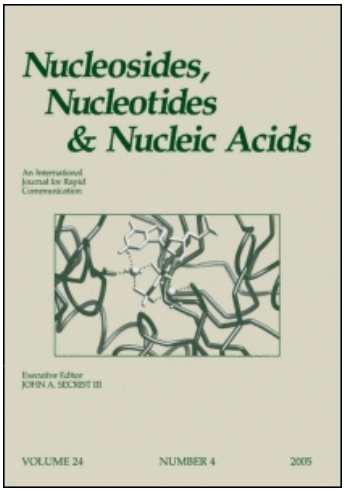

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Developing Synthetic Methods for Bioactive Phosphorus Compounds Using H-Phosphonate Chemistry: A Progress Report

Martin Bollmark,[1] Tommy Johansson,[1] Martin Kullberg,[1] Johan Nilsson,[1] Jacek Stawinski,[1,2,*] Jacek Cieslak,[2] Jadwiga Jankowska,[2] Michal Sobkowski,[2] Marzena Szymczak,[2] Malgorzata Wenska,[2] and Adam Kraszewski[2,*]

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ABSTRACT

In this paper a short account of our recent research concerning the development of new synthetic methods and reagents for the preparation of nucleotides and their analogues, is given.

Key Words: H-phosphonates; H-phosphonthioates; H-phosphonoselenoates; Pyridylphosphonates; Cyclic phosphonates.

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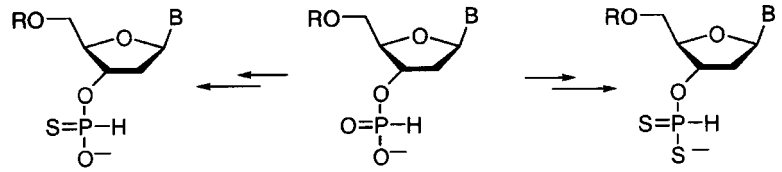
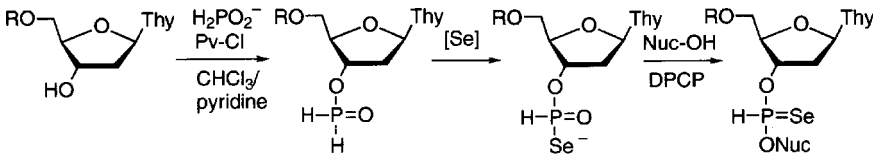
Synthesis of Nucleoside H-Phosphonothio- and H-Phosphonodithioate Monoesters



R = 4,4'-dimethoxytrityl

Transformation of nucleoside H-phosphonate monoesters into the corresponding H-phosphonothioate and H-phosphonodithioate derivatives and possible side-reactions that may accompany this process were studied using ^{31}P NMR spectroscopy. These provided new insight into a possible mechanism involved in this transformation and constituted the basis for development of efficient methods for the preparation of nucleoside H-phosphonothioate and nucleoside H-phosphonodithioate monoesters via sulfhydrolysis of activated H-phosphonate derivatives (aryl or mixed anhydrides).[1]

H-Phosphonoselenoates – A New Type of Synthetic Intermediates



R = 4,4'-dimethoxytrityl; Thy = thymin-1-yl; Nuc-OH = 5'-OH unprotected nucleside

Efficient protocols for the preparation of novel synthetic intermediates, H-phosphonoselenoate monoesters and the corresponding dinucleoside H-phosphonoselenoate diesters, have been developed.[2] Selenization of the in situ produced phosphinate intermediates with elemental selenium produced H-phosphonoselenoate monoesters from which the corresponding H-phosphonoselenoate diesters could be obtained in high yields.

Synthesis of Nucleoside 2′,3′-*O,O*-Cyclic Phosphorothioate and Phosphorodithioates

Phosphonylation of 5′-protected ribonucleosides with diphenyl H-phosphonate in pyridine furnished rapid formation of the corresponding 2′,3′-*O,O*-cyclic H-phosphonates, which upon sulfurisation and the subsequent removal of the 5′-protecting group, afforded nucleoside 2′,3′-*O,O*-cyclic phosphorothioates in high yields.[3]

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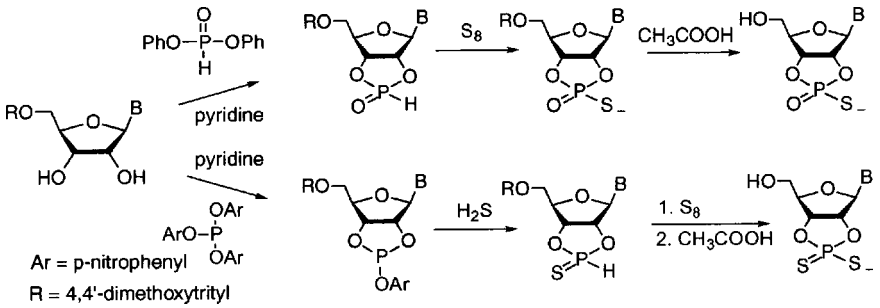
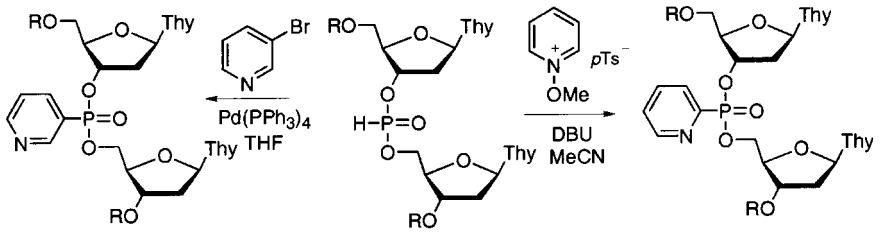


Also, a highly efficient method for the preparation of the phosphorodithio analogues of nucleoside 2′,3′-*O,O*-cyclic phosphates using tris(4-nitrophenyl) phosphite as a phosphitylating reagent, was developed.[4]

Pyridylphosphonates – New Nucleotide Analogues



Suitably protected dithymidine H-phosphonates afforded the corresponding dinucleoside 2-pyridylphosphonates upon treatment with N-methoxypyridinium tosylate in acetonitrile in the presence of 1,8-diazabicylo[5.4.0]undec-7-ene (DBU).[5] The reaction was rapid (ca. 5 min), practically quantitative and proceeded stereospecifically, most likely with retention of configuration at the phosphorus centre. For the preparation of dinucleoside 3-pyridylphosphonates, as well as their 2- and 4-pyridyl positional isomers, efficient palladium(0)-catalysed cross coupling strategy was developed.[6]

Other Studies

Phosphoropyridinium adducts derived from phosphate diesters, although postulated on many occasions as intermediates in various transformations of phosphorus compounds, remained until recently elusive.

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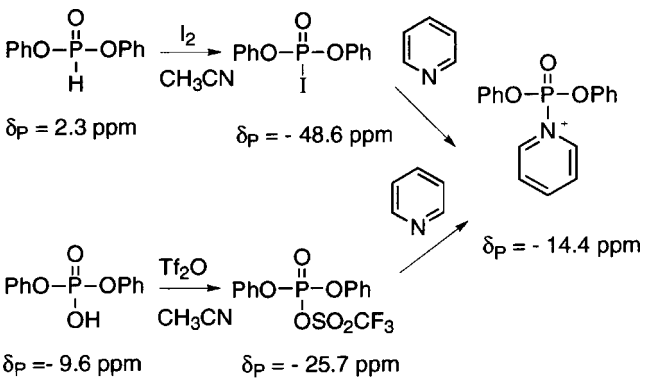

A ^{31}P NMR study on the reactions of diphenyl and diethyl chlorophosphates or bromophosphates with pyridine showed that equilibria of these reactions are heavily shifted to the left and thus concentrations of the putative diorganyl phosphoropyridinium chlorides/bromides are usually below the detection level of this spectroscopic method. However, when diphenyl iodophosphate was subjected to reaction with pyridine, we were able to observe the formation of a diorganyl phosphoropyridinium intermediate by ^{31}P NMR spectroscopy.[7]

As part of our basic research in H-phosphonate chemistry, configurational stability of dinucleoside H-phosphonates and the stereochemical course of their sulfurisation in the presence of diazabicyclo[5.4.0]undec-7-ene (DBU) were investigated using ^{31}P NMR spectroscopy.[8] It was found that irrespective of the type of protecting groups present in the nucleoside moieties, the H-phosphonate diesters investigated did not undergo any detectable epimerisation at the phosphorus centre, and their sulfurisation with elemental sulfur in the presence of DBU, proceeded stereospecifically.

In the reagents part, triphenylphosphine selenide (TPPSe) and its polymer-supported counterpart were found to be efficient selenium-transferring agents for the conversion of H-phosphonate diesters and phosphite triesters into the corresponding phosphoroselenoate derivatives.[9]

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