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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/gpss20</u>

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To cite this article: Sergei A. Lermontov, Igor M. Rakov & Sergei V. Shkavrov (1999) THE METHYL ESTER OF 3-AZIDOTETRAFLUOROPROPIONIC ACID - A NOVEL REAGENT FOR THE OXIDATIVE FLUORINATION OF GROUP 15 AND 16 ELEMENTS, Phosphorus, Sulfur, and Silicon and the Related Elements, 149:1, 75-83, DOI: 10.1080/10426509908037024

To link to this article: http://dx.doi.org/10.1080/10426509908037024

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THE METHYL ESTER OF 3-AZIDOTETRAFLUOROPROPIONIC ACID – A NOVEL REAGENT FOR THE OXIDATIVE FLUORINATION OF GROUP 15 AND 16 ELEMENTS

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(Received 24 September, 1998; In final form 17 December, 1998)

The methyl ester of 3-azidotetrafluoropropionic acid, N_3 -CF₂CF₂COOMe oxidatively fluorinates P(III), Sb(III) and Te(II) compounds to form the corresponding difluorides in good yield.

Keywords: Methyl 3-azidotetrafluoropropionate; oxidative fluorination; organophosphorus fluorides; organoantimony fluorides; organotellurium fluorides

Fluorinated compounds are of considerable interest in inorganic, organic, polymer, industrial and medicinal chemistry^[1-5]. Particularly valuable are mild and selective fluorinating agents and methods for the facile fluorination of organic and organoelement compounds^[4-6]. The great majority of fluorinating agents are of nucleophilic character. The reagents which are capable of electrophilic fluorination include F_2 itself ^[7], XeF₂ ^[8], PhIF₂ ^[9], acetyl hypofluorite, MeCOOF^[10], and N-fluoroamines and amides^[11]. Unfortunately, these reagents have various drawbacks and limitations such as hazardous handling (F₂, RCOOF), high cost and lack of selectivity (XeF₂, N-F compounds) or weak fluorinating ability (PhIF₂), and finally, they all are usually prepared *via* F₂. Therefore, new electrophilic fluorination

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ing agents that allow the facile introduction of fluorine under mild conditions into electron rich substrates are highly desirable and useful.

We have recently shown^[12] that the stable 2-hydroperfluoropropyl azide, $CF_3CHFCF_2N_3$, readily fluorinates various organophosphorus(III) compounds, affording difluorophosphoranes in high yield and hence, serving as an oxidative fluorinating agent.



In this paper we describe the reactions of 3-azidotetrafluoropropionic acid methyl ester MeOCO-CF₂CF₂-N₃, **1**, with some P(III), Sb(III) and Te(II) compounds. This azide (first prepared by C. G. Krespan and his co-workers^[13]) has the same N₃-CF₂- moiety as CF₃CHFCF₂N₃ and we could expect that the fluorinating properties would be similar. Besides, the boiling point of **1** is significantly higher than that of CF₃CHFCF₂N₃. This can be convenient in synthetic applications.

REACTIONS OF 1 WITH P(III) COMPOUNDS

We have found that the azide 1 reacts smoothly with trivalent phosphorus compounds, affording the corresponding products of oxidative fluorination. Thus, the trialkyl phosphites 2 and 3 react with the azide 1 at ambient temperature to form the phosphazenes 4 and 5. These phosphazenes are stable enough at room temperature but decompose readily upon heating in benzene producing the difluorophosphoranes 6 and further reaction products (Eq. 1).

Diethyl fluorophosphate 7 (R = Et) can easily be isolated in a pure state by distillation in 54% yield.

The hexaalkyltriaminophosphines, 9a-b, also readily react with the azide 1 to form quantitatively stable phosphazides 10a-b as primary products (no traces of the corresponding phosphazenes could be found in reaction mixtures). The phosphazide 10a is a crystalline compound which can be isolated in a pure state and analyzed. Its thermal decomposition gives the difluorophosphorane 11a in a good yield (Eq. 2)

$$(R_{2}N)_{3}P \xrightarrow{H_{4}H_{4}} (R_{2}N)_{3}P = N - N = N - CF_{2}CF_{2}C(0)OMe$$
2. 80 °C, 2 h 100%
9a-b 10a-b
a. R = Me
b. R = Et (2)
10a $\frac{110 \text{ °C}, 2 \text{ h}}{\text{toluene}}$ (Me₂N)₃PF₂ + XPF₆ X - unknown, phosphorus-
containing cation

Diethyl phosphite, 12, reacts with the azide 1 vigorously in a triethylamine solution to form diethyl fluorophosphate, 7, in 70% isolated yield (Eq. 3).

$$(EtO)_2 P(O)H \xrightarrow{1}_{Et_3N, 10 \text{ °C}} (EtO)_2 P(O)F \quad (3)$$
12
7
70%

An interesting Arbuzov-like rearrangement takes place during the reaction of the azide 1 with *iso*-butyl difluorophosphite, 13. *tert*-Butylphosphonic difluoride, 14, is formed as the main product (Eq. 4).

i-BuOPF₂
$$\frac{1}{50-70 \circ C, 5-8 \text{ h}}$$
 t-BuP(O)F₂ (4)
13 14 85 - 100%

The reaction proceeds with catalytic amounts of the azide 1 (20% mol.) and is followed by the isomerization of an initial i-Bu substituent into a tertiary one. The mechanism of this transformation is undoubtedly analogous to that described for $CF_3CHFCF_2N_3$ ^[12] and includes primary oxidative fluorination of 13 to the unstable tetrafluorophosphorane 15 followed by its disproportiontion into the alkylphosphonium salt 16 which is indeed the true catalyst of the rearrangement process (Scheme 1).



The disproportionation $15 \rightarrow 16 + \text{ROP}(O)$) F_2 (for R = Me) is described in the literature^[14]. The next step is a classical Arbuzov rearrangement accompanied by a catalyst recovery (Scheme 2).



On the whole the fluorinating properties of the azide 1 towards P(III) compounds are similar to those described for $CF_3CHFCF_2N_3$ ^[12] but display at least one peculiarity - the intermediate compounds 4, 5 and 10 are much more stable than in the case of $CF_3CHFCF_2N_3$ and in some cases can even be isolated and analyzed.

FLUORINATION OF Sb(III) AND Te(II) COMPOUNDS

We have found, that the reaction of the azide 1 with Ph_3Sb in toluene leads to a high yield of Ph_3SbF_2 , 17 (Eq. 5).

$$Ph_{3}Sb + 1 \xrightarrow{110 \circ C, 3-6 h} Ph_{3}SbF_{2}$$
(5)
17 67-100%

This reaction requires higher temperatures than the analogous reactions with organophosphorus compounds. The difluoride 17 can be isolated in a pure crystalline form.

The reaction of Ph_2Te with the azide 1 proceeds at higher temperatures and also gives the desired product of oxidative fluorination – difluoride Ph_2TeF_2 , 18, in a good yield. In contrast to Ph_3Sb , the reaction appeared to be sensitive to the presence of a dipolar aprotic solvent, namely of hexamethylphosphorotriamide (HMPTA). The addition of small amounts of HMPTA to a reaction mixture increased the yield of 18 significantly (Eq. 6).

Ph₂Te + 1
$$\xrightarrow{160 \circ C}$$
 Ph₂TeF₂
18 (6)
72% (9 h)
20% (3 h)
70% (3 h HMPTA added)

The mechanism of the fluorination reaction is undoubtedly similar to that described for $CF_3CHFCF_2N_3$ ^[12] (Scheme 3), and includes a Staudinger-like reaction – steps (a) and (b), and sigmatropic fluorine transfer with the formation of a stable nitrile and strong element-F bonds (c).

$$\frac{b}{-N_2} \left[Ph_3Sb + N_3 - CF_2CF_2COOMe \xrightarrow{a} [Ph_3Sb = N - N = N - CF_2CF_2COOMe] \xrightarrow{b} \\ F = CF_2COOMe \xrightarrow{c} Ph_3SbF_2 + NC - CF_2COOMe \xrightarrow{c} Ph_3SbF_2 + P$$

SCHEME 3

Thus, azide 1 can be regarded, to some extent, as a synthon of the following mixture: MeOCOCF₂CF₂N₃ \Rightarrow [F₂] + N₂+ MeOCOCF₂CN

EXPERIMENTAL

³¹P and ¹⁹F NMR spectra were recorded on a Bruker CXP-200 spectrometer. Chemical shifts are reported in δ -units downfield from external 85% H₃PO₄ and CF₃COOH, respectively. Melting points are uncorrected. Azide **1** was synthesized according to a literature procedure ^[13].

Fluorination of Trialkyl phosphites

A. Phosphite 2. A solution of $0.42 \text{ g} (2.09 \cdot 10^{-3} \text{ mol})$ of the azide 1 in 2 mL of dry benzene was added dropwise to a stirred solution of 0.595 g $(1.81 \cdot 10^{-3} \text{ mol})$ of 2 in 2 mL of dry benzene cooled by cold water, and the resulting mixture was kept for 20 min at rt. The ³¹P NMR spectrum of the resulting mixture contained the signal of 4 (-6.38, tt, ³J(P-F) = 18 Hz, ⁴J(P-F) = 4.3 Hz; 90%) and 10% of some unidentified impurities. After heating in refluxing benzene during 2 h the ³¹P NMR of the reaction mixture contained no signal of 4, but 70% of the difluuorophosphorane (CF₃CH₂O)₃PF₂, 6, (-77.25, t, ¹J(P-F) = 749 Hz; Lit.^[15] δ P -77.3, t, ¹J(P-F) = 747 Hz).

B. Phosphite 3 (R = Me). The analogous reaction of 0.316 g ($2.55 \cdot 10^{-3}$ mol) of 3 (R = Me) with 0.56 g ($2.79 \cdot 10^{-3}$ mol) of 1 in benzene gave the phosphazene 5 (R = Me) (δP 4.1 (tt, ${}^{3}J(P-F) = 15.4$ Hz, ${}^{4}J(P-F) = 5.3$ Hz) and the difluorophosphorane (MeO)₃PF₂, **6**, (δP -70, t, ${}^{1}J(P-F) = 722$ Hz) in 1: 1 ratio. Lit.^[16] for **6** (R = Me): ${}^{1}J(P-F) = 706$ Hz. After heating in refluxing benzene during 2 h the ${}^{31}P$ NMR spectrum of the reaction mixture contained the signal of (MeO)₂P(O)F, **7** (δP -6.2, d, ${}^{1}J(P-F) = 974$ Hz; Lit.^{[17] 1}J(P-F) = 949 Hz), **6**, and (MeO)₄P⁺PF₆- (δP 0, s, -143.3, heptet, ${}^{1}J(P-F) = 708$ Hz; Lit.^[18] (δP 0, s, -147, m, ${}^{1}J(P-F) = 700$ Hz) in 65: 10: 25 ratio.

C. Phosphite 3 (R = Et). In the analogous reaction of 1.94 g $(1.17 \cdot 10^{-2} \text{ mol})$ of (EtO)₃P with 2.8 g $(1.39 \cdot 10^{-3} \text{ mol})$ of 1 in benzene the reaction mixture consisted of 85% of the difluorophosphorane (EtO)₃PF₂, **6**, (δP -74.1, t, ¹*J*(P-F) = 725 Hz; Lit.^[19] δP -74.78, t, ¹*J*(P-F) = 722.7 Hz) and

15% of 7 (R = Et) (δP -8.2, d, ${}^{1}J(P-F) = 972$ Hz; Lit.^[17] δP -9.2, d, ${}^{1}J(P-F) = 963$ Hz). The reaction mixture was refluxed during 2 h and distilled *in vacuo*. 0.98 g (54%) of (EtO)₂P(O)F, 7, were obtained. Bp 60 - 65 °C/15 mm.; Lit.^[20] Bp 63 °C/12 mm.

Reaction of 1 with the triaminophosphines 9a and 9b

1.12 g $(5.57 \cdot 10^{-2} \text{ mol})$ of 1 in 3 mL of dry benzene were added dropwise to a cold water cooled solution of 0.808 g $(4.96 \cdot 10^{-3} \text{ mol})$ of **9a** in 4 mL of dry benzene. The mixture was stirred during 3 h and kept overnight. The ³¹P NMR spectrum contained only one signal: δP 42.77, S. Heating of the reaction mixture during 2 h at reflux left this signal unchanged. The solvent was evaporated *in vacuo* and the residue was recrystallized from a 1: 3 benzene: heptane mixture. Pure **10a** was obtained as colourless crystals, mp 94 – 95 °C.

³¹P NMR: δP 42.92, S.

¹⁹F NMR: δ F –18.7 (t), –42.0 (t) ³*J*(F-F) = 6.7 Hz.

¹H NMR: δH 2.59 (d, ${}^{3}J$ (H-P) = 9.4 Hz (18H); 3.77, S (3H)).

Anal. Calc. for For C₁₀H₂₁N₆O₂PF₄: C, 32.97, H, 5.81, N, 23.07, P 8.50. Found: C, 33.01, H, 5.71, N, 23.05, P, 8.52.

Heating of 10a in dry toluene during 2 h at reflux afforded a mixture of 70% of 11a (δP -63.9, t, ${}^{1}J(P-F) = 700$ Hz; Lit.^[21] δP 65.7, t, ${}^{1}J(P-F) = 700$ Hz; ${}^{1}J(P-F) = 700$ Hz; ${}^{1}J(P-F) = 707$ Hz^[16]), 20% of some PF₆- containing substance (δP 25.6, S; -143.5, heptet, ${}^{1}J(P-F) = 710$ Hz) and 10% of several minor impurities.

The analogous reaction of 0.54 g $(2.19 \cdot 10^{-3} \text{ mol})$ of **9b** and 0.56 g $(2.79 \cdot 10^{-3} \text{ mol})$ of **1** in benzene afforded **10b** quantitatively (δP 42.78, s). The substance remained unchanged after 2 h heating in refluxing benzene but our attempts to distill it failed.

Fluorination of diethyl phosphite, 12

A solution of 0.84 g $(4.18 \cdot 10^{-3} \text{ mol})$ of 1 in 2 mL of dry Et₃N was added dropwise to a water cooled solution of 0.43 g $(3.1 \cdot 10^{-3} \text{ mol})$ of **12** in 2 mL of Et₃N. After the completion of an exothermic reaction the mixture was stirred during 3 h at rt. The ³¹P NMR spectrum revealed the formation of 70% of (EtO)₂P(O)F, 7, (δP -8.5, d, ¹J(P-F) = 970 Hz) and 30% of several minor compounds.

The reaction of iso-butyl difluorophosphite, 13, with 1

0.5 g $(3.52 \cdot 10^{-3} \text{ mol})$ of **13** and 0.14 g $(7 \cdot 10^{-4} \text{ mol})$ of **1** were mixed in a steel bomb and heated at 50 °C during 5 h. The reaction mixture contained 85% of t-BuP(O)F₂, **14**, (δ P 32.1, t of decets, ¹J(P-F) = 1173 Hz; ³J_{P-H}= 19.7 Hz; Lit.^[22] δ P 31.8, t of decets, ¹J(P-F) = 1195 Hz; ³J(P-H) = 18.8 Hz), 15% of the starting **13** and traces of i-BuOP(O)F₂ (δ P -19.8, tt, ¹J(P-F) = 1004 Hz, ³J(P-H) = 8 Hz). Heating of the reaction mixture at 70 °C during 8 h afforded practically pure **14**.

Fluorination of Ph₃Sb

A solution of 0.194 g $(5.5 \cdot 10^{-4} \text{ mol})$ of Ph₃Sb and 0.35 g $(1.74 \cdot 10^{-3} \text{ mol})$ of the azide **1** in 3.5 mL of dry toluene was heated at reflux during 6 h. A known quantity of m-fluorotoluene was added as internal signal for NMR integration. The ¹⁹F NMR spectrum revealed the quantitative formation of the difluoride **17.** After removal of the solvent and recrystallization from n-heptane pure **17** was obtained. Mp 112–113 °C, ¹⁹F NMR: δ F –75.1, S. Lit.^[23] δ F –153.2 (CFCl₃) (s). Mp 120 – 122 °C ^[24]. Heating of the reaction mixture during 3 h afforded **17** in 67% yield.

Fluorination of Ph₂Te

A. A solution of 0.153 g $(5.43 \cdot 10^{-4} \text{ mol})$ of Ph₂Te and 0.35 g $(1.74 \cdot 10^{-4} \text{ mol})$ of **1** in 1.5 mL of dry CH₂Cl₂ was heated in a steel bomb at 160 °C during 9 h. ¹⁹F NMR revealed the formation of 72% of Ph₂TeF₂, **18** (NMR integration, using a known quantity of m-fluorotoluene as internal standard). After removal of the solvent and recrystallization from heptane the difluoride **18** was obtained in a pure state. Mp 146 - 148 °C, ¹⁹F NMR: -50.4, ¹*J*(Te-F) = 544 Hz; Lit.^[25] mp 152 °C.

B. Heating of the previous reaction mixture during 3 h afforded 18 in 20% yield. C.

A solution of 0.157 g $(5.57 \cdot 10^{-4} \text{ mol})$ of Ph₂Te, 0.35 g $(1.74 \cdot 10^{-3} \text{ mol})$ of 1 and 0.2 mL of dry HMPTA in 1.5 mL of CH₂Cl₂ was heated in a steel bomb at 160 °C during 3 h. The yield of 18 was 70% (NMR integration).

Acknowledgements

This work was supported by the Russian Foundation of Basic Research (Grant #98-03-32997).

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