Further Improvements of the Synthesis of Alkynes from Aldehydes

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Abstract: A highly convenient way to perform the synthesis of alkynes from aldehydes is reported. The procedure utilizes a new in situ preparation of dimethyldiazomethylphosphonate. As a consequence a commercially available reagent can now be used, circumventing a disadvantage of earlier protocols. The easy one-pot procedure avoids the use of strong bases, low temperatures and inert gas techniques.

Key words: alkynes, phosphonates, rearrangements

Utilizing dimethyldiazomethylphosphonate[3] (**1**, DAMP, Figure 1) as a reagent for the transformation of aldehydes into alkynes[4] is a widely used alternative to the longer known Corey–Fuchs method[5] and related procedures.[6,7] The phosphonate **1** is sometimes referred to as the Seyferth–Gilbert reagent though the corresponding diethyl ester was first synthesized by Regitz et al.[8] and the reagent was first used for the synthesis of alkynes by Colvin et al.[9] The mechanism of the transformation includes a Horner–Wadsworth–Emmons-type reaction, loss of nitrogen and rearrangement of the resulting alkenylidenecarbene into the alkyne.

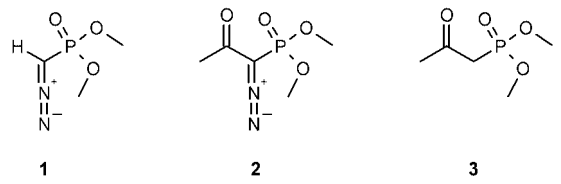
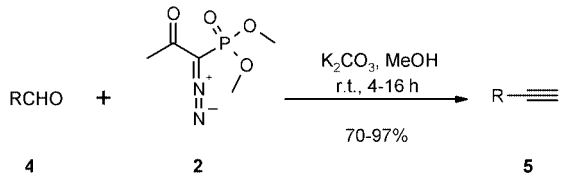


Figure 1

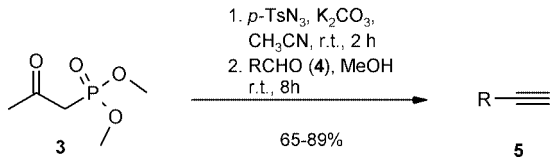
The major disadvantage of all reported procedures is the fact that reagent **1** is not commercially available and has to be prepared by one of several multistep procedures prior to use. Therefore, many researchers still hesitate to use this extremely mild and efficient method. Furthermore, strong bases such as *n*-butyllithium or potassium *tert*-butylate are required for deprotonation, low temperatures and inert gas techniques have to be applied. We recently described[10] an improved one-pot procedure of this reaction based on a protocol by Ohira[11] avoiding most of the mentioned disadvantages. A remaining problem is the fact that the employed dimethyl-1-diazo-2-oxopropylphosphonate (**2**, Figure 1) is still not commercially available, though it can be prepared in one step.[12] We herein present a further improvement of the reaction procedure so that commercially available dimethyl-2-oxopropylphosphonate (**3**, Figure 1) can directly be used as reagent. In addition, we compare the observed results with the older protocol employing **2** as reagent.

In our originally reported procedure (Method B) phosphonate **2** was added to a solution of K_2CO_3 and the aldehyde **4** in MeOH at room temperature (Scheme 1). After stirring for several hours the alkyne **5** could be isolated in good to excellent yields in analytical pure form usually after simple aqueous work-up.



Scheme 1

Compound **2** was obtained in 83% yield from dimethyl-2-oxopropylphosphonate (**3**) by diazo transfer with *p*-toluenesulfonylazide according to ref.[12] We reasoned that it should be possible to include the diazotation step into the reaction procedure by choosing appropriate conditions. Indeed, both processes can be combined to a convenient in situ method as shown in Scheme 2 (Method A).



Scheme 2

Dimethyl-2-oxopropylphosphonate (**3**) and *p*-toluenesulfonylazide were added to a suspension of K_2CO_3 in MeCN. After stirring for 2 hours at room temperature the in situ diazotation of the phosphonate yielding compound **2** was complete as judged by TLC.[13] To start the acetyl cleavage yielding compound **1** and the subsequent alkinylation reaction, aldehyde **4** dissolved in MeOH was added and the mixture was stirred overnight. Work-up included aqueous extraction to remove all water-soluble by-products. The residue after drying and evaporation of the solvent contained alkyne **5** together with *p*-

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toluenesulfonylamide produced in the diazotation step. The alkyne can easily be removed from the latter by repeated extraction of the residue with *n*-pentane. In the case of products not soluble in *n*-pentane column chromatography can be used for purification alternatively. Experiments utilizing water-soluble azides for the diazotransfer reaction resulted in lower yields.[14]

The described procedure is impressive both in simplicity and scope. As depicted in the Table 1 the yields lie in the range of 65–89%. As expected for a two-step procedure, these yields are lower compared to the non in situ protocol (Method B) when performed with the same substrates. Therefore, we recommend Method A for its simplicity, Method B for cases where high yields are desirable, e.g. in multistep procedures. The scope of the reaction is similar with both methods. Alkyl- (**4a**,**c**) and aryl- (**4b**) substituted aldehydes give good results. Compounds containing enolizable protons can be used without any problems. Furthermore, even compounds with stereogenic centers in α-position to the aldehyde react without observable epimerization (**4d**[15] and **4f**[16]) employing either method. In the case of **5d** no diastereomer could be detected. The optical purity of **5f** was checked by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$. Compound **4e** shows that metal complexed substrates can be used.[17] Only azulene-1-carbaldehyde **4g**[18] did not react even under enforced conditions (reflux) employing either Method A or B. This may be due to the electron-rich nature of aldehyde **4g** (see also examples in ref.[10]). However, some electron-rich aldehydes were shown to react after longer reaction times under the conditions of the older Method B.[19]

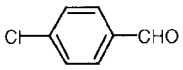
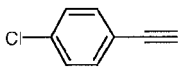
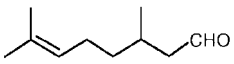
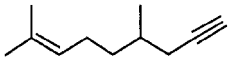
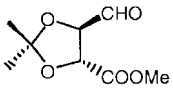
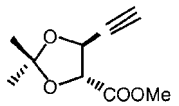
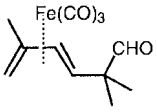
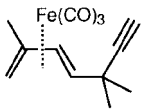
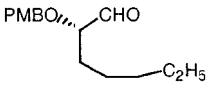
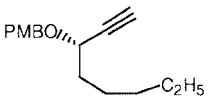
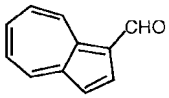
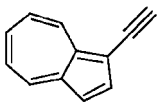
The shown procedure clearly holds promise to be not only one of the mildest but also most easily performable methods for the transformation of aldehydes into alkynes. The key reagent for the transformation is commercially available, the major disadvantage of earlier protocols. The possibility to employ compounds with stereogenic centers without observing any detectable epimerization makes it an interesting alternative in natural product synthesis. We believe it will become one of the standard protocols for that kind of transformation.

MeCN was distilled from CaH_2, MeOH was distilled from magnesium methanolate. Aldehydes **4a** and **4b** as well as K_2CO_3 and dimethyl-2-oxopropylphosphonate **3** were purchased from Aldrich, citronellal **4c** was purchased from Fluka. Aldehydes **4e** and **4g** can be prepared according to literature methods,[17,18] as was *p*-toluenesulfonylazide.[20] For aldehydes **4d** and **4f** see refs.[15,16] Column chromatography was carried out with Merck silica gel 60 (230–400 mesh). NMR spectra were recorded on a Jeol JNM-EX 400 spectrometer with TMS (^{1}H NMR) and $CDCl_3$ (^{13}C NMR) as internal standards. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer. Mass spectra were performed on a Varian MAT-CH-4B spectrometer (EI, 70 eV). Optical rotation was determined on a Schmidt & Haensch Polartronic E polarimeter. Melting points were taken on a Wagner & Munz melting point apparatus and are uncorrected. Elemental analyses were performed on a Heraeus C-H-N Mikromat.

Method A; General One-Pot Procedure

Dimethyl-2-oxopropylphosphonate **3** (1.2 mmol) was added to a suspension of K_2CO_3 (3.0 mmol) and *p*-toluenesulfonylazide (1.2

Table 1 Synthesis of Alkynes **5** from Aldehydes **4**

	4	5	Isolated yield (%)
a	*n*-$C_{11}H_{23}$CHO	*n*-$C_{11}H_{23}$–≡	89 (Method A) 96 (Method B)
b			83 (Method A) 97 (Method B)
c			72 (Method A) 96 (Method B)
d			65 (Method A) 73 (Method B)
e			68 (Method A) 70 (Method B)
f			73 (Method A) 80 (Method B)
g			0 (Method A) 0 (Method B)

mmol) in MeCN (15 mL). The mixture was stirred for 2 h. Then the aldehyde **4** (1.0 mmol), dissolved in MeOH (3 mL), was added. Stirring was continued for 8 h. The solvents were removed in vacuo and the residue was dissolved in Et_2O (10 mL) and water (10 mL). The aq layer was separated and the organic layer was washed with water (5 mL), brine (5 mL) and dried over anhyd Na_2SO_4. The solvent was removed in vacuo and the residue was triturated with *n*-pentane (5 mL) and decanted from insoluble material (3–7 times, depending on the solubility of the alkyne). After removal of the solvent the alkyne **5** remained in analytically pure form.

Method B; General Procedure
Dimethyl-1-diazo-2-oxopropylphosphonate **2** (1.2 mmol) was added to a solution of aldehyde **4** (1.0 mmol) and K_2CO_3 (2.0 mmol) in MeOH (15 mL) and stirring was continued for 8 h. The reaction mixture was diluted with Et_2O (25 mL), washed with an aq solution (5%) of $NaHCO_3$ (10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent in vacuo the alkyne **5** remained in analytically pure form.

Tridec-1-yne (5a)[21]
Yield: 160 mg (89%) [Method A], 172 mg (96%) [Method B]; colorless liquid.

IR (neat): 3320, 2120 cm^{-1} (lit.[21] 3320 cm^{-1}).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.26–1.56 (m, 18 H, CH_2), 1.93 (t, *J* = 3.0 Hz, 1 H, ≡CH), 2.18 (dt, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 2 H, ≡C-CH_2).

4-Chlorophenylacetylene (5b)[22]
Yield: 112 mg (83%) [Method A], 131 mg (97%) [Method B]; colorless crystals; mp 45 °C (lit.[22] 45 °C).

IR (KBr): 3295, 2956, 2109, 1488 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.10 (s, 1 H, ≡CH), 7.29 (d, *J* = 9.0 Hz, 2 H, CH_{ar}), 7.41 (d, *J* = 9.0 Hz, 2 H, CH_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.2 (CH), 82.5 (C-), 120.6 (C-C_{ar}), 128.7, 133.4 (CH_{ar}), 134.9 ($C_{ar}Cl$).

4,8-Dimethylnon-7-en-1-yne (5c)[23]
Yield: 109 mg (72%) [Method A], 145 mg (96%) [Method B]; colorless liquid.

IR (neat): 3310, 2980, 2950, 2850, 2110, 1450 cm^{-1} (lit.[23] 3313 cm^{-1}).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.0 Hz, 3 H, CH-C*H*$_3$), 1.25 (m, 1 H, CH_2), 1.45 (m, 1 H, CH_2), 1.61 (s, 3 H, =CH-C*H*$_3$), 1.65 (m, 1 H, CH_2), 1.68 (s, 3 H, =CH-C*H*$_3$), 1.94 (t, *J* = 3.0 Hz, 1 H, ≡CH), 1.98–2.20 (m, 4 H, CH_2, C*H*H, CH), 5.10 (t, *J* = 7 Hz, 1 H, =CH).

(4*S*,5*R*)-(–)-2,2-Dimethyl-4-ethinyl-5-methoxycarbonyl-1,3-dioxolane (5d)
Yield:[24] 107 mg (65%) [Method A], 120 mg (73%) [Method B]; colorless oil; $[\alpha]_D$ –57.6 (*c* 0.67, $CHCl_3$).

IR (neat): 3280, 2995, 2960, 2120, 1760, 1385 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 2.61 (d, *J* = 2.0 Hz, 1 H, CH), 3.82 (s, 3 H, OCH_3), 4.62 (d, *J* = 5.9 Hz, 1 H, CH-CO), 4.88 (d, *J* = 5.9 Hz, 1 H, CH-C).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3 (CH_3), 26.5 (CH_3), 52.7 (OCH_3), 68.4 (*C*H-C), 75.2 (CH), 79.7 (*C*H-CO), 80.2 (*C*CH), 113.1 [*C*(CH_3)$_2$], 169.7 (COO).

EI–MS: *m*/*z* = 184 [M^+], 169.

Anal. Calcd for $C_9H_{12}O_4$ (184.21): C, 58.69; H, 6.57. Found: C, 58.83; H, 6.51.

(+)-(4*E*)-Tricarbonyl[(4-7-η^4)-3,3,6-trimethylhepta-4,6-dien-1-yne]-iron(0) (5e)[17]
Yield: 183 mg (68%) [Method A], 188 mg (70%) [Method B];[17] yellow oil.

IR (neat): 3300, 2970, 2920, 2040, 1970, 1730, 1260 cm^{-1} (lit.[17] 2040 cm^{-1}).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.20 (d, *J* = 2.4 Hz, 1 H, H^{en}-7), 0.69 (d, *J* = 8.5 Hz, 1 H, H-4), 1.38 (s, 6 H, 3-CH_3), 1.73 (d, *J* = 2.4 Hz, 1 H, H^{ex}-7), 2.20 (s, 3 H, 6-CH_3), 2.26 (s, 1 H, H-1), 5.54 (d, *J* = 8.3 Hz, 1 H, H-5).

(3S)-(–)-3-(*para*-Methoxybenzyloxy)-oct-1-yne (5f)
Yield: 180 mg (73%) [Method A], 197 mg (80%) [Method B]; colorless oil; $[\alpha]_D$ –87.2 (*c* 2.08, $CHCl_3$).

IR (neat): 3300, 2960, 2920, 2870, 2090, 1600, 1580 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3 H, CH_3), 1.24–1.43 (m, 6 H, CH_2), 1.70 (m, 2 H, CH_2), 2.45 (s, 1 H, ≡CH), 3.80 (s, 3 H, OCH_3), 4.05 (m, 1 H, CH-O), 4.58 (dd, *J* = 11.4 Hz, 2 H, OCH_2-Ar), 6.87 (d, *J* = 8.3 Hz, 2 H, CH_{ar}), 7.28 (d, *J* = 8.3 Hz, 2 H, CH_{ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (CH_3), 23.5, 25.8, 32.4, 36.6 (CH_2), 56.2 (OCH_3), 69.0 (*C*H-C), 71.0 (OCH_2), 74.6 (CH), 84.1 (*C*CH), 114.7, 130.6 (C_{ar}), 130.9, 160.2 (COO) ppm.

EI–MS: *m*/*z* = 246 [M^+], 121.

Anal. Calcd for $C_{16}H_{22}O_2$ (246.36): C, 78.01; H, 9.00. Found: C, 78.03; H, 9.11.

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