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Synthesis of Brominated Imidazoles

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Bromination of imidazole in acetic acid containing sodium acetate gives 2,4,5-tribromoimidazole in a good yield. 4(5)-(2-Chloroethyl)imidazole, imidazole-4(5)-carbaldehyde, and 4(5)-hydroxymethylimidazole have been brominated by the same method. Debromination of 2,4,5-tribromoimidazole with sodium sulphite or butyllithium gives 4(5)-bromoimidazole. A simple synthesis of 4(5)-(2-bromoethyl)-imidazole is described.

In connection with studies on compounds capable of reactivating phosphorylated acetylcholinesterase, some imidazole derivatives were prepared because of their known catalytic activity.[1] In the present communication the synthesis of some imidazole derivatives containing bromo substituents is reported.

Bromination of imidazole to 2,4,5-tribromoimidazole occurs readily.[2] Attempted monobromination,[3,4] however, gives mixtures containing mono-, di-, and tribromo derivatives, indicating that deactivation of the imidazole ring by a bromo substituent is insignificant. Neither did we, using several different bromination procedures, achieve monobromination (see Experimental).

The yield of 2,4,5-tribromoimidazole is reportedly about 30 %.[2] This low figure is probably explained by a formation of unreactive imidazole hydrobromide and, to some extent, degradation.[5] We therefore investigated bromination in the presence of a base, which should neutralise the hydrogen bromide formed, as has been done in the bromination of other heterocyclics.[6]

Bromination of imidazole in acetic acid containing sodium acetate gave a good yield of 2,4,5-tribromoimidazole (78 %). Bromination of 4(5)-(2-chloroethyl)imidazole using the same method was also efficient and yielded the dibromo compound (76 %). Imidazole 4(5)-carbaldehyde, however, gave only a moderate yield of a monobrominated product. This proved to be the 5(4)-bromoimidazole 4(5)-carbaldehyde, as indicated by its NMR spectrum (Table

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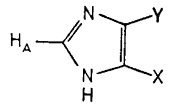
1) and by its oxidation to the known 5(4)-bromoimidazole 4(5)-carboxylic acid. In the latter bromination, 2,4,5-tribromoimidazole was also formed. This was also the main product isolated on bromination of 4(5)-hydroxymethylimidazole.

Selective debromination of 2,4,5-tribromoimidazole with sodium sulphite has been described by Balaban and Pyman,[2] who obtained 4(5)-bromoimidazole (57 %) together with dibromo- and sulphonated derivatives. On debromination of the crude reaction product, containing the tribromo derivative obtained on bromination of imidazole, 4(5)-bromoimidazole was formed in a 62 % yield. The same compound was also prepared by treatment of 2,4,5-tribromoimidazole with butyllithium at 0°, followed by hydrolysis of the trilithiated imidazole with methanol at −70°. Small amounts of 4(5)-bromo-5(4)-butylimidazole and 4,5-dibromoimidazole were also obtained. Also 4(5)-Bromoimidazole reacted with butyllithium. In a separate experiment a 98 % yield of imidazole was isolated after debromination. When the hydrolysis was carried out with deuteriated methanol, 4(5)-deuterio-imidazole was isolated.

For the synthesis of various *N*-substituted aminoethyl imidazoles we needed 4(5)-(2-bromoethyl)imidazole. This substance, which is more reactive than the corresponding chloro derivative, has been prepared in low over-all yields by multistep synthesis.[7–10] We prepared it by deamination of histamine in the presence of bromide. Deamination of primary amines generally gives a mixture of products and is of limited value in synthesis. However, 4(5)-(2-bromoethyl)imidazole was isolated in a 47 % yield after treatment of histamine with nitrous acid and potassium bromide. The bromoethylimidazole was extracted with chloroform, leaving the main by-product 4(5)-(2-hydroxyethyl)-imidazole in the aqueous phase. A minor by-product also extracted with chloroform was 4(5)-bromo-5(4)-(2-bromoethyl)imidazole. 4(5)-(2-Bromoethyl)-

Table 1. δ-Values (ppm) for ring- and aldehyde protons in some substituted imidazoles.



X	Y	H_A	H_Y	H_X	CHO	Solvent
COOH [11]	H	9.03	8.52	–	–	CF_3COOH
Br [11]	H	8.90	7.67	–	–	CF_3COOH
CHO	H	9.05	8.43	–	10.07	CF_3COOH
CHO	H	8.03	8.03	–	9.82	DMSO(d_6)
CHO	Br	8.15	–	–	9.75	DMSO(d_6)
CHO	Br	9.02	–	–	9.88	CF_3COOH
CH_2CH_2Br	H	8.68	7.43	–	–	CF_3COOH
CH_2CH_2Br	Br	8.68	–	–	–	CF_3COOH
H	H	8.78	7.56	7.56	–	D_2O [a]
D	H	8.87	7.62	–	–	D_2O [a]

[a] As the hydrochloride. Internal standard sodium trimethylsilylpropane-sulphonic acid.

imidazole is very reactive and should be stored as the hydrobromide salt. *N*-Alkylated derivatives may otherwise be formed from the free base by interalkylation.

Relevant NMR resonances from the imidazole derivatives prepared are given in Table 1.

EXPERIMENTAL

Melting points are corrected. NMR-spectra were recorded on a Varian A-60 instrument. Chemical shifts are given in ppm (δ) relative to TMS as an internal standard. Mass spectra were obtained on an LKB 9000 instrument at 70 eV (direct inlet). All compounds containing bromine and/or chlorine gave molecular ions with the expected isotope distribution. Reactions involving butyllithium were carried out anhydrously under purified argon. Tetrahydrofuran was distilled from lithium aluminium hydride immediately before use. Solutions of butyllithium (Merck, 20 % in hexane) were analysed by the double titration procedure of Gilman and Haubein.[12] The sodium acetate used contained about 1 % water. Concentrations were performed under reduced pressure.

Chromatography. TLC was performed on layers of silica gel (HF_{254} or DC-Fertigplatten F_{254}, Merck) and column chromatography on silica gel (0.05 – 0.2 mm, Merck). Imidazoles were detected by spraying with a 1 % solution of Echtblausaltz B (Merck) and then with M NaOH. Dragendorff's reagent and 2,4-dinitrophenylhydrazine (2,4-DNPH) were also used. TLC of imidazole, mono-, di-, and tribromoimidazole was obtained with ethyl acetate or ethyl acetate-water-methanol-acetone (95:5:5:25) as eluent.

2,4,5-Tribromoimidazole. Bromine (9.6 g) in anhydrous acetic acid (20 ml) was added during 30 min to a stirred solution of imidazole (1.36 g) and sodium acetate (20 g) in acetic acid (180 ml). When about one third of the bromine had been consumed, more sodium acetate (5 g) was added. Stirring was continued for 2.5 h. During this time tribromoimidazole began to separate. The acetic acid was evaporated and water (600 ml) was added. The white precipitate, consisting of tribromoimidazole, was collected, washed with water and dried. Yield: 4.30 g, 71 %, m.p. 221 – 222° (lit.[2] 220 – 222°). The mother liquor was concentrated and extracted with ether, yielding a mixture (0.75 g) containing imidazole, dibromoimidazole and tribromoimidazole. Fractional precipitation [2] permitted the isolation of dibromoimidazole (0.08 g, 2 %) and tribromoimidazole (0.40 g, 7 %).

Bromination of 4(5)-(2-chloroethyl)imidazole. The hydrochloride of the title compound (1.0 g) was brominated with bromine (2.2 g in 10 ml acetic acid) and sodium acetate (5.9 g) in acetic acid (125 ml) as described above for imidazole. The concentrated product was extracted with ether (3 × 150 ml). The presence of two Echtblau positive compounds in the ether extract was demonstrated with TLC (ethyl acetate). Chromatography on a silica gel column (80 g) with chloroform-ethyl acetate 1:1 yielded 2,4(5)-dibromo-5(4)-(2-chloroethyl)imidazole, 1.31 g, 76 %. Recrystallisation from benzene gave the pure compound, m.p. 102 – 105°. (Found: C 20.90; H 1.75; N 9.79. Calc. for $C_5H_5N_2ClBr_2$: C 20.83; H 1.75; N 9.72.) The other component is probably a monobromo derivative.

Bromination of imidazole 4(5)-carbaldehyde. The title compound (1.04 g) was brominated with bromine (3.95 g in 20 ml acetic acid) and sodium acetate (9.39 g) in acetic acid (100 ml) as above. The concentrated product was extracted with ether (3 × 150 ml) and then with acetone (3 × 150 ml). From the combined extracts a solid (2.0 g) containing three compounds (TLC, ethyl acetate) was obtained. These were separated on silica gel (80 g) using ethyl acetate, as eluent. One fraction (0.506 g) according to TLC (toluene-ethyl acetate, 1:1) and GLC-MS (5 % Lexan on Chromosorb W, 200°) contained a mixture of 2,4,5-tribromoimidazole (14 % total yield) and 2,5(4)-dibromoimidazole 4(5)-carbaldehyde (2 %). The main fraction (0.590 g) contained 5(4)-bromoimidazole 4(5)-carbaldehyde (32 %). An analytical sample, m.p. 216 – 217°, was prepared by crystallisation from butanone. (Found: C 27.67; H 1.62; N 16.42; Br 45.76. Calc. for $C_4H_3N_2OBr$: C 27.46; H 1.73; N 16.01; Br 45.67.) Part of the latter product was oxidised with permanganate to 5(4)-bromoimidazole 4(5)-carboxylic acid, m.p. 255 – 256° (lit.[13] 255°). The ethyl ester has m.p. 170 – 171° (lit.[14] 171°).

Bromination of 4(5)-hydroxymethylimidazole. The hydrochloride of the title compound (2.0 g) was brominated with bromine (4.79 g in 20 ml acetic acid) and sodium acetate (18.5 g) in acetic acid (125 ml) as above. The concentrated reaction mixture was extracted with ether (3 × 150 ml). The extract (1.84 g) contained at least six components according to TLC (ethyl acetate-water-methanol-acetone 95:5:5:25). One of these, 2,4,5-tribromoimidazole, was isolated in a yield of 23 % by chromatography on a silica gel column.

4(5)-Bromoimidazole (debromination with sulphite). Imidazole (1.36 g) was brominated as described above and the reaction mixture concentrated to dryness. The crude product and sodium sulphite (25 g) in water (125 ml) were refluxed for 3.5 h, cooled with ice water and extracted with ether (about 5 × 200 ml). The completeness of the extraction was checked by TLC. The ether solution was dried, concentrated and the crystalline product washed with light petroleum, yielding 4(5)-bromoimidazole, 1.82 g, 62 %, m.p. 130° (lit.[2] 130°).

4(5)-Bromoimidazole (debromination with butyllithium). Butyllithium (0.0144 mol in hexane, 8 ml) was transferred with a syringe to a solution of tribromoimidazole (1.10 g) in tetrahydrofuran (30 ml). The mixture was stirred for 1.25 h at 0° and then added with a syringe to methanol (50 ml) kept at −70°. The pale yellow solution was neutralised with hydrochloric acid, silica gel (0.5 g) was added and the solution was evaporated to dryness. Separation on a silica gel column using 40 g SiO_2/g substrate and chloroform-methanol (19:1) as eluent afforded 4(5)-bromoimidazole, m.p. 128 − 130° (lit.[2] 130°) 0.440 g, 83 %. A mixture (0.065 g) of 4(5)-bromo-5(4)-butylimidazole, 4(5)-bromoimidazole, and 4,5-dibromoimidazole in the approximate proportions 4:3:1 was eluted before the main fraction. The compounds were identified and their proportions determined by NMR and mass spectroscopy.

Attempted direct synthesis of 4(5)-bromoimidazole. The following methods have been tried without success. Bromination with dioxan.Br_2,[15] tetrahydrofuran.Br_2,[15] pyridine.Br_2,[15] iodine monobromine,[15] pyrrolidone-2-hydrotribromide,[15] copper(II) bromide,[15] bromination *via* thallium compounds,[16] and *via* *N*-lithioimidazole and *N*-acetyl imidazole. The method in alkaline medium described for nitroimidazoles by Kochergin *et al.*[17] was also tried.

Imidazole from 4(5)-bromoimidazole and butyllithium. A solution of 4(5)-bromoimidazole (0.522 g) in tetrahydrofuran (15 ml) was cooled to −70° and butyllithium (9.5 ml, 17.1 mmol) was added with a syringe. After 1 h at room temperature, the mixture was cooled to −70° and hydrolysed with 2 ml methanol. Concentrated hydrochloric acid (50 ml) was added and the solution evaporated to dryness, dissolved in 200 ml water and added to a Dowex 50W X-8 (200 − 400 mesh, H^+) column (21 × 3 cm). Elution with M HCl afforded first lithium salts and then imidazole hydrochloride, 0.365 g (98 %). 4(5)-Deuterio-imidazole was obtained in the same way using CH_3OD and careful neutralisation with 4 M HCl.

4(5)-(2-bromoethyl)imidazole. A saturated aqueous solution of sodium nitrite (2.42 g) was added during 2.5 h to a solution of histamine (3.0 g, free base) and potassium bromide (10.8 g) in 1.5 M sulphuric acid (40 ml) kept at −5°. After 3 h at room temperature, the pH was adjusted to 10 by adding 5 M sodium hydroxide, and the solution was extracted with chloroform (4 × 40 ml). Concentration of the chloroform extract yielded the title compound as a yellow oil (2.2 g, 47 %) which crystallised on cooling. This substance, which is not very stable due to intermolecular alkylation, was transferred to the hydrobromide. An analytical sample was prepared by silica gel chromatography (chloroform-methanol 9:1) of the free base. The eluted fractions were treated with hydrobromic acid before concentration. Recrystallisation from acetonitrile gave m.p. 149 − 150° (lit.[10] 156 − 158°). (Found: C 23.7; H 3.2; N 11.1. Calc. for $C_5H_7N_2Br_2$: C 23.5; H 3.2; N 10.9.) When an evaporated sample of the free base was left at room temperature overnight, intermolecular alkylation occurred. One component (10 %) was obtained from column chromatography and identified (NMR, MS) as a 4(5)-(2-bromoethyl)imidazole, *N*-alkylated by reaction with another monomer. The main by-product, 4(5)-(2-hydroxyethyl)imidazole, was obtained by extraction of the alkaline aqueous phase with butanol. When the nitrosation was carried out at 50°, another by-product, 4(5)-bromo-5(4)-(2-bromoethyl)imidazole, was obtained (15 %). The compound was identified by its NMR spectrum. Crystallisation from acetonitrile yielded the pure compound, m.p. 128 − 129°. (Found: C 23.7; H 2.4; N 11.2. Calc. for $C_5H_6N_2Br_2$: C 23.7; H 2.4; N 11.0.)

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