Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8355-8358, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01929-6

A New Efficient Method in Nucleoside Synthesis

Oliver Jungmann and Wolfgang Pfleiderer*

Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-78434 Konstanz, Germany

Abstract: A new stereo- and regioselective synthesis for adenosine analogous nucleosides is described. Starting from 2- and 6-substituted 4-amino-7(8H)-pteridinones, DBU deprotonation and the ribosylation with an α-haloribofuranose derivative leads to the corresponding pteridine-N-8-β-D-nucleosides in reasonably good yields[1]. Copyright © 1996 Published by Elsevier Science Ltd

More than eight decades have elapsed since Fischer and Helferich first reported the synthesis of certain purine nucleosides by glycosylation of silver salts of purines with acetobromoglucose[2]. In the meantime a tremendous number of nucleosides have been synthesized and the reaction of persilylated heterocyclic bases with peracylated sugars in the presence of Lewis acids has become a standard synthetic method[3] for the preparation of pyrimidine, purine as well as other heterocyclic nucleosides.

The synthesis of ribonucleosides via the Hilbert-Johnson-Birkofer procedure[4, 5] includes a neighbouring -group participation by a 2'-acyloxy group leading to the exclusive formation of the β-anomers (Tipson-Baker rule[6,7]). Unfortunately, when this method is extended to the synthesis of 2'-deoxyribonucleosides, α/β-anomeric mixtures are usually obtained, which have to be seperated by tedious chromatographical techniques.

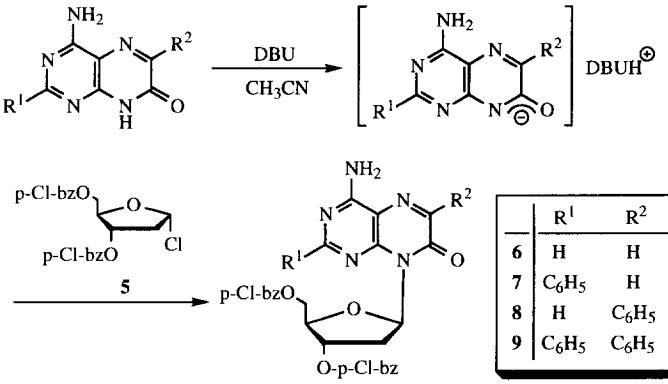
These difficulties have been overvcome by the phase-transfer glycosylation procedure introduced by F. Seela et al.[8] and the sodium salt approach practised by R. K. Robins et al.[9]. Both methods lead with various heterocycles and 1-chloro-2-deoxy-3,5-di-O-toluoyl-α-D-ribofuranose in a stereospecific manner to the blocked 2'-deoxy-β-D-ribonucleosides via an S_N2-mechanism.

For the pteridine series[10] we have been looking for an even simpler glycosylation procedure which allows the regio- and stereospecific synthesis of 7(8H)-pteridinone-N-8-β-D-ribo- and -2'-deoxyribonucleosides. Our interest was concentrated primarily towards the corresponding 4-amino derivatives which can be regarded as structural analogs of adenosine and 2'-deoxyadenosine, respectively. In earlier investigations some of the adenosine related ribonucleosides have been synthesized by applying the Hilbert-Johnson-Birkofer method[11, 12]. However, attempts to prepare the 2'-deoxy-ribonucleoside analogs failed and led to unsatisfactory results[12, 13].

After improvement of the synthesis of the known 4-amino-7(8H)-pteridinone **(1)**[12, 14] and its 2- and 6-phenyl derivatives **(2-4)**[12, 15], a suspension of the starting material in dry acetonitrile was treated with an equimolar amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and followed by the addition of 3,5-di-O-(4-chlorobenzoyl)-1-chloro-2-deoxy-α-D-ribofuranose **(5)**[16] (1.1 eq.) leading at room temperature to the corresponding 4-amino-8-(2-deoxy-β-D-ribofuranosyl)-7(8H)-pteridinones **(6-9)** which were isolated by crystallization from $CHCl_3/CH_3OH$ or by chromatographical workup in 34-54% yield. Besides the high β-

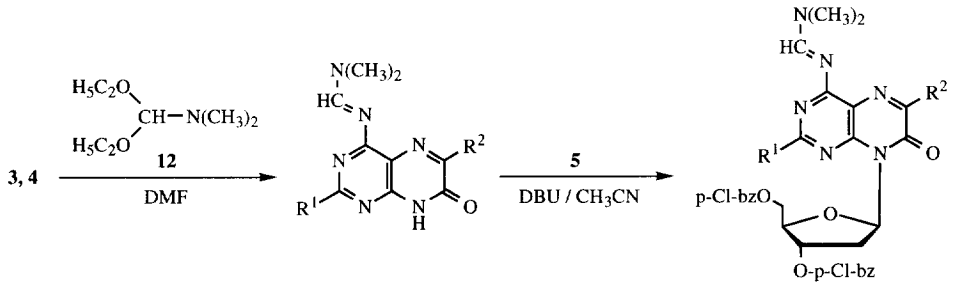
stereoselectivity, especially the regioselectivity of the reaction should be emphasized, which results in the exclusive formation of the blocked N-8- and no O-7-nucleosides.

	R^1	R^2
1	H	H
2	C_6H_5	H
3	H	C_6H_5
4	C_6H_5	C_6H_5



	R^1	R^2	%
6	H	H	34
7	C_6H_5	H	49
8	H	C_6H_5	45
9	C_6H_5	C_6H_5	54

The advantage of this new method is seen in an interesting solubilizing effect of the DBU on the relatively insoluble pteridines and the clean S_N2-type mechanism between the anion of the nucleobase and the halo-sugar **5** existing, according to the anomeric effect, predominately in the α-configuration at C(1). We also learned from the new results that the structure of the formerly published 4-amino-2-phenyl-8-(2-deoxy-3,5-di-O-p-toluoyl-α-D-ribofuranosyl)-7(8H)-pteridinone[12] - synthesized under Wittenburg conditions[17] applying $HgBr_2/HgO$ as catalysts in benzene - has to be revised from α-D- to the β-D-configuration.



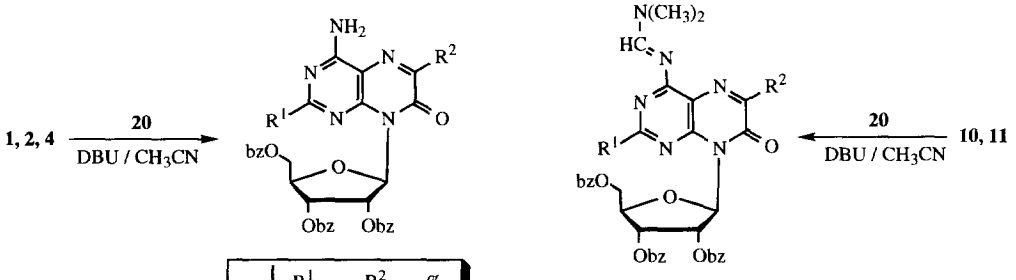
	R^1	R^2
10	H	C_6H_5
11	C_6H_5	C_6H_5

	R^1	R^2	%
13	H	C_6H_5	60
14	C_6H_5	C_6H_5	71

A further improvement in the glycosylation reaction was encountered by modifying the amino function in 4-amino-6-phenyl-7(8H)- (**3**) and 4-amino-2,6-diphenyl-7(8H)-pteridinone (**4**) by conversion into their dimethylaminomethylene derivatives **10** and **11**, respectively, showing an increased solubility in organic solvents as such. The heterocycles **3** and **4** reacted in high yield on treatment with 1.5 equivalents of N,N-dimethylformamide diethylacetal (**12**) in dry dimethylformamide[18] and the following stereoselective glycosylation of **10** and **11** with **5** readily provided in the presence of DBU within a few minutes the completely protected β-2'-deoxyribonucleosides **13** and **14** as yellow precipitates in 60 % and 71 % yield, respectively[19].

In the synthesis of the nucleosides **6-9** and **13**, the formation of the corresponding α-anomeres is comparatively low. After a complete workup of the reaction mixtures, which resulted predominately in a recovery of the starting materials **1-4** and **10**, further product fractions were isolated in less than 10 % of the overall yield, consisting of α/β-anomeric mixtures as confirmed by ^{1}H-NMR spectra. Only in the case of **14**, 21 % of an anomeric mixture was isolated from the mother liquor containing an equal quantity of the α- and β-nucleoside, which could however not be separated even by various chromatographical methods.

This synthetic method has been found to be applicable equally well for the preparation of the pteridine-N-8-β-D-ribonucleosides (**15-19**) since the nucleophilic displacement at the anomeric center of 2,3,5-tri-O-benzoyl-1-bromo-α-D-ribofuranose (**20**)[20] by the attack of the deprotonated aglycons **1**, **2**, **4**, **10** and **11** in form of their DBU salts is controlled by the intermediary acyloxonium cation leading to the formation of a β-glycosidic linkage. However, we have to confess that in the ribo-series this type of direct glycosylation via the DBU salt is only superior to the reported classical method[12], if the pteridines are amino protected as mentioned above.



	R^1	R^2	%
15	H	H	22
16	C_6H_5	H	34
17	C_6H_5	C_6H_5	33

	R^1	R^2	%
18	H	C_6H_5	52
19	C_6H_5	C_6H_5	68

During our recent studies we also noticed, that the earlier reported β-D-riboside[12] and the α- and β-D-2'-deoxyribosides of **3**[13] which were obtained under Hilbert-Johnson-Birkofer conditions are not in agreement with the physical data of the N-8-nucleosides synthesized via the DBU method. The observed alkali lability on treatment with aqueous base at pH > 10, which resulted in a recovery of the starting aglycon and the rearrangement with $HgBr_2$ in toluene[21] to the more stable N-8-derivatives points to an O-7 glycosidic bond.

All compounds have been structurally proven and well characterized by tlc, melting point, UV- and ^{1}H-NMR spectra, elementary analysis and pK_a determination. The configuration of the glycosidic bond of the newly synthesized nucleosides are based upon simple chemical shift data[22] and especially two dimensional NOESY ^{1}H NMR investigatons.

REFERENCES AND NOTES

1. For a comprehensive review of nucleoside syntheses: Townsend, L. B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, 1991-1994, Vol. 1-3; and references therein.
2. Fischer, E.; Helferich, B. *Ber. Dtsch. Chem. Ges.* **1914**, 47, 210.
3. Vorbrüggen, H.; Niedballa, U. *J. Org. Chem.* **1974**, 39, 3654, 3660, 3664, 3668, 3672; *J. Org. Chem.*

1976, 41, 2084; Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, 114, 1234; Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, 114, 1256; Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, 114, 1279.

4. Hilbert, G. E.; Johnson, T. B. *J. Am. Chem. Soc.* **1930**, 52, 2001 and 4489.
5. Birkofer, L.; Ritter, A. *Angew. Chem.* **1965**, 77, 414; *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 417.
6. Tipson, R. S. *J. Biol. Chem.* **1939**, 130, 55.
7. Baker, B. R.; Joseph, J. P.; Schaub, R. E.; Williams, J. H. *J. Org Chem.* **1954**, 19, 1786.
8. Seela, F.; Kehne, A. *Liebigs Ann. Chem.* **1983**, 876; Seela, F.; Steker, H. *Tetrahedron Lett.* **1984**, 25, 5017; Seela, F.; Steker, H. *Helv. Chim. Acta* **1985**, 68, 563; Seela, F.; Bindig, U. Liebigs Ann. Chem. **1989**, 895.
9. Kazimierczuk, Z.; Cottam, H.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, 106, 6379.
10. For a review of pteridine nucleoside syntheses: Pfleiderer, W. *Pteridine Nucleosides.* In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B.; Plenum Press: New York, 1994, Vol. 3, pp. 214-252.
11. Ott, M.; Pfleiderer, W. *Chem. Ber.* **1974**, 107, 339.
12. Harris, R; Pfleiderer, W. *Liebigs Ann. Chem.* **1981**, 1457.
13. Jungmann, O.; Pfleiderer, W. *Pteridines.* **1993**, 4, 100.
14. Söll, D.; Pfleiderer, W. *Chem. Ber.* **1963**, 96, 2977.
15. Weinstock, J.; Rosenbloom, J. P.; Hines, P. S. *J. Org. Chem.* **1968**, 33, 3339.
16. Kotick, M. P.; Szantay, C.; Bardos, T. J. *J. Org. Chem.* **1969**, 34, 3806.
17. Wittenburg, E. *Chem. Ber.* **1968**, 101, 1095 and 2132.
18. Zemlicka, J.; Holy, A. *Collect. Czech. Chem. Commun.* **1967**, 32, 3159.
19. *A Typical Procedure for the Glycosylation Reaction.* Starting from **4**, the synthesis of **14** is described. A mixture of **4**[12, 15] (3.15 g, 10 mmol) and of **12** (2.57 ml, 15 mmol) (Fluka®) is stirred at 60 °C for two hours. After cooling to room temperature, the yellow precipitate **11** is filtered off (1.59 g, 4.3 mmol, 43 %). Further 1.55 g (4.18 mmol, 42 %) of **11** are obtained by concentration of the filtrate to an oil and treatment with hot ethanol (50 ml). 1 g of **11** is recrystallized from 800 ml of iso-propanol, m. p. 269-270 °C. UV (CH_3OH), λ_{max} [nm] (lg ε): 385 (4.42), 303 (4.59), 225 (4.47). ^{1}H-NMR (250 MHz, DMSO-d_6): δ 3.21, 3.28 (2s, $2CH_3$); 7.50 (m, 6H of Phe); 8.31 (m, 2H of Phe); 8.47 (m, 2H of Phe); 8.93 (s, =C*H*-N(CH_3)$_2$); 12.89 (s, H-N(8)). To a suspension of **11** (3.7 g, 10 mmol) in dry acetonitrile (80 ml) is added DBU (1.49 ml, 10 mmol) and the solution is stirred at room temperature for 15 min followed by the addition of **5**[16] (4.73 g, 11 mmol). The reaction mixture is stirred at room temperature for 1 h before the formed N-8-β-D-nucleoside **(14)** is filtered off. Crystallization from $CHCl_3$/CH_3OH yields 5.42 g (7.1 mmol, 71 %) of **14**, m. p. 225-227 °C. UV (CH_3OH), λ_{max} [nm] (lg ε): 388 (4.36), 305 (4.88), 237 (4.72). $[\alpha]_D^{22}$ = -33.2° (c = 0.5, $CHCl_3$). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.58 (m, H_α-C(2')); 3.25, 3.32 (2s, $2CH_3$); 3.45 (m, H_β-C(2')); 4.60 (m, H-C(4')); 4.73, 4.75 (2d, H-C(5')); 4.80, 4.82 (2d, H-C(5')); 6.15 (m, H-C(3')); 7.23 (d, 2H of p-Cl-bz); 7.45 (m, 2H of p-Cl-bz, 6H of Phe); 7.93 (m, H-C(1')); 7.97 (m, 4H of p-Cl-bz); 8.29 (m, 2H of Phe); 8.48 (m, 2H of Phe); 8.90 (s, =C*H*-N(CH_3)$_2$).
20. Seela, F.; Lüpke, U.; Hasselmann, D. *Chem. Ber.* **1980**, 113, 2808.
21. Ulbricht, T. L. V.; Rogers, G. T. *J. Chem. Soc.* **1965**, 6125 and 6130.
22. Cao, X.; Pfleiderer, W.; Rosemeyer, H.; Seela, F.; Bannwarth, W.; Schönholzer, P. *Helv. Chim. Acta* **1992**, 75, 1267.

(*Received in Germany* 6 *August* 1996; *accepted* 24 *September* 1996)