The Synthesis of α-Fluoroalkylphosphonates

G. Michael Blackburn* **and Martin J. Parratt**
Department of Chemistry, The University, Sheffield S3 7HF, U.K.

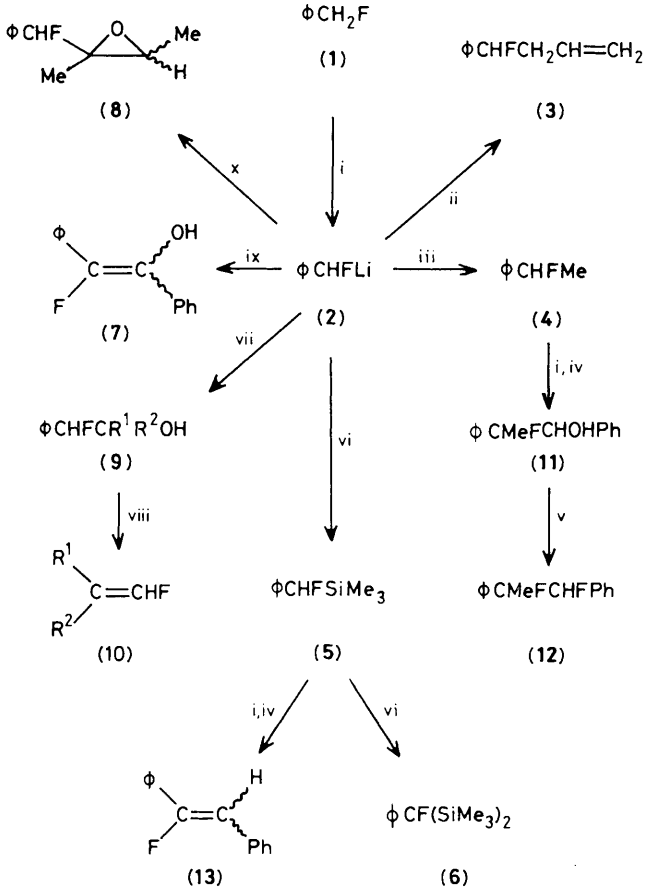
A general synthesis of α-fluoroalkylphosphonates is provided by the reaction of the dialkyl fluoromethylphosphonate carbanion with alkyl halides, aldehydes, ketones, and acyl halides.

α-Fluoroalkylphosphonates are effective isopolar and isosteric analogues of the corresponding phosphate monoesters.[1,2] Their development as models of biological phosphates[3,4] has been restricted until recently by the lack of synthetic methods for their formation. Routes involving C–F bond formation are founded on fluorination of phosphonate-stabilised carbanions[2,5,6] and the action of diethylaminosulphur trifluoride (DAST) on α-hydroxyalkylphosphonates.[1] Methods based on

Table 1. Substitution products from di-isopropyl fluoromethylphosphonate.

Reagents	Product	Yield %	Diastereoisomer ratio	^{31}P N.m.r.^{a} δ/p.p.m.
$CH_2{=}CHCH_2Br$ + (**1**)	(**3**)	45	—	15.5
Me_2SO_4 + (**1**)	(**4**)	60	—	16.6
Me_3SiCl or Me_3SiBr + (**1**)	(**5**)	40^{b}	—	19.3
	+ (**6**)	30^{b}	—	22.8
PhCOCl + (**1**)	(**7**)	46	4:3	0.7, 1.0
MeCOCHClMe + (**1**)	(**8**)	46	12:12:3:2	13.0, 11.8, 11.7, 13.4
DAST + (**11**)	(**12**)	65	1:1	11.6, 11.4
PhCHO + (**5**)	(**13**)	100	1:1	4.7, 3.3

^{a} ^{31}P Chemical shifts downfield from external 85% H_3PO_4 reference. ^{b} Spectroscopic yields.

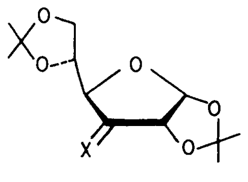


a; R^1 = H, R^2 = Ph
b; R^1 = H, R^2 = PhCH=CH
c; R^1 = H, R^2 = CH_2OCH_2OCH

Scheme 1. Reagents: i, LDA–THF at −78 °C; ii, $CH_2{=}CHCH_2Cl$; iii, Me_2SO_4; iv, PhCHO; v, DAST; vi, Me_3SiBr; vii, R^1R^2CO; viii, 50 °C; ix, PhCOCl; x, MeCOCHClMe.
Φ = $(Me_2CHO)_2PO$–

P–C(F) bond synthesis involve Arbusov or Michaelis–Becker reactions with bromofluoroalkanes,[2,7,8] while C–C(F)P bond formation has been achieved with Wadsworth–Emmons condensations of fluoromethylenebisphosphonates[9] and reactions of metallated derivatives of difluoromethylphosphonate diesters.[10–12] We here present our results on reactions between carbon electrophiles and di-isopropyl lithiofluoromethylphosphonate.

The phosphonate anion salt (**2**) is obtained from the easily prepared[13] di-isopropyl fluoromethylphosphonate (**1**) using lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C. The co-reactant is added at −78 °C and the reaction mixture brought to ambient temperature before work-up to give the desired products (Scheme 1). The carbanion acts as a nucleophile towards a variety of alkylating and acylating agents (Table 1). Simple alkylating agents lead to products of chain-extension, (**3**) and (**4**).† Silylation of (**2**) gives a mixture of mono- and bis-trimethylsilyl derivatives, (**5**) and (**6**) respectively, the latter resulting from the facile *trans*-protonation encountered elsewhere in this field.[2] Acylation of (**2**) affords β-keto-α-fluoroalkylphosphonates which exist exclusively as a *Z*/*E* mixture of enol forms (**7**) while reaction of (**2**) with α-halogenoketones gives a Darzens-type reaction leading to the β,γ-epoxy-α-fluorophosphonate (**8**).



(**9d**); X = ~OH, ~CHFΦ
(**10d**); X = CHF
(**14**); X = O

With aldehydes and ketones, the addition product of the phosphonate (**1**) is usually isolated as a mixture of diastereoisomeric α-fluoro-β-hydroxyphosphonates (**9**) (Table 2). If, however, the reaction mixture is warmed, a Wadsworth–Emmons type elimination results in the formation of a 1-fluoroalkene (**10**). Additions to chiral aldehydes and ketones show a useful degree of stereoselectivity at the β-carbon centre while at the α-carbon there appears to be no size discrimination between hydrogen and fluorine. Virtually complete stereoselectivity of addition to 1,2:5,6-di(*O*-isopropylidene)-α-D-ribohexofurano-3-ulose (**14**) results in production of only two diastereoisomers (**9d**). These can be assigned the *allo*-configuration resulting from addition to the less-hindered *si*-face of the ketone.[14]

Further elaborations of these primary products increases the variety of α-fluoroalkylphosphonates which can be constructed from (**1**). Thus, the 1-fluoroethylphosphonate (**4**) can be added to benzaldehyde to give the secondary alkylphosphonate (**11**). Treatment of α-fluoro-β-hydroxyphosphonates with DAST[1] can lead either to α,β-difluoroalkylphosphonates (**12**) or to products of dehydration. Lastly, the α-fluoro-α-trimethylsilylphosphonate (**5**) can be employed in a Peterson-type[15] condensation with aldehydes to generate α-fluorovinylphosphonate esters (**13**). These usefully have a higher *cis*–*trans* ratio of diastereoisomers than those made *via* Wadsworth–Emmons condensations using fluoromethylenebisphosphonate anions[9] (Table 1).

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† All new compounds have been adequately characterised by analytical and spectroscopic methods.

Table 2. Addition products of phosphonates with aldehydes and ketones.

Aldehyde/ketone + phosphonate	Product	Yield %	Diastereoisomer ratio	^{31}P N.m.r.[a] δ/p.p.m.
PhCHO + (**1**)	(**9a**)	46	1:1	14.9, 14.0
PhCH=CHCHO + (**1**)	(**9b**)	30	1:1	14.5, 14.0
$\overline{\mathrm{CH_2OCH_2OCH}}\text{-CHO}$ + (**1**)	(**9c**)	34	5:5:2:2	15.0, 13.0, 14.9, 13.8
(**14**) + (**1**)	(**9d**)	15	1:1	13.9, 12.8
PhCHO + (**4**)	(**11**)	44	5:4	18.9, 17.8

[a] ^{31}P Chemical shifts downfield from external 85% H_3PO_4 reference.

Work is in progress to achieve diastereosynthetic control of chirality at the α-carbon centre in these processes.

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