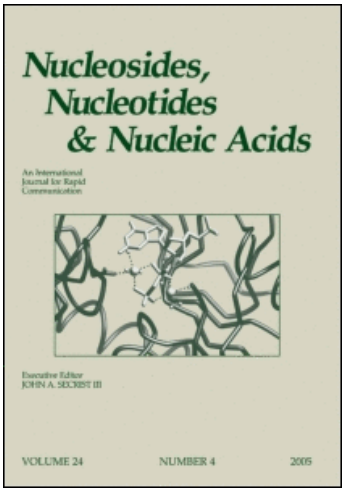


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

Inger Kers[a]; Jacek Cieslak[b]; Jadwiga Jankowska[b]; Adam Kraszewski[b]; Jacek Stawinski[a]
[a] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden
[b] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland

To cite this Article Kers, Inger , Cieslak, Jacek , Jankowska, Jadwiga , Kraszewski, Adam and Stawinski, Jacek(1999) 'New Methods for Multiple Modifications of a Phosphorus Centre. Their Relevance to Nucleotide and Oligonucleotide Analogues Synthesis', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1245 — 1246
To link to this Article: DOI: 10.1080/07328319908044678
URL: http://dx.doi.org/10.1080/07328319908044678

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1245–1246 (1999)

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

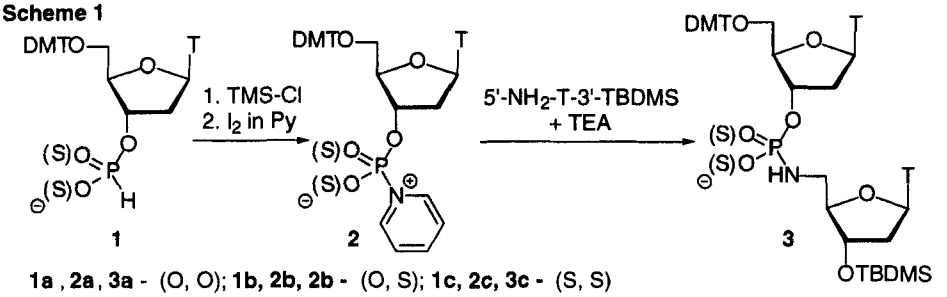
Inger Kers, Jacek Cieslak[a], Jadwiga Jankowska[a],
Adam Kraszewski[a]*and Jacek Stawinski*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden; [a]Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland

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 (^{31}P 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



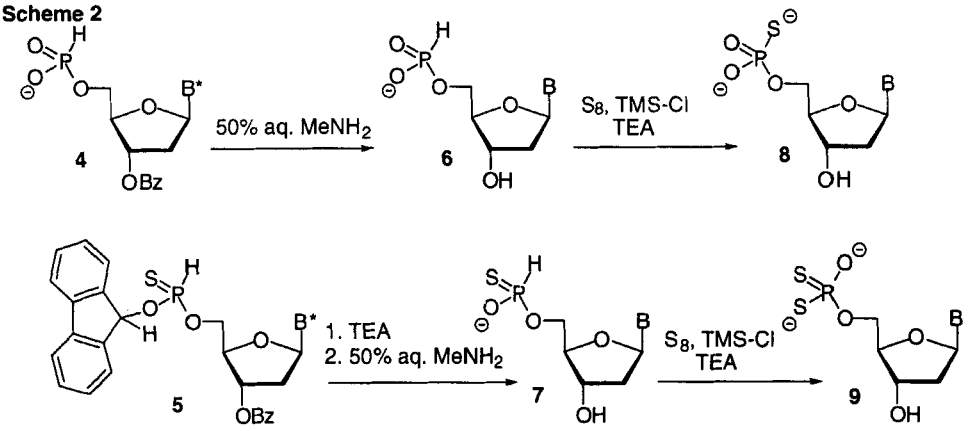
1 **2** **3**

1a , **2a**, **3a** - (O, O); **1b, 2b, 2b** - (O, S); **1c, 2c, 3c** - (S, S)

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* phosphonylation of suitably N,O-protected nucleosidic components with diphenyl H-phosphonate[2] (to produce H-phosphonate **4**) or *via* thiophosphonylation with 9-fluorenemethyl H-phosphonothioate[3] (to produce H-phosphonothioate **5**), followed by deprotection with aqueous methylamine (50%)[4]. In the instance of **5**, the initial removal of 9-fluorenemethyl 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%.

Acknowledgements

Financial support from the Swedish Natural Science Research Council and the State Committee for Scientific Research, Republic of Poland, is gratefully acknowledged.

REFERENCES

1. Kers, I.; Stawinski, J.; Kraszewski, A. *Tetrahedron Lett.* **1998**, *39*, 1219-1222.
2. Jankowska, J.; Sobkowski, M.; Stawinski, J.; Kraszewski, A. *Tetrahedron Lett.* **1994**, *35*, 3355-3358.
3. Jankowska, J.; Cieslak, J.; Kraszewski, A.; Stawinski, J. *Tetrahedron Lett.* **1997**, *38*, 2007-2010.
4. Reddy, M. P.; Farooqui, F.; Hanna, N. B. *Tetrahedron Lett.* **1995**, *36*, 8929-8932.