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 phe-nols. 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

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 morden 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 cotransporter 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[4-6], arylaluminates[7-9] and Grignard reagents[10-11]. Pummerer rearrangement[12] is a powerful reaction, featured with sulfonium-tethered [3,3]-sigmatropic rearrangement, offering efficient construction of carbon-carbon bonds without transition metal catalysis,[13-18] enabling functionalization at βposition of sulfinyl group (**Fig. 1b)**.[19] Base on our research of glycal,[20] *C*-aryl glycosides and 1,2-dihydrobenzofuran-fused *C*-aryl glycosides herein were constructed via interrupted Pummerer process between sulfoxide glycals and phenols (**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**A**) and electrophilic sulfur reagents (details in supporting information),[21]in which 2-sulfoxide glycals (**1a**) precursor was achieved with further oxidation from 2-alkyl sulfide glycals (**1B**).[22] The desired *C* -aryl glycoside**3** can be obtained in a 19% yield with the assistance of trifluoroacetic anhydride (TFAA) (**entry 1 , Table 1**). Other activating reagents, such as trifluoromethanesulfonic anhydride (Tf_2O), trimethylsilyl trifluoromethanesulfonate (TMSOTf), acetic anhydride (Ac_2O), and chlorotrimethylsilane (TMSCl) could not achieve the desired product, revealing the critical role of the activating reagents for sulfoxide (**entries 2-5, Table 1**). The yield of rearrangement product**3** was 34% after increasing the amount of TFAA to 3 equivalents (**entry 6, Table 1**). $MeNO_2$ is the best solvent among alternative solvents such as MeCN, $CHCl_3$, DCE, and acetone (**entries 7-11, Table 1**). The desired product **3**was obtained in a yield of 57%, when performed at 0°C (**entry 12, Table 1**). 73% and 81% desired rearrangement were afforded respectively, when *p* -cresol (**2b**) and 4-ethyl phenol (**2c**) were applied. (**entries 13-14, Table 1**). Notably, 87% of 1,2-dihydrobenzofuran-fused *C* -aryl glycoside **9** was achieved in a diastereomeric ratio of α :β = 2:1 with 2,6-lutidine addition (**entry 15, Table 1**).

Table 1 Optimization for *C* -aryl glycoside

Enter	Additive	Solvent (0.1 M)	3[g]	9a
1[a]	TFAA	DCM	19	-
2	Tf_2O	DCM	N/A	-
3	TMSOTf	DCM	N/A	-
4	Ac_2O	DCM	N/R	-
5	TMSCl	DCM	N/R	-
6[b]	TFAA	DCM	34	-
7	TFAA	$MeNO_2$	53	-
8	TFAA	MeCN	51	-
9	TFAA	Acetone	0	-
10	TFAA	$CHCl_3$	28	-
11	TFAA	DCE	42	-
12[c]	TFAA	$MeNO_2$	57	-
13[d]	TFAA	$MeNO_2$	73(3b)	
14[e]	TFAA	$MeNO_2$	81(3c)	
15[f]	TFAA	DCM	-	87(α:β = 2:1)

[a] **1a** (0.05 mmol) and **2a** (1.5 equiv.), TFAA (1.5 equiv.), DCM (0.1 M), 25 °C, 30 min. [b] TFAA (3.0 equiv.)[c] 0 °C.[d] **2b** (1.5 equiv.).[e] **2c** (1.5 equiv.).[f] 2,6-Lutidine (3 equiv.) was added.[g] Yields determined by ^{1}H NMR analysis with internal standard CH_2Br_2.α /β ratio was determined by ^{1}H NMR.

With the optimized conditions established, we proceeded to investigate the substrate scope of phenol for the

synthesis of *C* -aryl glycosides (**Scheme 1)** . Diverse phenol derivatives, bearing both electron-donating and electron-withdrawing substituents, participate in this transformation effectively, furnishing the desired products in moderate to good yields. Of noteworthy importance, phenols substituted with para-substituents, such as gem-dimethyl (**3j**), cyclohexanone (**3k**), cyclohexane (**3l**), benzene (**3m**), 4-bromobenzene (**3n**), ketones (**3o**), and vinyl (**3p**), were well compatible. Additionally, ortho-substituted phenols, comprising of methyl and halogen, were also great candidates (**3q-3t**). When a meta-substituent was present, the yield of the product remained at a respectable 68% (**3u**). Furthermore, the substitution of the allyl group was feasible as well (**3v**). Di-substituted phenols were also amenable substrates, providing good yields (**3w-3z**). Notably, bulky substituted phenols, such as adamantane, were also amenable to this reaction, as evidenced by the good yield of the desired product (**3aa**).

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.[23] 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% (**9p** and **9q**). 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 $MeNO_2$ (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.[24] Sotagliflozin is an inhibitor of both SGLT1 and SGLT2, and its oxygen at position one can be substituted with sulfur.[25] 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.), $MeNO_2$ (0.1 M), 0°C, 8-24 h. [a] 1) *m* -CPBA, CH_2Cl_2, 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, rearomatization 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

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 sulfonium-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 $MeNO_2$ (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 $NaHCO_3$ (sat. aq.) and extracted with DCM (three times), the combined organic layer was dried over Na_2SO_4 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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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 $NaHCO_3$ (sat. aq.) and extracted with DCM (three times). The combined organic layer was dried over Na_2SO_4, 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.

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