Direct Monobromination of Imidazole and *N*-Methylimidazole

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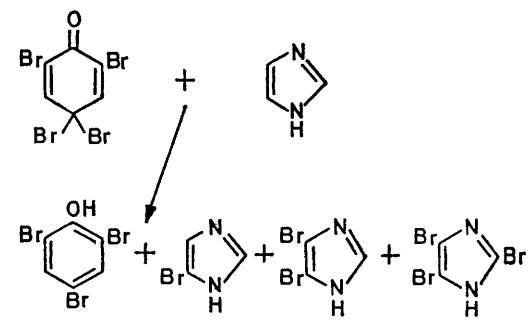
Monobromination of imidazole, *N*-methylimidazole, and indole is achieved in high yield by treatment with 2,4,4,6-tetrabromocyclohexa-2,5-dienone.

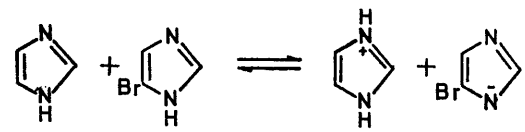
HALOGENATION reactions of the imidazole ring [1,2] are markedly affected by the reaction conditions, which determine whether imidazole reacts as conjugate acid, neutral molecule, or conjugate base. The direct bromination of imidazole and *N*-methylimidazole with molecular bromine usually yields only 2,4,5-tribromoimidazoles [3,4] (probably *via* *N*-bromo-compounds).[5,6] Ring opening occurs when imidazole reacts with bromine at low acidities,[7] or with *N*-bromosuccinimide.[8] For these reasons, monobromo- and dibromo-imidazoles can be obtained only by means of selective debromination of tribromoimidazoles; the procedures involved are tedious and low yields are obtained.

We have shown previously [9,10] that 2,4,4,6-tetrabromocyclohexa-2,5-dienone (I) can be used for selective monobromination of highly activated aromatic substrates; we now report the monobromination of imidazole, *N*-methylimidazole, and indole with this reagent.

Imidazole reacts readily with bromocyclohexadienone (I) in ethanol to give a mixture of bromoimidazoles in which 4-bromoimidazole predominates (Scheme 1). The formation of polybromoimidazoles can be explained in terms of an equilibrium between imidazole and monobromoimidazole [11] (Scheme 2). As a result, the conjugate base of the latter is formed, which should be susceptible to further bromination. In fact, addition



SCHEME 1



SCHEME 2

[1] J. J. Eisch, *Adv. Heterocyclic Chem.*, 1966, **7**, 1.
[2] M. R. Grimmett, *Adv. Heterocyclic Chem.*, 1970, **12**, 103.
[3] J. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, 1922, 947.
[4] J. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, 1924, 1564.
[5] H. Baumgaertel and H. Zimmermann, *Z. Naturforsch.*, 1963, **18b**, 406.
[6] P. Linda, *Tetrahedron*, 1969, **25**, 3297.
[7] M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1965, 1051.
[8] G. L. Schmir and L. A. Cohen, *Biochemistry*, 1965, **4**, 533.
[9] V. Caló, F. Ciminale, L. Lopez, G. Pesce, and P. E. Todesco, *Chimica e Industria*, 1971, **53**(5), 467.
[10] V. Caló, F. Ciminale, L. Lopez, and P. E. Todesco, *J. Chem. Soc.* (*C*), 1971, 3652.
[11] H. A. Staab and A. Mannschreck, *Tetrahedron Letters*, 1962, 913.

of imidazolium toluene-*p*-sulphonate [12] to the reaction medium, displacing the equilibrium to the left, causes a large increase in the ratio of mono- to poly-brominated products. In agreement with the foregoing hypothesis, bromination of *N*-methylimidazole (where the possibility of proton transfer is lacking) gives 5-bromo-1-methylimidazole, with only traces of the 4,5-dibromo-derivative. Bromination of indole leads to 3-bromoindole only, in 88% yield. The method appears more convenient than those previously reported (*i.e.* the use of dioxan dibromide [13] or the Weissgerber procedure [14]), allowing selective bromination and giving high yields even with very reactive heterocycles.

EXPERIMENTAL

Reagents and Products.—2,4,4,6-Tetrabromocyclohexa-2,5-dienone was synthesized as previously reported.[10] 4-Bromoimidazole had m.p. 131° (lit.,[3] 131°); picrate, m.p. 160° (lit.,[3] 160°). 4,5-Dibromoimidazole had m.p. 228° (lit.,[3] 225°). 2,4,5-Tribromoimidazole had m.p. 220° (lit.,[3] 220°). 5-Bromo-1-methylimidazole had m.p. 46° (lit.,[4] 46°); picrate, m.p. 188° (lit.,[4] 190°); τ ($CDCl_3$) 2·49 (2-H), 3·01 (4-H), and 6·42 (CH_3). 4,5-Dibromo-1-methylimidazole had m.p. 80° (lit.,[4] 80°); picrate m.p. 146° (lit.,[4] 149°); τ (CCl_4) 2·72 (2-H) and 6·46 (CH_3).

Imidazolium toluene-*p*-sulphonate, m.p. 146° (lit.,[12] 146—148°), was synthesized from equimolecular amounts of imidazole and toluene-*p*-sulphonic acid in ethanol and crystallized from the same solvent.

Bromination of Imidazole.—The dienone (I) (3 g) was added to the imidazole (0·5 g, 1 mol. equiv.) dissolved in ethanol (30 ml) with stirring at room temperature. The solution was directly chromatographed on a short column of silica gel [eluant benzene–acetone (5 : 2 v/v)]. Tribromophenol (2·3 g), tribromoimidazole (0·2 g, 27%), 4,5-dibromoimidazole (0·15 g, 28%), 4-bromoimidazole (0·14 g, 41%), and unchanged imidazole (0·34 g) were eluted in that order.

Bromination of Imidazole in the Presence of Imidazolium Toluene-p-sulphonate.—Imidazole (0·5 g) and imidazolium toluene-*p*-sulphonate (7 g, 3 mol. equiv.) were dissolved in ethanol (30 ml), and solid dienone (I) (3 g, 1 mol. equiv.) was added. After chromatography, tribromophenol (2·3 g), traces of tribromoimidazole, 4,5-dibromoimidazole (0·12 g, 13%), 4-bromoimidazole (0·46 g, 79%), and unchanged imidazole (0·24 g) were obtained.

Bromination of N-Methylimidazole.—Similar bromination with an equimolar amount of dienone (I) gave 5-bromo-1-methylimidazole (66% yield after chromatography) with traces of 4,5-dibromo- and tribromo-derivatives. The reaction between *N*-methylimidazole (0·5 g) and the dienone (I) (5 g, 2 mol. equiv.) in ethanol (30 ml) gave 4,5-dibromo-1-methylimidazole in 65% yield.

Bromination of Indole.—Indole (0·5 g) and sodium acetate (0·3 g, 0·1 mol. equiv.) were dissolved in anhydrous methanol (40 ml) and solid dienone (I) was addded (1·73 g, 0·1 mol. equiv.) with stirring at room temperature. Column chromatography [silica gel; eluant benzene–acetone (5 : 2 v/v)] gave 3-bromoindole (0·73 g, 88%), m.p. 65° (lit.,[13] 66°).

This work was supported by a grant from the Consiglio Nazionale delle Ricerche, Rome.

[2/963 *Received*, 1*st May*, 1972]

[12] H. A. Staab and K. Wendel, *Annalen*, 1966, **694**, 86.
[13] K. Piers, C. Meimaroglou, R. V. Jardine, and R. K. Brown, *Canad. J. Chem.*, 1963, **41**, 2399.
[14] R. Weissgerber, *Ber.*, 1913, **46**, 652.