PREPARATION OF *n*-BUTOXY($^{13}C_2$-ACETIC) ACID, 1-*n*-BUTOXY-2-HYDROXY($^{13}C_2$-ETHANE), (*n*-BUTOXY-2',2',3',3',4',4',4'-d_7)ACETIC ACID, AND 2-(*n*-BUTOXY-2',2',3',3',4',4',4'-d_7)ETHANOL

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Summary

(*n*-Butoxy-2',2',3',3',4',4',4'-d_7)acetic acid (1) and 2-(*n*-butoxy-2',2',3',3',4',4',4'-d_7)ethanol (2) have been prepared in high yield from *n*-butanol-2,2,3,3,4,4,4-d_7. *n*-Butoxy($^{13}C_2$-acetic) acid (3) and 1-*n*-butoxy-2-hydroxy($^{13}C_2$-ethane) (4) have also been synthesized using bromoacetic-$^{13}C_2$ acid as the source of labelled carbon. The main complication in the development of the process was partial conversion of butoxyacetic acid to butyl butoxyacetate during GC analysis, which hampered evaluation of trial reactions.

Key Words: butoxyacetic acid, 2-butoxyethanol, cellosolve, deuterium, carbon–13

Introduction

n-Butoxyacetic acid has been shown to be a metabolic product of the common glycol ether solvent 2-*n*-butoxyethanol (1). *n*-Butoxyacetic acid and 2-*n*-butoxyethanol labelled with deuterium in the butyl chain or with carbon–13 in the two-carbon segment would be useful in studying this metabolic process, however, these materials have not been previously reported in the literature. Known methods for preparing the unlabelled compounds are not economical or convenient for the small scale synthesis of the isotopically substituted materials. For instance, methods have been reported for producing 2-*n*-butoxyethanol from ethylene oxide (2), carbon

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monoxide (3), 2-chloroethanol (4), or other more complex intermediates such as tetra-*n*-butoxysilane (5), tri-*n*-butoxyborate (6), or various acetals (7). In many cases, mixtures of products are formed that are difficult to separate on a small scale 8). This problem has been solved by use of excess *n*-butanol to drive the desired reaction, although this solution is impractical when using a deuterated butanol as a reagent (9). A process that does conform to the requirements for efficient preparation of isotopically labelled 2-*n*-butoxyethanol is the reduction of the correspondingly labelled butoxyacetic acid (1).

Fewer routes are known for making *n*-butoxyacetic acid and these suffer many of the same drawbacks as the procedures for forming 2-*n*-butoxyethanol. In particular, there are examples of *n*-butoxyacetic acid synthesis involving carbon monoxide as a carbon source (10) and by oxidation of 2-*n*-butoxyethanol (11). More frequently, *n*-butoxide is used to displace the halogen of bromoacetic acid or chloroacetic acid, but an excess of the alcohol is again necessary for completion of these reactions (12). When the alcohol is deuterium labelled, use of any significant excess is unacceptable. Described herein is a process for the preparation of (*n*-butoxy-2',2',3',3',4',4',4'-d_7)acetic acid (**1**) and 2-(*n*-butoxy-2',2',3',3',4',4',4'-d_7)ethanol (**2**) in high chemical and isotopic yield beginning with *n*-butanol-2,2,3,3,4,4,4-d_7. The synthetic protocol for making *n*-butoxy($^{13}C_2$-acetic) acid (**3**) and 1-*n*-butoxy-2-hydroxy($^{13}C_2$-ethane) (**4**) is also reported. Some comments on unsuccessful efforts towards these substances are also included.

$CD_3CD_2CD_2CH_2OCH_2CO_2H$ **1** $CD_3CD_2CD_2CH_2OCH_2CH_2OH$ **2**

$CH_3CH_2CH_2CH_2O^{13}CH_2{}^{13}CO_2H$ **3** $CH_3CH_2CH_2CH_2O^{13}CH_2{}^{13}CH_2OH$ **4**

Experimental

General.

NMR spectra were obtained on a Varian VXR300 spectrometer. Infrared spectra were recorded on a Mattson Galaxy 5000 fourier transform spectrophotometer. GC/MS experiments were performed on a Hewlett Packard 5989A mass spectrometer coupled to a HP 5890A Series II gas chromatograph with a 20 m J&W DB-5MS column. Positive ion chemical ionization MS

experiments employed methane (Scott Gas, zero grade) as the ionizing reagent. Anhydrous tetrahydrofuran (THF, <0.005% water) was obtained from the Aldrich Chemical Company and was stored in the original Sure/Seal™ bottle under nitrogen. All other solvents were reagent grade, obtained from Fisher Scientific and used without further purification.

(*n*-Butoxy-2',2',3',3',4',4',4'-d_7)acetic acid (1)

Sodium hydride (Aldrich, 60% in mineral oil; 19.84 g, 496.0 mmol) was washed with hexane (3 x 30 mL), slurried in anhydrous THF (100 mL), and then heated to reflux with stirring under nitrogen. A solution of bromoacetic acid (Aldrich; 14.7662 g, 106.27 mmol) in anhydrous THF (100 mL) was added dropwise to the refluxing NaH slurry via pressure equalizing addition funnel over 90 min. (Caution! Copious evolution of hydrogen gas!) After the acid solution addition was complete, the addition funnel was charged with a solution of *n*-butanol-2,2,3,3,4,4,4-d_7 (Cambridge Isotope Laboratories; 8.0219 g, 98.82 mmol) in anhydrous THF (100 mL). The addition of the alcohol solution was allowed to occur dropwise over 60 min (gas evolution!), and the resultant thick gray slurry was heated at reflux under nitrogen for 24 h. After the reaction mixture cooled to room temperature, excess NaH was destroyed by careful addition of water (40 mL). (Caution! Copious evolution of hydrogen gas!) The crude product solution was then acidified with 12 M aq HCl (50 mL) and diluted with additional water (100 mL). The biphasic solution was then extracted with methylene chloride (350 mL) and the organic phase was washed once with satd. aq NH_4Cl (100 mL), dried (Na_2SO_4), filtered, and concentrated (30 °C/20 mm Hg). The residue thus obtained was fractionally distilled under reduced pressure to afford (*n*-butoxy-2',2',3',3',4',4',4'-d_7)acetic acid (9.9668 g, 72%): b.p. 110-119°/11 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (br s, 1H, $CO_2\underline{H}$), 4.10 (s, 2H, $O\underline{CH_2}CO_2$), 3.53 (s, 2H, $CD_2\underline{CH_2}O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 ($\underline{C}O_2H$), 71.6 ($O\underline{C}H_2CO_2H$), 67.6 ($\underline{C}H_2OCH_2CO_2H$), 30.3 (quintet, J_{C-D}=19.1, $CD_3CD_2\underline{C}D_2$), 17.7 (quintet, J_{C-D}=19.2, $CD_3\underline{C}D_2$), 12.5 (septet, J_{C-D}=19.2$C\underline{D}_3$); IR (neat) 3126 (br), 2218 (m), 1732 (s) cm^{-1}; MS (positive ion chemical ionization) *m/e* 140 (parent), 106, 94, 89, 80, 78 (base), 73, 64, 60, 50.

2-(*n*-Butoxy-2',2',3',3',4',4',4'-d_7)ethanol (2)

2-(*n*-Butoxy-2',2',3',3',4',4',4'-d_7)ethanol was prepared by the method of Jakiela and coworkers (14). Into a 250 mL round-bottomed flask fitted with reflux condenser and magnetic

stirrer was placed lithium aluminum hydride (LAH; Aldrich; 2.78 g, 73.25 mmol). The reaction vessel was purged with nitrogen and then the lithium aluminum hydride was slurried in anhydrous ether (75 mL). To the stirred LAH slurry was added a solution of (*n*-butoxy-2',2',3',3',4',4',4'-d_7)acetic acid (5.3944 g, 38.75 mmol) in THF (15 mL) dropwise via polyethylene cannula over 15 min followed by another portion of THF (10 mL). (Caution! Copious evolution of hydrogen gas!) The reaction mixture was stirred at ambient temperature under inert atomosphere for 16 h. Excess LAH was then destroyed by cautious addition of 20% aq NaOH solution (2.30 mL) followed by water (6.75 mL). (Caution! Copious evolution of hydrogen gas!) Stirring was continued for 3 h. The resultant white solid was removed from the crude product solution by filtration and washed with ether (3 x 10 mL). The combined organic solutions were concentrated on a rotary evaporator (25 °C/20 mm Hg) and the residue was distilled under reduced pressure to afford 1-(*n*-butoxy-2',2',3',3',4',4',4'-d_7)-2-hydroxyethane (4.2188 g, 87%): b.p. 56-61°/10 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (t, J=4.6 Hz, 2H, $OC\underline{H}_2CH_2OH$), 3.48 (t, J=4.7 Hz, 2H, $OCH_2C\underline{H}_2OH$), 3.42 (s, 2H, $CD_2C\underline{H}_2O$), 2.49 (br s, 1H, $O\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.8 ($O\underline{C}H_2CH_2OH$), 70.9 ($\underline{C}H_2OH$), 61.7 ($CD_2\underline{C}H_2O$), 30.5 (quintet, J_{C-D}=19.2, $CD_3CD_2\underline{C}D_2$), 17.9 (quintet, J_{C-D}=19.1, $CD_3\underline{C}D_2$), 12.6 (septet, J_{C-D}=19.6, $\underline{C}D_3$); IR (neat) 3429 (br s), 2217 (s) cm^{-1}; MS (positive ion chemical ionization) *m/e* 126 (parent), 108, 94, 92, 78, 75, 73, 64 (base), 63, 62, 60, 59.

_n_-Butoxy($^{13}C_2$-acetic) acid (3).

n-Butoxy($^{13}C_2$-acetic) acid (**3**) was prepared in similar fashion to acid **1** using 5.1777 g NaH (129.4 mmol), 4.0480 g bromoacetic-$^{13}C_2$ acid (Aldrich; 28.72 mmol), 20 mL *n*-butanol (Aldrich; 218.6 mmol), and 45 mL THF. The crude product was distilled under reduced pressure and the fraction boiling 125–137 °C at 22 mm Hg was collected. This fraction contained desired acid **3** as well as *n*-butyl *n*-butoxy($^{13}C_2$-acetate) (**5**). To saponify the ester, the collected distillate was taken up in ethanol (5.0 mL), treated with 20% NaOH (15.0 mL, 75 mmol), and heated to reflux for 2.5 h. Upon cooling to ambient temperature, the basic solution was acidified with 6 M HCl (20 mL, 120 mmol), and extracted with methylene chloride (21 x 30 mL). The combined organic phases were washed with brine (2 x 20 mL), dried (Na_2SO_4), filtered, and concentrated (30 °C/30 mm Hg). Distillation of the residue under reduced pressure afforded *n*-butoxy($^{13}C_2$-acetic) acid (**3**) (2.5052 g, 65%): b.p. 124-131°/22 mm Hg; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 10.05 (br s, 1H, $CO_2\underline{H}$), 4.10 (dd, $J_{^{13}C-H}$=143.5, 4.4 Hz, 2H, $O\underline{CH_2}CO_2$), 3.54 (td, J=6.6, $J_{^{13}C-H}$=3.1 Hz, 2H, $CH_3CH_2CH_2\underline{CH_2}O$), 1.59 (quintet, J=7.1 Hz, 2H, $CH_3CH_2\underline{CH_2}$), 1.37 (sextet, J=7.4 Hz, 2H, $CH_3\underline{CH_2}$), 0.91 (t, J=7.3 Hz, 3H, $\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3 (d, $J_{^{13}C-C}$=60.4, $\underline{C}O_2H$), 71.8 ($\underline{C}H_2OCH_2CO_2H$), 67.7 (d, $J_{^{13}C-C}$=60.4, $\underline{C}H_2CO_2H$), 31.4 ($CH_3CH_2\underline{C}H_2$), 19.0 ($CH_3\underline{C}H_2$), 13.7 ($\underline{C}H_3$); IR (neat) 3103 (br), 1701 (s) cm^{-1}; MS (positive chemical ionization) *m/e* 135 (parent), 119, 107, 88, 79 (base), 73.

1-*n*-Butoxy-2-hydroxy($^{13}C_2$-ethane) (4).

1-*n*-Butoxy-2-hydroxy($^{13}C_2$-ethane) (**4**) was prepared using the same procedure as for alcohol **2** using 0.5344 g LAH (14.08 mmol) in 15 mL ether, and 0.8556 g *n*-butoxy($^{13}C_2$-acetic) acid (6.3756 mmol) in 5.0 mL THF. The product was distilled under reduced pressure to afford 1-*n*-butoxy-2-hydroxy($^{13}C_2$-ethane) (**4**) (0.5928 g, 77%): b.p. 74-77°/22 mm Hg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.23-3.94 (m, 6H, $C\underline{H_2}O\underline{CH_2}\underline{CH_2}OH$), 2.37 (s, 1H, $O\underline{H}$), 1.55 (quintet, J=7.1 Hz, 2H, $CH_3CH_2\underline{CH_2}$), 1.34 (sextet, J=7.1 Hz, 2H, $CH_3\underline{CH_2}$), 0.89 (t, J=7.4 Hz, 3H, $\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.8 (d, $J_{^{13}C-C}$=40.3, $O\underline{C}H_2CH_2OH$), 71.0 ($\underline{C}H_2OCH_2CH_2OH$), 61.7 (d, $J_{^{13}C-C}$=40.3, $\underline{C}H_2OH$), 31.7 ($CH_3CH_2\underline{C}H_2$), 19.2 ($CH_3\underline{C}H_2$), 13.8 ($\underline{C}H_3$); IR (neat) 3410 (br) cm^{-1}; MS (electron impact) *m/e* 121 (parent, M + 1), 102, 88, 77, 57, 47, 41.

Results and Discussion

Of the known syntheses of *n*-butoxyacetic acid and 2-*n*-butoxyethanol, a route for which the corresponding deuterated precursor was available was that of Ghanayem and coworkers (1). In their report, 2-*n*-butoxyethanol was prepared by reduction of the corresponding ester, which in turn was formed by diazomethane treatment of *n*-butoxyacetic acid. The preparation of *n*-butoxyacetic acid was referenced to the work of Fridman (12). Unfortunately, the Fridman chemistry called for boiling stoichiometric amounts of sodium hydride and chloroacetic acid in a large excess of *n*-butanol as solvent to produce a 72% yield of *n*-butoxyacetic acid. Since the preparation of the deuterated analogues would have called for starting with a large excess of costly *n*-butanol-2,2,3,3,4,4,4-d_7 as solvent, a modified route was pursued.

With non-deuterated alcohol as an inexpensive model compound, a stoichiometric amount of *n*-butanol was used in a similarly high boiling aprotic solvent, toluene. This experiment,

however gave a messy product mixture including at least 11 components. Switching to the more reactive bromoacetic acid with excess potassium carbonate in acetone at reflux yielded none of the desired *n*-butoxyacetic acid, instead giving primarily *n*-butyl bromoacetate. To mitigate ester formation, an experiment was performed in which a pre-formed THF solution of lithium *n*-butoxide was added to a DMSO solution of iodoacetic acid sodium salt. This reaction ended with recovery of butanol and decomposition of the iodoacetate to molecular iodine. Attention then focused on improving solubility of the reactants.

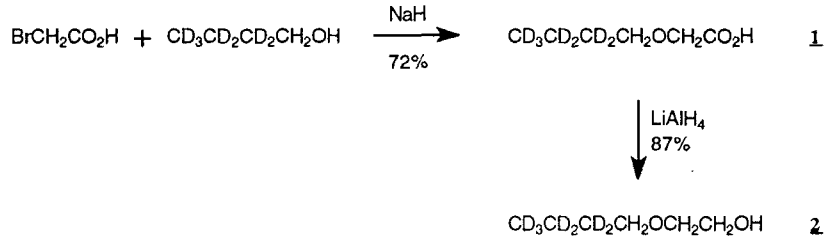
Treatment of ethyl bromoacetate with lithium *n*-butoxide in THF afforded a product mixture in which ethoxy ethylacetate and *n*-butoxy *n*-butylacetate could be clearly observed in NMR spectra of the crude reaction product. Not wanting ester exchange to create a difficult separation on a small amount of deuterated material, the experiment was repeated with *t*-butyl bromoacetate in place of ethyl bromoacetate. It was anticipated that the *t*-butyl group would effectively block the carboxyl carbon from attack. However, this experiment still produced *n*-butyl *n*-butoxyacetate according to GC and NMR analysis. This result indicated that a significant amount of valuable deuterated alcohol would be wasted by the procedure.

Turning back to displacements on the free carboxylic acid or its salts, experiments were conducted with stoichiometric alcohol and bromoacetic acid, and various amounts of sodium hydride at different scales. There initially appeared to be a capriciousness to the outcome of these reactions, sometimes producing *n*-butoxyacetic acid relatively cleanly and at other times giving significant quantities of *n*-butyl *n*-butoxyacetate. Effort on this pathway was spurred on by the report of Mathews and coworkers employing this basic route with two equivalents of sodium hydride for each acidic proton present in a related system (13). In following up on this work it was finally determined that *n*-butoxyacetic acid was partially converted to *n*-butyl *n*-butoxyacetate under the conditions of GC analysis (presumably in the 250 °C injection port). Large injections of *n*-butoxyacetic acid allowed most of the material to exit the GC unchanged, while very small samples were completely converted to the ester. The mechanism for this reaction is unknown, but the process was curtailed with the installation of a new silanized injection port liner. With this knowledge, formation of non-deuterated *n*-butoxyacetic acid was accomplished on the desired scale. The purity of the *n*-butoxyacetic acid was determined to be excellent by NMR spectroscopy, with no indication of the presence of ester.

While Ghanayem and coworkers resorted to a two-step conversion of the acid to the alcohol with an ester intermediate, a direct one-pot procedure was found to be equally effective. Under the conditions of Jakiela and coworkers for isolation of water soluble alcohols from LAH reaction mixtures, 2-*n*-butoxyethanol was obtained in high yield and purity on the desired scale (14).

With processes developed for making each of the desired compounds, 8.0 g of *n*-butanol-d_7 were put through the same reaction sequence as shown in Scheme I. As a result, 4.33 g of the deuterated *n*-butoxyacetic acid **1** and 4.09 g of deuterated 2-*n*-butoxyethanol **2** were isolated.

Scheme I

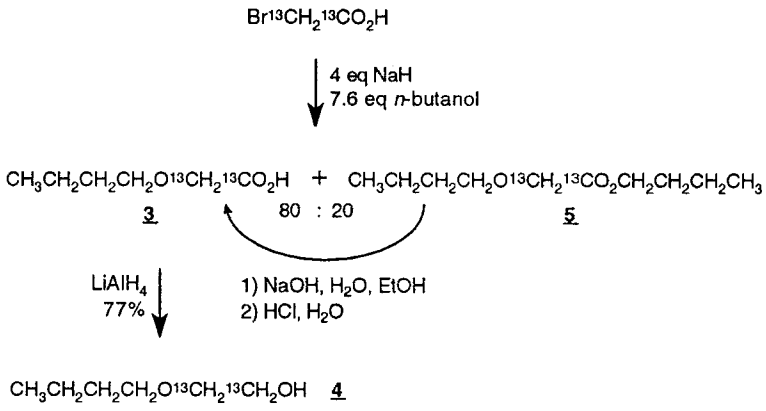


n-Butoxy($^{13}C_2$-acetic) acid (**3**) was prepared in a fashion similar to deuterated acid **1** except that an excess of *n*-butanol was used (Scheme II). Whereas the requisite deuterated alcohol precursor to **1** was far too costly to use in greater that stoichiometric amount, no such restriction applied in the present work. Use of excess *n*-butanol during the bromide displacement was expected to ensure complete reaction of the valuable ^{13}C–labelled bromoacetic acid. The additional alcohol did cause partial formation of ester **5** (80:20 ratio of acid:ester by NMR in crude etherification mixture), but saponification followed by acidification generated the free acid. *n*-Butoxy($^{13}C_2$-acetic) acid was isolated in 65% yield after distillation. The purity of acid **3** was determined to be 98+% by NMR and GC/MS analysis.

Reduction of acid **3** to alcohol **4** was straightforward (Scheme II). Again using the procedure of Jakiela and coworkers for isolation of water soluble alcohols from LAH reaction mixtures afforded 1-*n*-butoxy-2-hydroxy($^{13}C_2$-ethane) (**4**) in 77% yield (14). The purity of **4** thus obtained was 99+% by NMR and GC/MS.

In conclusion, the title compounds have been prepared in high yield with good isotope economy. The practicality of the process on small scale has also been demonstrated.

Scheme II



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