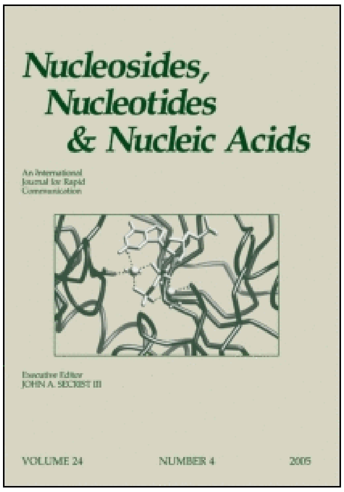

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A Mild Method for the Preparation of Nucleoside Phosphorofluoridate and Phosphorofluoridothioate Diesters

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A MILD METHOD FOR THE PREPARATION OF NUCLEOSIDE PHOSPHOROFLUORIDATE AND PHOSPHOROFLUORIDOTHIOATE DIESTERS

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ABSTRACT: Synthesis of unprotected dinucleoside phosphorofluoridate and phosphorofluoridothioates from the corresponding phosphorothioate and phosphorodithioate derivatives is described.

In recent years nucleotide analogues in which one of the non-bridging oxygen atoms is replaced by fluorine, *i. e.* phosphorofluoridates, have begun receiving attention. These compounds can been synthesized *via* several routes utilizing either P(III) or P(V) compounds as starting materials[1]. Although nucleosides phosphorofluoridate and nucleoside phosphorofluoridothioate diesters contain a very strong P-F bond, the fluorine atom (particularly that in phosphorofluoridate derivatives) may undergo a nucleophilic substitution. For this reason it would be desirable to introduce the fluorine atom to a target compound as late as possible in the synthesis, thus alleviating a potential problem of degradation, for example, during final deprotection.

Recently, we have developed a new method for the formation of the P-F bond *via* oxidative activation of the P-S linkage in the presence of fluoride anion[2]. Since the reaction of sulfur with iodine is highly chemoselective, the procedure should be valuable for the introduction of fluorine to unprotected phosphorus-containing natural products. This, and the possibility of replacing fluorine with other functionalities, makes the method of particular relevance to the synthesis of oligonucleotide analogues bearing labile modifications at the phosphorus centre.

The applicability of this procedure in the preparation of oligonucleotide analogues was assessed by carrying out some ^{31}P NMR experiments on unprotected nucleoside phosphorothioate **1a** and nucleoside phosphorodithioate **1b** diesters. To secure

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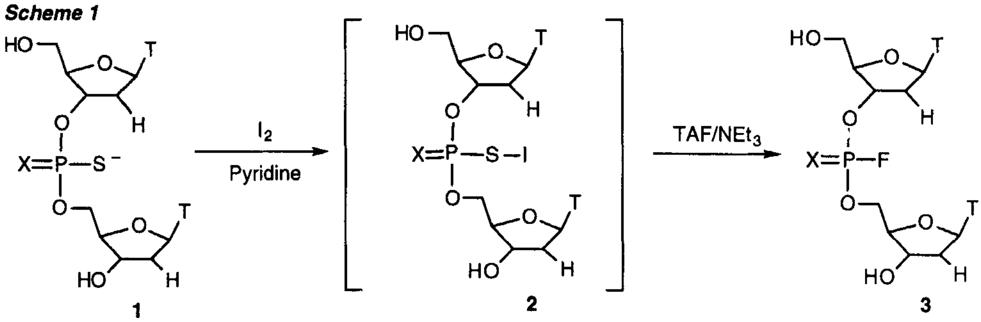
homogenous reaction conditions, the experiments were carried out in pyridine using triethylamine trishydrofluoride (TAF) as a source of fluoride anions. Upon the addition of iodine (2.5 equiv) to the pyridine solution of **1a** or **1b** containing TAF (1 equiv), a fast (ca 5 min) and clean reaction occurred to produce dinucleoside phosphorofluoridate **3a** (δ_P = -9.4 and -9.8 ppm, $^1J_{PF}$ = 977 and 985 Hz) or phosphorofluoridothioate **3b** (δ_P = 61.3 and 60.9 ppm, $^1J_{PF}$ = 1078 and 1085 Hz).

Scheme 1



1a, 2a, 3a, X = O; **1b, 2b, 3b**, X = S;

TAF = triethylamine tris(hydrofluoride)

We also carried out some preliminary studies on the replacement of the fluorine atom in phosphorofluoridates and phosphorofluoridothioates with O- and N-nucleophiles. It was found that 5', 3'-protected dinucleoside phosphorofluoridate **3a** and phosphorofluoridothioate **3b** reacted with alcohols significantly faster than simple dialkyl derivatives. For example, the reaction with *n*-butanol (5 equiv) in acetonitrile in the presence of DBU (5 equiv) cleanly produced the corresponding *n*-butyl phosphotriester and *n*-butyl phosphothiotriesters in 10 and 45 min, respectively. With triethylamine (5 equiv), the reaction was considerably slower, *e.g.* the dinucleoside phosphorofluoridothioate produced only 5-10% of the expected triester after 24 h. Pyridine was found to be unsuitable for these reactions as it mainly promoted degradation of the starting material. As expected, protected **3a** and **3b** derivatives were rather unreactive towards N-nucleophiles, *e.g.* *n*-butyl amine.

Acknowledgements

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