

Dedicated to Professor David Shugar on the occasion of his 80th birthday

Some recent trends and progress in nucleoside synthesis*

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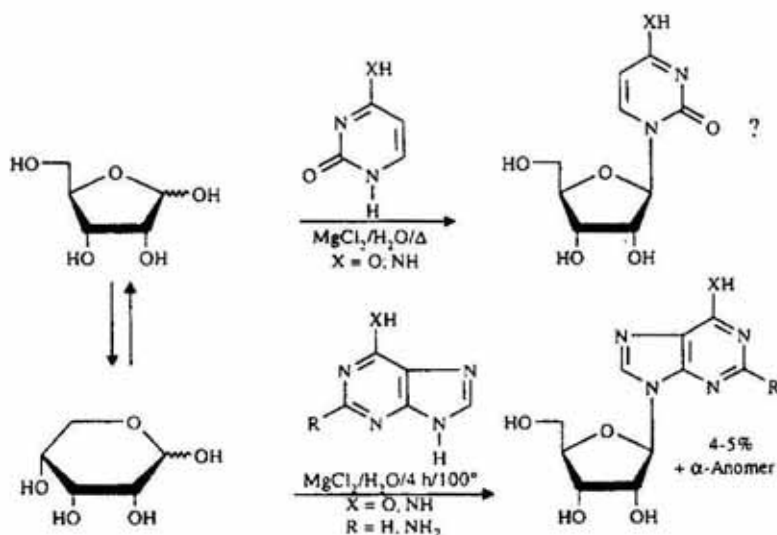
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Key words: nucleoside synthesis, persilylated sugars, heterocyclic bases, condensation

Some recent progress concerning the optimal combinations of Lewis acids and solvents for the synthesis of pyrimidine as well as purine nucleosides is reviewed. Furthermore, the novel condensation of persilylated free sugars and heterocyclic bases in the presence of trimethylsilyl triflate to the corresponding persilylated nucleosides is discussed.

For many years we have been fascinated by some experiments by Orgel *et al.* [1, 2] (Scheme 1). They heated D-ribose with purines in the presence of seawater containing the Lewis acid $MgCl_2$, whereupon small amounts of adeno-

sponding pyranose-purine nucleosides were detected. The same reaction conditions, however, failed completely with uracil or cytosine as none of the corresponding pyrimidine nucleosides were formed.



Scheme 1. Thermodynamically controlled, most stable products. After [1, 2].

sine and guanosine were formed, which thus appear to be the thermodynamically controlled most stable products. Apparently no corre-

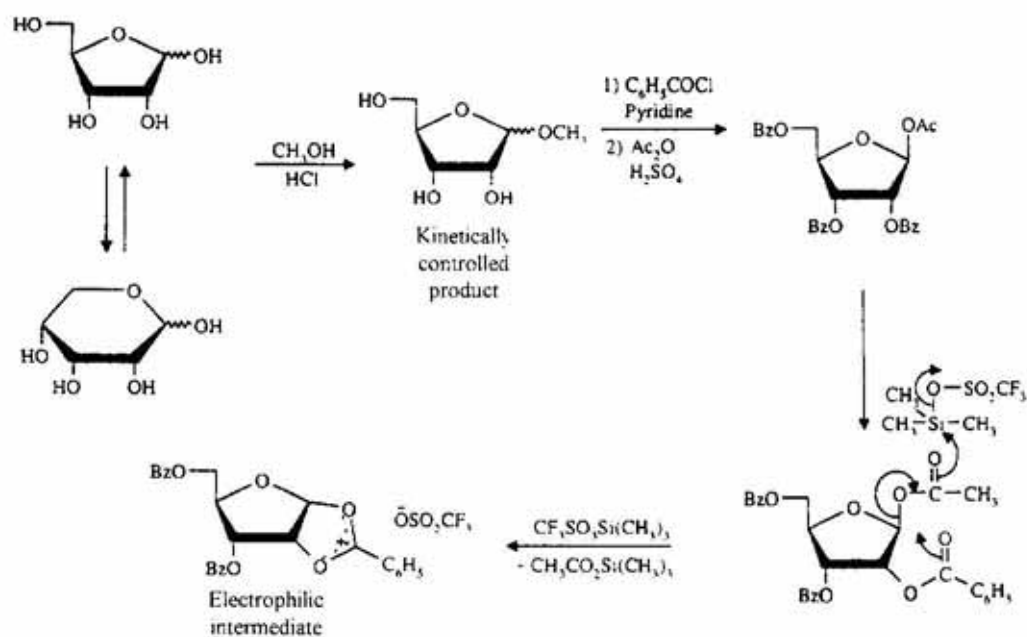
Since these simple reaction conditions in the polar and cheap water were thus obviously not suitable for the preparation of nucleosides,

*The major part of this lecture, especially the novel condensation of persilylated free sugars and heterocyclic bases was presented at the symposium on *The Chemistry of Therapeutic Oligomers* at the 209th ACS meeting in Anaheim, CA, April 2-6, 1995.

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Abbreviations: HMDS, hexamethyldisilazane; TCS, trimethylchlorosilane.

other methods have been devised in which bases and sugars were converted into unpolar protected derivatives to permit reactions in organic solvents.

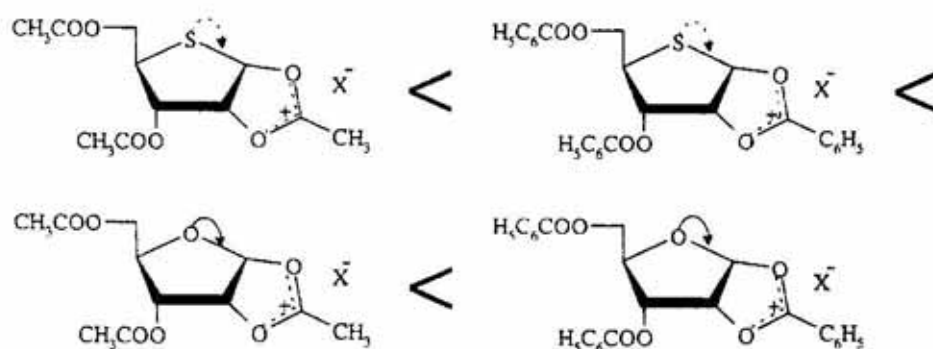
Turning to the sugar moieties (Scheme 2), D-ribose is converted by methanolic HCl (a kinetically controlled reaction) into 1-O-methylglycoside, which gives after benzylation and subsequent acetylation of the 1-O-methyl group, in altogether three steps, the stable and beautiful crystalline standard sugar 1-O-acetyl-2,3,5-tri-O-benzoyl- β -D-ribofuranose. Treatment of this standard sugar with trimethylsilyl triflate gives rise to the electrophilic sugar cation [3], able to react with any of the silylated bases affording thus the corresponding nucleosides, usually in excellent yields.

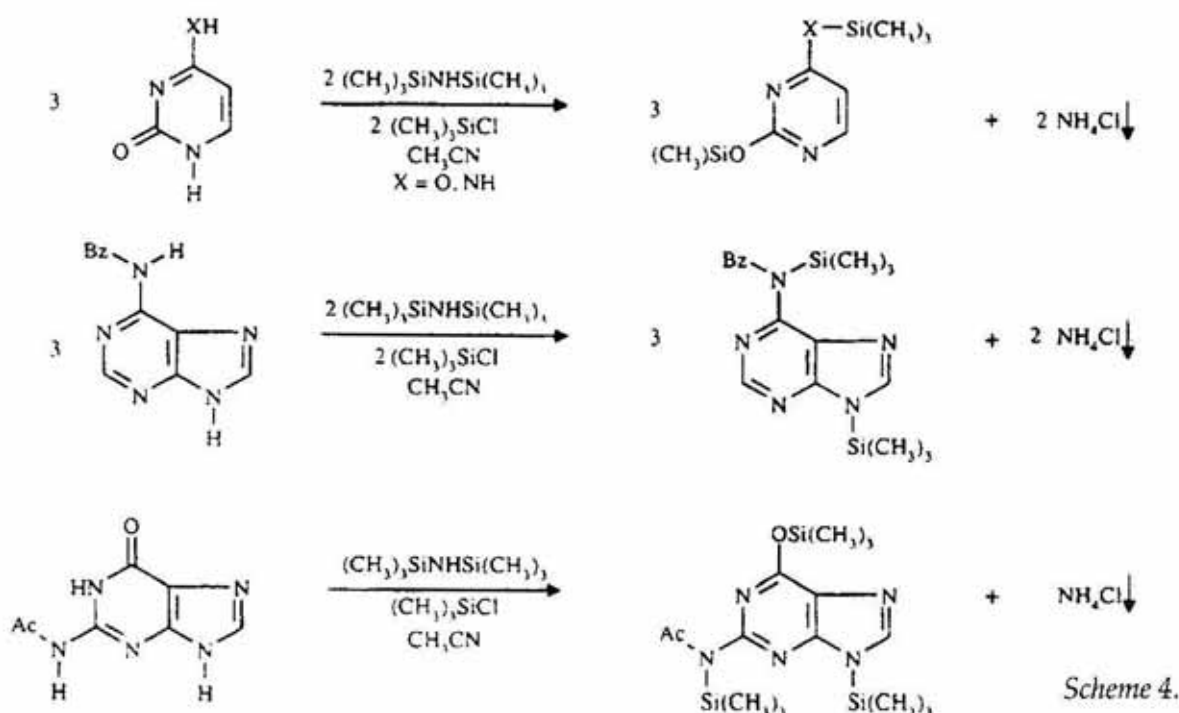


Scheme 2.

It is pertinent, however, to understand the factors which influence the stability of these sugar cations. Their stability increases roughly, in the order shown in Scheme 3, with the phe-

persilylated heterocycles (Scheme 4). The formed NH_4Cl either precipitates in acetonitrile at 24°C or sublimates on heating into the reflux condenser.

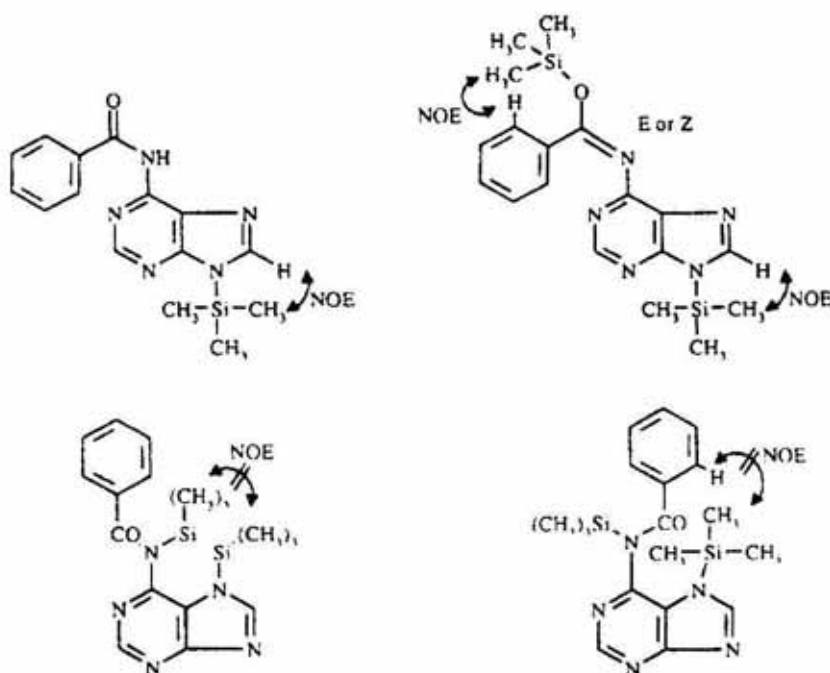
Scheme 3. Stability of sugar-cations. Control of β -selectivity.



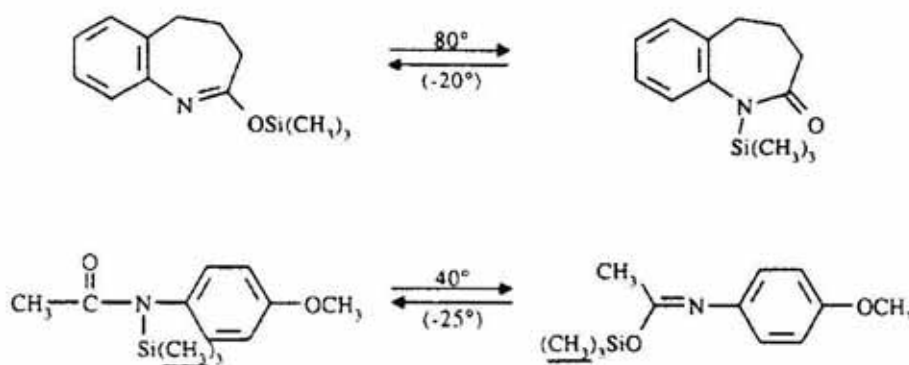
Since the structure of the persilylated purines have as yet not been determined, my colleagues at Schering Laboratories, Dr G. Michl and Miss G. Mayer (to be published) have studied (^1H and ^{29}Si NMR) persilylated N^6 -benzoyladenine (Scheme 5) and could prove by repeated NOE-measurements that the trimethylsilyl group is definitely attached to the N^9 -nitrogen of the purine system and that the N^6 -benzoyl group is O-trimethylsilylated. It could not be established, however, whether the homogene-

ous iminotrimethylsilyl ether moiety has the *E*- or *Z*-configuration. But due to the mobility of the trimethylsilyl group (Scheme 6), as established years ago by Klebe [7], this mobility makes the determination of the position of the trimethylsilyl groups rather irrelevant.

In the case of synthesis of purine nucleosides, e.g. of adenosine, one should furthermore realize that there seem to be always a number of kinetically controlled intermediates such as the N^3 -nucleosides, which gradually rearrange



Scheme 5.
Michl, G. & Mayer, G., unpublished



Scheme 6. Mobility of silyl groups ^1H NMR in pyridine solution. After [7].

(Scheme 7) to the thermodynamically controlled N^9 -nucleosides [3].

In the case of the synthesis of guanosine (Scheme 8), we obtained on heating in 1,2-dichloroethane preponderantly the desired N^9 -nucleoside [3] apparently *via* the N^7 -nucleoside. After saponification of the protecting groups, the crude product gave, after one crystallization, pure guanosine in 66% yield. This material contained only traces of the undesired N^7 -isomer as was demonstrated by high resolution ^1H NMR.

Later M.J. Robins [8, 9] claimed that on using our procedure he obtained guanosine containing about 30% of the N^7 -guanosine and devised a protection procedure for guanine, (Scheme 9), but obtained in effect only the same overall yield of guanosine as we [3] and other groups [10] did without that kind of guanine derivative.

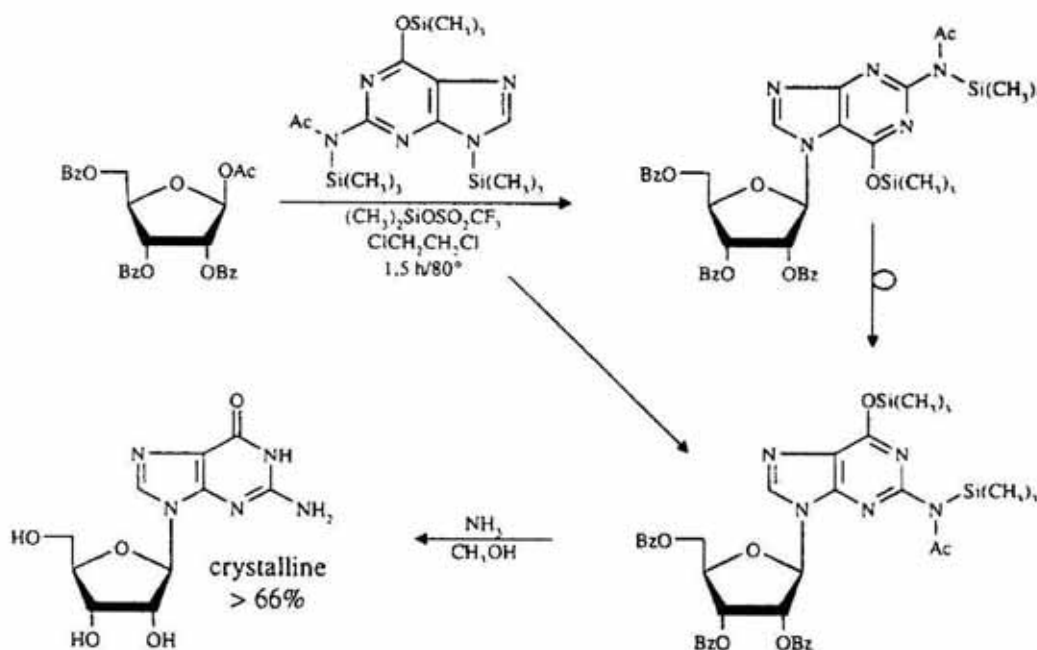
To summarize our present knowledge, as we discussed at the ACS-Meeting in S.F. in 1976

and in a detailed paper [11], the presence of σ -complexes between silylated pyrimidines and $(\text{CH}_3)_3\text{SiOSO}_2\text{CF}_3$ or SnCl_4 leads to increased formation of N^3 -nucleosides. Thus the polar solvent acetonitrile, which competes for the Lewis acids and thus diminishes σ -complex formation, is the favored solvent for the synthesis of pyrimidine nucleosides.

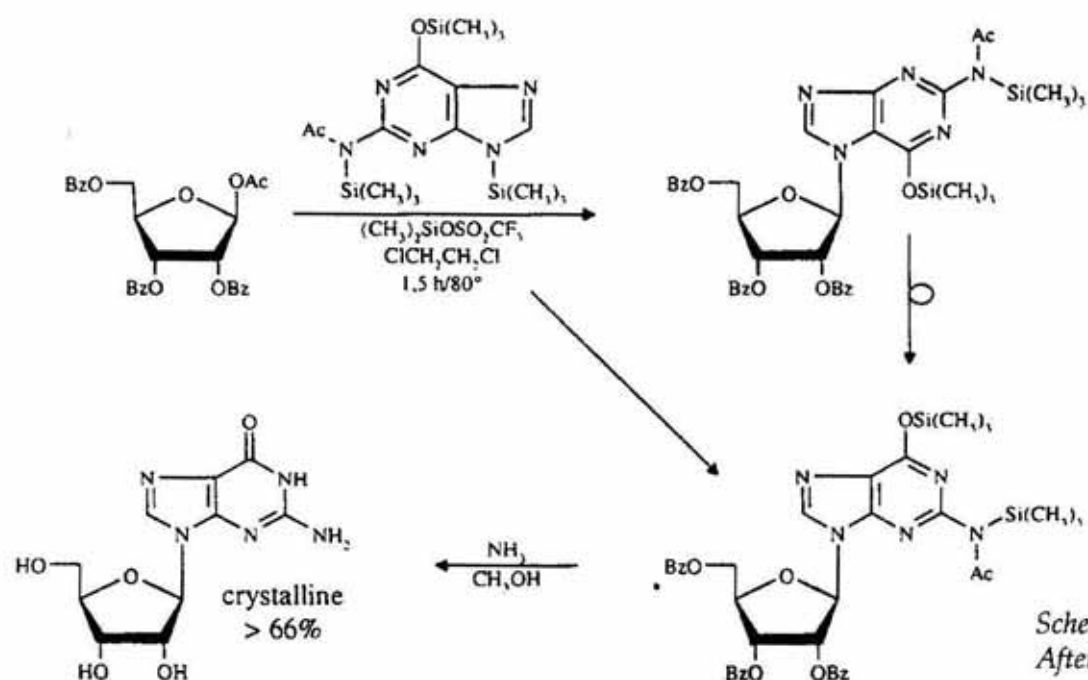
Since the synthesis of purine nucleosides, proceeds *via* a series of complex rearrangements of N^3 - *via* N^7 - to the desired N^9 -nucleosides involves such σ -complexes, less polar solvents such as 1,2-dichloroethane or toluene are favored for the synthesis of the natural N^9 -purine nucleosides.

How can the hitherto available methods be further improved? Are there new Friedel-Crafts catalysts, new solvents or sugar derivatives?

Some recent papers describe new catalysts such as SnCl_2 [12] (Scheme 10), but I do not



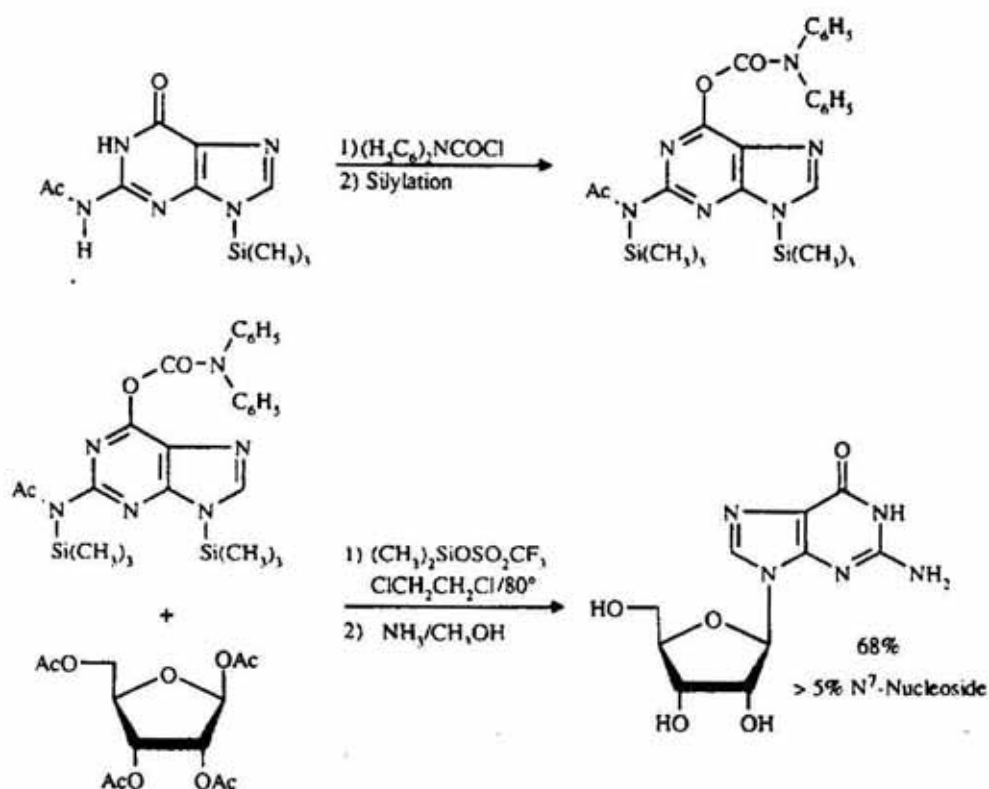
Scheme 7.

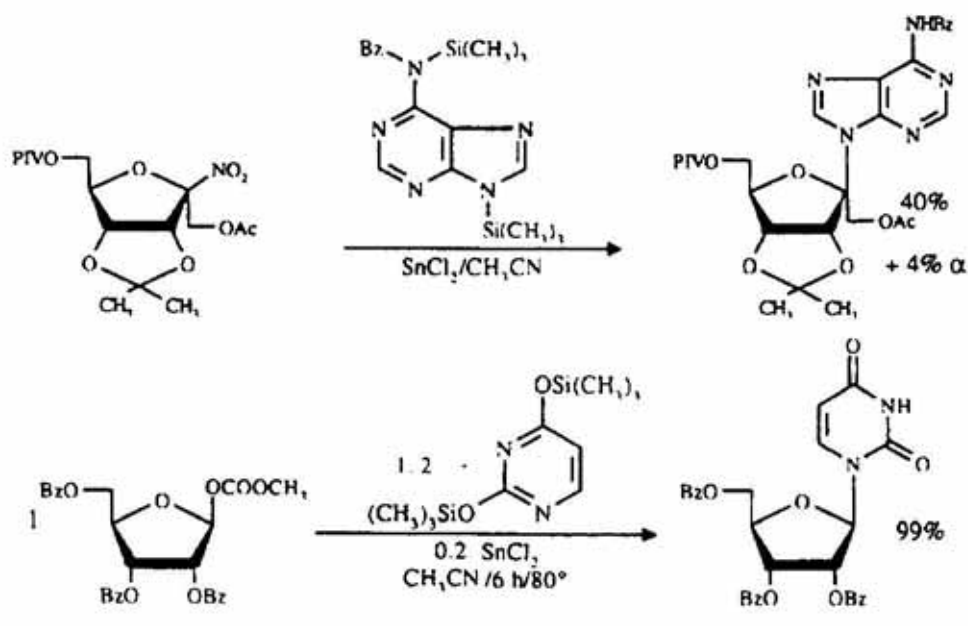


think that these catalysts offer any particular advantages. Neither do new and rather complicated Lewis acids as devised in recent years by Mukaiyama and his co-workers [13].

Concerning the use of quite different solvents we were intrigued by a recent publication [14] about the reaction of benzaldehyde-dimethylacetal with allyltrimethylsilane in liquid SO_2 (Scheme 11), which proceeded without a Lewis

acid. But to our disappointment the reaction of silylated uracil with the standard sugar afforded in liquid SO_2 at room temperature after one week in a thick walled glass vessel at 3 bar pressure only a moderate yield of protected uridine. Since a number of further experiments gave also disappointing yields we have abandoned liquid SO_2 as a solvent for nucleoside synthesis.





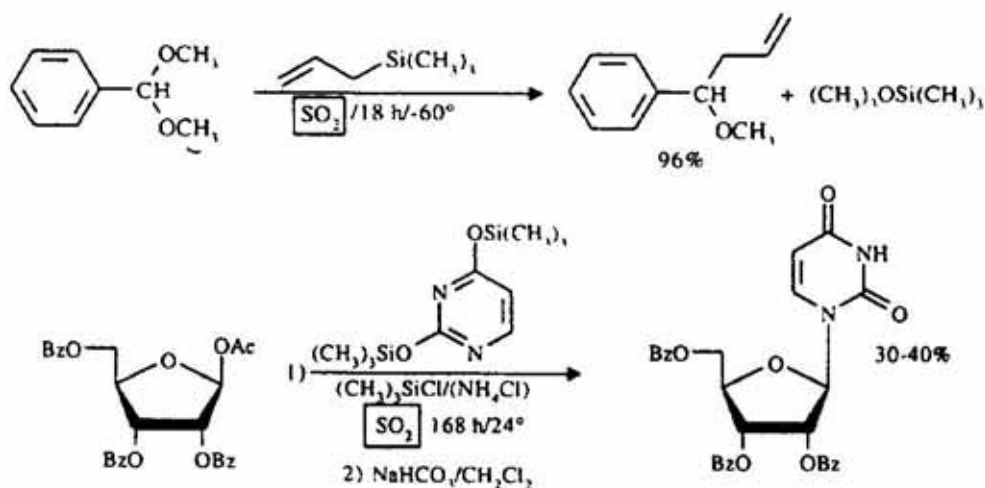
Let us now turn finally to the modification of the sugar moieties. Years ago we found that in a mixture of protected *O*-methyl-2-deoxy-furanosides and pyranosides a kinetically controlled reaction took place to give preferentially only an anomeric mixture of the furanosides [3] (Scheme 12).

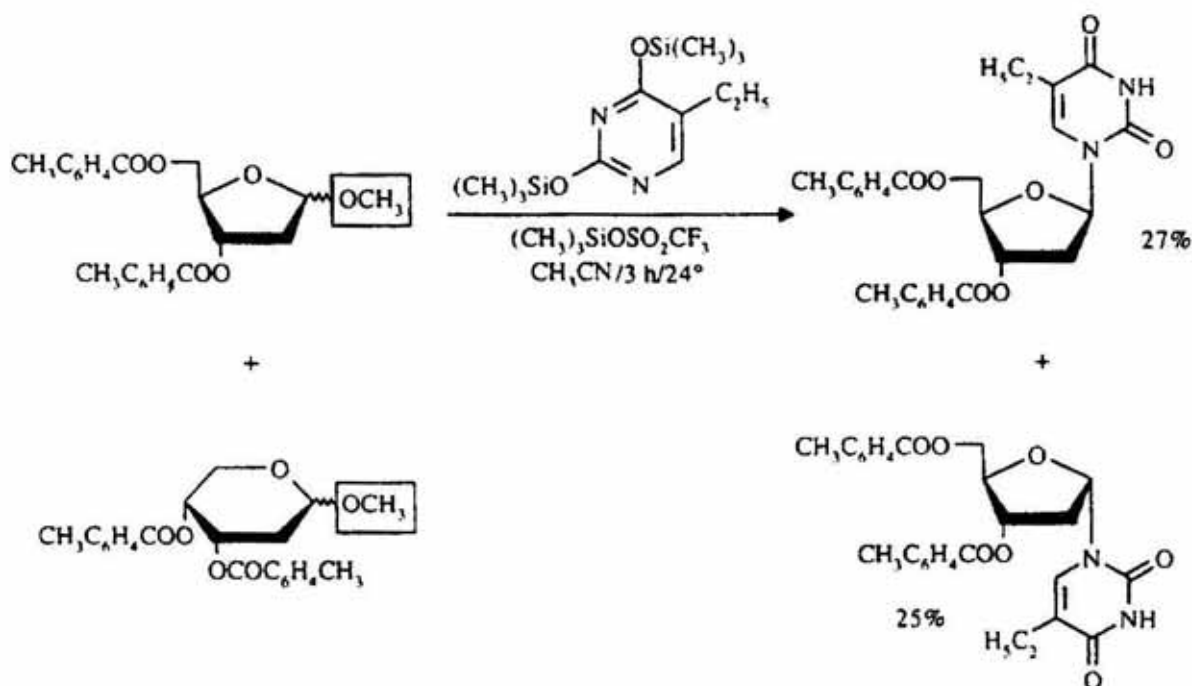
We furthermore described years ago that in the process of addition-elimination of protected 4-*O*-ethyl or 4-*O*-trimethylsilyluridines with ammonia, primary or secondary amines these groups reacted exactly analogously to result in an efficient silylation-amination to the corresponding cytidines (Scheme 13) establishing a close similarity of *O*-alkyl- and *O*-trimethylsilyl groups [16].

Since the silylation of pyrimidine or purine bases is accelerated by Lewis acids, silylation of the heterocyclic bases, formation of the sugar

cations and the subsequent nucleoside synthesis can be combined in a one step-one pot reaction [17] (Scheme 14). This method has become widely used.

We have wondered for years whether 1-*O*-trimethylsilyl sugars might not react exactly analogously to the corresponding 1-*O*-alkyl sugars, e.g. can one replace the 1-*O*-alkyl groups as well as the other protecting groups in sugars by *O*-trimethylsilyl groups? Consequently we have questioned whether the often multistep procedures for the preparation of protected sugar derivatives for nucleoside synthesis are necessary. We expected that persilylated free sugars such as *D*-ribose or *D*-glucose should react with trimethylsilyl triflate to form a stabilized 1-cation and hexamethyldisilozane. Due to the somewhat surprising fact that silylated alcohols such as trimethylsilylated methanol



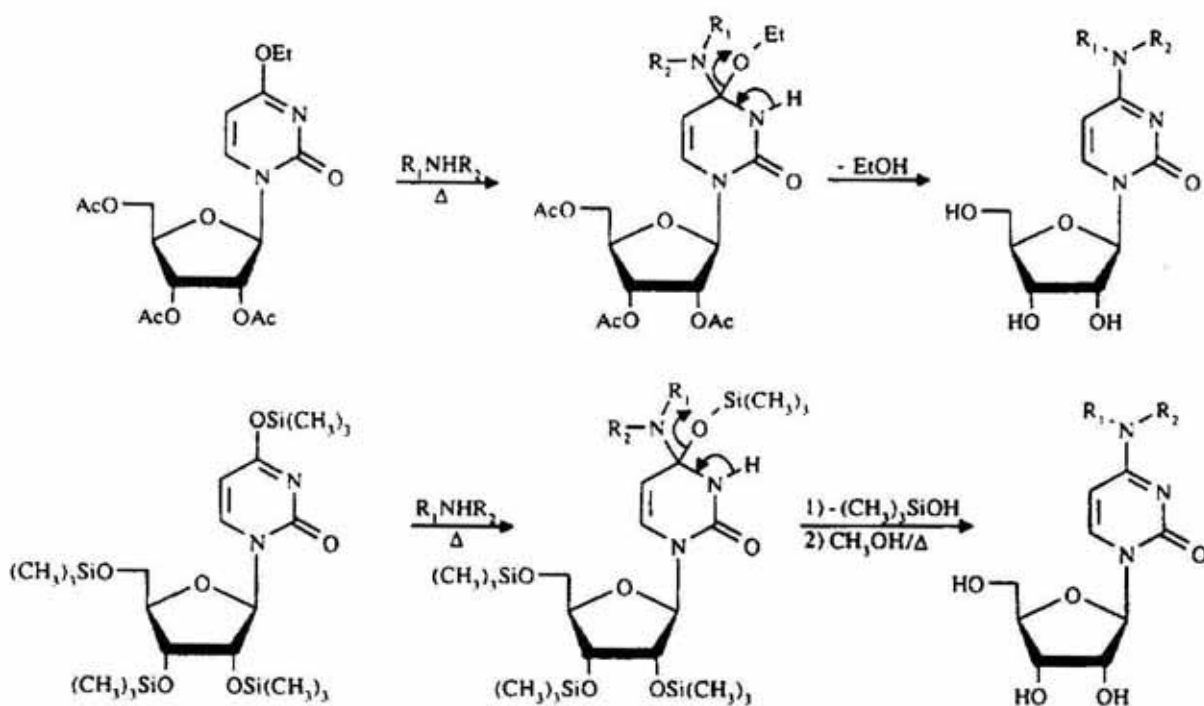


Scheme 12. After [3, 15].

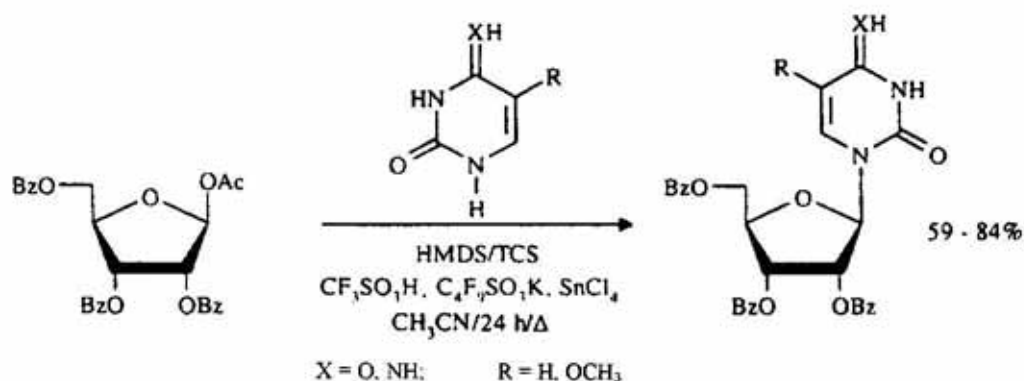
$\text{CH}_3\text{OSi}(\text{CH}_3)_3$ are weaker bases than the corresponding dialkyl ethers such as methyl-*tert*-butyl ether $\text{CH}_3\text{OC}(\text{CH}_3)_3$ [18, 19] (Scheme 15), we were confident that the persilylated sugar moieties would **not** be too basic to interfere with nucleoside synthesis.

Since all the different comparison samples in the 6-azauracil series were available [20], we did our first experiments with 6-azauracil (Scheme 16).

We heated initially equivalent amounts of D-glucose and 6-azauracil with hexamethyldisila-



Scheme 13. After [16].



Scheme 14. One pot/one step reactions, *in situ* silylation; the reactions proceed as well with purines. After [17].

zane and catalytic amounts of trimethylchlorosilane in boiling absolute acetonitrile until all the glucose and all the 6-azauracil had passed

showed after heating (transsilylation) with methanol the formation of the corresponding glucopyranoside of 6-azauracil.

Pauling electro-
negativities:

F = 4.0

C = 2.35

Si = 1.64

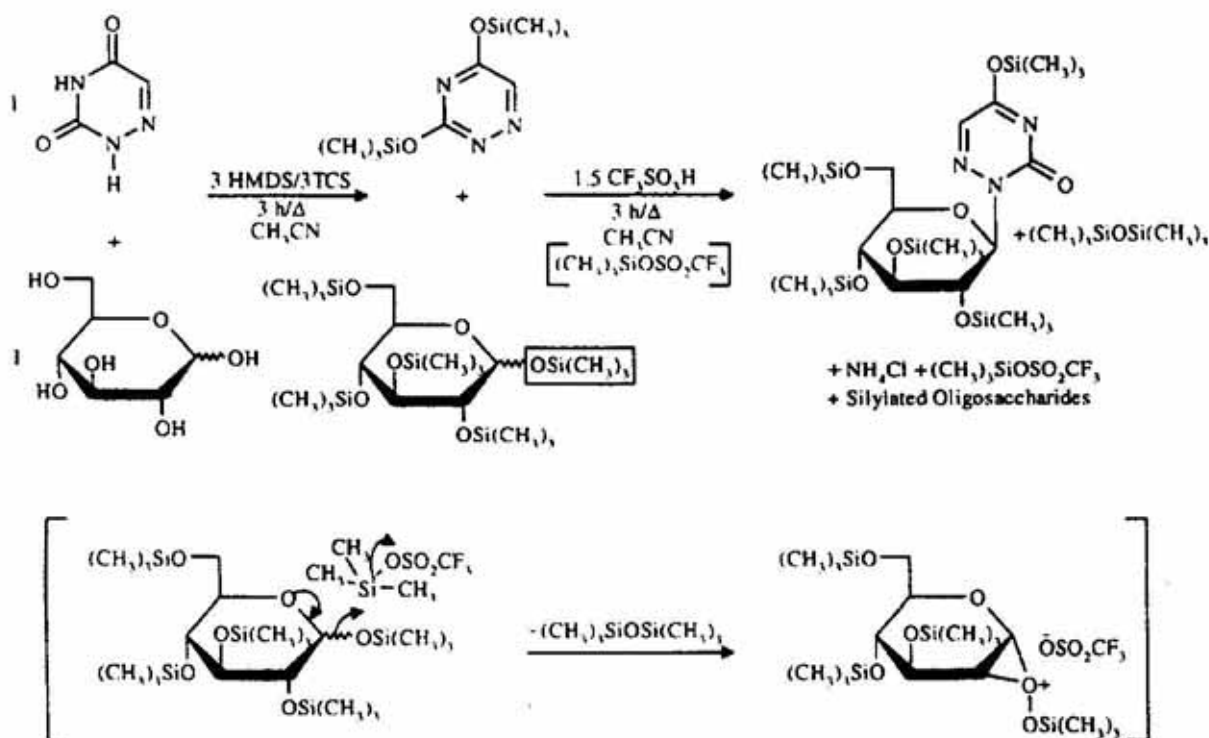
Scheme 15. Basicity of
silylethers. After [18, 19].

Basicities:

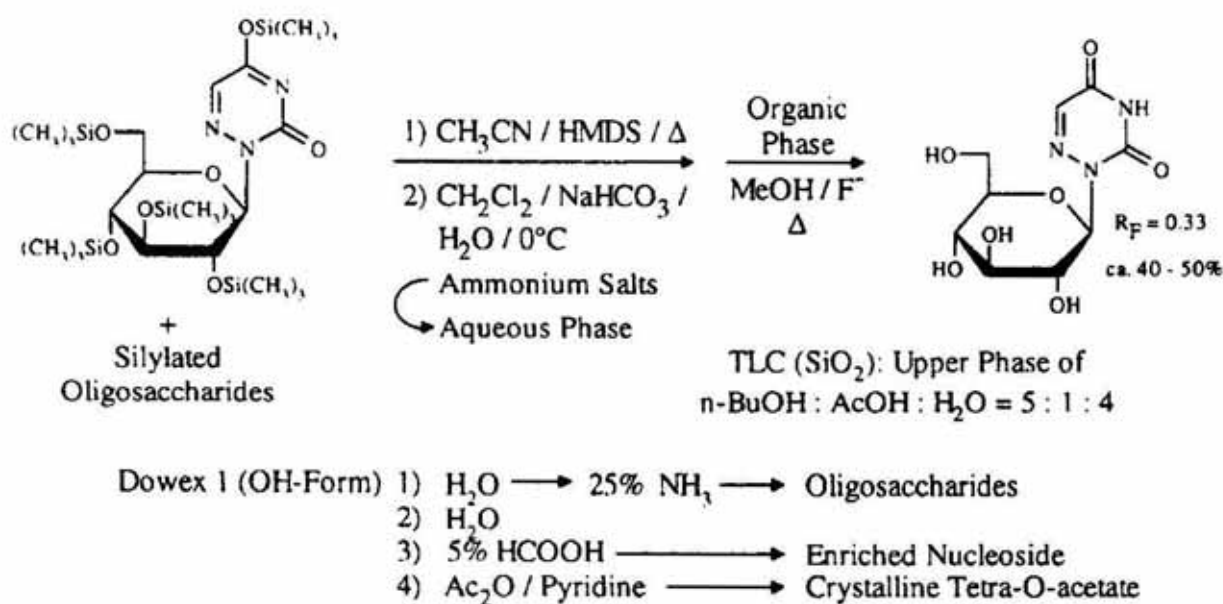
Et-O-C(CH₃)₃ > Et-O-Si(CH₃)₃

into solution. After evaporation and addition of acetonitrile, we added 1.1–1.5 equivalents of trimethylsilyl triflate to induce nucleoside synthesis, and heated the reaction mixture for 6–8 h. To our great satisfaction the TLC of a sample

The acetonitrile solution containing the persilylated nucleoside as well as some persilylated oligo- or polysaccharides was then neutralized with saturated aqueous NaHCO₃-solution (cf. Scheme 17) and after drying and evaporation



Scheme 16. After [22].



Scheme 17. After [22].

the crude product was heated in excess methanol to remove the trimethylsilyl groups by transsilylation. Since TLC indicated also the presence of considerable amounts of oligo- and polysaccharides lacking any 6-azauracil chromophore, the crude mixture was quickly filtered over a column of strongly basic Dowex 1. Elution with ammonia, and water gave the oligo- and polysaccharides, whereas the nucleoside containing an acidic NH-hydrogen was eluted with 5% formic acid. Although the eluted nucleoside was already rather pure, it refused to crystallize, as did a comparison sample obtained by saponification of authentic crystalline 2',3',4',6'-tetra-O-acetate [20].

Although the ^1H NMR-spectra of the two samples were nearly identical, we acetylated a small part of the nucleoside with acetic anhydride/pyridine and obtained after SiO_2 -chromatography authentic crystalline 2',3',4',6'-tetra-O-acetate.

Thus the anticipated nucleoside had really been formed in about 30–40% yield.

Repetition of the experiment with three equivalents of glucose afforded 65% of the corresponding crystalline 2',3',4',6'-tetra-O-acetate of the glucopyranoside of 6-azauracil.

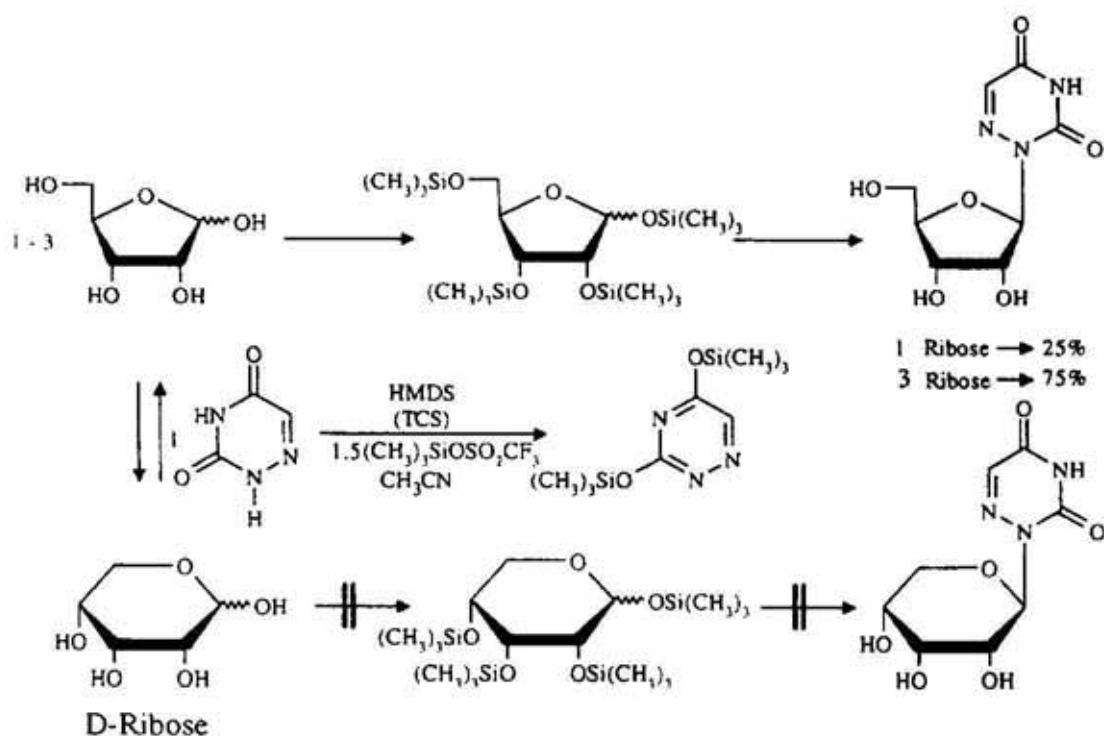
In this reaction SnCl_4 gave much lower yields, whereas ytterbium tris-triflate failed completely.

As discussed before (cf. Scheme 2), the furanose isomer of D-ribose forms the kinetically

favoured 1-cation. In addition, the primary 5-hydroxyl group in D-ribose is always silylated first, so that the preferential formation of persilylated D-ribofuranose could be anticipated. Therefore we heated 3 equivalents of D-ribose and 1 equivalent of 6-azauracil with HMDS (TCS) in acetonitrile and added again 1.1 equivalent of trimethylsilyl triflate to give after 8 h heating, according to TLC, practically exclusively 6-azauridine and only traces of the corresponding pyranoside-nucleoside (Scheme 18). The black mixture was treated with aqueous bicarbonate and methanol to remove the silyl groups and evaporated.

Extraction of the dark residue with boiling methanol and evaporation removed the polymeric material. Reextraction with boiling *n*-butanol dissolved some unpolar carbohydrate moieties lacking any heterocyclic chromophore. The residue from the butanol extraction was filtered in ethanol over a small column of silica gel and the yellowish extract evaporated. Subsequent chromatography over a column of SiO_2 with ethanol-25% NH_3 (9:1, v/v) afforded 68% of 6-azauridine, which crystallized partly from ethanol to give pure 6-azauridine, m.p. 159–161°C [20].

Likewise, the reactions of 3 equivalents of D-ribose with N^6 -benzoyladenine gave after workup for 16 h with methanolic ammonia, evaporation and chromatography on SiO_2 with ethanol-25% ammonia (9:1, v/v), 71% of free



Scheme 18.

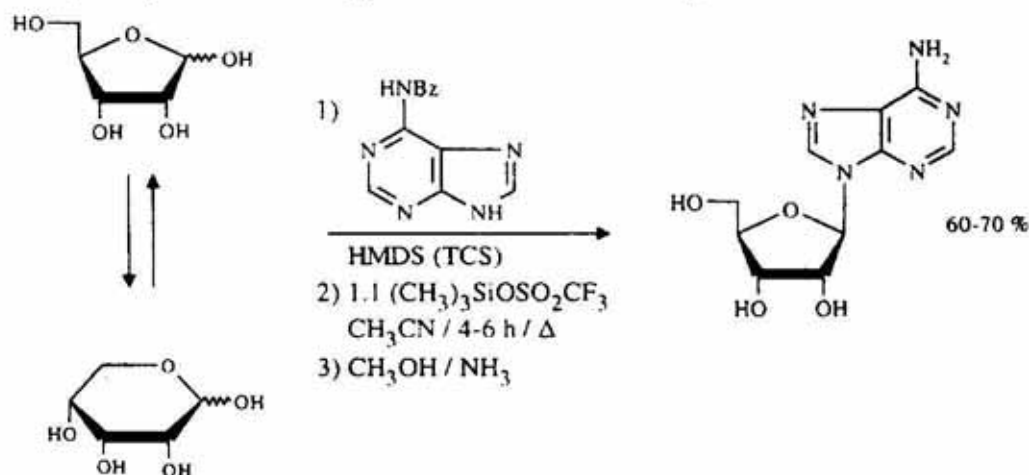
adenosine (Scheme 19), which was identical with an authentic sample.

It is obvious that other *N*-acylated bases such as *N*²-acetylguanine or *N*⁴-acylcytosine can be expected to react analogously.

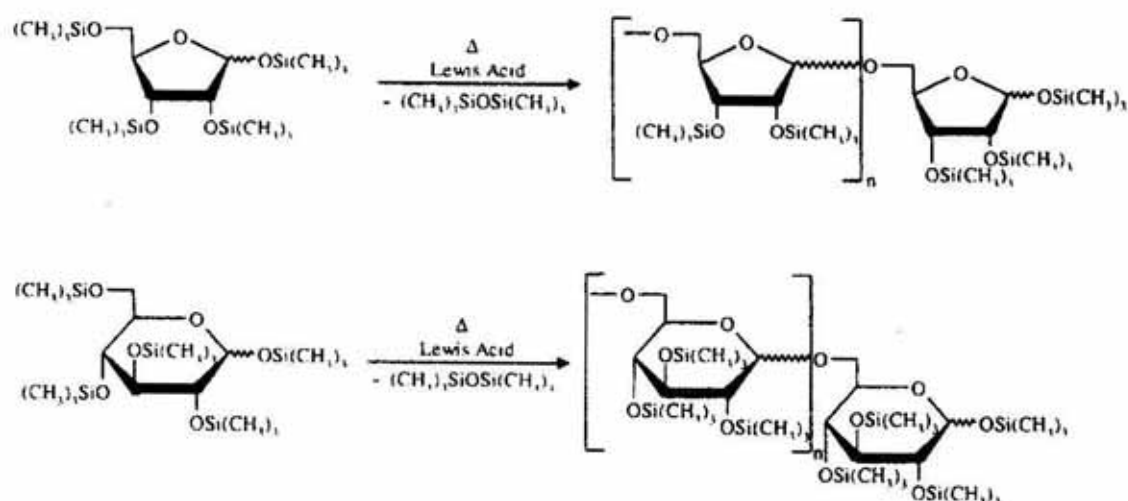
All attempts failed, however, to condense persilylated 2-deoxy-D-ribose and thymine in acetonitrile in the presence of 0.1–1.1 equivalents of trimethylsilyl triflate. The reaction mixture turned dark on heating and only thymine but no thymidine could be detected by TLC. Thus 2-deoxy sugars are apparently **not** suitable for this novel one step-one pot nucleoside synthesis.

Since part of the sugar moieties are consumed by side reactions and consequently a threefold excess of the sugar has to be employed, the question arises what are these side reactions of the persilylated sugars in the presence of trimethylsilyl triflate.

Apart from the possible polymerization of D-ribose and D-glucose to 1,5- or 1,6-linked poly-ribose or poly-glucose (cf. Scheme 20), the interaction of any free glycol systems in the sugar moieties in the presence of trimethylsilyl triflate to the corresponding acetals [21] seems to be more plausible (Scheme 21).



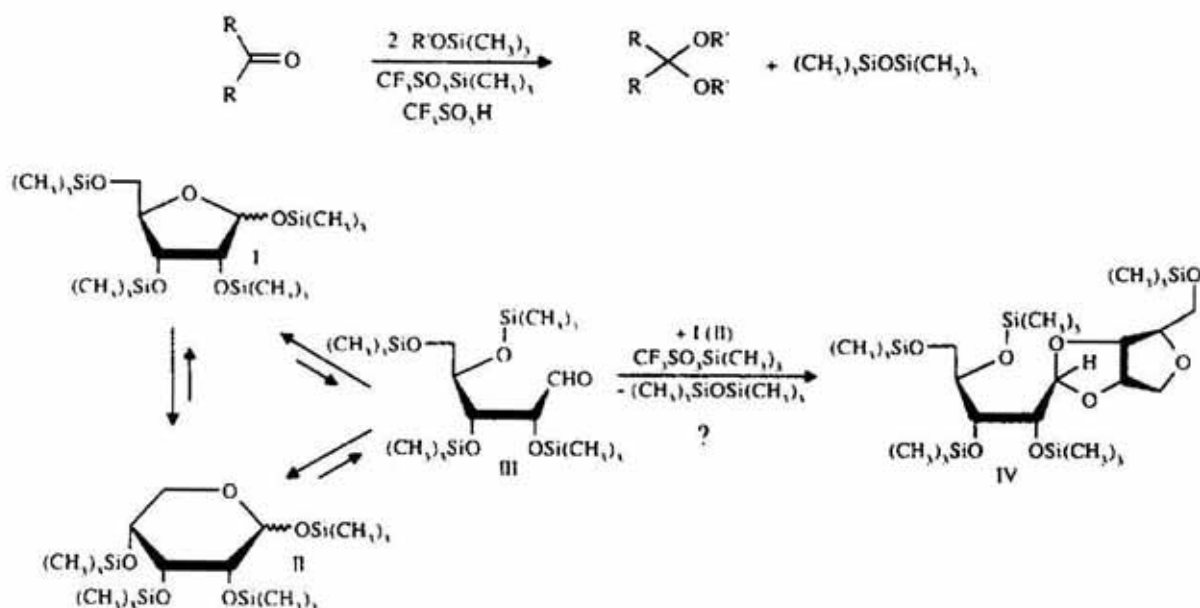
Scheme 19.



Scheme 20.

To summarize, free sugars and free bases (cf. Scheme 1) can be condensed in the form of their

their dedicated work and Mrs. Schwede for typing the manuscript.



Scheme 21.

persilylated derivatives to give after transsilylation the corresponding free nucleosides in up to 70% yield. In spite of the necessity of using an excess of the sugar, this new direct method of nucleoside synthesis will provide the fastest access to free nucleosides — in particular, when the corresponding protected (acylated or alkylated) sugar derivatives are not available [22].

I would like to thank my excellent, skillful and devoted technicians, Mr. Konrad Krolikiewicz and Mrs. Bärbel Bennua-Skalmowski, for all of

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