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PREPARATION OF CARBON-14 LABELED ORGANOPHOSPHATE PESTICIDES: CHLORFENVINPHOS

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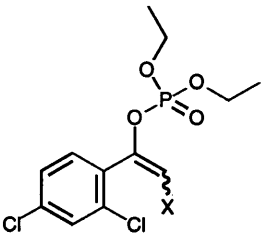
SUMMARY

Synthesis of [vinyl-^{14}C]chlorfenvinphos, utilizing [^{14}C]iodomethane as the source of the label, was accomplished in 28% radiochemical yield by the methylation of 2,4-dichlorobenzoyl chloride, chlorination of the resulting [^{14}C]-2,4-dichloroacetophenone, and condensation of the product with triethylphosphite. The product, isolated as a mixture of E and Z isomers (3.6 and 96.3%, respectively), was obtained in >99% purity and had specific activity 20 mCi/mmol.

Key Words: Chlorfenvinphos, organophosphate, pesticide, carbon-14

INTRODUCTION

Lanolin, which is used in many cosmetic preparations, has been found to contain substantial quantities of pesticide residues, among them chlorfenvinphos (1) (1). The metabolic pathways of orally administered chlorfenvinphos (1) and its bromo analog, bromfenvinphos (2), have been



1 X = Cl
2 X = Br

studied (2,3), and one report regarding the skin absorption, distribution, and excretion of 2 in the rat has appeared (4). These reports utilized 1 and 2 labeled with carbon-14 in the *O*-ethyl groups or at the benzylic position. To determine the skin penetration of chlorfenvinphos (1) the preparation of carbon-14 labeled material was undertaken.

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RESULTS AND DISCUSSION

Our synthetic approach was designed to place the carbon-14 label at a metabolically and chemically stable position on the molecule and, at the same time, to minimize the number of synthetic steps and the cost of radiolabeled starting material. Experimental details of the preparations of previously reported carbon-14 labeled chlorfenvinphos (1) are not available. However, the synthesis of the diisopropyl analog (3) of chlorfenvinphos by treatment of α,α-dichloro-2,4-dichloroacetophenone (4) with triisopropyl phosphite (5) was documented (5), as was the synthesis of unlabeled 4 from 2,4-dichloroacetophenone (6) (6), making 6 an attractive starting material (Chart 1). Since the cost of preparing universally labeled 6 would be very high, 6 labelled at the acetyl methyl was a suitable alternative as this carbon is not lost during degradation of 1 (5) or by metabolism (2,3). Thus, the required carbon-14 labeled 2,4-dichloroacetophenone ([α-^{14}C]-6) could be obtained by treatment of 2,4-dichlorobenzoyl chloride (7) with carbon-14 labeled iodomethane (8) in the presence of palladium catalyst (7) (Chart 2). The synthetic approach to carbon-14 labeled chlorfenvinphos (1), therefore, involved the preparation of carbon-14 labeled 2,4-dichloroacetophenone ([α-^{14}C]-6) (as in Chart 2), chlorination of [α-^{14}C]-6 to give carbon-14 labeled α,α-dichloro-2,4-dichloroacetophenone (4) (as in Chart 1), and reaction with triethyl phosphite (9) to afford carbon-14 labeled chlorfenvinphos ([α-^{14}C]-1). These steps are summarized in Chart 3.

Before embarking on the radiosynthesis, the reaction sequence was explored using unlabeled iodomethane. Treatment of dried iodomethane with freshly prepared zinc-copper couple (8) in dry benzene, and a 10% molar excess of anhydrous dimethyl formamide, under vacuum for one hour and under nitrogen for four hours at 60 °C, followed by reaction with a solution of 2,4-dichlorobenzoyl chloride (7) and 4% tetrakis(triphenylphosphine)palladium(0) in dry benzene, for one hour at ambient temperature, gave an orange-colored residue. Purification by flash chromatography (Baker flash SiO_2, 80% hexanes/chloroform) afforded 2,4-dichloroacetophenone (6) in 34% yield. Since at times the zinc-copper couple was inactive, it was essential to prepare it and carry out a trial reaction on the day before the master synthesis.

The chlorination of 6 was performed by treatment of an acetic acid solution with two equivalents of benzyltrimethylammonium tetrachloroiodate (9) at 70 °C for five hours under nitrogen; the product 4 was obtained in 80% yield. Crude 4 was treated with 1.1 equivalents of triethylphosphite in ether to give an oil (88% pure 1 by GC) which was purified by flash chromatography (Baker flash SiO_2, 90%→80% hexanes/ethylacetate). Combination of appropriate fractions afforded chlorfenvinphos 1

Chart 1

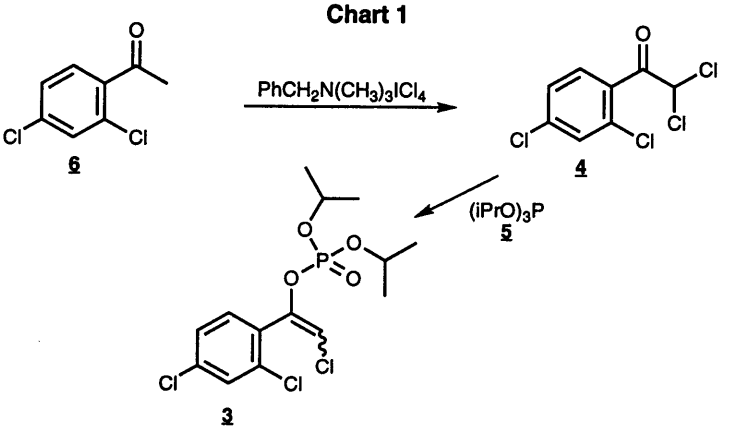


Chart 2

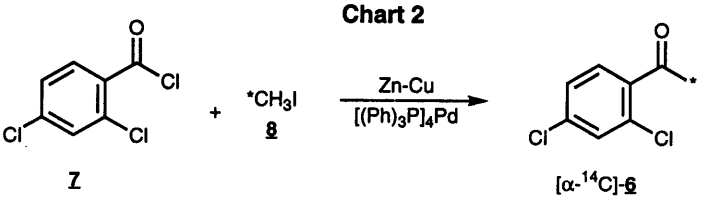
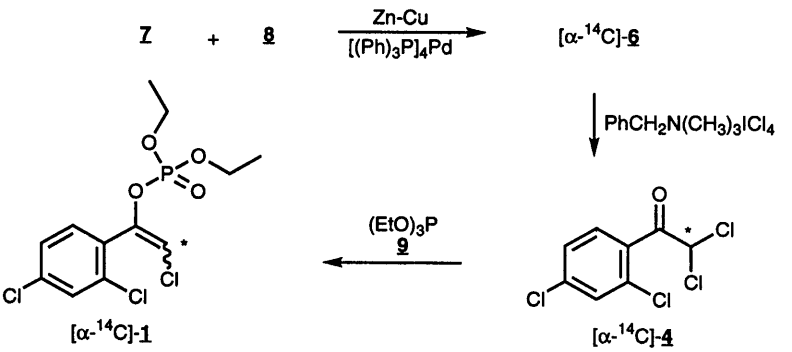


Chart 3



* denotes label

as a mixture of *E* and *Z* isomers (GC) in 49% yield. Separation of the isomers by preparative thin layer chromatography has been reported (2) but was not required in this case. The overall yield, based on iodomethane, the source of the radiolabel in the radiosynthesis, was 16%.

To confirm the viability of the zinc-copper couple a portion of the freshly prepared agent was used to perform the first step in the synthesis. Since the reaction proceeded well, the radiosynthesis was carried out, following the protocol described above, starting with 15 mCi iodomethane ([^{14}C]-**8**) and freshly distilled 2,4-dichlorobenzoyl chloride (**7**). The residue, after removal of the solids and the volatiles, accounted for the total radioactivity. Analysis by thin layer chromatography showed mainly (91%) of the desired product [^{14}C]-**6**. Analysis against an internal standard showed that approximately 40% of the total activity was contained in the product [^{14}C]-**6**. Purification by flash chromatography gave [^{14}C]-**6**. in 56% yield and >99% purity. Chlorination of [^{14}C]-**6** as above gave an 87% yield of 91% pure [^{14}C]-**4** which was used in the next step without purification. The final product [^{14}C]-**1**, 7.07 mCi, was purified to afford 4.25 mCi (58%) of >99% pure [^{14}C]-**1**. A less pure (96.5%) fraction (1.05 mCi) was also collected. The overall radiochemical yield was 28%; a higher yield could be obtained by repurification of the less pure fraction.

The radiochemical purity was ascertained by TLC/radioscan, and the chemical purity was determined by gas chromatography.

EXPERIMENTAL

TLC-radioscan analysis was performed using E. Merck SiO_2 60F-254 plates on a Berthold model LB Linear Analyzer or a Bioscan System 200 Imaging Scanner. GC analyses were carried out on a Hewlett-Packard 5890 II capillary chromatograph with FID detection. Samples were counted using Ultima Gold as scintillant on a Packard Tri-carb 4000 liquid scintillation spectrometer.

[α-^{14}C]-2,4-Dichloroacetophenone ([^{14}C]-**6**)

[^{14}C]Iodomethane ([^{14}C]-**8**) (15 mCi, 20 mCi/mmol, 0.75 mmol) was vacuum transferred into P_2O_5 then to a suspension of Zn(Cu) couple (74 mg, 1.13 mmol) in anhydrous DMF [100 µL, 1.1 eq to Zn(Cu)], and dry benzene (2.3 mL). This suspension was vigorously stirred for 1 h at room temperature under vacuum. The vacuum was broken with Ar, and stirring of the suspension was continued at 60 °C for 4 h under N_2. The reaction mixture was cooled to room temperature, and a solution of freshly distilled (95 °C/3 mm Hg) 2,4-dichlorobenzoyl chloride (**7**) (105 µL, 0.75 mmol) and tetrakis(triphenylphosphine)palladium(0) (45 mg, 0.03 mmol) in dry benzene (1.5 mL) was slowly added. This mixture was stirred at room temperature for 1 h under N_2, filtered, and concentrated to an

orange solid. Purification by flash chromatography on 6 mL SiO_2 in a 10 mL disposable pipette, eluting with 80% Hxn/$CHCl_3$, yielded 8.43 mCi (56%) of [^{14}C]-**6** with radiochemical purity >99%.

[α-^{14}C]-α,α,2,4-Tetrachloroacetophenone ([^{14}C]-4)

To a stirring solution of [α-^{14}C]-2,4-dichloroacetophenone ([^{14}C]-**6**) (8.43, 0.42 mmol) in HOAc (4.2 mL) was added benzyltrimethylammonium tetrachloride (528 mg, 1.42 mmol). The reaction mixture was heated at 70 °C under N_2 for 2.5 h, then cooled to room temperature, and filtered, and the HOAc was removed by vacuum transfer (~40 °C, 0.05 mmHg). To the resulting light-yellow oil was added 5% $NaHSO_4$ (4 mL) and 5% $NaHCO_3$ (15 mL), and the solution was extracted with Et_2O (3 × 15 mL). The combined Et_2O extract was dried over $MgSO_4$, filtered, and concentrated to a clear, colorless oil. The crude yield was 7.35 mCi with a radio-TLC (SiO_2 90% Hxn/EtOAc) purity of 91.3%.

[Vinyl-^{14}C]Chlorfenvinphos ([^{14}C]-1)

To a solution of [^{14}C]-**4** was slowly added triethylphosphite (**9**) (70 μL, 0.405 mmol) (7.35 mCi, 0.368 mmol) in Et_2O (0.5 mL). The mixture was stirred at room temperature under N_2. After 1.5 h, the volatiles were removed under a stream of N_2; the residue was purified by flash chromatography (Baker 40 μm flash SiO_2, 95% → 90% Hxn/EtOAc). A radiochemical yield of 4.25 mCi (58%) of a mixture of *E* and *Z* isomers (TLC-radioscan, SiO_2, 70% Hxn/EtOAc), 3.6% and 96.3%, respectively, was recovered. The purity of this mixture was >99%. A less pure (96.5%) fraction (1.07 mCi) was also collected.

CONCLUSIONS

The preparation of chlorfenvinphos labeled with carbon-14 at a chemically and metabolically stable site was accomplished in 28% isolated radiochemical yield utilizing carbon-14 labeled iodomethane, a relatively inexpensive starting material as the source of the label. The three-step sequence, in which 2,4-dichloroacetophenone is prepared by methylation of 2,4-dichlorobenzoyl chloride, chlorinated to α,α,2,4-tetrachloroacetophenone and condensed with triethylphosphite, provides an efficient route to the synthesis of carbon-14 labeled organophosphates.

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