SYNTHESIS OF [$^{14}C_1$]SQUARIC ACID

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The title work proceeds in five steps and 16% overall yield from sodium [1-^{14}C]acetate, which was converted by bromination followed by ethoxide displacement and reaction with phthaloyl dichloride to ethoxy[1-^{14}C]acetyl chloride. The thermal[2+2]cycloaddition of tetraethoxyethene with ethoxy[1-^{14}C]ketene, derived from base induced elimination from ethoxy[1-^{14}]acetyl chloride following the method of Bellus, provided an 80% yield of 1-(ethoxy[1-^{14}C]acetoxy)-2,3,3,4,4-pentaethoxy-1-[1-^{14}C]-cyclobutene. Acid hydrolysis and liquid-liquid extraction afforded [^{14}C]squaric acid.

Keywords: [$^{14}C_1$]Squaric acid; 1,2-dihydroxy[$^{14}C_1$]cyclobutene-3,4-dione; Ethoxy[1-^{14}C]ketene

INTRODUCTION

Squaric acid is a simple looking molecule which has captured the interest of many researchers since its discovery in 1959[1]. Its unique structure and chemistry have made investigations of the physical and biochemical properties of it and its relatives particularly intriguing[2,3]. Its synthesis[4] and wide-ranging reactivity have been reviewed[5], and its use, for instance, in the synthesis of zwitterionic dyes[6] is notable.

The synthesis of ^{14}C-labeled squaric acid reported here is based on the work of Bellus[7], which, of the many reported syntheses, appeared to be the most amenable to incorporation of a carbon isotopic label.

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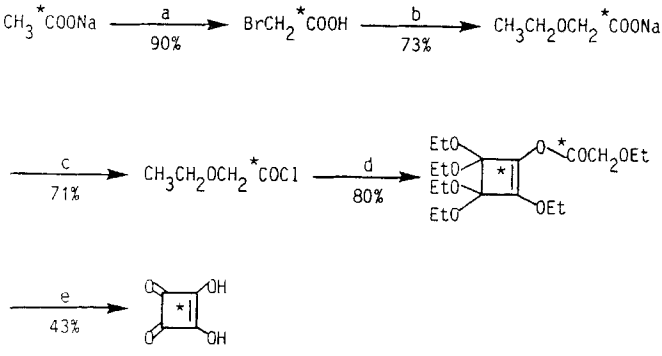
0362-4803/84/050409-05$01.00

Received August 23, 1983
Revised January 9, 1984

RESULTS AND DISCUSSION

The synthesis is outlined in the Scheme below. Bromination of sodium [1-^{14}C]acetate[8] was followed by displacement of bromide by ethoxide anion to provide ethoxy[1-^{14}C]acetic acid sodium salt. Triethylamine induced dehydrochlorination and *in situ* condensation[9] of the resultant ethoxy[1-^{14}C]ketene with tetraethoxyethene[10] in refluxing hexane, followed by esterification of the intermediate cyclobutenol by a second equivalent of acid chloride, resulted in an 80% yield of 1-(ethoxy[1-^{14}C]acetoxy)-2,3,3,4,4-pentaethoxy-1-[1-^{14}C]cyclobutene as a clear solution in hexane. Hydrolysis of the ester with aqueous HCl, followed by liquid-liquid extraction with ether yielded 11.2 mCi of [$^{14}C_1$] squaric acid (specific activity 7.27 mCi/mmole) as a white solid. The structure was confirmed by mass and UV-visible spectral comparison with an authentic unlabeled standard. Recovery of the second ethoxy[1-^{14}C]acetate equivalent released upon hydrolysis of the cyclobutene ester can potentially double the radiochemical yield of final product.



Steps: a) Br_2, P, AcCl, HCl; b) NaOEt, Et_2O; c) phthaloyl chloride, 120°; d) tetraethoxyethene, Et_3N, n-hexane, reflux; e) 6NHCl, 100°, 30 min.

EXPERIMENTAL

Sodium [1-^{14}C]acetate was obtained by carbonation of methylmagnesium bromide using $^{14}CO_2$, followed by standard workup procedures. Radioactivity measurements were carried out using Packard Tricarb 2425 and Beckman Model LS100C liquid scintillation spectrometers and Liquifluor (New England Nuclear) or 4a20 (Research Products International) cocktails. TLC analyses were carried out using Merck silica gel 60 F254 plates and radiochromatogram scans were performed on a Packard Model 7201 radiochromatogram scanner.

[$^{14}C_1$]Squaric Acid

Into a 150 mL flask containing sodium [1-^{14}C]acetate (5 mmol, 138 mCi) and red phosphorus (0.26 mmol, 8 mg) were transferred sequentially, with liquid nitrogen cooling, anhydrous hydrogen chloride (5 mmol, 125 mL), acetyl chloride (0.4 mmol, 0.028 mL, dried with P_2O_5) and bromine (9 mmol, 0.47 mL, dried with P_2O_5). The flask was sealed under vacuum and heated in a 100°C bath for 5 hr. The flask was opened and the product was purified by distillation in vacuo (<1 Torr) and collected in a -18° cooled container, affording bromo[1-^{14}C]acetic acid as a white solid (645 mg, 92% mass yield).

This product was diluted with 1.51 g unlabeled bromoacetic acid, and the diluted sample (15.0 mmol) dissolved in 5 mL ether. The solution was added dropwise to a solution of sodium metal (40 mg-atoms, 0.921 g) in absolute ethanol (30 mL). The ether was distilled off and the mixture was refluxed for 3 hrs, at which time TLC analysis (SiO_2, nBuOH: HOAc: H_2O, 50:5:10, R_f=0.44) showed no precursor remaining. The inorganics were removed by filtration under argon gas and the solvent was evaporated in vacuo. After vacuum drying (<1 Torr at 110°C for 2.5h), sodium ethoxy[1-^{14}C]acetate was obtained as an off-white solid (90.6 mCi, 73% yield).

To sodium ethoxy[1-^{14}C]acetate (11.3 mmol, 90.6 mCi) under an atmosphere of dry nitrogen, was quickly added phthaloyl dichloride (226 mmol, 33 mL). The flask was connected through a reflux condensor through two traps to the vacuum manifold. The reaction mixture was first heated to 80°C for 1 hr under slight vacuum, then to 120°C in 40 min and kept at 120°C for an additional 1 hr. The product was distilled slowly (in vacuo) into the Dry Ice/acetone cooled trap, first at ambient temperature, later at 70°C, affording 1.75 mL of clear oil. The oil was redistilled in vacuo at ambient temperature, yielding 1.60 mL of ethoxyl[1-^{14}C]acetyl chloride (clear oil, 9 mmol, 63.8 mCi, 71% yield).

To a refluxing solution of tetraethoxyethene[10] (4.5 mmol, 0.917 g) and triethylamine (10.5 mmol, 1.45 mL) in hexane (11.6 mL) was added dropwise (0.5 hr) a solution of ethoxy[1-^{14}C]acetyl chloride (9 mmol, 63.8 mCi) in n-hexane (4 mL). The mixture was refluxed for 4 hr after the addition and stirred overnight at ambient temperature. The resulting solid was filtered off, the filtrate (assay: 51.6 mCi) was washed with sodium chloride solution, concentrated in vacuo and used directly in the next step.

Hydrochloric acid (80 mL, 6N) was added to the product from the last step and the mixture heated to 100°C for 30 min. The aqueous solution was liquid-liquid extracted with ether overnight, and the crystalline product was isolated by filtration. The yield of [$^{14}C_1$]squaric acid as an off-white solid was 176 mg, 11.2 mCi (UV/gravimetric analysis), representing a 43% yield. Mass spectrum: Z(%), 114/116 (M+, 100/14.2), 86(47.7), 58 (46.2), 29 (54.0); UV-Vis (H_2O): E_{253} = 26,200 sh, E_{267} = 27,400.

ACKNOWLEDGEMENT

The authors express their gratitude to Mr. Richard Elliott for the preparation of tetraethoxyethene.

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