

TRIETHYL [1-¹⁴C]PHOSPHONOACETATE FROM [¹⁴C]CARBON DIOXIDE

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SUMMARY

Lithiation of diethyl methylphosphonate (1) with *n*-butyllithium followed by carbonation with [¹⁴C]carbon dioxide and esterification with diazoethane afforded high specific activity triethyl [1-¹⁴C]phosphonoacetate (4) in 62% yield.

Key Words: diethyl [1-¹⁴C]phosphonoacetic acid, triethyl [1-¹⁴C]phosphonoacetate, [1-¹⁴C]geranylgeraniol

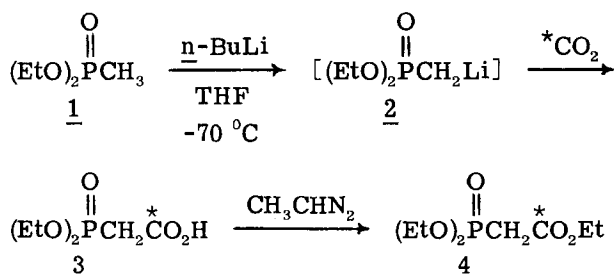
INTRODUCTION

The condensation of aldehydes and ketones with carbanions of phosphono esters is a widely used method for the preparation of α,β -unsaturated esters [1]. The adaptation of this method for the synthesis of ¹⁴C-labelled compounds requires access to ¹⁴C-labelled phosphono esters. Triethyl [¹⁴C]phosphonoacetate (4) is usually prepared by the Michaelis-Arbuzov reaction of ethyl [2-¹⁴C]bromoacetate with triethyl phosphite [2-5]. ¹³C-Labelled phosphonoacetates have been prepared in the same manner [6,7]. The report by Coutrot et al. [8] on the lithiation and carbonation of diethyl methylphosphonate (1) suggested an alternative and more economical approach to this useful ¹⁴C-labelled reagent.

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DISCUSSION

In connection with investigations in our laboratory on diterpene biosynthesis we undertook the preparation of ^{14}C -labelled geranylgeraniol [9, 10]. This and related isoprenoid alcohols are conveniently obtained by condensation of the appropriate prenyl acetone with triethyl ^{14}C phosphonoacetate followed by hydride reduction [2-4]. We have adapted the method of Coutrot et al. [8] to the preparation of high specific activity triethyl $[1-^{14}\text{C}]$ -phosphonoacetate by carbonation of α -lithio methylphosphonate (2) with ^{14}C carbon dioxide followed by esterification of the resulting phosphonoacetic acid (3) with diazoethane. Diethyl methylphosphonoacetate labelled in the 2 position has recently been prepared in a similar manner from ^{14}C methyl iodide [11].



A nine-fold excess of the α -lithio phosphonate (2) was generated by metallation of diethyl methylphosphonate (1) with n-butyllithium in tetrahydrofuran at $-70\text{ }^\circ\text{C}$ in order to maximize the uptake of the radioactive reagent. ^{14}C Carbon dioxide was liberated from 0.13 mmol (5 mCi) of barium ^{14}C carbonate with perchloric acid in a small gas generator (Figure 1) and passed into the solution of 2 at $-70\text{ }^\circ\text{C}$. Labelled phosphonoacetic acid 3 was isolated by extraction and converted to the ethyl ester with diazoethane. Purification by flash chromatography [12] on silica gel afforded triethyl $[1-^{14}\text{C}]$ phosphonoacetate (specific activity 38.4 mCi/mmol) of high chemical and radiochemical purity in 62% yield based on barium ^{14}C carbonate.

EXPERIMENTAL

Barium $[^{14}\text{C}]$ carbonate was purchased from Amersham Corporation. Diethyl methylphosphonate (**1**) and unlabelled triethyl phosphonoacetate were prepared by known procedures [13,14]. Diazoethane was generated from N-ethyl-N-nitrosourea [15] and used without distillation [16]. Radioactivity was measured with a Packard 2003 liquid scintillation counter. GC analyses were performed on a Varian model 3700 gas chromatograph connected to a Packard model 894 gas proportional counter. The 3.6-m by 2-mm glass column was packed with 3% OV17 on 100-120 mesh gas chrom Q. The analyses were carried out using a temperature program: 140 °C for 2 min followed by a gradient of 20°/min to 220 °C for 4 min.

A drawing of the apparatus used is shown in Figure 1. The reaction vessel was a 16 x 2.5 cm test tube fitted with a magnetic stirring bar, a rubber septum, a gas dispersion tube (5 mm OD, porosity 4-8 μ), and a syringe needle as gas outlet. A cold trap cooled to -70 °C and a drying tube filled with either Drierite (CaSO_4) or Aquasorb (P_2O_5 , Mallinkrodt) were placed between the carbon dioxide generator and the reaction vessel to exclude moisture. Any unreacted $[^{14}\text{C}]$ carbon dioxide was trapped by 0.1 N potassium hydroxide. A constant stream of argon was maintained throughout the entire experiment. A 25-mL portion of 35% aqueous perchloric acid that had been previously degassed at 60 °C by repeated evacuation and flushing with argon and 25.3 mg of barium $[^{14}\text{C}]$ -carbonate (0.13 mmol, 5 mCi) were placed in the carbon dioxide generator.

A solution of 190 μL (197 mg, 1.3 mmol) of diethyl methylphosphonate in 7 mL of tetrahydrofuran was stirred at -78 °C as 0.5 mL (1.15 mmol) of 2.3 M n-butyllithium in hexane was added dropwise. After 30 min the gas inlet was lowered to the bottom of the reaction vessel and the argon flow was adjusted to 10 mL/min. $[^{14}\text{C}]$ Carbon dioxide was generated by adding the aqueous perchloric acid dropwise to the barium $[^{14}\text{C}]$ carbonate at a rate such that the hydrolysis was complete within 4 min. Ca. 15 mL of perchloric acid

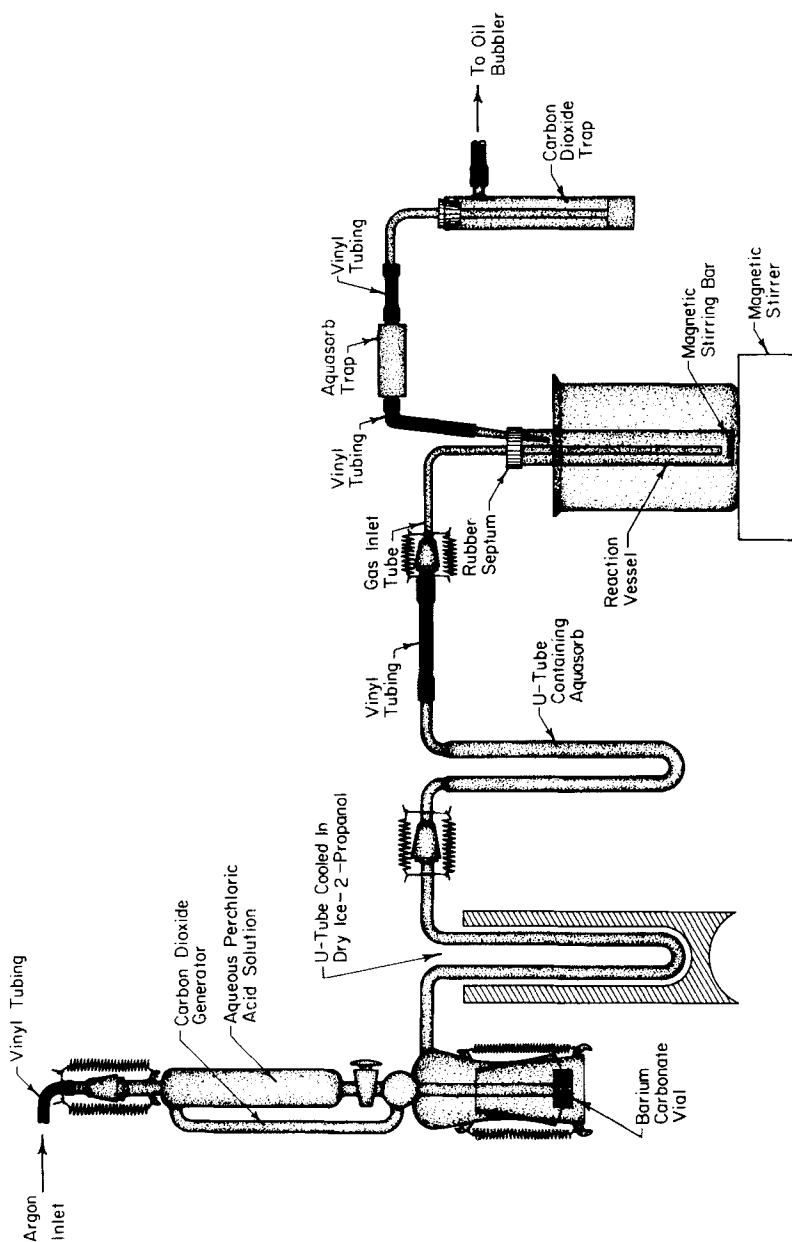


Figure 1

was rapidly added to the acid solution which was warmed with a heating gun to ensure complete evolution of [¹⁴C]carbon dioxide. The gas inlet was raised after 50 min and the reaction mixture was stirred at -70 °C for 2.5 h. The cooling bath was removed and the solution was allowed to warm to room temperature over one h. One mL of saturated sodium chloride solution and 2.5 mL of water were added and the organic layer was removed with a pipette. The aqueous layer was extracted with four 5-mL portions of 1:1 dichloromethane-ether, acidified with 10 drops of concentrated hydrochloric acid, and extracted again with five 5-mL portions of 1:1 dichloromethane-ether. The combined acidic extracts were treated with an excess diazoethane in ether and let stand overnight.

The ester solution was dried by filtering through a column of sodium sulfate (1 x 9 cm). Evaporation of the solvent under reduced pressure left a slightly yellow liquid which was diluted with 1 mL of 1:1 hexane-acetone and purified by flash chromatography [12] on a 15 x 1 cm column of silica gel with 100 mL of 1:1 hexane-acetone as eluant. Each of the 5-mL fractions was assayed for radioactivity and fractions 6 to 10, containing > 95% of the radioactivity, were pooled. Evaporation of the solvent left 18.2 mg (62%) of triethyl [1-¹⁴C]phosphonoacetate as a colorless liquid. The radiochemical yield was 3.12 mCi (62%), SA = 38.4 mCi/ mmol. Analysis of the product by GC showed the chemical and radiochemical purity to be greater than 98%.

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