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SYNTHESIS OF 2-CHLOROETHYL (^{13}C)-METHYL SULFIDE

Douglass F. Taber* and Robert P. Meagley

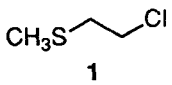
Department of Chemistry & Biochemistry, University of Delaware, Newark, DE 19716 USA

SUMMARY

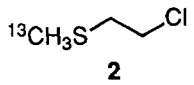
Incorporation of a stable isotope-labelled methylthio group into the mustard 2-chloroethyl methyl sulfide **2** was complicated by concomitant reaction with iodide ion, a necessary byproduct from the precursor stable isotope-labelled iodomethane. A two step procedure was therefore employed, initial displacement with mercaptoethanol **4** being followed by chlorination with thionyl chloride.

Key words: Mercaptoethanol, methylthio, mustard, $^{13}CH_3I$, sulfide.

In order to follow the destrucion of the sulfur mustard **1** through several half-lives, we desired to use the ^{13}C-labelled material **2**.

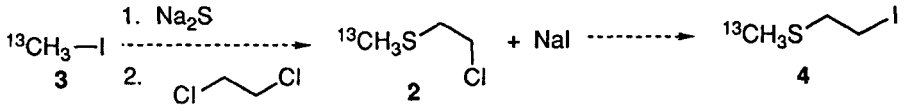


1



2

The incorporation of $^{13}CH_3I$ into organic molecules has been widely studied (1, 2). Originally, we had envisioned a one-pot preparation of the mustard, as outlined (**3** -> **2**). While there were reports of displacement by CD_3-S^- (3), however, we did not find any procedure for preparing the $^{13}CH_3$-S^- analogue. Further, in situ preparation of this reagent would not suffice. In any one-pot procedure, the desired product **2** would be exposed to NaI, with some halogen exchange inevitably taking place.



3 **2** **4**

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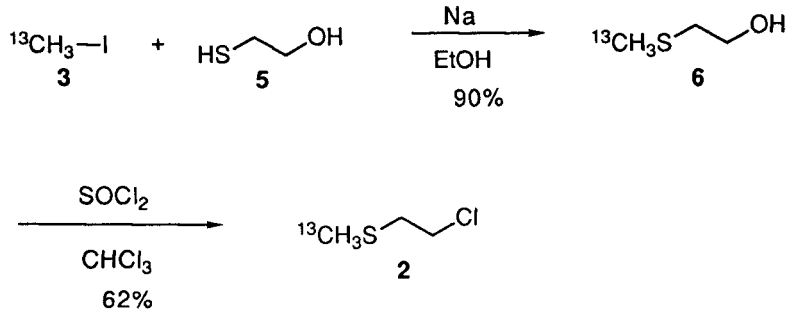
The availability of 2-mercaptoethanol suggested (4) an alternative approach (**Scheme 1**) to this problem. Following the procedure developed by Fong for the unlabelled material, alkylation of **5** with $^{13}CH_3I$ proceeded smoothly, to give alcohol **6**. Chlorination with $SOCl_2$ (by addition to **6** in *refluxing* $CHCl_3$)then provided **2**.

Scheme 1



In practice, we have found that neat **2** on storage at room temperature for several weeks develops a second, lower phase. This material (uncharacterized; perhaps the sulfonium dimer) appears to be in equilibrium with **2**. When some of the pure upper phase is removed for use, the ratio of the two phases is, over time, re-established.

EXPERIMENTAL SECTION

General: ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer. Chemical shifts are based on the setting of tetramethysilane at 0 ppm. Infrared spectra were determined on a Nicolet 5DXB System FT IR and are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry (HRMS) was performed on a VG 70-70 mass spectrometer.

(^{13}C-Methyl)-2-methylthioethanol **6**: Following the procedure of Fong (4), 2-mercaptoethanol (0.49 mL, 7.0 mmol) was added (N_2 atmosphere) to absolute ethanol (8 mL) in which Na metal (0.162 g, 7.0 mmol) had been dissolved. The mixture was cooled in an ice-water bath, then ^{13}C-iodomethane (1.0 g, 7.0 mmol) was added over 20 minutes. After 18 h (reaction comes to room temperature), the ethanol was removed by distillation. The residue was diluted with water (3 mL), then extracted with CH_2Cl_2 (6 x 3 mL). The organic extract was dried (Na_2SO_4), then concentrated on the rotary evaporator (120 mm, bath at room temperature). Traces of ethanol were removed by distillation (5 cm Vigreaux column, 115 mm, 35° C, followed by 55 mm, 100° C (bath)). The residual colorless oil (0.58 g, 6.3 mmol, 90% yield) appeared pure by NMR. ^1H NMR (δ): 2.10 (bs, 1 H), 2.11 (d,

J=138.7 Hz, 3 H), 2.71 (q, J=5.8 Hz, 2 H), 3.75 (t, J=5.8 Hz, 2 H); ^{13}C NMR (δ): 14.9 (x 85), 37.3, 59.6; IR (cm-1): 3380, 2915, 2361; MS calcd for $C_2{}^{13}CH_8OS$: 93.0329; found 93.0278.

^{13}C Methyl)-2-methylthio-1-chloroethane **2**: Following a modification of the procedure of Fong (4), (^{13}C-methyl)-2-methylthio ethanol **6** (3.24 g, 35 mmol) was dissolved in chloroform (5 ml) *and warmed to reflux.* A solution of thionyl chloride (3.6 ml, 49 mmol) in chloroform (5.9 ml) was *then* added dropwise over 30 minutes. Reflux was continued for an additional 45 minutes. The light yellow solution was concentrated on the rotary evaporator (120 mm, bath at room temperature), then distilled (5 cm Vigreux column). A foreshot of 0.1 ml (55-57° C, 40 mm) was followed by **2** as a colorless oil (57-50° C, 40 mm, 2.43 g, 62% from **6**). ^{1}H NMR (δ): 2.15 (d, J=139 Hz, 3 H), 2.85 (m, 2 H), 3.65 (m, 2 H); ^{13}C NMR (δ): 15.7 (x 81), 36.2, 42.6; IR (cm^{-1}): 2967, 2916, 2361, 1436, 1427; MS calcd. for $C_2{}^{13}CH_7SCl$ 110.999, found 111.001.

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REFERENCES

1. For a review of the use of $^{13}CH_3I$ in synthesis, see Finn R.D., BootheT.E., Vora M.M., Hildner J.C., Emran A.M., Kothari P.J. - Int. J. Appl. Radiat. Isot. 35:323 (1984).

2. For recent references to the use of $^{13}CH_3I$ in synthesis, see
   a. Anderson A.G. Jr., Hadock R.D. - J. Org. Chem. 56:550 (1991).
   b. Roth G.A., McClymont, E.L. - J. Labelled Compd. Radiopharm. 28:1073 (1990).

3. Kim J.K., Lingman E., Caserio M.C. - J. Org. Chem. 43:4545 (1978).

4. Fong H.O., Hardstaff W.R., Kay D.G., Langler R.F., Morse R.H., Sandoval D.-N. - Can. J. Chem. 57:1206 (1979).