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An improved glycal diazidation protocol with copper catalysis

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ABSTRACT

A new and efficient copper-catalyzed glycal diazidation method is described that resulted in the generation of 2,3-diazido sugar acid derivatives. Compared to previously known protocols, the present approach demonstrated improved reaction yields and substrate scopes, thereby allowing for access to potential anti-viral agents.

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Chemical modifications on the structural template of carbohydrates represent one of the important approaches to the discovery of bioactive compounds. In particular, considerable advances have been made in identifying anti-viral agents through preparation of analogues of *N*-acetylneuraminic acid (**1**, Neu5Ac, also known as sialic acid; Fig. 1A) [1]. For example, the anti-influenza clinical drug zanamivir (Relenza, **2**) possessing an unsaturated acid structural moiety was derived from **1** by incorporating a C4 guanidinium group [2]. Withers et al. reported several difluoro derivatives of **1** with potent anti-influenza activities (e.g., **3**, anti-H1N9, IC_{50} = 1.6–2.7 μM) [3]. Azido-containing compound **4** was an inhibitor of hPIV-3 HN (human parainfluenza virus type 3 haemagglutinin-neuraminidase) with an IC_{50} value of 4.8 μM [4].

Recently, our group synthesized a variety of 2,3-diazido derivatives of Neu5Ac (**1**) by developing a visible light-induced glycal diazidation protocol [5]. Among the analogues prepared according to our methodology, compounds **5** and **6** exhibited promising anti-HRV (**5**, IC_{50} = 0.93 μM) and anti-ZIKV (**6**, IC_{50} = 1.41 μM) activities, respectively. The above-mentioned diazidation reaction proceeded employing azidotrimethylsilane as the azide source and BI-OAc as the oxidant under the irradiation of 34 W blue LEDs, providing the corresponding 2,3-diazido products with moderate to excellent yields (66–94%; Fig. 1B). In the process of our research, we observed that the desired transformations could be promoted by thermal conditions as well, but with lower efficiency. We envisioned that addition of a metal catalyst would facilitate the glycal diazidation reaction, which is the subject of this work.

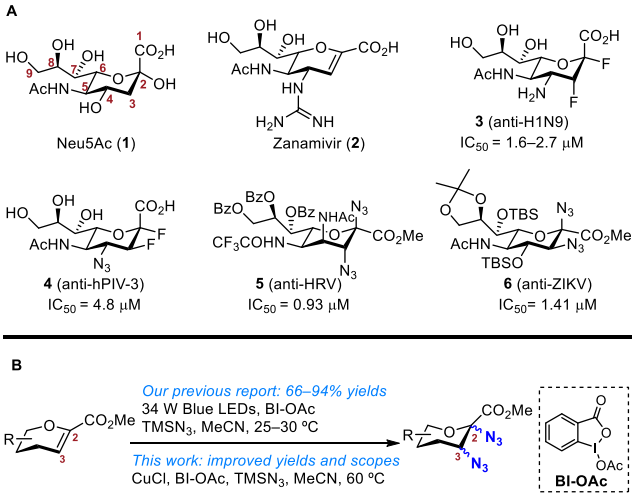

Fig. 1. (A) Structures of Neu5Ac (**1**) and its analogues with anti-viral activities; (B) Synthesis of diazido sugars by glycal diazidation.

Diazidation of alkenes with copper catalysis has been developed to yield the corresponding vicinal diazido compounds [6–12], which are useful synthetic intermediates for preparing amines and related heterocycles. In 2015, the groups of Greaney [6] and Loh [7] independently disclosed copper-catalyzed diazidation reactions with styrene-type substrates. Notably, in 2017, Bao et al. [9] demonstrated an environmentally benign, copper-catalyzed

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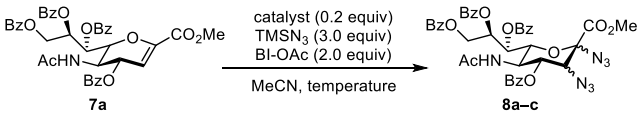
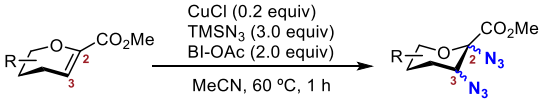
Table 1
Optimization of the reaction conditions.[a]

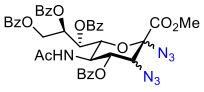


Entry	Catalyst	Temp. (℃)[b]	Time (h)	Yield (%)[c]
1[d]	None	25	17	0
2[d]	None	40	17	<5
3	None	60	17	32
4	None	80	17	20
5	$CuCl_2$	60	4	75
6	CuCl	60	1	96
7	$Cu(OAc)_2$	60	4	89
8	$Cu(acac)_2$	60	4	90
9	$Cu(OTf)_2$	60	4	83
10	CuOTf	60	4	68
11	CuCl	25	17	53
12	CuCl	40	4	85

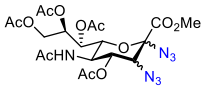
[a]Reactions were conducted on 0.075 mmol scale. [b]Ambient temperature or temperatures of oil bath. [c]Yield of isolated product. [d]Most starting material remained.

Table 2
Substrate scope of the copper-catalyzed glycal diazidation.[a]

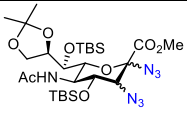




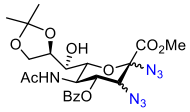
96% yield from **7a**
(dr =12:30:58)[b]
8a: 2β-N_3, 3β-N_3
8b: 2α-N_3, 3β-N_3
8c: 2β-N_3, 3α-N_3
85% yield (method A)[c]



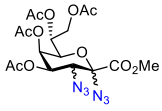
94% yield from **7b** (2.0 g scale)
(dr = 6:28:66)[b]
9a: 2β-N_3, 3β-N_3
9b: 2α-N_3, 3β-N_3
9c: 2β-N_3, 3α-N_3
90% yield (method A)[c]



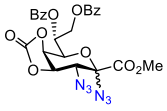
90% yield from **7c**
(dr = 47:12:41)
6: 2β-N_3, 3β-N_3
10a: 2α-N_3, 3β-N_3
10b: 2β-N_3, 3α-N_3
85% yield (method A)[c]



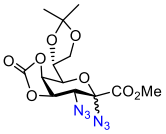
76% yield from **7d**
(dr = 23:31:46)[d]
11a: 2β-N_3, 3β-N_3
11b: 2α-N_3, 3β-N_3
11c: 2β-N_3, 3α-N_3
decomposition (method A)[c]



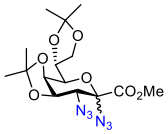
94% yield from **7e**
(dr = 85:4:11)[b]
12a: 2α-N_3, 3α-N_3
12b: 2β-N_3, 3α-N_3
12c: 2α-N_3, 3β-N_3
86% yield (method A)[c]



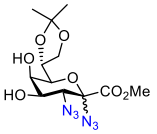
90% yield from **7f**
(dr = 44:56)
13a: 2α-N_3
13b: 2β-N_3
81% yield (method A)[c]



90% yield from **7g**
(dr = 39:61)
14a: 2α-N_3
14b: 2β-N_3
88% yield (method A)[c]



85% yield from **7h**
(dr = 82:18)
15a: 2α-N_3
15b: 2β-N_3
68% yield (method A)[c]



70% yield from **7i**
(dr = 75:25)[d]
16a: 2α-N_3
16b: 2β-N_3
decomposition (method A)[c]

[a]Yields and dr values were calculated based on isolated material unless otherwise stated. [b]Dr values were determined through HPLC analysis. [c]Method A: BI-OAc (2.0 equiv), $TMSN_3$ (3.0 equiv), MeCN, 34 W Blue LEDs, 25 °C. [d]Dr values were obtained by combination of column chromatography and ^1H NMR.

diazidation of a broad range of olefins including vinylarenes, unactivated alkenes, and dienes. Very recently, Zhu and co-workers [11] reported a copper-catalyzed 2,3-diazidation of indole derivatives in the presence of a directing group. To the best of our knowledge, copper-catalyzed diazido functionalization of the double bonds in glycals has been scarcely investigated. Here, we present an

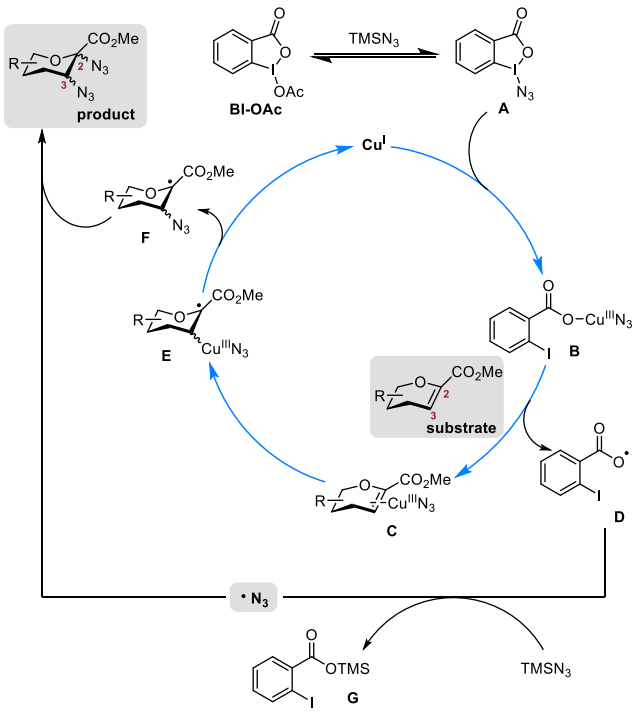


Fig. 2. Proposed mechanism of the copper-catalyzed glycal diazidation.

improved glycal diazidation protocol driven by copper catalysis compared to our previously reported conditions.

We began our studies using Neu5Ac-derived compound **7a** as a model substrate, which was readily prepared in decagram scales [5]. Initially, **7a** was treated with $TMSN_3$ (3.0 equiv) and BI-OAc (2.0 equiv) in acetonitrile without the use of visible light and catalyst under varied temperatures (Table 1). As a result, while most starting material remained at 25 ℃ and 40 ℃ (entries 1 and 2) after 17 h, complete conversion of **7a** was observed at elevated temperature, affording the corresponding diazido product as a diastereomeric mixture (i.e., **8a**–**c**) in 32% yield at 60 ℃ (entry 3) and 20% yield at 80 ℃ (entry 4), respectively. Subsequently, we investigated the reaction by adding different copper catalysts (entries 5–10) into the reaction system at 60 ℃. Pleasingly, the use of catalytic amount (0.2 equiv) of copper catalysts was beneficial for the glycal diazidation reaction, with

significantly improved yield of **8a**–**c** compared to that in entry 3. Among the catalysts evaluated, CuCl revealed to be the optimal one, which converted **7a** into diazido **8a**–**c** with 96% yield in 1 h (entry 6). Using CuCl as the catalyst, we further examined the effect of reaction temperature. Lower yields of **8a**–**c** were observed when conducting the reaction at 25 ℃ (53%, entry 11) and 40 ℃ (85%, entry 12). In addition, the effect of different solvents for the diazidation reaction was also surveyed (see the SI) and all the attempted solvents gave inferior results compared to that of MeCN (entry 6).

With the optimal conditions (CuCl, $TMSN_3$, BI-OAc, MeCN, 60 °C) in hand, we next explored the substrate scope of this copper-catalyzed glycal diazidation reaction. As shown in Table 2, subjecting the 4,7,8,9-tetra-*O*-Bz/Ac-protected substrates **7a** and **7b** derived from Neu5Ac to the aforementioned reaction conditions led to the formation of three diastereomers **8a**–**c** (96% yield, dr = 12:30:58) and **9a**–**c** (94% yield, dr = 6:28:66), respectively. Of note, the reaction of **7b** was performed on 2.0 g scale, which demonstrated the practicality of this method. In addition, diazidation of compound **7c** possessing 4,7-di-*O*-TBS and 8,9-*O*-acetonide moieties proceeded efficiently under the same conditions, generating a mixture of three diastereomers (i.e., **6**, **10a**, and **10b**) in 90% combined yield. Encouraged by these results, we examined the diazidation of glycals containing free hydroxyl groups, which were problematic substrates using our previously developed visible light-promoted diazidation method. To our delight, compound **7d** bearing a C7-hydroxyl group underwent diazidation smoothly to furnish the desired products **11a–c** (76% yield, dr = 23:31:46); by contrast, decomposition of **7d** was observed using visible light-promoted conditions (method A) [5]. On the other hand, glycals derived from 2-keto-3-deoxy-D-*manno*-octulosonic acid (Kdo) also proved to be suitable substrates for the copper-catalyzed diazidation reaction. Specifically, subjection of 4,5,7,8-tetra-*O*-Ac-protected Kdo glycal **7e** to the standard conditions delivered product **12** (dr = 85:4:11) in 94% yield. Substrates **7f**–**h** bearing cyclic 4,5-*O*-protecting groups were converted into the corresponding 2,3-diazido products (i.e., **13**–**15**) as two diastereomers in each case (85–90% yield). Similarly, Kdo glycal **7i** with two free hydroxyl groups was compatible with the copper-catalyzed reaction conditions, which gave **16a** and **16b** in 70% combined yield (dr = 75:25). Based on the above results, the overall reaction efficiency of the diazidation process was improved employing the present method, compared to that of the visible light-promoted approach reported in our laboratory [5]. Interestingly, the two methods provided differentiated diastereomeric constitutions or ratios of products for some substrates (e.g., **7a**–**c** and **7e**), the reason of which merits further investigations.

A possible mechanism for the copper-catalyzed glycal diazidation was proposed as shown in Fig. 2. Initial conversion of BI-OAc into BI-N_3 (**A**) takes place in the presence of $TMSN_3$. Compound **A** undergoes oxidative addition with Cu(I) to form Cu(III) intermediate **B**; [13] the latter would then coordinate with the glycal substrate and give **C** as well as the radical species **D**. The azidation step transforms **C** into radical intermediate **E**, which undergoes reductive elimination to yield carbon radical **F** and release Cu(I), completing the catalytic cycle. On the other hand, $TMSN_3$ would react with radical species **D** to provide TMS *o*-iodobenzoate (intermediate **G**); the resultant azido radical couples with **F** to furnish the 2,3-diazido products.

In summary, we have described a new copper-catalyzed diazidation reaction of sugar acid-derived glycals resulting in access to the corresponding 2,3-diazido carbohydrate products [14]. Notably, the present approach features higher reaction efficiency and greater substrate compatibility as compared to a related light-accelerated diazidation process previously developed by our group. In addition, generation of varied diastereomers of azido sugars and associated derivatives provides opportunities for identifying new anti-viral agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153010.

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153010.

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[14] Glycal substrates lacking the ester group at the anomeric position failed to provide the desired products with this protocol. For example, subjecting the commercially available 3,4,6-tri-O-acetyl-D-glucal under the standard reaction conditions resulted in no reaction over 48 h on a 500 mg scale, which implied the importance of the electronic-withdrawing ester group for the glycal diazidation method.