Catalytic Stereoselective Synthesis of Pyrimidine 2-Deoxyribonucleosides

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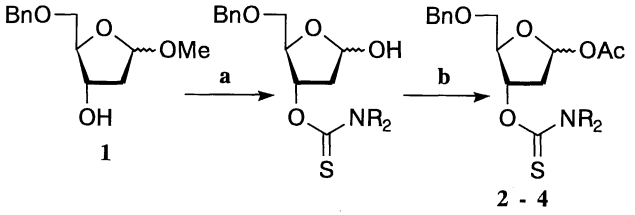
Highly stereoselective synthesis of β-D-deoxyribonucleosides from 1-O-acetyl-5-O-benzyl-2-deoxy-3-diethylthiocarbamoyl ribofuranoside (3) is performed by the reaction with silylated pyrimidine nucleobases in the presence of a catalytic amount of several Lewis acids.

Since certain sugar-modified nucleosides having potential antiviral and antitumor effects were discovered, a number of studies on nucleoside synthesis have been reported[1,2] and many ribonucleosides were synthesized stereoselectively by the participation of the neighboring group such as 2-O-acyl group.[3]

On the other hand, alternative strategies for the stereoselective synthesis of β-2-deoxyribonucleosides were desired because this method was not applicable to 2-deoxyribonucleosides with no 2-hydroxyl group. As a solution to this problem, S_N2-type N-glycosylation of silylated nucleobase with α-1-chloro-2-deoxyribose[4] was tried. But there was a difficulty in employing this method due to unstability of the glycosyl donor. Recently, another method by using a directing group on the 3-hydroxyl group was suggested.[5] This strategy was aimed to block the α-side of the sugars by the 3-O-directing group and β-nucleosides were synthesized stereoselectively. However, some problems still remained in yield or stereoselectivity of the produced nucleosides.

In this paper, we would like to report the results on highly stereocontrolled N-glycosylation reaction involving an intramolecular iminium ion intermediate by using thiocarbamate as a glycosyl donor.

5-O-Benzyl-1-O-methylribofuranoside (1), a glycosyl donor, was prepared according to the literature method.[6] Reaction of the sodium salt of 1 with thiocarbamoyl chlorides in THF provided the corresponding thiocarbamates in good yields. Methyl glycosides were cleaved under acidic conditions to give the corresponding lactols, which in turn were converted to the desired glycosyl donors by treatment with acetic anhydride, triethylamine and 4-dimethylaminopyridine in dichloromethane (Scheme 1). These donors 2 - 4 (α / β = ca. 2 / 3) are stable enough to be stored at room temperature for about one month.

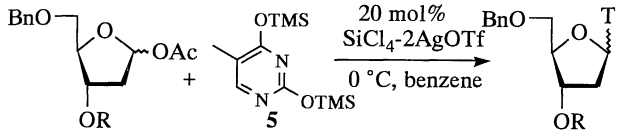


a) NaH, RCSCl, THF, r.t.; 0.3 N HCl-THF, 60 °C (R=Me; 86%, R=Et; 89%, NR_2=$N(C_2H_4)_2O$; 86%);
b) acetic anhydride, triethylamine, cat. DMAP (R=Me; **2** ; 92%, R=Et; **3** ; 96%, NR_2=$N(C_2H_4)_2O$; **4** ;91%).

Scheme 1.

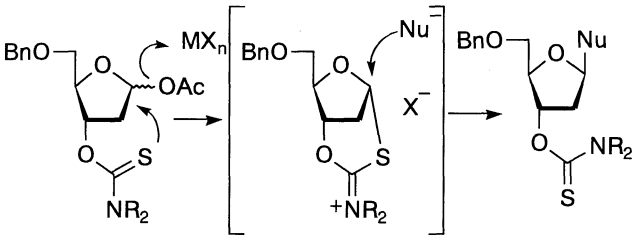
In the first place, the reaction of the above prepared glycosyl donors 2 - 4 with silylated thymine 5 was tried in the presence of a Lewis acid catalyst generated from 20 mol% of $SiCl_4$ and 40 mol% of AgOTf in benzene at 0 °C. Of several glycosyl donors examined (Table 1), 1-O-acetyl-5-O-benzyl-2-deoxy-3-diethylthiocarbamoyl ribofuranoside (3) gave the best result (Entry 4). On the other hand, simple benzoate or diethylcarbamate was less effective for obtaining β-isomer. This result suggested that the aforementioned intramolecular iminium ion intermediate would be formed by coordinating or by binding the sulfur atom of the thiocarbamate to the anomeric carbon.[7] Accordingly, the α-side of the glycosyl donor could be blocked as sketched in Scheme 2.

Table 1. Effect of thiocarbamate groups



Entry	R		time / h	Yield / %	α / β [a]
1	-COPh		24	55	26 / 74
2	$-CONEt_2$		24	81	9 / 91
3	$-CSNMe_2$	(2)	27	89	6 / 94
4	$-CSNEt_2$	(3)	**27**	**90**	**4 / 96**
5	$-CSN(C_2H_4)_2O$	(4)	27	90	6 / 94

[a] determined by NMR analysis.



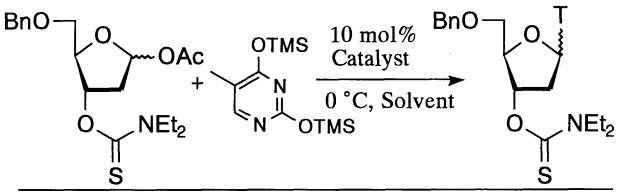
Scheme 2.

Next, several Lewis acid catalysts and solvents were examined (Table 2), and it was found that a combined use of 10 mol% of $SiCl_4$ and 20 mol% of $AgClO_4$ also gave a good result (Entry 5). Further, it became clear that the polar solvents diminished β-selectivity.

Several nucleosides were synthesized in high yields with high β-selectivities according to the above procedure (Table 3) whereas in the case of synthesis of cytidine derivative **8**, the yield was unsatisfactory probably because of poor nucleophilic ability of silylated N^4-benzoylcytosine. Therefore, this reaction was carried out by using a catalyst generated from 20 mol% of $SiCl_4$

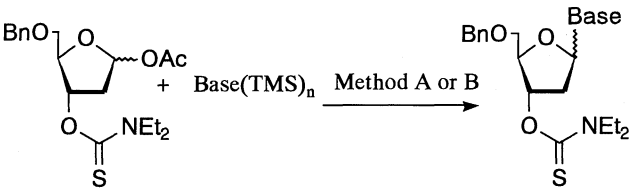
and 40 mol% of AgOTf in dichloromethane at room temperature in the coexistence of 3 mol% of SnI_4, and the desired nucleoside was obtained in good yield.

Table 2. Effect of Conditions



Entry	Catalyst	Solvent	time / h	Yield / %	α / β
1	$SiCl_4$-2AgOTf	Benzene	43	73	4 / 96
2	$SnCl_4$-2$AgClO_4$	Benzene	43	84	3 / 97
3	$TiCl_4$-2$AgClO_4$	Benzene	43	86	3 / 97
4	$SbCl_5$-2$AgClO_4$	Benzene	43	75	3 / 97
5	$SiCl_4$-2$AgClO_4$	Benzene	**29**	**90**	**4 / 96**
6	$SiCl_4$-2$AgClO_4$	CH_2Cl_2	24	84	6 / 94
7	$SiCl_4$-2$AgClO_4$	MeCN	21	85	38 / 62

Table 3. Synthesis of 2'-Deoxyribonucleosides

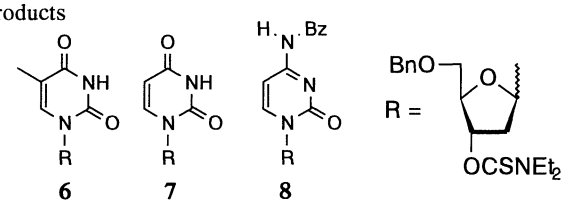


Method A: $SiCl_4$-2AgOTf (20 mol%), Benzene, 0 °C.
Method B: $SiCl_4$-2$AgClO_4$ (10 mol%), Benzene, 0 °C.

Entry	Base (eq.)	Method	time / h	Product	Yield / %	α / β
1	Thymine (1.5)	A	27	6	90	4 / 96
2	Thymine (1.5)	B	29	6	90	4 / 96
3	Uracil (1.5)	A	22	7	94	5 / 95
4	Uracil (1.5)	B	22	7	96	6 / 94
5	N^4-Benzoylcytosine (2.0)	A [a]	18	8	71	11 / 89

[a] Reaction was carried out in the coexistence of 3 mol% of SnI_4 in dichrolomethane at room temperature.

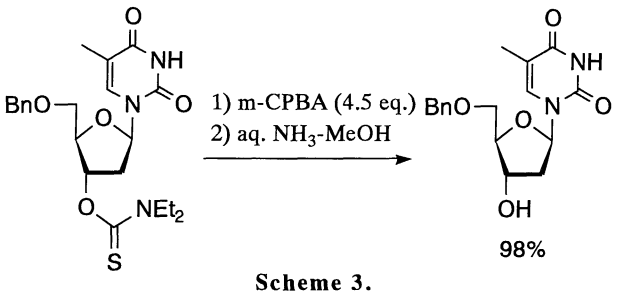
Products



6 **7** **8**

The following is a typical procedure: To a solution of AgOTf (0.060 mmol) in benzene (4 ml) was added $SiCl_4$ (0.030 mmol) in toluene (0.15 ml). This suspension was stirred at room temperature for 1 h, then a solution of trimethylsilylated pyrimidine nucleobase (0.225 mmol) in 1,2-dichloroethane (0.18 ml) and a solution of glycosyl donor (0.150 mmol) in benzene were added. The reaction mixture was stirred at 0 °C, then it was quenched by adding phosphate buffer (pH=7). The resulted mixture was filtered, and the organic layer was extracted with dichloromethane four times. Combined organic layer was washed with brine, then dried over Na_2SO_4. This solution was filtered and evaporated, then separation by preparative TLC afforded the deoxyribonucleosides.

The thiocarbamate was converted to the corresponding formate by the oxidation with 4.5 eq. of m-CPBA in dichloromethane followed by aqueous quenching. Further treatment with aq. NH_3 in methanol afforded the deprotected product in 98% yield (Scheme 3).



Scheme 3.

Thus, a new and efficient method for highly stereoselective preparation of β-deoxyribonucleosides under mild conditions was achieved by using a catalytic amount of several Lewis acids. Development of another valuable nucleoside synthesis based on this new strategy is now in progress.

References and Notes

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2 Recently, an effective synthetic method of β-ribonucleosides was reported, see T. Mukaiyama, T. Matsutani, and N. Shimomura, *Chem. Lett.*, **1993**, 1627; T. Mukaiyama, T. Matsutani, and N. Shimomura, *Chem. Lett.*, **1994**, 2089; N. Shimomura, T. Matsutani, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **67**, 3100 (1994).

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7 A structual assignment of the reaction intermediate, formed by the reaction of 3 with 1.1 eq. of TMSOTf, was made by ^1H and ^{13}C NMR spectrum after the removal of TMSOAc. The intermediate was assigned to be a single α-anomer and ^{13}C NMR indicated that the thiocarbamate carbon (186 ppm) diminished while the assumed iminium ion carbon (172 ppm) appeared.