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³¹P NMR Studies on Oxidative Transformations of Aryl Nucleoside H-Phosphonate Diesters

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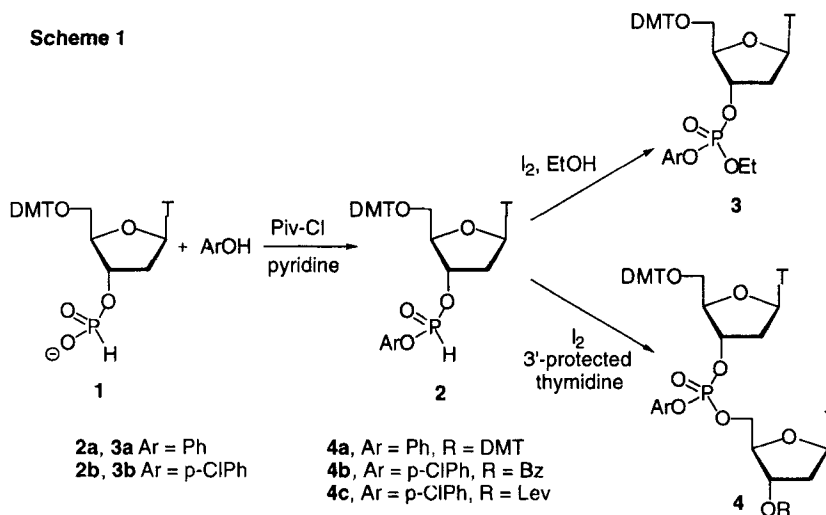
³¹P NMR STUDIES ON OXIDATIVE TRANSFORMATIONS OF ARYL NUCLEOSIDE H-PHOSPHONATE DIESTERS

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ABSTRACT: Various aspects of oxidative coupling of nucleoside aryl H-phosphonate diesters with nucleosides to produce important synthetic intermediates in the phosphotriester approach to oligonucleotide synthesis, dinucleoside aryl phosphotriesters, was investigated.

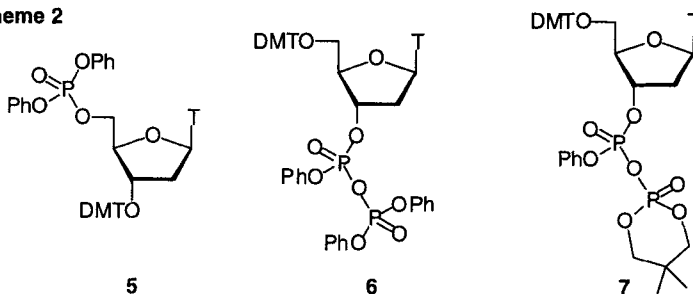
Aryl H-phosphonates **2**, due to the pronounced electrophilic character of their phosphorus center, are useful synthetic intermediates¹⁻³. As part of our interest in this type of H-phosphonate derivatives, we investigated various oxidative transformations of **2**.



Nucleoside aryl H-phosphonates **2** upon treatment with iodine (1.5 equiv.) and ethanol (1.5 - 6 equiv.) were cleanly converted to phosphotriesters **3**. An analogous oxidative coupling of **2** with 3'-protected nucleosides produced dinucleoside phosphate triesters **4** (Scheme 1), but this reaction was more sensitive to spurious water as it was apparent from the formation of varying amounts of the corresponding pyrophosphates. Under optimal reaction conditions (strictly anhydrous medium, presence of N-methylimidazole) aryl dinucleoside phosphates **4** were formed almost quantitatively, with only traces of phosphate diester present (^{31}P NMR). Compounds **4** could be isolated by silica gel column chromatography in 70-80% yield.

Since aryl nucleoside H-phosphonate diesters **2** are usually not stable enough to permit their isolation, these compounds were produced *in situ* from nucleoside H-phosphonate monoester **1** and a phenol, *via* a coupling agent promoted condensation. Along with pivaloyl chloride, diphenyl phosphorochloridate and 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane were also found to be useful reagents for this purpose.

Scheme 2



We observed, however, that aryl H-phosphonates **2** produced with different condensing agents, showed different reactivity in subsequent oxidative coupling reactions (*e.g.* formation of side products of type **5-7**). These, we assigned to the presence of various nucleophilic and electrophilic species derived from condensing agents that might react with nucleosidic components and/or intermediates generated during oxidation of **2** with iodine.

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