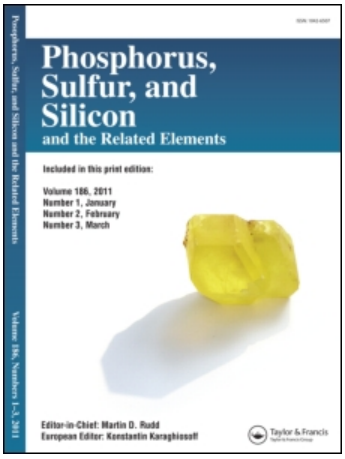


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

New Phosphitylating Reagents Containing Aryloxy Leaving Group. Applications in Nucleotide Chemistry

Jan Heliński[a]; Wojciech Dąbkowski[a]; Jan Michalski[a]
[a] Centre of Molecular & Macromolecular Studies, Polish Academy of Sciences, Łódź, Sienkiewicza

To cite this Article Heliński, Jan , Dąbkowski, Wojciech and Michalski, Jan(1993) 'New Phosphitylating Reagents Containing Aryloxy Leaving Group. Applications in Nucleotide Chemistry', Phosphorus, Sulfur, and Silicon and the Related Elements, 76: 1, 135 — 138
To link to this Article: DOI: 10.1080/10426509308032377
URL: http://dx.doi.org/10.1080/10426509308032377

Phosphorus, Sulfur, and Silicon, 1993, Vol. 76, pp. 135-138
Reprints available directly from the publisher
Photocopying permitted by license only
Printed in the United States of America

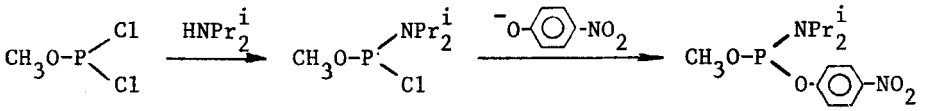
NEW PHOSPHITYLATING REAGENTS CONTAINING ARYLOXY LEAVING GROUP. APPLICATIONS IN NUCLEOTIDE CHEMISTRY

JAN HELIŃSKI, WOJCIECH DĄBKOWSKI and JAN MICHALSKI
Centre of Molecular & Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112

Synthetic oligonucleotides bearing modifications in the backbone have potentials as tools in studying and controlling biological processes.

The p-nitrophenoxy group attached to the tetracoordinate phosphorus center exhibits a high propensity to act as a leaving group in nucleophilic displacement reactions. This ability has been widely used in phosphorus chemistry and biochemistry.[1] In contrast to that, the use of the p-nitrophenoxy group in phosphitylation procedures has been little explored.[2] Systematic studies on the phosphitylating reagents containing aryloxy substituents, acting as leaving groups, have been undertaken in this Laboratory. We have shown in a preliminary paper that the p-nitrophenoxy group attached to the P^{III} center indeed acts as an excellent leaving group in the formation of the 3',5'-dinucleoside-P-methylphosphonites which are readily transformed into the corresponding P-methylphosphonates and P-methylthiophosphonates.[3]

In this paper we demonstrate the use of N,N-diisopropyl-O-methyl-O-4-nitrophenylphosphoroamidate 1 in the synthesis of oligonucleotides phosphates, thiophosphates and selenophosphates. The phosphoramidate 1 is readily available from the methoxydichlorophosphine and can be stored at ambient temperature without decomposition.



1

Internucleoside linkage formed with an aid of 1 can be constructed by two procedures, either via tetrazole activation of the diiso-

propylamino group or sodium hydride induced reaction. Both ways are remarkably selective. Potentialities of the reagent 1 are illustrated by the sequence of reactions described in Scheme 1, leading to the trinucleotide 2f containing thiophosphate and selenophosphate internucleoside linkages. The ^{31}P NMR spectrum of 2 is presented in Figure 1.

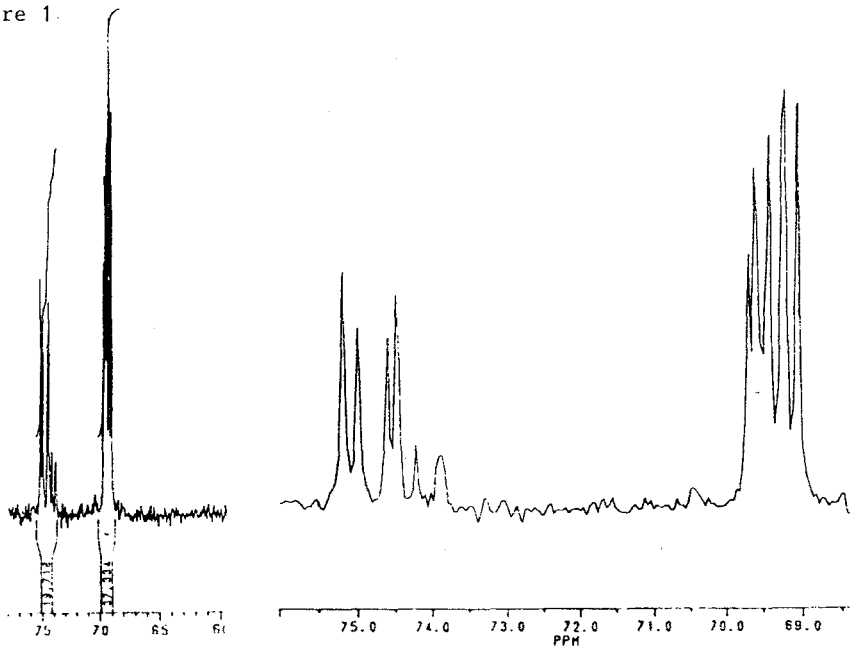
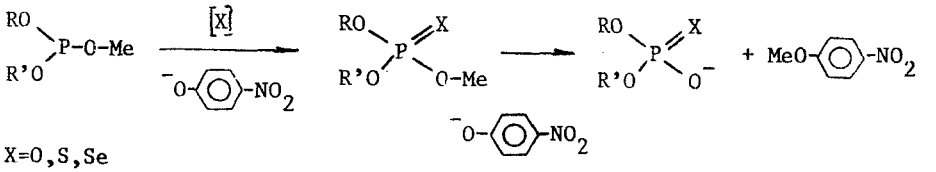
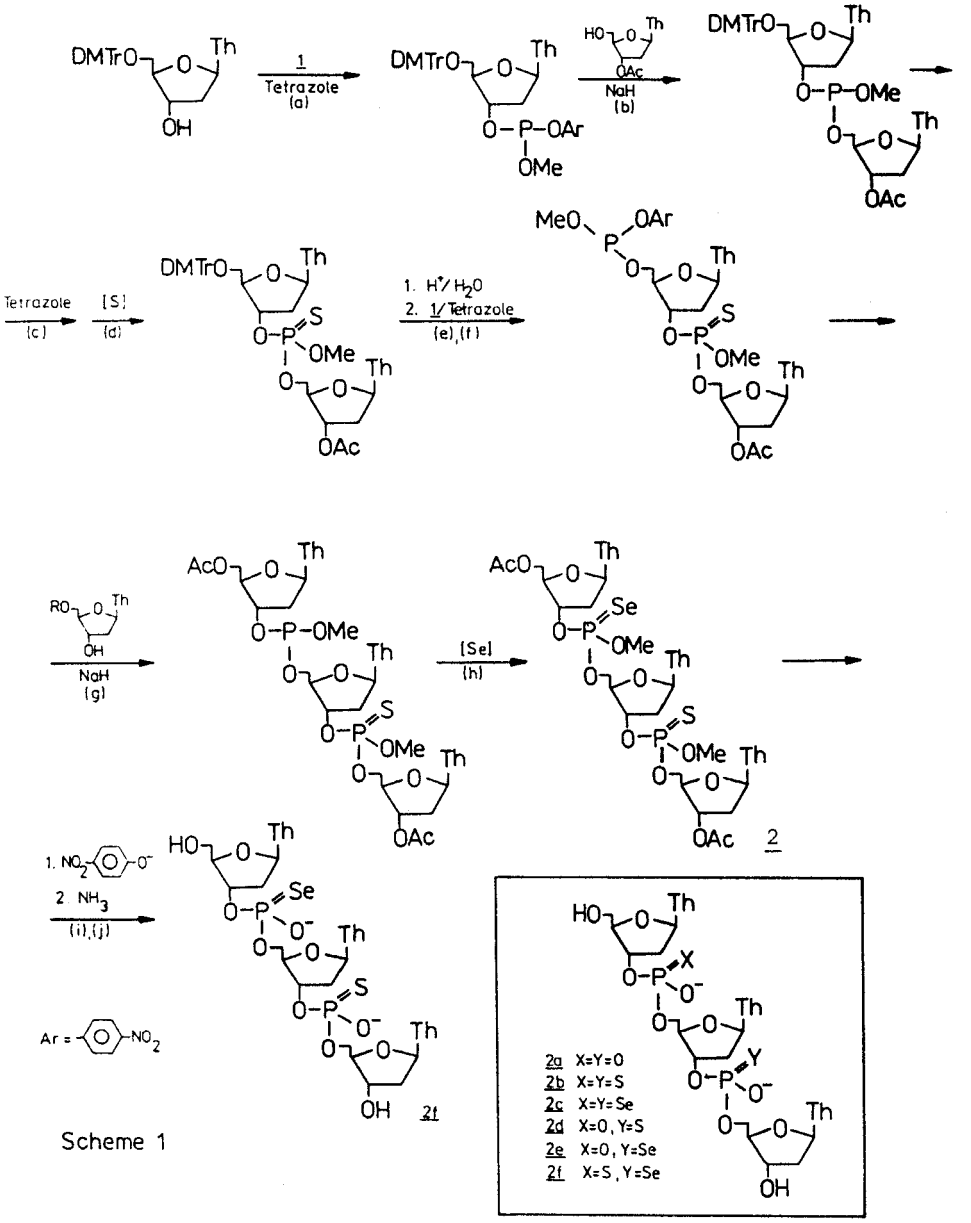


Figure 1. The 81-MHz ^{31}P NMR spectrum of the compound 2

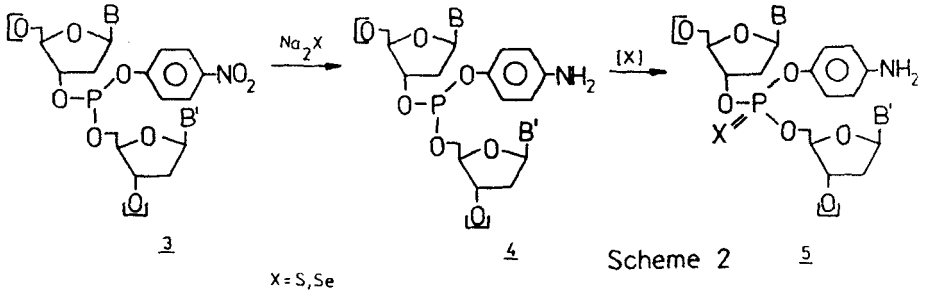
By this efficient methodology six structural combinations 2a-f are constructed. Yields and purity of the products are very high. Steps (a) and (f) involve activation by the tetrazole and steps (b) and (g) are activated by the sodium hydride. Two other additional features of this strategy are to be mentioned. The p-nitrophenol and even more its anion catalyse oxidations by elemental oxygen, sulfur and selenium. The p-nitrophenolate dealkylates tetracoordinate methyl esters more efficiently than the thiophenol.





These properties were utilized in steps (d), (h) and (i). The step (c), involving acidification by the tetrazole, is necessary to avoid dealkylation which otherwise proceeds at once after addition of the elemental sulfur. However, phosphitylation by the amidate 1 is not affected by the presence of anionic groups at the phosphorus center. This means that a modified strategy in which dealkylation by the p-nitrophenoxide preceds the phosphitylating step is possible.

The nucleosides phosphites containing p-nitrophenyl group 3 are smoothly reduced by sodium sulfide and sodium selenide to p-aminophenyl phosphites 4 These esters add immediately elemental sulfur or selenium to form in situ the correspondint thio or seleno-phosphates 5.



Scheme 2

The compound 5 (X=Se) can be efficiently oxidized under mild conditions to form its oxygen analogue 5 (X=O).

Applications of phosphitylating reagents containing aryloxy leaving groups in the synthesis of P-F modified nucleosides will be described in another paper presented during this Conference.

REFERENCES

1. Y. Hayakawa, M. Uchiyama and R. Noyori, Tetrahedron Lett., 25, 4003 (1984); Z. J. Leśnikowski and M. M. Jaworska, Tetrahedron Lett., 30, 3821 (1989).
2. R. Eritja, V. Smirnov and M. H. Caruthers, Tetrahedron, 46, 721 (1990).
3. J. Heliński, W. Dąbkowski and J. Michalski, Tetrahedron Lett., 32, 4981 (1991).