

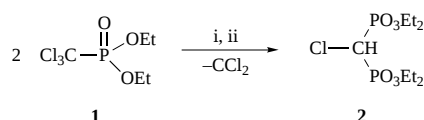
One-pot stereoselective synthesis of (Z)-diethyl α -chlorovinylphosphonates

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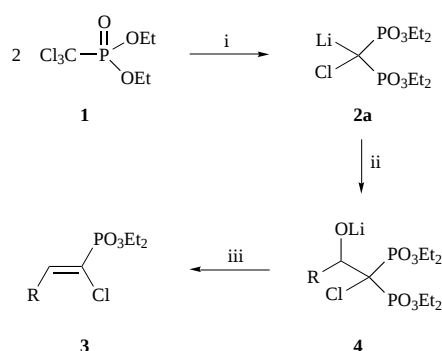
Diethyl trichloromethylphosphonate, treated with BuLi followed by an aldehyde (or cycloalkenone), was converted to α -chlorovinylphosphonates via the intermediate formation of a bisphosphonate and a Wadsworth–Emmons olefination. High (Z) stereoselectivity of the reaction is discussed in terms of the conformational preferences of the adducts.

The unceasing interest in α -phosphoryl, α -chlorocarbanions stems from the rich and diverse chemistry of these nucleophiles, and numerous studies of their preparation and synthetic applications have been published over the past two decades.¹ In a recent paper,² Dizièrè and Savignac reported a simple method for the preparation of alkyl-1-ynylphosphonates from diethyl trichloromethylphosphonate **1**. The method involves the



Scheme 1 Reagents and conditions: i, BuLi, Et₂O, –70 to –80 °C; ii, H₃O⁺, –70 °C

exchange of two α -chlorine atoms in **1** for Li and Me₃Si groups, addition of the lithiated derivative to an aldehyde with the spontaneous Peterson elimination³ of the adduct to an α -chlorovinylphosphonate **3**, followed by the dehydrochlorination of the latter product. Vinylphosphonates **3** were formed as mix-



Scheme 2 Reagents and conditions: i, BuLi, Et₂O, –78 °C; ii, RCHO, –78 °C to room temp.; iii, aq. NH₄Cl, room temp.

tures of *E* and *Z* stereoisomers, which eliminated HCl with different rates.

In the preceding paper of this series,⁴ we have reported the preparation of a useful substrate, tetraethyl (chloromethylene)bisphosphonate **2** directly from **1** (Scheme 1). In this work we report a one-pot synthesis of vinylphosphonates **3** from **1**, via the intermediate formation of **2**, in an approach similar to that used for the preparation of α -fluorovinylphosphonates from the α -fluoroanalogue of **2**.⁵ The method reported here is

complementary to the recent procedure of Savignac,² and offers better stereoselectivity of the formation of the alkenic bond.

Results and discussion

When an ethereal solution of diethyl trichloromethylphosphonate **1** was treated sequentially with BuLi, and aldehyde and aqueous NH₄Cl, α -chlorovinylphosphonates **3** were formed in high yields and with predominant (or exclusive) *Z* geometry (Scheme 2). Products **3** were purified by column chromatography (in some cases followed by distillation or crystallisation) and identified by NMR (³¹P, ¹H, ¹³C) spectroscopy and MS. The configuration was easily determined from the values of the vicinal ³J_{HP} coupling constant for the β -alkenic hydrogen in the ¹H NMR spectrum.⁶ Phenylacetaldehyde failed to react with **1** under the conditions specified in Scheme 2; unreacted phosphonate was recovered upon aqueous work-up, with only traces of product **3** observed in the ³¹P NMR spectrum. It seems likely that under strongly basic conditions of the first step of the sequence, phenylacetaldehyde undergoes deprotonation, complicating the course of the reaction. When, however, independently prepared **2**⁴ was lithiated and treated with phenylacetaldehyde, the expected vinylphosphonate **3** was easily formed, confirming the mechanism (Scheme 2), according to which lithiated **2** acts as the effective nucleophile. The vinylphosphonate (diethyl 1-chloro-3-phenylprop-1-enylphosphonate **3h**) underwent under the reaction conditions partial prototropic isomerisation to the corresponding allylic phosphonate (diethyl 1-chloro-3-phenylprop-2-enylphosphonate **3h'**). The equilibrium mixture consisted of 81% of the isomerised (allylic), and 19% of the unisomerised (vinylic) phosphonate which could not be separated by column chromatography or distillation.

Additional support for the mechanism shown in Scheme 2 was obtained by means of ³¹P NMR spectroscopy. Substrate **1** was dissolved in Et₂O in an NMR tube and the ³¹P NMR spectrum was recorded (single signal, δ_p 6.0). When a solution of BuLi was added to the tube, the signal of **1** gradually disappeared, giving way to a new signal at δ_p 35.6. The same signal was obtained when BuLi was added to a solution of **2** (δ_p 13.8) in Et₂O; the low-field signal was therefore assigned to the lithiated derivative **2a**. For a similar lithiated species, diethyl α -chloro, α -trimethylsilylmethylphosphonate, a key intermediate for the Peterson olefination, Dizièrè and Savignac reported the chemical shift value (in tetrahydrofuran THF) of δ_p = 46.9.² Table 1 includes vinylphosphonates **3** prepared according to Scheme 2, together with the characterisation of the products. It can be seen from Table 1 that stereoisomers *Z* are formed in high excess, or as the exclusive products. The results obtained for the reaction with benzaldehyde (first entry) demonstrate the advantage of using diethyl ether rather than THF as the reac-

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Table 1 Vinyl phosphonates **3**

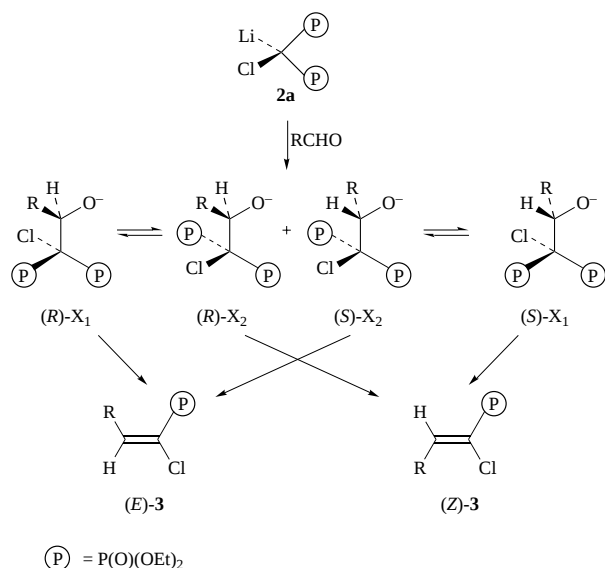
3	R	Yield (%) ^a	Z:E ^b	<i>n</i> _D ¹⁷	¹ H NMR ^c	¹³ C NMR ^c	³¹ P NMR ^d	MS
a^e	Ph	85	100:0	1.5355	7.35–7.40 (2 H, m, <i>o</i> -H ₂), 7.68 (1 H, d, ³ <i>J</i> _{HP} 15.3, β-H), 7.76–7.79 (3 H, m, <i>m</i> -H ₂ , <i>p</i> -H)	121.3 (d, <i>J</i> 344.1), 128.1 (s), 129.7 (s), 129.8 (s), 132.6 (d, <i>J</i> 16.9), 140.8 (d, <i>J</i> 19.1)	11.30	274, 276 (M ⁺ , 21, 7%), 239 (M ⁺ – Cl, 99%), 211 (M ⁺ – Cl – C ₂ H ₄ , 55%), 183 (M ⁺ – Cl – 2C ₂ H ₄ , 100%), 102 (M ⁺ – Cl – PO ₃ Et ₂ , 48%)
			81:19 ^f				11.30 (7.80)	304, 306 (M ⁺ , 17, 6%), 269 (M ⁺ – Cl, 94%), 241 (M ⁺ – Cl – C ₂ H ₄ , 22%), 213 (M ⁺ – Cl – 2C ₂ H ₄ , 100%), 132 (M ⁺ – Cl – PO ₃ Et ₂ , 53%)
b^g	4-MeOC ₆ H ₄	89	100:0	1.5534	3.82 (3 H, s, OMe), 6.91 (2 H, d, ³ <i>J</i> _{HH} 8.9, <i>m</i> -H ₂), 7.62 (1 H, d, ³ <i>J</i> _{HP} 15.3, β-H), 7.80 (2 H, d, ³ <i>J</i> _{HH} 8.9, <i>o</i> -H ₂)	55.0 (s), 113.7 (s), 116.8 (d, <i>J</i> 218.9), 125.5 (d, <i>J</i> 17.5), 131.9 (s), 140.5 (d, <i>J</i> 19.3), 160.7 (s)	12.1	319, 321 (M ⁺ , 6, 2%), 283 (M ⁺ – Cl, 100%), 255 (M ⁺ – Cl – C ₂ H ₄ , 27%), 227 (M ⁺ – Cl – 2C ₂ H ₄ , 91%)
c^h	4-O ₂ NC ₆ H ₄	90	95:5		7.72 (1 H, d, ³ <i>J</i> _{HP} 15.2, β-H), 7.89 (2 H, d, ³ <i>J</i> _{HH} 11.2, <i>o</i> -H ₂), 8.22 (2 H, d, ³ <i>J</i> _{HH} 11.2, <i>m</i> -H ₂)	123.4 (s), 128.1 (d, <i>J</i> 277.3), 130.5 (s), 138.2 (d, <i>J</i> 19.3), 142.2 (d, <i>J</i> 15.8), 147.7 (s)	9.55 (6.44)	352, 354, 356 (M ⁺ , 11, 14, 4%), 317, 319 (M ⁺ – Cl, 100, 97%), 289, 291 (M ⁺ – Cl – C ₂ H ₄ , 20, 19%), 261, 263 (M ⁺ – Cl – 2C ₂ H ₄ , 68, 67%), 29 (Et ⁺ , 35%)
dⁱ	4-BrC ₆ H ₄	85	100:0	1.5622	7.53 (2 H, d, ³ <i>J</i> _{HH} 9.0, <i>o</i> -H ₂), 7.62 (1 H, d, ³ <i>J</i> _{HP} 14.6, β-H), 7.65 (2 H, d, ³ <i>J</i> _{HH} 9.0, <i>m</i> -H ₂)	121.1 (d, <i>J</i> 213.7), 124.4 (s), 129.7 (s), 131.6 (s), 131.8 (s), 139.9 (d, <i>J</i> 19.2)	10.84	212, 214 (M ⁺ , 15, 5%), 177 (M ⁺ – Cl, 70%), 156, 158 (M ⁺ – 2C ₂ H ₄ , 100, 35%), 149 (M ⁺ – Cl – C ₂ H ₄ , 63%), 121 (M ⁺ – Cl – 2C ₂ H ₄ , 88%)
e^j	Me	93	97:3	1.4538	1.88 (3 H, dd, ³ <i>J</i> _{HH} 6.8, ⁴ <i>J</i> _{HP} 3.0, β-Me), 6.90 (1 H, dq, ³ <i>J</i> _{HH} 6.8, ³ <i>J</i> _{HP} 13.5)	14.5 (d, <i>J</i> 13.1), 123.1 (d, <i>J</i> 215.8), 141.8 (d, <i>J</i> 18.2)	10.21 (8.81)	282, 284 (M ⁺ , 15%), 247 (M ⁺ – Cl, 100%), 219 (M ⁺ – Cl – C ₂ H ₄ , 29%), 198, 200 (M ⁺ – C ₆ H ₁₂ , 77, 24%), 191 (M ⁺ – Cl – 2C ₂ H ₄ , 43%), 29 (Et ⁺ , 71%)
f^k	<i>n</i> -C ₆₇ H ₁₃	87	93:7	1.4558	0.85 (3 H, t, ³ <i>J</i> _{HH} 7.0, Me of C ₆ H ₁₃), 1.22–1.46 (10 H, m, 5 × CH ₂), 2.31 (2 H, ddt, ³ <i>J</i> _{HH} 7.1, 7.0, ⁴ <i>J</i> _{HP} 2.9, α-CH ₂ of C ₆ H ₁₃), 6.52 (minor, dt, ³ <i>J</i> _{HH} 7.1, ³ <i>J</i> _{HP} 38.2, β-H of <i>E</i> isomer), 6.85 (1 H, dt, ³ <i>J</i> _{HH} 7.1, ³ <i>J</i> _{HP} 13.8, β-H of <i>Z</i> isomer)	13.7 (s), 22.3 (s), 27.4 (s), 28.7 (s), 28.9 (s), 31.3 (s), 121.7 (d, <i>J</i> 215.2), 147.1 (d, <i>J</i> 16.5)	10.40 (8.87)	238, 240 (M ⁺ , 21, 7%), 210, 212 (M ⁺ – C ₂ H ₄ , 4%), 203 (M ⁺ – Cl, 32%), 182, 184 (M ⁺ – 2C ₂ H ₄ , 19, 6%), 147 (M ⁺ – Cl – 2C ₂ H ₄ , 100%), 29 (Et ⁺ , 27%)
g^l	MeCH=CH	85	85:15	1.4926	1.83 (3 H, d, ³ <i>J</i> _{HH} 5.5, δ-Me), 6.20 (1 H, dq, ³ <i>J</i> _{HH} 7.1, 14.3, δ-H), 6.45 (1 H, m, γ-H), 7.21 (1 H, dd, ³ <i>J</i> _{HH} 10.5, ³ <i>J</i> _{HP} 13.0, β-H)	18.6 (s), 117.3 (d, <i>J</i> 216.3), 125.4 (d, <i>J</i> 14.9), 140.6 (s), 142.2 (d, <i>J</i> 18.7)	11.53 (10.2)	288 (M ⁺ , 1%), 253 (M ⁺ – Cl, 97%), 197, 199 (M ⁺ – PhCH ₂ , 34, 8%), 151, 153 (M ⁺ – PO ₃ Et ₂ , 32, 11%), 115, (M ⁺ – PO ₃ Et ₂ – HCl, 100%), 91 (PhCH ₂ ⁺ , 14%)
h^m	PhCH ₂	14	100:0		3.68 (2 H, dd, ³ <i>J</i> _{HH} 7.2, ⁴ <i>J</i> _{HP} 3.0, γ-CH ₂), 7.04 (1 H, dt, ³ <i>J</i> _{HH} 7.2, ³ <i>J</i> _{HP} 13.3, β-H), 7.01–7.42 (5 H, m, Ph)	35.3 (d, <i>J</i> 12.8), 126.8 (s), 128.2 (d, <i>J</i> 215.7), 128.6 (s), 128.9 (s), other signals overlapping with those of the prop-2-enyl isomer	9.90	
hⁿ		60			4.57 (1 H, ddd, <i>J</i> _{HH} 8.8, 0.8, <i>J</i> _{HP} 13.3, α-H), 6.28 (1 H, ddd, <i>J</i> _{HH} 15.5, 0.8, <i>J</i> _{HP} 6.3, β-H), 6.75 (1 H, dd, <i>J</i> _{HH} 15.5, 0.8, γ-H), 7.01–7.42 (5 H, m, Ph)		17.80	

^a Isolated and purified product. ^b Determined by the integration of the ³¹P NMR signals in the spectrum of crude product. ^c For the sake of clarity, the ¹H and ¹³C NMR signals of the POEt ester groups are not included. In all cases those groups rise to the following signals. δ_H 1.30–1.37 (6 H, t, ³*J*_{HH} 6.9–7.1, 2 × Me of POEt), 4.08–4.24 (4 H, dq, ³*J*_{HH} 6.9–7.1, ³*J*_{HP} 14.3, 2 × CH₂ of POEt); δ_C 15.8–16.2 (d, *J* 6.3), 62.6–63.4 (d, *J* 4.9–5.3). ^d The chemical shift value for the *E* stereoisomer given in parentheses. ^e Purified by column chromatography followed by bulb-to-bulb (b-t-b) distillation; oven temp. (ot) 130–135 °C/0.1 mm. ^f Reaction carried out in THF. ^g Purified by column chromatography followed by b-t-b; ot 145–150 °C at 0.1 mmHg. ^h Purified by column chromatography followed by crystallisation from benzene; mp 54.5–55.5 °C. ⁱ Purified by column chromatography (CHCl₃–AcOEt; 4:1 v/v). ^j Purified column chromatography followed by b-t-b; ot 80 °C/0.1 mm. ^k Purified by column chromatography followed by b-t-b; ot 95–100 °C at 0.1 mmHg. ^l Purified by column chromatography followed by b-t-b; ot 85 °C at 0.1 mmHg. ^m Purified by column chromatography (CH₂Cl₂–AcOEt; 2:1, v/v).

tion medium. We believe, however, that the observed high stereoselectivity of the olefination step is primarily a consequence of the particular molecular system involved in our case in the condensation–olefination reaction.

In the reaction reported by the French authors,² the addition of the nucleophile to an aldehyde yields two diastereomeric adducts which undergo Peterson olefination leading to a pair (*E/Z*) of stereoisomeric alkenes. The stereoselectivity of the

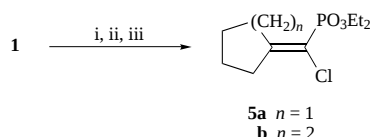
reaction is determined in this case by the stereoselectivity of the condensation step, usually not too high in reactions of phosphonate-stabilised carbanions.⁷ For the reaction involving the bisphosphonate carbanion (Scheme 2), on the other hand, the C–C bond making step results in a racemic adduct, for which two pairs of enantiomeric conformers are possible for the olefination step to occur (Scheme 3). Since the (*R*)-X₂/*(S)*-X₁(*S*)



Scheme 3

pair involves *syn*-periplanar (eclipsed) orientation of two pairs of 'small'/'large' substituents (H/PO₃Et₂, Cl/R), those conformers should be favoured relative to the (*R*)-X₁/*(S)*-X₂ pair which contains unfavourable 'large'/'large' (R/PO₃Et₂) non-bonded interactions. In consequence, the stereoselectivity of the olefination is in our case a function of the conformational equilibrium of the adduct and, as Table 1 shows, can lead (with a proper choice of the solvent) to the formation of the alkene product resulting from a single conformation of the precursor.

The reaction described in Scheme 2 can also be applied to ketones, but its outcome depends on the structure of the substrate. While cyclopentanone and cyclohexanone reacted smoothly yielding the corresponding alkenes **5** (Scheme 4),

Scheme 4 Reagents and conditions: i, BuLi, Et₂O, –78 °C;

ii, (n = 1,2), –78 °C; iii, NH₄Cl, room temp.

reaction with acetophenone led to the isolation of the intermediate **2** in 90% yield. Similarly, for cyclohex-2-enone, no product resulting either from the 1,2, or 1,4-addition could be detected. Further studies on the scope and limitations of the reactions utilising **1** and carbonyl compounds as starting materials are currently in progress.

Experimental

Solvents and commercially available substrates were purified by conventional methods. All condensation reactions were performed under dry nitrogen. Merck Kieselgel 60 (0.063–0.200) was used for column chromatography. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionisation potential of 70 eV. NMR spectra

were recorded on a Bruker AC 300 spectrometer in CDCl₃, and the chemical shift values (δ) are given in ppm relative to the solvent (¹H, δ 7.24; ¹³C, δ 77.0). ³¹P NMR chemical shifts are given relative to 85% H₃PO₄ as external standard. For structural assignments both ¹H-decoupled and ¹H-coupled ¹³C NMR spectra were recorded. *J* values are given in Hz.

Diethyl trichloromethylphosphonate **1** was prepared according to the literature procedure.⁸

General procedure for the preparation of diethyl α-chlorovinylphosphonates **3**

A solution of **1** (5.10 g, 0.020 mol) in dry diethyl ether (60 cm³) was cooled to –78 °C and a solution of butyllithium (1.6 mol dm^{–3} solution in hexane, 13.8 cm³, 0.022 mol) was added dropwise with stirring. The solution was stirred at –78 °C for 30 min and a solution of an aldehyde (1.1 equiv.) in diethyl ether (20 cm³) was added dropwise at the same temperature. After stirring at –78 °C for 1 h, the mixture was allowed to warm to room temp. and was stirred for another 20 h. Saturated aqueous NH₄Cl (30 cm³) was added, the aqueous layer was extracted with dichloromethane (3 × 25 cm³), and the combined organic solution was dried (MgSO₄) and evaporated under reduced pressure. Crude products were purified by column chromatography followed in some cases by bulb-to-bulb distillation or crystallisation.

Preparation of chlorodiethylphosphonomethylenecycloalkanes **5**

The reactions were performed in the same way as described for the preparation of product **3**.

Chlorodiethylphosphonomethylenecyclopentane **5a**

Purified by bulb-to-bulb distillation, oven temp. 85–90 °C at 0.15 mmHg. Yield 91%; *n*_D¹⁷ 1.4840; *m/z* 252, 254 (*M*⁺, 15, 5%), 224, 226 (*M*⁺ – C₂H₄, 14, 5%), 196, 198 (*M*⁺ – 2C₂H₄, 100, 32%), 161 (*M*⁺ – 2C₂H₄ – Cl, 28%); δ_H 1.32 (6 H, t, ³*J*_{HH} 7.1, 2 × Me of POEt), 1.64–1.77 (4 H, m, 3-H₂, 4-H₂), 2.51–2.53 (2 H, m, 2-CH₂), 2.73–2.75 (2 H, m, 5-CH₂), 4.06 (4 H, dq, ³*J*_{HH} 7.1, ³*J*_{HP} 14.3, 2 × CH₂ of POEt); δ_C 15.8 (d, *J* 6.5), 24.7 (s), 27.4 (s), 33.6 (s), 35.5 (d, *J* 11.9), 62.1 (d, *J* 5.1), 111.1 (d, *J* 218.6), 164.7 (d, *J* 18.7); δ_P 10.06.

Chlorodiethylphosphonomethylenecyclohexane **5b**

Purified by bulb-to-bulb distillation, oven temp. 95–100 °C at 0.15 mmHg. Yield 93%; *n*_D¹⁷ 1.4868; *m/z* 266, 268 (*M*⁺, 77, 25%), 238, 240 (*M*⁺ – C₂H₄, 44, 15%), 210, 212 (*M*⁺ – 2C₂H₄, 100, 34%), 175 (*M*⁺ – 2C₂H₄ – Cl, 23%); δ_H 1.31 (6 H, t, ³*J*_{HH} 7.1, 2 × Me of POEt), 1.53–1.66 (6 H, m, 3-H₂, 4-H₂, 5-H₂), 2.47–2.52 (2 H, m, 2-CH₂), 2.79–2.83 (2 H, m, 6-H₂), 4.06 (4 H, dq, ³*J*_{HH} 7.1, ³*J*_{HP} 14.3, 2 × CH₂ of POEt); δ_C 15.8 (d, *J* 7.3), 25.7 (s), 27.2 (s), 27.9 (s), 32.0 (d, *J* 3.2), 32.9 (d, *J* 12.9); δ_P 10.89.

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