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Synthesis of Nucleotide Analogues with Pyridylphosphonate and Pyridylphosphono thio ate Internucleotide Linkages

Tommy Johansson^a; Jacek Stawinski^a

^a Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden

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SYNTHESIS OF NUCLEOTIDE ANALOGUES WITH PYRIDYLPHOSPHONATE AND PYRIDYLPHOSPHONOTHIOATE INTERNUCLEOTIDE LINKAGES

Tommy Johansson and Jacek Stawinski Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

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Efficient synthetic methods for the preparation of dinucleoside 4-pyridyl-, 3-pyridyl-, and 2-pyridylphosphonates have been developed.

Keywords: H-Phosphonates; H-phosphonothioates; pyridylphosphonates.

INTRODUCTION

Pyridylphosphonic acids and their simple alkyl esters belong to a class of low-molecular weight phosphorus compounds with a wide range of important applications. In industrial processes, these compounds are most frequently used to inhibit corrosion or as disperse, antistatic, complexing, and emulsifying agents. Pyridylphosphonates also exhibit a broad spectrum of biological activity, which makes them important constituents of various preparations of pesticides (insecticides, fungicides, herbicides, etc.).

This diverse array of biological activity of pyridylphosphonates inspired us to incorporate this functionality into nucleotides as a potentially useful modification in designing new antisense and antigene agents. With this in mind, we have embarked on investigations aimed at the development of mild and efficient methods, compatible with fra gile natural products, for the synthesis of 2-pyridyl- (2), 3-pyridyl- (3), and 4-pyridylphosphonates (1), as well as their thio derivatives.

Address correspondence to Jacek Stawinski, Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden. E-mail: js@organ.su.se

$$R_1O-P-OR_2$$
 $R_1O-P-OR_2$ $R_1O-P-OR_2$ $R_1O-P-OR_2$

 $\textbf{FIGURE 1} \quad R_1,\, R_2 = a \text{ nucleosiole de moiety; } X = O \text{ or } S.$

RESULTS AND DISCUSSION

Most of synthetic methods for the preparation of pyridylphosphonates **1–3** make use of a nucleophilic attack of a phosphorus nucleophile on an electron deficient pyridine ring. All of them follow the disconnection patterns shown on Scheme 1, but differ in type of phosphorus nucleophile

$$\begin{array}{c}
O \\
P_1O-P-OR_2 \\
N
\end{array}$$

$$\begin{array}{c}
O \\
P_1O-P-OR_2 \\
O \\
P_1O-P-OR_2
\end{array}$$

$$\begin{array}{c}
O \\
H \\
N
\end{array}$$

$$\begin{array}{c}
O \\
N \\
N
\end{array}$$

$$\begin{array}{c}
O \\
P_1O-P-OR_2 \\
P_1O-P-OR_2
\end{array}$$

$$\begin{array}{c}
O \\
N \\
P_1O-P-OR_2
\end{array}$$

SCHEME 1

used for the reaction and the mode of activation of the pyridine ring to facilitate attack of a nucleophile.^{3–9}

Synthesis of Dinucleoside 4-Pyridylphosphonates

We found that dinucleoside H-phosphonates and dinucleoside H-phosphonothioates can be efficiently converted into 4-pyridyl-phophonate⁸ or 4-pyridyl-phosphonothioate derivatives under mild conditions in pyridine in the presence of trityl chloride and DBU.

Synthesis of Dinucleoside 2-Pyridylphosphonates

2-Pyridylphosphonates and their thio analogues bearing nucleoside moieties⁹ can be obtained in high yields by reacting the corresponding H-phosphonate or H-phosphonothioate derivatives with N-alkoxypyridinium salts in the presence of DBU. The reaction is rapid and clean, and it affords the target compounds in 80–90% yields after silica gel chromatography.

FIGURE 3

FIGURE 4

Synthesis of Dinucleoside 3-Pyridylphosphonates

³¹P NMR experiments showed that dinucleoside 3-pyridylphosphonates and 3-pyridylphosphonothioates were formed efficiently in a palladium-catalysed cross-coupling¹⁰ of H-phosphonate and H-phosphonothioate diesters with 3-bromopyridine. The reaction seemed to be stereospecific, and preliminary preparations afforded the target compounds in high yields (80–90%).

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