Cyanochlorination and Cyanogenation of Isoquinoline

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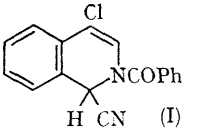
Summary Isoquinoline reacts with potassium cyanide and sulphuryl chloride to give, depending upon the reaction conditions, 4-chloro-1-cyano-, 1,3-dicyano-, 1-aminocarbonyl-3-cyano-, 3-cyano-, and 1-cyano-isoquinoline, thus illustrating a simple method for the direct introduction of chloro- and cyano-substituents into nitrogen heterocycles.

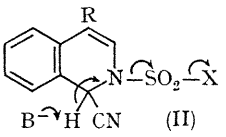
ISOQUINOLINE normally undergoes electrophilic substitution in the benzenoid ring. Derivatives substituted in the hetero-ring are usually prepared from non-heterocyclic precursors or by nucleophilic displacement of existing substituents. We now report a method of substitution involving successive nucleophilic and electrophilic attack on the hetero-ring.

Treatment of isoquinoline (1 mol.) in methylene chloride with aqueous potassium cyanide (3 mol.) and sulphuryl chloride (2 mol.) at 0° gave 4-chloro-1-cyanoisoquinoline, m.p. 122°, (15%) together with recovered isoquinoline (66%). The structure of the product was established by synthesis from 4-chloroisoquinoline[1] *via* the Reissert compound (I), m.p. 163—165°, which was cleaved with phosphorus pentachloride.[2] A possible mechanism for the reaction involves an intermediate (II; R = H, X = Cl or CN) resembling a sulphonyl Reissert derivative.[3]. Chlorination by sulphuryl chloride at C-4, assisted by the enamine structure, would give the ion (III). Loss of a proton would lead to (II; R = Cl) which could aromatise, as shown (II), by base-catalysed elimination[3] or fragmentation.

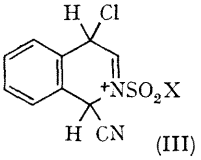
Some support for this mechanism was obtained by varying the reaction conditions. In the presence of a large excess of cyanide the major product (11%) was the amide (IV), m.p. 230—233°. This could arise by nucleophilic attack at C-3, by cyanide, on the iminium intermediate (III), followed by loss of hydrogen chloride and fragmentation as before. Hydrolysis of the 1-cyano-group would then give (IV). The structure of the amide (IV) was shown by conversion, with nitrous acid, into the corresponding acid, m.p. 200—203°, and decarboxylation to give 3-cyanoisoquinoline.[4] Since the amide lacked a low-field, n.m.r. singlet attributable to 1-H, the aminocarbonyl group must have occupied the 1-position. Dehydration of the amide with phosphorus oxychloride gave 1,3-dicyanoisoquinoline, m.p. 217—219°, which, together with 3-cyanoisoquinoline, occurred as a minor constituent in several of the original reaction mixtures. Finally treatment of isoquinoline with sulphuryl chloride and potassium cyanide in the presence of an excess of potassium hydroxide gave 1-cyanoisoquinoline (17%) with recovered isoquinoline (59%). In this reaction, presumably, the intermediate (II; R = H) was intercepted by hydroxide ion before chlorination could take place.



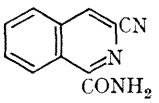
(I)



(II)



(III)



(IV)

No attempt has been made to achieve maximum yields of any one product. However, even in its present form, the method presents a simple and mechanistically unusual route to new isoquinoline derivatives and is capable of extension to other heterocyclic systems.

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