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Synthesis of *tert*-Butyl-[1-^{13}C]Glycolic Acid

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SUMMARY

A one step synthesis of *tert*-butyl-[1-^{13}C]glycolic acid was accomplished by a modification of the Corey and Eckrich procedure. *tert*-Butyl methyl ether was metallated by treatment with *sec*-butyl lithium and potassium *tert*-butoxide at -78°C. Carbonation with $^{13}CO_2$ yielded *tert*-butyl-[1-^{13}C]glycolic acid.

Keywords: *tert*-butyl-[1-^{13}C]glycolic acid; alkoxy-methyl anion; *tert*-butylmethyl ether, [^{3}C]carbon dioxide

INTRODUCTION

Glycolic acid and it derivatives can serve as a two carbon precursors for the preparation of a variety of important compounds. For example, O-alky derivatives of glycolic acid can be generated and subsequently reduced to give glycol ethers. More importantly *O*-acylated or *O*-alkylated glycolic acids have been used as precursors for the synthesis of dihydroxyacetone (DHA) and dihydroxyacetone phosphate (DHAP)[1,2]. Because DHAP is a substrate for many of aldolases, it has been used in the enzymatic synthesis of a variety of isotope-labeled sugars including 2-deoxyribose[3-5]. Thus a facile preparation of labeled glycolic acid is highly desirable. Recently O'Connor and coworkers[6] required ^{13}C-labeled glycolic acid as a precursor for the preparation of 2-phospho-[1,2-$^{13}C_2$]glycolic acid. They prepared labeled glycolic acid by treatment of commercial bromo-[1,2-$^{13}C_2$]acetic acid with sodium hydroxide. However, in an earlier report, Corey and Eckrich[7,8] described a more efficient one step route to the *tert*-butoxy-protected glycolic acid. They condensed the alkoxymethyl anion, derived from the reaction of *tert*-butyl methyl ether (**1**) with potassium *tert*-butoxide and *sec*-butyllithium, with carbon dioxide to

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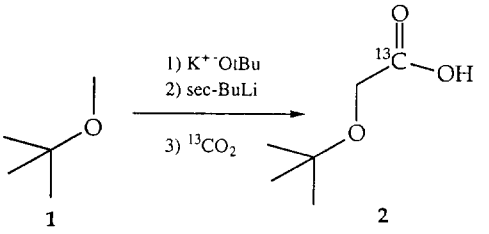
form the *tert*-butylglycolic acid (Scheme 1). We have optimized this process for labeling by limiting the quantities of the labeled precursor $^{13}CO_2$. Based on the $^{13}CO_2$ added we produced *tert*-butyl-[1-^{13}C]glycolic acid (**2**) in good yield (73%).



1 **2**

Scheme 1

RESULTS AND DISCUSSION

The anion generation was carried out essentially as described by Corey Eckrich[7,8]. However, they reported that potassium *tert*-butoxide was a suspension in *tert*-butyl methyl ether. We found that when freshly sublimed potassium *tert*-butoxide was transferred in a glove box, it dissolved to a homogeneous solution in *tert*-butyl methyl ether. To increase the yield based on the label, $^{13}CO_2$ was used as the limiting reagent raising the possibility of the addition of a second equivalent of the anion to form the corresponding ketone[7]. We found that while ketone formation occurred at higher temperatures, it was significantly suppressed at -78°C. Therefore, it was important to maintain and quench the reaction at low temperature. Straightforward purification of *tert*-butyl-[1-^{13}C]glycolic acid was accomplished by extraction under acidic conditions.

EXPERIMENTAL

Chemicals -- Treatment of ^{13}CO with CuO yields $^{13}CO_2$[9]. All other chemicals were purchased from Aldrich Chemical Co. Commercial *sec*-butyllithium (1.3 M solution in cyclohexane) was used without further purification. *tert*-Butyl methyl ether was dried by distillation from the Na^0/benzophenone under a dry argon atmosphere. Potassium *tert*-butoxide was sublimed and stored in an anaerobic glove box.

Analytical Methods –Proton (500 MHz) and proton decoupled ^{13}C NMR spectra were obtained using a Bruker AMX-500 NMR spectrometer. ^{1}H chemical shifts are reported in ppm using tetramethylsilane (0.00 ppm) as an internal reference; ^{13}C chemical shifts were referenced using the signal from $CDCl_3$ as an internal reference (δ = 77.0 ppm). Isotopic purity of *tert*-butyl-[1-^{13}C]glycolic acid was estimated from the fractional intensity of the ^{13}C satellites ($^{1}J_{C\text{-}C}$ = 60.5 Hz) on the natural abundance ^{13}C resonance from C2 of the labeled glycolic acid.

***tert*-Butyl-[1-^{13}C]glycolic acid** – This reaction was carried out in a two-necked round-bottomed flask (250 ml) that had a 24/40 ground glass joint and a 15 mm SolvSeal joint (J. Young Glass Company) connected through a Teflon valve. In an anaerobic glove box, potassium *tert*-butoxide (1.83 g, 14.98 mmol) and a magnetic stir bar were transferred into the reaction flask. The 24/40 ground glass joint was capped with a rubber septum, and the valve was closed. The sealed flask was then removed from the glove box and affixed to a stainless steal vacuum/pressure manifold through the SolvSeal joint. The flask was placed under a dry argon atmosphere, and freshly distilled *tert*-Butyl methyl ether (50 mL) was added to the flask with a syringe. The flask was cooled to -78°C with a dry ice/isopropanol bath. To this solution *sec*-butyllithium (11.5 mL, 14.98 mmol) was added dropwise over 2 minutes. The yellow-orange color of the *tert*-butyl methyl anion was immediately apparent. After an additional 2 hr of stirring the reaction mixture was an orange milky suspension $^{13}CO_2$ (0.51 g, 11.3 mmol) was placed into a stainless steal lecture bottle (250 ml) which was also affixed to the pressure/vacuum manifold. The reaction flask was evacuated, and the $^{13}CO_2$ was introduced into the reaction mixture over a 5 minute period. The $^{13}CO_2$ was added at a rate so that the pressure in the reaction flask did not exceed one atmosphere. After the addition of $^{13}CO_2$, the reaction mixture was allowed to stir for 30 min until the anion had been consumed as evidenced by dissipation of the orange color. The reaction was quenched with the addition of water (30 mL). The organic layer was extracted with additional water (2 X 30 mL). The combined aqueous layers were extracted with diethyl ether (2 X 30 mL). The aqueous layer (pH = 10) was cooled using an ice bath and methylene chloride (60 mL) was added. This two-phase solution was acidified to pH 3 by the dropwise

addition of cold aqueous hydrochloric acid (1 M). Extraction of the aqueous layer with additional methylene chloride (3 X 25 mL) gave *tert*-Butyl-[1-^{13}C]glycolic acid (1.1 g, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.05 (d, 2H, J = 5.13), 1.26 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ 175.15, 75.24, 60.18 (d, J, 60.5), 27.20.

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