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Electrochemical O-glycosylation using thioglycosides as glycosyl donors in the presence of a catalytic amount of sodium trifluoromethanesulfonate as a supporting electrolyte

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This Letter is dedicated to Professor Yoshihiko Ito in memorial

Abstract—Electrochemical O-glycosylation of primary alcohols with O-protected thioglycosides was performed in the presence of a small amount of sodium trifluoromethansulfonate (12.5 mol % to glycosyl acceptor) as a supporting electrolyte. The reaction was successfully carried out in an undivided cell to give *O*-glycosides in good yields with a high electro-efficiency (ca. 1 F/mol) at 15 °C in acetonitrile.

The biological significance of glycoconjugates has stimulated much synthetic activity in glycoside synthesis. One of the most essential and attractive reactions for glycosides is 'glycosylation reaction' in which a leaving group on the anomeric carbon of glycosyl donor is required to be stereoselectively replaced by an aglycon conveniently in good yields.[1] Though numerous methods by a combination of glycosyl donor, having a leaving group on the anomeric carbon, with its suitable activator are available to date, the development of new methods that promote glycosylation in a general and convenient manner is still very desirable. Thioglycosides, where an anomeric hydroxy group is replaced by an alkylthio or arylthio group, have recently attracted considerable attention as glycosyl donors, because of their stability, accessibility, and compatibility.[2] They offer sufficient temporary protection at the anomeric center and present several alternative possibilities for regioselective activation to generate glycosyl donor properties. For example, thioglycoside activators include *N*-iodosuccinimide/trifluoromethanesulfonic (triflic) acid combination (NIS/TfOH),[3] *N*-bromosuccimide (NBS)/TfOH,[4a] Et_3SiOTf,[4b] or 4 Å molecular sieves[4c,7] combination, dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (DMTST),[5] methyl triflate (MeOTf),[6] methylsulfenyl triflate (MeSOTf),[7] benzeneselenyl triflate (PhSeOTf),[8] iodonium dicollidine perchlorate (IDCP),[3] 1-(benzenesulfinyl)piperidine (BSP)/triflic anhydride (Tf_2O),[9] and more recently *N*-(phenylthio)caprolactam/(Tf_2O)[10] as well as earlier methods for activation including mainly mercury(II), copper(II), and lead(II) salts.[11] In these reactions, more than an equimolar (theoretical) amount of an activator was commonly required for completion of the reaction.

In our previous study on electrochemical glycosylation, we disclosed that electrochemical N-glycosylation was successfully carried out using O-protected arylthio(deoxy)ribose derivatives as donors and silylated pyrimidines as acceptors in the presence of only 10 mol % of NBS or Br_2, in which a bromonium ion (Br^+), formed from $Br^{\bullet}$ or Br^- by electrolysis, serves as an effective activator of thioglycoside **1** and bromine atom will be reused as a mediator of the reaction.[12]

As a matter of course the glycosylation by an activator generated in situ via electrolysis in the presence of a catalytic amount of mediator is more advantageous than

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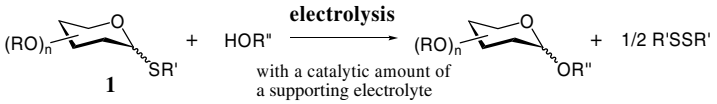
that using a stoichiometric amount of an activator. This led us to study further not only the electrochemical N-glycosylation but also the O-glycosylation using a small amount of a mediator or a supporting electrolyte. There are many reports on O-glycosylation with glycosyl donors activated by electrolysis using an excess amount of supporting electrolytes.[13]

Here we describe a convenient electrochemical O-glycosylation reaction of alcohols using thioglycosides **1** as glycosyl donors in the presence of a *small amount* of a supporting electrolyte (or a mediator) for activation of **1** as shown in Eq. 1.



(1)

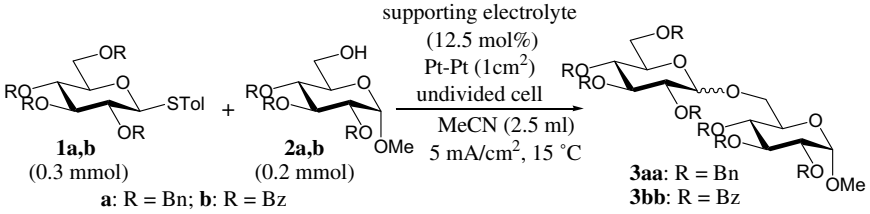
First, electrolysis was performed between benzyl protected *p*-tolylthioglucopyranoside **1a** and methyl 2,3,4-tri-*O*-benzylglucopyranoside **2a** to give methyl (2,3,4,6-tetra-*O*-benzyl-α- and β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3aa**,[14] in the presence of a small amount of a supporting electrolyte, which served as an activator of thioglycosides by electrolysis. Electrolysis with sodium trifluoromethanesulfonate (12.5 mol % of glycosyl acceptor) gave *O*-glycoside in good yield with a high electro-efficiency as well as that with lithium perchlorate (Table 1, entries 1, 3 and 4), although electrolysis in the presence of 10 mol % of NBS or Br_2 was ineffective.[15] Furthermore, sodium trifluoromethanesulfonate was revealed to be more effective than lithium perchlorate for the reaction of benzoyl protected *p*-tolylthioglucopyranoside **1b** with 2,3,4-tri-*O*-benzoylglucopyranoside **2b** to give methyl (2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **3bb**[13h] as shown in Table 1 (entries 6 and 8).

It has been reported by Yamago and Yoshida that the addition of benzoic acid is effective for decreasing by-products formation caused by hydrolysis due to an electrogenerated base.[13h] We found that sodium trifluoromethanesulfonate served as an efficient supporting electrolyte only with 12.5 mol % in acetonitrile (ca. 0.01 M).[17] It is assumed that the glycosylation would take place directly at the anode via electrochemical oxidation of thioglycosides as shown in Scheme 1.

Then, we applied this reaction to the O-glycosylation of various alcohols **2a**–**h** with thioglycosides **1b**–**e** to give the corresponding glycosides **3** in good yields. Results of the reaction with primary alcohols are summarized in Tables 2 and 3, and those with secondary alcohols are listed in Table 4.

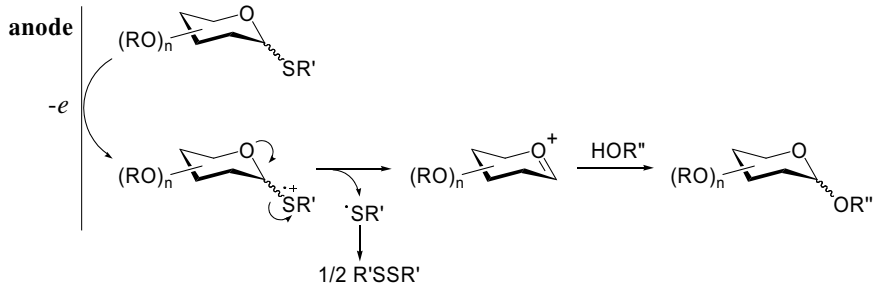
In the electrochemical glycosylation of secondary alcohols the yield of the corresponding glucosides was moderate. The difference of reactivity between primary alcohol and secondary alcohol was clearly observed in the glycosylation of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **2m** and methyl 3,4-di-*O*-benzyl-α-D-glucopyranoside **2n** with **1b**, in which the corresponding methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3 and 3,4-di-*O*-benzyl-α-D-glucopyranosides **3bm**, 3**bn** were obtained selectively in 88% and 67% yields, respec-

Table 1. Electrochemical O-glycosylation of **2a**,**b** with thioglycoside **1a**,**b**[a]



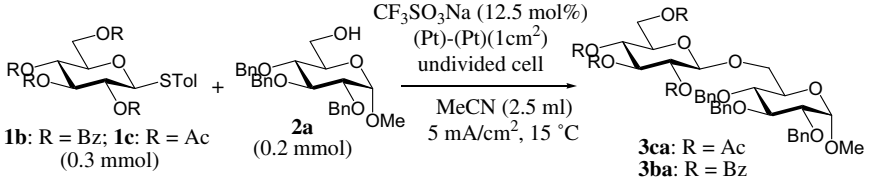
Entry	1	2	Electrolyte	Additive[b]	Electricity[c] (F/mol)	Applied voltage (V)	Yield of 3 (%)		α:β[d]
1	**1a**	**2a**	$LiClO_4$	—	1.0	5–10	**aa**	88	0.26:1
2	**1a**	**2a**	Bu_4NClO_4	—	1.0	2–10	**aa**	42	0.23:1
3	**1a**	**2a**	CF_3SO_3Na	—	1.0	8–30	**aa**	81	0.24:1
4	**1a**	**2a**	CF_3SO_3Na	—	1.3	5–25	**aa**	87	0.22:1
5	**1b**	**2b**	$LiClO_4$	—	1.0	5–100	**bb**	33	β only
6	**1b**	**2b**	$LiClO_4$	$PhCO_2H$ (0.2 mmol)	1.0	2–95	**bb**	71	β only
7	**1b**	**2b**	CF_3SO_3Na	—	1.0	5–15	**bb**	57	β only
8	**1b**	**2b**	CF_3SO_3Na	$PhCO_2H$ (0.2 mmol)	1.0	5–20	**bb**	84	β only

[a] Reactions were performed using **1a**,**b** (0.3 mmol) and **2a**,**b** (0.2 mmol). For reaction conditions, see Ref. 15.
[b] See Ref. 13h.
[c] Electricity based on thioglycoside **1a**,**b**.
[d] Determined by ^1H NMR.



Scheme 1. Direct electrochemical O-glycosylation of alcohols.

Table 2. Electrochemical O-glycosylation of **2a** with thioglycoside **1b**,**c**[a]



Entry	Thioglycoside	PhCOOH[b]	Electricity[c] (F/mol)	Applied voltage (V)	Yield of **3** (%)		α:β[d]
1	**1c**	—	1.0	5–20	**3ca**[16]	52[e]	β
2	**1c**	0.2 mmol	1.0	5–15	**3ca**[16]	55[e]	β
3	**1b**	—	1.0	10	**3ba**[14]	81	β

[a] Reactions were performed using **1b**,**c** (0.3 mmol) and **2a** (0.2 mmol) as described in Ref. 15.
[b] See Ref. 13h.
[c] Electricity based on thioglycoside **1**.
[d] Determined by ^{1}H NMR.
[e] *Ortho* ester **4ca** was obtained in ca. 20% yield together with **3ca**.

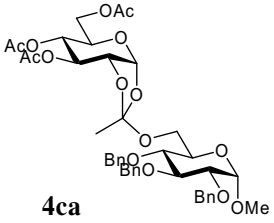
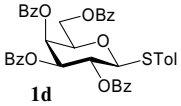
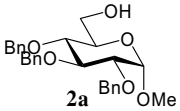
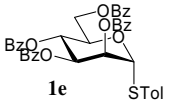
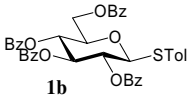
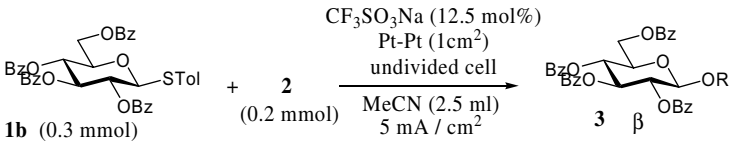


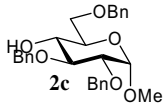
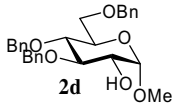
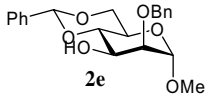
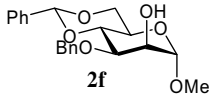
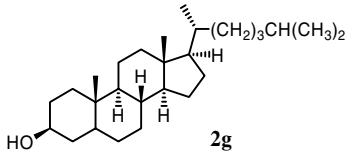
Table 3. Electrochemical O-glycosylation of primary alcohols **2** with thioglycoside **1b**,**d**,**e**[a]

Entry	Donor	Acceptor	Electricity[b] (F/mol)	Applied voltage (V)	Yield of **3** (%)	α:β[c]	
1	 **1d**	 **2a**	1.0	7–12	**3da**	80	β
2	 **1e**	**2a**	1.7	10–15	**3ea**[18]	76	α
3[d]	 **1b**	*n*-C_8H_{17}–OH **2h**	1.0	10	**3bh**	82	β

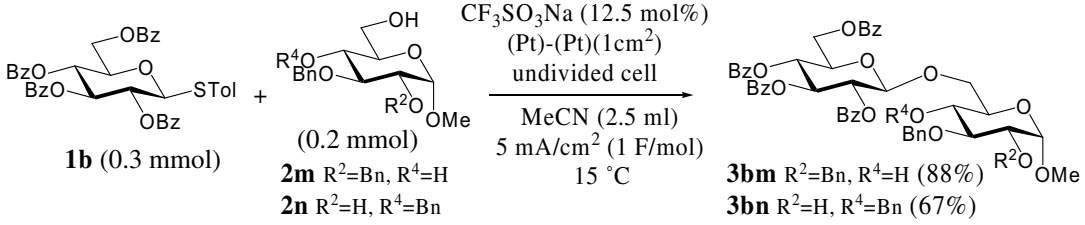
[a] Reactions were performed using acceptor **2a**,**h** (0.2 mmol) and donor **1b**,**d**,**e** (0.3 mmol) as described in Ref. 15.
[b] Electricity based on thioglycosides (donors).
[c] Determined by ^{1}H NMR.
[d] Performed at 60 °C.

Table 4. Electrochemical O-glycosylation of secondary alcohols **2c**–**g** with thioglycoside **1b**[a]



Entry	Acceptor R–OH	Temperature (°C)	Electricity[b] (F/mol)	Applied voltage (V)	Yield of **3** (%)
1	 **2c**	15	1.3	8	**3bc**[14] 54
2	 **2d**	15	1.0	5–10	**3bd**[18] 48
3	 **2e**	15	1.0	10–20	**3be** 35
4	 **2f**	15	1.0	10–20	**3bf** 47
5[c]	 **2g**	40	1.3	8–15	**3bg**[19] 46

[a] Reactions were performed using **1b** (0.3 mmol) and **2c**–**g** (0.2 mmol) as described in Ref. 15.
[b] Electricity based on thioglycoside **1b**.
[c] Performed in propanenitrile in the presence of benzoic acid (0.2 mmol).



Scheme 2. Regioselective electrochemical O-glycosylation of diols **2m** and **2n**.

tively, without any formation of the products reacted at the secondary alcohol (Scheme 2).

Acknowledgement

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References and notes

1. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem* **1994**, *50*, 21–123.
2. Oscarson, S. In *Carbohydrates in Chemistry and Biology*; Eanst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 93–116.
3. (a) Veenenman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278; (b) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334; (c) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313–4316.
4. (a) Sasaki, M.; Tachibana, K.; Nakanishi, H. *Tetrahedron Lett.* **1991**, *32*, 6873–6876; (b) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 191–192; (c) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434.
5. (a) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9–C12; (b) Andersson, F.; Fügedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919–3922.

6. Lünn, H. *Carbohydr. Res.* **1985**, *139*, 105–113, 115–121.
7. Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13–C17.
8. Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061–1064.
9. (a) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020; (b) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640–4646.
10. Durón, S. G.; Polat, T.; Wong, C.-H. *Org. Lett.* **2004**, *6*, 839–841.
11. (a) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 55–61; (b) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. *Chem. Lett.* **1979**, 487–490; (c) van Cleve, J. W. *Carbohydr. Res.* **1979**, *70*, 161–164; (d) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17–C22; (e) Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162–165; (f) Tsai, T. Y. R.; Jin, H.; Wiesner, K. *Can. J. Chem.* **1984**, *62*, 1403–1405; (g) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300–314; (h) Woodward, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 3215–3217; (i) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *43*, 3489–3493.
12. Nokami, J.; Osafune, M.; Ito, Y.; Miyake, F.; Sumida, S.; Torii, S. *Chem. Lett.* **1999**, 1053–1054.
13. Electrochemical O-glycosylation from thioglycosides (a) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinaÿ, P. *JCS., Chem. Commun.* **1990**, 718–719; (b) Mallet, J.-M.; Meyr, G.; Yvelin, F.; Jutand, A.; Amatore, C.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *244*, 237–246; (c) Amatore, C.; Jutand, A.; Meyr, G.; Bourhis, P.; Machetto, F.; Mallet, J.-M.; Sinaÿ, P.; Tabeur, C.; Zhang, Y.-M. *J. Appl. Electrochem.* **1994**, *24*, 725–729; (d) Balavoine, G.; Gref, A.; Fischer, J.-C.; Lubineau, A. *Tetrahedron Lett.* **1990**, *31*, 718–719; (e) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-C.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1217–1236; (f) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-C.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1237–1249; That from telluroglycosides, (g) Yamago, S.; Kokubo, K.; Yoshida, J.-i. *Chem. Lett.* **1997**, 111–112; (h) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J.-i. *J. Org. Chem.* **2002**, *67*, 8584–8592; Electrochemical glycosyl transfer from aryl 2,3,4,6-tetrabenzylglucopyranoside or aryl (2,3,4,6-deprotected)glucopyranoside to alcohols, (i) Noyori, R.; Kurimoto, I. *J. Org. Chem.* **1986**, *51*, 4322–4323.
14. Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597–7598.
15. An acetonitrile (2.5 mL) solution of thioglycoside **1** (0.3 mmol), alcohol **2** (0.2 mmol), and sodium trifluoromethanesulfonate (4.3 mg, 0.025 mmol) was electrolyzed in an undivided cell with two platinum plates (1 cm × 1 cm) as an anode and a cathode. Electrolysis was carried out under an inert atmosphere at a constant current (5 mA/cm^2) with stirring at 15 °C. After 1.0 F/mol of electricity was applied, acetonitrile was removed in vacuo. The reaction mixture was added with water and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the corresponding *O*-glycoside in the yields as shown in Tables. On the other hand, the electrolysis, performed by constant current (5 mA/cm^2, ca. 1 F/mol) with **1a** (0.2 mmol) and **2a** (0.3 mmol) in propanenitrile (2 mL) at 15 °C in the presence of 10 mol % of NBS or Br_2 in an undivided cell using platinum electrodes, gave unsatisfactory results (isolated yields of **3aa** < 40%).
16. Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51*, 4923–4932.
17. The yields (80–90%) were not influenced directly by the concentration of the supporting electrolyte (TfONa) (0.01 M–0.001 M). However, a higher applied voltage was required for a lower concentration electrolysis; for example, it became >30 V for 0.001 M to keep 5 mA/cm^2 of constant current density when 1 F/mol of electricity had been passed. Electrolysis under higher voltage has some disadvantages to keep the reaction temperature low (15 °C) and to carry out the electrolysis by low electricity.
18. Pornsuriyasak, P.; Demchenko, A. V. *Chem. Eur. J.* **2006**, *12*, 6630–6646.
19. Deng, S.; Yu, B.; Xie, J.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 7265–7266.