SYNTHESIS OF [2-^{13}C]PHENOL (1)

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SUMMARY

[2-^{13}C]cyclohexanone was synthesized through [^{13}C]cyanation of cyclopentanone followed by acetylation, reduction and ring expansion. Treatment with cupric bromide/lithium bromide and dehydrobromination of the resulting labeled 1,6-dibromohexanone in a "one pot" procedure gave [2-^{13}C]phenol.

Key words: carbon-13, cyclohexanone, cupric bromide-lithium bromide, 1,6-dibromocyclohexanone, phenol.

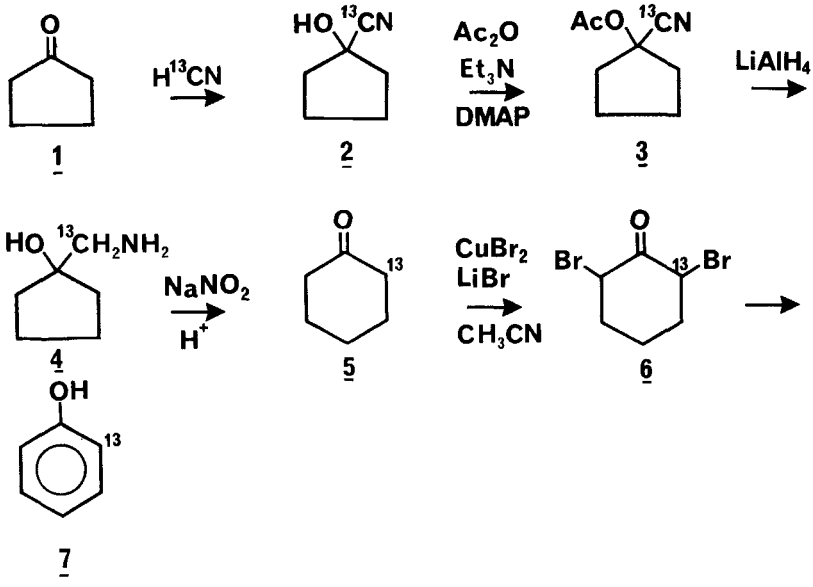
INTRODUCTION

Our research on the craze shape and fracture toughness (2) of bisphenol-A polycarbonate optical plastics required the development of a labeled probe for structural studies by carbon magnetic resonance (3). Towards this end, we devised a synthesis of [2-^{13}C]phenol in preference to its 1- or 4-^{13}C isotomers, upon noting that the bisphenol A (4) derived from it would afford better resolved signals, enhanced by the Nuclear Overhauser Effect. Since our earlier route to [1-^{13}C]benzenoid aromatics (5) could not be applied in this instance, we first obtained [2-^{13}C]cyclohexanone by ring expansion of cyclopentanone with H^{13}CN following the method of Geiss and Blech (6) with minor modifications. Treatment with cupric bromide-lithium bromide in refluxing

0362-4803/83/121349–06$01.00

Received August 31, 1983

acetonitrile, an approach used successfully to aromatize 3-keto steroids (7), accomplished the desired bromination to 1,6-dibromocyclohexanone and its subsequent dehydrobromination to phenol in a "one pot" sequence as depicted in Scheme I.



RESULTS AND DISCUSSION

The preparation of 1-amino[^{13}C]methylcyclopentanol, 4, as described by Geiss and Blech (6) did not prove reproducible on the tenfold larger scale required for our investigations, especially when NaCN was substituted for KCN. In trial runs without isotope, cyanohydrin formation did not exceed 70% and immediate acetylation with acetic anhydride catalyzed by acetyl chloride at reflux afforded product 3 of unsatisfactory purity for subsequent reduction. Nevertheless, we found that a series of minor modifications accomplished our objectives in comparable overall yield to the literature method. Cyanohydrin formation with liquid H^{13}CN, freshly prepared from Na^{13}CN, gave an acceptable mixture of product and unreacted starting material (75:25). Acetylation with

acetic anhydride in triethylamine at ambient temperature, under 4-dimethylaminopyridine catalysis (8) then gave crude 2 in 85% yield. Thereafter, lithium aluminum hydride reduction proceeded as expected, completing the conversion sequence to 4 in 67% yield from Na^{13}CN. The rearrangement to cyclohexanone, 3, was accomplished without difficulty but with a lower recovery of distilled product (50%) than expected, despite several efforts to optimize this reaction prior to committment of labeled precursor.

Dehydrogenation of 5 to phenol 7 presented a greater challenge. Although numerous industrial (9) processes have been reported to effect this transformation by gas phase and other catalytic methods, on careful examination, none appeared suitable for small scale application. In addition, the paucity of reports with experimental details in the general organic literature suggested further that a new method would have to be developed. Initially, we examined palladium chloride in stoichiometric amounts as a dehydrogenating reagent for hexanone (12), but obtained little product (15%). Dehydrogenation of cyclohexen-2-one, a more facile reaction by several published routes (12,13), was also considered but not attempted, since elaboration to the enone would have required a multistep sequence (14).

From prior experience with ring A steroid aromatizations (15) we adapted the method of Bondon and co-workers (7). Thus, when labeled cyclohexanone was treated with an excess of cupric bromide-lithium bromide in refluxing acetonitrile, we noted formation of 1,6-dibromocyclohexanone within three hours (80% conversion). Dehydrobromination proceeded over the next 24 hours, as shown in earlier studies by Sturtz and Raphalen (16), and left the desired product along with a small amount of 2-bromophenol. Fractional distillation gave [2-^{13}C] phenol in 50% yield, with a chemical purity greater than 95% as judged by gas chromatographic and spectroscopic analyses.

EXPERIMENTAL

General: Gas chromatographic analyses were performed on a Bendix-3000 instrument. NMR spectra were recorded using Varian EM360A and IBM NR80F Spectrometer. IR spectra were recorded on a Perkin-Elmer 727 Spectrometer.

1-[^{13}C]cyanocyclopentanol (2): A solution of sodium [^{13}C]cyanide (99 mol% ^{13}C, 17.5g, 0.35 mole) in 25 ml of water was added slowly to a warm (75°C) solution of 20 ml of conc. sulfuric acid in 100 ml of water. The distilled hydrogen cyanide was collected in a -78°C flask containing cyclopentanone (29.4 g, 0.35 mole) and pyridine (0.1 ml). The mixture was warmed up to 0°C with stirring for 2 hours. NMR ($CDCl_3$) δ:1.7-2.1 (m, CH_2) and 6.2 ppm (s, OH, integration showed that there was 25% starting ketone). IR (neat):3500 and 3150 (OH), 2060 (^{13}C≡N), 1740 (cyclopentanone) and 1160 cm^{-1} (C-O).

1-[^{13}C]cyanocyclopentyl acetate (3): Triethylamine (45g, 0.45 mole), acetic anhydride (40g, 0.4 mole) and 4-dimethylaminopyridine (3g) were added slowly with ice cooling to the cyanohydrin obtained from the above reaction. This mixture was stirred for 2 hours at room temperature (r.t.) and then was diluted with 200 ml of ether. The ether solution was washed with dil. hydrochloric acid, brine, sodium bicarbonate solution and again with brine. The organic layer was dried over $MgSO_4$ and evaporated to give 46g (85% yield) of product still contaminated with cyclopentanone, NMR ($CDCl_3$) δ:1.5-2.4 (2 sets of m, CH_2) and 2.0 ppm (s, CH_3CO_2). IR (Neat):2200 (weak, ^{13}C≡N) 1750 (C=O) 1240 and 1200 cm^{-1} (COC).

1-Amino[^{13}C]methylcyclopentanol (4): The crude acetate from the preceding reaction was dissolved in 100 ml of ether and added to a suspension of lithium aluminum hydride (38g, 1 mole) in 1L of ether under nitrogen. After refluxing for 3 hours, the mixture was treated carefully with 40 ml of water, 40 ml of

15% NaOH and then 80 ml of water. The solid was filtered off and the filtrate was dried over $MgSO_4$. Evaporation gave 27g of the amino alcohol (79%) NMR ($CDCl_3$) δ :1.4-2.0 (m, ring $\underline{CH}_2$), 1.8 (s, 3H, $\underline{OH}$ and $\underline{NH}_2$) and 2.7 ppm (d, J_{CH}=132 Hz, 2H, $^{13}\underline{CH}_2$, the high field branch was buried under the multiplet).

[2-^{13}C]Cyclohexanone (5): Sodium nitrite (25g) in 50 ml of chilled water was added slowly to a solution of 4 in 300 ml of 25% acetic acid in water at 0°C. The mixture was heated to 70°C for 3 hours and left to stir at r.t. overnight. Sodium hydroxide solution (6N) was added to pH7 followed by enough sodium chloride (solid reagent) to achieve saturation. The solution was extracted with 6X100 ml of ether. Careful distillation of the ether and fractionation of the product gave 12g of product (50% yield). NMR ($CDCl_3$) δ:1.5-2.1 (m, $\underline{CH}_2$), 2.3 (t, J=7 Hz, 6-$\underline{CH}_2$) and 2.3 ppm (dt, J=7 Hz. J_{CH}=132 Hz, $^{13}\underline{CH}_2$).

[2-^{13}C]phenol (7): [2-^{13}C]Cyclohexanone (9.8g, 0.1 mole), cupric bromide (95g) and lithium bromide (60g) were mixed in 500 ml of acetonitrile, and the mixture was heated to reflux for 4 hours. After 3 hours an aliquot was withdrawn, washed with water and evaporated. Gas chromatographic analysis (SE-30 column, 100°C) showed only one major peak, and the NMR spectrum was consistent with that of 1,6-dibromocyclohexanone (6): NMR ($CDCl_3$) δ:1.5-2.9 (m, $\underline{CH}_2$), 4.5 (dt, J=7 Hz, J_{CH}=130 Hz $^{13}\underline{CH}Br$, 50% uncoupled signal) and 4.9 ppm (dt, J=7 Hz, J_{eH}=130 Hz, $^{13}\underline{CH}Br$, 50% uncoupled), the latter two sets of signals indicating that one bromine is equatorial and the other axial. After 24 hours of further refluxing, analysis of a second aliquot showed mostly phenol plus 10% o-bromophenol, so the reaction mixture was evaporated and the residue was extracted with ether. The ether extract was washed with brine, dried over $MgSO_4$ and evaporated. Distillation (bp 70-72°C, 10 torr), gave 5 g of phenol, 7, (50%). GC of the material on OV-17 at 125°C showed the purity to be at least 95%. ^{1}H-NMR ($CDCl_3$) δ : 5.0 (m, OH), 6.5-7.3 (m, 4H) 6.7 (dd, with fine splittings, J=6 Hz, J_{CH}=156 Hz, $^{13}\underline{CH}$). ^{13}C-NMR ($CDCl_3$) δ : 115.5 (s, strong,

2-^{13}C), 120.8 (s, 4-C), 129.6 (d, J_{CCCC}=6.2 Hz, 5-C), 129.6 (d, J_{CC}=57.4 Hz, 3-C) and 155.0 ppm (d, J_{CC}=66.5 Hz, 1-C).

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