Solvent Polarity-Controlled Selective Synthesis of Methyl Pyranoside and Furanoside

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Supporting Information

ABSTRACT: A selective synthesis of methyl D-glucopyranoside or furanoside has been developed using 2,4,6-trichloro-1,3,5-triazine (TCT)-activated DMSO and D-glucose in methanol. At higher concentrations of DMSO, only pyranoside was formed and at lower concentrations of DMSO, only furanoside was formed. This method was also successfully applied to other sugars. In terms of reaction rates, selectivities, and yields, this method is better than most of the currently used methods.

KEYWORDS: sugar, glycosylation, DMSO, TCT, selective synthesis

INTRODUCTION

Methyl pyranoside and furanoside are basic starting materials in carbohydrate chemistry and in the development of new sweetener candidates. The Fischer reaction, which is catalyzed by protons and Lewis acids and mediated by methanol, is commonly employed to prepare methyl glycosides. These reactions require prolonged reaction times and give fair to good yields. Methyl furanosides are a kinetic product and not commercially available. Their preparative methods include the synthesis using ethyl dimethoxyborane, iodine-promoted glycosylation, synthesis using ethyl dimethoxyborane, and FeCl₃-promoted glycosylation. In these reactions, a multistep synthesis is required or else the formation of the side product methyl pyranoside is unavoidable. The separation of furanoside from its isomer pyranoside is tedious, and thus the preparation of these compounds would be much easier if the furanoside to pyranoside ratio could be increased or if only one of the products could be selectively synthesized. Herein, a selective synthesis for pyranoside or furanoside in excellent yield via tuning the ratio of MeOH/DMSO/2,4,6-trichloro-1,3,5-triazine (TCT) is described.

MATERIALS AND METHODS

General Experimental Information. All of the chemicals were obtained from commercial sources. The ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III spectrometer (600 and 150 MHz, respectively), using tetramethylsilane (TMS) as the internal standard (δ = 0).

General Procedure for the Preparation of Methyl D-Glucopyranoside (2). The procedure for the methylation of D-glucose (Table 1, entry 2) is representative for all conditions of entries 1, 3, and 4. To a solution of D-glucose (1, 300 mg, 1.0 equiv) and anhydrous DMSO (4 mL, 34 equiv) in anhydrous MeOH (2 mL) was added TCT (615 mg, 2.0 equiv) slowly over 0.5 h. The mixture was stirred at 25 °C, and the reaction was monitored by thin layer chromatography (TLC) until completion (0.5 h). Then, Na₂CO₃ (795 mg, 7.5 mmol) was added to the mixture and vigorously stirred for 0.5 h. Concentration under reduced pressure gave the crude product, which was then purified by silica gel chromatography (CH₂Cl₂/CH₃OH, 20:1) to afford 2 (298 mg, 92%, 2α/2β = 53/47) as a colorless syrup.

Methyl α-D-glucopyranoside (2α): ¹H NMR (600 MHz, D₂O) δ 4.81 (1H, d), 3.56 (1H, dd), 3.66 (1H, dd), 3.40 (1H, dd), 3.64 (1H, ddd), 3.87 (1H, dd), 3.75 (1H, dd), 3.53 (s, 3H); ¹³C NMR (150 MHz, D₂O) δ 99.20, 75.70, 71.51, 69.59, 60.50, 54.95.

Methyl β-D-glucopyranoside (2β): ¹H NMR (600 MHz, D₂O) δ 4.34 (1H, d), 3.25 (1H, dd), 3.48 (1H, dd), 3.36 (1H, dd), 3.45 (1H, ddd), 3.91 (1H, dd), 3.71 (1H, dd), 3.38 (s, 3H); ¹³C NMR (150 MHz, D₂O) δ 103.18, 75.86, 73.03, 71.16, 69.59, 60.50, 57.14.

General Procedure for the Preparation of Methyl D-Glucofuranoside (3). The procedure for the methylation of D-glucose (Table 1, entry 9) is representative for conditions of entry 10. To a solution of D-glucose (1, 300 mg, 1.0 equiv) and TCT (615 mg, 2.0 equiv) in anhydrous MeOH (5 mL) was added anhydrous DMSO (195 mg, 1.5 equiv) in anhydrous MeOH (10 mL) slowly over 0.5 h. The mixture was stirred at 25 °C, and the reaction was monitored by TLC until completion (0.5 h). Then, Na₂CO₃ (795 mg, 7.5 mmol) was added to the mixture and vigorously stirred for 0.5 h. Concentration under reduced pressure gave the crude product, which was then purified by silica gel chromatography (CH₂Cl₂/CH₃OH, 20:1) to afford 3 (315 mg, 97%, 3α/3β = 62:38) as a colorless syrup.

Methyl α-D-glucofuranoside (3α): ¹H NMR (600 MHz, D₂O) δ 5.03 (1H, d), 4.12 (1H, dd), 4.23 (1H, dd), 4.07 (1H, dd), 3.82 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, dd), 3.40 (s, 3H); ¹³C NMR (150 MHz, D₂O) δ 103.08, 79.45, 76.58, 74.65, 63.07, 55.11.

Methyl β-D-glucofuranoside (3β): ¹H NMR (600 MHz, D₂O) δ 4.83 (1H, d), 4.08 (1H, dd), 4.09 (1H, dd), 4.01 (1H, dd), 3.83 (1H, ddd), 3.56 (1H, dd), 3.74 (1H, dd), 3.31 (s, 3H); ¹³C NMR (150 MHz, D₂O) δ 109.00, 81.24, 77.73, 75.57, 69.56, 63.52, 55.90.

RESULTS AND DISCUSSION

In our previous research, a TCT-activated DMSO system was utilized in the conversion of benzyl alcohols to benzyl chloride and to benzyl ethers. It is speculated that the TCT-activated DMSO system could similarly catalyze the reaction between the carbohydrate anomeric hydroxyl group and an alcohol to form glycosides. Therefore, D-glucose was treated with 1.5 or 2.0 equiv of TCT in various ratios of DMSO to MeOH, and the results are summarized in Table 1. When the concentration of DMSO was 17 or 8.5 equiv/mL, pyranoside was synthesized in close to...
quantitative yield, and the $\alpha$ and $\beta$ isomers were about equally formed (Table 1, entries 1−4). Reducing the concentrations of DMSO to 4.3 or 1.7 equiv/mL resulted in an increase in the amounts of furanoside $3$ to 22, 16, 43, or 42% (Table 1, entries 5−8). Further decreasing the concentration of DMSO to 0.1 equiv/mL led to the formation of furanoside in nearly quantitative yields (Table 1, entries 9 and 10). When the amount of TCT was changed from 1.5 to 2.0 equiv, the $\alpha/\beta$ ratio changed from 62:38 to 43:57. The reaction time for the pyranoside was 6 h, and that for furanoside was 0.5 h.

After the above optimization, the yields for both methyl $\alpha$-glucopyranoside $2$ and $\alpha$-glucofuranoside $3$ were nearly quantitative. The reaction yield of acetone and sugar for $1,2;5,6$-di-isopropylidene-$\alpha$-$\beta$-glucopyranoside is $>90\%$. For the other currently used preparation methods, the highest reported yields for $\alpha$-glucopyranoside are all $<80\%$, and these products have to be separated from their isomer glucopyranoside (produced in $>20\%$ yield). The reason that $2$ and $3$ can be separately synthesized as the sole product with this method is probably because methanol is more polar than DMSO, and presumably when the concentration of DMSO in methanol is lower, the reaction medium is more polar and the $\alpha$-glucose exists in the furanose form. In contrast, when the concentration of DMSO is higher, $\alpha$-glucose exists in the pyranose form.

To validate this assumption, $^{13}$C NMR analysis of the $\alpha$-glucose in $3$, 17, and 170 equiv of DMSO-$d_6$ in CD$_3$OD was performed. With 170 equiv of DMSO-$d_6$, the $^{13}$C NMR spectrum revealed two hemiacetal isomers in a 13:87 ratio (Table 2, entry 2). After the addition of 0.1 equiv of TCT, only $\alpha$-$\beta$-glucopyranoside existed. No detectable amounts of methyl glucoside were formed within 15 min (Table 2, entry 3). With 3 equiv of DMSO-$d_6$, the $^{13}$C NMR spectrum showed two hemiacetal isomers in a 10:90 ratio (Table 2, entry 4). Five minutes after the addition of 0.1 equiv of TCT, there were two isomers and methyl $\alpha$-$\beta$-glucopyranoside in a 7:59:34 ratio (methyl $\alpha$-$\beta$-glucopyranoside, $\beta$-$\alpha$-glucopyranoside, $\alpha$-$\alpha$-glucopyranoside; Table 2, entry 5). This agrees with the fact that the formation rate of furanoside is higher than that of pyranoside.

With 17 equiv of DMSO-$d_6$, the $^{13}$C NMR spectrum indicated the existence of four hemiacetal in a 3:8:31:58 ratio.
Table 2. $^{13}$C NMR Analysis of $\alpha$-Glucose Isomers at Difference Concentration of DMSO-$d_6$ in CD$_3$OD at 25 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>concn$^a$</th>
<th>no. of major isomers</th>
<th>$C_\alpha$ (ppm) (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>340</td>
<td>2</td>
<td>92.15, 92.05 (38:62)</td>
</tr>
<tr>
<td>2</td>
<td>170</td>
<td>1</td>
<td>92.12, 92.02 (13:87)</td>
</tr>
<tr>
<td>3</td>
<td>170 + TCT$^b$</td>
<td>1</td>
<td>92.04</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1</td>
<td>95.51, 91.25 (10:90)</td>
</tr>
<tr>
<td>5</td>
<td>3 + TCT$^b$</td>
<td>2</td>
<td>99.49, 91.27, 91.23 (7:59:34)$^c$</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>1</td>
<td>94.00</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>2</td>
<td>95.56, 95.48, 91.31, 91.32 (3:8:31:58)$^d$</td>
</tr>
<tr>
<td>8</td>
<td>17 + TCT$^b$</td>
<td>2</td>
<td>94.88, 91.24 (53:47)</td>
</tr>
</tbody>
</table>

$^a$Conc, concentration of DMSO-$d_6$ in CD$_3$OD (equiv/mL). $^b$TCT = 0.1 equiv. Methyl $\alpha$-$\beta$-glucopyranoside/$\alpha$-$\beta$-glucofuranoside; Table 2, entry 7). These are probably the four possible isomers of $\alpha$-glucose. Five minutes after the addition of 0.1 equiv of TCT, there are two major isomers in a S3:47 ratio (Table 2, entry 8). This is in agreement with the fact that methyl pyranose and furanose were formed in roughly the same amounts (Table 1, entries 7 and 8). The isomer numbers indicated by the $^{13}$C NMR analysis with 170, 17, and 3 equiv of DMSO-$d_6$ correlate well with the major product numbers from Table 1, entries 1, 2, and 7—10. Further increasing the concentration of DMSO-$d_6$ in CD$_3$OD to 340 equiv exhibited $^{13}$C NMR signals of two isomers and decreasing that to 1.5 equiv exhibited $^{13}$C NMR signals of one isomer. This again indicates that the equilibrium between pyranose and furanose is related to the solvent ratio (Table 2, entries 1 and 6). A literature survey indicates that the NMR analysis of $\delta$-glucopyranose could be performed in D$_2$O.$^{22-26}$ dioxane-$d_6$.$^{27}$ and DMSO-$d_6$.$^{28}$ and that for $\delta$-glucopyranose in D$_2$O.$^{29,30}$ It is known that $\delta$-glucopyranose is dominant in aqueous solution.$^{31,32}$

To further verify the assumption that the ratio of pyranose to furanose is controlled by the polarities of the solvents, other alcohols were used in place of methanol as the solvent. For the ethylation of glucose, 8.5, 17, and 25.5 equiv of DMSO in EtOH were used as 0.1 equiv of DMSO in EtOH resulted in a poor yield. As expected, the $\delta$-glucopyranoses of the other alcohols were readily obtained as the sole product (Table 3, entries 1—12). However, the $\delta$-glucopyranoses could not be synthesized as the sole product. The proportions of the $\delta$-glucopyranoses decreased from 10% to 0% as the acceptor alcohols increased in carbon number from ethanol to $\delta$-pentanol with 1.7 equiv of DMSO (Table 3, entries 3, 6, 9, and 12). These results indicate that the solvent polarity is critical to the ratio of furanose and pyranose because all of these higher alcohols are less polar than methanol. Alkyl furanoses have been synthesized as the major products in solvents less polar than methanol, which has been attributed to metal complexation with the sugars because these glycosylation are often catalyzed by metal salts.$^{20}$$^{20}$

A plausible mechanism for the synthesis of methyl $\delta$-glucopyranoside is shown in Figure 1. First, the reaction of DMSO with TCT leads to I, which is attacked by the C-1 hydroxyl group of $\delta$-glucopyranose to form II. Because DMSO is a good leaving group, the DMSO group may then be replaced by MeOH to form methyl $\delta$-glucopyranoside via an $S_N$2 mechanism. Another possibility is the formation of carboxylation III from II and the attack of MeOH on the C-1 leading to methyl $\delta$-glucopyranoside via an $S_N$1 mechanism. Because only the C-1 carbon has a methoxy substituent, carboxylation III pathway is more likely. A similar mechanism is applicable to the formation of methyl $\alpha$-glucopyranoside.

The reaction conditions developed here were then applied to other carbohydrates, and the results are shown in Table 4. When $\delta$-fructose was treated with TCT (2.0 equiv) in 8.5 equiv/mL of DMSO in MeOH, no products formed after 6 h (Table 4, entry 1). Reducing the amount of DMSO to 0.1 equiv/mL (Table 4, entry 2) yielded a mixture of methyl $\delta$-fructopyranoside 6a and methyl $\delta$-fructofuranoside 6b (6a:6b = 73:27, Table 4, entry 2) in 82% yield. Increasing the reaction time from 6 to 24 h gave a higher yield (96%) and a similar product mixture (6a:6b = 68:32, Table 4, entry 3). When the concentration of DMSO was reduced to 0.07 equiv/mL, furanoside 6b became the major product (Table 4, entry 4). In these experiments, neither furanose nor pyranose could be produced as the sole product, but each could be produced as the major product by adjusting the concentration of DMSO in MeOH. The literature reports three methods for the preparation of methyl $\delta$-fructoses: an $I_2$/MeOH method (unspeciﬁed ratio of furanose and pyranose, 3 h, 61.5% yield),$^{33}$ a TsOH/MeOH method (furanoside, 12 h, 80% yield),$^{34}$ and an AcCl/MeOH method (furanoside::pyranose = 3:1, 16 h, 92% yield).$^{35}$ Our results compare favorably with these results in terms of yields and furanose and pyranose selectivities.

$\delta$-Mannose could not be transformed into the furanose even by changing the concentration of DMSO from 4.3 to 0.07 equiv/mL (Table 4, entries 5—7). This is probably because it has a C-2 axial OH and the MeOH/DMSO system cannot stabilize the $\delta$-mannofuranose. Methyl $\alpha$-$\beta$-mannopyranoside was the major product in 91% yield with 0.1 equiv/mL of DMSO in MeOH and TCT (2.0 equiv) (Table 4, entry 7). This result is better than previously reported methods: HCl/MeOH (pyranoside, 2 h, 70% yield)$^{36}$ and Amberlite IRA-120/MeOH (pyranoside, 10 min, 74% yield).$^{37}$

Treating $\delta$-arabinose with TCT (2.0 equiv) and 8.5 equiv/mL of DMSO led to only a 40% yield of pyranoside and furanoside (8a:8b = 90:10, Table 4, entry 8). When the reactions of $\delta$-arabinose with 0.1 or 0.07 equiv/mL of DMSO in MeOH were quenched after 1 h, furanoside was the major product in 73 and 97% yields, respectively (Table 4, entries 9 and 11). The pyranose was the major product (80:20) when the reaction time was increased from 1 to 24 h (Table 4, entry 10). This method is better than the current methods in terms of yield and reaction rates. These current methods are 1% HCl/MeOH/Ag$_2$CO$_3$ (pyranoside, 24 h, no yield reported),$^{37}$ Amberlite IRA-120/MeOH (pyranoside, 12 h, 37% yield),$^{38}$ and 0.18N HCl/MeOH (furanoside, 5.5 h, 79% yield).$^{39}$

Treating $\delta$-xylose with different concentrations of DMSO in MeOH and TCT (2.0 equiv) led to a selective synthesis of methyl $\delta$-xylofuranoside (Table 4, entries 12—15). With 8.5 equiv/mL of DMSO in MeOH, the yield was poor (Table 4, entry 12). Lowering the concentration of DMSO (0.07 equiv, Table 4, entry 13) and increasing the reaction time (24 h,}
Table 4, entry 14) improved the yield to >80%. The optimized conditions were 0.1 equiv of DMSO in MeOH, 2.0 equiv of TCT in 1 h, and the furanoside was selectively synthesized in 93% total yield (pyranoside/furanoside = 7:93, Table 4, entry 15). The reaction rate of this reaction is higher than that of the known methods. The known methods are MeOH/HCl/CaCO3 (furanoside, 12 h, quantitative),40 Amberlite IRA-120/MeOH (pyranoside, 12 h, 53% yield),38 and montmorillonite K-10 (pyranoside, 10 min, 87% yield).41

Methyl D-galactofuranoside could be obtained in 85% yield and methyl D-galactopyranoside in 80% yield by reacting D-galactose with TCT (2.0 equiv) and 0.1 or 8.5 equiv/mL of DMSO in MeOH (Table 4, entries 16 and 17). It is clear that the ratio of pyranoside to furanoside is controlled by the solvent polarities as in the case of methyl D-glucoside synthesis. In the above selective synthesis of methyl D-galactofuranoside, the ratio of furanoside to pyranoside was 93:7 in the crude product. The reported yields of methyl D-galactopyranoside synthesized using microwave irradiation are 100%42 and 84%.41 Two methods for the synthesis of methyl D-galactofuranoside as a major product catalyzed by FeCl3 (furanoside:pyranoside = 75:20)20 and in 75% yield are known.12 Our method has better selectivity for furanoside.

In summary, a highly selective method to synthesize methyl D-glucoside or pyranoside as the sole product via tuning the polarity of the solvent has been developed. The effect of the solvent polarity on the isomerization of D-glucose is supported by 13C NMR analysis.
system are better than the currently used methods. This is a rapid, convenient, and high-yielding procedure.

**ASSOCIATED CONTENT**

Supporting Information

Glycosylation procedures of six sugars and $^{13}$C NMR spectra of D-glucose at different concentrations of DMSO-$d_6$ in CD$_3$OD at 25 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

REFERENCES


