Imidazole Promoted Efficient Anomerization of β-D-Glucose Pentaacetate in Organic Solutions and Solid State

Meifeng Wang[♀b], *Liyin Zhang*[♀a], *Yiqun Li*[b]* *and Liuqun Gu*[a]*

[a] Department of Biomedical Engineering, Jinan University; [#]601, Huangpudadaoxi, Guangzhou, China

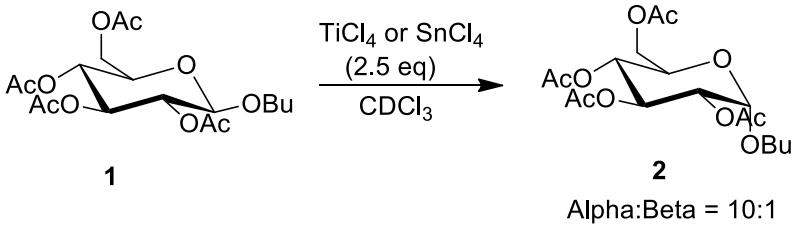
[b] Department of Chemistry, Jinan University; [#]601, Huangpudadaoxi, Guangzhou, China

KEYWORDS. Imidazole; Anomerization; organic solvents; β-D-Glucose pentaacetate; solid state.

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 reaction could proceed in both organic solvents and solid state at room temperature. Although mechanism is not yet clear, this unprecedent mild anomerization in solid state may open a new promising way for stereoseletive anomerization of broad glucosides and materials design in the future.

Carbohydrates play important role in various biological processes relating to virology, immunology, cancer and hence sugar-based molecules 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 $TiCl_4$ could also promote anomerization of Se-glycosides[4] 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 $SnCl_4$.



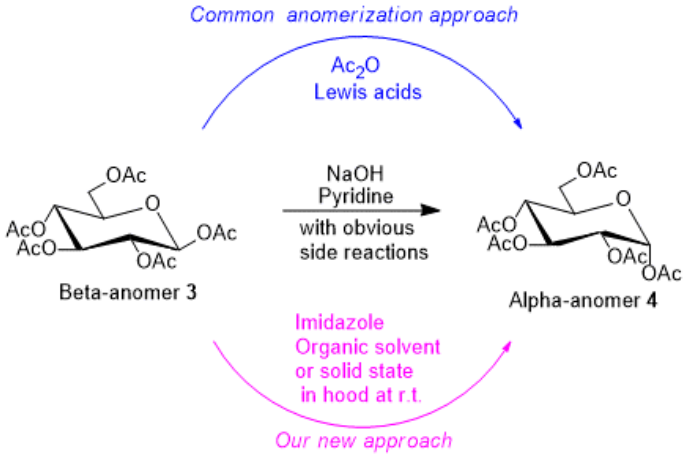
1 **2**

Alpha:Beta = 10:1

D-Glucose pentaacetate is an 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

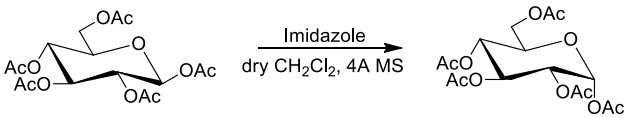
acids for α form is a classic anomerization method, based on a fact that a good stability of α-anomer towards a variety of acidic conditions which readily dissociate the β form (Scheme 2).[9,10] However, a single anomer was difficult to obtain due to the existence of the dissociation, and the involved ring-open processes promoted by Lewis acids might lead to problems in stereocontrol 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 anomerization of D-glucose pentaacetate from β-form to α-form 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 in both organic solvent and solid state at room temperature. To our best knowledge anomerization reaction of D-glucose pentaacetate or D-glucose in solid state under basic condition at room temperature was not yet reported in literature[12].

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



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

Entry	Imidazole (equiv.)[b]	Time (h)	Yield (%)[c]
1	0.5	1	22
2	1	1	40
3	2	1	92

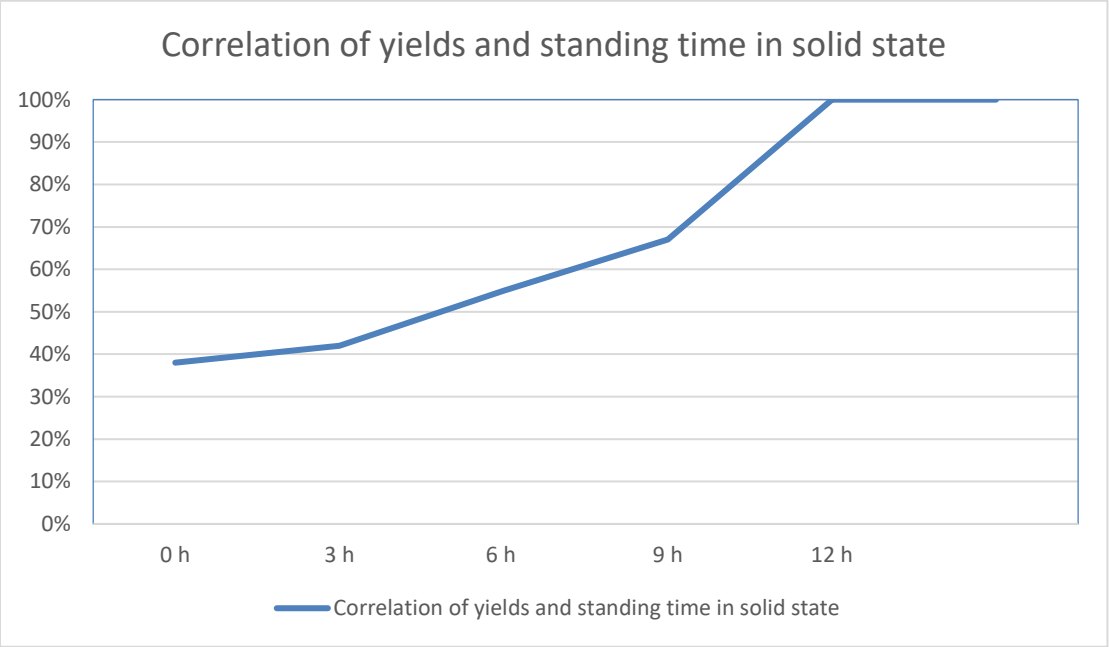
a: Reaction conditions: β-D-Glucose pentaacetate (1 mmol), activated 4Å molecular sieves (0.2 g), and imidazole (0.5 mmol to 2 mmol) were added into a pre-dried vial (20 mL), then anhydrous dichloromethane (2 mL) was added. The vial was sealed and the mixture was stirred at room temperature for 0.5 to 6 h as shown in the table. Evaporation of solvent to give a crude mixture, which was kept open in hood overnight for ^{1}H NMR analysis. 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[13]. 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.[14] 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 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. To further demonstrate the possibility in industrial use, a relatively large scale in 1 g in

acetone was performed. The anomerization occurred smoothly as well and almost full conversion yield (> 95%)[15] 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).

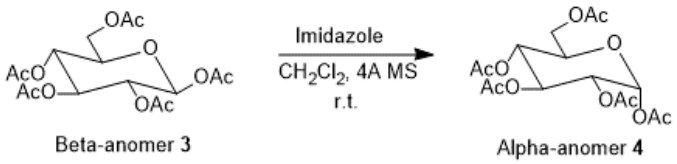
Figure 1: Correlation of yields and standing time in solid state



Yields were however inconsistent and sometime obvious differences were observed in our subsequent reproducing work when operating hands were changed. Excluding possibility of existence of moisture inside of molecular sieves or anhydrous dichloromethane, the problem was eventually located at different standing times after reactions were stopped and evaporation of solvents; continued anomerization in solid state was hypothesized logically. Yields were obtained

in 30% and > 99% at different standing time (0 h and 12 hrs) in solid state upon evaporation of all dichloromethane after the mixture was stirred for 1 hour; the sharp difference might well explain the previous inconsistence and encouraged us to further explore this unexpected anomerization reaction in solid state. Yields measured at 0 hr, 3 hrs, 6 hrs, 9 hrs, 12 hrs standing in solid state after 1 hr pre-mixing of β-D-glucose pentaacetate (0.5 mmol), imidazole (1 mmol) and 4Å molecular sieves upon evaporation of solvent. A good line correlation was observed between yield and standing time (Figure 1), which supported our hypothesis that anomerization indeed continue to proceed in solid state. With combination of anomerization in organic solution and solid state, yields of α-form were highly reproduceable quantitively after 12 hrs standing time in hood whether used dichloromethane was from any purification method. Under above conditions, solvent effect was intangible for non-protonic solvents like acetonitrile and hexane, while only moderate yield was achieved when using protonic solvent ethanol (See SI).

Table 3. **Investigation on effect of imidazole and molecular sieves on anomerization**.[a]

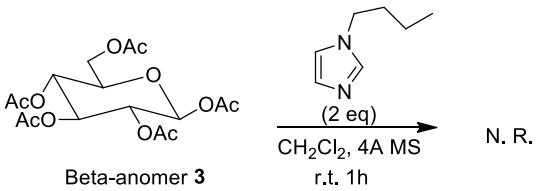


Beta-anomer 3 Alpha-anomer 4

Entry	Imidazole (Equiv.)	4Å Molecular sieves (g)	Standing time in solid state (h)	Yield (%)[b]
1	0	0	0	0
2	0	0	24	0
3	0	0	48	0
4	0	0	96	0
5	2	0	0	39
6	2	0	12	70

7	2	0	24	> 99
8	2	0.2	12	> 99
9	1	0.2	24	42
10	1	0.2	48	63
11	1	0.2	96	69

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



Mechanistic study was also performed in order to gain more clues. Replacement 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). Removal of imidazole and 4Å molecular sieves prohibited anomerization and gave no α-form product at all even (all β-D-glucose pentaacetate was recovered without any change) after 96 hrs standing in solid state (Entries 1 – 4, Table 3); it excluded a possibility of slow dissociation because of stability difference. In the absence of 4Å molecular sieves, anomerization reaction still could proceed as observed in organic solution albeit in a slower rate; almost pure α-form product could be obtained in 1 day (Entries 5 – 7, Table 3). Pores of 4Å molecular sieves might be benefit in absorbing of moisture and generation of more reactive amorphous state. In the presence of stoichiometric amount of imidazole, only 69% conversion was observed even after 96 hrs standing time (Entries 8 – 11, Table 3) and obvious impurity formed, which indicated excess amount of imidazole was pretty necessary for a clean satisfied yield.

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.[17] During the process, alcohol and carboxylic acid played an important role in assistance of acyl transfer by providing proton.[18] 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. Furthermore, in light of the existence of excess amount of imidazole and the excellent stability of N-acetylimidazole, the last step that acyl transfers back from N-acetylimidazole is unfavorable in our system. Hence it is postulated that a different mechanism was more probably in this anomerization in organic solution and solid state.

In conclusion, a "chemist-friendly" method for anomerization of β-D-glucose pentaacetate promoted by imidazole was developed; Even a relatively low yield was achieved after pre-mixing in organic solution, however continued reaction in solid state by simple keeping the crude mixture stand for 24 hours could still led to a consistent full conversion. A different mechanism with reported one was more probably based on evidences. Although current substrate scope was limited to β-D-glucose pentaacetate, the unprecedent mild anomerization in solid state may open a new promising way for stereoseletive anomerization of broad glucosides in the future.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

AUTHOR INFORMATION

Corresponding Author

*(L. Gu) E-mail: guliuqun@jnu.edu.cn or guliuqun@yahoo.com;

* (Y. Li). E-mail: tlyq@jnu.edu.cn

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).

REFERENCES

(1) Hanessian, S.; Lou, B. Stereocontrolled Glycosyl Transfer Reactions with Unprotected Glycosyl Donors. *Chem. Rev.* **2000**, *100* (12), 4443-4463. b) Das, R.; and Mukhopadhyay, B. Chemical O-Glycosylations: An Overview. *ChemistryOpen* **2016**, *5* (5), 401-433.
(2) Montero, E.; García-Herrero, A.; Asensio, J. L.; Hirai, K.; Ogawa, S.; Santoyo-Gonza´lez, F.; Canada, F. J.; Jime´nez-Barbero, J. The conformational behavior of non-hydrolyzable lactose analogues: the thioglycoside, carbaglycoside, and carba-iminoglycoside cases. *Eur. J. Org. Chem.* **2000**, (10), 1945-1952.
(3) Pilgrim, W.; and Murphy, P. V. SnCl4- and TiCl4-Catalyzed Anomerization of Acylated O- and S-Glycosides: Analysis of Factors That Lead to Higher α:β Anomer Ratios and Reaction Rates. *J. Org. Chem.* **2010**, *75* (20), 6747-6755.
(4) McDonagh, A. W.; Mahon, M. F.; and Murphy, P. V. Lewis Acid Induced Anomerization of Se-Glycosides. Application to Synthesis of α-Se-GalCer. *Org. Lett.* **2016**, *18* (3), 552-555.
(5) Doyle, L. M.; O'Sullivan, S.; Salvo, C. D.; McKinnney, M.; McArdle, P.; and Murphy, P. V. Stereoselective Epimerization of Glycosyl Thiols. *Org. Lett.* **2017**, *19* (21), 5802-5805.
(6) a) Lawandi, J.; Rocheleau, S.; Moitessier, N. Regioselective acylation, alkylation, silylation and glycosylation of monosaccharides. *Tetrahedron* **2016**, *72* (41), 6283-6319. b) Jensen, K. J. O-Glycosylations under neutral or basic conditions. *J. Chem. Soc., Perkin Trans. 1* **2002**, (20), 2219-2233.
(7) Ma, S.-L.; Wu, Y.-T.; Hurrey, M. L.; Wallen, S. L.; and Grant, C. S. Sugar Acetates as CO2-philes: Molecular Interactions and Structure Aspects from Absorption Measurement Using Quartz Crystal Microbalance. *J. Phys. Chem. B* **2010**, *114* (11), 3809-3817.

(8) Malaisse, W. J.; Jijakli, H.; Kadiata, M. M.; Sener, A.; and Kirk, O. Stimulation of insulin release by α-D-glucose pentaacetate. *Biochem. Biophys. Res. Commun.* **1997**, *231* (2), 435-436.
(9) Huang, G.; Tang, Q.; Li, D.; Huang, Y. and Zhang, D. Synthetic Methods of α-D-Glucose Pentaacetate. *Current Organic Synthesis* **2016**, *13* (1), 82-85.
(10) Lemieux, R. U. and Brice, C. Comparison of the properties of the pentaacetates and methyl 1,2-orthoacetates of glucose and mannose. *Can. J. Chem.* **1955**, *33*, 109-19.
(11) Lindberg, B. The beta to alpha transformation of fully acetylated glycosides by alkali. *ACTA CHEMICA SCANDINAVICA* **1950**, *4*, 49-51.
(12) $NaHCO_3$ was reported to catalyze solid state anomerization of D-glucose but mechanism study indicated that it proceeded via a protonic activating route because a stronger base Na_2CO_3 was inactive at all under the same conditions. See: Korolev, K. G.; Lomovsky, O. I.; Uvarov, N. F. and Salenko, V. L. Mechanochemical Transformations of the Crystalline Anomers of D-Glucose. *Chemistry for Sustainable Development*, **2004**, *12*, 339.
(13) Mandell, L.; Moncrief, J. W.; Goldstein, J. H. Novel process for anomerization of D-glucopyranose pentaacetate involving imidazole-catalyzed acyl transfer. *Tetrahedron Lett.* **1963**, *4*, 209.
(14) Recrystallization of both imidazole and β-D-glucose pentaacetate were also I, nvestigated and the effect was minor. The data of water effect was concluded as shown in **STable 1** in *Supporting Information*.
(15) 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).
(16) An obvious broad single peak appeared at δ11.5 ppm which lie in the range of carboxylic acids on ^1H NMR spectra in $CDCl_3$ from 5 mins to 60 mins.
(17) Mandell, L.; Moncrief, J. W.; Goldstein, J. H. Imidazole as a catalyst in acyl transfer. A model enzyme system for physiological transacetylation. *Tetrahedron* **1963**, *19*, 2025.
(18) a) Somayaji, V. and Brown, R. S. Distorted amides as models for activated peptide N-C:O units produced during enzyme-catalyzed acyl transfer reactions. 1. The mechanism of hydrolysis of 3,4-dihydro-2-oxo-1,4-ethanoquinoline and 2,3,4,5-tetrahydro-2-oxo-1,5-ethanobenzazepine. *J. Org. Chem.* **1986**, *51* (14), 2676-86. b) Kotzler, M. P.; Robinson, K.; Chen, H.-M.; Okon, M.; McIntosh, L. P.; and Withers, S. G. Modulating the Nucleophile of a Glycoside Hydrolase through Site-Specific Incorporation of Fluoroglutamic Acids. *J. Am. Chem. Soc.* **2018**, *140* (26), 8268-8276.