Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXV, No. 11

PREPARATION OF CARBON-14 AND TRITIUM LABELLED 2-SEC-BUTYLPHENYL N-METHYL CARBAMATE (BPMC)

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SUMMARY

BPMC is a widely used, carbamate type insecticide which was prepared both in ^{14}C and tritium labelled forms for metabolic pathway investigations. The specific acivity of the $[^{14}C]$BPMC was 26.7 mCi/mmol and that of the $[^{3}H]$BPMC was 58 Ci/mmol.

Key Words: ^{3}H and ^{14}C labelled 2-sec-butylphenyl N-methyl carbamate, BPMC, labelled insecticides.

INTRODUCTION

In order to investigate the metabolic fate of BPMC, it was necessary to synthetize ^{14}C and ^{3}H labelled BPMC at a metabolically stable positions. The synthesis routes are shown in figure 1.

0362–4803/88/111201–07$05.00
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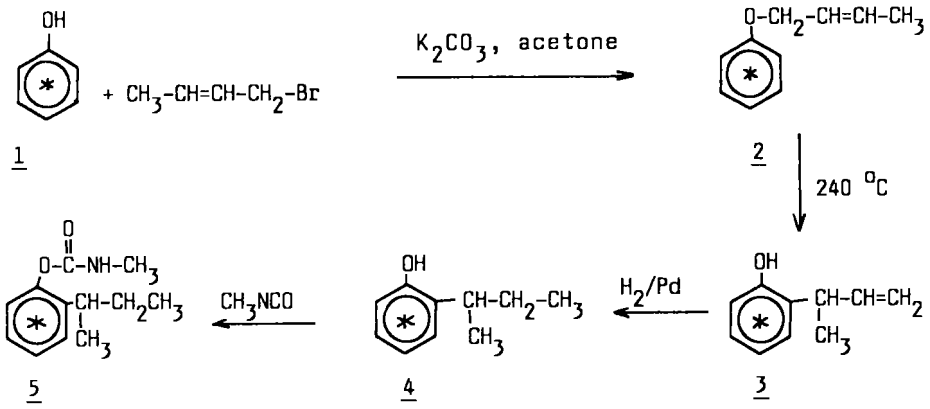
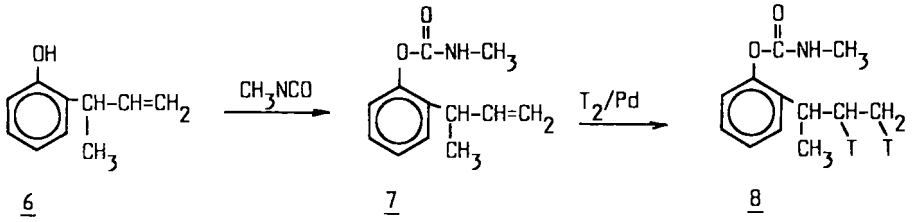
Received February 2, 1988
Revised March 24, 1988

Figure 1. Synthesis of [^{14}C]BPMC



Synthesis of [^{3}H] BPMC



The key step for the synthesis of [^{14}C] BPMC is the preparation of 2-sec-butyl [ring-U-^{14}C]phenol (4) from [U-^{14}C] phenol (1). It was very important to prepare compound 4 free of isomers to obtain the final products in radiochemically pure form.

There are several procedures in the literature concerning the production of compound 4 by direct alkylation of phenol, however these require strong reaction conditions (high temperature and pressure) and do not result in pure reaction product (1, 2, 3, 4). The application of the Claisen rearrangement of 2 seemed to be the most suitable method because during this reaction by-products are not formed (5).

MATERIALS AND METHODS

[U-^{14}C]Phenol (26.9 mCi/mmol) was synthetized from [U-^{14}C]benzene by one-electron oxidant cobalt(III)tri-

fluoroacetate in trifluoro acetic acid, using the procedure of Kochi et al. (6) and by hydrolizing the resultant [ring-U-^{14}C]phenyl trifluoroacetate (7). [U-^{14}C]Benzene was obtained from $Ba^{14}CO_3$ by a modification of Pietig and Scharpensel' method (8).

Crotyl bromide, methyl isocyanate and the solvents were dried and purified by distillation. All the other chemicals were purchased commercially and used without further purification.

Radioactivity measurements were carried out using an LKB 1217 Rackbeta liquid scintillation counter with Packard's Instagel scintillation cocktail. TLC analyses were generally run on Merck Kieselgel 60 F_{254} (0,2 mm) plates using the following solvent systems (given by volume):

A. Methylcyclohexane/acetic acid (20:1)

B. Benzene/ethanol/acetone (100:2:2)

The radiochemical analyses of the TLC plates were accomplished with Berthold LB 2723 scanner.

HPLC analyses were performed with a Waters (Model 6000 A) chromathography pump coupled with a Waters Lamda Max Model 480 LC Spectrophotometer (250 nm) and a Berthold LB 503 HPLC Radioactivity Monitor. The column used was Partisil M9 10/25 ODS.

Eluent : methanol/water (95:5).

Flow rate: 1 ml/min.

RESULTS AND DISCUSSION

Synthesis of ^{14}C labelled BPMC

^{14}C labelled crotyl phenyl ether (2) was prepared by the reaction of [U-^{14}C]phenol with crotyl bromide in the presence of K_2CO_3 in absolute acetone. It was a simple reaction and generally the products may be used without vacuum distillation. Compound 2 was heated at 240° to rearrange the

molecule according to Claisen and the resulting compound 3 was hydrogenated catalytically with Pd/charcoal. Finally compound 4 was carbamoylated with methyl isocyanate in dioxane. The overall radiochemical yield of ^{14}C BPMC from the starting compound 1 was 64.8 %. The isomer and the radiochemical purity of the final product were examined by TLC (system B) and HPLC.

Synthesis of tritium labelled BPMC

The preparation of [^{3}H]BPMC was started from non-radioactive phenol. The first two steps of the synthesis were identical with those of the synthesis of [^{14}C]BPMC. The obtained compound 6 was carbamoylated with methyl isocyanate and compound 7 was tritiated catalytically in dioxane using Pd/charcoal catalyst. The specific activity of 8 was 58 Ci/mmol.

EXPERIMENTAL

Crotyl [ring-U-^{14}C]phenyl ether (2)

0.94 g (10 mmol, 269 mCi) of [U-^{14}C]phenol, 1.35 g (10 mmol) of crotyl bromide and 1.4 g (10 mmol) of K_2CO_3 in dry acetone were stirred at room temperature for 20 hours, then were boiled for 3 hours. The precipitate was filtered and the filtrate was distilled in vacuo. The residue was dissolved in ether and the solution was washed with 0.5 N NaOH and twice with water. The ether solution was dried with anhydrous $MgSO_4$ and the ether was distilled.

Yield: 1.23 g, (82.9%)

The crude products was run on silica gel plates (Merck) using solvent system A. The radiochemical purity by radio-TLC was 97 %. If it appeared necessary the product was purified by distillation in vacuo (B.p. 75-77 ^{o}C/12 Torr).

2-(1-Methyl allyl) [ring-U-^{14}C]phenol (3)

1.23 g (8,29 mmol) of 2 were dissolved in 6 ml of N,N-diethylaniline distilled under argon and were heated at 240 °C for 4 hours under a blanket of argon. After cooling 10 ml of petroleum ether were added and the reaction mixture was extracted three times with 40 ml of 1 N HCl to remove N,N-diethylaniline. The organic layer was extracted twice with 30 ml of 0.5 N NaOH. The aqueous layer was treated with charcoal and was filtered. The solution was acidified with 1 N HCl and extracted three times with 20 ml of ether. The extract was dried with $MgSO_4$ and evaporated in vacuo below 45 °C to leave a viscous oily residue. Distillation in vacuo yielded 1.06 g, 7.17 mmol of 3 (86.5 %).
(B.p. 111-112°C/14 Torr).

Radio TLC (in system A) showed a radiochemical purity of 98 %. Rf: 0.13.

2-Sec-butyl [ring-U-^{14}C]phenol (4)

1.06 g of compound 3 were dissolved in 40 ml of abs. ethanol, 100 mg of 10 % Pd/charcoal catalyst were added and the mixture was hydrogenated until the hydrogen uptake was ended. The reaction mixture was filtered and evaporated in vacuo. The yield was 0.987 g, 6.58 mmol (91.8 %).

2-Sec-butyl [ring-U-^{14}C]phenyl methyl carbamate (5)

Without further purification the crude product of compound 4 was stirred in 0.3 ml of dioxane with 571 mg (10 mmol) of methyl isocyanate and 10 µl of triethylamine at 50°C for two hours. After evaporating of the solvent the residue was dissolved in 10 ml of benzene. The benzene solution was washed twice with 5 ml of cold 0.5 N NaOH and with 5 ml of water. The organic layer was dried with $MgSO_4$. The benzene

was evaporated and the residue was heated at 60 ^{o}C in 0.1 Torr vacuo to remove the traces of solvent and impurities. The product was obtained as a viscous colourless oil. The yield was 1.359 g, 6.53 mmol, 174,2 mCi (99,6 %). Specific activity of 5: 128.7 mCi/mg (26,7 mCi/mmol). The overall radiochemical yield from [U-^{14}C]phenol was 64.8 %. The radiochemical purity by radio TLC (system B) and HPLC was higher than 99 %.

2-(1-Methyl allyl)phenyl methyl carbamate (7)

740 mg (6 mmol) of non-radioactive 2-(1-methyl allyl)-phenol (6) were carbamoylated with 570 mg (10 mmol) methyl isocyanate in 0,3 ml absolute dioxane in the presence of 10 µl Et_3N by heating for an hour at 60^{o}C. The solvent and the volatile materials were evaporated (60^{o}C/0.05 Torr) and 7 was obtained as a viscous colourless oil.

2-(1-Methyl[2,3-^{3}H]propyl)phenyl methyl carbamate ([^{3}H]BPMC) (8)

20.50 mg (0.1 mmol) of 7 were tritiated in 0.7 ml dry dioxane in the presence of Pd/charcoal catalyst. After the tritium uptake ended the solution was filtered and the solvent was evaporated.

Yield: 19.4 mg (0.092 mmol, 5.33 Ci), specific activity: 58 Ci/mmol. Purity by radio TLC (in system B): higher than 98%.

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