Polyhalogenoaromatic Compounds. Part XXIV.[1] The Reaction of Chloropyridyl-lithium Compounds with Nitriles as a Route to Triazanaphthalenes [2]

By D. J. Berry, J. D. Cook, and B. J. Wakefield,* Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

The reactions of tetrachloro-4-pyridyl-lithium and tetrachloro-2-pyridyl-lithium with an excess of benzonitrile yield 5,6,8-trichloro-2,4-diphenylpyrido[3,4-d]pyrimidine and 6,7,8-trichloro-2,4-diphenylpyrido[3,2-d]pyrimidine, respectively, via the appropriate N-lithio-imines. The reaction of 2,3,6-trichloro-5-lithio-4-piperidinopyridine with an excess of benzonitrile gives a product formulated as N-[α-(2,5,6-trichloro-4-piperidino-3-pyridyl)benzylidene]-N'-(3,5,6-trichloro-4-piperidino-2-pyridyl)benzamidine.

Tetrachloropyrazine gives methyl- and phenyl-trichloropyrazine on treatment with methyl- and phenyl-lithium, respectively.

WE have previously reported the synthesis of 2,4-diaryl-5,6,7,8-tetrachloroquinazolines by the reaction of pentachlorophenyl-lithium with aromatic nitriles.[3,4] The analogous reactions of chloropyridyl-lithium compounds should, in principle, lead to triazanaphthalenes. We now report some successful and some unsuccessful attempts to utilise this potential route to such relatively inaccessible ring systems.

The reaction of tetrachloro-4-pyridyl-lithium (1)[5] with an excess of benzonitrile in diethyl ether under reflux, followed by hydrolysis with water, gave three products: 4-benzimidoyltetrachloropyridine (2) (11%), 4-(N-benzoylbenzimidoyl)tetrachloropyridine (3) (30·5%), and 5,6,8-trichloro-2,4-diphenylpyrido[3,4-d]-pyrimidine (4) (11%), whose formation is rationalised in Scheme 1. Reaction at room temperature followed by hydrolysis of the reaction mixture with hot 4M-hydrochloric acid instead of water gave 4-benzoyltetrachloropyridine (5) (49%) and the N-benzoylimine (3) (13%). The structure of the imine (2) was established by its molecular formula and n.m.r. spectrum, and by its

hydrolysis to the known 4-benzoyl compound (5).[6] The N-benzoylimine (3) was stable in 4M-hydrochloric acid, but was smoothly hydrolysed by 70% sulphuric acid to the ketone (5) and benzoic acid. The mass spectrum of the triazanaphthalene (4) showed a molecular ion of the calculated mass, with the appropriate isotope ratio for a compound containing three chlorine atoms, as well as fragment ions corresponding to the loss of one and two chlorine atoms; the n.m.r. spectrum showed only signals due to aromatic protons.

The isolation of the N-benzoylimine (3) was unexpected, since in the corresponding pentachlorophenyl series no analogous products were obtained.[3,4] Cyclisation is evidently fast compared with the addition of the second mole of nitrile in the benzene series, but slow in the pyridine series. The facile explanation, that a chlorine atom attached to the 3-position of a pyridine ring is less susceptible to nucleophilic attack than one attached to a benzene ring, seems hardly tenable. An alternative explanation is that in the pyridine series the intermediate (6) is stabilised by intramolecular attack at

[1] Part XXIII, J. D. Cook, N. J. Foulger, and B. J. Wakefield, J.C.S. Perkin I, 1972, 995.

[2] Preliminary communication, D. J. Berry, J. D. Cook, and B. J. Wakefield, Chem. Comm., 1969, 1273.

[3] D. J. Berry and B. J. Wakefield, J. Organometallic Chem., 1970, 23, 1.

[4] D. J. Berry and B. J. Wakefield, J. Chem. Soc. (C), 1971, 642.

[5] J. D. Cook and B. J. Wakefield, J. Organometallic Chem., 1968, 13, 15.

[6] S. S. Dua and H. Gilman, J. Organometallic Chem., 1968, 12, 299.

the reactive 4-position to give the spiro-Meisenheimer complex (7). There is precedent for the formation of spiro-Meisenheimer complexes from pyridine derivatives
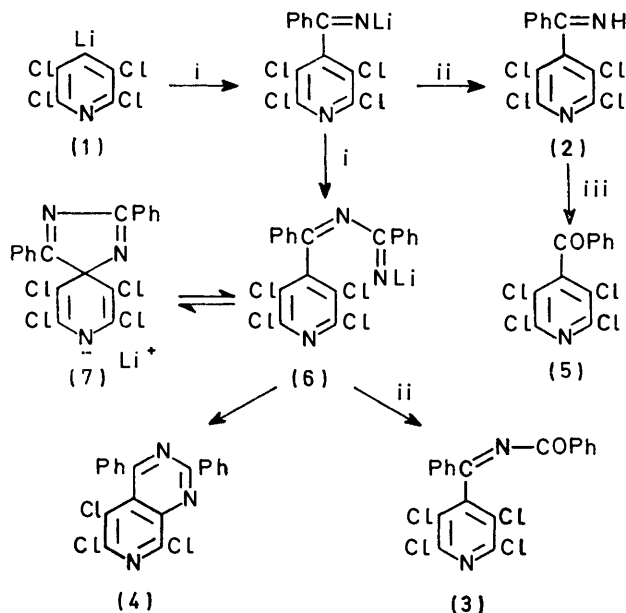
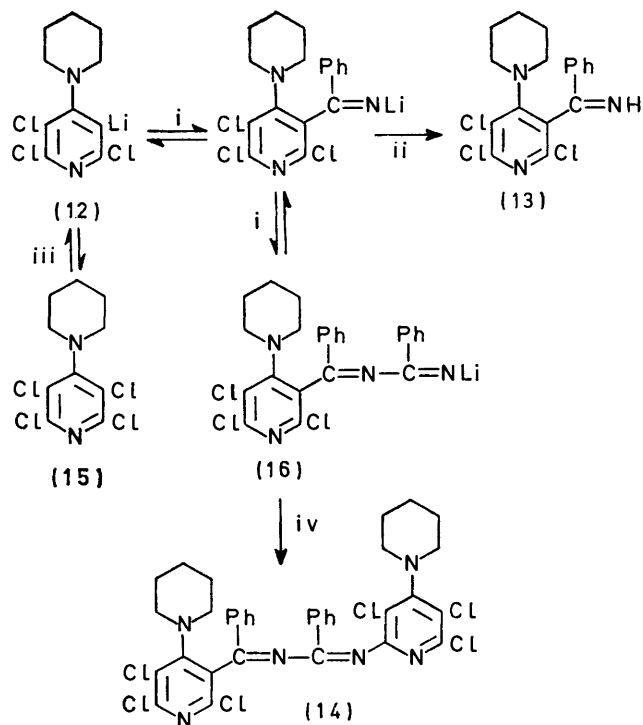SCHEME 1   Reagents: i, PhCN; ii, H$_2$O; iii, 4M-HCl

(*e.g.* ref. 7), and we have some evidence that the cleavage of the side chain from 2,3,5,6-tetrachloro-4-(2-hydroxy-ethoxy)pyridine with base, under very mild conditions, proceeds *via* the intermediate (8).[8]
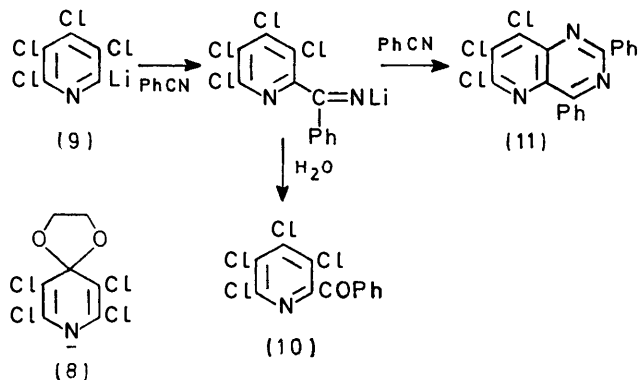
Treatment of tetrachloro-2-pyridyl-lithium (9)[5] with 1 mol. equiv. of benzonitrile, followed by hydrolysis with water, gave 2-benzoyltetrachloropyridine (10) * (12%). With an excess of benzonitrile, and more vigorous reaction conditions, the product was 6,7,8-trichloro-2,4-diphenylpyrido[3,2-*d*]pyrimidine (11) * (9%). No product analogous to the benzoylimine (3) was detected.

* In view of the fact that tetrachloro-2-pyridyl-lithium, prepared by metal–halogen exchange, is accompanied by the 3-lithio- and 4-lithio-isomers,[5] the possibility that compounds (10) and (11) are contaminated by isomeric products cannot be entirely excluded, particularly in view of the modest yields. However, they had sharp m.p.s and their spectra gave no indication of the presence of impurities. The yields are in fact higher than those cited, if based on a yield of *ca.* 40% for the lithio-compound.[5]

Treatment of 2,3,6-trichloro-5-lithio-4-piperidino-pyridine (12)[9] with 1 mol. equiv. of benzonitrile, followed by hydrolysis with water, gave the expected imine (13) (22%). However, when the reaction was repeated with an excess of benzonitrile, and under more vigorous conditions, a yellow, intractable solid was precipitated. The molecular formula of the solid, based on elemental analysis and mass spectrometry, was C$_{34}$H$_{30}$Cl$_6$N$_3$. We believe that it has the structure (14), and was formed as indicated in Scheme 2. Thus, the metal–halogen

SCHEME 2   Reagents: i, PhCN; ii, H$_2$O; iii, Bu^{n}Li; iv, (15)

exchange reaction[10] and the successive reactions with benzonitrile[3] are reversible, so that 4-piperidinotetra-chloropyridine (15) and the intermediate (16) may be present in the solution at the same time. Nucleophilic substitution by compound (16) at the expected 2-position of (15)[11] then gives the product (14), irreversibly. On the basis of this hypothesis, the yield of the product was 75%.

In an attempt to prepare derivatives of pteridine, *via* trichloropyrazinyl-lithium (18), we investigated the reaction of tetrachloropyrazine (17) with some organo-lithium compounds. However, methyl-lithium and phenyl-lithium gave the methyl (19) and phenyl

[7] C. A. Fyffe, *Tetrahedron Letters*, 1968, 659; G. Fraenkel and J. W. Cooper, *J. Amer. Chem. Soc.*, 1971, **93**, 7228.
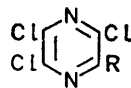
[8] B. J. Wakefield, unpublished observations.

[9] J. D. Cook and B. J. Wakefield, *J. Chem. Soc.* (C), 1969, 1973.

[10] H. J. S. Winkler and H. Winkler, *J. Amer. Chem. Soc.*, 1966, **88**, 964.

[11] S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (C), 1968, 1537.

derivatives (20), respectively, and n-butyl-lithium in a variety of solvents gave no recognisable products.

(17) R = Cl
(18) R = Li
(19) R = Me
(20) R = Ph

EXPERIMENTAL

For general directions, see ref. 1.

Reactions of Tetrachloro-4-pyridyl-lithium with Benzonitrile.—To a solution of tetrachloro-4-pyridyl-lithium [5] [from pentachloropyridine (2·0 g)] in diethyl ether (60 ml) at 20°, benzonitrile (5·2 ml) was added. The mixture was stirred at room temperature during 10 min and under reflux during 2 h. Following hydrolysis with water (50 ml) at room temperature and conventional work-up, the products were separated by chromatography on silica. Light petroleum eluted benzonitrile and traces of pentachloropyridine and tetrachloropyridines. Ether–light petroleum (1 : 99) eluted successively 5,6,8-*trichloro-2,4-diphenylpyrido*-[3,4-d]*pyrimidine* (4) (0·34 g, 11%), m.p. 180—181° (from light petroleum), τ 2·4 (m) (Found: C, 59·15; H, 2·55; Cl, 27·5%; M^+, 385. $C_{19}H_{10}Cl_3N_3$ requires C, 58·95; H, 2·6; Cl, 27·55%; M, 385); and 4-(N-*benzoylbenzimidoyl*)-*tetrachloropyridine* (3) (1·03 g, 30·5%), m.p. 157—158° (from light petroleum), τ 2·2 (m) (Found: C, 53·7; H, 2·5; N, 6·65. $C_{19}H_{10}Cl_4N_2O$ requires C, 53·75; H, 2·35; N, 6·7%). Chloroform–light petroleum (40 : 60) eluted 4-*benzimidoyl-tetrachloropyridine* (2) (0·28 g, 11%), m.p. 139—140° (from light petroleum), τ 2·45 (5H, m) and −0·05 (1H, s), $\nu_{max.}$ (Nujol) 3239 cm^{-1} (N–H str.) (Found: C, 45·3; H, 2·05; N, 8·75%; M^+, 318. $C_{12}H_6Cl_4N_2$ requires C, 45·0; H, 1·9; N, 8·75%; M, 318).

In another experiment, the reaction mixture was kept at room temperature during 2 h, and the crude product was heated under reflux in 4N-hydrochloric acid. The solid product was extracted with a little ether. The residue was recrystallised from benzene–light petroleum to give 4-benzoyltetrachloropyridine (5) (1·25 g, 49%), m.p. 134—135° (lit.,[6] 134—135°), τ 2·3 (m) (Found: C, 45·2; H, 1·85. Calc. for $C_{12}H_5Cl_4NO$: C, 44·9; H, 1·6%). Chromatography of the ether-soluble material (silica; 1 : 1 benzene–light petroleum) gave the N-benzoylimine (3) (0·43 g, 13%).

Hydrolysis of the N-Benzoylimine (3).—The N-benzoylimine (54 mg) and 70% sulphuric acid (3 ml) were heated to 100° during 1 h. The resulting homogeneous solution was poured into water (10 ml). Conventional work-up, including extraction of acidic material with alkali, gave benzoic acid (14 mg), identified by comparison with an authentic specimen, and 4-benzoyltetrachloropyridine (5) (24 mg), identical with the compound already described.

Reactions of Tetrachloro-2-pyridyl-lithium with Benzonitrile.—(i) To a solution of tetrachloro-2-pyridyl-lithium [5] [from pentachloropyridine (5·0 g)] in hexane (200 ml) at room temperature, benzonitrile (2·0 g) was added, and the mixture was stirred during 2 h. Hydrolysis with water (100 ml), followed by conventional work-up and chromatography on silica gave 2-*benzoyltetrachloropyridine* (10)

(0·80 g, 12%), m.p. 88—89° (from light petroleum) (Found: C, 45·0; H, 1·7; N, 4·4%; M^+, 319. $C_{12}H_5Cl_4NO$ requires C, 44·9; H, 1·6; N, 4·4%; M, 319).

(ii) To a similar solution of tetrachloro-2-pyridyl-lithium, benzonitrile (8·0 g) was added, and the mixture was heated under reflux during 2 h. Hydrolysis and work-up as before gave 6,7,8-*trichloro-2,4-diphenylpyrido*[3,2-d]*pyrimidine* (11) (0·70 g, 9%), m.p. 186—187° (from chloroform), τ 1·25 (2H, m) and 2·35 (8H, m) (Found: C, 59·1; H, 2·7; N, 11·2%; M^+, 385. $C_{19}H_{10}Cl_3N_3$ requires C, 58·95; H, 2·6; N, 10·9%; M, 385).

Reactions of 2,3,6-Trichloro-5-lithio-4-piperidinopyridine with Benzonitrile.—(i) To a stirred suspension of 2,3,6-tri-chloro-5-lithio-4-piperidinopyridine [9] [from tetrachloro-4-piperidinopyridine (4·5 g)] in diethyl ether (200 ml) at −70°, benzonitrile (1·55 g) in diethyl ether (20 ml) was added dropwise. The mixture was allowed to warm to room temperature during 1 h and then stirred during 30 min. Hydrolysis with water, followed by conventional work-up and chromatography on silica (eluant 20% ethyl acetate–light petroleum) gave 3-*benzimidoyl-2,5,6-trichloro-4-piperidinopyridine* (13) (1·2 g, 22%), m.p. 140° (decomp.), τ 0·1br (1H, s, NH), 2·4 (5H, m, ArH), 7·1br (4H, s, α-CH$_2$), and 8·5br (6H, s, β-, γ-CH$_2$) (Found: C, 53·5; H, 4·3; N, 11·5. $C_{16}H_{16}Cl_3N_3$ requires C, 53·85; H, 4·5; N, 11·8%).

(ii) To a similar solution of 2,3,6-trichloro-5-lithio-4-piperidinopyridine, benzonitrile (8·0 g) was added, and the mixture was heated under reflux during 3 h. Following hydrolysis with water (100 ml) the yellow product, formulated as N-[α-(2,5,6-*trichloro-4-piperidino-3-pyridyl*)*benzyl-idene*]-N′-(3,5,6-*trichloro-4-piperidino-2-pyridyl*)*benzamidine* (14), was washed with ether and dried; yield 5·5 g (75%), m.p. 270° (decomp.) (Found: C, 55·3; H, 3·8; N, 11·1%; M^+, 732. $C_{34}H_{30}Cl_6N_6$ requires C, 55·6; H, 4·1; N, 11·4%; M, 732.

Reactions of Tetrachloropyrazine with Organolithium Compounds.—(i) To tetrachloropyrazine [12] (2·18 g) in diethyl ether (100 ml) at −70°, a solution of methyl-lithium (1·2 mmol) in diethyl ether (12 ml) was added. The mixture was stirred at −25° to −30° during 45 min. Water (100 ml) was added, and conventional work-up followed by chromatography on silica gave starting material (eluted with 10% benzene–light petroleum) (1·0 g) and *trichloro-2-methylpyrazine* (19) (eluted with 15% benzene–light petroleum) (0·50 g, 51% based on starting material consumed), m.p. 49—50° after sublimation, τ 7·35 (s) (Found: C, 30·6; H, 1·5; N, 14·6. $C_5H_3Cl_3N_2$ requires C, 30·3; H, 1·5; N, 14·2%).

(ii) A similar experiment, with phenyl-lithium in place of methyl-lithium, gave *trichloro-2-phenylpyrazine* (20) (1·90 g, 73%), m.p. 42—43° (from ethanol), τ 2·3 (m) (Found: C, 46·1; H, 2·1; N, 10·8. $C_{10}H_5Cl_3N_2$ requires C, 46·3; H, 1·9; N, 10·8%).

(iii) Analogous experiments with n-butyl-lithium, and with diethyl ether, tetrahydrofuran, or methylcyclohexane as the solvent, did not yield identifiable products.

[12] R. D. Chambers J. A. H. MacBride, and W. K. R. Musgrave, *Chem. and Ind.*, 1966, 1721