Tetrahedron Letters,Vol.27,No.14,pp 1635-1638,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

A CONVENIENT SYNTHESIS OF 4(5)-MONO-, 4,5-DI-, AND 2,4,5-TRI-SUBSTITUTED IMIDAZOLES[1]

Brian Iddon* and Nazir Khan

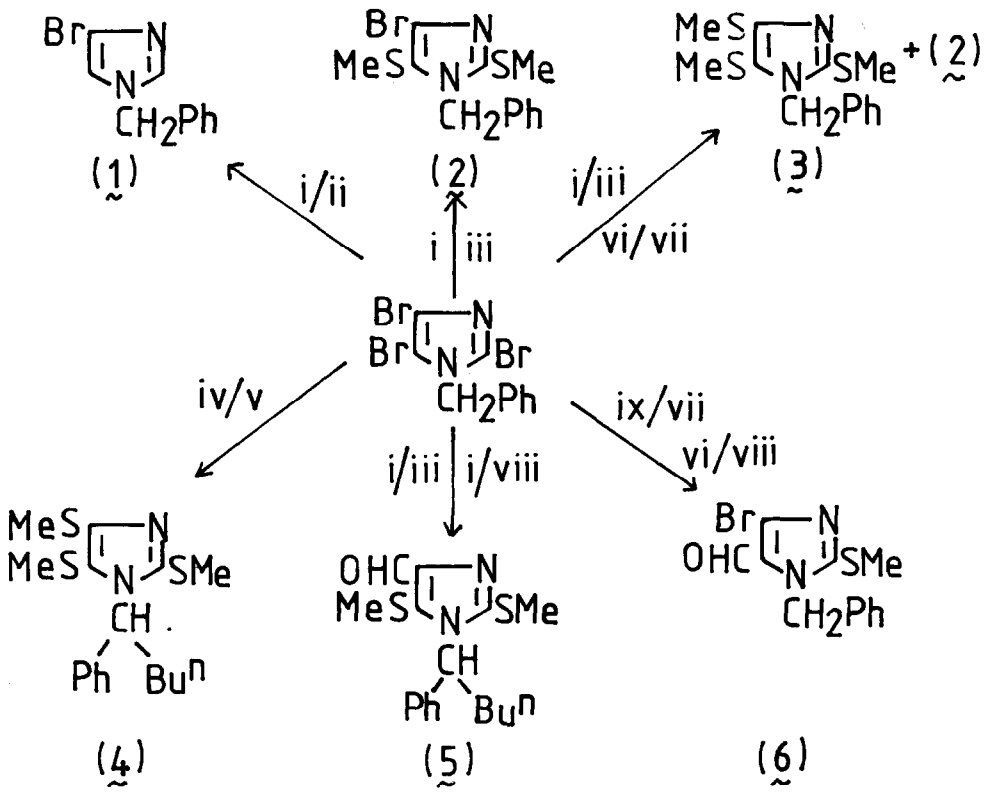
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT

Summary: A procedure is described for the stepwise introduction of substituents (hydrogen included) into the imidazole ring by FGI of the bromine atoms in 1-protected 2,4,5-tribromoimidazoles in the order 2 → 5 → 4 using halogen-metal exchange techniques.

Despite the considerable industrial importance of imidazoles and a widespread interest in their chemistry many simple imidazoles are not readily accessible.[5] It appeared to us, therefore, that a versatile synthesis of imidazole derivatives starting from a relatively cheap and, preferably, commercially available imidazole would be useful and we now describe such a synthesis which utilises 1-protected 2,4,5-tribromoimidazoles. These are available[3] in high yields through bromination of imidazole and protection on nitrogen by standard procedures of the 2,4,5-tribromoimidazole[6] obtained (71% yield: CAUTION - this compound and its 1-protected derivatives are reported to be neurotoxic[7]).

The potential of our strategy is illustrated by the reactions of 1-benzyl-2,4,5-tribromoimidazole (Scheme). Treatment of this compound with two mol. equivalents of n-BuLi in THF at -78°C followed by addition of either water or dimethyl disulphide gave 1-benzyl-4-bromoimidazole (1; 71% yield), m.p. 88-90°C [from light petroleum (b.p. 40-60°C)-ether] or 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (2; 72%), as a pale yellow oil, respectively.

Whereas 1,2- and 2,5-dilithiated imidazoles are known 2,4,5-trilithiated imidazoles are not.[4] Therefore, we treated 1-benzyl-2,4,5-tribromoimidazole with three mol. equivalents of n-BuLi (THF/-78°C) and quenched the reaction mixture with an excess of dimethyl disulphide with a view to preparing 1-benzyl-2,4,5-tris(methylthio)imidazole (3). However, the required compound (3) was obtained in only 5% yield and the major product was 1-benzyl-4-bromo-2,5-bis(methylthio)imidazole (2; 71%). This reaction was repeated using five mol. equivalents of n-BuLi. In this case a "tetra-anion" was generated by halogen-metal exchange of the



Reagents: (i) 2 x n-BuLi/THF/-78°C; (ii) H_2O; (iii) 2 x MeSSMe; (iv) 5 x n-BuLi/THF/-78°C; (v) 3 x MeSSMe; (vi) 1 x n-BuLi/THF/-78°C; (vii) 1 x MeSSMe; (viii) DMF; (ix) 1 x MeLi/THF/-78°C.

Scheme

three bromine atoms and metallation in the benzylic methylene group, as evidenced by the fact that quenching the reaction mixture with three mol. equivalents of dimethyl disulphide gave compound (4; 33% yield) as an oil. The n-butyl group is introduced into the protecting group *via* reaction of the CHLiPh moiety with the n-BuBr generated by initial halogen-metal exchange.

The difficulty experienced in replacement of the 4-Br atom in our system by Li is probably due to destabilisation of the C-4 anion by the adjacent lone pair (the "ALP effect" described by Kirk *et al.*[8]) as well as by the carbanionic character at C-5. This problem was overcome by reacting the 1-benzyl-2,4,5-tribromoimidazole successively with two mol. equivalents of n-BuLi (THF/-78°C), two mol. equivalents of dimethyl disulphide, then a further equivalent of n-BuLi followed by addition of a third mol. equivalent of dimethyl disulphide. This "one pot" procedure gave 1-benzyl-2,4,5-tris(methylthio)imidazole (3)

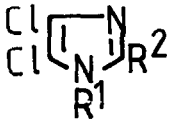
as an oil in 67% yield together with the 2,5-bis(methylthio)-compound (2; 12%).

In a similar way 1-benzyl-2,4,5-tribromoimidazole was reacted successively in one pot with two mol. equivalents of n-BuLi (THF/-78°C), two mol. equivalents of dimethyl disulphide, then two further mol. equivalents of n-BuLi followed by addition of NN-dimethylformamide (DMF), to give the tetra-substituted imidazole (5; 46% yield), m.p. 75-77°C (from ethanol). Treatment of the same starting material successively in one pot with one mol. equivalent of MeLi (addition of one mol. equivalent of n-BuLi results in replacement of both the 2- and 5-Br atoms[3]), one mol. equivalent of dimethyl disulphide, then one mol. equivalent of n-BuLi followed by addition of one mol. equivalent of DMF yields the imidazole-5-carbaldehyde (6; 60% yield), m.p. 76-78°C [from light petroleum (b.p. 60-80°C)].

Recently we[3] reported an application of this methodology to the synthesis of thieno-[2,3-d]imidazoles. In that work it proved possible to replace the 2-Br atom by hydrogen or another substituent, then interconvert the 5-Br atom into a formyl group and, finally, replace the 4-Br atom (by nucleophilic substitution, without protecting the aldehyde).

Using our methodology it should be possible to introduce stepwise a range of substituents (including H) into 1-protected 2,4,5-tribromoimidazoles in the order 2 → 5 → 4. Protecting groups can be removed by standard procedures. 4-Methoxybenzyl and 3,4-dimethoxybenzyl are more advantageous than benzyl as protecting groups since they are more readily removed. Thus, e.g., 2,4,5-tribromo-1-(4-methoxybenzyl)imidazole is deprotected quantitatively in hot trifluoroacetic acid. We have investigated a range of protecting groups and the results of this work will appear elsewhere.

Dirlam et al.[9] reacted the dianion (7) with various aromatic aldehydes and we checked and extended this work by the synthesis of compounds (8; 52%), m.p. 190-191°C (from ethanol) (lit.,[9] 190-191°C), (9; 48%), m.p. 160-162°C (from aqueous ethanol) (lit.,[10] 159-160°C), and (10; 42%), m.p. 112-114°C [from light petroleum (b.p. 40-60°C)], through reaction of the dianion (7) with DMF, CO_2, or elemental sulphur (see before), respectively. In a similar manner 2,4,5-tribromoimidazole gave dianion (11) with two mol. equivalents of n-BuLi (THF/-78°C) and this was reacted with 10% aq. HCl, DMF, CO_2, or elemental sulphur, respectively, to give compounds (12; 40%), m.p. 225-226°C (from aqueous ethanol) (lit.,[11] m.p. 225°C), (13; 43%), m.p. 192-194°C (from ethyl acetate), (14; 57%), m.p. 173-175°C (with decomp.) (from aqueous ethanol) [lit.,[10] m.p. 171-173°C (with decomp.)], and (15; 40%), m.p. 86-88°C [from ethyl acetate-light petroleum (b.p. 60-80°C)]. 4,5-Dibromoimidazole (12) was prepared in better yield (67%) by treating 2,4,5-tribromoimidazole with two mol.

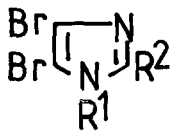


(7) $R^1 = R^2 = Li$

(8) $R^1 = H$, $R^2 = CHO$

(9) $R^1 = H$, $R^2 = CO_2H$

(10) $R^1 = H$, $R^2 = SBu^n$



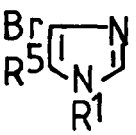
(11) $R^1 = R^2 = Li$

(12) $R^1 = H$, $R^2 = H$

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

(14) $R^1 = H$, $R^2 = CO_2H$

(15) $R^1 = H$, $R^2 = SBu^n$



(16) $R^1 = R^5 = Li$

(17) $R^1 = H$, $R^5 = C(OH)Ph_2$

equivalents of ethylmagnesium bromide (THF/reflux) and hydrolysing the product with 10% HCl.

When 4,5-dibromoimidazole was reacted successively with two mol. equivalents of n-BuLi (THF/-78°C), benzophenone, and acid, it gave only a 17% yield of carbinol (17), m.p. 166-167°C (from chloroform), via formation of the dianion (16). By judicious choice of reaction conditions it may be possible to improve on this yield, thereby allowing various 4,5-disubstituted imidazoles to be prepared from 2,4,5-tribromoimidazole without the need to protect the imidazole N-atom. We are pursuing this work further.

We thank the S.E.R.C. for a research studentship (to N.K.).

References

1. For our previous work in this area see refs. 2-4.
2. B. Iddon and B.L. Lim, J. Chem. Soc., Perkin Trans. I, 1983, 271, 279, and 735, and J. Chem. Soc., Chem. Comm., 1981, 1095.
3. B. Iddon, N. Khan, and B.L. Lim, J. Chem. Soc., Chem. Comm., 1985, 1428.
4. B. Iddon, Heterocycles, 1985, 23, 417.
5. A.F. Pozharskii, A.D. Garnovskii, and A.M. Simonov, Russ. Chem. Rev., 1966, 35, 122; K. Schofield, M.R. Grimmett, and B.R.T. Keene, "Heteroaromatic Nitrogen Compounds; The Azoles", Cambridge University Press, London and New York, 1976; M.R. Grimmett, Adv. Heterocycl. Chem., 1970, 12, 103 and 1980, 27, 241.
6. K.-E. Stensiö, K. Wahlberg, and R. Wahren, Acta Chem. Scand., 1973, 27, 2179.
7. R.D. Verschoyle, A.W. Brown, and C.A. Thompson, Arch. Toxicol., 1984, 56, 109.
8. K.L. Kirk, J. Heterocycl. Chem., 1985, 22, 57.
9. J.P. Dirlam, R.B. James, and E.V. Shoop, J. Org. Chem., 1982, 47, 2196.
10. J.P. Dirlam, R.B. James, and E.V. Shoop, J. Heterocycl. Chem., 1980, 17, 409.
11. I.E. Balaban and F.L. Pyman, J. Chem. Soc., 1922, 121, 947.

(Received in UK 10 January 1986)