



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

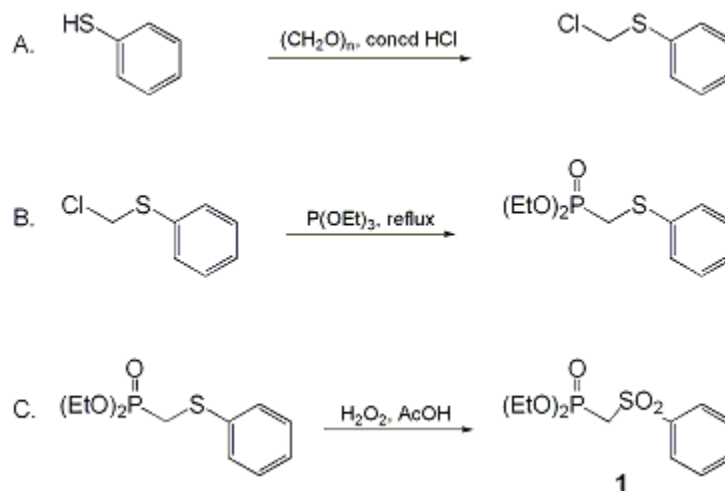
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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DIETHYL [(PHENYLSULFONYL)METHYL]PHOSPHONATE

[Phosphonic acid, [(phenylsulfonyl)methyl]-, diethyl ester]



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1. Procedure

A. Chloromethyl phenyl sulfide. As described in ref. 3, a 1-L, three-necked, round-bottomed flask fitted with a reflux condenser, 250-mL pressure-equalizing dropping funnel, and equipped with a large magnetic stirring bar is charged with 120 mL of *toluene* and 18.9 g (0.63 mol) of *paraformaldehyde* (Note 1). While the solution is stirred, 500 mL of *concd hydrochloric acid* is added to the suspension. The reaction mixture is heated to 50°C and the dropping funnel is charged with a solution of 55.1 g (51.3 mL, 0.5 mol) of *thiophenol* in 120 mL of *toluene*. The thiophenol solution is added dropwise over 1 hr. The reaction mixture is stirred at 50°C for 1 hr and subsequently at room temperature for an additional 3 hr. The reaction mixture is transferred to a separatory funnel and the organic phase is separated. The aqueous phase is extracted three times with 50-mL portions of *toluene* and the combined organic phase is washed with 100 mL of aqueous saturated *sodium chloride* solution. Most of the solvent is removed by distillation at atmospheric pressure and the remaining crude product is purified by fractional distillation under reduced pressure using a Vigreux column (15-20 cm) to yield 57.9 g (73%) of *chloromethyl phenyl sulfide* as a colorless liquid, bp 106-107°C (11 mm) (Note 2).

B. Diethyl [(phenylthio)methyl]phosphonate. As described in ref. 4, a 1-L, three-necked, round-bottomed flask fitted with a thermometer, a warm water (ca. 40-60°C) reflux condenser connected to an empty safety bottle and a safety bottle charged with *ethanol* (Note 3), a 200-mL pressure-equalizing dropping funnel, and equipped with a large magnetic stirring bar, is charged with 116.0 g (0.7 mol) of *triethyl phosphite* (Note 4). The dropping funnel is charged with 55.5 g (0.35 mol) of *chloromethyl phenyl sulfide* and the flask is heated under stirring to 130°C (internal temperature). The *chloromethyl phenyl sulfide* is added slowly at a constant rate over 40 min and the internal temperature is allowed to rise to 150-160°C. After complete addition, the resulting reaction mixture is stirred for an additional 12 hr under reflux and then cooled to room temperature. Excess *triethyl phosphite* is removed under reduced pressure (11 mm) through a short path distillation apparatus. The crude product is purified by fractional distillation under reduced pressure using a Vigreux column (20 cm) to afford 82.2 g (91%) of *diethyl [(phenylthio)methyl]phosphonate* as a colorless liquid, bp 130-135°C (0.08 mm) (Notes 5 and 6).

C. Diethyl [(phenylsulfonyl)methyl]phosphonate. A 1-L, three-necked, round-bottomed flask, fitted with a reflux condenser, thermometer, pressure-equalizing dropping funnel and equipped with a large

magnetic stirring bar is charged with 300 mL of acetic acid and 75.0 g (0.29 mol) of diethyl [(phenylthio)methyl]phosphonate. The dropping funnel is charged with 90 mL of an aqueous hydrogen peroxide, solution (30%) and the reaction mixture is heated under stirring to 50°C (internal temperature). The hydrogen peroxide solution is added slowly so that the internal temperature does not rise above 80°C (*Caution: This very exothermic reaction has an induction period!*) (Note 7). The reaction mixture is heated to 85°C for an additional 3 hr (Note 8), cooled to room temperature, and transferred to a 4-L beaker. Ice (1000 g) and then a concd sodium hydroxide solution (10 M) is added until the solution is basic, pH 8-9 (*Caution: Exothermic reaction!*) The reaction mixture is transferred to a separatory funnel, and the water phase is extracted five times with 200-mL portions of dichloromethane. The combined organic phase is washed with 50-mL portions of aqueous sodium hydrogen sulfite solution (10%) until no oxidizing agent remains (Note 9), and then dried over anhydrous magnesium sulfate. After removal of the magnesium sulfate by filtration, the solvents are evaporated under reduced pressure using a rotary evaporator. Purification of the crude product by flash chromatography (5 × 30-cm column) using 1:1 diethyl ether-hexanes to elute the non-polar impurities followed by 100% ethyl acetate to elute the product provides diethyl [(phenylsulfonyl)methyl] phosphonate (76.3 g, 90%) as colorless crystals, mp 51°C (Note 10).

2. Notes

1. Paraformaldehyde (96%) was purchased from Fisher Scientific Company and thiophenol (99%) was purchased from Sigma Chemical Company. Both reagents were used as received.
2. Chloromethyl phenyl sulfide shows the following physical data: ¹H NMR (400 MHz, CDCl₃) δ: 4.96 (s, 2 H), 7.35 (m, 3 H), 7.51 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 51.0, 127.9, 129.2, 130.9, 133.2; IR cm⁻¹: 1584, 1482, 1440, 1228; HRMS calcd for C₇H₇ClS (M⁺) 157.9957, found 157.9953. Anal. Calcd for C₇H₇ClS: C, 53.00; H, 4.45. Found: C, 52.97; H, 4.49. Chloromethyl phenyl sulfide is also commercially available (Aldrich Chemical Company, Inc.).
3. Volatile ethyl chloride is formed during the reaction, which evaporates through the reflux condenser and is trapped in an ethanol-filled safety bottle.
4. Triethyl phosphite was purchased from Aldrich Chemical Company, Inc., and used without further purification.
5. Diethyl [(phenylthio)methyl]phosphonate shows the following physical data: ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (t, 6 H, J = 7.1), 3.19 (d, 2 H, J = 14.1), 4.14 (m, 4 H), 7.26 (m, 1 H), 7.30 (m, 2 H), 7.45 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 16.2, 28.4 (J = 48), 62.5, 126.6, 128.8, 129.4, 135.4; IR cm⁻¹: 2982, 1582, 1482, 1440, 1392, 1255; HRMS calcd for C₁₁H₁₇O₃PS (M⁺) 260.0636, found 260.0630. Anal. Calcd for C₁₁H₁₇O₃PS: C, 50.76; H, 6.58. Found: C, 50.49; H, 6.51.
6. If the product does not show the required purity, a second distillation may be necessary.
7. The checkers used a water bath as heat source and did not observe a significant increase in reaction temperature during the addition of hydrogen peroxide.
8. The internal temperature may rise for a short time up to 100°C on heating.
9. Commercially available peroxide test strips (Aldrich Chemical Company, Inc.) are used to verify the presence of oxidizing agents.
10. The compound shows the following physical data: R_f = 0.31 (0.25-mm silica gel on glass, diethyl ether/methanol, 20:1, (v/v)); ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (td, 6 H, J = 7.0, 0.5), 3.77 (d, 2 H, J = 16.7), 4.16 (m, 4 H), 7.58 (m, 2 H), 7.68 (m, 1 H), 8.00 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 16.1, 53.7 (J = 38), 63.3, 128.2, 129.0, 134.0, 139.9; IR cm⁻¹: 2984, 1586, 1480, 1448, 1394, 1369, 1324, 1263, 1157; HRMS calcd for C₁₁H₁₈O₅PS (M⁺ +H) 292.0613, found 293.0602. Anal. Calcd for C₁₁H₁₇O₅PS: C, 45.20; H, 5.86. Found: C, 45.35; H, 6.13.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The sulfone group is well known as an activating group and enables the preparation of a vast array of functionalized products. In addition, this functional group is of enormous value in total synthesis.

These compounds are easily prepared by a range of mild and high-yield routes. The sulfone is a robust group and frequently confers useful properties such as crystallinity. Of importance is the ease of formation of carbanions α to the sulfone group. This enables efficient C-C bond formation via alkylation and aldol-like processes.⁵

Diethyl [(phenylsulfonyl)methyl]phosphonate (**1**) has served in many procedures as a versatile intermediate in synthesis. Thus **1** has been used in alkylation reactions by reaction of appropriate electrophiles with the metalated sulfone.⁶ In addition **1** may be used as the phosphonate component in Horner-Wadsworth-Emmons olefination reactions.^{7,8,9} The olefination step can be carried out with high (E)-selectivity, as illustrated in the accompanying procedure.¹⁰ α,β -Unsaturated phenyl sulfones are in general useful as Michael acceptors in reactions with a host of nucleophilic partners. In contrast to unsaturated carbonyl compounds, competing addition to the sulfone functionality cannot occur and the vinyl phenyl sulfone itself acts as a "two-carbon acceptor," which is not available using carbonyl-type Michael acceptors.⁵ Furthermore, unsaturated sulfones in which the sulfone is directly attached to an alkenyl or alkynyl group undergo a range of cycloadditions including [2+2], [3+2]⁸ and [4+2]⁹ processes. However, the sulfone is rarely required in the final target molecule and so methods for removal of the sulfone group have been developed.⁵ Finally, α,β -unsaturated sulfones are also an effective class of cysteine protease inhibitors.¹¹

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 10, 66*

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

Diethyl [(phenylsulfonyl)methyl]phosphonate:
Phosphonic acid, [(phenylsulfonyl)methyl]-, diethyl ester (9); (56069-39-7)

Chloromethyl phenyl sulfide:
Sulfide, chloromethyl phenyl (8);
Benzene, [(chloromethyl)thio]- (9); (7205-91-6)

Paraformaldehyde (9); (30525-89-4)

Thiophenol: Aldrich:
Benzethiol (8,9); (108-98-5)

Diethyl [(phenylthio)methyl]phosphonate:
Phosphonic acid, [(phenylthio)methyl]-, diethyl ester (9); (38066-16-9)

Triethyl phosphite:
Phosphorous acid, triethyl ester (8,9); (122-52-1)

Hydrogen peroxide (8,9); (7722-84-1)

Sodium hydrogen sulfite:
Sulfurous acid, monosodium salt (8,9); (7631-90-5)