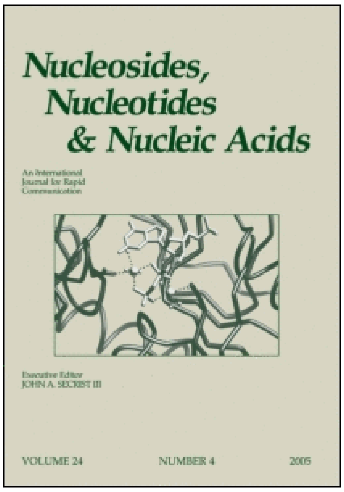

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Studies on the Conversion of Nucleoside H-Phosphonate Monoesters into the Corresponding H-Phosphonothioates

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STUDIES ON THE CONVERSION OF NUCLEOSIDE H-PHOSPHONATE MONOESTERS INTO THE CORRESPONDING H-PHOSPHONOTHIOATES

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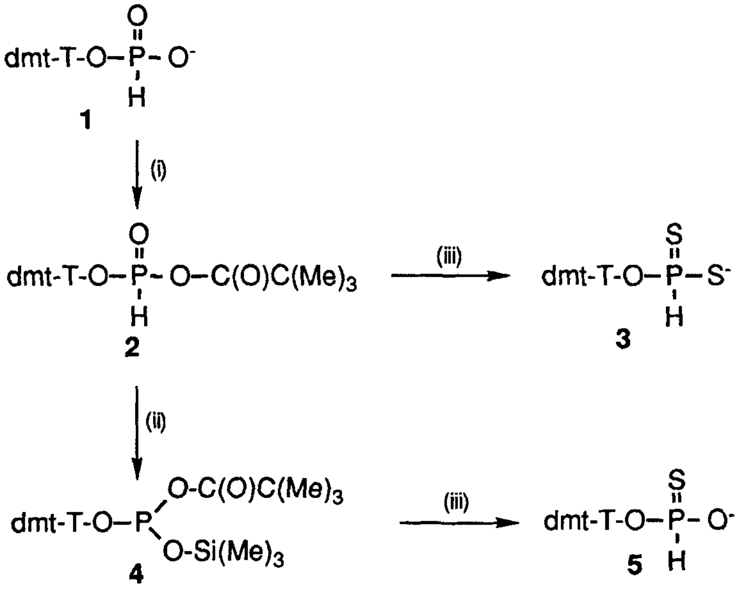

(i) Pivaloyl chloride in quinoline; (ii) Trimethylsilyl chloride in quinoline; (iii) Hydrogen sulfide in dioxane.

We have recently reported that reaction of nucleoside hydrogenphosphonates with coupling agents in pyridine, followed by addition of hydrogen sulfide, affords nucleoside H-phosphono*di*thioates as predominant products.[1] In order to steer the reaction towards H-phosphono*mono*thioates we replaced pyridine by quinoline, since it is known that in the latter solvent activation of H-phosphonate monoesters with acyl chlorides yields the mixed anhydride of type **2**[2] almost exclusively. Unfortunately, when nucleoside H-phosphonate **1** was treated with various amounts of pivaloyl chloride (PV-Cl) in quinoline/acetonitrile (1:4, v/v) followed by addition of hydrogen sulfide, the *di*thio H-phosphonate **3** was again the predominant product. Depending on the amount of coupling agent, the reaction afforded mainly **3** (3 equiv. of PV-Cl) or a mixture of **3** and the starting material **1** (ratio ~1:1) when 1.1 equiv. of PV-Cl was used. The amount of the *mono*thio H-phosphonate **5** was approximately the same in all reactions and constituted ~10% of all nucleotidic material.

Since the *di*thio compound **3**, most likely, is formed from the *mono*thio H-phosphonate **5**, which under reaction conditions undergoes activation with **2** or with PV-Cl, we attempted to convert the mixed anhydride **2** into the silylated species **4**. We assumed that this kind of intermediate should react with H_2S to produce exclusively the H-phosphono*mono*thioate **5**. To check if this was the case, the H-phosphonate **1** was activated in quinoline/acetonitrile (1:4, v/v) with 1.3 equiv. of PV-Cl and then 5 equiv. of trimethylsilyl chloride (after 2 min.) and 4 equiv. of H_2S (after 1 min.) were added consecutively. The ^{31}P NMR spectrum of the reaction mixture revealed that the *mono*thio H-phosphonate **5** was indeed the major product with only ~5% of the *di*thio compound **3** present. The amount of the undesired H-phosphonodithioate **3** was further decreased when 3 equiv. of PV-Cl was used for activation. As in the reactions without silylation, some minor side products were also present.

The same reaction sequence was repeated in pyridine/acetonitrile (1:4, v/v) as a solvent. In this case, as judged from the ^{31}P NMR spectra, the *di*thio and the *mono*thio compounds (**3** and **5**) were formed in almost equal amount.

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