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SYNTHESIS OF $[\beta,\beta,\gamma,\gamma,\delta,\delta,\delta{-}^{2}H_{7}]$-*n*-BUTYLBENZENE

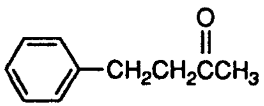
John T. Kendall and Thomas A. Spencer*
Department of Chemistry, Dartmouth College,
Hanover, New Hampshire 03755 USA

Summary

A convenient preparation of $[\beta,\beta,\gamma,\gamma,\delta,\delta,\delta{-}^{2}H_{7}]$-*n*-butylbenzene has been achieved by base-catalyzed isotopic exchange of 4-phenyl-2-butanone followed by application of Vedejs' procedure for Clemmensen reduction in a deuteriated medium.

Key words: 4-phenyl-2-butanone, deuterium, Clemmensen reduction, *n*-butylbenzene.

n-Butylbenzene containing at least several deuterium atoms in the side chain was required in substantial amount as a starting material to prepare certain aromatic derivatives for use as mass spectrometric standards. Synthesis of such a deuteriated *n*-butylbenzene could be envisaged via attachment of an appropriate prelabeled four-carbon unit to benzene, but such a reagent would be very expensive to prepare and use on the scale needed (1). A much more attractive route appeared to be use of the inexpensive benzylacetone (4-phenyl-2-butanone, **1**) as a reactant for introduction of deuterium labeling by isotopic exchange of alpha protons, followed by reduction of the carbonyl group. In this report are described the details of the conversions of **1** to $[1,1,1,3,3{-}^{2}H_{5}]$-4-phenyl-2-butanone (**2**) by treatment with NaOD in D_2O:CH_3OD and of **2** to $[\beta,\beta,\gamma,\gamma,\delta,\delta,\delta{-}^{2}H_{7}]$-*n*-butylbenzene (**3**) by Clemmensen reduction in a deuteriated medium.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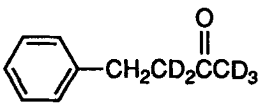
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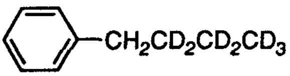
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Exchange of the five alpha protons of **1** was readily achieved by twice heating **1** in 3:2 D_2O:CH_3OD containing 0.3 equiv. NaOD for 22 h to afford 85% of **2** whose ^1H NMR spectrum showed a singlet for the benzylic protons, but only very weak absorption for residual methyl or alpha methylene protons. For the reduction of the carbonyl group of **2** a procedure of the type discovered by Yamamura (2) and developed by Vedejs (3) for conducting the Clemmensen reduction in an anhydrous deuteriated medium seemed particularly appropriate. Reduction of **2** by the customary Clemmensen (4,5) or Wolff-Kishner (6,7) methods in protiated media would risk loss of isotopic labeling by re-exchange. In addition, standard Clemmensen reduction under non-protic conditions on the scale needed would have required very large amounts of 40% DCl in D_2O. In one version of the Vedejs procedure (3), the amount of DCl required is simply generated *in situ* by reaction of D_2O with trimethylsilyl chloride and then added to a mixture of ketone and zinc in THF. By this method, 4,4-diphenylcyclohexanone afforded 1,1-dideuterio-4,4-diphenylcyclohexane containing 81% $^2H_2$ species in 70% yield (3).

When this convenient procedure was applied to **2**, [$\beta,\beta,\gamma,\gamma,\delta,\delta,\delta$-$^2H_7$]-*n*-butylbenzene (**3**) was obtained in 72% yield. Comparison of the ^1H NMR spectra of commercial *n*-butylbenzene and this **3** (shown below) indicated that largely complete deuteriation had been effected at the original carbonyl group position as well. Mass spectrometric analysis showed this **3** to contain 72% $^2H_7$, 24% $^2H_6$, and 4% $^2H_5$ species. This modified Clemmensen procedure (3) is recommended as a convenient and efficient method for deuterium labeling which is readily applicable to relatively large-scale (*e.g.*, 10-g) reactions.

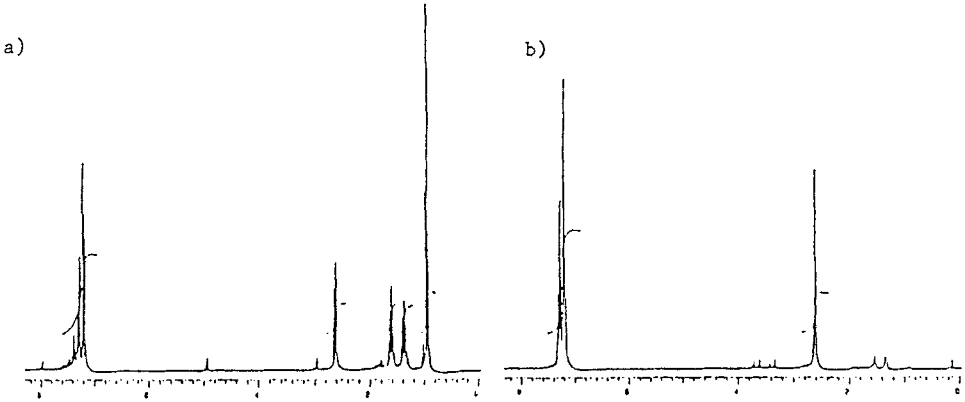

Figure 1. ^1H NMR spectra of: a) commercial *n*-butylbenzene; b) [$\beta,\beta,\gamma,\gamma,\delta,\delta,\delta$-$^2H_7$]-*n*-butylbenzene.

Experimental

All reagents were obtained from Aldrich and used as received. Zinc was activated (2) by stirring 325-mesh zinc dust in 2% HCl for 3 min, followed by washing with H_2O until the washes were neutral to pH paper, then with absolute ethanol, acetone, and ether and by drying overnight *in vacuo*. IR spectra were run as thin films. ^1H and ^{13}C NMR spectra were recorded at 299.95 and 75.43 MHz, respectively, in $CDCl_3$ on a Varian XL-300 spectrometer. Mass spectra were obtained on a Hewlett Packard 5890 Series II spectrometer with a HP 5971 detector and a HP Vectra 386/25 computer system.

[1,1,1,3,3-$^2H_5$]-4-Phenyl-2-butanone (2). A 500-mL, three-necked, round-bottomed flask was equipped with a Teflon-coated stir bar, thermometer, condenser and rubber septum. The flask was then charged with 100 mL of D_2O, 41 mL of CH_3OD, 29.5 g (200 mmol) of 4-phenyl-2-butanone and 5.0 mL (59 mmol) of a 30 wt.% solution of NaOD in D_2O. The resulting heterogeneous mixture was heated and stirred at reflux for 22 h, then allowed to cool to rt and 150 mL of ether was added. The two-phase mixture was stirred at rt for 1 h. The layers were separated and the aqueous layer washed with 75 mL of ether. The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4, and evaporated to afford partially (ca. 90%) deuteriated material. This crude product was heated again for 22 h in an identical deuteriated medium. The same workup afforded 30.3 g (98%) of a clear dark yellow oil which was distilled *in vacuo* through a 5-cm Vigreux column to yield 26.1 g (85%) of 2-phenyl-2-butanone as a colorless oil, bp 95-97°C (13 Torr), which was judged by ^1H NMR to be predominantly **2**. ^1H NMR ($CDCl_3$) δ 2.88 (2 H, s), 7.22 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 29.4, 125.9, 128.1, 128.3, 140.8, 208.0; IR 3010, 2920, 2220-2100, 1710, 1490, 1450, 1250, 1100, 1020, 755, 695 cm^{-1}.

[$\beta,\beta,\gamma,\gamma,\delta,\delta,\delta$-$^2H_7$]-*n*-Butylbenzene (3). A 1000-mL, three-necked, round-bottomed flask was equipped with a Teflon-coated stir bar, 250-mL pressure-equalizing dropping funnel and rubber septa. The apparatus was purged with argon and the flask was charged with 300 mL of THF. The flask was then cooled to 0°C in an icebath and 9.0 g (59 mmol) of **2** and 58.0 g (892 mmol) of activated zinc dust were added. A solution of 3.2 mL (170 mmol) of D_2O and 57 mL (450 mmol) of trimethylsilyl chloride in 150 mL of THF was prepared, allowed to stand for five min to allow complete generation of DCl, and then transferred to the dropping funnel and added dropwise over a period of ca. 3 h at 0°C with stirring, during which time the temperature of the reaction mixture was not allowed to exceed 10°C. The reaction mixture was allowed to stir at rt overnight, then was filtered and the filtrate was concentrated under reduced pressure. The resultant colorless solid was diluted with 200 mL of ether. The ethereal solution was washed with water (1 x 100 mL), 5% sodium carbonate (1 x 100 mL) and water (2 x 100 mL), dried over Na_2SO_4, and evaporated to afford 10.4 g of pale yellow oil which was short-path distilled to yield 6.0 g (72%) of **3** as a colorless oil, bp 66-67°C (24 torr): ^{1}H NMR ($CDCl_3$) δ 2.61 (2 H, s), 7.23 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 35.4, 125.5, 128.1, 128.3, 142.8; IR 3020, 2900, 2200, 2090, 1490, 1440, 1050, 730, 690 cm^{-1}; MS *m/z* 141 (M^+): isotopic composition determined as an average of results from scanning and single ion monitoring modes, in comparison to comparable mass spectra for unlabeled *n*-butylbenzene, to be 72% $^2H_7$, 24% $^2H_6$, and 4% $^2H_5$ species.

Acknowledgment

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