A mild and environmentally benign method for the synthesis of glycals in PEG-600/H_2O†

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Glycals were synthesized *via* a simple, mild, convenient and environmentally benign procedure, in which protected glycosyl bromides undergo the reductive elimination in the presence of zinc in PEG-600/H_2O at room temperature. The glycals were obtained in 75–92% isolated yields.

Introduction

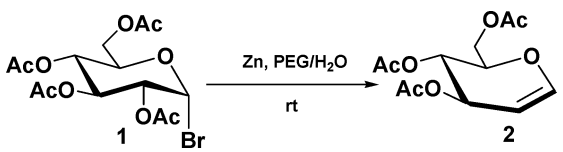
Glycals are useful synthetic intermediates in organic transformations such as in the synthesis of biologically active natural products,[1–2] *O*-glycosides,[3] *C*-glycosides,[4–5] *S*-glycosides,[6] *N*-glycosides[7] and cyclopropanated carbohydrates.[8] They have also been used in the glycosylation as glycosyl donors or acceptors.[9–10] Most 2-*C*-branched sugars can be synthesized through 1,2-cyclopropanation followed by selective ring opening *via* solvolysis[11–13] and a majority of the 1,2-cyclopropane derivatives were prepared from glycals. Moreover, they show remarkably versatile properties in different addition, rearrangement and substitution reactions. Glycals are also vital starting materials for stereoselective preparation of important 2-amino sugars, which are building blocks needed in glycoconjugate synthesis, as well as oxetanes or β-lactams.[14]

Many glycoconjugates can be synthesized *via* the glycal method, hence it is necessary to develop a simple, mild and environmentally benign method to produce a variety of glycals of different configurations. The traditional synthesis of glycals involves treating a peracetylated glycosyl bromide with zinc in acetic acid.[15] The Fischer–Zach method has been one of the most popular methods for synthesizing glycals, because the products of this method are suitable for the synthesis of carbohydrate derivatives and many other natural products.[15] Over the years, numerous synthetic methods for glycals have been developed, including the reduction of protected glycosyl halides by Na, lithium naphthalenide, Li-NH_3, Zn-Ag, $(Cp_2TiCl)_2$, Cr(II), Al-Hg, K-graphite, SmI_2,[16–17] or using thiophenyl glycoside, glycosyl sulfones and electrochemical approach.[18]

However, the present methods for synthesis of glycals possess some drawbacks such as use of expensive and toxic reagents, low reaction temperature, and complicated operation. Thus, a strong impetus has been given to develop a simple, mild, less toxic, economical, environmentally benign and user-friendly reaction protocol for their preparation. Herein, we describe a simple and convenient synthesis of glycals from easily available protected glycosyl bromides in good to excellent yields, giving access to further functionalized carbohydrate 2-*C*-analogs.

Results and discussion

In this study, upon treatment of the acetobromo-α-D-glucose **1** with Zn-$CuSO_4$ in acetic acid following the Fischer–Zach method, D-glucal **2** was obtained (entry 1, Table 1). However, this method required low temperature and intricate operation. When compound **1** was treated with Zn in H_2O at room temperature, we were able to get a modest yield (entry 2, Table 1). But, when the acetobromo-α-D-glucose **1** was treated with zinc in PEG-200, PEG-400 and PEG-600 at room temperature, tri-*O*-acety-D-glucal **2** was not obtained. Subsequently, compound **1** was treated with Zn in PEG-200/H_2O, PEG-400/H_2O, PEG-600/H_2O (Scheme 1); D-glucal **2** was obtained in all these reactions (entries 3–5, Table 1), and PEG-600/H_2O is a very efficient system with a good yield of **2**, and the reaction time was shortened to just 20 min (entry 5, Table 1). Meanwhile, to our delight, glucal can also be synthesized in neutral conditions (entry 5, Table 1), hence this method can be applicable to compounds possessing acid-sensitive protecting groups, which are incompatible with the classical Fischer–Zach method. This has demonstrated the use of both acid and base labile protecting groups during these reactions and purification steps, which should substantially facilitate the access to glycals for the study



Scheme 1 Synthesis of glucal **2** from the protected glycosyl bromide **1**.

Table 1 Optimization for synthesis of glycal **2** from the protected glycosyl bromide **1**

Entry	Conditions	Yield (%)
1	Zn, $CuSO_4$, NaAc, HAc, H_2O, –15 °C–0 °C, 6 h	67
2	Zn, H_2O, rt, 1 h	65
3	Zn, PEG-200, H_2O, rt, 20 min	50
4	Zn, PEG-400, H_2O, rt, 20 min	80
5	Zn, PEG-600, H_2O, rt, 20 min	88
6	Zn, PEG-600, H_2O, O_2, rt, 1 h	20

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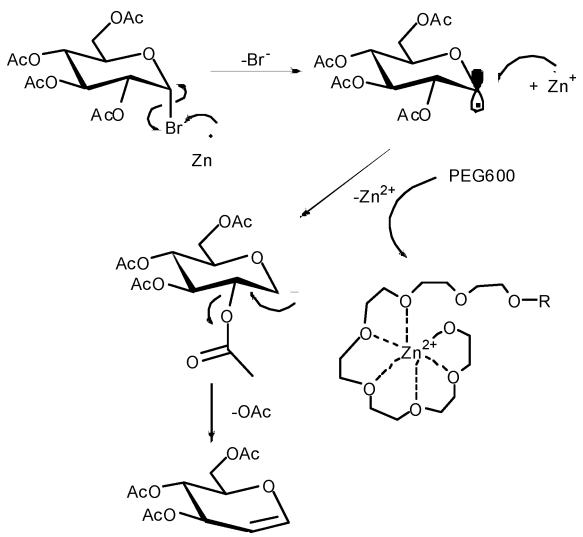
of important biological compounds. An advantage of the new methodology is that the groups of the starting material are typically both acid and base stable to a sufficient extent that a wide variety of reactions can be utilized in modifying the protecting groups of glycals.

To explore the synthetic potential and scope of the strategy, reactions involving 14 examples (**2**, **16–27**, Table 2) were performed on a preparative scale in the presence of zinc in PEG-600/H_2O (Scheme 2). To our delight, the acetobromosugars **3** and **4** reacted with Zn in PEG-600/H_2O, and the glycals **2** and **16** were afforded in good yields (entries 2 and 3 in Table 2). Encouraged by this result, the generality of the reaction was investigated for synthesis of benzoylated, 6-*O*-mesyl, 6-*O*-tosyl and 6-azido glycals under the same conditions.

The results showed that benzoylated glycals **17–19**, 6-*O*-mesyl glycal **21** and 6-*O*-tosyl glycals **22** and **23** were also obtained in good to excellent yields; benzoylated rhamnal **20** and 6-azido glycal **24** were accessible in good yields. Importantly, using this method, acetylated glycals **25–27** could also be obtained in good yields; the 1,4-glycosidic bond was not hydrolyzed. A variety of protecting groups, including acetyl, benzoyl, methanesulfonyl and *p*-tolylsulfonyl groups, were stable under the reaction conditions. In all cases the glycals (**2**, **16–27**) were obtained in 75–92% isolated yields (entries 1–14, Table 2).

Based on the product obtained in the presence of zinc in PEG-600/H_2O, a plausible mechanism is illustrated in Scheme 2. The glycosyl bromides generate the anomeric radical in the presence of zinc dust, further reduction of the anomeric radical then gives the anomeric anion with the excess zinc, which undergoes concomitant elimination with the C2-substituent affording the glycal. PEG-600 can chelate Zn^{2+}, hasten the formation of anomeric anion and shorten the reaction time. In order to identify the radical mechanism, we carried out the reaction under O_2 (entry 6, Table 1). It was found that oxygen could inhibit the formation of glycal; the yield was only 20%.



Scheme 2 Mechanism for the reaction of compound **1** with Zn in PEG-600/H_2O.

In the preparation of glycals, various methods have been used for enhancing the activity of zinc. However, in our procedure, we found that Zn had high activity and it did not need to

Table 2 Synthesis of substituted glycals from pyranosyl bromides

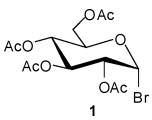
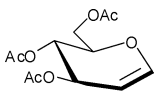
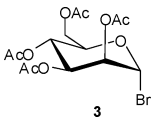
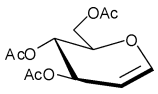
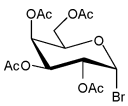
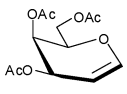
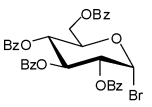
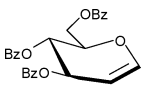
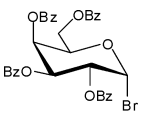
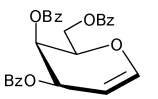
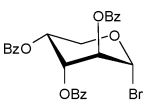
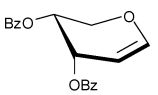
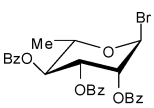
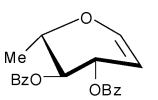
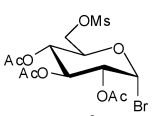
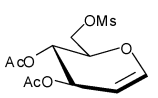
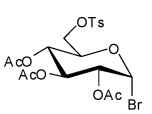
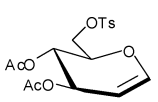
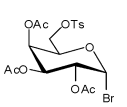
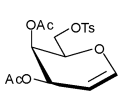
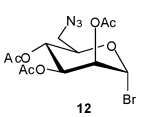
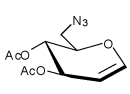
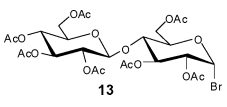
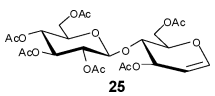
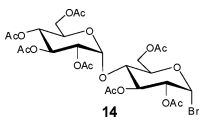
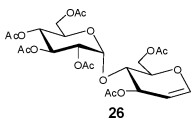
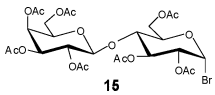
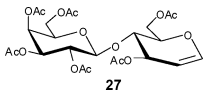
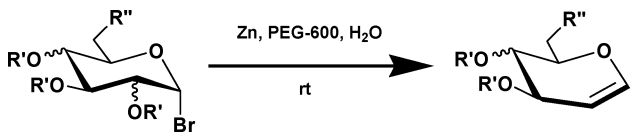
Entry	Substrate	Product	Yield (%)
1	 **1**	 **2**	88[a]
2	 **3**	 **2**	81[b]
3	 **4**	 **16**	80[b]
4	 **5**	 **17**	92[c]
5	 **6**	 **18**	90[d]
6	 **7**	 **19**	93[d]
7	 **8**	 **20**	75[c]
8	 **9**	 **21**	90[b]
9	 **10**	 **22**	89[b]
10	 **11**	 **23**	80[b]
11	 **12**	 **24**	76[b]
12	 **13**	 **25**	88[e]

Table 2 *(Contd.)*

Entry	Substrate	Product	Yield (%)
13	 **14**	 **26**	81[e]
14	 **15**	 **27**	80[e]

Reaction time: [a] 20 min; [b] 1 h; [c] 4 h; [d] 5 h; [e] 8 h.

be activated. Meanwhile, in comparison with the traditional synthetic method of glycals, we use PEG-600/H_2O to replace acetic acid, and the zinc dust consumption was reduced (6 equiv. reduced to 2 equiv.).



Scheme 3 Synthesis of glycals from pyranosyl bromides.

Conclusion

In summary, we have developed an environmentally friendly method for the synthesis of variously protected glycals. This method offers several advantages, *i.e.*, low toxicity of reagents, simplicity in operation and economy in operation, making it a useful and attractive strategy for the synthesis of glycals.

Experimental

General

Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354–92. ^{1}H NMR and ^{13}C NMR (600 and 150 MHz, respectively) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration and coupling constants (Hz). ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). ESI-HRMS spectra were recorded on BioTOF Q. Optical rotations were acquired on a Perkin Elmer-341 Digital Polarimeter. Glycals **2**, **16–22** and **24–27** are known compounds and their ^{1}H NMR data matched the literature data.[19–20] D-Glucose, D-mannose, D-galactose, D-arabinose, L-rhamnose, D-maltose, D-lactose and D-cellobiose were commercially available and used without further purification. Glycopyranosyl bromide **1**, **3–15** were prepared according to the reported procedure.[20a]

General procedure for the synthesis of glycals 2, 16–27. To a solution of glycopyranosyl bromide (1 mmol) in PEG-600/H_2O (1 : 1, 6.0 mL) were added zinc dust (2.0 mmol), followed by stirring at room temperature. TLC indicated that the reaction was complete. Usual workup and purification provided the corresponding compounds.

Product characterization data

3,4,6-Tri-*O*-acetyl-D-glucal[20] (2). $[\alpha]_D^{25}$ −21.9 (*c* 4.1, $CHCl_3$), lit. $[\alpha]_D^{23}$ −17 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 2.05 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 4.20 (dd, 1H, *J* = 12.4, 3.1), 4.26 (m, 1H), 4.40 (dd, 1H, *J* = 12.2, 5.8), 4.85 (dd, 1H, *J* = 9.5, 3.3), 5.22 (dd, 1H, *J*= 7.5, 6.0), 5.35 (dd, 1H, *J* = 4.2, 3.7), 6.47 (d, 1H, *J* = 6.2).

3,4,6-Tri-*O*-acetyl-D-galactal[20] (16). $[\alpha]_D^{25}$ −8.9 (*c* 0.1, EtOAc), lit. $[\alpha]_D^{23}$ −16.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 2.03 (s, 3H), 2.09 (s, 3H), 2.13 (s, 3H), 4.22 (dd, 1H, *J* = 11.6, 5.2), 4.28 (dd, 1H, *J* = 11.6, 7.2), 4.33 (m, 1H), 4.73 (m, 1H), 5.43 (dd, 1H, *J*= 3.8, 1.1), 5.56 (d, 1H, *J* = 1.0), 6.46 (d, 1H, *J* = 5.2).

3,4,6-Tri-*O*-benzoyl-D-glucal (17). $[\alpha]_D^{25}$ −59.1 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 4.68–4.71 (m, 3H), 5.12 (dd, 1H, *J* = 6.2, 3.6), 5.72 (dd, 1H, *J*= 4.4, 4.0), 5.80 (dd, 1H, *J* = 5.6, 5.3), 6.60 (dd, 1H, *J* = 6.1, 0.8), 7.39–7.44 (m, 6H), 7.52–7.57 (m, 3H), 7.99–8.05 (m, 6H).

3,4,6-Tri-*O*-benzoyl-D-galactal (18). $[\alpha]_D^{25}$ −42.8 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 4.57 (dd, 1H, *J* = 11.8, 4.8), 4.71 (m, 1H), 4.80 (dd, 1H, *J* = 11.8, 7.7), 4.99 (dd, 1H, *J* = 6.1, 1.7), 5.92–5.94 (m, 2H), 6.62 (d, 1H, *J* = 6.2), 7.33 (dd, 2H, *J* = 7.9, 7.7), 7.42 (dd, 4H, *J* = 7.7, 7.7), 7.50 (dd, 1H, *J* = 7.5, 7.3), 7.54–7.58 (m, 2H), 7.89 (d, 2H, J= 7.3), 8.00–8.07 (m, 4H).

3,4-Di-*O*-benzoyl-D-arabinal (19). $[\alpha]_D^{25}$ +225.5 (*c* 2.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 4.22–4.28 (m, 2H), 5.07 (dd, 1H, *J* = 5.6, 5.3), 5.44 (m, 1H), 5.81 (m, 1H), 6.62 (d, 1H, *J* = 5.9), 7.34 (d, 1H, *J* = 7.7), 7.36 (d, 1H, *J* = 7.6), 7.41 (d, 1H, *J* = 7.7), 7.42 (d, 1H, *J* = 7.6), 7.50–7.56 (m, 2H), 7.93 (d, 2H, *J* = 7.3), 8.02 (d, 2H, *J* = 7.4).

3,4-Di-*O*-benzoyl-L-rhamnal[20] (20). $[\alpha]_D^{25}$ +208.6 (*c* 0.6, $CHCl_3$), lit. $[\alpha]_D^{23}$ +229 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 1.45 (d, 3H, *J* = 6.5), 4.36 (m, 1H), 5.00 (dd, 1H, *J* = 5.9, 2.9), 5.51 (dd, 1H, *J* = 7.1, 6.7), 5.71 (m, 1H), 6.53 (d, 1H, *J* = 6.1), 7.40–7.44 (m, 4H), 7.52–7.57 (m, 2H), 8.01 (dd, 4H, *J* = 19.1, 7.9).

3,4-Di-*O*-acetyl-6-*O*-mesyl-D-glucal[20] (21). $[\alpha]_D^{25}$ −3.8 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 2.06 (s, 3H), 2.10 (s, 3H), 3.07 (s, 3H), 4.35 (m, 2H), 4.47 (dd, 1H, *J* = 11.6, 6.2), 4.89 (dd, 1H, *J* = 6.2, 3.5), 5.21 (dd, 1H, *J* = 7.4, 5.6), 5.35 (m, 1H), 6.48 (d, 1H, *J* = 6.2).

3,4-Di-*O*-acetyl-6-*O*-tosyl-D-glucal[20] (22). $[\alpha]_D^{25}$ +15.9 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 2.03 (s, 3H), 2.04 (s, 3H), 2.46 (s, 3H), 4.23 (m, 3H), 4.82 (dd, 1H, *J* = 6.2, 3.5), 5.13 (dd, 1H, *J* = 3.7, 3.7), 5.27 (dd, 1H, *J* = 6.2, 5.5), 6.35 (d, 1H, *J* = 6.0), 7.35 (d, 2H, *J* = 7.9), 7.80 (d, 2H, *J* = 8.4).

3,4-Di-*O*-acetyl-6-*O*-tosyl-D-galactal (23). $[\alpha]_D^{25}$ +2.7 (*c* 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ_H 2.01 (s, 3H), 2.05 (s, 3H), 2.46

(s, 3H), 4.14 (dd, 1H, $J = 10.5, 4.4$), 4.28 (dd, 1H, $J = 10.6, 7.7$), 4.32 (m, 1H), 4.72 (dd, 1H, $J = 6.1, 3.1$), 5.37 (s, 1H), 5.48 (s, 1H), 6.35 (d, 1H, $J = 6.1$), 7.36 (d, 2H, $J = 8.2$), 7.79 (d, 2H, $J = 8.2$). ^{13}CNMR ($CDCl_3$): δ_C 20.5, 20.7, 21.7, 63.5, 63.8, 66.7, 72.4, 98.9, 128.0, 129.9, 132.6, 145.2, 169.8, 170.1. ESI-HRMS exact mass calcd. for $C_{17}H_{20}NaO_8S$ [M + Na] 407.0771, found 407.0779.

3,4-Di-*O*-acetyl-6-deoxy-6-azido-D-glucal (24). $[\alpha]_D^{25}$ −45.7 (*c* 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ_H 2.06 (s, 3H), 2.10 (s, 3H), 3.56 (dd, 1H, $J = 11.0, 6.5$), 3.61 (dd, 1H, $J = 11.2, 5.0$), 4.29 (dd, 1H, $J = 11.8, 6.0$), 4.87 (dd, 1H, $J = 6.0, 3.5$), 5.28–5.31 (m, 2H), 6.50 (d, 1H, $J = 6.1$).

3,6,2′,3′,4′,6′-hexa-*O*-acetyl-D-cellobial (25). $[\alpha]_D^{25}$ −4.4 (*c* 0.3, $CHCl_3$.). ^{1}H NMR ($CDCl_3$): δ_H 2.00 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 3.69 (m, 1H), 3.99 (dd, 1H, $J = 7.4, 5.6$), 4.07 (dd, 1H, $J = 12.3, 2.2$), 4.14 (m, 1H), 4.19 (dd, 1H, $J = 11.9, 6.2$), 4.31 ((dd, 1H, $J = 12.4, 4.5$), 4.44 (dd, 1H, $J = 11.7, 2.5$), 4.69 (d, 1H, $J = 8.0$), 4.82 (dd, 1H, J= 6.1, 3.3), 4.98 (dd, 1H, $J = 9.4, 8.0$), 5.09 (dd, 1H, $J = 10.0, 9.4$), 5.19 (dd, 1H, $J = 9.6, 9.4$), 5.42 (m, 1H), 6.41 (d, 1H, $J = 6.1$).

3,6,2′,3′,4′,6′-hexa-*O*-acetyl-D-maltal (26)[20]. $[\alpha]_D^{25}$ +169.3 (*c* 0.6, $CHCl_3$), lit. $[\alpha]_D^{23}$ +65.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 2.01 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.10 (s, 3H), 2.13 (s, 3H), 4.03–4.05 (m, 2H), 4.11 (dd, 1H, $J = 12.3, 2.0$), 4.23 (dd, 1H, $J = 12.3, 4.1$), 4.29–4.32 (m, 1H), 4.33–4.39 (m, 2H), 4.82–4.84 (m, 2H), 5.06 (dd, 1H, $J = 10.0, 9.9$), 5.18 (dd, 1H, $J = 4.2, 4.1$), 5.41 (dd, 1H, $J = 10.0, 9.9$), 5.50 (d, 1H, $J = 4.0$), 6.44 (d, 1H, $J = 6.2$).

3,6,2′,3′,4′,6′-hexa-*O*-acetyl-D-lactal (27)[20]. $[\alpha]_D^{25}$ −8.5 (*c* 0.5, $CHCl_3$), lit. $[\alpha]_D^{23}$ −16.4 (*c* 1.4, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ_H 1.98 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.16 (s, 3H), 3.91 (dd, 1H, $J = 7.1, 6.4$), 4.00 (dd, 1H, $J = 7.4, 5.5$), 4.09 (dd, 1H, J= 11.2, 7.2), 4.14–4.17 (m, 2H), 4.20 (dd, 1H, $J = 11.8, 6.1$), 4.44 (dd, 1H, $J = 11.7, 2.5$), 4.66 (d, 1H, $J = 8.0$), 4.84(dd, 1H, $J = 6.1, 3.3$), 5.01 (dd, 1H, $J = 10.6, 3.5$), 5.19 (dd, 1H, $J = 10.4, 8.0$), 5.37 (d, 1H, $J = 2.6$), 5.41 (dd, 1H, $J = 4.1, 3.9$), 6.41 (d, 1H, $J = 6.1$).

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