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Large-Scale Preparation of [^{13}C]Methyl Phenyl Sulfide from [^{13}C]Methanol by a One-Step Process

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Abstract:

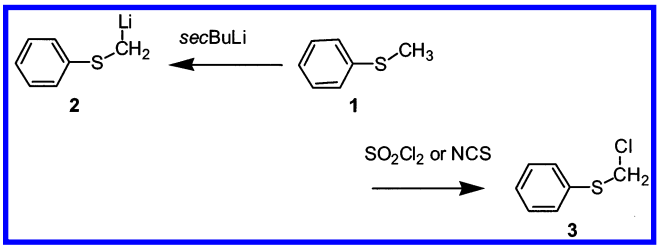
We have developed a large-scale "one-pot" procedure for the conversion of commercially available [^{13}C]- or [$^{2}H_3$,^{13}C]-methanol to [^{13}C]- or [$^{2}H_3$,^{13}C]methyl phenyl sulfide. [^{13}C]methyl phenyl sulfide is a potentially versatile, chemically stable, and nonvolatile labeling precursor. In addition, we report an efficient method for the oxidation of [^{13}C]methyl phenyl sulfide to [^{13}C]methyl phenyl sulfone. Finally, we have used [^{13}C]methyl phenyl sulfide to produce ^{13}C-labeled methyl iodide, containing exactly one or two deuterons.

Introduction

Stable isotope-labeled amino acids and nucleotides are required for structural and mechanistic studies of proteins and oligonucleotides. In addition, isotopically labeled biologically active compounds are required for many phases of drug discovery and development including elucidation of biosynthetic pathways, pharmacokinetics, and drug metabolism. For many applications, site-specific ^{13}C- or combined ^{13}C,^{2}H-labeling are required. Carbon-13 is enriched from its lighter isotope by cryogenic distillation of carbon monoxide; thus, all labeled carbons must be derived ultimately from ^{13}CO. The highly efficient conversion of CO to useful chemical precursors is a unique aspect of stable isotope-labeling chemistry. Because inefficiencies in these first steps add greatly to the expense of isotope labeling, considerable effort was devoted to the preparation of useful synthetic precursors giving rise to efficient large-scale methods for the synthesis of methane,[1] methanol,[2,3] methyl iodide,[3−7] sodium formate,[8] potassium cyanide,[9] and carbon dioxide. The most useful of the electrophilic one-carbon precursors, methyl iodide and carbon dioxide, are difficult to store and use efficiently because of their volatility.

Methyl phenyl sulfide has rich chemistry and if prepared with carbon and deuterium labels in the methyl group would be a potentially versatile labeled precursor (Scheme 1). For example, methyl phenyl sulfide (**1**) can be used as a nucleophilic synthon (**2**)[10−16] and is easily converted into an electrophilic synthon (**3**).[17−24] In addition, methyl phenyl sulfide would provide a chemically stable and nonvolatile carrier for the valuable label.

Scheme 1



Therefore, we would like to introduce a new very versatile labeled one-carbon precursor [^{13}C]methyl phenyl sulfide (**4**) which can also be used to prepare [^{13}C]methyl phenyl sulfone (**5**).[25−27] Choudhry and co-workers demonstrated the application of [^{14}C]methyl phenyl sulfone for the production

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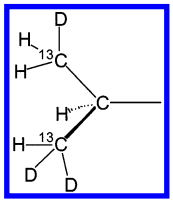


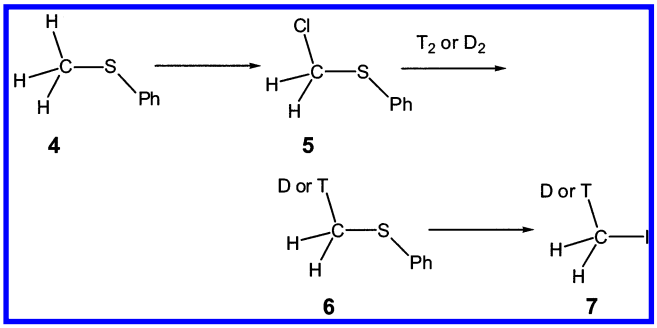
Figure 1.

of labeled ketones.[28] They prepared the sulfone by the reaction of sodium benzene sulfinate with [^{14}C]methyl iodide. There are many examples of the formation of unlabeled ketones by using methyl phenyl sulfone.[29,30] The unlabeled sulfone has also been alkylated[30] and used to generate alkenes.[31]

Our initial interest in ^{13}C-labeled methyl phenyl sulfide developed because we wanted to prepare ^{13}C-labeled methyl groups with exactly one or two deuteriums as shown in Figure 1. These isotopically differentiated methyl groups are attractive for a variety of applications. Our interest in these methyl groups stems from a need to produce a chirally differentiated isopropyl group as illustrated in Figure 1. These prochiral isopropyl systems can be found, for example, in the side chains of the natural amino acids valine and leucine.

Several methods for the production of methyl groups containing one or two deuteriums or tritiums have been described.[32−35] For example, $CHD(T)_2OH$ has been prepared by sodium borohydride reduction of formylesters[35] or hydrogenolysis of chloromethyl ethers.[32] The use of methyl phenyl sulfide appeared to be the best method for the production of both carbon and deuterium labeled methyl iodides. Rappaport and co-workers[33] used unlabeled methyl phenyl sulfide to produced these isotopically labeled methyl groups with single deuterium and tritium labels. This synthesis is illustrated in Scheme 2.

Scheme 2



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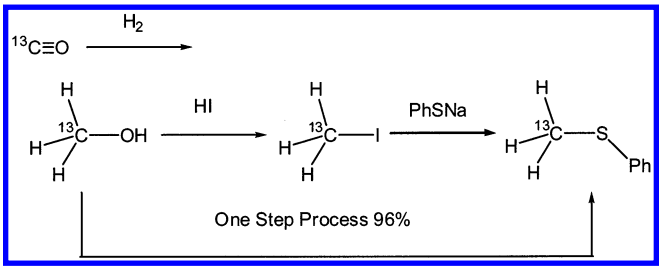
We have developed efficient large-scale one-pot procedures for the conversion of commercially available [^{13}C]- or [$^{2}H_3$,^{13}C]methanol to [^{13}C]- or [$^{2}H_3$,^{13}C]methyl phenyl sulfide (**1**). This process avoids otherwise inevitable losses resulting from the isolation of labeled methyl iodide. Methyl phenyl sulfide provides a chemically stable and nonvolatile carrier for the expensive label. In addition, we report an efficient method for the oxidation of [^{13}C]methyl phenyl sulfide to [^{13}C]methyl phenyl sulfone. Finally, we have produced ^{13}C-labeled methyl iodide, with exactly one or two deuterons from [^{13}C]methyl phenyl sulfide.

Results and Discussion

There are many procedures published for the synthesis of methyl phenyl sulfide. Of these, Herriott and Picker,[36] reported a high-yielding alkylation of thiophenol using methyl iodide. Although [^{13}C]methanol is available commercially, the National Stable Isotope Resource produces [^{13}C]methanol from [^{13}C]carbon monoxide on the 1−10 mol scale. Thus, we could derive methyl iodide from the readily available labeled methanol. A drawback and potential hazard of this synthesis stems from the fact that methyl iodide is both volatile and carcinogenic. Thus, we attempted the synthesis of the desired methyl phenyl sulfide on a mole scale by combining two synthetic steps into one process which avoids the need for the isolation of [^{13}C]methyl iodide (Scheme 3).

Scheme 3



[^{13}C]Methyl iodide is normally produced by refluxing [^{13}C]methanol in hydriodic acid (47−57%) and collecting the volatile components. This material is then dried by treatment with molecular sieves and redistilled to give [^{13}C]-methyl iodide in variable yields (62−94%).[3−7] Using essentially the same procedure methyl iodide has been produced in reported yield of 79,[4] 73,[5] 62,[6] 93,[7] and 94%.[3] The differences in reported yields are likely due to the extreme volatility of methyl iodide and the associated variable losses in handling. Because the subsequent reaction to produce methyl phenyl sulfide is carried out in a biphasic system of benzene and aqueous sodium hydroxide, we felt that the methyl iodide did not need to be dried and redistilled to give satisfactory yields of the desired methyl phenyl sulfide. We further surmised that isolation of the methyl iodide was not necessary and felt that it could be delivered directly to the second step of this reaction to avoid the isolation problems associated with methyl iodide. Indeed this proved to be the case, and we were able to produce methyl phenyl sulfide by this modification in a reproducible 96% yield.

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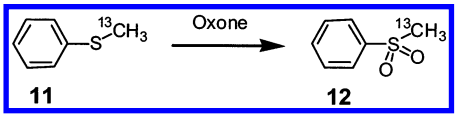
Having developed a high-yield method for the production of [^{13}C]methyl phenyl sulfide, we explored its conversion to [^{13}C]methyl phenyl sulfone. Many procedures exist for the preparation of sulfones from sulfides. Several reports exist for the oxidiation of sulfides to sulfoxide or sulfones by using oxone,[37−39] DCC/hydrogen peroxide[40] and sodium hypochlorite.[41] We found that an ethanol solution of the [^{13}C]methyl phenyl sulfide (**11**) added to aqueous oxone gave nearly a quantitative yield of [^{13}C]methyl phenyl sulfone (**12**) (Scheme 4).

Scheme 4



The required [^{2}H,^{13}C]- and [$^{2}H_2$,^{13}C]methyl iodides were derived from methyl phenyl sulfide as outlined below. The quantitative deprotonation of [^{13}C]- or [$^{2}H_3$,^{13}C]methyl phenyl sulfide was accomplished using *sec*-butyllithium at −78 °C,[42] which was then deuterated by quenching the reaction with deuterium oxide. The use of *sec*-butyllithium has significant advantages over the reported use of *n*-butyllithium because the requirement for cosolvents and additives is eliminated.[43] Also, this deprotonation/deuteration step allows for a one-step conversion to the desired product instead of the two-step process reported by Rappaport and co-workers.[33] On the basis of NMR analysis, the deuterium content of the product [^{2}H,^{13}C]- and [$^{2}H_2$,^{13}C]methyl phenyl sulfides was found to be equivalent to that of the deuterium oxide used, which in most cases was 100%-*d*. Finally, the labeled methyl iodides were produced in good yield by slowly heating benzyl iodide and methyl phenyl sulfide to 160 °C and collecting the volatiles using a liquid nitrogen-cooled trap (Scheme 5).[33]

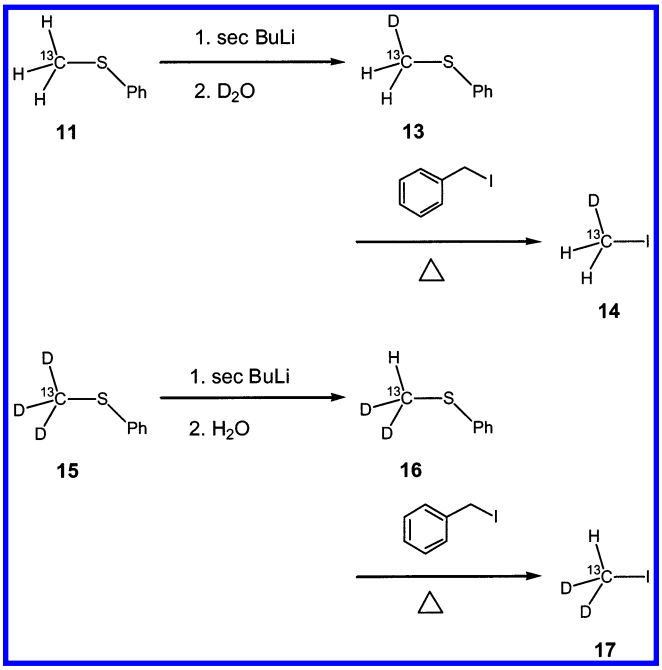
This work details simple high-yield large-scale methods for the production of isotopically labeled thioanisoles and isotopically labeled methyl iodides which are important labeled precursors that can be used for a variety of applications. The use of these intermediates for the synthesis of labeled amino acids and other important biochemicals will be reported elsewhere.

Experimental Section

All reagents and solvents were purchased from Aldrich Chemical Co. Dry tetrahydrofuran was prepared for each use by distillation of reagent grade tetrahydrofuran from potassium/benzophenone.

Melting points (mp) were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and

Scheme 5



^{13}C NMR) spectra were obtained using TMS (^{1}H NMR) or $CDCl_3$ (^{13}C NMR) as the internal standards. Thin-layer chromatography (TLC) was performed using either silica gel on glass plates (for analytical or preparative TLC, from Analtech) or silica gel (DCC) for preparative columns.

[^{13}C]Methyl Phenyl Sulfide (11). A 1-L, two-neck flask was fitted with an argon inlet adapter and an air-cooled condenser. This flask was charged with 46.2 g (1.40 mol) [^{13}C]methanol (99% ^{13}C) and 726 mL (4.20 mol, 3.00 equiv) HI (47% solution in water). The air-cooled condenser was fitted with an outlet adapter, which in turn was attached (via a short piece of Tygon tubing) to a long solvent trap immersed in an ice−water bath. This ice-cooled solvent trap was connected to an inlet adapter on a 2-L, two-neck flask containing a vigorously stirring biphasic mixture of 169.7 g (1.54 mol, 1.10 equiv) thiophenol and 140 g (3.50 mol, 2.50 equiv) of sodium hydroxide in 400 mL of benzene/300 mL of water. The second neck of this flask was fitted with a 2-propanol/dry ice-cooled condenser with an argon outlet. The [^{13}C]methanol/HI solution was heated at 70°C for 6 h under a slow, continuous stream of argon. After this time, the [^{13}C]methyl iodide, which had collected in the ice-cooled trap, was transferred into the 2-L flask containing the Na-thiophenoxide mixture. The [^{13}C]methanol/HI solution was then heated at 85 °C for 2 h, and then heating was discontinued. Again, any [^{13}C]methyl iodide which had collected in the ice-cooled trap was transferred to the Na-thiophenoxide mixture, and this mixture was allowed to stir overnight. The mixture was then transferred to a separatory funnel containing 400 mL of Et_2O, and the organic phase was washed with three 100-mL portions of water and then dried over Na_2SO_4. Removal of the solvents under reduced pressure gave 168 g (95.6%) of [^{13}C]methyl phenyl sulfide as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (d, 3H, $^{1}J_{CH}$ = 139.6 Hz), 7.11−7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.8, 126.7, 125.0, 15.9.

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[^{13}C,^{2}H$_3$]Methyl Phenyl Sulfide (16). [^{13}C,^{2}H$_3$]methyl phenyl sulfide was prepared from [^{13}C,^{2}H$_4$]methanol using the procedure described for **11**. From 36.6 g (0.987 mol) of [^{13}C,^{2}H$_4$]methyl alcohol, 540 mL (2.96 mol, 3.00 equiv) of HI (47% aqueous solution), 120 g (1.09 mol, 1.10 equiv) of thiophenol, and 98.7 g (2.47 mol, 2.50 equiv) of NaOH was obtained 125 g (98.6%) of [^{13}C,^{2}H$_3$]methyl phenyl sulfide as a clear, slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.26 (m, 5H); ^{13}C (75 MHz, $CDCl_3$) δ 138.4, 128.8, 126.7, 125.0, 15.1 (septet, $^{1}J_{DC} = 21.3$ Hz).

[^{13}C,^{2}H]Methyl Phenyl Sulfide (14). A 250-mL round-bottom flask fitted with a magnetic stir bar was charged with 5.00 g (39.9 mmol) of [^{13}C]methyl phenyl sulfide; 70 mL of THF was added, and the stirred solution was cooled to −78 °C in a dry ice bath. A 1.3 M solution of *sec*-BuLi (32.2 mL, 41.9 mmol, 1.05 equiv) was added via syringe, and the solution was stirred at −78 °C for 1.5 h. After this time, the reaction was quenched with 10 mL of $^{2}H_2O$. The mixture was poured into a separatory funnel containing enough water to dissolve the insoluble material, and the aqueous phase was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the product (4.98 g, 99%) was obtained through careful removal of the solvents under reduced pressure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (d, 2H, $^{1}J_{CH} = 139$ Hz), 7.13−7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 128.8, 126.6, 125.0, 15.61 (t, $^{1}J_{DC} = 21.5$ Hz).

[^{13}C,^{2}H$_2$]Methyl Phenyl Sulfide (17). Using the procedure described above, [^{13}C,^{2}H$_2$]methyl phenyl sulfide (**17**) was prepared from [^{13}C,^{2}H$_3$]methyl phenyl sulfide (**16**). From 10.0 g of **16** (78.0 mmol) and 72 mL of 1.3 M *n*-BuLi (93.6 mol, 1.2 equiv) stirring at −78 °C for 3 h was obtained, after a H_2O quench, 9.83 g (99%) of product as a clear, pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (d, 1H, $^{1}J_{CH} = 139$ Hz), 7.12−7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.8, 126.6, 125.0, 15.35 (pentet, $^{1}J_{DC} = 21.3$ Hz).

[^{13}C,^{2}H]Methyl Iodide (15). A two-neck 100-mL round-bottom flask was fitted with an Ar inlet adapter and a short-path condenser. To the flask was added 12.0 g (95.1 mmol) of [^{13}C,^{2}H]methyl phenyl sulfide, along with 41.5 g (0.190 mol, 2.00 equiv) of benzyl iodide. The reaction flask was heated gradually to 110 °C under a steady Ar stream. The reaction darkened as [^{13}C,^{2}H]methyl iodide passed from the reaction flask into a dry ice/2-propanol-cooled receiving flask. Heating was continued for 7 h and the collected product purified by cryogenic distillation to give 11.4 g (83%) of a clear, colorless liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (d, 2H, $^{1}J_{CH} = 151$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −23.5 (t, $^{1}J_{DC} = 23.0$ Hz).

[^{13}C,^{2}H$_2$]Methyl Iodide (17). A similar procedure was used to obtain [^{13}C,^{2}H$_2$]methyl iodide: 10.0 g (78.6 mmol) of [^{13}C,^{2}H$_2$]methyl phenyl sulfide and 34.3 g (0.157 mol, 2.00 equiv) of benzyl iodide were heated between 80 and 90 °C under a vacuum over a 7-h period. [^{13}C,^{2}H$_2$]methyl iodide was collected in a liquid N_2-cooled flask and purified by cryogenic distillation over 4 Å molecular sieves to yield 9.07 g (79.6%) of product as a clear, colorless liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15.(d, 1H, $^{1}J_{CH} = 151$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −23.5 (pentet, $^{1}J_{DC} = 23.2$ Hz)}.

[^{13}C]Methyl Phenyl Sulfone (13). Oxone (614.8 g; 0.84 mol/2.5 equiv/2.6 equiv oxidant) is dissolved in deionized water (750 mL), and ice (250 g) is added. [^{13}C]Methyl phenyl sulfide (45.0 g; 0.32 mol), dissolved in ethanol (200 mL), is added dropwise over a period of 3.5 h via a dropping funnel. The reaction is stirred at room temperature and monitored by TLC (ether, R_f 0.4). The product was completely formed after 4 h. Then the reaction mixture is poured into a separatory funnel, and the aqueous phase is extracted two times with ethyl acetate (600 mL). The combined organic phases are dried with Na_2SO_4 and then filtered, and solvents are evaporated. Remaining solvent was removed from the solid under vacuum using a liquid nitrogen-cooled trap. [^{13}C]-Methyl phenyl sulfone (53.3 g; 96.4%) was obtained as a white solid, pure by NMR (>98%), which could be used in subsequent reactions without further purification. ^{1}H [$CDCl_3$, 300 MHz] δ 3.06 (3H, $^{1}J_{CH} = 138$ Hz), 7.56−7.69 (3 H, m_{ABX}), 7.95 (2H, $J_{ABX} = 7.5$ Hz), ^{13}C [$CDCl_3$, 75 MHz] δ 44.66, 127.52, 129.55, 133.89, 140.81 (d, $^{2}J_{CC} = 8.7$ Hz) mp: 84−86° C [Lit. 85−88°].

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