5,6,7,8-Tetrahydroquinolines. Part 7. Synthesis of 8-Cyano-5,6,7,8-tetrahydroquinolines; Di-isopropylcyanamide, a New Reagent for Cyanation of Organometallics[1]

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Di-isopropylcyanamide (**1**) is an effective reagent for the conversion of 8-lithio-5,6,7,8-tetrahydroquinolines into 8-cyano-5,6,7,8-tetrahydroquinolines. 8,8-Dicyano derivatives are not formed. A convenient synthesis of the reagent from disodium cyanamide is described.

We have previously described the synthesis of 5,6,7,8-tetrahydroquinoline-8-thiocarboxamides and the corresponding nitriles by reaction of 8-lithio-5,6,7,8-tetrahydroquinolines with trimethylsilyl isothiocyanate.[1,2] This reaction has certain peculiarities and is particularly sensitive to the conditions used, which sometimes results in modest yields. We hope to report soon on our further researches in this area but meanwhile our continuing interest in thiocarboxamides as anti-secretory agents[3] led us to investigate an alternative synthesis *via* the nitriles. The literature contains few examples of the direct conversion of organometallics into the corresponding nitriles. Cyanogen bromide and cyanogen chloride have both been used but, in addition to their toxicity, they produce halogenated as well as cyanated products; alkyl thiocyanates have been used but yields are poor;[4] phenyl cyanate has been used but is unstable and must be made from cyanogen bromide;[5] tosyl cyanide has been used but the only convenient synthesis of this is from cyanogen chloride.[6] One report exists of the synthesis of nitriles using methyl(phenyl)cyanamide as a cyanating agent.[7] Using this reagent Lettré *et al.* prepared malononitrile derivatives from 2-methylpyridine (*i.e.* bis-cyanation) and, from 2-methylquinoline, either mono- or bis-nitriles or amidines depending on the conditions.

We speculated that it would be possible to control the outcome of the reaction by suitable modification of the cyanamide used. Here we report on the use of the readily prepared di-isopropylcyanamide to prepare 8-cyano-5,6,7,8-tetrahydroquinolines in high yield, uncontaminated by bis-nitrile or amidine by-products.

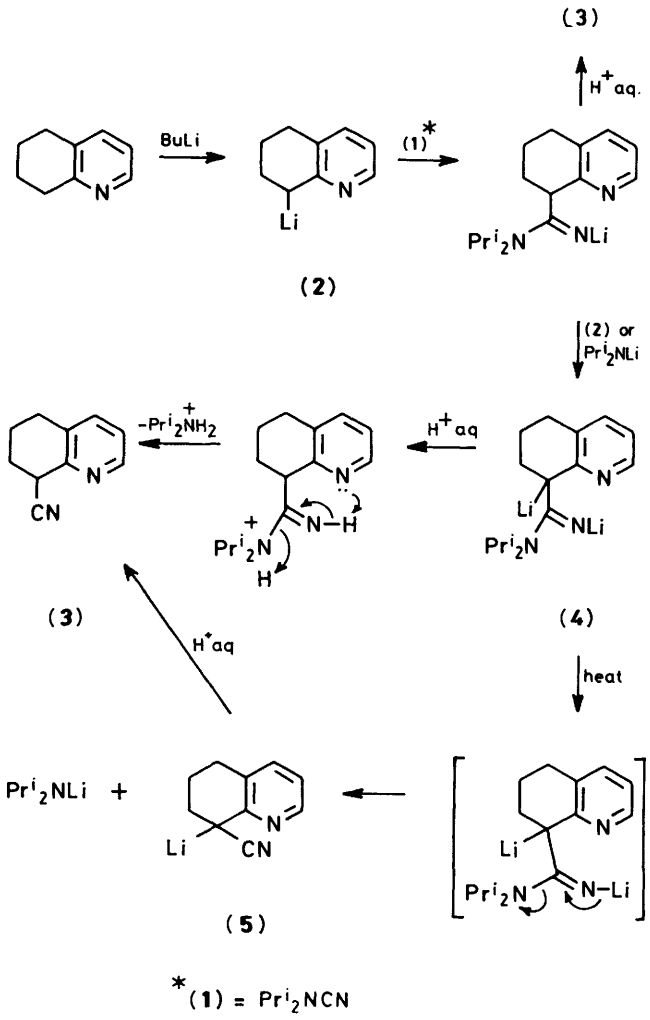
Results and Discussion

Di-isopropylcyanamide (**1**) is a stable, easily handled and relatively non-toxic reagent and may be made from cyanogen bromide and di-isopropylamine. We have found however, that it is much more conveniently and safely prepared *via* the alkylation of disodium cyanamide with isopropyl bromide in DMF (84% yield).

Treatment of 8-lithio-5,6,7,8-tetrahydroquinoline (**2**) with 1 equiv. of reagent (**1**) in a variety of solvents (toluene, ether, THF) at 0 °C followed by aqueous work-up gave a 50% yield of the 8-cyano derivative (**3**) and 50% recovered tetrahydroquinoline (n.m.r. analysis). This 50% conversion is a consequence of proton transfer[1] (Scheme 1) and several methods of circumventing it were successfully devised.

Method A. Inverse addition of anion (**2**) to 3 equiv. of reagent (**1**) in ether gave an 85% conversion into the nitrile (**3**). Under these conditions reaction with the cyanamide proved to be faster than proton abstraction.

Method B. Reaction of reagent (**1**) with the anion (**2**) in the presence of LDA (1 equiv.) (toluene, ether, THF) gave a 90% conversion into the nitrile (**3**). Here deprotonation competes successfully with attack by LDA on (**1**). Di-isopropylcyanamide is probably unique amongst cyanating agents in being sufficiently unreactive towards LDA to permit this procedure.



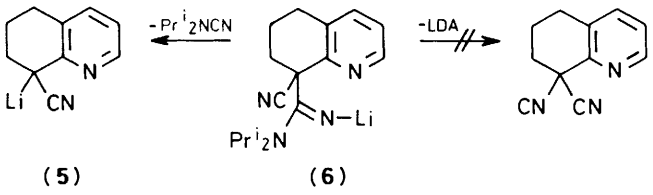
Scheme 1.

Method C. Treatment of the anion (**2**) in benzene at reflux with reagent (**1**) gave a 90% conversion into the nitrile (**3**). Under these conditions the initial adduct (**4**) evidently expels LDA which regenerates the anion (**2**) from tetrahydroquinoline (Scheme 1) as in Method B.

These procedures were successfully applied to 5,6,7,8-tetra-

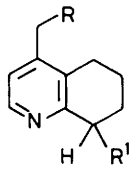
hydro-3-methylquinoline, 5,6-dihydro-7*H*-cyclopenta[*b*]pyridine and 1,2,3,4,5,6,7,8-octahydroacridine.

No isolable quantities of bis-cyanated tetrahydroquinolines were observed even in the presence of an excess of reagent (**1**) in contrast to the observations of Lettré *et al.*[7] and despite the presence of anions of the type (**4**) and (**5**) in the reaction mixtures. The lack of reactivity of (**4**) and (**5**) towards di-isopropylcyanamide may be due to the inherently lower nucleophilicity of (**4**) and (**5**) compared to (**2**) or it may reflect the relative nucleofugacities of (**5**) and LDA from (**6**), the hypothetical precursor of the bis-nitrile (Scheme 2).



Scheme 2.

Attempts to utilise other dialkyl cyanamides were less successful. Commercially available dimethylcyanamide gave some of the required nitrile (**3**) but this was accompanied by a large number of other products which were not further investigated. Although cyclohexyl(t-butyl)cyanamide and 1-cyano-2,2,6,6-tetramethylpiperidine (both made *via* the cyanogen bromide procedure) gave the nitrile (**3**) uncontaminated by by-products, the reactions were inconveniently slow, requiring 12 h at 25 °C for completion.



(**7**) R = R^1 = H
(**8**) R = H, R^1 = Li
(**9**) R = Li, R^1 = H
(**10**) R = H, R^1 = CN
(**11**) R = CN, R^1 = H

Application of these procedures to 4-methyl-5,6,7,8-tetrahydroquinoline (**7**) presents two problems. (*i*) Selective generation of the 8-lithio derivative (**8**) rather than the 4-lithiomethyl derivative (**9**)[1] and (*ii*) possible equilibration of (**8**) and (**9**) during the reaction.

Reaction of the anion (**8**) with di-isopropylcyanamide (**1**) at 0 °C in toluene gave the required 8-nitrile (**10**) uncontaminated by the 4-substituted derivative (**11**) but, as expected, in only 50% conversion. Attempts to increase this conversion by the methods used for the unsubstituted tetrahydroquinoline (*i.e.* inverse addition, increase of temperature or the addition of LDA) resulted in an increased conversion into nitrile (**10**) but at the expense of the generation of up to 35% of the isomeric nitrile (**11**). Production of (**11**) is a consequence of the conversion of the anion (**8**) into the anion (**9**), which transformation we hope to report on in a subsequent paper.

Synthesis of the desired nitrile (**10**) was finally accomplished by reaction of di-isopropylcyanamide (**1**) with the anion (**8**) in the presence of a useful new base, the lithium salt of 1-phenylpentyl(t-butyl)amine.[8] Under these conditions no more than 5% of the undesired isomer (**10**) was obtained.

The nitriles were converted into the corresponding thioamides in high yield by a modification of the Bayer dithiophosphate process,[9] thus providing an alternative synthesis of the drugs tiquinamide and isotiquimide.[1]

Experimental

General procedures are as described previously.[1] Tetrahydroquinolines and analogues were prepared as described previously[2] or purchased from Aldrich. Structural assignments are supported by n.m.r. spectra on a Varian EM360 and i.r. spectra on a Perkin-Elmer model 521 instrument.

Di-isopropylcyanamide (**1**).—A mixture of disodium cyanamide (62 g, 0.72 mol), isopropyl bromide (178 g, 1.44 mol) and DMF (400 ml) was maintained at 80 °C for 12 h. The mixture was allowed to cool, filtered and the filtrate poured onto water (2 l). The solution was extracted with hexane (6 × 500 ml) and the combined extracts were dried and evaporated. Distillation of the residue gave the title compound (75 g, 84%) b.p. 87—89 °C/15 mmHg (lit.,[10] 82 °C/10 mmHg), $\nu_{max.}$ (liquid film) 2 200 cm^{-1}; $\delta_H(CDCl_3)$ 3.2 (1 H, septet, *J* 7 Hz), 1.2 (6 H, d, *J* 7 Hz).

Cyclohexyl-t-butylcyanamide.—A solution of cyanogen bromide (53 g, 0.5 mol) in ether (200 ml) was added to a mixture of cyclohexyl-(t-butyl)amine (155 g, 1 mol) and ether (800 ml) at 0 °C and the mixture was allowed to warm to 25 °C overnight. The solution was filtered and the filtrate evaporated. Recrystallisation of the residue from hexane gave the *cyanamide* (72 g, 80%) m.p. 62—63 °C (Found: C, 73.6; H, 11.5; N, 15.4. $C_{11}H_{20}N_2$ requires C, 73.3; H, 11.2; N, 15.5%); $\nu_{max.}$ (liquid film) 2 180 cm^{-1}; $\delta_H(CDCl_3)$ 2.8 (1 H, m, CH), 1.6 (10 H, m, 5 × CH_2), and 1.25 (9 H, s, Bu^t).

1-*Cyano*-2,2,6,6-*tetramethylpiperidine.*—This was made by a similar procedure m.p. 50—52 °C (from hexane) (Found: C, 72.3; H, 10.9; N, 16.75. $C_{10}H_{18}N_2$ requires C, 72.2; H, 10.9; N, 16.9%); $\nu_{max.}$ (Nujol) 2 200 cm^{-1}; $\delta_H(CDCl_3)$ 1.5 (6 H, m, 3 × CH_2), and 1.3 (12 H, s, 4 × Me).

8-*Cyano*-5,6,7,8-*tetrahydroquinoline* (**3**).—*Method A.* A solution of 8-lithio-5,6,7,8-tetrahydroquinoline (**2**) (50 mmol), generated from 5,6,7,8-tetrahydroquinoline (6.5 ml, 50 mmol), butyl-lithium in hexane (1.6M; 31.3 ml), and ether (30 ml), was blown over by inert gas onto a solution of (**1**) (18.9 g, 0.15 mol) in ether (30 ml) maintained at 0 °C. After 0.5 h the mixture was cooled and quenched with water (100 ml). The organic phase was separated, dried, and evaporated. Distillation of the residue gave the title compound (**3**) (6.7 g, 85%), b.p. 135—140 °C/2 mmHg. The hydrochloride crystallised from ethanol as the quarter hydrate, m.p. 183 °C (Found: C, 60.8; H, 5.7; N, 14.0. $C_{10}H_{10}N_2$·HCl·0.25H_2O requires C, 60.5; H, 5.8; N, 14.1%).

Method B. A solution of LDA (50 mmol) generated from butyl-lithium in hexane (1.55M; 32.3 ml, 50 mmol), di-isopropylamine (7 ml, 50 mmol) and toluene (30 ml) and maintained at 5 °C was treated with a solution of 5,6,7,8-tetrahydroquinoline (3.33 g, 25 mmol) in toluene (5 ml). After 0.5 h the resulting anion (**2**) was treated with a solution of (**1**) (3.15 g, 25 mmol) in toluene (5 ml). After 0.5 h, work-up as in Method A gave the title compound in 90% yield.

Method C. A solution of 5,6,7,8-tetrahydroquinoline (6.5 ml, 50 mmol) in benzene (35 ml), maintained below 10 °C was treated with a solution of butyl-lithium in hexane (1.55M; 32.3 ml, 50 mmol). The resulting anion solution was heated to reflux

and treated with a solution of (**1**) (6.3 g, 50 mmol) in benzene (15 ml). After 15 min, work-up as in Method A gave the title compound in 71% yield.

7-*Cyano*-5,6-*dihydro*-7H-*cyclopenta*[b]*pyridine*.—This was obtained from 5,6-dihydro-7*H*-cyclopenta[*b*]pyridine following the procedure of Method B. The hydrochloride had m.p. 170 °C (sublimes) (from ethanol) (Found: C, 60.2; H, 5.1; N, 15.6. $C_9H_8N_2$·HCl requires C, 59.9; H, 5.0; N, 15.5%).

4-*Cyano*-1,2,3,4,5,6,7,8-*octahydroacridine*.—This was obtained from *sym*-octahydroacridine following the procedure of Method B, m.p. 88—90 °C from di-isopropyl ether (Found: C, 79.0; H, 7.8; N, 13.2. $C_{14}H_{16}N_2$ requires C, 79.2; H, 7.6; N, 13.2%).

8-*Cyano*-3-*methyl*-5,6,7,8-*tetrahydroquinoline*.—This was obtained from 3-methyl-5,6,7,8-tetrahydroquinoline following the procedure of Method B. The hydrochloride had m.p. 189 °C (lit.,[11] 189—190 °C) from propan-2-ol.

8-*Cyano*-4-*methyl*-5,6,7,8-*tetrahydroquinoline* (**10**).—A solution of *N*-benzylidene-t-butylamine[8,12] (19.3 g, 0.12 mol) in toluene (20 ml) was added to a solution of butyl-lithium in hexane (1.55M; 142 ml, 0.22 mol) maintained at 0 °C. After 0.5 h a solution of 4-methyl-5,6,7,8-tetrahydroquinoline (14.7 g, 0.1 mol) in THF (30 ml) was added. After a further 0.5 h a solution of (**1**) (14.0 g, 0.11 mol) in THF (30 ml) was added and the mixture stirred for 0.5 h and then quenched with water (100 ml). The aqueous phase was extracted with toluene (3 × 100 ml) and the combined toluene extracts were washed with water, dried, and evaporated. Trituration of the residue with hexane gave a crystalline mixture (14.1 g, 84%) of the title compound (**10**) and the isomeric nitrile (**11**) in the ratio of 95:5 (n.m.r. analysis). The crude mixture was dissolved in methanol and treated with an excess of ethereal hydrogen chloride. Removal of the resulting crystals by filtration gave the title compound [free from (**11**)] as the *hydrochloride* (15.9 g, 76%), m.p. 253—255 °C (Found: C, 63.0; H, 6.7; N, 13.1. $C_{11}H_{12}N_2$·HCl requires C, 63.3; H, 6.3; N, 13.4%).

4-*Methyl*-5,6,7,8-*tetrahydroquinoline*-8-*thiocarboxamide*.—A mixture of the nitrile (**10**) (73 g, 0.35 mol), diethyl dithiophosphate (60 ml, 0.36 mol), and dichloroethane (350 ml) was treated with hydrogen chloride at reflux over 4 h. The mixture was cooled to ambient temperature. The resulting crystals were filtered off, washed with dichloroethane, and recrystallised from methanol to give the title compound as the hydrochloride (74.5 g, 88%), m.p. 213 °C (lit.,[2] 212—213 °C).

Acknowledgements

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References

1 Part 6, R. Crossley and R. G. Shepherd, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1917.
2 A. C. W. Curran and R. G. Shepherd, *J. Chem. Soc., Perkin Trans 1*, 1976, 983.
3 D. E. Beattie, R. Crossley, A. C. W. Curran, G. T. Dixon, D. G. Hill, A. E. Lawrence, and R. G. Shepherd, *J. Med. Chem.*, 1977, **20**, 714.
4 C. Rodriguez, A. M. Lamazouere, and J. Sotiropoulos, *C. R. Acad. Sci., Ser. C*, 1980, 179.
5 R. E. Murray and G. Zweifel, *Synthesis*, 1980, 150.
6 D. Kahne and D. B. Collum, *Tetrahedron Lett.*, 1981, **22**, 5011.
7 H. Lettré, P. Jungmann, and J. C. Salfeld. *Chem. Ber.*, 1952, **85**, 397.
8 I. A. Cliffe, R. Crossley and R. G. Shepherd submitted to *Synthesis*.
9 G.P. 1, 111, 172/1961
10 American Cyanamid Co., *New Products Bulletin*, Coll. vol. 1, 1952, 73.
11 R. Crossley, A. C. W. Curran, and D. G. Hill, *J. Chem. Soc. Perkin Trans. 1*, 1976, 977.
12 B. L. Emling, R. J. Horvath, A. J. Saraceno, E. F. Ellermeyer, L. Haile, and L. D. Hudac, *J. Org. Chem.*, 1959, **24**, 657.

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