Cyanochlorination and Cyanation of Isoquinolines

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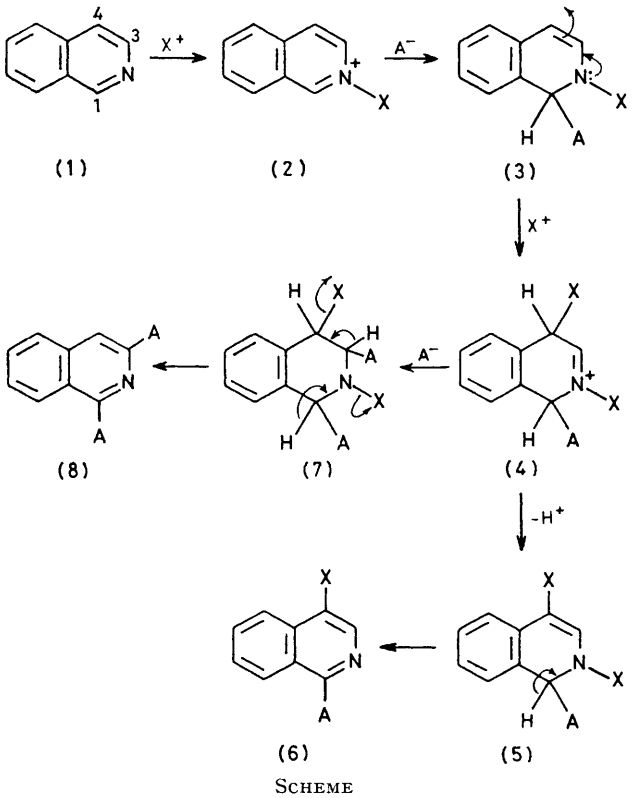
Treatment of isoquinoline with sulphuryl chloride and potassium cyanide gave, in one preparative step, 4-chloro-1-cyanoisoquinoline and 1-carbamoyl-3-cyanoisoquinoline in yields dependent upon the proportions of reagents. 4-Chloroisoquinoline, 1,3-dicyanoisoquinoline, 3-cyanoisoquinoline, and 1-cyanoisoquinoline were also produced under different reaction conditions. The formation of the various products is explained in terms of successive electrophilic and nucleophilic attack by the reagents on the hetero-ring of isoquinoline followed by elimination reactions to regenerate an aromatic system. Cyanochlorination and cyanation of several isoquinoline derivatives and of quinoline were briefly studied.

ELECTROPHILIC substitution in the heterocyclic ring of isoquinoline (1) is rendered difficult by the electron-attracting effect of the nitrogen atom. Nucleophilic

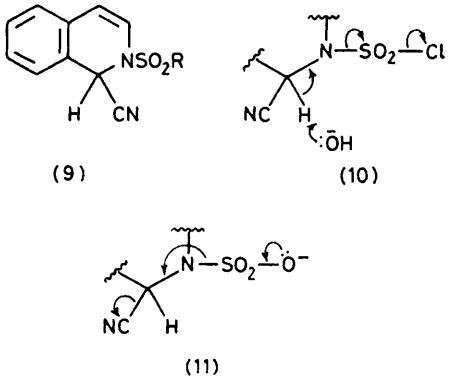


SCHEME

substitution is feasible but normally requires attack by a powerful nucleophile, for example, the amide ion. In principle, substitution in the heterocyclic ring might be effected by successive attack with electrophilic and nucleophilic species (see Scheme). An electrophile, X^+, would react readily with the basic nitrogen atom to yield a cation (2) susceptible to attack at C-1 by a nucleophile, A^-, thereby giving the enamine (3). This might react further with X^+ to give the iminium ion (4) and thence the substituted enamine (5). Finally, elimination of HX would generate the disubstituted aromatic system (6). Alternatively, attack by A^- on (4) followed by elimination of two molecules of HX could produce the derivative (8). Clearly, for this scheme to succeed as a one-step, preparative route to substituted isoquinolines, the mutual reaction of the nucleophile and electrophile, to form AX, must proceed slowly compared with their reaction with the heterocycle. We now report [1] a new route to mono- and di-substituted isoquinolines based on these ideas.

RESULTS AND DISCUSSION

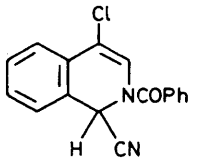
The first two steps in the Scheme are well illustrated by the formation of the familiar Reissert derivatives.[2] For example, isoquinoline reacts with benzoyl chloride and aqueous potassium cyanide to give the derivative (3; X = PhCO, A = CN) in good yield without serious loss of reagents by hydrolysis or formation of benzoyl cyanide. Also sulphonyl Reissert compounds [3] (9) react with base to yield, by elimination of sulphinate anion, 1-cyanoisoquinolines, a process analogous to the transformation (5)→(6). With these examples in mind we studied the reaction of isoquinoline (1) with aqueous



potassium cyanide and sulphuryl chloride, SO_2Cl_2. The latter can act electrophilically both as an acid chloride and a chlorinating agent. Also its bifunctional character allows formation of intermediates which might undergo fragmentation (10) and elimination (11) processes not available to alkane or arene sulphonyl derivatives.

Sulphuryl chloride (2 molar equivalents) was added at 0—5 °C to a vigorously stirred two-phase mixture of aqueous potassium cyanide (3 equiv.) and isoquinoline (1 equiv.) in dichloromethane. The organic phase was extracted with acid to remove unreacted isoquinoline

(66%) and evaporated to afford 4-chloro-1-cyanoisoquinoline (6; A = CN, X = Cl) (15%). The structure of this product was tentatively deduced from the i.r. ($\nu_{max.}$ 2 236 cm^{-1}, CN stretch) and n.m.r. (τ 1.3, s, 3-H) spectra and proved by synthesis from 4-chloroisoquinoline [4] *via* the Reissert derivative (12) which was



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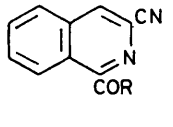

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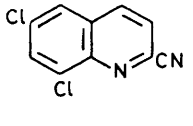

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cleaved [5] with phosphorus pentachloride. With increased amounts of sulphuryl chloride and potassium cyanide (5 molar equivalents of each) the consumption of isoquinoline was more complete (55% recovered) and the yield of 4-chloro-1-cyanoisoquinoline was increased (19%). However, two new products were isolated in low yield (*ca.* 0.4%). One was identified as 3-cyanoisoquinoline by comparison with authentic material. The other was shown to be 1,3-dicyanoisoquinoline (8; A = CN) by comparison with a sample obtained by dehydration of 1-carbamoyl-3-cyanoisoquinoline (see below) with phosphorus oxychloride.

Treatment of isoquinoline with sulphuryl chloride (2.5 molar equivalents) and a large excess of potassium cyanide (7 equiv.) resulted in a lower yield (3%) of 4-chloro-1-cyanoisoquinoline and the formation of 1-carbamoyl-3-cyanoisoquinoline (13; R = NH_2) as the major product (18%). This is consistent with the Scheme in that an increased concentration of A^- would facilitate the path (4)→(7)→(8) at the expense of (4)→(5)→(6). 4-Chloroisoquinoline was also formed as a minor (0.3%) product. This may have arisen from an intermediate of the type (5) by the elimination process (11).

The structure (13; R = NH_2) for the new, major product was established as follows. The i.r. spectrum showed absorption attributable to cyano (2 238 cm^{-1}) and carbamoyl (3 388 and 1 663 cm^{-1}) groups while the absence of any signal [6] near τ 0.85 in the n.m.r. spectrum indicated substitution at C-1 in the isoquinoline nucleus. A distinction between the possible 1,3- or 1,4-disubstituted isomers was made by degradation. Treatment of the carboxamide (13; R = NH_2) with sodium nitrite in acetic acid gave the corresponding acid (13; R = OH) which decarboxylated thermally to yield the known 3-cyanoisoquinoline.

Various other reaction conditions were investigated with the results recorded in the Experimental section. One experiment deserves comment here. When isoquinoline was treated with sulphuryl chloride and potassium cyanide in the presence of an excess of potassium hydroxide, substantial amounts (17%) of 1-cyanoisoquinoline were produced. Presumably, under these conditions, an intermediate of the type (3) is intercepted and aromatised [see (10)] before chlorination can occur.

Other heterocyclic systems were briefly studied although the low yields of products discouraged detailed investigation. 3-Methylisoquinoline was converted inefficiently, with sulphuryl chloride and potassium cyanide, into 1-cyano-3-methylisoquinoline and 4-chloro-1-cyano-3-methylisoquinoline, the substitution pattern of the latter being assigned largely by analogy with the foregoing results. 4-Bromoisoquinoline gave a crystalline, inseparable mixture judged spectroscopically to consist of 4-bromo-1-cyanoisoquinoline and 4-chloro-1-cyanoisoquinoline. 5-Nitroisoquinoline gave 1-cyano-5-nitroisoquinoline as the sole identified product; apparently, the nitro-group inhibits chlorination of the enamine intermediate C-4. Quinoline reacted only slowly with sulphuryl chloride and potassium cyanide; the reaction mixture yielded a small amount of a product, tentatively assigned the structure (14), together with unreacted quinoline (91%).

The foregoing results are entirely consistent with the mechanistic ideas formulated, in general terms, in the Scheme. Despite the diverse reaction paths implicit in this Scheme, the reactions of isoquinoline with sulphuryl chloride and potassium cyanide have some preparative merit in providing routes, involving only one preparative step, to compounds such as 4-chloro-1-cyanoisoquinoline and 1-carbamoyl-3-cyanoisoquinoline which are not readily accessible by other methods.

EXPERIMENTAL

General Methods.—N.m.r. spectra were measured, unless otherwise stated, for deuteriochloroform solutions at 60 MHz with tetramethylsilane as internal standard. I.r. spectra were run with potassium bromide discs (for solids) or thin films (for liquids) and u.v. spectra were measured in ethanol. M.p.s were determined with a Kofler hot-stage apparatus.

Preparation of 4-Chloro-1-cyanoisoquinoline from Isoquinoline, Sulphuryl Chloride, and Potassium Cyanide.—Isoquinoline (5.16 g) in dichloromethane (40 ml) and potassium cyanide (7.8 g) in water (20 ml) were stirred at 0—5 °C. Sulphuryl chloride (10.8 g) was added dropwise and stirring continued for 4 h. The organic layer was washed successively with water, 2N hydrochloric acid, water, 2N sodium hydroxide, and water, and then dried (Na_2SO_4). Evaporation gave a yellow solid which was purified by chromatography (Grade III neutral alumina). Crystallisation from ethanol gave *4-chloro-1-cyanoisoquinoline* as needles (1.10 g), m.p. 121.5—122.5 °C (Found: C, 63.8; H, 2.9; N, 14.9. $C_{10}H_5ClN_2$ requires C, 63.7; H, 2.7; N, 14.9%); $\nu_{max.}$ 2 236 and 1 618 cm^{-1}; *m/e* 188 and 190; τ 1.3 (s, 3-H), 1.5—1.8 (m, 2 H, aryl-H), and 1.8—2.2 (m, 2 H, aryl-H). The aqueous layer from the reaction mixture was basified and extracted with chloroform to yield isoquinoline (3.30 g). With increased amounts of sulphuryl chloride (5 mol. equiv.) and potassium cyanide (5 mol. equiv.) the yield of 4-chloro-1-cyanoisoquinoline increased to 19% and the recovery of isoquinoline dropped to 55%: also isolated were 3-cyanoisoquinoline (0.4%), m.p. 118—120 °C, identified by comparison with an authentic sample, and 1,3-dicyanoisoquinoline (0.4%), m.p. 215—216 °C, identical with a sample prepared from 1-carbamoyl-3-cyanoisoquinoline (see below).

Preparation of 4-Chloro-1-cyanoisoquinoline from 4-Chloroisoquinoline.—A mixture of 4-chloroisoquinoline [4] (0.57 g) in dichloromethane (4 ml) and potassium cyanide (0.70 g) in water (2 ml) was treated with benzoyl chloride (0.90 g) in the usual way.[7] *2-Benzoyl-4-chloro-1-cyano-1,2-dihydroisoquinoline* (0.37 g) was obtained as rhombs, m.p. 163—165 °C (ethyl acetate) (Found: C, 69.7; H, 3.8; N, 9.4. $C_{17}H_{11}ClN_2O$ requires C, 69.2; H, 3.7; N, 9.5%); $\nu_{max.}$ 2 238 and 1 664 cm^{-1}; τ 2.2—2.9 (m, aryl-H), 3.13 (s, 3-H), and 3.44 (s, 1-H). This Reissert compound (0.17 g) was heated with phosphorus pentachloride (0.19 g) at 130—135 °C for 2.5 h. The reaction mixture was dissolved in chloroform and treated with water. The chloroform layer was washed with dilute aqueous sodium hydroxide and then water, and the product was isolated by preparative t.l.c. [alumina PF_{254} plates developed with benzene–ethyl acetate (95 : 5)]. 4-Chloro-1-cyanoisoquinoline (32 mg) was obtained, m.p. 121—122 °C (ethanol), undepressed upon admixture with the sample prepared earlier.

Preparation of 1-Carbamoyl-3-cyanoisoquinoline from Isoquinoline.—Isoquinoline (2.55 g) in dichloromethane (100 ml) and potassium cyanide (6.5 g) in water (30 ml) were stirred at 0—5 °C. Sulphuryl chloride (3.2 ml) was added dropwise. A second portion of potassium cyanide (2.6 g) in water (20 ml) was added followed by sulphuryl chloride (0.8 ml), and stirring was continued for 5 h. The organic layer was extracted with 2N hydrochloric acid and the extract combined with the aqueous layer. Basification of the combined solutions with aqueous sodium hydroxide caused precipitation of the product as a white solid which was filtered off. The filtrate yielded more product after extraction with chloroform and preparative t.l.c. *1-Carbamoyl-3-cyanoisoquinoline* was obtained as needles (0.70 g), m.p. 230—233 °C (ethanol) (Found: C, 66.8; H, 3.9; N, 21.5. $C_{11}H_7N_3O$ requires C, 67.0; H, 3.6; N, 21.3%); $\nu_{max.}$ 2 238, 1 663, and 3 388 cm^{-1}; *m/e* 197; τ[$(CD_3)_2SO$] 1.17 (s, 4-H), 1.0—1.3 (m, 1 H, aryl-H), and 1.45—2.15 (m, 5 H, NH_2 + aryl-H). Further preparative t.l.c. also provided 4-chloro-1-cyanoisoquinoline (3%), 4-chloroisoquinoline (0.3%), and 1-cyanoisoquinoline (2%), m.p. 86—88 °C, identical with an authentic sample.[3]

Conversion of 1-Carbamoyl-3-cyanoisoquinoline into 3-Cyanoisoquinoline.—1-Carbamoyl-3-cyanoisoquinoline (75 mg) in acetic acid (4 ml) and water (1 ml) was treated with sodium nitrite (0.20 g) portionwise with occasional warming. The mixture was heated at 80—95 °C for 3 h, then basified and extracted with chloroform. The aqueous solution was acidified and extracted with chloroform to give *3-cyanoisoquinoline-1-carboxylic acid* (30 mg), m.p. 200—203 °C (benzene–ethanol) (Found: C, 66.7; H, 3.4; N, 13.9. $C_{11}H_6N_2O_2$ requires C, 66.7; H, 3.05; N, 14.1%); $\nu_{max.}$ 2 253 and 1 755 cm^{-1}; *m/e* 198. This acid (20 mg) was heated under reflux in Dowtherm (a eutectic mixture of diphenyl ether and biphenyl) for 1 h. The product (7 mg), m.p. 120—122 °C, isolated by t.l.c., was identified as 3-cyanoisoquinoline by comparison with authentic material.[8]

Conversion of 1-Carbamoyl-3-cyanoisoquinoline into 1,3-Dicyanoisoquinoline.—The carboxamide (0.51 g) was heated under reflux with phosphorus oxychloride (10 ml) for 3.5 h. Chloroform and aqueous sodium hydroxide were added to the reaction mixture. The chloroform layer was washed with water, dried (Na_2SO_4), heated with charcoal, and evaporated to dryness to give *1,3-dicyanoisoquinoline* (0.31 g), m.p. 215—216 °C (ethanol) (Found: C, 73.7; H, 3.15; N, 23.9. $C_{11}H_5N_3$ requires C, 73.7; H, 2.8; N, 23.45%); $\nu_{max.}$ 2 247 and 1 613 cm^{-1}; *m/e* 179; τ 1.59 (s, 4-H) and 1.8—2.2 (m, aryl-H).

Reactions of Isoquinoline with Sulphuryl Chloride and Potassium Cyanide under Varied Conditions.—The cyanochlorination of isoquinoline (as above) was studied with various amounts of sulphuryl chloride and potassium cyanide with and without added sodium or potassium hydroxide. Minor products were isolated by preparative t.l.c. using PF_{254} silica plates developed with benzene–ethyl acetate (95 : 5). The following R_F values were recorded: 4-chloro-1-cyanoisoquinoline, 0.03; 1-carbamoyl-3-cyanoisoquinoline, 0.04; isoquinoline, 0.20; 4-chloroisoquinoline, 0.24; 1-cyanoisoquinoline,[3] 0.35; 3-cyanoisoquinoline, 0.39; 1,3-dicyanoisoquinoline, 0.46. The isolated products (yields based on isoquinoline) from the reactions of isoquinoline (1 equiv.) with different proportions of reagents (mol. equiv.) were as follows: SO_2Cl_2 (2)–KCN (3) gave 4-chloro-1-cyanoisoquinoline (15%) and isoquinoline (66% recovery); SO_2Cl_2 (5)–KCN (5) gave 4-chloro-1-cyanoisoquinoline (19%), 1,3-dicyanoisoquinoline (0.4%), 3-cyanoisoquinoline (0.4%), and isoquinoline (55%); SO_2Cl_2 (18)–KCN (25)–NaOH (32) gave 4-chloro-1-cyanoisoquinoline (22%), 1,3-dicyanoisoquinoline (1%), 3-cyanoisoquinoline (1%), 1-carbamoyl-3-cyanoisoquinoline (2%), and 1-cyanoisoquinoline (1%); SO_2Cl_2 (2.5)–KCN (7) gave 4-chloro-1-cyanoisoquinoline (3%), 4-chloroisoquinoline (0.3%), 1-carbamoyl-3-cyanoisoquinoline (18%), and 1-cyanoisoquinoline (2%); SO_2Cl_2 (2.5)–KCN (3)–KOH (5) gave 4-chloro-1-cyanoisoquinoline (12%), 1-cyanoisoquinoline (7%), and isoquinoline (55%); SO_2Cl_2 (4)–KCN (3)–KOH (15) gave 1-cyanoisoquinoline (17%) and isoquinoline (59%).

Reaction of 3-Methylisoquinoline with Sulphuryl Chloride and Potassium Cyanide.—Following the standard procedure (see above), 3-methylisoquinoline (2.4 g) in dichloromethane (20 ml) and potassium cyanide (2.9 g) in water (10 ml) were treated with sulphuryl chloride (2.5 ml). The products were separated by chromatography (Grade III neutral alumina). Elution with benzene and then benzene–ethyl acetate gave, successively, *4-chloro-1-cyano-3-methylisoquinoline* (120 mg), m.p. 124 °C (ethanol) (Found: C, 65.4; H, 3.5; N, 13.7. $C_{11}H_7ClN_2$ requires C, 65.2; H, 3.5; N, 13.8%), $\nu_{max.}$ 2 233 cm^{-1}; *m/e* 202; τ 1.55—2.3 (aryl-H) and 7.17 (s, CH_3): then *1-cyano-3-methylisoquinoline* (56 mg), m.p. 105—106 °C (light petroleum, b.p. 40—60 °C) (Found: C, 78.5; H, 4.9; N, 16.6. $C_{11}H_8N_2$ requires C, 78.55; H, 4.8; N, 16.7%); $\nu_{max.}$ 2 233 cm^{-1}; *m/e* 168; τ 1.8 (m, 8-H), 2.25 (s, 4-H), 2.05—2.45 (m, aryl-H), and 7.30 (s, CH_3). 3-Methylisoquinoline (1.70 g) was recovered from the basic fraction of the reaction mixture.

Reaction of 4-Bromoisoquinoline with Sulphuryl Chloride and Potassium Cyanide.—The reaction was carried out as in the preceding experiment. Chromatography of the reaction mixture from 4-bromoisoquinoline [9] (2.08 g) gave a crystalline solid (0.25 g), m.p. 114—120 °C (ethanol) raised to 122—127 °C by crystallisation. Mass spectrometry [*e.g. m/e* 233 and 231 (1 : 1), and 188 and 190 (3 : 1)] indicated that this was a mixture of 4-bromo-1-cyanoisoquinoline and 4-chloro-1-cyanoisoquinoline (*ca.* 3 : 1). 4-Bromoisoquinoline (1.5 g) was recovered.

Reaction of 5-Nitroisoquinoline with Sulphuryl Chloride and Potassium Cyanide.—5-Nitroisoquinoline (1.0 g) gave, in the usual way (see above), *1-cyano-5-nitroisoquinoline* (0.22 g), m.p. 198.5—199 °C (ethanol) (Found: C, 60.5; H, 2.8; N, 21.0. $C_{10}H_5N_3O_2$ requires C, 60.3; H, 2.5; N,

21.1%); $\nu_{max.}$ 2 236 cm^{-1}; *m/e* 199; $\tau(CF_3CO_2H)$ 0.55 (d, 3-H), 0.75—1.10 (m, 3 H, aryl-H), and 1.67 (m, 1 H, aryl-H). 5-Nitroisoquinoline (0.6 g) was recovered. With potassium cyanide (4 mol. equiv.) and sulphuryl chloride (6 mol. equiv.), 5-nitroisoquinoline (1.0 g) yielded 1-cyano-5-nitroisoquinoline (0.27 g); 5-nitroisoquinoline (0.55 g) was recovered.

Reaction of Quinoline with Sulphuryl Chloride and Potassium Cyanide.—Quinoline (5.16 g) gave, as before, a product (25 mg) tentatively identified as *6,8-dichloro-2-cyanoquinoline*, m.p. 195—196 °C (ethanol) (Found: C, 53.5; H, 2.1; N, 12.4. $C_{10}H_4Cl_2N_2$ requires C, 53.8; H, 1.8; N, 12.55%); $\nu_{max.}$ 2 243 cm^{-1}; τ 1.73 (d, *J* 8.6 Hz, 4-H), 2.25 (d, *J* 8.6 Hz, 3-H), 2.09 (d, *J* 2.0 Hz, 7-H), and 2.20 (d, *J* 2.0 Hz, 5-H). Quinoline (4.7 g) was recovered.

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