Highly Stereoselective Preparation of α-Glucosides Utilizing Anomerization Reaction with $MgBr_2 \cdot OEt_2$ and a Catalytic Amount of Titanium(IV)tetrahalides

Teruaki Mukaiyama, Kazuya Takeuchi, and Hiromi Uchiro
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

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The anomerization reactions of several β-D-glucopyranosides proceed smoothly in the coexistence of $MgBr_2 \cdot OEt_2$ and a catalytic amount of titanium(IV)halides to afford the corresponding α-D-glucopyranosides. The desired alkyl α-glucosides and α-anomer of disaccharides such as Glcα1-6Glc were obtained in high yields with high stereoselectivities.

The preparation of anomerically pure glycosides is one of the characteristic and important problems in carbohydrate chemistry. In general, 1,2-trans-glycosides are effectively synthesized utilizing so-called neighboring group participation by the introduction of an acyloxy group at C-2 position of glycosyl donor. On the other hand, preparation of 1,2-cis-glycoside by glycosylation procedure is more difficult and has been first achieved by a halide-catalysed glycosylation reaction using glycosyl halide (in situ anomerization method) with a non-participating C-2 substituent.

In recent years, highly stereoselective glycosylation reactions were developed and it was observed that the process of anomerization was essential for the exclusive formation of α-isomer.[1] Therefore, it was considered that the anomerization reaction was a key step in achieving a new and general method for the preparation of anomerically pure α-glycosides.

In 1928, it was firstly reported by Pacsu that $TiCl_4$ promoted the transformation of fully acetylated alkyl β-D-glucopyranosides to their α-isomers,[2] and after that, this reaction was also applied to fully benzoylated ones.[3] Koto et al found that methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside was anomerized rapidly into the α-anomer when 1 equivalent of $TiCl_4$ was used and also studied the significant effect of substituents on the anomerization in detail.[4] Nakanishi et al reported the preparation of alkyl α-D-glycopyranosides by anomerization reaction using excess amount of $FeCl_3$.[5] When a stoichiometric amount of strong Lewis acids such as $TiCl_4$ or $SbCl_5$[6] were used, lowering of yield was observed because complicated side reactions took place at the same time. Although all of the above reactions were useful for preparation of the corresponding alkyl α-D-glycopyranosides, it is difficult to anomerize the glycosidic linkage of a disaccharide in high yield with high stereoselectivity. Therefore, the above procedures were not successfully employed in oligosaccharide synthesis and then it was thought that a catalytic procedure would be quite effective for anomerization reaction.

In the first place, the anomerization reaction of methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **1** was examined in the presence of 1 equivalent of various Lewis acids in dichloromethane at rt (Table 1). Lewis acids were considered to coordinate with ring or glycosidic oxygen atom forming the acyclic or cyclic oxocarbenium ion intermediates consequently (Scheme 1). After screenig several Lewis acids, it was thought that the dominant reaction pathway (path I or II) depended on the characteristic properties of center metals. When $SnCl_4$, $BF_3 \cdot OEt_2$ and $SbCl_5$ were used, the anomerization would take place mainly via path II and the desired α-glucosides were obtained in low to moderate stereoselectivities. Because this type of anomerization proceeded reversibly to form cyclic intermediate from both anomers and therefore the anomeric mixture of glycosides were obtained in thermodynamic equiribrium ratio. In these reactions, a byproduct, 1-hydroxy sugar, was isolated after hydrolysis of the intermediate resulted by the exocyclic carbon-oxygen bond cleavage.[5] On the contrary, the (IV) group metal chlorides ($TiCl_4$, $ZrCl_4$, $HfCl_4$) exhibited high activity for anomerization reaction and the desired α-glucosides were obtained very rapidly[4] in high yields with high stereoselectivities. In these cases, the anomerization was assumed to proceed via an acyclic oxocarbenium ion, which was in turn underwent intramolecular recyclization irreversibly to form α-glycosides (path I). These results indicated that a suitable choice of Lewis acid was essential for the preparation of anomerically pure glycosides by the above procedure. Of these (IV) group metal halides, $TiCl_4$ gave the best result. Then, the effects of reaction temperature were examined (see Table 2). In the presence of 1 equivalent of $TiCl_4$, the anomerization reaction proceeded smoothly at -28°C in 10 min

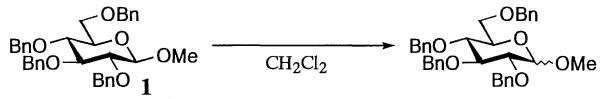


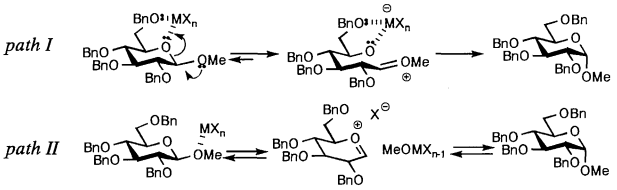
Table 1. Effect of metal halide

Entry	MX_n (100 mol%)	recover /%	α / β	time /h
1	$TiCl_4$	85	97 / 3	0.25
2	$ZrCl_4$	93	85 / 15	2.5
3	$HfCl_4$	86	89 / 11	1.5
4	$SnCl_4$	70	79 / 21	4
5	$BF_3 \cdot OEt_2$	90	33 / 67	4
6	$SbCl_5$	63	76 / 24	4
7	$SiCl_4$	N.R.		
8	$GeCl_4$	N.R.		

Table 2. Effect of reaction temperature[a]

Entry	temp /°C	recover /%	α / β	time /min
1	- 45	98	44 / 56	10
2	- 35	94	85 / 15	↑
3	- 28	98	90 / 10	↑
4	0	93	95 / 5	↑

[a] 100 mol% of $TiCl_4$ was used.

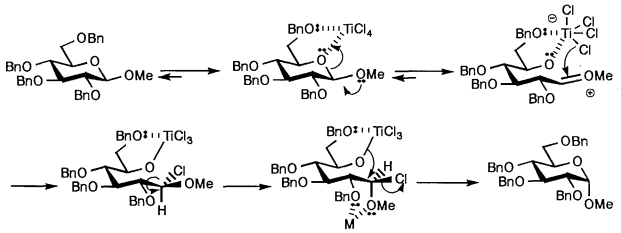


Scheme 1. Reaction Mechanism of Anomerization.

and the glycosides were recovered almost quantitatively. Next, several titanium(IV) compounds such as $Cl_2Ti(OTf)_2$, Cp_2TiCl_2, $Cl_3Ti(^iPrO)$, (acac)TiO were examined. Unexpectedly, $Cl_2Ti(OTf)_2$, much stronger Lewis acid than $TiCl_4$, and the other titanium compounds were not effective and the anomerization did not take place under -28°C. Anomerization of the glycosidic bond of **1** occurred only when $TiCl_4$ was used.

Based on the above results, the mechanism of this $TiCl_4$-mediated anomerization was reconsidered in some detail. So far, it was not yet made clear why the C(1)-C(2) bond of acyclic intermediate was caused to rotate. Then, it was assumed that a shift of chloride ion of $TiCl_4$ to C(1) carbon of an acyclic intermediate was facilitated to form halo-acetal by the coordination of $TiCl_4$ to C(6) and to ring oxygen atoms (Scheme 2). From this assumption, the second metal salts were added to interact with halo-acetal to rotate at the C(1)-C(2) bond due to their chelation to the glycosidic and C(2) oxygen atoms (Table 3). Then, it was found that the combined use of $TiCl_4$ and $MgBr_2{\cdot}OEt_2$ was quite effective (Entry 4) and the amount of $TiCl_4$ could be decreased when the anomerization was carried out at rt.

The effect of the amount of $MgBr_2{\cdot}OEt_2$ is shown in Table 4. The stereoselectivity increased as the amount of $MgBr_2{\cdot}OEt_2$ increased. Moreover, the anomerization proceeded much faster



Scheme 2. Mechanism of $TiCl_4$-mediated Anomerization.

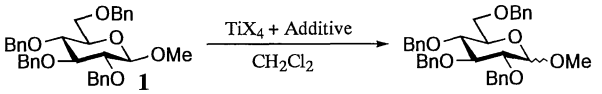


Table 3. Effect of combination with $TiCl_4$

Entry	Additive (mol%)	temp /°C	recover /%	α / β	time /min
1[a]	None	-28	96	55 / 45	30
2[a]	$Ti(^iPrO)_4$ (50)	-28	N.R.		
3[a]	$LiClO_4$ (50)	-28	95	54 / 46	30
4[a]	$MgBr_2{\cdot}OEt_2$ (50)	-28	99	78 / 12	30
5[a]	$MgBr_2{\cdot}OEt_2$ (100)	-28	98	93 / 7	30
8[b]	$MgBr_2{\cdot}OEt_2$ (100)	rt	98	92 / 8	50

[a] 50 mol% of $TiCl_4$ was used. [b] 5 mol% of $TiCl_4$ was used.

Table 4. Effect of the amount of $MgBr_2{\cdot}OEt_2$[c]

Entry	TiX_4	$MgBr_2{\cdot}OEt_2$ /mol%	recover /%	α / β	time /min
1	$TiCl_4$	None	98	59 / 41	30
2	↑	10	99	69 / 31	30
3	↑	40	95	82 / 18	30
4	↑	100	99	92 / 8	20
5	$TiBr_4$	None	98	80 / 20	30
6	↑	10	97	80 / 20	30
7	↑	50	97	86 / 14	30
8	↑	100	95	93 / 7	30
9	None	100	N.R.		

[c] 10 mol% of TiX_4 was used at room temperarure.

when $TiBr_4$ was used instead of $TiCl_4$ (Entry 1 and 5) and the effect of $MgBr_2{\cdot}OEt_2$ was similar to the above result.

Finally, this anomerization reaction was applied to several alkyl glucosides and per-*O*-benzyl derivative of disaccharide having primary glycosidic linkage (see Table 5). This system was effective for such alkyl groups as cyclohexylmethyl, cyclohexyl and tert-butyl (Entry1~3). Successful result was also obtained for anomerization of glycosidic linkage of disaccharide such as Glcβ1-6Glc and thus the desired anomerically pure α-glucoside was prepared in high yield (Entry 5). However, no anomerization occurred in the case of trifluoroethyl glucoside (Entry 4) indicating that electron density of glycosidic oxygen played an important role on this type of anomerization reaction.

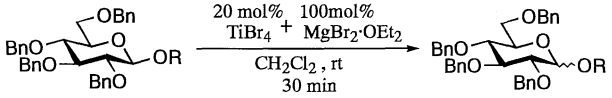
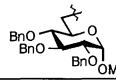


Table 5. Effect of aglycons

Entry	R	recover /%	α / β
1	Cyclohexylmethyl	93	94 / 6
2	Cyclohexyl	93	94 / 6
3	tert-Butyl (α/β=10/90)	83	85 / 15
4	trifluoroethyl (α/β=25/75)	95	25 / 75
5		86	>99 / 1

The typical experimental procedure is as follows: to a stirred suspension of titanium tetrabromide (3.7 mg, 0.01 mmol) and magnesium bromide diethyletherate (25.8 mg, 0.1 mmol) in dichloromethane (3 ml) was successively added dichloromethane solution (1.5 ml) of methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (55.5 mg, 0.1 mmol) at rt. The reaction mixture was stirred for 30 min at rt, then it was quenched by adding saturated sodium hydrogen carbonate. By usual work-up and purification with preparative TLC (silica gel), the desired glucoside was afforded (52.7 mg, 95% yield) and the ratio of anomers was determined by HPLC analysis.

Thus, an anomerization reaction of various β-D-glucopyranosides was successfully carried out by the combined use of $MgBr_2{\cdot}OEt_2$ and a catalytic amount of titanium(IV) halides. It is noted that this reaction was also quite effective to anomerize primary glycosidic linkage of disaccharide in high yield with high stereoselevtivity.

Further study on the anomerization of various glycoside according to the present procedure is now in progress.

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References

1 H. Uchiro and T. Mukaiyama, *Chem. Lett.*, **1996**, 271; H. Uchiro, K. Miyazaki, and T. Mukaiyama, *Chem. Lett.*, **1997**, 403.
2 E. Pacsu, *Chem. Ber.*, **61**, 1508(1928).
3 R. E. Reeves and L. W. Mazzeno, Jr., *J. Am. Chem. Soc.*, **76**, 2219(1954).
4 N. Morishima, S. Koto, and S. Zen, *Chem. Lett.*, **1979**, 749; S. Koto, N. Morishima, R. Kawahara, K. Ishikawa, and S. Zen, *Bull. Chem. Soc. Jpn.*, **55**, 1092(1982).
5 N. Ikemoto, O. K. Kim, L-C. Lo, V. Satyanarayana, M. Chang, and K. Nakanishi, *Tetrahedron Lett.*, **33**, 4295(1992).
6 I. Karasawa and R. Onishi, *J. Agr. Chem. Soc. Jpn.*, **35**, 813(1961).