SYNTHESIS OF O,S-DIETHYL 2-(BROMOMETHYL-^{13}C)-2-METHYLTHIOMALONATE, A MODEL SUBSTRATE FOR METHYLMALONYL-CO A MUTASE REACTIONS

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Summary

O,S-Diethyl methylthiomalonate was efficiently condensed with paraformaldehyde-^{13}C in the presence of sodium methoxide to give 2-[^{13}C]-hydroxymethylated product, which was converted to 2-[^{13}C]-bromomethyl product by treatment with triphenylphosphine and carbon tetrabromide.

Key words: ^{13}C-paraformaldehyde, Malonate Condensation, Vitamin B_{12} Model, ^{13}C-NMR.

In connection with our mechanistic model study on the coenzyme B_{12} dependent mutase reactions by means of C-13 NMR technique, we required the title compound. The unlabelled compound was previously synthesized by condensing dibromomethane with the carbanion derived from the corresponding methylmalonate ester.[1] Because of the unavailability of the C-13 labelled dibromomethane and the necessary economy of any labelled precursor, a new synthetic route which is more efficient and direct was required.

We now wish to report a convenient synthesis of the title compound (3) (scheme). Reaction of O,S-diethyl methylthiomalonate (1), prepared from the commercially available diethyl methylmalonate in three steps according to a literature procedure[2], with paraformaldehyde-^{13}C in the presence of catalytic amount of sodium methoxide in methanol at 60°C gave the desired hydroxymethyl adduct (2) in 70% yield. The proton NMR of 2 clearly showed the features expected from C-13 incorporation at the hydroxymethyl moity; doublet at δ1.45 (^{3}J H-C-C-^{13}C = 4.5Hz) for the quarternary methyl group and two signals at δ3.96 and 3.77 (each d of d, J=144, 10Hz, 1H) for the geminal protons at labelled hydroxymethyl group. The required conversion of the alcohol 2 to the bromo-compound (3) was satisfactorily accomplished by a modified procedure of Hooz and Gilani.[3] Thus, when 2 was treated over-

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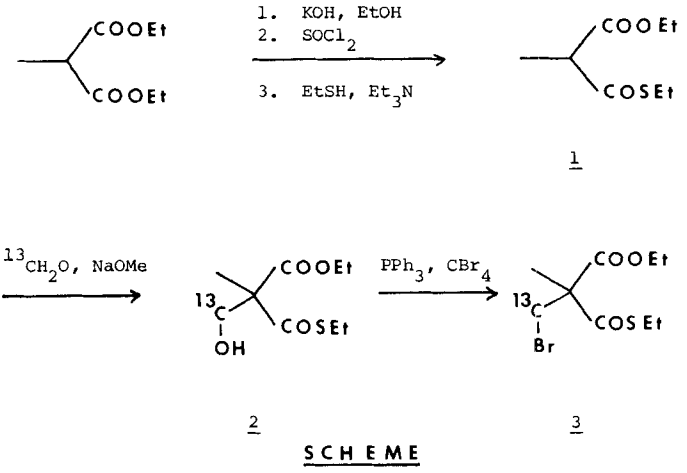
night with two equivalents of dry triphenylphosphine and carbon tetrabromide in dry benzene at the reflux temperature, the bromomethyl product (3) was obtained in 88% yield after a chromatographic purification on silica-gel. The ^{1}H-NMR of 3 again showed a doublet at δ1.65 (^{3}J=5.5Hz, 3H) for the quarternary methyl group and the two signals at δ4.02 and 3.75 (each d of d, J=154, 11Hz, 1H) for the C-13 labelled bromomethyl moiety. The C-13 NMR of 3 showed only one signal at δ37.6.



SCHEME

EXPERIMENTAL

Paraformaldehyde-^{13}C(90 atom% of ^{13}C) was purchased from Merck & Co., Inc. Isotopes. Reagents and solvents were dried according to the standard procedure prior to use. Proton NMR spectra were recorded on a Varian T-60 spectrometer, and ^{13}C-NMR on a Varian XL-200. Chemical shifts are expressed in δ units, with TMS as standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 Spectrophotometer, and Mass Spectra were recorded by a Hewlett-Packard GC-MS Data System Model 5982-A.

O,S-Diethyl 2-(hydroxymethyl-^{13}C)-2-methylthiomalonate (2). To a stirred solution of O,S-diethyl methylthiomalonate[2] (1; 774 mg. 4.08 mmol) and 4 drops of sodium methoxide

(10% solution in dry MeOH) in dry methanol (10 ml), was added paraformaldehyde-^{13}C (140 mg, 4.5 mmol).[4] After stirring for 9 hr. at 60°C, ether (20 ml) was added to the mixture. The precipitate was removed by filtration and washed with ether. The combined filtrate was successively washed with dil. HCl, brine and water, dried ($MgSO_4$), and evaporated to give the crude product, which was purified by a silica-gel column (10% ethyl acetate in toluene). Liquid product (602 mg, 70%): ^{1}H-NMR ($CDCl_3$) δ4.20 (q, J=7Hz, 2H, -CO_2CH_2-), two signals centered at 3.96 and 3.77 (each 1H, d,d, J=144, 10Hz, -$^{13}CH_2O$-), 2.90(q, J=7Hz, 2H, -$COSCH_2$-), 1.45 (d, J=4.5 Hz, 3H, quart.-CH_3), 1.30(br.t., J=7 Hz, 6H); IR(CCl_4) 3570, 1730, 1680 cm^{-1}; MS(15eV) m/e 221 (M^+, not observed), 175(M^+-EtOH, base), 160(M^+-SEt), 132(M-COSEt).

O,S-Diethyl 2-(bromomethyl-^{13}C)-2-methylthiomalonate (3). To a well stirred solution of alcohol 2 (233mg, 1.05 mmol) and carbon teterabromide (570 mg, 2.15 mmol) in dry benzene (20ml), was added triphenylphosphine (735 mg, 2.22 mmol) in 10 ml of dry benzene. The mixture was heated at the reflux temperature for 6 hr. After cooling at 0°C, the precipitate was filtered and washed with ether. The combined organic phase was evaporated to dryness and subjected to preparative TLC (SiO_2, 10% ethyl acetate in toluene) to afford a liquid product (263 mg, 88%): ^{1}H-NMR($CDCl_3$) δ4.22(q, J=7H, 2H, -CO_2CH_2-), two signals at 4.02 and 3.75 (each 1H, d,d, J=154, 11Hz, -$^{13}CH_2Br$), 2.95(q, J=7Hz, 2H, -$COSCH_2$-), 1.65 (d, J=5.5Hz, 3H, quart.-CH_3), 1.26 (br. t, J=7Hz, 6H); ^{13}C-NMR($CDCl_3$) δ37.6(s); IR (neat) 1740, 1680 cm^{-1}; MS (15 eV) m/e 285/283 (M^+), 224/222 (M^+-EtS), 204 (M^+-Br).

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