A General Synthesis of *N*-Glycosides. 6.[1] On the Mechanism of the Stannic Chloride Catalyzed Silyl Hilbert–Johnson Reaction

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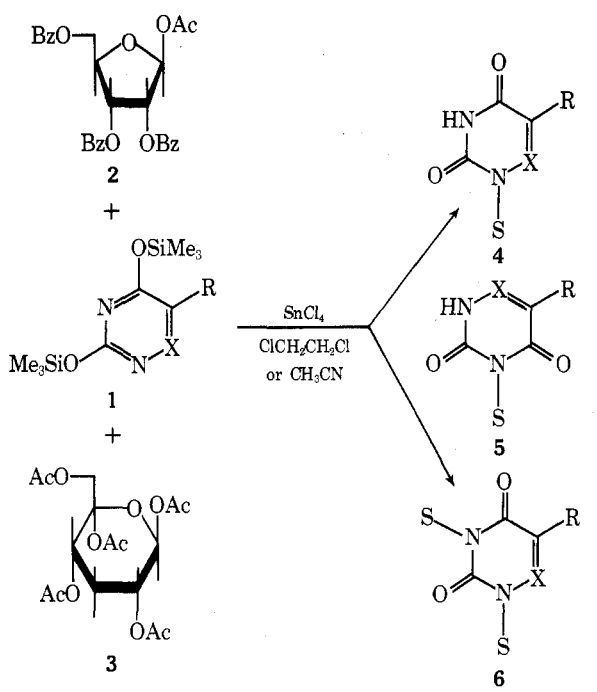
The influence of 5 and 6 substituents in silylated uracils on nucleoside synthesis and the formation of donor–acceptor complexes between the silylated bases and $SnCl_4$ is discussed.

In our previous publications on the $SnCl_4$-catalyzed silyl Hilbert–Johnson reaction we reported the surprisingly fast and high yield ribosilylation of silylated 5-nitrouracil **1c**[2a] and the striking influence of an additional 5-methyl group in silylated 6-methyluracil on the N_1/N_3 ratio[2b] during nucleoside formation.

Because we thought that the influence of such 5-substituents in uracil should be due mainly to electronic effects, we have varied the substituents in the 5 and 6 position of uracils and treated the silylated uracils **1** and **7** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (ABR, **2**) and **1** with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (PAG, **3**) under standard conditions to give besides the desired N_1-nucleosides **4**, the N_3-nucleosides **5**[3] and the N_1,N_3-nucleosides **6** (Scheme I, Tables I and II).

Scheme I

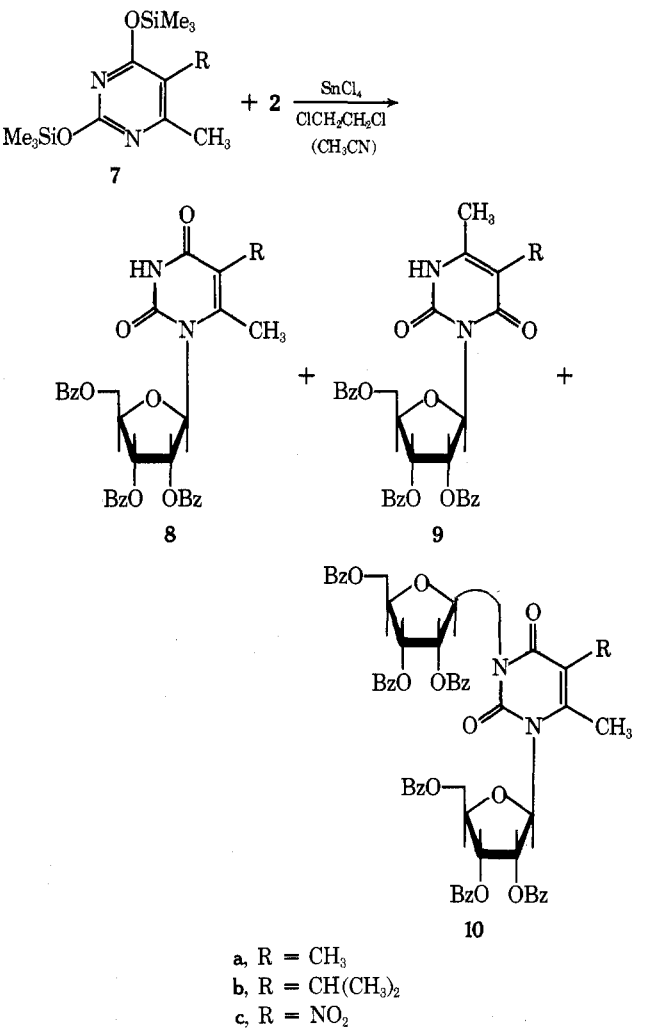


S = acylated β-D-ribofuranose or β-D-glucopyranose

a, R = H; X = CH
b, R = H; X = N
c, R = NO_2; X = CH
d, R = OCH_3; X = CH
e, R =  ; X = CH

Electron-donating substituents in the 5 position such as OCH_3 and NR_2 groups apparently strongly increase the basicity of the silylated uracils. Consequently, on addition of $SnCl_4$ in 1,2-dichloroethane, stable 1:1 donor–acceptor or π complexes[4] are formed between $SnCl_4$ and silylated 5-methoxyuracil **1d** or silylated 5-morpholinouracil **1e** which only react further with protected 1-*O*-acyl sugars if additional $SnCl_4$ is added to effect the formation of sugar cations.

Scheme II



a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = NO_2

Even with larger amounts of $SnCl_4$ the rates of ribosilylation (Table I) of **1d** or **1e** were much lower (2 h) than with silylated 5-nitrouracil **1c** (5 min) where no complex formation with $SnCl_4$ seems to occur. However the electron density of N_1 in silylated 5-nitrouracil **1c** is apparently still large enough for a rapid reaction with the sugar cation.

Since these donor–acceptor complexes are expected to be less stable in more polar solvents, nucleoside formation in acetonitrile is usually much faster and needs less $SnCl_4$ than in 1,2-dichloroethane. Furthermore, owing to decreased complex stability in acetonitrile in most cases less N_3- or N_1,N_3-nucleosides are obtained than in $ClCH_2CH_2Cl$.

Silylated uracil **1a** and 6-azauracil **1b** show reactivities (rate

Table I. Reaction of 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (ABR, 2, 10 mmol) with Silylated Uracils 1 and 7 (11 mmol) in the Presence of $SnCl_4$ at 23 °C

	$SnCl_4$ mmol		Reaction time, h		N_1 %		N_3 %		N_1, N_3 %	
Uracil (silylated)	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
Uracil	6.84	6.84	12	12	84	89	9	4	Traces	Traces
	13.68		1		73		11		7	
6-Azauracil	1.71	1.71	4	12	97	93[c]			1	
	13.68		1		90		2		3	
5-Nitrouracil	1.71	1.71	0.1	0.1	97	98				
5-Methoxyuracil	13.68	8.55	2.5	12	53[5]	90	27	3	13	Traces
5-Morpholinouracil	13.68	13.68	2	1	39[6]	53	18	32	42	12
5-Isopropyl-6-methyl-uracil	12.00	12.00	72	24	18	53	41	25		
6-Methyl-5-nitrouracil	8.55	8.55	0.9	0.6	84	73			14	19

[a] In 1,2-dichloroethane. [b] In acetonitrile. [c] The reaction in acetonitrile leads apparently to decomposition of the heterocycle thus resulting in lower yields.

Table II. Reaction of 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (PAG, 3, 10 mmol) with Silylated Uracils 1 (11 mmol) in the Presence of $SnCl_4$ at 23 °C

	$SnCl_4$, mmol		Reaction time, h		N_1 %		N_3 %		N_1, N_3 %	
Uracil (silylated)	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
Uracil	6.84	6.84	12	12	58	90	34	1	8	6
6-Azauracil	6.84	6.84	12	12	82	81				
5-Nitrouracil	6.84	6.84	5	12	82	77				
5-Methoxyuracil	13.68	6.84	3.5	12	61	83	25	15	Traces	

[a] In 1,2-dichloroethane. [b] In acetonitrile.

Table III. Analytical Data of the New Compounds

Registry no.	Nucleoside	$[\alpha]^{23}D$[a]	H-1′, ppm[b]	Formula (mol wt)	Anal., % calcd (found) C	H	N
58581-71-8	3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methoxyuracil	+21	6.68 (J < 1 Hz)	$C_{31}H_{26}N_2O_{10}$ (586.58)	63.48 (63.43)	4.47 (4.63)	4.78 (4.63)
58581-72-9	1,3-Bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-methoxyuracil	−41	6.65 (J < 1 Hz) 6.55 (J < 1 Hz)	$C_{57}H_{46}N_2O_{17}$ (1031.01)	66.40 (66.17)	4.50 (4.72)	2.72 (2/6(
58581-73-0	1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-morpholinouracil	−140.6	6.52 (J = 7 Hz)	$C_{34}H_{31}N_3O_{10}$ (641.65)	63.65 (63.73)	4.87 (5.18)	6.55 (6.54)
58581-74-1	3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-morpholinouracil	7.4	6.69 (J < 1 Hz)	$C_{34}H_{31}N_3O_{10}$ (641.65)	63.65 (63.47)	4.87 (5.01)	6.55 (6.44)
58581-75-2	1,3-Bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-morpholino-uracil	−54.4	6.68 (J = 2 Hz) 6.60 (J = 7 Hz)	$C_{60}H_{51}N_3O_{17}$ (1086.09)	66.35 (66.07)	4.73 (4.91)	3.87 (3.84)
58581-76-3	1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-isopropyl-6-methyl-uracil[c]	−19.3	5.70 ($W_{1/2}$ = 3 Hz)	$C_{34}H_{32}N_2O_9$ (612.61)	66.66 (66.86)	5.27 (5.79)	4.57 (4.18)
58581-77-4	3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-isopropyl-6-methyl-uracil	+14.8	6.72 ($W_{1/2}$ = 3 Hz)	$C_{34}H_{32}N_2O_9$ (612.61)	66.66 (67.02)	5.27 (5.89)	4.57 (4.08)
58581-78-5	1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitro-6-methyl-uracil[d]	2.7	6.60 (J < 1 Hz)	$C_{31}H_{25}N_3O_{11}$ (615.57)	60.49 (60.29)	4.09 (4.27)	6.83 (6.84)
58581-79-6	1,3-Bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitro-6-methyl-uracil[e]	−39.3	6.56 (J < 1 Hz) 5.80 (J < 1 Hz)	$C_{57}H_{45}N_3O_{18}$ (1060.01)	64.59 (64.46)	4.28 (4.33)	3.97 (3.85)

[a] *c* 1, in $CHCl_3$. [b] In $CDCl_3$. [c] Mp 158–160 °C, 195–197 °C from ethanol. [d] Mp 202–204 °C from CH_2Cl_2–pentane. [e] Mp 191–193 °C from CH_2Cl_2–pentane.

of nucleoside synthesis, formation of N_3- and N_1,N_3-nucleosides) between the extremes of silylated 5-nitrouracil **1c** and silylated 5-morpholinouracil **1e.**

The effect of the 5-methyl group in silylated 5,6-dimethyluracil[2b] **7a** is mainly a steric one, i.e., altering the complex formation between the base and $SnCl_4$ compared to silylated 6-methyluracil. This steric effect is even more pronounced in silylated 5-isopropyl-6-methyluracil **7b,** where the bulky isopropyl group hinders the formation of these complexes leading to increased amounts of the N_1-nucleosides **8b** besides **9b** (Scheme II, Table I).

In silylated 5-nitro-6-methyluracil **7c** the electronic and steric effect of the 5-nitro group dominates over the steric effect of the 6-methyl group[2b] in either solvent leading to 80%

Table IV. Analytical Data of the New Compounds

Registry no.	Nucleoside	Mp, °C	$[\alpha]^{23}D^a$	H-1′[b]	Formula (mol wt)	Anal., % calcd (found) C	H	N
58581-68-3	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-nitrouracil	129–131[c]	−45.7	5.93	$C_{18}H_{21}N_3O_{13}$ (487.39)	44.36 (44.21)	4.34 (4.44)	8.62 (8.50)
58581-69-4	1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-methoxyuracil	208–209[d]	−20.5	5.92	$C_{19}H_{24}N_2O_{12}$ (472.42)	48.31 (48.48)	5.12 (5.20)	5.93 (5.81)
58581-70-7	3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-methoxyuracil	204–205[d]	+2.4	6.22	$C_{19}H_{24}N_2O_{12}$ (472.41)	48.31 (48.25)	5.12 (5.31)	5.93 (5.97)

[a] *c* 1, $CHCl_3$. [b] $CDCl_3$, parts per million (J = 9 Hz). [c] From ethanol. [d] From ethyl acetate.

of the N_1-riboside **8c** and to ca. 15% of the N_1,N_3-bisriboside **10c** (Scheme II, Table I).

As expected, similar effects were observed with silylated cytosine, which has an electron-releasing 4-trimethylsilylamino group and did therefore not react with ABR (**2**) under our standard conditions in 1,2-dichloroethane with 0.5 equiv of $SnCl_4$ at 24 °C. Only after addition of a further 0.7 equiv of $SnCl_4$ did the reaction proceed to afford after 4 h a ca. 95% yield of amorphous cytidine 2′,3′,5′-tri-*O*-benzoate.

Reactions with penta-*O*-acetyl-β-D-glucopyranose (PAG, **3**) instead of **2** gave similar results, although the reaction times are longer because of the diminished reactivity of the corresponding cation (Table II). Thus a complex combination of electronic and steric factors influences and determines the rate of the reaction of silylated uracils with peracylated sugars as well as the ratio of N_1- (**4**), N_3- (**5**), and N_1,N_3- (**6**) nucleosides in the presence of $SnCl_4$.

These observations confirm our previous assumption that the $SnCl_4$-catalyzed silyl Hilbert–Johnson reaction between the hard[7] sugar cation and the hard[7] nitrogen of the silylated bases is similar to Friedel–Crafts acylations, where such phenomena have also been observed. Thus the basic *N,N*-dimethylaniline forms with Friedel–Crafts catalysts, e.g., BF_3, stable donor–acceptor complexes which prevent or impede the acylation by hard[7] acyl cations.[8]

Experimental Section

All melting points were taken on a Kofler melting point microscope and are uncorrected. The NMR spectra were determined on Varian A-60 and HR-100 instruments. The thin layer chromatography was performed on Merck silica plates GF_{254} using systems previously described.[2] The purification of the solvents, $SnCl_4$, and the sugar components ABR and PAG as well as the silylation of the uracils were performed essentially as described.[2]

5-Methoxyuracil was prepared according to Chesterfield et al.,[9] 5-morpholinouracil[10] from 5-bromouracil following the procedure of Ueda,[6] and 5-nitro-6-methyluracil[11] by nitration of 6-methyluracil. 5-Isopropyl-6-methyluracil, mp 289–292 °C. (Anal. Calcd: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.17; H, 7.51; N, 16.48) was prepared by desulfurization of 5-isopropyl-6-methyl-2-thiouracil[12] with chloroacetic acid.

General Procedure for the Preparation of Nucleosides. To a solution of 10 mmol of peracylated sugar and 11 mmol of silylated uracil in 100 ml of 1,2-dichloroethane (or acetonitrile) a solution of $SnCl_4$ in 100 ml of 1,2-dichloroethane (or acetonitrile) was added and the reaction mixture stirred at 23 °C and monitored by TLC. On completion the reaction mixture was poured on an excess $NaHCO_3$ solution and extracted with methylene chloride. After drying (Na_2SO_4) and evaporation, the residue was either crystallized or chromatographed on a column of silica gel (E. Merck, Darmstadt, 40–50-fold amount, 0.063–0.2 mm or 70–230 mesh) using hexane–ethyl acetate, chloroform–5% 2-propanol, or ethyl acetate–methanol mixtures as eluents.

In Tables III and IV the physical and analytical data of the new protected nucleosides are summarized.

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Registry No.—2, 604-69-3; **3,** 58581-81-0; $SnCl_4$, 7646-78-8; uracil, 66-22-8; 6-azauracil, 461-89-2; 5-nitrouracil, 611-08-5; 5-methoxyuracil, 6623-81-0; 5-morpholinouracil, 37454-52-7; 5-isopropyl-6-methyluracil, 58581-82-1; 6-methyl-5-nitrouracil, 16632-21-6.

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