A Novel Synthesis of α-Fluoroalkylvinyl- or α-Fluoroepoxyalkyl-phosphonates

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α-Fluoroalkylvinyl- or α-fluoroepoxyalkyl-phosphonates can be synthesized by the reaction of diethyl lithium phosphite with fluorinated β-oxoalkylphosphonium salts, depending upon the α-substituents R^1 and R^2 in the alkylidene moiety of the phosphorane used to prepare the phosphonium salts and the base used.

Vinylphosphonates are useful intermediates in the synthesis of biologically active compounds and may undergo many useful organic transformations.[1] β-Fluoroalkylvinylphosphonates, which are applicable to the synthesis of a variety of fluorine containing compounds, have been reported by Ishihara *et al.*[2] However, to the best of our knowledge, α-fluoroalkylvinyl- and α-fluoroepoxyalkyl-phosphonates have not been reported previously. They would be expected to be useful intermediates for the preparation of fluorinated biologically active compounds, and an effective method for their synthesis would be valuable.

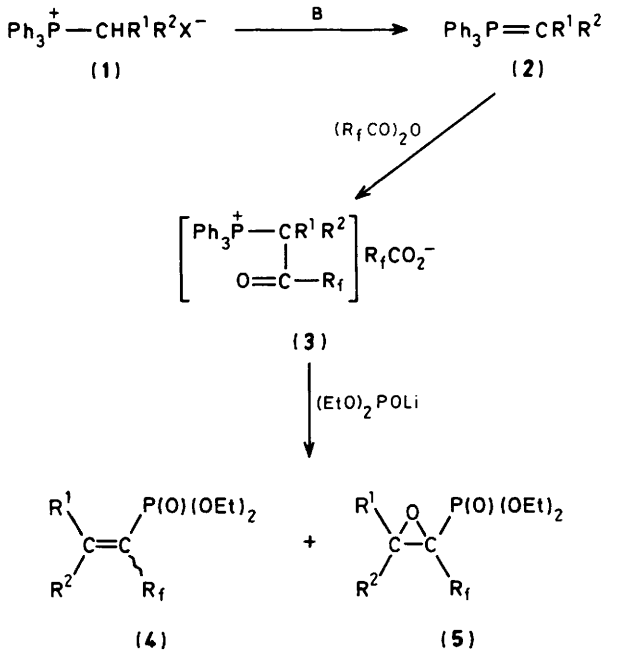
Results and Discussion

Recently we found that carbon nucleophiles could attack fluorinated β-oxophosphonium salts leading to the formation of tetrasubstituted fluoroalkenes[3] and fluoroenynes.[4] In our continuing investigations to exploit the synthetic utility of fluorinated β-oxophosphonium salts in organic synthesis, we report a novel one-pot synthesis of α-fluoroalkylvinyl- or α-fluoroepoxyalkyl-phosphonates using attack of fluorinated β-oxophosphonium salts by the heteronucleophile diethyl lithium phosphite.

The phosphoranes (**2**), generated from the corresponding phosphonium salts (**1**) and n-butyl-lithium or methyl-lithium in tetrahydrofuran, were acylated by the addition of perfluoroalkanoic anhydrides to give the fluorinated β-oxophosphonium salts (**3**), which in the reaction medium were attacked by diethyl lithium phosphite followed by elimination of triphenylphosphine or triphenylphosphine oxide to give α-fluoroepoxyalkyl- or α-fluoroalkylvinyl-phosphonates. The reaction sequence is shown in Scheme 1 and the results are summarized in the Table.

The effect of the structure of the groups R^1 and R^2, the counter-ion X, and the base used on the selectivity of the reaction has been studied. The results in Table 1 indicate that the selectivity could be controlled to give exclusively either (**4**) (runs c–g) or (**5**) (run b) depending upon R^1 and R^2 in the alkylidene moiety of the phosphoranes and the base used. Change in the counter-ion X had no effect on the selectivity of the reaction. Usually the α-fluoroalkylvinyl-phosphonates (**4**) were obtained exclusively or predominately. Comparison of runs a and a′ shows that the yield of (**4**) decreased markedly while the yield of (**5**) increased if methyl-lithium was used instead of n-butyl-lithium. No reasonable explanation for this result is apparent.

The mechanism may be rationalized as follows. The reaction is initiated by nucleophilic attack of diethyl lithium phosphite on the carbonyl carbon atom of the fluorinated β-oxophosphonium salt to give the intermediate (**6**). If $R^1 = R^2 = Me$, the oxygen anion with the least sterically hindered position attacks the neighbouring carbon atom, followed by elimination



Scheme 1.

of triphenylphosphine to give (**5**). In the other cases, with a more bulky group R^1, formation of the betaine (**7**) could result from 180° rotation around the C–C bond. Subsequent decomposition of the betaine (**7**) with elimination of phosphine oxide in a *syn* fashion would afford (**4**) (Scheme 2).

Compounds (**5**) are fluoro-analogues of phosphomycin;[5] they could be synthesized conveniently by this reaction and may possess some biologically activity.

Experimental

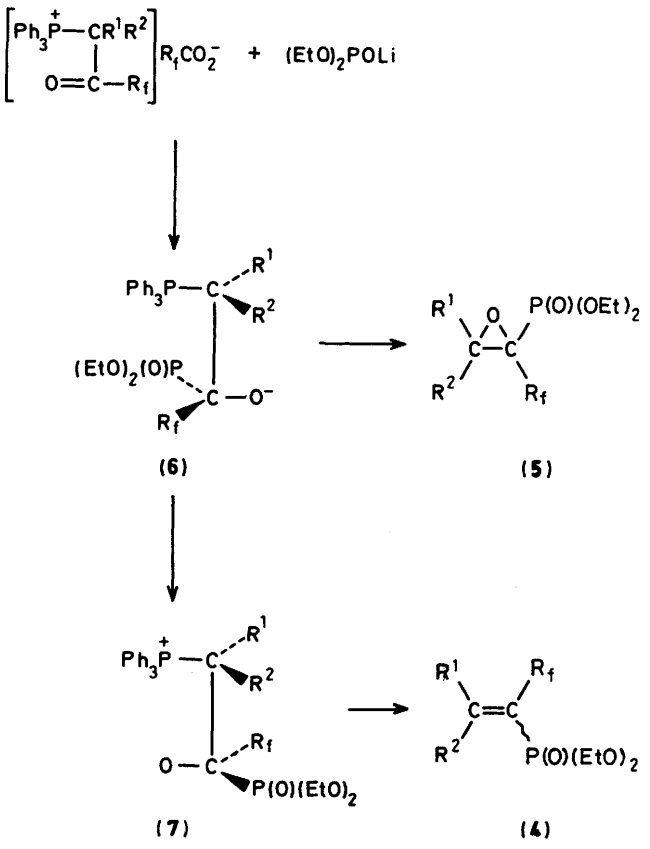
All b.p.s are uncorrected. IR spectra of liquid products were obtained as films on a Shimadzu IR-440 spectrometer. ^1H and ^{19}F NMR spectra were recorded on a Varian EM-360 (60 MHz) or JEOL FX-90Q (90 MHz) spectrometer with $SiMe_4$ and CF_3CO_2H (positive for upfield shifts) as external references, respectively. Mass spectra were measured on a GC-MS-4021 spectrometer.

General Procedure.—n-Butyl-lithium (3.0 mmol) or methyl-lithium (3.0 mmol) in dry tetrahydrofuran (THF) was added dropwise to a stirred suspension of the phosphonium salt (**1**) (3.0 mmol) in absolute THF (30 ml) at −20 °C under nitrogen.

Table. Preparation of α-fluoroalkylvinyl- or α-fluoroepoxyalkylphosphonates

Run	R^1	R^2	R_f	X	B	% Yield[a] (4)	% Yield[a] (5)	$Z:E$[b]
a	Me	Me	CF_3	I	Bu^{n}Li	52	13	
a′	Me	Me	CF_3	I	MeLi	2	51	
b	Me	Me	C_2F_5	I	MeLi	0	42	
c	–(CH$_2$)$_4$–		CF_3	Br	Bu^{n}Li	45	0	
d	–(CH$_2$)$_4$–		C_2F_5	Br	Bu^{n}Li	42	0	
d′	–(CH$_2$)$_4$–		C_2F_5	Br	MeLi	41	0	
e	–(CH$_2$)$_5$–		CF_3	I	Bu^{n}Li	72	0	
e′	–(CH$_2$)$_5$–		CF_3	I	MeLi	78	0	
f	Ph	Me	CF_3	Cl	Bu^{n}Li	68	0	100:0
g	Ph	Me	C_2F_5	Cl	Bu^{n}Li	56	0	85:15

[a] Isolated yields. All products were characterized by microanalyses, and IR, NMR, and mass spectroscopy. [b] $Z:E$ ratio estimated from NMR data.



Scheme 2.

The mixture was stirred for 30 min at 0 °C and cooled to −78 °C; the perfluoroalkanoic anhydride (2.5 mmol) was slowly added until the characteristic ylidic colour had disappeared. The mixture was stirred at −78 °C for 5 min and a solution of diethyl lithium phosphite [prepared by the reaction of ethyl hydrogen phosphite (0.41 g, 3.0 mmol) and methyl-lithium (3.0 mmol) in THF (10 ml) for 30 min at −78 °C] was slowly added. The mixture was allowed to warm to room temperature, stirred for a further 2 h, and diluted with light petroleum (b.p. 60–90 °C). Filtration and evaporation of filtrate gave a residue which was purified by column chromatography on silica gel with light petroleum (b.p. 60–90 °C)–ethyl acetate (10:1) as eluant to give the products (**4**) or/and (**5**).

Diethyl (1-*cyclopentylidene*-2,2,3,3,3-*pentafluoropropyl*)*phosphonate* (**4d**) was obtained in 42% yield, b.p. 92–94 °C at 0.2 mmHg; δ_H 1.33 (6 H, t, *J* 7.1 Hz), 1.68–3.02 (8 H, m), 4.15 (2 H, q, *J* 7.1 Hz), and 4.27 (2 H, q, *J* 7.1 Hz); δ_F 6.5 (3 F, s), and 28.0 (2 F, s) ppm; ν_{max} 1 600s, 1 300s, and 1 110s cm^{-1}; *m*/*z* 337 (M^+ + 1, 100%), 336 (M^+, 10%), 317 (M^+ − F, 10%), and 267 (M^+ − CF_3, 2%) (Found: C, 43.3; H, 5.8. $C_{12}H_{18}F_5O_3P$ requires C, 42.9; H, 5.4%).

Diethyl (1-*cyclohexylidene*-2,2,2-*trifluoroethyl*)*phosphonate* (**4e**) was obtained in 72% yield, b.p. 98–100 °C at 0.1 mmHg; δ_H 1.34 (6 H, t, *J* 7.0 Hz), 1.63–3.07 (10 H, m), 4.05 (2 H, q, *J* 7.0 Hz), and 4.17 (2 H, q, *J* 7.0 Hz); δ_F −24.6 (3 F, s) ppm; ν_{max} 1 600s, 1 300s, 1 110s, 980s cm^{-1}; *m*/*z* 301 (M^+ + 1, 100%), 300 (M^+, 9%), 281 (M^+ − F, 10%), and 231 (M^+ − CF_3, 7%) (Found: C, 47.8; H, 7.0. $C_{12}H_{20}F_3O_3P$ requires C, 48.0; H, 6.7%).

Diethyl (2-*phenyl*-1-*trifluoromethylprop*-1-*enyl*)*phosphonate* (**4f**) was obtained in 68% yield, b.p. 93 °C at 0.5 mmHg; δ_H 1.28 (6 H, t, *J* 7.0 Hz), 2.46 (3 H, br s), 4.05 (2 H, q, *J* 7.0 Hz), 4.17 (2 H, q, *J* 7.0 Hz), and 7.00–7.40 (5 H, m); δ_F −25.0 (3 F, s) ppm; ν_{max} 1 610s, 1 300s, 1 120s, and 980s cm^{-1}; *m*/*z* 322 (M^+, 55%) and 253 (M^+ − CF_3, 12%) (Found: C, 51.95; H, 5.7. $C_{14}H_{18}F_3O_3P$ requires C, 52.2; H, 5.6%).

Diethyl (1-*pentafluoroethyl*-2-*phenylprop*-1-*enyl*)*phosphonate* (**4g**) was obtained in 56% yield, b.p. 95 °C at 0.7 mmHg; δ_H 1.00 (6 H, t, *J* 7.0 Hz), 2.27 (3 H, br s), 3.76 (2 H, q, *J* 7.0 Hz), 3.80 (2 H, q, *J* 7.0 Hz), and 7.20–7.40 (m, 5 H); δ_F 4.2 (3 F, s), 22.2 (*E*-isomer), and 24.2 (*Z*-isomer) (total 2 F, s) ppm; ν_{max} 1 590s, 1 330s, 1 130s, and 980s cm^{-1}; *m*/*z* 372 (M^+, 100%) and 253 (M^+ − C_2F_5, 30%) (Found: C, 48.4; H, 4.9. $C_{14}H_{18}F_3O_3P$ requires C, 48.4; H, 4.9%).

Diethyl (2-*methyl*-1-*trifluromethylprop*-1-*enyl*)*phosphonate* (**4a**) was obtained in 52% yield, b.p. 116 °C at 8 mmHg; δ_H 1.38 (6 H, t, *J* 7.0 Hz), 2.13 (3 H, q, *J* 2.0 Hz), 2.39 (3 H, q, *J* 2.0 Hz), 4.01 (2 H, q, *J* 7.0 Hz), and 4.12 (2 H, q, *J* 7.0 Hz); δ_F −25.0 (3 F, s) ppm; ν_{max} 1 620s, 1 300s, 1 110s, and 970s cm^{-1}; *m*/*z* 261 (M^+ + 1, 100%), 245 (M^+ − CH_3, 14%), and 191 (M^+ − CF_3, 11%) (Found: C, 41.1; H, 6.6. $C_9H_{16}F_3O_3P$ requires C, 41.55; H, 6.2%).

Diethyl (3,3-*dimethyl*-2-*trifluoromethyloxiran*-2-*yl*)*phosphonate* (**5a**) was obtained in 13% yield, b.p. 118 °C at 8 mmHg; δ_H 1.30 (6 H, t, *J* 7.0 Hz), 1.75–1.95 (6 H, m), 4.02 (2 H, q, *J* 7.0 Hz), and 4.13 (2 H, q, *J* 7.0 Hz); δ_F −18.2 (3 F, s) ppm; ν_{max} 1 290s, 1 090s, and 990s cm^{-1}; *m*/*z* 277 (M^+ + 1, 100%), 261 (M^+ − CH_3, 9%), and 208 (M^+ − CF_3, 4%) (Found: C, 39.1; H, 6.1. $C_9H_{16}F_3O_4P$ requires C, 39.1; H, 5.8%).

Diethyl (3,3-*dimethyl*-2-*pentafluoroethyloxiran*-2-*yl*)*phosphonate* (**5b**) was obtained in 42% yield b.p. 84 °C at 2 mmHg; δ_H 1.36 (6 H, t, *J* 7.2 Hz), 1.88–1.99 (m, 6 H), 4.16 (2 H, q, *J* 7.2 Hz), and 4.27 (2 H, q, *J* 7.2 Hz); δ_F 8.0 (3 F, s) and 35.9 (2 F, s) ppm; ν_{max} 1 300s, 1 090s, and 990s cm^{-1}; *m*/*z* 327 (M^+ + 1, 19%), 326 (M^+, 10%), 81(100%), and 69(29%) (Found: C, 36.6; H, 5.0. $C_{10}H_{16}F_5O_4P$ requires C, 36.8; H, 4.9%).

Diethyl (1-*cyclopentylidene*-2,2,2-*trifluoroethyl*)*phosphonate* (**4c**) was obtained in 45% yield, b.p. 80–82 °C at 0.1 mmHg; δ_H 1.34 (6 H, t, *J* 7.0 Hz), 1.70–3.01 (8 H, m), 4.08 (2 H, q, *J* 7.0 Hz) and 4.19 (2 H, q, *J* 7.0 Hz); δ_F −21.0 (3 F, s) ppm; ν_{max} 1 620s, 1 290s, 1 100s, and 980s cm^{-1}; *m*/*z* 287 (M^+ + 1, 100%), 286 (M^+, 22%), 267 (M^+ − F, 27%), and 217 (M^+ − CF_3, 5%) (Found: C, 45.9; H, 6.4. $C_{11}H_{18}F_3O_3P$ requires C, 46.2; H, 6.3%).

Acknowledgements

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