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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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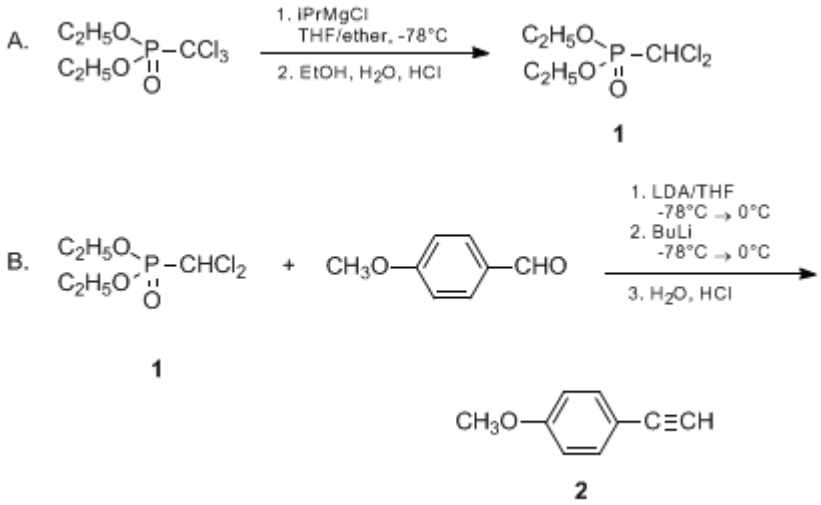
DIETHYL (DICHLOROMETHYL)PHOSPHONATE. PREPARATION AND USE IN THE SYNTHESIS OF ALKYNES: (4-METHOXYPHENYL)ETHYNE

[Phosphonic acid, (dichloromethyl)-, diethyl ester to prepare Benzene, 1-ethylnyl-4-methoxy-]



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1. Procedure

A. *Diethyl (dichloromethyl)phosphonate*, **1**. An oven-dried, 1-L, four-necked, round-bottomed flask (or a 1-L, three-necked flask with a Claisen head fitted in a side neck) is fitted with an efficient mechanical stirrer, thermometer, reflux condenser with a bubbler, and a 200-mL, pressure-equalizing addition funnel with a nitrogen inlet. Under a gentle flow of nitrogen the flask is charged with 400 mL of tetrahydrofuran (THF) (Note 1). The addition funnel is charged with a 1.9 M solution of isopropylmagnesium chloride in diethyl ether (83 mL, 0.158 mol) (Note 2). The mixture is cooled to −78°C with a dry ice/acetone bath (Note 3), and isopropylmagnesium chloride is added over a few minutes with stirring. At this temperature, a solution of diethyl (trichloromethyl)phosphonate (38.3 g, 0.150 mol) (Note 4) in tetrahydrofuran (50 mL) is added dropwise over 15 min. The resulting solution is stirred for an additional 15 min at −78°C producing a clear orange solution. Anhydrous ethanol (12 g, 0.260 mol) in tetrahydrofuran (15 mL) is added dropwise at −78°C, producing a clear yellow solution. The resulting mixture is stirred for a few minutes, then allowed to warm slowly to −40°C. The reaction mixture is poured into a beaker containing a stirred mixture of 3 M hydrochloric acid (70 mL), and an equal volume of crushed ice and dichloromethane (70 mL). The yellow color initially dissipates, but the solution becomes yellow orange upon warming to room temperature. The organic layer is separated, and the aqueous layer is extracted with dichloromethane (2 × 60 mL). The extracts are combined and dried over anhydrous magnesium sulfate. After the filtration, the solvents are evaporated on a rotary evaporator. The bright yellow, crude liquid (36.3 g) is transferred to a pear-shaped flask fitted with a 10-cm Vigreux column and distilled under reduced pressure to give 26.6 g (80%) of diethyl (dichloromethyl)phosphonate, **1**, as a pale yellow liquid, bp 115–119°C/9 mm, >90% pure by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy (Note 5) and (Note 6).

B. *(4-Methoxyphenyl)ethyne*, **2**. An oven-dried, 1-L, four-necked, round-bottomed flask is fitted as above, flushed with nitrogen, and charged with a solution of butyllithium in hexane (1.56 M, 92 mL, 0.143 mol) (Note 7). The solution is cooled with stirring to −20°C with a dry ice/acetone bath and a

solution of diisopropylamine (15.1 g, 0.149 mol) (Note 8) in tetrahydrofuran (220 mL) (Note 1), is added dropwise over 15 min. The resulting clear solution is cooled to −78°C and treated by the dropwise addition of a solution of **1** (30 g, 0.136 mol) and 4-methoxybenzaldehyde (18.1 g, 0.133 mol) (Note 8) in tetrahydrofuran (60 mL) over 30 min. The resulting brown solution is stirred at −78°C for an additional 30 min, then allowed to warm slowly to 0°C over 60 min. The resulting mixture is then cooled to −78°C and a solution of butyllithium (1.56 M in hexane, 183 mL, 0.285 mol) (Note 7) is added dropwise over 20 min. The resulting brown solution is stirred at −78°C for an additional 30 min, then allowed to warm slowly to 0°C over 60 min. At this temperature, the reaction mixture is quenched by the dropwise addition of 3 M hydrochloric acid to pH 5–6 (125–130 mL). The brown color has practically disappeared and the solution is yellow orange. The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 × 50-mL). The extracts are combined, washed with water (3 × 10 mL), and dried over anhydrous magnesium sulfate. Magnesium sulfate is removed by filtration and the solvents are evaporated on a rotary evaporator. The residue is dissolved in hexane (200 mL) and filtered after 30 min. Solvent is again completely evaporated under reduced pressure. Crude product **2** thus obtained is purified by column chromatography on silica gel (Note 9) to afford 11.0 g (63%) of pure (4-methoxyphenyl)ethyne as a colorless liquid, bp 70–72°C (3 mm) that gives white crystals on standing in the freezer (Note 10).

2. Notes

1. Tetrahydrofuran is obtained from S.D.S. Company and is purified by distillation from sodium and benzophenone.
2. Isopropylmagnesium chloride (2 M in diethyl ether) is available from Aldrich Chemical Company, Inc., and is standardized before use by titration against a solution of benzyl alcohol in toluene with cuproine (2,2'-biquinoline).
3. An alternative cooler was also used by the submitters consisting of a Dewar partially filled with liquid nitrogen.
4. Diethyl (trichloromethyl)phosphonate (97%) either purchased from Aldrich Chemical Company, Inc., or prepared according to a described procedure[2] is used.
5. The crude liquid could be distilled using a Kugelrohr apparatus. The main fraction (27.5 g, 83% yield) consists of a clear orange liquid that was collected at 145–155°C (oven temperature)/9–10 mm. ^{1}H NMR (200 MHz, $CDCl_3$) indicates that this material is of the same purity as that from conventional distillation.
6. The product displays the following spectroscopic data: ^{31}P NMR (81 MHz, $CDCl_3$) δ: +10.9; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.29 (t, 6 H, CH_3), 4.22 (dq, 4 H, CH_2), 5.6 (d, 1 H, $^{2}J_{H\text{-}P}$ = 2, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.2 (d, $J_{C\text{-}P}$ = 5.9, CH_3), 60.7 (d, $J_{C\text{-}P}$ = 178, CH), 65.0 (d, $J_{C\text{-}P}$ = 7.4, CH_2) ppm.
7. Butyllithium (1.6 M solution in hexane) is available from Janssen Chimica or Aldrich Chemical Company, Inc., and is standardized before use by titration against a solution of benzyl alcohol in toluene with cuproine (2,2'-biquinoline) or with (±)-2-butanol and 1,10-phenanthroline in diethyl ether.
8. Diisopropylamine (99%) and 4-methoxybenzaldehyde (98%) were purchased from Aldrich Chemical Company, Inc., and used without purification.
9. The crude product is purified by chromatography (200 g of silica gel, Silitech 32–63 μm, purchased from ICN Biomedicals; column diameter, 5.5 cm). Elution is performed first with hexanes (200 mL) and then with hexanes-diethyl ether (20:1). Alternatively, the submitters purified the product by distillation from a pear-shaped flask using an 8-cm fractionating column.
10. The product displays the following spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.02 (s, 1 H), 3.80 (s, 3 H), 6.8 (AA'BB', 2 H), 7.4 (AA'BB', 2 H); ^{13}C NMR (50, MHz, $CDCl_3$) δ: 55.2 (OCH_3), 75.8 (CCH), 83.6 (CCH), 113.9 [CH (Ar)], 114.0 (C-C≡CH), 133 [CH (Ar)], 159.9 (COCH-3) ppm.

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 procedure described in Part A represents a convenient synthesis ofdiethyl (dichloromethyl)

phosphonate, **1**, for large-scale preparations (up to 1 mol). The use of isopropylmagnesium chloride instead of butyllithium[3,4] reduces the amount of by-products,[5] simplifies the purification step, and improves the yield. An alternative synthetic method for **1** is chlorination of diethyl (chloromethyl) phosphonate;[6,7] however, yields and selectivities are lower than in the procedure described here. Diethyl (dichloromethyl)phosphonate, **1**, or the corresponding lithiated derivative, are useful intermediates in organic synthesis: 1,1-dichloroalkenes[3,4,6] as well as terminal alkynes[4] have been prepared.

Part B shows the use of **1** as starting material for the synthesis of (4-methoxyphenyl)ethyne. The generation of the phosphorylated carbanion is performed through metalation with lithium diisopropylamide (LDA). A mixture containing the phosphorus reagent **1** and the aldehyde is added directly to LDA, in order to trap the unstable phosphorylated, lithiated carbanion, thus preventing decomposition and side reactions. The formation of (4-methoxyphenyl)ethyne described here is an example of a general synthetic method for the conversion of aldehydes into acetylenes, on a large scale, by means of diethyl (dichloromethyl)phosphonate, **1**. The methodology is well suited for the synthesis of a wide variety of acetylenic compounds, such as $C_9H_{19}C{\equiv}CH$, $(C_2H_5)_2CHC{\equiv}CH$, $C_6H_5CH{=}CHC{\equiv}CH$,[4] and analogous terminal alkynes. Several methods for the preparation of alkynes based on phosphorus reagents have been reported previously. Each of these procedures can be regarded as an extension of the Wittig-Horner olefin synthesis. In the final step the olefins are converted into the corresponding alkynes. The first method that employed the PPh_3-CBr_4 couple (or PPh_3- CBr_4- zinc dust) was introduced by Corey and Fuchs[8] (1972). The amounts of PPh_3 involved (2 or 4 equiv and of PPh_3O formed during the reaction, are obstacles for large scale synthesis. Dimethyl diazomethylphosphonate first prepared by Seyferth[9] in 1971 was shown, by Colvin and Hamill[10] in 1977, then by Gilbert and Weerasooriya[11] in 1982, to be an effective reagent for the transformation of aldehydes, alkyl aryl ketones or diaryl ketones into alkynes. However, this reagent is rather difficult to prepare (four steps, 46% yield), and very hazardous to handle (explosive decomposition on distillation), and therefore is unsuitable for preparative scale synthesis.

References and Notes

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

Benzene, 1-ethylnyl-4-methoxy-

sodium and benzophenone

cuproine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

nitrogen (7727-37-9)

toluene (108-88-3)

zinc (7440-66-6)

Benzyl alcohol (100-51-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

isopropylmagnesium chloride (1068-55-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

(±)-2-butanol (78-92-2)

lithium diisopropylamide (4111-54-0)

1,10-phenanthroline (66-71-7)

diisopropylamine (108-18-9)

4-methoxybenzaldehyde (123-11-5)

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

Dimethyl diazomethylphosphonate

Diethyl (dichloromethyl)phosphonate,
Phosphonic acid, (dichloromethyl)-, diethyl ester (3167-62-2)

(4-Methoxyphenyl)ethyne (768-60-5)

diethyl (trichloromethyl)phosphonate (866-23-9)

diethyl (chloromethyl)phosphonate (3167-63-3)