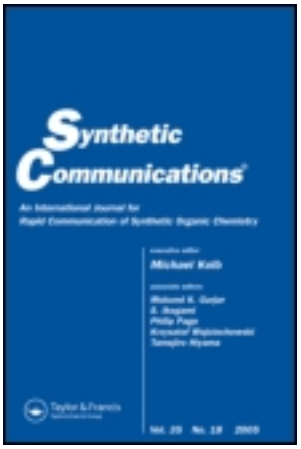

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New Preparation of Diethyl Methylformyl-2-phosphonate Dimethylhydrazone: A Reagent for Aldehyde Homologation

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NEW PREPARATION OF DIETHYL METHYLFORMYL-2-PHOSPHONATE DIMETHYLHYDRAZONE: A REAGENT FOR ALDEHYDE HOMOLOGATION

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The phosphonate reagent diethyl methylformyl-2-phosphonate dimethylhydrazone contains a protected aldehyde group instead of the usual ester group. It can be used for the two-carbon homologation of aldehydes to α, β-unsaturated aldehydes. The reagent can be prepared in good overall yield (82%) and purity by deprotection of commercially available diethyl-2,2-(diethoxy)ethylphosphonate with p-toluenesulfonic acid in 1.5% aqueous acetone to give diethyl formylmethyl-2-phosphonate, followed by a simple preparation of the dimethylhydrazone derivative with N,N-dimethylhydrazine.

Keywords: Aldehyde homologation; diethyl methylformyl-2-phosphonate dimethylhydrazone

INTRODUCTION

A recurring theme in the synthesis of various polyketide natural products and other compounds is two-carbon homologation of aldehydes to α,β-unsaturated aldehydes.[1] Previously, a new phosphonate reagent, diethyl methylformyl-2-phosphonate dimethylhydrazone (**1**), was developed for this conversion.[2] A typical homologation cycle entails condensation of the reagent with the starting aldehyde, followed by removal of the dimethylhydrazone protective group with a biphasic mixture of 1 M HCL and petroleum ether. This robust two-step process works with aliphatic, α,β-unsaturated, and aromatic aldehydes.[2]

The previous synthesis of phosphonate reagent **1**, from commercially available diethyl methylphosphonate and was accomplished by lithiation of diethyl methylphosphonate, and formylation with dimethylformamide,[3] and then the aldehyde functional

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The mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture.

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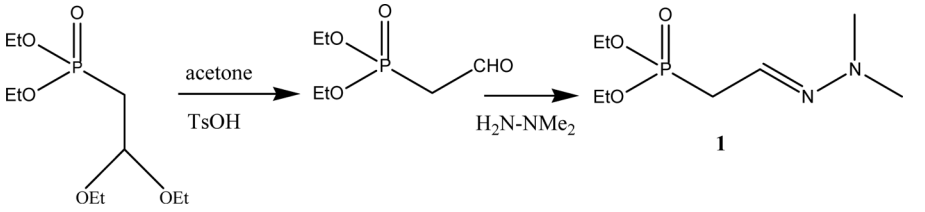

Figure 1. Preparation of phosphonate 1.

group was protected as the dimethylhydrazone derivative.[2] The overall yield for this short synthetic pathway was only 50%, so an alternative preparation of the reagent was sought.

In this article, a new preparation of diethyl methylformylphosphonate dimethylhydrazone (**1**) is reported, which results in greater overall yield (82%) of the reagent (Fig. 1).

RESULTS AND DISCUSSION

Acetals of aldehydes have been deprotected by transfer to acetone in the presence of certain catalysts;[4–7] therefore, deprotection of commercially available diethyl-2,2-(diethoxy)ethylphosphonate[8] would yield the required diethyl formylmethylphosphonate. A deprotection procedure, which needed only a small amount of water, would be preferable because the product, diethyl formylmethyl-2-phosphonate, is difficult to extract from water. Also, hydrolysis of the ethyl esters on phosphorous can occur in water.[9]

Of the catalyst possibilities, the use of amberlyst-15 seemed attractive because the catalyst could be removed by filtration.[4] Unfortunately, decomposition of the resin was observed when conducting the deprotection reaction in this laboratory. The deprotection was successfully carried out with a *p*-toluenesulfonic acid catalyst in acetone[7] containing only 1.5% water. The product contained 8% unused starting material, diethyl-2,2-(diethoxy)ethylphosphonate. Deprotection of the acetal with aqueous HCl also resulted in unreacted starting material.[6]

The aldehyde functional group was then protected as the dimethylhydrazone derivative as done previously.[2] The product still contained about 8% unused starting material, carried through the synthesis. The presence of starting material did not pose a problem when the phosphonate reagent was used for aldehyde homologation.

Alternative names for the aldehyde phosphonate and aldehyde phosphonate dimethylhydrazones **1** are given in the references.[10] The simpler and more intuitive names are used in this article.

EXPERIMENTAL

Chemicals and General Methods

Diethyl-2,2-(diethoxy)ethylphosphonate was purchased from Alfa Aesar (Ward Hill, MA). Other organic reagents, including *p*-toluenesulfonic acid, were obtained from Aldrich and were used without further purification. Nonaqueous reactions were

performed under an atmosphere of dry argon in oven-dried glassware. Removal of solvent was accomplished by rotary evaporation at water aspirator pressure.

Analysis of Reaction Products

Progress of synthetic reactions was monitored by gas chromatography (GC). All reaction products were identified by GC and mass spectrometry (MS), and the structures were additionally verified by NMR. Yields were corrected for purity.

The Hewlett-Packard (HP) 5890 series II gas chromatograph was equipped with flame ionization detector and split/splitless inlet and was interfaced to an HP ChemStation data system. The column was a DB-5 capillary (30 m × 0.25 mm, 0.25-μm film thickness, J&W Scientific, Folsom, CA). Carrier gas was He. The oven temperature was programmed from 50 to 280 °C at 10 °C/min, and the detector temperature was 280 °C. The inlet temperature was 220 °C, and 1.0-μL sample injections were made in splitless mode.

Electron-impact mass spectra (70 eV) were obtained with an HP 5973 MSD instrument, interfaced to an HP 6890 GC equipped with a splitless inlet. Several columns were used but gave results comparable to that used for GC. The oven temperature was programmed from 50 to 250 °C at 10 °C/min; the inlet temperature was 220 °C, and the transfer line temperature was 250 °C.

^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were collected on a Bruker (Bellerica, MA) Avance 500 spectrometer using a 5-mm inverse broadband probe. Samples were dissolved in either $CDCl_3$ or C_6D_6 (where indicated) and all spectra (^{1}H and correlation spectroscopy at 500 MHz, ^{13}C and distortionless enhancement by polarization transfer at 125 Mhz) were acquired at 300 K. Chemical shifts are reported as parts per million from tetramethylsilane with absolute frequency $\Xi = 500.11$ MHz. Coupling constants (J) are in hertz. Assignments were made with the help of ^{1}H and ^{13}C predictive software[11] and by analogy to known compounds.

Diethyl methylformylphosphonate dimethylhydrazone (1). Diethyl-2,2-(diethoxy)ethylphosphonate (5.31 g, 20.9 mmol) was added to acetone (200 mL), followed by water (3 mL) and *p*-toluenesulfonic acid (1.3 g, 6.8 mmol). The mixture was stirred at rt under an argon atmosphere for 4 days. A solution of $NaHCO_3$ (570 mg, 6.8 mmol in 6 mL water) was added with stirring to quench the reaction and neutralize any acid present. The pH was checked and found to be 7. After removal of solvent, aqueous oil remained. The oil was saturated by the addition of NaCl (25 g). The aqueous oil was repeatedly extracted with CH_2Cl_2 (100 mL, then 2 × 50 mL), and the combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and filtered. Solvent was removed to afford 5.59 g of crude diethyl methylformyl-2-phosphonate. Without further purification, the crude product was converted to the dimethylhydrazone (DMH) derivative by adding it to a mixture of CH_2Cl_2 (75 mL) containing anhydrous $MgSO_4$ (5.3 g, 44 mmol), and then *N,N*-dimethylhydrazine (1.76 g, 2.2 mL, 22 mmol) was added in one portion. The mixture was stirred (48 h) until analysis by GC showed complete protection of the aldehyde as the DMH derivative. Filtration, removal of solvent, and Kugelrohr distillation (oven temperature 62 °C, 0.05 Torr) afforded 4.41 g of oil containing **1** (purity 86%, yield corrected for purity 82%). The

oil also contained 8% starting material, diethyl-2,2-(diethoxy)ethylphosphonate. MS of product: (EI) m/z (%) 222 (M^+, 32), 180 (9), 152 (91), 125 (100), 122 (74), 108 (27), 97 (37), 85 (85), 71 (15), 58 (8), 44 (91). ^{1}H NMR δ1.30 (6H, t, $J = 7.0$, C**H**$_3$-CH$_2$-O), 2.77 (6H, s, N-CH$_3$), 2.81 (1H, dt, $J_{1-2} = 5.8$, H-2), 4.09 (4H, q, $J = 7.0$, CH$_3$-C**H**$_2$-O), 6.47 (1H, br d, $J_{1-2} = 5.8$, H-1). ^{13}C NMR δ16.4 (**C**H$_3$-CH$_2$-O), 31.3 (C-2), 42.9 (N-CH$_3$), 61.9 (CH$_3$-**C**H$_2$-O), 126.1 (C-1). The MS and NMR spectral data were consistent with the reference spectral data from previous work.[2]

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10. Diethyl methylformylphosphonate can also be named (2-oxo-ethyl)-phosphonic acid diethyl ester. Diethyl methylformylphosphonate dimethylhydrazone can also be named [2-(dimethyl-hydrazino)-ethyl]-phosphonic acid diethyl ester.
11. ACD ^{1}H and ^{13}C predictive software, version 6.0, is available from Advanced Chemistry Development, Toronto, Ontario, Canada.