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SYNTHESIS OF (1,2^{13}C)-2-CHLOROETHYL PHENYL SULFIDE

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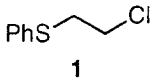
SUMMARY

Incorporation of a double ^{13}C label into the mustard 2-chloroethyl phenyl sulfide **2** is straightforward, but analysis is complicated by ^{13}C-^{13}C coupling. An alternative is reported, in which the ease of scrambling of sulfur mustards is used to advantage to prepare precisely 50% (1, 2-^{13}C) enriched **2**, with each carbon of the ethyl chain labelled to provide optimal signal to noise in the ^{13}C spectrum.

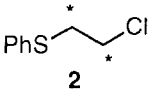
Key words: Phenylthioethanol, phenylthio, mustard, double, sulfide.

INTRODUCTION

In order to follow the decontamination of the sulfur mustard **1**, an agent simulant, through several half-lives (1), we desired to use the doubly ^{13}C-labelled material **2.** We wanted, however, sulfide that would appear as two clean singlets in the ^{13}C NMR spectrum. Fully labelled material would of course appear as a pair of doublets, due to ^{13}C-^{13}C coupling. As multiple products are formed in the course of the decontamination, we preferred to be able to analyze *single* pairs of peaks.



1



2

Hypothetically, the perfect material would be a one-to-one mixture of 1-(^{12}C)-2-(^{13}C) with 1-(^{13}C)-2-(^{12}C). We could have prepared each of these substances separately and then combined them. It seemed more expedient,

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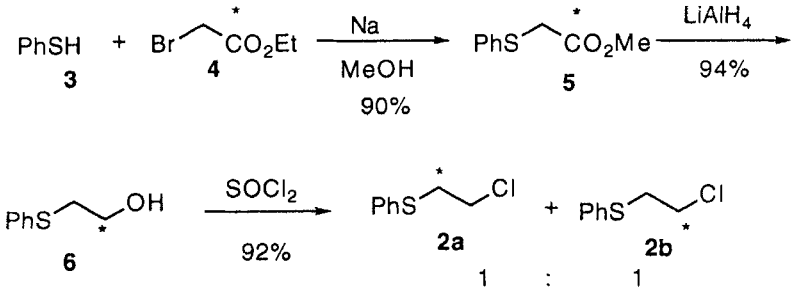
however, to take advantage of the well-known (2, 3) scrambling of 2-haloethyl sulfides to prepare the desired mixture directly (2 c.). To this end (**Scheme 1**), labelled ethyl bromoacetate **4** was exposed to an excess of thiophenol in the presence of ethanolic sodiumn ethoxide to give the labelled sulfide **5**. Reduction then provided alcohol **6**.

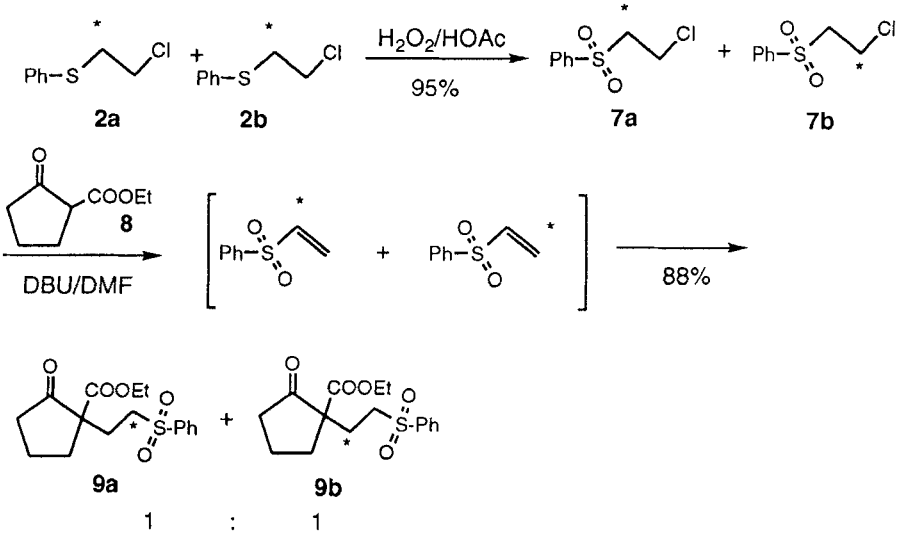
Scheme 1



Previous attempts to prepare the chloride from **6** (4) have invariably led to scrambling. In this case, scrambling is exactly what is required to produce the desired material. Chlorosulfide **2** showed two dominant peaks in the ^{13}C spectrum, at 36 ppm and 42 ppm respectively.

Applications of sulfide **2** (**Scheme 2**) extend well beyond the current decontaminateion studies. This "doubly-labelled" sulfide is a useful synthon

Scheme 2



for preparing other contiguously "double-labelled" materials. Thus, oxidation of **2** to **7**, followed by exposure to **8** in DMF and DBU, gave **9** (5). As expected, **9** showed two dominant peaks in the ^{13}C spectrum, at 26 ppm and 52 ppm respectively.

EXPERIMENTAL

General: ^{1}H and ^{13}C Jvert NMR spectra were obtained on a Bruker AM-250 spectrometer in $CDCl_3$ solution. In the Jvert experiment, methyl groups and methines are down, and methylenes and quaternary carbons are up. 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. Column chromatography was carried out with TLC-mesh silica gel, using the procedure we have described (6). The dominant ^{13}C peaks are indicated with an asterisk(*). The starting ethyl bromoacetate (Cambridge Isotope Laboratory) was 99%^{13}C at the carbonyl carbon.

Methyl 1-^{13}C-2-thiophenyl acetate **5**: To sodium methoxide, which was made by dissolving sodium (172 mg, 7.48 mmol) in methanol (4 mL), was added thiophenol (789 mg, 7.18 mmol). The reaction mixture was stirred at room temperature for 30 minutes and cooled with an ice-water bath. Ethyl 1-^{13}C-bromoacetate (1.0 g, 5.98 mmol) in methanol (2 mL) was added to above mixture and the reaction was brought to gentle reflux for 40 minutes. The reaction was quenched with water (10 mL), and the resulting mixture was extracted with chloroform (15 mL x 4). The extract was washed with saturated aqueous sodium bicarbonate solution (10 mL), saturated aqueous sodium sulfate solution (10 mL), dried with sodium sulfate and concentrated. The residue was chromatographed to give 909 mg of product (84%) as a colorless oil. TLC R_f= 0.44 (10% ethyl acetate / petroleum ether). ^{1}H NMR (δ): 3.64 (d, J= 5.5Hz, 2H), 3.70 (d, J=3.9Hz, 3H), 7.50-7.20 (m, 5H). ^{13}C NMR (δ): down: 129.8, 129.0, 126.8, 52.4; up: 176.0*, 134.9, 36.9. IR (cm^{-1}, neat): 3005, 2951, 1698, 1583, 1482, 1438, 1249, 1134, 1007. MS (m/z, %): 183 (70), 151 (2),123 (100), 109 (15), 77 (14). HRMS (m/z): 183.0430 (calcd for $C_8{}^{13}C_1H_{10}O_2S$: 183.0435).

2-^{13}C-2-Thiophenyl ethanol **6**: To the suspension of lithium aluminum hydride (628 mg, 15.0 mmol) in ethyl ether (60 mL) was added compound **5** in ether (10 mL) via syringe at 0°C. The resulting reaction mixture was

stirred and warmed to room temperature overnight. The mixture was cooled to 0°C and water (0.54 mL) was added, and the reaction mixture was stirred for one hour. 10% Aqueous sodium hydroxide (0.54 mL) was added, and the mixture was stirred for another hour. An additional 1.1 mL of water was added, and the mixture was stirred for one hour. The reaction mixture was filtered with ether (40 mL). The filtrate was dried over sodium sulfate and concentrated, and the residue was chromatographed to provide 1.47 g of the product (94%) as a colorless oil. TLC Rf= 0.15 (10% ethyl acetate / petroleum ether). ^{1}H NMR (δ): 2.76 (s, 1H), 3.06 (dt, J=6.15Hz, 3.01Hz, 2H), 3.70 (dt, J=144.4, 6.17Hz, 2H), 7.50-7.20 (m, 5H). ^{13}C NMR (δ): down: 129.8, 128,9, 126.4; up: 134.9, 63.8, 60.2*. IR (cm^{-1}, neat): 3362, 3057, 2923, 2870, 1583, 1480, 1438, 1286, 1025; MS (m/z, %): 155 (75), 123 (100), 110 (45), 109 (16), 77 (32). HRMS (m/z): 155.0481 (calcd. for $C_7{}^{13}C_1H_{10}O_2S$: 155.0486).

1-^{13}C-2-Chloroethyl phenyl sulfide **2a** and 2-^{13}C-2-Chloroethyl phenyl sulfide **2b:** To a solution of compound **6** (1.47 g, 9.34 mmol) in methylene chloride (20 mL) was added thionyl chloride (2.00 g, 16.8 mmol) gradually in an ice-water bath. After stirring at room temperature for two hours, the reaction mixture was concentrated and chromatographed to give 1.50 g of the product (92%) as a colorless oil. TLC Rf= 0.67 (10% ethyl acetate / petroleum ether). ^{1}H NMR (δ): **2a** 7.38-7.18 (m, 5H), 3.58 (dt, J=159.6, 8.0Hz, 2H), 3.12 (t, J=8.0Hz, 2H). **2b** 7.38-7.18 (m, 5H), 3.59 (t, J=8.0Hz, 2H), 3.19 (dt, J=142.4, 8.0Hz, 2H). ^{13}C NMR (δ): down: 130.3, 129.0, 126.9; up: 134.1, 42.2*, 36.0*. IR (cm^{-1}, neat): 3059, 2962, 2853, 1584, 1481, 1439, 1263, 1210, 1088, 1025. MS (m/z, %): 173 (40), 137 (15), 122 (10), 109 (100), 77 (40). HRMS (m/z): 173.0162 (calcd. for $C_7{}^{13}C_1H_9ClS$: 173.0159).

1-^{13}C-2 Chloroethyl phenyl sulfone **7a** and 1^{13}C-2- Chloroethyl phenyl sulfone **7b:** A mixture of compound **2** (500 mg, 2.90 mmol), 30% hydrogen peroxide (2.30 g, 20.3 mmol) and acetic acid (2.1 mL) was heated to reflux for 45 minutes. The reaction mixture was cooled to room temperature and stirred overnight. The mixture was quenched with water (10 mL) and extracted with methylene chloride (10 mL x 4). The extracts were washed with saturated aqueous sodium bicarbonate (10 mL), dried over sodium sulfate, and concentrated. The residue was chromatographed to give 562 mg of the product (95%) as a colorless oil. TLC Rf= 0.22 (10% ethyl acetate / petroleum ether).^{1}H NMR (δ): **7a** 7.85-7.58 (m, 5H), 3.77 (dt, J=149.1, 7.8Hz, 2H), 3.52 (t, J=7.8Hz, 2H). **7b** 7.85-7.58 (m, 5H), 3.77 (t, J=7.8Hz, 2H), 3.52 (dt, J=115.0, 7.8Hz, 2H). ^{13}C NMR(δ): down: 134.3, 129.6, 128.2; up: 127.8, 58.1*, 35.6*. IR (cm^{-1}, neat): 3062, 2925, 1718, 1588, 1448, 1324, 1266, 1151, 1086, 1024.

MS (m/z, %): 205 (50), 189 (8), 176 (21), 157 (16), 142 (50), 141 (100), 125 (46), 94 (20), 77 (65). HRMS (m/z): 205.0036 (calcd. for $C_7{}^{13}C_1H_9ClO_2S$: 205.0034).

Ethyl 1-(1'-^{13}C-2'-phenylsulfonylethyl)-2-oxocyclopentanecarboxylate **9a** and Ethyl 1-(2'-^{13}C-2'-phenylsulfonylethyl)-2-oxocyclopentanecarboxylate **9b**: To a solution of ethyl 2-oxocyclopentanecarboxylate (407 mg, 2.61 mmol) in DMF (2.5 mL) was added DBU (416 mg, 2.74 mmol) under N_2. After 10 minutes at room temperature, a solution of **7** (533 mg, 2.61 mmol) in DMF (1.5 mL) was added. The reaction was completed by stirring at room temperature for 50 minutes. After quenching with 10% aqueous HCl (5 mL) and saturated aqueous sodium chloride (5 mL), the mixture was extracted with ethyl acetate (10 mL x 4). The extract was dried over sodium sulfate and concentrated. The residue was chromatographed to afford 721 mg of the product (88%) as a light yellow oil. TLC R_f= 0.12 (20% ethyl acetate / petroleum ether). ^{1}H NMR (δ): **9a** 7.85-7.58 (m, 5H), 4.11 (q, J=7.3Hz, 2H), 3.43 (dm, J_{CH}=138.7Hz, 2H), 3.16 (m, 2H), 2.25-1.80 (m, 6H), 1.09 (t, J=7.3Hz, 3H). **9b** 7.85-7.58 (m, 5H), 4.11 (q, J=7.3Hz, 2H), 3.43 (m, 2H), 3.16 (dm, J_{CH}=133.4Hz, 2H), 2.25-1.80 (m, 6H), 1.09 (t, J=7.3Hz, 3H). ^{13}C NMR (δ): down: 133.8, 129.3, 128.0, 13.9; up: 213.8, 170.9, 138.5, 61.7, 51.9*, 37.8, 34.3, 26.6, 26.4*, 19.6. IR (cm^{-1}, neat): 3059, 2926, 2360, 1750, 1725, 1586, 1448, 1308, 1260, 1150, 1087. GC-MS (m/z, %): 297 (20), 252 (5), 224 (50), 184 (17), 155 (58), 125 (39), 110 (88), 77 (100). HRMS (FAB) (m/z): 326.1158 (MH^+) (calcd. for $C_{15}{}^{13}C_1H_{21}O_5S$: 326.1143).

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REFERENCES

1. Taber D.F., Meagley R.P. - J. Labelled Compd. Radiopharm. 31:849 (1992).

2. For leading references to the preparation of 2-chloroethyl sulfides, see:
   a. Raber D.J., Neal W.C. Jr., Dukes M.D., Harris J.M., Mount D.M.- J. Am. Chem. Soc. 100: 8137 (1978).

b. McManus S.P., Nemeati-Mazreah N., Hovanes B.A., Paley M.S., Harris J. M. - J. Am. Chem. Soc. 107: 3393 (1985).
c. Sedaghat-Herati M.R., McManus S.P., Harris J.M.- J. Org. Chem. 53: 2539 (1988).

3. Peterson L.A., Harris T.M., Guengerich F.P. - J. Am. Chem. Soc. 110: 3284 (1988).

4. McManus S.P., University of Alabama, personal communication. We would like to thank Professor McManus for sharing his results with us prior to publication.

5. a. For leading references to the homologation of phenyl sulfides, see Harada T., Karasawa A., Oku A. - J. Org. Chem. 51: 842 (1986).
b. Chu D.T. W. - J. Org. Chem. 48: 3571 (1983).

6. Taber D. F. -J. Org. Chem. 47:1351(1982).