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HYDROFLUORINATION OF ANHYDROTHYMIDINE *VIA* SOLUBLE ALUMINUM DERIVATIVES

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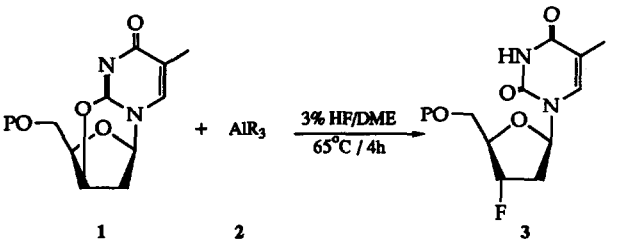
Abstract: A new method to stereospecifically hydrofluorinate anhydrothymidine has been discovered which allows the product to be obtained in higher yields than the current literature method.

The installation of fluorine is notorious among the halogens for being the most difficult to accomplish. Indeed, various reagents have been developed solely to effect this transformation.[1] In terms of nucleosides and the interest this class of compounds has garnered, fluoro derivatization has become a desirable avenue of pursuit in the quest for medicinally interesting compounds. One specific example, 3'-deoxy-3'-fluorothymidine (FLT, **3d**), has been shown to possess exceptional anti-HIV activity. [2] The approach used to incorporate fluorine into this molecule has been used with other similar compounds[3] and involves heating the anhydronucleoside in an HF/dioxane mixture in the presence of aluminum fluoride. This approach suffers from low, variable yields (0-30%) and the requirement of high dilution (0.5%). These problems most likely arise from the extreme insolubility of aluminum fluoride in dioxane. Indeed, aluminum fluoride is insoluble in organic solvents in general. Therefore, it seemed prudent to investigate other aluminum reagents which would be soluble and thus able to exert their effect more easily. We report herein the first example of stereospecific hydrofluoroination of anhydrothymidine and some of its hydroxyl-protected derivatives using *soluble* forms of aluminum. This modification drastically reduces by-products by allowing the reactions to be run at much lower temperatures (*i.e.* 60°C vs 200°C). Additionally, greater productivity is achieved for the reaction due to the higher concentrations allowable by this approach (*i.e.* 10 wt.% vs 0.5 wt.%).



1 2 3

Table 1:[1]

P	2	2/1	[2](Wt%)	Yield (%)
Trityl	$AlMe_3$ [3]	.5/1	4	28
	Et_2AlF [4]	1.2/1	10	65[2]
	iPr_3Al [3]	1.5/1	10	52
	(t-butoxy)3Al	1.5/1	10	10
Acetyl	Et_2AlF [4]	1.5/1	7	70
Methanesulfonyl	Et_2AlF [4]	1.5/1	9	60
Hydrogen	DIBAL-H [5]	1.1/1	4	24
	Al(acac)3	1.5/1	5	23
	(n-hexyl)3Al [4]	1/1	5	17

[1] All compounds were characterized by 300 MHz ^{1}H-NMR, M.S. and I.R. and shown to be consistent with the assigned structure. Additionally, all protected fluoro-compounds were converted to the known 3'-deoxy-3'-fluorothymidine (FLT).[2] Includes formation of 44% of unprotected fluoro nucleoside. [3]Toluene solution. [4]Heptane solution. [5]THF solution.

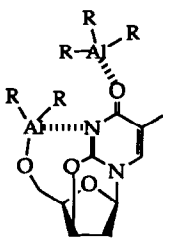
As outlined in Table 1, when a mixture of **1** and the soluble aluminum species **2** react in a solution of 3% HF in 1,2-dimethoxyethane (DME), the fluorinated product **3** is formed. Other solvents capable of dissolving HF may also be used, but for our purposes ease of removal made DME the solvent of choice. We found that HF concentrations significantly higher than 3% promoted by-product formation and lower concentrations reduced the productivity of the process. Table 1 is representative of the results obtained with various aluminum compounds.

Several observations deserve comment. The first relates to the solubility of **1** in DME; in general, greater solubility of **1** resulted in increased yields. For the case where P=trityl (**1a**), we found that this protecting group was removed slowly under the fluorination conditions. Interestingly, no deprotected starting material (*i.e.* **1d**)was ever observed. The acetyl and

methanesulfonyl groups were found to be very stable to the fluorinating conditions and very clean products were obtained.

The assumption has been made that to some degree conversion of the alkyl aluminum species **2** to some R_nAlF_{3-n} occurs . Since aluminum fluoride is insoluble in DME and not known to promote the reaction at these temperatures or concentrations, the reaction presumably stops if and when complete conversion occurs. Some evidence for this is suggested by the reaction between anhydronucleoside **1a** and trimethylaluminum. The expectation that aluminum with methyl ligands would react more rapidly with HF than an aluminum compound having higher order alkyl ligands appears to be supported by the low yield observed with trimethylaluminum. With regard to alkoxy ligand substitution, the reduced Lewis acidity of aluminum tri-t-butoxide presumably accounts for the marginal yield observed for the fluorination of **1a** with this compound.

Our own particular requirement was for the unprotected fluoronucleoside, **3d**. Thus, an examination of the fluorination on the unprotected anhydronucleoside **1d** was undertaken. Direct fluorination of **1d** would constitute the most desirable approach; however, as indicated in Table 1, yields for these reactions represented the lowest of all the compounds examined. We feel that this is a manifestation of the insolubility of the anhydronucleoside in the reaction medium. One strategy to potentially solve this problem involves reaction of the hydroxyl group in **1d** with the Lewis acid to form a new and discrete complex. This approach, in theory, would seem to have the advantage of promoting fluorination by placing the Lewis acid in a spatial orientation proximal to the thymine ring thereby permitting intramolecular coordination with nitrogen, in addition to the usual intermolecular coordination with oxygen.



Additionally, while this new complex should be soluble in the reaction medium, simple hydrolysis upon completion of the reaction would liberate the desired product. The experiment described in Table 1 showing fluorination of **1d** promoted by diisobutylaluminum hydride was an attempt to form diisobutylaluminumanhydrothymidine. The indicated yield (24%) is significantly higher than when this reaction was performed with diethylaluminum fluoride (yield = 5%) and indicates that there may be some merit to this strategy. Other variations of this approach are being pursued as well as examining the application of this technology to the fluorination of other anhydronucleosides.

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(4) Typical Experimental: To a solution of the anhydrothymidine derivative in 3%HF/DME (10 wt.%) in a polyethylene screw cap bottle equipped with a magnetic stir bar, is added **2**. The container is closed and placed in an oil bath at 65°C with stirring for 4h. An equivalent volume of water and enough calcium carbonate to neutralize any remaining HF (1g/gram of **2**) is added. If the starting anhydrothymidine was **1d** the fluorinated product is either precipated and filtered from a concentrated aqueous solution or alternatively purified using chromatographic means (silica gel, using 4:1 methylene chloride - acetone as eluant). When protected anhydrothymidine derivatives were used, the fluorinated products could be extracted from the aqueous solution into methylene chloride and isolated or deprotected using conventional means as desired.

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