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A convenient reagent for aldehyde to alkyne homologation

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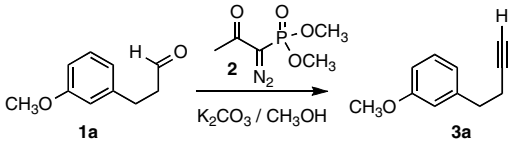
ABSTRACT

A convenient reagent for the one-carbon homologation of an aldehyde to the corresponding alkyne is reported. This reagent allows this conversion to conveniently be carried out on a large scale under ambient conditions.

1. Introduction

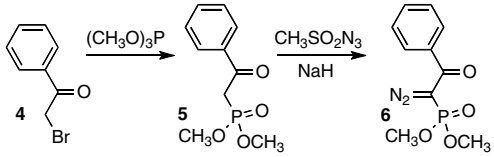
In 1989, Ohira[1] reported a convenient procedure for the homologation of an aldehyde such as **1a** (Eq. 1) to the corresponding alkyne **3a**, by condensation with dimethyl diazomethyl phosphonate, generated in situ from the diazo phosphonate **2**. Subsequently, Bestmann[2] described a more detailed study of this transformation.



(1)

Although we[3] and many others[4] have found the Ohira–Bestmann reagent to be convenient, in recent years, its use has often been displaced by alternative protocols[5] for effecting this homologation. Although the reagent 2 is convenient and easy to prepare from its precursor dimethyl 2-oxopropylphosphonate, the latter is sufficiently expensive (~$2/mmol)[6] that alternative reagents such as TMSCH=N_2 are competitive.

It occurred to us that as the acyl group is lost before the diazophosphonate reacts with the aldehyde, it might be possible to use a bulkier acyl group that would give intermediates that were less expensive and easier to handle. The phosphonate **5** (Eq. 2) immediately came to mind. Easy to prepare[7] from the inexpensive 2-bromoacetophenone **4** (or potentially the even less expensive 2-chloroacetophenone), **5** is also easy to purify by extraction into aqueous base followed by distillation. We have found that the derived[8,9] diazophosphonate **6** can be used directly,[4c] without any purification other than extraction. It is particularly noteworthy that in contrast to the preparation of the Ohira reagent, diazo transfer can be effected with the atom-economical methanesulfonyl azide.[8]



(2)

We were pleased to observe (Table 1) that the crude diazo phosphonate 6 efficiently converted a variety of aldehydes to the corresponding alkynes. The α,β-unsaturated aldehyde (entry 7) gave the methoxy-substituted alkyne. If desired, the methyl benzoate generated as a byproduct of the reaction could be removed by saponification during workup.

The procedure described here for the homologation of an aldehyde to its corresponding alkyne is inexpensive, and can be conveniently carried out on a large scale. In particular, with a burgeoning interest of 'click chemistry',[11] there is a need of the inexpensive preparation of terminal alkynes. We expect that the diazo phosphonate **6** will become a useful tool in the armamentarium of organic synthesis.

2. Experimental

Safety note: Differential scanning calorimetry on the ethyl ester corresponding to **6**, prepared at an early stage of this project, showed a substantial exotherm at 70 °C. The diazo phosphonate **6** should not be warmed past room temperature. The commonly used diazo phosphonate **2** showed a similar exotherm at about the same temperature, so it also must be handled with due caution.

2.1. Dimethyl 2-oxo-2-phenylethylphosphonate (5)

Following the published procedure,[7] to a solution of 2-bromoacetophenone (98%, 12.2 g, 60.0 mmol) in THF (6.0 mL) was added trimethylphosphite (97%, 8.8 mL, 72.4 mmol) dropwise over 5 min.

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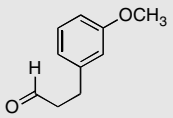
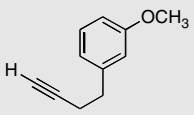
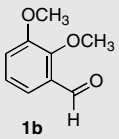
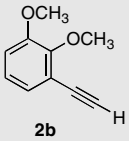
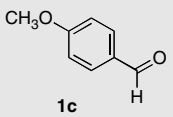
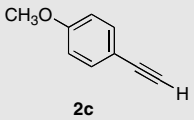
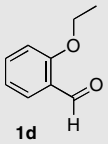
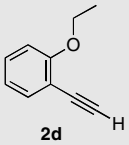
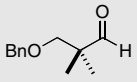
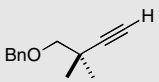
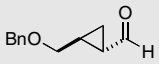
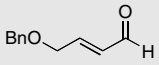
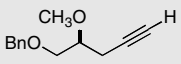
Table 1
Homologation of aldehydes with **6**

Entry	Aldehyde	Alkyne	Yield (%)
1	 **1a**	 **2a**	77[a]
2	 **1b**	 **2b**	79[b]
3	 **1c**	 **2c**	72[c]
4	 **1d**	 **2d**	73[d]
5	 **1e**	 **2e**	81
6	 **1f**	 **2f**	92
7	 **1g**	 **2g**	75[e]

[a] Ref. 10a.
[b] Ref. 10b.
[c] Ref. 10c.
[d] Ref. 10d.
[e] Ref. 10e.

The resulting mixture was heated to reflux overnight, then concentrated. The product was a ~7:3 mixture of dimethyl-2-oxophenylphosphonate and dimethyl 1-phenylethenyl ester by ^{1}H NMR. The mixture was diluted with H_2O (200 mL) and CH_2Cl_2/petroleum ether (PE) (1:19) (10 mL), and was then stirred with solid NaOH pellets (9.6 g, 240.0 mmol) at 0 °C for 2 h (NaOH dissolved). The mixture was diluted with 700 mL of H_2O, and washed with 4 × 900 mL of CH_2Cl_2/PE (1:19). The aqueous phase was acidified with concentrated aqueous HCl (11 M, 22 mL) at 0 °C. The reaction mixture was partitioned between CH_2Cl_2 and, sequentially, H_2O and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude phosphonate was received as a dark orange oil. Distillation (0.5 torr (pot) = 180–190 °C) delivered the known[7b] keto phosphonate as a pale yellow oil (7.7 g, 33.8 mmol, 55% yield). The phosphonate **5** was used in the diazo transfer reaction without further purification. TLC R_f = 0.26 (MTBE/CH_2Cl_2, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 3.78 (d, J = 11.0 Hz, 6H), 3.64 (d, J = 22.6 Hz, 2H); ^{13}C NMR[12] (100 MHz, $CDCl_3$) δ d 52.7 (d, J = 6.6 Hz), 128.3, 128.6, 133.4; u 36.4, 37.7, 136.0 (d, J = 2.5 Hz), 191.4 (d, J = 6.6 Hz).

2.2. Dimethyl 1-diazo-2-oxo-2-phenylethylphosphonate (6)

To a solution of dimethyl-2-oxo-2-phenylphosphonate **5** (99%, 1% CH_2Cl_2 by ^{1}H NMR , 4.7 g, 20.4 mmol) in MeCN (20 mL) was added NaH (60% in mineral oil, 0.99 g, 24.8 mmol) portionwise over 2 min at 0 °C. Mesyl azide[8c] (99%, 3.2 g, 26.2 mmol) was then added in one portion. The mixture was stirred for 3 h at 0 °C, and then partitioned between CH_2Cl_2 and, sequentially, 1 M aqueous NaOH (200 mL) at 0 °C and saturated aqueous $NaHCO_3$ at 0 °C. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude diazo compound was received as a thick orange oil (5.3 g). A portion of the crude diazo compound (94.6 mg) was chromatographed to yield an analytical sample of the known[9] diazo phosphonate **6** (87.1 mg) as a thick yellow oil. The isolated yield was 94% based on **5**. TLC R_f = 0.41 (MTBE/CH_2Cl_2, 2:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 3.81 (d, J = 11.8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ d 53.9 (d, J = 5.8 Hz), 127.2, 128.5, 132.4; u 29.5, 136.6 (d, J = 3.2 Hz), 187.2 (d, J = 9.0 Hz). Diazo phosphonate **6** was stable in the freezer (−20 °C).

2.3. Procedure A: (2*S*)-1-*O*-benzyl-2-methoxypent-4-yn-1-ol (2g)

To a mixture of the aldehyde 1 g (116 mg, 0.7 mmol) and K_2CO_3 (395 mg, 2.9 mmol) in MeOH (3 mL) were added the crude diazo **6** (85.8% pure, 301 mg, 1.0 mmol) and MeOH (7 mL) in one portion at 0 °C. The resulting mixture was stirred at 0 °C–rt overnight. The reaction mixture was chromatographed to yield the known alkyne **2g**[10d] (101 mg, 0.5 mmol, 75% yield) as a pale yellow oil. TLC R_f = 0.24 (MTBE/PE, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 4.57 (s, 2H), 3.51–3.57 (m, 1H), 3.60–3.64 (m, 2H), 3.44 (s, 3H), 2.48–2.51 (m, 2H), 1.98 (t, 1H, J = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 57.6, 78.3, 127.5, 127.6, 128.3; u 20.8, 69.9, 70.6, 73.4, 80.5, 138.0.

2.4. Procedure B (saponification of methyl benzoate): (1*S*,2*S*)-(2-ethynylcyclopropyl)methyl benzyl ether (2f)

To a mixture of the aldehyde **1f** (103 mg, 0.5 mmol) and K_2CO_3 (312 mg, 2.3 mmol) in MeOH (2 mL) were added the crude diazo **6** (92% pure, 226 mg, 0.8 mmol) and MeOH (3.4 mL) in one portion at 0 °C. The resulting mixture was stirred at 0 °C–rt overnight. Then, solid NaOH pellets (256 mg, 6.4 mmol) were added, and the reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to rt, concentrated, and chromatographed to yield alkyne **2f** (92 mg, 0.5 mmol, 92% yield) as a colorless oil. TLC R_f = 0.42 (MTBE/PE, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.38 (m, 5H), 4.56 (s, 2H), 3.55–3.64 (m, 2H), 1.81 (d, 1H, J = 2.0 Hz), 1.46–1.52 (m, 1H), 1.32–1.38 (m, 1H), 0.97–1.02 (m, 1H), 0.53–0.58 (q, 1H, J = 5.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ d 4.7, 17.5, 127.4, 127.7, 128.2; u 12.4, 66.2, 70.6, 72.8, 83.8, 138.3; IR (film): 3294, 3028, 2860, 2360, 2117 cm^{-1}; MS 185 (M^+−1 19), 155 (31), 141 (65), 129 (61), 105 (100); HRMS calcd for $C_{13}H_{13}O$ 185.0966, obsd 185.0966.

Acknowledgments

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Supplementary data

Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.114.

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12. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as 'd' from methylene and quaternary carbons as 'u'.