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Tin(II) Chloride Catalyzed Synthesis of Ribofuranosides

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Catalytic synthesis of several D-ribofuranosides from 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose and trimethylsilylated nucleophiles such as 3β-cholestanyl trimethylsilyl ether and phenyl trimethylsilyl sulfide is efficiently promoted by tin(II) chloride under mild conditions. When allyltrimethylsilane, azidotrimethylsilane, etc., are used as nucleophiles, combined use of catalytic amounts of $SnCl_2$ and $SiCl_4$ also afforded the corresponding ribofuranosides in good yields.

The synthesis of D-ribofuranosides from 1-O-acylribofuranoses or ribofuranosyl fluorides is generally accomplished by using rather strong Lewis acids. For example, an equimoler amount of $SnCl_4$ was required for the synthesis of ribofuranosides, and ribosylations must be carried out at a lower temperature because of instabilities of products and starting materials under the conditions. On the other hand, it was recently reported that the catalyst systems composed of silver salts having stable counter anions ($^-ClO_4$, $^-SbF_6$, and ^-OTf), rather weak Lewis acids, and neutral compounds such as $Ph_2Sn{=}S$ and Lawesson's reagent are effective for the synthesis of β-D-ribofuranosides from 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose (**1**) or 2,3,5-tri-O-benzyl-D-ribofuranose and alkyl trimethylsilyl ethers or alcohols.[1)]

In this communication we would like to describe an efficient method for the synthesis of ribofuranosides from **1** and various trimethylsilylated nucleophiles by using a catalytic amount of $SnCl_2$, a weakly acidic salt, at room temperature under milder conditions.

In the first place, the reaction of **1** with 1.2 equiv. of cyclohexyl trimethylsilyl ether was tried in the presence of 20 mol% of $SnCl_2$ in dichloromethane at room temperature and the corresponding ribofuranoside was obtained in 86% yield. It was found that ribosylation of cyclohexyl trimethylsilyl ether could be effectively carried out by using even a catalytic amount of a weak Lewis acid as $SnCl_2$. Several acyl groups, leaving groups, at C-1 position of ribofuranose were screened in the above reaction using 20 mol% of $SnCl_2$ (see Table 1) and it was shown that ribofuranoses having iodoacetyl and 2'-methoxyethoxyacetyl groups at C-1 position gave good chemical yields. When the same reactions were carried out in the presence of 10 mol% of $SnCl_2$, on the other hand, the yields decreased, especially in the case of 2'-methoxyethoxyacetyl group (Table 1, Entries 5 and 12). It suggested that the activity of $SnCl_2$ as a catalyst might decrease because of the interaction between $SnCl_2$ and trimethylsilyl 2'-methoxyethoxyacetate formed during the reaction. Accordingly, 1-O-iodoacetylribofuranose was selected as a glycosyl donor in the following experiments.

Next, the same reaction was tried with 1-O-iodoacetylribofuranose and 1.5 equiv. of cyclohexyl trimethylsilyl ether in order to improve chemical yield, and the corresponding ribofuranoside was obtained in

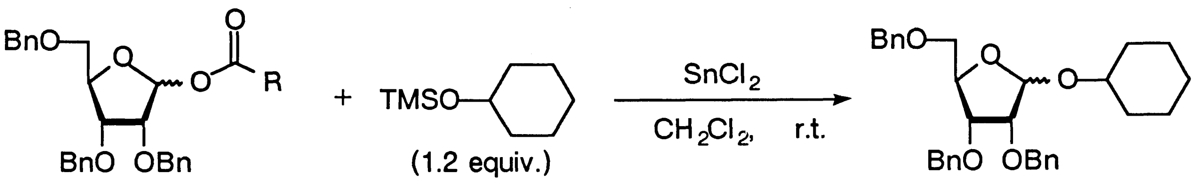


Table 1. Effect of Acyl Groups

Entry	R	$SnCl_2$ / mol%	Time / h	Yield / % [a]	α / β [b]
1	CH_3	20	4	69	9 / 91
2	CH_2I	20	4	**86**	**7 / 93**
3 [c]	CH_2I	20	4	**87**	**8 / 92**
4 [d]	CH_2I	20	4	**90**	**7 / 93**
5	CH_2I	10	5	80	8 / 92
6 [d]	CH_2I	10	4	**93**	**7 / 93**
7 [c, d]	CH_2I	10	4	50	20 / 80
8	CH_2Br	20	4	trace	
9	CH_2Cl	20	4	trace	
10	CH_2OCH_3	20	4	79	26 / 74
11	$CH_2OCH_2CH_2OCH_3$	20	4	**90**	**9 / 91**
12	$CH_2OCH_2CH_2OCH_3$	10	4	51	72 / 28
13	CH_2Ac	20	4	trace	

a) Isolated yield. b) Determined by HPLC analysis. c) Propionitrile was used as a solvent instead of dichloromethane. d) One and a half equiv. of cyclohexyl trimethylsilyl ether was used.

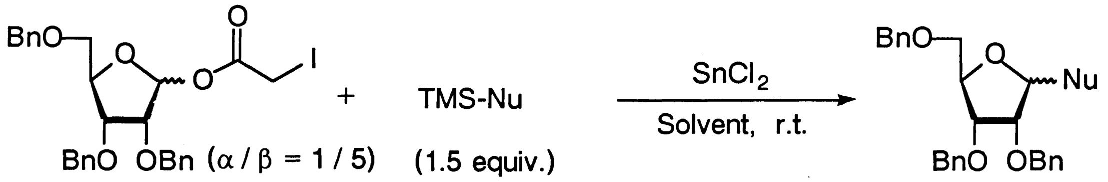
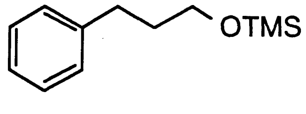
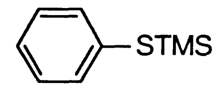


Table 2. Synthesis of D-Ribofuranosides by Using Tin(II) Chloride

Entry	TMS-Nu	$SnCl_2$ / mol%	Solvent	Time / h	Yield / % [a]	α / β [b]
1		10	CH_2Cl_2	4	95	8 / 92
2		10	EtCN	2	71	28 / 72
3	1-Octadecyl-OTMS	10	CH_2Cl_2	4	93	8 / 92
4		10	EtCN	2	83	19 / 81
5	3β-Cholestanyl-OTMS	30	CH_2Cl_2	3	91	8 / 92
6		30	EtCN	2	85	7 / 93
7		20	CH_2Cl_2	8	91	27 / 73 [c]
8		20	EtCN	4	46	63 / 37 [c]

a) Isolated yield. b) Determined by HPLC analysis. c) Determined by ^1H-NMR analysis.

better yield (Table 1, Entries 4 and 6). Good results were also given in the reactions with some alkyl trimethylsilyl ethers (see Table 2). Further, when phenyl trimethylsilyl sulfide was used as a nucleophile, the corresponding ribofuranoside2) was also obtained in good yield (Table 2, Entry 7).

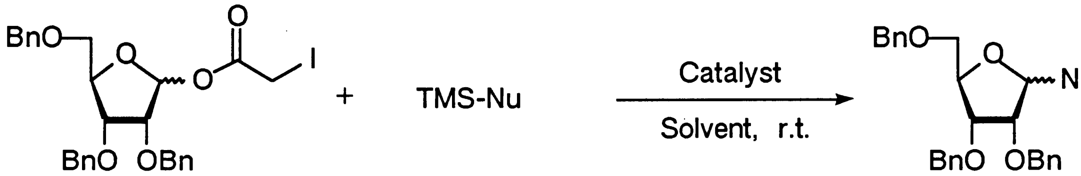
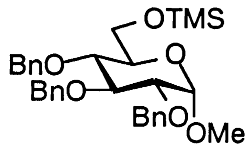
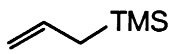
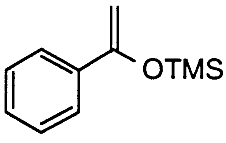


Table 3. Synthesis of D-Ribofuranosides by Combined Use of $SnCl_2$ and $SiCl_4$

Entry	TMS-Nu / equiv.		$SnCl_2$ / $SiCl_4$ / mol%	Solvent	Time / h	Yield / % a)	α/β b)
1		1.5	30 / 0	CH_2Cl_2	5	77	37 / 63
2		1.5	10 / 0	CH_2Cl_2	24	47	44 / 56
3		1.5	10 / 2	CH_2Cl_2	5	88	10 / 90
4c)		1.5	10 / 2	CH_2Cl_2	5	73	33 / 67
5d)		1.5	10 / 2	CH_2Cl_2	5	63	42 / 58
6		1.5	0 / 2	CH_2Cl_2	5	0	
7		1.5	30 / 0	EtCN	2	92	18 / 82
8		1.5	10 / 0	EtCN	4	80	24 / 76
9		1.5	10 / 2	EtCN	0.5	96	18 / 82
10		3.0	20 / 0	CH_2Cl_2	24	36	93 / 7 e)
11		3.0	20 / 4	CH_2Cl_2	7	69	95 / 5 e)
12		3.0	20 / 20	CH_2Cl_2	4	87	95 / 5 e)
13		3.0	20 / 20	EtCN	1	88	96 / 4 e)
14		3.0	20 / 0	CH_2Cl_2	20	trace	
15		3.0	20 / 4	CH_2Cl_2	20	trace	
16		3.0	20 / 20	CH_2Cl_2	5.5	80	60 / 40
17		3.0	20 / 20	EtCN	1.5	91	72 / 28
18	$TMSN_3$	2.0	20 / 0	CH_2Cl_2	18	42	46 / 54 f)
19		2.0	20 / 4	CH_2Cl_2	5	77	61 / 39 f)
20		2.0	20 / 20	CH_2Cl_2	2	94	62 / 38 f)
21		3.0	0 / 20	CH_2Cl_2	2	trace	
22		2.0	20 / 20	EtCN	1	91	29 / 71 f)
23		2.0	20 / 20	EtCN	0.25	92	37 / 63 f)

a) Isolated yield. b) Determined by HPLC analysis. c) Trichloromethylsilane was used instead of tetrachlorosilane. d) Chlorotrimethylsilane was used instead of tetrachlorosilane. e) It was determined by mass spectrum that the minor product separated by HPLC was α-anomer. f) Ratios were determined by isolated yields.

When methyl 2,3,4-tri-O-benzyl-6-O-trimethylsilyl-α-D-glucoside was used as a nucleophile, however, the corresponding ribofuranoside was obtained in moderate yield (Table 3, Entry 1). Then, 2 mol% of $SiCl_4$3) was used together with 10 mol% of $SnCl_2$ in the above experiment, and the corresponding ribofuranoside was obtained in better yield (Table 3, Entry 3). It was shown that $SiCl_4$ is more effective compared with other silyl chlorides such as TMSCl or $MeSiCl_3$ as a co-catalyst in the above experiment (Table 3, Entries 4 and 5). In this case, a coordinated complex between $SiCl_4$ and $SnCl_2$ would generate more active catalytic silicon center.

Concerning other nucleophiles such as allyltrimethylsilane, enol trimethylsilyl ether derived from acetophenone, and azidotrimethylsilane, the corresponding ribofuranosides$^{4)}$ were obtained in satisfactory yields (Table 3). In the case of allyltrimethylsilane, α-anomer was predominantly yielded by kinetic control because α-anomer does not isomerize to β-anomer under the conditions. On the other hand, TLC observation indicated that isomerization from α-anomer to β-anomer took place during O-, S-, and N-glycosylations (for example, Table 3, Entries 22 and 23). By TLC analysis, it was observed that cyclohexyl and 3-phenylpropyl α-ribofuranosides formed in the early stage of the O-glycosylation rapidly isomerized to β-anomers while the isomerization of disaccharide took place slowly.

When propionitrile was used as a solvent instead of dichloromethane, the reactions proceeded smoothly to give better chemical yields in a shorter time as shown in Table 3. But in cases of the nucleophiles shown in Table 1 and 2, chemical yields decreased in propionitrile.

A typical experimental procedure is as follows: to a stirred suspension of $SnCl_2$ (0.015 mmol) in CH_2Cl_2 (2.5 ml) was added a solution of 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose (**1**; 0.15 mmol) and cyclohexyl trimethylsilyl ether (0.225 mmol) in CH_2Cl_2 (3.5 ml) at room temperature. After stirring for 4h, saturated aqueous $NaHCO_3$ (5 ml) was added to quench the reaction. Usual work up and separation by TLC afforded the corresponding β-anomer (86%) and α-anomer (7%).

Thus, catalytic synthesis of various D-ribofuranosides including C-, S-, and N-ribofuranosides was successfully carried out from 1-O-iodoacetylribofuranose and trimethylsilylated nucleophiles by using a catalytic amount of $SnCl_2$, a rather weak Lewis acid, under milder conditions. Moreover, it was found that combined use of $SnCl_2$ (10-20 mol%) and $SiCl_4$ (2-20 mol%) was effective in cases of the reactions of 1-O-iodoacetyl-ribofuranose with methyl 6-O-trimethylsilylglucoside, allyltrimethylsilane, enol trimethylsilyl ether derived from acetophenone, and azidotrimethysilane to afford the corresponding ribofuranosides in satisfactory yields.

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References

1) T. Mukaiyama and N. Shimomura, *Chem. Lett.*, **1993**, 781; N. Shimomura and T. Mukaiyama, *ibid.*, **1993**, 1941.

2) Two isomers, α- and β-anomer, were identified by comparing these ^{1}H-NMR data with those of the following literature; T. Kametani, K. Kawamura, and T. Honda, *J. Am. Chem. Soc.*, **109**, 3010 (1987).

3) Aldol reaction was already carried out by combined use of $SnCl_2$ and TMSCl in the following literature; N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, **1989**, 145.

4) Two isomers, α- and β-anomer, in cases of allyltrimethylsilane and trimethylsilyl ether derived from acetophenone were identified by comparing these ^{13}C-NMR data with those of the following literatures; T. Mukaiyama and S. Kobayashi, *Carbohydr. Res.*, **171**, 81 (1987); T. Mukaiyama, S. Kobayashi, and S. Shoda, *Chem. Lett.*, **1987**, 1529; T. Mukaiyama, T. Shimpuku, T. Takashima, and S. Kobayashi, *ibid.*, **1989**, 145.

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