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THE REACTION BETWEEN CYANIDE ION AND NITRONES

A NOVEL IMIDAZOLE SYNTHESIS

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On allowing equimolecular amounts of potassium cyanide and N-methyl-C-phenylnitrone (I) to stand overnight at room temperature in aqueous ethanolic solution, a colourless crystalline solid, m.p. 156-157°, separated in excellent yield. The compound had a molecular formula $C_{16}H_{14}N_2$. It was not possible to identify any functional groups from the i.r. absorption spectrum, but the n.m.r. spectrum showed signals attributable to ten aromatic protons (two phenyl groups), three aliphatic protons (one methyl group), and probably one additional aromatic proton. These findings suggested that the compound was 1-methyl-4,5-diphenylimidazole (III) (lit. m.p. 158°), the truth of which was confirmed by mixed melting-point and comparison of i.r. spectra using an authentic sample(1).

By carefully monitoring the progress of the reaction on t.l.c. plates, it became clear that a well-defined intermediate was rapidly produced (within the first 30 min.), and more slowly converted into the imidazole. The reaction was a very clean one and, throughout its progress, only the intermediate and the imidazole were detected. On quenching the reaction mixture into water after 1 hr., it was possible to isolate this intermediate in good yield. It formed colourless crystals, m.p. 38-39°, had a molecular formula $C_9H_8N_2$, and was identified as α-cyanobenzylidenemethylamine (II) (lit. m.p. 37°) by comparison with an authentic sample(2).

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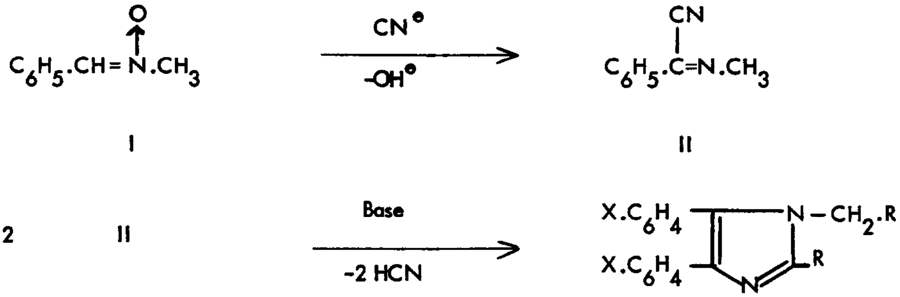
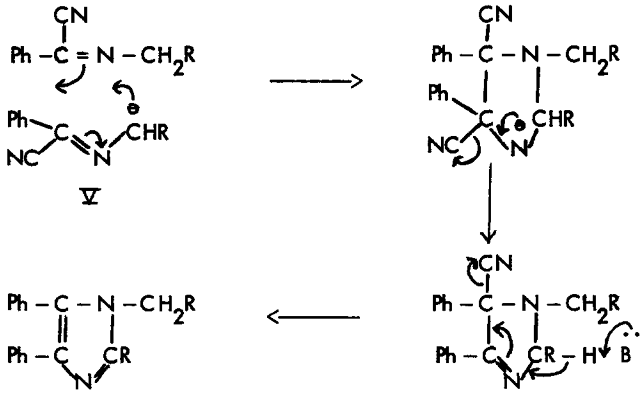
This compound arises from nucleophilic attack by cyanide ion on the highly polar nitrone system, which is well known in the case of the *C*,*N*-diphenylnitrones(3). The latter yield α-cyanobenzylideneanilines, which are stable under mildly basic conditions; α-cyanobenzylidenemethylamine, on the other hand, is converted in excellent yield into 1-methyl-4,5-diphenylimidazole by the action of potassium hydroxide in cold aqueous ethanol, thus confirming its role as the reaction intermediate. Two molecules of α-cyanobenzylidenemethylamine combine to produce one molecule of the imidazole with elimination of two molecules of hydrogen cyanide, a fact that has been established not only by identifying cyanide ion in the reaction solution but monitoring its concentration as ring-closure proceeds.



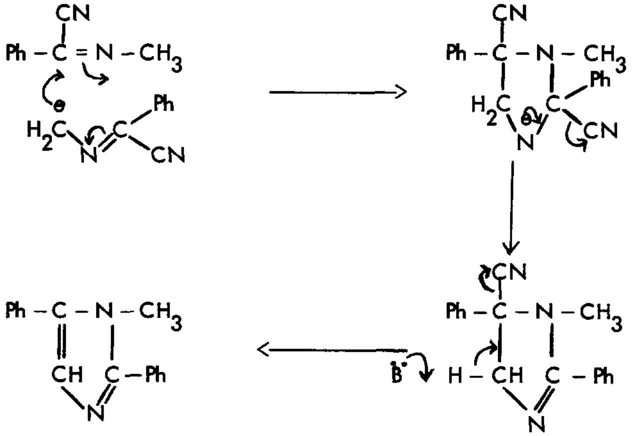
III (R = X = H)
IV (R = CH_3; X = Cl)

Incorporation of the *N*-alkyl group of the initial *N*-alkyl-*C*-phenylnitrone (or of the intermediate α-cyanobenzylidenealkylamine) into the imidazole ring structure at the 2- position is confirmed by the action of potassium cyanide on C-4-chlorophenyl-N-ethylnitrone. The product in this case contains one ethyl group and one methyl group (as shown by the n.m.r. spectrum), and is formulated as 4,5-*bis*-4'-chlorophenyl-1-ethyl-2-methylimidazole (IV).

As a result of the base-catalysed nature of the reaction, it is postulated as being initiated through the carbanion V, whose formation is assisted by electron-delocalisation through the adjacent cyano and phenyl groups. Subsequent cyclisation invokes a Woodward-Hoffmann intermolecular [4 + 2] cyclo-addition of this carbanion with a molecule of the uncharged α-cyanobenzylidenealkylamine, followed by elimination of cyanide ion and proton under the influence of base (B).


V

It is conceivable, on the other hand, that the two proposed ring fragments might add to each other in the opposite sense, giving rise to an isomeric product, e.g. 1-methyl-2,5-diphenylimidazole (VI). However, this compound(5) has a m.p. 197.5 - 198.5° and has not been detected (t.l.c.) in cyclisation experiments involving α-cyanobenzylidenemethylamine or N-methyl-C-phenylnitrone.


VI

Cold thionyl chloride converted N-methylbenzamide into N-methylbenzimidoyl chloride in 93% yield(4). By stirring a petrol solution of the latter with a cold solution of potassium cyanide in formamide, it was converted in 89% yield into α-cyanobenzylidenemethylamine. A very practical, alternative route to the imidazole therefore exists, which avoids recourse to the nitrone.

The full scope of these reactions and their mechanism are now being investigated, and findings will be published elsewhere.

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