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Synthesis of 2′,3′-dideoxynucleosides via C–S bond cleavage: N-glycosylation of 2,3-dideoxy-1-[(2-pyridylmethyl)thio]glycoside

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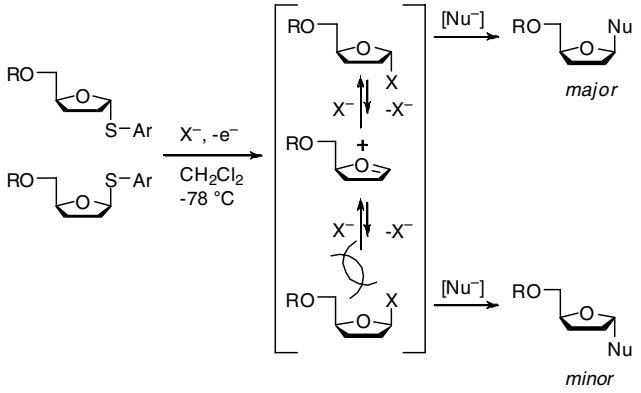
Abstract—N-Glycosylation of 2,3-dideoxy-1-[(2-pyridylmethyl)thio]glycosides (**1a**) using several activators is described. NBS-promoted glycosylation reaction utilizing either the α- or β-thiodideoxyglycoside proceeded smoothly at −78 °C to give the corresponding dideoxynucleoside in a β-selective manner, presumably through a common glycosyl donor.

2′,3′-Dideoxynucleosides are important structural blocks of many natural products. For example, some of their derivatives exhibit potent antiviral activity against HIV,[1] and some 2′,3′-dideoxynucleotides are used as DNA labeling reagents for Sanger's DNA sequencing method.[2] In the synthesis of 2′,3′-dideoxynucleosides, stereoselective formation of an anomeric linkage is significant because only β-anomers show valid bioactivity. The glycosylation of nucleobases using thioglycosides is one of the most effective methods for preparing nucleosides, and has been investigated intensively.[3] The stereochemical outcome at the anomeric position is mainly determined by neighboring group effects from the group at C2 in the glycosyl donors. However, anchimeric assistance cannot be used in the synthesis of 2′-deoxynucleosides because of the lack of a directing group at C2′. Therefore, the development of efficient methods for the stereoselective synthesis of β-anomers of 2′,3′-dideoxynucleosides is still an important issue.

Recently, we reported a halide salts-mediated electrooxidative N-glycosylation ([X^-]/[X^+]-mediated N-glycosylation) of 2,3-dideoxy-1-arylthioglycosides.[4] In the presence of ammonium chloride or bromide, N-glycosylation of 2,3-dideoxy-1-arylthioglycosides took place smoothly to give 2′,3′-dideoxynucleoside in a β-selective manner. In this study, we found that the electrooxidative glycosylation of both α and β-thio-substituted isomers proceeded in a quite similar level of reactivity and β-selectivity, and NMR analysis of the reaction mixture shows the formation of an equilibrium mixture of α- and β-haloglycosides as intermediates, suggesting that β-2′,3′-dideoxynucleoside might be formed by the subsequent S_N2-type attack of nucleobases to the thermodynamically favorable α-isomer (Scheme 1).

Our next interest was whether this phenomenon is specific to the electrooxidative reaction or not. We focused on the stereochemistry of chemical activators promoted N-glycosylation of 2,3-dideoxy-1-thioglycosides. At the start of the study, we newly designed glycosyl donor **1a**, bearing a pyridylmethyl group on S, expecting that the bidentate coordination of S and N atoms to the Lewis acidic activator would promote the C–S bond



Scheme 1. [X^-]/[X^+]-Mediated electrooxidative N-glycosylation.

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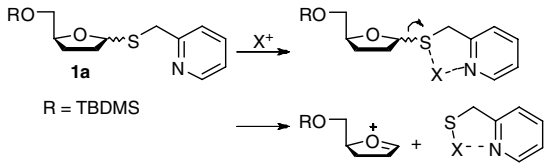
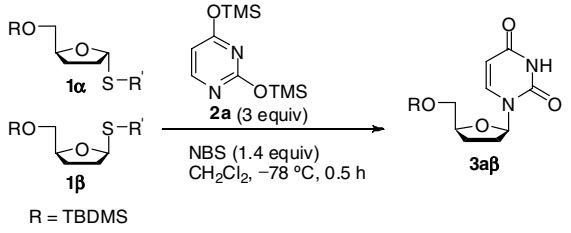


Scheme 2.

cleavage (Scheme 2). Herein, we report the N-glycosylation of **1a** promoted with several activators.

First, N-glycosylation of glycosyl donor **1a** using NBS as an activator was conducted and compared with the glycosylation of analogous 2,3-dideoxy-1-thioglycosides **1b** and **1c**, bearing no directing group on S (Table 1).[5] Upon treatment of **1a**α and TMS–uracil with NBS in CH_2Cl_2 at −78 °C, N-glycosylation took place smoothly to give **3a** in 90% yield and the β/α ratio was 3.9 (entry 1). When the β-1-thioglycoside **1a**β was used, the nucleoside **3a** was obtained in good yield with a similar β/α ratio (entry 2). Similarly to our previously reported electrooxidative glycosylation, the β-isomer **3a**β was obtained predominantly from either **1a**α or **1a**β. N-Glycosylation of thioglycosides **1b** and **1c** was performed in a similar manner to afford the nucleoside **3a** in the β/α ratio range of 2.8–3.7 (entries 3–6). The highest β-selectivity was attained by the glycosylation with **1a** as a glycosyl donor (entries 1 and 2).

Table 1. N-Glycosylation of glycosyl donors **1a**–**c** with NBS



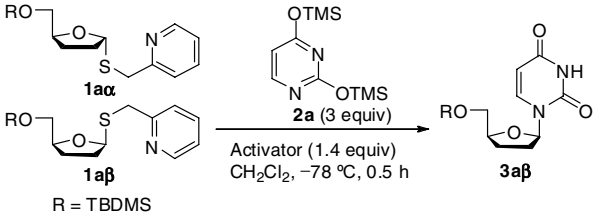
Entry	Thioglycoside **1**	Yield[a] (%)	β/α[b]
1	**1a**α	90	3.9
2	**1a**β	88	4.0
3	**1b**α	92	3.1
4	**1b**β	98	3.7
5	**1c**α	95	2.8
6	**1c**β	98	3.3

[a] Combined yield of α- and β-anomers.
[b] Determined by ^{1}H NMR.

Next, we investigated the effect of activators. The glycosylation of thioglycoside **1a**α and **1a**β with several other activators was conducted (Table 2). When the glycosylation of thioglycoside **1a**α was carried out using *N*-bromophthalimide (NBP), the β/α ratio was almost the same as the reaction using NBS, but the yield of nucleoside **3a** decreased to 73% (entry 1). The yield of nucleoside **3a** drastically decreased to 39% when the glycosylation of thioglycoside **1a**α was carried out with *N*-bromosaccharin (entry 2). *N*-Chlorosuccinimide (NCS) was ineffective, and the starting material **1a**α was recovered quantitatively, probably due to the poor solubility of NCS in CH_2Cl_2 (entry 3). The glycosylation of thioglycoside **1a**β with *N*-iodosuccinimide (NIS) took place but the yield and β/α ratio of nucleoside **3a** drastically decreased (entry 4). Since NBS showed the best reactivity and β-selectivity in the glycosylation, the glycosylation using other bromine activators was undertaken (entries 5–7). The glycosylation of thioglycoside **1a**α with bromine took place to afford nucleoside **3a** in 76% yield with 4.0 ratio of β/α (entry 5). When the reaction was carried out using pyridium tribromide perbromide, nucleoside **3a** was obtained in 67% yield and the β/α ratio was 4.4 (entry 6). Utilizing 2-benzothiazolyl sulfanylbromide, nucleoside **3a** was obtained in 60% yield with good β-selectivity (β/α = 5.0, entry 7), while the reactivity was lower than in the reaction using NBS. Among the thus far investigated activators, NBS was the most effective for the N-glycosylation reaction.

During the course of the optimization studies, it was revealed that the yields and the selectivity of the glycosylation were significantly dependent upon the amount of the activator (Table 3). On decreasing the amount of NBS to 0.6 equiv, the β-selectivity of **3a** increased to 5.4 (from **1a**β) and 5.1 (from **1a**α).[6] In these cases, the glycosylation proceeded with 0.6 molar equivalent of NBS.

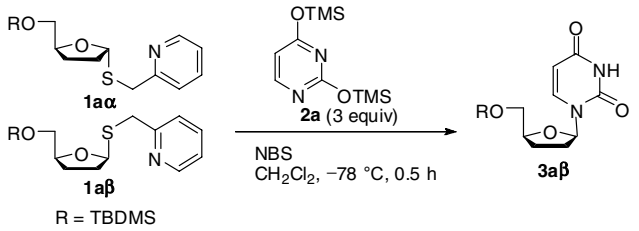
Table 2. Effect of activators in N-glycosylation of glycosyl donor **1a**



Entry	Donor	Activator	Yield[a] (%)	β/α[b]	Recovered **1** (%)
1	**1a**α	NBP[c]	73	3.9	ND
2	**1a**α	NBSac.[d]	39	4.3	ND
3	**1a**α	NCS	ND	—	95
4	**1a**β	NIS	25	1.2	66
5	**1a**α	Br_2	76	4.0	14
6	**1a**α	$PyHBr_3$	67	4.4	ND
7	**1a**α	BTSBr[e]	60	5.0	ND

[a] Combined yield of α- and β-anomers.
[b] Determined by ^{1}H NMR.
[c] *N*-Bromophthalimide.
[d] *N*-Bromosaccharin.
[e] 2-Benzothiazolyl sulfanylbromide.

Table 3. Effect of the amount of NBS in N-glycosylation of glycosyl donor **1a**



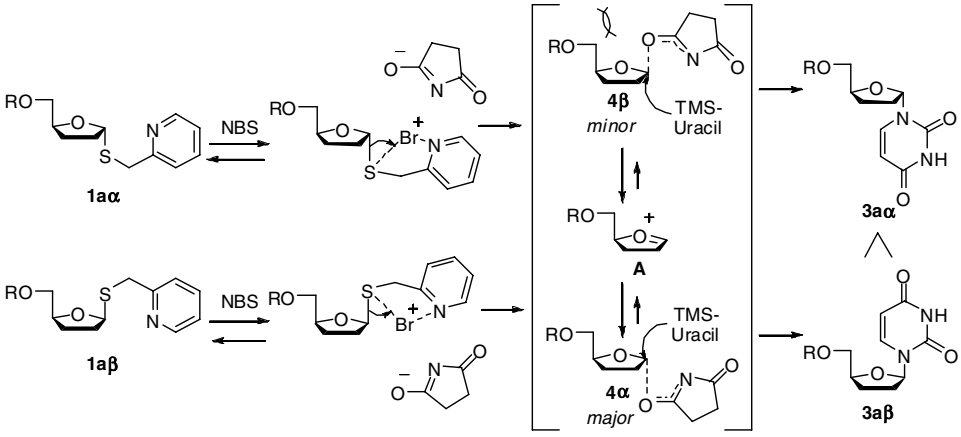
Entry	Donor	NBS (equiv)	Yield[a] (%)	β/α[b]	Recovered **1** (%)
1	**1a**β	0.6	66	5.4	6
2	**1a**β	1.1	80	5.2	N.D.
3	**1a**β	1.4	88	4.0	N.D.
4	**1a**α	0.6	57	5.1	5
5	**1a**α	1.1	73	3.8	N.D.
6	**1a**α	1.4	90	3.9	N.D.

[a] Combined yield of α- and β-anomers.
[b] Determined by ^{1}H NMR.

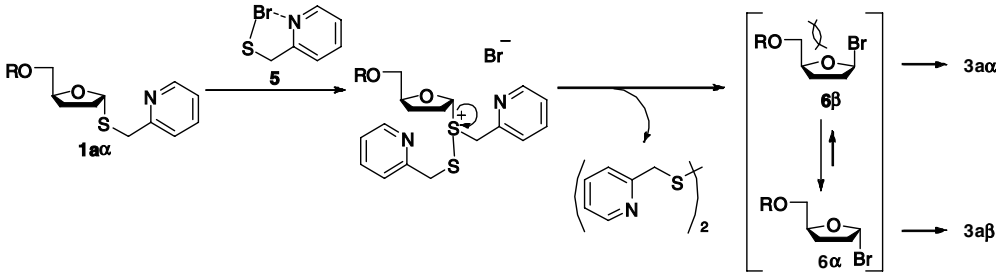
To observe the intermediates, the reaction mixture of **1a** and NBS was measured by ^{1}H NMR at −50 °C, and anomeric proton was observed at 5.44 ppm (d, $J = 4.2$ Hz) from each isomer. It is different from that of the haloglycosides, suggesting that succinimide ion might be the counter anion. A plausible mechanism is shown in Scheme 3. The reaction of **1a**α and **1a**β with NBS would cause the C–S bond cleavage to afford a common intermediate, oxonium cation **A**, through the coordination of the pyridyl and sulfur moieties to [Br^+]. The succinimide ion would be associated with **A** reversibly, generating an equilibrium mixture of **4**α and **4**β. The intermediate **4**α is probably generated predominantly due to the steric hindrance. As a result, the subsequent S_N2 reaction with TMS–uracil would afford **3a**β as the major product. As mentioned above, the N-glycosylation with 0.6 equiv of NBS resulted in increase of the β/α ratio up to 5.1–5.4. This result suggests that there might be some other species acting as activators. Probably, (2-pyridyl)methylsulfanylbromide (**5**), generated in situ by C–S bond cleavage of **1a**, might react with **1a** to give an equilibrium mixture of α- and β-1-bromoglycosides (**6**α and **6**β), and subsequent attack of **2** also afforded **3** in a β-selective manner (Scheme 4).[7]

Finally, glycosylation of thioglycoside **1a**β with several nucleobases was undertaken (Table 4). TMS–thymine **2b** gave the corresponding nucleoside **3b** in 72% yield and with good β-selectivity (β/α = 5.4, entry 1). TMS–cytosine **2c** gave the corresponding nucleoside **3c** in 72% yield with moderate β-selectivity (β/α = 3.4, entry 2). When TMS–adenine **2d** was used as a base, the reaction proceeded to afford the corresponding nucleoside **3d** in 58% yield with low β-selectivity (β/α = 1.9, entry 3). Unfortunately, **3d** was obtained as a mixture of regioisomers (*N*9 and *N*7 isomers).

In summary, the NBS-promoted N-glycosylation of 2,3-dideoxyglycosides **1a** was found to proceed smoothly to afford the corresponding 2′,3′-dideoxynucleosides. From each **1a**α or **1a**β, the reaction proceeded with

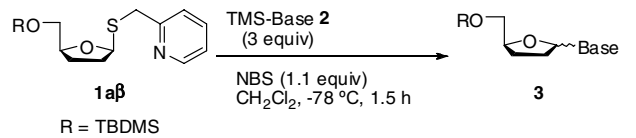


Scheme 3. A plausible mechanism.



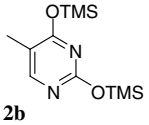
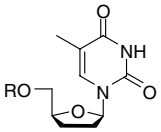
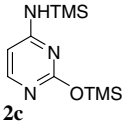
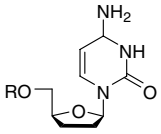
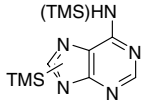
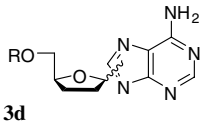
Scheme 4. An another plausible path to the β-glycoside **3a**β.

Table 4. N-Glycosylation of glycosyl donor **1a**β using several TMS-bases



1aβ **3**

R = TBDMS

Entry	2	3	Yield[a] (%)	β/α[b]
1	 **2b**	 **3b**	72	5.4
2	 **2c**	 **3c**	72	3.4
3	 **2d**	 **3d**	58[c]	1.9[d]

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Mixture of *N*9-α + *N*7-α + *N*9-β + *N*7-β.
[d] Ratio of (*N*9-β + *N*7-β)/(*N*9-α + *N*7-α).

moderate to high β-selectivity. Further investigation of this reaction is currently in progress in our laboratory.

Acknowledgements

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References and notes

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4. Mitsudo, K.; Kawaguchi, T.; Miayahara, S.; Matsuda, W.; Kuroboshi, M.; Tanaka, H. *Org. Lett.* **2005**, *7*, 4649–4652.
5. The stereoisomers of **1a**–**c** could be separated easily by silica gel column chromatography, and the pure isomers were used for the following reactions.
6. General procedure of the N-glycosylation of **1a** with TMS–uracil (**2a**): To a solution of **2a** (34 mg, 0.30 mmol) in CH_2Cl_2 (0.5 mL) was added thioglycoside **1a**β (38 mg, 0.11 mmol) in dry CH_2Cl_2 (2.5 mL) at −78 °C under argon and the mixture was stirred for 10 min at this temperature. To the mixture was added dropwise a solution of NBS (22 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C and stirred for 0.5 h at −78 °C. The reaction was quenched by adding aq satd. $Na_2S_2O_3$ (3.0 mL) at −78 °C and the resulting mixture was gradually warmed to room temperature and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 5:1 → 3:1 → 2:1 → 1:1) to afford **3a** (29 mg, 80%, β/α = 5.2) as a colorless liquid (Table 3, entry 2).
7. The haloglycoside **6** might be a better intermediate than the intermediate **4** for β-selective glycosylation reaction. Our previouly reported $[X^-]/[X^+]$-mediated electrooxidative N-glycosylation of 2,3-dideoxyglycosides proceeded with high β-selectivity to afford 2′,3′-dideoxynucleosides **3a**–**d** (β/α = 4.4–13.8), wherein the haloglycoside would be formed as the major intermediate.[4]