Imidazole Promoted Efficient Anomerization of β-D-Glucose Pentaacetate

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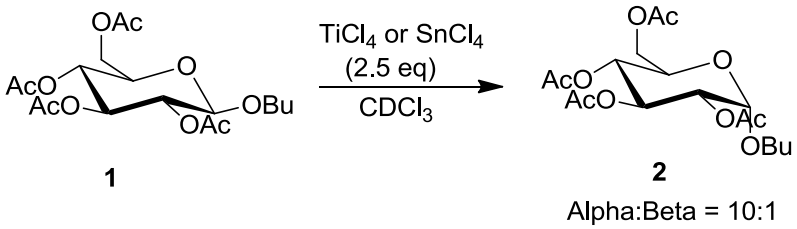
KEYWORDS. Imidazole; Anomerization; Glycosides; β-D-Glucose pentaacetate; Mechanism.

ABSTRACT. Anomerization of glycosides were rarely performed under basic condition due to lack of efficiency. Here an imidazole promoted anomerization of β-D-glucose pentaacetate was developed; and the reaction was very efficient and full conversion could be achieved within an hour in several anhydrous solvents. Subsequently a new intramolecular mechanism was proposed based on investigation and following which anomerization of broad β-C(O)-O-glucosides might be expected in the future.

Carbohydrates play important role in various biological processes relating to virology, immunology, cancer and hence sugar-based moleculars attracted increasing attention of medicinal chemists.[1] Different conformational preferences can influent biological properties

remarkably.[2] Despite much effort in recent years, stereocontrolled synthesis of glycosides with a single anomer is still challenging and a universal method for which is out of the realm till now.[1] Recently P. V. Murphy group found that $TiCl_4$ or $SnCl_4$ could promote anomerization of O-glycosides or S-glycosides as Lewis acids at relative low concentration of glycoside substrates (Scheme 1).[3] Further study indicated TiCl4 could also promote anomerization of Se-glycosides4 and stereoselective epimerization of glycosyl thiols[5] in the presence/absence of additives. An increased amount (more than 2 equiv.) of $TiCl_4$ was a must to ensure completion of reaction typically and acceptable yields were achieved only for reactions carried out at higher dilution, which are not welcomed in potential industrial application.

Scheme 1. Anomerization of O-glycoside by $TiCl_4$ or $SnCl_4$.



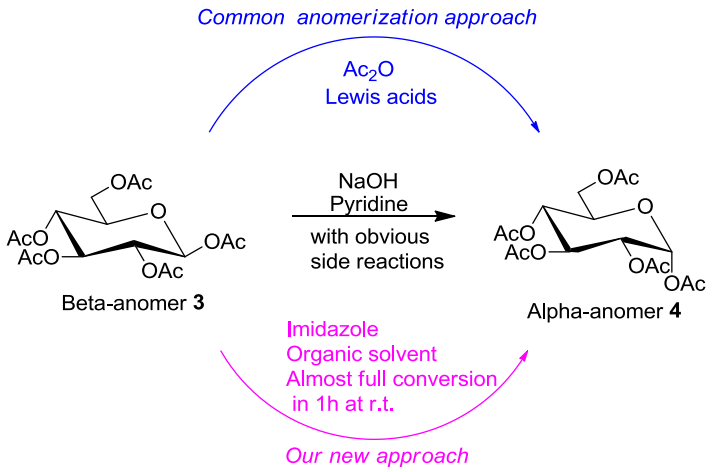
1 **2**

Alpha:Beta = 10:1

D-Glucose pentaacetate is important intermediate for synthesis of different types of glycosides.[1,6] During glycosylation, although β-D-glucose pentaacetate was found to react faster with nucleophiles in the presence of Lewis acids,[6b] its α anomer showed better performance in more applications like CO_2 absorption[7] and stimulation of insulin release[8]. α-D-Glucose pentaacetate was usually prepared from acetylation of D-glucose, or anomerization of β-anomer with acetyl anhydride catalyzed by Lewis acids.[9] Treating β-D-glucose pentaacetate with Lewis acids for α form is a classic anomerization method, based on a fact that a good stability of α-anomer towards a variety of acidic conditions which readily dissociate the β form (Scheme 2).[9,10] However, a single anomer was difficult to obtain due to the existence of the dissociation, and the

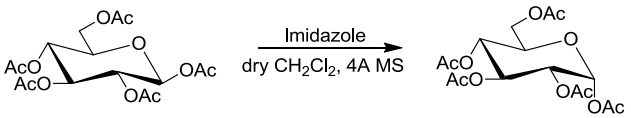
involved ring-open processes promoted by Lewis acids might lead to problems in stereocontroll especially for oligomers of sugar.

Scheme 2. Comparison of reported approaches with ours in anomerization of β-D-glucose pentaacetate.



In 1950, Lindberg found alkali (NaOH in pyridine) could promote β to α anomerization of D-glucose pentaacetate albeit with strong side reactions[11]. Since then, basic reaction conditions were generally considered to be out of choice in anomerization of glycosides due to lack of efficiency, here we report a new imidazole promoted efficient anomerization method. The reaction was performed at room temperature and β-anomer could be transformed into α form within an hour. Evidences indicated an intramolecular mechanism without ring-open process was more probably which may open a new promising way for stereoseletive anomerization of broad glucosides in the future.

Table 1. Optimization of loading of imidazole and reaction time.[a]



Beta-anomer **3** Alpha-anomer **4**

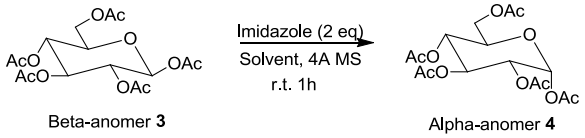
Entry	Imidazole (equiv.)[b]	Time (h)	Conversion yield (%)[c]
1	0.5	1	22
2	1	1	40
3	2	1	92
4	2	0.5	93
5	2	3	92
6	2	6	80

a: Reaction conditions: β-D-glucose pentaacetate (1 mmol), activated 4Å molecular sieves (0.2 g), and imidazole (0.5 mmol to 2 mmol) were added into a pre-dried vial (20 mL), then anhydrous dichloromethane (2 mL) was added. The vial was sealed and the mixture was stirred at room temperature for 0.5 to 6 h as shown in the table. b: Equivalent of β-D-glucose pentaacetate. c: Determined by crude ^{1}H NMR.

Imidazole was observed to promote anomerization of glucose pentaacetate in $CDCl_3$ during study of its catalyzed acetyl transfer reactions by Goldstein[12]. However, we met problems in achieving reproducible conversion yields in the above reactions under same conditions. After thorough study of potential affecting factors, we eventually found that the reaction is pretty sensitive to water and consistent conversion yields could be achieved by performing the reaction in the presence of activated 4Å molecular sieves.[13] With anhydrous dichloromethane as solvent, effect of loading of imidazole was evaluated at room temperature in the presence of activated 4Å molecular sieves. The conversion yield was higher along with increase amount of imidazole and over 93% yield could be achieved in half an hour when ratio of β-D-glucose pentaacetate : imidazole = 1 : 2 (Entries 1 – 3, Table 1). Prolonged reaction time to 3 hrs had negligible effect on the conversion yield (Entries 3 – 5, Table 1); while too long reaction didn't benefit the

conversion yield and obvious side products were observed probably because sugar ring open reactions occurred (Entries 4 and 5, Table 1).

Table 2. **Investigation on solvent effect**.[a]



Beta-anomer **3** Alpha-anomer **4**

Entry	Solvent	Conversion yield (%)[b]
1	CH_2Cl_2	92
2	THF	68
3	Acetone	77
4	MeCN	81
5	$CHCl_3$	83
6	EtOAc	51
7	DMSO	43
8	Hexane	33
9	EtOH	9
10[c]	Acetone	>95

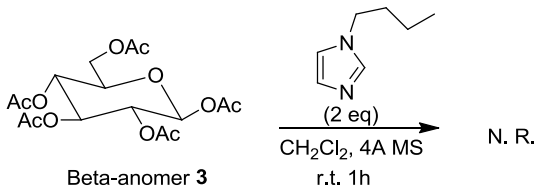
a: Reaction conditions: β-D-glucose pentaacetate (1 mmol), activated 4Å molecular sieves (0.2 g), and imidazole (2 mmol) were added into a pre-dried vial (20 mL), then anhydrous solvent (2 mL) was added. The vial was sealed and the mixture was stirred at room temperature for 0.5 to 6 h as shown in the table. b: Determined by crude ^{1}H NMR. c: 1 gram of β-D-glucose pentaacetate was used.

The anomerization was further optimized in different organic solvents with imidazole (2 equiv.) in the presence of 4Å molecular sieves (Table 2). In general the anomerization reactions proceeded well in most of common organic solvents; excellent performances were observed in dichloromethane, acetone and chloroform although the best was achieved in dichloromethane. The low efficiency in hexane and ethanol was largely due to the low solubility of β-D-glucose

pentaacetate or imdazole in both of the solvents. To further demonstrate the possibility in industrial use, a relative large scale in 1 g in acetone was performed. The anomerization occurred smoothly as well and almost full conversion yield (> 95%)[14] was observed.

A liquid mixture of β-D-glucose pentaacetate and its α-form after recrystallization of either form was usually disposed as a waste in industry for production of a pure form because of high cost in separation of the two anomers. To our delight, the presence of imidazole could fully convert all β-form in the mixture (α:β = 2.2:1) into α-form within an hour and a mixture became pure α-form (detail sees supporting information).

Scheme 3. No anomerization occurred with 1-butyl imidazole instead of imidazole.



Mechanistic study was also performed in order to answer three key concerns: 1) was the C-O bond in the sugar ring ever open during anomerization? 2) Did the (O)C-OAc ever break or not? 3) What is the role of imidazole during anomerization? Repalcement of imidazole with 1-butyl imidazole led to no reaction and all β-D-glucose pentaacetate was recovered, which indicated the necessary role of free nucleophilic amine part in imidazole (Scheme 3). A ^{1}H NMR tracking reaction in $CDCl_3$ was performed in order to gain insights on the anomerization pathway. Small amount of N-acetylimidazole was observed as Goldstein reported, however anomerization process seemed very slow and stopped after a few minutes in three repeated trials possibly because significant carboxylic acid byproducts formed[15]. Goldstein proposed an acyl transfer and sugar ring-open mechanism catalyzed by imidazole in the presence of aliphatic alcohol, which was claimed to be a similar mechanism with enzyme catalyzed acyl transfer reaction under

biological conditions.[16] During the process, alcohol and carboxylic acid played an important role in assistance of acyl transfer by providing proton.[17] The acyl transfer reaction was proposed follow pathway A (Figure 1): a hydrolysis reaction occurs from intermedicate I assisted by a proton interacting with oxygen on 1-C, and the formed 1-β-hydroxyl D-glucose tetraacetate undergoes equilibration via aldehyde form to give α-form of 1-hydroxyl D-glucose tetraacetate. We question that the last step that acyl transfers back from N-acetylimidazole is unfavorable in light of the existence of excess amount of imidazole and the excellent stability of N-acetylimidazole.

Meanwhile in our system, evidences that β-D-glucose pentaacetate kept without any change with imidazole hydrogen chloride as promoter and moisture inside reaction mixture affected conversion yield significantly, indicated that the presence of proton inhibited anomerization. With glues in hands, we postulated an alternative anomerization pathway B (Figure 1): imidazole attacks acyl group on 1-C of β-D-glucose pentaacetate to give intermediate I. The newly formed O- attacks 1-C again to form a four-membered ring intermediate II in which an interaction of electron-negative 1-C and electron-positive imidazole ring might contribute to the stabilization. The original C-O bond on 1-C breaks off and imidazole moiety leaves, forming α-form of D-glucose pentaacetate.

In conclusion, a practical method for anomerization of β-D-glucose pentaacetate promoted by imidazole was developed. The reaction was very efficient and full conversion could be achieved within an hour in several anhydrous solvents. A new intramolecular mechanism was proposed and following which we envisaged that anomerization of broad β-C(O)-O-glucosides might be possible.

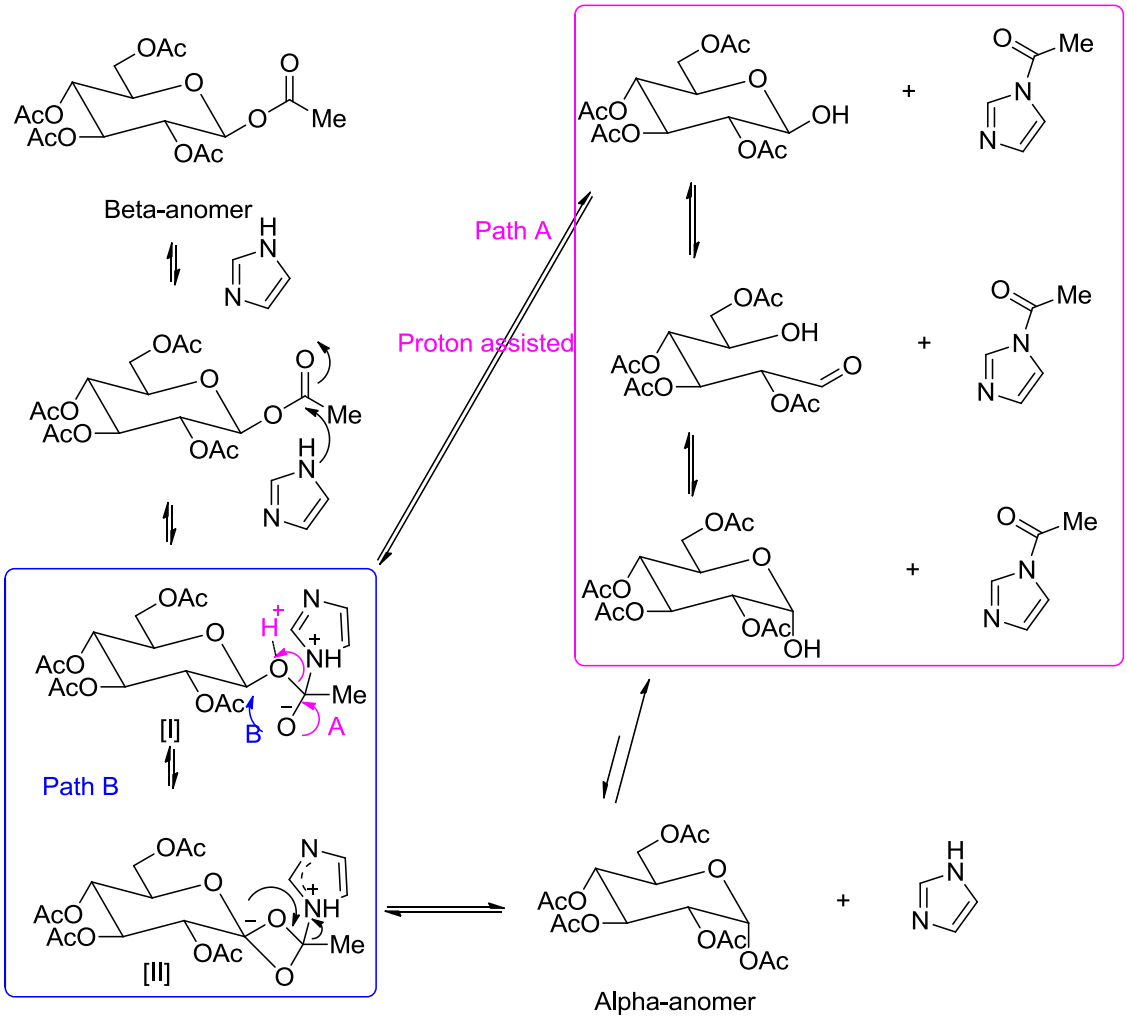


Figure 1. Two possible pathways for imidazole promoted anomerization.

EXPERIMENTAL SECTION

General procedure for imidazole promoted anomerization of β-D-Glucose pentaacetate

β-D-Glucose pentaacetate (0.390 g, 1.0 mmol) and imidazole (0.136 g, 2.0 mmol) were added into a solution of activated molecular sieves (4 Å) (0.200 g) in anhydrous dichloromethane (or other solvent) (2 mL) at room temperature, then the mixture continued to be stirred for 1 hour (or

longer time) at room temperature. Subsequently the reaction was stop stirring and 400 μL of which was transferred to a single-necked flask. Removel of solvent under *vaccum* gave a crude product for ^{1}H NMR to determine a conversion yield.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ♀These authors contributed equally.

ACKNOWLEDGMENT

We acknowledge a startup funding from Jinan University to L. Gu (No: 88015155 and 88016607).

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(13) Recrystallization of both imidazole and β-D-glucose pentaacetate were also investigated and the effect was minor. The data of water effect was concluded as shown in **STable 1** in *Supporting Information*.
(14) The better yield achieved in 1 g scale was probably due to less moisture in the vial (reactions were all performed in closed cap instead of protecting nitrogen gas for convenience).
(15) An obvious broad single peak appeared at δ11.5 ppm which lie in the range of carboxylic acids on ^{1}H NMR spectra in $CDCl_3$ from 5 mins to 60 mins.
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