Synthesis of 1-Aryloxymethyl- and 1-Arylthiomethyl-imidazoles

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A convenient synthesis of 1-aryloxymethylimidazoles (1; X = O) from sodium imidazolide, dichloromethane or bromochloromethane, and sodium phenolates is described. 1-Aryloxymethyl- and 1-arylthiomethyl-imidazoles were also prepared by alkylation of imidazole with chloromethyl ethers or chloromethyl thioethers.

4(5)-ARYLOXYMETHYLIMIDAZOLES and their thio-analogues have been known for some time,[1] but only recently have the 2-aryloxymethylimidazoles been reported.[2] We describe here the synthesis of the 1-substituted analogues (1; X = O or S).

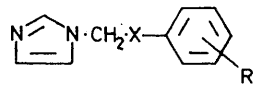
From general considerations, compounds of type (1) should be obtainable either by alkylation of imidazole with a phenoxymethyl halide or reaction of a 1-halogenomethylimidazole (3) with phenolates. Indeed, reaction of the chlorides (2a)[3] or (2b)[4] with imidazole yielded the corresponding ethers (5) and (6) (Table 1),† characterised by analysis and ^{1}H n.m.r. and mass spectroscopy.

Since a number of analogues of (1) were required for hypolipidaemic screening, the alternative possibility was investigated in order to circumvent the repetitive synthesis of phenoxymethyl halides. 1-Halogenomethylimidazoles (3) have not been reported although the corresponding alcohol is claimed but not characterised.[5] Sodium imidazolide (4) has been utilised for the synthesis of *N*-alkylimidazoles[6] and the possibility of finding conditions which would allow the synthesis of (3; Hal = Cl) *in situ* by reaction of the imidazolide (4) with dichloromethane or bromochloromethane was therefore investigated.

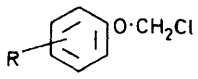
Conditions were eventually found which enabled the ethers (5)—(12) (Table 1), to be prepared readily in fair yield, by the reaction of dichloromethane (or bromochloromethane) with sodium imidazolide followed by treatment of the resultant mixture with substituted sodium phenolates (see Experimental section). The corresponding methylene diethers (13)—(20) were also produced in these reactions, presumably from residual dichloromethane (Table 2). The imidazolyl methyl ethers (5) and (6) prepared by this method were identical with the materials synthesised from substituted phenoxymethyl chlorides (2a and b).

The mass spectra of compounds (5) and (6) provided further evidence for the structures. The base peak in both spectra at *m/e* 81 (1-methyleneimidazolium) indicated α-cleavage of the ether link, and a peak corresponding to the phenolic portion was also observed.

Various investigations by n.m.r. spectroscopy to determine whether 1-chloromethylimidazole had been produced proved inconclusive owing to the complexity of the primary reaction mixture. That the diphenoxymethanes produced in the sodium imidazolide reactions originated by reaction of phenolates with residual dichloromethane was confirmed by treating dichloromethane with sodium *p*-chlorophenolate in dimethylformamide under similar conditions.

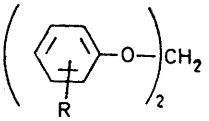


	X	R
(1)	O or S	
(5)	O	4-Me
(6)	O	2,4-Cl_2
(7)	O	4-Et
(8)	O	4-Cl
(9)	O	4-CO_2Et
(10)	O	4-OMe
(11)	O	3,5-Bu^t_2
(12)	O	H
(21)	S	4-Me
(22)	S	4-Cl
(23)	S	3,4-Benzo



(2) a; R = 4-Me
b; R = 2,4-Cl_2

(3) R = CH_2Hal
(4) R = Na



	R
(13)	4-Me
(14)	2,4-Cl_2
(15)	4-Et
(16)	4-Cl
(17)	4-CO_2Et
(18)	4-OMe
(19)	3,5-Bu^t_2
(20)	H

Numerous attempts to obtain the corresponding thioethers (1; X = S) by the sodium imidazolide method produced only traces of the required compounds. The alternative method utilising the thio-analogues of (2)[7] to alkylate imidazole proved satisfactory, yielding compounds (21)—(23) (Table 3).

None of the compounds described exhibited hypolipidaemic properties in experimental animals.

† Satisfactory analytical and spectroscopic data were obtained for all new compounds. The data (Tables 1—3) are available as Supplementary Publication No. SUP 21426 (4 pp.). For details of Supplementary Publications, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

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EXPERIMENTAL

N.m.r. spectra were obtained with a Varian A60 and mass spectra with an MS 902 instrument.

Alkylation of Imidazole with Active Halides.—The standard procedure involved stirring under reflux a mixture of the halide, an excess of imidazole, and anhydrous potassium carbonate in acetone for *ca.* 6 h. Removal of inorganic salts by filtration, and concentration of the filtrate yielded a syrup which was taken up in ether, and the solution was washed well with water The basic product was extracted into N-hydrochloric acid, the combined acidic extracts were basified with N-sodium hydroxide, and the product was isolated with ether and purified by chromatography on silica and/or recrystallisation.

Alkylation of Dichloromethane with Sodium Imidazolide and Preparation of the Ethers (5)—(12).—A solution of sodium imidazolide (16 g, 0.18 mol) [6] in dimethylformamide (100 ml) was added during 30 min with cooling to dry dichloromethane (or bromochloromethane) (80 ml) in a flask (250 ml) fitted with stirrer, calcium chloride tube, and dropping funnel. The mixture was then rapidly transferred to a rotary evaporator and the excess of dichloromethane was removed under vacuum at room temperature. (If this mixture was warmed to 40 °C none of the required product could be isolated). The resultant slurry was then returned to a flask (500 ml) fitted as above and incorporating a condenser. The mixture was treated immediately with the sodium phenolate in ethanol [phenol (0.1 mol), sodium (2.3 g), and ethanol (51 ml)] over 15 min at room temperature, heated under reflux for 45 min, and cooled. The solvent was removed under reduced pressure and the residue was separated into basic and neutral fractions as described above, affording the ethers (5)—(12) in 22—35% yield. The corresponding diphenoxymethanes (13)—(20) were obtained in 13—66% yield and characterised by m.p. or b.p. and n.m.r. spectra (Table 2).

Bis-(p-chlorophenoxy)methane (16).—A solution of *p*-chlorophenol (12.8 g, 0.1 mol) in sodium ethoxide solution [sodium (0.1 g atom) in ethanol (51 ml)] was treated with dry dimethylformamide (100 ml) and dichloromethane (40 ml), and the mixture was heated under reflux for 45 min. Solvents were removed under reduced pressure, the residue was diluted with water, and the product was isolated with ether. Crystallisation from aqueous ethanol afforded needles (7.4 g, 55%), m.p. 71—72° (lit.,[8] 67—69°).

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