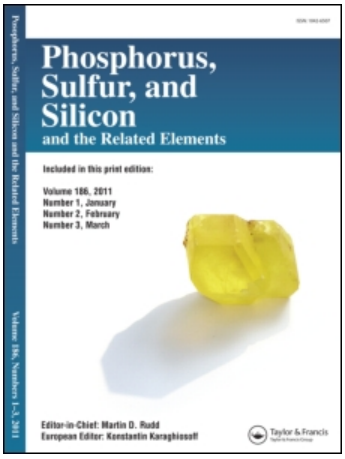

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New Methods for the Formation of the P-N and P-F Bonds, their Relevance to Nucleotide and Oligonucleotide Analogues Synthesis

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Two approaches have been developed for the formation of phosphoramidates with the nitrogen atom in bridging positions of the internucleotide linkage. One of them makes use of H-phosphonamidates as intermediates and the other is based on the oxidative coupling of H-phosphonate monoesters or their analogues with appropriate amines. Also, a new, convenient entry to nucleoside methylphosphonamidates, consisting of an oxidative coupling of nucleoside 3'-methylphosphinates with 5'-aminonucleosides, was investigated. Finally, iodine promoted desulfurization or deselenization of the appropriate phosphorothioate and phosphoroselenoate diesters in the presence of fluoride anion, was found to provide new means for the formation of the P-F bond.

Keywords: Phosphorofluoridates; Phosphoramidates; H-Phosphonates

INTRODUCTION

A potent biological activity of numerous phosphorus compounds constitutes a strong rationale for their increasingly growing applications, *inter alia*, as agrochemicals and medicinal compounds.[1,2] In the latter group the most important are derivatives of nucleosides with antiviral and antitumor properties.[1] To minimize cytotoxic effects of a potential antiviral and antitumor drug a fine adjustment of its chemical properties (*e.g.* changing the pKa values of the ioniseable functions, changing the electronegativity of substituents, their size, hydrophobicity *etc.*), is often required. In this respect

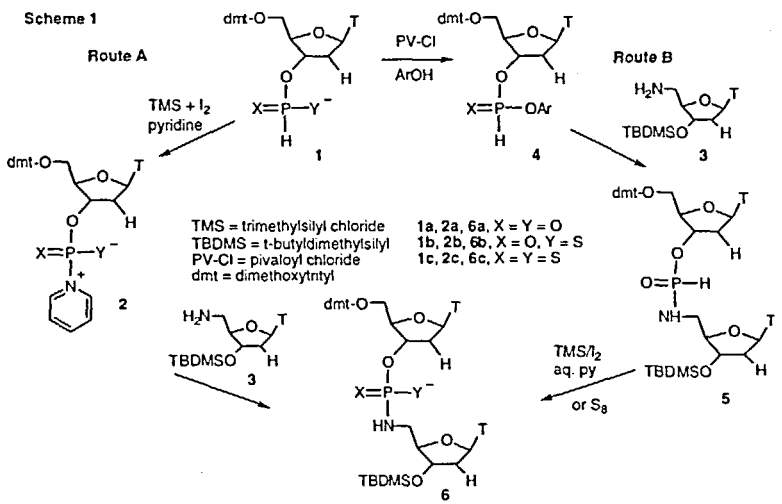
modifications at the phosphorus centre may provide the necessary tuning in interactions with enzymes, additionally modified by stereochemical factors. Changes at the phosphorus centre can also influence the transport of a drug, its preferential degradation in normal cells or activation in virus infected ones.

RESULTS AND DISCUSSION

To provide new entries and/or to develop a novel type of oligonucleotide analogues with improved properties as antisense or antigene agents, we have recently been engaged in the development of new synthetic methods for the multiple modifications of the phosphorus center in biologically important phosphate derivatives. These involve, *inter alia*, new methodologies for the formation of the P-S, P-Se, P-F, and P-N bonds. In this report, a short account of new methods for the synthesis of nucleoside phosphoramidates, methylphosphonamidates, and phosphorofluoridates developed in our Laboratories, is given.

Methods for the formation the P-N bond using H-phosphonate monoesters

Oligonucleotide N3'–>P5' phosphoramidates have recently attracted attention due to their favourable properties as antisense/antigen agents.[3,4] Two methods for the synthesis



of phosphoramidates with the P-N bond in a bridging position of the phosphodiester

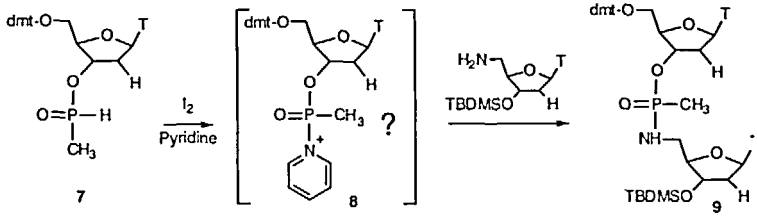
function was investigated in our Laboratory. Route A (Scheme 1) involved oxidative coupling of nucleoside H-phosphonate **1a** or its thio analogues (**1b** and **1c**) with aminonucleoside **3** to produce **6**, and route B made use of the H-phosphonamidate **5** intermediate, followed by its oxidation. Route A worked smoothly affording various phosphoramidates **6a-c** in high yields.[5] In the other approach, the generation of intermediates of type **5** in a direct coupling between **1a** and alkyl amines was hampered by extensive side reactions of amines with condensing agents. However, the conversion of **1** into aryl H-phosphonate **4**,[6] followed by aminolysis with **3** efficiently produced the desired H-phosphonamidate **5** (^{31}P NMR experiments), which after sulfurization with S_8 afforded phosphoramidothioate **6b**. Oxidation of **5** with iodine/water, was found to be significantly slower than that for H-phosphonate diesters and required a prior conversion of **5** into its trimethylsilyl esters.

Synthesis of methylphosphonamidates from methylphosphinates

We have reported that nucleoside methylphosphinates **7**, produced from a suitably protected nucleoside and methylphosphinate, can serve as useful substrates for the preparation of nucleoside methylphosphonates and nucleoside methylphosphonothioate monoesters.[7]

Recently, we have also found that phosphinate **7** in pyridine may undergo an iodine promoted oxidative coupling, with aminonucleosides (Scheme 2) to produce

Scheme 2

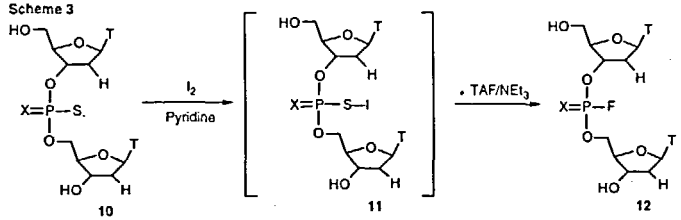


nucleoside methylphosphonamidate analogue **9**. To prevent protonation of aminonucleosides under the reaction conditions, the presence of triethylamine is required. Alkyl amines also react smoothly to the corresponding methylphosphonamidates under these conditions. The reaction is fast and clean and thus it may constitute a novel and general entry to this class of compounds.

Formation of the P-F bond *via* oxidative activation of the P-S linkage

Natural product analogues carrying =P(O)-F or =P(S)-F group have received relatively little attention despite their potentially useful properties.[8] Aiming towards the introduction of a fluorine atom to unprotected biophosphates, starting from readily available substrates, we found that dinucleoside phosphorothioate **10a** quantitatively afforded the phosphorofluoridate **12** when treated with iodine in the presence of fluoride anion.[9]

Scheme 3



This, and the possibility of replacing fluorine with other functionalities, make the method of particular relevance to the synthesis of oligonucleotide and other analogues bearing labile modifications at the phosphorus centre.

Acknowledgments
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