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SYNTHESIS OF ^{14}C-LABELED ESCHENMOSER'S SALT: DIMETHYL([^{14}C]METHYLENE)AMMONIUM IODIDE.

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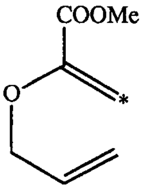
Summary

A six step synthesis of dimethyl([^{14}C]methylene)ammonium iodide (Eschenmoser's salt) is described. Sodium [2-^{14}C]acetate was used as the starting material. The overall yield of the final product was 30% with specific activity 8 mCi/mol.

Key words: Eschenmoser's salt, carbon-14, iodoform, methylene iodide.

Introduction

In the course of studies on the mechanism and transition structure of the aliphatic Claisen rearrangement, samples of specifically-labeled 2-methoxycarbonyl-3-oxa-1,5-hexadiene were needed. The synthetic route to 2-methoxycarbonyl-3-oxa-1,5-[1-^{14}C]hexadiene (1) required the use of ^{14}C-labeled Eschenmoser's salt (2), which, to our knowledge was, hitherto, unknown. We now report the synthesis of 2.



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$*CH_2{=}N(CH_3)_2I$ 2

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Discussion

Synthesis of 2 was carried out as shown in Scheme 1.

Scheme 1

$$^{14}CH_3CO_2Na \xrightarrow{a} {}^{14}CH_3COCl \xrightarrow{b} {}^{14}CH_3COC_6H_5 \xrightarrow{c}$$

$$^{14}CHI_3 \xrightarrow{d} {}^{14}CH_2I_2 \xrightarrow{e} [(CH_3)_3N^{14}CH_2I]I \xrightarrow{f} \underline{2}$$

Reagents: a, phthaloyl chloride; b, benzene, $AlCl_3$; c, KI, 5% NaClO; d, As_2O_3, NaOH; e, $(CH_3)_3N$ in ethanol; f, sulfolane and heating.

Commercially available sodium [2-^{14}C]acetate was converted to [2-^{14}C]acetyl chloride by reaction with phthaloyl chloride (1). Friedel-Crafts reaction with benzene and anhydrous aluminium chloride gave [^{14}C]acetophenone in excellent yield.

Subsequent treatment with a solution of sodium hypochlorite and potassium iodide (2) gave [^{14}C]iodoform. It is worth noting that in the method used here the ^{14}C label is fully utilised; in contrast, had we used [1-^{14}C]acetone for preparing [^{14}C]iodoform, half of the label would have been lost as acetic acid.

[^{14}C]iodoform was reduced to [^{14}C]methylene iodide by reaction with sodium arsenite in alkaline solution (4). Crude [^{14}C]methylene iodide was used in preparation of ([^{14}C]iodomethyl)trimethylammonium iodide which was later suspended in anhydrous tetramethylene sulfone (sulfolane) and heated at about 150 °C to give [^{14}C]Eschenmoser's salt (5).

Experimental

[2-^{14}C]Acetyl chloride was prepared in 83% yield using the procedure described in literature (1).

[^{14}C]Acetophenone.

To a mixture of 50 mL of anhydrous benzene (distilled from calcium hydride) and 11 g (0.083 mol) of anhydrous aluminium chloride, cooled in an ice-water bath, 5.0 g (0.064 mol) of freshly prepared [2-^{14}C]acetyl chloride was added dropwise. After addition was complete the reaction mixture was refluxed for 0.5 h, cooled to room temperature and poured onto crushed ice mixed with 10 mL of concentrated hydrochloric acid. The benzene layer was separated, washed with water, 1 N sodium hydroxide, water followed by brine, and dried over magnesium sulfate. The benzene was evaporated and the product was distilled under normal pressure at 200-205 °C to give 6.54 g (0.054 mol, 85%, 32 mCi/mol) of [^{14}C]acetophenone.

[^{14}C]Iodoform.

To a solution of 36 g (0.24 mol) of potassium iodide in 110 mL of distilled water, was added 100 mL of diethylene glycol followed by 6.54 g (0.054 mol) of [^{14}C]acetophenone (32 mCi/mol). The reaction mixture was cooled in an ice-water bath while being stirred, and 200 mL of 5% solution of sodium hypochlorite was added during 1 hour. Stirring was continued for 1 hour at room temperature, after which 200 mL of water was added and the resulting yellow solid was filtered and crystallized from ethanol to give 13.1 g (0.033 mol, 61%, 32 mCi/mol) of [^{14}C]iodoform, mp 119-120 °C (dec), (lit (2) mp 119 °C).

[^{14}C]Methylene iodide.

A solution of sodium arsenite was prepared from 3.55 g of arsenious oxide and 7 g of sodium hydroxide dissolved in 35 mL of distilled water. A mixture of half of this solution and 13.1 g (0.033 mol) of [^{14}C]iodoform (32 mCi/mol), was placed in the reaction flask and heated to 60-65 °C. Then, the rest of sodium arsenite solution was added dropwise and the reaction mixture was stirred at 60-65 °C for 1 hour and cooled to 50 °C. The lower layer containing [^{14}C]methylene iodide separated. The aqueous layer was removed, cooled to room temperature, extracted with diethyl ether and the ether extract was combined with [^{14}C]methylene iodide.

The ether solution of [^{14}C]methylene iodide was washed with water and dried over calcium chloride protected from light overnight. The ether was evaporated under reduced pressure to give 8.38 g (0.031 mol, 95%, 32 mCi/mol) of [^{14}C]methylene iodide.

([^{14}C]Iodomethyl)trimethylammonium iodide.

The [^{14}C]methylene iodide was diluted with 25.1 g of unlabeled methylene iodide. The diluted reagent was added to a mixture containing 75 mL of 33% solution of trimethylamine in ethanol, 50 mL of anhydrous ethanol, and 15 mL of dioxane, and was left in the dark at room temperature for 10 days. The product which precipitated was filtered , washed with diethyl ether and air dried to give 39.7 g (0.121 mol, 97%, 8 mCi/mol) of ([^{14}C]iodomethyl)-trimethylammonium iodide, mp 180-185 °C/ca. 240 °C (dec.), lit (5) mp 190 °C/ca.240 °C (dec.).

Dimethyl([^{14}C]methylene)ammonium iodide (Eschenmoser's salt).

A suspension of 39.7 g (0.12 mol) of ([^{14}C]iodomethyl)trimethylammonium iodide (8 mCi/mol) in 125 mL of tetramethylene sulfone (distilled from calcium hydride) was heated under a stream of argon to 160 °C. The solid dissolved at about 130 °C; methyl iodide, which was formed in the reaction, was removed by the argon stream and collected in a cold trap. Decomposition was complete in about 20 min. The mixture was then cooled in an ice-water bath, and the product which crystallized was filtered, washed quickly with anhydrous carbon tetrachloride, and dried under vacuum to give 17.3 g (0.093 mol, 77%, 8 mCi/mol) of dimethyl([^{14}C]methylene)ammonium iodide, mp 240 °C (dec.), lit(5) mp 240 °C (dec.).

Acknowledgement

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References

1. Lawson J. A. ; Colwell W. T.; DeGraw J. I.; Peters R. H.; Dehn R. L.; Tanabe M.- Synthesis 1975: 729.
2. Baker K. V.; Brown J. M.; Cooley N. A.- J. Labld. Compd. Radiopharm. 25: 1229 (1988).
3. Jones A. R.- J. Labld. Compd. 11: 77 (1975).
4. Vogel A. I.- Practical Organic Chemistry, J. Wiley, N.Y. 1962, p. 300.
5. Schreiber J.; Maag H.; Hashimoto N.; Eschenmoser A.- Angew. Chem. Int. Ed. Engl. 10: 330 (1971).