Novel synthesis of trifluoromethylated allylic phosphonates

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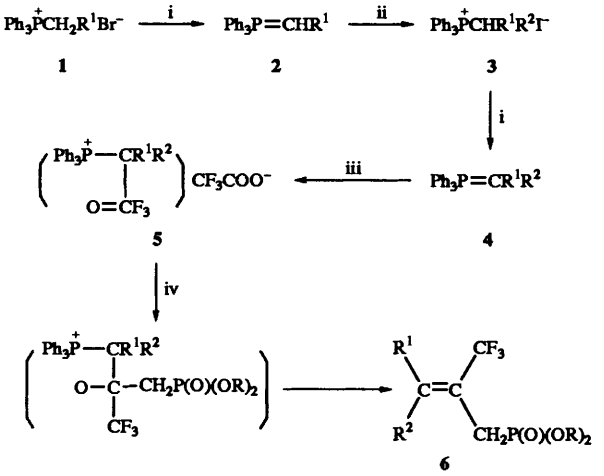
Trifluoromethylated allylic phosphonates have been synthesized under mild conditions in 56–72% yield by a one-pot reaction of (dialkoxyphosphinoyl)methyllithium with trifluoromethylated β-oxophosphonium salts.

Of phosphoryl-stabilized carbanions the synthetic applications of which are wide,[1] allylic phosphonates occupy an important position.[2] Thus, they are used in Wittig–Horner reactions for the synthesis of functionalized 1,3-dienes,[3] and as new and versatile substrates[2] for carbon–carbon bond formation. Further, allylic phosphonates upon hydrogenolysis and in conjunction with alkylation provide a stereo selective synthesis of *trans* olefins;[4] they may also be used in the synthesis of (*E*)-γ-amino-α,β-unsaturated phosphonates.[5] However, to the best of our knowledge trifluoroalkylated allylic phosphonates have not been reported previously although they would be expected to be useful intermediates for the synthesis of fluorine-containing biological active compounds.

Results and discussion

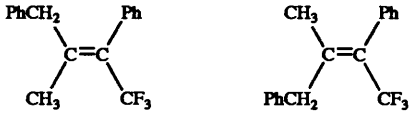
In previous papers we have reported that fluorinated β-oxoalkylphosphonium salts when attacked by nucleophiles give rise to tetrasubstituted fluoroalkenes,[6] fluoroenynes[7] and α-fluoroalkylvinyl or α-fluoroepoxyalkyl phosphonates.[8] In our continuing investigations into the exploitation of the synthetic utility of fluorinated β-oxoalkylphosphonium salts in organic synthesis we now report a novel synthesis of trifluoromethylated allylic phosphonates under mild conditions in 60–72% yields by the reaction of (dialkoxyphosphinoyl)methyllithium with trifluoromethylated β-oxoalkylphosphonium salts. The reaction sequence is shown in Scheme 1.



Scheme 1 *Reagents and conditions:* i, BuLi, THF, −20 °C–room temp.; ii, R^2I, room temp.; iii, $(CF_3CO)_2O$, −78 °C; iv, $LiCH_2P(O)(OR)_2$, THF, −78 °C–room temp.

The phosphoranes **4**, generated from the corresponding phosphonium salts **3** and butyllithium in tetrahydrofuran (THF), were acylated by the addition of trifluoroacetic anhydride to afford the trifluoromethylated β-oxoalkylphosphonium salts **5** which in the reaction medium were attacked by (dialkoxyphosphinoyl)methyllithium. Elimination of triphenylphosphine oxide gave **6** in 56–72 yields. The results are summarized in Table 1.

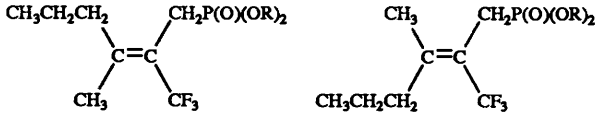
The configurations of compounds **6a–c** were ascertained on the basis of their ^{19}F NMR data. Thus, it has been reported that if the trifluoromethyl group is *trans* with respect to the methyl group (**II**), the chemical shifts of the trifluoromethyl group are downfield, while for the corresponding *cis* compounds (**I**), the



−22.6 −24.1

I **II**

chemical shifts are in the upfield.[9] Therefore, the assignments of configuration to compounds **6b** are as shown. The high



−21.5 −22.7

Z-**6b** *E*-**6b**

stereoselectivity of the reaction may be rationalized in terms of Cram's rule. Thus, the oxygen of the carbonyl group orientates itself between the small (R^2) and medium (R^1) sized groups, and the large group (Ph_3P^+) orientates itself *anti* to the carbonyl oxygen. The reaction is initiated by nucleophilic attack of (dialkoxyphosphinoyl)methyllithium on the carbon of the carbonyl group; if R^1 is a bulky group the attack is from the rear (the side of the plane containing the small group) of **7**, forming the intermediate **8** (Scheme 2).† After rotation at the C–C bond, intermediates **9** are formed with elimination of triphenylphosphine oxide to give **10** as the *Z*-isomer **6a**.

Experimental

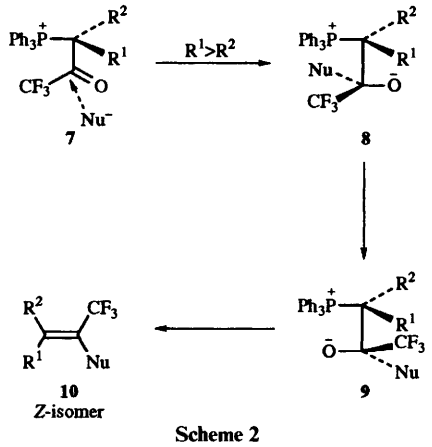
IR spectra of all products were obtained as films on a Perkin-Elmer 983G spectrometer. ^1H and ^{31}P NMR spectra were recorded on a Bruker AM-300 spectrometer (δ in ppm from tetramethylsilane and external 85% phosphoric acid for ^1H, and ^{31}P NMR, respectively, in $CDCl_3$, J values are given in Hz). ^{19}F NMR spectra were taken on a Varian EM-360L spectrometer (δ in ppm from external trifluoroacetic acid, in

† An alternative explanation would be a Felkin conformation with the C–PPh_3 bond at 90° to the carbonyl plane and attack occurring alongside the smaller group R^2. This gives the same result.

Table 1

Compound 6	R^1	R^2	R	Method[a]	Yield[b] (%)	Ratio[c] Z:E
a	Ph	Me	Pr^i	A	60	100:0
b	Pr	Me	Pr^i	A	60	78:22
c	Pr	Me	Et	A	56	74:26
d	Me	Me	Et	B	65	
e	Me	Me	Pr^i	B	70	
f	$-(CH_2)_4-$		Et	B	64	
g	$-(CH_2)_4-$		Pr^i	B	72	

[a] Method A: **1** was used as starting material. Method B: **3** was used as starting material. [b] Isolated yields. [c] The ratios of isomers were estimated on the basis of their ^{19}F and ^{31}P NMR spectra.



Scheme 2

$CDCl_3$, positive for upfield shifts). Mass spectra were measured on an HP 5989a spectrometer.

General procedure for the preparation of compound 6

Method A. A solution of the phosphorane **2**, generated from the phosphonium bromide **1** (3.0 mmol) and butyllithium (3.3 mmol) at −20 °C in absolute THF (30 cm^3), was stirred at 0 °C under nitrogen while methyl iodide (0.43 g, 3 mmol) was slowly added to it. After the mixture had been stirred at 20 °C for 1 h and then cooled to −20 °C, a second portion of butyllithium (3 mmol) was added to it. After this the mixture was again stirred for a further 1 h and then cooled to −78 °C when trifluoroacetic anhydride (3 mmol) was slowly added to it. Stirring was continued at −78 °C for 1 h after which (dialkoxyphosphinoyl)-methyl lithium (3 mmol) was slowly added to the mixture which was then allowed to warm to room temperature. After being stirred for a further 1 h and then stored overnight, the mixture was filtered and diluted with light petroleum (bp 60–90 °C, 100 cm^3). Filtration and evaporation gave a residue which was purified by column chromatography on silica gel with light petroleum (bp 60–90 °C)–acetone (10:1) as eluent to give the products **6**.

Method B. A procedure similar to that in method A was used, but without the first two operations, since the intermediates **3** are available.

Diisopropyl 3-phenyl-2-trifluoromethylbut-2-enylphosphonate **6a**.—Colourless oil; ν/cm^{-1} 2950, 1655, 1250 and 1230; *m/z* (rel. int.) 365 (M^+ + 1, 39), 345 (10), 323 (10), 261 (25) and 159 (100); δ_H 7.27–7.34 (m, 3 H), 7.13 (d, *J* 6.8, 2 H), 4.74–4.80 (m, 2 H), 2.91 (d, *J* 22.3, 2 H), 2.17–2.19 (m, 3 H) and 1.35 (d, *J* 6.2, 12 H); δ_F −24.1 (s); δ_P 23.22 (s) (Found: C, 55.9; H, 6.5. Calc. for $C_{17}H_{24}F_3O_3P$ (364.34): C, 56.04; H, 6.59%).

Diisopropyl 3-methyl-2-trifluoromethylhex-2-enylphosphonates **6b**.—Colourless oil; ν/cm^{-1} 2960, 1655, 1250 and 1230; *m/z* (rel. int.) 331 (M^+ + 1.52), 289 (30), 226 (100) and 186 (88); δ_H 4.66 (m, 2 H), 2.74 (d, *J* 21.9) and 2.72 (d, *J* 21.9) (2 H), 2.22 (t, *J* 7.0, 2 H), 1.90–1.93 (m, 3 H), 1.44–1.52 (m, 2 H), 1.28–1.33 (m, 12 H), 0.94 (t, *J* 7.2, 3 H); δ_F −22.7 (s, 0.66 F, *E*), −21.5 (s, 2.34 F, *Z*); δ_P 23.65 (s, 0.78 P, *Z*), 24.02 (0.22 P, *E*) [Found: C, 51.2; H, 7.8. Calc. for $C_{14}H_{26}F_3O_3P$ (330.33): C, 50.91; H, 7.93%)].

Diethyl 3-methyl-2-trifluoromethylhex-2-enylphosphonates **6c**.—Colourless oil; ν/cm^{-1} 2950, 1650, 1250 and 1230; *m/z* (rel. int.) 303 (M^+ + 1, 53), 283 (100), 254 (17) and 186 (36); δ_H 4.06–4.16 (m, 4 H), 2.81 (d, *J* 21.8) and 2.79 (d, *J* 21.8) (2 H), 2.21–2.61 (m, 2 H), 1.90–1.95 (m, 3 H), 1.46–1.53 (m, 2 H), 1.32 (t, *J* 7.0, 6 H) and 0.94 (t, *J* 7.2, 3 H); δ_F −22.2 (s, 0.78 F, *E*), −21.1 (s, 2.22 F, *Z*); δ_P 25.71 (s, 0.74 P, *Z*) and 26.04 (0.26 P, *E*) [Found: C, 47.9; H, 7.4. Calc. for $C_{12}H_{22}F_3O_3P$ (302.27): C, 47.68; H, 7.34%].

Diethyl 3-methyl-2-trifluoromethylbut-2-enylphosphonates **6d**.—Colourless oil; ν/cm^{-1} 2960, 1660, 1250 and 1230; *m/z* (rel. int.) 275 (M^+ + 1, 61), 206 (98), 178 (100) and 138 (27); δ_H 4.06–4.23 (m, 4 H), 2.79 (d, *J* 21.8, 2 H), 1.91–1.97 (m, 6 H) and 1.31 (t, *J* 7.0, 6 H); δ_F −21.5 (s); δ_P −25.93 (s) [Found: C, 43.6; H, 6.5. Calc. for $C_{10}H_{18}F_3O_3P$ (274.22): C, 43.90; H, 6.62%].

Diisopropyl 2-trifluoromethyl-3-methylbut-2-enylphosphonates **6e**.—Colourless oil; ν/cm^{-1} 2950, 1655, 1245 and 1225; *m/z* (rel. int.) 303 (M^+ + 1, 3), 260 (5) and 178 (100); δ_H 4.60–4.76 (m, 2 H), 2.74 (d, *J* 21.8, 2 H), 1.90–1.97 (m, 6 H) and 1.26–1.34 (m, 12 H); δ_F −21.5 (s); δ_P −20.2 (s) (Found: C, 47.4; H, 7.3. Calc. for $C_{12}H_{22}F_3O_3P$ (302.27): C, 47.68; H, 7.34%).

Diethyl 2-cyclopentylidene-3,3,3-trifluoropropylphosphonates **6f**.—Colourless oil; ν/cm^{-1} 2950, 1660 and 1250; *m/z* (rel. int.) 301 (M^+ + 1, 34) and 281 (100); δ_H 4.06–4.15 (m, 4 H), 2.74 (d, *J* 21.7, 2 H), 2.53 (br s, 4 H), 1.67–1.76 (m, 4 H) and 1.29–1.33 (m, 6 H); δ_F −17.5 (s); δ_P −26.13 (s) [Found: C, 47.9; H, 6.6. Calc. for $C_{12}H_{20}F_3O_3P$ (300.26): C, 48.00; H, 6.71%].

Diisopropyl 2-cyclopentylidene-3,3,3-trifluoropropylphosphonates **6g**.—Colourless oil; ν/cm^{-1} 2950, 1660 ad 1245; *m/z* (rel. int.) 329 (M^+ + 1, 100), 309 (6) and 287 (22); δ_H 4.65–4.75 (m, 2 H), 2.69 (d, *J* 21.8, 2 H), 2.53 (br s, 4 H), 1.67–1.75 (m, 4 H), 1.25–1.34 (m, 12 H); δ_F −17.3 (s); δ_P −24.17 (s) [Found: C, 51.3; H, 7.4. Calc. for $C_{14}H_{24}F_3O_3P$ (328.31): C, 51.22; H, 7.37%].

Acknowledgements

Thanks are due to the National Natural Science Foundation of China, Laboratory of Organometallic Chemistry and Academia Sinica for financial support.

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Paper 4/05866F
Received 26*th September* 1994
Accepted 4*th January* 1995