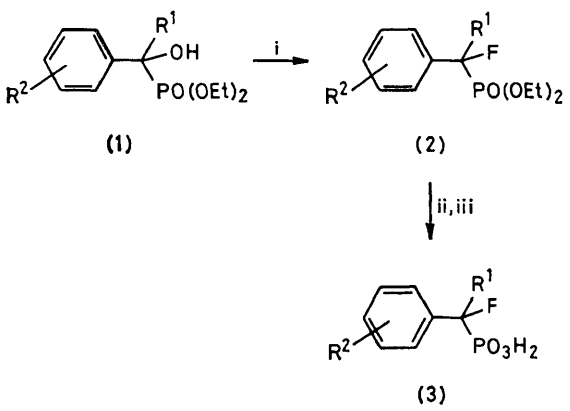
A Novel Synthesis of α- and γ-Fluoroalkylphosphonates

By G. MICHAEL BLACKBURN* and DAVID E. KENT
(*Department of Chemistry, The University, Sheffield* S3 7HF)

Summary α-Hydroxybenzylphosphonate esters are efficiently converted into α-fluorobenzylphosphonate esters by diethylaminosulphur trifluoride while the corresponding α-hydroxyallyl- and α-hydroxycinnamylphosphonates undergo fluorination with allylic rearrangement; the corresponding phosphonic acids are formed by de-esterification using bromo- or iodotrimethylsilane.

ISOSTERIC analogues of biological phosphates have played a significant role in studies of biosynthetic pathways and enzyme mechanisms. Although phosphorus–carbon bonds have greater hydrolytic stability than phosphorus–nitrogen or phosphorus–sulphur bonds, alkanephosphonates have enjoyed relatively small success as biological analogues.[1] Their limitations can be analysed in terms of the relative electronegativity of the methylene group,[2] which increases in the series $-CH_2- < -S- < -NH- < -O-$. This change is manifest in a weakened acidity for phosphonates relative to phosphates,[3] reduced P=O stretching frequency,[4] downfield ^{31}P n.m.r. chemical shift,[5] and diminished apicophilicity.[6]

All of these changes appear to be reversible as a result of halogen substitution at α- and, to a lesser extent, β-positions in alkanephosphonates. Consequently, a strong case can be made for the development of α-halogeno-alkanephosphonates as analogues of biological phosphates.[7] Consideration both of size and of electronegativity indicates a preference for fluorine substitution in this regard. However, while many perfluoroalkanephosphonates are known, few specifically-fluorinated phosphonates have been described.[8,9] We now report a general synthesis of α-fluorobenzylphosphonate esters and their parent acids.



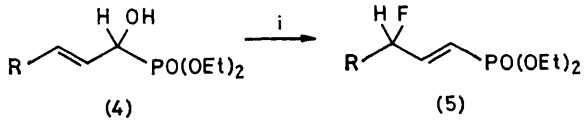
a; R^1 = H, R^2 = H, *m*-Cl, *p*-Cl, *p*-Me
b; R^1 = Me, R^2 = H, *p*-Cl
c; R^1 = H, R^2 = 2,4,6-Me_3

SCHEME 1. i, Et_2NSF_3, ii, Me_3SiX, iii, MeOH.

Hydroxybenzylphosphonate diesters (**1**) are readily produced by the action of dialkyl phosphites on aryl aldehydes and aryl ketones. The conversion of the hydroxy- into the fluoro-function is achieved by the action of 1 equiv. of diethylaminosulphur trifluoride,[10] DAST, in dichloromethane solution at 0 °C and, as gauged by ^1H n.m.r. spectroscopy, is virtually quantitative. The products (**2**) are readily isolable by distillation *in vacuo*. They can be converted smoothly into the parent α-fluorobenzylphosphonic acids (**3**), isolated as their crystalline cyclohexylammonium salts, by treatment with bromo- or iodotrimethylsilane followed by methanolysis of the bis-silyl esters.[11]

The transformation appears to be compatible with a variety of substituents in the aryl function; difficulty was encountered only for the phosphonate (**1a**; R^2 = *p*-MeO–) derived from anisaldehyde, which may well indicate a carbonium-ion-like mechanism. There is no sign of steric hindrance in the transformation, such as has been observed for certain steroidal alcohols.[12] Thus, the tertiary alcohols (**1b**) and the extremely crowded mesitylene derivative (**1c**) are readily fluorinated under standard conditions (Scheme 1).

1-Hydroxyallyl- and -cinnamyl-phosphonate esters (**4**) also give monofluoro-products (**5**) in high yield. However, analysis of proton, fluorine, and phosphorus n.m.r. spectra shows unambiguously that these species are formed by an S_N2' substitution process and all have the 3-fluoro-*trans*-prop-1-enylphosphonate structure (Scheme 2).



R = H, Me, Ph

SCHEME 2. i, Et_2NSF_3, CH_2Cl_2, 0 °C.

Coupled with the observation that diethyl 2-hydroxypropan-2-ylphosphonate reacts with DAST exclusively by dehydration to give diethyl 2-propenylphosphonate, the above facts suggest that the fluorination process involves a transition state with significant carbocation character, such as has been observed for fluorination of certain tricyclic systems.[13]

Lastly, it is noteworthy that the fluorination process is not restricted to α-hydroxyphosphonates. Treatment of α-hydroxybenzyldiphenylphosphine oxide with DAST gives the α-fluorobenzyldiphenylphosphine oxide quantitatively. Such fluorinated phosphine oxides may well have application for fluoro-olefin synthesis *via* the Wittig reaction.[14]

The i.r., n.m.r., and pK_a characteristics of these α-fluorophosphonates uniformly have values intermediate between those for the parent benzylphosphonates and those for the corresponding phenyl phosphate species (Table).

These physical data thus establish the potential of the CHF group as an isosteric substituent for oxygen of com-

TABLE[a,b]

Compound	Ester $\nu_{P=O}$/cm^{-1}	^{31}P δ	Acid pK_a′
$PhOPO(OR)_2$	1275	+6·8	6·25
$PhCHFPO(OR)_2$	1266	+14·71	6·5
p-$MeC_6H_4CHFPO(OR)_2$	1261	+16·0	6·99
$PhCH_2PO(OR)_2$	1254	+27·06	7·6

[a] Ester, R = Et; Acid, R = H. [b] Chemical shifts (in p.p.m.) relative to 85% phosphoric acid.

parable electronegativity and provide a good basis for the further development of α-fluoroalkanephosphonates as analogues of biological phosphates.

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