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Stabilization of Glycosyl Sulfonium Ions for Stereoselective *O*-Glycosylation

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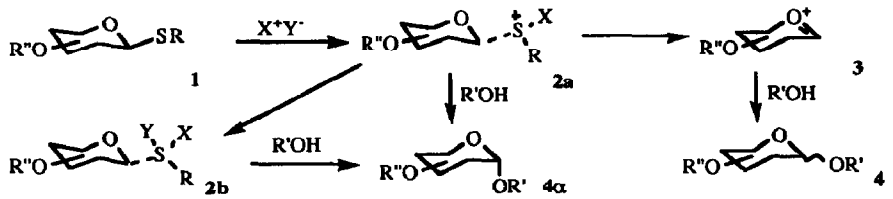
Summary: Bis(trifluoroacetoxy)iodobenzene can be used for studying the stereoselectivity of O-glycosylation from thioglycosides and the use of reagent-stabilized sulfonium ions to prohibit the formation of oxonium ions is also discussed.

O-glycosides play very important roles in a variety of biological recognition processes[1] and many strategies have been developed for the preparation of *O*-glycosides.[2] Methods include the use of glycosyl donors such as halides,[3] 4-pentenyl glycosides,[4] phosphate derivatives,[5] sulfides,[6] and acylated compounds.[7] For diastereoselective glycosylation, excellent approaches include the trichloroacetimidate method,[8] the use of silicon connections,[9] fluoride donors,[3] and glycal derivatives,[10] as well as the formation of the glycosidic bond with the aid of neighboring group participation.[11]

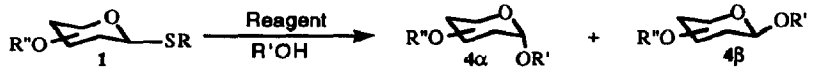
Scheme 1

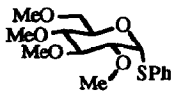
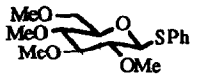
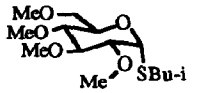


Oxidative or alkylative couplings of thioglycosides and alcohols have been studied.[6] In the process of activating thioglycosides, the resulting sulfonium ions **2a** are often fragmented to oxonium ions 3 that react with glycosyl acceptors via S_N1 reactions (Scheme 1), resulting in little diastereoselectivity. We envisage that the reactivity of sulfonium ions **2a** can be modulated by the change of activating reagents XY or sulfur substituents R.[12] Moreover, the stabilization of sulfonium ions **2a-b** may inhibit the formation of oxonium ions 3 and force S_N2-type glycosylation to give **4α** stereoselectively. In this paper, we describe a procedure in which a mild oxidative reagent is used for the conversion of thioglycosides **1** to reactive glycosyl donors **2a-b** ($X^+ = CF_3CO_2I^+Ph$, $Y^- = CF_3CO_2^-$), producing diastereoselective glycosylation.

This method involves the treatment of **1** with bis(trifluoroacetoxy)iodobenzene (BTIB) in the presence of alcohols to give high yields of *O*-glycosides, in which the stereocenters of glycosylation are mainly inverted for both the α- and β-thioglycosides (Table 1).[13] Reagent effects on the reactivity and stereoselectivity of glycosylation were studied by comparing several oxidants such as BTIB, *N*-bromosuccinimide (NBS),[6a] *N*-iodosuccinimide (NIS),[6m] and hydroxy(tosyloxy)-iodobenzene (HTIB). The reaction of **1a** with NBS or HTIB (entries 1 and 3) in the presence of ethanol gave a mixture of **4α** and **4β** with little selectivity. By using acid catalyzed NIS, the ratio was improved to 1:8 (entry 2), but the best selectivity was obtained with BTIB as an activator (entries 4-6). Similar results were also observed from other thioglycosides (entries 7-14).

Table 1



Entry	Substrate	Reagent	R'OH	Yield[a]	4α:4β[b]
1	 **1a**	NBS	EtOH	85%	4:5
2		NIS, TfOH	EtOH	85%	1:8
3		HTIB	EtOH	82%	1:1
4		BTIB	EtOH	81%	1:15
5		BTIB	MeOH	82%	1:9
6		BTIB	i-PrOH	87%	1:8
7	 **1b**	NBS	EtOH	76%	6:1
8		BTIB	EtOH	92%	13:1
9		BTIB	MeOH	92%	15:1
10		BTIB	i-PrOH	80%	16:1
11	 **1c**	NBS	EtOH	90%	1:2
12		BTIB	EtOH	90%	1:7
13	 **1d**	NBS	EtOH	90%	6:1
14		BTIB	EtOH	80%	30:1

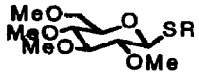
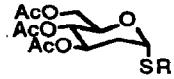
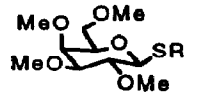
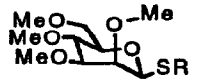
a) Isolated yields. b) The ratios were determined by NMR and GC/Mass analysis.

The mechanism of diastereoselective glycosylations remains unclear. It is quite reasonable that reaction is initiated by nucleophilic attack of sulfur on the electrophilic center of oxidants to give **2a** (Scheme 1). In the case which BTIB was used, complex **2b** was formed along with trifluoroacetic acid which prohibited the production of oxonium ions **3**. The diastereoselective glycosylation of **2a-2b** could then take place by an S_N2 reaction with inversion at the anomeric center.

Since these conditions are very mild,[14] different functional groups survive (Table 2), leading to both high yields and high diastereoselectivities from thioglucosides (entries 15-20), thiogalactoside (entry 23), and thiomannoside (entry 24). Although

an excess of alkohols is required, the results confirm that activating agents can indeed modulate the reactivity of sulfonium ions for diastereoselective *O*-glycosylation.

Table 2

Entry	Substrate	R	Yield[a]	4α:4β[b]
15		Ph	80%	>30:1
16		Ph	90%	~15:1
17		*n*-Bu	90%	>30:1
18		*i*-Bu	80%	>30:1
19		*p*-MeO-C_6H_4	78%	23:1
20		*p*-Cl-C_6H_4	75%	14:1
21		*n*-Bu	90%	~1:30
22		Ph	85%	1:12
23		*n*-Bu	95%	14:1
24		*n*-Bu	80%	>30:1

a) Isolated yields. b) The ratios were determined by NMR and GC/Mass analysis.

In conclusion, the use of sulfonium ion intermediates **2** allows the synthesis of *O*-glycosides diastereoselectively, while addressing the important problem of stereocontrolled glycosylation by prohibiting the formation of oxonium ions. Consequently, it becomes possible to design glycosyl donors with different sulfide moieties to investigate their effects on the stereochemistry of glycosylation as well as their use for the preparation of oligosaccharides.

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