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Large-scale preparation of ^{13}C-labeled 2-(phenylthio)acetic acid and the corresponding labeled sulfoxides and sulfones

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We have developed large-scale efficient procedures for the conversion of commercially available [^{13}C]- or [$^{2}H_3$,^{13}C]methanol and $^{13}CO_2$ or ^{13}C-labeled bromoacetic acid to 2-(phenylthio)[1,2-$^{13}C_2$]-, [1-^{13}C]-, and [2-^{13}C]acetic acid. The resulting derivatives are versatile, chemically stable, and nonvolatile two-carbon labeling precursors. We have used the ^{13}C-isotopomers of 2-(phenylthio)acetic acid in the synthesis of ^{13}C-labeled acrylic acid, methacrylic acid, and *trans*-crotonic acid.

Keywords: stable isotope labeling; ^{13}C-labeled synthons; 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid

Introduction

Stable isotopes ^{13}C, ^{15}N, ^{17}O, ^{18}O, and ^{2}H have the benefit that they are detected by mass spectrometry and, with the exception of ^{18}O, by NMR spectroscopy, yielding information about both the extent and the position of the stable isotope labels. ^{13}C-labeled compounds have proven to be especially useful in studying complex biological systems. For example, stable isotope labels have been used to obtain detailed information about the biosynthetic pathways[1–4] leading to useful products such as enzyme cofactors, vitamins, antibiotics, and anticancer drugs. In addition, ^{13}C-labeled compounds are useful in many phases of drug development including hit-to-lead optimization, pharmacokinetics, and elucidation of drug metabolism pathways.[5–7]

Carbon-13 is enriched from its lighter isotope by cryogenic distillation of carbon monoxide; thus, all ^{13}C-labeled carbons must ultimately be derived from ^{13}CO. Highly efficient conversion of ^{13}CO to useful chemical precursors is essential to stable-isotope-labeling chemistry. Because inefficiencies in the initial steps of conversions add greatly to the expense of isotope labeling, considerable effort has been devoted to the preparation of useful synthetic precursors and has led to efficient methods for the large-scale synthesis of one-carbon, stable-isotope-labeled synthons including methane,[8] methanol,[9,10] methyl iodide,[11–14] [^{13}C]methyl phenyl sulfide,[15] sodium formate,[16,17] potassium cyanide,[18–20] carbon dioxide, carbon disulfide,[21] and urea.[22] Similarly efficient methods for the synthesis of two-carbon-labeled synthons are essential for the economical preparation of complex labeled compounds. By far, the most useful of the two-carbon-labeled synthons have been [1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]acetic acid that are prepared on the large scale by the carbonylation of methanol where the carbonyl carbon is derived from carbon monoxide and the alkyl carbon is derived from methanol.[23] Efficient large-scale methods have also been reported for the conversion of ^{13}C-labeled acetic acid into the corresponding labeled ethanol,[24] ethyl iodide, bromoacetic acid,[25] and glycine.[26]

Another potentially useful two-carbon precursor if prepared with isotopic labels would be 2-(phenylthio)acetic acid, which has been used extensively in organic synthesis. For example, 2-(phenylthio)acetic acid has been used to make beta-lactones,[27] beta-lactams,[28] and benzo[*b*]thiophenes[29] in the synthesis of natural products and anticancer therapeutics. The dianion of 2-(phenylthio)acetic acid provides access to a wide variety of β-hydroxysulfides, providing key intermediates for the synthesis of olefins, oxiranes, and ketones.[30] In addition, Reeves and coworkers[31] have used 2-(phenylthio)acetic acid in the conversion of carboxylic acids to trifluoromethyl ketones.

Described in this manuscript is the synthesis of 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid (**1**) and its conversion to its corresponding ethyl ester **2**. We also describe simple conditions for the conversion of ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate (**2**) to its corresponding sulfoxide **3** and sulfone **4** (Scheme 1). Our synthetic routes are also useful for the preparation of the ^{13}C-isotopomers labeled at either C1 or C2 of the acetyl group.

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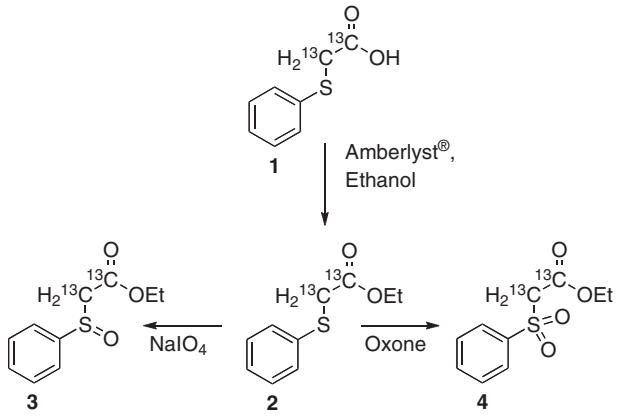


Scheme 1. The conversion of 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid to its ethyl ester and oxidation of ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate to its corresponding sulfoxide and sulfone.

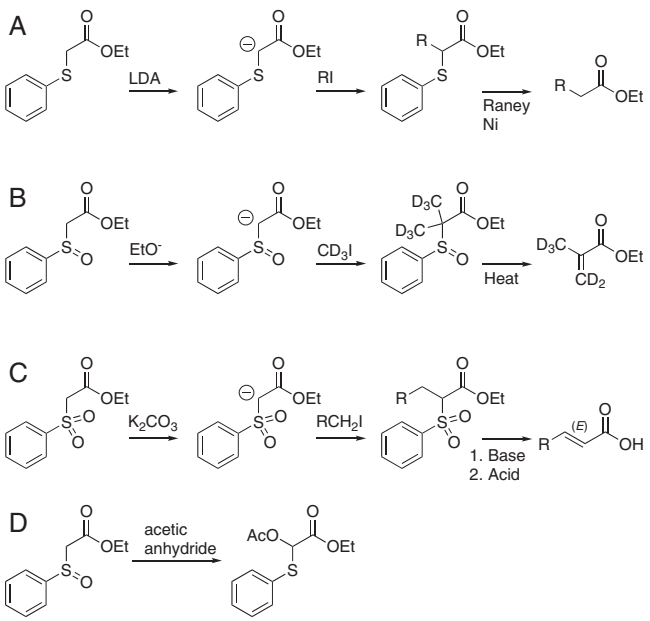
We have found that all of these compounds are versatile labeling precursors. Representative applications of these reagents to labeling chemistry are diagrammed in Scheme 2. For example, ethyl 2-(phenylthio)acetate can be converted to a nucleophile by treatment with lithium diisopropylamide.[32] The corresponding anion can be readily alkylated to extend the carbon chain. The phenylthio group can be removed by treatment with Raney Ni to yield extended-chain carboxylic acids.[33,34] The relative acidity of the methylene protons can be adjusted by oxidizing the sulfide (Scheme 2A) to sulfoxide (Scheme 2B) or sulfone (Scheme 1C). Similarly, the oxidation of the sulfur activates it for elimination to yield alkenes (Scheme 2B and 2C). For example, we have prepared deuterated acrylates by alkylation of ethyl 2-(phenylsulfinyl)acetate followed by thermal elimination of the sulfoxide.[35,36] In our experience, elimination of the sulfone under basic conditions yields predominately the *trans* product as detected by NMR. For example, we have prepared *trans*-[U-$^{13}C_4$]crotonic acid by treatment of 3-(phenylsulfonyl)[U-$^{13}C_4$]butanoic acid with aqueous sodium hydroxide. ^{13}C NMR analysis of the [U-$^{13}C_4$]crotonic acid showed >99.5% the trans isomer. Finally, treatment of the sulfoxide with acetic anhydride under Pummerer conditions[37–39] produces a protected aldehyde (Scheme 2D). Specifically, we have used ^{13}C-isotopomers of 2-(phenylthio) acetic acid in the synthesis of ^{13}C-labeled acrylic acid,[35,36] methacrylic acid,[35,36] and *trans*-crotonic acid.

Results and discussion

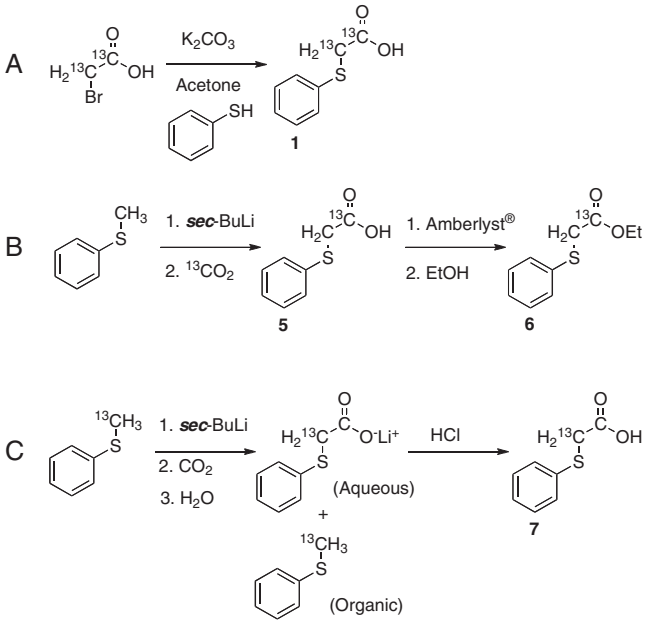
Synthesis of 2-(phenylthio)[1,2-$^{13}C_2$]-, 2-(phenylthio)[1-^{13}C]-, and 2-(phenylthio)[2-^{13}C]acetic acid

Spinelli and coworkers previously reported the preparation of isotopically labeled 2-(phenylthio)acetic acid that they used for the synthesis of [2-^{13}C]benzo[*b*]thiophene-3-one.[29] In that paper, the authors describe the preparation of 2-(phenylthio)[2-^{13}C] acetic acid in a 86% yield through the treatment of an aqueous solution of sodium bromo[2-^{13}C]acetate with sodium thiophenoxide at 90–100 °C. In our studies, we have identified more efficient conditions for the near-quantitative conversion of ^{13}C-labeled bromoacetic acid to ^{13}C-labeled 2-(phenylthio)acetic acid (Scheme 3A). We prepared 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid in 99% yield by mixing of bromo[1,2-$^{13}C_2$]acetic acid with benzenethiol in a suspension of potassium carbonate in acetone (Scheme 3A). Similarly, by starting with bromo[1-^{13}C]- and bromo [2-^{13}C]acetic acid, we have used this procedure to prepare 2-(phenylthio)[1-^{13}C]- and 2-(phenylthio)[2-^{13}C]acetic acid in near-quantitative yields. As such, the route we have identified is convenient for converting commercial ^{13}C-labeled bromoacetic acids to the corresponding ^{13}C-labeled 2-(phenylthio)acetic acids.

We have also identified an efficient route to 2-(phenylthio)[1-^{13}C] acetic acid from $^{13}CO_2$ and methyl phenyl sulfide (Scheme 3B). A solution containing 2 equivalents of (phenythio)methyl lithium in THF is treated with $^{13}CO_2$ to form 2-(phenylthio)[1-^{13}C]acetic acid



Scheme 2. Useful application of ethyl 2-(phenylthio)acetate to prepare simple carboxylic acids (A), acrylates (B), crotonates (C), and mixed thioacetals (D).



Scheme 3. Synthesis of 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid from bromo[1,2-$^{13}C_2$] acetic acid (A). Conversion of methyl phenyl sulfide (B) or [^{13}C]methyl phenyl sulfide (C) to the corresponding to 2-(phenylthio)[1-^{13}C]- or 2-(phenylthio)[2-^{13}C]acetic acid.

with an excellent yield (97%). The second equivalent of (phenythio)methyl lithium is required because one equivalent is consumed in the reaction by the formation of the dianion of the product 2-(phenylthio)[1-^{13}C]acetic acid. Quenching the reaction leaves a mixture of methyl phenyl sulfide and 2-(phenylthio)[1-^{13}C]acetic acid, which are easily separated by a simple acid/base extraction. Rapid addition or addition of an excess of $^{13}CO_2$ generates 2-(phenylthio)[1,3-$^{13}C_2$]malonate that decarboxylates during the workup. Thus, for good recovery of the label, it is essential to be careful about the stoichiometry of the reagents. We also prepared C2-labeled isotopomers of 2-(phenylthio)acetic acid in good yield (theoretical 50%) using this route by starting with a twofold excess of [^{13}C]methyl phenyl sulfide and being careful to recover the excess (Scheme 3C). To prepare 2-(phenylthio)[1-^{13}C]acetic acid by the methyl phenyl sulfide route requires a pressure/vacuum manifold to handle labeled $^{13}CO_2$, which may not be commonly available in a standard organic chemistry laboratory. However, considering the lower overall yields (81%[26]) of expensive isotope and number of steps involved in the preparation of labeled bromoacetic acid, the methyl phenyl sulfide route achieves a greater overall recovery of the isotope, making it particularly economical for large-scale syntheses. The efficiency of the methyl phenyl sulfide route can also be appreciated by considering the published price of the labeled precursors, which is most straightforward for 2-(phenylthio)[1-^{13}C] acetic acid. Bromo[1-^{13}C]acetic acid (~$30.15/mmol, Aldrich Chemical Co) is more than an order of magnitude more expensive than $^{13}CO_2$ (~$2.36/mmol, Aldrich Chemical Co).

Synthesis of ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate, ethyl 2-(phenylsulfinyl)[1,2-$^{13}C_2$]acetate, and ethyl 2-(phenylsulfonyl)[1,2-$^{13}C_2$]acetate

As outlined in Schemes 1 and 2, we have described the use of Amberlyst® to catalyze the conversion of labeled 2-(phenylthio) acetic acids **1** and **5** to their corresponding ethyl esters **2** and **6** in 96–98% yield. Using a modest excess (1.2 equiv) of sodium periodate, ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate is oxidized to its corresponding sulfoxide, ethyl 2-(phenylsulfinyl)[1,2-$^{13}C_2$]acetate (**3**) in near-quantitative yield (99%). Finally, we have described the oxidation of ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate (**2**) to ethyl 2-(phenylsulfonyl)[1,2-$^{13}C_2$]acetate (**4**) in 89% yield using an excess of oxone.

Conclusion

In this paper, we have described two routes to produce 2-(phenylthio)[1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]acetic acid and the conversion to their corresponding ethyl esters. In addition, we have described the oxidation of labeled ethyl 2-(phenylthio)acetates to their corresponding sulfones and sulfoxides. All of these compounds are versatile, chemically stable, and nonvolatile two-carbon-labeling precursors.

Experimental

General

[^{13}C]Carbon monoxide and [^{13}C]carbon dioxide enriched to 99.2% were supplied by the Los Alamos ICONS facility. All labeled precursors were prepared by the National Stable Isotope Resource at Los Alamos using published methods. Bromo[1,2-$^{13}C_2$]acetic acid was prepared from [1,2-$^{13}C_2$]acetic acid by the method of Roberts and Poulter[25] and purified by sublimation. [1,2-$^{13}C_2$]Acetic acid[23], [^{13}C]methanol,[9,10] and [^{13}C]methyl phenyl sulfide[15] were prepared as described. Anhydrous THF (Aldrich Sure/Seal™), *sec*-butyllithium 1.4 M in cyclohexane (Aldrich Sure/Seal™), potassium carbonate powder −325 mesh, and Amberlist® 15 H^+-form were purchased from Sigma-Aldrich (Milwaukee, WI USA) and used without purification. Because it is difficult to precisely determine the concentration of *sec*-butyllithium, we monitored our reaction mixtures to ensure complete formation of the desired anion in the following manner. A small aliquot of the reaction mixture was quenched with D_2O and deuterium incorporation analyzed by ^{13}C NMR ($^1J_{DC}$ = 18 Hz). Proton-decoupled ^{13}C (75 MHz) and ^{1}H (300 MHz) NMR spectra were obtained at 25 °C using a Bruker DRX-300 NMR spectrometer (Bruker BioSpin Corporation, Billerica, MA USA). Samples were dissolved in $CDCl_3$, and the resonance signals from $CDCl_3$ (^{13}C, 77.23 ppm) or $CHCl_3$ (^{1}H, 7.27 ppm) were used as an internal chemical shift standards. High-resolution mass spectra were obtained using a Thermo-Finnigan LTQ FT mass spectrometer (Thermo Scientific, San Jose, CA, USA). Samples were dissolved in methylene chloride containing formic acid (0.1% V/V).

2-(Phenylthio)[1,2-$^{13}C_2$]acetic acid (1) and 2-(phenylthio)[1-^{13}C]acetic acid (5)

Bromo[1,2-$^{13}C_2$]acetic acid (51.0 g, 0.362 mol, 1.00 equiv) was dissolved in acetone (765 mL) in a 2-L round-bottom flask and was cooled to 0 °C. After 15 min of stirring, potassium carbonate (150 g, 1.09 mol, 3.00 equiv) was added slowly while the reaction mixture was vigorously stirred. After another 15 min of stirring, benzenethiol (97%, 40.7 mL, 43.9 g, 0.398 mol, 1.1 equiv) was added slowly. The reaction mixture progressively thickened, making the stirring difficult. After 10 min, an aliquot was taken out of the reaction mixture, placed in a test tube with water and dichloromethane, then acidified to pH = 2 using 1 N HCl. The organic layer was separated and then dried over sodium sulfate; it was then filtered and subsequently evaporated under reduced pressure using a rotary evaporator. The resulting solid was dissolved into $CDCl_3$ and analyzed by ^{13}C NMR. The disappearance of bromo[1,2-$^{13}C_2$]acetic acid (C1 δ = 168 ppm, C2 δ = 26 ppm) and subsequent appearance of the desired 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid (C1 δ = 175 ppm, C2 δ = 35 ppm) were noted so the reaction was found to be complete at this time. The volatiles were removed from the reaction mixture under reduced pressure using a rotary evaporator. The resulting solids were then washed with dichloromethane (500 mL) to remove excess benzenethiol. Dichloromethane (500 mL) was added to the solids. The heterogeneous mixture was then cooled to 0 °C over 10 min of stirring; then, the mixture was acidified to pH = 2 using 1 N HCl. The organic layer was separated, and the aqueous layer was washed with more dichloromethane (2×, 100 mL). The organic layers were combined, dried over sodium sulfate, filtered, and evaporated using a rotary evaporator to yield **1** as a colorless solid (60.96 g, 99.0%) that was used without further purification. Using the same procedure, **5** was prepared from bromo[1-^{13}C]acetic acid in 99.6% yield. Compound **1** ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.66 (dd, $^2J_{CH}$ = 5.3 Hz, $^1J_{CH}$ = 141.3 Hz, 2H, S^{13}CH$_2$), 7.17–7.49 (m, 5H$_{arom}$), 10.68 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 36.8, (d, $^1J_{CC}$ = 59.5 Hz, S^{13}CH$_2$), 127.5 (C$_{arom}$), 129.4 (C$_{arom}$), 130.2 (d, $^3J_{CC}$ = 2.2 Hz, C$_{arom}$), 134.6 (C$_{arom}$), 176.5 (d, $^1J_{CC}$ = 59. Hz, ^{13}C=O). HRMS (ESI+) (Calculated 171.0384) Found 171.0383 (M^+). Melting point of 63.9 °C, literature value 63.5 °C[40]. Compound **5** ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.67 (d, $^2J_{CH}$ = 5.3 Hz, 2H, SCH$_2$), 7.18–7.50 (m, 5H$_{arom}$), 10.96 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 36.8, (d, $^1J_{CC}$ = 59.5 Hz, SCH$_2$), 127.5 (C$_{arom}$), 129.4 (C$_{arom}$), 130.3 (C$_{arom}$), 134.6 (d, $^3J_{CC}$ = 1.1 Hz, C$_{arom}$), 176.1 (^{13}C=O). Melting point of 64.0 °C, literature value 63.5 °C[40].

Ethyl 2-(phenylthio)[1-^{13}C]acetate (6) and ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate (2)

2-(Phenylthio)[1-^{13}C]acetic acid (**5**) (126 g, 0.745 mol) was dissolved in ethanol (700 mL) in a 2-L round-bottom flask. Amberlyst® 15 H^+-form (31.75g, 25 wt.%) was rinsed with ethanol and then added to the reaction mixture. This mixture was then refluxed for 8.5 h until the reaction was complete. Completion was determined by hourly analysis via ^{13}C NMR noting the disappearance of a resonance at 176.1 ppm (^{13}C=O of **5**)

and the appearance of a resonance at 169.9 ppm (^{13}C=O of **6**). The reaction mixture was filtered through a celite-packed frit funnel to remove the Amberlyst®. The volatiles were removed using a rotary evaporator to yield **6** as a slightly yellow and viscous liquid (142 g, 96.6%), which was used without further purification. Using the same procedure, **2** was prepared from 2-(phenylthio)[1,2-$^{13}C_2$]acetic acid (**1**) in 98.1% yield. Compound **6** ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.22$ (t, $^3J_{HH} = 7.2$ Hz, 3H, CH_3), 3.63 (d, $^2J_{CH} = 5.5$ Hz, 2H, SCH_2), 4.16 (dq, $^3J_{CH} = 3.2$ Hz, $^3J_{HH} = 7.2$ Hz, 2H, OCH_2), 7.20–7.43 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.3$ (d, $^3J_{CC} = 2.0$ Hz, CH_3), 36.9, (d, $^1J_{CC} = 61.9$ Hz, SCH_2), 61.7 (d, $^2J_{CC} = 2.5$ Hz, CH_2), 127.1 (C_{arom}), 129.2 (C_{arom}), 130.2 (C_{arom}), 135.2, 169.9 (^{13}C=O). Compound **2** ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.22$ (t, $^3J_{HH} = 7.2$ Hz, 3H, CH_3), 3.63 (dd, $^2J_{CH} = 5.4$ Hz, $^1J_{CH} = 141.3$ Hz, 2H, $S^{13}CH_2$), 4.16 (dq, $^3J_{CH} = 3.2$ Hz, $^3J_{HH} = 7.2$ Hz, 2H, OCH_2), 7.20–7.43 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.3$ (d, $^3J_{CC} = 2.0$ Hz, CH_3), 36.9, (d, $^1J_{CC} = 61.9$ Hz, $S^{13}CH_2$), 61.7 (d, $^2J_{CC} = 2.5$ Hz, CH_2), 127.1 (C_{arom}), 129.2 (C_{arom}), 130.2 (C_{arom}), 135.2 (C_{arom}), 169.9 (d, $^1J_{CC} = 61.9$ Hz, ^{13}C=O).

Ethyl 2-(phenysulfinyl)[1,2-$^{13}C_2$]acetate (3)

Ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate (**2**) (10.0 g, 0.05 mol, 1.0 equiv) was dissolved in a 50% solution of methanol in distilled water (100 mL). Then, sodium periodate (13.0 g, 0.06 mol, 1.2 equiv) was added. The resulting solution was stirred at room temperature using a magnetic stir bar. Product formation was monitored by ^{13}C NMR noting the disappearance of resonance doublets at 36.9 ($S^{13}CH_2$ of **2**) and 169.9 ppm (^{13}C=O of **2**) and the appearance of resonance doublets at 61.7 ($S^{13}CH_2$ of **3**) and 164.5 ppm (^{13}C=O of **3**). A white precipitate formed after approximately 30 min. The mixture becomes very thick, and more solvent (100 mL) was added to allow continuous stirring. After approximately 24 h, the reaction was determined to be complete by ^{13}C NMR. The white precipitate was then filtered, and most of the methanol was removed using a rotary evaporator. The aqueous phase was extracted with ethyl acetate (3×, 200 mL). The organic layer was dried over sodium sulfate and filtered, and the volatiles were removed by a rotary evaporator to obtain a clear, colorless oil (10.7 g, 99%) that was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.19$ (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3), 3.81 (dddd, $^1J_{CH} = 141.8$ Hz, $^{AB}J_{HH} = 39.3$ Hz; 13.8 Hz; 6.1 Hz, 2H, $S^{13}CH_2$), 4.13 (dq, $^3J_{HH} = 7.1$ Hz, $^3J_{CH} = 3.2$ Hz, 2H, OCH_2), 7.21–7.83 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.7$ (d, $^3J_{CC} = 2.0$ Hz, CH_3), 61.1 (d, $^1J_{CC} = 60.2$ Hz, $S^{13}CH_2$), 61.7 (d, $^2J_{CC} = 2.0$ Hz, CH_2), 123.9, 129.1, 131.5, 142.4 (d, $^2J_{CC} = 2.2$ Hz, C_{arom}), 164.5 (d, $^1J_{CC} = 60.2$ Hz, ^{13}C=O).

Ethyl 2-(phenylsulfonyl)[1,2-$^{13}C_2$]acetate (4)

Oxone (44.6 g, 0.072 mol, 3.0 equiv) was dissolved in distilled water (200 mL) and the solution stirred with a magnetic stir bar. Ethyl 2-(phenylthio)[1,2-$^{13}C_2$]acetate (**2**) (4.8 g, 0.024 mol, 1.0 equiv) was dissolved in a 50% solution of ethanol in ethyl acetate (50 mL) and added dropwise to the stirred oxone solution. The resulting solution was incubated at room temperature for 3 h with continued stirring. Product formation was monitored by ^{13}C NMR noting the disappearance of resonance doublets at 36.9 ($S^{13}CH_2$ of **2**) and 169.9 ppm (^{13}C=O of **2**) and the appearance of resonance doublets at 61.1 ($S^{13}CH_2$ of **4**) and 162.4 ppm (^{13}C=O of **4**). After oxidation was complete, the solution was extracted (3×, 200 mL) with ethyl acetate. The organic layer was dried over sodium sulfate and then filtered. The volatiles were removed using a rotary evaporator to obtain a clear, colorless oil (4.94 g, 88.6%) that was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.18$ (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3), 4.14 (dd, $^2J_{CH} = 6.6$ Hz, $^1J_{CH} = 140.1$ Hz, 2H, $S^{13}CH_2$), 4.14 (dq, $^3J_{CH} = 3.3$ Hz, $^3J_{HH} = 7.1$ Hz, 2H, OCH_2), 7.52–7.98 (m, $5H_{arom}$). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.9$ (d, $^3J_{CC} = 2.2$ Hz, CH_3), 61.1, (d, $^1J_{CC} = 60.7$ Hz, $S^{13}CH_2$), 61.7 (dd, $^3J_{CC} = 1.0$ Hz, $^2J_{CC} = 2.7$ Hz, OCH_2), 128.6 (C_{arom}), 129.3 (C_{arom}), 134.4 (C_{arom}), 138.8 (d, $^3J_{CC} = 8.3$ Hz, C_{arom}), 162.4 (d, $^1J_{CC} = 60.7$ Hz, ^{13}C=O).

2-(Phenylthio)[1-^{13}C]acetic acid (5)

This reaction was carried out using a pressure/vacuum manifold to which the $^{13}CO_2$ supply cylinder, a 250-mL stainless steel lecture bottle, a vacuum/pressure gauge, and the reaction flask could be affixed and isolated by metering valves. The 250-mL lecture bottle was evacuated and tared. [^{13}C]Carbon dioxide (3.6 g, 0.08 mol, 1.0 equiv) was condensed into the lecture bottle, and the quantity of $^{13}CO_2$ was verified by the change in mass of the lecture bottle. The rest of the reagents were scaled to the amount of $^{13}CO_2$. Then, methyl phenyl sulfide (19.9 g, 0.16 mol, 2.0 equiv) was added to a 1-L round-bottom flask equipped with a magnetic stir bar and placed under a stream of argon. Anhydrous THF (300 mL) was added to the flask, and this solution was cooled to −78 °C. To this solution, *sec*-butyllithium (1.4 M, 129 mL, 0.180 mol, 2.2 equiv) was added dropwise over 10 min and monitored to ensure complete formation of the anion as described earlier. The reaction flask containing the (phenylthio)methyl lithium was evacuated three times until the solvent boiled vigorously (0.1–0.2 mBar ≈ vapor pressure of THF at −78 °C). Then, $^{13}CO_2$ was slowly introduced into the reaction vessel through a metering valve over approximately 30 min. During the addition of $^{13}CO_2$, the pressure in the reaction flask was always below atmospheric pressure. The addition of $^{13}CO_2$ was judged complete when the pressure in the system returned to ~0.1–0.2 mBar after which the reaction was stirred for 1 h. The mixture was then brought to room temperature while stirring for an additional 2 h. The reaction was quenched by adding distilled water (100 mL). The reaction mixture was extracted with hexane (3×, 100 mL) to remove methyl phenyl sulfide. The aqueous layer was then acidified using hydrochloric acid (6 N) to pH = 2. At this time, compound **5** precipitated as a white solid. The heterogeneous aqueous layer was then extracted with ethyl acetate (3×, 200 mL). The ethyl acetate layer was then dried over solid sodium sulfate and filtered, and volatiles were removed using a rotary evaporator to yield a yellowish solid (13.1 g, 97% based on $^{13}CO_2$) that can be used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.67$ (d, $^2J_{CH} = 5.3$ Hz, 2H, SCH_2), 7.18–7.50 (m, $5H_{arom}$), 10.96 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 36.8$, (d, $^1J_{CC} = 59.5$ Hz, SCH_2), 127.5 (C_{arom}), 129.4 (C_{arom}), 130.3 (C_{arom}), 134.6 (d, $^3J_{CC} = 1.1$ Hz, C_{arom}), 176.1 (^{13}C=O). Elemental analysis of **5**: Calculated: $^{13}CC_7H_8O_2S$: C, 57.37; H, 4.77; S, 18.95. Found: C, 57.44; H, 4.73; S, 18.88. Melting point of 63.9 °C, literature value 63.5 °C[40].

2-(Phenylthio)[2-^{13}C]acetic acid (7)

The [^{13}C]methyl phenyl sulfide[15] (20.1 g, 0.160 mol, 2.0 equiv) was added to a 1-L round-bottom flask equipped with a magnetic stir bar and placed under a stream of argon. Anhydrous THF (200 mL) was added to the flask, and this solution was cooled to −78 °C. To this solution, *sec*-butyllithium (1.4 M, 129 mL, 0.180 mol, 2.2 equiv) was added dropwise over a 10-min period and monitored to ensure complete formation of the anion as described earlier. An excess of CO_2 was bubbled through the reaction until a white precipitate formed. The mixture was then allowed to come to room temperature while stirring for an additional 2 h. The reaction was quenched by adding distilled water (100 mL). The reaction mixture was extracted with hexane (3×, 100 mL) to remove unreacted [^{13}C]methyl phenyl sulfide, which was recovered by evaporation of the solvent using a rotary evaporator. The aqueous layer was acidified using hydrochloric acid (6 N) to pH = 2, which caused **7** to precipitate as a colorless solid. The heterogeneous aqueous layer was then extracted with ethyl acetate (3×, 200 mL). The combined ethyl acetate fractions were dried over solid sodium sulfate, filtered, and evaporated to yield a colorless solid (13.53 g, 99.6%) that was used without further purification. The recovered [^{13}C]methyl phenyl sulfide (8.4 g, 84%) was used in subsequent reactions without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.66$ (d, $^1J_{CH} = 141.3$ Hz, 2H, $S^{13}CH_2$), 7.17–7.49 (m, $5H_{arom}$), 10.68 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 36.8$, (s, $S^{13}CH_2$), 127.5, 129.4, 130.2 $^3J_{CC} = 1.9$ Hz, 134.6, 176.5 (d, $^1J_{CC} = 59.5$ Hz, C=O); Melting point of 64 °C, literature value 63.5 °C[40].

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Conflict of Interest

The authors did not report any conflict of interest.

References

[1] H. Seto, T. Sato, H. Yonehara, *J. Am. Chem. Soc.* **1973**, *95*, 8461.
[2] S. C. Wenzel, R. M. Williamson, C. Gruenanger, J. Xu, K. Gerth, R. A. Martinez, S. J. Moss, B. J. Carroll, S. Grond, C. J. Unkefer, R. Mueller, H. G. Floss, *J. Am. Chem. Soc.* **2006**, *128*, 14325.
[3] D. R. Houck, J. L. Hanners, C. J. Unkefer, *J. Am. Chem. Soc.* **1991**, *113*, 3162.
[4] S. J. Gould, D. E. Cane, *J. Am. Chem. Soc.* **1982**, *104*, 343.
[5] C. J. Unkefer, R. A. Martinez, *Drug Test. Anal.* **2012**, *4*, 303.
[6] A. R. Branfman, M. F. McComish, R. J. Bruni, M. M. Callahan, R. Robertson, D. W. Yesair, *Drug Metab. Dispos.* **1983**, *11*, 206.
[7] T. A. Baillie, A. W. Rettenmeier, *J. Clin. Pharmacol.* **1986**, *26*, 481.
[8] M. Alei, Jr., *J. LabelledCompd. Radiopharm.* **1980**, *17*, 115.
[9] D. G. Ott, V. N. Kerr, T. W. Whaley, T. Benziger, R. K. Rohwer, *J. Labelled Compd.* **1974**, *10*, 315.
[10] T. E. Walker, W. E. Wageman, *Magn. Reson. Chem.* **1986**, *24*, 157.
[11] T. W. Whaley, G. H. Daub, V. N. Kerr, T. A. Lyle, E. S. Olson, *J. Labelled Compd. Radiopharm.* **1979**, *16*, 809.
[12] M. Pomerantz, R. Fink, *J. Labelled Compd. Radiopharm.* **1979**, *16*, 275.
[13] M. A. G. El-Fayoumy, H. C. Dorn, M. A. Ogliaruso, *J. Labelled Compd. Radiopharm.* **1977**, *13*, 433.
[14] J. D. Roberts, R. E. McMahon, J. S. Hine, *J. Am. Chem. Soc.* **1950**, *72*, 4237.
[15] R. A. Martinez, M. A. Alvarez, S. P. Velarde, L. A. P. Silks, P. L. Stotter, J. G. Schmidt, C. J. Unkefer, *Org. Process Res. Dev.* **2002**, *6*, 851.
[16] B. D. Andresen, *J. Org. Chem.* **1977**, *42*, 2790.
[17] R. E. Royer, G. H. Daub, D. L. Vander Jagt, *J. Labelled Compd. Radiopharm.* **1976**, *12*, 377.
[18] D. G. Ott, V. N. Kerr, T. G. Sanchez, T. W. Whaley, *J. Labelled Compd. Radiopharm.* **1980**, *17*, 255.
[19] T. E. Walker, C. J. Unkefer, D. S. Ehler, *J. Carbohydr. Chem.* **1988**, *7*, 115.
[20] T. W. Whaley, D. G. Ott, *J. Labelled Compd.* **1975**, *11*, 307.
[21] V. N. Kerr, D. G. Ott, *J. Labelled Compd. Radiopharm.* **1978**, *14*, 793.
[22] T. W. Whaley, D. G. Ott, *J. Labelled Compd.* **1975**, *11*, 167.
[23] D. G. Ott, V. N. Kerr, *J. Labelled Compd. Radiopharm.* **1976**, *12*, 119.
[24] V. N. Kerr, D. G. Ott, *J. Labelled Compd. Radiopharm.* **1978**, *15*, 503.
[25] J. L. Roberts, C. D. Poulter, *J. Org. Chem.* **1978**, *43*, 1547.
[26] D. G. Ott, *Syntheses with Stable Isotopes of Carbon, Nitrogen, and Oxygen*, John Wiley & Sons, New York, **1981**.
[27] T. J. Donohoe, R. M. Harris, O. Williams, G. C. Hargaden, J. Burrows, J. Parker, *J. Am. Chem. Soc.* **2009**, *131*, 12854.
[28] S. D. Sharma, S. Kanwar, *Org. Process Res. Dev.* **2004**, *8*, 658.
[29] D. Spinelli, P. Zanirato, E. Di Miceli, L. Lamartina, F. Guerrera, *J. Org. Chem.* **1997**, *62*, 4921.
[30] P. A. Grieco, C. L. J. Wang *J. Chem. Soc., Chem. Commun.* **1975**, 714.
[31] J. T. Reeves, J. J. Song, Z. Tan, H. Lee, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2008**, *73*, 9476.
[32] S. E. Schaus, J. Brnalt, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 4876.
[33] D. E. Ward, V. Jheengut, G. E. Beye, *J. Org. Chem.* **2006**, *71*, 8989.
[34] W. W. Win, R. W. Franck, *J. Org. Chem.* **1997**, *62*, 4510.
[35] M. A. Alvarez, R. A. Martinez, C. J. Unkefer, The University of California, USA; Los Alamos National Security, LLC. U.S. Pat. Appl. Publ. #20070106085, **2007**, p. 9 pp.
[36] M. A. Alvarez, R. A. Martinez, C. J. Unkefer, University of California, USA; Los Alamos National Security, LLC. U.S. Pat. Appl. Publ. #20070191635, **2007**.
[37] R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282.
[38] R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401.
[39] B. Laleu, M. S. Machado, J. Lacour, *Chem. Commun. (Cambridge, U. K.)* **2006**, 2786.
[40] W. J. Kenny, J. A. Walsh, D. A. Davenport, *J. Am. Chem. Soc.* **1961**, *83*, 4019.