Efficient Electrochemical *N*-Glycosylation of Silylated Pyrimidines with Protected Arylthioriboses in the Presence of a Catalytic Amount of NBS or Br_2

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Electrolysis of silylated pyrimidines with protected arylthioribose, in the presence of a catalytic amount of NBS or Br_2 as a mediator in an undivided cell, gave the corresponding *N*-glycosides (nucleosides) in good yield.

The glycosylation reaction of various nucleophiles (glycosyl acceptor) with sugar derivatives (glycosyl donor) to give *C*-,[1] *O*-,[2] and *N*-glycosides is one of the most important reactions in organic syntheses. Many chemists devote much effort to discover a convenient glycosylation procedure by use of suitable promotors as well as glycosyl donors. A reaction via oxonium ion under neutral conditions (without using Lewis acid) is well recognized as a characteristic electroorganic reaction.[3] Thus, an electrochemical reaction seems to be one of the most effective ways to promote glycosylation. Noyori,[4] Amatore,[5] Balavoine,[6] and Yoshida[7] have already succeeded in electrochemical glycosylation of several types of alcohol with various stable glycosyl donors such as arylglycosides,[4] aryl- or alkyl-thioglycosides,[5] arylthio- or arylseleno-glycosides[6] and aryltelluroglycosides,[7] using supporting electrolytes such as $LiClO_4$, Bu_4NBF_4, Bu_4NClO_4 to give the corresponding *O*-glycosides effectively.

N-Glycosides such as nucleosides are very attractive in medicinal chemistry. However, electrochemical *N*-glycosylation of nucleoside bases with glycosyl donors to give *N*-glycosides has not been explored. Therefore, we investigated electrochemical *N*-glycosylation of nucleoside bases in order to discover a useful method for the synthesis of nucleosides, which are very important from an economic and environmental view point.

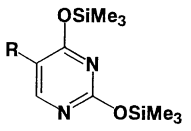
Electrolysis was carried out by employing arylthioriboses **2-5** as stable glycosyl donors, and silylated pyrimidines, bis(trimethylsilyl)thymine **1a** and bis(trimethlsilyl)-5-fluorouracil **1b** as soluble glycosyl acceptors, in the presence of a catalytic amount of supporting electrolyte in an undivided cell. We discovered that when tetrabutylammonium bromide (Bu_4NBr) was used as a supporting electrolyte, the desired *N*-glycosylation took place to give nucleosides in a modelate yield. However, the electrolysis using common supporting electrolytes, such as lithium perchlorate ($LiClO_4$), tetraethylammonium perchlorate (Et_4NClO_4), and tetraethylammonium tosylate (Et_4NOTs), was unsuccessful.[8]

The result suggests that the bromonium ion, formed by the electrolysis of the supporting electrolyte Bu_4NBr, serves as an effective mediator for the formation of the oxonium ion from arylthioribose via oxidative desulfurization, which then reacts with **1** to give nucleosides. Consequently, we examined the electrochemical *N*-glycosylation using a catalytic amount of *N*-bromosuccimide (NBS)[9] as a mediator, which was found to be more effective than Bu_4NBr. The results are listed in Table 1 (entries 1-12).

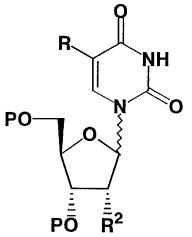
Table 1. *N*-Glycosylation of silylated nucleoside base **1** with thioglycosides **2**, **3**, **4** and **5**[a]

Entry	Donor (α/β)[b]	Acceptor	C.D.[c]	F/mol[d]	Electrolyte (10 mol%)	Product	Yield/%[e] (α/β)[b]
1	**2p** (2/3)	**1a**	25	3	NBS	**6a**	73 (1.9/1)
2	**2p** (2/3)	**1a**	25	3	Bu_4NBr	**6a**	65 (2.2/1)
3	**2t** (1/1)	**1a**	25	3	NBS	**6a**	86 (2.3/1)
4	**2t** (1/1)	**1a**	25	3	Bu_4NBr	**6a**	73 (2.2/1)
5	**2t** (1/1)	**1b**	5	1	NBS	**6b**	74 (2.7/1)
6	**2t** (1/1)	**1b**	25	3	Bu_4NBr	**6b**	53 (2.2/1)
7	**3p** (1/3)	**1a**	25	3	NBS	**7a**	79 (4.2/1)
8	**3p** (1/3)	**1b**	5	1.5	NBS	**7b**	82 (3.2/1)
9	**3t** (1/3)	**1a**	25	3	NBS	**7a**	76 (5.2/1)
10	**3t** (1/4)	**1a**	25	3	Bu_4NBr	**7a**	41 (1.9/1)
11	**3t** (1/4)	**1b**	5	1.5	NBS	**7b**	92 (1.8/1)
12	**3t** (2/5)	**1b**	25	3	Bu_4NBr	**7b**	43 (1.8/1)
13[f]	**3t** (1/2)	**1b**	25	3	Br_2	**7b**	73 (2.7/1)
14[f]	**4** (2/3)	**1b**	25	3	NBS	**8b**	65 (2.6/1)
15[f]	**4** (2/3)	**1b**	25	2	Br_2	**8b**	68 (2.0/1)
16[f]	**5** (1/2)	**1b**	25	4.5	NBS	**9b**	68 (β)
17[f]	**5** (1/2)	**1b**	25	4	Br_2	**9b**	85 (β)

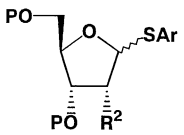
[a] All reactions were performed with donor **2**, **3**, **4** or **5** (1 mmol) and acceptor **1** (1.2 mmol), using platinum plate (1 cm^2) electrodes, in 2 mL of dry propanenitrile at room temperature unless otherwise noted. [b] Determined by ^1H NMR (400 MHz) integration of the mixture. [c] Current density (mA/cm^2). [d] Electricity. [e] isolation by column chromatography on silica gel. [f] Performed at 10 °C.



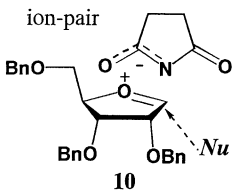
1a R = CH_3
1b R = F



	P	R^2	R
6a	Bn,	H,	CH_3
6b	Bn,	H,	F
7a	Bn,	OBn,	CH_3
7b	Bn,	OBn,	F
8b	Ac,	H,	F
9b	Ac,	OAc,	F



	P	R^2	Ar
2p	Bn,	H,	Ph
2t	Bn,	H,	*p*-Tol
3p	Bn,	OBn,	Ph
3t	Bn,	OBn,	*p*-Tol
4	Ac,	H,	*p*-Tol
5	Ac,	OAc,	*p*-Tol



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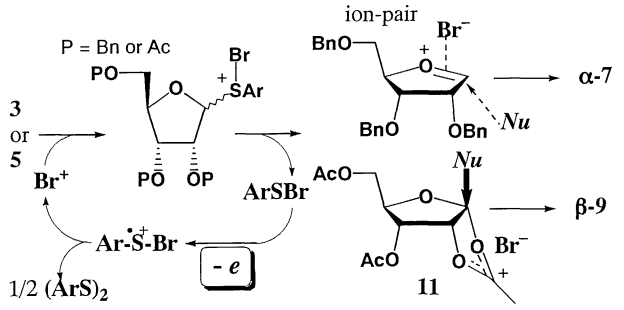
By employing the present glycosylation method, α-isomers were preferentially obtained in both dibenzylated 2-deoxyribose derivatives **2** and tribenzylated ribose derivatives **3**. This selectivity has already been shown in the reaction using stoichiometric amount of NBS,[9] in which the formation of an ion-pair with a counter ion (succimide anion) at the sterically less hindered β-site (*trans* to the most interactive substituent) is favorable to generation of the oxonium ion intermediate **10**. In this reaction, the nucleophile should be introduced from the opposite α-site (*cis* to the most interactive substituent) to give the α-isomer as a major product, bearing a sterically disadvantageous configuration. On the other hand, the triacetylated ribose derivatives **5** gave the β-isomer selectively due to the formation of the intramolecularly stabilized oxonium ion **11** (entry 16). This is in contrast to the reaction of diacetylated 2-deoxyribose derivative giving the α-isomer selectively (entry 14). The electrogenerated bromonium ion-assisted *N*-glycosylation is a versatile tool for nucleoside synthesis, on functioning a mediatory system, as shown in Scheme 1.



Scheme 1.

This finding prompted us to investigate further a similar electrolysis with a catalytic amount of bromine (Br_2)[10] as the mediator. The results are also shown in Table 1 (entry 13, 15, 17). It can be assumed that the actual activator in the *N*-glycosylation using thioglycoside and NBS[8] is also an in situ generated bromine species.

In conclusion, the electrochemical *N*-glycosylation undergoes preferentially in the presence of a catalytic amount (10 mol%) of NBS or bromine as a mediator. The stereoselectivity (β/α) of this glycosylation was similar to that of chemical glycosylation using a stoichiometric amount of NBS. It is most likely that the activation of the thioglycosides does not take place directly on the surface of the anode but indirectly in the bulk solution by the electrochemical mediatory system.

Further investigation of the synthetic applications of this electrochemical glycosylation is now in progress.

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