The Synthesis of α-Fluorovinylphosphonates

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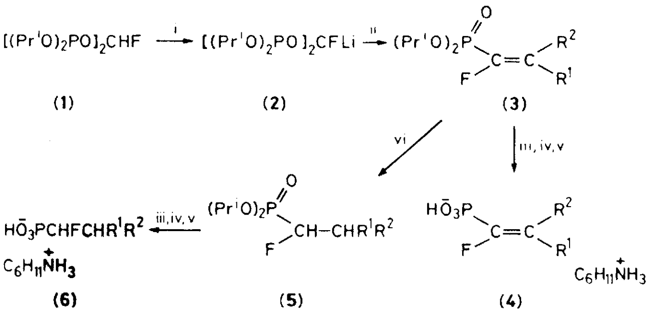
A general synthesis of α-fluorovinylphosphonates results from Wadsworth–Emmons condensation of tetra-alkyl fluoromethylenebisphosphonates with aldehydes and ketones with stereoselectivity favouring the less hindered product which can be reduced to give α-fluorophosphonates in good yield.

α-Fluorination of phosphonates has been shown[1–3] to reduce the disparity in important physical properties between phosphate esters and the corresponding alkylphosphonate esters. The development of α-fluoroalkylphosphonates as analogues

Table 1. ^{31}P N.m.r. chemical shifts for compounds (**3**), (**4**), and (**5**).

			Vinylphosphonate (**3**)		^{31}P n.m.r. δ/p.p.m.[a]			Alkylphosphonate (**5**)	
Compound	R^1	R^2	Yield, %	$E:Z$	E-(**3**)	Z-(**3**)	(**4**)[b]	Yield, %	^{31}P n.m.r. δ/p.p.m.[a]
a	Ph	H	76	6	3.3	4.7	−0.0	59	16.6
b	*trans*-PhCH=CH	H	67	20	7.0	1.2	−0.4		
c	Me_2CH	H	95	5	2.0	3.3	+1.3	100	16.9
d	(*R*)-$OCMe_2OCH_2CH$-	H	56	10	1.2	1.2	−1.3	100	15.4
e	Me	Me	73	—	2.8		+0.6	100	16.1
f	Me_2CH	Me	68	3	4.0	3.6		100	16.7
g	Ph	Me	66	4	3.5	2.5	+0.5	59	15.2

[a] Chemical shifts relative to external 85% H_3PO_4. [b] Major (*E*) isomer,



Scheme 1. i, BuLi, n-heptane; ii, R^1COR^2; iii, Me_3SiBr; iv, MeOH; v, $C_6H_{11}NH_2$; vi, H_2, Pd–C, EtOH.

of biological phosphates[4,5] has been restricted by the limited availability of general syntheses of such compounds. Some use has been made of the action of diethylaminosulphur trifluoride on α-hydroxyalkylphosphonates,[1] the fluorination of phosphonate carbanions,[2,6,7] and Arbusov-type reactions of *gem*-bromofluoroalkanes.[2,3,8]

Both Machleidt's work with triethyl phosphonofluoroacetate[8] and Engel's use of tetra-alkyl methylenebisphosphonate[9] suggested that a Wadsworth–Emmons[10] condensation based on tetra-alkyl fluoromethylenebisphosphonate[2] might provide a general synthesis of α-fluorovinylphosphonates leading to α-fluoroalkylphosphonates on reduction. A recent report of the condensation of diethyl difluoromethylphosphonate with aldehydes and ketones[11] prompts the presentation of our results at this time.

The tetraisopropyl ester of fluoromethylenebisphosphonic acid (**1**) was used routinely although the tetraethyl ester has proved to be equally satisfactory. The phosphonate anion (**2**) is generated with n-butyl-lithium in heptane and condenses smoothly[9] with aliphatic, aromatic, and α,β-unsaturated aldehydes giving good yields of alkenes (**3**) (Scheme 1). The proportion of the less-hindered *E*-isomer, giving a $^3J_{HF}$ value typically of 40 Hz, varied from 80 to 95%. The anion (**2**) also condenses with a variety of ketones, although the reaction failed in the case of 3,3-dimethylbutan-2-one and camphor, probably because of steric hindrance. A lower product stereoselectivity was observed for ketones compared with aldehydes and the major isomer appears to have the phosphoryl group *trans* to the more bulky ketone substituent.

All of the α-fluorovinylphosphonate esters (**3**) prepared are distillable liquids. They are converted into the parent phosphonic acids by treatment with bromo- or iodo-trimethylsilane[12,13] followed by methanolysis of the bis-silyl-esters and purified by crystallisation of their cyclohexylammonium salts (**4**) (Scheme 1).† The ^{31}P n.m.r. chemical shifts of these compounds are close to those for monoalkyl phosphates (Table 1).

Catalytic hydrogenation of the α-fluorovinylphosphonate esters (**3**) affords α-fluoroalkylphosphonates (**5**) in high yield which can be transformed into the cyclohexylammonium salts (**6**) of the phosphonic acids in the usual way (Scheme 1). These reductions showed two unusual features. Firstly, hydrogenation of the 4:1 mixture of *E*:*Z* diastereoisomers (**3g**) formed from acetophenone gave a 3:1 ratio of diastereoisomers of di-isopropyl 1-fluoro-2-phenylpropylphosphonate (**5g**) showing that the reduction proceeds with *cis*- and *trans*-addition of hydrogen. Secondly, the hydrogenation of 1-fluoro-2-phenylvinylphosphonates (**3a**, **3g**) gives minor amounts of fluorine-free alkylphosphonates together with the major products (**5a**, **5g**). However, this loss of fluorine appears to be restricted to β-arylvinylphosphonates.

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† All new compounds described have been characterised by analytical and spectroscopic data.