First Synthesis of Nucleosidyl Phosphorofluoridothioates and a Convenient Synthesis of Nucleosidyl Phosphorofluoridates

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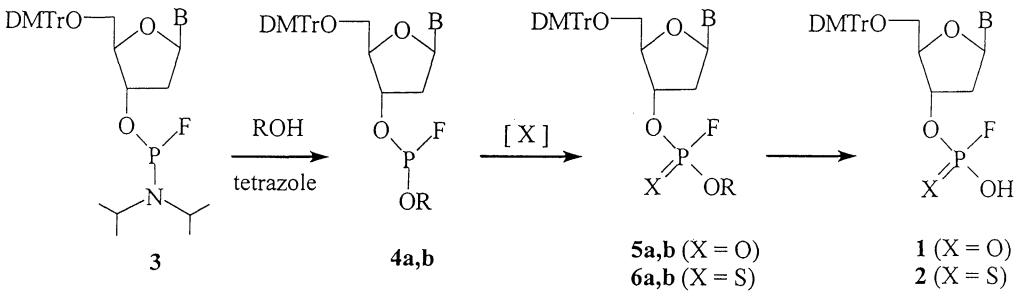
The first synthesis of 3'- or 5'-nucleosidyl phosphorofluoridothioates RO-P(S)(OH)F have been accomplished via nucleosidyl phosphoramidofluoridates RO-P(NPr^i_2)F. An analogous convenient procedure has been employed to prepare 3'- or 5'-nucleosidyl phosphorofluoridates RO-P(O)(OH)F.

Nucleosidyl phosphorofluoridates, in contrast to other phosphorohalidates, exhibit higher stability towards nucleophilic displacements of the fluoride group. Recently interest in compounds of this type has arisen in molecular biology and their useful antiviral properties have been disclosed.[1,2] Witmann was the first to prepare nucleosidyl phosphorofluoridates RO-P(O)(OH)F (R= nucleosidyl) **1**, **7**, from 3' or 5'-nucleotides by the reaction with 2,4-dinitrofluorobenzene.[3] This method has been applied by other authors in nucleotide and sugar chemistry.[4] Fluorophosphoric acid F-P(O)$(OH)_2$ can be condensed with nucleosides in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride[1,2] to give compounds **1**. This reaction is likely to involve the intermediate formation of phosphorus-sulfonic anhydride $ArSO_2OP(O)(OH)F$. Nucleosidyl phosphorofluoridates have been also obtained by the reaction of tetrabutylammonium fluoride with nucleosidyl-O-aryl-3-alkyl-thiophosphates.[5] The sulfur analogues of nucleosidyl phosphoro-fluoridates **1** and **7**, namely RO-P(S)(OH)F (R = nucleosidyl) **2** and **8**, have not previously been described.

In this paper we present a general and highly efficient method leading to fluoridates **1**, **7** and their sulfur analogues RO-P(S)(OH)F **2**, **8**. Nucleosidyl phosphoramidofluoridites **3** and **9** have recently become readily available by methods which have been developed in this Laboratory.[6] Compounds **3** react with tert-butanol (1 eq.) or 2-cyanoethanol (1 eq.) in CH_3CN in presence of tetrazole (4 eq.) at r.t. for 10 min. to give the corresponding phosphorofluoridites **4a** or **4b** in quantitative. Preservation of tert-butyl group in the reaction leading to compounds **4a** is noteworthy. Oxidation of phosphorofluoridites **4a** or **4b** by tert-butyl hydroperoxide gives tert-butylphosphorofluoridates **5a** or 2-cyanoethylphosphorofluoridates **5b**, respectively. Fluoridates **5a** were transformed into the desired nucleosidyl phosphoro-fluoridates **1** by thermal elimination of 2-methyl-1-propen (80°C, 2 h, CH_3CN) while fluoridates **5b** were transformed to compounds **1** by β-elimination of vinyl cyanide [pyridine-triethylamine (3:1 v/v), r.t., 10 min.] (Scheme 1).

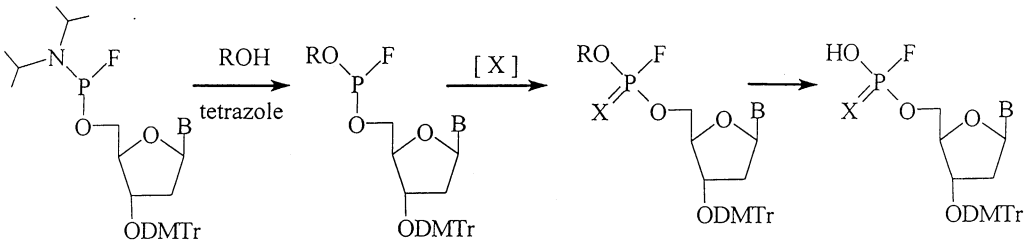
Analogous synthetic pathways led to nucleosidyl phosphoro-fluoridothioates **2**. After the addition of elemental sulfur to phosphorofluoridites **4a** or **4b** intermediate fluoridothionates **6a** or **6b** were formed and converted into the nucleosidyl phosphoro-fluoridothioates **2** by elimination of the tert-butyl or 2-cyanoethyl groups, respectively. The compounds **1** and **2** were separated by preparative thin layer chromatography, using CH_2Cl_2:CH_3COCH_3 (10:3 v/v) as an eluent.

Reactions delineated in Scheme 1 can be carried out as one-flask procedure and compounds **1** and **2** were isolated in over 90% yield as sodium or ammonium salts. ^{31}P and ^{19}F NMR data of compounds **4a,b**, **6a,b** and **2** are shown in Note 7. Similar series of reactions in regard to 5'-nucleosides shown in Scheme 2 was performed in conformable preparative procedures.



a: R = Bu^t b: R = CH_2CH_2CN B: Th, Ad(Bz)

Scheme 1.



9 **10a,b** **11** (X = O) **12** (X = S) **7** (X = O) **8** (X = S)

a: R = Bu^t **b**: R = CH_2CH_2CN B: Th, Ad(Bz)

Scheme 2.

Phosphorofluoridothionates **6a** and **6b** were converted by trifluoroacetyl anhydride into the corresponding oxo derivatives **5a** and **5b** in almost quantitative yield.[8]

6a,b $\xrightarrow{(CF_3CO)_2O}$ **5a,b**

Compounds **2** and **8** have a chiral phosphorus center. The corresponding diastereomers are formed as 1:1 mixture. Structures of all compounds were confirmed by ^{31}P and ^{19}F NMR spectroscopy and FAB-MS.

In conclusion we describe the first synthesis of nucleosidyl fluoridothionates and the new convenient synthesis of nucleosidyl phosphorofluoridates. Separation of the former compounds into pure diastereomers is currently being studied.

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References and Notes

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7 Selected spectroscopic data: $^{31}P(CDCl_3$, 81.014 Mhz) NMR (H_3PO_4 external standard), ^{19}F ($CDCl_3$, 188.154 Mhz) NMR (CCl_3F external standard, J_{P-F} in Hz. **4a [B=Ad(Bz)}** ^{31}P NMR: δ=139.88, 124.93, 138.53, 123.66; ^{19}F NMR: δ=-47.33, -53.76, -47.91, -54.31; J_{P-F}=1210.9, 1204.7; **4a (B=Th)** ^{31}P NMR: 139.21, 124.34, 140.72, 125.77; ^{19}F NMR: δ=-54.56, -48.14, -55.22, -48.82; J_{P-F}=1210.50, 1204.78; **6a {B=Ad(Bz)}** ^{31}P NMR: δ=59.23, 45.87, 58.74, 45.36; ^{19}F NMR: δ=-31.13, -36.87, -31.35, -37.11; J_{P-F} 1081.9, 1084.2; **6b (B=Th)** ^{31}P NMR: δ=60.18, 46.77, 59.75, 46.39; J_{P-F}=1082.67, 1085.91; **2 {B=Ad(Bz)}** ^{31}P NMR: δ=60.50, 47.50, 60.33, 47.33, ^{19}F NMR: δ=-27.40, -32.99, -27.57, -33.15; J_{P-F}= 1053.23, 1053.24.

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