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Preparation of carbon-14 labelled ampropylfos (1-[^{14}C]-α-aminopropanephosphonic acid)

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Summary

1-[^{14}C]-α-Aminopropanephosphonic acid, with a specific activity of 1.736 μCi mg^{-1}, has been prepared from 1-[^{14}C]-propanal, triphenyl phosphite, and benzyl carbamate by interaction in toluene in the presence of boron trifluoride-etherate, followed by hydrolysis. The product was shown by single crystal X-ray diffraction to be structurally identical to an unlabelled specimen.

Key Words: carbon-14; agrochemical; fungicide; aminophosphonic acid

Introduction

Ampropylfos (α-aminopropanephosphonic acid) (**1**) has shown potentially useful activity when applied as a seed dressing for the control of *Drechslera* spp. and other fungal pathogens of cereal crops.[1] It is virtually non-toxic to mammals (oral LD_{50} to rat $> 5000\,mg\,kg^{-1}$),[2] and has been mentioned as one of a number of possible replacements for the highly toxic organomercurials.[3] In this paper, we describe the preparation of 1-[^{14}C]-ampropylfos for use in metabolic and environmental studies, the results of which are summarized elsewhere.[2]

$$Et–CH(NH_2)–PO_3H_2$$
(1)

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Discussion

Of the various methods that are available for the preparation of α-aminoalkanephosphonic acids,[4] we have generally found it convenient[5] to use the one-pot procedure described by Oleksyszyn and Tyka,[6] based on the interaction of triphenyl phosphite, an aliphatic aldehyde, and ethyl (or benzyl) carbamate in glacial acetic acid, followed by hydrolysis of the first-formed phosphonate ester with hydrochloric acid. The free aminophosphonic acid is then liberated by treatment with propylene oxide. In the case of α-aminopropanephosphonic acid we also found that reaction in toluene, using benzyl carbamate as a reactant and boron trifluoride-etherate as catalyst, was a good alternative method.[7] This modified procedure was used in the present synthesis to give a product with 1-[^{14}C] labelling (Scheme 1) and with no detectable contaminants. The melting point found for the recrystallized product (275–276°C) was some 10°C higher than that which we had previously observed for the unlabelled compound[5,7] and that reported by Tyka,[6,8] indicating a higher degree of purity for our radiolabelled product. Other variations in the literature data for this compound include, however, melting points of 271°C [9] and 286°C.[10] The reasons for these differences are not clear but may be due to differences in crystal size and rate of heating, the compound being zwitterionic and having multiple intermolecular hydrogen bonding interactions. The possible presence of water of crystallization in the lower melting specimens was excluded by elemental analysis and there were no spectroscopically detectable impurities; single-crystal X-ray diffraction studies furthermore showed both the labelled and unlabelled products to be structurally identical.[11] The labelled product was obtained as a fine white crystalline solid, with specific activity of 1.736 μCi mg^{-1}.

$$(PhO)_3P + Et^{14}CHO + PhCH_2OCONH_2 \xrightarrow{\text{i), ii), iii)}} Et\text{-}^{14}CH(NH_2)\text{-}PO_3H_2$$

(i) BF_3-Et_2O; ii) conc. HCl; iii) propylene oxide

Scheme 1.

Experimental

Starting materials

1-[^{14}C]-propanal with radiochemical purity >95% was supplied by Amersham International plc. Other reagents were obtained from Aldrich Chemical Company. Triphenyl phosphite was redistilled before use and toluene was dried over sodium.

Analytical methods

Microanalysis for carbon, hydrogen, and nitrogen was carried out on a Perkin-Elmer 240B instrument. Nmr data were recorded for solutions in D_2O on a Bruker WP80 spectrometer operating at 80.018, 20.12, or 32.395 MHz for ^{1}H, ^{13}C, and ^{31}P spectra, respectively. Chemical shifts are relative to sodium trimethylsilylpropionate (^{1}H and ^{13}C spectra) or 85% H_3PO_4 (for ^{31}P).

Preparation

Triphenyl phosphite (26.7 g, 0.0861 mol), benzyl carbamate (13.0 g, 0.0861 mol) and 1-[^{14}C]-propanal (5.0 g, 0.0862 mol, 22.5 mCi) were mixed in toluene (80 ml) and boron trifluoride-etherate (45% w/w, 2.5 ml) in toluene (50 ml) was added dropwise with stirring at room temperature (15 min). The mixture was heated at 85–90°C under reflux (5 h) after which toluene was removed under reduced pressure on a rotary evaporator. Concentrated hydrochloric acid (120 ml) was added to the residue and the mixture was heated at 105°C under reflux (8 h). Phenol and other by-products were removed by extraction with toluene (3×20 ml) and the aqueous layer was evaporated under reduced pressure to yield a yellowish oil which was dissolved in methanol (15 ml). The methanol solution was warmed under reflux and propylene oxide (10 ml) was added to give an immediate precipitate which was filtered off, washed with acetone, and dried to give the crude product (7.1 g, 59%), m.p. 255–258°C. Recrystallization from aqueous ethanol gave two crops of product which were oven-dried at 60°C and found to be essentially identical: (i) 3.72 g (31% yield) (Found: C, 25.3; H, 7.2; N, 10.2. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%), m.p. 275–276°C, δ_H (D_2O) 1.05 (t, 3 H, CH_3, $^{3}J_{HCCH}$ 7 Hz), 1.45–2.15 (m, 2 H, CH), 2.85–3.45 (m, 1 H, CH); δ_C (D_2O) 13.06 (d, CH_3, $^{3}J_{PC}$ 9.2 Hz), 24.71 (d, CH_2,

$^{2}J_{PC}$ 1.8 Hz), 53.66 (d, CH, $^{1}J_{PC}$ 142.8 Hz); δ_P (D_2O) 13.5; specific activity 1.736 μCi mg^{-1} (calc. from activity of propanal used: 1.784 μCi mg^{-1}); ii) 1.81 g (15% yield), m.p. 274–275°C, with similar characteristics.

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