Oligosaccharide Synthesis Based on a One-pot Electrochemical Glycosylation–Fmoc Deprotection Sequence

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We have found that tetrabutylammonium triflate (Bu_4NOTf) serves as an effective electrolyte for electrochemical glycosylation using thioglycosides. Based on this method, a one-pot electrochemical glycosylation–Fmoc group deprotection sequence has been developed. This sequence has been successfully applied to the synthesis of a pentasaccharide.

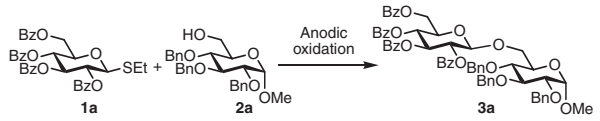
The chemical synthesis of oligosaccharides plays a crucial role in recent carbohydrate studies.[1] Among many glycosyl donors for chemical glycosylations, thioglycosides serve as powerful building blocks from a practical point of view, because thioglycosides are stable under atmospheric conditions and are compatible with a variety of reaction conditions. Indeed, many chemical glycosylation strategies are based upon the use of thioglycosides as both donors and acceptors.[2] However, such strategies suffer from the use of strong oxidizing reagents for activation of thioglycosides, which might affect other functional groups during the reaction.[3]

Electrochemical oxidation is a powerful method for oxidizing organic compounds under mild conditions.[4] Electrochemical glycosylations using various glycosyl donors have been reported by several groups.[5] A single-electron-transfer (SET) reagent was also effective for glycosylations.[6] Thus, it was evident that electron-transfer reactions are useful for activation of glycosyl donors.

Recently, we reported that electrochemical oxidation of thioglycosides followed by the reaction with glycosyl acceptors led to effective glycosylation.[7] Tanaka and co-workers also reported the electrochemical activation of thioglycosides in the absence of a nucleophile.[8] Nokami and co-workers revealed that thioglycosides having benzoyl groups are readily activated electrochemically in the presence of catalytic amount of NaOTf.[9] Very recently, we revealed that glycosyl triflates are accumulated in the electrochemical oxidation of thioglycosides using Bu_4NOTf by low-temperature NMR studies.[10] Although various methods based on electrochemical glycosylations have been reported, the development of new methods that are practically useful for synthesis of a variety of oligosaccharides is still needed. In this paper, we report a method based on one-pot electrochemical glycosylation–Fmoc deprotection sequence and its application to the synthesis of a pentasaccharide.

We initiated our study by investigating several solvent/electrolyte systems for the reaction of glycosyl donor **1a** (0.1 mmol) and glycosyl acceptor **2a** (0.1 mmol) under constant current conditions at room temperature (Table 1).[11] The glycosylation using Bu_4NClO_4 as a supporting electrolyte in CH_3CN (Entry 1) and CH_2Cl_2 (Entry 2) gave 1,6-anhydroglucoside and methyl tetrabenzoylglucoside as major products. The electrochemically generated acid seems to be responsible for the formation of these products, because ClO_4^- is known to generate a very strong acid under electrolytic conditions.[12] Use of Bu_4NBF_4 gave the desired disaccharide **3a** in moderate yields (Entries 3 and 4). The yields were further improved using Bu_4NOTf as an electrolyte (Entries 5 and 6). CH_2Cl_2 was found to be superior to CH_3CN as solvent. Therefore, hereafter we use a Bu_4NOTf/CH_2Cl_2 system for glycosylation reactions.

Table 1. Effect of solvent/electrolyte systems for electrochemical glycosylation



Entry	Solvent	Electrolyte	Selectivity	Yields/%
1	CH_3CN	Bu_4NClO_4	β only	trace
2	CH_2Cl_2	Bu_4NClO_4	β only	30
3	CH_3CN	Bu_4NBF_4	β only	65
4	CH_2Cl_2	Bu_4NBF_4	β only	44
5	CH_3CN	Bu_4NOTf	β only	70
6	CH_2Cl_2	Bu_4NOTf	β only	79

The electrochemical glycosylation with several donors **1a**, **4**, and **5** and acceptors **2a** and **2b** were examined and the results are summarized in Figure 1. In some cases, the reaction suffered from low yields of the products, but yields were improved using an excess amount of a donor (1.2–1.5 equiv).

For sequential oligosaccharide synthesis, it is necessary to introduce at least one temporary protecting group to hydroxy groups of glycosyl donors. Several protecting groups such as, *tert*-butyldimethylsilyl (TBS), *p*-methoxybenzyl (PMB), and 9-fluorenylmethoxycarbonyl (Fmoc)[13] were examined to protect one of the hydroxy groups. Among these protecting groups, only

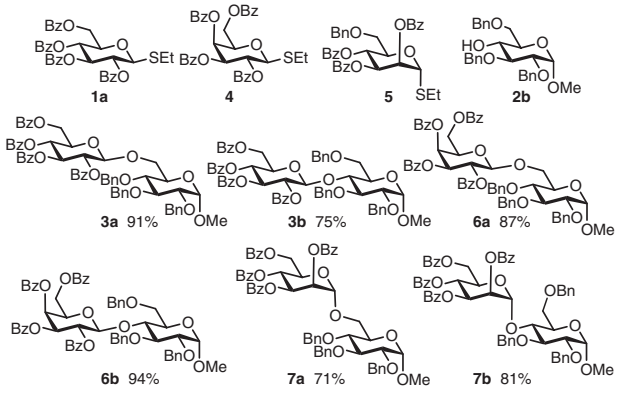
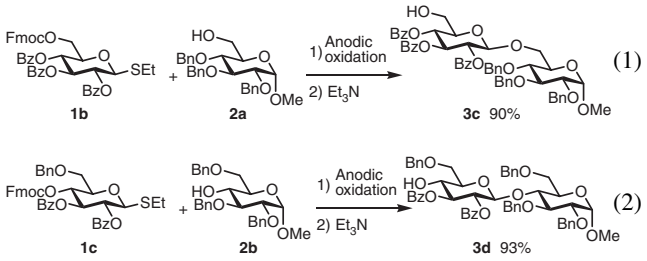


Figure 1. Disaccharide obtained by the electrochemical glycosylation.

Fmoc group was revealed to survive under the electrochemical oxidation conditions. The electrochemical glycosylations using glycosyl donors **1b** and **1c** were performed under normal conditions and thus-obtained mixtures were treated with Et_3N in the same pot (eqs 1 and 2). Quantitative removal of the Fmoc group afforded disaccharides **3c** (90%) and **3d** (93%), which could be used for the next glycosylation as accepters.



In order to demonstrate the utility of the present method involving electrochemical glycosylations followed by the one-pot Fmoc group deprotection sequence, pentasaccharide **10** was synthesized (Figure 2). The use of 1.2 equiv of thioglycoside donor **1b** for each glycosylation steps gave the corresponding pentasaccharide **10** as a single product in 63% yield over 6 steps (See Supporting Information for the details).[14]

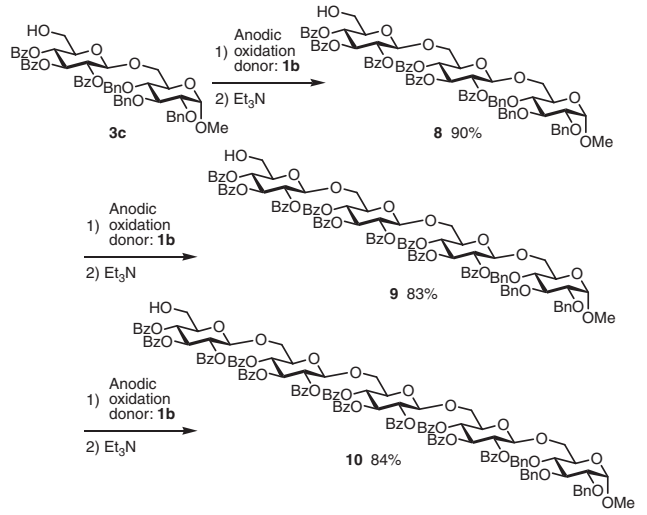


Figure 2. Sequential oligosaccharide synthesis using the electrochemical glycosylations.

In summary, we have developed a highly efficient electrochemical glycosylation reaction using Bu_4NOTf as an electrolyte. The combination of the electrochemical glycosylation with the subsequent one-pot Fmoc group deprotection serves as a highly practical method for the synthesis of oligosaccharides. The scope and limitations of the present method and its application to the synthesis of biologically active oligosaccharides are under investigation in our laboratory.

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14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/.

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