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Nucleosides; XLI[1]. A Simple Synthesis of Pyrimidine α-Nucleosides via Direct Glycosylation

S.N. MIKHAILOV

Institute of Molecular Biology of the U.S.S.R. Academy of Sciences, Moscow, B-334, U.S.S.R.

W. PFLEIDERER*

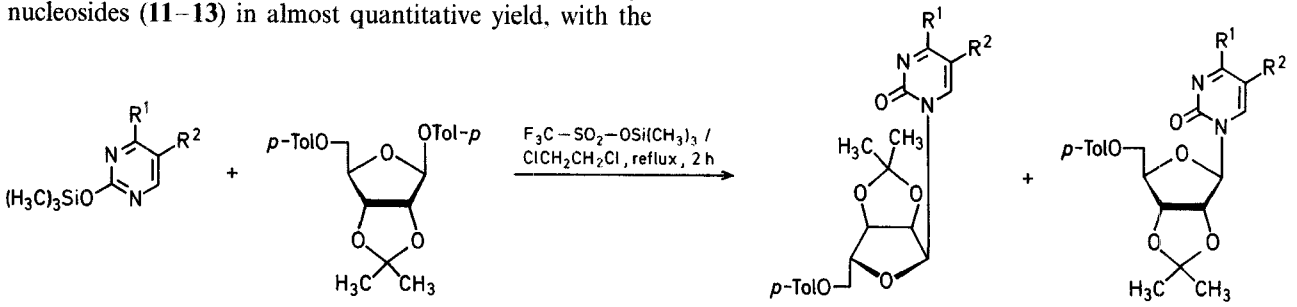
Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-7750 Konstanz, Federal Republic of Germany

Among the various procedures used for nucleoside synthesis[2] the method developed by Vorbrüggen and coworkers[3,4] is applied most often. The method involves glycosylation of trimethylsilyl derivatives of nucleic bases with completely acylated sugars in the presence of Lewis acids, preferentially tin(IV) chloride or trimethylsilyl triflate, respectively. The stereospecificity of the reaction is determined by the transient 1,2-acyloxonium ion: *trans*-derivatives with respect to the 2-*O*-acyl group are formed[2]. Recent observations[5,6,7] indicate the possibility of stereoselective syntheses of α- or β-nucleosides starting from sugar derivatives with non-participating groups.

In the present investigations, the crystalline, easily available 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-toluoyl-β-D-ribofuranose (**4**)[8,9] is used as a starting compound. Condensation of bis-trimethylsilyl derivatives of the pyrimidine bases **1**–**3** with **4** in 1,2-dichloroethane in the presence of trimethylsilyl triflate gave mixtures of the corresponding α-(**5**–**7**) and β-nucleosides (**11**–**13**) in almost quantitative yield, with the α/β-ratio ranging from 9:1 to 6:1. Unfortunately, only thymine α-nucleoside **6** could be obtained in pure state by direct crystallization of its mixture. The separation of the anomeric mixtures **5** + **11** and **7** + **13**, respectively, was not possible even by various chromatographic means, but, after deacylation of each mixture, the partially blocked α-ribonucleosides **8**–**10** were isolated in 63–44% overall yield. The structures of the synthesized compounds **5**–**10** were deduced from the analysis of their ^{1}H-N.M.R. spectra (Table). The empirical rules formulated for proving the anomeric configuration of nucleosides using N.M.R. spectroscopy are applicable to these products: the chemical shifts of the H-1′ for the 1′,2′-*cis*-substituted furanoses are located downfield[10] as compared to those for 1′,2′-*trans*-substituted furanoses, indicating a preferred formation of the α-ribonucleosides from the spectra of the mixtures. Furthermore, the results are in agreement with Imbach's rule[11], since the difference between the chemical shifts of protons of the methyl groups of the dioxolane ring is mostly $\Delta\delta < 0.15$ ppm for α-nucleosides and $\Delta\delta > 0.15$ ppm for β-nucleosides, respectively. Also, the 4′-proton forms a triplet and the spin-spin coupling constants $J_{3',4'}$ are close to zero, as is characteristic for α-nucleosides[12].

The U.V. spectra of the nucleosides **8**–**10** are typical for *N*-1-substituted derivatives of pyrimidine nucleic bases. Acetonides **11**–**13** may be deblocked in the usual way to give the free α-nucleosides.

The developed procedure for the synthesis of α-ribonucleosides via direct glycosylation supplements the well known method of the preparation of 1′,2′-*cis*-nucleosides using the cyanamide approach[13].



1-3

	R^1	R^2
1	$OSi(CH_3)_3$	H
2	$OSi(CH_3)_3$	CH_3
3	N(Si(CH3)3)(CO–C6H5)	H

4

5-7

11-13

	R^1	R^2
5,8,11	OH	H
6,9,12	OH	CH_3
7,10,13	NH–CO–C6H5	H

8-10

Table. ^{1}H-N.M.R. Spectra of 1-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-pyrimidines and their 5′-*O*-*p*-Toluoyl Derivatives (δ-values in ppm)

Compound (Solvent)	1′-H ($J_{1',2'}$)	2′-H ($J_{2',3'}$)	3′-H ($J_{3',4'}$)	4′-H ($J_{4',5'}$)	5′-H (J)	5″-H (J)	NH	OH ($J_{OH,5'}$)	6-H ($J_{6,5}$)	5-Subst.	*o*-	*p*-Toluoyl *m*- (J)	*p*-	Isopropylidene ($\Delta\delta$, ppm)
5 (CDCl$_3$)	6.32(d) (4.2)	4.96(dd) (6.0)	4.83(d) (0.0)	4.65(t) (3.4)	4.53(dd) (3.4)	4.36(dd) (−12.2)	9.08(br.s)		7.51(d) (8.0)	5.71(dd)[a]	7.90(d) (8.1)	7.28(d)	2.39(s)	1.45(s) 1.30(s) (0.15)
6 (CDCl$_3$)	6.33(d) (4.3)	4.93(dd) (5.8)	4.83(d) (0.0)	4.66(t) (3.6)	4.52(dd) (3.4)	4.36(dd) (−12.2)	8.08(br.s)		7.34(q) (1.2)	1.93(d)	7.90(d) (8.1)	7.28(d)	2.40(s)	1.45(s) 1.30(s) (0.15)
7 (CDCl$_3$)	6.38(d) (4.1)	5.14(dd) (5.9)	4.87(d) (0.0)	4.71(t) (3.9)	4.53(dd) (3.7)	4.38(dd) (−12.2)	9.22(br.s)		7.96(d) (7.6)	[b]	7.92(d) (8.2)	7.28(d)	2.40(s)	1.38(s) 1.27(s) (0.11)
											8.10 – 7.40(m, 5H, Bz)			
8 (DMSO-d_6)	6.09(d) (4.3)	4.76(dd) (6.1)	4.82(d) (0.0)	4.31(t) (3.0)	3.54(m) (3.0)		11.34(br.s)	5.16(t) (4.9)	7.49(d) (8.0)	5.61(d)				1.34(s) 1.24(s) (0.10)
9 (DMSO-d_6)	6.11(d) (4.3)	4.75(dd) (5.9)	4.82(d) (0.0)	4.32(t) (3.3)	3.54(m) (3.3)		11.32(br.s)	5.14(t) (4.9)	7.32(q) (1.2)	1.77(d)				1.34(s) 1.25(s) (0.09)
10 (DMSO-d_6)	6.18(d) (4.0)	4.87(m)		4.38(t) (3.0)	3.59(m) (3.0)		11.19(br.s)	5.18(t) (5.0)	8.04(d) (7.6)	7.40(d)	8.01 – 7.47(m, 5H, Bz)			1.30(s) 1.24(s) (0.06)

[a] Long-range coupling $J_{5,NH}$ = 2.0 Hz.

[b] Overlapped by the signals of benzoyl groups.

U.V.-Absorption spectra: Cary-Recording Spectrometer (Model 118) of Applied Phys. ^{1}H-N.M.R.-spectra: Bruker WM 250. Chromatography: T.L.C. on thin layer plates silica gel F 1500 LS 254 from Schleicher & Schüll; column chromatography on silica gel 60, particle size 0.063–0.2 mm from Merck/Darmstadt. The substances were dried in a vacuum dessicator over phosphorus pentoxide or in an oven at 100°C. Melting points are not corrected.

General Method of Glycosylation:
A mixture of uracil, thymine, or N^4-benzoylcytosine (7 mmol) and hexamethyldisilazane (15 ml) is heated under reflux for 16 h. The resulting solution is evaporated under reduced pressure to remove the excess of hexamethyldisilazane. The residue is dissolved in dry 1,2-dichloroethane (25 ml), then 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-toluoyl-β-D-ribofuranose (**4**; 2.13g, 5 mmol) and 1 molar solution of trimethylsilyl triflate in dry 1,2-dichloroethane (5.5 ml) are added, and the resulting solution is heated under reflux for 2 h. The solution is cooled, chloroform (25 ml) and saturated sodium hydrogen carbonate solution (25 ml) are added, and the mixture is stirred at 20°C for 20 min. The organic layer is separated, the aqueous layer extracted with chloroform (20 ml), the combined organic layers are washed with water (10 ml), and then dried with sodium sulfate. The filtrate is evaporated and the residue chromatographed over a column of silica gel (50 g). The column is first washed with chloroform (500 ml) and then eluted with a mixture of chloroform/methanol (98:2) to give a mixture of α- and β-anomers as the main fraction in 90–95% yield. According to the ^{1}H-N.M.R. spectra, 10–15% of the β-isomers were present in these mixtures.

1-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluoyl-α-D-ribofuranosyl)-thymine (6):
The anomeric mixture of isomers **6** + **12** is recrystallized twice from ethanol to give colourless crystals, which contain 1 mol of ethanol and do not show a defined melting point; yield: 1.5 g (65%).

$C_{21}H_{24}N_2O_7 \cdot C_2H_5OH$ (462.5)	calc.	C 59.73	H 6.54	N 6.06
	found	59.28	6.07	6.21

After drying for 16 h at 100°C or recrystallization from aqueous methanol the substance looses the molecule of ethanol; m.p. 140–142°C.

$C_{21}H_{24}N_2O_7$ (416.4)	calc.	C 60.57	H 5.81	N 6.73
	found	60.20	5.78	6.68

1-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-uracil (8):
A solution of the crude anomeric mixture **5** + **11** (2 mmol) in 5 molar ammonia solution in dry methanol (10 ml) is kept for 24 h at 20°C and then concentrated under reduced pressure. The residue is shaken with chloroform (20 ml) and water (20 ml). The aqueous layer is again treated with chloroform (20 ml) and finally the combined organic layers extracted with water (20 ml). The combined water layers are concentrated under reduced pressure, coevaporated with ethanol, and the residue is crystallized from ethanol to give colourless crystals; yield: 0.35 g (63%); m.p. 199–201°C (Lit.[10], m.p. 201–202°C); R_f = 0.3 (19/1 chloroform/methanol).

U.V. (water, pH 7): λ_{max} (log ε) = 206 (3.94); 262 nm (4.01); (water, pH 13): 261 nm (3.89).

1-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-thymine (9):
This compound is prepared analogously to the preceeding procedure from crude mixture **6** + **12** (2 mmol) to give on crystallization from ethanol, colourless crystals; yield: 0.30 g (50%); m.p. 212–213°C (Lit.[10], m.p. 212–213°C); R_f = 0.3 (19/1 chloroform/methanol).

U.V. (water, pH 7): λ_{max} (log ε) = 208 (3.94); 267 nm (4.00); (water, pH 13): 266 nm (3.89).

N^4-Benzoyl-1-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)-cytosine (10):
To a cooled solution of crude mixture **7** + **13** (2 mmol) in dry methanol (14 ml) is added a 0.5 molar solution of sodium methoxide in dry methanol (0.5 ml) and the solution is kept at 0°C for 30 min. The solution is then neutralized with acetic acid. The combined filtrates are evaporated in vacuum to dryness and the crystalline residue recrystallized from acetone; yield: 0.23 g (30%).

Better yields are obtained after purification by column chromatography on silica gel (30 g) with chloroform (500 ml) followed by 97.5/2.5 chloroform/methanol. The first fraction contains the β-nucleoside (R_f = 0.27; 19/1 chloroform/methanol) and the main fraction, the α-nucleoside **10**. Evaporation to dryness and crystallization from acetone or ethanol gives colourless crystals: yield: 0.31 g (40%); m.p. 217–219°C; R_f = 0.14 (19/1 chloroform/methanol).

$C_{19}H_{21}N_3O_6$ (387.4)	calc.	C 58.90	H 5.46	N 10.85
	found	59.03	5.44	10.83

U.V. (10% methanol, pH 7): λ_{max} (log ε) = 259 (4.36); 303 nm (4.10); (10% methanol, pH 13): [280 (3.99)]; 315 nm (4.26).

Received: October 1, 1984

* Address for correspondence.

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