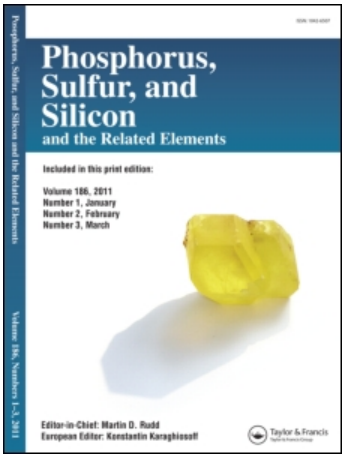

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New Synthetic Methods for Nucleotide Analogues Based on H-Phosphonate Chemistry: A Progress Report

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NEW SYNTHETIC METHODS FOR NUCLEOTIDE ANALOGUES BASED ON H-PHOSPHONATE CHEMISTRY: A PROGRESS REPORT

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New synthetic methods, based on H-phosphonate chemistry, have been developed for functionalization of oligonucleotides and for the preparation of various nucleotide analogues bearing sulfur and selenium at the phosphorus center.

Keywords: H-Phosphonates; H-phosphonothioates; selenization

INTRODUCTION

The interest in modified oligonucleotides has boomed during the last decade due to the therapeutic potential of this class of compounds as antisense and antigene agents, causing a high demand for DNA and RNA mimics, bearing various modifications at the phosphorus center.

Over the years, our laboratories have been involved in development of new, efficient methodologies and reagents for the preparation of biologically important phosphate and their analogues, based on H-phosphonate chemistry.[1] Here, we present some of our recent methods for modifications of a phosphorus center in nucleotides.

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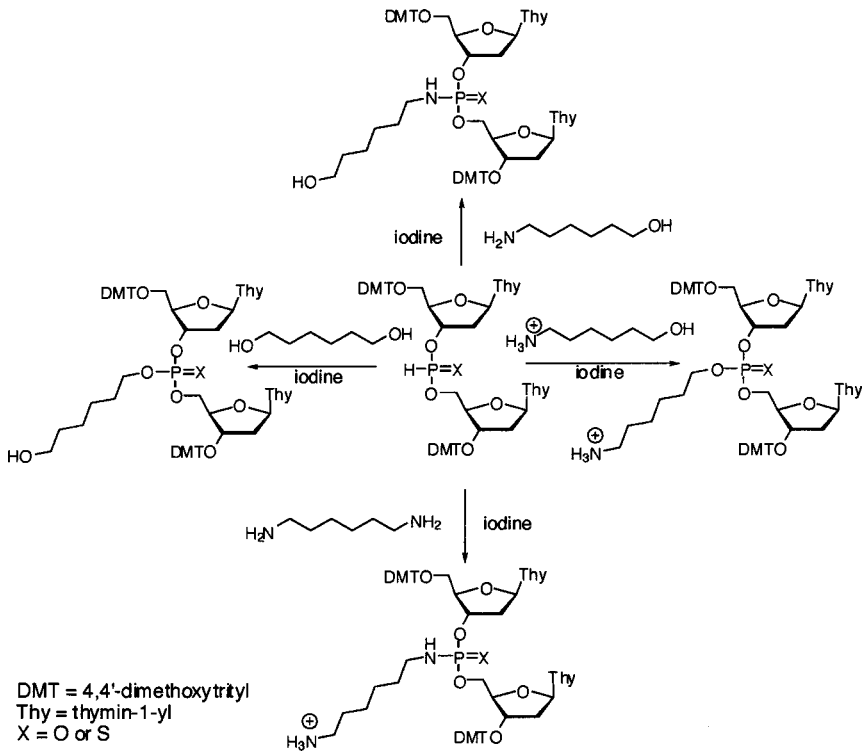
RESULTS AND DISCUSSION

Oxidative Coupling of H-Phosphonate and H-Phosphonothioate Diesters

Functionalization of oligonucleotides with diols, amino alcohols, and other bifunctional reagents enables the attachment of various reporter groups to DNA and RNA fragments for the purpose of producing hybridization probes or other medical diagnostics.[2] Recently, we have developed a chemoselective method for the oxidative coupling of dinucleoside H-phosphonates with amino alcohols.[3] Now we have extended this methodology to H-phosphonothioate derivatives and to other bifunctional reagents (Scheme 1).



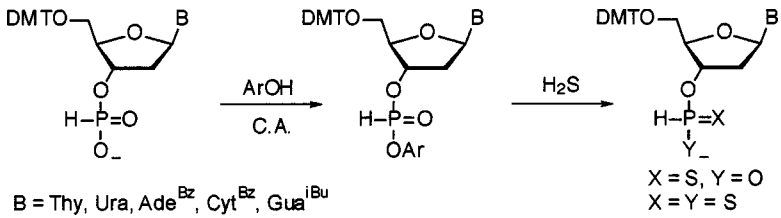
SCHEME 1

We found that H-phosphonate and H-phosphonothioate diesters in pyridine reacted rapidly (ca 5 min) with N-nucleophiles in the presence of iodine (1.5 equiv) to produce the corresponding phosphoramidate and

phosphorothioamidate diesters in high yields. H-Phosphonothioates were significantly less reactive toward O-nucleophiles compared to H-phosphonate derivatives (few minutes *vs* few hours), and the reaction mixtures were often contaminated by the corresponding pyrophosphates. A particularly sluggish reaction (several hours) was the oxidative coupling of H-phosphonodithioate diesters with amino alcohols hydrochlorides. Using ^{31}P NMR spectroscopy, we found that this was due to conversion of the initially formed phosphorothioiodidate into rather unreactive phosphorothiochloridate. Investigations of a stereochemical course of these reactions showed that in pyridine a complete epimerization at the phosphorus center occurred,[4] while in acetonitrile, the reactions appeared to be stereospecific.

Synthesis of H-Phosphonomonothioate and H-Phosphonodithioate Monoesters

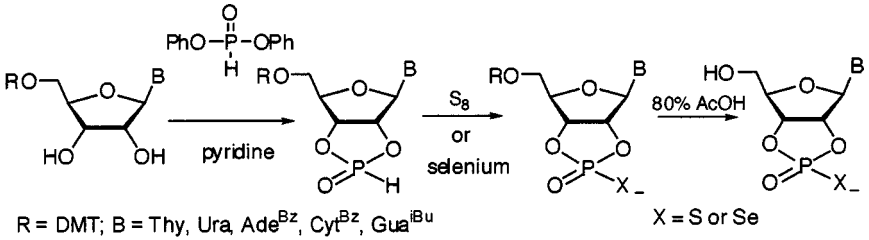
A new method for the preparation of nucleoside H-phosphonothioates and nucleoside H-phosphonodithioate, which makes use of sulfhydrolysis of aryl H-phosphonate intermediates with hydrogen sulfide, has been developed. Depending on the nature of the aryl group used, either H-phosphono*mono*thioate or H-phosphono*di*thioate monoesters can be prepared in high yields.[5]



SCHEME 2

Thio- and Seleno Analogues of Nucleoside 2,′3′-Cyclic Phosphates

The reaction of 5′-protected ribonucleosides with diphenyl H-phosphonate in pyridine furnished rapid formation of the corresponding 2′,3′-cyclic H-phosphonates, which upon sulfurization and the subsequent removal of the 5′-protecting group afforded nucleoside 2′,3′-*O*,*O*-cyclophosphorothioates in high yields.[6] When selenium is used instead of sulfur for the oxidation, the corresponding cyclic phosphoroselenoates are formed.

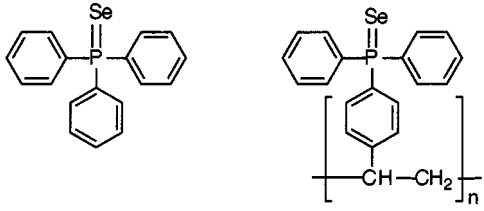


R = DMT; B = Thy, Ura, Ade^{Bz}, Cyt^{Bz}, Gua^{iBu}

SCHEME 3

Triphenylphosphine Selenide as a Selenium-Transferring Reagent

Triphenylphosphine selenide and its polymer-supported counterpart were found to be efficient selenium-transferring reagents for the conversion of H-phosphonate diesters and phosphite triesters into the corresponding phosphoroselenoate derivatives.[7] The reaction is fast and occurs under mild conditions.



SCHEME 4

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