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# Catalytic Stereoselective Synthesis of α- or β-Ribofuranosides by Combined Use of Silver Salts and Lithium Perchlorate or Diphenyltin Sulfide

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Catalytic stereoselective synthesis of 1,2-cis- or 1,2-trans-ribofuranosides from 1-O-iodoacetylribofuranose and alkyl trimethylsilyl ethers is efficiently promoted by combined use of silver salts and lithium perchlorate or diphenyltin sulfide ($Ph_2Sn=S$) under mild conditions.

It was recently developed in our laboratory that the Friedel-Crafts alkylation, esterification[1] and glycosylation reactions[2] are smoothly carried out by the promotion of active acidic species generated from Lewis acids and silver salts. It was also reported that effective activations of secondary and tertiary alcohols take place in the Friedel-Crafts alkylation and in the dehydration reaction by using $AgClO_4$ alone.[3]

Glycosylation reactions starting from 1-O-acylribofuranose are generally promoted by strong Lewis acids [4] and it is expected that an applicability in the synthesis of various glycosides, especially acid sensitive derivatives, would be widened if glycosylation reaction is promoted by weak Lewis acids. Silver perchlorate is considered as one of weak Lewis acids and is already employed as a promoter of glycosylation reaction by Ley [5] and Inazu [6] using more than one equivalent of $AgClO_4$.

We have recently reported an efficient method for stereoselective synthesis of 1,2-cis- and 1,2-trans-ribofuranosides from 2,3,5-tri-O-benzyl-1-O-trimethylsilyl-D-ribofuranose and alkyl trimethylsilyl ethers by use of 150 mol% of $Ph_2Sn=S$ and 3 mol% of $Me_3SiOTf$.[7] On the other hand, 1,2-cis-ribofuranosides were obtained in high yields with high stereoselectivities by addition of $LiClO_4$. A starting material, 1-O-trimethylsilylribofuranose, in the above glycosylation reactions, however, is often unstable to store; therefore, further improvement in these methods are required.

In this communication we would like to report on catalytic and highly stereoselective glycosylation reaction of 1-O-acylribofuranose and alkyl trimethylsilyl ethers promoted by combined use of silver salts, rather weak Lewis acids, and $LiClO_4$ or $Ph_2Sn=S$.

In the first place, the reaction of 2,3,5-tri-O-benzyl-1-O-bromoacetyl-D-ribofuranose with 3-phenylpropyl trimethylsilyl ether was tried by using 20 mol% of silver salt such as $AgClO_4$, $AgSbF_6$, or AgOTf, and the corresponding ribofuranosides were obtained in moderate yields (72%, 59%, or 41%, respectively) with low selectivities (α/β=67/37, 49/51, or 72/28, respectively). Then, several acyl groups (iodoacetyl, chloroacetyl, methoxyacetyl, acetoacetyl, and acetyl), leaving groups, at C-1 position of ribofuranose were screened in the above experiments using 20 mol% of $AgClO_4$, in which iodoacetyl group gave the best result (yield: 73%, 12%, 17%, 40%, and 64% respectively, α/β: 37/63, 64/36, 56/44, 76/24, and 25/75 respectively). Thus, the results indicated that 1-O-acylribofuranose was effectively activated by silver salt alone, though stereoselectivity was

poor. Then in order to improve stereoselectivity, some additives as $LiClO_4$ and $Ph_2Sn{=}S$, shown in the our previous paper,[7] were employed in the above reaction.

When the reaction was carried out in coexistence of $LiClO_4$ (300 mol%)[8] with various trimethylsilyl ethers as nucleophiles, the corresponding 1,2-cis-ribofuranosides were obtained in high yields with high stereoselectivities by using 10 mol% of $AgClO_4$ as summarized in Table 1. Further, the reaction also proceeded very smoothly when $AgSbF_6$ or AgOTf was used instead of $AgClO_4$ (see Table 3); namely, 1,2-cis-ribofuranosides were synthesized stereoselectively just by using silver salt and $LiClO_4$ making simpler procedure compared with our previous results using 1-O-trimethylsilylribofuranose.[7] In the present reaction, intermediate carbocation (2) at C-1 position of ribofuranose would be efficiently stabilized by the perchlorate anion located at β-side of the anomeric center. Then, the anomeric carbon is exclusively attacked from α-side by trimethylsilylated nucleophiles to afford the corresponding 1,2-cis-ribofuranosides.

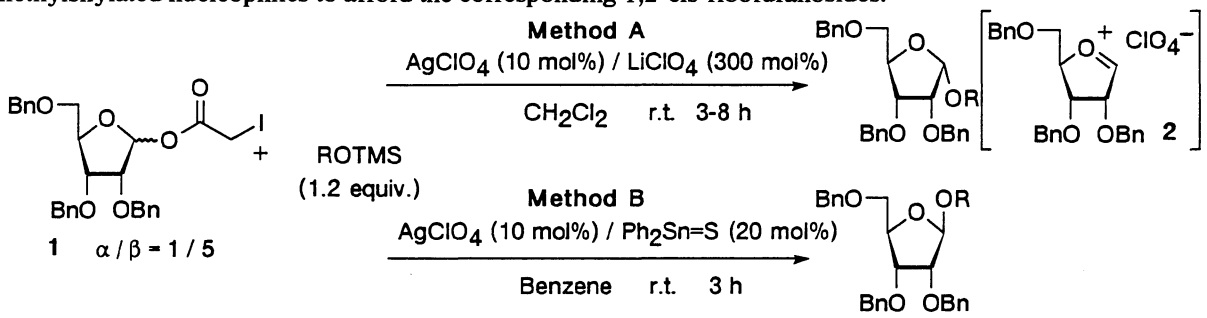
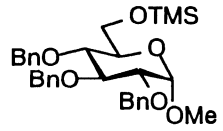
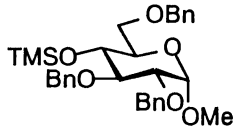
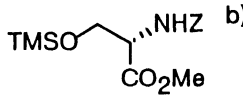
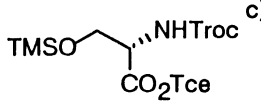



Table 1. Synthesis of 1,2-cis and 1,2-trans-Ribofuranosides

| Entry | ROTMS | Method A | | Method B | |
|---|---|---|---|---|---|
| | | Yield / % | α / β [a] | Yield / % | α / β [a] |
| 1 | Ph-$(CH_2)_3$-OTMS | 96 | 96 / 4 | 91 | 5 / 95 |
| 2 | Cyclohexyl-OTMS | 98 | 97 / 3 | 93 | 4 / 96 |
| 3 | 3β-Cholestanyl-OTMS | 92 | 97 / 3 | 83 | 5 / 95 |
| 4 |  | 99 | 88 / 12 | 88 | 11 / 89 |
| 5 |  | 99 | 88 / 12 | 59 | 31 / 69 |
| 6 |  [b] | 96 | 83 / 17 | 96 | 9 / 91 |
| 7 |  [c] | 81 | 85 / 15 | 82 | 8 / 92 |

a) Determined by HPLC analysis. b) Z = benzyloxycarbonyl. c) Troc = 2,2,2-trichloroethoxycarbonyl, Tce =2,2,2-trichloroethyl.

On the other hand, the corresponding 1,2-trans-ribofuranosides were stereoselectively obtained in high yields, when the reaction was carried out in the presence of $Ph_2Sn=S$ (150 mol%) in dichloromethane. After screening several solvents, it was made clear that benzene was the solvent of choice in chemical yield and in stereoselectivity (see Table 2). Finally, it was found that the reaction proceeded smoothly even when 20 mol% of $Ph_2Sn=S$ and 10 mol% of AgOTf were used (see Table 3); namely,the glycosylation reaction proceeded smoothly by combined use of catalytic amounts of silver salts, rather weak Lewis acids, and $Ph_2Sn=S$ without using typical Lewis acids such as $Me_3SiOTf$ shown in our previous work.[7] At present, the reaction is assumed to proceed by the promotion of the new active acidic species (**3**) generated from silver salt and $Ph_2Sn=S$ as shown in the following scheme.

$$AgX + Ph_2Sn=S \longrightarrow \underset{\mathbf{3}}{Ph_2\overset{+}{S}n\text{-}SAg\ X^-}$$

Table 2. Effect of Solvents in Synthesis of 1,2-trans-Ribofuranosides [a]

| Entry | Solvent | Yield / % | α / β [b] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 85 | 8 / 92 |
| 2 | Benzene | 96 | 6 / 94 |
| 3 | 1,2-Dichloroethane | 90 | 6 / 94 |
| 4 | $Et_2O$ | 83 | 32 / 68 |
| 5 | $CH_3CN$ | 32 | 39 / 61 |

a) The reactions were carried out at room temperature by using 20 mol% of $AgClO_4$, 150 mol% of $Ph_2Sn=S$ and 3-phenylpropyl trimethylsilyl ether (1.2 equiv.) as a nucleophile. b) Determined by HPLC analysis.

Table 3. Effect of Silver Salts in Synthesis of Cyclohexyl Ribofuranoside

| Entry | Silver salt (10 mol%) | Method A | | Method B | |
|---|---|---|---|---|---|
| | | Yield / % | α / β [a] | Yield / % | α / β [a] |
| 1 | $AgClO_4$ | 97 | 98 / 2 | 92 | 5 / 95 |
| 2 | $AgSbF_6$ | 95 | 97 / 3 | 88 | 4 / 96 |
| 3 | AgOTf | 98 | 97 / 3 | 92 | 4 / 96 |
| 4 | $AgPF_6$ | N.T.[b] | | N. R. | |
| 5 | $AgBF_4$ | N.T. | | N. R. | |

a) Determined by HPLC analysis. b) N.T. = not tested.

The followings are typical procedures for the preparation of both anomers of cyclohexyl 2,3,5-tri-O-benzyl-D-ribofuranosides. Method A: To a stirred suspension of $AgClO_4$ (0.015 mmol) and $LiClO_4$ (0.45 mmol) in dichloromethane (2.5 ml) was added a solution of 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose [9] (**1**; 0.15 mmol) and cyclohexyl trimethylsilyl ether (0.18 mmol) in dichloromethane (3.5 ml) at room temperature. After stirring for 8 h, saturated aqueous $NaHCO_3$ (5 ml) was added to quench the reaction. Usual work up and separation by TLC afforded the corresponding 1,2-cis-anomer (95%) and 1,2-trans-anomer (3%). Method B: To a stirred solution of $AgClO_4$ (0.015 mmol) and $Ph_2Sn=S$ (0.03 mmol) in benzene (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 (0.18 mmol) in benzene (3.5 ml) at room temperature. After stirring for 3 h, saturated aqueous $NaHCO_3$ (5 ml) was added to the reaction mixture. Usual work up and separation by TLC afforded the corresponding 1,2-trans-anomer (89%) and 1,2-cis-anomer (4%).

Thus, highly stereoselective preparation of 1,2-cis or 1,2-trans-ribofuranoside was successfully carried out starting from 1-O-iodoacetylribofuranose and alkyl trimethylsilyl ether by use of a catalytic amount of silver salt in the coexistence of $LiClO_4$ or by combined use of catalytic amounts of $Ph_2Sn{=}S$ and silver salt. Additionally, it is noted that 2,3,5-tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose (1) is easily prepared as stable colorless needles.

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9) 2,3,5-Tri-O-benzyl-1-O-iodoacetyl-D-ribofuranose (1) was prepared according to the following procedure. To a stirred suspension of KF (18 equiv.) in acetonitrile was added a solution of 2,3,5-tri-O-benzyl-D-ribofuranose and iodoacetyl chloride (1.65 equiv.) in dichloromethane. After stirring for 12 h at room temperature, filtration and separation by column chromatography on silica gel afforded 1 in 79% yield. 1β: Mp 79-81°C (recrystallized from benzene-hexane); $^1H$ NMR (270 MHz, $CDCl_3$) δ=3.45 (1H, d, J=10.4 Hz), 3.50 (1H, d, 10.4 Hz), 3.59 (1H, dd, J=11.0, 4.5 Hz), 3.72 (1H, dd, J=11.0, 3.1 Hz), 3.92 (1H, d, J=4.6 Hz), 4.13 (1H, dd, J=7.8, 4.6 Hz), 4.35-4.45 (1H, m), 4.42 (1H, d, J=11.9 Hz), 4.50 (1H, d, J=12.4 Hz), 4.55 (1H, d, J=12.4 Hz), 4.57 (1H, d, J=11.9 Hz), 4.62 (1H, d, J=12.2 Hz), 4.76 (1H, d, J=12.2 Hz), 6.18 (1H, s), 7.2-7.5 (15H, m). C-1 proton of 1α: $^1H$ NMR (270 MHz, $CDCl_3$) δ=6.30 (1H, d, J=4.3 Hz).

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