



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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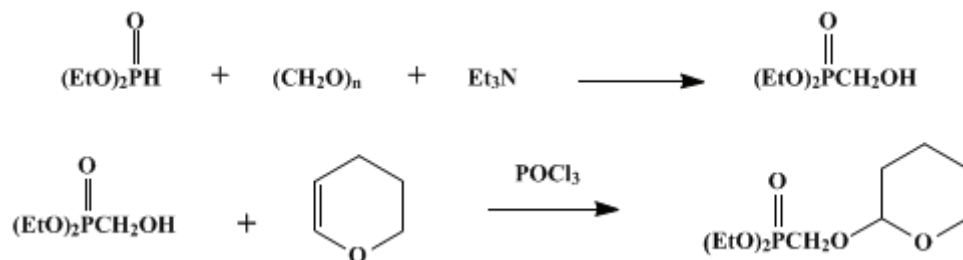
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 7, p.160 (1990); Vol. 64, p.80 (1986).*

## DIETHYL [(2-TETRAHYDROPYRANYLOXY)METHYL] PHOSPHONATE

[Phosphonic acid, [(tetrahydro-2 *H*-pyran-2-yl)oxy]methyl-, diethyl ester]



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### 1. Procedure

A. *Diethyl hydroxymethylphosphonate*. To a 250-mL, round-bottomed flask equipped with a magnetic stirring bar and an efficient reflux condenser are added 69 g (64.4 mL, 0.5 mol) of *diethyl phosphite* (Note 1), 15 g (0.5 mol) of *paraformaldehyde*, and 5.1 g (0.05 mol) of *triethylamine*. The mixture is placed in an oil bath preheated to 100–120°C. The temperature is increased to 120–130°C, and the mixture is stirred at this temperature for 4 hr. The stirring bar is removed, the flask is transferred to a rotary evaporator, and most of the *triethylamine* is removed by heating under reduced pressure of ca. 15 mm and with a bath temperature of ca. 80°C. Kugelrohr distillation at 125°C (0.05 mm) (Note 2) gives 41.4–54.9 g (49–65%) of material of sufficient purity for the next step (Note 3) and (Note 4).

B. *Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate*. A mixture of 33.63 g (0.2 mol) of *diethyl hydroxymethylphosphonate*, 21 g (0.25 mol) of *dihydropyran*, and 150 mL of *diethyl ether* is placed in a stoppered flask, and 20 drops of *phosphorus oxychloride* is added while the contents are swirled manually. After 3 hr at room temperature the reaction is monitored by TLC (Note 5). The mixture is diluted with *diethyl ether*, transferred into a separatory funnel, and shaken successively with 100 mL of saturated *sodium bicarbonate* solution, 100 mL of water, and 100 mL of saturated *sodium chloride* solution. The *ether* solution is dried over *MgSO<sub>4</sub>*, filtered, and the *ether* is removed with a rotary evaporator. Kugelrohr distillation of the residue (110°C, 0.05 mm) gives 42.4–46.9 g (84–93%) of material of sufficient purity for use in homologation reactions (Note 6) and (Note 7).

### 2. Notes

1. *Diethyl phosphite*, *paraformaldehyde*, and *triethylamine* were obtained from Aldrich Chemical Company, Inc. *Dihydropyran* was obtained from MCB, Inc.

2. Attempted isolation of *diethyl hydroxymethylphosphonate* by standard vacuum-distillation technique is accompanied by extensive decomposition. The use of Kugelrohr apparatus allows the isolation to be accomplished at a lower temperature, and therefore the product is obtained in higher yield. Alternatively, the checkers found that distillation using a 2-in. wiped-film molecular still. (Pope Scientific, Inc.) significantly raised product yields, especially when the reaction was performed on a larger scale (Note 3) and (Note 6).

3. The checkers found that reactions run on up to four times the present scale and rectified using a molecular still (wall temperature 110–120°C, 0.10 mm) gave yields of 89–94%. *Warning: On this larger scale (i.e., four times the present scale) a brief runaway was experienced and some material that escaped from the condenser was caught in a trap; however, the yield was still excellent (94%).*

4. On TLC [silica, visualization with 1.5% *phosphomolybdic acid* spray and heating] the product has a

retardation factor of ca. 0.1 with ethyl acetate development and ca. 0.3 with methanol–dichloromethane [5:95] development. The  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) is as follows  $\delta$ : 1.31 (t, 6 H,  $J = 6.8$ ), 3.87 (d, 2 H,  $J = 7$ ), 4.13 (m, 4 H), 5.34 (br s, 1 H, OH).

5. Five drops of reaction mixture is added to a mixture of 20 drops of diethyl ether and 1 drop of triethylamine. On TLC (Note 4) the product has  $R_f \sim 0.4$  with ethyl acetate development. If TLC indicates the presence of diethyl hydroxymethylphosphonate an additional 5 g of dihydropyran and 10 drops of phosphorus oxychloride are added. The reaction is checked by TLC for completeness after 1 hr and is worked up at that time.

6. The checkers found that reactions run on up to nine times the present scale could be effected with only a small reduction in yield. Molecular still distillation (wall temperature 105–115°C, 0.10 mm) gave yields of 81–83%.

7. GLC analysis ( $0.5 \times 200$  cm 3% OV-17, 170°C, helium flow = 30 mL/min) shows the product with a retention time of 5 min and a purity greater than 97% The  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ) is as follows  $\delta$ : 1.35 (t, 6 H,  $J = 7$ ), 1.4–1.9 (m, 6 H), 3.4–4.45 (m, 8 H), 4.7 (m, 1 H).

### 3. Discussion

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate is useful in the Wittig–Horner synthesis of enol ethers, which are intermediates in one-carbon homologations of carbonyl compounds.<sup>2</sup> This procedure is an adaptation of a general method for preparing dialkyl hydroxymethylphosphonates.<sup>3</sup> An *O*-tetrahydropyranyl derivative also has been prepared from dibutyl hydroxymethylphosphonate, and diethyl hydroxymethylphosphonate has been *O*-silylated with *tert*-butylchlorodimethylsilane and imidazole.<sup>2</sup> Another useful congener in this series has been prepared by an Arbuzov reaction of methoxyethoxymethyl (MEM) chloride and triethyl phosphite.<sup>2</sup>

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 18

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### References and Notes

1. Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.
  2. Kluge, A. F.; Clousdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.
  3. Zaripov, R. K.; Abramov, V. S. *Tr. Khim.-Met. Inst., Akad. Nauk Kaz. S.S.R.* **1969**, *5*, 50; *Chem. Abstr.* **1970**, *72*, 21745y.
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### Appendix

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

methoxyethoxymethyl (MEM) chloride

ether,  
diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

Phosphorus Oxychloride (21295-50-1)

MgSO<sub>4</sub> (7487-88-9)

dihydropyran

Imidazole (288-32-4)

triethylamine (121-44-8)

Triethyl phosphite (122-52-1)

diethyl phosphite (762-04-9)

helium (7440-59-7)

phosphomolybdic acid (51429-74-4)

Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate,  
Phosphonic acid, [(tetrahydro-2 H-pyran-2-yl)oxy]methyl-, diethyl ester (71885-51-3)

Diethyl hydroxymethylphosphonate (3084-40-0)

dibutyl hydroxymethylphosphonate

tert-butylchlorodimethylsilane (18162-48-6)

paraformaldehyde (30525-89-4)