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Synthesis of 1,2,3,4-Tetrahydrocarbazole-9a-^{13}C and Carbazole-9a-^{13}C

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SUMMARY

The synthesis of 1,2,3,4-tetrahydrocarbazole-9a-^{13}C and carbazole-9a-^{13}C *via* cyclohexanone-1-^{13}C, prepared in turn from carbon dioxide-^{13}C and 1,5-pentanedimagnesium bromide is described.

Key Words: 1,2,3,4-tetrahydrocarbazole-9a-^{13}C, carbazole-9a-^{13}C, cyclohexanone-1-^{13}C, 1,5-pentanedimagnesium bromide, carbon dioxide-^{13}C.

INTRODUCTION

In earlier publications (1) we described the synthesis of several ^{13}C-labeled compounds (2) for use in studies on the effectiveness of hydrogen transfer solvents in coal liquification processes. Since nitrogen heterocyclic compounds are abundant in coal liquids and because their presence can influence the hydrogen transfer process, the study of ^{13}C-labeled heterocyclic compounds is an obvious extension in gaining a better understanding of the coal liquification process (3).

In this paper we describe the preparation of the specifically labeled title compounds synthesized from cyclohexanone-1-^{13}C (**1**) as shown in Scheme I.

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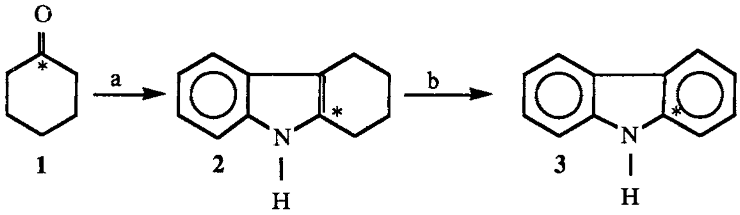
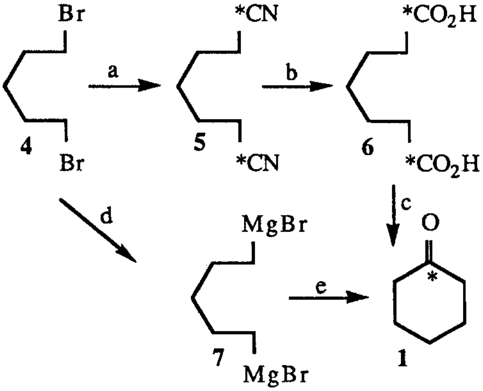
Scheme I



^{a} $C_6H_5NHNH_2$, CH_3CO_2H, Δ. ^{b}Pd/C, Δ.

The reactions of scheme I are easily carried out and provide **2** and **3** in 77% and 85% yields respectively (4). The synthesis of **2** and **3** requires cyclohexanone-1-${}^{13}C$ (**1**) which previously had been prepared through the sequence (**4**→**5**→**6**→**1**) shown in Scheme II.

Scheme II



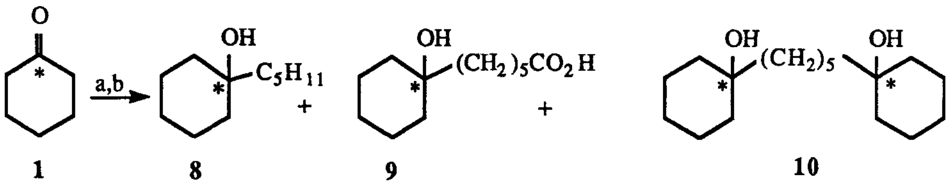
${}^{a}K^{13}CN$. ${}^{b}H_3O$, Δ. ${}^{c}Ba(OH)_2$, Δ. ^{d}Mg, ethyl ether, Δ. ${}^{e}\,{}^{13}CO_2$; $H_3\overset{+}{O}$.

The overall conversion of **4** to **1** using this sequence ranges from 57 - 76% yield (5). Although this is a good yield, the sequence requires the use of two moles of labeled potassium cyanide for each mole of **1** produced. The lost label may be recovered as barium carbonate. This factor plus the added expense of cyanide, labeled cyanide costs more than double that of labeled carbon dioxide, prompted selection of the alternate sequence (**4**→**7**→**1**) shown in Scheme II. Selection of this latter route was based on reports that carbonation of 1,5-pentanedimagnesium bromide (**7**) provides cyclohexanone, in unspecified yield, using only one mole of carbon dioxide (6).

Carbonation of **7** at -78 °C gave **1** in 24-38% isolated yield. Operation at low temperature is essential to prevent condensation of **1** with unreacted Grignard reagent or derivatives of the reagent

(7). If the carbonation of **7** is carried out at warmer temperatures, e.g. -8 °C, none of **1** is isolated and the series of alcohols **8**, **9** and **10** shown in Scheme III appears as reaction products.

Scheme III



^{a}BrMg(CH$_2$)$_5$MgBr. ^{b}H$_3\overset{+}{}$O.

The acidic fraction from the carbonation of **7**, as the corresponding methyl esters, was shown by GC/MS studies to be a complex mixture of ^{13}C-labeled carboxylic acids. The following were identified as present in the reaction mixture in their order of emergence from a SE-54 capillary column: hexanoic acid-1-^{13}C, 1,7-heptanedioic acid-1,7-^{13}C, undecanoic acid-1-^{13}C, and 1,12-dodecanedioic-1,12-^{13}C-acid (major product). ^{13}C-NMR studies also showed that at least one keto acid (^{13}C-labeled keto group) of unknown structure had formed.

EXPERIMENTAL

Cyclohexanone-1-^{13}C (1). In a dry (8) 500 mL, 3-neck flask was placed 13.6 g (0.56 mol) magnesium turnings (9), a Teflon-coated magnetic stirring bar, and sufficient anhydrous ethyl ether to completely cover the turnings. To this mixture, under nitrogen (10), was added approximately 5 g of 1,5-pentane dibromide. After the reaction was initiated, stirring was started and the remainder of the dibromide (64.37 g, 0.28 mol), diluted with an equal volume of ether, was added dropwise. Reflux was maintained for 1 h after addition was complete. The reaction was cooled and the mixture was then transferred to a stainless steel reactor (11) and diluted with an additional 0.5 L of anhydrous ethyl ether (12). The reactor was cooled to -78 °C, using a Dry Ice/acetone bath and $^{13}CO_2$ gas was added at 20 psi. After addition was complete, the reaction mixture was allowed to reach room temperature. The unreacted $^{13}CO_2$ was recovered as Ba^{13}CO$_3$ by sweeping into a Ba(OH)$_2$ solution with nitrogen.

The stainless steel reactor was disconnected and the contents were poured onto ice. HCl was added and the reaction product was extracted with ethyl ether. The combined ether extracts were washed with 5% NaOH solution, and with water, dried (MgSO$_4$), filtered, and distilled. The first cut was ether. The second cut was cyclohexanone-1-^{13}C (**1**): bp 153 °C [lit. (13) 155 °C for unlabeled ketone]; ^{1}H-NMR ($CDCl_3$) δ 1.3-1.85 (m, 3, CH_2), 2.35-2.7 (m, 2, CH_2CO); ^{13}C-NMR ($CDCl_3$) ppm 211.4, 41.9, 27.1, 25.1; IR (Neat) 2925, 2860, 1720 cm^{-1}; mass spectrum m/e(relative intensity), 99(30), 71(19), 70(27), 55(100), 42(67). The yield varied from 24-38% of (**1**).

The pot residue was analyzed by GC-MS (14) and GC (15). It was found to contain in order of elution 1-decene, decane, **4**, **8**, bromodecane, 1-pentadecene, pentadecane, 1-bromopentadecane,eicosane, **8**, and **10**.

The alkali washings were combined, acidified with concentrated HCl and extracted into ether, dried ($MgSO_4$), filtered, and concentrated to yield a complex mixture of acids. GC-MS (14) and GC (15) analysis of the methyl esters, prepared with diazomethane, in order of emergence showed hexanoic acid, 17-heptanedioic acid (**6**), undecanoic acid, 1,12-dodecanedioic acid, and 1-hexanoic acid-1-cyclohexanol (**9**) as well as several unidentified acids.

1,2,3,4-Tetrahydrocarbazole-9a-^{13}C (2). A mixture of **1** (5 g, 0.03 mol) and acetic acid (50 mL) were placed in a 250-mL three-necked flask equipped with a reflux condenser, mechanical stirrer and dropping funnel (4). To the stirred solution at reflux was added dropwise 5.6 g of phenylhydrazine during 0.5 h. Reflux was maintained for 1 h after addition was complete. The mixture was cooled with an ice slurry and extracted 3 times with ethyl ether. The ether extracts were combined, washed with 5% HCl, dried ($MgSO_4$), concentrated and Kugelrohr distilled to give 6.6 g. of **2**: mp 119-120 °C [lit. (16) 120 °C for unlabeled amine]; IR (KBr) 3400 (sharp, NH), 2925, 2840 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.4-7.5 (m, 2, ArH), 7.1-7.2 (m, 3, ArH, NH), 2.6-2.7 (m, 2, CH_2), 1.8-1.9 (br s, 2, CH_2); ^{13}C-NMR ($CDCl_3$) ppm 135.5, 134.1, 127.7, 120.9, 119.1, 119.0, 117.7, 117.6, 110.4, 110.3, 109.5, 23.4, 23.3, 23.2, 23.1, 22.8, 20.88, 20.86; mass spectrum m/e (relative intensity), 172.1 (11.3), 171.1 (3.9), 144.1 (25.4); exact mass (M^+) 172.1081, required for $C_{12}\,^{13}CH_{13}N(M^+)$ 172.1081.

Carbazole-9a-^{13}C (3). A mixture of **2** (2 g, 0.012 mol) were heated at 320 °C until H_2 evolution ceased. The reaction mixture was cooled, ether was added and the resulting slurry was filtered through Dicalite to remove the catalyst. The filtrate was concentrated and the resulting solid was Kugelrohr distilled to give 1.7 g of **7**; mp 247 °C [lit. (16) 247-8 °C for unlabeled carbazole]; IR (KBr) 3415 (NH, sharp), 3050 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.2-8.1 (m); ^{13}C-NMR (DMSO-d_6) ppm 139.6, 125.8, 120.3, 119.6, 119.5, 119.4, 111.0, 110.6, 110.2; mass spectrum m/e (relative intensity) 168.1(32), 167.1(4), 141.1(2.2), 140.1(2.2); exact mass (M^+) 168.0766, required for $(C_{11}\,^{13}CH_9N(M^+)$ 168.0768.

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7. Vigorous stirring is required to insure efficient contact of Grignard reagent and carbon dioxide.

8. Glassware was heated overnight at 125 °C, assembled hot, and allowed to cool under dry nitrogen.

9. Magnesium (99.98%, Reade Manufacturing Company, Inc.) was received stored under argon in a sealed package. Transfer to smaller containers was made in a glove bag filled with argon.

10. The Nitrogen was dried by passing through molecular sieves that had been activated by heating overnight at 320 °C under vacuum.

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12. Experience indicated this additional ether is needed to obtain a good yield of **1** presumably through improved stirring and minimizing contact of **1** with unreacted Grignard reagent.

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14. These data were collected using a Finnigan 1020B on a 30 m x 0.25 mm Supelco wax column.

15. GC analyses were performed on a Varian 3700 using a SE-54 capillary column and on a Micro-Tek 220 using a 5% Carbowax 20 m on acid-washed Gas Pac. Both instruments were equipped with FID detectors.

16. Ref. 13, p. C-231.