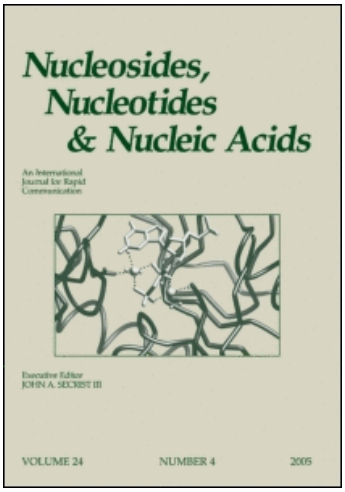

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Some Examples of the Use of Trifluoromethane Sulfonic Anhydride in Nucleic Acid Chemistry

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SOME EXAMPLES OF THE USE OF TRIFLUOROMETHANE SULFONIC ANHYDRIDE IN NUCLEIC ACID CHEMISTRY

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Abstract - Trifluoromethane sulfonic anhydride has been used for the inversion of configuration at the 3'-position of 2'-deoxypurine nucleosides, for the modification of the base moiety of purine and pyrimidine nucleosides, for nucleophilic substitution in the sugar moiety, for the synthesis of O^2,3'-cyclothymidine and for sugar-base condensation reactions. Reaction can be carried out under very mild conditions. The conditions for these reactions are quite different so that a good selectivity can be obtained when different reactive groups are present.

The use of the extremely reactive triflate leaving group has allowed substitution reaction under very mild conditions which are normally impossible or very difficult with ordinary leaving groups. It is rather surprising that this reagent has only been used sporadically in nucleic acid chemistry i.e. for the synthesis of nucleosides fluorinated in the sugar moiety[1].

Inversion of configuration at the 3'-position of 2'-deoxypurine nucleosides (A)

While this reaction is straightforward for pyrimidine nucleosides because of anchimeric assistance of the base[2], the reaction with purine nucleosides is more problematic. In this case, intramolecular attack of the base on the 3'-activated carbon atom gives N^3,3'-cyclonucleosides which are sensitive to opening of the pyrimidine ring with nucleophiles[3]. The methods which are described for the synthesis of 9-(2-deoxy-ß-D-threo-pentofuranosyl)adenine are low yielded[4], lengthy[5] or not attractive for large scale preparations[6].

A 5'-O-benzoyl group however, can replace the function of the pyrimidine ring to inverse the configuration at the 3'-position of purine nucleosides using triflate as a leaving group. The reaction proceeds via a hemi-orthoester as intermediate. The product distribution is dependent on the reaction[7]. By manipulating these conditions, predominantly 2 or 3 is formed. This reaction proceeds with a total yield of 90 %.

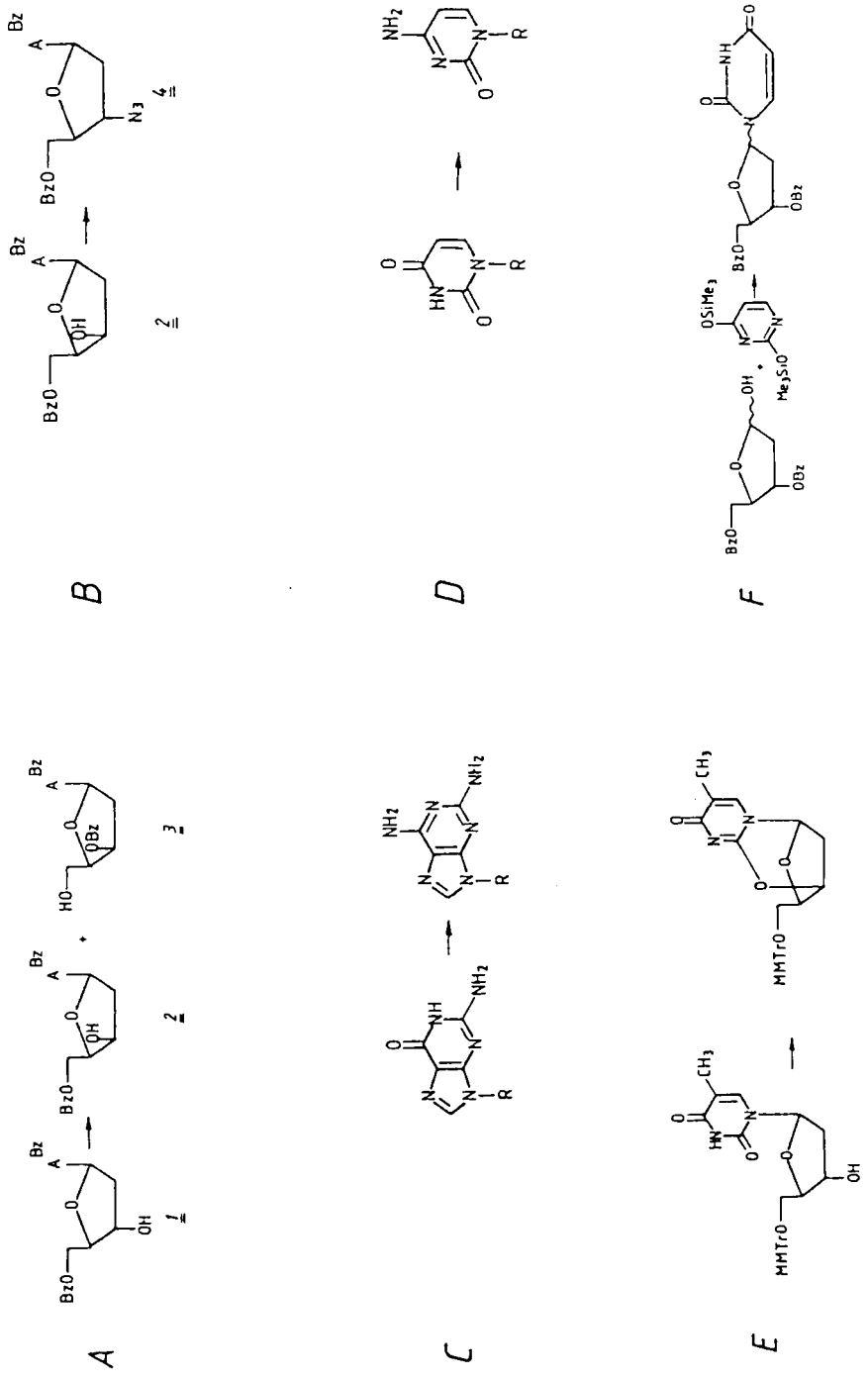
Nucleophilic substitution in the sugar moiety (B)

This reaction has been used mainly for the synthesis of fluorinated nucleosides[8]. Only one other example is given here. 3'-Azido-2',3'-dideoxyadenosine has been synthesized before by a transglycosylation procedure[9], by reaction of lithium azide on the 3'-O-mesylate of 2[10] and by a direct introduction with CBr_4, $\emptyset_3P$, LiN_3[11].

The conversion of 2 into 4, using trifluoromethanesulfonic anhydride and lithium azide can be done in one step, at room temperature in 85 % isolated yield. A combination of reaction A and B was used for the syn-

Table 1. Reaction conditions: reactions were carried out in two successive steps without isolation of the intermediate. Conditions for both steps (a) and (b) are described.

Reaction	CH_2Cl_2/Pyrid (ml/mmol)	$(CF_3SO_2)_2O$ (equiv.)	(a)	(b)	Yield
A	15/1	1.5	-30°C - 0°C 30 min	H_2O 2 h RT	90 %
B	9/1	1.2	-30°C - 0°C 15 min	LiN_3, DMF 2 h RT	85 %
C	9/1	1.5	2 h RT	NH_3-dioxane 16 h RT	80 - 90 %
D	4/1	2	3 h RT	NH_3-CH_3OH 16 h RT	50-75 %
E	9/1	1.2	-15°C 10 min	H_2O 1 h 0°C	80 %
F	10/2 eq.	1.5	15 min RT	silylated base CH_2Cl_2, reflux, 2 days	50 % [?]



thesis of 3'-azido-2',3'-dideoxyinosine from 5'-O,N^6-dibenzoyl-2'-deoxyadenosine[7].

Substitution reactions at the base moiety (C,D)

Examples of substitution reactions on the heterocyclic base of nucleosides (purines as well as pyrimidines) are legion[12]. In these examples the carbonyl function of the base is activated by thiation, sulphonation, phosphorylation or by conversion into a chlorine derivative. The use of the reactive triflate leaving group allows this conversion to proceed at low or ambient temperature in good yield. The combination of method A and method C on appropriately protected 2'-deoxyguanosine has allowed the synthesis of 3'-azido-ddDAP[13] in satisfactory yield.

Synthesis of O^2,3'-cyclopyrimidine nucleosides (E)

Because of the increasing interest in 3'-substituted-2',3'-dideoxynucleosides as anti-HIV agents, a fast and easy method is needed for their synthesis. Recently, D. Baker reported the use of DAST for the synthesis of O^2,3'-anhydronucleosides[14]. This reaction can also be carried out with trifluoromethanesulfonic anhydride as activating reagent. The reaction has to be intercepted by addition of H_2O, because of the ease with which the pyrimidine base reacts itself.

Although opening of the O^2,3'-anhydro bond with nucleophiles is more difficult than nucleophilic substitution on mesylates[15], this method represents a useful alternative for the synthesis of AZT-analogues.

Sugar-base condensation reactions (F)

Simple and selective methods exist for the synthesis of nucleosides by sugar-base condensation reactions[16]. For the synthesis of 2'-deoxynucleosides, crystalline protected 1-α-chlorofuranose is needed as starting material. Activation of the sugar is also possible with trifluoromethane sulfonic anhydride so that the moisture sensitive 1-halosugar doesn't need to be synthesized each time prior to the condensation reaction. However, the results of the condensation reactions (Table 1) are only preliminary and no attempts were made yet to improve the yields and the selectivity.

CONCLUSION

Modifications of nucleosides via activation with the fluoromethanesulfonic anhydride represent an easy and time-saving alternative to previously

known methods (Table 1). Yields are approximately the same as with the classical procedures.

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