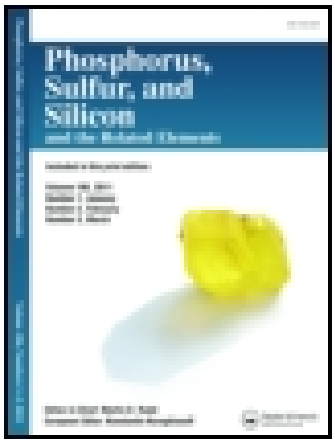


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis of P-Fluorodithioacids of Phosphorus and Their Synthetic Application

Izabela Tworowska [a], Wojciech Dabkowski [a] & Jan Michalski [a]

[a] Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

Published online: 27 Oct 2010.

To cite this article: Izabela Tworowska, Wojciech Dabkowski & Jan Michalski (2002) Synthesis of P-Fluorodithioacids of Phosphorus and Their Synthetic Application, Phosphorus, Sulfur, and Silicon and the Related Elements, 177:6-7, 1855-1858, DOI: 10.1080/10426500212294

To link to this article: http://dx.doi.org/10.1080/10426500212294

Phosphorus, Sulfur and Silicon, 2002, Vol. 177:1855–1858

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290093298

SYNTHESIS OF P-FLUORODITHIOACIDS OF PHOSPHORUS AND THEIR SYNTHETIC APPLICATION

Izabela Tworowska, Wojciech Dabkowski, and Jan Michalski
Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

(Received July 29, 2001; accepted December 25, 2001)

Oligonucleotides containing 3′-S-*P(S) and* 5′-S-*P(S) fragments in the deoxy-series are available only by tedious multistep procedures. We have developed a novel and efficient methodology based on ring opening of anhydronucleosides by phosphorus dithioacids. This approach allows efficient synthesis of modified dinucleotides of the ribo-series.*

Keywords: 1,3,2-Dithiaphospholane method; anhydronucleosides; phosphorodithioic acids; thionucleotides

INTRODUCTION

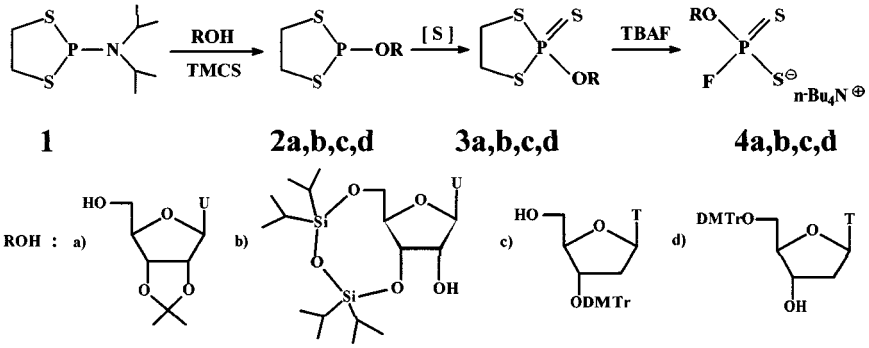
The rapid development of antisense chemotherapy[1] and studies to elucidate the mechanism of rybozyme action[2] have encouraged organic chemists to undertake the synthesis of oligonucleotide analogues in which the sugar residues and internucleotide linkages are modified. Interest in oligonucleotides containing 3′-*S*- or 5′-*S*-phosphorothioate linkages has recently increased. These compounds have been prepared 1) via nucleophilic displacement of 3′-iodo-, 5′-tosyl-, or 5′-bromo-5′-deoxynucleosides by nucleoside 3′-phosphorothioates,[3] 2) via phosphoroamidide chemistry,[4] 3) via Michaelisa-Arbusov reaction between a nucleosid-5′-yl phosphite and a nucleosid-3′-yl-*S*-disulfide.[5] Methods presented to date, though elegant, are laborious and difficult to carry out.[3–6] For this reason we have sought an alternative strategy avoiding 3′-*S*- or 5′-*S*-thionucleosides. Our long-standing interest in the chemistry of modified nucleotides containing P—F bond also stimulated this

Address correspondence to J. Michalski, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland. E-mail: jmich@bilbo.cbmm.lodz.pl

work.[7] It is known that readily available 2,3′-anhydrothymidine reacts with a variety of nucleophiles, usually under harsh conditions.[8] Our laboratory has been involved in the design and synthesis of modified nucleotides, with the fluorine ligand attached to a tetracoordinate or tricoordinate phosphorus center. Continuing our efforts to explore this field, we report a new synthesis of nucleosidyl phosphorodithioates in both DNA and RNA series. Our approach is based on the reaction of anhydronucleosides with a variety of phosphorofluoridodithioic acids.[9] Efficient synthesis of the latter is based on 1,3,2-dithiaphospholane derivatives, which are known to undergo facile ring opening by nucleophilic reagents.[10]

RESULTS AND DISCUSSION

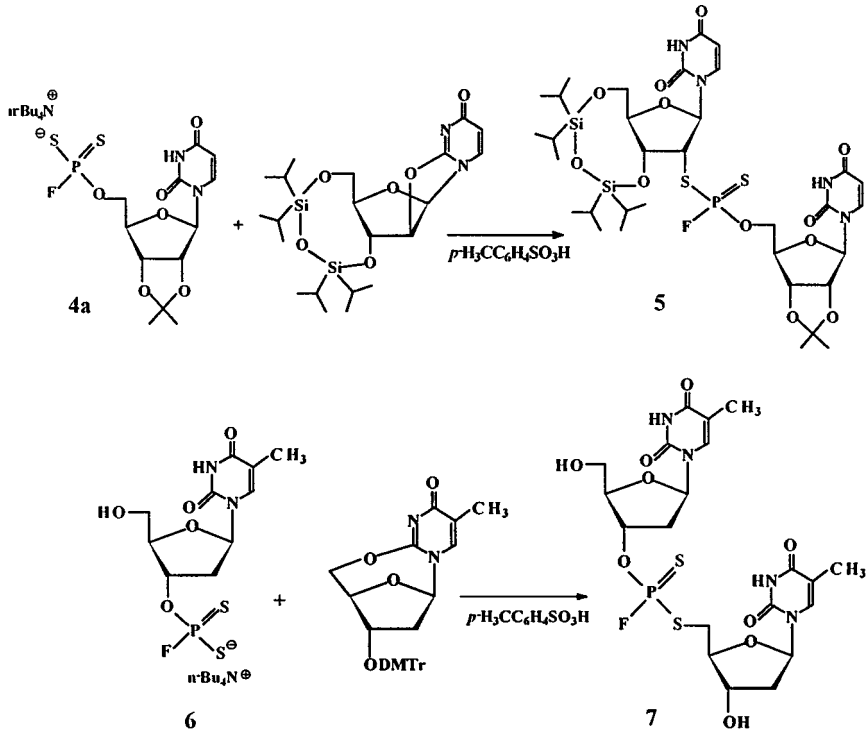
Compound **1** was prepared from 1,2-ethanediol and diisopropylphosphoramidous dichloride and allowed to react with a nucleoside in the presence of trimethylchlorosilane (TMCS),[11] yielding the nucleosidyl-*O*-(1,3,2-dithiaphospholane) **2**. The latter was sulfurized by elemental sulfur to give compound **3**. The crucial step leading to the derived phosphorofluoridodithioates **4** is the reaction with *tetra*-butylammonium fluoride (TBAF). All reactions presented in Scheme 1 proceed in very high yield. Yields of the final products exceeded 95%. This strategy allowed us to prepare a number of novel organic structures and can also be extended to analogues of **4** containing a P═Se group.



SCHEME 1

The reaction proceeds in THF solution at room temperature. While methods used previously are less suitable, ours gives easy access to this class of compounds and opens a door to the study of their interesting chemistry.

Having such excellent access to phosphorofluoridodithioic acids, we used them in reactions with anhydronucleosides in both DNA and RNA series. Scheme 2 illustrates opportunities connected with our strategy.



SCHEME 2

Ring opening reactions proceed at ambient temperature in over 95% yield. The expected inversion of configuration at 3′- or 2′-carbon atoms was observed in all our experiments. The dinucleotides **5**, **7**, obtained from **4a** or **6**, are formed as a 1:1 mixture of diastereoisomers and can be purified by silica gel chromatography. As expected, they are relatively stable towards nucleophilic reactions. The special feature of this ring opening is the high rate of the reaction with free dithioic acid and the sluggish reaction rate with their salts. This means that protonation is vital to form a good leaving group. The dithioic acids were prepared *in situ* by treating their salts with excess of *p*-toluenesulfonic acid monohydrate. The low nucleophilicity of sulfonic acids is well known. Water introduced in this way does not interfere with the ring opening reaction but effects the removal of acid sensitive protective groups. We are currently exploring the use of anhydronucleoside to construct

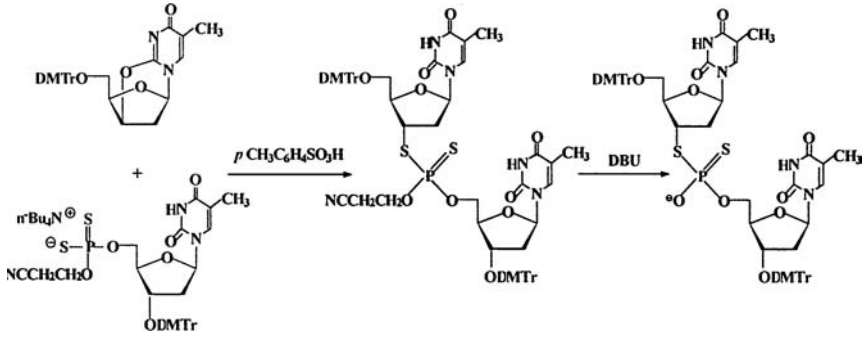


FIGURE 1

analogues of oligonucleotides containing phosphorothiolate linkages by this methodology in the RNA series. The representative example (see Figure 1) is the synthesis of dithymidine-2′-*S*-phosphorodithioate performed in very high yield and purity.

In conclusion, our approach proves to be generally applicable to various classes phosphorus dithioacids and anhydronucleosides.

REFERENCES

[1] J. S. Cohen, ed., *Oligonucleotides: Antisense Inhibitors of Gene Expression*, (Macmillan, London, 1989).
[2] W. A. Picken, D. B. Olsen, F. Benseler, and F. Eckstein, *Science*, **253,** 314 (1991).
[3] S. Chladek and J. Nagyvary, *J. Am. Chem. Soc*., **94,** 2079 (1972); A. Okruszek, M. Olesiak, and W. J. Stec, *Phosphorus Sulfur Silicon, Relat. Elem*., **111,** 81 (1996).
[4] M. Mag, S. Lüking, and J. W. Engels, *Nucleic Acids Res*., **19,** 1437 (1991).
[5] X. Li, G. K. Scott, A. D. Baxter, R. J. Taylor, J. S. Vyle, and R. Cosstick, *J. Chem. Soc. Perkin Trans.*, **1,** 2123 (1994).
[6] X. Liu and C. B. Reese, *Tetrahedron Lett*., **37,** 925 (1996).
[7] W. Dąbkowski and I. Tworowska, *Chem. Lett*., 727 (1995); W. Dąbkowski and I. Tworowska, *Tetrahedron Lett*., **36,** 1095 (1995).
[8] S. Czernecki and J. M. Valery, *Synthesis*, 239 (1991).
[9] W. Dąbkowski, M. Michalska, and I. Tworowska, *Chem. Commun*., 427 (1998); W. Dąbkowski, M. Michalska, and I. Tworowska, *Nucleosides & Nucleotides*, **17**(9–11), 1635 (1998); I. Tworowska and W. Dąbkowski, *Chem. Commun*., 2611 (1998); I. Tworowska and W. Dąbkowski, *Nucleosides & Nucleotides*, **18**(4 & 5), 977 (1999).
[10] A. Okruszek, A. Sierzchała, M. Sochacki, and W. J. Stec, *Tetrahedron Lett.*, **33,** 7585 (1992); S. F. Martin and A. S. Wagman, *J. Org. Chem*., **58,** 5897 (1993).
[11] W. Dąbkowski, I. Tworowska, J. Michalski, and F. Cramer, *Chem. Commun.*, 877 (1997).