

SYNTHESIS OF 16-IODO-CARBOXYL-¹⁴C₁₆HEXADECANOIC ACID

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SUMMARY

Iodo-hexadecanoic acid labelled with carbon 14 in the carboxyl group was obtained with good yield in three steps from [¹⁴C] NaCN using bromopentadecyl tetrahydropyranyl ether **2**. Specific radioactivity: 0.0166 mCi/mg; 6.34 mCi/mmol. Radiochemical yield: 69.6 % of the theoretical amount.

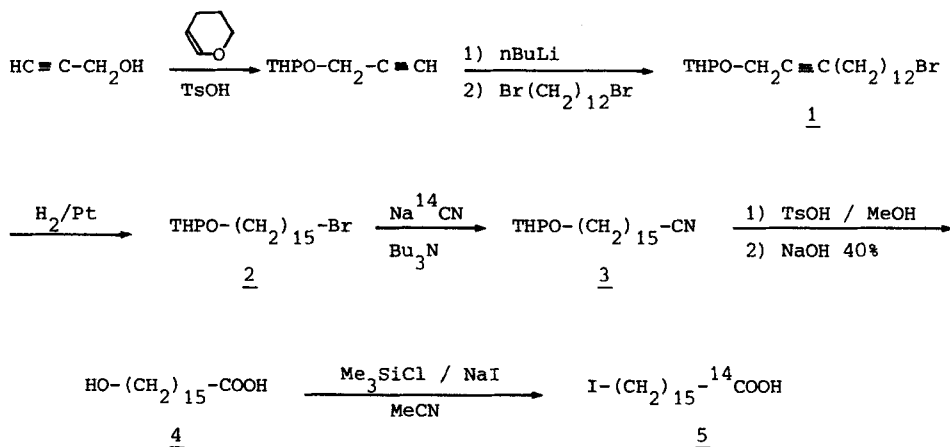
Key Words: Labelled fatty acid, ¹⁴C fatty acid, Iodised fatty acid.

INTRODUCTION

In order to investigate myocardic metabolism of fatty acids, ¹⁴C-labelled iodo-hexadecanoic acid was synthesized with good yield from sodium [¹⁴C]-cyanide (25 mCi). The starting material **1** was obtained by an original method from dibromododecane and a protected propargylic alcohol. The labelling reaction started with sodium cyanide and was carried according to a phase transfer catalysis process (1). This method allowed a minimal cyanide ratio (1.2 equivalent with regard to bromide compound **2**) to be used without a reduction in yield and the purification of **3** was easily achieved. Silylation and iodation were carried out to afford the title compound **5** in good yield.

EXPERIMENTAL:

Infrared spectra (IR) were recorded on thin film using Perkin Elmer Spectrometer model 397. NMR spectra were obtained as CDCl_3 solution using a Bruker WP 80 spectrometer. Radioactivity measurement was performed on an Intertechnique ABAC SL 40 Liquid Beta Scintillation Spectrometer. Thin layer chromatography (TLC) utilized silicagel 1R2F F&W Flex plate and column chromatography was carried out from Merck Kieselgel 60 (ASTIM 70-230 mesh). Elemental analyses were performed by the Central Analytical Service of the C.N.R.S.



THP = Tetrahydropyranyl

Scheme 1: Synthetic pathway

Solvents were redistilled just before utilization from lithium aluminium hydride for tetrahydrofuran (THF) and from calcium hydride for hexamethyl phosphoric triamide (HMPT). $^{14}\text{C}[\text{NaCN}]$ (25 mCi, 41 mCi/mmol) was purchased from C.E.A. (Saclay).

15-Bromo-2-pentadec-2-yn-1-tetrahydropyranyl ether 1:

In a dry 250 ml flask equipped with a dropping funnel, a thermometer, a septum and a magnetic stirrer, was placed a solution of 7 g (0,05 mol) of pro-2-yn-1-tetrahydropyranyl ether in 50 ml of dry THF under argon (2). The mixture was cooled to 0°C and 1 equivalent of a solution of *n*-butyl lithium in hexane was added dropwise, the temperature being kept below 10°C. To the red solution, HMPT (10 ml, 0.056 mol) was added by syringe. After stirring at room temperature for 0.5 h., the solution was transferred to a dropping funnel under argon and added over 2 h. to a magnetically stirred solution of 32.8 g (0,1 mol) of 1,12-dibromododecane. The temperature was kept between 20°C and 25°C. After 3 h, a TLC showed completion of the reaction. The mixture was then hydrolysed by 300 ml of saturated NH₄Cl solution and extracted with pentane (4 x 100 ml). The combined extracts were washed with water (2 x 100 ml). After drying over anhydrous sodium sulphate, removal of the solvent under vacuum gave 35.1 g of an oil which was purified by chromatography on silicagel using pentane-ethyl acetate (9.5:0.5) to give 20.6 g of 1,12-dibromododecane, 11.9 g (62 %) of 1 and 1.1 g of a minor by-product.

Compound 1: IR 2280, 2230, 1040 cm⁻¹; nmr δ ppm 1.1-2.3 (m, 28 H); 3.1-3.8 (t and m, 4 H), 4.1 (m, 2 H), 4.7 (m, 1H). Anal. calc. for C₂₀H₃₅BrO₂: C, 62.01; H, 9.04; Br, 20.67; Found: C; 62.03; H, 9.24; Br, 20.53. The minor product was obtained by reaction on both side of the starting material as showed by its nmr spectra: δ ppm: 1.2-1.9 (m, 32 H), 2.1-2.4 (m, 4 H), 3.3-4.1 (m, 4 H), 4.2 (m, 4 H), 4.8 (m, 2 H).

15-Bromo-pentadecyl-1-tetrahydropyranyl ether 2:

Compound 1 (11.6 g, 0.03 mol) and 50 mg of PtO₂ was added to 200 ml of ethyl acetate and the mixture hydrogenated with H₂ at atmospheric

pressure. The reduction took 2 h-2.5 h. After filtration of the catalyst and concentration of the mixture, compound **2** was obtained in 98 % yield. I.R.:

1025; nmr δ ppm 1.1-2.2 (m, 32 H), 3.1-4 (t and m, 6 H), 4.3-4.6 (m, 1 H).

Anal. Calc. for $C_{20}H_{39}BrO_2$: C, 61.38; H, 9.97; Br, 20.46; Found: C, 61.46; H, 10.17; Br, 20.32.

16-(2-Tetrahydroxypranyl)-oxy-hexadecanitrile **3**:

A mixture of **2** (3.91, 0.01 mol), 33 % aqueous NaCN (2 ml, 0.012 mol) and a few drops of tributylamine as a catalyst was refluxed and vigorously stirred at 100°C for 24 h. At this time, a TLC showed completion of the reaction.

After cooling, the solid was filtered and purified by chromatography on silicagel using hexane-ethyl acetate to give 2.99 g (89 %) of **3**.

Mp. = 46°-47°C. I.R.: 2240, 1015; nmr δ ppm: 1.2-2.9 (m, 32 H), 2.3 (t, 2 H), 3.2-4.1 (m, 4 H), 4.6 (m, 1 H). Anal. Calc. for $C_{21}H_{39}NO_2$: C, 74.77; H, 11.57; N, 4.15; O, 9.49. Found: C, 74.43; H, 11.70; N, 4.23; O, 9.29.

The labelled nitrile was prepared in the same manner using 25 mci of [^{14}C]NaCN (0.61 mmol) in 0.8 ml of water, 199 mg (0.507 mmol) of **2** and the same phase transfer catalyst. Extraction with ether, drying over anhydrous sodium sulphate and removal of the solvent under reduced pressure gave a white solid, 170 mg (99 %).

16-Hydroxy- [carboxyl- ^{14}C]hexadecanoic acid **4**:

Into a 20 ml flask, fitted with a condenser, was placed a solution of the labelled nitrile (0.507 mmol, 170 mg) and of the unlabelled material (2.28 mmol, 770 mg) in 5 ml of methanol. After addition of a little amount of p-toluene sulfonic acid, the solution was stirred for 5 h. at room temperature and 10 ml of 40 % aqueous NaOH was then poured into the flask. The mixture was refluxed for 24 h. After cooling, neutralization by addition of 12 N HCl and work up, 750 mg (99 %) of 16-hydroxy- [carboxyl- ^{14}C]hexadecanoic acid was obtained. Mp. = 96°C.

16-Iodo-carboxyl-¹⁴C hexadecanoic acid 5 (3):

The hydroxyacid **4** (750 mg, 2.78 mmol) was dissolved by heating in 20 ml of freshly distilled acetonitrile. Sodium iodide (1.8 g, 12 mmol) and trimethylsilyl chloride (1.55 ml, 12 mmol) was added and the brown mixture heated under reflux at 70°C for 90 mn. After cooling, 50 ml of 20 % sodium thiosulphate was added to remove the excess of iodine. Extraction with ether, drying over anhydrous sodium sulphate and removal of the solvent under reduced pressure gave 1050 mg (98 %) of white labelled 16-iodo-hexadecanoic acid. TLC (chloroform-acetone 80:20) confirmed the purity and the identity with the unlabelled compound. R_f = 0.8, M_p. = 74°C. Specific radioactivity: 0.0166 mCi/mg; 6.34 mCi/mmol. Overall radiochemical yield: 69.6 % of the theoretical amount.

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