, the scope of these reactions, we next turned our attention to 2,4,5-tribromoimidazole (**1**) in order to establish the possibility of stepwise exchange of the three bromine atoms in this compound using halogen-metal exchange strategies.



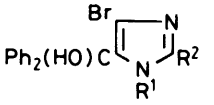
(**1**) X = Br
(**2**) X = Cl



	X	R
(**3**)	Cl	CH(OH)Ar
(**4**)	Br	H
(**5**)	Br	CHO
(**6**)	Cl	CHO
(**7**)	Br	CO_2H
(**8**)	Cl	CO_2H
(**9**)	Br	SBu
(**10**)	Cl	SBu

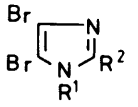
Treatment of 2,4,5-tribromoimidazole (**1**) with 2 mol equiv. of butyl-lithium (in THF at −78 °C) followed by addition of either 10% hydrochloric acid, DMF, carbon dioxide, or elemental sulphur gave moderate yields of compounds (**4**) (40%), (**5**) (43%), (**7**) (57%), and (**9**) (40%), respectively. A better yield (67%) of the dibromo compound (**4**) was obtained by successive treatment of the tribromo compound (**1**) with ethylmagnesium bromide (in THF) and 10% hydrochloric acid. This is probably the most convenient method for preparing this simple imidazole reported to date. Patents[12] describe its synthesis in 63% yield by debromination of 2,4,5-tribromoimidazole with triphenylphosphine but in our hands this reaction gave only a 25% yield of the dibromo compound (**4**).

Further treatment of this dibromo compound (**4**) with 2 mol equiv. of butyl-lithium (in THF at −78 °C) followed by quenching of the intermediate 1,5-dilithiated imidazole with benzophenone and work-up in the usual way gave only a 17%



(11) $R^1 = R^2 = H$

(12) $R^1 = CH_2OMe$, $R^2 = SPh$



(13) $R^1 = CH_2Ph$, $R^2 = H$

(14) $R^1 = CH_2OMe$, $R^2 = H$

(15) $R^1 = CH_2OEt$, $R^2 = H$

(16) $R^1 = CH_2C_6H_4OMe\text{-}4$, $R^2 = H$

(17) $R^1 = CH_2C_6H_3(OMe)_2\text{-}3,4$, $R^2 = H$

(18) $R^1 = CPh_3$, $R^2 = H$

(19) $R^1 = CH_2CO_2Et$, $R^2 = H$

(20) $R^1 = CH_2CH_2SO_2Ph$, $R^2 = H$

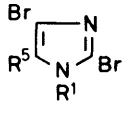
(21) $R^1 = SO_2Ph$, $R^2 = H$

(22) $R^1 = SO_2C_6H_4Me\text{-}4$, $R^2 = H$

(23) $R^1 = CH_2Ph$, $R^2 = SMe$

(24) $R^1 = CH_2OMe$, $R^2 = SMe$

(25) $R^1 = CH_2C_6H_4OMe\text{-}4$, $R^2 = C(OH)Ph$

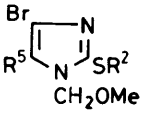


(26) $R^1 = CH_2Ph$, $R^5 = H$

(27) $R^1 = CH_2OMe$, $R^5 = H$

(28) $R^1 = CH_2Ph$, $R^5 = SMe$

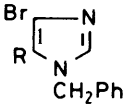
(29) $R^1 = CH_2OMe$, $R^5 = SMe$



(30) $R^2 = CH_2Ph$, $R^5 = H$

(31) $R^2 = CH_2Ph$, $R^5 = CHO$

(32) $R^2 = Ph$, $R^5 = CHO$

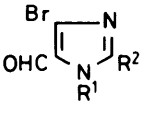


(33) R = CHO

(34) R = CO_2H

(35) R = CO_2Me

(36) R = SH



(37) $R^1 = CH_2Ph$, $R^2 = SCH_2Ph$

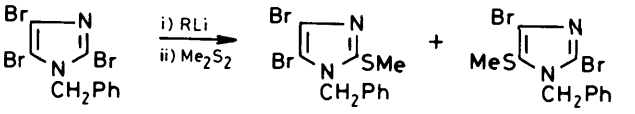
(38) $R^1 = CH_2Ph$, $R^2 = SPh$

(39) $R^1 = CH_2C_6H_4OMe\text{-}4$, $R^2 = H$

(40) $R^1 = CH_2C_6H_3(OMe)_2\text{-}3,4$, $R^2 = H$

yield of the methanol (**11**). When 4(5)-bromo-5(4)-chloroimidazole was treated with butyl-lithium under the same conditions and the 4(5)-chloroimidazol-5(4)-yl-lithium produced quenched with benzophenone, only 4(5)-butyl-5(4)-chloroimidazole was isolated (59% yield). Clearly, in this case, the intermediate lithium compound reacted faster with the butyl bromide, released by the initial halogen-metal exchange reaction, than with the benzophenone, a result that might be overcome by switching to t-butyl-lithium. Obviously it would be an advantage to be able to synthesize substituted imidazoles using these techniques—*i.e.* without the need to protect the imidazole nitrogen atom. However, to date, we have made no further progress in this direction because our attention has been concentrated on the greater synthetic usefulness of 1-protected 2,4,5-tribromoimidazoles. These compounds are available in high yield by treating 2,4,5-tribromoimidazole with PCl (P = protecting group) in the presence of a base (see preceding paper).

Table. Reactions of 1-benzyl-2,4,5-tribromoimidazole with organolithium reagents[a]



(23) (28)

Reagent	Solvent	Ratio (23):(28)	Yield (%)
BuLi	Et_2O	4:1	68
BuLi	THF	4:1	67
PhLi	THF	1:0	72
MeLi	THF	1:0	70
s-BuLi	THF	1:0	68

[a] Reaction time—30 min; temperature −78 °C in all cases.

Contrary to our earlier report[9] that 2,4,5-tribromo-1-ethoxymethylimidazole reacts with 1 mol equiv. of butyl-lithium in ether at −70 °C regioselectively in the 2-position we have now found that this is not the case. Both the 2- and 5-bromine atoms undergo halogen-metal exchange under these conditions. Similarly, when 1-benzyl (or 1-methoxymethyl)-2,4,5-tribromoimidazole is treated with butyl-lithium under these conditions and the products quenched with water, mixtures (analysed by ^1H n.m.r. spectroscopy) of compounds (**13**) and (**26**) and (**14**) and (**27**), respectively, are obtained. If the lithiated products are quenched with dimethyl disulphide, mixtures of compounds (**23**) and (**28**) and (**24**) and (**29**) (ratio 4:1 in each case; by ^1H n.m.r. spectroscopy), respectively, are obtained instead. The reactions of 1-benzyl-2,4,5-tribromoimidazole with various organolithium compounds in THF at −78 °C are summarised in the Table. The results show that organolithium reagents other than butyl-lithium regioselectively attack only the 2-bromine atom.

An equally useful synthesis of 1-protected 4,5-dibromoimidazoles (**13**)—(**17**) and one which provides higher yields (72—80%) of products involves treating the appropriate 1-protected 2,4,5-tribromoimidazole with 1 mol equiv. of ethylmagnesium bromide in refluxing ether or THF followed by hydrolysis of the product. The Grignard derivative prepared in this way from 2,4,5-tribromo-1-(4-methoxybenzyl)imidazole was treated also with benzophenone, to give the methanol (**25**) (83% yield). In this case, however, the ether was distilled off from the Grignard compound and replaced with refluxing benzene before addition of the quenching reagent. Grignard derivatives of imidazoles are not well-known.[10] As far as we are aware, the first examples of C—MgX compounds were reported as recently as 1981 by an Egyptian group,[13] although 2,4,5-tribromoimidazole forms a N–MgBr derivative with ethylmagnesium bromide.[14]

Having established conditions whereby 1-protected 2,4,5-tribromoimidazoles can be made to react regioselectively with organometallic reagents by displacement of the 2-bromine atom the next step was to study the reactions of 1-protected 4,5-dibromoimidazoles.

When 2-benzylthio-4,5-dibromo-1-methoxymethylimidazole[1] was treated with 1 mol equiv. of ethylmagnesium bromide in refluxing ether and the product hydrolysed with water, an 81% yield of 2-benzylthio-4-bromo-1-methoxymethyl-

imidazole (**30**) was obtained. The same product (66% yield) was obtained from the same starting material by treating it successively with 1 mol equiv. of butyl-lithium (in ether at −78 °C) and water. The methanol (**12**) (41% yield) was obtained similarly by treating 4,5-dibromo-1-methoxymethyl-2-phenylthioimidazole successively with butyl-lithium, benzophenone, and water.

1-Benzyl-4-bromoimidazol-5-yl-lithium was prepared likewise and reacted with DMF, carbon dioxide, methyl chloroformate, and elemental sulphur to give compounds (**33**)—(**36**), respectively, in 53—68% yields. The ester (**35**) was hydrolysed to the acid (**34**) by a standard procedure. The 5-bromoaldehydes (**31**), (**32**), and (**37**)—(**40**) were obtained similarly in moderate yields starting from either 2-benzyl(or phenyl)thio-4,5-dibromo-1-methoxymethylimidazole,[1] 1-benzyl-2-benzyl-(or phenyl)thio-4,5-dibromoimidazole,[1] 4,5-dibromo-1-(4-methoxybenzyl)imidazole (**16**), or 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole (**17**), respectively (ether or THF can be used as the solvent for these reactions). Surprisingly, when 4,5-dibromo-1-methoxymethylimidazole was treated successively with butyl-lithium and DMF it failed to yield 4-bromo-1-methoxymethylimidazole-5-carbaldehyde: 4-bromo-1-methoxymethylimidazole was isolated instead.

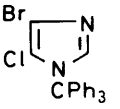
We have seen no evidence for attack at the imidazole 4-bromine atom in any of the reactions described in this paper. This is probably due to destabilisation of imidazole C-4 anions by the adjacent N-3 lone pair (the ALP effect as described by Kirk *et al.*[15]). Generation of a C-4 anion would be further inhibited by carbanionic character at C-5. When a carbon–lithium bond at C-4 possesses significant covalent character the ALP effect can be overcome. An interesting example of the ALP effect is seen when 4- and 5-bromo-1-methylimidazole are treated with butyl-lithium.[16] The former compound undergoes exclusive metallation in the 2-position whereas the latter compound undergoes exclusive halogen-metal exchange.

In our work there was no evidence either to suggest that our 1-protected 4,5-dibromoimidazoles undergo metallation in the 2-position.* Neither was there any evidence for attack in the 1- or 2-protecting groups [*e.g.* in the benzene rings of imidazoles carrying a 1-(4-methoxy- or 3,4-dimethoxy-benzyl) protecting group or in the compounds substituted by a 2-methylthio group].

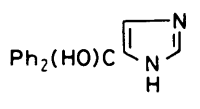
Noteworthy is the fact that, whereas the series of 1-ethoxymethylimidazoles are liquids at ambient temperatures, their 1-methoxymethyl isomers are all solids and thus are easier to handle.

It proved impossible to synthesize 2,4,5-tribromo-1-tritylimidazole but 4,5-dibromoimidazole (**4**) reacted with trityl chloride in benzene in the presence of triethylamine to give an excellent yield of 4,5-dibromo-1-tritylimidazole (**18**). 4-(5)-Bromo-5(4)-chloroimidazole reacted similarly with trityl chloride to give a mixture of two products. We believe that the isomer formed in the largest amount is 4-bromo-5-chloro-1-tritylimidazole (**41**). Likewise, compounds (**19**)—(**22**) were synthesized by treating 4,5-dibromoimidazole (**1**) with either ethyl 2-bromoacetate, 2-phenylsulphonylethyl chloride, benzenesulphonyl chloride, or 4-methylbenzenesulphonyl chloride, respectively (see also preceding paper).

4,5-Dibromo-1-tritylimidazole failed to react with an excess of either methyl-, butyl-, or s-butyl-lithium, presumably due to a combination of steric hindrance and the ALP effect. Kirk[15] reported the synthesis of 1-tritylimidazole-4-carbaldehyde though halogen-metal exchange of 4-iodo-1-tritylimidazole with butyl-lithium (3 mol equiv. were required to overcome the ALP effect) followed by *rapid* quenching of the intermediate 4-lithiated imidazole with DMF. Noteworthy is the synthesis[17] of 2-fluoro-1-tritylimidazole-4-carbaldehyde by *metallation* of 2-fluoro-1-tritylimidazole (with Bu^{t}Li at −78 °C in THF!) followed by reaction of the intermediate lithium compound with DMF.



(**41**)



(**42**)

Reports appeared in 1982[18] that imidazol-4(5)-ylidiphenylmethanol (**42**) can be prepared in moderate yield *via* treatment of 4(5)-bromoimidazole with lithium naphthalenide followed by quenching the intermediate with benzophenone. After several attempts we were able to prepare the methanol (**42**) in this way, but attempts to quench the intermediate with DMF, triethyl orthoformate, methyl iodide, acetone, or dimethyl disulphide all failed.

To conclude, we have established conditions which allow the 2- and 5-bromine atoms in 1-protected 2,4,5-tribromoimidazoles to be replaced stepwise and regioselectively in the order 2 ⟶ 5 using halogen metal exchange strategies.

Experimental

The spectroscopic instruments used and the general experimental conditions employed were the same as those described previously.[1,19] Temperatures recorded for our halogen-metal exchange reactions are those recorded by a thermometer placed in the reaction mixture and rates of addition of reagents were controlled to maintain these temperatures.[20]

2,4,5-Tribromoimidazole (71% yield),[9,21] 2-bromo-4,5-dichloroimidazole (74%),[11,22] 4(5)-bromoimidazole (62%),[9,21] 4(5)-bromo-5(4)-chloroimidazole (56%),[22] and 2,4,5-tribromo-1-ethoxymethylimidazole (100% crude)[9] were prepared by literature procedures. 2,4,5-Tribromo-1-methoxymethylimidazole, 1-benzyl-2,4,5-tribromoimidazole, 2,4,5-tribromo-1-(4-methoxybenzyl)imidazole, 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)imidazole, 1-benzyl-2-benzyl(and phenyl)thio-4,5-dibromoimidazole, and 2-benzyl(and phenyl)thio-4,5-dibromo-1-methoxymethylimidazole were prepared as described in the preceding paper.[1]

4,5-*Dichloroimidazole*-2-*carbaldehyde* (**6**).—1.78M-Butyllithium in hexane (36.4 ml, 64.8 mmol) was added dropwise to a stirred solution of 2-bromo-4,5-dichloroimidazole (7.0 g, 32.4 mmol) in anhydrous THF (60 ml) at −78 °C under nitrogen and the resulting mixture was stirred for a further 30 min at −78 °C. DMF (2.5 ml, 2.36 g, 32.4 mmol) was added dropwise and the mixture was allowed to warm slowly to ambient temperature. It was acidified with 10% hydrochloric acid and extracted with chloroform to give the aldehyde (**6**) (2.78 g, 52%), m.p. 190—191 °C (from ethanol) (lit.,[11] m.p. 190—191 °C).

The following compounds were prepared similarly: 4,5-dichloroimidazole-2-carboxylic acid (**8**) (48%) (the lithiated imidazole was quenched with an excess of solid carbon dioxide), m.p. 160—162 °C (from aqueous ethanol) (lit.,[23] m.p. 159—160 °C): 2-*butylthio*-4,5-*dichloroimidazole* (**10**) (42%) (the lithiated imidazole was quenched with 1 mol equiv. of elemental sulphur), m.p. 112—114 °C (from light petroleum); δ($CDCl_3$) 0.98 (3 H, t, Me), 1.56 (4 H, m, 2 × CH_2), 3.11 (2 H, t, SCH_2), and 9.83 (1 H, br s, exchangeable, NH) (Found: C, 37.5; H, 4.4; N, 12.6%; M^+, 223.9942. $C_7H_{10}Cl_2N_2S$ requires C, 37.3; H, 4.5; N, 12.4%; *M*, 223.9947): 4,5-dibromoimidazole (**4**) (40%), m.p. 225—226 °C (from aqueous ethanol) (lit.,[24] m.p. 225 °C) [the product was extracted with ethyl acetate in this case and,

* See note added in proof on p. 1450.

after removal of this solvent, chloroform (30 ml) was added to the residue and the crude product filtered off]; 4,5-*dibromoimidazole*-2-*carbaldehyde* (**5**) (43%) (the lithiated imidazole was quenched with 1 mol equiv. of DMF), m.p. 192—194 °C (from ethyl acetate), $\nu_{max.}$ 1 650 cm^{-1} (CO) (Found: C, 19.1; H, 0.85; N, 11.3%; M^+, 252. $C_4H_2Br_2N_2O$ requires C, 18.9; H, 0.8; N, 11.0%; *M*, 252): 4,5-dibromoimidazole-2-carboxylic acid (**7**) (57%) (the lithiated imidazole was quenched with an excess of solid carbon dioxide), m.p. 173—175 °C (with decomp.) (from aqueous ethanol) [lit.,[23] m.p. 171—173 °C (with decomp.)], $\nu_{max.}$ 1 675 cm^{-1} (CO): 4,5-*dibromo*-2-*butylthioimidazole* (**9**) (40%) (the lithiated imidazole was quenched with 1 mol equiv. of elemental sulphur), m.p. 86—88 °C (from light petroleum) [in this case the product was extracted with chloroform, then chromatographed on silica; ethyl acetate–light petroleum (b.p. 60—80 °C) eluted the product]; δ($CDCl_3$) 0.96 (3 H, t, Me), 1.55 (4 H, m, 2 × CH_2), and 2.90 (2 H, t, SCH_2) (Found: M^+, 311.8932.* $C_7H_{10}Br_2N_2S$ requires *M*, 311.8967): 4(5)-*bromoimidazol*-5(4)-*yldiphenylmethanol* (**11**) (17%) (lithiated imidazole quenched with 1 mol equiv. benzophenone), m.p. 166—167 °C (from chloroform) [after extraction with chloroform the light brown oil obtained was triturated with light petroleum (b.p. 60—80 °C) to yield the crude product] (Found: M^+, 328.0178. $C_{16}H_{13}BrN_2O$ requires *M*, 328.0211).

Reaction of 4(5)-*Bromo*-5(4)-*chloroimidazole with Butyl-lithium.*—1.78M-Butyl-lithium (23.5 ml, 41.88 mmol) was added dropwise to a stirred solution of 4(5)-bromo-5(4)-chloroimidazole (3.8 g, 20.94 mmol) in THF (75 ml) at −78 °C and the resulting mixture was stirred at −78 °C for a further 30 min. Then a solution of benzophenone (3.81 g, 20.94 mmol) in THF (10 ml) was added dropwise at −78 °C and the mixture was allowed to warm to ambient temperature. Addition of 10% hydrochloric acid and extraction with chloroform gave a light-brown oil which solidified on trituration with light petroleum (b.p. 60—80 °C), to give 4(5)-*butyl*-5(4)-*chloroimidazole* (1.95 g, 59%), m.p. 107—108 °C (from ethanol) (M^+, 158.0602. $C_7H_{11}ClN_2$ requires *M*, 158.0611) (this compound proved extremely difficult to combust and it was not possible to obtain an acceptable microanalysis result, although the result obtained was in agreement with the structure proposed).

1-*Protected Derivatives of* 4,5-*Dihalogenoimidazoles.*—(a) 4,5-*Dibromo*-1-*tritylimidazole* (91%), m.p. 180—182 °C (from ethanol); δ($CDCl_3$) 6.90—7.30 (m, ArH) (Found: C, 56.2; H, 3.5; N, 6.0%; M^+, 466. $C_{22}H_{16}Br_2N_2$ requires C, 56.4; H, 3.4; N, 6.0%; *M*, 466) and 4-*bromo*-5-*chloro*-1-*tritylimidazole* (64%), m.p. 172—174 °C (from ethyl acetate); δ($CDCl_3$) 7.10—7.70 (m, ArH) (Found: C, 62.3; H, 4.1; N, 6.5%; M^+, 422. $C_{22}H_{16}BrClN_2$ requires C, 62.35; H, 3.8; N, 6.6%; *M*, 422) were prepared using trityl chloride in a manner similar to that used previously[9] to synthesize 2,4,5-tribromo-1-ethoxymethylimidazole. *Ethyl* 2-(4,5-*dibromoimidazol*-1-*yl*)*acetate* (91.5%), m.p. 94—96 °C (from chloroform–light petroleum); $\nu_{max.}$ 1 730 cm^{-1} (CO); δ($CDCl_3$) 1.31 (3 H, t, Me), 4.30 (2 H, q, CH_2), 4.76 (2 H, s, NCH_2), and 7.60 (1 H, s, 2-H) (Found: C, 26.9; H, 2.5; N, 9.0%; M^+, 310. $C_7H_8Br_2N_2O_2$ requires C, 26.95; H, 2.6; N, 9.0%; *M*, 310) was prepared in a manner similar to that described previously for the synthesis of ethyl 2-(2,4,5-tribromoimidazol-1-yl)acetate and 4,5-*dibromo*-1-(2-*phenylsulphonylethyl*)*imidazole* (66%), m.p. 155—156 °C (from chloroform); δ(CF_3CO_2H) 3.96 (2 H, m, CH_2), 4.98 (2 H, m, CH_2), 7.50—8.10 (5 H, m, ArH), and 9.31 (1 H, s, 2-H) (Found: C, 33.4; H, 2.5; 7.2%; M^+, 392. $C_{11}H_{10}Br_2N_2O_2S$ requires C, 33.5; H, 2.55; N, 7.1%; *M*, 392) was prepared in a manner similar to that described previously for the synthesis of 2,4,5-tribromo-1-(2-phenylsulphonylethyl)imidazole.[1]

(b) 4,5-*Dibromo*-1-*phenylsulphonylimidazole.* A mixture of 4,5-dibromoimidazole (4.0 g, 17.7 mmol), sodium carbonate (1.87 g, 17.7 mmol), and benzenesulphonyl chloride (2.4 ml, 3.12 g, 17.7 mmol) in acetone (100 ml) was stirred overnight at ambient temperature; it was then filtered and the solvent distilled off under reduced pressure. Chloroform was added to the residue, the resulting solution was filtered, and distillation of the chloroform gave 4,5-*dibromo*-1-*phenylsulphonylimidazole* (5.7 g, 88%), m.p. 180—182 °C (from chloroform–light petroleum); δ($CDCl_3$) 7.50—8.15 (5 H, m, ArH) and 8.20 (1 H, s, 2-H) (Found: C, 29.4; H, 1.7; N, 7.7%; M^+, 364. $C_9H_6Br_2N_2O_2S$ requires C, 29.5; H, 1.65; N, 7.65; *M*, 364).

4,5-*Dibromo*-1-(4-*tolylsulphonyl*)*imidazole* (92%) was prepared similarly, m.p. 151—153 °C (from ethyl acetate); δ($CDCl_3$) 2.50 (3 H, s, Me), 7.40 (2 H, dd, ArH), 7.90 (2 H, dd, ArH), and 8.20 (1 H, s, 2-H) (Found: C, 31.8; H, 2.2; N, 7.4%; M^+, 378. $C_{10}H_8Br_2N_2O_2S$ requires C, 31.6; H, 2.1; N, 7.4%; *M*, 378).

None of the compounds whose preparations are described in this Section required purification by chromatography.

Reaction of 2,4,5-*Tribromo*-1-*methoxymethylimidazole with Butyl-lithium.*—1.78M-Butyl-lithium in hexane (8.0 ml, 14.32 mmol) was added dropwise to a solution of 2,4,5-tribromo-1-methoxymethylimidazole (5.0 g, 14.32 ml) in anhydrous ether (75 ml) at −78 °C under nitrogen and the resulting mixture was stirred at −78 °C for 30 min. Dimethyl disulphide (1.34 g, 14.32 mmol) was then added dropwise and the mixture was allowed to warm slowly to ambient temperature. Water (25 ml) was added and work-up in the usual way gave a pale yellow oil (3.15 g, 70%) whose ^1H n.m.r. spectrum showed it to be a mixture of 4,5-dibromo-1-methoxymethyl-2-methylthioimidazole (**24**) and 2,4-dibromo-1-methoxymethyl-5-methylthioimidazole (**29**) (ratio 4:1).

1-Benzyl-2,4,5-tribromoimidazole was treated successively with various organolithium reagents and dimethyl disulphide in either ether or THF and the results are shown in the Table (see Discussion).

4,5-*Dibromo*-1-*ethoxymethylimidazole* (**15**).—2,4,5-Tribromo-1-ethoxymethylimidazole (4.0 g, 11.0 mmol) was added to a stirred solution of ethylmagnesium bromide (11.0 mmol) [prepared from ethyl bromide (0.85 ml, 1.20 g, 11.0 mmol) and magnesium turnings (0.26 g, 11.0 mol)] in ether (50 ml) at ambient temperature under nitrogen and the resulting mixture was heated under reflux for 2 h. To the cooled mixture was added 20% aqueous ammonium chloride (30 ml, excess) after which the organic layer was separated from the aqueous layer; the latter was then extracted several times with chloroform. The organic layer and extracts were combined and dried ($MgSO_4$) and distillation of the solvents gave the *product* (**15**) as a pale yellow oil (2.5 g, 80%), b.p. 120—125 °C at 0.5 mmHg (Kugelrohr single path distillation); δ_H($CDCl_3$) 1.20 (3 H, t, Me), 3.55 (2 H, q, OCH_2), 5.32 (2 H, s, NCH_2), and 7.65 (1 H, s, 2-H); δ_C($CDCl_3$) 14.28 (q, Me), 64.63 (t, OCH_2), 75.33 (t, NCH_2), 103.31 (s, C-5), 117.38 (s, C-4), and 137.56 p.p.m. (d, C-2) (Found: C, 25.4; H, 2.9; N, 10.0%; M^+, 282. $C_6H_8Br_2N_2O$ requires C, 25.4; H, 2.8; N, 9.9%; *M*, 282).

The following compounds were prepared similarly: 4,5-dibromoimidazole (**4**) (67%), m.p. 224—225 °C (from aqueous ethanol), identical with the sample prepared as described before (THF used as the solvent: mixture heated under reflux for 3 h; acidified with 10% hydrochloric acid; product extracted with ethyl acetate and, after removal of this solvent, triturated with chloroform): 4,5-*dibromo*-1-*methoxymethylimidazole* (**14**) (73%)

* Based on ^{79}Br.

(solvent Et_2O; product chromatographed on alumina and eluted with chloroform–light petroleum), m.p. 65—67 °C (from light petroleum); $\delta_H(CDCl_3)$ 3.35 (3 H, s, OMe), 5.20 (2 H, s, NCH_2), and 7.60 (1 H, s, 2-H); $\delta_C(CDCl_3)$ 56.01 (q, Me), 76.89 (t, CH_2), 103.47 (s, C-5), 117.29 (s, C-4), and 137.62 p.p.m. (d, C-2) (Found: C, 22.3; H, 2.2; N, 10.4%; M^+, 268. $C_5H_6Br_2N_2O$ requires C, 22.2; H, 2.2; N, 10.4%; *M*, 268): 1-*benzyl*-4,5-*dibromoimidazole* (**13**) (80%) (solvent Et_2O; mixture heated under reflux for 4.0 h and hydrolysed with 10% hydrochloric acid; product extracted with Et_2O), m.p. 56—57 °C (from carbon tetrachloride–light petroleum); $\delta(CDCl_3)$ 5.10 (2 H, s, NCH_2), 7.00—7.70 (5 H, m, ArH), and 7.50 (1 H, s, 2-H) (Found: C, 38.0; H, 2.5; N, 9.0%; M^+, 314. $C_{10}H_8Br_2N_2$ requires C, 38.0; H, 2.55; N, 8.9%; *M*, 314): 4,5-*dibromo*-1-(4-*methoxybenzyl*)-*imidazole* (**16**) (73%) (solvent Et_2O; mixture heated under reflux for 3 h and hydrolysed with 10% hydrochloric acid; product extracted with Et_2O), m.p. 64—65 °C (from carbon tetrachloride–light petroleum); $\delta(CDCl_3)$ 3.80 (3 H, s, OMe), 5.04 (2 H, s, NCH_2), 6.85 (2 H, d, *J* 8 Hz, ArH), 7.15 (2 H, d, *J* 8 Hz, ArH), and 7.45 (1 H, s, 2-H) (Found: C, 37.9; H, 2.9; N, 8.2%; M^+, 344. $C_{11}H_{10}Br_2N_2O$ requires C, 38.2; H, 2.9; N, 8.1%; *M*, 344): 4,5-*dibromo*-1-(3,4-*dimethoxybenzyl*)*imidazole* (**17**) (72%) (solvent THF; mixture heated under reflux for 3 h after stirring at ambient temperature for 1 h following addition; hydrolysed with 10% hydrochloric acid; product extracted with chloroform), m.p. 111—113 °C (from ethanol); $\delta(CDCl_3)$ 3.90 (6 H, s, 2 × OMe), 5.03 (2 H, s, NCH_2), 7.45 (1 H, s, 2-H), and 6.60—6.90 (3 H, m, ArH) (Found: C, 38.6; H, 3.2; N, 7.5%; M^+, 374. $C_{12}H_{12}Br_2N_2O_2$ requires C, 38.3; H, 3.2; N, 7.45%; *M*, 374).

4,5-*Dibromo*-1-(4-*methoxybenzyl*)*imidazol*-2-*yldiphenylmethanol* (**25**).—2,4,5-Tribromo-1-(4-methoxybenzyl)imidazole (15.0 g, 35.29 mmol) was added portionwise to a stirred solution of ethylmagnesium bromide (35.29 mmol) in anhydrous ether (100 ml) at ambient temperature, then the mixture was heated under reflux for 4 h. Anhydrous benzene (100 ml) was added and the ether was distilled off. Benzophenone (6.42 g, 35.29 mmol) in anhydrous benzene (15 ml) was added dropwise to the cooled mixture after which it was heated under reflux for 2 h. 10% Hydrochloric acid (50 ml) was added to the cooled (ice-bath) mixture and the organic layer was separated off. The aqueous layer was extracted several times with ether. The ethereal extracts and organic layer were combined and dried ($MgSO_4$), and distillation of the solvents gave the *product* (**25**) as a colourless oil (15.45 g, 83%) which solidified with time, m.p. 125—127 °C (from ethanol); $\nu_{max.}$ 3 525 cm^{-1} (OH); $\delta(CDCl_3)$ 3.72 (3 H, s, OMe), 5.02 (2 H, s, NCH_2), 6.65 (4 H, s, ArH), and 7.21 (10 H, s, ArH) (Found: C, 54.4; H, 3.8; N, 5.4%; M^+, 526. $C_{24}H_{20}Br_2N_2O_2$ requires C, 54.5; H, 3.8; N, 5.3%; *M*, 526).

2-*Benzylthio*-4-*bromo*-1-*methoxymethylimidazole* (**30**). This was prepared similarly by treating 2 benzylthio-4,5-dibromo-1-methoxymethylimidazole (2.0 g, 5.1 mmol) in anhydrous ether (30 ml) with ethylmagnesium bromide (5.1 mmol) heated under reflux for 3 h (after addition). The mixture was hydrolysed with 20% ammonium chloride (25 ml) and the *product* (1.3 g, 81%) was extracted with chloroform; it had m.p. 60—62 °C (from ethanol–light petroleum); $\delta(CDCl_2)$ 3.10 (3 H, s, Me), 4.21 (2 H, s, SCH_2), 4.88 (2 H, s, NCH_2), 7.00 (1 H, s, 5-H), and 7.21 (5 H, s, ArH) (Found: C, 46.2; H, 4.2; N, 8.8%; M^+, 312. $C_{12}H_{13}BrN_2OS$ requires C, 46.0; H, 4.2; N, 8.9%; *M*, 312).

The same compound (1.05 g, 66%), m.p. 59—62 °C (from ethanol–light petroleum), identical with the sample prepared as described in the preceding experiment, was prepared also by treating 2-benzylthio-4,5-dibromo-1-methoxymethylimidazole (2.0 g, 5.1 mmol) in anhydrous ether (50 ml) with 1.6M-butyllithium in hexane (3.2 ml, 5.1 mmol) at −78 °C under nitrogen for 30 min. Water (25 ml) was added to the resulting mixture which was worked up in the usual way.

4-*Bromo*-1-*methoxymethyl*-2-*phenylthioimidazol*-5-*yldiphenylmethanol* (**12**).—1.6M-Butyl-lithium in hexane (8.0 ml, 12.6 mmol) was added dropwise to a stirred solution of 4,5-dibromo-1-methoxymethyl-2-phenylthioimidazole (4.0 g, 10.5 mmol) in anhydrous ether (50 ml) at −78 °C under nitrogen, after which the mixture was stirred at −78 °C for a further 40 min. Benzophenone (1.9 g, 10.5 mmol) in ether (15 ml) was added dropwise to the mixture which was then allowed to warm up slowly to ambient temperature; it was then stirred overnight. 10% Aqueous ammonium chloride (25 ml) was added, the organic layer was separated off, and the aqueous layer was extracted with chloroform (3 × 25 ml). The ethereal layer and extracts were combined and dried ($MgSO_4$), and distillation of the solvents gave a pale yellow oil which was chromatographed on alumina. Light petroleum–chloroform eluted the *methanol* (**12**) (2.1 g, 41%), m.p. 123—124.5 °C (from ethanol); $\delta(CDCl_3)$ 3.25 (3 H, s, Me), 5.35 (2 H, s, NCH_2), and 7.15—7.50 (15 H, m, ArH) (Found: C, 59.2; H, 4.45; N, 5.95%; M^+, 480.0508. $C_{24}H_{21}BrN_2O_2S$ requires C, 59.9; H, 4.4; N, 5.8%; *M*, 480.0495).

4-*Bromo*-1-*methoxymethyl*-2-*phenylthioimidazole*-5-*carbaldehyde* (**32**).—1.6M-Butyl-lithium in hexane (17.8 ml, 28.5 mmol) was added dropwise to a stirred solution of 4,5-dibromo-1-methoxymethyl-2-phenylthioimidazole (9.0 g, 23.8 mmol) in anhydrous ether (200 ml) at −78 °C under nitrogen and the mixture was stirred for a further 2 h at this temperature. DMF (1.73 g, 1.85 ml, 23.8 mmol) was added to the mixture which was then allowed to warm up slowly to ambient temperature; it was then stirred overnight. 10% Aqueous ammonium chloride (100 ml) was added and work-up as described in the preceding experiment (with the exception that ether was used to extract the product) gave a brown oil which was chromatographed on alumina. Light petroleum–ethyl acetate eluted the *aldehyde* (**32**) (4.0 g, 51%) as an oil; $\nu_{max.}$ 1 660 cm^{-1}; $\delta(CDCl_3)$ 3.36 (3 H, s, Me), 5.70 (2 H, s, NCH_2), 7.20—7.65 (5 H, m, ArH), and 9.66 (1 H, s, CHO) (Found: C, 44.0; H, 3.4; N, 8.3%; M^+, 326. $C_{12}H_{11}BrN_2O_2S$ requires C, 44.05; H, 3.4; N, 8.6%; *M*, 326).

The following compounds were prepared similarly with amendments to the above procedure indicated in parentheses: 2-*benzylthio*-4-*bromo*-1-*methoxymethylimidazole*-5-*carbaldehyde* (**31**) (54%), m.p. 53—55 °C (from light petroleum); $\nu_{max.}$ 1 660 cm^{-1} (CO); $\delta(CDCl_3)$ 3.31 (3 H, s, OMe), 4.51 (2 H, s, SCH_2), 5.48 (2 H, s, NCH_2), 7.30 (5 H, m, ArH), and 9.60 (1 H, s, CHO) (Found: C, 45.6; H, 3.7; N, 7.9%; M^+, 340. $C_{13}H_{13}BrN_2O_2S$ requires C, 45.8; H, 3.8; N, 8.2%; *M*, 340): 1-*benzyl*-2-*benzylthio*-4-*bromoimidazole*-5-*carbaldehyde* (**34**) (54%), colourless oil; $\nu_{max.}$ 1 660 cm^{-1} (CO); $\delta(CDCl_3)$ 4.41 (2 H, s, SCH_2), 5.32 (2 H, s, NCH_2), 6.90—7.50 (10 H, m, ArH), and 9.50 (1 H, s, CHO) (Found: M^+, 386. $C_{18}H_{15}BrN_2OS$ requires *M*, 386): 1-*benzyl*-4-*bromo*-2-*phenylthioimidazole*-5-*carbaldehyde* (**38**) (52%), m.p. 73—75 °C (from ethanol); $\nu_{max.}$ 1 660 cm^{-1} (CO); $\delta(CDCl_3)$ 5.60 (2 H, s, NCH_2), 7.00—7.50 (10 H, m, ArH), and 9.63 (1 H, s, CHO) (Found: C, 54.4; H, 3.6; H, 7.6%; M^+, 372. $C_{17}H_{13}BrN_2OS$ requires C, 54.7; H, 3.5; N, 7.5%; *M*, 372): 4-*bromo*-1-(4-*methoxybenzyl*)*imidazole*-5-*carbaldehyde* (**39**) (50%) (in this case the product was chromatographed under medium pressure on silica instead of alumina: same solvent elution system), m.p. 62—64 °C (from ethanol); $\nu_{max.}$ 1 660 cm^{-1} (CO); $\delta(CDCl_3)$ 3.80 (3 H, s, OMe), 5.48 (2 H, s, NCH_2), 6.86 (2 H, d, ArH), 7.07 (1 H, s, 2-H), 7.21 (2 H, d, ArH), and 9.78 (1 H, s, CHO) (Found: C, 48.9; H, 3.9; N, 9.3%; M^+, 294. $C_{12}H_{11}BrN_2O_2$ requires C, 48.8; H, 3.75; N, 9.5%; *M*, 294): 4-*bromo*-1-(3,4-*dimethoxybenzyl*)*imidazole*-5-*carbaldehyde* (**40**) (55%), m.p. 159—160 °C (from ethanol); $\nu_{max.}$ 1 660 cm^{-1} (CO); $\delta(CDCl_3)$ 3.78 (6 H, s, OMe), 5.40 (2 H, s, NCH_2), 6.85 (3 H, s, ArH), 7.55 (1 H, s, 2-H), and 9.80 (1 H, s, CHO) (Found: C, 48.2; H, 4.2; N, 8.5%; M^+, 324. $C_{13}H_{13}BrN_2O_3$ requires C, 48.0; H, 4.0; N, 8.6%; *M*, 324): 1-*benzyl*-4-*bromoimidazole*-5-*carbal-*

dehyde (**33**) (53%), m.p. 59—60 °C (from ethyl acetate–light petroleum); $\nu_{max.}$ 1 660 cm^{-1} (CO); δ($CDCl_3$) 5.48 (2 H, s, NCH_2), 6.90—7.70 (5 H, m, ArH), 7.54 (1 H, s, 2-H), and 9.75 (1 H, s, CHO) (Found: C, 49.9; H, 3.4; H, 10.6%; M^+, 264. $C_{11}H_9BrN_2O$ requires C, 49.8; H, 3.4; N, 10.6%; *M*, 264): 1-*benzyl*-4-*bromoimidazole*-5-*carboxylic acid* (**34**) (67%) (mixture stirred at −78 °C for 2 h prior to addition of an excess of solid carbon dioxide; mixture allowed to warm up slowly to room temperature then water added to hydrolyse product and product precipitated on addition of 10% hydrochloric acid to aqueous layer), m.p. 193—194 °C (from ethanol); $\nu_{max.}$ 1 700 (CO) and 3 400 cm^{-1} (OH); δ[$(CD_3)_2SO$] 3.75 (1 H, br s, CO_2H, exchangeable), 5.84 (2 H, s, NCH_2), 7.25—7.75 (5 H, m, ArH), and 8.40 (1 H, s, 2-H) (Found: C, 47.0; H, 3.4; N, 10.2%; M^+, 280. $C_{11}H_9BrN_2O_2$ requires C, 47.0; H, 3.2; N, 10.0%; *M*, 280): *methyl* 1-*benzyl*-4-*bromoimidazole*-5-*carboxylate* (**35**) (61%) (mixture stirred at −78 °C for 2 h prior to addition of methyl chloroformate; mixture allowed to warm slowly to ambient temperature, then water added before product was extracted with ether), as a pale yellow oil, b.p. 145—151 °C at 0.5 mmHg (Kugelrohr single-path distillation apparatus); $\nu_{max.}$ 1 705 cm^{-1} (CO); δ($CDCl_3$) 3.76 (3 H, s, Me), 5.40 (2 H, s, NCH_2), 6.80—7.70 (5 H, m, ArH), and 7.48 (1 H, s, 2-H) (Found: M^+, 294. $C_{12}H_{11}BrN_2O_2$ requires, *M*, 294): and 1-*benzyl*-4-*bromoimidazole*-5-*thiol* (**36**) (68%) (mixture stirred at −78 °C for 2 h prior to addition of 1 mol equiv. of elemental sulphur; mixture allowed to warm slowly to ambient temperature, then hydrolysed with water and product precipitated from aqueous layer by addition of 10% hydrochloric acid), decomposed at 130 °C (recrystallised from ethanol); δ($CDCl_3$) 5.20 (2 H, s, NCH_2), 6.52 (1 H, s, SH), and 7.40 (6 H, s, ArH) (Found: C, 44.3; H, 3.35; N, 10.5%; M^+, 268. $C_{10}H_9BrN_2S$ requires C, 44.6; H, 3.4; N, 10.4%; *M*, 268).

Hydrolysis of Methyl 1-*Benzyl*-4-*bromoimidazole*-5-*carboxylate* (**35**).—The hydrolysis with 10% aqueous sodium hydroxide, heated under reflux for 1 h, and work-up in the standard way also gave the acid (**34**) (85%), m.p. 192—194 °C (from ethanol), identical with the sample prepared as described before.

Reaction of 4,5-*Dibromo*-1-*methoxymethylimidazole* (**14**) *with Butyl-lithium.*—1.78M-Butyl-lithium in hexane (4.4 ml, 7.78 mmol) was added dropwise to a stirred solution of 4,5-dibromo-1-methoxymethylimidazole (2.1 g, 7.78 mmol) in ether (50 ml) at −78 °C and the resulting mixture was stirred at this temperature for 30 min. DMF (0.6 ml, 0.57 g, 7.78 mmol) was added dropwise at −78 °C and the mixture was allowed to warm slowly to ambient temperature; it was then stirred for a further 30 min before addition of water (30 ml). Work-up in the usual way gave a pale-yellow oil (1.27 g) which was shown by ^1H n.m.r. spectroscopy to be a mixture of 4-bromo-1-methoxymethylimidazole and starting material (ratio 2:1).

The mass spectrum of this mixture confirmed this result: M^+ (product), 189.9733. $C_5H_7BrN_2O$ requires *M*, 189.9723. The mixture was not investigated further.

Imidazol-4(5)-*yldiphenylmethanol* (**42**) (*with T. McC.Paterson*).—A solution of lithium naphthalenide in anhydrous THF (30 ml) was prepared by successive addition of naphthalene (4.48 g, 35.0 mmol) and lithium (0.31 g, 44.7 mol) to the stirred THF under nitrogen. Then 4(5)-bromoimidazole (1.1 g, 7.48 mmol) was added during 5 min to this solution kept at −10 C to −15 °C. Benzophenone (6.38 g, 35.0 mmol) in THF (15 ml) was added dropwise during 5 min to the resulting green solution, which immediately turned blue, and the temperature of the mixture was allowed to rise to 20 °C whereupon it was stirred at this temperature for 1 h. Water (25 ml) was added and the mixture was acidified to pH 1.0 by addition of concentrated hydrochloric acid. The aqueous layer was separated and addition of solid sodium hydrogencarbonate to it resulted in a white precipitate which was recrystallised from ethyl acetate–light petroleum (b.p. 80—100 °C) to give the product (0.7 g, 38%), m.p. 166—167 °C (lit.,[18] m.p. 168—169 °C); $\nu_{max.}$ 3 220 cm^{-1} (NH); δ($CDCl_3$) 6.68 [1 H, s, 4(5)-H], 7.50—7.70 (10 H, m, ArH), and 7.68 (1 H, s, 2-H).

Note added in proof. In these reactions careful control of temperature and addition of reagents is important. All reagents should be added at −78 °C (internal temperature) or *at a lower temperature* at such a rate that the temperature is not allowed to rise. Addition of reagents using a syringe and septum cap is recommended. If the quenching reagent (*e.g.* DMF) is not added shortly after addition of the butyl-lithium (*i.e.* within 15—30 min), transmetallation reactions can occur.

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