A CONVENIENT METHOD FOR SYNTHESIS OF ^{14}C-CARBONYL METHYLCARBAMATES

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SUMMARY

While [^{14}C-carbonyl]-methyl isocyanate has been used widely for the preparation of radioactive insecticidal methylcarbamates, yields are often low, and in some cases reactions completely unsuccessful, because of the sensitivity of the isocyanate to moisture. This paper described a process whereby the [^{14}C]-methyl isocyanate, in its break-seal container as received from the supplier, is reacted with the appropriate oxime or phenolic intermediate without exposing the isocyanate to atmospheric moisture. Results are presented for the insecticides carbaryl, carbofuran, aldicarb and methomyl demonstrating consistent yields of 85 to 95% using a procedure of uncommon simplicity.

Key Words: ^{14}C-Carbonyl Methylcarbamates, Carbaryl, Carbofuran, Aldicarb, Methomyl, Mass Spectra

INTRODUCTION

Carbon-14 labeling of the carbonyl group in carbamate anticholinesterase toxicants provides an excellent tool for studying the disposition of these chemicals in various biological systems. In particular, knowledge of the metabolism of methylcarbamate insecticides has greatly increased because of the use of this and other radiolabeling techniques (1,2). In addition to the accountability and ease of quantitation afforded by radiotracer techniques, ^{14}C-carbonyl labeling of the carbamates gives rapid data relative to an animal's ability to directly detoxify methylcarbamates through hydrolysis of the ester linkage, as this detoxication results in expiration of [^{14}C]-carbon dioxide (3).

Methods of radiosynthesis of methylcarbamates have been recently reviewed (2). One widely used method of producing ^{14}C-carbonyl methylcarbamates involves ester-

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ification of the appropriate phenolic or oxime starting material with [^{14}C-carbonyl]-methyl isocyanate (4). However, unless extreme caution is used in handling the volatile, moisture-labile methyl isocyanate, the simple one-step reaction can be frustrating as well as expensive due to loss of the desired radiocarbon. The purpose here is to report a facile, efficient means of synthesis of aromatic and aliphatic methylcarbamates which circumvents many of the problems encountered in handling small quantities of radioactive methyl isocyanate. By this method ^{14}C-carbonyl labeling was accomplished with the insecticides carbaryl (1-naphthyl methylcarbamate), carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate), aldicarb (2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)oxime, and methomyl (S-methyl-N-[(methylcarbamoyl)-oxy] thioacetimidate.

MATERIALS AND METHODS

Phenolic and oxime starting materials for syntheses were obtained by alkaline hydrolysis of analytical grade methylcarbamates used in residue analysis. Subsequently, thin-layer chromatography (TLC) on silica gel plates (Silgel F-254, Brinkman Instruments, Des Plains, IL. 60016) as detailed in Table I afforded purification. In this manner, 1-naphthol, carbofuran phenol (2,3-dihydro-2,2-dimethyl-7-hydroxybenzofuran), aldicarb oxime (2-methyl-2-(methylthio)propionaldehyde oxime) and methomyl oxime (S-methyl-N-hydroxy thioacetimidate) were isolated using systems A, B, C and D, respectively. [^{14}C-Carbonyl]-methyl isocyanate, 5.38 mCi/mM, was obtained from New England Nuclear, Boston, MA. 02118. Reagent grade triethylamine was used as a catalyst. Benzene, dried over sodium, served as the solvent for the reaction.

Reactions of the various phenols or oximes with the radiolabeled methyl isocyanate were carried out in the glass break-seal vial (similar to K-892750, Kontes Glass Co., Vineland, N.J. 08360), as supplied by New England Nuclear. This vial, as illustrated below in Figure 1, consisted of two compartments. Compartment A contained 1.06 mg of the radioactive methyl isocyanate. Compartment B was dried with desiccated air and a two fold molar equivalent of the

Table I. R_f values of starting materials and products isolated by silica gel TLC systems.

Compound	Solvent system A	B	C	D
Carbaryl	.58	.46	.58	.74
Naphthol	.84	.69	.81	.86
Carbofuran	.57	.41	.58	.71
Carbofuran phenol	.88	.65	.84	.83
Aldicarb	.36	.24	.38	.61
Aldicarb oxime	.90	.65	.84	.89
Methomyl	.11	.13	.14	.36
Methomyl oxime	.57	.34	.55	.72

A - 4:1 diethyl ether - hexane

B - 7:3 benzene - diethyl ether

C - 9:1 diethyl ether - hexane

D - 9:1 diethyl ether - acetone

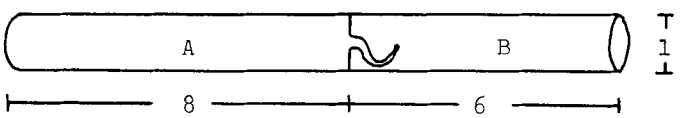

Figure 1. The break-seal vial used as a reaction vessel. Dimensions are expressed in centimeters.

proper phenolic or oxime reactant was added along with 0.01 ml of triethylamine and 0.5 ml of dry benzene. In addition, a 1 cm section of 0.5 cm diameter glass rod was carefully inserted and compartment B was tightly sealed with a teflon-covered cork. Compartment A was immersed in a dry ice-acetone bath which served to condense the methyl isocyanate and create a reduced pressure within compartment A. By holding the tube horizontally so that the tip of the break-seal was immersed in the benzene solution, the seal was easily broken by the glass rod upon a sudden movement of the vial. Because of the negative pressure, the ben-

zene solution containing the nonradioactive reactant and the catalyst was rapidly withdrawn into compartment A. When this transfer was essentially complete, the reaction vial was placed in a water bath at 45°C for about 18 hours. The tube was then opened and the ^{14}C-carbonyl methylcarbamate isolated by silica gel TLC using the solvent systems previously described. Radioactive products were located on the plates by radioautography. These were quantitated by direct counting of the silica gel in 3a70B scintillation cocktail (Research Products International Corporation, Elk Grove Village, IL. 60007) by means of a Packard Model 3380 liquid scintillation spectrometer.

Mass spectra of the purified synthetic products were obtained using a Finnigan Model 1015-C quadrupole instrument. Samples were introduced via the solid probe inlet and were ionized with a 70 eV electron beam.

RESULTS AND DISCUSSION

The radiopurity of the crude reaction mixtures of synthesized methylcarbamates were 94 and 92% for carbaryl and carbofuran, and 88 and 86% for aldicarb and methomyl, respectively. The reproducibility of this synthetic method was demonstrated by yields of carbaryl ranging from 93.9 to 94.6% radiopurity in 4 separate attempts. Radioactive impurities occurred as 3 distinct products with only slight TLC mobility (R_f <.10) in the indicated solvent systems.

In addition to thin layer cochromatography with authentic standards, mass spectra of the synthetic products confirmed their authenticity. Major fragment ions in these spectra are indicated in Table II. The spectra of all compounds indicated ions of m/e 58, corresponding to CH_3NHCO^+ which originated from the methylcarbamyl moiety. With the exception of aldicarb, the spectrum of each compound exhibited molecular and phenolic or oxime ions. In contrast, the thiomethylene group of aldicarb was labile apparently in preference to molecular ionization or decarbamylation.

All spectra were identical, except for the minor [^{14}C] contribution, to reference spectra of authentic compounds recorded in this laboratory. In addition, the spectrum of carbaryl coincided with that previously published (5). The mass

Table II. Major ions in the mass spectra of the synthesized methylcarbamates. Percent abundances are listed in parentheses.

Compound	
Carbaryl	*201(3), 144(100), 127(3), 116(33), 115(43), 89(6), 63(6), 58(5) and 57(5)
Carbofuran	*221(6), 164(100), 149(74), 131(18), 123(19), 122(21), 121(13), 91(12), 77(12), 58(11) and 57(10).
Aldicarb	144(47), 100(30), 89(21), 87(50), 86(100), 85(63), 76(37), 58(62), 55(32) and 41(90).
Methomyl	*162(1), 105(76), 88(29), 58(100), 47(30), 44(29), 42(37) and 41(33).

* Molecular ions.

spectrum of aldicarb differed in base peak, and consequently in abundance of other ions, from spectra reported elsewhere (6,7). Possibly, the variance resulted from differences in ionization or mass separation techniques.

In conclusion, the above method offers an uncommonly simple means of obtaining radiolabeled methylcarbamates. This method should be of wide utility because of the extensive use of methylcarbamate compounds as drugs and pesticides. Moreover, the potential for synthesis of small quantities of these materials at low cost should extend the availability of this radiolabel to any interested investigator.

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