THE PREPARATION OF 3-PHENOXY[1-^{14}C]- AND 3-PHENOXY[3-^{14}C]PROPENE

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ABSTRACT

Preparations of specifically labeled α- and γ-[^{14}C]allyl phenyl ether are described.

INTRODUCTION

In connection with studies of heavy-atom kinetic isotope effects (KIE) in the Claisen rearrangement, it was necessary to prepare the title compounds. One of these, 3-phenoxy[1-^{14}C]propene (**1**) has been prepared before by Schmid, also in connection with the Claisen rearrangement, but in establishing its pericyclic nature rather than in measuring KIE (1). We found it useful to modify Schmid's preparation so that we could adapt its modified form for also preparing the second, needed compound, 3-phenoxy[3-^{14}C]propene (**2**), which, to our knowledge has not been reported. Although we used standard methods, gathered from the literature, for preparing each of these labeled ethers, we felt that it would be helpful to report the details of each sequence, collectively, for the use of others.

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Steps in the preparation of 1 are numbered and shown in Scheme 1. Each step was carried out first with unlabeled materials. Steps 1 and 2 were as described by Schmid (1), although we found it simpler to carry out the hydrolysis of step 2 in sealed ampules placed in an oven, rather than to use the autoclave as described (1). Step 3 followed a procedure (unlabeled) described by Arndt (2), step 4 is a general method from Houben-Weyl (3), step 5 is a general method by Brown (4), and step 6 is a general method from Vogel (5). In regard to steps 3-6, we found these to be more useful for making the quaternary ammonium iodide than Schmid's sequence, in which the final step is the autoclave reaction of 1-iodo-3-phenoxypropane with trimethylamine. Last, step 7 was as described by Schmid (1).

Steps in the preparation of 2 are numbered and shown in Scheme 2. The chlorination of acetic acid (step 1) is described in Houben-Weyl (6). Step 2 was according to Stuetzel (7), while the use of $AlCl_3$ in increasing the efficiency of reduction by $LiAlH_4$ (step 3) is described by Brown (8). The remaining steps 4-10 were as described in Scheme 1.

For convenience of other users, all of the steps of Scheme 1 and steps 1-3 of Scheme 2 are given in detail.

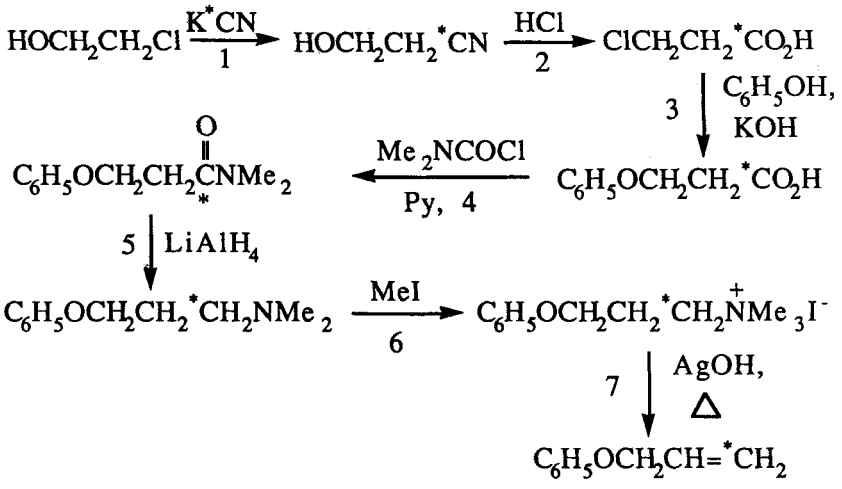
EXPERIMENTAL

Scheme 1.

3-Hydroxypropio[^{14}C]nitrile (step 1). A solution of 17.6 g (0.219 mol) of 2-chloroethanol in 90 mL of ethanol was heated to reflux. To the solution was added 25.8 mg (0.396 mmol) of solid K[^{14}C]N (Pathfinder Labs, Inc., 17 mCi/mmol) in one increment, followed by the dropwise addition of a solution of 14.1 g (0.217 mol) of KCN in 22 mL of water. Heating and stirring were continued for 20 h. The solution was cooled, diluted with 200 mL of acetone and the precipitate of KCl was filtered off. Solvent was removed in a rotary evaporator and the oily brown residue was distilled under water aspirator pressure at 127-130° C, giving 10.8 g (0.152 mol, 69.4% based on 2-chloroethanol) of 3-hydroxypropionitrile, having a calculated activity of approx 32 mCi/mol.

Scheme 1

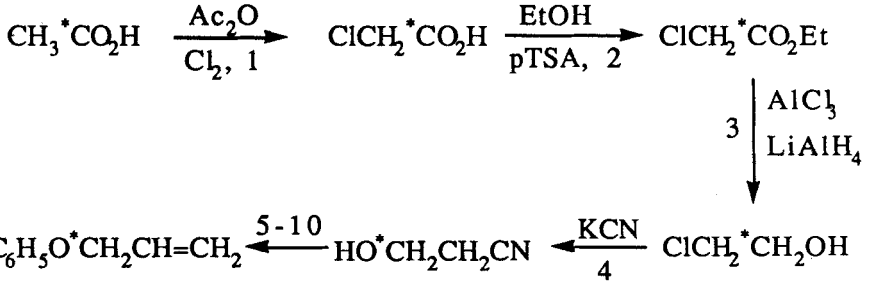
Preparation of 3-Phenoxy[1-^{14}C]propene



1

Scheme 2

Preparation of 3-Phenoxy[3-^{14}C]propene



2

3-Chloro[1-^{14}C]propionic acid (step 2). The 3-hydroxypropionitrile was divided into three portions, each of which was sealed with 25 mL of conc. HCl in an ampule and heated in an oven at 120°C for 8 h. Repetitive use of this technique with unlabeled reactant assured us of its safety. The cooled ampules were opened and the desired product was extracted with 10 x 50 mL of ether. Drying ($MgSO_4$) and workup of the ether solution gave 3-chloro[1-^{14}C]propionic acid, which was distilled under water-aspirator pressure at 111-115°C, giving 13.9 g (0.128 mol, 84.2%) of product.

3-Phenoxy[1-^{14}C]propionic acid (step 3). Three solutions were made as follows: (A), 49 g (0.52 mol) of phenol and 29.4 g (0.52 mol) of KOH in 20 mL of water; (B), 13.9 g of the labeled and 13.9 g of unlabeled 3-chloropropionic acid, total 0.256 mol, in 20 mL of water; (C), 14.0 g of KOH in 20 mL of water. Solutions A and B were heated to about 70°C. Portions of solutions B and C were added alternately to solution A over a period of 30 min. Finally, the mixture was heated for 5 min, cooled, and acidified with conc. HCl. Phenol and 3-phenoxypropionic acid were extracted into ether (3 x 100 mL), from which the 3-phenoxypropionic acid was extracted with 6 x 30 mL of 2N $NaHCO_3$ solution. The $NaHCO_3$ solution was acidified very slowly with conc. HCl, and the precipitate was filtered off and dried in air to give 12.2 g (73.5 mmol, 28.7%) of 3-phenoxy[1-^{14}C]propionic acid, having a calculated activity of approx 16 mCi/mol, and mp 95.5 - 96°C; lit. mp 97-98°C (2).

N,N'-Dimethyl-3-phenoxy[1-^{14}C]propionamide (step 4). The labeled 3-phenoxypropionic acid was dissolved in a mixture of 100 mL of benzene and 20 mL of pyridine. To the solution was added 20 mL (0.217 mol) of dimethylcarbamyl chloride (Aldrich). The mixture was stirred for 2 h at room temperature and then heated at reflux for 3 h. The completion of reaction was monitored for the absence of 3-phenoxypropionic acid by TLC (silica gel, ether development). The solution was cooled, washed with dilute HCl, water, 2 N $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated to give 12.9 g (66.7 mmol, 90.7%) of the amide, mp 48-50°C.

1-Dimethylamino-3-phenoxy[1-^{14}C]propane (step 5). A solution of the amide from step 4 in 150 mL of dry ether was added to a suspension of 1.7 g (44.8 mmol) of $LiAlH_4$ in 100 mL of ether, at such a rate as to maintain gentle boiling. Stirring was continued for 4 h after addition, when TLC showed that no amide remained. Water was added slowly, followed by 20 mL of 10% NaOH solution. A precipitate of $Al(OH)_3$ was filtered off, the ether layer was separated from the filtrate and the aqueous layer was extracted with 5 x 50 mL of ether. The combined ether solutions were extracted with 15% HCl, and the acidic solution was made alkaline with 15% NaOH solution. Extraction with ether and workup gave 8.18 g (45.6 mmol, 68.4%) of 1-dimethylamino-3-phenoxy[1-^{14}C]propane as an oil.

3-Phenoxy[1-^{14}C]propyltrimethylammonium iodide (step 6). A solution of the crude product from step 5 and 3.5 mL (56.2 mmol) of methyliodide in 20 mL of dry ethanol was allowed to stand at room temperature for 6 h. Evaporation of volatiles and crystallization of the product from hot ethanol gave 11.15 g (34.7 mmol 76%) of the desired quaternary ammonium iodide, mp 173-175°C. Lit. mp 172-172°C (1).

3-Phenoxy[1-^{14}C]propene (step 7). Silver oxide was prepared from 22.3 g of $AgNO_3$ and 5.2 g of NaOH in 500 mL of water. All of the quaternary ammonium iodide was dissolved in 200 mL of water which was stirred for 20 h with the silver oxide. Silver iodide formed and was filtered off and washed with water. Combined water solutions were evaporated under reduced pressure and at a temperature not over 45°C. The brown residue was slowly heated to 160°C to distill off water, Me_3N and the product. The distillate was extracted with 4 x 50 mL of ether, and the ether solution was washed with dilute HCl and water, dried over $MgSO_4$ and evaporated in a rotary evaporator at room temperature. The liquid product was dissolved in 10 mL of petroleum ether, bp 30-60°C, and the solution was filtered through a column of neutral alumina. Evaporation gave 2.78 g (20.8 mmol, 60%) of 3-phenoxy[1-^{14}C]propene. This was diluted with 4.64 g of unlabeled 3-phenoxypropene and the mixture was distilled at 89-92°C

under water-aspirator pressure, giving 7.0 g (90% recovery) of 3-phenoxy[1-^{14}C]propene, having a calculated activity of 6 mCi/mol. Overall yield based on 2-chloroethanol was 4.7%.

Scheme 2.

[1-^{14}C]Chloroacetic acid (step 1). A mixture of 4.15 g (40.7 mmol) of acetic anhydride, 66.4 mg (1.11 mmol) of [1-^{14}C]acetic acid (activity 9.04 mCi/mmol, total 10 mCi, Pathfinder Labs.), and 13.8 g (0.230 mol) of acetic acid was placed in a 50 mL three-necked, round-bottom flask, fitted with a gas-inlet tube, thermometer and condenser cooled with circulating ice-water. The mixture was stirred and heated at 105°C and Cl_2 gas was passed into the mixture for 17 h. The mixture was cooled and distilled to give 25.8 g (0.273 mol, 87.4%) of [1-^{14}C]chloroacetic acid, bp 182-187°C, having a calculated activity of approx 32 mCi/mol.

Ethyl chloro[1-^{14}C]acetate (step 2). The chloroacetic acid was dissolved in a mixture of 70 mL of dry ethanol and 150 mL of chloroform containing 1.64 g of p-toluenesulfonic acid (pTSA). This mixture was stirred and heated under gentle reflux in a Dean-Stark apparatus for 12 h. The mixture was cooled, transferred to a separatory funnel, and washed with water, 1% $NaHCO_3$ solution, and again with water. After drying over $MgSO_4$ and distilling, 27.0 g (0.220 mmol, 80.6%) of ethyl chloro[1-^{14}C]acetate was obtained, bp 138°C.

2-Chloro[1-^{14}C]ethanol (step 3). To a suspension of 8.3 g (0.219 mol) of $LiAlH_4$ in 200 mL of dry ether cooled to 0°C was added dropwise a solution of 9.75 g (73.1 mmol) of anhydrous $AlCl_3$ in 200 mL of dry ether. This mixture was stirred for 30 min at 0°C, and to it was added dropwise a solution of the labeled ethyl chloroacetate in 100 mL of dry ether, during which the temperature was kept between -3 and 1°C. The mixture was then stirred for 4.5 h at 5°C and to it was added 150 mL of dilute HCl. The acidic mixture was transferred to a separatory funnel, 20 g of NaCl was added (chloroethanol is soluble in water), and the product was extracted with 10 x 100 mL portions of

ether. Workup of the ether solution and distillation of the product gave 11.0 g (0.136 mol, 62%) of 2-chloro[1-^{14}C]ethanol. Lit. yld was 83%, estimated by glpc (8).

The overall yield at this stage was 43.7%. The remaining steps (4-10) were carried out essentially as in Scheme 1, resulting in the formation of 3-phenoxy[3-^{14}C]propene (**2**) in an overall yield of 2.1%.

ACKNOWLEDGEMENT

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