A convenient reagent for aldehyde to alkyne homologation

Douglass F. Taber*, Sha Bai, Peng-fei Guo
Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, United States

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A B S T R A C T
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, Ohira1 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, Bestmann2 described a more detailed study of this transformation.

CH₃O

\(-\)

O

N₂

OCH₃

\(\text{K₂CO₃/CH₃OH}\)

\(\text{CH₃O}\)

O

OCH₃

\(2\)

\(3\)

\(\text{NaH}\)

\(\text{P} \) \(\text{O}\)

\(\text{CH₃O}\)

O

OCH₃

\(6\)

\(\text{N₂}\)

\(\text{CH₃SO₂N₃}\)

We were pleased to observe (Table 1) that the crude diazo phosphonate 6 efficiently converted a variety of aldehydes to the corresponding alkynes. The \(\alpha,\beta\)-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.
The resulting mixture was heated to reflux overnight, then concentrated. The product was a ~7:3 mixture of dimethyl-2-oxophenylphosphonate and dimethyl 1-phenylethynyl ester by 1H NMR. The mixture was diluted with H2O (200 mL) and then partitioned between CH2Cl2 and, sequentially, 1 M aqueous NaOH (200 mL) at 0°C and saturated aqueous NaHCO3 at 0°C. The combined organic extracts were dried (Na2SO4) 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 diazo phosphonate 6 (87.1 mg) as a thick yellow oil. The isolated yield was 94% based on 5. TLC Rf = 0.24 (MTBE/CH2Cl2, 2:8); 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ d 53.9 (d, J = 5.8 Hz), 172.8, 128.3, 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: (2S)-1-0-benzyl-2-methoxypent-4-yn-1-ol (2g)

To a mixture of the aldehyde 1 g (116 mg, 0.7 mmol) and K2CO3 (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 (101 mg, 0.5 mmol, 75% yield) as a pale yellow oil. TLC Rf = 0.24 (MTBE/PE, 1:9); 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ d 57.6, 78.3, 127.5, 126.7, 126.8; u 20.8, 69.9, 70.6, 73.4, 80.5, 138.0.

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

To a mixture of the aldehyde 1f (103 mg, 0.5 mmol) and K2CO3 (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, 0.55 mmol, 92% yield) as a colorless oil. TLC Rf = 0.42 (MTBE/PE, 1:9); 1H NMR (400 MHz, CDCl3) δ 7.24–7.38 (m, 5H), 4.56 (s, 2H), 3.53–3.64 (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); 13C NMR (400 MHz, CDCl3) 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 calcld for C13H13O 185.0966, obsd 185.0966.

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Supplementary data

Experimental procedures and ¹H NMR and ¹³C 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.

References and notes

8. For diazo transfer with methanesulfonyl azide see: (a) Taber, D. F.; Ruckle, R. E., Jr.; Hennessey, M. J. J. Org. Chem. 1986, 51, 4077. For the preparation of methanesulfonyl azide see: (b) Boyer, J. H.; Mack, C. H.; Goebel, N.; Morgan, L. R., Jr. J. Org. Chem. 1958, 23, 1051; (c) Danheiser, R. L.; Miller, R. F.; Briscois, R. G.; Park, S. J. J. Org. Chem. 1990, 55, 1959. Note that it is convenient to carry out this preparation in acetone. We remove the acetone on high vacuum at room temperature, and do not further purify the methanesulfonyl azide.
12. ¹³C 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'.