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# Reaction of N,N-disubstituted perfluoroalkanethioamides with trialkyl phosphites. A new method for the synthesis of polyfluorinated α-aminophosphonates

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ABSTRACT

The first examples of the reactions of perfluoroalkanethiocarboxylic acid amides and trialkyl phosphites are presented. The reactions are shown to be dependent on the perfluoroalkyl chain length and the presence of proton-donating reagents. New fluorinated α-aminophosphonate derivatives are obtained in moderate to good yields.



The reactivity of thiocarbonyl compounds with nucleophiles is characterized by the duality between carbophilic and thiophilic reactions.[1] Studies on the reactivity of their fluorinated analogs have shown that the presence of electron-withdrawing perfluoroalkyl groups adjacent to the thiocarbonyl function enhances their electrophilicity and favors the thiophilic addition of nucleophiles.[2–5]

Alkyl perfluorodithiocarboxylates react with alkyllithium and Grignard reagents via thiophilic addition/fluoride elimination sequences to give perfluoroketene dithioacetals in good yields.[2] The reaction of perfluoroalkanethiocarboxylic acid amides with alkyllithium reagents proceeds in the same manner affording perfluoroketene-*N*,*S*-acetals.[3] Fluorinated thiocarbonyl compounds also react with *S*-nucleophiles. The thiophilic addition of a bisulfite ion to hexafluorothioacetone and trifluoromethyl trifluorodithioacetate gives Bunte salts.[4] The reaction of methyl trifluorodithioacetate with *tert*-butyl thiol in the presence of a catalytic amount of base leads to the trifluoroethane dithioacetal disulfide resulting from the thiophilic attack.[5] It has been reported that the reaction of hexafluorothioacetone and methyl trifluorodithioacetate with trialkyl phosphites gives rise to the corresponding phosphonium ylides.[4,5] Although the reactions of various thiocarbonyl compounds, both nonfluorinated and fluorinated, with phosphites have been described,[6] thus far, there have been no studies involving thioamides.

Herein we report the first examples of the reaction between fluorine-containing thioamides and trialkyl phosphites.

Initially, the reaction of perfluorothioamide **1a** with triethyl phosphite was examined. Heating a mixture of thioamide **1a** (1 equiv) and triethyl phosphite (2 equiv) at 100 °C for 2 h led to the formation of fluorophosphorane **2** (Scheme 1).[7]

Compound **2** was isolated by fractional distillation in vacuo in 67% yield. The spectroscopic data were consistent with the proposed structure.[8] In the $^{19}F$ NMR spectrum of **2** the fluorine atom attached to the phosphorus atom appeared as a doublet at −30.4 ppm with a coupling constant ($^1J_{F,P}$) of 840.0 Hz. The corresponding doublet with the same coupling constant was observed in the $^{31}P$ NMR spectrum at −55.5 ppm. Fluorophosphorane **2** spontaneously transformed into phosphonate **3a** at room temperature over one week. This transformation was also accomplished by thermolysis of **2** at 150 °C for 0.5 h or by treatment with water in 1,4-dioxane at room temperature (Scheme 1).

Phosphonate **3a** could also be prepared by the treatment of thioamide **1a** (1 equiv) with triethyl phosphite (3 equiv) at 150 °C for 5 h without the isolation of the intermediate fluorophosphorane **2** (Scheme 2).[9] Fractional distillation of the crude mixture gave phosphonate **3a**[10] in 74% yield (Table 1, entry 1). The scope of this reaction was then extended to other trialkyl phosphites and thioamides bearing different perfluoroalkyl substituents ($CF_3$, $C_2F_5$). Applying the conditions described above, novel fluorinated vinyl phosphonates **3a–e** were synthesized for the first time in moderate to good yields (Table 1).

The formation of compounds **3a–e** proved to be stereoselective, only one set of signals was observed in the $^{19}F$ and $^{31}P$ NMR spectra

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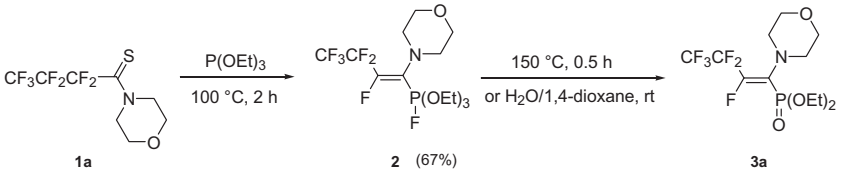
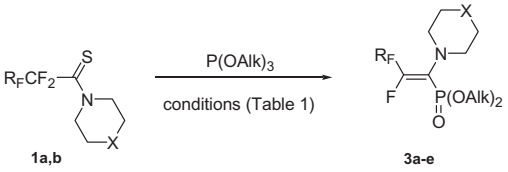
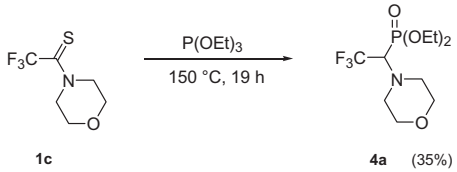



**Scheme 1.** Reaction of thioamide **1a** with triethyl phosphite.




**Scheme 2.** Synthesis of phosphonates **3a**–**e**.

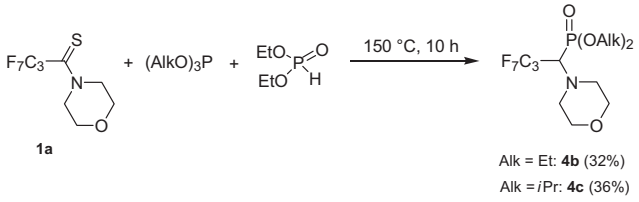



**Scheme 3.** Reaction of thioamide **1c** with triethyl phosphite.

of each compound. The stereochemistry of vinyl phosphonates **3a**–**e** was determined on the basis of the vicinal $^{13}C$–$^{31}P$ coupling constant (Fig. 1). It is recognized that for various vinyl phosphonates the $^{3}J_{C1-P}$ coupling constant is generally smaller than $^{3}J_{C2-P}$ in $^{13}C$ NMR spectra (6–8 and 20–25 Hz, respectively).[11] Therefore, the large coupling constant $^{3}J_{C-P}$ (17.1 Hz) shows that the $CF_3$ group is trans relative to the phosphorus atom in **3d**. The stereochemistry of compounds **3a**–**c,e** was assigned on the basis of $^{3}J_{P,F}$ coupling constants in comparison with those of vinyl phosphonate **3d**.

In contrast to thioamides **1a,b**, the reaction of the trifluoromethyl derivative **1c** and triethyl phosphite proceeded without elimination of a fluoride ion to give the saturated phosphonate **4a**[12] (Scheme 3). It should be noted that this reaction required a longer period of heating (19 h at 150 °C) and excess phosphite (9 equiv).

The preparation of saturated phosphonates with longer perfluoroalkyl substituents was performed by adding proton-donating diethyl phosphonate. It was found that heating a mixture of thioamide **1a** (1 equiv), triethyl phosphite (3 equiv), or triisopropyl phosphite (3 equiv) and diethyl phosphonate (2 equiv) at 150 °C for 10 h afforded the corresponding phosphonates **4b,c** which were isolated by fractional distillation in vacuo (Scheme 4).




**Scheme 4.** Synthesis of phosphonates **4b**,**c**.

It is worth noting that compounds **4a–c** are new fluorinated phosphonate derivatives bearing an *N*,*N*-dialkylamino group.

The results obtained allow us to propose the following reaction mechanism (Scheme 5). Thiophilic attack on the thioamide by the trialkyl phosphite results in formation of zwitterion **5**, which can undergo transformation via two pathways. Elimination of trialkyl thiophosphate from **5** gives carbene **6** (Path A). The reaction of **6**

**Table 1**
Reactions of thioamides **1a**,**b** with trialkyl phosphites

| Entry | Substrate | $R_F$ | X | Alk | Temp (°C) | Time (h) | Product (yield)[a] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | $C_2F_5$ | O | Et | 150 | 5 | **3a** (74%) |
| 2 | **1a** | $C_2F_5$ | O | Me | 100[b] | 11 | **3b** (46%) |
| 3 | **1a** | $C_2F_5$ | O | *i*Pr | 150 | 8 | **3c** (60%) |
| 4 | **1b** | $CF_3$ | $CH_2$ | Et | 150 | 7 | **3d** (48%) |
| 5 | **1b** | $CF_3$ | $CH_2$ | *i*Pr | 150 | 8 | **3e** (45%) |

[a] Isolated yield.
[b] Reaction carried out at 100 °C since trimethyl phosphite is not stable at 150 °C.

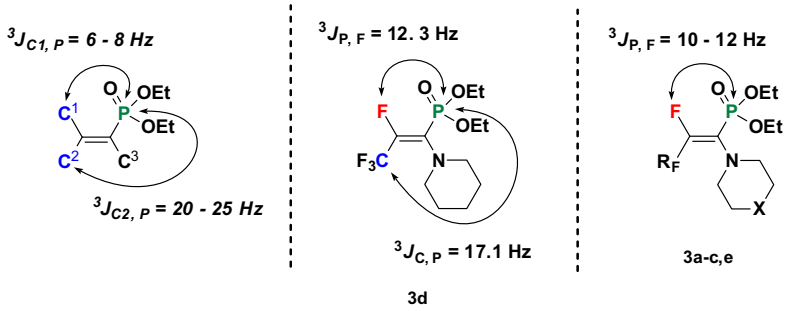



**Figure 1.** Determination of the stereochemistry of vinyl phosphonates **3a**–**e**.