SYNTHESIS OF 1,3,5-TRIMETHOXY[1-^{14}C]BENZENE

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SUMMARY

Utilizing the facile acylative annulation of 2-methoxypropene with [1-^{14}C]malonyl dichloride (5), the synthesis of 1,3,5-trimethoxy[1-^{14}C]benzene (8) was accomplished through a seven-step sequence starting from potassium [^{14}C]cyanide with an overall yield of 60%.

Thus, reaction of bromoacetic acid with potassium [^{14}C]cyanide gave sodium [^{14}C]cyanoacetate (1). Hydrolysis of 1 with sodium hydroxide solution provided the sodium salt of [1-^{14}C]malonic acid (2). Treatment of 2 with calcium chloride gave the calcium salt 3, which was acidified with concentrated sulfuric acid in ether to give [1-^{14}C]malonic acid (4). Reaction of 4 with oxalyl chloride in refluxing ether gave [1-^{14}C]malonyl dichloride (5). Annulative acylations of 2-methoxypropene with 5 gave the crucial intermediate 5-methoxy[1-^{14}C]resorcinol (7), together with 4-hydroxy-6-methyl-[2 (or 4)-^{14}C]2H-pyran-2-one (6), in a ratio of 3:1. However, 6 could be advantageously converted to 7a by initial O-methylation with dimethyl sulfate, followed by rearrangement of the product, 4-methoxy-6-methyl[2(or 4)-^{14}C]2H-pyran-2-one (6a), upon treatment with sodium methoxide. Finally, bis-O-methylation of 7 and 7a with dimethyl sulfate in refluxing acetone gave the title compound 8.

KEY WORDS: 1,3,5-Trimethoxy[1-^{14}C]benzene, 5-methoxy[1-^{14}C]resorcinol, [1-^{14}C]malonic acid, 4-hydroxy-6-methyl-[2(or 4)-^{14}C]2H-pyran-2-one

INTRODUCTION

1,3,5-Trimethoxybenzene is the key intermediate in the synthesis of a series newly developed ACAT (acyl coenzyme A: cholesterol acyltransferase) inhibitors,

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which are potential hypocholesterolemic agents[1]. In the course of pharmacokinetics and drug metabolism studies, the carbon-14 labeled forms of these compounds were required. This paper describes the synthesis of 1,3,5-trimethoxy[^{14}C]benzene, the precursor to the labelled target compounds.

DISCUSSION AND RESULTS

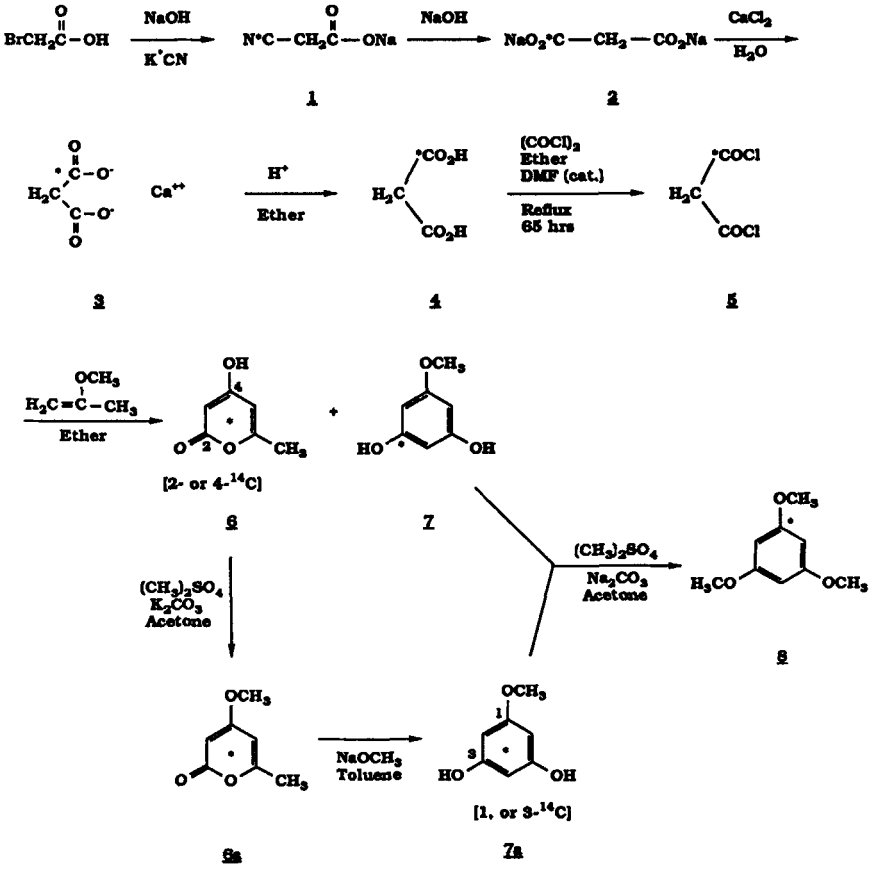
A reasonable route to ^{14}C-labeled 1,3,5-trimethoxybenzene would be the methylation of labeled phloroglucinol (1,3,5-trihydroxybenzene). The syntheses of [2,4,6-^{14}C]phloroglucinol, as well as a number of unlabeled syntheses[2], have been reported. However, these syntheses, mostly based on acylative condensations of various active methylene compounds followed by decarboxylation, generally seem to require rather strenuous conditions, often with low or unreported yields.

In an effort to develop a convenient and reproducible procedure for the ^{14}C-labeled synthesis of 1,3,5-trimethoxybenzene, we found that the facile annulative acylation of enol ether with malonyl dichloride, reported by Effenberger, et. al., highly suitable. The reaction was incorporated into the synthetic sequence as shown in Scheme I. The scheme may be viewed as a seven-step sequence in which the yield was enhanced by conversion of 6, the minor product of annulation, to the major product 7. An overall radiochemical yield of 53%, based on the [1-^{14}C]potassium cyanide initially used, was achieved.

EXPERIMENTAL

Potassium [^{14}C]cyanide was purchased from American Radiolabeled Company. Radioactivity was determined with a Packard Tri-Carb 4530 liquid scintillation counter, using Beckman Ready-Gel as the counting medium. TLC plates, E. Merck silica gel 60 F-254, were scanned on a Berthold LB2832 automatic TLC linear analyzer. Column chromatography was performed using E. Merck silica gel, 230-400 mesh.

SCHEME I: Synthesis of 1,3,5-trimethoxy[1-^{14}C]benzene



[1-^{14}C]Malonic acid[3] (4). Bromoacetic acid (6.7 g, 48.2 mmol) was dissolved in 14 mL of water, and the solution was neutralized with 2 N NaOH to pH 7. Potassium [^{14}C]cyanide (2.86 g, 500 mCi, 43.8 mmol) was added, and the reaction mixture was heated at 100°C for one hour. The reaction mixture was then treated with 10.2 mL of 12.5 N NaOH and heated at 100°C for an additional two hours. The solution was cooled to room temperature, and $CaCl_2$ (13.44 g in 20 mL H_2O) was added dropwise. The resulting white precipitate was stirred at room temperature overnight. The precipitate was collected by filtration and dried to give 3 as a white powder. Compound 3 was suspended in 200 ml of ether, and concentrated H_2SO_4 (5.8 mL) was added dropwise. The suspension was stirred at room temperature overnight. The precipitate was removed by filtration, and the

filtrate was evaporated to give [1-^{14}C]malonic acid (4) (4.28 g, 470 mCi, 41.2 mmol, 94%) as a white solid.

[1-^{14}C]Malonyl dichloride[4] (5). [1-^{14}C]Malonic acid (4.29 g, 41.2 mmol) was dissolved in 150 mL of ether. A catalytic amount of DMF was added to the solution followed by oxalyl chloride (42.4 g, 333.8 mmol). The reaction mixture was heated under reflux for 65 hours. Ether and excess oxalyl chloride were removed using a rotary evaporator. The residual liquid was purified using bulb to bulb vacuum distillation to give [1-^{14}C]malonyl dichloride (5; 5.8 g, 41.1 mmol, 99.8%).

5-Methoxy[1-^{14}C]resorcinol (7)[5] and 4-hydroxy-6-methyl-[2 or (4)-^{14}C]-2H-pyran-2-one (6)[5]. A solution of 2-methoxypropene, (13.4 g, 185.8 mmol) in 45 mL of ether was cooled to -20°C. The solution was treated dropwise with a solution of [1-^{14}C]malonyl dichloride (5; 5.8 g, 41.1 mmol) in 45 ml of ether. The reaction mixture was stirred at -20°C for 3 hours and was then treated with a solution of KOH (10.4 g, 178.3 mmol) and 464 mg of triethylbenzylammonium chloride in 45 mL of water. The solution was warmed to room temperature and stirred for 4 hours. The layers were separated and the aqueous layer was acidified with concentrated HCl. The aqueous layer was extracted with ether (5 x 20 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated to give a solid. TLC analysis using hexane/ethyl acetate (1:1) showed 7, 57% and 6, 20%, as the two main radioactive components. The mixture was chromatographed over 45 g of silica gel using hexane/ethyl acetate (1:1) as the eluant. Evaporation of the appropriate fractions gave 3.0 g of product 7 and 1.83 g of product 6.

1,3,5-Trimethoxy[1-^{14}C]benzene (8)[6]. A mixture of 5-methoxy[1-^{14}C]resorcinol (7; 3.0 g, 21.4 mmol), K_2CO_3 (8.88 g, 64.2 mmol), and dimethyl sulfate (40.5 g, 321.1 mmol) in 150 mL of acetone was heated under reflux for 44 hours. The reaction mixture was filtered, and the precipitate was washed well with acetone. The filtrate was concentrated *in vacuo* to a residue. The residue was

chromatographed over silica gel using hexane/ethyl acetate (1:1) as the eluant. Fractions were analyzed by TLC (hexane/ethyl acetate, 1:1) and those containing pure 8 were combined. The solvents were removed in vacuo to give 2.7 g of 1,3,5-trimethoxy[1-^{14}C]benzene (8)[7].

A mixture of the minor product 6 (1.83 g, 14.5 mmol), 1.1 g of Na_2CO_3, and 1.83 g of dimethyl sulfate in 100 mL of acetone was heated at reflux for 4 hours. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The resulting dark brown glue 6a was dissolved in toluene, and sodium methoxide (3.1 g, 58 mmol) was added. The reaction mixture was heated under reflux for 4 hours. After cooling, the mixture was added to 100 mL of water and extracted with ether. The aqueous phase was acidified and extracted with CH_2Cl_2 (3 x 20 mL). The combined CH_2Cl_2 phases were dried (Na_2SO_4) and concentrated to give 7a. Na_2CO_3 (1.2 g, 12 mmole) and excess dimethyl sulfate were added to the filtrate, and the reaction mixture was heated under reflux for an additional 24 hours. The reaction mixture was filtered, and the filtrate was evaporated to a residue. The residue was chromatographed over silica gel using hexane/ethyl acetate (1:1), as the eluant. Fractions were analyzed by TLC (hexane/ethyl acetate, 1:1) and those containing pure 8 were combined. The solvents were removed in vacuo to give 1.2 g of 1,3,5-trimethoxy[1-^{14}C]-benzene[8] (8). ^{1}H NMR ($CDCl_3$) δ3.73(s, 9H), 6.02(s, 3H); specific activity, 10.52 mCi/mmol.

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8. According to our later studies with unlabeled materials, it should be possible to obtain 8 with a yield exceeding 90% by heating a mixture of 7, methyl iodide, and potassium carbonate in toluene under reflux for 24 hours.