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Electrooxidative Glycosylation through C–S Bond Cleavage of 1-Arylthio-2,3-dideoxyglycosides. Synthesis of 2′,3′-Dideoxynucleosides

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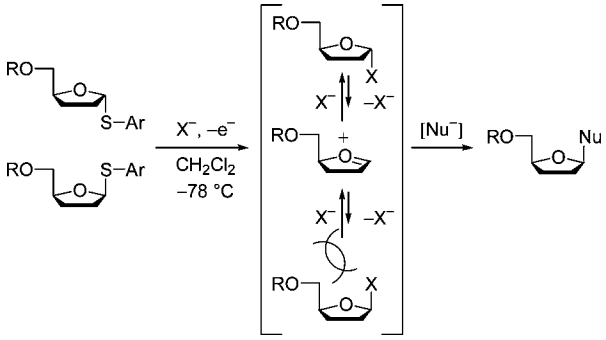
ABSTRACT



The electrooxidative glycosylation of newly designed 1-arylthio-substituted 2,3-dideoxyglycosides is described. The halide salt-mediated electrooxidation utilizing either of the α- or *β*-thiodideoxyglycosides proceeded smoothly at −78 °C to give dideoxynucleosides in a *β*-selective manner, presumably through a 1-halo-substituted glycosyl donor.

2′,3′-Dideoxynucleosides are of considerable interest because several of these derivatives exhibit potent antiviral activity against HIV (Figure 1).[1] In the synthesis of 2′,3′-dideoxynucleosides, selective formation of the *β*-glycosidic linkage is critical since only the *β*-anomers show significant biological activity. The glycosylation of nucleobases using thioglycosides is one of the most effective methods for preparing nucleosides and has been investigated intensively.[2] The stereochemical outcome at the anomeric position is mainly determined by neighboring group effects from the group at

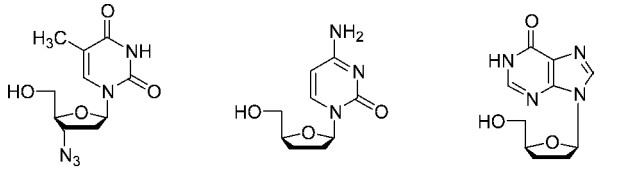


Figure 1. Potent anti-HIV reagents.

(1) (a) Herdewijn, P.; Balzarini, J.; De Clercq, E. 2′,3′-Dideoxynucleoside Analogues as Antiviral Agents. In *Advances in Antiviral Drug Design*; De Clerck, E., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 1. (b) De Clercq, E. *Trends Pharmacol. Sci.* **1990**, *11*, 198. (c) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D. B.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096. (d) Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Daugeuet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868. (e) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500.

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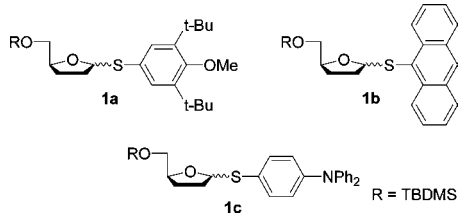
C2 in the glycosyl donors. However, anchimeric assistance cannot be used in the synthesis of 2′-deoxynucleosides because of the lack of a participatory group at C2′. Therefore, the development of efficient methods for the synthesis of β-anomers of 2′,3′-dideoxynucleosides (in a stereoselective manner) is still an important issue.

Divalent sulfur compounds have received much attention as targets for electrooxidation.[3] Various transformations have been reported, including glycosylations by electrooxidation of thio-substituted glycosyl donors.[4,5] However, to our knowledge, there have been no reports of the electrooxidative synthesis of 2′,3′-dideoxynucleosides, which as a consequence led us to investigate such an approach. Herein, we report on the electrooxidative glycosylation of 2,3-dideoxythioglycosides to obtain 2′,3′-dideoxynucleosides in a β-selective manner.

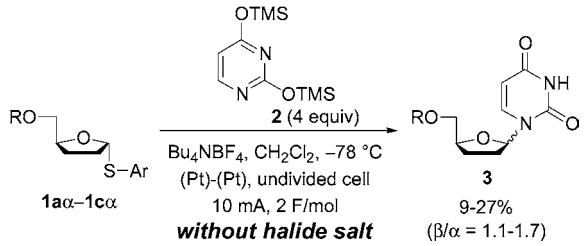
Since the glycosyl donors for glycosylation reactions should be stable yet highly reactive after activation, we designed a series of thioglycosides **1a**−**c** that had readily oxidizable electron-rich arylthio moieties at the anomeric position (Scheme 1).[6]

Scheme 1. Glycosyl Donors **1a**−**c**



We first investigated the direct electrooxidative glycosylation of α-anomers **1a**α−**1c**α. A 2 F/mol[7] amount of electricity was passed through a CH_2Cl_2 solution of the glycosyl donors **1a**α−**1c**α and the silylated uracil **2** (4 equiv) in the presence of tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) as a supporting electrolyte (Scheme 2). However,

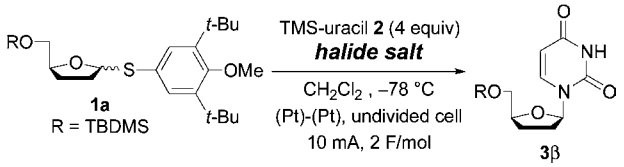
Scheme 2. Direct Electrooxidative Glycosylation



the coupling products **3** were obtained in only 27%, 25%, and 9% yields, respectively, and the β/α ratios were in the range of 1.1−1.7.

These disappointing results prompted us to investigate the indirect electrooxidative glycosylation. To our delight, we found that the reaction efficiency and stereoselectivity of glycosylation reaction was highly improved by the halide salt-mediated electrooxidation ([X^-]/[X^+]-mediated electrooxidation). Electrolysis of the glycosyl donor **1a**α with TMS-uracil **2** was performed in CH_2Cl_2 containing Bu_4NCl (1.5 equiv) as the halide salt to afford nucleoside **3**β in low yield (19%), but the β/α ratio was significantly improved to 4.8 (Table 1, entry 1). Addition of Bu_4NBr improved the

Table 1. [X^-]/[X^+]-Mediated Electrooxidative Glycosylation



entry	1a	additive	yield[a] (%)	β/α[b]	recovered **1a**[a] (%)
1	**1a**α	Bu_4NCl	19	4.8	33
2	**1a**α	Bu_4NBr	79	3.6	9
3	**1a**β	Bu_4NBr	72	4.1	trace
4	**1a**α	Bu_4NI	18	1.7	44

[a] Isolated yield. [b] Determined by ^{1}H NMR.

reaction efficiently to afford nucleoside **3**β in 79% yield with moderate β-selectivity (β/α = 3.6, entry 2). By way of contrast, with Bu_4NI, the reaction proceeded to give nucleoside **3**β in low yield with poor β-selectivity (entry 4). Noteworthy is that the isomer **3**β was obtained predominantly from the electrooxidative glycosylation of each stereoisomer **1a**α or **1a**β (entries 2 and 3), suggesting that the reactions proceeded through the same intermediate from each stereoisomer.

(2) Glycosylation using thioglycosides: (a) Motawia, S. M.; Pedersen, B. E. *Liebigs Ann. Chem.* **1990**, 599. (b) Okabe, M.; Sun, C. R.; Tam, K. Y.; Torado, J. L.; Coffen, L. D. *J. Org. Chem.* **1988**, *53*, 4780. (c) Kawakami, H.; Ebata, T.; Koseki, K.; Matsumoto, K.; Itoh, K. *Heterocycles* **1990**, *31*, 2041. (d) Farina, V.; Benigni, A. D. *Tetrahedron Lett.* **1988**, *29*, 1239. (e) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (f) Chu, K. C.; Babu, R. J.; Lee, J. S. *J. Org. Chem.* **1990**, *55*, 1418. (g) Kim, U. C.; Misco, F. P. *Tetrahedron Lett.* **1992**, *39*, 5733. (h) Sujino, K.; Sugimura, H. *Synlett* **1992**, 553. (i) Young, R. J.; Shaw-Ponter, S.; Hardy, G. W.; Mills, G. *Tetrahedron Lett.* **1994**, *35*, 8687. (j) Sujino, K. Sugimura, H. *Tetrahedron Lett.* **1994**, *12*, 1883.

(3) Review: (a) Torii, S. Electrooxidation of Sulfur Compounds. *Monographs in Modern Chemistry, Vol. 15: Electro-Organic Syntheses. Methods and Applications, Part 1: Oxidation*; VCH Publishers: Deerfield Beach, FL, 1985. Our previous work: (b) Torii, S.; Tanaka, H.; Kasaoka, M.; Saito, N.; Shiroi, T.; Nokami, J.; Tada, N. *Denki Kagaku* **1983**, *51*, 139.

(4) Electrochemical *O*-glycosylation: (a) Noyori, Y.; Kurimoto, I. *J. Org. Chem.* **1986**, *51*, 4320. (b) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1990**, 718. (c) Balavoin, G.; Gref, A.; Fischer, J.-C.; Lubineau, A. *Tetrahedron Lett.* **1990**, *31*, 5761. (d) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-C.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1217. (e) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-C.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1237. (f) Yamago, S.; Kokubo, K.; Yoshida, J. *Chem. Lett.* **1997**, 111. (g) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755.

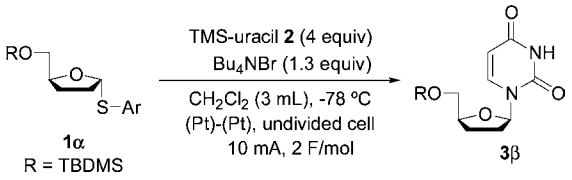
(5) Electrochemical *N*-glycosylation: Nokami, J.; Osafune, M.; Ito, Y.; Miyake, F.; Sumida, S.; Torii, S. *Chem. Lett.* **1999**, 1053.

(6) The stereoisomers of **1a**−**c** could be separated easily by silica gel column chromatography, and the pure isomers were used for the following reactions.

(7) *F* (Faraday constant) is the amount of electric charge of one mol of electrons (1 *F* = 9.64853415 × 10^4 C/mol).

[X⁻]/[X⁺]-mediated electrooxidative glycosylation of glycosyl donors **1b** and **1c** was carried out in a similar manner (Table 2). Bu_4NBr was used as the halide salt. The glycos-

Table 2. [X⁻]/[X⁺]-Mediated Electrooxidative Glycosylation of **1b**α and **1c**α



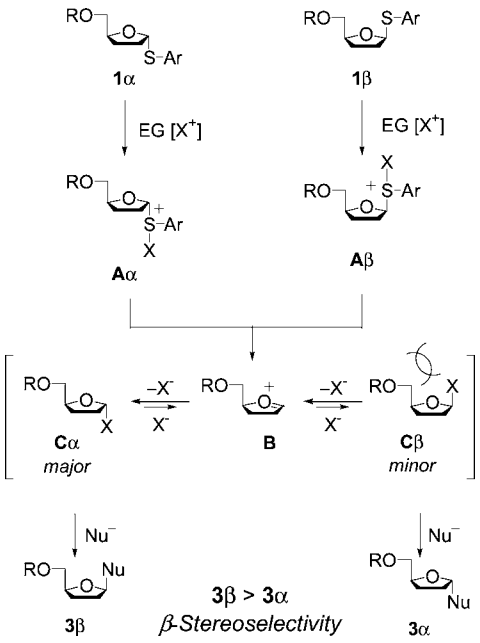
entry	thioglycoside **1**	yield[a] (%)	β/α[b]
1	**1b**α	*c*	
2	**1c**α	86	3.6

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Complex mixture containing **3**.

ylation of **1c**α proceeded smoothly to form the nucleoside **3** in 86% yield (β/α = 3.6, entry 2), while only a complex mixture was obtained from **1b**α (entry 1).[8]

The electrooxidative glycosylation of both **1a**α and **1a**β afforded nucleoside **3** with a similar level of reactivity and stereoselectivity. This result indicates that the reaction probably does not proceed via an S_N2 mechanism. A plausible mechanism is illustrated in Scheme 3. The EG [X⁺]

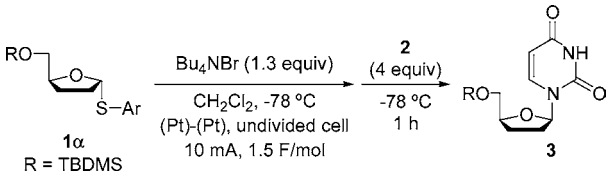
Scheme 3. A Plausible Mechanism



(X = Cl, Br), generated by electrooxidation of X⁻, attacks the sulfur atom of **1**α and **1**β to give sulfenium ion **A**α and

(8) Brominated anthracenyl groups were observed by ^{1}H NMR.

Table 3. [X⁻]/[X⁺]-Mediated Stepwise Electrooxidative Glycosylation



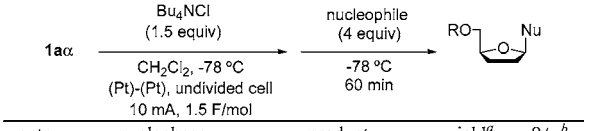
entry	thioglycoside **1**	yield[a] (%)	β/α[b]	recovered **1**[a] (%)
1	**1a**α	81	5.1	
2	**1b**α	*c*		7
3	**1c**α	45	4.1	24

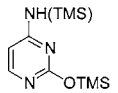
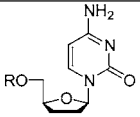
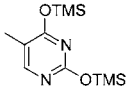
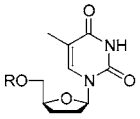
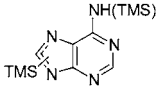
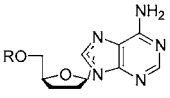
[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Complex mixture.

Aβ, respectively. The C−S bond of **A** is then cleaved to form the same intermediate, oxonium cation **B**. Halide ion X⁻ probably reacts with **B** reversibly, generating the second intermediate **C**α and **C**β. The intermediate **C**α is probably generated predominantly due to steric hindrance. As a result, the subsequent S_N2 reaction with a nucleophile affords **2**β as the major product. To support this hypothesis, the electrooxidation of **1a**α without nucleoside **2** was conducted in the presence of Bu_4NCl, and ^{1}H NMR was recorded at −50 °C. The anomeric proton of the chlorinated dideoxysugar **C**α was observed at 6.42 ppm (doublet, J = 3.3 Hz).[9]

In this reaction, the oxonium cation **B** reacts with the nucleophile competitively to give a mixture of the nucleosides **3**α and **3**β in poorly selective manner. One way to suppress the undesired process would be to effect the preoxidation of **1** without nucleobase **2**. Therefore, we conducted the electrooxidation of **1**α without nucleophile and then nucleophile was added to the electrolysis solution.

Table 4. Electrooxidative Glycosylation with Several Nucleophiles



entry	nucleobase	product	yield[a]	β/α[b]
1		 **4**	60%	13.8
2		 **5**	63%	12.4
3		 **6**	68%[c]	4.4[d]

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Mixture of N9-α + N7-α + N9-β + N7-β. [d] Ratio of (N9-β + N7-β)/(N9-α + N7-α).

The results of the two-step sequence involving the halide salt-mediated electrooxidation of glycosyl donors **1a**α−**1c**α and subsequent reaction with TMS-uracil **2** are summarized in Table 3. Electrolysis of glycosyl donor **1a**α in CH_2Cl_2 was performed under a constant current condition (10 mA, 24 min, 1.5 F/mol) at −78 °C in an undivided cell. Then, to this reaction mixture was added TMS-uracil **2** in CH_2Cl_2. The reaction proceeded smoothly to afford the corresponding nucleoside **3** in 81% yield with a β/α ratio of 5.1 (entry 1). The glycosyl donor **1c**α also gave nucleoside **3** in 45% yield and the β/α ratio was 4.1 (entry 3). On the other hand, only a complex mixture was obtained from glycosyl donor **1b**α (entry 2).

Finally, we carried out the electrooxidative glycosylation in the presence of other nucleobases. The reaction with TMS-thymine and TMS-cytosine gave the corresponding nucleosides **4** and **5** with high β-selectivity ($\beta/\alpha = 13.8$, 12.4, Table 4, entries 1 and 2). When TMS-adenine was employed as a nucleobase, the reaction proceeded similarly to afford the corresponding nucleoside **6** in a 68% yield with moderate β-selectivity ($\beta/\alpha = 4.4$, entry 3). Unfortunately, nucleoside **6** was produced as a mixture of regioisomers (N9 and N7 isomers).

In summary, the halide salt-mediated electrooxidative glycosylation using 2,3-dideoxyglycosides was found to proceed smoothly to afford 2′,3′-dideoxynucleosides with moderate to high β-selectivity. Further investigation of this strategy is currently in progress in our laboratory.

Acknowledgment. We thank the SC-NMR Laboratory of Okayama University for ^1H and ^{13}C NMR analysis.

Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The anomeric proton of **C**β was also observed at 6.35 ppm (doublet, $J = 3.9$ Hz)