CHEMISTRY LETTERS, pp. 1627-1630, 1993.

Catalytic Stereoselective Synthesis of β-Ribonucleosides from Methyl Ribofuranosyl Carbonate and Trimethylsilylated Nucleoside Bases by Combined Use of Silver Salts and Diphenyltin Sulfide

Teruaki MUKAIYAMA, Takafumi MATSUTANI, and Naoyuki SHIMOMURA
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

Catalytic stereoselective synthesis of several ribonucleosides from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate and trimethylsilylated nucleoside bases is efficiently carried out by combined use of silver salts and diphenyltin sulfide ($Ph_2Sn=S$) under mild conditions.

There have been known several methods for the synthesis of ribonucleosides, and the reactions of 1-O-acylribofuranosides or 1-halogenoribofuranosides with nucleoside bases are generally carried out using rather strong Lewis acids such as $SnCl_4$,[1] Me_3SiClO_4, Me_3SiOTf,[2] and SiF_4[3] as promoters. It is expected that the synthetic scope of various nucleosides, especially of acid sensitive derivatives, would be widened if N-glycosylation reaction is effectively catalyzed by weak Lewis acids under mild conditions.

We have recently reported a useful method for stereoselective synthesis of 1,2-trans-ribofuranosides from 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose and alkyl trimethylsilyl ethers by combined use of silver salts and $Ph_2Sn=S$.[4] As of present, the reaction has been assumed to proceed under rather mild conditions by promotion of the active catalyst (**11**) generated from both very weakly acidic substances as silver salts and $Ph_2Sn=S$.

In this communication we would like to describe a convenient method for synthesis of β-ribofuranosides carried out by the above mentioned catalyst system using methyl ribofuranosyl carbonates as starting materials. The ribofuranosyl carbonate would be activated smoothly even by weak Lewis acids because carbonyl oxygen in carbonate has a stronger affinity for Lewis acids compared with that in acetate. Concerning the use of alkyl or aryl carbonates as glycosyl donors, equimolar amounts of catalysts[5] or pyrolytic conditions[6] are required to achieve the glycosylation reactions so as to form corresponding glycosides.

In the first place, the reaction of 2,3,5-tri-O-benzyl-D-ribofuranosyl methyl carbonate (α/β = 1/3) with 2,4-bis(trimethylsilyloxy)pyrimidine (**2**; 2 equiv.) was tried in the presence of 20 mol% of silver salts such as $AgClO_4$, $AgSbF_6$, AgOTf, or AgOTs and 40 mol% of $Ph_2Sn=S$ in acetonitrile at room temperature. The above mentioned silver salts gave good results except in the case of AgOTs ($AgClO_4$: y.86%, α/β = 21/79; $AgSbF_6$: y.78%, α/β = 19/81; AgOTf: y.85%, α/β = 21/79; AgOTs: y.6%, α/β = 52/48). The better yield and β-selectivity were given when acetonitrile was used as a solvent, yet the stereoselectivity did not reach enough to the satisfactory level.

Next, stereoselective synthesis of β-ribonucleosides from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate (**1**)[7] and trimethylsilylated nucleoside bases by utilizing the assistance of neighboring effect was studied. First, the reaction of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate (**1**) with 2,4-bis(trimethylsilyloxy)pyrimidine (**2**; 2 equiv.) was tried by using 20 mol% of AgOTf and 40 mol% of $Ph_2Sn{=}S$ in acetonitrile at 40 °C, 60 °C, and 80 °C, respectively, and the desired product was obtained in high yields with perfect β-selectivity in each case (Table 1).

The effect of solvent was screened in the above reaction (at 60 °C) and acetonitrile gave the best result. Further, it was found that the present reaction was efficiently promoted by using even 10 mol% of AgOTf and 20 mol% of $Ph_2Sn{=}S$ (Table 1).

We further examined two other leaving groups, acetoxy and iodoacetoxy groups, at the C-1 position of 2,3,5-tri-O-benzoyl-β-D-ribofuranose, but those were found less efficient than the methoxycarbonyloxy group in the present procedure (Table 1).

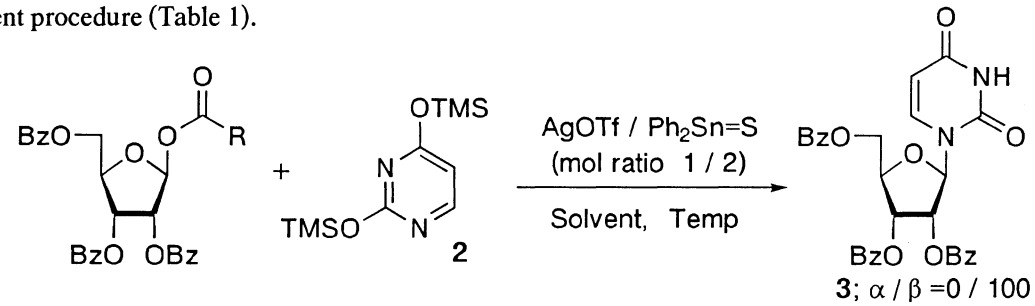


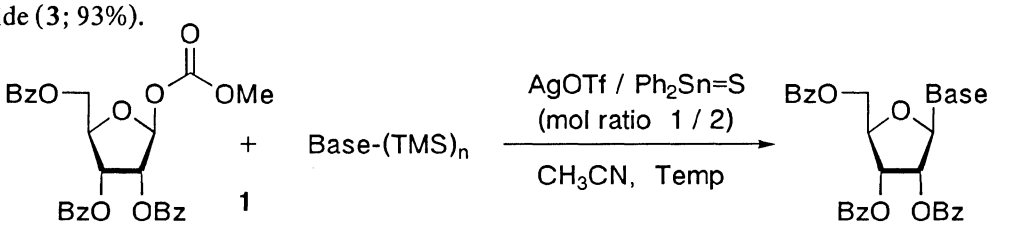
Table 1. Synthesis of 2',3',5'-Tri-O-Benzoyluridine

Entry	R	AgOTf / mol%	2 / equiv.	Temp /°C	Time / h	Solvent	Yield / % [a]
1	OMe	20	2.0	40	20.0	CH_3CN	98
2	OMe	20	2.0	60	3.5	CH_3CN	97
3	OMe	20	2.0	80	2.0	CH_3CN	99
4	OMe	20	1.2	60	7.5	1,2-Dichloroethane	98
5	OMe	20	1.2	60	5.0	Benzene	36
6	OMe	20	1.2	60	5.5	CH_3CN	99
7	OMe	10	1.2	60	6.0	CH_3CN	93
8	CH_3	10	1.2	60	6.0	CH_3CN	56
9	CH_2I	10	1.2	60	6.0	CH_3CN	38

a) Isolated yield.

Additionally, several nucleosides were synthesized by the above procedure in good yields with β-selectivity (Table 2). In the case of synthesis of 2',3',5'-tri-O-benzoyladenosine (**8**), the reaction was carried out in the presence of 20 mol% of $AgClO_4$ and 40 mol% of $Ph_2Sn{=}S$ in propionitrile and the corresponding nucleoside (**8**) was isolated (49%) along with N-debenzoyl compound (**9**; 34%),[8] which was converted to **8** on heating in xylene with benzoic anhydride. Similarly, nucleoside (**5**) was isolated (32%) along with N-debenzoyl compound (**6**; 57%).[8]

The following is a typical procedure for the preparation of 2',3',5'-tri-O-benzoyluridine; to a stirred suspension of AgOTf (0.015 mmol) and $Ph_2Sn{=}S$ (0.03 mmol) in acetonitrile (2 ml) was added a solution of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate (**1**; 0.15 mmol) and 2,4-bis(trimethylsilyloxy)pyrimidine (0.18 mmol, 0.8 M 1,2-dichloroethane solution) in acetonitrile (3 ml) at room temperature. After the reaction mixture was heated at 60 °C for 6 h, it was cooled down to room temperature and saturated aqueous $NaHCO_3$ (5 ml) was added. Usual work up and separation by TLC afforded the β-ribonucleoside (**3**; 93%).

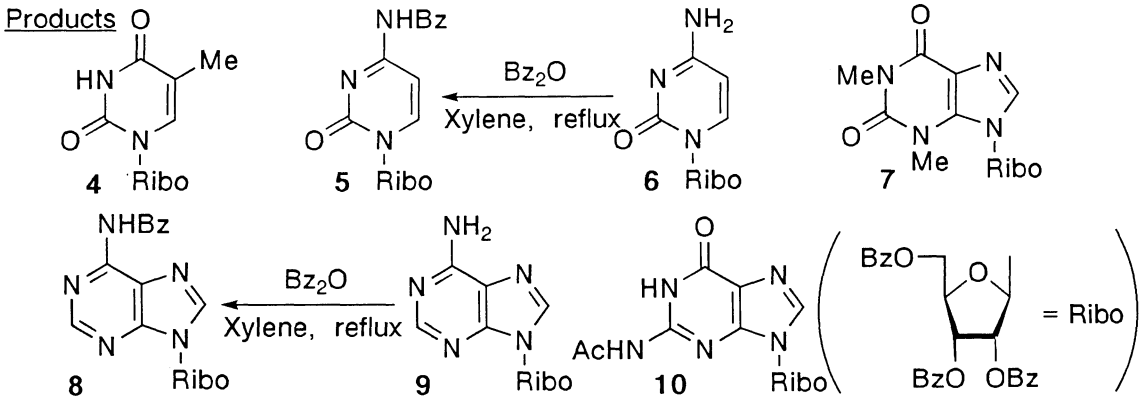


Base-$(TMS)_n$ = trimethylsilylated nucleoside base

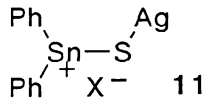
Table 2. Synthesis of 2',3',5'-Tri-O-Benzoylribonucleosides

Entry	Base / equiv.		AgOTf / mol%	Temp /°C	Time / h	Product	Yield / % [a]
1	Thymine	1.2	10	60	5	**4**	96
2 [b]	N^4-Benzoylcytosine	1.5	30	60	4.5	**5**	32
						6	57
3	Theophylline	1.5	10	60	1.5	**7**	96
4 [c]	N^6-Benzoyladenine	1.5	20	reflux	14	**8**	49
						9	34
5 [d]	N^2-Acetylguanine	1.5	30	reflux	16	**10**	77

a) Isolated yield. b) 30 mol% of $AgClO_4$ was used instead of AgOTf. In order to quench the reaction, Na_2HPO_4/KH_2PO_4 buffer was used instead of saturated aqueous $NaHCO_3$. c) 20 mol% of $AgClO_4$ was used instead of AgOTf in C_2H_5CN. d) The reaction was carried out in C_2H_5CN.



Active Species



11

Thus, highly stereoselective preparation of various β-ribonucleosides was successfully carried out starting from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate and trimethylsilylated nucleoside bases under mild conditions by using catalytic amounts of silver salts and $Ph_2Sn=S$. It is also noted that 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate, a starting material, is stable and readily available from D-ribofuranose.

The present research is partially supported by Grant-in-Aids for Scientific Research on Priority Areas (No. 03242104) from Ministry of Education, Science and Culture.

References

1) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654, 3660, 3664, 3668, 3672 (1974); F. W. Lichtenthaler, P. Voss, and A. Heerd, *Tetrahedron Lett.*, **1974**, 2141.

2) H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, **114**, 1234 (1981); H. Vorbrüggen and K. Krolikiewicz, *Angew. Chem., Int. Ed. Engl.*, **14**, 421 (1975).

3) R. Noyori and M. Hayashi, *Chem. Lett.*, **1987**, 57.

4) T. Mukaiyama and N. Shimomura, *Chem. Lett.*, **1993**, 781.

5) K. Suzuki, H. Maeta, T. Matsumoto, and G. Tuchihashi, *Tetrahedron Lett.*, **29**, 3571 (1988); A. Marra, J. Esnault, A. Veyrieres, and P. Sinaÿ, *J. Am. Chem. Soc.*, **114**, 6354 (1992).

6) Y. Ishido, S. Inaba, A. Matsuno, T. Yoshino, and H. Umezawa, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1382.

7) 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl methyl carbonate (**1**) was prepared according to the following procedure: To a stirred solution of 2,3,5-tri-O-benzoyl-D-ribofuranose and chloroformic acid methyl ester (5 equiv.) in dichloromethane was added triethylamine dropwise at 0 °C. After stirring for 4 h at 0 °C, saturated aqueous $NaHCO_3$ was added to the reaction mixture. Usual workup and separation by column chromatography on silica gel afforded the crude carbonate (**1**). Pure β-anomer was afforded by recrystallization from benzene-hexane or Et_2O-hexane (58%). **1**: Mp 97.5-98.5 °C; ^1H NMR (270 MHz, $CDCl_3$) δ=3.77 (3H, s), 4.55 (1H, dd, J=12.2, 4.3 Hz), 4.72 (1H, dd, J=12.2, 4.0 Hz), 4.77-4.87 (1H, m), 5.84 (1H, d, J=5.0 Hz), 5.93 (1H, dd, J=1H, dd J=6.9, 5.0 Hz), 6.33 (1H, s), 7.25-7.65 (15H, m), 7.89 (2H, bd, J=7.9 Hz), 8 01 (2H, bd, J=7.9 Hz), 8.10 (2H, bd, J=7.9 Hz).

8) It is assumed that compound **6** and **9** were produced by an attack of the methoxide, generated by decomposition of the methoxycarbonyloxy group, on compound **5** and **8**, respectively.

(Received June 22, 1993)