Synthesis of the Bestmann–Ohira Reagent

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Abstract: The conversion of an aldehyde to a terminal alkyne by means of a one-carbon chain extension is a key reaction in organic synthesis. By using dimethyl 1-diazo-2-oxopropylphosphonate, the Bestmann–Ohira reagent, the transformation can be achieved in one pot. A reliable, convenient sequence for the preparation of the Bestmann–Ohira reagent is described.

Key words: alkenes, diazo compounds, carbenoids, phosphorus

Alkenylidenes are versatile reactive intermediates in organic synthesis that have been utilized in the synthesis of natural products numerous times. One outstanding application is the transformation of an aldehyde to a chain-extended alkyne via a Fritsch–Buttenberg–Wiechell-type rearrangement.¹ While two-step processes, e.g. the Corey–Fuchs procedure,² are highly popular, one-pot conversions, e.g. using the Colvin³ or Gilbert–Seyferth reagent,⁴ have been less regularly applied. The convenient Bestmann–Ohira reagent (1) is an alternative that allows the addition of the reagent to the aldehyde under mild reaction conditions thus avoiding the use of a strong base under low-temperature conditions (Scheme 1).³ A variety of different aldehydes have been successfully subjected to the transformation. Versatile building blocks such as the 2,3-O-isopropylidene-D-glyceraldehyde⁶ or the Garner aldehyde derived⁷ alkenes 2 or 3, respectively, have been synethesized using this procedure. No racemization of aldehydes (and hence alkynes) was observed in these and similar cases. Herein we describe a reliable, scalable synthesis of the reagent 1 that has been successfully tested in our laboratories numerous times.

First, a synthesis of the β-oxophosphonate 4 was essential (Scheme 2). Acylation of the α-lithiated phosphonate 5 was the first option.⁸ Nevertheless, the procedure proved to be unreliable (the yields varying between 24–80%) and in addition the workup (a time-consuming filtration) was problematic. Direct Michaelis–Arbuzov reaction⁹ between trimethyl phosphate and chloroacetone (6) is not possible, since isopropenyl dimethyl phosphate is the major (Perkow) product.¹⁰ On the other hand, iodoacetone is not commercially available, but would lead to the desired product. Noyori et al. developed a practical variant that allowed the in situ formation of iodoacetone from starting material 6; subsequent treatment with trimethyl phosphate furnished the product 4.¹¹ The oxophosphonate 4 was ready to use after filtration and distillation. Small amounts of impurities sometimes remained after the first distillation leading to a slow discolorization. Repeating the workup procedure yielded the pure product (62–71%; up to 100-g scale).

Sulfonyl azides are well-established reagents for diazo transfer,¹² with tosyl azide being the most frequently used.
To simplify the workup procedure, Baum et al. reported an alternative (Scheme 3); commercially available sulfonyl chloride 7 was easily transformed to the corresponding azide 8 under phase-transfer conditions (73–91%). A modified procedure from Vandewalle et al. was used for the diazo transfer. Deprotonation of the oxophosphonate 4 with sodium hydride in toluene was followed by treatment with reagent 8 in THF instead of using tosyl azide and benzene. The reaction led to the desired Bestmann–Ohira reagent (1) in 77% yield (40–50 g scale). For complete purification, column chromatography was essential; however, for most applications a simple filtration through Celite is sufficient.

Summing up, a short, reliable procedure for the versatile Bestmann–Ohira reagent (1) is reported. The required starting materials are commercially available and have been conveniently transformed in up to 50 g scale to the final product.

The reactions were carried out by using standard Schlenk techniques under dry N₂ with magnetic stirring. Glassware was oven dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use; THF was freshly distilled from Na/ benzophenone. Common solvents for chromatography (PE, EtOAc) were distilled prior to use; PE refers to petroleum ether (bp 40–60 °C). Flash chromatography was performed on silica gel 60, 0.040–0.063 mm (230–400 mesh). TLC (monitoring the course of the reactions) was performed on pre-coated plastic sheets (Polygram SIL G/UV254, Macherey-Nagel) with detection by UV (254 nm) or by coloration with cerium molybdenum soln [phosphomolybdic acid (25 g), Ce(SO₄)₂·H₂O (10 g), conc H₂SO₄ (60 mL), H₂O (940 mL)]. ¹H and ¹³C NMR spectra were recorded at r.t. in CDCl₃, with a Bruker ARX 300/500. Chemical shifts are given in ppm relative to TMS as internal standard (¹H) or relative to the resonance of the solvent (¹³C: CDCl₃, δ = 77.0). Higher order δ and J values are not corrected. ¹³C signals were assigned by means of H–H and C–H COSY spectroscopy. Microanalyses were performed at the Institut für Organische Chemie, Stuttgart. IR spectra were obtained on a Perkin-Elmer 283.

Dimethyl 2-Oxoproplyphosphonate (4)
To a stirred suspension of KI (164 g, 980 mmol) in acetone (200 mL) and MeCN (250 mL) was added chloroacetone (6; 78 mL, 980 mmol). Stirring was continued for 1 h at r.t. Trimethyl phosphate (116 mL, 980 mmol) was slowly added. After 12 h at r.t., the mixture was heated to 50 °C to ensure complete conversion. Filtration through a pad of Celite and evaporation of the solvents under reduced pressure yielded the crude product. Distillation furnished the phosphonate 4 as a colorless liquid; yield: 101.3 g (62%) (Lit.¹¹b 71%). The spectroscopic data were in full agreement with those previously reported: bp 69–70 °C/0.47 mbar (Lit.¹¹b 85–88 °C/0.67 mbar).

IR (film): 3002, 2959, 2923, 2854, 1710 (C=O), 1463, 1361, 1260 (P=O), 1080, 825 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 2.29 (s, 3 H, CH₃), 3.07 (d, J_H,P = 22.8 Hz, 2 H, H₁), 3.76 (d, J_H,P = 11.0 Hz, 6 H, OCH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 31.8 (s, C₁), 42.6 (d, J_C,P = 127.4 Hz, C₁), 53.4 (d, J_C,P = 6.4 Hz, OCH₃), 197.7 (d, J_C,P = 3.1 Hz, C=O).

**p-Acetamidobenzensulfonyl Azide (8)**
To a stirred suspension of chloride 7 (100 g, 430 mmol) in CH₂Cl₂ (800 mL) was added TBAC (300 mg), followed by a solution of NaN₃ (42 g, 660 mmol) in H₂O (200 mL). Stirring was continued at r.t.; two clear phases formed overnight. The organic layer was washed with H₂O (2 × 150 mL), dried (MgSO₄), and the solvent removed under reduced pressure. A colorless solid was obtained that was directly used without any further purification; yield: 93.4 g (91%) (Lit.¹³ 73%).

IR (film): 3304, 2923, 2130 (N=N=N), 1680, 1586, 1528, 1405, 1370, 1260, 1127, 1087, 840, 752 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.25 (s, 3 H, CH₃), 7.78 (d, J_H,P = 8.9 Hz, 2 H, ar H₃), 7.90 (d, J_H,P = 8.9 Hz, 2 H, ar H₃), 8.00 (br, 1 H, NH).

¹³C NMR (126 MHz, CDCl₃): δ = 24.8 (CH₃), 119.7 (arom C₃₄), 128.3, 132.4 (arom CH₃), 144.1 (arom C₆₄), 169.4 (C=O).

**Dimethyl 1-Diazo-2-oxoproplyphosphonate (1)**
A 1-L, three-necked flask was equipped with an overhead stirrer and an addition funnel. The flask was charged with phosphonate 4 (54.0 g, 325 mmol) in toluene (300 mL) and the soln cooled to 0 °C. NaN₃ (13.1 g of 55% in paraffin; 300 mmol) was added in portions. After the gas evolution had ceased, a soln of azide 8 (71.8 g, 300 mmol) in THF (100 mL) was added dropwise; the highly viscous suspension slowly colored to yellow-brown and stirring became easier. After 16 h the mixture was diluted with petroleum ether, filtered through a pad of Celite, rinsed thoroughly with Et₂O, and the solvents removed under reduced pressure. For many applications the remaining slightly impure yellow oil can be directly used. Flash chromatography (silica gel, PE–EtOAc, 1:1) furnished the product I; yield: 44.5 g (77%) (Lit.¹¹b 80%).

IR (film): 3055, 2923, 2913, 2130 (N=N=N), 1680, 1586, 1528, 1405, 1370, 1260, 1127, 1087, 840, 752 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 2.24 (s, 3 H, CH₃), 3.81 (d, J_H,P = 11.9 Hz, 6 H, OCH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 27.5 (C₃), 54.0 (d, J_C,P = 5.8 Hz, OCH₃), 60.8 (br, C₁), 190.3 (d, J_C,P = 3.2 Hz, C₂).


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References


(15) The reagent is meanwhile commercially available from Digital Chemistry DSC (www.digitalchem.com).


(17) A discussion has taken place on whether the use of NaN₃ in CH₂Cl₂ causes explosions during workup (see sodium azide under http://pubs.acs.org./cen/safety). However, changing the solvent (e.g. to THF) should not lead to a false sense of safety.