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Stereoselective synthesis of trifluoromethylated vinyl- and dienylphosphonates with γ-alkoxycarbonyl moiety

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Abstract

Trifluoromethylated vinyl- and dienylphosphonates with γ-alkoxycarbonyl moiety have been synthesized via sequential transformations of bisphosphonates in 68–76% (three steps) yields with *Z*-isomers exclusively or predominantly.

Keywords: Trifluoromethylated vinylphosphonates; Trifluormethylated dienylphosphonates; Trifluoroacylated bisphosphonates; Alkoxycarbonyl moiety; Stereoselective synthesis

1. Introduction

In the last several decades, much interest has been attracted to the new synthetic methodologies for the synthesis of functionalized vinylphosphonates, and their synthetic applications have been widely studied [1]. Furthermore, a large number of these compounds have been shown to exhibit biological usefulness [2,3] and are useful building blocks that have been used for the synthesis of hetero- and carbocyclic compounds [1,4,5]. Recently vinylphosphonates bearing an ene moiety are useful intermediates which have been employed in the synthesis of bicyclic compounds and of cadalane and valerenic acid sesquiterpenoids [4,5]. Organofluorine compounds are increasingly being applied in pharmaceuticals, agrochemicals and other fields [6–8] since the introduction of fluorine or trifluoromethyl group into biologically active compounds often gives rise to unique physiological activities [9,10]. However, the methodology for the synthesis of fluorinated vinylphosphonates is still limited [11–15].

2. Results and discussion

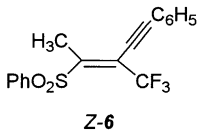
In our continuing investigation to explore the new methods for the synthesis of functionalized phosphonates [16–21], herein we report the synthesis of trifluoromethylated vinyl- and dienylphosphonates with γ-alkoxycarbonyl moiety via sequential transformations of bisphosphonates in 68–76% (three steps) yields with *Z*-isomers exclusively or predominantly (Scheme 1).

Treatment of tetraethyl ethyl-1,1-bisphosphonate (**1**) with *n*-butyllithium in tetrahydrofuran (THF) afforded the bisphosphoryl-stabilized carbanion (**2**) which was acylated by the addition of trifluoroacetic anhydride to give trifluoroacylated phosphonate (**3**). Without isolation, **3** was attacked by organozinc reagents followed by elimination of phosphonic acid anion affording substituted trifluoromethylated vinylphosphonates (**4**) with γ-alkoxycarbonyl moiety. The results are summarized in Table 1.

When the organozinc compound with a double bond moiety was used, the substituted trifluoromethylated dienylphosphonates were obtained with *Z*-isomer exclusively (Scheme 2).

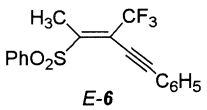
The results are listed in Table 2. It is interesting to note that in this reaction only α-position addition product was obtained. The detail mechanism is being pursued.

It has been reported that the ^{19}F NMR data of similar compounds *Z*-**6** and *E*-**6** are as follows [22].



Z-**6**

δ = -53.4 ppm



E-**6**

δ = -59.0 ppm

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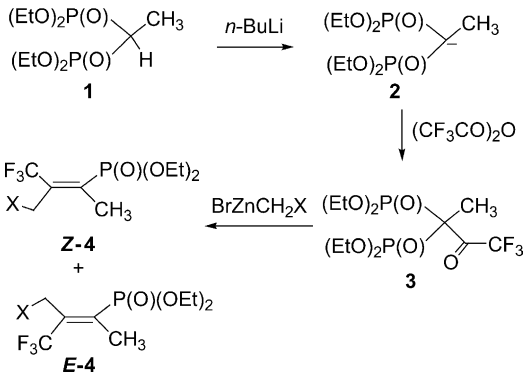


Scheme 1.

If the trifluoromethyl group is *trans* with respect to the phenylsulfonyl group, the chemical shifts of the trifluoromethyl group appear upfield (*E*-**6**), while those *cis* with respect to the phenylsulfonyl group are shifted downfield (*Z*-**6**). Hence, we assume that CF_3 signal of *E*-**4f** is shifted upfield (−61.5 ppm) while that of compound *Z*-**4f** is shifted downfield (−59.5 ppm). Similarly in other products only one isomer was obtained exclusively and their CF_3 signals are located in the range of −59.5 to −60.2 ppm. Hence, the configurations of other products could be ascertained as *Z*-isomers.

Similarly, the CF_3 signals of **5a** and **5b** are located at −56.5 ppm, hence the configurations of **5a** and **5b** could be also ascertained as *Z*-isomers.

The stereochemical results may be rationalized as shown in Scheme 3. The mechanism for the formation of **4** is analogues to that of the bisphosphonates reported in the literature [23] (Scheme 3).

Table 1
Trifluoromethylated vinylphosphonates prepared

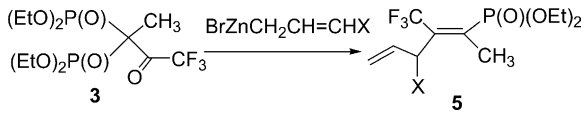
Compound	X	Yield (%)[a]	Ratio (*Z*:*E*)[b]
4a	CO_2Me	76	100:0
4b	CO_2Et	68	100:0
4c	CO_2Pr^i	69	100:0
4d	CO_2Bu^t	73	100:0
4e	CO_2CMe_2Et	71	100:0
4f	$CO_2CH_2CF_3$	75[c]	85:15

[a] Isolated yields.
[b] The ratios of *E*- and *Z*-isomers are estimated on the basis of ^{19}F NMR data.
[c] *Z*/*E* mixture.

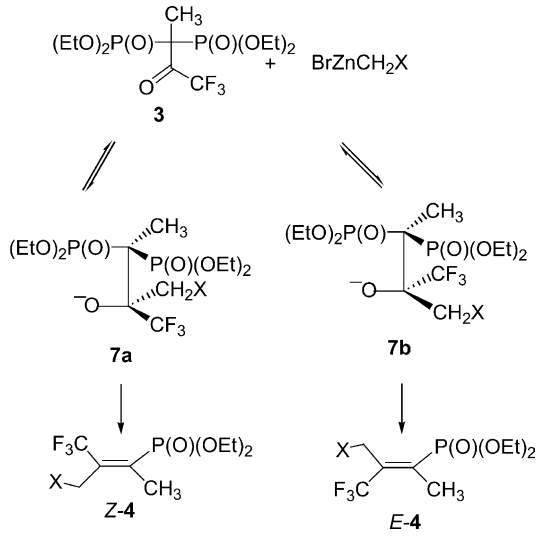
Table 2
Trifluoromethylated dienylphosphonates prepared

Compound	X	Yield (%)[a]	Ratio (*Z*:*E*)[b]
5a	CO_2Me	72	100:0
5b	CO_2Et	70	100:0

[a] Isolated yields.
[b] No *E*-isomer was detectable by TLC or ^{19}F NMR spectra.



Scheme 2.



Scheme 3.

The reaction is initiated by nucleuophilic attack of organozinc reagents on the carbon–oxygen double bond of the carbonyl group, forming two diasteroisomeric betaines **7a** and **7b** in equilibrium. The size of reactive groups is $PO_3Et_2 > CH_2X > CF_3 > CH_3$. Since the intermediate **7a** involves an eclipsed orientation of two pairs of 'small/large' substituents (CH_3/CH_2X, CF_3/PO_3Et_2), this conformer should be favorable relative to the stereoisomer **7b**, which contains unfavorable 'large/large' (PO_3Et_2/CH_2X) nonbonding interactions. Therefore, the stereoselectivity of olefination in our cases is a function of the conformational equilibrium of the adducts. Each of these intermediates decomposes via a *syn*-elimination, affording alkenes *Z*-**4** or *E*-**4**. In our case, formation of isomer **7a** will be favored over isomer **7b** and the *Z*-isomer was obtained exclusively or predominantly.

In summary this methodology provides a convenient synthesis of trifluoromethylated vinyl- and dienylphosphonates with γ-alkoxycarbonyl moiety in 68–76% (three steps) yields with *Z*-isomers exclusively or predominantly.

3. Experimental

All boiling points are uncorrected. The IR spectra of liquid products were obtained as films on a Digilab FTS-20E spectrometer. ^1H 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). The published ^{19}F NMR spectra were taken on a

Varian EM-360 (60 MHz) spectrometer and recalculated using the standard chemical shift of reference δ (F) (CF_3CO_2H) −76.5 ppm with respect to δ ($CFCl_3$) 0.00 ppm. Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer.

Tetraethyl ethyl-1,1-bisphosphonate (**1**) was prepared according to the known method [24].

3.1. General procedure for the preparation of substituted trifluoromethylated vinylphosphonates

Treatment of tetraethyl ethyl-1,1-bisphosphonate (**1**) (0.6 g, 2 mmol) with *n*-butyllithium (2.2 mmol in 2 ml hexane) in absolute THF (25 ml) at −78 °C under nitrogen gave the phosphoryl-stabilized carbanion 2, which was stirred at −78 °C for 0.5 h. under nitrogen. Trifluoroacetic anhydride (0.28 ml, 2 mmol) was added to it in one portion. After stirring at −78 °C for 1 h, the reaction mixture was allowed to warm to 20 °C and the organozinc reagents [6 mmol, prepared from 6 mmol of bromoacetic ester and 6 mmol (0.39 g) of zinc powder][1] was added to the mixture, which was stirred for another 4 h. The reaction mixture was poured into 2N HCl solution (10 ml) and the water layer was extracted with dichloromethane (4 ml × 20 ml). The combined organic layer was washed with water (2 ml × 10 ml) and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography eluting with petroleum ether (60–90 °C): ethyl acetate (4:1) to give the product **4**.

3.1.1. Diethyl 3,3,3-trifluoro-2-(methoxycarbonylmethyl)-1-methyl-prop-1-enyl-phosphonate (*4a*)

Yield: 76%; bp = 100 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2990, 1750, 1540, 1320, 1250, 1130, 1020, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 1.26 (t, J = 7.1 Hz, 6H), 2.04 (dq, J = 14.5, 2.4 Hz, 3H), 3.64 (s, 3H), 3.91 (s, 2H), 4.10–3.98 (m, 4H). ^{19}F NMR ($CDCl_3$/TFA): δ –59.8 (s, 3F). MS *m/z* (rel. int.): 319 ($M^+ + 1$, 1), 318 (M^+, 1), 286 (26), 258 (36), 231 (36), 230 (49), 203 (100), 180 (79). Anal. calcd. For $C_{11}H_{18}F_3O_5P$ (318.22): C, 41.52: H, 5.70. Found: C, 41.26; H, 5.60%.

3.1.2. Diethyl 3,3,3-trifluoro-2-(ethoxycarbonylmethyl)-1-methyl-prop-1-enyl-phosphonate (*4b*)

Yield: 68%; bp = 102 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2990, 1740, 1320, 1200, 1030, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 1.23 (t, J = 7.2 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H), 2.09 (dq, J = 14.6, 2.5 Hz, 3H), 3.95 (s, 2H), 4.18–4.04 (m, 6H). ^{19}F NMR ($CDCl_3$/TFA): δ −60.2 (s, 3F). MS *m/z* (rel. int.): 333 ($M^+ + 1$, 4), 287 (26), 203 (49), 202 (76), 166 (100), 135 (38), 103 (40). Anal. calcd. For $C_{12}H_{20}F_3O_5P$ (332.25): C, 43.38: H, 6.07. Found: C, 43.18; H, 6.10%.

3.1.3. Diethyl 3,3,3-trifluoro-2-(i-propoxycarbonylmethyl)-1-methyl-prop-1-enyl-phosphonate (*4c*)

Yield: 69%; bp = 120 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2990, 1740, 1450, 1320, 1200, 1030, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 1.20 (d, J = 6.2 Hz, 6H), 1.30 (t, J = 7.1 Hz, 6H), 2.08 (dq, J = 14.7, 2.4 Hz, 3H), 3.92 (s, 2H), 4.12–4.05 (m, 4H), 4.99 (hept, J = 6.2 Hz, 1H). ^{19}F NMR ($CDCl_3$/TFA): δ −59.5 (s, 3F). MS *m/z* (rel. int.): 347 ($M^+ + 1$, 91), 305 (39), 287 (100), 259 (23), 231 (26), 203 (24), 202 (25), 43 (49). Anal. calcd. For $C_{13}H_{22}F_3O_5P$ (346.28): C, 45.09: H, 6.40. Found: C, 45.00; H, 6.38%.

3.1.4. Diethyl 3,3,3-trifluoro-2-(t-butoxycarbonylmethyl)-1-methyl-prop-1-enyl-phosphonate (*4d*)

Yield: 73%; bp = 125 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2990, 1740, 1460, 1320, 1250, 1130, 1030, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 1.30 (t, J = 7.1 Hz, 6H), 1.40 (s, 9H), 2.07 (dq, J = 14.6, 2.2 Hz, 3H), 3.85 (s, 2H), 4.11–4.05 (m, 4H). ^{19}F NMR ($CDCl_3$/TFA): δ −59.8 (s, 3F). MS *m/z* (rel. int.): 304 (18), 287 (100), 260 (78), 259 (44), 231 (48), 204 (21), 203 (28), 57 (53). Anal. calcd. For $C_{14}H_{24}F_3O_5P$ (360.31): C, 46.67: H, 6.71. Found: C, 46.37; H, 6.76%.

3.1.5. Diethyl 3,3,3-trifluoro-2-[(1,1-dimethylpropoxycarbonyl)methy]-1-methyl-prop-1-enyl-phosphonate (*4e*)

Yield: 71%; bp = 120 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2980, 1740, 1390, 1250, 1130, 1030, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 0.82 (t, J = 7.5 Hz, 3H), 1.28 (t, J = 7.1 Hz, 6H), 1.36 (s, 6H), 1.72 (q, J = 7.5 Hz, 2H), 2.05 (dq, J = 14.6, 2.0 Hz, 3H), 3.86 (s, 2H), 4.10–4.03 (m, 4H). ^{19}F NMR ($CDCl_3$/TFA): δ −59.8 (s, 3F). MS *m/z* (rel. int.): 305 (23), 287 (100), 260 (57), 259 (46), 203 (37), 202 (23), 71 (65), 43 (35). Anal. calcd. For $C_{15}H_{26}F_3O_5P$ (374.33): C, 48.13: H, 7.00. Found: C, 47.96; H, 6.85%.

3.1.6. Diethyl 3,3,3-trifluoro-2-[(1,1,1-trifluoroethoxycarbony)methyl]-1-methyl-prop-1-enyl-phosphonate (*4f*)

Yield: 75% (*E/Z* mixture); bp = 115 °C/0.8 mmHg; Z:*E* = 85:15. IR (film) (cm^{-1}): 2990, 1770, 1420, 1320, 1140, 970. ^{1}H NMR ($CDCl_3$/TMS): δ 1.31 (t, J = 7.1 Hz, 6H), 1.98 (dq, J = 15.3, 2.5 Hz, 0.15 × 3H), 2.10 (dq, J = 14.5, 2.4 Hz, 0.85 × 3H), 4.18–4.03 (m, 6H), 4.35 (q, J = 8.2 Hz, 0.15 × 2H), 4.47 (q, J = 8.4 Hz, 0.85 × 2H). ^{19}F NMR ($CDCl_3$/TFA): δ −59.5 (s, 0.85 × 3F), −61.5 (s, 0.15 × 3F), −72.5 (t, J = 8.4 Hz, 0.85 × 3F), −73.2 (T, J = 8.4 Hz, 0.15 × 3F). MS *m/z* (rel. int.): 386 (M^+, 8), 385 ($M^+ - 1$, 4), 287 (46), 258 (49), 230 (55), 203 (35), 202 (100), 138 (37). Anal. calcd. For $C_{12}H_{17}F_6O_5P$ (386.22): C, 37.32: H, 4.44. Found: C, 37.22; H, 4.40%.

[1] The effect of the amount of organozinc reagent used was investigated with tetraethyl ethyl-1,1-bisphosphonate (**1**) and $BrZnCH_2CO_2CH_2CF_3$ as reactants. When the amount of organozinc reagent used was increased from 2 to 6 mmol, the yield was increased from 56 to 75%.

3.2. General procedure for the preparation of substituted trifluoromethylated dienylphosphonates

The procedure is same with aforementioned method.

3.2.1. Diethyl 3-methoxycarbonyl-2-trifluoromethyl-1-methyl-penta-1,4-dienylphosphonate (**5a**)

Yield: 72%; bp = 130 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2990, 1750, 1440, 1200, 1020, 970, 800. ^{1}H NMR ($CDCl_3$/TMS): δ 1.30 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.10 (dq, J = 14.4, 2.2 Hz, 3H), 3.70 (s, 3H), 4.16–4.04 (m, 4H), 5.22–5.19 (m, 1H), 5.26–5.24 (m, 1H), 6.07–6.04 (m, 1H), 6.17–6.12 (m, 1H). ^{19}F NMR ($CDCl_3$/TFA): δ −56.5 (s, 3F). MS *m/z* (rel. int.): 346 ($M^+ + 2$, 9), 345 ($M^+ + 1$, 56), 314 (16), 313 (100), 312 (25), 284 (14), 228 (11), 127 (11). Anal. calcd. For $C_{13}H_{20}F_3O_5P$ (344.26): C, 45.36: H, 5.86. Found: C, 45.61; H, 5.71%.

3.2.2. Diethyl 3-ethoxycarbonyl-2-trifluoromethyl-1-methyl-penta-1,4-dienylphosphonate (**5b**)

Yield: 70%; bp = 132 °C/0.8 mmHg; Z:*E* = 100:0. IR (film) (cm^{-1}): 2990, 1750, 1640, 1320, 1190, 1020, 970, 800. ^{1}H NMR ($CDCl_3$/TMS): δ 1.21 (t, J = 7.2 Hz, 3H), 1.34–1.26 (m, 6H), 2.10 (dq, J = 14.2, 2.1 Hz, 3H), 4.24–4.06 (m, 6H), 5.25–5.17 (m, 2H), 6.04–6.01 (m, 1H), 6.18–6.15 (m, 1H). ^{19}F NMR ($CDCl_3$/TFA): δ −56.5 (s, 3F). MS *m/z* (rel. int.): 358 (M^+, 1), 312 (36), 284 (35), 256 (31), 228 (100), 127 (43), 111 (31), 57 (53). Anal. calcd. For $C_{14}H_{22}F_3O_5P$ (358.29): C, 46.93: H, 6.19. Found: C, 46.92; H, 6.23%.

Acknowledgements

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