## 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<sup>III</sup> derivatives 1, which are transformed into the corresponding P<sup>IV</sup> 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 <sup>31</sup>P NMR spectroscopy.<sup>1</sup> Dithioacids containing a fluorine ligand attached directly to the phosphorus atom are rare.<sup>2</sup> 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<sup>3a-c</sup> or phosphonofluoridothioate<sup>3d</sup> monoesters, there is only one synthetic method available for the preparation of nucleoside phosphonofluoridodithioate monoesters.<sup>3e</sup> Stawinski and Bollmark have devised a synthesis of nucleoside phosphonofluoridodithioate monoesters via oxidation of nucleoside phosphonodithioate with I2 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<sup>4</sup> 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<sup>III</sup> 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.<sup>5</sup>



Scheme 1 Reagents and conditions: i, S<sub>8</sub>, 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).<sup>†</sup> The compounds **1a** and **2a** have been prepared according to the modified procedure of Okruszek and Olesiak.<sup>5b</sup> The condesation of **1** (R = NPr<sup>i</sup><sub>2</sub>) with 5'-dimethoxytritylthymidine was performed in the presence of TMSCl yielding **1a** in very high yield.<sup>6†</sup>

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.<sup>7</sup>

An analogous synthetic pathway led to  $3c_8$  starting from 1c (Scheme 1). Synthesis of the 2-citronellyloxy-1,3,2-dithiaphospholane 1c was achieved by the coupling of 1 (R = NPri<sub>2</sub>) with citronellol in the presence of TMSCl as activator.<sup>6</sup>

The phosphonofluoridodithioate  $3d\P$  can be conveniently prepared from 1d, which is readily available from 1 (R = NPr<sup>i</sup><sub>2</sub>) *via* condensation with 2-cyanoethanol in the presence of TMSCI. Compound 1d was transformed into 2d¶. Ring opening with TBAF gave the dithioacid 1d (Scheme 1) which, after removal in the presence of Et<sub>3</sub>N of the 2-cyanoethyl group, gave the phosphonofluoridodithioic acid 4 [ $\delta_{P}$ (CDCl<sub>3</sub>) 67.50(d);  $\delta_{F}$ (CDCl<sub>3</sub>) -0.42 (d,  $J_{P-F} = 1108.96$ )].

$$\begin{array}{c}
\mathsf{R} \quad \mathsf{O}^{-} \mathsf{H} \overset{\uparrow}{\mathsf{N}} \mathsf{E} \mathsf{t}_{3} \\
\mathsf{S}^{-} \mathsf{H} \overset{\downarrow}{\mathsf{N}} \mathsf{E} \mathsf{t}_{3} \\
\mathbf{4}
\end{array}$$

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

<sup>†</sup> The solvents were reagent grade and were distilled and dried by conventional methods before use. NMR spectra were recorded on a Bruker AC200 spectrometer (<sup>31</sup>P 81.014 MHz, H<sub>3</sub>PO<sub>4</sub> external standard; <sup>19</sup>F 188.15 MHz, CFCl<sub>3</sub>). The compounds **1a** and **2a** were prepared according to the modified procedure of Okruszek and Olesiak [ref. 5(*b*)]. *Typical procedure* for **1** ( $\mathbf{R} = NPr^{i_2}$ ): A solution of  $Pr^{i_2}NPCl_2$  (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<sub>3</sub>N (20 mmol) in dry THF (50 ml) with stirring for 2 h. After 2 h, Et<sub>3</sub>N·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<sub>3</sub>) 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 chromato-graphy [ $\delta_{\rm P}$ (CDCl<sub>3</sub>) 119.64 (d);  $\delta_{\rm F}$ (CDCl<sub>3</sub>) -4.92 (d,  $J_{\rm PF}$  1103.74)].

<sup>‡</sup> 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 <sup>†</sup>.

§ Selected data for 1c:  $\delta_{\rm P}({\rm CDCl}_3)$  142.75. For 2c:  $\delta_{\rm P}({\rm CDCl}_3)$  120.53. For 3c  $\delta_{\rm P}({\rm CDCl}_3)$  120.24 (d);  $\delta_{\rm F}({\rm CDCl}_3) - 8.53$  (d,  $J_{\rm PF}$  1094.22). Compounds 1c, 2c and 3c were prepared according to the procedure described in note  $\dagger$ .

¶ *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);  $\delta_P(CDCl_3) - 6.07$  (d,  $J_{PF}$  1096.30). Compounds **1d**, **2d** and **3d** were prepared according to the procedure described in note  $\dagger$ .

|| 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  $\dagger$ .

\*\* Selected data for 1f:  $\delta_{\rm P}({\rm CDCl}_3)$  10.71. Compound 1f was prepared by the reaction of 1 (R = Cl) with TMSCN. For 2f:  $\delta_{\rm P}({\rm CDCl}_3)$  108.0. For 3f:  $\delta_{\rm P}({\rm CDCl}_3)$  60.18 (d),  $\delta_{\rm F}({\rm CDCl}_3)$  -41.01 (d,  $J_{\rm PF}$  1070.1). Compounds 2f and 3f were prepared according to the procedure described in note  $\dagger$ . For 2f, the sulfurization procedure using B<sub>2</sub>S<sub>3</sub> is superior to that employing elemental sulfur.

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