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.
DIETHYL [(2-TETRAHYDROPYRANYLOXY)METHYL] PHOSPHONATE

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

Submitted by Arthur F. Kluge1

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, 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-tetrahydropyran-2-yloxy)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 MgSO4, 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 $^1$H NMR spectrum (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 × 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 $^1$H NMR spectrum (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-tetrahydropyranloxy)methyl]phosphonate is useful in the Wittig–Horner synthesis of enol ethers, which are intermediates in one-carbon homologations of carbonyl compounds. This procedure is an adaptation of a general method for preparing dialkyl hydroxymethylphosphonates. An O-tetrahydropyranyl derivative also has been prepared from dibutyl hydroxymethylphosphonate, and diethyl hydroxymethylphosphonate has been O-silylated with tert-butylchlorodimethylsilane and imidazole. Another useful congener in this series has been prepared by an Arbuzov reaction of methoxyethoxymethyl (MEM) chloride and triethyl phosphite.

This preparation is referenced from:


References and Notes


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)
MgSO₄ (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)

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