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Synthesis of isotopically labeled 1,3-dithiane

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The 1,3-dithiane is a protected formaldehyde anion equivalent that could serve as a useful labeled synthon. We report a facile synthesis of 1,3-[2-¹³C]- and 1,3-[2-¹³C, 2-²H₂]dithiane in two steps from [¹³C]- or [¹³C, ²H₃]methyl phenyl sulfoxide. We have previously reported the high yield synthesis of [¹³C]methyl phenyl sulfide from [¹³C]MEOH and the oxidation of [¹³C]methyl phenyl sulfide to [¹³C]methyl phenyl sulfoxide. Here, we describe the facile exchange of deuterium from ²H₂O into [¹³C]methyl phenyl sulfoxide to yield [¹³C, ²H₃]methyl phenyl sulfoxide. Thus, from [¹³C]MEOH and ²H₂O, all possible C2 stable isotopomers of 1,3-dithiane are available. Our synthetic route is also amenable to preparation of radiolabeled 1,3-dithianes.

Keywords: stable isotope labeling; ¹³C-labeled synthons

Introduction

Carbon-13 is enriched from its lighter isotope by cryogenic distillation of carbon monoxide. Because all labeled carbons must be derived ultimately from ¹³CO, considerable effort has been devoted to the preparation of useful synthetic precursors giving rise to efficient large-scale methods for the synthesis of one-carbon compounds including methane,¹ MEOH,^{2–4} methyl iodide,^{4–8} [¹³C]methyl phenyl sulfide,⁹ sodium formate,^{10,11} potassium cyanide,^{4,12–14} carbon dioxide, carbon disulfide,¹⁵ and urea.¹⁶ If prepared efficiently, C2-labeled 1,3-dithiane is a very useful one-carbon donor that allows for the construction of many useful labeled chemicals and biochemicals.

There are numerous examples for the use of unlabeled 1, 3-dithiane (Scheme 1) for the synthesis of a wide variety of compounds. The 1,3-dithiane is a protected formaldehyde equivalent. Lithiated 1,3-dithiane is a 'formyl anion equivalent' that has been used extensively in synthetic chemistry.¹⁷ For example, lithiated 1,3-dithiane been added to alkyl halides in order to produce aldehydes and either symmetrical or unsymmetrical ketones^{18–20} as shown in Scheme 2.

In addition, α -hydroxyketones, β -hydroxyketones, 1,2-diketones, and α -keto acid derivatives have also been produced from this protected formaldehyde^{21,22} (Scheme 3). There are over 1000 references where unlabeled 1,3-dithiane has been used as a synthetic precursor to synthesize a variety of important molecules.^{23–25} The importance of formyl anion equivalents in the synthesis of natural products has been reviewed recently.¹⁷

While there are numerous examples in the literature where 1, 3-dithiane has been used to make a variety of important synthetic precursors and biochemicals, isotopically labeled 1,3-dithiane has seen only limited use^{26,27} because of the lack of a commercial source for this important compound. Therefore, the availability of this new precursor will allow researchers to take advantage of the wealth of chemistry that has been performed using unlabeled 1,3-dithiane. 1,3-Dithiane is normally made from aqueous formaldehyde, paraformaldehyde, dialkoxymethane,²⁸ or trioxane. The example shown in Scheme 4 illustrates the synthesis of 1, 3-[2-¹³C]dithiane (**1**) from [¹³C]paraformaldehyde.²⁷

Using this route, the overall reported yield from [¹³C] paraformaldehyde is 51%. From our experience, yields from the expensive precursor [¹³C]paraformaldehyde are variable due in part to the volatility of the intermediates. We have developed a new route to 1,3-[2-¹³C]dithiane from [¹³C]methylphenyl sulfoxide that produces less volatile intermediates increasing the overall yield to 80% (Scheme 5).

Results and discussion

We have previously reported a large-scale and efficient one-pot synthesis for [¹³C]methyl phenyl sulfide from [¹³C]MEOH.⁹ We see [¹³C]methyl phenyl sulfide as a versatile, chemically stable, and nonvolatile labeling precursor. Here, we report its oxidation to [¹³C]methyl phenyl sulfoxide, which serves as a precursor for the synthesis of 1,3-[2-13C]dithiane. While many conditions have been used to oxidize sulfides to sulfoxides, we found simply treating [¹³C]methyl phenyl sulfide with aqueous hydrogen peroxide using ethanol as a solvent gave near guantitative yields of [¹³C]methyl phenyl sulfoxide. 1,3-[2-¹³C]Dithiane (1) was prepared in two steps from $[^{13}C]$ methyl phenyl sulfoxide (2) as shown in Scheme 5. The Pummerer rearrangement²⁹⁻³¹ proceeds quantitatively in the presence of trifluoroacetic anhydride to vield the mixed thioacetal 3. Heptane is added to the reaction flask, and the dichloromethane and excess trifluoroacetic anhydride and trifluoroacetic acid are then

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Scheme 1. 1,3-Dithiane.



Scheme 2. Application of 1,3-dithiane in the synthesis of aldehydes and ketones.

removed by distillation. Propanedithiol is then added to the reaction flask, and the mixture is refluxed until the reaction is complete as determined by ¹³C-NMR spectroscopy. The overall yield of the carbon-13 label from [¹³C]MEOH via our synthetic route of 80% may seem a modest improvement from Baxter and Abbot's²⁷ route from [¹³C]paraformaldehyde (overall yield 51%) until one considers the cost of the labeled starting material. Based on current published prices, [13C]paraformaldehyde (~\$22.31/ mmol, Cambridge Isotope Laboratories, Inc., Andover MA, USA) is 4.6-fold more expensive than [¹³C]MEOH (~\$4.83/mmol, Cambridge Isotope Laboratories, Inc., Andover MA, USA). Coupled with the overall yields, to prepare a gram of 1, 3-[2-¹³C]dithiane would require \$361 to purchase the precursor for the paraformaldehyde route and only \$50 to purchase the precursor for our route, which would be particularly attractive for large-scale synthesis.

To provide an alternate route to deuterated aldehydes, we have also prepared deuterated 1,3-dithiane. Although $[^{13}C, ^{2}H_{3}]$ methyl phenyl sulfoxide (**4**) can be produced from $[^{13}C, ^{2}H_{3}]$



Scheme 4. Synthesis of 1,3-[2-¹³C]dithiane (1) from [¹³C]paraformaldehyde.



Scheme 5. Synthesis of 1,3-[2-13C]- and 1,3-[2- $^{2}H_{2}$, 2- ^{13}C]dithiane from [^{13}C] methyl phenyl sulfoxide.

methyl phenyl sulfide, we have developed a much less expensive route to the desired deuterated 1,3-dithianes. The methyl protons in [¹³C]methyl phenyl sulfoxide (**1**) are quantitatively exchanged by heating in deuterium oxide and catalytic sodium deuteroxide. The [²H₃, ¹³C]methyl phenyl sulfoxide (**4**) is then treated as before to yield the 1,3-[2-²H₂, 2-¹³C]dithiane (**6**) in high yield. Based on the commercial availability of [¹⁴C] iodomethane and ³H₂O, our route could be used to make 1, 3-[2-¹⁴C]- or 1,3-[2-¹⁴C, 2-³H₂]dithiane.



Scheme 3. Application of 1,3-dithiane in the synthesis of α -hydroxyketones, β -hydroxyketones, 1,2-diketones, and α -keto acid derivatives.

Conclusion

In this paper, we have described an efficient synthetic route to isotopically-labeled 1,3-dithiane. In addition, we have described the exchange of deuterium into [¹³C]methyl phenyl sulfoxide. Thus, both 1,3-[2-¹³C]-, and 1,3-[2-²H₂, 2-¹³C]dithiane are synthesized from a single non-volatile starting material, [¹³C] methyl phenyl sulfide. An improved preparation of isotopically labeled 1,3-dithiane will allow for the efficient synthesis of many useful labeled aldehydes and ketones.

Experimental

General

[¹³C]Carbon monoxide and [¹³C]carbon dioxide enriched to 99.2% were supplied by the Los Alamos ICONS facility. [¹³C]MEOH^{2,3} and [¹³C]methyl phenyl sulfide⁹ were prepared by the National Stable Isotope Resource at Los Alamos using published methods. All other chemicals were purchased from commercial sources as reagent grade and used without purification. Proton-decoupled ¹³C (75 MHz) and ¹H (300 MHz) NMR spectra were obtained at 25°C at using a Bruker DRX-300 NMR spectrometer. Samples were dissolved in CDCl₃ and the resonance signal from CDCl₃ (¹³C, 77.23 ppm) or CHCl₃ (¹H, 7.27 ppm) used as an internal chemical shift standard. Proton-decoupled ¹³C-NMR specta were used to determine the extent of deuteration in [¹³C, ²H₃]methyl phenyl sulfoxide. To minimize the effects of NOE and differences in T₁ between protonated and deuterated species, the ¹H-decoupler was turned off during a 60 s delay between pulses.

[¹³C]Methyl phenyl sulfoxide (2)

In a 1-L round bottom flask [¹³C]methyl phenyl sulfide (10.0 g, 77.6 mmol, 1 eq) was dissolved in ethanol (50 mL). The solution was cooled in an icewater bath. Hydrogen peroxide (30% by mass, 23.8 g, 7.92 g, 233 mmol, 3 eq) was added dropwise via addition funnel. The reaction was permitted to stir at room temperature. The reaction was monitored by ¹³C-NMR following the disappearance of [¹³C]methyl phenyl sulfide $(\delta = 16 \text{ ppm})$ and appearance of the desired [¹³C]methyl phenyl sulfoxide $(\delta = 44 \text{ ppm})$. After 24 h, the reaction was complete. The reaction mixture was then transferred to a 1-L Erlenmeyer flask containing dichloromethane (100 mL) and cooled in an ice/water bath. Remaining H₂O₂ was decomposed by dropwise addition of aqueous sodium bisulfite (15%) until oxidant was no longer visualized using potassium iodide/starch paper. The layers were separated, and the organic layer was dried with sodium sulfate and then vacuum filtered. The volatiles were removed using a rotary evaporator followed by evacuation under reduced pressure to constant weight. Compound 2 was recovered as a colorless solid (11.0 g, 99% yield) that was used without further purification. ¹H-NMR (CDCl₃, 300 MHz): $\delta = 2.73$ (d, 3H, ¹J_{CH} = 139.6 Hz), 7.44–7.75 (m, 5H). ¹³C-NMR (CDCl₃, 75 MHz): $\delta = 44.3 (^{13}CH_3)$, 123.8, 129.7, 131.3, 146.0.

(Phenylthio) [¹³C]methyl 2,2,2-trifluoroacetate (3)

In a 500-mL oven-dried round bottom flask [¹³C]methyl phenyl sulfoxide (18.0 g, 0.125 mol, 1.0 eq) was dissolved in dichloromethane (181 mL). The reaction vessel was flushed with argon and was cooled using an ice-water bath. After the solution had stirred for 60 min, the internal temperature of the solution was 4°C. Trifluoroacetic anhydride (210 g, 1.0 mol, 8.0 eq) was added via syringe to the stirring solution. Product formation was monitored by ¹³C-NMR noting the disappearance of [¹³C] methyl phenyl sulfoxide (δ = 44 ppm) and appearance of (phenylthio)[¹³C] methyl trifluoroacetate (δ = 73 ppm). The reaction was judged to be complete after 2.5 h. Heptane (93 mL) was then added to the reaction mixture. The reaction vessel was covered with an air-cooled reflux condenser and placed into a heating mantle. A simple distillation apparatus was placed above the air-cooled reflux condenser. The reaction was refluxed for 4.5 h, until the dichloromethane and trifluoroacetic anhydride and acid were distilled away from the reaction solution. Because of its

reactivity, attempts at isolation of **3** were not successful. For this reason, **3** was used in the following reaction as a solution in heptane.

1,3-[2-¹³C]Dithiane (1)

In a 250 mL oven-dried round bottom flask phenylthio [¹³C]methyl trifluoroacetate (17.1 g, 0.072 mol, 1 eg) was dissolved in heptane (102 mL). The reaction vessel was placed under a reflux condenser $(T = -3^{\circ}C)$ under a nitrogen atmosphere. To the stirring solution 1, 3-propanedithiol (7.8 g, 0.072 mol, 1.1 eq) was added in a single portion. Amberlyst[®] ion exchange resin (17.1 g, 1:1 wt ratio of labeled starting material) was added as a solid through a powder funnel. The reaction flask was placed into a heating mantle ($T = 135^{\circ}C$) and allowed to reflux. Product formation was monitored by ¹³C-NMR noting the disappearance of (phenylthio)¹³C]methyl trifluoroacetate ($\delta = 73 ppm$) and the subsequent appearance of the desired 1,3-[2-¹³C]dithiane (δ = 32 ppm) The reaction was judged to be complete after 18 h. The hot reaction mixture was filtered quickly using vacuum and a Büchner funnel to remove the Amberlyst® resin. Heptane (50 mL) was removed by simple distillation to leave the product in 52 mL heptane (6 mL/gram of 1). The reaction mixture was allowed to cool to room temperature and then washed with 1 M agueous sodium hydroxide (50 mL). The aqueous layer was then extracted with heptane (100 mL). The combined organic layers were cooled in a freezer at -19°C for 1 h and filtered to yield 1 as colorless crystals. Pentane (15 mL) was added to the filtrate and the mixture placed back into the freezer, where more of compound 1 crystallized and was recovered by filtration. The crystals were combined to obtain $1,3-[2-^{13}C]$ dithiane (1) (7.0 g, 80%) having an m.p. range of 52–54°C. ¹H-NMR (CDCl₃, 300 MHz): δ = 2.08 (m, 2H), 2.84 (m, 4H), 3.79 (d, 2H, ¹J_{CH} = 149.6 Hz). ¹³C-NMR (CDCl₃, 75 MHz): δ = 26.6 (d, ²J_{CC} = 2.8 Hz, CH₂CH₂S¹³CH₂), 29.9 (d, ³J_{CC} = 1.1 Hz, $CH_2CH_2S^{13}CH_2$), 31.9 (s, $S^{13}CH_2S$). Elemental analysis of **1**: Calculated: ^{T3}CC₃H₈S₂: C, 40.45; H, 6.65; S, 52.90. Found: C, 40.45; H, 6.51; S, 52.90.

$[^{2}H_{3}, ^{13}C]$ Methyl phenyl sulfoxide (4)

A 100-mL round bottom reaction flask was equipped with a magnetic stir bar, filled with ²H₂O, and stoppered. After stirring overnight, the roundbottom flask was then emptied, flushed with argon, then ²H₂O (30 mL, 99% ²H) was added, stirring under an argon atmosphere. The [¹³C]methyl phenyl sulfoxide (2) (1.52 g, 10.8 mmol, 1 eq) was added to the ${}^{2}H_{2}O_{1}$ forming a heterogeneous mixture. An air-cooled reflux condenser was fixed to the reaction flask and the reaction mixture, and placed in an argon atmosphere. Sodium deuteroxide (0.22 g, 40% in D₂O, 2.2 mmol, 0.20 eq) was added via syringe. The reaction mixture was then placed into a heating mantle, and refluxed for 4 h. As the reaction mixture came to reflux, it became homogeneous. After heating at reflux for 4 h, the reaction mixture was cooled and extracted with dichloromethane (3x, 15 mL). The organic layers were combined and dried using sodium sulfate, filtered, and then volatiles were removed by vacuum using a rotary evaporator to yield **4** as a light tan oil (1.53 g, 99%); ¹³C NMR analysis showed >99% deuterium incorporation into 4. The resulting product was used without further purification. ¹H-NMR (CDCl₃, 300 MHz): δ = 7.45–7.81 (m, 5H). ¹³C-NMR (CDCl₃, 75 MHz): $\delta = 43.2$ (septet, ¹ $J_{CD} = 21.2$ Hz, ¹³CD₃), 123.6, 129.4, 131.1, 145.6.

(Phenylthio) [²H₂, ¹³C]methyl 2,2,2-trifluoroacetate (5)

(Phenylthio)[¹³C, ²H₂]methyl trifluoroacetate **(5)** was prepared from [¹³C, ²H₃]methyl phenyl sulfoxide (1.53 g, 0.011 mol) using the same procedure reported for **3**. Because of its reactivity, attempts at isolation of **5** were not successful. For this reason, **5** was used in the following reaction as a solution in heptane.

$1,3-[2-^{2}H_{2}, 2-^{13}C]$ Dithiane (6)

1,3-[2-²H₂, 2-¹³C]Dithiane (**6**) was prepared from (phenylthio)[²H₂, ¹³C] methyl trifluoroacetate (**5**) (2.54 g 0.011 mol) using the same procedure and with comparable yields reported previously for **1**. ¹H-NMR (CDCl₃, 300 MHz): δ = 2.08 (m, 2H), 2.83 (m, 4H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 26.7 (d, ²J_{CC} = 2.8 Hz, CH₂CH₂S¹³CD₂), 29.9 (s, CH₂CH₂S¹³CH₂), 31.6

(pentet, ${}^{1}J_{CD}$ = 22.9 Hz, $S^{13}CD_{2}S$). Elemental analysis of **6**: Calculated: ${}^{13}CC_{3}^{2}H_{2}H_{6}S_{2}$: C, 39.80; H, 8.15; S, 52.05. Found: C, 39.69; H, 8.11; S, 51.92.

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Conflict of Interest

The authors did not report any conflict of interest.

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