

SYNTHESIS OF CYCLOPROPYL CYANIDE-2,2-D₂

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SUMMARY

A convenient method for the synthesis of cyclopropyl cyanide-2,2-d₂ has been elaborated. Reduction of methyl 3-cyanopropionate with lithium borodeuteride followed by reaction of the resulting alcohol with triphenylphosphine and carbon tetrachloride gave 4-chlorobutyronitrile-4,4-d₂. Conversion of the chloride to the iodide with sodium iodide followed by cyclization with sodium hydride afforded cyclopropyl cyanide-2,2-d₂ in 30% overall yield with deuterium incorporation of >95%.

INTRODUCTION

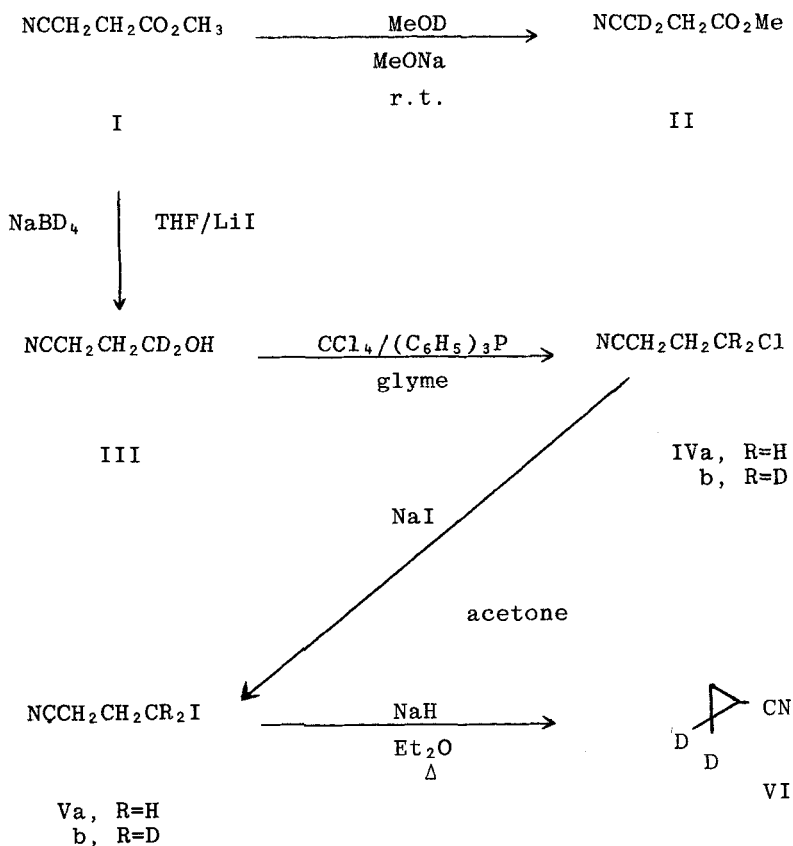
In connection with some mass spectral studies,¹ cyclopropyl cyanide-2,2-d₂ (VI) was synthesized.

Cyclopropyl cyanide has usually been prepared by one of two methods,^{2,3} both proceeding from 4-chlorobutyronitrile (IVa). The method of Lampman,² involving the conversion of IVa to 4-iodobutyronitrile (Vb) with sodium iodide in acetone followed by cyclization with sodium hydride, was chosen for the preparation of VI as it was felt to be more amenable to small-scale synthesis than the commonly used sodium amide ring closure³ of IVa. The

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simplest approach to either of the two possible prerequisite 4-chlorodideutero-butyronitriles appeared to be *via* methyl 3-cyanopropionate (I) either by selective deuterium exchange of the 2,2-hydrogens followed by reduction to 4-hydroxybutyronitrile-3,3- d_2 and chlorination, or by deuteroreduction to 4-hydroxybutyronitrile-4,4- d_2 (IVb) and chlorination (Scheme I).

SCHEME I



While mild base-catalyzed deuterium exchange on I proved highly selective, it gave only the undesired methyl 3-cyanopro-

pionate-3,3-d₂ (II) with deuterium incorporation of >97%. Alternatively, reduction of I with lithium borodeuteride generated *in situ* from sodium borodeuteride and lithium iodide⁴ proceeded smoothly at room temperature to give 4-hydroxybutyronitrile-4,4-d₂ (III) in 86% yield. The alcohol (III) was chlorinated with triphenylphosphine/carbon tetrachloride⁵ and the chloride was converted to the iodide. Cyclization of the crude 4-iodobutyronitrile-4,4-d₂ (Vb) with sodium hydride in ether afforded the desired cyclopropyl cyanide-2,2-d₂ (VI) in 40.1% yield with deuterium incorporation of >95%.

EXPERIMENTAL⁶

All reactions were carried out in purified solvents under anhydrous conditions. The ¹H and ¹³C nmr spectra were obtained on either a Varian A60A nmr spectrometer, a Varian XL-100 nmr spectrometer equipped with a Digilab nmr-3 FT accessory or a JEOL PS-100 nmr spectrometer. Mass spectra were run on a CEC 21-104 mass spectrometer. Gas chromatographic analyses (glc) were carried out using a Bendix model 2300 gas chromatograph with 5 ft x 0.25 in. copper columns packed with 5% SE-30 on Chromosorb G-HP (80-100 mesh) using He carrier gas at a 60 ml/min. flow rate.

Methyl 3-cyanopropionate-3,3-d₂ (II)

To 6.6 ml (0.162 mol) of methanol-d (Wilmad Glass Co., 99.0% CH₃OD) under nitrogen was added 60 μl of 2.6 M sodium methoxide in methanol-d followed by 450 mg (4 x 10⁻³ mol) of methyl 3-cyanopropionate (I).⁷ The resulting solution was allowed to stand for three days at room temperature. The methanol was removed under reduced pressure and the oil/solid residue washed with methylene chloride (5 x 2 ml). The methylene chloride washings were filtered, washed with deuterium oxide (0.5 ml) and dried (Na₂SO₄). Removal of the solvent afforded 419 mg (91%) of crude

II (>98% pure by glc).

The ^1H nmr of I showed (CDCl_3) 2.65 ppm (s,4,- CH_2CH_2 -), 3.65 ppm (s,3,- CH_3) while that of II gave (CDCl_3) 2.68 ppm (s,2), 3.7 ppm (s, 3,- CH_3). Proton decoupled ^{13}C nmr indicated that II was >80% deuterated on the 3-carbon. The ^1H nmr of I, determined using an nmr shift reagent, gave (CDCl_3 , EuFOD) 6.72 ppm (m,2), 7.19 ppm (m,2), 7.45 (s,3,- CH_3) and II under the same conditions showed 6.72 ppm (m,2), 7.45 (s,3,- CH_3). On the basis of these data the shifted methylene resonance of I at 6.72 ppm was assigned to the 2-protons and that at 7.19 ppm to the 3-protons. Thus, II was deuterated on the 3-position with >97% d_2 with <1% d on the 2-position.⁸

4-Hydroxybutyronitrile-4,4- d_2 (III)

Tetrahydrofuran (100 ml) was added with stirring to 1.57 g (0.0375 mol) of sodium borodeuteride (Merck Sharp and Dohme Canada, Ltd., 98% NaBD_4) and 5.02 g (0.0375 mol) lithium iodide. The resulting cloudy mixture was cooled to $0-5^\circ$ and 5.65 g (0.05 mol) of methyl 3-cyanopropionate (I) in 25 ml tetrahydrofuran was added over 0.5 hr. The mixture was then stirred for four days at room temperature. Addition of 6.25 g (0.104 mol) of glacial acetic acid in 25 ml tetrahydrofuran at $0-5^\circ$ over 1.25 hour, followed by stirring at $0-5^\circ$ for 0.25 hour and at room temperature for one hour gave, on removal of the solvent at room temperature under reduced pressure, a clear oil. Treatment of the oil with 50 ml of methylene chloride, followed by cooling to $0-5^\circ$ and addition of 10 ml of water gave a two-phase solution which was kept cold and basified to pH 8-9 with 50% aqueous sodium hydroxide (w/w, 3.5 ml). The layers were separated. The aqueous layer was washed with 25 ml of methylene chloride, followed by the addition of 10 ml of water and 10 ml of saturated sodium chloride. The pH was readjusted to 8-9 with 10% sodium hydroxide

and the solution was continuously extracted for 24 hours with methylene chloride. The combined methylene chloride fractions were dried (Na₂SO₄). Removal of the solvent afforded 4.16 g of crude III which was distilled to give 3.74 g (86%) of III: bp 87-90° (2.7 mm). Glc showed purity >98% and nmr indicated a minimal isotopic composition of 90% d₂.⁸

4-Chlorobutyronitrile-4,4-d₂ (IVb)⁹

To a stirred solution of 13.60 g (0.0519 mol) of triphenylphosphine and 19.16 g (0.124 mol) of carbon tetrachloride in 50 ml of glyme was added over 0.25 hour 3.61 g (0.0415 mol) of 4-hydroxybutyronitrile-4,4-d₂ (III) in 24 ml of glyme. The solution was heated under gentle reflux for one hour with efficient stirring. The mixture was cooled and the insoluble triphenylphosphine oxide was collected by filtration and washed with cold glyme. The filtrate was concentrated by distillation (90 mm) through a 10 cm Vigreux column. A further portion of triphenylphosphine oxide which deposited was separated and washed with a small portion of cold glyme. The filtrate was reconcentrated and the remaining oil was distilled to give 3.64 g (95.7%) of IVb: bp 90-7° (21 mm). Glc showed purity >98% and nmr indicated minimal isotopic composition of 90% d₂.⁸

4-Iodobutyronitrile-4,4-d₂ (Vb)

To 9.95 g (0.0664 mol) of sodium iodide at 0-5° was added with stirring 30 ml of acetone, followed by 3.51 g (0.0332 mol) of 4-chlorobutyronitrile-4,4-d₂ (IV) at room temperature. The mixture was heated under reflux for 48 hours. The acetone was removed under reduced pressure leaving a solid/oil which was treated with 50 ml of methylene chloride followed by 25 ml of water. The methylene chloride layer was separated and the water layer was washed with methylene chloride (2 x 10 ml). The

methylene chloride extracts were dried (MgSO_4) and the solvent was removed to give 5.94 g (91%) of crude Vb. Glc showed purity >98% and nmr indicated minimal isotopic composition of 90% \underline{d}_2 . Mass spectral analysis showed 94.6% \underline{d}_2 , 5.2% \underline{d}_1 and 0.1% \underline{d}_0 .

Cyclopropyl Cyanide-2,2- \underline{d}_2 (VI)

Ether (45 ml) was added to 2.25 g (0.0469 mol) of a 50% dispersion of sodium hydride in mineral oil previously washed *in situ* with ether (3 x 3 ml). To the stirred mixture was added over 0.25 hour 5.56 g (0.0282 mol) of 4-iodobutyronitrile-4,4- \underline{d}_2 (Vb) in 15 ml of ether. The reaction was heated under reflux with stirring for 36 hours, after which glc showed the reaction to be essentially complete.¹⁰ The mixture was cooled to 0-5⁰ and 10 ml of water was added slowly. The ether layer was separated, and the aqueous portion and insoluble tar were washed with ether (3 x 10 ml). The combined ether washings were dried (MgSO_4) and the ether was removed by distillation (760 mm) through a 10 cm Vigreux column. The residual oil was distilled through a 4 cm Vigreux column with the receiver cooled in dry ice to give 0.781 g (40.1%) of VI: bp 65-8⁰ (79 mm). Glc indicated a purity >92% and nmr showed a minimal isotopic composition of >90% \underline{d}_2 .⁸

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REFERENCES

1. Glenn, D. F. and Edwards, III, W. B., J. Org. Mass Spec., in press.
2. Lampman, G. M., Horne, D. A. and Hager, G. D., J. Chem. Eng. Data, 14, 396 (1969).

3. Schlatter, M. J., Org. Syn. Coll. Vol. 3, 223 (1955).
4. Kollonitsch, J., Fuchs, O., Gábor, V., Nature, 173, 125 (1954).
5. Weiss, R. G., Snyder, E. I., Chem. Commun., 1358 (1968).
6. The structure and site of labeling of all deuterated materials were confirmed by comparison of their nmr and mass spectra with those of authentic nondeuterated samples.
7. Available from Chemicals Procurement Laboratories, Inc.
8. The lack of an abundant ion containing both deuteriums made nmr data more reliable than the mass spectral data.
9. Hart, H., Corbin, J. L., Wagner, C. R. and Wu, C., J. Amer. Chem. Soc., 85, 3269 (1963). These authors prepared IVb of unreported deuterium content with a yield of <40%.
10. Since the rate of reaction has been found to vary, it is important that the mixture be checked by glc, as the presence of moderate amounts of unreacted V gave an impurity which was difficult to separate from VI.