C-Aryl Glycosylation via Interrupted Pummerer Rearrangement

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Abstract

C-aryl glycosides are an important kind of carbohydrate derivatives for drug discovery, due to their distinctive attributes of resistance to hydrolysis from enzymes. Herein, C-aryl glycosylation was established for the synthesis of 2-sulfur C-aryl glycals and 1,2-dihydrobenzofuran-fused C-aryl glycosides via interrupted Pummerer process, featured with sulfonium-tethered [3,3]-sigmatropic rearrangement between sulfoxide glycals and phenols. This protocol offers a broad substrate scope with diverse glycosyl and phenols. Dapagliflozin, Empagliflozin, and Ipragliflozin analogs were straightforward achieved, respectively.

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C-Aryl Glycosylation via Interrupted Pummerer Rearrangement

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In memory of Prof. Xiyan Lu

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Keywords

Glycal; Glycosylation; Interrupted Pummerer; Rearrangement; Sulfoxide

Comprehensive Summary

C-aryl glycosides are an important kind of carbohydrate derivatives for drug discovery, due to their distinctive attributes of resistance to hydrolysis from enzymes. Herein, C-aryl glycosylation was established for the synthesis of 2-sulfur C-aryl glycals and 1,2-dihydrobenzofuran-fused C-aryl glycosides via interrupted Pummerer process, featured with sulfonium-tethered [3,3]-sigmatropic rearrangement between sulfoxide glycals and phenols. This protocol offers a broad substrate scope with diverse glycosyl and phenols. Dapagliflozin, Empagliflozin, and Ipragliflozin analogs were straightforward achieved, respectively.

Background and Originality Content

C-aryl glycosides, possessing an aryl moiety on the anomeric carbon, are extensively existed in natural products and pharmaceuticals (Fig. 1a). Superior biological activity with resistance to metabolic degradation sparked C-aryl glycosides increasing interest in modern drug discovery. Puerarin is a well-known anti-inflammatory agent, which has been demonstrated as 5-HT2C receptor antagonist.¹ Gliflozin, a series of C-aryl glycoside drugs, are inhibitors of sodium-glucose co-transporter 1 and 2 (SGLT1 and SGLT2), serving for type 1 and type 2 diabetes therapy.² 1,2-Dihydrobenzofuran-fused C-aryl glycosides, Chafurosides A and B, originating from oolong tea, are potent DNFB inhibitors displaying suppressive effect on type I and IV anaphylaxis.³ Therefore, the protocol are highly desirable for the synthesis of C-aryl glycosides. The representative route for C-aryl glycoside construction is nucleophilic substitution from arylmetal species to-
ward glycosyl electrophiles, such as arylzincates\textsuperscript{4-6}, arylaluminates\textsuperscript{7-9} and Grignard reagents\textsuperscript{10-11}. Pummerer rearrangement\textsuperscript{12} is a powerful reaction, featured with sulfonium-tethered [3,3]-sigmatropic rearrangement, offering efficient construction of carbon-carbon bonds without transition metal catalysis,\textsuperscript{13-18} enabling functionalization at β position of sulfinyl group (\textbf{Fig. 1b}). Base on our research of glycal,\textsuperscript{20} C-aryl glycosides and 1,2-dihydrobenzofuran-fused C-aryl glycosides herein were constructed via interrupted Pummerer process between sulfoxide glycals and phenols (\textbf{Fig. 1c}).

**Figure 1** a Significant C-aryl glycosides b Traditional synthesis of C-aryl glycosides c The strategy of C-aryl glycosides via interrupted Pummerer.

**Results and Discussion**

Results

First, 2-alkyl/aryl sulfide glycals were established with the reaction of 3,4,6-tri-O-benzyl-D-glucal (1\textsuperscript{A}) and electrophilic sulfur reagents (details in supporting information),\textsuperscript{21} in which 2-sulfoxide glycals (1\textsuperscript{a}) precursor was achieved with further oxidation from 2-alkyl sulfide glycals (1\textsuperscript{B}).\textsuperscript{22} The desired C-aryl glycoside\textsuperscript{3} can be obtained in a 19% yield with the assistance of trifluoroacetic anhydride (TFAA) (\textbf{entry 1, Table 1}). Other activating reagents, such as trifluoromethanesulfonic anhydride (Tf\textsubscript{2}O), trimethylsilyl trifluoromethanesulfonate (TMSOTf), acetic anhydride (Ac\textsubscript{2}O), and chlorotrimethylsilane (TMSCl) could not achieve the desired product, revealing the critical role of the activating reagents for sulfoxide (\textbf{entries 2-5, Table 1}). The yield of rearrangement product\textsuperscript{3} was 34% after increasing the amount of TFAA to 3 equivalents (\textbf{entry 6, Table 1}). MeNO\textsubscript{2} is the best solvent among alternative solvents such as MeCN, CHCl\textsubscript{3}, DCE, and acetone (\textbf{entries 7-11, Table 1}). The desired product\textsuperscript{3} was obtained in a yield of 57%, when performed at 0°C (\textbf{entry 12, Table 1}). 73% and 81% desired rearrangement were afforded respectively, when p-cresol (2\textsuperscript{b}) and 4-ethyl phenol (2\textsuperscript{c}) were applied. (\textbf{entries 13-14, Table 1}). Notably, 87% of 1,2-dihydrobenzofuran-fused C-aryl glycoside\textsuperscript{9} was achieved in a diastereomeric ratio of α:β = 2:1 with 2,6-lutidine addition (\textbf{entry 15, Table 1}).

**Table 1** Optimization for C-aryl glycoside

<table>
<thead>
<tr>
<th>Enter</th>
<th>Additive</th>
<th>Solvent (0.1 M)</th>
<th>3\textsuperscript{a}</th>
<th>9a</th>
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</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>TFAA</td>
<td>DCM</td>
<td>19</td>
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<tr>
<td>2</td>
<td>Tf\textsubscript{2}O</td>
<td>DCM</td>
<td>N/A</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ac\textsubscript{2}O</td>
<td>DCM</td>
<td>N/R</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>TMSCl</td>
<td>DCM</td>
<td>N/R</td>
<td>-</td>
</tr>
<tr>
<td>6\textsuperscript{b}</td>
<td>TFAA</td>
<td>DCM</td>
<td>34</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>TFAA</td>
<td>MeNO\textsubscript{2}</td>
<td>53</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>TFAA</td>
<td>MeCN</td>
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<td>TFAA</td>
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<td>0</td>
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<td>-</td>
</tr>
<tr>
<td>11</td>
<td>TFAA</td>
<td>DCE</td>
<td>42</td>
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</tr>
<tr>
<td>12\textsuperscript{c}</td>
<td>TFAA</td>
<td>MeNO\textsubscript{2}</td>
<td>57</td>
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<td>TFAA</td>
<td>MeNO\textsubscript{2}</td>
<td>73(3b)</td>
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<tr>
<td>14\textsuperscript{e}</td>
<td>TFAA</td>
<td>MeNO\textsubscript{2}</td>
<td>81(3c)</td>
<td>-</td>
</tr>
<tr>
<td>15\textsuperscript{f}</td>
<td>TFAA</td>
<td>DCM</td>
<td>-</td>
<td>87(α:β = 2:1)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1\textsuperscript{a} (0.05 mmol) and 2\textsuperscript{a} (1.5 equiv.), TFAA (1.5 equiv.), DCM (0.1 M), 25 °C, 30 min. \textsuperscript{b} TFAA (3.0 equiv.)\textsuperscript{c} 0 °C. \textsuperscript{d} 2\textsuperscript{b} (1.5 equiv.). \textsuperscript{e} 2\textsuperscript{c} (1.5 equiv.). \textsuperscript{f} 2,6-Lutidine (3 equiv.) was added. Yields determined by \textsuperscript{1}H NMR analysis with internal standard CH\textsubscript{2}Br\textsubscript{2}. α:β ratio was determined by \textsuperscript{1}H NMR.

With the optimized conditions established, we proceeded to investigate the substrate scope of phenol for the
The nucleophilicity of intermediate furnishes product through an intramolecular nucleophilic substitution at the cationic sulfur center with phenol, yielding 1,2-dihydrobenzofuran-fused C-aryl glycosides in moderate to good yields. Notably, even glycals containing long-chain alkyl-dodecyl and vinyl were well compatible. Additionally, ortho-substituted phenols, including methyl and halogen substituents, were also great candidates. Several drug analogues, including Ipragliflozin, Empagliflozin, and Dapagliflozin, were straightforward achieved through this protocol.

The investigation entailed an extensive study of glycals within the purview of Scheme 1. The substrates encompassed derivatives from glucose (6a and 6d-6j), rhamnose (6b), and xylose (6c). Notably, the reaction conditions exhibited excellent tolerance towards both alkyl ether and acetyl protecting groups. Remarkably, even glycals containing long-chain alkyl-dodecyl (6a and 6d-6j) demonstrated remarkable efficacy as reaction partners, resulting in the formation of aryl glycosides in good yields.

Upon the addition of 2,6-lutidine to the reaction system, 1,2-dihydrobenzofuran-fused C-aryl glycosides were observed. These glycosides, which have been isolated from natural products and exhibit significant biological activity (as depicted in Fig. 1), are limited in their synthetic literature. The substrate scope of phenols was explored as illustrated in Scheme 1, and a wide range of phenol derivatives proved compatibility for this reaction. Notably, the reaction proceeded smoothly regardless of the presence of electron-donating or electron-withdrawing groups as substituents on the phenol ring (9a-9g), yielding 1,2-dihydrobenzofuran-fused C-aryl glycosides in moderate to good yields. The reaction was favorable for para-substituted phenols, such as gem-dimethyl (9h), benzene (9s), and 4-bromobenzene (9t). Furthermore, ortho-substituted phenols, including methyl and halogen substituents, were also well-tolerated (9i-9l). Meta-substituted phenols afforded the desired product in yields of 61–63% (9m-9o). Notably, disubstituted phenols, such as 9m-9o, were also found to be good partner. Several drug analogues, including Ipragliflozin, Empagliflozin, and Dapagliflozin, were straightforward achieved through this protocol (9u-9w).

Scheme 1 Scope of C-Glycosylation with glycal

Reaction conditions: TFAA (3.0 equiv.) was added to a mixture of 1/4 (0.2 mmol) and 2/5/8 (1.5 equiv.) in MeNO₂ (0.1 M) at 0 °C and stirred for 8-24 h. a) stirred at -10 °C for 24 h. b) 2,6-Lutidine (3 equiv.) was added. c) 2,6-Lutidine (3 equiv.) was added in DCM (0.1 M).

Dapagliflozin, a potent and metabolically stable SGLT2 inhibitor, is selective, but its usage carries the risk of hypoglycemia and weight loss. By replacing the initial oxygen of dapagliflozin with sulfur, the adverse effects of hypoglycemia and weight loss can be nullified. Sotagliflozin is an inhibitor of both SGLT1 and SGLT2, and its oxygen at position one can be substituted with sulfur. Under our reaction conditions, we achieved 11a (68%), 11b (72%), and 11c (69%), demonstrating the feasibility of the protocol. Scale-up preparation of 11c further shown the practicability. Interestingly, when the sulfide carbohydrate (11c) was oxidized to sulfone, 13c was achieved with the help of potassium hydroxide via an intramolecular nucleophilic reaction. The structure of 13c was further confirmed through X-ray analysis.

Scheme 2 Synthesis of drug analogs

Reaction conditions: 1 (0.2 mmol) and 10 (1.5 equiv.), TFAA (3.0 equiv.), MeNO₂ (0.1 M), 0°C, 8-24 h. a) 1) m-CPBA, CH₂Cl₂, 0 °C, 2 h; 2) KOH, THF, 60 °C, 5 h, 85% (2 steps for 13c).

A plausible mechanism is shown in Fig. 2. Activation of the 2-alkyl sulfoxide glycals 1 followed by nucleophilic substitution at the cationic sulfur center with phenol 2 formed intermediate I-B, which underwent a regiocontrolled C-C bond formation through a temporarily sulfonium-tethered intramolecular process. Without 2,6-lutidine, rearratization of I-C furnishes product 3. While with 2,6-lutidine, the enhanced nucleophilicity of intermediate I-D led to the formation of product 9 through an intramolecular nucleophilic reaction.
addition to thioonium.

**Figure 2** Plausible mechanism.

Conclusions

In summary, we have developed a straightforward protocol for the divergent synthesis of C-aryl glycosides and 1,2-dihydrobenzofuran-fused C-aryl glycosides, utilizing an interrupted Pummerer reaction followed by a sultonium-tethered [3,3]-sigmatropic rearrangement with glycals sulfoxides and phenols. These reactions are characterized by their employment of widely available starting materials and reagents, mild reaction conditions, and remarkable tolerance towards a diverse range of functional groups, which afford an efficient C-aryl glycoside library for drug discovery. Further pharmaceutic exploration is undergoing in our laboratory.

Experimental

**General procedures for the synthesis of products 11c in Gram scale**

To a solution of 1 (1.46 g, 3.0 mmol, 1 equiv.) in MeNO₂ (0.1M) was added 10c (1.18 g, 4.5 mmol, 1.5 equiv.) and TFAA (1.25 mL, 9.0 mmol, 3.0 equiv.) at 0°C. The reaction mixture was stirred for 16 h. After the reaction was completed (monitored by TLC), the mixture was quenched with NaHCO₃ (sat. aq.) and extracted with DCM (three times), the combined organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (PE/EA=1:0 to 10:1) affording product 11c (1.39 g, 63%) as a pale-yellow oil.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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References


22. 1 was synthesized from C through the oxidation of m -CPBA: To a solution of C in DCM (1 g/10 mL) was added m -CPBA (1.1 equiv.) at -40 °C and stirred for 20 min at -40 °C. After the reaction was completed, the mixture was quenched with NaHCO₃ (sat. aq.) and extracted with DCM (three times). The combined organic layer was dried over Na₂SO₄, concentrated to dryness and purified by column.
chromatography (PE/EA=1:0 to 1:1) to afford the desired product in 65-91 % yields (PE/EA=3:1, Rf = 0.3). See Supporting Information for details.


The Authors

After acceptance, please insert a group photo of the authors taken recently.

**Left to Right:** Authors Names

Entry for the Table of Contents

*C-Aryl Glycosylation via Interrupted Pummerer Rearrangement* Jiagen Li, a and Xuefeng Jiang,* a, b, c *Chin. J. Chem.* 2023, xxx-xxx.

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