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Stereoselective Synthesis of 1,2-*cis*-*N*-Glycosides by the *N*-Bromosuccinimide Promoted Reaction of Thioglycosides with Silylated Pyrimidine Bases

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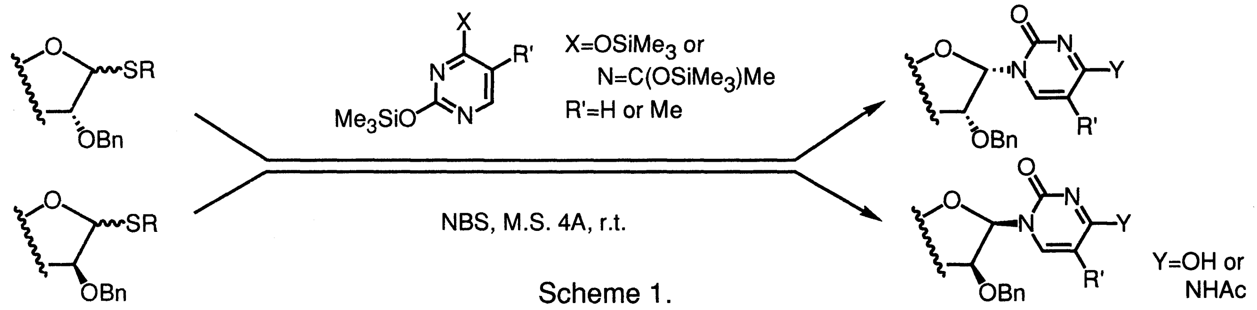
The coupling of *O*-benzylated 1-thioglycosides, derived from D-glucose, D-mannose, D-ribose, D-xylose, and D-arabinose, with silylated pyrimidine bases by activation with *N*-bromosuccinimide uniformly afforded the corresponding 1,2-*cis*-*N*-glycosides with good selectivity.

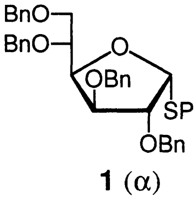
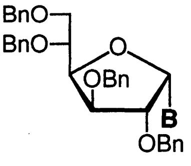
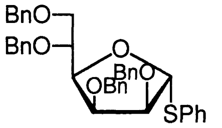
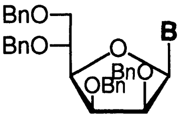
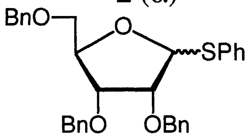
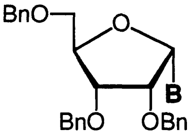
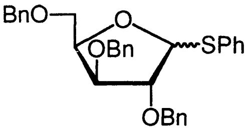
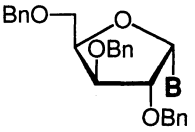
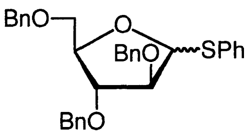
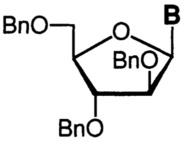
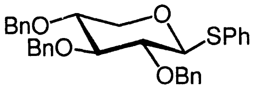
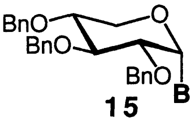
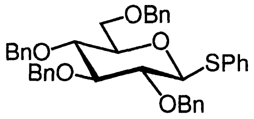
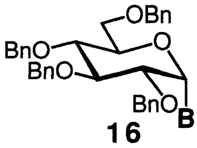
There has been considerable interest in the synthesis of nucleoside analogs as potent antiviral1) and antibiotic2) agents. The coupling of a sugar moiety with a nucleoside base has been shown to be useful for obtaining these derivatives. Most of these studies, except those concerning 2'-deoxynucleoside derivatives, have dealt with the synthesis of 1,2-*trans*-*N*-glycosides because most natural nucleosides and nucleoside antibiotics contain a 1,2-*trans*-*N*-glycosyl bond, and little attention has been paid to the synthesis of 1,2-*cis*-*N*-glycosides, including β-D-arabinofuranosyl nucleosides and α-ribazole (5,6-dimethyl(1-α-D-ribofuranosyl)benzimidazole; a component of vitamin B_{12}). For example, the stereocontrolled synthesis of 1,2-*trans*-*N*-glycosides has been established as the well-known Lewis acid catalyzed reaction of fully acylated sugars with silylated nucleoside bases, utilizing the participating effect of the 2-*O*-acyl group.3a,b) Moreover, alternative methods such as the zinc chloride mediated nucleophilic opening of 1,2-anhydro sugars have been developed.4) By contrast, although several methods exist for the synthesis of 1,2-*cis*-*N*-glycosides via the S_N 2 type reaction of glycosyl halides5) or other activated glycosyl intermediates6) bearing a 1,2-*trans* relationship, a general and applicable method to a wide range of sugars is lacking. As a part of our program to develop a convenient method for the synthesis of nucleoside derivatives employing thioglycoside as a glycosyl donor,7) we report herein the stereocontrolled synthesis of 1,2-*cis*-*N*-glycosides from *O*-benzylated 1-thioglycosides and silylated nucleoside bases by the use of *N*-bromosuccinimide(NBS) as an activator (Scheme 1).



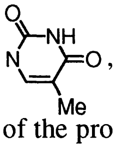
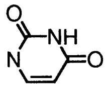
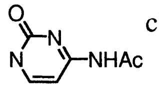
Scheme 1.

The starting thioglycosides **1**–**7** were prepared by applying known methods.8–11) We first examined several thiophilic reagents; dimethylmethylthiosulfonium triflate(DMTST),12) iodonium dicollidine perchlorate

Table 1. Synthesis of *N*-glycosides by the coupling of thioglycosides with silylated bases[a]

Run	1-Thioglycoside (α/β)	**B**[b]	Activator[c] (equiv.)	Solvent	Time/h	Product[d]	Yield/%[e]	α:β[f]
1	 **1** (α)	Th	DMTST (2.0)	CH_2Cl_2	5	 **8**	74	58:42
2		Th	IDCP (1.1)	CH_2Cl_2	26		74	60:40
3		Th	NBS (1.1)	CH_2Cl_2	26		87	96:4
4		Th	NIS-TMSOTf (1.15-1.1)	CH_2Cl_2	0.5		78	57:43
5		Th	NIS-TMSOTf (1.15-0.1)	CH_2Cl_2	1		70	71:29
6	 **2** (α)	Th	NBS (1.1)	CH_2Cl_2	0.5	 **9**	86	14:86
7	 **3** (1/2.2)	Th	NBS (1.1)	CH_2Cl_2	7	 **10**	92	92:8
8	 **4** (1.4/1)	Th	NBS (1.1)	CH_2Cl_2	6	 **11**	88	84:16
9	 **5** (3.0–1.4/1)	Th	NBS (1.1)	CH_2Cl_2	4.5	 **12** (B=Th)	89	13:87
10		Th	NBS (1.1)	Et_2O	2.5		85	21:79
11		Th	NBS (1.1)	THF	2.5		91	47:53
12		Th	NBS (1.1)	CH_3CN	5		92	26:74
13		Th	NBS (1.1)	Benzene	5		93	16:84
14		Th	NBS (1.1)	$CHCl_3$	3.5		91	9:91
15		Ur	NBS (1.1)	$CHCl_3$	2.5	**13** (B=Ur)	85	11:89
16		Cy^{Ac}	NBS (1.1)	$CHCl_3$	2.5	**14** (B=Cy^{Ac})	81	10:90
17	 **6** (β)	Th	NBS (1.1)	CH_2Cl_2	6.5	 **15**	88	93:7
18	 **7** (β)	Th	NBS (1.1)	CH_2Cl_2	7	 **16**	58[g]	78:22
19		Th	NBS (1.1)	CH_2Cl_2	45		78	79:21

a) The reaction was carried out at r.t. under Ar using 2 equiv. of silylated base in the presence of M.S. 4A.

b) Th: , Ur: , Cy^{Ac}: 

c) DMTST=$Me_2SSMeOSO_2CF_3$, IDCP=$I(collidine)_2ClO_4$, NIS=*N*-iodosuccinimide, TMSOTf=$Me_3SiOSO_2CF_3$

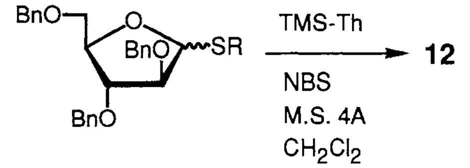
d) All of the products gave spectral data in full accord with the assigned structure. e) Isolated yield.

f) The ratios were determined by 400 MHz ^1H NMR. g) The starting material **7** was recovered in 14% yield.

(IDCP),[13] NBS[11] and NIS-TMSOTf,[14] as an activator in the reaction of thioglycoside **1** with silylated thymine as shown in Table 1 (runs 1–5). Although all reagents employed efficiently promoted the desired *N*-glycoside formation, regarding the stereochemical outcome only NBS afforded a high level of α-selectivity. Then, the generality of this method was explored by examining the reaction of other thiofuranosides **2–5**, derived from different sugars, with silylated thymine. In these examples, the reaction proceeded at room temperature and provided 1,2-*cis*-*N*-glycosides in a good yield with good selectivity regardless of the anomeric configuration of the starting thioglycosides (runs 6–9). The reaction of D-arabinose derivative **5** seems to be useful for the synthesis of β-D-arabinofuranosyl nucleosides, widely known as antiviral and antitumor agents. However, the stereoselectivity was not necessarily satisfactory in terms of practical value. As an attempt to enhance the selectivity, we examined the effect of the solvent on the reaction of **5** with silylated thymine (runs 10–14 in Table 1). Polar solvents rather decreased the ratio of the β anomer and, in particular, the use of THF led to the marked loss of the selectivity, whereas chloroform proved to slightly improve the β-selectivity. Under this optimum condition, 1-(β-D-arabinofuranosyl)uracil and cytosine derivatives, **13** and **14**, were synthesized with a similar stereoselectivity (runs 15 and 16). This 1,2-*cis*-selective *N*-glycosylation is applicable to some 1-thiopyranosides to afford the expected products predominantly (runs 17–19), though in the case of the D-glucopyranose derivative **7** the yield and selectivity were less satisfactory.

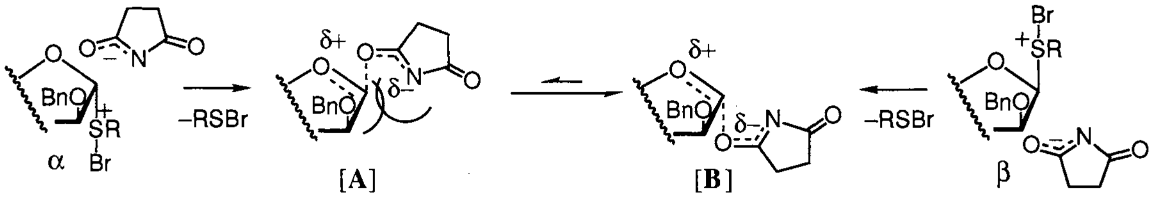
Although a mechanism has recently been discussed for the IDCP promoted, 1,2-*cis* selective *O*-glycosylation using thioglycosides,[15] we propose a somewhat different mechanism for the present NBS-promoted *N*-glycosylation. The occurrence of 1,2-*cis* selectivity only using NBS as the activator suggests that the succinimide anion plays an important role in the appearance of the selectivity as counter species for an oxonium ion intermediate. To understand the mechanism of the stereoselection in more detail, we explored the effect of the leaving group on the reaction of 1-thio-D-arabinofuranoside derivatives as model compounds, as shown in Table 2. Several features are noteworthy: (1) The reaction of phenyl β-1-thioglycoside proceeded more rapidly with higher stereoselectivity than that of phenyl α-1-thioglycoside (runs 1 vs. 2 in Table 2). (2) The substituent on the phenyl group influenced the reaction rate but not the anomeric ratio (runs 2–4). (3) After the treatment of ethyl α-1-thioglycoside with NBS for 1h, the silylated base was added to the reaction mixture. This slightly enhanced the β-selectivity (runs 5 vs. 6). Scheme 2 shows the proposed mechanism for the selective formation of the 1,2-*cis*-*N*-glycosides. Two intermediates consisting of oxonium and succinimide ions, **A** and **B**, are in equilibrium. However, the formation of the 1,2-*trans* intermediate **B** would be sterically and electrically preferable to that of the 1,2-*cis* intermediate **A**. Accordingly, the subsequent back-side attack with the nucleoside base on these intermediates leads to the 1,2-*cis*-*N*-gly-

Table 2. The effect of the leaving group of thioglycoside[a)]



Run	Thioglycoside		Time	12	
	R	α/β	h	Yield/%	α:β
1	Ph	β	0.5	87	8:92
2	Ph	α	5	92	26:74
3	*p*-ClC6H4	α	6	90	25:75
4	*p*-MeOC6H4	α	2.5	95	26:74
5	Et	α	1	94	15:85
6[b)]	Et	α	1	84	9:91

a) The reaction was carried out by addition of NBS to the thioglycoside and silylated thymine in CH_2Cl_2 at r.t. in the presence of M.S. 4A, unless otherwise noted. b) Prior to addition of silylated thymine, the thioglycoside was treated with NBS for 1 h.



Scheme 2.

coside preferentially. In the reaction using THF as solvent (run 11 in Table 1), the intermediates **A** and **B** are probably difficult to form due to its strong Lewis basicity. Consequently, the reaction will proceed via the S_N 1 type pathway to give rise to the anomeric mixture of the *N*-glycoside in nearly equal ratios.

In conclusion, the NBS-promoted coupling of thioglycosides with silylated nucleoside bases has proven to be a general phenomenon applicable to the synthesis of a wide range of 1,2-*cis*-*N*-glycosides. Further studies on the usefulness of this method in the preparation of nucleoside analogs, including α-ribazole, are in progress.

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