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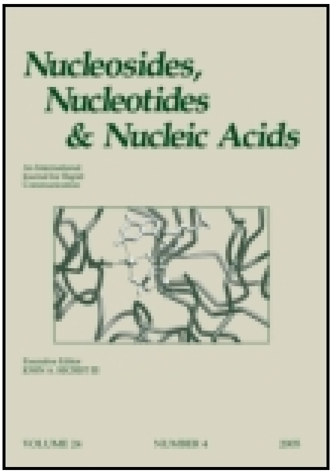

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New Phosphitylating Reagents Containing P-F Bond and Their Application in the Synthesis of P-Fluoro Nucleosidyl Phosphates, Thiophosphates and Selenophosphates

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NEW PHOSPHITYLATING REAGENTS CONTAINING P-F BOND AND THEIR APPLICATION IN THE SYNTHESIS OF P-FLUORO NUCLEOSIDYL PHOSPHATES, THIOPHOSPHATES AND SELENOPHOSPHATES

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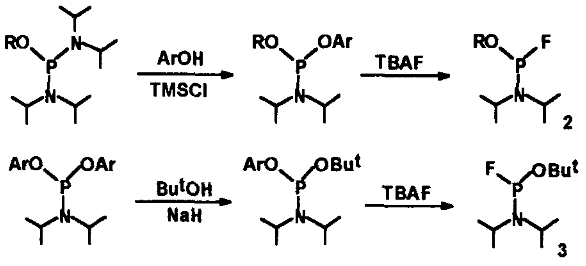
Abstract: An efficient and general synthesis of phosphorofluoridates RO-P(X)(OH)F (X=O) and their analogues (X=S, Se) based on two new phosphitylating reagents: 2-cyanoethyl-N,N-diisopropylfluorophosphoroamidite F-P(NPr$^i_2$)OCH$_2$CH$_2$CN and tert-butyl-N,N-diisopropylfluorophosphoroamidite F-P(NPr$^i_2$)OBu^t is described.

Compounds of the general formula R-O-P(X)(F)OH **1** where X=O (R=nucleosid-3'-yl or nucleosid-5'-yl) have been first obtained by Wittmann [1]. Wittmann method and procedures described afterward are not fully satisfactory. We searched for more general synthesis of **1** especially providing approach towards thio- and selenofluorophosphates [2].

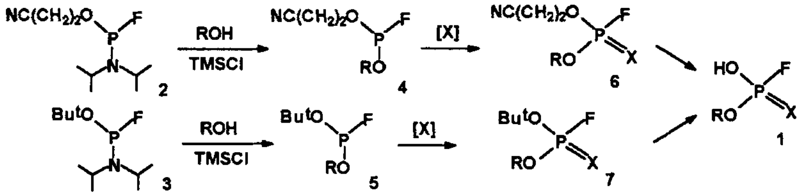
In this communication we present an expedient general method based on a phosphoroamide approach. New phosphitylating reagents containing P-F bond **2** and **3** were synthesized and applied in the synthesis of compounds **1** (X = O, S, Se). The synthetic strategy for the preparation of the phosphitylating reagents **2** and **3** is delineated below.



R : CH$_2$CH$_2$CN, Ar : 4-nitrophenyl

Preparation of amidites **2** and **3** can be performed in one-flask procedure in over 90% yield. Both compounds are stable colourless liquids which can be purified by destillation *in vacuo* or by silica gel column chromatography and stored at room temperature.

Phosphitylating reagents **2** and **3** react with alcohols in the presence of activators such as tetrazole, benzoyl chloride or trimethylsilyl chloride (TMSCl) at room temperature to give phosphorofluorides **4** and **5** in very high yield. TMSCl proved to be superior to others.



R : a) 2'-deoxynucleosid-3'-yl b) 2'-deoxynucleosid-5'-yl c) citronellyl d) cholesteryl

Oxidation of phosphorofluoridites **4** and **5** by hydrogen tert-butyl peroxide or addition of elemental sulfur in the presence of triethylamine gave the corresponding phosphorofluoridates **6** and **7** which undergo thermal elimination of 2-methyl-1-propen (80°C, 2h) or β-elimination of vinyl cyanide [pyridine-triethylamine (3:1 v/v), r.t., 10 min] to form the final compounds **1** (X=O, S) in excellent yield. All these reactions are best performed as one-flask procedures. It is noteworthy that in the coupling procedure (**3** → **5**) activated by TMSCl the tert-butyl group in unaffected. Preliminary experiments showed that this procedure is applicable for the synthesis of **1** (X=Se).

Examination of the phosphitylation procedure by ^{31}P and ^{19}F NMR spectroscopy using phosphorofluoridite **2** clearly shows intermediate formation of fluorophosphorotetrazolidite $FP(OCH_2CH_2CN)CHN_4$ **8**. Formation of fluorochlorophosphine $FP(OCH_2CH_2CN)Cl$ **9** was observed when amidite **2** was allowed to react with benzoyl chloride or TMSCl. It is most likely that the compounds **8** and **9** act as phosphitylating species towards alcohols.

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