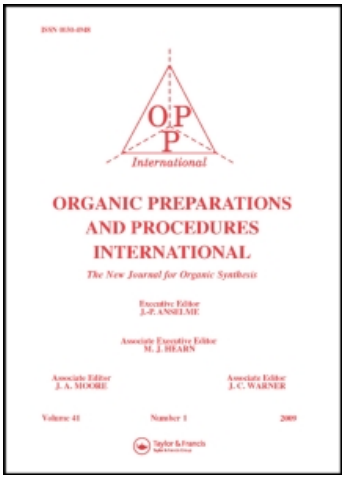

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SYNTHESIS OF CARBON-13 LABELLED DIALKYLCARBINOLS AND DIALKYLKETONES

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SYNTHESIS OF CARBON-13 LABELLED DIALKYLCARBINOLS AND DIALKYLKETONES

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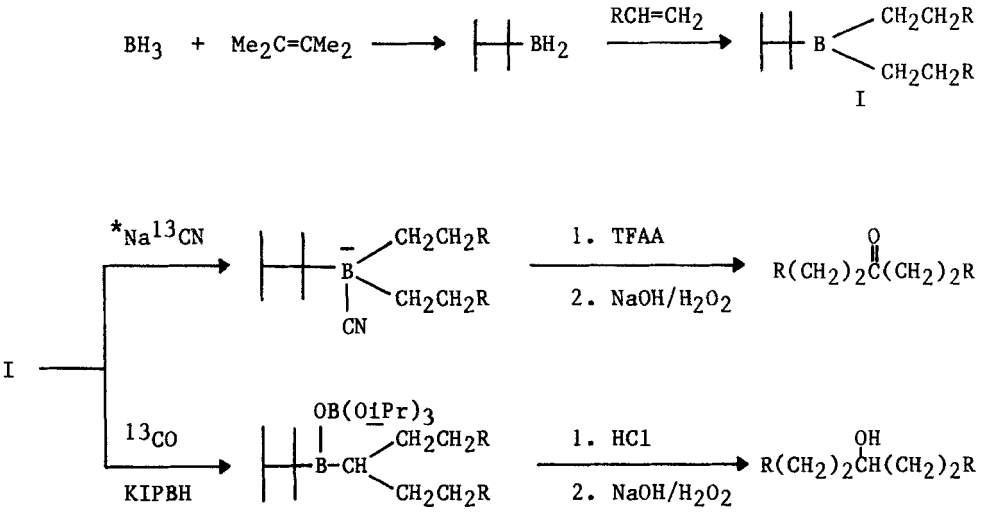
As part of a program to synthesize carbon-11 labeled, 17β-estradiol and related hormones, we investigated the reaction of organoboranes with carbon-13 labeled carbon monoxide and sodium cyanide. Organoboranes have proven to be ideal intermediates for the syntheses of labeled compounds containing a wide variety of functional groups.[1] The availability of starting materials, the tolerance of functionality, and the facile incorporation of desired nuclides are among the advantages of the new organoborane procedures.[1-5]

We now report that the carbonylation[6-8] and cyanidation[6,9,10] of dialkylthexylboranes using carbon-13 enriched reagents produces the regiospecifically labeled secondary alcohols and ketones, respectively. The reactions offer significant advantages over traditional labeling methods involving carbonation of organometallic reagents[11] and the cyanide substitution reactions.[12]

The syntheses of carbon-13 labeled secondary alcohols were carried out via the carbonylation of dialkylthexylboranes with carbon-13 enriched carbon monoxide in the presence of potassium triisopropoxyborohydride

(KIPBH). [13] The synthesis of carbon-13 labeled ketones were carried out *via* the reaction of dialkylthexylboranes with carbon-13 labeled sodium cyanide. The synthetic sequences are summarized below



R = (a) $CH_3(CH_2)_4CH_2$-; (b) $CH_3O\overset{O}{\overset{\|}{C}}(CH_2)_7CH_2$-; (c) $C_6H_5O(CH_2)_2CH_2$-

EXPERIMENTAL SECTION

The ^1H and ^{13}C-NMR spectra were obtained on a JEOL FX-90Q Fourier Transform NMR spectrometer. Chemical shift values are expressed in parts per million (δ) downfield from Me_4Si. The IR spectra were obtained on a Digilab Model 20 c/v FTIR. Melting points were recorded using Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, Tennessee. Commercially available samples of 1-nonene (Aldrich), 1-octene (Aldrich) and methyl 10-undecenoate (Eastman Kodak) were distilled prior to use. 5-Phenoxy-1-pentene[14] and BH_3 THF[15] were prepared according to published procedures. ^{13}C-enriched CO (90%, MSD isotopes) was used as received. ^{13}C-enriched sodium cyanide (90%, MSD Isotopes) was oven-dried and powdered prior to use. Tetrahydrofuran was dried over CaH_2 and distilled over Na/-benzophenone under nitrogen. The reaction flasks were dried in an oven at 130°, and then assembled under a dry nitrogen flow while cooling. All the reagents were added *via* nitrogen-flushed dry syringe.

Dialkylthexylboranes. General Procedure.- The particular dialkylthexylborane was prepared according to the standard procedures[2,8,9] by successive addition of dry THF (18 ml), BH_3 THF (5 mmol, 2.65 M solution), 2,3-dimethyl-2-butene (5 mmol, 0.6 ml), and olefin (10 mmol) to a cooled (0°) flask fitted with a magnetic stirrer and a septum inlet.

Carbonylation.[5,8] General Procedure.- The organoborane (5 mmol, 0.25 M solution) was cooled to -5° and potassium triisopropoxyborohydride (4.75 mmol, 3.7 ml of a 1.28 M solution) was then added without stirring. [Caution: Excess KIPBH will inhibit the uptake of CO]. The system was flushed with carbon-13 enriched carbon monoxide without stirring. The reaction mixture was then stirred vigorously for 40 minutes. During this period the carbon-13 enriched carbon monoxide atmosphere was maintained over the solution using a 17 gauge syringe needle connected to a rubber bladder containing the ^{13}C-enriched CO. The system was then flushed with nitrogen and concentrated hydrochloric acid (2 ml) was added via a Teflon needle (to inhibit Fenton's reaction). After 1 hr, aqueous sodium hydroxide (12 ml of a 3 N solution) and H_2O_2 (2.0 ml of a 30% solution) were added dropwise at 0°. The solution was brought to room temperature and stirred for 2 hr. The reaction mixture was then poured into water (25 ml) and the product extracted into pet ether (30-60°) or ether (150 ml). The solution was washed with water (3 x 15 ml), dried over anhydrous $MgSO_4$ and then the solvent removed under reduced pressure. The ^{13}C-labeled alcohols were purified by column chromatography.

10-Nonadecanol-10-^{13}C.- The dioctylthexylborane (5 mmol, 0.25 M) was carbonylated as described in the general procedure. The product was purified on a silica gel column (80 g) by eluting, sequentially, with pet ether 30-60° (300 ml) and 5% EtOAc-pet ether to yield 0.67 g (49.7%) of white

solid, mp 64.5-65° (lit.[16] 64-64.5°).

^{1}H-NMR ($CDCl_3$): δ 3.56(broad s,1H,CHOH), 2.58(s,1H,OH), 1.27(s,16H,-aliphatic CH_2), 0.88(t,6H,CH_3); ^{13}C-NMR ($CDCl_3$): δ 72.143 (CHOH), 37.608, 32.028, 29.833, 29.751, 29.697, 29.770, 22.790, 14,234.

Anal. Calcd for C, 80.20; H, 14.17. Found: C, 80.12; H, 13.92

Di-[10-Carbomethoxy-1-decyl]-^{13}C-carbinol.- The organoborane (5 mmol, 0.25 M) was carbonylated as described in the general procedure. The product was purified on a silica gel column (80 g) by eluting, sequentially, with pet ether 30-60° (400 ml), 5% EtOAc-pet ether (500 ml), and 20% EtOAc-pet ether to yield 0.98 g (48.2%) of white solid, mp 78-79°.

^{1}H-NMR ($CDCl_3$): δ 3.75(s,1H,CHOH), 3.66(s,6H,OCH_3), 2.308(t,4H,CH_3OCOCH_2), 1.61(s,1H,OH), 1.278(s,36H,aliphatic CH_2); ^{13}C-NMR ($CDCl_3$): δ 174.370 (CH_3OC=O), 71.980 (CHOH), 51.475, 37.554, 29.751, 29.643, 29.562, 29.453, 29.291, 29.183, 15.715, 24.984.

Anal. Calcd for C, 70.16; H, 11.19. Found: C, 70.27; H, 11.46

Di-[5-phenoxy-1-pentyl]-^{13}C-carbinol.- The organoborane (5 mmol, 0.25 M) was carbonylated as described in the general procedure. The product was purified on a silica gel column (80 g) by eluting, sequentially, with pet ether 30-60° (300 ml), 10% EtOAC-pet ether (500 ml) and 20% EtOAC-pet ether to yield 0.7 g (41.4%) of white solid, mp 63.64°.

^{1}H-NMR ($CDCl_3$): δ 7.19-7.27 (m,10H,ArH), 6.93(t,4H,OCH_2), 3.63(broad s,1H, CHOH), 2.04(s,1H,OH), 1.82(broad t,4H,OCH_2CH_2), 1.46(s,12H,aliphatic CH_2); ^{13}C-NMR ($CDCl_3$): δ 159.120, 129.459, 120.547, 114.534 (aryl carbons), 71.745 (CHOH) 67.682 (OCH_2), 37.473, 29.318, 26.203, 25.499.

Anal. Calcd for C, 77.48, H, 9.04. Found: C, 77.05, H, 9.10

Cyanidation.[10] General Procedure.- Carbon-13 labelled sodium cyanide (0.53 g, 11 mmol) was placed in a bent tube which was connected to one of the side necks of a 250 ml three-necked flask which had been deoxygenated

by repeated evacuation and readmission of nitrogen. The dialkylthexylborane was prepared as described in the general procedure. The cyanide was then added by rotating the bent tube. The mixture was stirred using an ultrasonic bath for 1 hr at 25°. The flask was cooled to -78° and trifluoroacetic anhydride (TFAA) (12 mmol, 1.7 ml) was added with stirring. The cooling bath was removed and the mixture was allowed to come to room temperature. The mixture was cooled to 0° and 3N NaOH (12 ml), and then 50% H_2O_2 (8 ml) were added slowly. The cooling bath was removed and oxidation continued for 3 hr at 25° and then 15 min at 50°. The mixture was extracted into pet ether (200 ml), washed sequentially with 2N NaOH (2 x 25 ml), 2N HCl (2 x 25 ml), and water (4 x 25 ml), dried ($MgSO_4$), filtered, and the solvent removed to yield the crude ketone.

Di-n-octyl ketone-^{13}C.- 1-Octene (20 mmole, 2.3 g) was used to prepare 10 mmoles of organoborane which was reacted with ^{13}C-labeled cyanide to produce 1.89 g (75%) of the ^{13}C-labeled ketone which was eluted with pet ether (300 ml) and then benzene on a silica gel (100 g) column. Recrystallization from methanol gave pure product, m.p. 47-48° (lit.[6] 48-48.5°).

^{1}H-NMR ($CDCl_3$): δ 2.38(t,4H,CH_2CO), 1.26(s,12H,CH_2), 0.87(t,6H,CH_3); ^{13}C-NMR ($CDCl_3$): δ 211.723 (*C=O), 42.917 ($\underline{C}H_2CO$), 31.947, 29.508, 29.399, 29.264, 24.009, 22.763, 14.179.

Di-[10-carbomethoxy-1-decyl]ketone-^{13}C.- Methyl-10-undecenoate (20 mmole, 4.0 g) was used to prepare 10 mmoles of the organoborane which yielded 2.97 g (70%) of the ^{13}C-labeled ketone which was eluted successively with 10% pet ether (400 ml) and EtOAc-pet ether. Recrystallization from methanol gave pure product, m.p. 73.5-76°.

^{1}H-NMR ($CDCl_3$): δ 3.668(s,6H,CH_3O), 2.306(m,4H,$\underline{CH_2}COCH_2$) 1.6(broad t,4H, $MeOCOCH_2$), 1.27(s,12H,aliphatic CH_2); ^{13}C-NMR ($CDCl_3$): δ 211.290 (*C=O) 178.352 ($\underline{C}H_3OCO$), 51.529 (CH_3O), 42.917 ($CH_2CO\underline{C}H_2$), 34.195 (CH_3OCOCH_2),

29.481, 29.372, 29.160, 25.038, 24.009 (CH_2); IR (KBr): 1735 (OC=O) and 1705 (C=O)cm^{-1}.

Anal. Calcd for C, 70.38, H, 10.87. Found: C, 70.35, H, 10.83.

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