A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

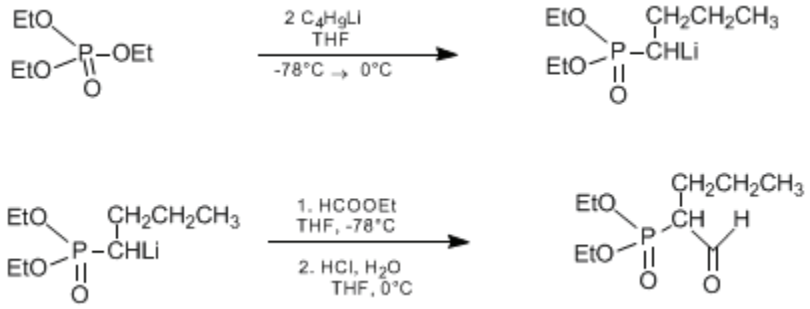
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.072.0241

Organic Syntheses, Coll. Vol. 9, p.239 (1998); Vol. 72, p.241 (1995).

DIETHYL 1-PROPYL-2-OXOETHYLPHOSPHONATE

[Phosphonic acid (1-formylbutyl)-, diethyl ester]



Submitted by Philippe Savignac and Carl Patois[1].
Checked by David R. Jones and Amos B. Smith, III.

1. Procedure

A four-necked, 500-mL, round-bottomed flask is fitted with an efficient mechanical stirrer, thermometer, reflux-condenser with a bubbler, and a 200-mL, pressure-equalizing dropping funnel with a nitrogen inlet. The flask is flame-dried, flushed with nitrogen (the checkers used argon throughout), and charged with 100 mL of tetrahydrofuran (THF) (Note 1). The dropping funnel is charged with 140 mL of a 1.5 M solution of butyllithium in hexane (0.210 mol) (Note 2). The flask is cooled to −20°C with a dry ice/acetone bath (Note 3), stirring is started, and butyllithium is added to tetrahydrofuran over a few minutes. The resulting yellow solution is cooled to −78°C. The cooling bath is then kept just below the bottom of the flask while a solution of triethyl phosphate (18.2 g, 0.1 mol) (Note 4) in tetrahydrofuran (50 mL) is added dropwise from the dropping funnel over 15 min at such a rate that the temperature of the reaction mixture slowly rises to 0°C (Note 5). The resulting solution is stirred for an additional 15 min at 0°C. By this time, the yellow color has practically disappeared and the solution is clear. The reaction mixture is cooled to −78°C and a solution of ethyl formate (7.9 g, 0.107 mol) (Note 6) in tetrahydrofuran (20 mL) is added dropwise at this temperature. The reaction mixture is stirred for 30 min, then allowed to warm up slowly to 0°C, and quenched by the dropwise addition of 80 mL of 3 M hydrochloric acid. The organic layer is separated, and the aqueous phase is extracted with three 50-mL portions of dichloromethane. The extracts are combined with the original organic layer, and dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration, and the solvents are removed on a rotary evaporator. The yellow, crude liquid is distilled through a short column (Note 7) to give 21.0 g (94%) of diethyl 1-propyl-2-oxoethylphosphonate (Note 8) as a pale yellow oil (Note 9), bp 110–115°C/0.05 mm (Note 10).

2. Notes

1. Tetrahydrofuran available from S.D.S. Company was purified by distillation from sodium and benzophenone.
2. The submitters used butyllithium in hexane available from Janssen Chimica and standardized before use by titration against a solution of benzylic alcohol in toluene and cuproine (2,2'-biquinoline). The checkers used butyllithium (1.6 M in hexane) available from Aldrich Chemical Company, Inc., which was standardized before use by titration with diphenylacetic acid in THF.
3. An alternative cooler was used by the submitters, consisting of a Dewar partially filled with liquid nitrogen.
4. The submitters used triethyl phosphate, 99%, available from Janssen Chimica without further purification. The checkers used triethyl phosphate (99+ %) available from Aldrich Chemical Company, Inc., without further purification.
5. The reaction mixture must be only slightly cooled by placing it just above the cooling bath, so that the

reaction proceeds smoothly.
6. The submitters used ethyl formate, 97%, available from Janssen Chimica, without further purification. Dimethylformamide (DMF) can be used instead of ethyl formate with the same operating conditions. The checkers used ethyl formate (99%), available from Aldrich Chemical Company, Inc., without further purification.
7. The submitters used an 8-cm fractionating column equipped with a condenser for distillation.
8. The product displays the following spectroscopic data: m/e = 222; ^{31}P NMR ($CDCl_3$) δ: +19.4 (CHO form), +24.2 (=CHOH form); ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 3 H), 1.30 (t, 6 H), 1.1–2.3 (m, 4 H), 2.9 (m, 1 H), 4.1 (dq, 4 H), 9.6 (d, 1 H). In the presence of the enol form, the ^{1}H spectrum is more complex and exhibits the signal of the aldol proton at 7.3 ppm. ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_3-CH_2), 15.8 (CH_3-CH_2-O), 21.3 (CH_2), 25.5 (CH_2), 52.6 (d, J_{PC} 126.0, P-CH, CHO form), 61.0 and 62.6 (O-CH_2), 99.2 (d, J_{PC} 195.7, P-C=C, CHOH form), 156.6 (d, J_{PC} 29.0, P-C=C, CHOH form), 196.0 (C=O). When several grains of solid potassium carbonate were added to the NMR sample, the ^{1}H and ^{13}C NMR spectra were consistent with the spectral data provided by the submitters for the keto form of the title compound.
9. The distilled product was found to be slightly yellow. It should be stored at 0°C; under these conditions, the purified product is stable for at least several months.
10. The large temperature range is due to the distillation of a mixture of the keto-enol tautomers.

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

This procedure, based on the alkylation-metalation of a trialkyl phosphate by alkyllithiums,[2] illustrates a general route to diethyl 1-formylalkylphosphonates. The method is general and characterized by good yields, mild conditions, and easy preparation of phosphonic aldehydes in pure form starting from readily available materials. It has been shown to be applicable to a wide variety of organolithium reagents, linear (MeLi, EtLi, PrLi) or branched (i-BuLi, isopentyllithium). It is superior to the multistep synthesis previously described which includes an Arbuzov reaction with a protected aldehyde, acidic hydrolysis, enaminophosphonate alkylation, and acidic hydrolysis.[3] Diethyl 1-formylalkylphosphonates are useful intermediates in the Wittig-Horner synthesis of α,β-unsaturated aldehydes and in the synthesis of aminoalkylphosphonates by reductive amination.[4]

References and Notes

1. Laboratoire de Chimie du Phosphore et des Métaux de Transtition, DCPH, Ecole Polytechnique, 91128 Palaiseau Cedex, France.
2. Teulade, M. P.; Savignac, P. *Tetrahedron Lett.* **1987**, *28*, 405; Teulade, M. P.; Savignac, P. *Janssen Chim. Acta* **1988**, *6(2)*, 3; *Chem. Abstr.* **1989**, *110*, 95397m.
3. Nagata, W.; Hayase, Y. *J. Chem. Soc. C.* **1969**, 460.
4. Savignac, P.; Collignon, N. In "Phosphorus Chemistry"; Quin, L. D.; Verkade, J., Eds.; ACS Symposium Series, No. 171; American Chemical Society: Washington, D.C., 1981, p. 255.

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

sodium and benzophenone

i-BuLi

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

nitrogen (7727-37-9)

toluene (108-88-3)

benzylic alcohol (100-51-6)

Diphenylacetic acid (117-34-0)

ethyl formate (109-94-4)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

argon (7440-37-1)

triethyl phosphate (78-40-0)

2,2'-biquinoline (119-91-5)

Diethyl 1-propyl-2-oxoethylphosphonate,
Phosphonic acid (1-formylbutyl)-, diethyl ester (112292-30-5)

isopentyllithium

Copyright © 1921-2005, Organic Syntheses, Inc. All Rights Reserved