PREPARATION OF [^{18}O]-CHLOROCARBONYLSULFENYL CHLORIDE

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Summary

[^{18}O]-Chlorocarbonylsulfenyl chloride with an isotopic purity of 92% was prepared in three steps starting with the [^{18}O]-hydrolysis of 2-ethyl-1,3-dioxolane to [^{18}O]-propanal, which was then converted to [^{18}O]-*O*-1-methylpropyl *S*-methyl dithiocarbonate, which was then chlorinated to give the title compound. Distilled yields for the three steps were 57%, 49%, and 40% respectively.
Key Words: [^{18}O]-chlorocarbonylsulfenyl chloride, [^{18}O]-xanthate, [^{18}O]-propanal

Introduction

Chlorocarbonylsulfenyl chloride (**1**), a versatile bifunctional reagent[1], is used in this laboratory for the preparation of *N*-dithiasuccinoyl (Dts) protected derivatives of amines and amino acids[2-4]. In order to determine the fate of the carbonyl oxygen during some transformations[3,5,6] involving **1**, we required the reagent enriched with oxygen-18. The present communication describes an efficient route to [^{18}O]-**1** of excellent isotopic purity.

Results and Discussion

The preferred preparation of **1**, developed by Weiss[7], involves controlled hydrolysis of trichloromethanesulfenyl chloride (**2**) in the presence of sulfuric

$$\underset{\mathbf{2}}{Cl_3CSCl} + H_2O \xrightarrow{H_2SO_4} \underset{\mathbf{1}}{ClC(=O)SCl} + 2\ HCl$$

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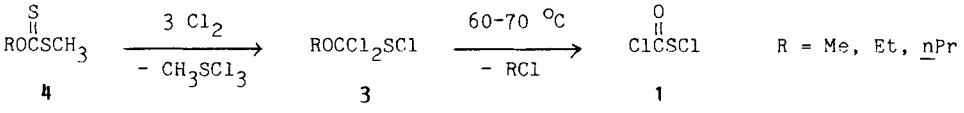
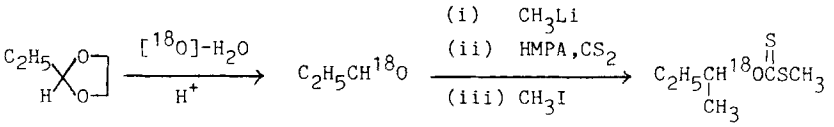
acid. When an adaptation of this procedure was carried out using [^{18}O]-water and fuming sulfuric acid, **1** was obtained in good yield but with only 17 atom% ^{18}O. This isotopic purity agreed with that expected from complete exchange of the [^{16}O]-sulfuric acid and the [^{18}O]-water. Although in principle the synthesis could be repeated with [^{18}O]-sulfuric acid, the high expense of that reagent together with the inefficient utilization of isotope argue against such an approach. Also, attempts using other strong acids to promote hydrolysis of **2** were unsuccessful.

A second literature preparation of **1** involves[8] thermolysis of alkoxydichloromethanesulfenyl chlorides (**3**), in turn obtained[9] by chlorination of O-alkyl S-methyl dithiocarbonates (xanthates) with primary alkoxy groups (**4**). For our purposes, we abandoned the primary xanthate system, but rather selected the secondary O-1-methylpropyl S-methyl dithiocarbonate (**5**) as the precursor to **1**. This choice was dictated both by the chemistry and the need for alkyl groups that would be converted to co-products easily separable from **1**.



4 **3** **1**

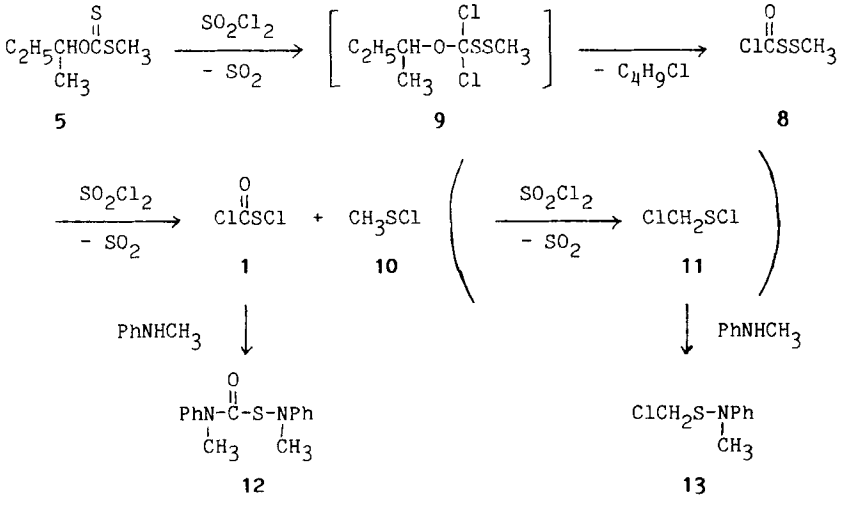
The introduction of label was accomplished by [^{18}O]-hydrolysis of 2-ethyl-1,3-dioxolane (**6**) to [^{18}O]-propanal (**7**) in a manner similar to the preparation[10] of [^{18}O]-ethanal from 1,1-dipropoxyethane and [^{18}O]-water. The optimal catalyst was found to be sulfuric acid rather than hydrogen chloride; the increased yield of **7** outweighing the slight (1 to 2%) isotopic dilution due to the sulfuric acid. Next, propanal (**7**) was taken directly to **5**, with an isotopic purity of 92%, by sequential reactions with methyl lithium, carbon disulfide and iodomethane. One equivalent of hexamethylphosphoramide (HMPA) was found to be necessary for the lithium 2-butoxide intermediate to react completely with the carbon disulfide.



6 **7** **5**

(Methylthio)thiocarbonyl chloride[11,12] also reacted with the lithium 2-butoxide to give **5**, but the yield was lower and considerable amounts of dimethyl trithiocarbonate[12,13] contaminated the product. The procedure used is preferred, in terms of the number and ease of purification steps, over the alternative of reducing **7** to 1-propanol with subsequent conversion to **4** by standard methods[12,14,15].

The chlorination of xanthates with secondary alkoxy groups has been attempted previously[9], but any presumed secondary alkoxydichloromethanesulfenyl chloride was found to readily lose hydrogen chloride and could not be isolated. Our attempts to chlorinate **5** gave product mixtures containing **1**, probably formed by loss of hydrogen chloride and butenes from 1-methylpropoxydichloromethanesulfenyl chloride. However, since alkenes react[1] with **1**, it was not possible to isolate the pure sulfenyl chloride. Therefore, **5** was chlorinated under milder conditions using sulfuryl chloride in n-pentane, found to be less reactive and more suitable than the same reagent in dichloromethane. Although the stoichiometry involves only two equivalents, three to four equivalents of sulfuryl chloride were needed to drive the reaction to completion. The chlorination could be stopped at (methyldithio)carbonyl chloride (**8**)[12], which forms by rapid loss of 2-chlorobutane from the intermediate **9**. The structure of



9 can be inferred by analogy to our earlier result[16] with primary alkoxy xanthates (**4**), where the initial chlorination adduct was established to rearrange to the isolable alkoxydichloromethyl methyl disulfane. Separate experiments showed that pure **8** could be chlorinated to **1** plus methanesulfenyl chloride (**10**)[12,17]. Reduced pressure distillation of the product mixture from the chlorination of **5** with sulfuryl chloride gave desired **1** in fair yield, whereas distillation at atmospheric pressure gave only small amounts of **1**. The crude **1** was contaminated primarily with chloromethanesulfenyl chloride (**11**)[18], which presumably arises by reaction of **10** with excess sulfuryl chloride. Redistillation gave chemically pure **1** with an isotopic purity of 92%, as determined by mass spectral analysis of the N-methylaniline derivative **12** (Table 1). Thus, no isotopic dilution occurred during the final step of the synthesis.

Table 1. Mass Spectra of N,N'-Dimethyl-N,N'-Diphenylcarbamoylsulfenamide (**12**)

		Source of Cl(C=O)SCl		
		Control	Hydrolysis of **2**	Chlorination
		$[^{16}O]$	with $[^{18}O]$-H_2O	of $[^{18}O]$-**5**
Ion	m/z	Relative Intensity		
$M^{+\cdot}$ (^{18}O or ^{34}S)	274	0.6	2.2	12
$M^{+\cdot}$ (^{16}O and ^{32}S)	272	10	8.1	1.5
$PhN(Me)COS^+$ (^{18}O)	168	-	0.7	1.5
$PhN(Me)COS^+$ (^{16}O)	166	1.7	1.8	-
$PhN(Me)CO^+$ (^{18}O)	136	1.0	21	91
$PhN(Me)CO^+$ (^{16}O)	134	100	100	6.4
Isotopic purity			17%	92%

Spectra obtained on a Kratos/AEI MS-30 using solid probe insertion at 25-50 °C, and an ionizing voltage of 70 eV. Ions common to all three spectra included: m/z 138 [$PhN(Me)S^+$, 3-6%], 106 [$PhN(Me)^+$, 70-100%], 77 [Ph^+, 50-70%]. Isotopic purity was calculated from $\frac{\text{(intensity at m/z 136)}}{\text{(sum of intensities at m/z 134 and 136)}}$.

Experimental Section

General. Proton NMR and IR spectra were observed[12] on samples dissolved in $CDCl_3$, using a Varian HFT80 and a Perkin-Elmer 297 instrument respectively. Electron ionization mass spectra were obtained on a Kratos/AEI MS-30 at a source temperature of 200 °C, sample insertion conditions and ionizing voltages as specified in the text.

Chemical purities of samples containing **1** were assessed by combining known weights of sample plus toluene and diluting in $CDCl_3$, followed by (a) integration of proton-containing impurities with respect to toluene in the NMR spectrum; and (b) conversion to N-methylanilide **12** as quantitated[12] by NMR and HPLC. Compound **12** showed δ 7.1-7.4 (m, 10 H), 3.38 (s, 3 H), 3.27 (s, 3 H). Compound **13** is new; it showed δ 6.7-7.3 (m, 5 H), 4.76 (s, 2 H), 3.48 (s, 3 H).

Materials. [^{18}O]-Water was obtained from MSD Isotopes (97.2%) and Cambridge Isotopes (98%). HMPA was dried by distillation from calcium hydride, and stored over 4 Å molecular sieves. Other solvents and chemicals were reagent grade and used without further purification. Chloromethanesulfenyl chloride (**11**) was made by chlorination of dimethyl disulfide; bp 120 °C (740 mm) [lit.[18] bp 50 °C (40 mm)], NMR: δ 5.12 (s). Unlabelled **5** was prepared in 70% yield from potassium 2-butyl xanthate and iodomethane; bp 50 °C (1 mm) [lit.[19] bp 78 °C (11 mm)], NMR: δ 5.64 (m, 1 H), 2.54 (s, 3 H), 1.5-1.8 (m, 2 H), 1.35 (d, 3 H, J = 6.3 Hz), 0.94 (t, 3 H, J = 7.1 Hz). In pilot experiments where **5** was treated with SO_2Cl_2, **8** was detected in the NMR at δ 2.58 (s), as was 2-chlorobutane at δ 3.98 (m, 1 H), 1.6-1.9 (m, 2 H), 1.50 (d, 3 H, J = 6.6 Hz), 1.01 (t, 3 H, J = 6.8 Hz).

[^{18}O]-Chlorocarbonylsulfenyl Chloride (**1**) by Hydrolysis of Trichloromethanesulfenyl Chloride (**2**). A 7 mL screw-cap test tube was charged successively with [^{18}O]-water (0.5 mL, 28 mmol), fuming sulfuric acid containing 20% sulfur trioxide (3.4 g, ∿40 mmol), and **2** (1.1 mL, 10 mmol), and this mixture was stirred vigorously for 7 hr at 50 °C. Shorter reaction times or less water resulted in the recovery of unreacted **2** whereas a longer reaction time led to decomposition to gases and elemental sulfur. The upper phase (0.93 g, 72%) was separated by centrifugation, and shown to be >98% pure **1**, free of starting **2**. Converted[12] to

12 (0.25 mmol scale, 88% yield); isotopic purity 17% (Table 1).

2-Ethyl-1,3-dioxolane (**6**). Propanal (100 mL, 1.39 mol), 1,2-ethanediol (83 mL, 1.5 mol) and benzene (300 mL) were refluxed with p-toluenesulfonic acid (1 g) under a Dean-Stark trap until 25 mL (1.39 mol) of water had been collected. After removal of the benzene through a 40 cm Vigreux column, the product was distilled at bp 108 °C (lit.[20] bp 107 °C). Redistillation gave 72 g (51%) of **6**. NMR: δ 4.82 (t, 1 H, J = 4.6 Hz), 3.84-4.00 (m, 4 H), 1.68 (dq, 2 H, J = 4.6, 7.7 Hz), 0.96 (t, 3 H, J = 7.7 Hz).

[^{18}O]-Propanal (**7**). A mixture of [^{18}O]-water (1.24 g, 62 mmol), **6** (6.34 g, 62 mmol) and fuming sulfuric acid (20 mg, 0.2 mmol) was heated with stirring in a short-path distillation apparatus with a cooled receiving flask. As the oil bath reached 90 °C the aldehyde began to distill at bp 48-52 °C. The bath was maintained at 90-100 °C until all the propanal had distilled and the residue was homogeneous. The crude product was redistilled to give 2.10 g (57%) of **7**, bp 48-51 °C, dried overnight over 4 Å molecular sieves at -10 °C. IR (C=O region) 1700(s), 1725(m) cm^{-1} (cf. [^{16}O]-**7** 1730(s) cm^{-1}; other bands superimposable).

[^{18}O]-O-1-Methylpropyl S-Methyl Dithiocarbonate (**5**). A solution of methyl lithium in ether (1.6 M, 20.8 mL, 33.3 mmol) was added under nitrogen, over 20 min, to a solution of **7** (2.04 g, 34.0 mmol) in dry ether (20 mL) at -50 °C. After stirring for 20 min at -20 °C, HMPA (5.9 mL, 34 mmol) was added followed by cooling to -40 °C. Next, a solution of carbon disulfide (2.1 mL, 35.7 mmol) in dry ether (10 mL) was added, during which time the solution turned brown, then red. After 15 min at 22 °C, the solution was cooled to -20 °C and a solution of iodomethane (2.64 mL, 42.4 mmol) in ether (5 mL) was added. After 45 min at 22 °C, the reaction mixture was washed with water (50 mL) to remove the precipitate that had formed, dried ($MgSO_4$), and evaporated to give a red oil (4.51 g, 82%), further purified by distillation, bp 61-66 °C (2.8 mm) to yield the yellow **5** (2.71 g, 49%) with less than 6% (w/w) of dimethyl trithiocarbonate [NMR: δ 2.76 (s)]. Deviations from the ratios of reactants described above adversely affected the yield and purity of **5**. Mass spectral analysis (gas probe 150 °C, 20 eV) showed an isotopic purity of 92%: m/z 166([^{18}O]-M$^{+\cdot}$, 18%), 164([^{16}O]-M$^{+\cdot}$, 1%),

111 ($M^{+\cdot}$ - C_4H_7, 41%), 104 ($M^{+\cdot}$ - COS, 30%), 91 ($CH_3S(C{=}S)^+$, 43%), 62 ($C^{18}OS$, 100%), 60 ($C^{16}OS$, 7%), 57 ($C_4H_9^+$, 92%), 56 ($C_4H_8^{+\cdot}$, 90%).

[^{18}O]-Chlorocarbonylsulfenyl Chloride (**1**). Sulfuryl chloride (4.85 mL, 60 mmol) was quickly added, at 25 °C, with vigorous evolution of gas, to a solution of [^{18}O]-**5** (2.51 g, 15.1 mmol) in n-pentane (25 mL). The resulting golden solution was stirred overnight and evaporated to give 3.24 g of a yellow oil that included 1.6 g (81%) of **1** by an N-methylaniline assay[12]. Distillation, bp 24-32 °C (25 mm), yielded 1.40 g (70%) of a crude product that was determined to be comprised of 63% of the desired **1**, 20% of **11**, and the remainder unidentified butyl-containing compounds which did not react with N-methylaniline. The amount of **11** in the crude product was much lower at the corresponding stage of a preparation starting with unlabelled **5** that was prepared from potassium 2-butyl xanthate and iodomethane. Redistillation, bp 40 °C (40 mm) (cf. [^{16}O]-**1** lit.[8] bp 52-57 °C (140 mm); lit.[7,12] bp 97-101 °C) gave **1** of >90% purity with 90% recovery of the amount of that material present in the crude product. Converted to **12** (0.25 mmol scale, 75% yield, cf. 88% with [^{16}O]-**1**); isotopic purity 92% (Table 1). IR 1740 (C=O), 815 cm^{-1} (cf. [^{16}O]-**1** 1785, 815 cm^{-1}). Mass spectral analysis (gas probe 25 °C, 70 eV) showed an isotopic purity of 92%. The base peak due to $C^{18}OS$ was at m/z 62 (100%), with $C^{16}OS$ at m/z 60 (6%). The four possible molecular ions were at m/z 136 (5%), 134 (26%), 132 (38%), and 130 (3%) and ions due to $ClCO^+$ were at m/z 99 (16%), 97 (41%), and 95 (4%).

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