Interaction of triethyl phosphite with 3-fluoropropanoyl chloride: the concurrent formation of 1:2 and 2:1 reaction products

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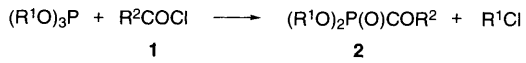
The major products of the interaction between triethyl phosphite and 3-fluoropropanoyl chloride at room temperature are diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enylphosphonate 3 and diethyl 1-(diethoxyphosphoryl)-3-fluoropropyl phosphate 4, which result from concurrent 1:2 and 2:1 reactions, respectively.

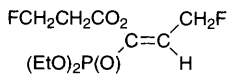
Trialkyl phosphites enter readily into the Michaelis–Arbuzov reaction with acyl chlorides **1** (R^2 = alkyl, aryl) at room temperature or below,[1] to give the corresponding dialkyl acylphosphonates **2** (Scheme 1).[2,3] The latter are useful intermediates in the formation of the corresponding oximes[4] and thence, by reduction, α-aminoalkylphosphonates.[4–7] Acylphosphonates and their derivatives have also attracted interest as biologically active molecules[3] and the oximes as chelating agents for transition[8–11] and lanthanide[12] metals. In view of the possible influence of fluorine substitution on the biological activity and complexing properties of molecules of these types we have turned our attention to methods for the preparation of fluorinated derivatives, and have recently reported a series of α-aminoarylmethylphosphonic acids with a range of fluoro, fluoroalkyl and fluoroalkoxy substituents in the aromatic ring.[13]

In the course of investigations into methods for the preparation of fluorinated aliphatic derivatives, we attempted the preparation of diethyl 3-fluoropropanoylphosphonate **2** (Scheme 1; R^1 = Et, R^2 = FCH_2CH_2) by mixing equimolar quantities of triethyl phosphite and 3-fluoropropanoyl chloride (no solvent) under dry nitrogen at 0–5 °C, followed by stirring of the mixture overnight at room temperature. We have generally found this procedure to give good yields of the desired products (*e.g.* 70–90%, after distillation) in the preparations of unsubstituted dialkyl acylphosphonates.[14] Examination of the total initial products obtained from triethyl phosphite and 3-fluoropropanoyl chloride by ^{31}P NMR spectroscopy showed, however, that the major components of the mixture (*ca.* 25 mol% of each) were the 2:1 and 1:2 reaction products **3** (δ_P 7.2) and **4** (δ_P 19.7, −0.6, J_{PP} 20 Hz), respectively. Diethyl 3-fluoropropanoylphosphonate **5** (δ_P −2.9) was also present (*ca.* 20 mol%), together with minor amounts (*ca.* 3–5 mol% each) of triethyl phosphate (δ_P −0.3), diethyl phosphite (δ_P 7.9) and a further by-product (δ_P 19.8) which is tentatively assigned as the α-hydroxy-1,1-bis(phosphonate) **6**. About 15 mol% of other, unidentified phosphorus-containing compounds were also present. The major products **3** and **4** were separated by column chromatography, and were characterised by elemental analysis, NMR spectroscopy (^1H, ^{13}C, ^{19}F and ^{31}P) and mass spectrometry.



1 **2**

Scheme 1



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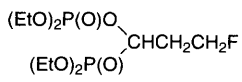

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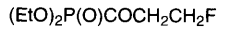

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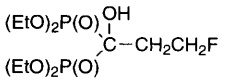
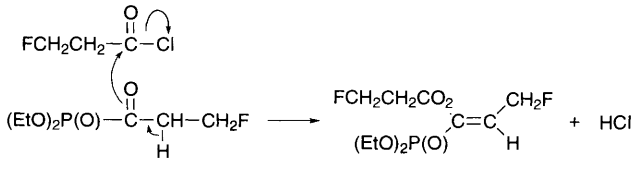


6

The formation of diethyl (*E*)-1-(3-fluoropropanoyloxy)-3-fluoroprop-1-enylphosphonate **3** is most reasonably explained (Scheme 2) 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 type[15] reports the formation of 1-acyloxylvinylphosphonates from dialkyl acetylphosphonates 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 the 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. Assignment of (*E*)-stereochemistry to the elimination product **3** can be made on the basis of the magnitude of the coupling observed between phosphorus and the *cis*-related vinylic proton ($^3J_{PH}$ *ca.* 11 Hz), which is within the range established for *cis*-coupling in vinylphosphonates ($^3J_{PH}$ 10–30 Hz).[16] A considerably higher value ($^3J_{PH}$ 30–50 Hz) would be expected if the phosphorus and vinylic proton bore a *trans*-relationship to each other.[16] Further confirmation of (*E*)-configuration in the product **3** is given by the magnitude of coupling between the allylic fluorine atom and phosphorus ($^4J_{PF}$ *ca.* 1 Hz), which is similar to that in other related phosphonates.[17] None of the (*Z*)-isomer was detectable by NMR spectroscopy.

The formation of diethyl 1-(diethoxyphosphoryl)-3-fluoropropyl phosphate **4** can be assumed to occur (Scheme 3) *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 2), and is a prerequisite for the reaction shown in Scheme 3 to occur. The presence of traces of adventitious moisture cannot be totally excluded, but water alone does not appear to be sufficient to promote this type of reaction since we have found no evidence for the formation of 2:1 reaction products in the preparations of



5 **3**

Scheme 2

unsubstituted dialkyl acylphosphonates by standard procedures.[14] Analogous products have, however, been obtained in the reactions of trialkyl phosphites with aroyl chlorides in the presence of added proton donors, *e.g.* alcohols or carboxylic acids,[18,19] and in the reactions of trimethyl or triethyl phosphite with perfluoroacyl chlorides in THF at −78 °C, followed by quenching with water–methanol.[20] In each case a carbanion intermediate was assumed to be formed and to be trapped by the protic reagent.

The formation of hydrogen chloride (Scheme 2) may also be expected to lead to dealkylation of triethyl phosphite to give diethyl phosphite,[21] which can itself undergo addition with an acylphosphonate to give the corresponding α-hydroxy-1,1-bis(phosphonate)[22] (in this case, compound **6**). As mentioned above, the presence of a minor amount of this by-product was indicated by a signal (δ_P 19.8) in the ^{31}P NMR spectrum of the total initial product.

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 a 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 2).

The generality of these types of reaction is now under investigation, together with a more detailed study of the reaction mechanisms involved.

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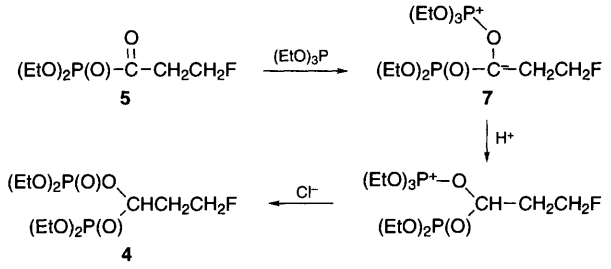

Scheme 3

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