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Electrochemical formation of glycals in THF

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Abstract—A new method is presented to produce unsaturated sugars from glycosyl bromides. This work offers a simplification of existing electrochemical approaches to these types of species and is amenable to scale up for large-scale production. In addition, this work is intended to provide a means of employing electrochemistry that can be duplicated in most organic chemistry laboratories using readily available glassware and equipment. © 2001 Elsevier Science Ltd. All rights reserved.

Glycals are versatile and useful intermediates in organic synthesis. They have been employed in natural product synthesis,¹ *C*-glycoside formation² and oligosaccharide preparation.³ Traditionally these unsaturated sugars have been prepared via the reduction of glycosyl halides by various metallic or organometallic reagents.⁴ Electrochemistry has also been utilized, but the procedure required the use of a mercury cathode, a divided electrochemical cell, and acidic conditions.⁵ We sought to develop a convenient and general set of conditions that would avoid the use of mercury, and could be employed by electrochemists and non-electrochemists alike. In this letter we report the achievement of these objectives by utilizing controlled current electrolysis.

We initially investigated the reduction of acetobromoglucose (1) to tri-(O)-acetyl glucal (2) as a model reaction. As depicted in Scheme 1, a concern is the ability of transient acetate (produced as the reaction progresses) to form elimination and substitution products (3 and 4). Our initial investigations, conducted in a divided electrochemical cell, led us to conclude that we could limit these unwanted side-reactions by increasing the current density (and thus limiting the reaction time) of the reduction. We realized that the utilization of undivided cells would not only allow us to reach the high currents desired, but also greatly simplify the reaction conditions.

Though electrochemical oxidations are commonly performed in single cells, electrochemical reductions under these conditions are less common. However, the recent development of sacrificial anodes⁶ has greatly increased the practicality of undivided cells for constant current reductions. By using a reticulated vitreous carbon (RVC) cathode⁷ and a consumable zinc anode under constant current conditions we were able to achieve the rapid (reactions typically last less than 20 min) conversion of **1** to glycal **2** in excellent yield (Scheme 2). We



Scheme 1. Reactivity patterns of glycosyl bromides.

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RVC cathode, zinc anode Controlled current electrolyisis in undivided cell

Scheme 2. Electrochemical reduction of glycosyl bromides. See Fig. 1 and Table 1.

have since applied these conditions to a variety of other substrates and the results are shown in Table 1. The yields vary from fair to excellent. Note that this method is also applicable to compounds possessing acid-sensitive protecting groups (entry 9), which are incompatible with the classical Fischer–Zach zinc/acetic acid method of glycosyl halide reduction.⁸ In addition, these conditions appear to be tolerant of potentially sensitive protecting groups such as benzyl ethers (entry 10) which

Table 1. Electrochemical formation of glycals from glycosyl bromides

Entry	glycosyl halide	product	yield (%) ^a
1	AcO AcO AcO AcO Br	AcO AcO AcO	90
2	AcO OAc AcO OAc AcO Br	AcO AcO AcO	84
3	BzO BzO BzO BzO BzO Br	BzO BzO BzO	74
4	AcO OAc AcO AcO Br	AcO OAc AcO	48
5	H ₃ C OAc AcO O AcO Br	AcO AcO	42
6	AcO AcO AcO Br	AcO AcO	44
7	AcO AcO AcO OAc AcO OAc AcO	AcO AcO AcO OAc OAc OAc	57
8	AcO AcO AcO Br AcO O O OAc OAc	AcO AcO AcO AcO OAc	68
9	ACO Br	Aco Zo	55
10	BnO AcO AcO AcO Br	BnO AcO AcO	47
	Entry 1 2 3 4 5 6 7 8 9 10	Entryglycosyl halide1 $AcO \\ AcO \\ AcO \\ AcO \\ Br2AcO \\ AcO \\ AcO \\ Br3BzO \\ BzO \\ BzO \\ Br3BzO \\ BzO \\ Br4AcO \\ AcO \\ AcO \\ Br5AcO \\ AcO \\ AcO \\ AcO \\ Br6AcO \\ AcO \\ Br7AcO \\ AcO \\ Br9AcO \\ AcO \\ Br10BnO \\ AcO \\$	Entryglycosyl halideproduct1 $A_{CO}^{ACO} \rightarrow O_{AC}^{O}$ $A_{CO}^{ACO} \rightarrow O_{AC}^{O}$ 2 $A_{CO}^{ACO} \rightarrow O_{AC}^{O}$ $A_{CO}^{ACO} \rightarrow O_{AC}^{O}$ 3 $B_{ZO}^{BZO} \rightarrow O_{Br}^{O}$ $B_{ZO}^{BZO} \rightarrow O_{Br}^{O}$ 4 $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ 5 $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ 6 $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ 7 $A_{CO}^{CO} \rightarrow O_{AC}^{O} \rightarrow O_{AC}^{O}$ $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ 8 $A_{CO}^{CO} \rightarrow O_{AC}^{O} \rightarrow O_{AC}^{O}$ $A_{CO}^{CO} \rightarrow O_{AC}^{O}$ 9 $A_{CO}^{CO} \rightarrow O_{AC}^{O} \rightarrow O_{AC}^{O}$ $A_{CO}^{O} \rightarrow O_{AC}^{O}$ 10 $A_{CO}^{ACO} \rightarrow O_{AC}^{O} \rightarrow O_{AC}^{O}$ $B_{DO}^{O} \rightarrow O_{AC}^{O}$

^alsolated yield after column chromatography.



Figure 1. Electrochemical cell employed in preparative electrolysis.

can be cleaved using reductive electrochemistry.⁹ A typical experimental setup is illustrated in Fig. 1.

The reaction likely involves direct reduction of the carbon-bromine bond at the cathode followed by rapid elimination of the neighboring acetate group to provide the glycal. However, we cannot rule out the possible role of highly activated zinc (formed at the cathode surface due to oxidation of the zinc anode followed by reduction of the resulting zinc salts at the cathode) produced as the reaction proceeds. There also exists the possibility of the zinc salts participating as Lewis acidic species to activate the carbon-bromine bond towards cleavage. We intend to pursue further investigations into these possibilities.

In conclusion, we have developed a simplified electrochemical approach to glycals employing constant current electrochemistry conducted in a single cell using a consumable zinc anode. This approach allows for the use of inexpensive and readily available materials to quickly produce large amounts of unsaturated sugars. This method also avoids the use of acidic conditions or large amounts of organometallic reagents.

General procedure: A small (30 mL) cylindrical cell (Fig. 1) was charged with 20 mL of freshly distilled THF and 1.0 g of LiClO₄ (final concentration: 0.5 M). The solution was thoroughly deaerated with a stream of nitrogen and fitted with a RVC cathode and zinc anode. 300 mg of the appropriate glycosyl halide (prepared as previously described¹⁰) was introduced and a controlled current of 400–500 mA was passed through the cell until the reaction was judged complete by TLC (2–4 F/mol).¹¹ The crude electrolyte was then concentrated and the residue partitioned between water (30 mL) and ether (30 mL). The layers were separated and the aqueous layer was extracted with additional ether (2×30

mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel using ether/pentane solutions as eluant. All products had NMR spectra in agreement with previously published data.^{8b,10b}

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- 11. The cell warms at this point due to the high electrical current. This can be controlled by immersing the cell in an ice bath. We found that this heating has no deleterious effect on the reaction.