Synthesis of α- and γ-Fluoroalkylphosphonates

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α-Fluorobenzylphosphonate esters are conveniently made by treating α-hydroxybenzylphosphonate esters with diethylaminosulphur trifluoride. The reaction is not subject to steric impedance and is extended to the α-fluorination of an α-hydroxybenzylphosphine oxide. For α-hydroxyallyl and α-hydroxycinnamylphosphonates, the replacement of the hydroxy group by fluorine proceeds *via* an S_N2' rearrangement to give the γ-fluoroalk-1-enylphosphonates exclusively. Dehydration rather than substitution occurs in the case of alcohols of secondary alkylphosphonates.

Phosphonates have been widely employed as analogues of biological phosphates.[1] While there is little doubt that they provide a satisfactory steric simulation of the prototype and the desirable stability of the P–C bond under most conditions, in many areas their biological performance falls short of that anticipated on these grounds. We have argued the case for allotting equal priority to polar and to steric features of phosphonates[2] and suggested that a satisfactory solution to the problem could be the use of α-halogenoalkylphosphonates. The preference for α-fluorine substitution rather than α-chlorination is dictated by consideration of the relative chemical inertness of alkyl fluorides relative to chlorides and of the smaller Van der Waals radius for fluorine (0.135 nm) than for chlorine (0.180 nm). Although a considerable number of α-fluoroalkylphosphonates is known,[3] the methods employed in their preparation are often particular for perfluorinated carbon substrates and few lend themselves to broad utility. We have accordingly undertaken the task of developing general methods for the synthesis of α-fluoroalkylphosphonates and describe here a route for the preparation of α-fluorobenzylphosphonate esters and the corresponding phosphonic acids. A preliminary account of this work has been published earlier.[4]

Experimental

^{1}H N.m.r. spectra were recorded at 220 MHz on a Perkin-Elmer R34 spectrometer or at 400.13 MHz using a Bruker WH400 instrument and using tetramethylsilane as an internal reference. ^{31}P N.m.r. spectra were recorded at 40.48 MHz using a Jeol JNM-PS-100 spectrometer with proton decoupling. Positive chemical shifts are downfield from 85% phosphoric acid as an external reference. I.r. spectra were recorded on a Perkin-Elmer 157G grating instrument. High resolution mass spectra were run on a Kratos MS80 instrument with a Kratos DS55 data system. pK_a' Values were measured by titration using a Radiometer PHM 28, Autoburette ABU12, and Titrator TT11 with a Titrigraph SBR2c and with a Russell CTWL combination electrode. M.p.s were measured on a Kofler hot stage apparatus and are otherwise uncorrected.

Standard laboratory reagents were distilled or crystallised as appropriate before use and solvents were dried by regular procedures.

Diethyl α-Hydroxy-2,4,6-trimethylbenzylphosphonate (**1**).—2,4,6-Trimethylbenzaldehyde (5 g, 34 mmol) was mixed with diethyl phosphite (5 g, 36 mmol) and the mixture was heated with stirring at 100 °C for 8 h then allowed to cool overnight. The crystalline solid was collected by filtration, washed with light petroleum (40—60 °C), and recrystallised from ethanol to give the *product* as colourless needles (2.5 g, 26%), m.p. 90—92 °C (Found: C, 58.7, H, 7.8. $C_{14}H_{23}O_4P$ requires C, 58.74; H, 8.04%); $\delta_H(CDCl_3)$ 1.09 (3 H, t, $^3J_{HH}$ 7.1 Hz, $MeCH_2$), 1.23 (3 H, $^3J_{HH}$ 7.1 Hz, $MeCH_2$), 2.20 (3 H, s, 4-Me), 2.41 (6 H, br s, 2-, 6-Me), 3.59—4.11 (4 H, m, CH_2O), 4.87 (1 H, br s, OH), 5.45 [1 H, d, $^2J_{PH}$ 17.1 Hz, CH(OH)P], and 6.78 (2 H, s, 3-, 5-H).

Diethyl 1-Hydroxyprop-2-enylphosphonate.—The title compound was prepared from acrylaldehyde and diethyl phosphite as described by Pudovik[5] to give a colourless oil, b.p. 158—159 °C, 13 mmHg (lit.,[5] b.p. 154—155 °C, 10 mmHg), δ_H-($CDCl_3$) 1.32 (6 H, m, 2 × Me), 4.15 (4 H, m, 2 × CH_2OP), 4.50 (1 H, dd, $^2J_{PH}$ 14.7 Hz, $^3J_{HH}$ 5.0 Hz, 1-H), 5.25 (1 H, dd, $^2J_{gem}$, 4.9 Hz, $^3J_{cis}$ 9.8 Hz, 3-H_{trans}), 5.48 (1 H, dd, $^2J_{gem}$ 4.9 Hz, $^3J_{trans}$ 17.0 Hz, 3-H_{cis}), and 5.98 (1 H, ddd, $^3J_{1,2}$ 5 Hz, $^3J_{cis}$ 9.8 Hz, $^3J_{trans}$ 17.0 Hz, 2-H).

Diethyl α-Fluorobenzylphosphonate (**2**).—Diethyl α-hydroxybenzylphosphonate[6] (1.0 g, 4.1 mmol) in dichloromethane (10 ml) was added dropwise with stirring to a solution of diethylaminosulphur trifluoride[7] (DAST) (0.78 g, 0.6 ml, 4.8 mmol) in dichloromethane (5 ml) cooled to −78 °C under a dry nitrogen atmosphere during 0.5 h. The mixture was allowed to warm to room temperature and stirred for a further 0.5 h, when it was carefully quenched into ethanol (40 ml) containing pyridine (1.5 ml). After 0.5 h this mixture was poured into ice-cold water (200 ml) and extracted into dichloromethane (3 × 100 ml). The combined extracts were washed with dilute hydrochloric acid (2 × 50 ml) and water (50 ml), dried, (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product (0.9 g) as a mobile yellow oil. This was distilled under reduced pressure in a short path bulb-to-bulb apparatus (Kugelrohr) to give the product as a colourless viscous oil (0.45 g, 44.9%), b.p. 110 °C, 0.4 mmHg (lit.,[8] b.p. 122 °C, 0.5 mmHg) (Found: C, 53.7; H, 6.5. Calc. for $C_{11}H_{16}FO_3P$: C, 53.72; H, 6.50%); $\delta_H(CDCl_3)$ 1.24 (6 H, m), 4.04 (4 H, m), 5.68 (1 H, dd, $^2J_{PH}$ 7 Hz, $^2J_{FH}$ 44 Hz), 7.38 (3 H, m), and 7.48 (2 H, m).

Diethyl α-Fluoro-4-methylbenzylphosphonate (**3**).—From diethyl α-hydroxy-4-methylbenzylphosphonate[9] (2.0 g, 7.7 mmol) and DAST (1.34 g, 1.06 ml, 8.3 mmol) under the above reaction and work-up conditions was obtained the product (**3**) as a colourless oil (0.8 g, 39.7%) (Found: C, 55.7; H, 6.85. $C_{12}H_{18}FO_3P$ requires C, 55.38; H, 6.92%); $\delta_H(CDCl_3)$ 1.18 (6 H, m), 2.28 (3 H, s), 4.00 (4 H, m), 5.56 (1 H, dd, $^2J_{PH}$ 7.2 Hz, $^2J_{FH}$ 45 Hz), 7.12 (2 H, m), and 7.30 (2 H, m); $\nu_{max.}$(film) 1 261 cm^{-1}.

Diethyl 3-Chloro-α-fluorobenzylphosphonate (**4**).—From diethyl 3-chloro-α-hydroxybenzylphosphonate[10] (2.0 g, 7.2 mmol) and DAST (1.43 g, 1.1 ml, 8.88 mmol) under standard reaction and work-up conditions was obtained the *product* (**4**) as a colourless oil (1.69 g, 84.4%) (Found: C, 46.65; H, 5.55.

$C_{11}H_{15}ClFO_3P$ requires C, 47.07; H, 5.34%); $\delta_H(CDCl_3)$ 1.28 (6 H, m), 4.20 (4 H, m), 5.67 (1 H, dd, $^2J_{PH}$ 9 Hz, $^2J_{FH}$ 46 Hz), 7.32 (3 H, m), and 7.47 (1 H, s).

Diethyl 4-Chloro-α-fluorobenzylphosphonate (**5**).—From diethyl 4-chloro-α-hydroxybenzylphosphonate[11] (2.0 g, 7.2 mmol) and DAST (1.43 g, 1.1 ml, 8.88 mmol) under standard reaction and work-up conditions was obtained the *product* (**5**) as a pale yellow oil (1.41 g, 69.5%) (Found: C, 47.1; H, 5.3. $C_{11}H_{15}ClFO_3P$ requires C, 47.07; H, 5.34%); $\delta_H(CDCl_3)$ 1.26 (6 H, m), 4.09 (4 H, m), 5.66 (1 H, dd, $^2J_{PH}$ 8.5 Hz, $^2J_{FH}$ 46 Hz), and 7.39 (4 H, m).

Diethyl α-Fluoro-2,4,6-trimethylbenzylphosphonate (**6**).—From diethyl α-hydroxy-2,4,6-trimethylbenzylphosphonate (1.5 g, 5.2 mmol) and DAST (1.17 g, 0.9 ml, 7.3 mmol) under standard reaction and work-up conditions was obtained the *product* (**6**) as a colourless oil (0.9 g, 59.6%) (Found: M^+, 288.1284. $C_{14}H_{22}FO_3P$ requires M, 288.1291); $\delta_H(CDCl_3)$ 1.25 (6 H, m), 2.37 (3 H, m), 2.47 (6 H, m), 4.15 (4 H, m), 6.36 (1 H, dd, $^2J_{PH}$ 11.1 Hz, $^2J_{FH}$ 45.5 Hz), and 7.01 (2 H, m).

Diethyl α-Fluoro-α-methylbenzylphosphonate (**7**).—From diethyl α-hydroxy-α-methylbenzylphosphonate[12] (2.0 g, 7.7 mmol) and DAST (1.43 g, 1.1 ml, 8.88 mmol) under standard reaction and work-up conditions was obtained the *product* (**7**) as a colourless mobile oil (900 mg, 44.6%) (Found: C, 55.1; H, 6.9. $C_{12}H_{18}FO_3P$ requires C, 55.38; H, 6.92%); $\delta_H(CDCl_3)$ 1.1—1.34 (6 H, m), 1.95 (3 H, dd, $^3J_{PH}$ 13.5 Hz, $^3J_{FH}$ 25 Hz), 4.23 (4 H, m), and 7.52 (5 H, m).

Diethyl 4-Chloro-α-fluoro-α-methylbenzylphosphonate (**8**).—From 4-chloro-α-hydroxy-α-methylbenzylphosphonate[13] (2.0 g, 6.9 mmol) and DAST (1.43 g, 1.1 ml, 8.88 mmol) under standard reaction and work-up conditions was obtained the *product* (**8**) as an oil (1.40 g, 69.5%) (Found: C, 48.65; H, 6.05. $C_{12}H_{17}ClFO_3P$ requires C, 48.89; H, 5.77%); $\delta_H(CDCl_3)$ 1.30 (6 H, m), 1.89 (3 H, dd, $^3J_{PH}$ 15 Hz, $^3J_{FH}$ 25 Hz), 4.18 (4 H, m), and 7.55 (4 H, m).

Attempted Reaction of DAST with Diethyl α-Hydroxy-4-methoxybenzylphosphonate.—Diethyl α-hydroxy-4-methoxybenzylphosphonate,[14] m.p. 112—114 °C (2.0 g) and DAST (1.43 g) were admixed under standard conditions to give a colourless oil. ^1H N.m.r. spectroscopy of this crude product showed a complex mixture of compounds including a minor component, δ5.5 and 5.7 (1 H, dd, J_{PH} 8 Hz, J_{HF} 46 Hz), and predominant (>80%) loss of the signal (δ 3.8) associated with the MeO group. Attempts to purify this mixture were unsuccessful.

(E)-*Diethyl 3-Fluoroprop-1-enylphosphonate* (**9**).—From diethyl 1-hydroxyprop-2-enylphosphonate[5] (2.0 g, 10.3 mmol) and DAST (1.82 g, 1.4 ml, 11.3 mmol) using standard reaction and work-up conditions was obtained the *product* (**9**) as a mobile oil (0.51 g, 24.9%) (Found: M^+, 196.0683. $C_7H_{14}FO_3P$ requires M, 196.0665); $\delta_H(CDCl_3)$ 1.32 (6 H, m), 4.10 (4 H, m), 5.0‡ (2 H, d, $^2J_{FH}$ 46 Hz), 6.01 (1 H, m), and 6.80 (1 H, m).

(E)-*Diethyl 3-Fluorobut-1-enylphosphonate* (**10**).—From diethyl 1-hydroxybut-2-enylphosphonate[5] (2.0 g, 9.6 mmol) and DAST (1.69 g, 1.3 ml, 10.5 mmol) using standard reaction and work-up conditions was obtained the *product* (**10**) as an oil (0.95 g, 47%) (Found: M^+, 210.0818. $C_8H_{16}FO_3P$ requires M, 210.0821); $\delta_H(CDCl_3)$ 1.37 (6 H, m), 1.49 (3 H, dd, $^3J_{FH}$ 24.6 Hz, $^3J_{Me\text{-}H}$ 5.2 Hz), 4.12 (4 H, m), 4.98 (1 H, ddd, $^3J_{1,2}$ 18.3 Hz, $^2J_{PH}$ 13.9 Hz, $^4J_{FH}$ 2.8 Hz, 1-H), 5.24 (1 H, dm, $^2J_{FH}$ 47.2 Hz, $^2J_{H\text{-}Me}$ 5.2 Hz), and 6.79 (1 H, dddd, $^3J_{FH}$ 22.2 Hz, $^3J_{2,1}$ 18.3 Hz, $^3J_{PH'}$ 16.7 Hz).

Diethyl (E)-*3-Fluoro-3-phenylprop-1-enylphosphonate* (**11**).—From diethyl 1-hydroxycinnamylphosphonate[5] (1.5 g, 5.5 mmol) and DAST (1.04 g, 0.8 ml, 6.5 mmol) using standard reaction and work-up conditions was obtained the *product* (**11**) as a viscous oil (0.89 g, 59.6%) (Found: M^+, 272.0975. $C_{13}H_{18}FO_3P$ requires M, 272.0978); $\delta_H(CDCl_3)$ 1.30 (6 H, t, ^3J = 7.1 Hz) 4.09 (4 H, m), 5.95 (1 H, dddd, $^2J_{FH}$ 46.6 Hz, $^3J_{3,2}$ 3.3 Hz, $^4J_{3,1}$ 3.5 Hz), 6.05 (1 H, dt, $^3J_{1,2}$ 18.42 Hz, $^2J_{PH'}$ 9 Hz, $^4J_{FH'}$ 1.4 Hz), 6.87 (1 H, dddd, $^3J_{PH'}$ 21.0 Hz, $^3J_{2,1}$ 18.42 Hz, $^3J_{FH}$ 16.6 Hz, $^3J_{2,3}$ 3.3 Hz), and 7.37 (5 H, m).

Attempted Preparation of Diethyl 1-Fluoro-1-methylethylphosphonate.—From diethyl 1-hydroxy-1-methylethylphosphonate[15] (2.0 g, 10.2 mmol) and DAST (1.69 g, 1.3 ml, 10.5 mmol) using standard reaction and work-up conditions was obtained diethyl propen-2-ylphosphonate as the sole product (1.4 g, 77.1%), b.p. 66 °C, 0.6 mmHg (lit.,[16] b.p. 64.5—65 °C, mmHg); $\delta_H(CDCl_3)$ 1.32 (6 H, m), 1.94 (3 H, d, $^3J_{PH}$ 16 Hz), 4.08 (4 H, m), 5.75 (1 H, d, $^3J_{PH}$ 44 Hz), and 5.96 (1 H, d, $^3J_{PH}$ 22 Hz).

α-Fluorobenzyl(diphenyl)phosphine Oxide (**12**).—From α-hydroxybenzyl(diphenyl)phosphine oxide[17] (2.7 g, 8.7 mmol) and DAST (1.43 g, 1.1 ml, 8.88 mmol) under standard reaction and work-up conditions was obtained the *product* (**12**) as a white crystalline solid (2.7 g, 99%), m.p. 169—171 °C (Found: C, 73.1; H, 5.4. $C_{19}H_{16}FOP$ requires C, 73.55; H, 5.16%); $\delta_H(CDCl_3)$ 6.28 (1 H, dd, $^2J_{FH}$ 44.4 Hz, $^2J_{PH}$ 3 Hz) and 7.20—7.90 (15 H, m); $\delta_P(CDCl_3)$ 23.5 (d, $^2J_{PF}$ 71.7 Hz).

α-Fluorobenzylphosphonic Acid Biscyclohexylammonium Salt (**13**).—To diethyl α-fluorobenzylphosphonate (2.0 g, 8.1 mmol) in anhydrous tetrachloromethane (10 ml) was added iodotrimethylsilane (3.37 g, 2.4 ml, 16.9 mmol) under dry nitrogen with vigorous stirring and external cooling. The mixture was stirred at room temperature for 0.5 h then the volatiles were removed under reduced pressure to yield the bis-silylester as a dark viscous oil. This was treated with methanol (5 ml) and cyclohexylamine (2.99 g, 2.05 ml, 30 mmol) with external cooling. The volatiles were removed under reduced pressure to yield a crude brown solid (2.3 g, 99%). The pure *product* was obtained on repeated recrystallisation from methanol (0.67 g, 21.3%), m.p. 196—198 °C (Found: C, 54.3; H, 7.45; N, 4.85. $C_{19}H_{34}FN_2O_3P$ requires C, 53.79; H, 7.32; N, 4.84%); $\delta_H(CD_3OD)$ 1.1—2.9 (22 H, m), 5.44 (1 H, dd, $^2J_{FH}$ 46.4 Hz, $^2J_{PH}$ 9.1 Hz), 7.27 (3 H, m), and 7.52 (2 H, d); $\delta_P(CD_3OD)$ 11.89 (d, $^2J_{PF}$ 79.35 Hz); pK_{a^2} = 6.50 ± 0.2.

α-Fluoro-4-methylbenzylphosphonic Acid Biscyclohexylammonium Salt (**14**).—From diethyl α-fluoro-4-methylbenzylphosphonate (1.7 g, 6.5 mmol), iodotrimethylsilane (2.76 g, 1.96 ml, 13.8 mmol), and cyclohexylamine (2.41 g, 1.65 ml, 24.2 mmol) under standard reaction and work-up conditions was obtained the *product* (**14**) as a white crystalline solid (0.45 g, 20.4%), m.p. 186—188 °C (Found: C, 59.85; H, 8.95; N, 6.95. $C_{20}H_{36}FN_2O_3P$ requires C, 59.70; H, 8.95; N, 6.97%); $\delta_H(CD_3OD)$ 1.10—2.90 (25 H, m), 5.39 (1 H, dd, $^2J_{FH}$ 50.2 Hz, $^2J_{PH}$ 9.3 Hz), 7.10 (2 H, d), and 7.41 (2 H, d); $\delta_P(CD_3OD)$ 9.78 (d, $^2J_{PF}$ 71.72 Hz); pK_{a^2} = 7.0 ± 0.2.

4-Chloro-α-fluorobenzylphosphonic Acid Biscyclohexylammonium Salt (**15**).—From diethyl 4-chloro-α-fluorobenzylphosphonate (0.5 g, 1.8 mmol), iodotrimethylsilane (0.74 g, 0.53 ml, 3.72 mmol), and cyclohexylamine (0.66 g, 0.45 ml, 6.6 mmol) under standard reaction and work-up conditions was obtained the *product* (**15**) (550 mg, 73%), m.p. 182—183 °C (Found: C, 54.1; H, 8.15; N, 6.45. $C_{19}H_{33}ClFN_2O_3P$ requires C, 53.96; H, 7.81; N, 6.63%); $\delta_H(CD_3OD)$ 1.10—2.90 (22 H, m), 7.30 (2 H, d,

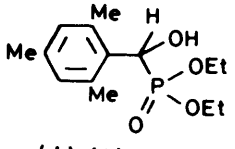
^3J 7.0 Hz), and 7.58 (2 H, br); $\delta_P(CD_3OD)$ 12.12 (d, $^2J_{PF}$ 77.8 Hz); pK_{a^2} = 6.91 ± 0.2.

Results and Discussion

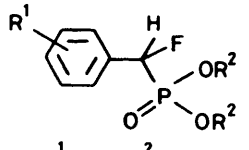
The requisite α-hydroxyphosphonate esters were conveniently prepared by the sodium methoxide-catalysed condensation of diethyl phosphite with a range of arylaldehydes,[9] aryl methyl ketones,[13] and α,β-unsaturated aldehydes,[5] and were routinely characterised by ^{1}H n.m.r. spectroscopy. The most sterically crowded of these species, the product (**1**) derived from mesitaldehyde, showed a marked magnetic non-equivalence of the ester methyl signals not observed for the other esters. The substitution of the α-hydroxy group by fluorine generally proceeded smoothly and efficiently by reaction with a small excess of diethylaminosulphur trifluoride (DAST) in methylene dichloride solution at sub-zero temperature [Equation (1)]. The

$$ArCH(OH)PO(OEt)_2 + Et_2NSF_3 \xrightarrow[CH_2Cl_2]{-78\,^\circ C \rightarrow 0\,^\circ C} ArCHFPO(OEt)_2 \quad (1)$$

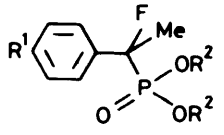
crude reaction mixtures were routinely examined by ^{1}H n.m.r. spectroscopy which showed a high conversion into the desired α-fluoroalkanephosphonate esters (**2**—**8**) for all of the benzylic



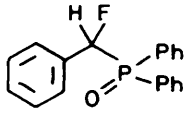
(±)-(**1**)



(**2**) R^1 = H; R^2 = Et
(**3**) R^1 = 4-Me; R^2 = Et
(**4**) R^1 = 3-Cl; R^2 = Et
(**5**) R^1 = 4-Cl; R^2 = Et
(**6**) R^1 = 2,4,6-Me_3; R^2 = Et
(**13**) R^1 = R^2 = H
(**14**) R^1 = 4-Me; R^2 = H
(**15**) R^1 = 4-Cl; R^2 = H



(**7**) R^1 = H; R^2 = Et
(**8**) R^1 = Cl; R^2 = Et



(**12**)

phosphonates with one exception. The reaction between DAST and diethyl α-hydroxy-4-methoxybenzylphosphonate failed to give any of the desired α-fluorophosphonate product while the ^{1}H n.m.r. spectrum of the crude reaction mixture showed the loss of the singlet due to the methoxy group. The α-fluorobenzylphosphonate esters were obtained as oils and adequately purified by bulb-to-bulb distillation under reduced pressure.

The three β,γ-unsaturated-α-hydroxyphosphonates obtained[5] from acrylaldehyde, crotonaldehyde, and cinnamaldehyde also reacted smoothly and efficiently with DAST. While the ^{1}H n.mr. spectra of the crude reaction mixtures showed a characteristic pattern of fluorine-coupled signals, detailed analysis of the purified products (**9**)—(**11**) showed that in each case the fluorine was located at C-3 of an α,β-unsaturated phosphonate ester having the *E*-configuration for the alkene. This conclusion was confirmed by examination of the proton-decoupled ^{31}P n.m.r. spectra of the three esters (**9**)—(**11**), each of which was a singlet devoid of the large coupling ($^2J_{PF}$ *ca.* 85 Hz) characteristic of α-fluorophosphonates.

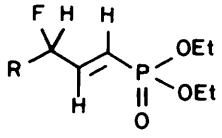
In an attempt to extend the generality of the fluorination process to alkanephosphonate esters, diethyl 1-hydroxy-1-methylethylphosphonate (**16**) was treated with DAST as before. N.m.r. analysis of the crude reaction mixture revealed none of the desired fluorination product and showed a high conversion of (**16**) into its dehydration product, diethyl propen-2-ylphosphonate (**17**) [Equation (2)].

$$Me_2C(OH)P(O)(OEt)_2 \xrightarrow[77\%]{DAST} CH_2{=}CMeP(O)(OEt)_2 \quad (1)$$
(**16**) (**17**)

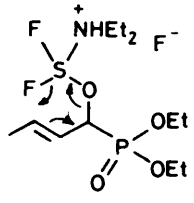
Finally, to explore the wider applicability of this method of synthesis of fluorine compounds as potential Wittig reagents for fluoro-olefination,[18] α-hydroxybenzyl(diphenyl)phosphine oxide [17] was smoothly and quantitatively converted by treatment with DAST into α-fluorobenzyl(diphenyl)phosphine oxide (**12**).

In all of these experiments, the phosphonate ester function proved to be inert towards DAST at temperatures up to 80 °C. Nonetheless, routine precautions were observed in case of formation of any potentially toxic phosphonofluoridate material. In order to probe the mechanism of the transformation [Equation (1)], the trimethylsilyl ethers obtained by the addition of diethyl trimethylsilyl phosphite to benzaldehyde, acetone, and acetophenone[19] were treated with DAST as before. In all cases, the starting silyl ethers were recovered quantitatively.

Taken together, all of the above information indicates that DAST reacts initially with the α-hydroxy group to generate a sulpho ester. The absence of steric hindrance, the facile dehydration of compound (**16**), and the perceived demethyl-



(**9**) R = H
(**10**) R = Me
(**11**) R = Ph



(**16**)

ation of the anisaldehyde-derived phosphonate all indicate a subsequent displacement process with a large measure of carbocation character. A thorough investigation of the solvolyses of the methanesulphonates of four α-hydroxyphosphonates, giving results very much in line with those of the present study, has led Creary[20] to conclude that the diethyl phosphoryl substituent, $-PO(OEt)_2$, has a stabilising effect on an adjacent cation, despite its generally recognised electron-withdrawing character, which is associated with a σ_p value[21] of +0.52. In this context it is noteworthy that recent MO calculations[22] have suggested considerable contribution to the order of the phosphoryl bond from a *triple* bond, $\bar{P}{\equiv}\overset{+}{O}$. This could well populate d orbitals capable of energetically favourable overlap with the vacant orbital of an adjacent carbocation, $\overset{+}{C}{-}\bar{P}{\equiv}\overset{+}{O}$.

The formation of the γ-fluorophosphonates (**9**)—(**11**) involves a rearrangement that could, in principle, involve any of three mechanisms: (i) an S_N2' process, (ii) electrocyclic rearrangement of an intermediate ester (**16**), or (iii) formation of an allyl cation followed by capture of fluoride. The complete absence of any α-fluorination product, especially for the

Table 1. Second dissociation constants for some phosphonic acids and related phosphate aryl monoesters

Compound	pK_{a^2}
$4\text{-}ClC_6H_4OPO_3H_2$	6.10 ± 0.2
$PhOPO_3H_2$	6.20 ± 0.2
$PhCHFPO_3H_2$	6.50 ± 0.2
$3\text{-}ClC_6H_4CHFPO_3H_2$	6.86 ± 0.2
$4\text{-}MeC_6H_4CHFPO_3H_2$	6.99 ± 0.2
$4\text{-}ClC_6H_4CHFPO_3H_2$	6.91 ± 0.2
$PhCH_2PO_3H_2$	7.60 ± 0.2

cinnamaldehyde-derived phosphonate, argues against the last of these possibilities. A correct choice might only finally be made through investigation of the stereoselectivity of the formation of compounds (**10**) and (**11**) from chiral precursors.

In a number of cases, the diethyl α-fluoroalkylphosphonates (**2**), (**3**), and (**5**) were converted into the biscyclohexylammonium salts of the corresponding phosphonic acids (**13**)—(**15**) by the well established trans-esterification procedure using iodotrimethylsilane[23] followed by methanolysis of the bistrimethylsilyl ester. While ^1H n.m.r. monitoring showed the transformation to be quantitative, isolated yields of the crystalline products were only modest.

The effectiveness of the CHF group as an isosteric and isoelectronic replacement for the ester oxygen in phospho monoesters, $ROPO_3H_2$, relative to the weakly electronegative CH_2 group can be assessed by reference to three physical characteristics of the α-fluoro phosphonates and their esters: (i) the acidity of the second dissociation constant, pK_{a^2}; (ii) the i.r. frequency for stretching the P=O bond; and (iii) the ^{31}P n.m.r. chemical shift.

Values for pK_{a^2} for the acids (**13**)—(**15**) were obtained by potentiometric titration and are compared with those for standard phosphonic acids* and for phenyl phosphate[24] (Table 1). It is evident that α-fluorination has markedly shifted the second dissociation constant of the alkanephosphonates closer to that of phenyl phosphate though a significant difference remains. Clearly, it can be anticipated that the α,α-difluoroalkylphosphonates should have acidities very similar to those of the corresponding phosphate monoesters.

The phosphoryl group stretching frequencies for the α-fluoroalkylphosphonates fall into a narrow band about halfway between those of diethyl phenyl phosphate and of diethyl benzylphosphonate (Table 2). Taking the average of the five values and applying the formula [Equation (3)] devised by Thomas[25] to give phosphorus inductive constants, π, for substituents at a phosphonyl centre gives a value of 2.7(3) for the (Ar)CHF group.

$$\nu_{P=O} = 930 + 40\Sigma\pi \text{ cm}^{-1} \quad (3)$$

This value compares to those[26] for MeO of 2.9, PhO of 3.0, $ArCH_2$ of 2.5, and Me of 2.1. Without going more deeply into the validity of this treatment, it is evident that monofluorination has not wholly raised the P=O stretching frequency to that of phosphate triesters, which suggests that difluorination might be a more advantageous pattern of substitution for mimicry of phosphate esters.

Finally, the ^{31}P chemical shift, a complex parameter influenced by several diverse factors,[27] does exhibit an approximately linear relationship between chemical shift for $XPO(OEt)_2$ and the electronegativity of first (and some second) row elements X. One can note three features of the phosphorus

* Measured using samples provided by Mr. D. Ingleson.

Table 2. I.r. and ^{31}P n.m.r. data for some dialkyl phosphonates and related dialkyl aryl phosphate esters.

Ester	$\nu_{P=O}(cm^{-1})^a$	$\delta^{31}P$(p.p.m.)^b	$^2J_{PF}$ (Hz)
$PhOPO(OEt)_2$	1 275	+6.8	
$PhCHFPO(OEt)_2$ (**2**)	1 266	+14.71	85.5
$4\text{-}MeC_6H_4CHFPO(OEt)_2$ (**3**)	1 261	+16.00	87.0
$3\text{-}ClC_6H_4CHFPO(OEt)_2$ (**4**)	1 264	+14.10	82.4
$4\text{-}ClC_6H_4CHFPO(OEt)_2$ (**5**)	1 263	+15.14	83.1
$2,4,6\text{-}Me_3C_6H_2CHFPO(OEt)_2$ (**6**)	1 265	+16.2	86.0
$PhCFMePO(OEt)_2$ (**7**)	1 260	+17.43	87.4
$4\text{-}ClC_6H_4CFMePO(OEt)_2$ (**8**)	1 261	+17.81	87.0
(*E*)-$CH_2FCH{=}CHPO(OEt)_2$ (**9**)	1 252	+16.92	0
(*E*)-$MeCHFCH{=}CHPO(OEt)_2$ (**10**)	1 250	+17.26	0
(*E*)-$PhCHFCH{=}CHPO(OEt)_2$ (**11**)	1 243	+16.62	0
$PhCH_2PO(OEt)_2$	1 254	+27.06	

^{a} Liquid film. ^{b} $CDCl_3$ Solution.

chemical shifts of the phosphonate esters under study. Firstly, α-fluorine substitution effects an upfield shift in the phosphorus resonance to a position roughly halfway between that for phosphate triesters and for dialkyl alkylphosphonates (Table 2). Secondly, additional methyl substitution at the α-carbon atom, as in compounds (**7**) and (**8**), causes a second-order downfield shift which may reflect changes in bond-angles consequent on the steric crowding close to phosphorus. Lastly, the α,β-unsaturated phosphonates, (**9**)—(**11**), also show an upfield shift, possibly suggestive of phosphorus d orbital interaction with the π-system.

The considerations outlined in the introduction give support to the idea that α-fluorination of alkylphosphonates should give compounds whose properties suitably resemble those of the corresponding phosphate esters. The experimental evidence here presented fully validates this concept, but also shows that at a quantitative level the physical measurements differ significantly from those of the corresponding phosphates. It would therefore appear that the introduction of a second α-fluorine substituent should provide better analogues of biological phosphate esters whilst retaining the desired resistance to phosphonyl transfer processes.

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