

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.

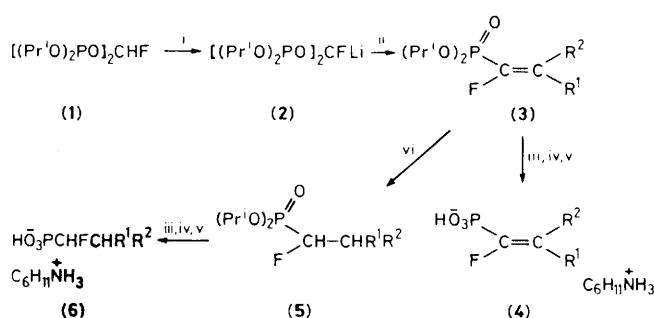
α -Fluorination of phosphonates has been shown^{1–3} to reduce the disparity in important physical properties between phos-

phate 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).

Compound	R ¹	R ²	Vinylphosphonate (3)		^{31}P n.m.r. $\delta/\text{p.p.m.}^a$			Alkylphosphonate (5)	
			Yield, %	<i>E</i> : <i>Z</i>	<i>E</i> -(3)	<i>Z</i> -(3)	(4) ^b	Yield, %	^{31}P n.m.r. $\delta/\text{p.p.m.}^a$
a	Ph	H	76	6	3.3	4.7	-0.0	59	16.6
b	<i>trans</i> -PhCH=CH	H	67	20	7.0	1.2	-0.4		
c	Me ₂ CH	H	95	5	2.0	3.3	+1.3	100	16.9
d	(<i>R</i>)-OCMe ₂ OCH ₂ CH-	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 ₂ CH	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% H₃PO₄. ^b Major (*E*) isomer,



Scheme 1. i, BuLi, n-heptane; ii, R¹COR²; iii, Me₃SiBr; iv, MeOH; v, C₆H₁₁NH₂; vi, H₂, 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 phosphonofluoroacetate⁸ and Engel's use of tetra-alkyl methylenebisphosphonate⁹ suggested that a Wadsworth-Emmons¹⁰ condensation based on tetra-alkyl fluoromethylenebisphosphonate² 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 ketones¹¹ 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 smoothly⁹ 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 $^3J_{\text{HF}}$ 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 cyclohexyl-

ammonium 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.