Azoles. Part 6.[1,2] A Convenient Synthesis of Polysubstituted Imidazoles from 1-Protected 2,4,5-Tribromoimidazoles

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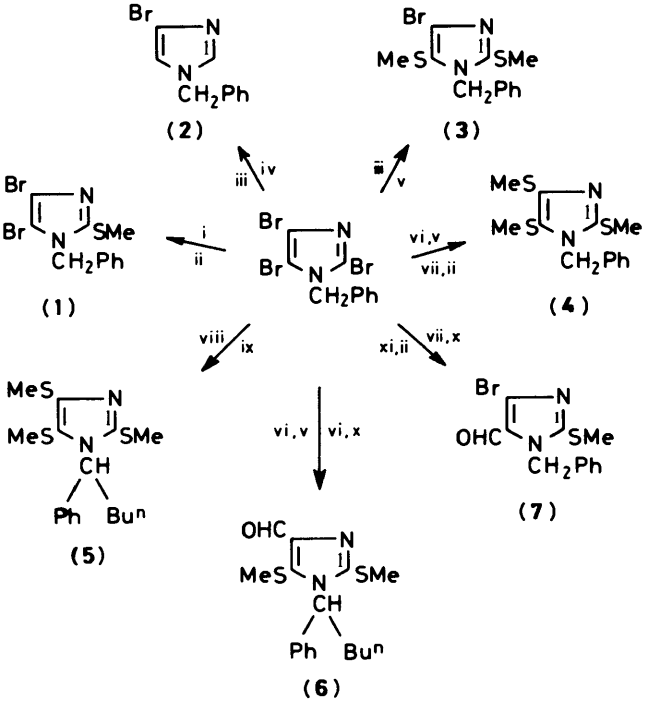
Starting from 1-benzyl-2,4,5-tribromoimidazole 'one-pot' methods are described for the synthesis of 1-benzyl-4,5-dibromo-2-methylthioimidazole (**1**) (72%), 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (**3**) (72%), 1-benzyl-2,4,5-tris(methylthio)imidazole (**4**) (67%), 1-benzyl-4-bromoimidazole (**2**) (71%), 4-bromo-2,5-bis(methylthio)-1-(1-phenylpentyl)imidazole (71%), 2,5-bis(methylthio)imidazole-4-carbaldehyde (**6**) (46%), and 1-benzyl-4-bromoimidazole-5-carbaldehyde (**7**) (60%). *N*-1-Deprotection reactions are also reported.

The first polylithiated imidazoles were reported in 1973.[3-5] Metallation of 1-methylimidazole with 2 mol equiv. of butyl-lithium followed by addition of trimethylsilyl chloride gives a low yield (32%) of 1-methyl-2,5-bis(trimethylsilyl)imidazole.[3] Chadwick's group[6,7] have studied 2,5-dilithiation of several 1-protected imidazoles. *N*,*N*-Dimethylimidazole-1-sulphonamide, *e.g.* can be dimetallated in 15 min with butyl-lithium below −15 °C in dimethoxyethane in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.[6] Quenching the intermediate 2,5-dilithiated derivative with suitable electrophiles and removal of the protecting group with 2M-hydrochloric acid provides a useful route to 2,5-disubstituted imidazoles. If the 2,5-dilithiated compound is quenched with only 1 mol equiv. of the electrophile, reaction occurs regioselectively in the 5-position and hydrolysis followed by deprotection provides a route to 4(5)-monosubstituted imidazoles.[6] Unfortunately, the reagent, namely dimethylsulphamoyl chloride, necessary to protect imidazoles for these reactions is expensive. In our view polylithiated imidazoles are more conveniently prepared by halogen-metal exchange reactions involving polybromoimidazoles. 3-Bromo-2,5-dilithio-1-methylimidazole has been prepared previously[8] in this way from 2,4,5-tribromo-1-methylimidazole and butyl-lithium and hydrolysed to 4-bromo-1-methylimidazole.

In Part 5[1] we have reported how several 1,2- and 2,5-dilithiated imidazoles can be prepared *via* halogen-metal exchange reactions of polybromoimidazoles. We now report how the three bromine atoms in 1-protected 2,4,5-tribomoimidazoles can be replaced stepwise in the order 2 ⟶ 5 ⟶ 4. The starting materials are available in high yields through elemental bromination of imidazole (commercially available at a modest price) and protection on nitrogen by standard procedures of the 2,4,5-tribromoimidazole[4] obtained (**CAUTION**: this compound and its 1-protected derivatives, which are deprotected *in vivo* to give 2,4,5-tribromoimidazole, are neurotoxins[9]). Our strategy provides a convenient route to 4(5)-mono-, 4(5),5(4)-di-, and 2,4(5),5(4)-tri-substituted imidazoles.

1-Protected 2,4,5-tribromoimidazoles do not react regioselectively with 1 mol equiv. of butyl-lithium (in ether or THF at −78 °C): both the 2- and 5-bromine atoms undergo exchange under these conditions.[1] With other organolithium reagents, however, regioselective attack at the 2-bromine atom can be achieved.[1] Thus, 1-benzyl-2,4,5-tribromoimidazole (see Scheme) reacts successively with 1 mol equiv. of phenyl-lithium (in THF at −78 °C) and dimethyl sulphide to give a 72% yield of 1-benzyl-4,5-dibromo-2-methylthioimidazole (**1**) (Scheme).

Treatment of 1-benzyl-2,4,5-tribromoimidazole with 2 mol equiv. of butyl-lithium (in ether or THF at −78 °C) followed by addition of either water or dimethyl sulphide gave 1-benzyl-4-bromoimidazole (**2**) (71% yield) and 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (**3**) (72%), respectively.



Scheme. *Reagents and conditions:* i, 1 × PhLi–THF, −78 °C; ii, 1 × $(MeS)_2$; iii, 2 × BuLi–Et_2O, −78 °C; iv, H_2O; v, 2 × $(MeS)_2$; vi, 2 × BuLi–THF, −78 °C; vii, 1 × BuLi–THF, −78 °C; viii, 5 × BuLi–THF, −78 °C; ix, 3 × $(MeS)_2$; x, DMF; xi, 1 × MeLi–THF, −78 °C

Trilithiated imidazoles have not been reported as far as we are aware.[5] Therefore, we treated 1-benzyl-2,4,5-tribromoimidazole with 3 mol equiv. of butyl-lithium (in THF at −78 °C) and quenched the intermediate polylithiated imidazole with an excess of dimethyl disulphide with a view to preparing 1-benzyl-2,4,6-tris(methylthio)imidazole (**4**). The required compound (**4**) was produced in only 5% yield and the major product was 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (**3**) (71%). When this reaction was repeated using 5 mol equiv. of butyl-lithium and an excess of dimethyl disulphide the tetrasubstituted imidazole (**5**) (33% yield) was isolated. Presumably the tetralithiated intermediate reacts with the butyl bromide

generated in the initial halogen-metal exchange reaction prior to addition of the dimethyl disulphide.

Our difficulty in exchanging the 4-bromine atom for lithium in these systems is probably due to destablisation of any carbanionic character at C-4 both by the adjacent N-3 lone pair (the 'ALP effect' described in a series of papers by Kirk's group [10]) as well as by the carbanionic character at C-5.

To overcome this problem 1-benzyl-2,4,5-tribromoimidazole was treated successively with 2 mol equiv. each of butyl-lithium (in THF at −78 °C) and dimethyl disulphide and the intermediate 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (**3**) was treated further in the same pot with 1 mol equiv. each of butyl-lithium and dimethyl disulphide, which gave 1-benzyl-2,4,5-tris(methylthio)imidazole (**4**) in 67% yield together with the 2,5-bis(methylthio) compound (**3**) (12%).

In a similar way we prepared the 2,5-bis(methylthio) compound (**3**), and then in the same pot added successively 2 mol equiv. of butyl-lithium and 1 mol equiv. of *N,N*-dimethylformamide (DMF), which gave the tetra substituted imidazole (**6**) (46% yield). Introduction of an alkyl group into the 1-protecting group in this way should prove advantageous since the resulting 1-protecting group is rendered sensitive to acid, whereas 1-benzyl groups require reductive removal. The latter deprotection procedures may be inconvenient and can prove costly.

To illustrate further the scope of this new strategy for the synthesis of imidazoles we have prepared compound (**7**) (Scheme) in 60% yield through successive treatment of 1-benzyl-2,4,5-tribromoimidazole in 'one-pot' with the following reagents: (i) 1 mol equiv. of methyl-lithium; (ii) 1 mol equiv. of dimethyl sulphide; (iii) 1 mol equiv. of butyl-lithium; and (iv) 1 mol equiv. of DMF.

The merits or otherwise of the use of different protecting groups for the imidazole nitrogen-atom have been discussed elsewhere.[11–13] They can be removed by standard procedures. 4-Methoxybenzyl used, *e.g.* by Buckle and Rockell [14] for *N*-protection of 1,2,3-triazoles and 3,4-dimethoxybenzyl, used previously, *e.g.* for *N*-protection of pyrroles,[15] are more advantageous than benzyl as protecting groups since they are removed under relatively mild acidic conditions, whereas benzyl is not. We treated 2,4,5-tribromo-1-(4-methoxybenzyl)-imidazole [16] and 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)-imidazole [16] with hot trifluoroacetic acid (addition of anisole is not necessary) and obtained a high yield of 2,4,5-tribromo-imidazole in each case. 2,4,5-Tribromo-1-methoxymethyl-imidazole [16] and 2-benzylthio-4-bromo-1-methoxymethyl-imidazole [1] were deprotected, also in high yields, with hydrochloric acid in aqueous ethanol whilst 4,5-dibromo-1-tritylimidazole readily lost its trityl group in methanol in the presence of aqueous acetic acid (see Experimental section for details).

Gommper and Guggenberger [17] recently synthesised some novel diazadithiafulvalenes using 2,4,5-tris(ethylthio)imidazole.[18] A variety of starting materials of this type should be available by an extension of our methodology.

Experimental

The spectroscopic instruments used and the general experimental conditions employed were the same as those reported by us previously.[1,19] 1-Benzyl-2,4,5-tribromoimidazole, 2,4,5-tribromo-1-(4-methoxybenzyl)imidazole, 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)imidazole, and 2,4,5-tribromo-1-methoxymethylimidazole were prepared as described in Part 4,[16] whilst 2-benzylthio-4-bromo-1-methoxymethylimidazole and 4,5-dibromo-1-tritylimidazole were prepared as described in Part 5.[1]

1-Benzyl-4,5-dibromo-2-methylthioimidazole (**1**).—2.4M-Phenyl-lithium in cyclohexane–ether (5.3 ml, 12.72 mmol) was added dropwise to a stirred solution of 1-benzyl-2,4,5-tribromoimidazole (5.0 g, 12.65 mmol) in anhydrous THF (75 ml) at −78 °C under nitrogen and the resulting mixture was stirred for a further 30 min. Dimethyl disulphide (1.2 g, 12.76 mmol) was added dropwise and the mixture was allowed to warm slowly to ambient temperature. Water (25 ml) was added, the organic layer was separated off, and the aqueous layer was extracted several times with chloroform. The organic layer and extracts were combined, dried ($MgSO_4$), and distilled to give an oil which was flash chromatographed on silica. Elution with ethyl acetate–light petroleum (b.p. 60—80 °C) yielded the *title compound* (3.32 g, 72%), as a pale yellow oil; δ($CDCl_3$) 2.55 (3 H, s, SMe), 5.12 (2 H, s, NCH_2), and 7.00—7.50 (5 H, m, ArH) (Found: C, 36.25; H, 2.5; N, 7.8%; M^+, 360. $C_{11}H_{10}Br_2N_2S$ requires C, 36.5; H, 2.8; N, 7.7%; *M*, 360).

1-Benzyl-4-bromoimidazole (**2**).—1.78M-Butyl-lithium in hexane (68.2 ml, 0.12 mol) was added dropwise to a stirred solution of 1-benzyl-2,4,5-tribromoimidazole (20.0 g, 50.63 mmol) in ether (175 ml) at −78 °C under nitrogen and the resulting mixture was stirred for a further 1 h at this temperature. Water (50 ml) was added and work-up using standard procedures (ether as the extraction solvent) gave an oil which was chromatographed on alumina. Ethyl acetate–light petroleum eluted the *product* (**2**) (8.5 g, 71%), m.p. 88—90 °C (from ether–light petroleum); δ($CDCl_3$) 5.05 (2 H, s, NCH_2), 6.85 (1 H, s, 5-H), and 7.05—7.50 (6 H, m, ArH) (Found: C, 50.95; H, 3.8; N, 11.9%; M^+, 236. $C_{10}H_9BrN_2$ requires C, 50.65; H, 3.8; N, 11.8%; *M*, 236).

1-Benzyl-4-bromo-2,5-bis(methylthio)imidazole (**3**).—This was prepared similarly as a pale yellow oil (72%); δ($CDCl_3$) 2.01 (3 H, s, 5-SMe), 2.63 (3 H, s, 2-SMe), 5.23 (2 H, s, NCH_2), and 7.00—7.60 (5 H, m, ArH) (Found: M^+, 327.9744. $C_{12}H_{13}BrN_2S_2$ requires *M*, 327.9704).

A similar reaction, with the exception that 5 mol equiv. of butyl-lithium were used and an excess of dimethyl disulphide, gave 2,4,5-*tris(methylthio)*-1-(1-*phenylpentyl)imidazole* (**5**) (33%) as an oil; δ($CDCl_3$) 0.90 (3 H, t, Me), 0.70—1.60 (4 H, m, 2 × CH_2), 1.85 (3 H, s, 5-SMe), 2.50 (2 H, m, CH_2), 2.52 (3 H, s, 4-SMe), 2.56 (3 H, s, 2-SMe), 5.70 (1 H, dd, CH), and 7.30 (5 H, m, ArH) (Found: M^+, 352.1100. $C_{17}H_{24}N_2S_3$ requires *M*, 352.1100). The product balance was an intractable tar.

1-Benzyl-2,4,5-tris(methylthio)imidazole (**4**).—1.78M-Butyl-lithium in hexane (28.4 ml, 50.6 mmol) was added dropwise to a stirred solution of 1-benzyl-2,4,5-tribromoimidazole (10.0 g, 25.3 mmol) in THF (150 ml) at −78 °C under nitrogen and the resulting mixture was stirred at −78 °C for a further 30 min. Dimethyl disulphide (4.7 g, 50.6 mmol) was added dropwise and the mixture was allowed to warm slowly to room temperature. The mixture was cooled again to −78 °C, 1.78M-butyl-lithium in hexane (14.2 ml, 25.3 mmol) was added dropwise, the resulting mixture was stirred for 30 min, dimethyl disulphide (2.35 g, 25.3 mmol) was added dropwise, and the mixture was allowed to warm slowly to room temperature. Water (50 ml) was added and work-up in the usual way gave an oil which was flash chromatographed on silica. Ethyl acetate–light petroleum (b.p. 60—80 °C) eluted: (i) 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (**3**) (1.02 g, 12%), identical with the sample prepared as described before; and (ii) 1-*benzyl*-2,4,5-*tris(methylthio)imidazole* (**4**) (5.04 g, 67%); δ($CDCl_3$) 2.00 (3 H, s, 5-SMe), 2.50 (3 H, s, 4-SMe), 2.58 (3 H, s, 2-SMe), 5.20 (2 H, s, NCH_2), and 7.00—7.50 (5 H, m, ArH) (Found: M^+, 296.0499. $C_{13}H_{16}N_2S_3$ requires *M*, 296.0476).

2,5-*Bis*(*methylthio*)-1-(1-*phenylpentyl*)*imidazole*-4-*carbaldehyde* (**6**).—Using the techniques described in the preceding experiments 1-benzyl-2,4,5-tribromoimidazole (5.0 g, 12.65 mmol) in THF (100 ml) was treated successively with the following reagents: (i) 1.78M-butyl-lithium in hexane (14.2 ml, 25.3 mmol); (ii) dimethyl disulphide (2.35 g, 25.3 mmol); (iii) 1.78M-butyl-lithium in hexane (17.0 ml, 30.4 mmol); (iv) DMF (1.1 g, 15.7 mmol); and (v) water (30 ml). Work-up in the usual way gave an oil which was flash chromatographed on silica. Ethyl acetate–light petroleum (b.p. 60—80 °C) eluted the *aldehyde* (**6**) (1.94 g, 46%) as a pale yellow oil which solidified, m.p. 75—77 °C (from ethanol); $\nu_{max.}$ 1 690 cm^{-1} (CO); $\delta(CDCl_3)$ 0.90 (3 H, t, Me), 1.05—1.60 (4 H, m, 2 × CH_2), 2.10 (3 H, s, 5-SMe), 2.62 (3 H, s, 2-SMe), 2.50 (2 H, m, CH_2), 5.80 (1 H, dd, CH), 7.30 (5 H, m, ArH), and 10.05 (1 H, s, CHO) (Found: C, 60.95; H, 6.6; N, 8.8%; M^+, 334. $C_{17}H_{22}N_2OS_2$ requires C, 61.0; H, 6.6; N, 8.4%; *M*, 334).

1-*Benzyl*-4-*bromo*-2-*methylthioimidazole*-5-*carbaldehyde* (**7**).—Using the techniques described in the preceding experiments 1-benzyl-2,4,5-tribromoimidazole (5.0 g, 12.65 mmol) in THF (75 ml) was treated successively with the following reagents: (i) 1.84M-methyl-lithium in ether–cyclohexane (6.9 ml, 12.65 mol); (ii) dimethyl disulphide (1.2 g, 12.65 mmol); (iii) 1.78M-butyl-lithium in hexane (7.1 ml, 12.65 mmol); (iv) DMF (0.92 g, 12.65 mmol); and (v) water (50 ml). Work-up and chromatography as described before gave *aldehyde* (**7**) (2.38 g, 60%), m.p. 76—78 °C [from light petroleum (b.p. 60—80 °C)]; $\nu_{max.}$ 1 660 cm^{-1} (CO); $\delta(CDCl_3)$ 2.73 (3 H, s, SMe), 5.53 (2 H, s, NCH_2), 7.33 (5 H, m, ArH), and 9.60 (1 H, s, CHO) (Found: C, 46.1; H, 3.6; N, 8.9%; M^+, 310. $C_{12}H_{11}BrN_2OS$ requires C, 46.3; H, 3.6; N, 9.0%; *M*, 310).

Deprotection of 2,4,5-*Tribromo*-1-(3,4-*dimethoxybenzyl*)*imidazole*.—A mixture of the title compound (2.5 g, 5.49 mmol), trifluoroacetic acid (6 ml), concentrated sulphuric acid (1 ml), and anisole (25 ml) was heated under reflux overnight. The solvents were distilled off under reduced pressure and water (25 ml) was added to the residue. The precipitated solid was filtered off and recrystallised from aqueous ethanol to give 2,4,5-tribromoimidazole (1.36 g, 81%), m.p. 218—220 °C, identical in other respects with an authentic sample.

2,4,5-Tribromo-1-(4-methoxybenzyl)imidazole (2.5 g, 5.85 mmol) was deprotected similarly using trifluoroacetic acid (15 ml) by heating at 67 °C for 6—7 h, and gave 2,4,5-tribromoimidazole (1.65 g, 93%), m.p. 220—221 °C, identical in other respects with an authentic sample.

Deprotection of 2-*Benzylthio*-4-*bromo*-1-*methoxymethylimidazole*.—A mixture of the title compound (1.0 g, 3.19 mmol), 50% aqueous ethanol (50 ml), and concentrated hydrochloric acid (25 ml) was heated under reflux for 5 h, after which the ethanol was distilled off under reduced pressure, and sodium carbonate was added to the aqueous mixture until gas evolution ceased. Extraction with chloroform gave a pale yellow oil which solidified. Recrystallisation of the resulting solid from ethanol gave 2-*benzylthio*-4-*bromoimidazole* (0.7 g, 81%), m.p. 113—114 °C; $\delta(CDCl_3)$ 4.18 (2 H, s, SCH_2), 7.03 (1 H, s, 5-H), and 7.10—7.50 (5 H, m, ArH) (Found: C, 44.8; H, 3.4; N, 10.6%; M^+, 268. $C_{10}H_9BrN_2S$ requires C, 44.6; H, 3.4; N, 10.4%; *M*, 268).

2,4,5-Tribromo-1-methoxymethylimidazole similarly gave 2,4,5-tribromoimidazole (86%), m.p. 218—220 °C, identical in other respects with an authentic sample.

Deprotection of 4,5-*Dibromo*-1-*tritylimidazole*.—A solution of the title compound (5.0 g, 10.68 mmol) in methanol (50 ml) containing 5% acetic acid (25 ml) was heated under reflux for 4 h. The methanol was distilled off under reduced pressure and water (50 ml) was added to the residue. The precipitate was filtered off, washed well with chloroform, and recrystallised from ethyl acetate, to give 4,5-dibromoimidazole (1.85 g, 77%), m.p. 225—226 °C, identical in other respects with an authentic sample.

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References

1 Part 5, B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1987, preceding paper.
2 Preliminary communications are given in ref. 2 cited in the preceding reference.[1]
3 P. Jutzi and W. Sakriss, *Chem. Ber.*, 1973, **106**, 2815.
4 K.-E. Stensiö, K. Wahlberg, and R. Wahren, *Acta Chem. Scand.*, 1973, **27**, 2179.
5 B. Iddon, *Heterocycles*, 1985, **23**, 417.
6 D. J. Chadwick and R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 1984, 481; see also A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, 1986, **42**, 2351.
7 A. J. Carpenter, D. J. Chadwick, and R. I. Ngochindo, *J. Chem. Res.*, 1983, (*S*), 196; (*M*), 1913.
8 M. El Borai, A. H. Moustafa, M. Anwar, and F. I. Abdel Hay, *Pol. J. Chem.*, 1981, **55**, 1659.
9 R. D. Verschoyle, A. W. Brown, and C. A. Thompson, *Arch. Toxicol.*, 1984, **56**, 109; J. M. Barnes, *Sci. Basis Med., Ann. Rev.*, 1969, 183; V. H. Parker, *Biochem. Pharmacol.*, 1973, **22**, 1203; R. B. Beechey, *Biochem. J.*, 1966, **98**, 284.
10 See K. L. Kirk, *J. Heterocycl. Chem.*, 1985, **22**, 57.
11 C. van der Stelt, P. S. Hofman, and A. B. H. Funcke, *Eur. J. Med. Chem. Chim. Ther.*, 1978, **13**, 251.
12 R. I. Ngochindo, Ph.D. Thesis, University of Liverpool (1982).
13 N. Khan, Ph.D. Thesis, University of Salford (1985).
14 D. R. Buckle and C. J. M. Rockell, *J. Chem. Soc., Perkin Trans. 1*, 1982, 627.
15 M. I. Jones, C. Froussois, and D. A. Evans, *J. Chem. Soc., Chem. Commun.*, 1976, 472.
16 Part 4, B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1437.
17 R. Gommper and R. Guggenberger, *Tetrahedron*, 1986, **42**, 839.
18 K. H. Büchel and H. Erdmann, *Chem. Ber.*, 1976, **109**, 1625.
19 Part 1, B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 271.

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