A Stable Reagent for Synthesis of Conjugated Enynes from Enals

Yan Zhang, Yun Li, Yikang Wu*

State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. of China
Fax +86 (0)2164166128; E-mail: yikangwu@mail.sioc.ac.cn

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Abstract: Several conjugated enynes, which were not accessible if using the Ohira–Bestmann reagent, were synthesized from the corresponding enals using a newly developed reagent that has a longer shelf lifetime and can be activated under mild conditions.

Key words: alkynes, Wittig reactions, elimination, carbenes, phosphates

Dimethyldiazomethylphosphonate (**1**, Figure 1) is a mild and useful reagent for the conversion of aldehydes into corresponding alkynes.[1] However, it is not very stable and thus has to be prepared prior to use.[1f] To overcome this shortcomings, Ohira[2a] and Bestmann[2b] introduced a modified reagent **2**, which can be readily prepared and is much easier to handle. On treatment with K_2CO_3 in MeOH, **2** undergoes facile reaction with the in situ formed methoxide anion to generate MeOAc and the anion of **1**. The latter then reacts further with the aldehyde present in the reaction mixture, yielding corresponding terminal alkyne.

While the Ohira–Bestmann reagent **2** is much more convenient to use than **1** and indeed works very well in many cases, it is not applicable to substrates sensitive to MeOH/methoxide (e.g., conjugated enals).[2b,c] In another project, we needed to gain access to certain conjugated enynes from the corresponding enals. Repeated failure with **2** prompted us to design a new reagent **3** (Figure 1), which carries a hydroxyl group at the terminal of a three-carbon chain and allows for generation of the desired diazomethane anion by cleavage of the acyl functionality via lactonization instead of the intermolecular attack by a methoxide ion as required for **2**. Those side reactions caused by methoxide hence can be avoided altogether.

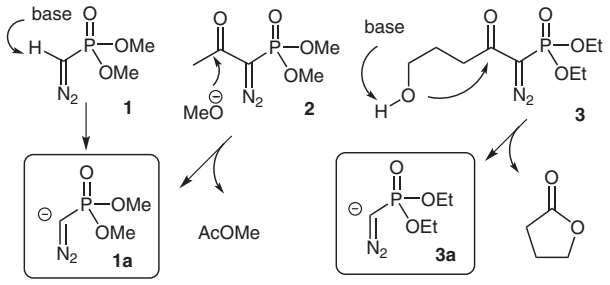

Figure 1 The structures of **1**, **2**, **3**, and the anions generated

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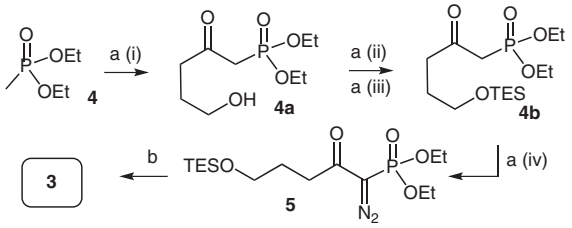
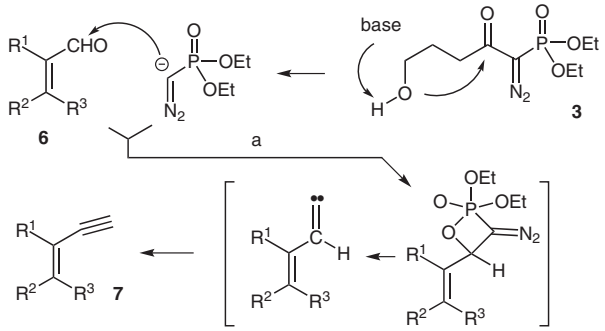
One of the feasible routes to the new reagent **3** is shown in Scheme 1. Deprotonation of the known **4**[3] with *n*-BuLi followed by treatment with γ-butyrolactone introduced the desired acyl chain. The hydroxyl group was then masked[4] as a Et_3Si (TES) ether to suppress the possible intramolecular attack of the hydroxyl group on the acyl group leading to formation of γ-butyrolactone (the same process as desired in later reaction with aldehydes to yield alkynes) during introduction of the diazo group. The TES protecting group was then cleaved with AcOH–H_2O in THF at 0 °C to give the new reagent **3**, a compound that can be stored at room temperature for months without any discernible decomposition.[5,6]



Scheme 1 *Reagents and conditions*: a) (i) *n*-BuLi, THF, γ-butyrolactone, –78 °C; (ii) LDA; (iii) TESCl, 87% from **4**; (iv) TsN_3, K_2CO_3, 68%; b) AcOH, H_2O, THF, 0 °C, 70% from **5**.

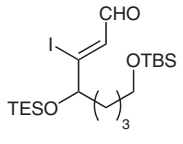
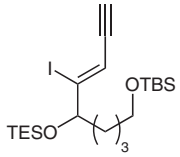
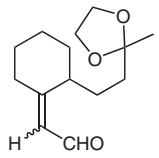
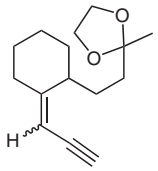
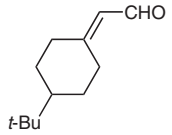
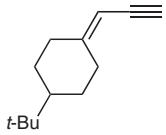
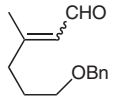
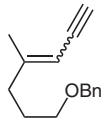
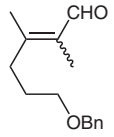
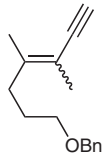
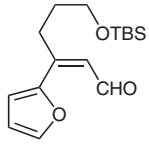
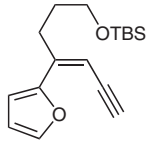
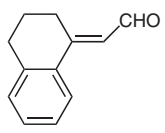
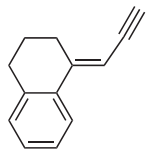
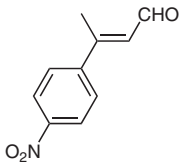
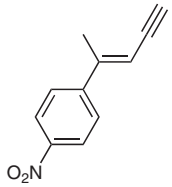
Conversion of aldehydes into alkynes with **3** was then tested on conjugated enals (Scheme 2), the most difficult subtype to which the Ohira–Bestmann reagent **2** is entirely inapplicable. As cleavage of the acyl group in **3** to release the diazomethane anion **3a** does not rely on the intermolecular attack of methoxide ion and the relative high temperature required in experiments with **2** is no longer necessary, the reactions were performed at –78 °C to minimize potential complications.



Scheme 2 *Reagents and conditions*: a) NaHMDS, THF, 18-crown-5, –78 °C.

Preliminary results with **3** are outlined in Table 1. Compared with the broadly employed **2**, which is entirely inapplicable to these enals, the newly developed reagent **3** showed unambiguous advantages. In most cases the desired conjugated enynes were formed in moderate to good yields. Except **6a**, which reacted well without any added crown ether, all other substrates required addition of substantial amounts of 15-crown-5 ether to facilitate the reaction.[7,8]

Table 1 Results of Reaction of **3** with **6** Leading to **7**[a]

Entry	Substrate	Product	Yield (%)
1	 **6a**	 **7a**	83[b]
2	 **6b**	 **7b**	68[c]
3	 **6c**	 **7c**	42[d]
4	 **6d**	 **7d**	22[e]
5	 **6e**	 **7e**	38[f]
6	 **6f**	 **7f**	63[g]
7	 **6g**	 **7g**	35[h]
8	 **6h**	 **7h**	78

[a] Confer the general procedure given in ref. 8.
[b] No 15-crown-5 was used in this run.
[c] Along with 20% of recovered **6b**.
[d] Along with 25% of recovered **6c**.
[e] Along with 28% of recovered **6d**.
[f] Along with 15% of recovered **6e**.
[g] Along with 50% of recovered **6f**.
[h] Along with 17% of recovered **6g**.

It was noted that in most runs where significant amounts of starting aldehydes were recovered at the end of the reaction, some unidentified intermediates (most likely, the adducts before elimination of the phosphate and N_2) were also obtained in substantial quantities.

In conclusion, a new reagent for conversion of aldehydes into alkynes was developed, which contains a self-activation mechanism and thus may generate reactive diazomethane anion at low temperature on treatment with NaHMDS in the presence of 15-crown-5. Compared with the classic reagent **1**, the newly developed **3** is remarkably more stable, without any difficulty to store at ambient temperature for months. Fresh preparation of the reagent every time in need as with **1** is thus avoided. On the other hand, because activation of this reagent (i.e., the cleavage of the acyl group to generate the diazomethane anion) does not rely on intermolecular attack of methoxide ion as with the Ohira–Bestmann reagent **2**, all the side reactions stemming from the presence of MeOH/methoxide are hence eliminated. As a consequence, the additional limitations on the types of substrates associated with **2**, which appear to be the price one has to pay for its facile preparation, storage, and use compared with **1**, are circumvented. Conjugated enynes as those shown in Table 1, which are not attainable with **2**, can now be smoothly obtained from the corresponding enals.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(5) **Synthesis of Compound 3**
n-BuLi (2.5 M in hexanes, 15.76 mL, 39.4 mmol) was added to a solution of **4** (6.0 g, 39.4 mmol) in dry THF (40 mL) stirred at –78 °C under argon. The mixture was stirred at the same temperature for 1 h before a solution of γ-butyrolactone (2.15 mL, 28 mmol) in dry THF (5 mL) was introduced. The originally slightly cloudy mixture now became clear. The bath temperature was allowed to rise slowly to ambient temperature. The stirring was then continued for another 2 h. After that, the bath was re-cooled to –78 °C before a solution of LDA (28 mmol, freshly prepared from 4.0 mL of *i*-Pr_2NH and 11.2 mL of 2.5 M *n*-BuLi) in dry THF (20 mL) was introduced. The mixture was stirred for 30 min. TESCl (9.4 mL, 56 mmol) was then added. The mixture was stirred at ambient temperature overnight. Aq sat. NH_4Cl was added, followed by EtOAc. The phases were separated. The organic layer was washed with H_2O and brine before being dried over anhyd Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE–EtOAc = 1:1 to 1:2) on silica gel gave the intermediate acyl phosphate **4b** as a colorless oil (8.57 g, 87% from **4**).
A portion of this oil (**4b**, 7.596 g, 21.5 mmol) was dissolved in THF (30 mL). With cooling (ice-water bath) and stirring, powdered K_2CO_3 (3.3 g, 23.9 mmol) was added, followed by TsN_3 (4.7 g, 23.9 mmol). The mixture was stirred at the bath temperature for 2 h and then at ambient temperature overnight before being diluted with Et_2O, washed with aq sat. NH_4Cl, and dried over anhyd Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE–EtOAc = 3:1) on silica gel gave **5** as a colorless oil (5.53 g, 68% from the intermediate acyl phosphate).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.25–4.08 (m, 4 H), 3.65 (t, *J* = 6.0 Hz, 2 H), 2.66 (t, *J* = 7.3 Hz, 2 H), 1.86 (quin, *J* = 6.6 Hz, 2 H), 1.39 (t, *J* = 7.1 Hz, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.59 (q, *J* = 7.9 Hz, 6 H). FT-IR (film): 3412, 2955, 2123, 1659, 1253, 1019, 977, 742, 589 cm^{-1}. ESI-MS: *m/z* = 401.1 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{15}H_{31}N_2O_5PSiNa$: 401.1632 $[M + Na]^+$; found: 401.1634.
AcOH (11 mL) was added slowly to a solution of **5** (2.5 g, 6.76 mmol) in THF–H_2O (20 mL, 1:1 v/v) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at the same temperature for another 10 min. Na_2CO_3 was carefully added to neutralize the acid. The mixture was extracted with EtOAc. The combined organic layers were concentrated on a rotary evaporator. The residue was chromatographed (PE–EtOAc = 1:2) on silica gel to give **3** as yellowish oil (1.25 g, 4.73 mmol, 70%).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30–4.10 (m, 4 H), 3.66 (t, *J* = 6.1 Hz, 2 H), 2.72 (t, *J* = 6.9 Hz, 2 H), 2.10–1.90 (br s, 1 H), 1.92 (quin, *J* = 6.5 Hz, 2 H), 1.39 (t, *J* = 7.0 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.2 (d, J_{C-P} = 14 Hz), 63.5 (d, J_{C-P} = 6 Hz), 61.3, 35.9, 27.1, 15.9 (d, J_{C-P} = 7 Hz). FT-IR (film): 3443, 2986, 2118, 1656, 1369, 1251, 1032, 977, 593 cm^{-1}. ESI-MS: *m/z* = 287.0 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_9H_{17}N_2O_5PNa$: 287.0767 $[M + Na]^+$; found: 287.0769.

(6) For the reaction of diakyl methylphosphate with γ-butyrolactone, see: Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325.

(7) In the absence of the crown ether, the reaction was very slow; most of the starting enal (except **6a**) remained unchanged after 4–5 h at –78 °C along with some uncharacterized intermediates and small amounts of the desired enyne.

(8) **General Procedure for the Conversion of 6 into 7**
NaHMDS (2.0 M in THF, 55 μL, 0.11 mmol) was added to a solution of **3** (29 mg, 0.11 mmol) in dry THF (1.0 mL) stirred at –78 °C under argon. The mixture was stirred at the same temperature for 30 min, when a solution of enal **6** (0.073 mmol) in dry THF (0.5 mL) was added slowly (the mixture darkened soon). 15-Crown-5 ether (22 μL, 0.11 mmol) was then added in one portion. The mixture was stirred at the same temperature for 1 h. Aq sat. NH_4Cl was added, followed by Et_2O. The phases were separated. The organic layer was dried over anhyd Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography on silica gel gave the corresponding **7**.