

A Simple and Clean Method for *O*-Isopropylidene of Carbohydrates

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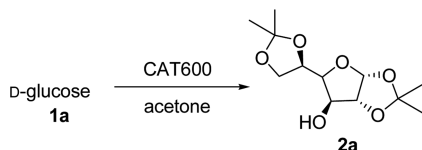
Protection of hydroxyl functions by *O*-isopropylidene is an important method in the field of carbohydrate chemistry. Due to its convenient application in synthetic, configurational and conformational studies,¹ the *O*-isopropylidene derivatives of sugars play an important role in the research of building blocks, such as glycosyl acceptors² and glycosyl donors.³ Additionally, these derivatives of sugars are important in the synthesis of various natural products.^{4,5} For example, 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**2i**) has been utilized for the total synthesis of (+)-7-*epi*-goniofufurone, a potent cytostatic agent.⁶ Similarly, 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (**2a**) is the starting material in the total synthesis of 1-deoxynajirimycin, an α -glucosidase inhibitor for diabetes treatment.⁷ More interestingly, the *O*-isopropylidene derivative of D-glucose is also well known for its antiinflammatory and antipyretic activities with very low toxicity.⁸ In addition, many other di-and/or mono-*O*-isopropylidene derivatives have been used widely in total syntheses of some bioactive macromolecules.⁹ Therefore, studies on these sugar derivatives have continuously attracted interest in recent years, with a strong demand on the development of some green methods for the large-scale preparation of these compounds in industry.

Traditionally, the *O*-isopropylidene derivatives of sugars are synthesized through the reaction of the corresponding sugar and anhydrous acetone in the presence of an acid catalyst such as concentrated H₂SO₄ or anhydrous ZnCl₂.¹⁰ Over the years, many catalysts have been reported for the *O*-isopropylidene of sugars to prepare their *O*-isopropylidene derivatives. The most commonly used catalysts are Lewis acidic metal salts, such as CuSO₄,¹¹ FeCl₃,¹² AlCl₃,¹³ SnCl₂,¹⁴ ceric ammonium nitrate (CAN).¹⁵ Given that most of these catalysts do not produce a satisfactory yield, a series of efficient catalysts have been investigated. As literatures reported, vanadyl triflate (VO(OTf)₂·xH₂O),¹⁶ bromodimethylsulfonium bromide (BDMS),¹⁷ tetrabutylammonium tribromide (TBATB),¹⁸ phosphotungstic acid (PTA),¹⁹ and [Cp*IrCl₂]₂ (Cp* = pentamethylcyclopentadienyl)²⁰ can catalyze the *O*-isopropylidene of sugars with a high yield. However, many of these catalysts need inert atmospheric condition, and bring the environmentally harmful factors in the reaction. In addition, some heterogeneous catalysts, such as Zeolite HY,²¹ montmorillonite clay,²² triphenylphosphine polymer-bound/iodine complex,²³ and sul-

furic acid immobilized on silica gel²⁴ are also applied to this reaction. But most of the reported catalysts require complex preparation, and have one or more disadvantages such as lower catalytic activity, harsh condition requirements, and environmentally hazardous. Hence, a clean, recoverable catalyst is required for simple preparation of these important *O*-isopropylidene derivatives.

With the development of green chemistry, solid catalysts are becoming popular because of their easy separability from products, recoverability, and environmental friendliness. Ion exchange resin as a low-cost heterogeneous catalyst has been used to many significant reactions.^{25,26} Focusing attention on the polystyrene ion exchange resin bearing the sulfonic acid group, Amberlite IR-120 (CAS No. 78922-04-0), was also tested as an effective catalyst for the per-*O*-acetylation of sugars in the early years.²⁷ In our previous study, a commercial macroporous acidic cation exchange resin with a sulfonated polystyrene parent, CAT600, which is an analogue of Amberlite IR-120, was found to be able to catalyze the synthesis of 1,1-diacetate in high yield and short time.²⁸ Herein, it was of interest to clarify whether CAT600 could catalyze the *O*-isopropylidene of sugars, so we applied CAT600 to this reaction for finding a cheap and reusable catalyst. The results are presented in this note.

Initially, the mixture of D-glucose (**1a**, 360 mg, 2 mmol), anhydrous acetone (10 mL) and CAT600 (20 mg) was stirred at 40 °C. Samples were taken at regular intervals (per 1 h) to perform GC analysis and calculate the yield of 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (**2a**). Since the target product was not found until 1 h with a low yield (2%), more amount of catalyst were used in the reaction. As shown in entries 2 to 5 in Table 1, the yield increased from 6% to 11% with increasing the dose of CAT600 from 50 mg to 100 mg, and it did not change even though the dose of CAT600 was added up to 150 mg. Therefore, 100 mg was selected as an optimized dose of CAT600 and was used to further screen other reaction conditions such as reaction time and temperature. As time progressed, the yields presented an increasing trend from 11% at 1 h to 84% at 10 h, and then it stabilized in 84% (entries 4 and 6-8 in Table 1). Thus, a 10 h reaction time was selected to optimize the reaction temperature. When the reaction temperature was to 30 °C, a low yield of 49% (entry 9 in Table 1) was obtained, whereas a yield of 83% was obtained at 50 °C (entry 10 in Table 1). In the other

Table 1. Optimization of the reaction conditions for the *O*-isopropylideneation of D-glucose^a

| Entry | CAT600 (mg) | Reaction time (h) | Temperature (°C) | Yield (%) ^b |
|-------|-------------|-------------------|------------------|------------------------|
| 1 | 20 | 1 | 40 | 2 |
| 2 | 50 | 1 | 40 | 6 |
| 3 | 75 | 1 | 40 | 9 |
| 4 | 100 | 1 | 40 | 11 |
| 5 | 150 | 1 | 40 | 11 |
| 6 | 100 | 9 | 40 | 80 |
| 7 | 100 | 10 | 40 | 84(84 ^c) |
| 8 | 100 | 11 | 40 | 84 |
| 9 | 100 | 10 | 30 | 49 |
| 10 | 100 | 10 | 50 | 83 |
| 11 | - | 10 | 40 | None |

^aReaction condition: D-glucose (2 mmol), acetone (10 mL). ^bDetermined by GC. ^c50 mg of 4 Å molecular sieve was added under the same condition.

hand, the *O*-isopropylideneation of D-glucose is a nucleophilic addition that followed elimination of H₂O, we suspected that adding a dehydration agent to the reaction mixture may lead that the reaction balance lean to products. 4 Å molecular sieve (50 mg) as a dehydration agent herein was added to the mixture under the reaction condition of entry 7. Unfortunately, an increased yield was not obtained. Considering that the high yield of 84% had been achieved, therefore the reaction condition, 2 mmol of sugar, 100 mg of CAT600, 40 °C for 10 h in 10 mL of anhydrous acetone, was selected as an optimized condition. To prove the catalysis effect of CAT600, a blank test was carried out (entry 11 in Table 1). As predicted, the desired product was not found in the absence of CAT600 in the optimized reaction condition.

After optimizing the reaction conditions, D-fructose (**1b**) was used to further verify this catalysis system. We found delightedly that the reaction period of **1b** (1.1 h) is shorter obviously than that of **1a** (10 h). Through a simple purification procedure including filtration, extraction and recrystallization, the product **2b** as a white needle crystal was obtained in a yield of 73%. **2b** was characterized by ¹H NMR and ¹³C NMR, and the spectral data closely matched the reported data.²⁹

To further evaluate this catalysis system, D-glucose (**1a**) and D-fructose (**1b**) were used as substrates respectively in the recycle tests of CAT600. This catalyst was easily separated by filtration after the reaction. And then it was washed several times by acetone, and dried for 30 min at 40 °C for reusing in next reaction. As we can see in Table 2, the recoverability was performed well in the *O*-isopropylideneation of D-glucose and D-fructose. Especially, the yield decreased slightly to 68% from 73% (entries 1-8 in Table 2)

Table 2. Reusability of CAT600 in the *O*-isopropylideneation of D-glucose and D-fructose

| Substrate | No. of run | Reaction time (h) | Yield (%) ^a |
|-------------------------|------------|-------------------|------------------------|
| D-Glucose ^b | 1 | 10 | 84 |
| | 2 | 10 | 81 |
| | 3 | 10 | 74 |
| | 4 | 10 | 65 |
| | 5 | 10 | 52 |
| | 6 | 18 | 46 |
| D-Fructose ^c | 1 | 1.1 | 73 |
| | 2 | 1.1 | 74 |
| | 3 | 1.1 | 70 |
| | 4 | 1.1 | 75 |
| | 5 | 1.1 | 72 |
| | 6 | 1.1 | 70 |
| | 7 | 1.1 | 71 |
| | 8 | 1.1 | 68 |

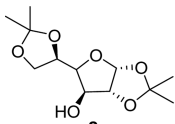
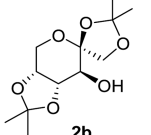
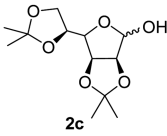
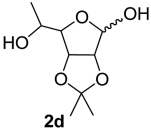
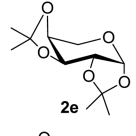
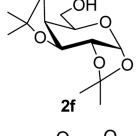
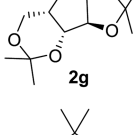
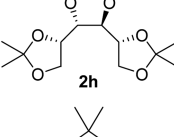
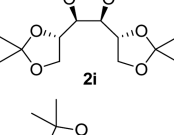
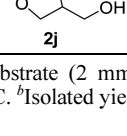
^aThe yield of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2a**) was determined by GC and the yield of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2b**) was from isolation. ^bReaction condition: D-glucose (**1a**) (2 mmol), acetone (10 mL) and CAT600 (100 mg) at 40 °C for 10 h. ^cReaction condition: D-fructose (**1b**) (2 mmol), acetone (10 mL) and CAT600 (100 mg) at 40 °C for 1.1 h.

after the catalyst was reused 8 times in the synthesis of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**2b**). This decline of yield was caused by the loss of CAT600 during recycling. But it was only slightly different in the *O*-isopropylideneation of D-glucose, the yield decreased to 52% from 84% (entries 1-5 in Table 2) after 5 runs. From the outcome of the reactions, we could conclude that the recoverability of CAT600 was dependent on the time of reaction. Since the resin catalyst lived on a certain mechanical strength, it was observed that some CAT600 grains were crushed after a long time stirring. So the shorter the reaction time was, the better the reusability of CAT600 was. It was worth mentioning that the discarded CAT600 can be easily recycled and reactivated by some resin processing plants in a very low cost.

Then a larger scale experiment was conducted with D-fructose (**1b**, 3.6 g, 20 mmol) under the same condition. To our satisfaction, the desired product (**2b**) was obtained in the similar yield, which indicated that this catalysis system was promising to enlarge on a large-scale reaction. To illustrate the generality of our catalysis system, a series of mono-saccharides (**1a-1g**) were used as substrates for the *O*-isopropylideneation (Table 3). All of them achieved corresponding products (**2a-2g**) with high yields from 74%-95% (entries 1-7 in Table 3). Further, we used sugar alcohols (**1h**, **1i**) and glycerin (**1j**) to this system. The *O*-isopropylidene derivatives (**2h-2j**) of them were also gained in good yields within a short reaction time (entries 8-10 in Table 3).

In summary, an efficient catalysis system for the synthesis of *O*-isopropylidene derivatives of sugars and polyhydroxy alcohols has been developed with sulfonated polystyrene cation exchange resin CAT600 as a catalyst. The key advant-

Table 3. Synthesis of *O*-isopropylidene derivatives catalyzed by CAT600^a

| polyhydroxy substrates | | CAT600 | | O-isopropylidene derivatives | |
|------------------------|--------------------------|---|-------------------|------------------------------|------|
| 1a~1j | | dry acetone, 40 °C | | 2a~2j | |
| Entry | Starting material | Product | Reaction time (h) | Yield (%) ^b | Ref. |
| 1 | D-Glucose 1a |  | 10 | 74 | 21 |
| 2 | D-Fructose 1b |  | 1.1 | 73 | 29 |
| 3 | D-Mannose 1c |  | 3 | 89 | 23 |
| 4 | L-Rhamnose 1d |  | 3 | 77 | 17 |
| 5 | L-Arabinose 1e |  | 3 | 95 | 21 |
| 6 | D-Galactose 1f |  | 10 | 74 | 21 |
| 7 | D-Xylose 1g |  | 3 | 85 | 17 |
| 8 | D-Glucitol 1h |  | 3 | 83 | 30 |
| 9 | D-Mannitol 1i |  | 3 | 76 | 30 |
| 10 | Glycerin 1j |  | 1 | 90 | 31 |

^aReaction condition: substrate (2 mmol), CAT600 (100 mg) and dry acetone (10 mL) at 40 °C. ^bIsolated yield.

ages of this protocol are simple workup, good yields and the recoverability, the innocuity and low cost of the catalyst. As a green, general and efficient reaction system, this method is expected to attract much attention for the preparation of

various *O*-isopropylidene sugar derivatives in a large scale.

Experimental Section

General Methods. Sulfonated polystyrene cation exchange resin CAT600 was donated by Xian Electric Power Resin Factory, China. It showed a parameter as the density of SO₃H groups in 4.9-5.1 mmol/g, specific surface area in 35.0-38.5 m²/g, average pore size in 50-100 Å. Unless otherwise stated, other chemicals (AR) were purchased from commercial sources and used without purification. ¹H NMR spectra were recorded using CDCl₃ as a solvent on a Bruker Avance 300 MHz spectrometer (75 MHz for ¹³C NMR). GC analysis was performed on a Shimadzu GC-2010 apparatus equipped with an Rxi-1MS capillary column (30 m × 0.25 mm × 0.25 μm) connected to a hydrogen flame ionization detector. The GC condition was used as follows: a sampling/detector temperature of 250 °C, a column temperature of 190 °C, nitrogen as carrier gas, nitrogen pressure 100 kPa, total flow rate: 50 mL/min, hydrogen flow rate: 40 mL/min, air flow rate: 400 mL/min. The temperature programme: 190 °C for 3 min, then rose to 250 °C with the rate 10 °C/min, finally held at 250 °C for 1 min.

General Procedure for the *O*-Isopropylideneation. To a suspension of the substrate (2 mmol) in dry acetone (10 mL), CAT600 (100 mg) was added. Then the mixture was stirred at 40 °C till the TLC (*n*-hexane-EtOAc 2:1) showed the completion of the reaction. The catalyst was separated by filtration, washed with acetone, dried, and reused for a consecutive run under the same reaction conditions. The filtrate was condensed to dry in vacuum, and the residue was dissolved in CH₂Cl₂ (10 mL) and washed with 3 × 5 mL brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to afford the crude product. Then the desired pure product was obtained by recrystallization from *n*-hexane. While, the silica gel column chromatography was used if the product existed in the liquid form.

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