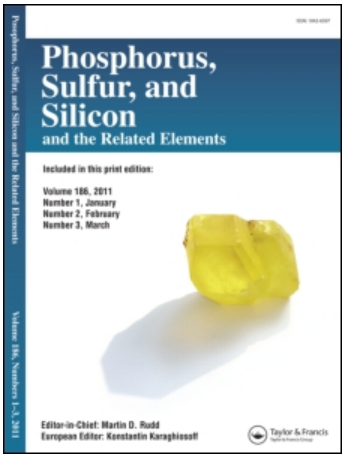

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Novel Unique Activating Reagents in Synthesis of Biophosphates Via Phosphoroamidite Route

WOJCIECH DABKOWSKI[a], IZABELA TWOROWSKA[a], JAN MICHALSKI[a], ELŻBIETA PONIATOWSKA[a] and FRIEDRICH CRAMER[b]

[a]*Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90–363 Łódź, Sienkiewicza 112, Poland and*
[b]*Max-Planck-Institut für experimentelle Medizin, 3400 Göttingen, Hermann-Rein Strasse 3, Germany*

Trimethylhalogenosilanes Me_3SiX (X=Cl,Br) are remarkably efficient activators in the reaction of P(III) amidites with nucleosides and other alcohols of biological interest to give P(III) esters in excellent yield. This activation is illustrated by synthesis of P(III) compounds containing a phosphorus-fluorine bond. Under specially chosen conditions the interaction between trimethylhalogenosilanes, 2'-deoxy-nucleosidylphosphoroamidites and nucleosides allows synthesis of 5'-phosphonate -linked deoxydinucleotides. 2,4-Dinitrophenol is an effective activator in "amidite" coupling.

Keywords: Trimethylchlorosilane; trimethylbromosilane; phosphoroamidites; phosphorofluoridites; phosphonate deoxydinucleotides

INTRODUCTION

The use of organosilicon compounds in both organic synthesis and homogenous catalysis remains a subject of current interest. This interest extends into the field of phosphates of biological and medicinal interest. In the modern synthesis of biophosphates and their structural analogues the phosphoroamidite route is one of the most efficient and highly suitable for solid phase synthesis [1]. P(III)-amides derived from diisopropylamine are relatively stable and easy to handle. They react with alcohols in the presence of activators. Tetrazole, the most widely used activator, must often be used in large excess and be of high purity. Purification involves hazardous sublimation. In our recent studies on the synthesis of modified nucleotides we were confronted with the challenge of finding an alternative mode of activation without using tetrazole or similar compounds.

In our earlier work it has been shown that the reaction of phosphorus hexamethyltriamide with trimethylbromo- or iodosilanes provides a convenient synthesis of the corresponding N,N,N',N'-tetramethylphosphoroamidous halides [2].

$$(Me_2N)_3P + Me_3SiX \rightleftharpoons (Me_2N)_2PX + Me_2NSiMe_3$$

This reaction occurs immediately at room temperature in dichloromethane solution. At -50°C no formation of the phosphoroamidous halides was observed. However, the ^{31}P NMR signals of $P(NMe_2)_3$ were drastically changed in result of the addition of trimethylhalidosilane, indicating a strong interaction of both species. ^{31}P NMR spectra and conductometric measurements prove the equilibrium.

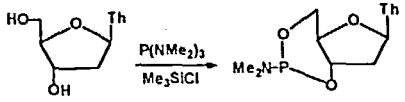
$$(Me_2N)_3P + Me_3SiX \rightleftharpoons [(Me_2N)_3P^+\text{-}SiMe_3]\,X^-$$

The signal of the complex (δ ^{31}P 64 ppm) is accompanied by satellites arising from ^{31}P-^{29}Si spin-spin coupling. The relatively high value of the coupling constant (115 Hz) speaks for P-Si bonding in the complex. When X=I the equilibrium is fully shifted toward the complex. In the case of X=Br, the low temperature ^{31}P NMR spectra prove that reaction takes an analogous course the equilibrium in contrast lies on the side of substrates. It can be anticipated that when X=Cl this equilibrium will be even more highly shifted towards substrates [3]. Became of rapid reversibility of the reaction leading to P(III)-X species suggested to us that trimethylhalogenosilanes may serve as a tool in phosphitylation of alcohols.

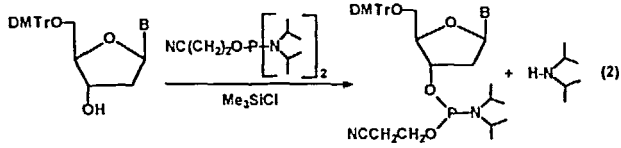
RESULTS AND DISCUSSION

The reaction of P(III) amidites with an equivalent amount of nucleoside proceeds in the presence of TMSCl in very high yield and at rates comparable or higher than those when tetrazole is used. Phosphitylations activated by TMSCl proceed at room temperature in solvents like THF, dichloromethane or acetonitrile. On average, the amount of activator required for an efficient coupling is ca. 30%-60% of the stoichiometrical ratio. Most of our experiments were performed with P(III) amides derived from diisopropylamine in order to conform to the most popular phosphitylation procedures. The rate of the reaction can controlled by the ratio of an activator.

Selected examples (1) [4], (2) [5], (3) [5], (4) [6], (5), (6) illustrating our methodology are chosen from nucleotide chemistry.

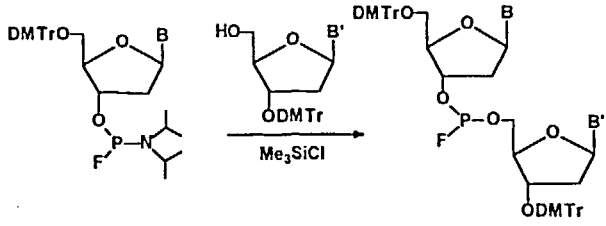


(1)



(2)

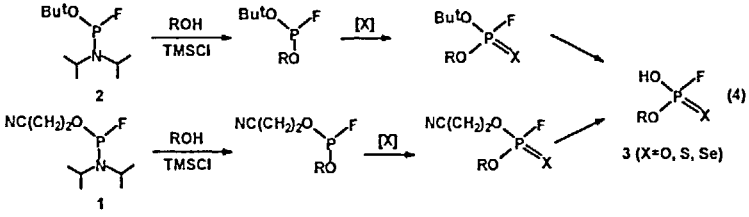
P(III) derivatives containing a phosphorus fluorine bond and ligands of biological importance have been insufficiently. Our new method of activation with trimethylchlorosilane provides an excellent access to this class of organophosphorus compounds. An example of the effectiveness of our approach is the synthesis of dinucleosidyl phosphorofluoridites.



(3)

More recently we have synthesized two new phosphitylating reagents: 2-cyanoethyl N,N-diisopropylfluorophosphoramidite F-P(NPr$^i_2$)OCH$_2$CH$_2$CN **1** and tert-butyl N,N-diisopropylfluorophosphoramidite F-P(NPr$^i_2$)OBu^t **2** [7] by standard methods via P(III) intermediates containing 4-nitrophenoxy ligands [7]. They can be prepared in high yield and show high stability at ambient temperature.

Phosphitylating reagents **1** and **2** react with alcohols in the presence of activators such as tetrazole, benzoyl chloride or TMCS at room temperature in very high yield. In our hands TMCS proved to be superior to others.



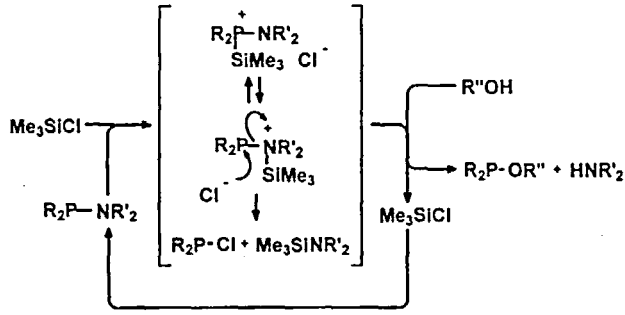
(4)

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

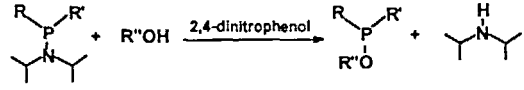
Application of phosphitylating reagents **1** and **2** allows highly effective synthesis of phosphorofluoridates, phosphorofluoridothioates and phosphorofluoridoselenoates **3** (Scheme 4) in three steps. Oxidation of intermediate of phosphorofluoridites, addition of elemental sulfur or selenium gave the corresponding phosphorofluoridates which undergo thermal elimination of 2-methyl-1-propene or β-elimination of vinyl cyanide to form the final compounds **3** in excellent yield (Scheme 4). All these reactions are best performed as one-flask procedures. It is noteworthy that in all coupling procedures activated by TMCS the tert-butyl and DMTr groups are unaffected.

Exploring the system: phosphoroamidites - alcohols - trimethylhalogenosilanes, we discovered formation of 5'-phosphonate - linked thymidine deoxydinucleotide. This type of structure is formed when 3'-O-DMTr-thymidine is allowed to react with Me$_3$SiBr prior to addition of 5'-O-DMTr-thymidin-3'-yl N,N-diisopropylphosphoroamidite.

The mechanism of activation by TMCS is presumed to involve this reaction with P(III) amide. The first step produces the salt-like species $R_2P^{\cdot}(SiMe_3)NR'_2Cl^{-}$ and $R_2P\text{-}N^{\cdot}R'_2(SiMe_3)Cl^{-}$. These react either directly with alcohol to give ester $R_2P\text{-}OR^{\cdot}$ or via intermediate formation of $R_2P\text{-}Cl$. In both cases TMCS is regenerated. The catalytic cycle involved in the activation is proposed below.



Our recent efforts are directed towards finding another simple activating reagents in „amidite" coupling reactions, 2,4-dinitrophenol is one of them.



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[5] Yield of the reaction product was almost quantitative.

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