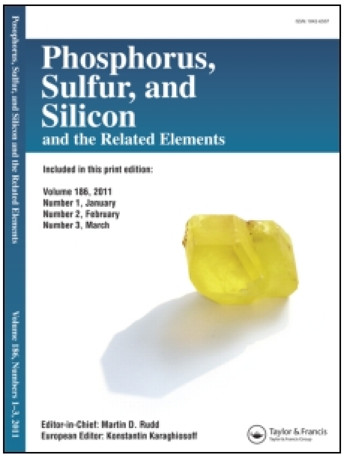

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NOVEL ROUTES TO TRI- AND TETRACOORDINATE PHOSPHORUS-FLUORINE COMPOUNDS DIRECTED TO SYNTHESIS OF P-F MODIFIED NUCLEOTIDES

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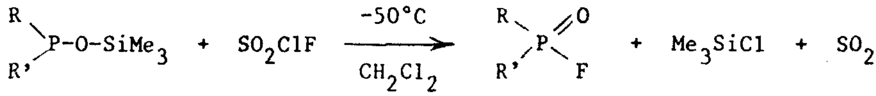
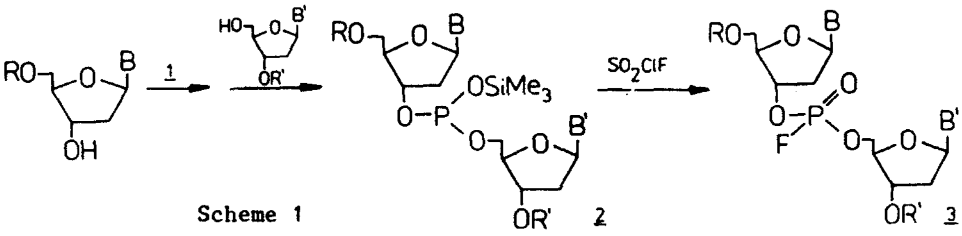
Fluoroderivatives of phosphorus are important in the chemistry and biochemistry of both elements.[1] Recently, our attention has been focused on the synthesis of non-ionic oligodeoxynucleoside-phosphorofluoridates and their thio- and selenoanalogues. Existing methods were, in our opinion, not suited for the synthesis of oligonucleoside-phosphorofluorides. So we devised new ones.

We have found that trimethylsilylphosphites react with sulfuryl chloride fluoride SO_2ClF in a fully chemoselective manner.[2]



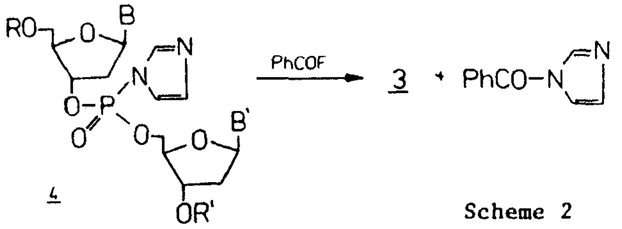
$$\mathrm{RR'P{-}O{-}SiMe_3} + \mathrm{SO_2ClF} \xrightarrow[\mathrm{CH_2Cl_2}]{-50^\circ C} \mathrm{RR'P(O)F} + \mathrm{Me_3SiCl} + \mathrm{SO_2}$$

Phosphorofluoridates of very high purity are formed in almost quantitative yield. The side products are volatile and readily separable. Dideoxynucleoside trimethylsilylphosphites 2 are readily available.[3] They are prepared in very good yield by the classic procedure of Letsinger and Caruthers with aid of a new phosphitylating reagent $(Pr^i_2N)_2P{-}OSiMe_3$ 1.[4] This reagent requires the tetrazole as an activating agent. Reaction of 1 with sulfurylchloride fluoride leading to 3 is almost quantitative.



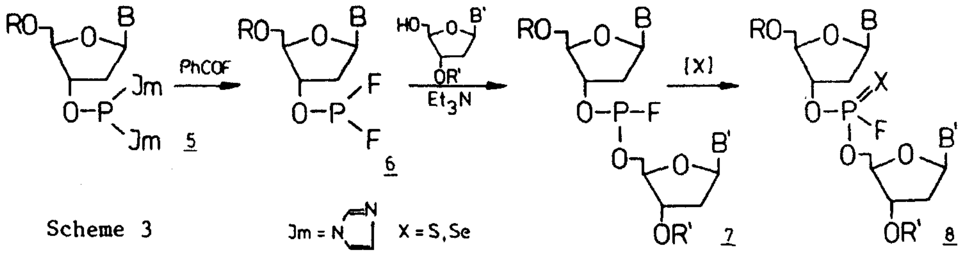
Scheme 1

Another efficient synthesis of dideoxynucleoside phosphorofluoridates 3 employs the reaction of dideoxynucleoside phosphorimidazolides 4 with acyl fluorides.



Scheme 2

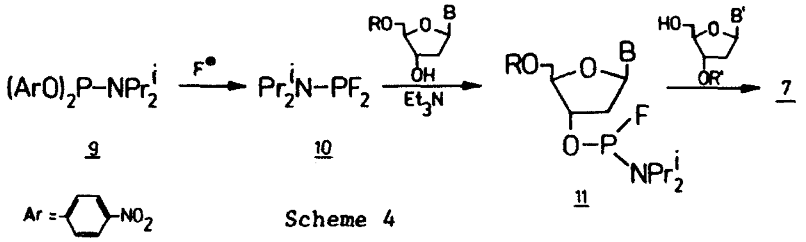
This type of reaction is general for the tetracoordinate and the tricoordinate phosphorus-N-imidazole compounds and similar systems. An example is the reaction of diimidazolide 5 with two equivalents of benzoyl fluoride.



Scheme 3

The difluoride 6 readily undergoes selective phosphitylation, leading to the dideoxynucleoside-phosphorofluoridite 7 which can be easily transformed into 8 (X=S,Se) by addition of elemental sulfur or selenium. The overall yield is very good.

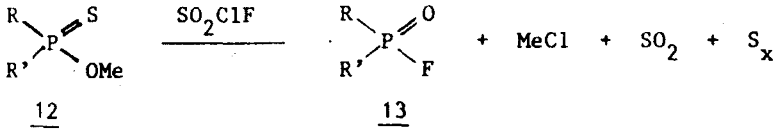
A third an alternative route to 3 and 8, involves new phosphitylating reagents containing a p-nitrophenoxy leaving group.



Scheme 4

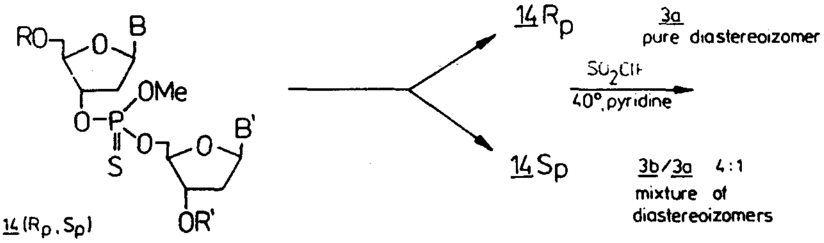
The reaction of 9 with $Bu_4\overset{+}{N}\overset{-}{F}$ allows quantitative formation of the difluoride 10 which reacts in a highly selective way to give 11. Surprisingly the monofluoride 11 can be transformed into 7 by activating of the amido group without breaking the P-F bond.

We discovered that thionoesters 12 undergo transformation into the fluoridates 13 when allowed to react with sulfurylchloride fluoride.[5]

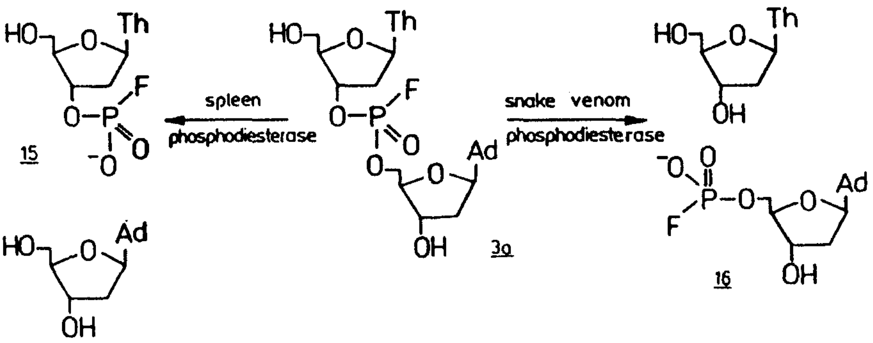


R,R' = EtO, MeO

The fluoridates 3 have a chiral center at the phosphorus atom. Methods Methods shown in Schemes 1, 2, 3 and 4 lead to a mixture of diastereoizomers without any noticeable preference. Pure diastereoizomers of 14 R_P and S_P are readily available[6] and their reaction with SO_2ClF is either fully stereoselective (14 R_P) or highly stereoselective (14 S_P).



The fluoridates 3 are stable in aqueous media and can be deprotected by standard protocols into 3a. Surprisingly the fluoridates 3a are good substrated for specific diesterases. To our knowledge this is the first case in which nonionic dinucleotides are readily hydrolyzed by snake venom and spleen diesterases. Enzymatic hydrolysis of 3a provides an additional proof of their structure.



The mono and dideoxynucleoside phosphorofluoridates can be used as building units for oligonucleotides of biological interest. Our preliminary studies show that the P-F bond is able to survive deprotection and coupling procedures.

The ionic monofluoridates **15** and **16** are identical with compounds prepared by Wittman method[7] and recently by Sund and Chattopadhyaya.[8] Phosphorofluoridate of the type **3** is presumably formed in the reaction of a dinucleoside phosphorothioate with 2,4-dinitrofluorobenzene.[9]

REFERENCES

1. R. Filler and Y. Kobayashi in *Biomedical Aspects of Fluorine Chemistry*, Eds Kodansha (Ed.), *Elsevier Biomedicinal, Tokyo*, 1983.
2. W. Dąbkowski and J. Michalski, *J. Chem. Soc., Chem. Commun.*, 1987, 755.
3. W. Dąbkowski, J. Michalski and W. Qing, *Angew. Chem.* Int.Ed.Engl., 1990, **29**, 522.
4. W. Dąbkowski, F. Cramer and J. Michalski, *Tetrahedron Lett.*, 1988, **29**, 3301.
5. A. Łopusiński and J. Michalski, *J. Am. Chem. Soc.*, 1982, **104**, 290.
6. F. Eckstein and G. Gish, *Trends in Biochemical Sciences*, 1989, **14**, 97 and references cited therein, M. Koziołkiewicz, B. Uznański and W. J. Stec, *Chemica Scripta* 1986, **26**, 251.
7. R. Wittman, *Chem. Ber.*, 1963, **96**, 771.
8. Ch. Sund and J. Chattopadhyaya, *Tetrahedron*, 1983, **45**, 7523.
9. W. J. Stec, G. Zon and B. Uznański, *J. Chromatogr.*, 1985, **326**, 263.