New efficient synthesis of phosphonofluorodithioates ROP(S)(S$^-$)F and their structural analogues

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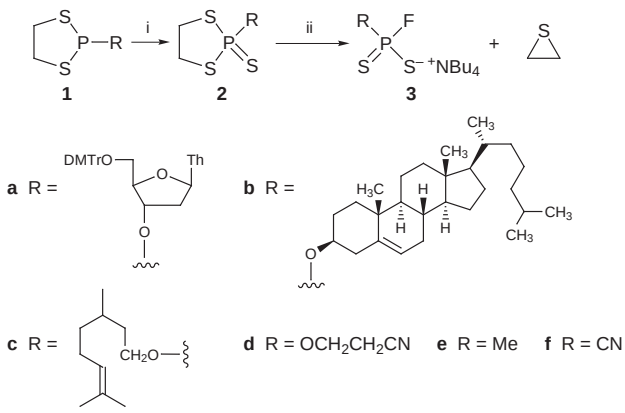
The title compounds 3 are formed in very high yield from a one-pot sequential reaction of 1,3,2-dithiaphospholane P^{III} derivatives 1, which are transformed into the corresponding P^{IV} compounds 2 by addition of elemental sulfur and finally into fluoridodithioates 3 by TBAF.

Phosphorus dithioacids play an important role as reagents, ligands and stereochemical probes in ^{31}P NMR spectroscopy.[1] Dithioacids containing a fluorine ligand attached directly to the phosphorus atom are rare.[2] The method of choice for the preparation of simple phosphonofluoridodithioates is not applicable for the preparation of phosphonofluoridodithioate monoesters derived from natural products. Unlike for nucleoside phosphonofluoridate[3a–c] or phosphonofluoridothioate[3d] monoesters, there is only one synthetic method available for the preparation of nucleoside phosphonofluoridodithioate monoesters.[3e] Stawinski and Bollmark have devised a synthesis of nucleoside phosphonofluoridodithioate monoesters *via* oxidation of nucleoside phosphonodithioate with I_2 in pyridine in the presence of TMSCl, followed by addition of triethylamine trishydrofluoride (TAF) to give the nucleoside phosphonofluoridodithioate.[3e]

The importance of phosphoro-fluorine compounds in pure and applied chemistry stimulated our interest in the synthesis of phosphorus dithioacids with P–F bonds. Our studies on the synthesis of phosphonodithioates from 3′-thiothymidine by anhydro-ring opening of 2,3′-anhydrothymidine[4] required an efficient synthesis of *O*,*O*-disubstituted phosphonodithioic acids. We now disclose a novel synthesis of the title compounds **3** containing a wide variety of substituents attached to the phosphorus center (Scheme 1). Our method is based on 1,3,2-dithiaphospholane derivatives **1** which are readily available from ethane-1,2-dithiol and an appropriate P^{III} compound.

The protocol we have developed involves two consecutive reactions carried out in one pot: sulfurization of compound **1** to form compound **2** and finally the reaction with TBAF to open the dithiaphospholane ring with spontaneous elimination of ethylene sulfide and formation of the desired acid **3** (Scheme 1). The roots of this approach are derived from methodology described by Stec.[5]



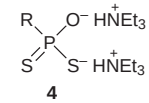
Scheme 1 *Reagents and conditions*: i, S_8, benzene; ii, TBAF, THF.

To illustrate the power and versality of this strategy several examples are presented which include the fluoro dithioacids **3** containing alkyl and alkoxyl (nucleosidyloxy) moieties attached to the phosphorus center. The first example comes from nucleotide chemistry (Scheme 1).† The compounds **1a** and **2a** have been prepared according to the modified procedure of Okruszek and Olesiak.[5b] The condesation of **1** (R = NPr$^i_2$) with 5′-dimethoxytritylthymidine was performed in the presence of TMSCl yielding **1a** in very high yield.[6]†

According to this method *O*-cholesteryl phosphonofluoridodithioate **3b** was obtained in quantitative yield (Scheme 1).‡ 2-Cholesteryloxy-2-thioxo-1,3,2-dithiaphospholane **2b** was the first prepared by Stec and coworkers.[7]

An analogous synthetic pathway led to **3c**§ starting from **1c** (Scheme 1). Synthesis of the 2-citronellyloxy-1,3,2-dithiaphospholane **1c** was achieved by the coupling of **1** (R = NPr$^i_2$) with citronellol in the presence of TMSCl as activator.[6]

The phosphonofluoridodithioate **3d**¶ can be conveniently prepared from **1d**, which is readily available from **1** (R = NPr$^i_2$) *via* condensation with 2-cyanoethanol in the presence of TMSCl. Compound **1d** was transformed into **2d**¶. Ring opening with TBAF gave the dithioacid **1d** (Scheme 1) which, after removal in the presence of Et_3N of the 2-cyanoethyl group, gave the phosphonofluoridodithioic acid **4** [δ_P($CDCl_3$) 67.50(d); δ_F($CDCl_3$) −0.42 (d, $J_{P–F}$ = 1108.96)].



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The methylphosphonofluoridodithioate **3e**‖ was prepared from compound **1e**[8] (Scheme 1). The preparation of the latter involves the condensation of ethane-1,2-dithiol with methyl(dichloro)phosphine.

The same strategy allowed us to prepare a novel inorganic structure, the cyanophosphonofluoridodithioate **3f**** (Scheme 1). The cyano derivative **1f** was prepared by the reaction **1** (R = Cl) with trimethylsilyl cyanide.

In summary we have developed a novel, efficient and general method for the synthesis of phosphonofluorodithioates **3**. Yields of the final products are very good, exceeding 95%. They show high stability at ambient temperature and can be conveniently converted into free acids by the action of toluene-*p*-sulfonic acid. Acids **3** are strong nucleophiles and thus serve as useful precursors to a wide variety of hitherto unknown functionalized heteroatom systems and ligands. The new route leading to phosphonofluorodithioic acids **3** described here is noteworthy in its flexibility. It can also be extended to analogues of **2** containing a P=Se group.

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Notes and references

† The solvents were reagent grade and were distilled and dried by conventional methods before use. NMR spectra were recorded on a Bruker AC200 spectrometer (^{31}P 81.014 MHz, H_3PO_4 external standard; ^{19}F

188.15 MHz, $CFCl_3$). The compounds **1a** and **2a** were prepared according to the modified procedure of Okruszek and Olesiak [ref. 5(*b*)]. *Typical procedure* for **1** (R = NPr^i_2): A solution of $Pr^i_2NPCl_2$ (10 mmol) in dry THF (10 ml) was added dropwise at room temperature under a nitrogen atomosphere to the solution of ethane-1,2-dithiol (10 mmol) and Et_3N (20 mmol) in dry THF (50 ml) with stirring for 2 h. After 2 h, $Et_3N{\cdot}HCl$ was filtered off and the filtrate evaporated *in vacuo*. The residue was distilled under reduced pressure.

For **1a**: A solution of 5′-DMTr-thymidine (10 mmol) in dry THF (10 ml) was added dropwise at room temperature under a nitrogen atmosphere to a solution of **1** (R = NPr^i_2) (10 mmol) and TMSCl (0.6 mmol) in dry THF (20 ml). After 1 h the mixture was evaporated *in vacuo* and the residue was purified by column chromatography [$\delta_P(CDCl_3)$ 150.67].

For **2a**: To a solution of **1a** in THF was added elemental sulfur, and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed using acetone–CH_2Cl_2 as eluent to give pure **2a** [$\delta_P(CDCl_3)$ 122.65].

For **3a**: To a solution of **2a** (10 mmol) in dry THF was added a solution of TBAF (11 mmol) in THF at room temperature. After 1 h the mixture was evaporated *in vacuo* and the residue was purified by column chromatography [$\delta_P(CDCl_3)$ 119.64 (d); $\delta_F(CDCl_3)$ −4.92 (d, J_{PF} 1103.74)].

‡ *Selected data* for **1b**: $\delta_P(CDCl_3)$ 147.24. For **2b** $\delta_P(CDCl_3)$ 118.33. For **3b**: $\delta_P(CDCl_3)$ 118.65 (d); $\delta_F(CDCl_3)$ −3.36 (d, J_{PF} 1096.38). Compounds **1b**, **2b** and **3b** were prepared according to the procedure described in note †.

§ *Selected data* for **1c**: $\delta_P(CDCl_3)$ 142.75. For **2c**: $\delta P(CDCl_3)$ 120.53. For **3c** $\delta_P(CDCl_3)$ 120.24 (d); $\delta_F(CDCl_3)$ −8.53 (d, J_{PF} 1094.22). Compounds **1c**, **2c** and **3c** were prepared according to the procedure described in note †.

¶ *Selected data* for **1d**: $\delta_P(CDCl_3)$ 150.19. For **2d**: $\delta_P(CDCl_3)$ 123.34. For **3d**: $\delta_P(CDCl_3)$ 120.84 (d); $\delta_F(CDCl_3)$ −6.07 (d, J_{PF} 1096.30). Compounds **1d**, **2d** and **3d** were prepared according to the procedure described in note †.

‖ *Selected data* for **1e**: $\delta_P(CDCl_3)$ 42.78. Compound **1e** was prepared as described by Peake *et al.* (ref. 7). For **2e**: $\delta_P(CDCl_3)$ 90.58. For **3e**: $\delta_P(CDCl_3)$ 129.8 (d); $\delta_F(CDCl_3)$ −25.55 (d). Compounds **2e** and **3e** were prepared according to the procedure described in note †.

** *Selected data* for **1f**: $\delta_P(CDCl_3)$ 10.71. Compound **1f** was prepared by the reaction of **1** (R = Cl) with TMSCN. For **2f**: $\delta_P(CDCl_3)$ 108.0. For **3f**: $\delta_P(CDCl_3)$ 60.18 (d), $\delta_F(CDCl_3)$ −41.01 (d, J_{PF} 1070.1). Compounds **2f** and **3f** were prepared according to the procedure described in note †. For **2f**, the sulfurization procedure using B_2S_3 is superior to that employing elemental sulfur.

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