A Significant Effect of a Lithium Salt in the Stereocontrolled Synthesis of α-D-Ribofuranosides

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Lithium bis[(trifluoromethyl)sulfonyl]imide was found to be a new and effective additive in the stereocontrolled synthesis of α-D-ribofuranosides from 2,3,5-tri-*O*-benzyl-D-ribofuranose and several alcohols while β-anomers were formed in the absence of the lithium salt. A hypothetical mechanism of this reverse stereocontrol to yield α-D-ribofuranosides by the influence of the lithium salt is discussed.

In the previous paper, trityl salt catalyzed glycosylation reaction of several alcohols with 2,3,5-tri-*O*-benzyl-D-ribo furanose was described;[1] that is, several β-ribofuranosides were prepared in high yields with high stereoselectivities while completely reversed stereoselecition was observed in the coexistence of lithium perchlorate in the above reaction. A similar effect of lithium perchlorate induced reverse stereoselection in the synthesis of α-D-ribofuranosides has also been reported from our laboratory[2] and these results were explained by assuming the following characteristic properties of the perchlorate anion. Namely, the perchlorate anion is bulky and highly stabilized by delocalization of electron, which leads the anion to locate in anti position to the 2-hydroxyl group of the intermediate cationic species generated from sugar derivertives. Therefore, the nucleophiles would selectively approach from its α-side.[3] It has been strongly needed to develop a new and effective additive for this purpose since lithium perchlorate is not a completely safe compound. Then, several new additives were examined in order to replace lithium perchlorate. As a result, this reverse effect was realized by the use of lithium bis[(trifluoromethyl)sulfonyl] imide[4,5] and we would like to report on the influence of this new additive in highly stereoselective synthesis of α-D-ribofuranosides.

First, several reactions were carried out in the coexistence of 10 mol% of the trityl catalyst and 150 mol% of various lithium salts in order to find new effective additives other than lithium perchlorate by taking the reaction of 2,3,5-tri-*O*-benzyl-D-ribo furanose **1** with cyclohexanol as a model (Table 1). Then, every lithium salts having super-acid class counter anion were effective for changing the stereoselection. This effect was shown to be more obvious when a solvent which dissolves lithium salts such as nitroethane was used. On the other hand, tetra-n-butyl ammonium perchlorate which is even more soluble in dichloromethane was quite ineffective. In addition, reactivities were notably lowered when lithium nitrate or iodide were used. Then, several lithium salts with super-acid class counter anions were further examined and lithium bis[(trifluoromethyl) sulfonyl]imide was found to be a new and effective additive, and was superior to lithium perchlorate mentioned in the previous papers. By the addition of this lithium salt, the model reaction proceeded very smoothly to give the desired α-D-ribofuranoside in excellent selectivity and yield.

Next, the amount of lithium salt was examined (Table 2) and it became clear that more than one equivalent of lithium bis[(trifluoromethyl)sulfonyl] imide was essentially needed for realizing high stereoselectivity.

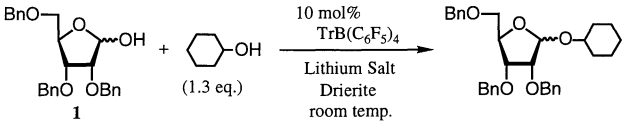


Table 1. Effect of lithium salts and solvents

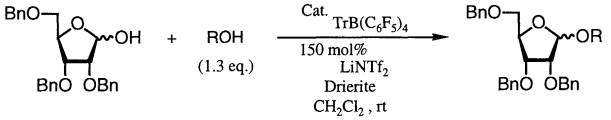
Solvent	Lithium salt[a]	Time / h	Yield / %	α / β
CH_2Cl_2	None	4	81	7 / 93
	$LiClO_4$	4	90	95 / 5
	LiOTf	6	80	32 / 68
	$LiBF_4$	6	85	40 / 60
	$LiNO_3$	20	34	15 / 85
	LiI	20	trace	–
	$LiNTf_2$	**4**	**94**	**>100 / 1**
$EtNO_2$	None	4	51	5 / 95
	$LiClO_4$	4	73	96 / 4
	LiOTf	6	67	71 / 29
	$LiBF_4$	6	80	80 / 20
	$LiNO_3$	20	28	34 / 66
	LiI	20	trace	–
	$LiNTf_2$	**4**	**60**	**97 / 3**
CH_2Cl_2	$^nBu_4NClO_4$	4	90	7 / 93

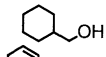
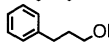
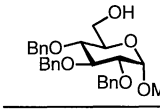
[a] 150 mol% of Lithium salts were used.

Table 2. Effect of the amount of $LiNTf_2$

Solvent	$LiNTf_2$ / mol%	Time / h	Yield / %	α / β
CH_2Cl_2	0	4	81	7 / 93
	50	4	84	61 / 39
	100	4	92	99 / 1
	120	4	94	>100 / 1
	150	4	94	>100 / 1
	200	4	93	>100 / 1

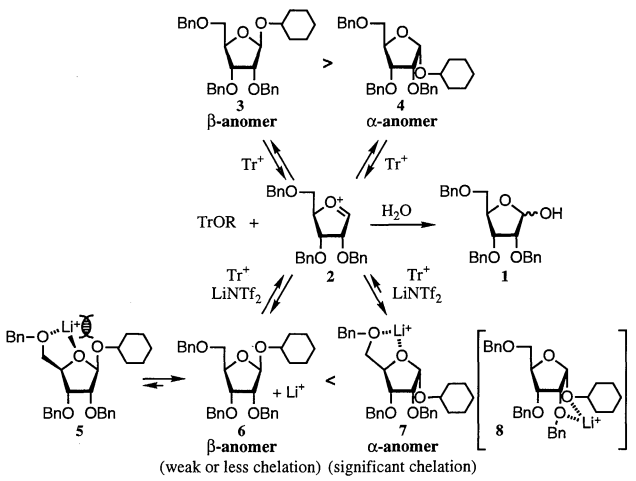
Table 3. Synthesis of α-D-Ribofuranosides



ROH	Cat. / mol%	Time / h	Yield / %	α / β
$CH_3(CH_2)_7OH$	10	24	94	>100 / 1
	15	24	95	99 / 1
	15	24	95	>100 / 1
	10	4	94	>100 / 1
3β-Cholestan-1-ol	10	12	94	>100 / 1
	10	24	90	99 / 1

Several examples of the present glycosylation reaction are demonstrated in Table 3. In every case, the desired α-D-ribofuranosides were obtained in high yield with almost perfect stereoselectivity although more catalysts and longer reaction time were required in the cases of using primary alcohols as nucleophiles.

In order to make the mechanism of this reverse effect clear, some experiments on anomerization of α- and β-ribofuranosides obtained by model reaction were tried first. Here, in the presence of 10 mol% of the trityl catalyst in dichloromethane, pure α-anomer (α/β=>99/1) isomerized to β-anomer rich mixture (α/β=6/94) whereas slight isomerization with the ratio of (α/β=6/94) took place in the case of pure β-anomer (α/β=1/>99). This is probably due to the thermodynamic control. In these cases, about 10% of 1-hydroxy sugar (2,3,5-tri-*O*-benzyl-D-ribofuranose) formed as by-product. On the other hand, the result was quite different in the coexistence of 150 mol% of lithium bis[(trifluoromethyl)sulfonyl]imide. Thus, the isomerization of pure α-anomer was completely inhibited (α/β=>99/1) while pure β-anomer almost completely isomerized to the α-anomer (α/β=>99/1). In these cases, about 2% of 1-hydroxy sugar formed in a similar manner as above.



Scheme 1. A hypothesis of anomerization mechanism.

The present anomerization mechanism was assumed to proceed via key intermediate, oxocarbenium ion **2**, as shown in Scheme 1. In the presence of the trityl cation, an existing equilibrium between the glycosylation products **3** and **4** may shift to yield more thermodynamically-stable β-anomer **3**-rich mixture (α/β=6/94) via the intermediate **2**. At the same time, a small amount of the remaining intermediate **2** yielded 1-hydroxy sugar **1** on quenching. This observation indicated that a ring-opening mechanism[6] is not essentially needed in the anomerization step. On the other hand, in the coexistence of lithium bis[(trifluoro methyl)sulfonyl]imide, the α-anomer was exclusively formed (α/β=>99/1). It is probably due to the selective stabilization of the α-anomer by forming a coordinated complex including lithium cation as follows. There are two possible chelate complexes : 1) lithium cation coordinates with the oxygen atoms at C-5 position and furanose ring as shown in **7**, or 2) lithium cation interacts between two oxygen atoms at anomeric and C-2 positions as shown in **8**. In either case, the β-anomer would not be able to form similar coordinated complex different from the α-anomer. Namely, in the case of 1), it is difficult to make a chelate complex since two oxygen atoms located in anti position, and in the case of 2), the steric repulsion between cis-fused two five-membered rings and the substituent at anomeric position would inhibit the formation of a stable chelate complex as shown in **5**. Therefore, a regeneration of the oxocarbenium ion intermediate **2** from the β-anomer would take place easily, while the α-anomer was hard to generate the intermediate **2** because of the above chelation. As a result, the α-anomer would be exclusively formed. In addition, it was observed that, the formation of 1-hydroxy sugar on quenching (about 2%) was smaller than that in the absence of lithium salt (about 10%). This result indicated that this chelation effect reduced the amount of existing oxocarbenium ion intermediate **2**.

The typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (18.4 mg, 0.02 mmol), lithium bis[(trifluoromethyl)sulfonyl] imide (86.1 mg, 0.30 mmol) and Drierite (450 mg) in dichloromethane (2 ml) was successively added to a dichloromethane (1 ml) solution of cyclohexanol (26.0 mg, 0.26 mmol) and a dichloromethane (1 ml) solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose **1** (84.1 mg, 0.2 mmol) at room temperature. The reaction mixture was stirred for 4 hours then it was cooled to 0 °C and was quenched by adding triethylamine (0.5 ml) and saturated aqueous sodium hydrogen carbonate. By usual work-up and purification with preparative TLC (silica gel), Cyclohexyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside (94.5 mg, 94% yield) was isolated. The ratio of two anomers was determined by HPLC analysis.

Thus, it is noted that lithium bis[(trifluoromethyl)sulfonyl] imide is a new and effective additive superior to lithium perchlorate which works to afford α-D-ribofuranosides in perfect stereocontrol. A hypothetical mechanism of lithium salts induced reverse effect on the stereoselectivity in the synthesis of α-D-ribofuranosides is now proposed.

A development of another useful glycosylation reaction based on this new hypothesis is now in progress.

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References and Notes

1 H.Uchiro and T. Mukaiyama, *Chem. Lett.*, **1996**, 79.
2 T. Mukaiyama, S. Kobayashi, and S. Shoda, *Chem. Lett.*, **1984**, 907; T. Mukaiyama, T. Shimpuku, T. Takashima, and S. Kobayashi, *Chem. Lett.*, **1989**, 145; S. Suda and T. Mukaiyama, *Chem. Lett.*, **1991**, 431; T. Mukaiyama, K. Matsubara, and S. Suda, *Chem. Lett.*, **1991**, 981; T. Mukaiyama and K. Matsubara, *Chem. Lett.*, **1992**, 1041; T. Mukaiyama and N. Shimomura, *Chem. Lett.*, **1993**, 781.
3 T. Mukaiyama, K. Matsubara, and M. Hora, *Synthesis*, **1994**, 1368.
4 J. Foropoulos Jr. and D. D. Desmarteau, *Inorg. Chem.*, **23**, 3720(1984).
5 Its application in organic synthesis, S. T. Handy, P. A. Grieco, C. Mineur, and L. Ghosez, *Synlett*, **1995**, 565; H. Kobayashi, J. Nie, and T. Sonoda, *Chem. Lett.*, **1995**, 307.
6 N. Morishima, S. Koto, and S. Zen, *Chem. Lett.*, **1979**, 749; M. Kawana, H. Kuzuhara, and S. Emoto, *Bull. Chem. Soc. Jpn.*, **54**, 1492(1981).