Regiospecific and stereoselective synthesis of (1*E*,3*Z*)-3-cyano-butadienylphosphonates

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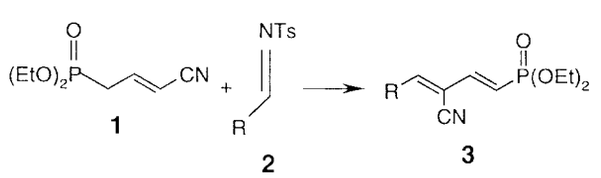
Treatment of a catalytic amount of DBU (20 mol%) with a mixture of diethyl 3-cyanoallylphosphonate **1** and *N*-tosylsulfonylimines **2** gave diethyl 3-cyanobuta-1,3-dienylphosphonates **3** in 72–83% yields. All the products (**3a–3h**) are assigned 1*E*,3*Z* configurations on the basis of the crystal structure of diethyl (1*E*,3*Z*)-3-cyano-4-naphthylbuta-1,3-dienylphosphonate (**3h**), the proton NMR spectra and the proposed reaction mechanism.

Introduction

The syntheses of phosphonic acids and their derivatives have attracted much interest, since a large number of these have been shown to exhibit important biological properties including antibiotic, antileukaemic and insecticidal activity depending on the nature of the substituent on the phosphonate group.[1] They are also utilized as useful intermediates in the synthesis of biologically active compounds.[2] Much attention has been paid to the synthesis of functionalized vinylphosphonates and their synthetic utilities have been widely studied in the last two decades.[3] Recently vinylphosphonates and 1,3-dienylphosphonates bearing an ene moiety are useful intermediates that have been employed in the synthesis of bicyclic compounds and in the synthesis of cadalane and valerenic acid sesquiterpenoids.[4] The existing synthetic methods use the classic Knoevenagel condensation mediated by titanium compounds[4b] and the palladium-catalyzed coupling reaction.[5,6] Therefore to develop an effective method for the preparation of vinylphosphonates would be valuable.

Results and discussion

In our continuing investigation to explore the new synthetic methodologies for carbon–carbon double bond formation,[7,8] particularly for the synthesis of unsaturated phosphonates,[9–13] we report here a new olefination methodology and its application to the regiospecific and stereoselective synthesis of (1*E*,3*Z*)-3-cyanobuta-1,3-dienylphosphonates. The reaction is shown in Scheme 1. Treatment of a catalytic amount of DBU



Scheme 1 *Reagents and conditions*: cat. DBU (20 mol%), THF, −30 °C to 0 °C.

(20 mol%) with a mixture of diethyl 3-cyanoallylphosphonate **1** and *N*-tosylsulfonylimines **2** gave diethyl 3-cyanobuta-1,3-dienylphosphonates **3** in 72–83% yields with 1*E*,3*Z* isomers exclusively. The results are summarized in Table 1.

The reaction mechanism of the catalytic cycle may be rationalized as in Scheme 2. The phosphoryl-stabilized carbanion **4**, generated from the corresponding phosphonate **1** and DBU, reacted with *N*-tosylsulfonylimines affording the adducts

Table 1 Preparation of (1*E*,3*Z*)-3-cyanobuta-1,3-dienylphosphonates

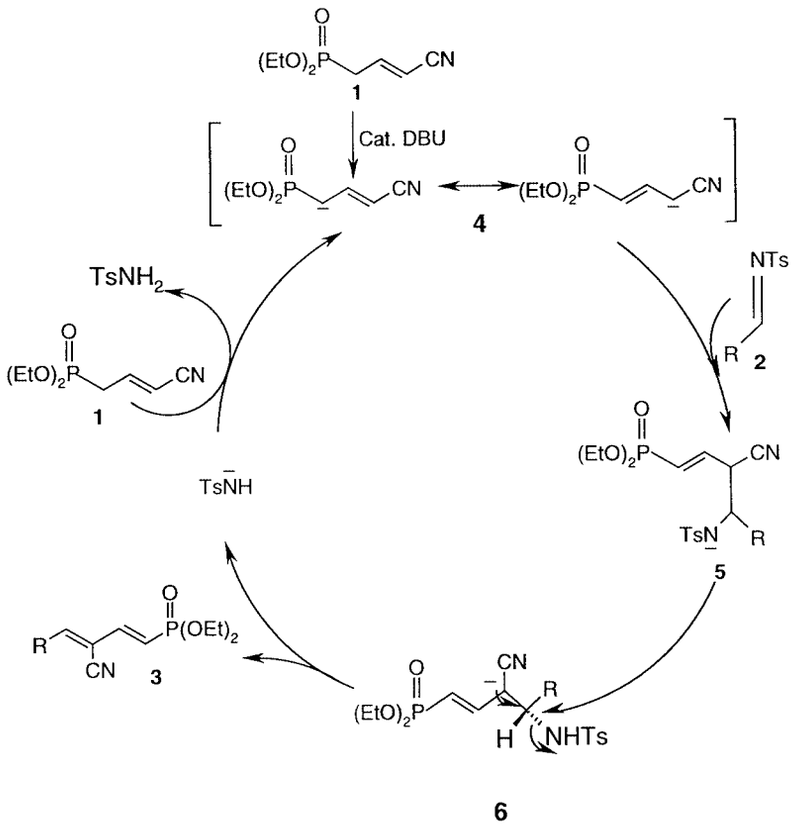
Compound	R	Yield (%)[a]
3a	C_6H_5	72
3b	4-ClC_6H_4	72
3c	2,4-$Cl_2C_6H_3$	75
3d	4-$(CH_3)_2NC_6H_4$	83
3e	4-$C_2H_5C_6H_4$	81
3f	4-$CH_3OC_6H_4$	76
3g	4-$CH_3C_6H_4$	80
3h	Naphthyl	78

[a] Isolated yields.

5. After intramolecular hydrogen transfer, **5** gave **6**. Elimination of the toluene-*p*-sulfonamide anion gave the products **3**. The toluene-*p*-sulfonamide anion abstracted a proton from **1** to give toluene-*p*-sulfonamide and regenerated the carbanion **4**. Thus, the catalytic cycle was completed.

The stereochemical results may be rationalized as shown in Scheme 3. The reaction is initiated by nucleophilic attack of the phosphoryl-stabilized carbanion **4** on the imine carbon in **2** forming **7a** and **7b**, which after intramolecular hydrogen transfer afforded **8a** and **8b** (Scheme 3). The vinylphosphonate group may be eclipsed with the hydrogen atom, and the CN group staggered between the R and the NHTosyl group and *vice versa* for the other conformer, *i.e.* with the vinylphosphonate group staggered between the R and the NHTosyl group and with the CN eclipsed with the hydrogen atom. Slight rotation of the NHTosyl group to become orthogonal, forming **9a** and **9b**, enables it to leave as shown. Since the intermediate **8a** involves the smaller CN group staggered between the R and NHTosyl groups, this conformer should be favored relative to the conformer **8b** which contains the bulkier vinylphosphonate group staggered between the R and NHTosyl groups. Each of those intermediates decomposes *via* an elimination, affording **3-(1*E*,3*Z*)** or **3-(1*E*,3*E*)**. In our case, elimination *via* **9a** was favored over **9b** and the **1*E*,3*Z***-isomer was obtained exclusively.

The crystal of diethyl (1*E*,3*Z*)-3-cyano-4-naphthylbuta-1,3-dienylphosphonate was grown from petroleum ether (60–90 °C)–ethyl acetate (10:1). X-Ray crystallographic analysis showed that the structure of diethyl 3-cyano-4-naphthylbuta-1,3-dienylphosphonate (**3h**) has a 1*E*,3*Z* configuration (Fig. 1). The vicinal couplings in the 1H NMR spectra of the phosphonates **3a–3g** are all within the range 18.0–17.2 Hz showing that the hydrogen atoms across the C1–C2 double bonds are *trans*. Thus these compounds also have a 1*E* configuration. On



Scheme 2

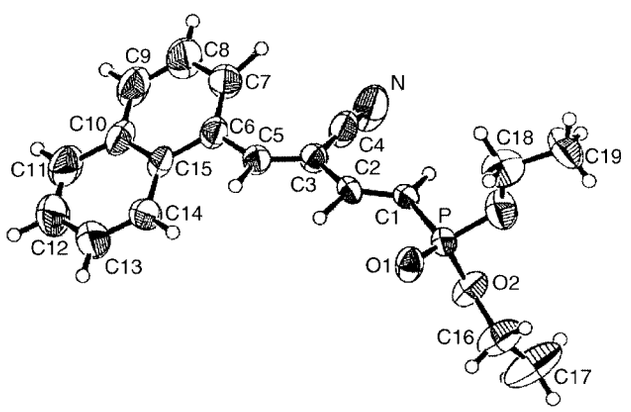


Fig. 1 The X-ray molecular structure of compound **3h**.

the basis of the proposed mechanism and the lack of physical and spectral evidence for the existence of mixtures, the configurations at C3 for phosphonates **3a–3g** are also assigned a 3*Z* configuration.

It is interesting to note that the reaction was regiospecific and the carbanion reacted with imines occurring at the 3-position. No product resulting from the 1-position was observed. Thus steric effects may play an important role in regioselectivity.

In conclusion, this olefination is different from the traditional Horner–Wadsworth–Emmons reaction. The former eliminates toluene-*p*-sulfonamide forming carbon–carbon double bonds while the latter eliminates phosphonic acid anions. Thus in our method the phosphonate moiety remains in the products and this new methodology provides a convenient, effective, regiospecific and stereoselective synthesis of the title compounds. The structure of diethyl (1*E*,3*Z*)-3-cyano-4-naphthylbuta-1,3-dienylphosphonate **3h** was established by X-ray crystallography.

Experimental

Mps are uncorrected. The IR spectra of solid products were obtained as KBr disks on a Digilab FTS-20E spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer (δ values in ppm from tetramethylsilane, in $CDCl_3$, *J*-values are given in Hz). Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.

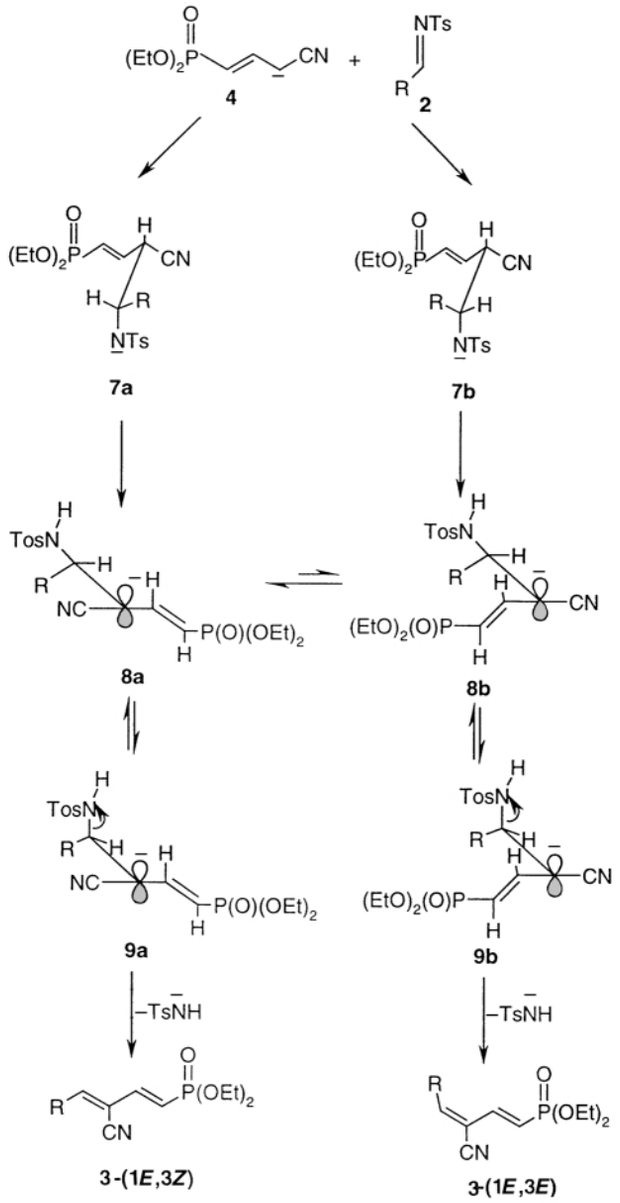
Diethyl 3-cyanoallylphosphonate (1)

Compound **1** was prepared according to the similar procedure for the synthesis of diethyl 3-ethoxycarbonylallylphosphonate.[14] It is a known compound but no data are reported in the literature.[15] Yield 44%; bp: 112–120 °C/0.5 mmHg (unstable when heating); $Z:E = 56:44$;[16] δ_H 6.59 (ddd, *J* 16, 15.8, 8.0, 0.56 × 1H, *Z*), 6.52 (ddd, *J* 16, 8.0, 7.8, 0.44 × 1H, *E*), 5.51 (dd, *J* 8.0, 7.8, 0.56 × 1H, *Z*), 5.47 (dd, *J* 15.8, 8.0, 0.44 × 1H), 4.11 (m, 4H), 2.96 (dd, *J* 23.0, 8.0, 0.44 × 2H), 2.74 (dd, *J* 23.0, 8.0, 0.56 × 2H), 1.32 (t, *J* 7.0, 3H), 1.31 (t, *J* 7.0, 3H); *m*/*z*: 204 ($M^+ + 1$, 12%), 203 (M^+, 8), 176 (7), 158 (7), 137 (28), 109 (100), 91 (27) and 67 (56) (Found: C, 46.69; H, 6.85; N, 7.03. $C_8H_{14}NO_3P$ (203.18) requires C, 47.29; H, 6.95; N, 6.89%).

General procedure for the preparation of (1*E*,3*Z*)-buta-1,3-dienylphosphonates (3)

To a mixture of diethyl 3-cyanoallylphosphonate **1** (0.203 g, 1 mmol), *N*-tosylarylimine **2** (1 mmol), and THF (10 ml) in a capped vessel under nitrogen at −30 °C was injected 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (30 mg, 0.2 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 30 min. TLC showed that the reaction was complete. The mixture was filtered on a short column of silica gel to remove the precipitate which was identified as toluene-*p*-sulfonamide. The filtrate was concentrated and chromatographed on silica gel, and eluted with petroleum ether (60–90 °C)–ethyl acetate (2:1) to give the product **3**.

Diethyl (1*E*,3*Z*)-3-cyano-4-phenylbuta-1,3-dienylphosphonate (3a). Mp: 91–92 °C; ν_{max}/cm^{-1} 2990, 2220, 1610, 1600, 1240,



Scheme 3

1050, 1030, 960; δ_H 7.87–7.83 (m, 2H), 7.47–7.43 (m, 3H), 7.28 (s, 1H), 7.22 (dd, *J* 20.6, 16.9, 1H), 6.22 (dd, *J* 16.6, 15.7, 1H), 4.15–4.05 (m, 4H), 1.33 (t, *J* 7.1, 6H); *m*/*z*: 292 (M^+ + 1, 63%), 291 (M^+, 75), 262 (14), 234 (33), 154 (85), 153 (100), 127 (46), 111 (53) and 82 (40) (Found: C, 61.70; H, 6.04; N, 4.56. $C_{15}H_{18}NO_3P$ (291.29) requires C, 61.85; H, 6.23; N, 4.81%).

Diethyl (1*E*,3*Z*)-3-cyano-4-(4-chlorophenyl)buta-1,3-dienyl phosphonate (3b). Mp: 102–103 °C; ν_{max}/cm^{-1} 2980, 2220, 1610, 1590, 1240, 1050, 1030, 960; δ_H 7.73 (d, *J* 8.6, 2H), 7.36 (d, *J* 8.6, 2H), 7.16 (s, 1H), 7.15 (dd, *J* 23.8, 17.2, 1H), 6.20 (dd, *J* 16.6, 16.6, 1H), 4.10–4.00 (m, 4H), 1.28 (t, *J* 7.0, 6H); *m*/*z*: 327 (M^+ + 2, 37%), 325 (M^+, 100), 295 (10), 268 (19), 242 (20), 216 (16), 187 (39), 153 (31), 111 (36) and 82 (32) (Found: C, 55.23; H, 5.35; N, 4.09. $C_{15}H_{17}ClNO_3P$ (325.73) requires C, 55.31; H, 5.26; N, 4.30%).

Diethyl (1*E*,3*Z*)-3-cyano-4-(2,4-dichlorophenyl)buta-1,3-dienylphosphonate (3c). Mp: 97–99 °C; ν_{max}/cm^{-1} 2980, 2230, 1610, 1580, 1240, 1060, 1030, 970; δ_H 8.07 (d, *J* 8.5, 1H), 7.62 (s, 1H), 7.47 (d, *J* 2.1, 1H), 7.35 (dd, *J* 8.5, 2.1, 1H), 7.26 (dd, *J* 20.7, 16.9, 1H), 6.29 (dd, *J* 16.8, 15.1, 1H), 4.20–4.05 (m, 4H), 1.34 (t, *J* 7.0, 6H); *m*/*z*: 363 (M^+ + 4, 11%), 361 (M^++2, 62), 359 (M^+, 100), 268 (51), 223 (45), 187 (49), 151 (29), 111 (39) and 82 (47) (Found: C, 50.00; H, 4.39; N, 3.73. $C_{15}H_{16}Cl_2NO_3P$ (360.18) requires C, 50.02; H, 4.48; N, 3.89%).

Diethyl (1*E*,3*Z*)-3-cyano-4-(4-dimethylaminophenyl)buta-1,3-dienylphosphonate (3d). Mp: 126–128 °C, ν_{max}/cm^{-1} 2980, 2210, 1620, 1590, 1260, 1030; δ_H 7.78 (d, *J* 9.0, 2H), 7.19 (dd, *J* 20.8, 16.8, 1H), 7.09 (s, 1H), 6.66 (d, *J* 9.0, 2H), 5.99 (dd, *J* 16.5, 16.5, 1H), 4.12–4.03 (m, 4H), 3.05 (s, 6H), 1.32 (t, *J* 7.1, 6H); *m*/*z*: 335 (M^+ + 1, 48%), 334 (M^+, 100), 259 (6), 196 (52) and 153 (5) (Found: C, 61.14; H, 6.75; N, 8.12. $C_{17}H_{23}N_2O_3P$ (334.35) requires C, 61.07; H, 6.93; N, 8.38%).

Diethyl (1*E*,3*Z*)-3-cyano-4-(4-ethylphenyl)buta-1,3-dienylphosphonate (3e). Mp: 61–62 °C; ν_{max}/cm^{-1} 2980, 2220, 1600, 1240, 1050, 1030, 970, 960; δ_H 7.79 (d, *J* 8.2, 2H), 7.29 (d, *J* 8.2, 2H), 7.26 (s, 1H), 7.19 (dd, *J* 20.7, 16, 1H), 6.23 (dd, *J* 16.6, 16.6, 1H), 4.16–4.07 (m, 4H), 2.69 (q, *J* 7.6, 2H), 1.35 (t, *J* 7.0, 6H), 1.25 (t, *J* 7.4, 3H); *m*/*z*: 320 (M^+ + 1, 100%), 319 (M^+, 40), 290 (3), 262 (3), 236 (2), 181 (5), 166 (9), 111 (4) and 82 (2) (Found: C, 63.99; H, 7.10; N, 4.22. $C_{17}H_{22}NO_3P$ (319.34) requires C, 63.94; H, 6.94; N, 4.39%).

Diethyl (1*E*,3*Z*)-3-cyano-4-(4-methoxyphenyl)buta-1,3-dienylphosphonate (3f). Mp: 71–72 °C; ν_{max}/cm^{-1} 2990, 2220, 1600, 1510, 1250, 1020; δ_H 7.84 (d, *J* 8.8, 2H), 7.20 (dd, *J* 20.5, 16.8, 1H), 7.19 (s, 1H), 6.94 (d, *J* 8.9, 2H), 6.13 (dd, *J* 16.4, 16.4, 1H), 4.14–4.04 (m, 4H), 3.85 (s, 3H), 1.32 (t, J 7.0, 6H); *m*/*z*: 322 (M^+ + 1, 18%), 321 (M^+, 100), 183 (71), 140 (29) and 111 (21) (Found: C, 59.39; H, 6.33; N, 4.33. $C_{16}H_{20}NO_4P$ (321.31) requires C, 59.81; H, 6.27; N, 4.36%).

Diethyl (1*E*,3*Z*)-3-cyano-4-(4-methylphenyl)buta-1,3-dienylphosphonate (3g). Mp: 85.5–86.5 °C; ν_{max}/cm^{-1} 2980, 2220, 1600, 1240, 1050, 1030, 960; δ_H 7.75 (d, *J* 8.1, 2H), 7.25 (d, *J* 7.8, 2H), 7.24 (s, 1H), 7.21 (dd, *J* 20.7, 16.5, 1H), 6.20 (dd, *J* 16.2, 16.2, 1H), 4.15–4.06 (m, 4H), 2.39 (s, 3H), 1.34 (t, *J* 7.0, 6H); *m*/*z*: 306 (M^+ + 1, 100%), 305 (M^+, 75), 167 (71), 138 (25), 111 (46) and 82 (26) (Found: C, 62.99; H, 6.81; N, 4.34. $C_{16}H_{20}NO_3P$ (305.31) requires C, 62.94; H, 6.60; N, 4.59%).

Diethyl (1*E*,3*Z*)-3-cyano-4-naphthylbuta-1,3-dienylphosphonate (3h). For crystallographic and refinement data see Table 2.† Mp: 100–101 °C; ν_{max}/cm^{-1} 2990, 2220, 1600, 1240, 1050, 1020, 970; δ_H 8.14 (d, *J* 7.4, 1H), 8.12 (s, 1H), 7.99–7.89 (m, 3H), 7.63–7.54 (m, 3H), 7.42 (dd, *J* 20.7, 17, 1H), 6.33 (dd, *J* 16.2,16.2, 1H), 4.21–4.11 (m, 4H), 1.38 (t, *J* 7.1, 6H); *m*/*z*: 341 (M^+, 51%),

Table 2 Crystallographic and refinement data for **3h**†

Compound	**3h**
Chemical formula	$C_{19}H_{20}NO_3P$
Formula weight	341.35
Crystal system	Monoclinic
Space group	$P2_1/c$ (no. 14)
μ	λ(Mo-Kα) = 0.71069 Å
R values	0.070
Unit cell dimensions	
a/Å	7.943(3)
b/Å	27.493(3)
c/Å	8.752(2)
β/°	103.73(3)
Unit cell volume *V*/Å^3	1856(1)
Temperature of data collection	291 K
Z	4
Measured/independent reflections and *R*(int)	3615/3366, R_{int} = 0.040

† CCDC reference number 207/364. See http://www.rsc.org/suppdata/p1/1999/3495 for crystallographic files in .cif format.

203 (100), 176 (13) and 111 (15) (Found: C, 66.97; H, 5.76; N, 4.01. $C_{19}H_{20}NO_3P$ (341.35) requires C, 66.86; H, 5.91; N, 4.10%).

Acknowledgements

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Notes and references

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16 Both *E* and *Z* isomers can be used in this reaction, since the reaction is *via* carbanion **4** (see Scheme 2). The coupling constants of the vinyl Hs in all products **3** are within the range 18.0–17.2 Hz, showing that H-atoms across the C2–C3 double bond are *trans* (1*E*).

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