Diethyl (3-Trimethylsilyl-2-propynyl)phosphonate, a New Reagent for the Preparation of Terminal Conjugated Enynes

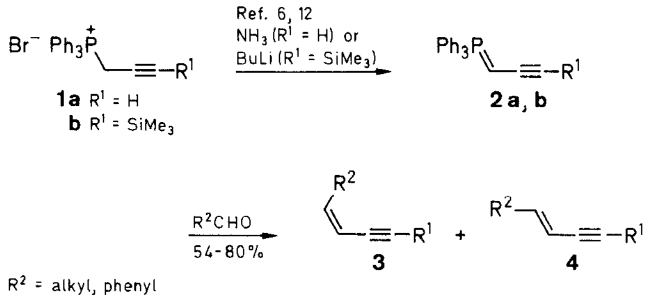
Andrew W. Gibson, Guy R. Humphrey, Derek J. Kennedy, Stanley H.B. Wright*
Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Herts., EN11 9BU, England

The preparation and use of diethyl (3-trimethylsilyl-2-propynyl)phosphonate as a reactant with aldehydes and ketones for the synthesis of terminal conjugated enynes is reported. The reagent is readily obtained and purified by simple procedures amenable to scale up. The scope of the Horner-Wadsworth-Emmons reaction using the reagent has been briefly explored.

Terminal conjugated enynes occur in marine algae[1,2] and the Sea Hare *Aplysia dactylomela*,[3] and it has been suggested that the enynes are precursors of the bromoallenes present in the related mollusc *Aplysia brasiliana*[4] and the red alga genus *Laurencia*.[5] Terminal conjugated enynes are important intermediates for the synthesis of naturally occurring acetylenes,[6,7] acetylenic analogues of Leukotrienes,[8] and peptides in which double bond isosteres replace amide groups.[9-11]

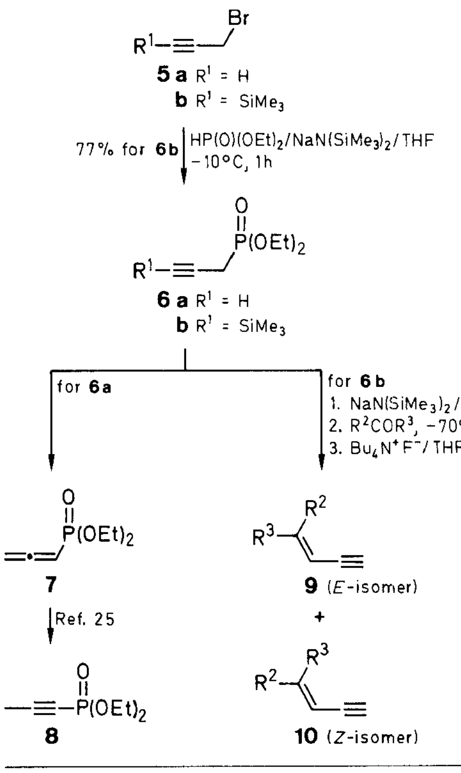
In order to investigate the biomimetic conversion of enynes into bromoallenes by the Bu'Lock mechanism,[2,5] we required an efficient method for the preparation of terminal enynes. Terminal enynes have been obtained from chlorodienes,[6] 4-bromoalkynes,[12] diynes[13] and from vinyl methyl ketones.[14] Other methods for the preparation of terminal enynes or the silyl protected derivatives include the reaction of 2-iodo-1-trimethylsilylacetylenes with a vinyl copper derivative,[15] the palladium catalysed coupling of trimethylsilylacetylene with vinyl halides[4,16] or an enol triflate,[17] and the palladium catalysed reaction of ethynylzinc chloride with vinyl halides.[18] Terminal enynes may also be obtained by reaction of Grignard reagents with pyridazine 1-oxide.[19-21] More recently, the Peterson reaction has been used to generate terminal enynes or silyl derivatives.[22]The plethora of methods which have been used for the preparation of terminal enynes reflects the limitations of the available reagents for the simple Wittig reaction.

The preparation of enynes **3**, **4** by a Wittig reaction, between aromatic and conjugated unsaturated aliphatic aldehydes and the ylide **2a** derived from triphenyl (2-propynyl)phosphonium bromide **1a** was first described by Eiter and Oediger.[15] However, the yields were poor, and Corey[6] demonstrated that with an aliphatic aldehyde (cyclohexanecarboxaldehyde) a cumulene derivative was obtained. Corey then described a more versatile reagent, the silyl derivative **1b**, which reacted with aliphatic and aromatic aldehydes without isomerisation, to furnish enynes **3**, **4** in good yields (Scheme **1**). Recently another ylide reagent, triphenyl(3-trimethylsilyl-2-propynyl)-arsonium bromide was reported which reacts with ketones to give enynes in good yield.[23]



Scheme 1

The instability[7] of the salt **1b**, together with the restricted scope of the Wittig reaction using this reagent suggested that the Horner-Wadsworth-Emmons variant[24] of the reaction would be a superior method for the preparation of enynes. This method would offer the advantages of increased nucleophilicity of the phosphonate carbanion and water soluble phosphate byproducts. Thus, it was with some surprise that we found no reference to this approach in the literature.



9,10	R^2	R^3	9,10	R^2	R^3
a	H	4-MeOC$_6$H$_4$	d	H	CH$_2$=CHCH$_2$CMe$_2$
b	H	Ph	e	Me	Ph
c	H	*n*-C$_{11}$H$_{23}$	f	Bu	Bu

Scheme 2

Diethyl 2-propynylphosphonate (**6a**) rapidly isomerises *via* the allene **7** to the 1-propynylphosphonate **8**[25] (Scheme **2**). However, we wish to report that alkylation of diethyl phosphite with 3-bromo-1-trimethylsilylprop-1-yne (**5b**) gave the trimethylsilyl derivative **6b** as a stable distillable liquid in high yield. The phosphonate **6b** reacted with aromatic aldehydes to afford, after

Table 1. Compounds 9, 10 Prepared

Products 9, 10	Yield (%)	(E/Z) ratio	mp (°C)[a] or bp (°C)/Torr[b]	Molecular Formula[c] or Lit. Data	MS (70 eV)[d] m/z (%)
a	92	95:5	45–47	51[14]	158 (M^+, 94), 115 (100)
b	90	87:13	85–92/0.5	80–90/4[19]	128 (M^+, 100)
c	85	72:28	147–155/0.6	$C_{15}H_{26}$ (206.4)	206 (M^+, 1), 79 (100)
d	71	73:27	75/15	$C_{10}H_{14}$ (134.2)	119 ($M-CH_3$, 28), 77 (100)
e	85	78:22	100/0.7	90–95/4[19]	142 (M^+, 54), 141 (100)
f	76	–	81–82/4	$C_{12}H_{20}$ (164.3)	164 (M^+, 100)

[a] Uncorrected, measured with a Büchi apparatus.

[b] Kugelrohr oven temperature.

[c] Satisfactory HRMS data obtained: $m/z = \pm 0.005$ (M^+).

[d] Recorded on a V.G. Micromass 7070 spectrometer.

Table 2. NMR Spectra of Enynes 9 (E-Isomers)

Compound	^{1}H-NMR (CD_2Cl_2/TMS)[a] δ, J (Hz)	^{13}C-NMR (CD_2Cl_2/TMS)[b] δ
9a	3.06 (dd, 1H, J = 0.8, 2.2, 1-CH), 3.79 (s, OMe), 5.99 (dd, 1H, J = 2.2, 16.5, 3-CH), 6.98 (brd, 1H, J = 16.5, 4-CH), 7.3–6.9 (m, 4H_{arom})	56.3 (OMe), 79.3 (1-CH), 84.3 (2-C), 105.5 (3-CH), 143.7 (4-CH), 114.8, 115.2, 128.6, 161.6 (C_{arom})
9b	3.0 (dd, 1H, J = 0.6, 2.4, 1-CH), 6.06 (dd, 1H, J = 2.4, 16.3, 3-CH), 6.94 (brd, 1H, J = 16.3, 4-CH), 7.1–7.4 (m, 5H_{arom})	80.1 (1-CH), 83.8 (2-C), 107.9 (3-CH), 144.1 (4-CH), 127.3, 129.7, 130.0, 136.9 (C_{arom})
9c	0.89 (~t, 3H, J = 7, Me), 1.3 (brs, 18H, $(CH_2)_9$), 2.1 (dq, 2H, J = 1.6, 7.2, 5-CH_2), 2.8 (ddt, 1H, J = 0.6, 1.2, 2.2, 1-CH), 5.45 (ddt, 1H, J = 1.2, 1.8, 16, 3-CH), 6.28 (ddt, 1H, J = 0.4, 7.2, 16, 4-CH)	15.0 (Me), 23.8, 29.7, 30.2, 30.5, 30.6, 30.7, 30.8, 33.07, 34.1 ($((CH_2)_{10})$), 76.4 (1-CH), 82.5 (2-C), 109.5 (3-CH), 148.2 (4-CH)
9d	0.91 (s, 6H, Me_2), 1.97 (dt, 2H, J = 1.2, 7.5, 6-CH_2), 2.73 (dd, 1H, J = 0.6, 2.2, 1-CH), 4.9 (m, 2H, 8-CH_2), 5.29 (dd, 1H, J = 2.2, 16.5, 3-CH), 5.67 (m, 1H, 7-CH), 6.15 (dd, 1H, J = 0.6, 16.5, 4-CH)	27.0 (Me_2), 47.6 (6-CH_2), 47.9 (5-C), 76.9 (1-CH), 84.2 (2-C), 106.3 (8-CH_2), 118.2 (3-CH), 135.8 (7-CH), 156.5 (4-CH)
9e	2.32 (dd, 3H, J = 0.5, 1.2, Me), 3.3 (dq, 1H, J = 0.5, 1.8, 1-CH), 5.88 (dq, 1H, J = 1.2, 1.8, 3-CH), 7.2–7.5 (m, 5H_{arom})	19.2 (Me), 80.1 (2-C), 83.7 (1-CH), 106.3 (3-CH), 151.2 (4-C), 126.4, 129.3, 129.4, 141.8 (C_{arom})
9f	0.9 (t, 3H, J = 6.9, Me), 0.92 (t, 3H, J = 6.9, Me), 1.4 (m, 8H, $2(CH_2)_2$), 2.1 (t, 2H, J = 8.1, CH_2), 2.32 (t, 2H, J = 8.1, CH_2), 3.0 (brd, 1H, J = 2.2, 1-CH), 5.23 (m, 1H, 3-CH)	14.7 (Me_2), 23.5, 23.6, 30.9, 31.0, 33.8, 36.6 ($2(CH_2)_3$), 80.3 (1-CH), 82.5 (2-C), 104.4 (3-CH), 160.1 (4-C)

[a] Spectra also show the Z-isomers **10**; **10a:** δ = 3.39 (dd, 1H, J = 1, 3 Hz, 1-CH), 3.8 (s, 3H, OMe), 5.55 (dd, 1H, J = 3, 12 Hz, 3-CH), 6.66 (brd, 1H, J = 12 Hz, 4-CH); **10b:** δ = 3.31 (dd, 1H, J = 1, 2.8 Hz, 1-CH), 5.59 (dd, 1H, J = 2.8, 12 Hz, 3-CH), 6.63 (brd, 1H, J = 12 Hz, 4-CH); **10c:** δ = 2.31 (dq, 2H, J = 1.3, 7.5 Hz, 5-CH_2), 3.1 (m, 1H, 1-CH), 6.02 (ddt, 1H, J = 1, 7.5, 11 Hz, 4-CH); **10d:** δ = 1.11 (s, 6H, Me_2), 2.16 (dt, 2H, J = 1.2, 7.5 Hz, 6-CH_2), 3.1 (dd, 1H, J = 1, 2.6 Hz, 1-CH); **10e:** δ = 2.18 (dd, 3H, J = 0.8, 1.5 Hz, Me), 2.9 (dq, 1H, J = 0.8, 2.5 Hz, 1-CH), 5.61 (dq, 1H, J = 1.5, 2.5 Hz, 3-CH)

[b] Recorded on a Bruker AM250 spectrometer.

desilylation, the enyne E-isomers **9a** and **9b** in high yield (Table 1). Reaction of the reagent with aliphatic aldehydes was less stereoselective (E/Z ratio ~ 2.5:1), but high yields of the enynes **9c, 10c** and **9d, 10d** were obtained. Aromatic and aliphatic ketones also reacted with the phosphonate reagent **6b** to give good yields of the enynes **9e, 10e** and **9f** demonstrating the scope of the reaction with the new reagent (Scheme **2**).

Diethyl (3-Trimethylsilyl-2-propynyl)phosphonate (6b):

To a stirred solution of $NaN(SiMe_3)_2$ in THF (1 M, 10 mL, 10 mmol) at −10 °C is added diethyl phosphonate (1.38 g, 10 mmol) in THF (3 mL). The solution is stirred for 15 min at −10 °C and then treated with 3-bromo-1-trimethylsilylprop-1-yne[26] (**5b**; 1.91 g, 10 mmol) in THF (3 mL) maintaining the temperature at −10 °C. The mixture is stirred at −10 °C for 1 h, diluted with H_2O (15 mL) and extracted with EtOAc (2 × 15 mL). The extract is washed with aq HCl (2 M, 25 mL), H_2O (20 mL) and then dried (Na_2SO_4). The solution is evaporated and the oil distilled to give the phosphonate **6b** as a mobile liquid; yield: 1.9 g (77%) bp 115–120 °C/0.2 Torr.

$C_{10}H_{21}O_3PSi$	calc.	C 48.36	H 8.53
(248.3)	found	48.39	8.53

^{1}H-NMR (CD_2Cl_2/TMS): δ = 1.17 (dt, 3H, J = 0.6, 7 Hz, Me), 2.64 (d, 2H, J = 22.2 Hz, CH_2P), 3.98, 4.01 (2 dq, 1H each, J = 0.6, 7 Hz, 2 CHO).

^{13}C-NMR (CD_2Cl_2/TMS): δ = 0.4 (s, MeSi), 17.15 (d, J = 5.5 Hz, Me), 19.9 (d, J = 144.3 Hz, CH_2P), 64.0 (d, J = 6.5 Hz, CH_2O), 88.5 (d, J = 8.3 Hz, C≡), 96.95 (s, SiC≡).

MS: m/z = 248 (M^+, 6%), 177 (100%).

4-Phenyl-3-buten-1-yne (9b); Typical Procedure:

A solution of $NaN(SiMe_3)_2$ in THF (1 M, 9.3 mL, 9.3 mmol) is added to a solution of the phosphonate **6b** (2.3 g, 9.3 mmol) in THF (20 mL) at −60 °C over 10 min. The red solution is stirred at −70 °C for 15 min and then treated with benzaldehyde (0.78 g, 7.4 mmol) in THF (15 mL), added over 15 min. The mixture is stirred at −70 °C for 15 min and then allowed to warm to r.t. over 1 h. The mixture is diluted with H_2O (50 mL) and extracted with EtOAc (2 × 30 mL). The extract is washed with H_2O (2 × 40 mL) and dried (Na_2SO_4). A solution of $Bu_4N^+F^-$ in THF (1 M, 8.5 mL, 8.5 mmol) is added to the dried solution and the mixture stirred at r.t. for 1.5 h. The solution is washed with H_2O (2 × 40 mL), aq HCl (2 M, 40 mL), H_2O (40 mL) and then dried (Na_2SO_4). The solution is evaporated and the residue in hexane (15 mL) chromatographed on silica gel (20 g) to give the enyne **9b** as an orange oil; yield: 0.85 g (90%); bp 85–92 °C/0.7 Torr.

Other compounds were prepared similarly (Table 1). The NMR data for the enynes **9** are collected together (Table 2).

We thank P. V. Byway for mass spectral data.

Received: 19 October 1990; revised: 21 January 1991

(1) Moore, R.E., in: *Marine Natural Products*, Vol. 1, Scheuer, P.J. (ed.), Academic Press, New York, 1978, p. 43.
Waraszkiewicz, S.M.; Sun, H.H.; Erickson, K.L. *Tetrahedron Lett.* **1976**, 3021.
Sun, H.H.; Waraszkiewicz, S.M.; Erickson, K.L. *Tetrahedron Lett.* **1976**, 4227.

(2) Erickson, K.L., in: *Marine Natural Products*, Vol. 5, Scheuer, P.J., (ed.), Academic Press, New York, 1983, p. 131.

(3) Vanderah, D.J.; Schmitz, F.J. *J. Org. Chem.* **1976**, *41*, 3480.

(4) Feldman, K.S. *Tetrahedron Lett.* **1982**, *23*, 3031.

(5) Kennedy, D.J.; Selby, I.A.; Cowe, H.J.; Cox, P.J.; Thomson, R.H. *J. Chem. Soc., Chem. Comm.* **1984**, 153.

(6) Corey, E.J.; Ruden, R.A. *Tetrahedron Lett.* **1973**, 1495.

(7) Ahmed, M.; Barley, G.C.; Hearn, M.T.W.; Jones, E.R.H.; Thaller, V.; Yates, J.A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1981.

(8) Young, R.N.; Champion, E.; Gauthier, J.Y.; Jones, T.R.; Leger, S.; Zamboni, R. *Tetrahedron Lett.* **1986**, *27*, 539.

(9) Hann, M.M.; Sammes, P.G.; Kennewell, P.D.; Taylor, J.B. *J. Chem. Soc., Chem. Commun.* **1980**, 234.
Hann, M.M.; Sammes, P.G.; Kennewell, P.D.; Taylor, J.B. *J. Chem. Soc., Perkin Trans 1* **1982**, 307.

(10) Johnson, R.L. *J. Med. Chem.* **1984**, *27*, 1351.

(11) Kaltenbronn, J.S.; Hudspeth, J.P.; Lunney, E.A.; Michniewicz, B.M.; Nicolaides, E.D.; Repine, J.T.; Roark, W.H.; Stier, M.A.; Tinney, F.J.; Woo, P.K.W.; Essenburg, A.D. *J. Med. Chem.* **1990**, *33*, 838.

(12) Eiter, K.; Oediger, H. *Liebigs Ann. Chem.* **1965**, *682*, 62.

(13) Holmes, A.B.; Raphael, R.A.; Wellard, N.K. *Tetrahedron Lett.* **1976**, 1539.

(14) Loetzbeyer, J.; Bodendorf, K. *Chem. Ber.* **1967**, *100*, 2620.

(15) Normant, J.F.; Commercon, A.; Villieras, J. *Tetrahedron Lett.* **1975**, 1465.

(16) Myers, A.G.; Kuo, E.Y.; Finney, N.S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

(17) Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320.

(18) King, A.O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Comm.* **1977**, 683.

(19) Igeta, H.; Tsuchiya, T.; Nakai, T. *Tetrahedron Lett.* **1969**, 2667.

(20) Okusa, G.; Kumagai, M.; Itai, T. *J. Chem. Soc., Chem. Comm.* **1969**, 710.

(21) Crombie, L.; Kerton, N.A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2136.

(22) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568.
Corey, E.J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719.
Overman, L.A.; Thompson, A.S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

(23) Shen, Y.; Liao, Q. *J. Organomet. Chem.* **1988**, *346*, 181.

(24) Latest review Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863.

(25) Kondratev, Y.A.; Knobel, Y.K.; Irvin, S.Z. *Zh. Obshch. Khim.* **1967**, *37*, 1094.

(26) Miller, R.B. *Synth. Commun.* **1972**, 267.