1. Introduction

During the course of an investigation on the mechanistic application of kinetic isotope effects, it became desirable to prepare 2-aryl-ethanols labeled with carbon-14 at the specific position of the aryl ring. Benzoic (ring-1-14C) acid and toluene (ring-1-14C) were the only commercially available starting materials for the purpose. 2-Phenylethanol (ring-1-14C), 1-phenyl-2-propanol (ring-1-14C), 2-methyl-2-phenyl-1-propanol (ring-1-14C), and 2-methyl-2-(4-bromophenyl)-1-propanol (ring-1-14C) were prepared from the former starting material by the standard sequences of synthetic procedures. Introduction of a methoxyl group on a phenyl ring at the para to the carbon-14 was a matter of synthetic strategy. We report here the synthesis of 2-(4-methoxyphenyl) ethanol (ring-1-14C) (I) starting from toluene (ring-1-14C) (II).

2. Results

The synthetic scheme of I from II was summarized in Fig. 1. The strategy took advantage of two molecular rearrangements: the Baeyer-Villiger rearrangement of 4-methylacetophenone (III) to 4-methylphenyl (ring-1-14C) acetate (IV) and the Wolff rearrangement of 4-methoxy-a-diazoacetophenone (IX) to methyl 4-methoxyphenylacetate (X), and the both worked quite well.

![Synthesis of 2-(4-Methoxyphenyl)ethanol (ring-1-14C)](image)
4-Methylacetophenone \([\text{ring-4-}^{14}\text{C}]\) (III) was obtained by the Friedel-Crafts acetylation of toluene \([\text{ring-1-}^{14}\text{C}]\) (II) in a good yield. The Baeyer-Villiger rearrangement of III to 4-methylphenyl\([\text{ring-4-}^{14}\text{C}]\) acetate (IV) was performed with perbenzoic acid in chloroform. The reaction took as long as 141 days at a room temperature, and the yield after hydrolysis to 4-methylphenol \([\text{ring-4-}^{14}\text{C}]\) (V) amounted to 60% from III. Oxidation of the methyl group of V was carried out with lead dioxide in an alkaline solution to give 4-hydroxybenzoic \([\text{ring-1-}^{14}\text{C}]\) acid (VI) in a 58% yield. After methylation of the phenol group with dimethyl sulfate, 4-methoxybenzoin \([\text{ring-1-}^{14}\text{C}]\) acid (VII) was converted to the acid chloride (VIII) and then to 4-methoxy-\(\alpha\)-diazoacetophenone \([\text{ring-1-}^{14}\text{C}]\) (IX) with diazomethane. The Wolff rearrangement of IX to methyl 4-methoxyphenylacetate \([\text{ring-1-}^{14}\text{C}]\) (X) was undertaken in the presence of silver benzoate as a catalyst in triethylamine-methanol. X was obtained in a 83% yield. Reduction of X with lithium aluminum hydride gave the desired I. The radioactivity of I was determined for its \(p\)-nitrobenzenesulfonate (XI); 8.8 g of XI (1.381 mCi/mol) was obtained from 0.5 mCi of II. The overall yield for this nine-step synthesis of I from II amounted to 13.6%. The present preparation can be applied as a useful method to introduce an oxygen function at the para to the alkyl side chain of the labeled benzene ring.

3. Experimental

3.1 4-Methylacetophenone \([\text{ring-4-}^{14}\text{C}]\) (III)

4-Methylacetophenone \([\text{ring-4-}^{14}\text{C}]\) (III) was obtained by the Friedel-Crafts acetylation of toluene \([\text{ring-1-}^{14}\text{C}]\) (II) in a good yield. The Baeyer-Villiger rearrangement of III to 4-methylphenyl\([\text{ring-4-}^{14}\text{C}]\) acetate (IV) was performed with perbenzoic acid in chloroform. The reaction took as long as 141 days at a room temperature, and the yield after hydrolysis to 4-methylphenol \([\text{ring-4-}^{14}\text{C}]\) (V) amounted to 60% from III. Oxidation of the methyl group of V was carried out with lead dioxide in an alkaline solution to give 4-hydroxybenzoic \([\text{ring-1-}^{14}\text{C}]\) acid (VI) in a 58% yield. After methylation of the phenol group with dimethyl sulfate, 4-methoxybenzoin \([\text{ring-1-}^{14}\text{C}]\) acid (VII) was converted to the acid chloride (VIII) and then to 4-methoxy-\(\alpha\)-diazoacetophenone \([\text{ring-1-}^{14}\text{C}]\) (IX) with diazomethane. The Wolff rearrangement of IX to methyl 4-methoxyphenylacetate \([\text{ring-1-}^{14}\text{C}]\) (X) was undertaken in the presence of silver benzoate as a catalyst in triethylamine-methanol. X was obtained in a 83% yield. Reduction of X with lithium aluminum hydride gave the desired I. The radioactivity of I was determined for its \(p\)-nitrobenzenesulfonate (XI); 8.8 g of XI (1.381 mCi/mol) was obtained from 0.5 mCi of II. The overall yield for this nine-step synthesis of I from II amounted to 13.6%. The present preparation can be applied as a useful method to introduce an oxygen function at the para to the alkyl side chain of the labeled benzene ring.

3.2 4-Methylphenol \([\text{ring-4-}^{14}\text{C}]\) (V)

A mixture of 12.0 g of III, 44.8 g of perbenzoic acid, and 100 ml of chloroform was prepared in an Erlenmeyer flask equipped with a ground glass stopper. The flask was kept in the dark at a room temperature for 141 days. After the addition of another 100 ml of chloroform, the mixture was washed thoroughly with 100 ml of 10% sodium bisulfite solution. The water layer was extracted with ether, and the combined organic layer was washed with saturated sodium bicarbonate solution, and then dried with anhydrous sodium sulfate. After the solvent was removed, 10 g of sodium hydroxide, 50 ml of water, and 50 ml of ethanol were added to the residue, and the mixture was refluxed for one hour. The solvent was removed under vacuum, 50 ml of water was added to the residue, and the mixture was neutralized with 20% hydrochloric acid. Extraction with ether, drying with anhydrous sodium sulfate, removal of the ether, and distillation under vacuum gave 5.8 g (60%) of V: bp 96.5-98.0°C/17.5 Torr.

3.3 4-Hydroxybenzoic \([\text{ring-1-}^{14}\text{C}]\) acid (VI)

A mixture of 5.8 g of V, 39.4 g of lead dioxide, 58 g of sodium hydroxide, and 12 ml of water was stirred at 200-220°C for one hour. Into the reaction mixture, after standing at a room temperature and before the mixture solidified, was added 100 ml of water by portions while stirring. The mixture was refluxed for 30 min, and the solid was removed by filtration and washed with 50 ml of water. The filtrate was neutralized with concd hydrochloric acid and extracted with ether. After the ether was removed, the residue was recrystallized from 80 ml of water. VI was obtained in a 58% yield (4.3 g).

3.4 4-Methoxybenzoic \([\text{ring-1-}^{14}\text{C}]\) acid (VII)

Into a stirred mixture of 4.3 g of VI, 5 g of sodium hydroxide, and 30 ml of water, was added 7.9 g of dimethyl sulfate dropwise for 30 min below 10°C. Then the mixture was stirred at 90°C for three hours. Upon cooling colorless crystals precipitated and were filtered. The crystals were stirred in 30 ml of water with 3 g
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3.5 4-Methoxybenzoyl [ring-1-¹⁴C] chloride (VIII)

VIII was obtained from 9.0 g of VII with 60 ml of thionyl chloride in the usual manner: bp 138.0-139.0°C/13 Torr (8.3 g, 82%).

3.6 4-Methoxy-α-diazoacetophenone [ring-1-¹⁴C] (IX)

VIII (8.3 g) in 20 ml of anhydrous ether was added dropwise for 20 min into a stirred solution of 6.1 g of diazomethane in 300 ml of ether at 0°C, and the reaction mixture was stirred further three hours. Removal of the ether gave yellow crystals, which was recrystallized from a mixture of 40 ml of anhydrous benzene and 200 ml of hexane below 60°C within 5 min. IX was obtained in a 84% yield (7.2 g): mp 85.0-88.0°C (dec).

3.7 Methyl 4-methoxyphenylacetate [ring-1-¹⁴C] (X)

A solution of silver benzoate (0.7 g) in 7 ml of dry triethylamine was added dropwise into a solution of 7.2 g of IX in 70 ml of anhydrous methanol. Further, two 0.25 g portions of silver benzoate were added into the reaction mixture. After the evolution of nitrogen gas ceased, a small quantity of Norite was added, refluxed several minutes, filtered, and washed with a small volume of ether. The solvent was removed from the filtrate, and the residue was taken up in 50 ml of ether. The ether layer was washed with sodium bicarbonate solution and dried with anhydrous sodium sulfate. X was obtained by distillation in a 83% yield (6.1 g): bp 135-141°C/12.5 Torr.

3.8 2-(4-Methoxyphenyl)ethanol [ring-1-¹⁴C]

Reduction of X was carried out with lithium aluminum hydride in the usual manner. I was obtained in a 82% yield (4.2 g): bp 138-142°C/12.0 Torr.

3.9 2-(4-Methoxyphenyl)ethyl [ring-1-¹⁴C] p-nitrobenzenesulfonate (XI)

Anhydrous pyridine (20 ml) was added at once onto a mixture of 2.0 g of X and 4.4 g of crystals of p-nitrobenzenesulfonyl chloride cooled with an ice-salt mixture, and the reaction mixture was stirred at that temperature for one hour. The mixture was poured into ice-water, and the precipitates were filtered, washed, and dried. Crude XI was obtained in a 90% yield (4.2 g). Recrystallization from hexane-carbon tetrachloride (1:1) gave the pure material: mp 98.0-99.0°C. Radioactivity was assayed as 1.381 mCi/mol.

References
3) Y. Yukawa, S.-G. Kim, and H. Yamata-ka: ibid., 373 (1973)
5) At present toluene [ring-1-¹⁴C] is commercially available (New England Nuclear), but benzoic [ring-1-¹⁴C] acid is not routinely available.
8) C. Graebe and H. Kraft: Ber., 39, 397 (1906)
10) M.S. Newman and P.F. Beal, III: ibid., 72, 5163 (1950)