Synthesis of the Bestmann–Ohira Reagent

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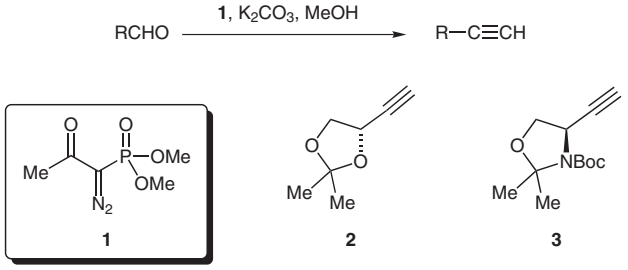
Abstract: The conversion of an aldehyde to a terminal alkyne by means of a one-carbon chain extension is a key reaction in organic synthesis. By using dimethyl 1-diazo-2-oxopropylphosphonate, the Bestmann–Ohira reagent, the transformation can be achieved in one pot. A reliable, convenient sequence for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

Key words: alkynes, diazo compounds, carbenoids, phosphorus

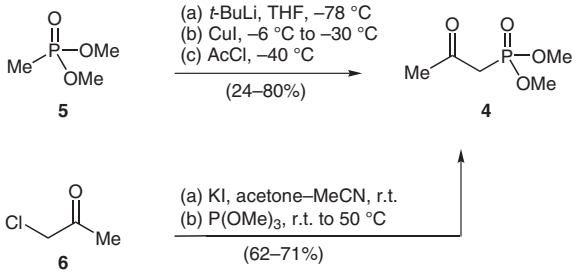


Scheme 1 One-pot procedure for the conversion of an aldehyde to an alkyne using reagent **1**

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 Colvin[3] 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).[5] A variety of different aldehydes have been successfully subjected to the transformation. Versatile building blocks such as the 2,3-*O*-isopropylidene-D-glyceraldehyde[6] or the Garner aldehyde derived[7] alkynes **2** or **3**, respectively, have been synthesized 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 reaction[9] between trimethyl phosphite 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 phosphite 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.



Scheme 2 Syntheses of β-oxophosphonate **4**

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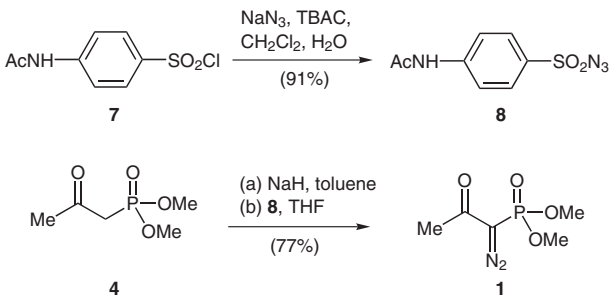

Scheme 3 Diazo-transfer reagent **8** and its use for the synthesis of **1**

To simplify the workup procedure, Baum et al. reported an alternative (Scheme 3);[13] 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.[14] 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.[15]

The reactions were carried out by using standard Schlenk techniques under dry N_2 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 column 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/UV_{254}, Macherey–Nagel) with detection by UV (254 nm) or by coloration with cerium molybdenum soln [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), H_2O (940 mL)]. ^1H and ^{13}C NMR spectra were recorded at r.t. in $CDCl_3$ 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 (^{13}C: $CDCl_3$ δ = 77.0). Higher order δ and *J* values are not corrected. ^{13}C 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-Oxopropylphosphonate (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 phosphite (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;[16] 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, $CDCl_3$): δ = 2.29 (s, 3 H, H3), 3.07 (d, $^2J_{H,P}$ = 22.8 Hz, 2 H, H1), 3.78 (d, $^3J_{H,P}$ = 11.0 Hz, 6 H, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.8 (s, C3), 42.6 (d, $^1J_{c,p}$ = 127.4 Hz, C1), 53.4 (d, $^2J_{c,p}$ = 6.4 Hz, O*C*H_3), 197.7 (d, $^2J_{c,p}$ = 3.1 Hz, *C*=O).

***p*-Acetamidobenzenesulfonyl Azide (8)**

To a stirred suspension of chloride **7** (100 g, 430 mmol) in CH_2Cl_2 (800 mL) was added TBAC (300 mg), followed by a solution of NaN_3 (42 g, 660 mmol) in H_2O (200 mL) (**CAUTION**: AZIDES CAN CAUSE EXPLOSIONS![17]). Stirring was continued at r.t.; two clear phases formed overnight. The organic layer was washed with H_2O (2 × 150 mL), dried ($MgSO_4$), 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, 3266, 3187, 3112, 2130 (N=N=N), 1680, 1586, 1528, 1405, 1370, 1317, 1266, 1170, 1087, 840, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 7.78 (d, ^3J = 8.9 Hz, 2 H, arom C*H*), 7.90 (d, ^3J = 8.9 Hz, 2 H, arom C*H*), 8.00 (br, 1 H, N*H*).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.8 (*C*H_3), 119.7 (arom C_{ipso}), 128.9, 132.4 (arom *C*H), 144.1 (arom C_{para}), 169.4 (C=O).

Dimethyl 1-Diazo-2-oxopropylphosphonate (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. NaH (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 discolored 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 Et_2O, and the solvents removed under reduced pressure. For many applications the remaining slightly impure yellow oil can be directly used. Flash column chromatography (silica gel, PE–EtOAc, 1:1) furnished the product **1**; yield: 44.5 g (77%) (Lit.[14] 80%).

IR (film): 2959, 2855, 2222, 2123 (C=N_2), 1736, 1658, 1461, 1366, 1273, 1182, 1023, 836, 804 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, H3), 3.81 (d, $^3J_{H,P}$ = 11.9 Hz, 6 H, OCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.5 (C3), 54.0 (d, $^3J_{C,P}$ = 5.8 Hz, O*C*H_3), 60.8 (br, C1), 190.3 (d, $^3J_{C,P}$ = 3.2 Hz, C2).

Anal. Calcd for $C_5H_9N_2O_4P$ (192.11): C, 31.26; H, 4.72; N, 14.58. Found: C, 31.40; H, 4.83; N, 14.01.

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