A Convenient Stereoselective Synthesis of 1,3-Dienylphosphonates and 1-En-3-ynylphosphonates and Their Phosphine Oxide Analogs

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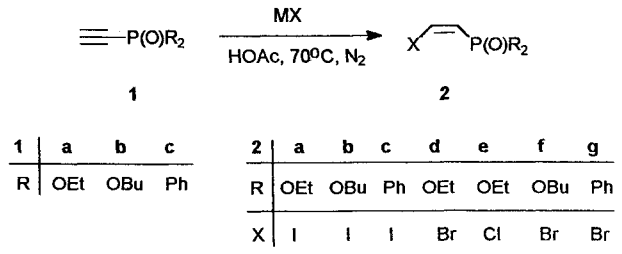
Ethynylphosphonates (or phosphine oxides) react with a lithium halide in acetic acid at 70 °C to yield (*Z*)-2-halovinylphosphonates (or phosphine oxides), which give (1*Z*, 3*E*)-dienylphosphonates and (1*Z*)-en-3-ynylphosphonates (phosphine oxides) after coupling with alkenes and alkynes, respectively, in the presence of a palladium catalyst.



Scheme 1

Table 1. Hydrohalogenation of Ethynylphosphonates and Ethynylphosphine Oxides

Substrate	MX (equiv.)	Time (h)	Product	Yield (%)
1a	LiI (1.2)	14	**2a**	85
1a	NaI (1.2)	17	**2a**	73
1a	LiBr (4.0)	19	**2d**	50
1a	LiCl (4.0)	30	**2e**	30
1b	LiI (1.2)	15	**2b**	84
1b	LiBr (4.0)	19	**2f**	40
1c	LiI (1.2)	14	**2c**	94
1c	LiBr (4.0)	17	**2g**	92

[a] Yield of isolated product.

Stereodefined conjugated dienes and enynes represent a class of important synthetic intermediates and a variety of natural products of biological interest, such as sorbic acid, abscisic acid, etc.[1] Dienylphosphonates containing a (*Z*)-olefinic moiety are of synthetic interest due to their potential usefulness as an enophile or a Michael acceptor and could be regarded as a phosphorus analog of abscisic acid. Their syntheses suffer from the preparation of stereodefined vinyl halides which require lengthy procedures.[2] Recently, we developed a stereoselective hydrohalogenation reaction of 2-propynoates yielding (*Z*)-3-halopropenoates as the sole product.[3] We report here that this is also an efficient stereoselective route to (*Z*)-2-halovinylphosphonates (or phosphine oxides), which could be used as the starting materials for introducing the *Z*-olefinic moiety into dienylphosphonates and enynylphosphonates (or phosphine oxides).

Heating diethyl ethynylphosphonate **(1a)** with lithium iodide in acetic acid at 70 °C under a nitrogen atmosphere for 14 hours afforded **2a** as the sole product in good yield (Table 1). The assignment of the configuration of the product was based on the analysis of the ^{1}H NMR spectral data; the coupling constants $J_{H\text{-}1,H\text{-}2}$ (9.2 Hz) and $J_{P,H\text{-}2}$ (44.8 Hz) confirmed the *Z*-configuration of C=C double bond[4] (Table 2).

The corresponding bromo and chloro analogs were also prepared stereoselectively using a similar procedure, although the yields were lower (Table 1). The reaction of ethynyldiphenylphosphine oxide **(1c)** with metal halides under the same condition gave the (*Z*)-isomers **2c** and

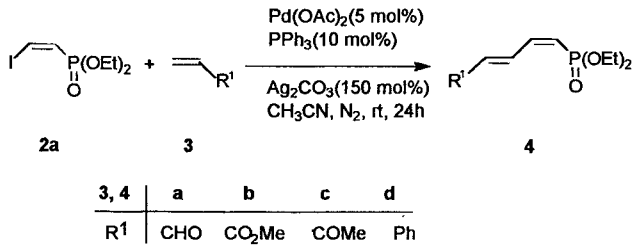
Table 2. 2-Halovinylphosphonates (or Phosphine Oxides) **2** Prepared

Product[a]	mp (°C)	IR (neat) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS *m/z* (%)
2a	oil	3050, 1570, 1240, 1045, 1020	1.37 (t, 6H, *J* = 7.1), 4.18 (q, 4H, *J* = 7.1), 7.07 (dd, 1H, *J* = 9.2, 12.4), 7.62 (dd, 1H, *J* = 9.2, 44.8)	290 (M^+, 75), 135 (100)
2b	oil	3050, 1570, 1230, 1010, 970	0.95 (t, 6H, *J* = 7.8), 1.44 (m, 4H), 1.68 (m, 4H), 4.10 (q, 4H, *J* = 7.8), 7.07 (dd, 1H, *J* = 10.0, 12.4), 7.61 (dd, 1H, *J* = 10.0, 44.8)	346 (M^+, 3), 83 (100)
2c	107–108[b]	3050, 1580, 1440, 1200, 730[c]	7.05 (dd, 1H, *J* = 10.0, 57.5), 7.00–7.10, 7.68–7.78 (m, 10H)[d]	354 (M^+, 47), 203 (100)
2d	oil	3060, 1580, 1250, 1060, 1020	1.37 (t, 6H, *J* = 7.2), 4.17 (m, 4H), 6.60 (dd, 1H, *J* = 9.2, 10.4), 7.18 (dd, 1H, *J* = 9.2, 40.8)	245 [$M^+(^{81}Br)+1$, 94], 243 [$M^+(^{79}Br)+1$, 100]
2e[e]	oil	3050, 1580, 1250, 1020, 970	1.30 (t, 6H, *J* = 7.7), 4.10 (q, 4H, *J* = 7.7), 6.03 (dd, 1H, *J* = 9.0, 10.2), 6.90 (dd, 1H, *J* = 9.0, 40.0)	201 [$M^+(^{37}Cl)+1$, 40], 199 [$M^+(^{35}Cl)+1$, 100]
2f	oil	3030, 1580, 1250, 1060, 1020	0.88 (t, 6H, *J* = 7.5), 1.42 (m, 4H), 1.70 (m, 4H), 4.10 (q, 4H, *J* = 7.5), 6.61 (t, 1H, *J* = 9.2), 7.18 (dd, 1H, *J* = 9.2, 40.8)	301 [$M^+(^{81}Br)+1$, 21], 299 [$M^+(^{79}Br)+1$, 22], 189 (100)
2g	99.5–100.5[b]	3050, 1595, 1470, 1450, 1200[c]	6.61 (dd, 1H, *J* = 9.1, 18.0), 6.71 (dd, 1H, *J* = 9.1, 64.9), 7.0–7.9 (m, 10H)[d]	308 [$M^+(^{81}Br)$, 11], 306 [$M^+(^{79}Br)$, 9], 227 (100)

[a] **2a**, **2b** and **2d** gave HRMS ±0.0029; satisfactory microanalyses for **2c** and **2g** obtained: C ±0.26, H −0.19, except for **2f** (C +0.41, H +0.47).
[b] Recrystallized from acetone/hexane.
[c] Recorded in $CDCl_3$.
[d] Recorded in C_6D_6.
[e] Lit.[5] oil.

2g in excellent yields possibly due to the more electron-withdrawing effect of the diphenylphosphinyl group. Unlike the alkynoates, the reaction did not take place for substituted alkynylphosphonates under the same condition.

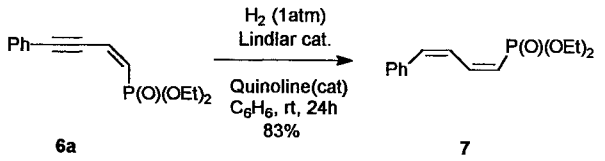
Having the stereodefined (*Z*)-2-iodovinylphosphonates in hand, we desired to introduce the *Z*-olefinic moiety into the dienylphosphonates. Under the modified Heck reaction conditions,[6] coupling of **2a** with alkenes did afford the desired product, (1*Z*, 3*E*)-dienylphosphonates **4** with high stereoselectivity and yields (Table 3).



Scheme 2

The stereochemistry of the above coupling products was confirmed to be in the *Z*-form by the $J_{P,H-2}$ values of their ^{1}H NMR spectra which were between 46–50 Hz[4] (Table 4).

Compounds **6** could be further transformed into (1*Z*,3*Z*)-dienylphosphonates under suitable conditions. As an example, diethyl (1*Z*, 3*Z*)-4-phenylbuta-1,3-dienylphosphonate (**7**) could be prepared by catalytic hydrogenation of **6a** with Lindlar catalyst[9] in 83% yield. The *Z*-stereochemistry of the new C=C double bond was confirmed by analysis of the ^{1}H NMR spectra in which $J_{H-3,H-4}$ was determined to be 11.6 Hz, indicating the *Z*-stereochemistry.



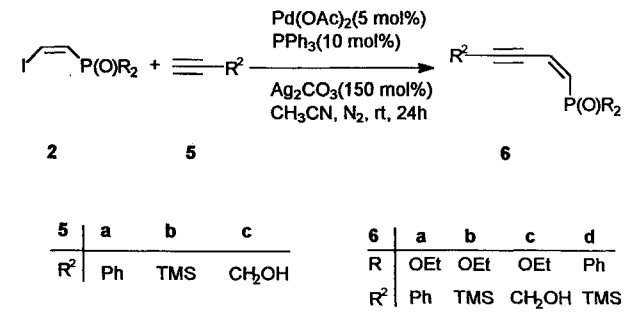
Scheme 4

Table 3. 1,3-Dienylphosphonates **4** Prepared

Product[a]	Yield (%)	IR (neat) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS *m/z* (%)
4a	92	3000, 2720, 1685, 1570, 1050	1.36 (t, 6H, J = 7.0), 4.16 (q, 4H, J = 7.0), 5.99 (t, 1H, J = 13.8), 6.27 (dd, 1H, J = 8.0, 15.5), 7.03 (dt, 1H, J = 49.1, 12.0), 8.24 (dd, 1H, J = 11.4, 15.5), 9.72 (d, 1H, J = 8.0)	218 (M^+, 31), 133 (100)
4b	90	3000, 1720, 1630, 1580, 1050	1.35 (t, 6H, J = 7.1), 3.78 (s, 3H), 4.13 (q, 4H, J = 7.1), 5.90 (dd, 1H, J = 13.1, 15.4), 6.07 (d, 1H, J = 15.4), 6.89 (dt, 1H, J = 49.5, 12.3), 8.14 (dd, 1H, J = 11.4, 15.4)	248 (M^+, 13), 190 (100)
4c[b]	90	3000, 1675, 1620, 1570, 1050	1.39 (t, 6H, J = 7.0), 2.40 (s, 3H), 4.18 (q, 4H, J = 7.0), 5.97 (dd, 1H, J = 12.5, 15.3), 6.25 (d, 1H, J = 16), 6.98 (dt, 1H, J = 49.0, 12.0), 8.19 (dd, 1H, J = 11.2, 15.8)	232 (M^+, 18), 133 (100)
4d	93	3050, 1630, 1590, 1570, 1050	1.35 (t, 6H, J = 7.0), 4.14 (q, 4H, J = 7.0), 5.5 (dd, 1H, J = 12.7, 16.7), 6.79 (d, 1H, J = 15.4), 7.03 (dt, 1H, J = 49.8, 12.0), 7.36–7.60 (m, 5H), 7.82 (dd, 1H, J = 11.4, 15.4)	266 (M^+, 84), 128 (100)

[a] All the products are obtained as oils. Satisfactory HRMS values obtained: ±0.0028.
[b] Lit.[7] oil.

We next turned our attention to the synthesis of (1*Z*)-en-3-ynylphosphonates. When we tried to couple **2a** with phenylacetylene using Sonogashira's conditions,[8] the reaction failed to give the desired product. The use of triethylamine or 1,5-diazabicyclo[3.4.0]non-5-ene as the base also gave fruitless results. Finally, under the same conditions employed in the coupling of **2a** with alkenes described above, the desired products (1*Z*)-en-3-ynylphosphonates **6** were obtained with the retention of the configuration of C=C double bond.



Scheme 3

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360 or XL-200 spectrometer for solutions in $CDCl_3$ or C_6D_6 with TMS as internal standard. IR spectra were taken on a Shimadzu IR-440 spectrometer and mass spectra (MS) were run on a Finnigan 4021 GC/MS/DC instrument. Petroleum ether used refers to boiling range 60–90°C.

Phosphonate **1a**[10] and phosphine oxide **1c**[11] were prepared according to the literature methods. Phosphonate **1b** was prepared in a similar procedure as for **1a**:[10] Yield: 75%, oil.

1b:

IR (neat): ν = 3200, 2950, 1270, 1030 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 90 MHz): δ = 0.95 (t, 6H, J = 7.7 Hz), 1.3–1.6 (m, 8H), 2.90 (d, 1H, J = 12.8 Hz), 4.1 (q, 4H, J = 7.7 Hz).

MS: *m/z* (%) = 219 (M^+ + 1, 5), 107 (100).

HRMS: *m/z* calc. for $C_6H_{12}O_3P(M^+ - C_4H_7)$: 163.0524; found 163.0513.

2-Halovinylphosphonates (or Phosphine Oxides) 2; Typical Procedure:

A mixture of **1a** (260 mg, 1 mmol) and LiI (160 mg, 1.2 mmol) in AcOH (2 mL) was heated at 70°C under N_2 with stirring. The reaction was monitored by TLC. After 14 h, H_2O (5 mL) was added. The mixture was neutralized with solid K_2CO_3, extracted with EtOAc (3 × 20 mL), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel (petroleum ether/acetone, 10:1) to afford **2a** as a colorless oil (230 mg, 85%).

Table 4. 1-En-3-ynylphosphonates (or Phosphine Oxide) **6** Prepared

Product[a]	mp (°C)	Yield (%)	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS m/z (%)
6a	oil	81	3050, 2200, 1600, 1580, 1450	0.95 (t, 6H, J = 7.0), 4.18 (q, 4H, J = 7.0), 6.08 (dd, 1H, J = 13.0, 17.4), 6.56 (dd, 1H, J = 13.0, 46.9), 7.35–7.50 (m, 5H)	264 (M^+, 94), 155 (100)
6b	oil	70	3020, 2115, 1580, 1440, 1010	0.22 (s, 9H), 1.35 (t, 6H, J = 7.1), 4.16 (q, 4H, J = 7.1), 6.10 (dd, 1H, J = 13.6, 17.5), 6.33 (dd, 1H, J = 13.6, 46.9)	260 (M^+, 10), 189 (100)
6c	oil	53	3350, 2200, 1580, 1440, 1020	1.35 (t, 6H, J = 7.1), 4.14 (q, 4H, J = 7.1), 4.42 (s, 2H), 5.99 (dd, 1H, J = 13.3, 17.3), 6.41 (dd, 1H, J = 13.3, 47.9)	217 ($M^+ - 1$, 9), 133 (100)
6d	115–117[b]	83	3030, 2100, 1560, 1440, 1000[c]	0.01 (s, 9H), 6.15 (dd, 1H, J = 13.5, 73.5), 6.17 (dd, 1H, J = 13.5, 19.5), 7.0–7.9 (m, 10H)[d]	324 (M^+, 40), 309 (100)

[a] HRMS for **6a**: +0.0013; satisfactory microanalyses for **6b–d** obtained: C ± 0.26, H ± 0.18, P ± 0.38.
[b] Recrystallized from acetone/hexane.
[c] Measured in $CDCl_3$.
[d] Measured in C_6D_6.

1,3-Dienylphosphonates 4; Typical Procedure:
To a solution of **2a** (290 mg, 1 mmol) and acrolein (224 mg, 4 mmol) in MeCN (3 mL) under N_2 atmosphere were added Ag_2CO_3(415 mg, 1.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and Ph_3P (26 mg, 0.1 mmol). The mixture was stirred at r.t. and monitored by TLC. After the reaction was complete (24 h), the mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/acetone, 10:1) to afford **4a** as a colorless oil (205 mg, 94%).

1-En-3-ynylphosphonates (or Phosphine Oxides) 6. Typical Procedure:
To a solution of **2a** (290 mg, 1 mmol) and phenylacetylene (150 mg, 1.5 mmol) in MeCN (3 mL) under N_2 atmosphere were added Ag_2CO_3 (415 mg, 1.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and Ph_3P (26 mg, 0.1 mmol). The mixture was stirred at r.t. and monitored by TLC. After the reaction was complete (20 h), the mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/acetone, 10:1) to afford **6a** as a colorless oil (220 mg, 81%).

Diethyl (1*Z*, 3*Z*)-4-Phenylbuta-1,3-dienylphosphonate (7):
A mixture of **6a** (265 mg, 10 mmol), quinoline (0.10 mL) and Lindlar catalyst[9] in benzene (5 mL) was stirred under H_2 atmosphere (1 atm.) at r.t. for 24 h. The mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/acetone, 3:1) to afford **7** as a colorless oil (220 mg, 83%).

IR (neat): ν = 3050, 1630, 1590, 1450, 1050 cm^{-1}.

^1H NMR (C_6D_6/TMS, 300 MHz): δ = 1.22 (t, 6H, J = 7.4 Hz), 4.11 (q, 4H, J = 7.4 Hz), 5.66 (dd, 1H, J = 12.9, 15.4 Hz), 6.75 (d, 1H, J = 11.7 Hz), 7.0–7.5 (6H, m), 7.93 (1H, t, J = 11.7 Hz).

MS: m/z (%) = 266 (M^+, 70), 128 (100).

$C_{14}H_{19}O_3P$	calc.	C 63.10	H 7.20	P 11.64
(266.3)	found	63.08	7.55	11.42

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(1) Cornforth, J.W.; Milborrow, B.V.; Ryback, G. *Nature* **1965**, *206*, 715.
Roberts, D.L.; Heckman, R.A.; Hege, B.P.; Bellin, S.A. *J. Org. Chem.* **1968**, *33*, 3566.
(2) Xu, Y.; Jin, X.; Huang, G.; Huang, Y. *Synthesis* **1983**, 556.
Xu, Y.; Jin, X.; Huang, G.; Wang, Y. *Huaxue Xuebao (Engl. Ed.)*, **1985**, 273, *Chem. Abstr.* **1987**, *106*, 5148.
Al-Badri, H.; About-Jaudet, E.; Collignon, N. *Synthesis* **1994**, 1072.
(3) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643.
Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709.
Lu, X.; Zhu, G.; Ma, S. *Chin. J. Chem.* **1993**, *11*, 267; *Chem. Abstr.* **1994**, *120*, 216690.
(4) Petrov, A.A.; Lonin, B.I.; Ignatyev, V.M. *Tetrahedron Lett.* **1968**, 15.
(5) Williamson, M.P.; Castellano, S.; Griffin, C.E. *J. Phy. Chem.* **1968**, *72*, 175.
(6) Abelman, M.M.; Overman, L.E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.
Abelman, M.M.; Oh, T.; Overman, L.E. *J. Org. Chem.* **1987**, *52*, 4130.
(7) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.
(8) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
(9) Lindlar, H.; Dubius, R. *Org. Synth.* **1966**, *46*, 89.
(10) Monaghan, D.T.; Momills, M.C.; Chamberlin, A.R.; Cotman, C.M. *Brain Res.* **1983**, *278*, 137.
(11) Charrier, C.; Chodkiewiecz, W.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1966**, 1002.