Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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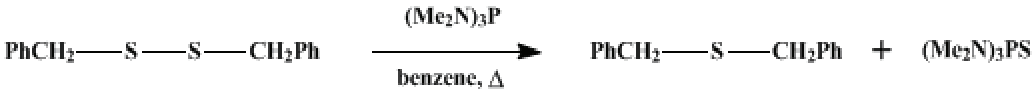
SULFIDE SYNTHESIS: BENZYL SULFIDE

[Benzene, 1,1-[thiobis(methylene)]bis-]



$$PhCH_2{-}S{-}S{-}CH_2Ph \xrightarrow[\text{benzene, }\Delta]{(Me_2N)_3P} PhCH_2{-}S{-}CH_2Ph + (Me_2N)_3PS$$

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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 100-ml., one-necked, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser topped with a drying tube is charged with 3.92 g. (0.0240 mole) of freshly-distilled hexamethylphosphorous triamide (Note 2), 15 ml. of dry benzene (Note 3), and 4.93 g. (0.0200 mole) of benzyl disulfide (Note 4). The mixture is refluxed for 1 hour (Note 5) and (Note 6), during which time it may develop a slight yellow color. After cooling to room temperature, the solution is concentrated on a rotary evaporator (Note 7), and the residue is chromatographed over 75 g. of silica gel (Note 8). After eluting with 8:2 (v/v) hexane–chloroform at 3–4 ml. per minute (Note 9) and monitoring the eluant by GC (Note 10), an initial fraction containing no product is collected (typically 100 ml.). Successive fractions (*ca.* 1.45 1.) contain the product. These are combined and evaporated (Note 11); 20 ml. of absolute ethanol is added to the residue, and the mixture is heated on a steam bath for *ca.* 30 seconds to form a homogeneous solution. The solution is filtered hot through a Büchner funnel (medium-porosity fritted disk), which is washed with three 3-ml. portions of absolute ethanol. The solvent is then removed to constant weight of residue by rotary evaporation, yielding 4.15–4.27 g. (96.7–99.5%) of benzyl sulfide as a white solid or colorless oil that crystallizes on standing (cooling on dry ice for *ca.* 1 minute may be required), m.p. 46.5–47.5°. This product is of sufficient purity for most purposes (Note 12). Further elution of the column with 1.1 1. of chloroform (same flow rate as above) and removal of solvent by rotary evaporation afford 3.94–4.06 g. (101–104%) of crude (*ca.* 95% pure) tris (dimethylamino) phosphine sulfide (Note 13).

2. Notes

1. To avoid benzene, dry toluene or acetonitrile can be used as solvents following the same procedure.
2. The hexamethylphosphorous triamide was obtained from the Eastman Kodak Company, distilled under reduced pressure (water aspirator), yielding a clear, colorless oil, b.p. 46–48° (7 mm.) and stored under nitrogen (rubber septums should be avoided as they tend to deteriorate on prolonged contact with phosphine vapors). Hexamethylphosphorous triamide not freshly distilled often requires much longer reaction times. Since this chemical is an irritant, all operations with it should be performed in a well-ventilated hood. Hexamethylphosphoric triamide is classified as a carcinogen.[2] It should not be confused with hexamethylphosphorous triamide used in this preparation.
3. The benzene was dried over type 3Å molecular sieves. Use of a greater amount of solvent slows the reaction rate. The checker flamed the reaction flask under nitrogen and ran the reaction under a nitrogen atmosphere.
4. The benzyl disulfide was obtained from the Eastman Kodak Company. Some batches, not homogeneous by GC, were recrystallized from absolute ethanol (*ca.* 2.5 ml. per g.), yielding colorless crystals, m.p. 69–71° (lit.,[3] m.p. 70–71.5°).
5. The temperature of the oil bath is 100–105°; the reaction mixture is *ca.* 88°.
6. After 1 hour, the reaction is complete as monitored by GC on an Hewlett-Packard F&M 5751

research chromatograph (1.85 m. × 0.313 cm. stainless-steel column of 10% Apiezon L on Chromosorb W AW/DMCS; column temperature 250°). TLC was found to be of little use in monitoring the reaction, as the R_f values for benzyl disulfide and benzyl sulfide are virtually identical for a variety of solvent systems tried. ^{1}H NMR (C_6H_6) shows that these two compounds have coincidental chemical shifts for the benzylic protons: δ 3.4 (singlet).

A 20% excess of hexamethylphosphorous triamide was utilized to increase the reaction rate. When a 10% excess of the phosphine was used, the reaction was not quite complete (as monitored by GC) even after 3 hours. If the reaction is not allowed to go to completion, the chromatographed product will contain benzyl disulfide. Note that the desulfurization rate for hexaethylphosphorous triamide is comparable to that for hexamethylphosphorous triamide. However, the chromatographic separation following the reaction is much more efficient when hexamethylphosphorous triamide is used.

7. The pressure should be reduced gradually and cautiously to avoid the "bumping" often characteristic of benzene distillations.

8. To 75 g. of silica gel (see below) that has been freshly heated at 120–130° for 18 hours and cooled in a desiccator (see below) is added *ca.* 200 ml. of a 8:2 (v/v) hexane–chloroform mixture. The resulting slurry is stirred to remove air bubbles and added to a 26-mm. column (in which a flat base of glass wool and sand has been prepared) in one portion with tapping of the column. Any remaining silica gel is also added to the column by washing with more of the solvent mixture, resulting in a *ca.* 28-cm. column of silica gel. A sand layer is then carefully added to the top of the column, and the solvent is drained to the sand level. The reaction residue is placed on the column as is, and the reaction flask is rinsed with small portions of hexane–chloroform which are also loaded onto the column.

The volume of column packing used represents a length–width ratio of *ca.* 10:1. Since column efficiency improves as the length–width ratio is increased (for a given volume of packing), these approximate dimensions should be maintained. For example, when a length–width ratio of *ca.* 9:1 was applied (with the same amount of silica gel), there was not complete separation, and the yield of pure benzyl sulfide was less than optimum (93%).

The packing material is Silica Gel 60, Cat 7734 (70–230 mesh ASTM), for column chromatography, an EM Reagent of E. Merck, Darmstadt, available from Brinkmann Instruments Ltd. (Canada). Lower grades of silica gel such as the 60–120 mesh grade of BDH Chemicals Ltd. were found to be much less efficient, not effecting a complete separation of the compounds. The amount of Silica Gel 60 utilized and found to be most efficient was 75 g., or 8.5 g. of silica gel per g. of reaction mixture. The checkers used Mallinckrodt CC-7 Special (100–200 mesh) column packing, a flow rate of 8.5 ml. per minute, a 9:1 ratio of hexane–chloroform eluant and obtained a lower product yield (77%).

Eighteen hours at 120–130° was found to dry various batches of Silica Gel 60 to the same activity. The silica gel was cooled in a desiccator over 8-mesh Drierite available from Anachemia Chemicals Ltd. This procedure should be performed so that the silica gel is used immediately after cooling; otherwise, the activity will decrease with time even if the silica is left in the desiccator.

The solvent mixture of 8:2 (v/v) was found to be the most effective, with increased concentrations of chloroform not effecting a complete separation. The two solvents should therefore be mixed thoroughly. Chloroform (A.C.S. grade) and an isomeric mixture of hexanes (A.C.S. grade) supplied by Fisher Scientific Company are quite suitable.

9. Increased flow rate resulted in a poorer chromatographic resolution.

10. The chromatography may be monitored by collection of 50-ml. fractions analyzed by GC (same conditions as in (Note 6)).

11. The residue will be a white solid or colorless oil.

12. The solidified residue is homogeneous by GC, and its IR and ^{1}H NMR spectra and GC are identical to those of recrystallized authentic benzyl sulfide. The product may be recrystallized from *ca.* 25 ml. of absolute ethanol to yield colorless plates, m.p. 47–48° (lit.,[4] m.p. 50°), which give a satisfactory combustion analysis.

13. This material has IR and ^{1}H NMR spectra identical to those of an authentic sample prepared by the procedure of Stuebe and Lankelma.[5]

3. Discussion

The disulfide linkage is found in a large number of natural products,[6,7,8,9] and chemical manipulations of this functionality are of considerable interest.[10,11,12,13,14] In contrast to desulfurization methods utilizing various phosphines[15,16,17,18] and phosphites,[19,20,21,22,23,24,25,26,27,28,29] aminophosphines have proved to be efficient desulfurizing agents for a variety of alkyl, aralkyl, alicyclic, and certain diaryl disulfides.[30] In addition, the reaction conditions are mild enough to be compatible with a variety of common functional groups. Hence, the desulfurization procedure given here for benzyl disulfide merely demonstrates the practibility of this method for which the synthetic scope and mechanism have already been developed.[30]

References and Notes

1. Department of Chemistry, McGill University, P.O. Box 6070, Montreal, Quebec, Canada H3A 2K6.
2. J. A. Zapp, Jr., *Science*, **190**, 422 (1975).
3. F. H. McMillan and J. A. King, *J. Am. Chem. Soc.*, **70**, 4143 (1948).
4. C. Forst, *Justus Liebigs Ann. Chem.*, **178**, 370 (1875).
5. C. Stuebe and H. P. Lankelma, *J. Am. Chem. Soc.*, **78**, 976 (1956).
6. L. Young and G. A. Maw, "The Metabolism of Sulfur Compounds," Wiley, New York, 1958;
7. R. F. Steiner, "The Chemical Foundations of Molecular Biology," Van Nostrand, Princeton, 1965;
8. K. G. Stern and A. White, *J. Biol. Chem.*, **117**, 95 (1937);
9. K. Jost, V. Debabov, H. Nesvadba, and J. Rudinger, *Collect. Czech. Chem. Commun.*, **29**, 419 (1964).
10. W. A. Pryor and K. Smith, *J. Am. Chem. Soc.*, **92**, 2731 (1970);
11. J. L. Kice, "Mechanisms of Reactions of Sulfur Compounds," Vol. 3, Wiley, New York, 1968, p. 91;
12. N. Kharasch and A. J. Parker, *Q. Rep. Sulfur Chem.*, **1**, 285 (1966);
13. N. Kharasch, Ed., "Organic Sulfur Compounds," Vol. 1, Pergamon Press, New York, 1961;
14. A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583, 589 (1959).
15. A. Schönberg, *Ber. Dtsch. Chem. Ges.*, **68**, 163 (1935);
16. A. Schönberg and M. Barakat, *J. Chem. Soc.*, 892 (1949);
17. F. Challenger and D. Greenwood, *J. Chem. Soc.*, 26 (1950);
18. C. Moore and B. Trego, *Tetrahedron*, **18**, 205 (1962).
19. H. Jacobson, R. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955);
20. A. Poshkus and J. Herweh, *J. Am. Chem. Soc.*, **79**, 4245 (1957);
21. C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **79**, 5326 (1957);
22. C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **81**, 1243 (1959);
23. C. Moore and B. Trego, *J. Chem. Soc.*, 4205 (1962);
24. R. Harvey, H. Jacobson, and E. Jensen, *J. Am. Chem. Soc.*, **85**, 1618 (1963);
25. K. Pilgram, D. Phillips, and F. Korte, *J. Org. Chem.*, **29**, 1844 (1964);
26. K. Pilgram and F. Korte, *Tetrahedron*, **21**, 203 (1965);
27. A. J. Kirby, *Tetrahedron*, **22**, 3001 (1966);
28. R. S. Davidson, *J. Chem. Soc.* C, 2131 (1967);
29. D. N. Harpp and R. A. Smith, *J. Org. Chem.*, **44**, 4140 (1979).
30. D. N. Harpp and J. G. Gleason, *J. Am. Chem. Soc.*, **93**, 2437 (1971); D. N. Harpp, J. Adams, J. G. Gleason, D. Mullins, and K. Steliou, *Tetrahedron Lett.*, 3989 (1978).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

ethanol (64-17-5)

Benzene (71-43-2)

acetonitrile (75-05-8)

chloroform (67-66-3)

nitrogen (7727-37-9)

toluene (108-88-3)

phosphine (7723-14-0)

hexane (110-54-3)

benzyl disulfide (150-60-7)

Hexamethylphosphorous triamide (1608-26-0)

hexamethylphosphoric triamide (680-31-9)

Hexaethylphosphorous triamide (2283-11-6)

Benzyl sulfide,
Benzene, 1,1-[thiobis(methylene)]bis- (538-74-9)

tris(dimethylamino) phosphine sulfide (3732-82-9)