CHEMISTRY LETTERS, pp. 449-452, 1974. Published by the Chemical Society of Japan

HEXURONIC ACID AND AMINOSUGAR NUCLEOSIDES VIA STANNIC CHLORIDE-CATALYZED GLYCOSIDATIONS OF SILYLPYRIMIDINES WITH PERACYL-SUGARS[1)]

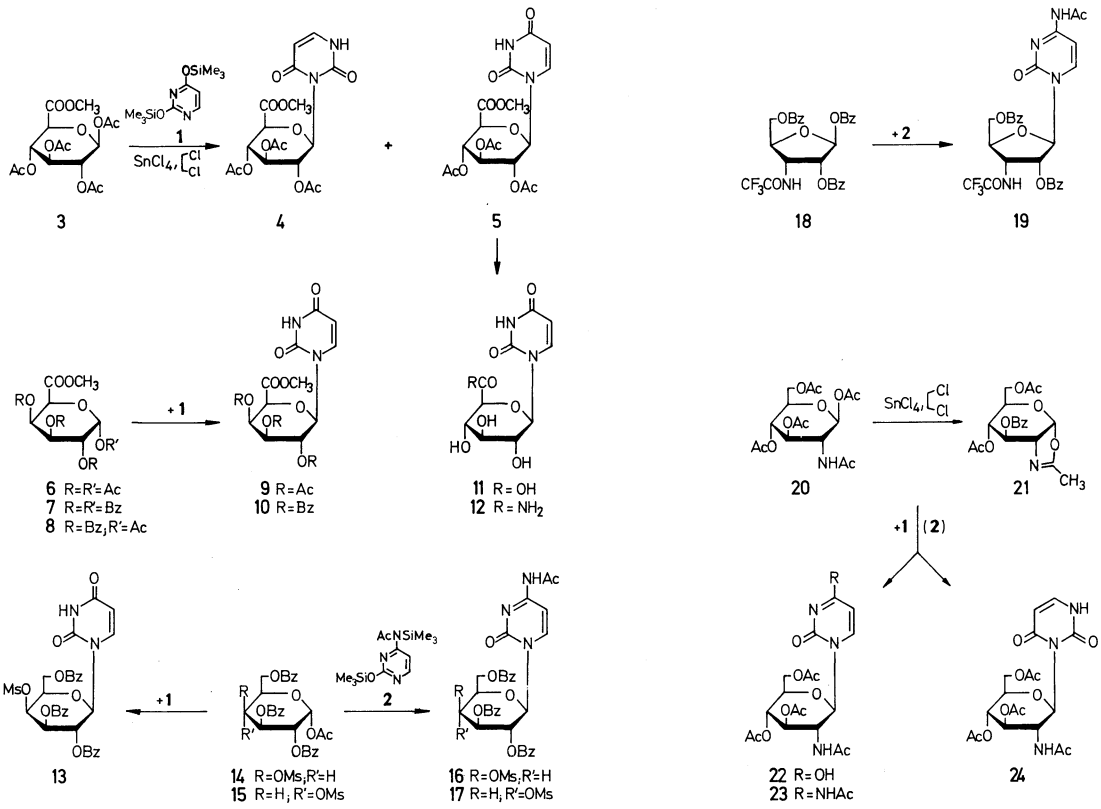
Frieder W. LICHTENTHALER, Arnold HEERD, and Kurt STROBEL
Institut für Organische Chemie, Technische Hochschule Darmstadt,
61 Darmstadt, Germany

On the basis of ten $SnCl_4$-catalyzed N-glycosidations of silylated uracil (1) and N-acetylcytosine (2) with per-O-acyl-glycoses from uronic acids, aminosugars and simple hexoses, the scope of the procedure is evaluated, a major concern being the formation of N-3 nucleosides from 1.

Of the various newer procedures for the synthesis of pyrimidine nucleosides [2)] the most recently advanced [3)] Friedel-Crafts catalyzed N-glycosidation of silylated pyrimidines with per-O-acyl-glycoses has commanded particular interest [4-13)], featuring the utilization of readily accessible silyl nucleobases and of fully acetylated sugars as distinct advantages. Hence, not only standard pyrimidines have been glycosidated in this way with a variety of pentose and hexose derivatives [4-8)], but also aza- [6, 9)], thio- [3, 10)], and seleno-analogs [11)] as well as pyrazine [12)] and fused pyrimidine heterocycles [13)]. We here report the first applications of this procedure to the synthesis of pyrimidine nucleosides from hexuronic acids and aminosugars, together with some of the limitations of the method.

In glycosidations of 2, 4-bis(trimethylsilyl)uracil (1) via this procedure, the formation of N-1-, and N-3-substituted ß-glycosyl-uracils appears to be of much more serious concern than that of α-nucleosides. Thus, reaction of methyl tetraacetyl-ß-D-glucuronate 3 with 1 in a 1 : 1.2 : 2.3 ratio of sugar, base and stannic chloride (5 h, 70°C) gave two major products in approximately equal amounts, readily separated by PLC and characterized in crystalline form, yet in low yield (cf. Table). One product proved to be the expected 1-(methyl tri-O-acetyl-ß-D-glucuronyl)uracil 5 on the basis of spectral data and its ready conversions into the unblocked 1-(glucuronyl 11 by 0.1 N sodium hydroxide (3 h, 25°) or into the corresponding glucuronamido derivative 12 by methanolic ammonia [14)] The second component turned out to be the N-3-glycosylated uracil nucleoside 4 rather than an α-anomer of 5, as evidenced by a shift of λ_{max} from 265 nm (water) to 294 nm (0.1 NaOH) [16)] and a quartet for H-6 at τ 2.68, attributable to coupling with the vicinal H-5 (8 Hz) and N^1-H protons (4 Hz).

An increase in the amount of nucleobase used in the glycosylation appears to raise the proportion of N-1-substituted uracil nucleosides, as evidenced by the isolation of galacturonyl-uracil 9 from 6 in 58 % yield (cf. Table), yet two minor components were detectable (tlc). Even



more propitious proceeded the uracilations of the benzoyl derivatives 7, 8 and 14, affording only traces of UV-active material other than 10 and 13, resp., and allowing their isolation in yields over 70 % (cf. Table).

As expected from the ready formation of the oxazoline 21 from tetraacetyl-2-acetamido-2-deoxy-ß-D-glucose (20) with ferric chloride in dichloromethane at room temperature [17], the conversion 20 → 21 is also effected by stannic chloride (or titanium tetrachloride) in dichloroethane. Hence, when subjecting either 20 or 21 to $SnCl_4$-catalyzed uracilation with 1, the actual glycosidations are occuring at the intermediate stage of an $SnCl_4$-oxazoline complex, and the product distributions are identical. Under standard conditions, i.e. 7 h at 70° with a 1 : 1,3 : 1.4 ratio of 20/21, silylbase 1 and catalyst, the mixture obtained consisted of N-1 nucleoside 22 with approximately 10 % each of the corresponding N-3-isomer 24 [amorph, $[\alpha]_D^{23}$ - 67° (c 0.5, methanol)], oxazoline 21 and tri-O-acetyl-2-acetamido-2-deoxy-D-glucopyranose, the latter being formed from 21 during aqueous workup. Better results were obtained on raising the amount of silyl-uracil to two, and decreasing the catalyst to 0.5 molar equivalents; the ensuing reaction mixture contained only traces of 21 and the N-3-nucleoside and allowed the isolation of 22 in 59 % yield (cf. Table).

With respect to the site of N-glycosidation, reactions of N^4,-O-bis(trimethylsilyl)-N^4-acetylcytosine (2) with per-O-acyl sugars appear to take a much more uniform course. Accordingly, the two blocked hexopyranoses 14 and 15 afforded, in yields of over 80 %, the N-1-nucleo-

TABLE: Nucleosides prepared by stannic chloride catalyzed glycosidations of 2,4-bis(trimethylsilyl)derivatives of uracil (1) and N-acetylcytosine (2) with 1-O- acyl-glycoses.

Product[a]	Educts: Silyl-Pyrimidine	Educts: Sugar Component[b]	Molar ratio of Sugar : Base : $SnCl_4$	Conditions: time (h)	Conditions: temp. (°C)	Yield %	mp (°C)	$[\alpha]_D$	(solvent, °C)
4 5	1	3	1 : 1.2 : 2.3	5	70	10 15	179-180 209-210	+ 6 - 7	(CH_3OH, 20) (CH_3OH, 20)
9	1	6	1 : 1.6 : 2.3	5	70	58	amorph	+ 37	(CH_3OH, 20)
10	1	7 or 8	1 : 1.6 : 2.3	5	70	75	220-223	+ 160	($CHCl_3$, 20)
13	1	14	1 : 1.3 : 2.6	12	60	71	204-206		
22	1	20 or 21	1 : 2.0 : 0.5	5	70	50	glass	- 32	($CHCl_3$, 19)
16	2	14	1 : 1.1 : 2.6	12	60	85	266-268(dec)	+ 99	(DMF, 23)[c]
17	2	15	1 : 1.1 : 2.6	12	60	81	240-241(dec)	+ 24	(DMF, 24)
19	2	18	1 : 1.5 : 2.6	16	25	69	255	+ 23	(Me_2CO, 20)
23	2	20 or 21	1 : 2.0 : 0.5	5	70	71	218-220	- 10	($CHCl_3$, 25)[d]

a) All new compounds gave elementary analysis results within 0.3 % of theory, as well as UV (methanol) and NMR data (DMSO-d_6) that were consistent with the structures assigned.

b) The newly prepared acyl sugars were obtained as follows: 8, mp 225 - 226° and $[\alpha]_D^{20}$ + 277° (c 0.5, $CHCl_3$), from its methyl glycoside or from 7 [S. Morell and K.P. Link, J. Biol. Chem., 108, 766 (1935)] by acetolysis (58 %); 14, mp 143 - 144° and $[\alpha]_D^{20}$ + 92° (c 1, $CHCl_3$), from its methyl glycoside [E.J. Reist et al., J. Org. Chem., 30, 2312 (1965)] by acetolysis (79 %); 15, mp 175 - 178° and $[\alpha]_D^{20}$ + 126° (c 1, $CHCl_3$), from its methyl glycoside [F.W. Lichtenthaler and P. Heidel, Angew. Chem., 81, 998 (1969)] by BF_3-catalyzed acetolysis (47 %); 18, mp 164° and $[\alpha]_D^{22}$ + 43° (c 1, $CHCl_3$), from 1,2-O-isopropylidene-3-trifluoroacetamido-3-deoxy-α-D-ribofuranose [A.M. Fujiwara et al., J. Heterocycl. Chem., 7, 891 (1970)] by benzoylation, deacetalization by acid and benzoylation (48 % for 3 steps).

c) In conformity with data reported previously [K.A Watanabe et al., J. Org. Chem., 35, 231 (1970)].

d) Data correlate well with those of C.L. Stevens and K. Nagarajan, J. Med. Chem., 5, 1124 (1962).

sides 16 and 17,, key intermediates for efficient syntheses of 4'-aminohexosyl-cytosines of gluco- and galacto-configuration [18] Similarly, the 3-aminoribose derivative 18 and glucosamine pentaacetate 20 could be converted into their N-acetylcytosine nucleosides 19 and 23, resp., in satisfactory yields (cf. Table); some minor products detectable by tlc in the reaction mixtures (conceivably α-anomers and/or N-3-isomers) were readily removed by the usual isolation procedure.

The results presented here are of purely preparative nature and, hence, unsuitable for far-reaching mechanistic conclusions. Yet, the highly stereoselective formation of ß-glycosidic linkages clearly indicates that the stereochemistry is controlled by the vicinal 2-acyloxy group via trans-opening of cyclic acyloxonium intermediates, a course that is substantiated by the ready formation of oxazoline 21 from 20 under these conditions. Furthermore, on the basis of the accumulated evidence, some rationalizations may be made that are of considerable relevance to the preparative utility of this stannic chloride catalyzed N-glycosidation procedure:

1. Whilst bis-trimethylsilyl-N^4-acetylcytosine 2 is readily N-1-glycosidated with 1-O-acyl-glycoses by $SnCl_4$ in dichloroethane, N-1 and N-3-glycosidation can occur with bis-trimethylsilyl-uracil (1), impairing yields considerably.
2. The use of benzoyl instead of acetyl groups for O-protection in the sugar educt not only favors the isolation of crystalline products at the blocked nucleoside stage — of advantage for removal of side products formed — but also appears to disfavor N-3-glycosidation of bis-(trimethyl)uracil.

3. Though somewhat less reactive, 1-O-benzoylglycoses may be utilized for this procedure just like their 1-O-acetyl analogs.

Acknowledgments. - The authors wish to express their appreciation to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for supporting this investigation and the State of Hessia for a graduate fellowship (to A. H.)

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(Received February 4, 1974)