Notes

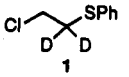
Preparation of 2-Chloroethyl-1,1-d_2 Phenyl Sulfide without Appreciable Scrambling

Douglass F. Taber* and Yanong Wang

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

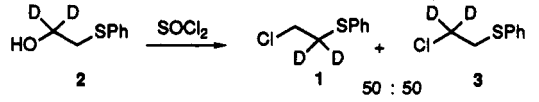
Received May 3, 1993

Stable isotope-labeled sulfur mustards[1] are important tools[2] for the study of the mechanism of nucleophilic displacement reactions. We report a simple route to a long-sought but heretofore elusive[2,3] member of this series, 2-chloroethyl-1,1-d_2 phenyl sulfide (1).[4]



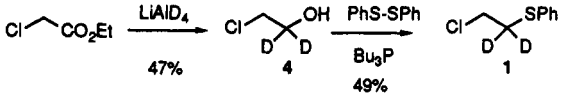
1

Originally, we had sought to prepare the regioisomer 3 of 1 by chlorination of alcohol 2. All attempts so to do, however, led to scrambling, to give a 50:50 mixture of 1 with 3.



2 1 50 : 50 3

As an alternative, we turned to 2-chloroethanol-1,1-d_2 (4), readily prepared[4] from ethyl chloroacetate by reduction with $LiAlD_4$. Exposure of 4 to tributylphosphine and



47% 4 49% 1

diphenyl disulfide in pyridine (rt, 12 h)[5] smoothly gave 1, scarcely contaminated with 3 (49:1 by ^1H NMR: δ 3.57 and δ 3.19, respectively, in $CDCl_3$).

This alternative approach now makes 1 readily available. As noted,[4] sulfide 1 in its purified form is reasonably stable. After 3 days in $CDCl_3$ at room temperature, the ratio of 1 to 3 had deteriorated to 25:1. After an additional three months at −10 °C, this ratio was unchanged.

Experimental Section[6]

[1,1-$^2H_2$]-2-Chloroethanol (4). To a suspension of $LiAlD_4$ (2.5 g, 59.5 mmol) in THF (85 mL) was added a solution of ethyl chloroacetate (11.5 g, 93.9 mmol) in THF (10 mL) at a rate to keep the reaction mixture gently refluxing. The mixture was maintained at reflux for 12 h, after which it was chilled in an ice–water bath and quenched by sequential dropwise addition of water (2.16 mL), 10% aqueous NaOH (2.16 mL), and water (6.48 mL), with stirring between each addition. The mixture was filtered with Et_2O, and the filtrate was dried (Na_2SO_4) and fractionally distilled to yield 3.65 g (47% yield) of 4 as a colorless oil: bp_{760} = 130 °C. ^1H NMR δ: 3.67 (s, 2H) 2.22 (bs, 1H). ^{13}C NMR δ: 45.7.

[1,1-$^2H_2$]-[(2-Chloroethyl)thio]benzene (1). Tributylphosphine (1.47 g, 6.1 mmol) and diphenyl disulfide (1.45 g, 6.7 mmol) were added sequentially to a solution of alcohol 4 (500 mg, 6.1 mmol) in pyridine (5 mL) at rt. After 12 h, the mixture was partioned between petroleum ether and, sequentially, 10% aqueous HCl and 10% aqueous NaOH. The organic extract was dried (Na_2SO_4) and concentrated (bath at rt). The residue was chromatographed on silica gel, and the fraction having TLC (10% EtOAc/petroleum ether) R_f = 0.67 was distilled bulb-to-bulb (pot temperature = 120 °C at 2.0 mm) to give 516 mg (49% yield) of 1 as a colorless oil. ^1H NMR δ: 7.37–7.18 (m, 5H), 3.57 (s, 2H). ^{13}C NMR (δ): 134.1, 130.5, 129.2, 127.0, 42.1. After the $CDCl_3$ solution was stored at rt for 3 days, signals for 3 could also be observed. ^1H NMR δ: 7.37–7.18 (m, 5H), 3.19 (s, 2H). ^{13}C NMR (δ): 134.1, 130.5, 129.2, 127.0, 36.0.

Acknowledgment. We thank CRDEC/Aberdeen and Battelle for support of this work. We thank S. P. McManus for helpful discussions and for sharing his results with us prior to publication.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds 1 and 4 (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(1) Taber, D. F.; Meagley, R. P. *J. Labelled Cmpds. Radiopharm.* **1992**, *31*, 849.

(2) (a) Raber, D. J.; Neal, W. C., Jr.; Dukes, M. D.; Harris, J. M.; Mount, D. M. *J. Am. Chem. Soc.* **1978**, *100*, 8137. (b) Harris, J. M.; Mount, D. L.; Smith, M. R.; Neal, W. C., Jr.; Dukes, M. D.; Raber, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8147. (c) McManus, S. P.; Neamati-Mazreah, N.; Hovanes, B. A.; Paley, M. S.; Harris, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3393. (d) McManus, S. P.; Neamati-Mazreah, N.; Karaman, R. M.; Harris, J. M. *J. Org. Chem.* **1986**, *51*, 4876. (e) Rosnati, V.; Saba, A.; Angius, A.; Casarini, D. *J. Org. Chem.* **1987**, *52*, 4094. (f) Sedaghat-Herati, M.R.; Harris, J. M.; McManus, S. P. *Tetrahedron* **1988**, *44*, 7479. (g) Sedaghat-Herati, M. R.; McManus, S. P.; Harris, J. M. *J. Org. Chem.* **1988**, *53*, 2539.

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

(4) For an alternative preparation of 3, see: McManus, S. P.; Karaman, R. M.; Sedaghat-Herati, M. R.; Hovanes, B. R.; Ding, X.-T.; Harris, J. M. *J. Org. Chem.*, previous paper in this issue. We thank Professor McManus for sharing his results with us prior to publication.

(5) (a) Cleary, D. G. *Synth. Commun.* **1989**, 737. (b) Nagakawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1049.

(6) A general experimental procedure was recently published: Taber, D. F.; Deker, P.B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990.

0022-3263/93/1958-6470$04.00/0