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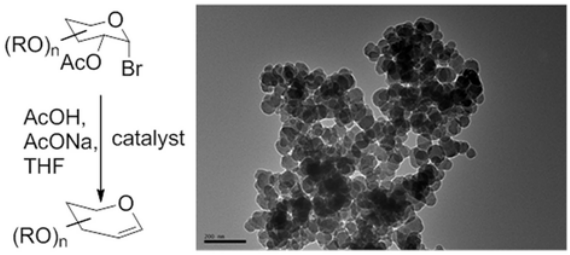

A simple and efficient method for synthesis of pyranoid glycals utilizing zinc nanoparticles reductive elimination glycopyranosyl bromides in acetate buffers is described. A variety of pyranoid glycals derivatives were obtained, especially for the synthesis of 6-deoxy, 4,6-*O*-benzylidene and disaccharides glycals with good yields.

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A Convenient and Efficient Synthesis of Glycals by Zinc Nanoparticles

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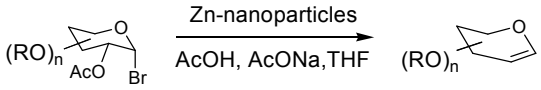
A simple and efficient method for synthesis of pyranoid glycals utilizing zinc nanoparticles reductive elimination glycopyranosyl bromides in acetate buffers is described. A variety of pyranoid glycals derivatives were obtained, especially for the synthesis of 6-deoxy, 4,6-*O*-benzylidene and disaccharides glycals with good yields.

The biological functions of glycoconjugates and oligosaccharides are critical and extensive in cell growth, cell adhesion, cell communication, inflammatory response, and immune defense.[1] The efficient stereoselective construction of glycosidic linkages for the preparation of complex oligosaccharides and glycoconjugates is a challenging focus in organic synthesis and glycochemistry.[2] Due to the presence of the enol ether functionality, among the wide variety of glycosylation strategies, glycals are important intermediates, and they have been commonly employed in the formation of glycosidic bonds, for example, glycals are multifunctional donors for O-glycosides,[3] C-glycosides,[4] S-glycosides,[5] N-glycosides.[6] Meanwhile they serve as irreplaceable building blocks for 2-deoxy-hexoses and 2-deoxy-2-amino-hexoses synthesis[7] and natural products such as palytoxin, halichondrin, spongistatin, etc.[8] Glycals were discovered by Fisher and Zach,[9] in spite of their long existence, they remain a type of great interest sugar because of the addition[10], oxidation[11] and rearrangement[12] reactions that they undergo. Recently, the uses of glycals in combinatorial chemistry have been found.[13]

Over the years, numerous efforts have been made to construct glycals, including reduction of glycosyl halides by metals such as Zn-AcOH,[9] Li-NH_3,[14] $(Cp_2TiCl)_2$,[15] Cr(II),[16] Zn-MeOH-vitamin-B_{12},[17] and Al-Hg[18] or using thiophenyl glycoside,[19] glycosyl sulfones,[20] glycosyl sulfoxides,[21] and electrochemical approach.[22] However, many of these aforementioned methods have long suffered from lack of generality because of several drawbacks. Firstly, use of moisture-sensitive, expensive, and toxic metal reagents generating intricate laboratory operations may limit the applications of these protocols. Secondly, harsh reaction conditions such as strong acidic conditions confine the utilization of acid-labile substrates. Thirdly, because of the low reactivity of metal dust in some cases, excess loading of metals and acetic anhydride reagents were employed, resulting in the following workup tedious such as metal-scavenging and acid-base neutralization to remove the superfluous metals and acidic reagents. In this regard, a user-friendly, convenient, less toxic and general protocol for the synthesis of glycal is desirable.

In recent years, owing to numerous advantages of metal nanoparticles particularly the high surface to volume ratio leading to high reaction activity, metal nanoparticles have been recognized as powerful reactants in organic synthesis.[23] Herein, an approach based on a non-toxic, air- and moisture-stable zinc nanoparticles as reduction agent is developed. Mild reaction conditions and high reactivity of zinc nanoparticles leads to high yield of products, ease of work-up, and ecologically clean procedure for the construction of diverse pyranoid glycal derivatives, especially for the synthesis of 6-deoxy,4,6-*O*-benzylidene and disaccharides glycals.



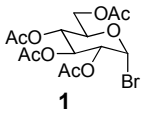
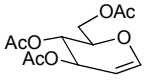
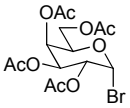
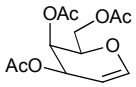
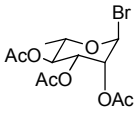
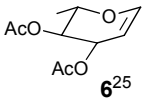
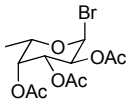
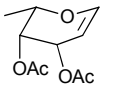
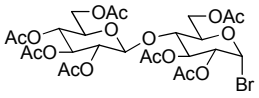
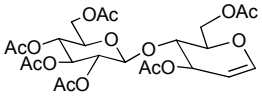
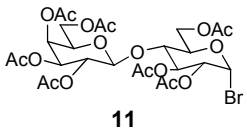
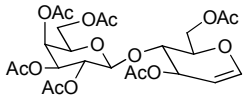
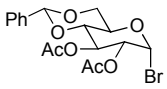
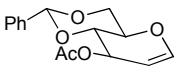
Scheme 1. Synthesis of glycal from glycopyranosyl bromide

For the synthesis of glycals, we utilized zinc nanoparticles reductive elimination of glycopyranosyl bromides under acetate buffers, as depicted in Scheme 1. Our approach presented here is mild with easily available reagents. In initial studies, acetobromo-α-D-glucose **1** chosen as starting materials was carried out in the presence of zinc nanoparticles (50 nm, commercial available, see supporting information) under AcOH/AcONa/THF buffers at room temperature for 1 h (Scheme 1). TLC analysis indicated complete conversion of the starting material **1** and formed **2**[24] as the sole product in yield of 90% (Table 1, Entry a). This result motivated us to continue our study to investigate the substrate scope of the reaction. Thus, the mild protocol was further applied to synthesis of other glycals with a variety of substituents. Similarly, the desired products were afforded for substrates with other groups and the results are summarized in Table 1.

As shown in Table 1, various desired glycals were obtained under the same condition in good yields. Treatment of the tetra-*O*-acetyl-α-D-galacopyranosyl bromide **3** with zinc nanoparticles in acetate buffers afforded Tri-*O*-acetyl-D-galactal **4**[24a] in 93% isolated yield and the rapid conversion was achieved in less than 1 h (Table 1, Entry b). Encouraged by the results obtained with zinc nanoparticles reductive elimination glycopyranosyl bromide **1** and **3** providing corresponding glucal **2** and galactal **4**, we turned our attention to 6-deoxy glycals. As illustrated in Table 1, 3,4-Di-*O*-acetyl-L-rhamnal **6**[25] and 3,4-di-*O*-acetyl-L-fucal **8**[26] were readily afforded in excellent yield 93% and 85%, respectively (Table 1, entries c, and d). Compared with previous reports with tedious workup,[27] in this study,

benefited from the high reaction activity of zinc nanoparticles increasing the reaction selectivity and then to give pure and high yield of desired product, 3,6,2',3',4',6'-Hexa-*O*-acetyl-α-D-cellobial **10**[28] and 3,6,2',3',4',6'-hexa-*O*-acetyl-α-D-lactal **12**[28] were successfully afforded after recrystallization in hexane and ethyl acetate in 91% and 86% isolated yield (Table 1, entries e, and f). Furthermore, it's possible to scale up to commercial applications because the reaction could be conducted on a gram scale without a decrease of yield (**10**, 91%).

Table 1. Synthesis of various substituted glycals from glycosyl bromides[a].

Entry	Substrate	Product	Time(h)	Yield[b] (%)
a	 **1**	 **2**[24]	1	90
b	 **3**	 **4**[24a]	1.5	93
c	 **5**	 **6**[25]	2.5	93
d	 **7**	 **8**[26]	1	85
e	 **9**	 **10**[28]	12	91
f	 **11**	 **12**[28]	10	86
g	 **13**	 **14**[27a]	2	37

[a] Reaction conditions: 1.0 mmol glycopyranosyl bromides, 2.0 mmol zinc nanoparticles, 6.0 mmol AcONa and 0.4 mL AcOH, in 4 mL THF at r.t.
[b] Isolated yield

To ascertain the substrate tolerance and generality of the reaction, 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl bromide **13** with bearing acid-sensitive 4,6-*O*-benzylidene group as substrate was treated under the same reaction conditions (Scheme 1). After 2 h, TLC detection showed that we obtained 47% yield of 3-*O*-acetyl-4, 6-*O*-benzylidene-D-glucal **14**[27a] (Table 1, Entry g). To improve the

yield of **14**, 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl bromide **13** was then conducted in different buffer systems at room temperature for 2 h, and the results are summarized in Table 2. As illustrated in Table 2, we found that the reaction carried out in AcOH/Et_3N·HCl/THF acquiring a better result that desired product 3-*O*-acetyl-4,6-*O*-benzylidene-D-glucal **14** was obtained in 68% yield (Table 2, Entry 5). We ascribe the improvement to the buffer's pH value. The reaction is highly efficient in acidic condition, whereas the product is stable in neutral. The optimized AcOH/Et_3N·HCl/THF buffer system reaches the balance between reactivity and stability. Although the result is less than satisfactory, it may provide an available access to the formation of the glycals with acid-sensitive groups.

Table 2. Optimization of reaction conditions for synthesis of **14**.

Entry	Conditions	Yield[b] (%)	Time(h)
1	AcOH / AcONa / THF	47	2
2	AcOH / THF	33	2
3	Et_3N·HCl / THF	trace	2
4[a]	AcOH / Et_3N·HCl / THF	68	2

[a] Reaction conditions: 1.0 mmol glycopyranosyl bromides, 2.0 mmol zinc nanoparticles, 6.0 mmol Et_3N·HCl and 0.4 mL AcOH, in 4 mL THF at r.t for 2 h .
[b] Isolated yield

Conclusions

In summary, we have successfully established an efficient and practical protocol for the preparation of glycals with zinc nanoparticles under mild conditions. The high reactivity of zinc nanoparticles leads to complete and clean reaction simplifying the process of purification as well as fewer acetic acid solutions reducing difficulty of the post-processing. Thus, this protocol has proved to be general in the preparation of a variety of glycals and their derivatives, especially for the synthesis of 6-deoxy, 4,6-*O*-benzylidene and disaccharides glycals. In addition, the procedure could be conducted on a gram scale, highlighting its possible industrial application. Further studies on broadening substrates to clearly understand the synthetic applications are ongoing.

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Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

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