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Development of Glycosylation Using the Glucopyranose 1,2-Orthobenzoate under Electrochemical Conditions

Kohei Kawa, Tsuyoshi Saitoh, Eisuke Kaji, and Shigeru Nishiyama*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan

nisiyama@chem.keio.ac.jp

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ABSTRACT

Substituted glucopyranose 1,2-orthobenzoate undergoes β-selective glycosylation. The developed orthobenzoate derivative was stable under standard workup conditions and efficiently provided a variety of glycosides by EGA (electrogenerated acid), produced by anodic oxidation of cyclohexanol. Upon comparison with Lewis and Brønsted acids, EGA superiorly affected activation of the orthoester to afford desired glycosides possessing such aglycons as sugars, steroids, and adamantanes.

Carbohydrates play central roles in a wide variety of biological systems and as components of important bioactive natural products. Because of the importance of these substances, elucidation of their complex biological properties requires extensive structure−activity relationship studies. As a result, methods for the structural derivatization of sugar chains have received widespread attention in recent years.[1] Also, methods for creating glycoside linkages and glycans have been devised as a means to uncover the biological roles played by carbohydrates and to prepare derivatives for biological testing.[2]

In this regard, pioneering efforts from several laboratories have shown that electrochemistry provides a powerful tool for functionalizing sugars.[3] Electrochemical methods for the synthesis of complicated glycosides have several meritorious features including the environmentally benign conditions that are required and the ability to control reactivity by adjusting electric potentials. Although a few examples have been described in which this technique has been applied to the synthesis of natural products, further investigations aimed at optimizing the conditions for the chemical selectivity of the process are required.

During the course of investigations into the synthesis of biologically active substances, we observed that anodic or DDQ oxidations of benzyl ethers generate the corresponding benzaldehydes (eq 1, Figure 1).[4] Inanaga described a similar reaction of 3,4-dimethylbenzyl 2-deoxyglycosides that leads to glycosylation through alcohol capture of an oxocarbenium ion intermediate **X** (eq 2, Figure 1).[5]

(1) Gantt, R W.; Peltier-Pain, P.; Thorson, J. S. *Nat. Prod. Rep.* **2011**, *28*, 1811–1853.

(2) (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531. (b) Jacobsson, M.; Malmberg, J.; Ellervik, U. *Carbohydr. Res.* **2006**, *341*, 1266–1281. (c) Stalforth, P.; Lepenies, B.; Adibekian, A.; Seeberger, P. H. *J. Med. Chem.* **2009**, *52*, 5561–5577. (d) Liptak, A.; Borbas, A.; Bajza, I. In *Protective Group Manipulation in Carbohydrate Synthesis. In Comprehensive glycosciences*; Kamering, J. P., Boons, G.-J., Lee, Y. C., Suzuki, A., Taniguchi, N., Vorangen, A.G. J., Eds.; Elsevier: Oxford, 2007; pp 203−259. (e) Thorson, J. S.; Vogt, T. In *Glycosylated Natural Products. In Carbohydrate-based Drug Discovery*; Wong, C. H., Ed.; Wiley-VCH: Weinheim, 2003; pp 685−711. (f) Tanis, V. M.; Moya, C.; Jacobs, R. S.; Little, R. D. *Tetrahedron* **2008**, *64*, 10649–10663.

(3) (a) Noyori, R.; Kurimoto, I. *J. Org. Chem.* **1986**, *51*, 4320–4322. (b) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1990**, 718–719. (c) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922–10928. (d) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J. *J. Org. Chem.* **2002**, *67*, 8584–8592.

(4) (a) Saitoh, T.; Suzuki, E.; Takasugi, A.; Obata, R.; Ishikawa, Y.; Umezawa, K.; Nishiyama, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5383–5386. (b) Sumi, T.; Saitoh, T.; Natsui, K.; Yamamoto, T.; Atobe, M.; Einaga, Y.; Nishiyama, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5443–5446.

(5) (a) Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 85–88. (b) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Chem. Lett.* **1993**, 2013–2016. (c) Ishikawa, A.; Lee, Y. J.; Ito, Y. *Org. Biomol. Chem.* **2010**, *8*, 3596–3608.

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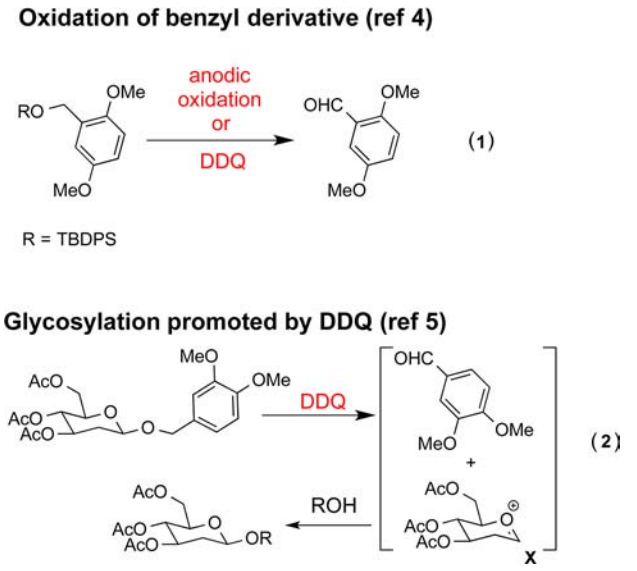
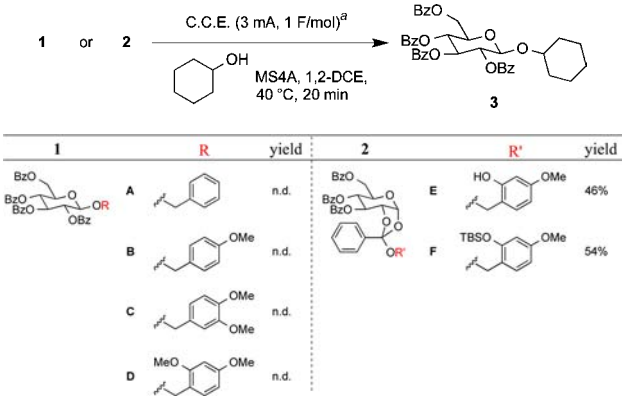


Figure 1. Oxidation of benzyl derivatives.

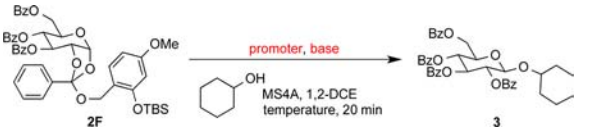
These earlier studies prompted us to develop a new electrochemical glycosylation. By utilizing the Koenig–Knorr reaction for benzyl glycoside synthesis, benzyl 2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranoside derivatives and the corresponding orthoesters were produced by reaction of a benzoyl protected 1-bromo-sugar with benzyl alcohols in the presence of Ag_2CO_3, and in moderate-to-good yields. Although several glycosylation procedures employing orthoesters have been described,[6] 1,2-*O*-(1-*N*-1-phenylethylidene-amino-oxy)-2,2-dimethylpropyridene-3,4,6-tri-*O*-pivaloyl-α-D-glucopyranose (oximate ortho-ester) was stable and used for glycosylation with alcohols involving steroids.[7] Similarly, the orthoester **2F**, prepared in this investigation, was easy to handle even when standard workup procedures and silica gel chromatography were utilized. When benzyl glycosides **1** or the corresponding orthoesters **2** were submitted to the constant current electrolysis conditions (C.C.E., 3 mA/cm^2, 1 F/mol) in the presence of cyclohexanol, only the latter substances reacted to generate the expected cyclohexyl-glycoside **3** in moderate yield. Benzyl glycosides, produced by the standard migration of the benzyloxy group in the orthoester moiety to the corresponding anomeric position, were not obtained (Table 1).

Table 1. Oxidation Reactions of Benzyl Glycoside and Orthoesters



[a] Conditions: Cell, undivided; substrate, 0.01 M; supporting salt (Bu_4NClO_4), 1 M concentration; anode, GC plate; cathode, Pt wire.

Table 2. Comparison of Reactivity of **2F** under Several Conditions



				yield (%)	
entry	promoter	base	temp (°C)	**3**	**2F**
1	C.C.E.[a]		40	54	–
2	BF_3OEt_2	–	r.t.	68	–
3	TfOH	–	r.t.	58 (β:α = 10:1)	–
4	DDQ	–	40	–	–
5	CAN	–	r.t.	–	89
6	C.C.E.[a]	2,6-litidine	40	–	67
7		DIPA		–	85

[a] Conditions: Cell, undivided; substrate, 0.01 M; supporting salt, 1 M concentration; anode, GC plate; cathode, Pt wire; current, 3 mA; 1 F/mol.

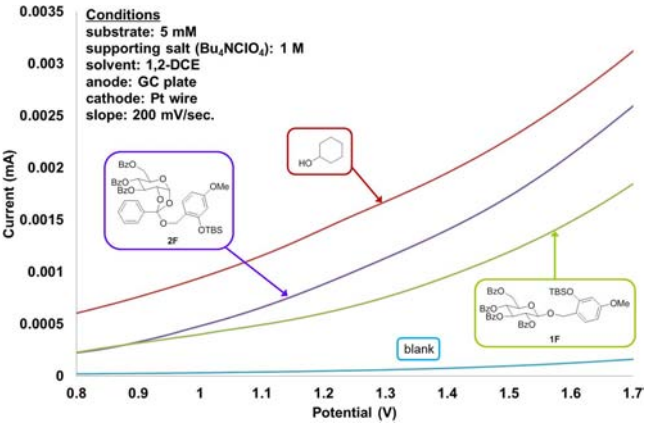
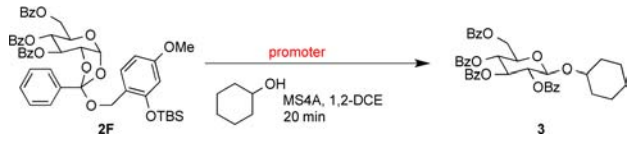


Figure 2. Comparison of LSV spectrum.

(6) (a) López, J. C.; Ventura, J.; Uriel, C.; Gómez, A. M.; Fraser-Reid, B. *Org. Lett.* **2009**, *11*, 4128–4131. (b) Yu, B.; Yang, Z. *Tetrahedron Lett.* **2000**, *41*, 2961–2964. (c) Yoshioka, T.; Uematsu, T. *Carbohydr. Res.* **1985**, *143*, 282–287. (d) Backinowsky, L. V.; Tsvetkov, Y. E.; Balan, N. F.; Byramova, N. E.; Kochetkov, N. K. *Carbohydr. Res.* **1980**, *85*, 209–221. (e) Honma, K.; Hamada, A. *Carbohydr. Res.* **1979**, *73*, 297–301. (f) Kochetkov, N. K.; Bochkov, A. F.; Sokolovskaya, T. A.; Snyatkova, V. J. *Carbohydr. Res.* **1971**, *16*, 17–27.

Table 3. EGA Activation of Glycosylation Reaction



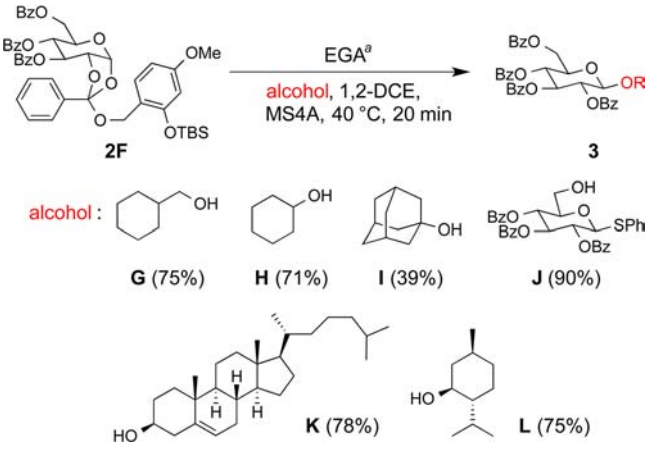
				yield (%)	
entry	promotor	equiv	supporting salt	**3**	**2F**
1	EGA[a]	3	Bu_4NClO_4	71	–
2		0.3		65	–
3	EGA[a]	3	Bu_4NPF_6	52	–
4		0.3		12	27
5	EGA[a]	3	Bu_4NBF_4	39	–
6		0.3		–	26
7	$HClO_4$	3	–	54	–
8	(ref 11)	0.3		18	36
9	BF_3OEt_2	3	–	68	–
10		0.3		12	16

[a] Preparation: Cell, divided; substrate, 0.01 M; supporting salt, 1 M concentration; anode, GC plate; cathode, Pt wire; current, 3 mA; 1 F/mol.

If these reactions proceed by a plausible pathway, involving oxidative conversion of the benzylic moiety as depicted in Figure 1, benzaldehyde derivatives should be generated as side products. However, production of cyclohexyl-glycoside **3** indicated that oxocarbenium ion **X** (Figure 1, eq 2) served as intermediates in these processes, although no benzaldehyde derivatives were formed. To determine if this finding was a consequence of overoxidation to polymers, the benzaldehydes were submitted to the electrochemical oxidation conditions for time periods over 3 h. In each case, the aldehyde was recovered and only deprotection of the silyl group was observed to occur, when contained in substrates.

These observations indicated that an acid generated in the electrolytic reaction system promoted the glycosylation reaction, rather than the anodic oxidation process.[8] To confirm this possibility, electrochemical and typical chemical reactions of orthoester **2F** were examined (Table 2). The results demonstrated that no desired reaction took place when either DDQ or CAN was used as the chemical oxidant (entries 4, 5) and that the desired glycosylation product **3** was smoothly produced when Lewis or Brønsted acids were utilized as promoters (entries 2, 3).

Scheme 1. Glycosylation Promoted by EGA Using Various Alcohols



[a] Preparation: Cell, undivided; substrate, 0.01 M; supporting salt, 1 M concentration; anode, GC plate; cathode, Pt wire; current, 6 mA; 3 F/mol.

Furthermore, **2F** remained unreactive when bases were present in the electrochemical reaction mixture (entries 6, 7). Thus, it appeared that acid generated *in situ* in the electrochemical oxidation reaction mixture served as a catalyst for the glycosylation reaction.

The electrochemical behavior of the glycosyl donor **2F** and cyclohexanol were inspected using LSV measurements (Figure 2). The results showed that oxidation of cyclohexanol took place preferentially in contrast to the glycosyl donor **2F** at *ca.* 40 °C. Consequently, oxidation of cyclohexanol rather than **2F** occurs to generate an acid catalyst. This proposal was supported by the observation that glycosylation with **2F** did not take place under the reaction conditions without cyclohexanol.

Thus, the glycosylation reactions were promoted by an electrochemically generated acid (EGA),[9] which might be anhydrous $HClO_4$, produced *via* the reaction of the proton generated at the anode, and ClO_4^- from the supporting salt. To understand the effect of the EGA, glycosylation of **2F** was carried out by addition of the EGA, prepared in advance by using electrolysis conditions (Table 3, entries 1–6) in a divided cell to avoid the effect of the amine generated by reduction of a quaternary ammonium cation at the cathode.[9,10] EGA, carrying the ClO_4 anion (entries 1, 2), effected better results than others (entries 3–6). In comparison with Lewis and Brønsted acids (entries 7–10), even a catalytic amount of EGA (entry 2) promoted a more effective reaction (Table 3). In addition, no glycosylation took place in the absence of cyclohexanol, when the EGA was prepared under the pre-electrolysis conditions.

To explore the utility of this process, the glycosylation protocol was applied to various alcohols (Scheme 1).

(7) (a) Kunz, H.; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41–48. (b) Kunz, H.; Pfrengle, W. *Chem. Commun.* **1986**, 713–714.

(8) Although 2 F/mol of electricity was required in a plausible reaction mechanism, **3** was obtained with only 1 F/mol of electricity. This phenomenon also supported this idea.

(9) (a) Uneyama, K. In *Electrochemistry 1*; Steckhan, E., Ed.; Springer: Berlin/Heidelberg, 1987; Vol. 142, pp 167–188. (b) Torii, S. *Electroorganic Synthesis, Part 1, Oxidation Methods, Applications*; Verlag Chemie: Weinheim, 1985; pp 188–192. (c) Uneyama, K.; Isimura, A.; Torii, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1859. (d) Nielsen, M. F. In *Encyclopedia of Electrochemistry*; Shäfer, H. J., Ed.; Wiley-VHC: Weinheim, 2004; Vol. 8, pp 451–488. (e) Matsuo, K.; Shimazaki, H.; Sanada, T.; Shimada, K.; Hagiwara, S.; Suga, S.; Kashimura, S.; Yoshida, J. *Chem. Lett.* **2013**, *42*, 843–845.

(10) Whereas the desired reaction did not occur when an undivided cell was employed (starting material recovered: 91%), the desired reaction was conducted in a divided cell (71% yield, 20 min).

(11) $HClO_4$ was purchased as 70% aqueous solution. To reduce the amount of water contained, experiments were carried out in the presence of MS4A.

With the exception of adamantanol **3I**, which is a sterically encumbered alcohol, the other alcohols **G**−**L** participated in successful glycosylation reactions with **2F** to afford the corresponding glycosides **3G**−**L** in moderate to high yields.

In conclusion, the study described above has uncovered novel electrochemically induced glycosylation reactions of the glucopyranose orthobenzoate **2F** with a variety of glycosyl acceptors that were promoted by an alcohol-derived EGA. Moreover, the results showed that the orthoester prepared is stable under standard purification conditions. Although the mechanistic details about how it is generated in this process are still unresolved, the EGA serves as a superior catalyst than Lewis and Brønsted acids for this process.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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