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A CONVENIENT PREPARATION OF GLYCOLIC-1-^{14}C ACID

Lane A. Clizbe* and Elmer J. Reist

SRI International
Bio-Organic Chemistry Laboratory
333 Ravenswood Ave.
Menlo Park, CA 94025

SUMMARY

An operationally simple preparation of glycolic-1-^{14}C acid from $^{14}CO_2$ has been developed using a tin-lithium exchange reaction to generate the required hydroxymethyl anion equivalent. Glycolic-1-^{14}C acid was then produced in high yield and good radiochemical purity upon hydrogenolytic removal of the benzyl group.

Key Words: Glycolic-1-^{14}C acid, benzyloxymethyllithium, tin-lithium exchange

INTRODUCTION

In conjunction with a variety of projects in our laboratory, we needed a simple synthesis of glycolic-1-^{14}C acid from $^{14}CO_2$. There have been few reports in the literature[1] on the preparation of this particular labelled intermediate, and it was obvious from the outset that the classical synthesis[2] would be far too cumbersome for our needs. This route proceeds through a Hell-Volhard-Zelinski reaction with acetic-1-^{14}C acid to make chloroacetic-1-^{14}C acid, and then by treatment with $CaCO_3$, giving glycolic-1-^{14}C acid. The most promising recent synthesis[3] involved reaction of the Grignard reagent from benzyl chloromethyl ether with $^{14}CO_2$. However, the preparation of Grignard reagents from chloromethyl ethers is notoriously inconsistent, as evidenced by the paucity of references to their preparation[4], and in our hands, that route gave poor yields of impure product. Moreover, the synthesis of benzyl chloromethyl ether[5] gives varying amounts of benzyl chloride as a contaminant, which can be difficult to remove completely by distillation. This is not usually a problem in its use as a benzyloxymethylating agent, but is highly undesirable when the objective is the preparation of a Grignard reagent. We therefore sought alternative chemistry that utilized more easily purifiable intermediates. Among a number of hydroxymethyl anion synthons in the literature[6], we decided to employ the tin-lithium exchange reaction reported by Still and others[7] for this purpose.

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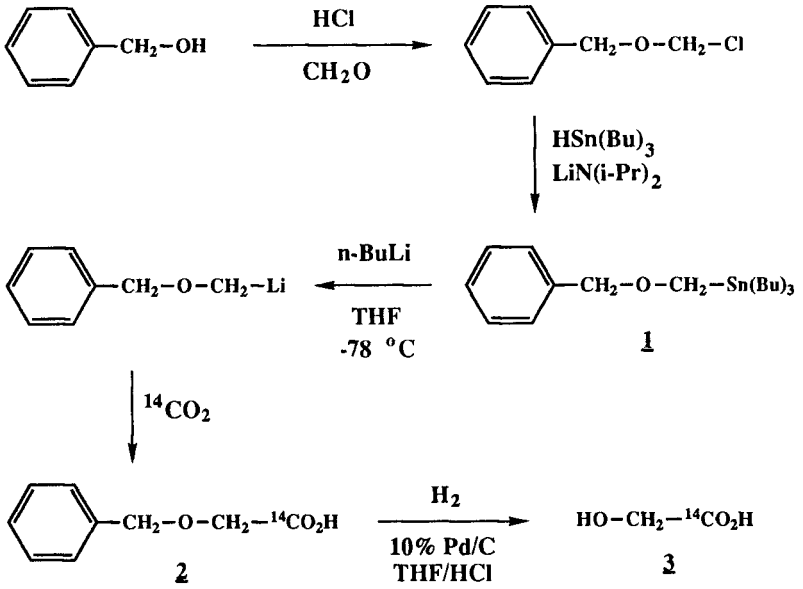
Scheme: Synthesis of Glycolic-1-^{14}C acid



CHEMISTRY

There are several reports in the literature describing the synthesis of (benzyloxymethyl)-tributylstannane[7a] (1); we have also found that it can be prepared from benzyl chloromethyl ether[5] and the tributylstannyl anion (see Experimental Section). This stannane is easily purified and characterized, and has good long-term storage stability. The desired benzyloxymethyllithium was produced cleanly by an exchange reaction with n-butyllithium in anhydrous THF at low temperature, and it condensed readily with $^{14}CO_2$ (generated from $Ba^{14}CO_3$ and concentrated H_2SO_4) to give a 78% isolated yield of glycolic-1-^{14}C acid benzyl ether (2) with a radiochemical purity of 94.5 % (see Scheme). Hydrogenolysis of the benzyl ether in tetrahydrofuran containing a few drops of HCl, using 10% Pd/C catalyst, occurred smoothly to give glycolic-1-^{14}C acid (3) in 97% yield and in 96.6% radiochemical purity. Because of poisoning, it was usually necessary to add a second batch of catalyst, after which the reduction would proceed rapidly. In practice, the crude glycolic-1-^{14}C acid was used without further purification.

In summary, then, we wish to report an operationally simple synthesis of glycolic-1-^{14}C acid which allows the preparation of this useful radiolabelled intermediate in reliably good yield and in high radiochemical purity.

EXPERIMENTAL SECTION

General

^{1}H NMR spectra were obtained on unlabelled compounds only and were recorded in $CDCl_3$ on a Varian Gemini - 300 mHz spectrometer, referenced to TMS. $Ba^{14}CO_3$ was obtained

from Wizard Laboratories, W. Sacramento, CA, at a specific activity of 58 mCi/ mmol. Thin layer chromatograms were obtained using Whatman Silica Gel 60 A LK6F 5 x 20 cm plates. Authentic samples were included in chromatograms as confirmation of compound identity. Radiochemical purity determinations were made using a Bioscan QC-Scan thin layer chromatography radioscanner. Specific acitivity determinations were made by liquid scintillation counting.

Synthesis of Tributyl[(phenylmethoxy)methyl]stannane (1)

A solution of 5.31 g (52.5 mmol) of diisopropylamine in 100 mL of anhydrous THF under argon was cooled with an ice-water bath, and was treated dropwise with 38 mL of n-butyllithium (49.4 mmol, 1.3 M solution in hexanes). The reaction mixture was stirred for 5 min, then 14.55 g (13.5 mL, 50 mmol) of tributyltin hydride was added dropwise over a few minutes. The reaction mixture was stirred for 15 min, then cooled with a dry ice-acetone bath, and a solution of 15.66 g (100 mmol) of benzyl chloromethyl ether[5] in 15 mL of dry THF was added dropwise over 15 min. The reaction mixture was stirred in the cold for 45 min, then quenched by the addition of 100 mL of water. The reaction mixture was extracted with 2 x 100 mL of hexanes, and the combined extracts were dried over anhydrous sodium sulfate. Filtration and concentration gave a yellow oil, which was washed through a plug of silica gel in a sintered glass funnel with 200 mL of 5% ethyl acetate in hexanes. Concentration then gave 23.3 g of a clear, nearly colorless oil. Vacuum distillation afforded 15.73 g (77%) of stannane 1 as a colorless oil (bp 126-144 °C/0.1 mm): NMR (δ^{CDCl_3}) 7.33 (m, 5H), 4.43 (s, 2H), 3.76 (s and d due to Sn coupling, 2H), 1.51 (m, 6H), 1.33 (m, 6H), 0.91 (m, 15H).

Synthesis of 2-(Phenylmethoxy)acetic-1-^{14}C acid (2)

A solution of 2.50 g (6.08 mmol) of tributyl[(phenylmethoxy)methyl]stannane (1) in 50 mL of anhydrous THF was cooled in a dry ice-acetone bath under argon, and 5.26 mL of n-butyllithium (1.14 M in hexanes, freshly titrated with diphenylacetic acid) were added dropwise over a few minutes. The light yellow solution was then stirred in the cold for 10 min. From 1.202 g (6.03 mmol, 350 mCi) of barium carbonate-^{14}C and concentrated sulfuric acid, $^{14}CO_2$ was generated. The reaction mixture was degassed with three freeze-thaw cycles (liquid nitrogen and dry ice-acetone), and the $^{14}CO_2$ was condensed into the reaction mixture by vacuum transfer using a liquid nitrogen bath. The reaction was stirred for 15 min in a dry ice-acetone bath, allowed to warm to room temperature over 1 hr, then quenched by the addition of 25 mL of sat. NH_4Cl. The solution was acidified with 25 mL of 3N HCl, extracted with 4 x 25 mL of ether, and the combined organic extracts were washed with 5 x 25 mL of 1N NaOH. The aqueous layer was acidified to pH 2 with 100 mL of 3N HCl, and extracted with 6 x 25 mL of ether. The organic extracts were dried over anhydrous sodium sulfate, decanted, and the drying agent was washed repeatedly with small amounts of ether. The combined organics were then concentrated to give 1.01 g (78% yield) of 2-(phenylmethoxy)acetic-1-^{14}C acid (2) as a clear oil: radiochemical purity 94.5%; TLC (silica gel, $CHCl_3$:CH_3OH:CH_3CO_2H 85:10:5) R_f 0.59; NMR (unlabelled compound, δ^{CDCl_3}) 7.37 (m, 5H), 4.66 (s, 2H), 4.15 (s, 2H).

Synthesis of Glycolic-1-^{14}C acid (3)

To a solution of 1.01 g (6.00 mmol) of 2-(phenylmethoxy)acetic-1-^{14}C acid (2) in 20 mL of

THF was added 3 drops of 3N HCl and 200 mg of 10% Pd/C, and the reaction mixture was placed under an atmosphere of hydrogen (balloon). After stirring overnight, the reaction was incomplete, so an additional 100 mg of 10% Pd/C was added, and the reaction was stirred for another 2 hr. Filtration and concentration gave a clear, light yellow oil, which was placed under high vacuum, to give 452 mg (97%) of glycolic-1-^{14}C acid (3) as a light yellow solid: radiochemical purity 96.6%; TLC (silica gel, $CHCl_3$:CH_3OH:CH_3CO_2H 85:10:5) R_f 0.08; specific activity: 50.6 mCi/mmol; NMR (unlabelled compound, δ^{CDCl_3}) 4.04 (s).

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