

A FACILE SYNTHESIS OF [1-¹³C]BENZONITRILE
BY BROMINATION-DEHYDROBROMINATION OF [1-¹³C]1-CYANOCYCLOHEXENE
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SUMMARY

[1-¹³C]1-Cyanocyclohexene can be bisbrominated by N-bromosuccinimide and then aromatized by triethylamine to give [1-¹³C] benzonitrile in 90% yield. This allylic bisbromination-dehydrobromination reaction is generally applicable to the transformation of other 1-substituted cyclohexenes into benzenoid derivatives.

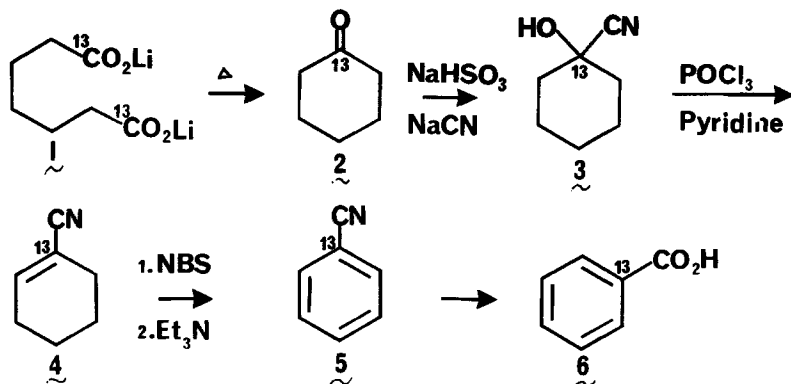
Key words: [1-¹³C]Benzonitrile, Bromination-Dehydrobromination, N-Bromosuccinimide, ¹³C-Labeling.

INTRODUCTION

In the course of preparing site specifically labeled ¹³C precursors for biosynthetic studies, we have developed an improved procedure for [1-¹³C]benzonitrile (2), a key intermediate in the elaboration of correspondingly labeled benzoic acid and its derivatives. The traditional methods for 1-labeled aromatic ring constructions have been based upon the high temperature dehydrogenation of [1-¹⁴C] or [1-¹³C]1-methylcyclohexene over supported noble metal catalysts on a 100 mmol or smaller reaction scale (2-8). These approaches proved to be unworkable when applied to [1-¹³C]1-cyanocyclohexene, the synthon of choice in our investigations.

So, following the overall synthetic scheme depicted below, we bisbrominated [1-¹³C] 1-cyanocyclohexene with two equivalents of N-bromosuccinimide (NBS) in carbon tetrachloride and dehydrohalogenated the reaction product without prior isolation by addition of triethylamine. [1-¹³C]benzonitrile was recovered in 93% crude yield on a 300 mmol scale, affording pure product in 85% yield after distillation (9). In carrying out model reactions with unlabeled cyanocyclohexene, we had found that the dibromo adduct could not be isolated. Nor did our attempts to react it in a one-pot sequence with bases other than triethylamine succeed in furnishing pure benzonitrile in yields above

40%, as might have been expected from the literature on NBS mediated introduction of supplementary double bonds (10).



DISCUSSION

[1- ^{13}C]Benzonitrile obtained in this manner is indistinguishable from the unlabeled article of commerce, except by spectroscopic means. Its NMR and IR spectra were found to be consistent with the assigned structure and site of ^{13}C labeling. Hydrolysis of the benzonitrile with aqueous hydroxide afforded [1- ^{13}C]benzoic acid^{2,3d}. Its spectral characteristics also were consistent with the assigned structure.

We believe the aromatization sequence reported here for [1- ^{13}C]-benzonitrile to be one of general applicability in the synthesis of other benzene derivatives from precursors amenable to allylic bromination-dehydrobromination. Thus, for example, isotopically labeled 1-ethylcyclohexene and 1-cyano-2-methyl-cyclohexene have been converted into ethyl benzene and tolunitrile, respectively, in 70% or better yields. However, the mechanism of this transformation remains to be elucidated. It may be a more complex reaction, than simple base-catalyzed elimination of HBr, requiring light, trace metal ions, and adducts of triethylamine with carbon tetrachloride. The effects of these factors on the yield were not examined.

EXPERIMENTAL

All isotopically labeled precursors were obtained from KOR isotopes and all other reagents from Aldrich. They were used without further purification. Gas liquid chromatography (GLC) was performed on a 3%

OV-17/Gas Chrom Q column in a Bendix-3000 gas chromatograph. Nitrogen was used as a carrier gas at 10psi; injector temperature was 175°C, oven temperature was 125°C, and FID detector temperature 125°C. IR spectra were recorded on a Perkin-Elmer 727 Spectrophotometer. ¹H and ¹³C-NMR spectra were taken on Varian EM360A and JEOL FX-90Q NMR spectrometers, respectively.

[1-¹³C]1-Cyanocyclohexene (4). [1-¹³C]Cyclohexanone (90.5% ¹³C) was prepared in 85% yield from [1,7-¹³C₂]pimelic acid by the literature procedure (11) and converted to [1-¹³C]1-cyanocyclohexene in 74% yield (two steps) by dehydration with phosphorus oxychloride of the intermediate cyanohydrin (12). The residual oil was distilled, bp 86° (18 torr), and GLC analysis indicated a purity of 98.2%; IR: 2963 (m), 2220 (m), 1620 (w), 1365 (m), 1228 (s), 1048 (m), 1020 (m) cm⁻¹. NMR (CDCl₃): 1.5-1.7 (m, 4H, 4 and 5-CH₂), 2.0-2.4 (m, 4H, 3 and 6-CH₂) and 6.5 ppm (m, more complex than unlabeled, 2-CH).

[1-¹³C]Benzonitrile (5). N-Bromosuccinimide (113g, 633 mmol; from a freshly opened bottle) was added to a mechanically stirred solution of [1-¹³C]1-cyanocyclohexene (32.5g, 301 mmol, 90.5% ¹³C) in carbon tetrachloride (415 mL) and the suspension was refluxed for 16 h in an oil bath. Throughout this time the reaction flask (2 L, three-neck, round bottom, fitted with a reflux condenser) was illuminated by a 15 watt incandescent reading lamp placed at a 15 cm distance. The reaction mixture was cooled to room temperature and triethylamine (91g, 900 mmol) was added dropwise over 1 h. The reaction mixture was again refluxed for 4 h, allowed to cool and treated with 415 ml of pentane with rigorous stirring. The solids were separated by suction filtration and washed with additional small portions of pentane. Concentration of the combined organic filtrates under reduced pressure to a 100 mL volume gave a red syrup which was passed through a 5x10 cm short column of silica gel and eluted with 200 ml of 10% diethyl ether in hexane. Evaporation of the eluates at 35°C (12 torr) afforded crude [1-¹³C]benzonitrile (29g, 93%). Fractional distillation, bp 69° (10 torr), yielded product (26.5g, 85%). Analysis of this material by GLC indicated a purity of 98.7%; IR: 3075 (m), 2220 (s), 1600 (m), 1485 (s), 1445 (s), 755 (s), 685 (s). ¹H-NMR (CDCl₃): 7.3-7.8 ppm, a single spike above a multiplet, (unlabeled material showed two spikes). ¹³C-NMR (CDCl₃): 112.4 (s, 1-¹³C), (C=N peak too weak), 129.1 (s, 3-C), 132.0 (d, J_{CC}=59Hz, 2-C, integration showed 90% ¹³C at 1-C) and 132.7 ppm (d,

$J_{1,4}=12\text{Hz}$, 4-C).

[1-¹³C]Benzoic acid (6). [1-¹³C]Benzonitrile (8g, 76.5 mmol) was refluxed with 125 mL of 10% NaOH under a gentle purge stream of nitrogen. Upon cooling to room temperature, the resulting solution was brought to pH 4.5 with vigorous stirring and chilled to 0°. The product was collected by filtration and dried *in vacuo* to give 8g (85%) of product: mp 122-123°C, undepressed by admixture with unlabeled benzoic acid; IR: identical with IR of unlabeled material. ¹H-NMR (CDCl₃): 7.2-7.7 (m, more complex than unlabeled, 3H) and 7.9-8.3 ppm (m, 2H). ¹³C-NMR (CDCl₃): 128.6 (s, 3-C), 129.6 (s, 1-¹³C), 130.4 (d, $J_{CC}=58\text{Hz}$, 2-C, only the 131.7 ppm peak was discernible, the other buried under large 1-¹³C peak), 133.9 (d, $J_{1,4}=9.8\text{Hz}$, 4-C) and 174.5 ppm (d, $J_{CC}=73\text{Hz}$, CO₂H, integration showed 90% ¹³C at 1-¹³C).

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