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NEW SIMPLIFIED NUCLEOSIDE SYNTHESIS[1]

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Pyrimidine- and purine-nucleosides can be synthesized efficiently by the reaction of silylated heterocyclic bases with peracylated sugars in the presence of Friedel-Crafts catalysts[2-4]. However, these procedures still demand the prior silylation of the heterocyclic bases to the highly moisture sensitive silyl derivatives. Furthermore the perfluoroalkane sulfonic and perchloric acids or their corresponding salts have to be converted to trimethylsilyltriflate, nonaflate or the labile perchlorate[4] - if not commercial trimethylsilyltriflate or the readily available $SnCl_4$ are used.

We have now discovered that silylation of the heterocyclic bases, the preparation of $(CH_3)_3SiSO_3C_nF_{2n+1}$ or $(CH_3)_3SiClO_4$ as well as the reaction with the peracylated sugar derivatives can be combined to effect nucleoside formation in one simple synthetic step in high yields.

Under these one step conditions the amounts of hexamethyldisilazane (HMDS) and trimethylchlorosilane (TCS) have to be chosen in such a way that each reactive heterocyclic hydroxy, mercapto or amino group as well as the free acids $C_nF_{2n+1}SO_3H$, $HClO_4$ or their corresponding salts are silylated with formation of NH_4Cl and the corresponding alkali chlorides. The preparation of the intermediate reagents involved are depictured in the following equations:

(1) $3\ CF_3SO_3H + TCS + HMDS \rightarrow 3\ (CH_3)_3SiSO_3CF_3 + NH_4Cl$

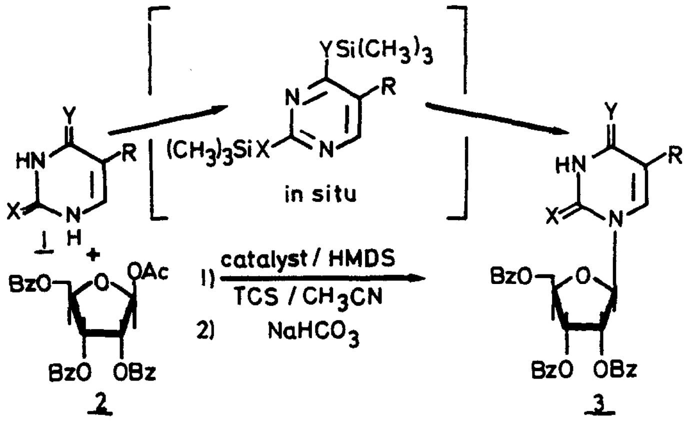
(2) $C_4F_9SO_3K^5 + TCS \rightarrow (CH_3)_3SiSO_3C_4F_9 + KCl$

(3) $NH_4ClO_4{}^6 + TCS \rightarrow (CH_3)_3SiClO_4{}^6 + NH_4Cl$

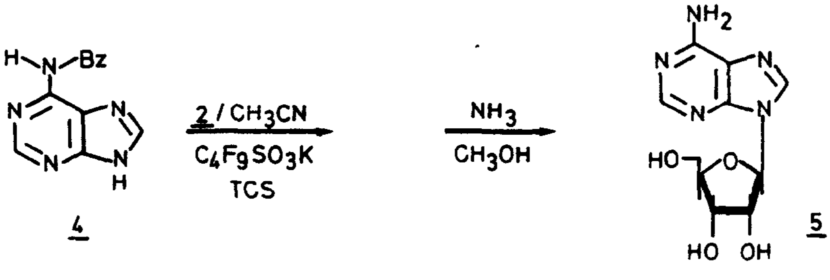
(4) $NaBF_4 + TCS \rightarrow (CH_3)_3SiBF_4{}^7 + NaCl$

Since salts like NH_4ClO_4[6] or $C_4F_9SO_3K$[5] are not very soluble in acetonitrile and the precipitating NaCl, KCl or NH_4Cl can thus occlude unreacted reagent, an excess of these salts is usually employed. In the case of the better soluble $NaClO_4 \cdot H_2O$[6] additional amounts of HMDS and TCS have to be used to eliminate the water. Surprisingly even $NaBF_4$ in combination with $(CH_3)_3SiCl$ (equation 4) must yield the unstable[7] $(CH_3)_3SiBF_4$ as intermediate, since nucleosides were formed albeit in moderate yield.

We investigated first the formation of uridine-2',3',5'-tri-O-benzoate 3a starting from uracil 1a and 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose 2 in absolute acetonitrile and obtained 3a in yields of up to 84% (Table I). Free trifluoromethane sulfonic acid, potassium nonaflate and $SnCl_4$ gave the highest yields. The more basic[2f] 5-methoxyuracil 1c, cytosine 1d as well as N^6-benzoyladenine 4, were reacted with 2 in the presence of potassium nonaflate and TCS to give the 3c, 3d and 5 in ca. 60-70% yield (Table I).



a X=O, Y=O, R=H; b X=S, Y=O, R=H;
c X=O, Y=O, R=OCH3; d X=O, Y=NH, R=H;



On conducting the reaction between 1a, 2 and $SnCl_4$ in 1,2-dichloroethane instead of acetonitrile besides 3a ca. 30% of the N_3-nucleoside as well as ca. 5-10% N_1,N_3-bis-riboside were formed. This is probably due to the increased salt concentration[2b,f] in the reaction mixture. Further experiments with bases like 4-pyridone and sugars like β-penta-O-acetylglucose and 1-O-methyl-3,5-bis-O-p-toluoyl-2-deoxy-D-ribose will be reported in the full paper.

Table I. Ribonucleosides

Base / Sugar (1 equ.)	Acid or Salt	TCS / HMDS (equ.)	Reaction Time Temperature	Acylated Nucleoside (Yield)
1a/2	CF_3SO_3H[a]	1,2/1,1	1 h/83°C	3a (81%)
1a/2	$C_4F_9SO_3K$[b]	3,1/0,7	14 h/83°C	3a (84%)
1a/2	$SnCl_4$[a]	0,8/0,8	2 h/24°C	3a (83%)
1a/2	NH_4ClO_4[b]	3,1/0,7	19 h/83°C	3a (40%)
1a/2	$NaClO_4\ H_2O$[b]	4,7/2,3	19 h/83°C	3a (58%)
1a/2	$NaBF_4$[b]	3,1/0,7	2 h/83°C	3a (43%)
1b/2	$SnCl_4$[a]	0,8/0,8	7 h/24°C	3b (59%)
1c/2	$C_4F_9SO_3K$[b]	3,1/0,7	20 h/83°C	3c (71%)
1d/2	$C_4F_9SO_3K$[b]	3,1/0,7	27 h/83°C	3d (56%)
4/2	$C_4F_9SO_3K$[b]	3,1/0,7	21 h/83°C	5 (63%)[c]

[a] 1,2 equivalents

[b] 2,4 equivalents

[c] Yield of free crystalline adenosine after saponification with CH_3OH/NH_3.

The following preparative procedure may serve as an example:

5-Methoxyuridine-2',3',5'-tri-O-benzoate 3c. To 0,63 g (5 mmol) 5-methoxyuracil, 2,57 g (5 mmol) 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose and 4,06 g (12 mmol) $C_4F_9SO_3K^5$ in 70 ml abs. CH_3CN, 1,63 g (1,89 ml = 15 mmol) TCS and 0,57 g (0,74 ml = 3,5 mmol) HMDS were added and the reaction mixture refluxed for 20 h with careful exclusion of moisture. After dilution with CH_2Cl_2, extraction with $NaHCO_3$- and NaCl-solution, evaporation gave a light brown residue (3,72 g) which was crystallized from ethyl acetate-hexane in several crops to give 2,09 g (71,4%) 3c, mp. 206-208°C.

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5) We thank Dr. H. Niederprüm, Inorg. Chemical Division, Bayer AG, D-5090 Leverkusen, Germany, for the generous supply of these reagents. Small samples of $C_4F_9SO_3K$ can be obtained free of charge from Bayer AG (Dr. Niederprüm), however the compound is also available in commercial quantities from Bayer AG.

6) A recent explosion of dimethylammoniumperchlorate [M. Menzer and H.G. Kazmirowski, Z. Chem. 17, 344 (1977)] should be taken as a warning to be extremely careful while working with perchlorates!

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