

Synthesis, Mechanism of Formation and Insecticidal Activity of Novel Fluorinated Organophosphorus Compounds

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The major products of the interaction between triethyl phosphite and 3-fluoropropanoyl chloride at room temperature are diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enylphosphonate (**3**) and diethyl 1-(diethoxyphosphoryl)-3-fluoropropyl phosphate (**4**). The compounds **3** and **4** were separated by chromatography, and structurally characterized by elemental analysis, NMR spectroscopy (¹H, ¹³C, ¹⁹F and ³¹P) and mass spectrometry. Possible reaction mechanisms are proposed. The major products **3** and **4** were tested for insecticidal activity. **3** gave 100% control of *Musca domestica* L. and *Phaedon cochledriae* Fab. at a dose of 20 µg/per insect.

Keywords synthesis, reaction mechanism, insecticidal activity, fluorinated organophosphonate

Introduction

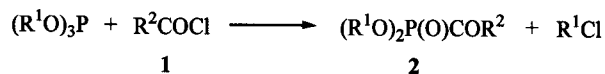
Organophosphorus compounds are widely used as insecticides, herbicides and fungicides. In view of the possible influence of fluorine substitution on the biological activity of organophosphorus compounds we have turned our attention to the study of the synthesis and biological activity of fluorinated organophosphorus compounds.

In the course of investigation on the fungicidal activity of guanidine derivatives, including the *N*-(ω -guanidinoalkyl) aminoalkanephosphonic acids and their amino-phosphonic precursors, Hudson *et al.* found that certain members of the α -aminoalkanephosphonic acids showed the best activity and were patented as agricultural fungicides, especially as seed-dressing agents.¹ Of these compounds, α -aminopropanephosphonic acid is the most active and is now listed under the name ampropylfos as an available alternative to organomercury compounds for the

control of covered smut, loose smut in oats.² In view of the influence of fluorine substitution on the fungicidal activity of α -aminoalkanephosphonic acid, we attempted the preparation of fluorinated α -aminopropanephosphonic acid via diethyl 3-fluoropropanoylphosphonate (Scheme 1, R¹ = Et, R² = FCH₂CH₂) (**2**).³ The latter was a key intermediate in the formation of the corresponding oxime and thence, by reduction and hydrolysis, fluorinated α -aminopropanephosphonic acid. Examination of the total initial products obtained from triethyl phosphite and 3-fluoropropanoyl chloride showed, however, that the major components of the mixture were diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enylphosphonate (**3**) and diethyl 1-(diethoxyphosphoryl)-3-fluoropropyl phosphate (**4**).

In this paper, the preparation, mechanism, spectroscopy and insecticidal activity of novel fluorinated organophosphorus compounds obtained from the interaction between triethyl phosphite and 3-fluoropropanoyl chloride are reported.

Scheme 1



Results and discussion

Preparation of organophosphorus compounds **3** and **4**

Trialkyl phosphites enter readily into the Michaelis-

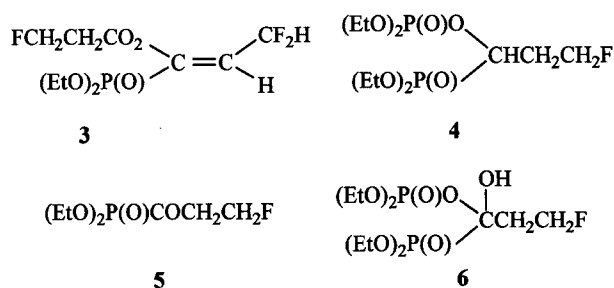
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Arbuzov reaction with acyl chlorides (**1**) at room temperature or below, to give the corresponding dialkyl acylphosphonates (Scheme 1) (**2**).^{4,5} Examination of the total initial products obtained from triethyl phosphite and 3-fluoropropanoyl chloride by ³¹P NMR spectroscopy showed, however, that the major components of the mixture (*ca.* 25 mol% of each) were the reaction products (Scheme 2) **3** (δ_{P} 7.2) and **4** (δ_{P} 19.7, -0.6 , J_{PP} 20 Hz). Diethyl 3-fluoropropanoylphosphonate (**5**) (δ_{P} -2.9) was also present (*ca.* 20 mol%), together with minor amounts (*ca.* 3–5 mol%) of triethyl phosphate (δ_{P} -3.0), diethyl phosphite (δ_{P} 7.9) and a further by-product (δ_{P} 19.8), which is tentatively assigned as α -hydroxy-1,1-bis(phosphonate) (**6**). Other (unidentified amounted up to *ca.* 15%) phosphorus-containing compounds were also present. The initial products were complicated and the volatile by-products were firstly removed at reduced pressure and then the residue was subjected to column chromatography to give **3** and **4**.

Scheme 2



Characterization of organophosphorus compounds **3** and **4**

¹H and ¹³C NMR data for both **3** and **4** are described in the experimental section. The ³¹P NMR chemical shifts are for **3** (δ_{P} 7.9) and **4** (δ_{P} 19.7, -0.6 , J_{PP} 20 Hz). ¹⁹F NMR signals appear at δ -52.36 , -56.72 for **3**, and δ -54.93 for **4**. Assignment of (*E*)-stereochemistry to the product **3** can be made on the basis of the magnitude of the coupling observed between phosphorus and the *cis*-related vinylic proton ($^3J_{\text{PH}}$ *ca.* 11 Hz), which is within the range established for *cis*-coupling in vinylphosphonates ($^3J_{\text{PH}}$ 10–30 Hz).⁶ A considerably higher value ($^3J_{\text{PH}}$ 30–50 Hz) would be expected if the phosphorus and vinylic proton bore a *trans*-relationship to each other.⁶ Further confirmation of (*E*)-configuration in the

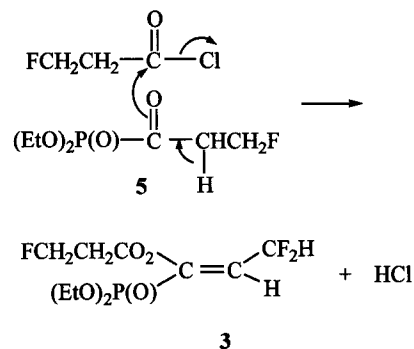
product **3** is given by the magnitude of coupling between the allylic fluorine atom and phosphorus ($^4J_{\text{PF}}$ *ca.* 1 Hz), which is similar to that in other related phosphonates.⁷ None of the (*Z*)-isomer was detectable by NMR spectroscopy.

The positive-ion fast atom bombardment mass spectra of compounds **3** and **4** gave characteristic pseudomolecular ions, $[\text{MH}]^+$, which appear as the base peak for **4**, and with a relative intensity of 89.5% for **3**.

Reaction mechanism

The formation of diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enylphosphonate (**3**) is most reasonably explained (Scheme 3) by assuming relatively fast electrophilic attack by a second molecule of acyl halide on the carbonyl oxygen atom of the first-formed acylphosphonate **5** and the loss of a proton from the α -methylene group of the latter. The only previous reference to acylations of this type⁸ reported the formation of 1-acyloxyvinylphosphonates from dialkylacylphosphonate and acyl chlorides in the presence of triethylamine, the latter being assumed to generate the enolate anion of the acylphosphonate as a reactive intermediate. Deprotonation of the methylene group of 3-fluoro derivative (**5**) clearly occurs in the absence of added base and is likely to be favoured by the combined electron-attracting effects of the adjacent fluoromethyl and carbonyl groups.

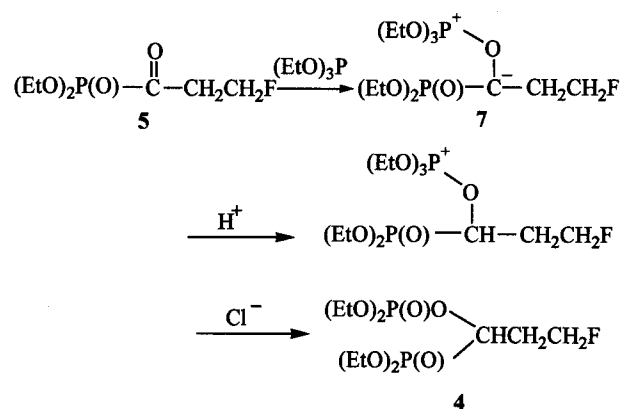
Scheme 3



The formation of diethyl 1-(diethoxyphosphoryl)-3-fluoropropyl phosphate (**4**) can be assumed to occur (Scheme 4) via nucleophilic attack of a second molecule of phosphite on the carbonyl group of the acylphosphonate **5** to give a carbanion **7**, followed by protonation and

dealkylation. A source of acid is available from the elimination reaction leading to the formation of the 1-acyloxypropenylphosphonate (**3**) (Scheme 3), and is a prerequisite for the reaction shown in Scheme 4 to occur. The presence of a trace of adventitious moisture cannot be totally excluded, but water alone does not appear to be sufficient to promote this type of reaction. Analogous products have, however, been obtained in the reaction of trialkyl phosphites with acyl chlorides in the presence of added proton donors, *e. g.*, alcohols or carboxylic acids,^{9,10} and in the reaction of trimethyl or triethyl phosphite with perfluoroacyl chlorides in THF at -78°C , followed by quenching with methanol.¹¹ In each case a carbanion intermediate was assumed to be formed and to be trapped by the protic reagent.

Scheme 4



The formation of hydrogen chloride (Scheme 3) may also be expected to lead to dealkylation of triethyl phosphite to give diethyl phosphite,¹² which can itself undergo addition reaction with an acylphosphonate to give the corresponding α -hydroxy-1,1-bis(phosphonate)¹³ (in this case, compound **6**).

In conclusion, the present results exemplify a novel interdependence between two types of reaction that can occur between trialkyl phosphites and acyl chlorides, one occurring in the molecular ratio of 1:2 and normally requiring the presence of tertiary base, and the other occurring in the molecular ratio of 2:1, and requiring the presence of a proton donor. The critical factor in the overall course of reaction in the present case appears to be the presence of fluorine in the 3-position of the propanoyl chain and the consequent ease with which the acylated

propenylphosphonate **3** is formed, making hydrogen chloride available in the reaction system (Scheme 3).

Insecticidal activity

Activity against *Musca domestica* L. (housefly) and *Phaedon cochledriae* Fab. (mustard beetle) was assessed by topical application of solutions of the compounds in acetone. The results showed that at $20\ \mu\text{g}$ per insect, diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enylphosphonate (**3**) gave 100% control of both species (LD_{50} for mustard beetle = $5.0\ \mu\text{g}$ per insect). Diethyl 1-(diethoxyphosphoryl)-3-fluoropropyl phosphate (**4**) was less active, giving 8% and 25% control only of these two species, respectively, at the same rate of application (8% in housefly is equivalent to control mortality). Whereas vinyl phosphates are known to be active insecticides,¹⁴ it is surprising to observe activity in a vinylphosphonate such as compound **3**, which does not possess an obviously suitable leaving group for it to be an acetylcholinesterase inhibitor. The reason for activity in **3** is as yet uncertain but the possibility of molecular rearrangement in which P—C is replaced by P—O should be considered.

Experimental

Starting materials

3-Chloropropan-1-ol and triethyl phosphite were obtained from Aldrich. The 3-chloropropan-1-ol was converted successively, by described procedures, into 3-fluoropropan-1-ol, 3-fluoropropanoic acid¹³ and 3-fluoropropanoyl chloride, b. p. $51\text{--}52^{\circ}\text{C}$ at $8.93 \times 10^3\ \text{Pa}$ (lit.¹⁵ b. p. 52°C at $9.33 \times 10^3\ \text{Pa}$).

Spectroscopy and instrumentation

NMR spectra were recorded on a Bruker AM250 instrument for solutions in CDCl_3 . Chemical shifts are in ppm downfield from TMS (^1H and ^{13}C spectra), C_6F_6 (^{19}F spectra), and 85% H_3PO_4 (external reference, ^{31}P spectra). Mass spectra were obtained on a Kratos Profile instrument, using a glycerol matrix and with a Cs^+ ion gun operating at 10 kV. Microanalyses were carried out with a Carlo Erba 1106 elemental analyzer.

Reaction of 3-fluoropropanoyl chloride with triethyl phosphite

3-Fluoropropanoyl chloride (11.3 g, 0.10 mol) was added dropwise, under nitrogen, to triethyl phosphite (17.0 g, 0.1 mol) at 0—5 °C with vigorous stirring. Stirring was continued overnight at room temperature and volatile products were then removed at 66.6 Pa. The colourless liquid residue was subjected to column chromatography on silica gel, with a mixture of ethyl acetate and light petroleum (1:3, *V*:*V*) as eluant, to give a main fraction which was concentrated and dried over anhydrous magnesium sulphate to give diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enyl-phosphonate (**3**) (6.0 g, 59.2%); ¹H NMR (CDCl₃, 250 MHz) δ: 1.34 (t, *J* = 7.06 Hz, 6H), 2.89 (dt, *J* = 5.72, 25.43 Hz, 2H), 4.06—4.23 (m, 4H), 4.76 (dt, *J* = 5.73, 46.35 Hz, 2H), 4.95 (ddd, *J* = 3.10, 5.40, 46.34 Hz, 2H), 6.61 (overlapping ddt, *J* = 5.4, 11.00, 16.05 Hz, 1H); ¹³C NMR (CDCl₃, 63 MHz) δ: 16.10 (d, *J* = 6.67 Hz), 35.18 (d, *J* = 22.77 Hz), 63.15 (d, *J* = 5.03 Hz), 77.39 (dd, *J* = 15.16, 165.01 Hz), 78.77 (d, *J* = 168.62 Hz), 131.52 (dd, *J* = 24.84, 22.08 Hz), 139.89 (dd, *J* = 226.99, 10.00 Hz), 166.99 (s); ¹⁹F NMR (CDCl₃, 235 MHz) δ: -52.36 (d, *J* = 0.59 Hz), -56.72 (d, *J* = 0.71 Hz); ³¹P NMR (CDCl₃, 101 MHz) δ: 7.20 (d, *J* = 1.16 Hz); MS *m/z* (%): 287 ([MH]⁺, 89.5). Anal. calcd for C₁₀H₁₇F₂O₆P: C 42.0, H 5.9; found C 41.7, H 5.8.

Further elution from the column with methanol gave a second (crude) product which was purified by chromatography on alumina, using ethyl acetate/light petroleum (2:1, *V*:*V*), to give diethyl 1-(diethoxyphosphinyloxy)-3-fluoropropyl phosphonate (**4**) (3.89 g, 33.3%). ¹H NMR (CDCl₃, 250 MHz) δ: 1.20—1.40 (m, 12H), 2.04—2.48 (m, 2H), 4.08—4.30 (m, 8H), 4.65 (m, *J* = 47.14 Hz, 2H), overlapping with 4.71—4.86 (m, 1H); ¹³C NMR (CDCl₃, 63 MHz) δ: 16.08 (d, *J* = 6.98 Hz), 16.05 (d, *J* = 7.09 Hz), 16.43 (d, *J* = 5.75 Hz), 16.48 (d, *J* = 5.64 Hz), 32.09 (dd, *J* = 21.01, 2.53 Hz), 63.15 (d, *J* = 7.14 Hz), 63.18 (d, *J* = 6.29 Hz), 64.30 (d, *J* = 5.92 Hz), 64.33 (d, *J* = 5.91 Hz), 69.06 (ddd, *J* = 172.79, 5.09, 7.16 Hz), 79.38 (dd, *J* = 166.57, 12.12 Hz); ¹⁹F NMR (CDCl₃, 235 MHz) δ: -54.93 (d, *J* = 1.61 Hz); ³¹P NMR (CDCl₃, 101

MHz) δ: 19.68 (d, *J* = 20.34 Hz), -0.60 (d, *J* = 21.29 Hz); MS *m/z* (%): 351 ([MH]⁺, 100). Anal. calcd for C₁₁H₂₅FO₇P: C 37.72, H 7.19; found C 37.86, H 7.19.

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