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Note

An efficient method for the synthesis of pyranoid glycals

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ABSTRACT

A simple and efficient procedure was designed for the preparation of pyranoid glycals. In a novel fashion, a series of protected glycopyranosyl bromides underwent reductive elimination in the presence of zinc dust and ammonium chloride in CH_3CN at 30–60 °C. The corresponding glycals were obtained with excellent isolated yields (72–96%) in a short time (20–50 min). Furthermore, the transformation was compatible with different protection patterns and conveniently scalable (86% for 45 g aceto-bromoglucose) which made it very applicable in organic synthesis.

As versatile and useful intermediates, glycals are widely used in organic synthesis of *O*-glycosides [1–3], C-glycosides [4–8], S-glycosides [9], N-glycosides [10–13], and even natural products [14–17]. They have also been used in the synthesis of iminosugars [18], sugar-heterocycle hybrid molecules [19], bioactive molecules [20,21], and other sugar based building blocks [22]. Besides, the unsaturated part of the glycals allows many straightforward modifications in the sugar rings such as rearrangement, epoxidation, addition and substitution. For example, 2,3-unsaturated glycosides and 1,2-anhydroglycosides can be prepared from glycals conveniently [23–26]. In addition, glycals are often used as starting materials for the synthesis of 2-deoxy glycosides and 2-*C*-branched sugars [27–29]. A traditional method for preparing glycals is the Fischer-Zach method, which uses zinc dust in acetic acid for reductive elimination of acylated glycosyl bromides [30]. Over the recent years, many synthetic methods for glycals have been developed, including the reduction of protected glycosyl halides by $(Cp_2TiCl)_2$ [31], Cr(II) [32], Al-Hg [33], Zn-PEG/600-H_2O [34], Zn–NaH_2PO_4 [35], Zn-β-CD-H_2O [36], Zinc-nanoparticles [37] or using thiophenyl glycosides, glycosyl sulfones and electrochemical approach. [38], [39] However, the above methods often suffer from some disadvantages like low yields, long reaction times, stringent conditions and using of expensive and toxic reagents. Thus, it is still interesting for the glycochemists to develop a simple, efficient and economical reaction protocol for glycal preparation.

In our previous research, Zn–NH_4Cl–CH_3CN had been successfully applied in the deprotection of the 2,2,2-trichloroethyl group at the anomeric oxygen of carbohydrates, where most protective groups including ethers, esters, silyl ethers, and ketals remained intact. [40] Therefore, we tried to synthesize the glycals through the reductive elimination of protected glucopyranosyl bromides. As we predicted, when tetra-*O*-acetyl-D-glucopyranosyl bromide was treated with Zn dust and NH_4Cl in CH_3CN (at reflux), tri-*O*-acetyl-D-glucal was obtained as the sole product. Inspired by this preliminary result, we established optimal conditions with following steps. First, several solvents were tested; and we found the conversion proceeded much better in acetonitrile than other solvents (Table 1, entries 1–5). Subsequently, the reaction of **1** was carried out in the presence of different amounts of Zn/NH_4Cl in CH_3CN at different temperature. After many trials, we were able to get the tri-*O*-acetyl-D-glucal with the highest yield (96%) in a short time (20 min) using 7.5 equivalent of Zn/NH_4Cl (1:1) at 60 °C (Table 1, entry 8). When smaller amount of Zn/NH_4Cl was used, the reaction required substantially longer time and the yield was decreased (Table 1, entries 5–6). In addition, the reaction did not occur at all without the NH_4Cl (Table 1, entry 12), which indicated that NH_4Cl is indispensable to this reaction.

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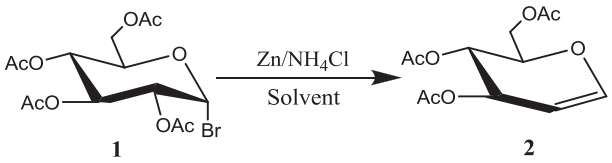
Table 1
Optimization of the synthesis of 3,4,6-tri-*O*-acetyl-D-glucal from the tetra-*O*-acetyl-α-D-glucopyranosyl bromide.



1 **2**

Entry	Promoter (Zn/NH_4Cl) (equiv)	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
1	6/6	DCM	40	240	NR[b]
2	6/6	Toluene	80	60	80
3	6/6	THF	80	50	78
4	6/6	CH_3OH	60	30	75
5	6/6	CH_3CN	80	20	90
6	4/4	CH_3CN	80	90	70
7	7.5/7.5	CH_3CN	80	20	94
8	7.5/7.5	CH_3CN	60	20	96
9	7.5/7.5	CH_3CN	40	90	85
10	7.5/5	CH_3CN	60	30	82
11	7.5/3	CH_3CN	60	90	51
12	7.5/0	CH_3CN	60	240	NR[b]

[a] Isolated yields.
[b] NR, no reaction.

To examine whether or not this method has generality, reactions involving 15 examples (Entries 1–15 in Table 2) were performed on a preparative scale. As show in Table 2, treatment of the acetobromosugars **1** and **3**–**7** with Zn/NH_4Cl in CH_3CN, affording the glycals **2** and **17**–**20** in good to excellent yields. As the glycopyranosyl bromides **5**–**7** were unstable at 60 °C, lower temperature was used to carry out the transformations (Entries 4–6 in Table 2). Meanwhile, the benzoyl-protected glycals **21**–**23**, were also obtained in excellent yields. Starting materials carrying unstable protecting groups such as methanesulfonyl, *p*-tolylsulfonyl and azido groups were also tolerated under the reaction conditions (Entries 10–12 in Table 2). Importantly, using this method, disaccharide glycals **27**–**29** were accessible in very good yields; while the 1,4-glycosidic bonds were not attacked. The structures of all the synthetic glycals were elucidated from NMR and mass spectral data, and also by comparison with the reported data [27–30]. In all cases the glycals (**2**, **17**–**29**) were obtained in 72–96% isolated yields at a short time (20–50 min). Notably, the reaction could be conducted on a large scale (45 g acetobromoglucose) with excellent yield (**2**, 86%). In the previous synthesis of glycals, various methods have been used for enhancing the activity of zinc. However, in our procedure, the zinc dust did not need to be pre-activated and the reaction avoided the acidic conditions, which further simplified the reaction procedure.

In summary, we have developed an efficient and convenient method for the synthesis of variously protected glycals using Zn/NH_4Cl as an inexpensive system. This method offers several advantages, such as low toxicity of reagents, simplicity in operation, high yields and short reaction time. Furthermore, the efficient applicability of this methodology to gram-scale amount of the starting acetobromoglucose substrates makes this approach highly practical.

1. Experimental

All reagents were purchased with purity of AR and used as such. All the solvents for chromatography were distilled before use. Silica gel (10–40 μm, Yantai, China) was used for column chromatography. TLC plates (10–40 μm, Yantai, China) were applied to monitor reactions. ^1H and ^{13}C NMR spectra were respectively recorded on 500 MHz and 125 MHz with a Bruker DRX 500 spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million (ppm) with TMS as the internal standard. MS experiments were performed on LTQ-XL (Thermo Scientific, USA) with an electrospray (ESI) ion source. Glycopyrannosyl bromide was prepared following the literature. [41]

2. General procedure for the synthesis of glycals

Under nitrogen, the glycopyranosyl bromide (1.0 mmol) was dissolved in CH_3CN, and then zinc dust (7.5 mmol) and ammonium chloride (7.5 mmol) were added, followed by stirring at corresponding temperature. Upon completion of the reaction (monitored by TLC), inorganic salts and excessive zinc dust were removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel flash column chromatography to afford the corresponding glycal in pure form.

3. Product characterization data

3.1. 3,4,6-Tri-O-acetyl-D-glucal **(2)** [34]

White solid: mp 49–151 °C; ^1H NMR($CDCl_3$): δ(ppm) 6.47 (d, 1H, $J = 6.2$ Hz), 5.35 (dd, 1H, $J = 4.2$, 3.7 Hz), 5.22 (dd, 1H, $J = 7.5$, 6.0 Hz), 4.85 (dd, 1H, $J = 9.5$, 3.3 Hz), 4.40 (dd, 1H, $J = 12.2$, 5.8 Hz), 4.26 (m, 1H), 4.20 (dd, 1H, $J = 12.4$, 3.1 Hz), 2.08 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.55, 170.36, 169.53, 145.59, 98.95, 73.90, 67.38, 67.12, 61.32, 20.95, 20.75, 20.68. MS (ESI): *m/z* Calculated for $[M+Na]^+$ $C_{12}H_{16}O_7Na$ 295.09, found 295.17.

3.2. 3,4,6-Tri-O-acetyl-D-galactal **(17)** [34]

Colorless syrup. ^1H NMR($CDCl_3$): δ(ppm) 6.47 (dd, 1H, $J = 4.7$, 1.4 Hz), 5.56 (d, 1H, $J = 0.8$ Hz), 5.43–5.42 (m, 1H), 4.74–4.73 (m, 1H), 4.34–4.20 (m, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.20, 169.93, 169.82, 145.13, 98.61, 72.52, 63.63, 63.45, 61.65, 20.49, 20.43, 20.34. MS (ESI): *m/z* Calculated for $[M+Na]^+$ $C_{12}H_{10}O_7Na$ 295.08, found 295.17.