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Studies on Sulfurization of Nucleoside H-Phosphonate and H-Phosphonothioate Esters Using 3H-1,2-Benzodithiol.3-one 1,1-dioxide

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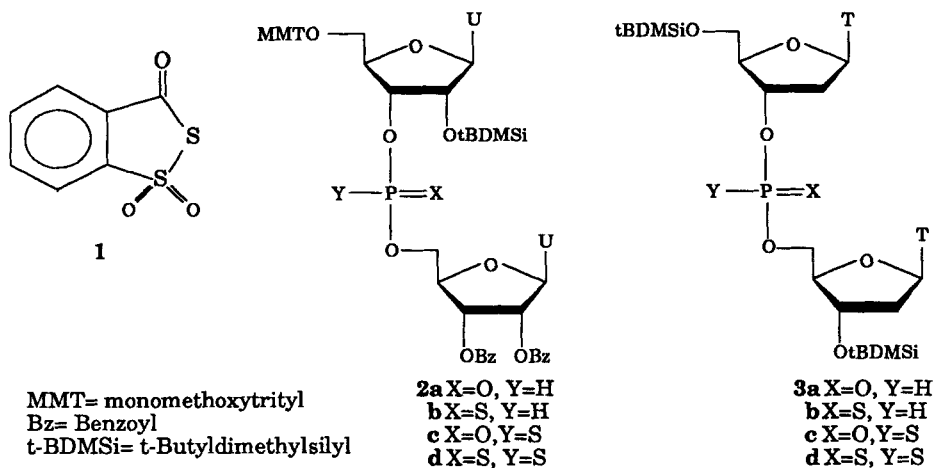
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STUDIES ON SULFURIZATION OF NUCLEOSIDE H-PHOSPHONATE AND H-PHOSPHONOTHIOATE ESTERS USING 3*H*-1,2-BENZODITHIOL-3-ONE 1,1-DIOXIDE

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Oligonucleotides in which one or two of the non-bridging phosphate oxygens has been exchanged for sulfur are of great medical interest. One of a convenient method for producing such thiophosphates is sulfurization of H-phosphonate diesters with elemental sulfur. Recently 3*H*-1,2-benzodithiol-3-one 1,1-dioxide **1** has been proposed as a new sulfurizing reagent for the conversion of phosphite triesters to phosphorothioates¹. Since this reagent offers some advantages over sulfur in solid-phase oligonucleotide synthesis, we



decided to check its utility in H-phosphonate chemistry. To this end we synthesized two H-phosphonate diesters (**2a**, **3a**) and two H-phosphonothioates

(**2b**, **3b**) and investigated their reactivity towards **1** under various experimental conditions.

When 3 eq. of **1** were added to a solution of **3a** in acetonitrile, t.l.c. revealed that during 1 hour practically no reaction occurred. To see if a base would speed up the reaction, 3 eq. of triethylamine (TEA) were added to the reaction mixture. After 5 min., t.l.c (chloroform / methanol 9:1, v/v) showed a quantitative conversion of the substrate **3a** to a polar product (the base line material). The same experiment was repeated and followed by ^{31}P NMR. It was found that the product of the reaction was the corresponding phosphorothioate **3c** ($\delta = 57.3$ ppm and 57.2 ppm). In a few optimization reactions the amount of **1** and a base were minimized to 1.5 and 2 equiv. respectively.

To check the stereochemical course of the reaction, a pure diastereomer of **2a** ($\delta = 9.2$ ppm $^1\text{J}_{\text{P-H}} = 733$ Hz) was sulfurized with **1**. Only one diastereoisomer of the thiophosphate **2c** was formed ($\delta = 57.7$ ppm), and it was the same that is obtained from oxidation with elemental sulfur.

When the H-phosphonothioate **2b** and **3b** were oxidized with **1** in the presence of a base, the reaction was even faster than with ordinary H-phosphonate. In contradiction to oxidation with elemental sulfur², however, approximately 20 % of the thiophosphates **2c** and **3c** were formed along with the desired dithiophosphates **2d** and **3d**. A mechanism which leads to formation of **2c** and **3c** is unknown and is under investigation in this laboratory.

In conclusion, it was found that (i) 3H-1,2-benzodithiol-3-one 1,1-dioxide **1** is ca. 10 times faster than sulfur in sulfurization of H-phosphonate and H-phosphonothioate diesters, (ii) the stereochemical course of sulfurization with **1** is the same as with elemental sulfur, (iii) sulfurization of H-phosphonothioates with reagent **1** affords phosphorodithioates (**2d**, **3d**) together with ca. 20 % of undesired phosphoromonothioates (**2c**, **3c**).

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