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PREPARATION OF ^{14}C- AND ^{18}O-ENRICHED ALLYL ALCOHOL (PROPANOL FREE)

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Summary

Preparations of specifically labeled [1-^{14}C]-, [3-^{14}C]- and [1-^{18}O]allyl alcohol are described. The syntheses were achieved, respectively, in 7, 11 and 9 steps, with overall yields of 33%, 10% and 38%. Commercially available K^{14}CN, CH$_3$^{14}COONa and H$_2$^{18}O were used as the starting materials.

Key words: allyl alcohol, allyl vinyl ether, Carbon-14, Oxygen-18.

Introduction

^{14}C- and ^{18}O-enriched allyl alcohol were required for syntheses of ^{14}C- and ^{18}O-enriched allyl vinyl ether, which is the substrate in the aliphatic Claisen rearrangement. No method is described in the literature for preparation of ^{14}C-labeled allyl alcohol. Methods leading to specifically ^{2}H-labeled allyl alcohols have been reported, but require the reduction of labeled acryloyl chloride (1) or methyl propiolate (2). These methods were not usable for our purposes because the product is contaminated with labeled propanol that is impossible to remove by distillation. For the same reason the reduction of ^{18}O-labeled acrolein to give ^{18}O-labeled allyl alcohol (3) was not acceptable to us. Consequently, we synthesized [1-^{14}C]allyl alcohol (propanol free) as outlined in Scheme 1:

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$$\mathrm{ClCH_2CH_2OH} \xrightarrow{a} \underset{\underline{1}}{\mathrm{HOCH_2CH_2{}^{14}CN}} \xrightarrow{b} \underset{\underline{2}}{\mathrm{ClCH_2CH_2{}^{14}COOH}}$$

$$\xrightarrow{c} \underset{\underline{3}}{\mathrm{ClCH_2CH_2{}^{14}COOEt}} \xrightarrow{d} \underset{\underline{4}}{\mathrm{ClCH_2CH_2{}^{14}CH_2OH}} \xrightarrow{e}$$

$$\underset{\underline{5}}{\mathrm{ICH_2CH_2{}^{14}CH_2OH}} \xrightarrow{f} \underset{\underline{6}}{\mathrm{{}^-I(Me)_3\overset{+}{N}CH_2CH_2{}^{14}CH_2OH}} \xrightarrow{g}$$

$$\underset{\underline{7}}{\mathrm{CH_2{=}CH^{14}CH_2OH}} \text{ (overall 33%, based on } \mathrm{K^{14}CN})$$

Reagents: a, $K^{14}CN$; b, hydrochloric acid; c, EtOH, TsOH; d, $LiAlH_4$, $AlCl_3$; e, NaI, acetone; f, Me_3N in ethanol; f, AgOH, and heating.

Scheme 1

When 2-chloro[1-^{14}C]ethanol (4) was used as the starting material, we obtained [3-^{14}C]allyl alcohol with an overall yield of 10%, based on sodium [1-^{14}C]acetate (Scheme 2).

$$\mathrm{CH_3{}^{14}COONa} \longrightarrow \longrightarrow \underset{\underline{8}}{\mathrm{ClCH_2{}^{14}CH_2OH}} \longrightarrow \longrightarrow \underset{\underline{9}}{\mathrm{{}^{14}CH_2{=}CHCH_2OH}}$$

Scheme 2

To synthesize ^{18}O-labeled allyl alcohol, a slightly different route was used (Scheme 3):

$$\mathrm{ClCH_2CH_2CN} \xrightarrow{a} \underset{\underline{10}}{\mathrm{ClCH_2CH_2C^{18}OOEt}} \xrightarrow{b} \underset{\underline{11}}{\mathrm{ClCH_2CH_2CH_2{}^{18}OH}}$$

$$\longrightarrow \longrightarrow \underset{\underline{12}}{\mathrm{CH_2{=}CHCH_2{}^{18}OH}} \text{ (overall 38%, based on } \mathrm{H_2{}^{18}O})$$

Reagents: a, $H_2{}^{18}O$, EtOH, $HCl_{(g)}$; b, $LiAlH_4$, $AlCl_3$.

Scheme 3

Experimental

3-Hydroxypropio[1-^{14}C]nitrile (<u>1</u>) and **3-chloro-[1-^{14}C]propionic acid** (<u>2</u>) were synthesized as described previously (4).

Ethyl 3-chloro[1-^{14}C]propionate (3).

To 16.5 g (0.152 mol) of 3-chloro[1-^{14}C]propionic acid (15 mCi/mol) dissolved in 150 mL of benzene, were added 25 mL (0.426 mol) of anhydrous ethanol and 0.87 g of p-toluenesulfonic acid. The mixture was refluxed for 20 h, while a Dean-Stark trap was used to collect water. The benzene solution was cooled to room temperature and was washed with sodium bicarbonate solution followed by water. The solution was dried over $MgSO_4$ and evaporated. Distillation gave 16.9 g (0.123 mol, 81%, 15 mCi/mol) of ethyl 3-chloro[1-^{14}C]-propionate, bp 160 °C.

3-Chloro[1-^{14}C]propanol (4).

To a suspension of 7.10 g of lithium aluminum hydride in anhydrous diethyl ether cooled to 0 °C was slowly added a solution of 8.20 g of anhydrous aluminum chloride in diethyl ether. The mixture was stirred at 0 °C for 1 h. Then 16.9 g (0.123 mol) of ethyl 3-chloro-[1-^{14}C]propionate (15 mCi/mol) dissolved in ether was added dropwise. After addition was complete the mixture was stirred at 0 °C for 4 h. Dilute hydrochloric acid solution was added and the product was extracted into diethyl ether. The ether solution was dried over $MgSO_4$ and evaporated. Distillation under normal pressure gave 10.4 g (0.096 mol, 78%, 15 mCi/mol) of 3-chloro[1-^{14}C]propanol. After distillation 5.70 g of unlabeled 3-chloropropanol was placed in the distillation apparatus and distilled into the labeled product, giving 15.9 g (0.146 mol, 10 mCi/mol) of 3-chloro[1-^{14}C]propanol, bp 155 °C.

3-Iodo[1-^{14}C]propanol (5).

A solution of 58.0 g of sodium iodide in 400 mL of anhydrous acetone was heated to boiling and 15.9 g (0.168 mol) of 3-chloro-[1-^{14}C]propanol (10 mCi/mol) was added dropwise. Heating and stirring were continued for 24 h after which the mixture was cooled and the acetone was evaporated. Water was added and the product was extracted into diethyl ether. The ether layer was dried over $MgSO_4$ and evaporated to give 31.2 g (0.168 mol, 100%, 10 mCi/mol) of 3-iodo[1-^{14}C]propanol.

3-Trimethylammonium[1-^{14}C]propanol iodide (6).

To 100 mL of a 33%-solution of trimethylamine in ethanol was added 31.2 g (0.168 mol) of 3-iodo[1-^{14}C]propanol (10 mCi/mol). The mixture was kept at room temperature for 24 h to precipitate 38.3 g

(0.156 mol, 75%, 10 mCi/mol) of 3-trimethylammonium[1-^{14}C]-propanol iodide, mp 197-200 °C, after air drying, (lit(5) mp 200-203 °C).

[1-^{14}C]Allyl alcohol (7).

Silver oxide was prepared from 55 g of silver nitrate and 26 g of sodium hydroxide, and suspended in 500 mL of distilled water containing 38.3 g (0.156 mol) of 3-trimethylammonium[1-^{14}C]-propanol iodide (10 mCi/mol). The suspension was stirred at room temperature for 24 h. The silver salt was filtered off and washed with distilled water until the pH of the washings was 7. The water solution was evaporated under reduced pressure, to give a brown residue which was heated slowly to 160 °C. Water, trimethylamine and [1-^{14}C]allyl alcohol distilled. The distillate was then extracted continuously with diethyl ether for 24 h. The ether extract was dried over anhydrous K_2CO_3 overnight. Distillation of the ether under normal pressure gave 6.4 g (0.11 mol) of crude [1-^{14}C]allyl alcohol. To this was added 4.0 g of unlabeled allyl alcohol and the mixture was dried over anhydrous K_2CO_3 for 3 days. Distillation under normal pressure gave 9.62 g (0.166 mol, 70%, 6 mCi/mol) of 7, bp 95 °C.

[3-^{14}C]Allyl alcohol (9).

2-Chloro[1-^{14}C]ethanol (8). Sodium [1-^{14}C]acetate (4.1mCi/mmol) was heated with 95% stearic acid to give [1-^{14}C]acetic acid (6) which was then converted into [1-^{14}C]chloroacetic acid (77%). Esterification with ethanol gave ethyl chloro[1-^{14}C]acetate (96%) , which was reduced to 2-chloro[1-^{14}C]ethanol (8) in 86% yield (4). Then, following the procedures already described, the following compounds were prepared: 3-hydroxy[3-^{14}C]propionitrile (64%), 3-chloro-[3-^{14}C]propionic acid (79%), ethyl 3-chloro[3-^{14}C]propionate (88%), 3-chloro[3-^{14}C]propanol (92%), 3-iodo[3-^{14}C]propanol (100%), 3-trimethylammonium[3-^{14}C]propanol iodide (75%). The latter was converted into 9 in 57% yield.

[1-^{18}O]Allyl alcohol (12).

Ethyl 3-chloro[^{18}O-carbonyl]propionate (10) was prepared as follows. Hydrogen chloride was bubbled through a mixture containing 8.0 mL (0.10 mol) of 3-chloropropionitrile, 1.8 mL (0.10 mol) of 50% ^{18}O-labeled water and 20 mL of anhydrous ethanol until TLC shown no nitrile to be present. The hydrogen chloride supply was disconnected and the mixture was refluxed for 2 h. After the mixture was cooled to room temperature, 50 mL of diethyl ether was added and the ammonium chloride that precipitated was filtered off. Solvents were evaporated, and the residue was dissolved in diethyl ether. The ether solution was washed with water followed by dilute sodium bicarbonate solution and water, dried over $MgSO_4$ and evaporated. Distillation gave 9.20 g (0.067 mol, 67%, 50% ^{18}O-carbonyl labeled) of ethyl 3-chloro[^{18}O-carbonyl]propionate, bp 158 °C.

3-Chloro[1-^{18}O]propanol (11) and its conversion to 12. The ethyl 3-chloro[^{18}O-carbonyl]propionate was reduced to 3-chloro[1-^{18}O]propanol in 86% yield using the same procedure as described for compound 4. Thereafter, the following were prepared: 3-iodo[1-^{18}O]propanol (100%), 3-trimethylammonium[1-^{18}O]propanol iodide (91%). The latter was converted into 12 in 72% yield.

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