CHEMISTRY LETTERS, pp. 2089-2092, 1994. © 1994 The Chemical Society of Japan

Tin(II) Chloride Catalyzed Synthesis of β-D-Ribonucleosides

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

Several β-D-ribonucleosides are stereoselectively synthesized in high yields from methyl 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl carbonate and trimethylsilylated nucleoside bases such as pertrimethylsilylated uracil and adenine under mild conditions by using a catalytic amount of tin(II) chloride, a weak Lewis acid.

The study of nucleoside synthesis is a matter of great interest and thus a lot of research works have been made. It is still desired, however, to develop a method which will work out more efficiently under milder conditions. There have been three typical methods for chemical synthesis of nucleosides: (1) condensation of a sugar and a heterocycle which corresponds to a nucleoside base (glycosylation), (2) construction of the heterocycle after introduction of the functional group to C-1 position of a sugar, and (3) derivation from a natural nucleoside to the desired one. Among many methods, glycosylation reaction is the simplest one with wide application. Particularly, the Vorbrüggen modification[1] of the Hilbert-Johnson reaction[2] has widely been employed for preparation of many modified nucleosides by treating silylated nucleoside bases with sugar derivatives having leaving groups at the anomeric center. The above reaction was carried out by using a catalytic amount of TMSOTf (trimethylsilyl trifluoromethanesulfonate) or $TMSClO_4$, and it was assumed that the stable counter anion (e.g., ^-OTf, $^-ClO_4$) was necessary in order to achieve the catalytic glycosylation reaction.

Recently, it was reported that the catalyst systems composed of silver salts having stable anions such as ^-OTf and $^-ClO_4$, rather weak Lewis acids, and neutral compounds such as diphenyltin sulfide ($Ph_2Sn=S$) and Lawesson's reagent were effective for the synthesis of β-D-ribonucleosides from methyl 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl carbonate (**1**) and pertrimethylsilylated nucleoside bases.[3] However, there still remained an important problem to develop such a method as to be carried out more efficiently under milder conditions.

On the other hand, a useful method for the synthesis of β-D-ribofuranosides from 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose and trimethylsilylated nucleophiles was reported from our laboratory by using tin(II) chloride or combined use of tin(II) chloride and tetrachlorosilane ([$SnCl_2/SiCl_4$] catalyst system) where no stable counter anion such as ^-OTf or $^-ClO_4$ was involved.[4] In this method, a catalytic amount of tin(II) chloride, a weak Lewis acid, promoted O-glycosylation reaction. Therefore, it was also thought that the catalytic synthesis of β-D-ribonucleosides might be carried out from **1** and trimethylsilylated nucleoside bases by using tin(II) chloride or [$SnCl_2/SiCl_4$] catalyst system although from 0.6 to 2.6 molar amounts of $SnCl_4$[5] were generally used for β-D-ribonucleosides synthesis. Then, synthesis of β-D-ribonucleosides was tried by using tin(II) chloride or [$SnCl_2/SiCl_4$] catalyst system.

In this paper, we would like to describe an efficient method for the stereoselective syntheses of β-D-ribonucleosides from **1** and trimethylsilylated nucleoside bases by using a catalytic amount of tin(II) chloride, a weak Lewis acid, under mild conditions.

In the first place, the reaction of **1** with 1.2 equiv. of trimethylsilylated uracil (**2**) was tried in the presence of 20 mol% of $SnCl_2$ and 20 mol% of $SiCl_4$ at 60 °C in acetonitrile, propionitrile, or 1,2-dichloroethane as a solvent, and the corresponding β-D-ribonucleoside was obtained respectively in good yield except in the case of 1,2-dichloroethane (MeCN, 2.5 h: 94% yield; EtCN, 5 h: 99% yield; CH_2ClCH_2Cl, 6.5 h: 13% yield). Next, the above reaction was carried out by using tin(II) chloride, a weak Lewis acid, under the same conditions, but yet no good result was given (Table 1, Entries 1 and 2). This indicated that a higher temperature was required for the completion of the reaction when tin(II) chloride was used alone. Then, the suitable reaction temperature and amount of tin(II) chloride were examined in detail, and employment of 40 mol% of tin(II) chloride at 60 °C or 20 mol% of tin(II) chloride at 80 °C gave excellent results (Table 1, Entries 3 and 4). No regioisomer, 3-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)uracil, was observed by TLC analysis.

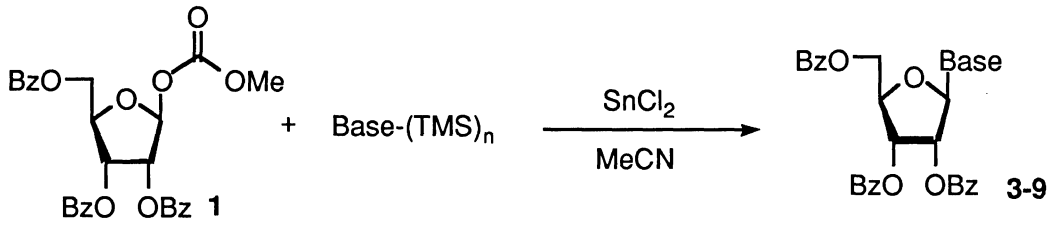
When the reaction of **1** with trimethylsilylated thymine (1.2 equiv.) was carried out by using 20 mol% of tin(II) chloride in acetonitrile at 80 °C, the corresponding β-D-ribonucleoside was obtained in quantitative yield. In the reaction of **1** with trimethylsilylated theophylline (1.2 equiv.),[6] the desired product was obtained in excellent yield when heated at 60 °C because trimethylsilylated theophylline is generally a more reactive nucleophile than trimethylsilylated uracil or thymine.

When trimethylsilylated N^4-benzoylcytosine was used as a nucleophile in the reaction of **1** by using 40 or 50 mol% of tin(II) chloride in acetonitrile at 60 °C, the desired β-D-ribonucleoside was obtained in moderate yields (40 mol%, 3.5 h: 72% yield; 50 mol%, 10 h; 65% yield), respectively. While, when the above reaction was carried out by using 50 mol% of tin(II) chloride at 80 °C, the corresponding β-D-ribonucleoside was obtained in satisfactory yield (84% yield) without accompanying N^4-debenzoyl compound.[7] The result suggested that the reaction proceeded under milder conditions compared with those using [$AgClO_4$/Ph_2Sn=S] catalyst system.[3]

In the case of synthesis of adenosine derivative (**7**), the reaction was carried out in the presence of 50 mol% of tin(II) chloride in acetonitrile at 60 °C and the desired nucleoside **7** (19% yield) was isolated along with N^6-debenzoyl compound **8** (39% yield). It was assumed that compound **8** was produced by an attack of methoxide anion, generated by decomposition of the methoxycarbonyloxy group, on compound **7**. In order to achieve a better yield, the reaction was carried out in acetonitrile under reflux, and the yields of **7** and **8** were 37% and 33%, respectively. Finally, it was found that the yields were increased up to satisfactory level by carrying out the reaction in propionitrile under reflux. Moreover, no regioisomer was detected.

The N^2-acetylguanosine derivative (**9**) was also synthesized in better yield compared with that in the previous work[3] from **1** and pertrimethylsilylated N^2-acetylguanine by using 30 mol% of tin(II) chloride in acetonitrile[8] at 80 °C, probably due to the present mild reaction conditions.

A typical experimental procedure is as follows; to a suspension of $SnCl_2$ (0.03 mmol) in acetonitrile (2 ml) was added a solution of **1** (0.15 mmol) and **2** (0.18 mmol) in acetonitrile (2 ml) at room temperature. After heating the reaction mixture at 80 °C for 6 h, saturated aqueous $NaHCO_3$ was added at room temperature to quench it. The mixture was filtered through a celite pad, then extracted with AcOEt, and the extracts were washed with sat. aqueous NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by TLC (silica gel) to give 2',3',5'-tri-O-benzoyl-β-D-uridine (**3**: 99% yield).

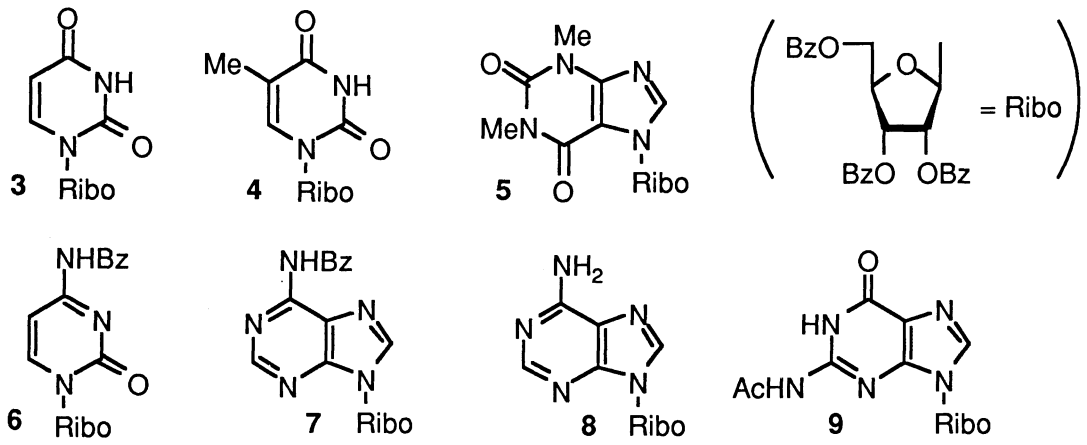


Base-$(TMS)_n$ = trimethylsilylatd nucleoside base

Table 1. Synthesis of 2',3',5'-Tri-O-benzoyl-β-D-ribonucleosides

Entry	Base / equiv.		$SnCl_2$ / mol%	Temp / °C	Time / h	Product	Yield / % [a]
1	Uracil	1.2	20	60	8.0	**3**	69
2 [b]	Uracil	1.2	20	60	10.5	**3**	66
3	Uracil	1.2	40	60	9.5	**3**	99
4	Uracil	1.2	20	80	6.0	**3**	99
5	Thymine	1.2	20	80	6.5	**4**	quant.
6	Theophylline	1.2	20	60	2.75	**5**	99
7	N^4-Benzoylcytosine	1.5	50	80	4.3	**6**	84
8 [b]	N^6-Benzoyladenine	1.5	50	reflux	7.0	**7**	42
						8	44
9	N^2-Acetylguanine	1.5	30	80	6.0	**9**	82

a) Isolated yield. b) The reaction was carried out in propionitrile.



Thus, syntheses of typical β-D-ribonucleosides were now successfully performed by the reactions of new glycosyl donor **1** and trimethylsilylated nucleoside bases in the presence of catalytic amounts of tin(II) chloride (20–50 mol%) under mild conditions because tin(II) chloride is a much weaker Lewis acid compared with Lewis acids having counter anions such as $^{-}ClO_4$ and ^{-}OTf.

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) H. Vorbrüggen and K. Krolikiewicz, *Angew. Chem., Int. Ed. Engl.*, **14**, 421 (1975); H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, **114**, 1234 (1981); H. Vorbrüggen and G. Höfle, *ibid.*, **114**, 1256 (1981); H. Vorbrüggen and B. Bennua, *ibid.*, **114**, 1279 (1981).

2) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4489 (1930).

3) T. Mukaiyama, T. Matsutani, and N. Shimomura, *Chem. Lett.*, **1993**, 1627; N. Shimomura, T. Matsutani, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, submitted.

4) N. Shimomura, M. Saitoh, and T. Mukaiyama, *Chem. Lett.*, **1994**, 433.

5) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654, 3660, 3664, 3668, and 3672 (1974); F. W. Lichtenthaler, P. Voss, and A. Heerd, *Tetrahedron Lett.*, **24**, 2141 (1974); M. Saneyoshi and E. Satoh, *Chem. Pharm. Bull.*, **27**, 2518 (1979).

6) Use of 1.5 equiv. of trimethylsilylated theophylline was required in the reaction of **1** with the [AgOTf/Ph_2Sn=S] catalyst system.

7) Compound **6** (32% yield) was isolated along with N^4-debenzoyl compound (57% yield) in the reaction using the [$AgClO_4$/Ph_2Sn=S] catalyst system.

8) The same reaction was carried out in refluxing propionitrile when combined use of AgOTf and Ph_2Sn=S was used.

(Received July 28, 1994)