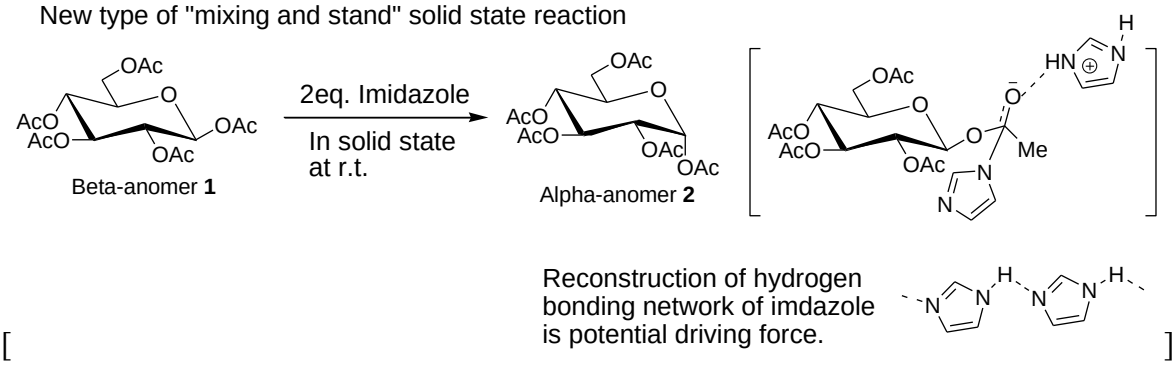
Imidazole Promoted Efficient Anomerization of β-D-Glucose Pentaacetate in Solid State and Reaction Mechanism

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

[a] Department of Biomedical Engineering, Jinan University; [#]601, Huangpu Avenue West, Guangzhou, China

[b] Department of Chemistry, Jinan University; [#]601, Huangpu Avenue West, Guangzhou, China.

Supporting Information Placeholder



ABSTRACT: Anomerization of glycosides was rarely performed under basic condition. Here, an imidazole promoted anomerization of β-D-glucose pentaacetate in solid state at room temperature was discovered. This unprecedent anomerization occurred after simple premixing and reaction proceeded continuously in solid state to full conversion without stirring or mechanomixing. A proposed mechanism involved with inter/intramolecular acyl transfer promoted by imidazoles in a concerted manner may promote the discovery of more new transformations in solid state.

Carbohydrates play an 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] Even after full acetylation of all hydroxyl groups, the anomeric effect is still persistent. D-Glucose pentaacetate is an important intermediate for the synthesis of different types of glycosides.[1,3] During glycosylation, β-D-glucose pentaacetate was found to react faster with nucleophiles in the presence of Lewis acids[4]; but its α anomer showed better performance in other applications like CO_2 absorption[5] and stimulation of insulin release[6]. α-D-Glucose pentaacetate was usually prepared from anomerization of β-anomer with acetic anhydride catalyzed by Lewis acids.[7] Treating β-D-glucose pentaacetate with Lewis acids for α form is a classic anomerization method, based on the fact that a good stability of α-anomer towards a variety of acidic conditions which readily dissociate the β form.[8,9]

However, only less than a handful of anomerizations of D-glucose pentaacetate conditions was reported under basic reaction. It was M. L. Wolfrom and D. R. Husted who reported the first case, in which a good conversion of β-form sugar to α-form was observed in dioxane or diethyl ether when mixing with solid sodium hydroxide and a suitable drying agent.[10] In 1950, the followed study indicated anomerization in pyridine was 6 – 7 times faster and a heterogeneous catalysis mechanism was proposed[11]. Treatment of β-2,4-dinitrophenyl 2,3,4,6-tetra-O-acetyl-D-glucopyranoside with K_2CO_3 in DMF could also lead to an excellent anomerization to the α-form.[12] Epimerization of β-D-glucose pentaacetate to the α-form in dilute deuterochloroform solution was observed by J. H. Goldstein.[13] Here we report an imidazole promoted efficient anomerization in solid state at room temperature (**Scheme 1**); to our best knowledge, anomerization reaction of D-glucose pentaacetate in solid state under basic conditions was not yet reported in a literature. It should be noted that this reaction in solid state is different from current popular mechanochemistry because no mechanical mixing was used during reaction; in fact, it looks more like accelerated aging reactions without a stimuli[14]. It belongs to a new type of "mixing and stand" solid state reaction[15].

We noticed that imidazole could promote the anomerization of β-D-glucose pentaacetate in anhydrous dichloromethane during our methodology exploration and such anomerization was ever observed in 1963 by Goldstein[13]. After thorough study of potential affecting factors, we found that the reaction was pretty sensitive to water and consistent yields could only be achieved in the presence of activated 4Å molecular sieves (MS);[16] the best yield (92%) was obtained when the ratio of β-D-glucose pentaacetate to imidazole = 1 : 2 (see **STable 1** and **2** in *Supporting Information*).

In our subsequent reproduced work when operating hands were changed, yields were however surprisingly inconsistent. Excluding possibility of existence of moisture, the problem was eventually located at different standing times after evaporation of solvents; continued anomerization in solid state was hypothesized logically. Yields were obtained in 30% and > 99% at 0 h and 12 hrs standing respectively in solid state upon evaporation of all dichloromethane after the mixture was premixed for 1 hour; the sharp difference could well explain the previous inconsistence and that encouraged us to further explore this unexpected anomerization reaction in solid state. Yields measured at 0 hr, 3 hrs, 6 hrs, 9 hrs, and 12 hrs standing in solid state after 1 hr pre-mixing of β-D-glucose pentaacetate (1 mmol), imidazole (2 mmol) and 4Å MS upon evaporation of solvent. A good line correlation was observed between yield and standing time (**Figure 1**), which supported our hypothesis that anomerization indeed continues to proceed in solid state. With these optimized conditions in solid state, yields of α-form were highly reproduceable quantitively after 12 hrs standing time in hood, no matter dichloromethane was from any purification method. Solvent effect was intangible for aprotic solvents like acetonitrile and acetone, while only moderate yield was achieved when using protic solvent ethanol. Such observance showed that the existence of protons inhibits anomerization in solid state, but reactions in solid state have a better tolerance.

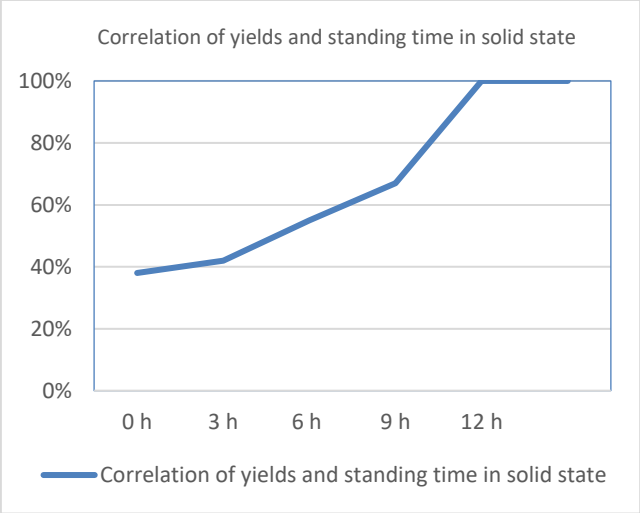


Figure 1. Correlation of yields and standing time in solid state.

There are several potential advantages for this new type of solid-state reaction that doesn't need mechanical mixing except more tolerance to moisture: 1) Less energy consumption. Continuous magnetic stirring or mechanical mixing are usually necessary for organic transformations for hours or days, consuming remarkable energy. 2) Minimized solvent use possible. A pre-mixing in solvent was necessary for this new solid-state reaction, however solvent usage might be possibly minimized by pre-mixing in high concentration or saturated solution particularly for future large-scale processes. 3) Highly accessible for green and safer solvents. High yields and excellent selectivity are usually only achievable in certain solvents such as halogenated solvents for most of the organic transformations, hence replacement with a suitable green and safer solvent without compromise on yield and selectivity is always difficult. But for this new solid-state reaction, any aprotic solvents including green solvent acetone are usable with an excellent yield. 4) Better solvent recycling potential. A pre-mixing of all reagents in solvent only for 30 mins to 1 hour means loss of solvent and potential new contaminants could be minimized, which is crucial for a better solvent recycling.

Table 1. Optimization of anomerization in solid state

Entry	Imidazole (Equiv.)	4Å Molecular sieves (g)	Standing time in solid state (h)	Yield (%)
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

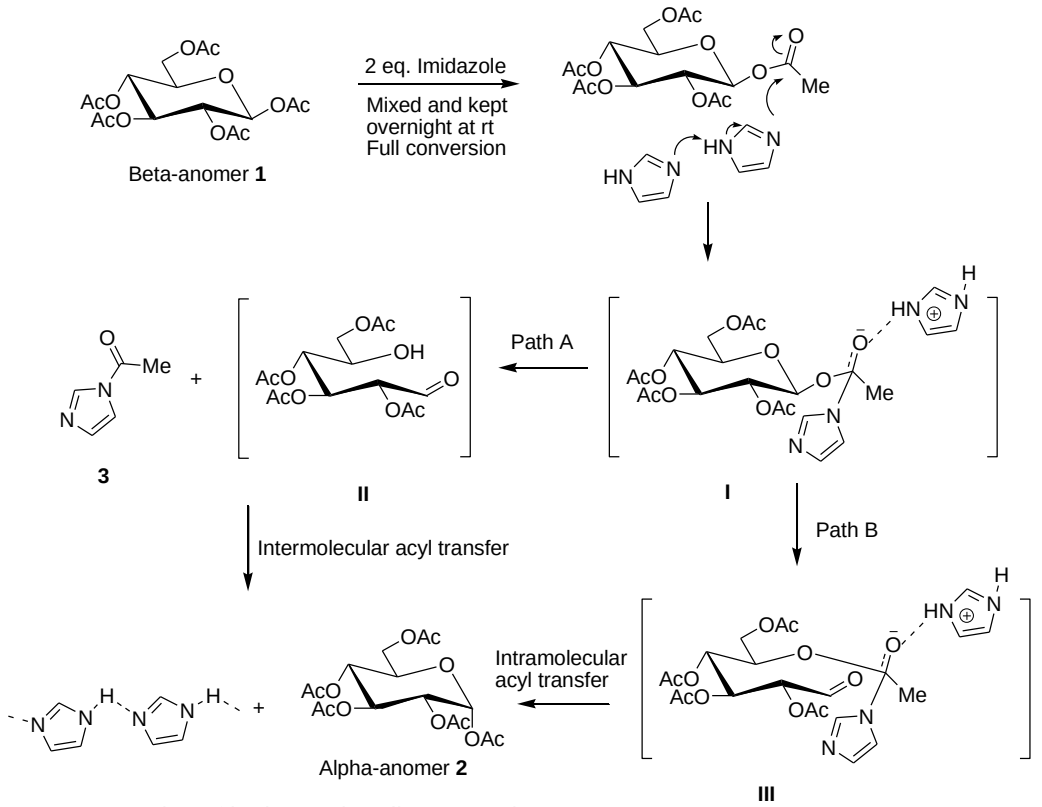
Due to the potential advantages, a further understanding of the mechanism will be of much importance to future exploration of this new type reaction. Replacement of imidazole with 1-butyl imidazole led to no reaction, indicating the necessary role of intermolecular hydrogen bonding network of imidazole because similar intermolecular hydrogen bonding cannot form for N-substituted imidazole due to the lack of hydrogen donor. Evidence that β-D-glucose pentaacetate kept without any change with imidazole hydrogen chloride as a promoter proved the role of free nucleophilic amine part of imidazole. Removal of both imidazole and 4Å MS prohibited anomerization, even after 96 hrs standing in solid state (Entries 1 – 4, **Table 1**), hence it excluded a possibility of slow dissociation in solid state driven by stability difference. Without 4Å MS, anomerization reaction still could proceed albeit in a slower rate (Entries 5 – 7, **Table 1**). In the presence of 1 equivalent imidazole, only 69% conversion was observed even after 96 hrs standing time (Entries 8 – 11, **Table 1**), which indicated 2 equivalents of imidazoles were pretty necessary for an outstanding yield. A parallel study in the presence of light and under dark condition gave the same yield from crude ^{1}H NMR, and this data indicates that the photoanomerization mechanism could be excluded (see SI).

Goldstein proposed an intermolecular acyl transfer catalyzed by an imidazole and a subsequent sugar ring-open reaction, making the dissociation of two anomers possible.[13] A key evidence is the detection of N-acetylimidazole **3** in dilute deuterochloroform solution by NMR[13]. A following comprehensive mechanistic study from Withers' group suggested anion form of intermediate II (**Scheme 1**) could be an active intermediate;[18] and an acetyl pyridinium specie likely plays a key role in pyridine-catalyzed anomerization[19].

However, there are still some facts in our system that could not be well explained by reported mechanism: 1) In our observance, 2 equivalents of imidazoles were quite necessary for a completed anomerization. 2) We observed a full and clean anomerization in optimized condition. Meanwhile quantitative transferring acetyl group from **3** in dilute solution or under heterogeneous system is very challenging and uncommon according to basic physical organic chemistry knowledge. 3) The

Scheme 1. Proposed bisimidazole promoted anomerization mechanism

Bisimidazole promoted anomerization pathways under basic condition.



anomerization in solid state proceeded without mechanomixing or heating, and we are curious what is the driving force.

To better explain key features observed, a bisimidazole promoted mechanism involving two possible pathways via intermolecular or intramolecular acetyl transfer is proposed here (**Scheme 1**). Bisimidazole mechanism involving concerted deprotonation step was proposed before to better explain the need for 2 equivalents imidazoles in the promotion of N-formylation via formyl transfer[20] and peptide cyclization via ester transfer[21]. We envisage that two molecules of imidazole also play concerted roles in the activation of β-D-glucose pentaacetate, one acts as nucleophilic reagent and the another one stabilizes the oxygen atom of carbonyl group of C_1 acetyl moiety as descripted in intermediate **I**. A subsequent release of **3** could lead to the generation of aldehyde intermediate **II**, isomerization of intermediate **II** and a following ring-closed reaction plus an intermolecular acetyl transfer back to C_1 moiety of sugar complete the anomerization forming α-form **2**. This pathway A is a modified version of the reported mechanism proposed by Goldstein and Withers, and this proposed bisimidazole promotion is more energetic feasible[21]. Another possible pathway (Path B) from intermediate **I** is an intramolecular acetyl migration along with imidazoles from oxygen anion on C_1 to that on C_5 (after ring-open reaction), forming intermediate **III**. Although no experimental evidence is available yet, it is theoretically very possible and might be even kinetic favorable than path A because intramolecular functional group transfer is usually more feasible than intermolecular transfer. In fact, acetyl migrations within monosaccharides[22,23] and oligosaccharides[23] were already observed under mild basic conditions; a biomimetic approach to asymmetric acyl transfer catalysis was also developed[24]. Such double intramolecular acetyl transfer away and back to C_1 moiety after isomerization could far more easily lead to a full and clean anomerization forming α-form **2**. The C_1-O_1 bond within "the required 4-membered transition state" would be pulled much longer and simultaneously broke, in other words, the look-like 4-membered transition state is actually a much less hindered 8-membered transition state (after C_1-O_1 bond broke). Reconstruction of the imidazole hydrogen bonding network could be a major driving force to transform intermediate **II** or intermediate **III** to product **2**; imidazole hydrogen bonding networks were known to be the major form in solution[25,26] or solid state[27]. Very recently, NMR evidence of downfield shift for imidazole N-proton[21] and observance of a peculiar behaviour of imidazole during scanning tunnelling microscopy-break junction experiments[28] also indicated the existence of in-situ generated hydrogen bonding network of imidazole. Through the measurement of a $^{2h}J_{NN}$ coupling, Andreas group also confirmed the existence of the imidazole–imidazole hydrogen bonding in the pH-sensing histidine side chains of M2 protein from influenza.[29] Both reaction pathways are competitive in solution or in solid state although path B is more favorable kinetically.

Above mechanism (**Scheme 1**) could also explain the extraordinary reaction performance in solid state with a better tolerance to moisture: 1) all active species are much less mobile in

solid state, which benefits path A; 2) moisture has a much lower chance to interact with intermediates **I**, **II**, **III** and **3**, minimizing hydrolysis side reactions.

In this mechanism imidazole monomer is proposed as an active catalyst; however, in organic solution ($CHCl_3$ or acetone) the dominant form was known to be dimer/trimer of imidazole formed via hydrogen bonding[30,31]. The role of dimer/timer forms in this anomerization cycle is not yet clear, and future investigation on their roles in this reaction will be of much importance to understanding imidazole catalysis at atom level. One of reasonable roles of dimer/trimer is acceleration of reconstruction of hydrogen bonding networks as core units.

In conclusion, an imidazole promoted anomerization of β-D-glucose pentaacetate in solid state was developed. This is the first one in solid state to our best of knowledge. A bisimidazole promoted mechanism involving both intermolecular acetyl transfer and intramolecular acetyl transfer was most probably based on new evidences and reported literatures. In term of many potential advantages such as tolerance to moisture/air, less energy consumption, minimized solvent use possible, highly accessible for green and safer solvents and better solvent recycling potential in future large-scale synthesis, this unprecedent new "mixing and stand" type of solid-state reaction looks promising as a new green and sustainable methodology in organic transformations. The potential driven force of reconstruction of imidazole hydrogen network may be applicable in more organic transformations promoted by imidazole and could inspire more discovery on imidazole-based solid-state transformations in the future.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra for all crudes and all experimental details, materials, and methods, including photographs of crudes with/without 4Å MS and experimental setup.

The Supporting Information is available free of charge on the ACS Publications website.

Supporting information (PDF)

Video of a parallel study (MP4)

AUTHOR INFORMATION

Corresponding Author

Yiqun Li: tlyq@jnu.edu.cn ;
Liuqun Gu: guliuqun@yahoo.com;
ORCID: 0000-0002-4254-6824.

Present Addresses

†Hunan Engineering Technology Research Center for Comprehensive Development and Utilization of Biomass Resources, Hunan University of Science and Engineering, Yongzhou 425199, China.

Author Contributions

L. Gu conceived concept and designed experiments; L. Zhang and M. Wang carried out all experiments, collected data and prepared supporting information. L. Gu and Y. Li co-supervised this project; L. Gu proposed reaction mechanism and drafted this manuscript; both L. Gu and Y. Li edited it. All authors have given approval to the final version of the manuscript.

♀These authors contributed equally.

Notes

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