Published in final edited form as:

Tetrahedron Lett. 2008 November 24; 49(48): 6904–6906. doi:10.1016/j.tetlet.2008.09.114.

A Convenient Reagent for Aldehyde to Alkyne Homologation

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Abstract

An 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.

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.

(1)

Although we³ and many others⁴ have found the Ohira-Bestmann reagent to be convenient, in recent years its use has often been displaced by alternative protocols⁵ 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=N₂ 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 prepare⁷ 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.

Experimental Section

*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 the about the same temperature, so it also must be handled with due caution.*

Dimethyl 2-oxo-2-Phenylethylphosphonate (**5**)

Following the published procedure⁷, 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-phenylethenyl ester by ¹H NMR. The mixture was diluted with H₂O (200 mL) and CH₂Cl₂/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 H₂O, and washed with 4×900 mL of CH₂Cl₂/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 CH₂Cl₂ and, sequentially, H₂O and saturated aqueous NaHCO₃. The combined organic extracts were dried (Na₂SO₄) 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/CH₂Cl₂, 2:8); ¹H NMR (400 MHz, CDCl₃) 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 NMR¹² (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).

Dimethyl 1-Diazo-2-oxo-2-phenylethylphosphonate (6)

To a solution of dimethyl-2-oxo-2-phenylphosphonate **5** (99%, 1% CH_2Cl_2 by ^1H 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. Mesityl 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, 1M 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 known⁹ 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); ^1H 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).

Procedure A: (2S)-1-O-Benzyl-2-methoxypent-4-yn-1-ol (2g)

To a mixture of the aldehyde **1g** (116 mg, 0.7 mmol) and K_2CO_3 (395 mg, 2.9 mmol) in MeOH (3 mL) was 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); ^1H 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.

Procedure B (Saponification of Methyl Benzoate): (1S,2S)-(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) was 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); ^1H 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 ($\text{M}^+ - 1$ 19), 155 (31), 141 (65), 129 (61), 105 (100); HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{O}$ 185.0966, obsd 185.0966.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank John Dykins for high resolution mass spectra (supported by NSF0541775), and the National Institutes of Health (GM060287) for financial support.

References

1. Ohira S. *Syn. Comm* 1989;19:561.
2. Muller S, Liepold B, Roth GJ, Bestmann HJ. *Synlett* 1996:521–522.
3. Taber DF, Wang Y. *J. Am. Chem. Soc* 1997;119:22.
4. For the use of **2** by others, see (a) Kramer CS, Zeitler K, Muller TJ. *J. Org. Lett* 2000;2:3723. (b) Pietruszka J, Witt A, Frey W. *Eur. J. Org. Chem* 2003;16:3219. (c) Roth GJ, Liepold B, Muller SG, Bestmann HJ. *Synthesis* 2004;1:59. (d) Lepage O, Kattinig E, Furstner A. *J. Am. Chem. Soc* 2004;126:15970. [PubMed: 15584724] (e) Dickson HD, Smith SC, Hinkle KW. *Tet. Lett* 2004;45:5597. (f) Dirat O, Clipson A, Elliott JM, Garrett S, Jones AB, Reader M, Shaw D. *Tet. Lett* 2006;47:1729. (g) Quesada E, Raw SA, Reid M, Roman E, Taylor RJK. *Tetrahedron* 2006;62:6673. (h) Torssell S, Wanngren E, Somfai P. *J. Org. Chem* 2007;72:4246. [PubMed: 17451274] (i) Muruganantham R, Mobin SM, Namboothiri INN. *Org. Lett* 2007;9:1125. [PubMed: 17302426] (j) Vinntonyak VV, Maier ME. *Angew. Chem. Int. Ed* 2007;46:5209. (k) Shangguan N, Kiren S, Williams LJ. *Org. Lett* 2007;9:1093. [PubMed: 17319675] (l) Furstner A, Bouchez LC, Funel J, Liepins V, Poree F, Gilmour R, Beaufils F, Laurich D, Tamiya M. *Angew. Chem. Int. Ed* 2007;46:9265. (m) Negru M, Schollmeyer D, Kunz H. *Angew. Chem. Int. Ed* 2007;46:9339.
5. (a) Trost BM, Waser J, Meyer A. *J. Am. Chem. Soc* 2007;129:14556. [PubMed: 17985906] (b) Barth R, Mulzer J. *Angew. Chem. Int. Ed* 2007;46:5791. (c) Monti C, Sharon O, Gennari C. *Chem. Commun* 2007:4271. (d) Tortosa M, Yakelis NA, Roush WR. *J. Am. Chem. Soc* 2008;130:2722. [PubMed: 18254629]
6. For 2-oxopropylphosphonate preparation, see (a) Cotton FA, Schunn RA. *J. Am. Chem. Soc* 1963;85:2394. (b) Kitamura M, Tokunaga M, Noyori R. *J. Am. Chem. Soc* 1995;117:2931. (c) Pietruszka J, Witt A. *Synthesis* 2006:4266.
7. (a) Fang FG, Feigelson GB, Danishefsky SJ. *Tet. Lett* 1989;30:2743. (b) Moorhoff CM. *Synth. Commun* 2003;12:2069.
8. For diazo transfer with methanesulfonyl azide, see (a) Taber DF, Ruckle RE Jr, Hennessy MJ. *J. Org. Chem* 1986;51:4077. For the preparation of methanesulfonyl azide, see (b) Boyer JH, Mack CH, Goebel N, Morgan LR Jr. *J. Org. Chem* 1958;23:1051. (c) Danheiser RL, Miller RF, Brisbois RG, Park SZ. *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.
9. Regitz M, Martin R. *Tetrahedron* 1985;41:819.
10. (a) Zhang L, Kozmin SA. *J. Am. Chem. Soc* 2004;126:10204. [PubMed: 15315407] (b) Marti T, Peterson BR, Furer A, Mordasini-Denti T, Zarske J, Jaun B, Diederich F. *Helv. Chim. Acta* 1998;81:109. (c) Rosiak A, Frey W, Christoffers J. *Eur. J. Org. Chem* 2006;17:4044. (d) Stiles M, Burckhardt U, Haag A. *J. Org. Chem* 1962;27:4715. (e) Schuppan J, Wehlan H, Keiper S, Koert U. *Chem. Eur. J* 2006;12:7364.
11. For early references to click chemistry, see (a) Kolb HC, Finn MG, Sharpless KB. *Angew. Chem. Int. Ed* 2001;40:2004. (b) Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew. Chem. Int. Ed* 2002;41:2596. (c) Tornøe CW, Christensen C, Meldal M. *J. Org. Chem* 2002;67:3057. [PubMed: 11975567] (d) Speers AE, Adam GC, Cravatt BF. *J. Am. Chem. Soc* 2003;125:4686. [PubMed: 12696868] For more recent references, see (d) Ye C, Gard GL, Inter RW, Syvret RG, Twamley B, Shreeve JM. *Org. Lett* 2007;9:3841. [PubMed: 17715932] (e) Turner RA, Oliver AG, Lokey RS. *Org. Lett* 2007;9:5011. [PubMed: 17956112] (f) Zhang Q, Takacs JM. *Org. Lett* 2008;10:545. [PubMed: 18189407]
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”.

Table 1

Homologation of aldehydes with 6.

Entry	Aldehyde
1	<p>1a</p>

Entry

Aldehyde

2

3

Entry

4

Aldehyde

Entry

Aldehyde

5

1e

6

1f

7

1g^aRef 10a.^bRef 10b.^cRef 10c.^dRef 10d.

^eRef 10e.