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A NEW SYNTHESIS OF PHOSPHOROFLUORIDATES OF BIOLOGICAL INTEREST. THE REACTION OF PHOSPHOROAZOLIDES WITH BENZOYL FLUORIDE

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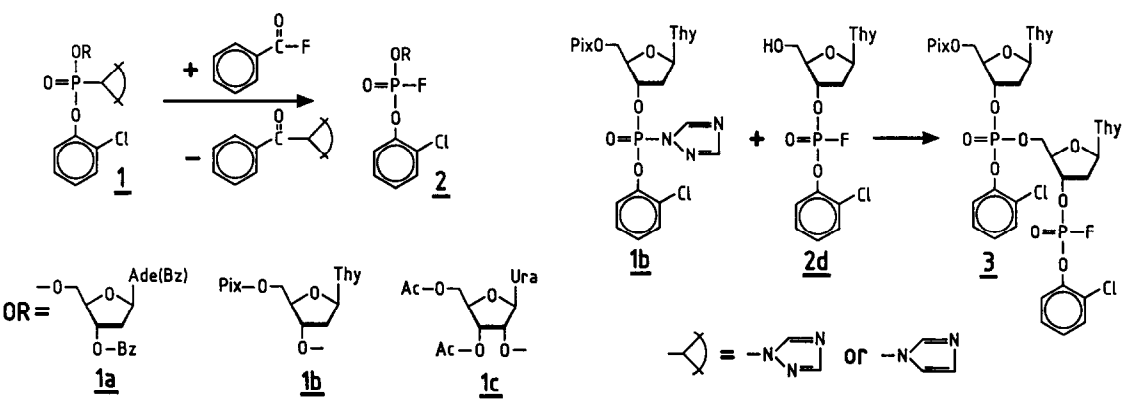
Phosphoroazolides, including nucleoside derivatives, can be converted smoothly into the corresponding phosphorofluoridates by reaction with benzoyl fluoride. From these compounds oligonucleotides containing →P-F instead of →P-OH can be prepared.

Fluoro derivatives of phosphorus are of great importance in the chemistry of both these elements. Fluoro derivatives of compounds of the pentavalent phosphorus, namely phosphorofluoridates and their structural analogues can be potent enzyme inhibitors[1]. Nucleotides containing a P-F bond were first prepared by Wittmann[2] employing 1-fluoro-2,4-dinitrobenzene. This method proceeds with moderate yield and is not suitable for preparation of phosphorofluoridate diesters.

In this paper we wish to report a new synthesis of nucleoside phosphorofluoridates. Investigating the application of phosphoroazolides[3] 1 to the synthesis of nucleoside derivatives of phosphoric sulfonic anhydride[4] we discovered that 1 is converted to the fully protected mononucleotide 2 using benzoyl fluoride. After removal of the pixyl- (9-phenyl-9-xanthenyl-) protecting group from 2b to get 2d, it was added to 1b (triazolide) to give the dinucleotide derivative 3, thus incorporating fluorine in oligonucleotides with chiral and uncharged phosphorus (Table 1); these compounds may be of interest in biology and biophysics[5].



This reaction demonstrates the low phosphorylating ability of the phosphorofluoridate 2d in comparison with the phosphorotriazolide 1b. However, in presence of an activator, such as N-methylimidazole, slow phosphorylation of alcohols by phosphorofluoridates is observed. In the presence of N-methylimidazole, the compounds 2 and 4 may exist in equilibrium, shifted strongly towards 2. Similar intermediates have been observed spectroscopically, using ^{31}P-NMR, upon reaction of N-methylimidazole with the nucleoside derivatives of phosphoric sulfonic an-

hydride[4]. The method can be easily applied for the rapid and effective synthesis of further fluoro compounds of pentavalent phosphorus (5 → 6; Table 1). The ^{31}P-NMR spectra of the material was consistent with the assigned structure and also identical with the spectra obtained from material prepared via another route.

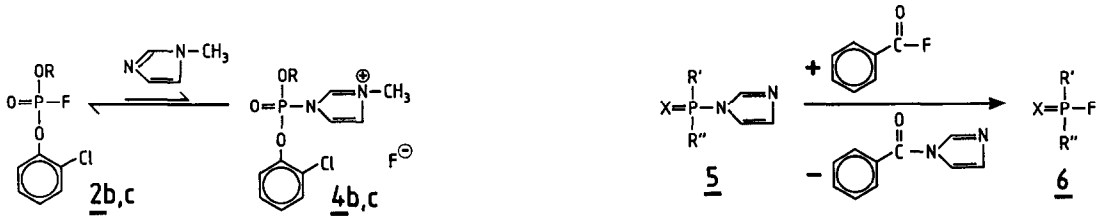


Table 1: Spectroscopic data and yields of compounds 2 to 6.

Compound				^{31}P-NMR[a] (ppm)	J_{P-F} (Hz)	Yield[b] (%)
2a				-14.45/-14.70	985.93/991.88	93
2b				-15.36/-15.47	992.35/995.76	95
2c				-15.26/-15.69	992.86/995.16	91
3				-5.65/-10.36/-12.8	- /1017.101/988.81	97
4b				-14.32/-14.41		
4c				-13.38/-13.97		
6	R': EtO	R'': EtO	X: O	-8.60	970.10	98
	CF_3CH_2O	CF_3CH_2O	O	-10.22	995.10	99
	iPrO	iPrO	O	-10.26	968.31	97
	PhO	PhO	O	-19.73	995.99	100
	t-Bu	Ph	O	+58.63	1048.08	98
	EtO	EtO	S	+63.38	1072.31	95
	CH_3	F[c]	S	+104.75	1147.96	100

[a] relative to the external standard 85% H_3PO_4; [b] estimated by ^{31}P-NMR spectroscopy; [c] starting from the diimidazolide.

A typical synthesis of 2 and 6 is: Benzoyl fluoride (0.01 mol) was added to a solution of 1 or 5 (0.01 mol) in dry CH_2Cl_2 (20 ml) at 0°C and the reaction mixture was kept 1 h at room temperature. After 1 h TLC analysis on silica gel plates developed in CH_2Cl_2/ethyl acetate/triethylamine or ^{31}P-NMR showed complete conversion of 1 or 5 into 2 or 6. The solvent was removed in vacuo and the residue treated with a minimum amount of dry 1,4-dioxane. The precipitated acylazolide was filtered off. The residue was purified by column chromatography (2a, b, c) or distillation (6).

In conclusion, the conversion of 1 into 2 may be regarded as a new and mild procedure for the introduction of the fluorine atom in the internucleotide bond.

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