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Nucleosides, Nucleotides and Nucleic Acids

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New Methods for Multiple Modifications of a Phosphorus Centre. Their Relevance to Nucleotide and Oligonucleotide Analogues Synthesis

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NEW METHODS FOR MULTIPLE MODIFICATIONS OF A PHOSPHORUS CENTRE. THEIR RELEVANCE TO NUCLEOTIDE AND OLIGONUCLEOTIDE ANALOGUES SYNTHESIS

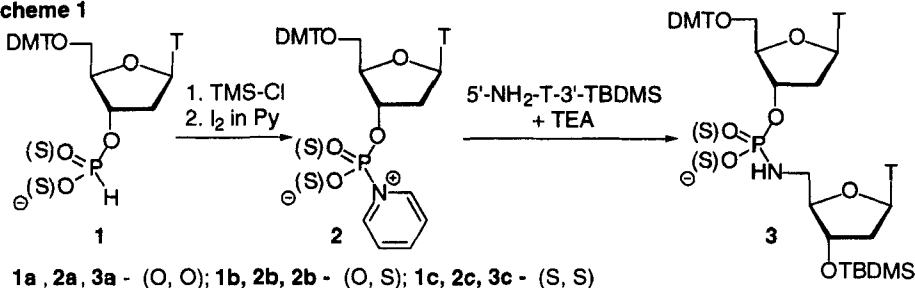
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ABSTRACT: Nucleoside phosphoramidates and their analogues with the P-N bond in bridging positions of the phosphoramidate linkage were prepared by a new method utilizing the corresponding pyridine adducts of metaphosphates. Also, a new procedure was developed for the synthesis of unprotected nucleoside phosphoromono- and phosphorodithioates.

Pyridine adduct of metaphosphates **2a-c** could be produced efficiently (³¹P NMR analysis) by treating H-phosphonate monoesters or their thio analogues (**1a-c**) consecutively with trimethylsilyl chloride (TMS-Cl, 3 equiv.) and iodine (1.5 equiv.).

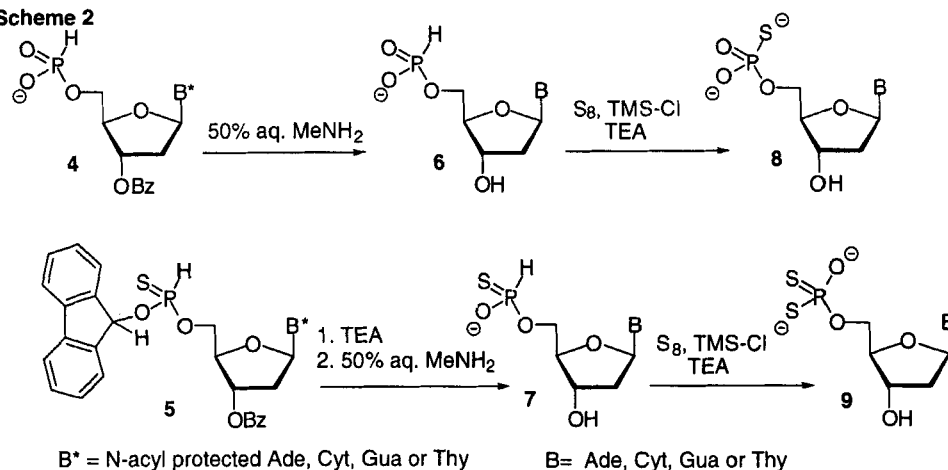
Scheme 1



The addition of a pyridine solution of 5'-amino-3'-tert-butyldimethylsilyl-5'-deoxy-thymidine (1 equiv.) and triethylamine (TEA, 5 equiv.) to intermediates **2a-c**, furnished fast and clean reaction to dinucleoside phosphoramidates **3a-c**¹ (Scheme 1). Compounds of type **3** with the N3'→P5' internucleotide linkage, can be obtained analogously using the appropriate starting materials. Isolated yields of **3** were 70-90%.

Also, a simple and efficient method for the synthesis of nucleoside phosphorothioates **8** and nucleoside phosphorodithioates **9**, utilizing sulfurization of unprotected nucleoside H-phosphonates **6** and nucleoside H-phosphonothioate **7**, was developed (Scheme 2).

Scheme 2



The key intermediates in this approach, compounds **6** and **7**, were prepared *via* phosphorylation of suitably N,O-protected nucleosidic components with diphenyl H-phosphonate² (to produce H-phosphonate **4**) or *via* thiophosphorylation with 9-fluorenmethyl H-phosphonothioate³ (to produce H-phosphonothioate **5**), followed by deprotection with aqueous methylamine (50%)⁴. In the instance of **5**, the initial removal of 9-fluorenmethyl group with triethylamine, was found to be advantageous. The sulfurization of unprotected nucleotidic synthons **6** and **7** in pyridine with elemental sulfur in the presence of TMS-Cl and triethylamine furnished within a few minutes **8** and **9**, respectively. The isolated yields 70-90%.

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