

SYNTHESIS OF ALKYL GLYCOSIDES USING TRIALKYL BORATES

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Abstract-Some trialkyl borates worked as highly reactive glycosyl acceptors of glycosyl acetates. Several allyl glycosides were obtained in good yields by the reaction of glycosyl acetates with triallyl borate using ytterbium(III) trifluoromethanesulfonate as the activator.

In order to synthesize glycosides and oligosaccharides related to natural products and their analogues for the investigation of their biological functions, glycosidation is one of the most important synthetic methods.¹ Most of the known glycosidation methods are based on the activation of a leaving group at the anomeric center of a glycosyl donor.² In some cases, the alcohol derivatives such as ROSnBu_3 and ROSiMe_3 are used to increase the reactivity of the glycosyl acceptors.² 1-*O*-Acyl sugars are useful glycosyl donors because they are stable and easy to prepare, but some of them are difficult to activate. It was reported that 2,3,4,6-tetra-*O*-benzyl-**D**-glucopyranosyl acetate (**1**) is not easily activated by the lanthanide trifluoromethanesulfonates.³

We have already reported that the glycosidation reactivity of **1** with alcohols was dramatically increased by the addition of only a 3 mol % amount of boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$) in the presence of ytterbium(III) trifluoromethanesulfonate ($\text{Yb}(\text{OTf})_3$).⁴ This reactivity enhancement was caused by the formation of a $\text{BF}_3\text{-ROH}$ complex, which made us consider that compounds having a B-OR bond were likely to be highly reactive acceptors. In this communication, we describe glycosidations of glycosyl acetates using the trialkyl borates ($\text{B}(\text{OR})_3$) as new glycosyl acceptors.

We investigated the reaction of **1** with triallyl borate ($\text{B}(\text{OCH}_2\text{CH}=\text{CH}_2)_3$)⁵ as one of the trialkyl borates. The reaction using $\text{Yb}(\text{OTf})_3$ in dichloromethane (CH_2Cl_2) gave the expected corresponding allyl glucoside in 86% yield, and this result showed that $\text{B}(\text{OCH}_2\text{CH}=\text{CH}_2)_3$ worked as the highly reactive glycosyl acceptor of **1**.⁶ Furthermore, the reaction between **1** and $\text{B}(\text{OCH}_2\text{CH}=\text{CH}_2)_3$ was examined in detail. The reaction using tin(II) trifluoromethanesulfonate ($\text{Sn}(\text{OTf})_2$) as the trifluoromethanesulfonate salt in CH_2Cl_2 also predominantly gave the α -allyl glucoside in excellent yield. Triphenylmethyl perchlorate (TrtClO_4) and cyclopentadienylzirconium trifluoromethanesulfonate tetrahydrofuran complex ($\text{Cp}_2\text{Zr}(\text{OTf})_2 \cdot \text{THF}$) were also effective for this reaction. On the other hand, the reactions using zinc trifluoromethanesulfonate ($\text{Zn}(\text{OTf})_2$) and halide salts such as $\text{BF}_3 \cdot \text{OEt}_2$ and tin (IV) chloride (SnCl_4) gave the glucoside in low yields. CH_2Cl_2 , acetonitrile (MeCN), tetrahydrofuran (THF), and benzene (PhH) were used as the solvent. The reactions using these solvents in the presence of $\text{Yb}(\text{OTf})_3$ afforded the allyl glycosides in good yields.

The reaction using MeCN predominantly gave the β -anomer. This β -stereoselectivity could be explained by the generation of the α -D-glucosylacetonitrilium ion as Fraser-Reid *et al.* reported.⁷ We used the reaction conditions involving Yb(OTf)₃ in CH₂Cl₂ because Yb(OTf)₃ is very stable and can be recycled. The reaction using trimethyl borate (B(OMe)₃) and triphenyl borate (B(OPh)₃) with Yb(OTf)₃ in CH₂Cl₂ also afforded the corresponding methyl and phenyl glucosides in 98 and 68% yields, respectively. These results are summarized in Table 1.

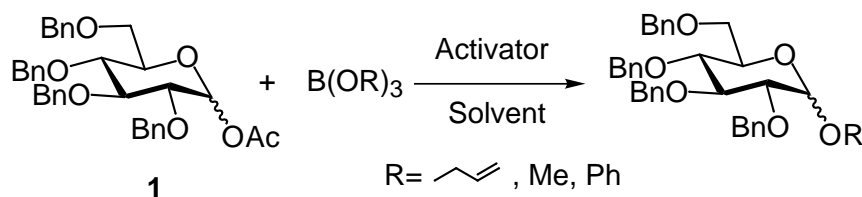


Table 1. The reaction of **1** with B(OR)₃ using several activators and solvents

Entry ^{a)}	R	Activator	Solvent	Yield(%)	α/β
1		Yb(OTf) ₃	CH ₂ Cl ₂	86	6/5
2		BF ₃ •OEt ₂	CH ₂ Cl ₂	44	2/3
3		TiCl ₄	CH ₂ Cl ₂	none	
4		SnCl ₄	CH ₂ Cl ₂	21	N.d.
5		TrtClO ₄	CH ₂ Cl ₂	70	4/1
6		Cp ₂ Zr(OTf) ₂ •THF	CH ₂ Cl ₂	70	1/1
7		Zn(OTf) ₂	CH ₂ Cl ₂	trace	
8		Mg(OTf) ₂	CH ₂ Cl ₂	62	3/2
9		Sn(OTf) ₂	CH ₂ Cl ₂	85	7/3
10		Yb(OTf) ₃	MeCN	73	1/3
11		Yb(OTf) ₃	THF	73	1/1
12		Yb(OTf) ₃	PhH	74	1/1
13	Me	Yb(OTf) ₃	CH ₂ Cl ₂	98	3/2
14	Ph	Yb(OTf) ₃	CH ₂ Cl ₂	63	3/1

a) Molar ratio; **1**: Activator: B(OR)₃ = 1:1:1. N.d.=Not determined.

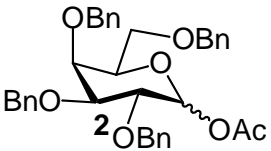
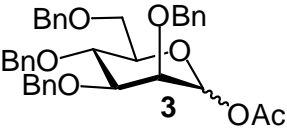
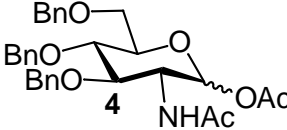
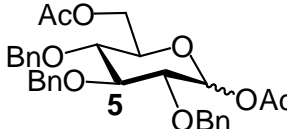
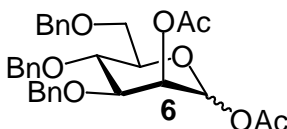
The effect of the molar ratio among **1**, Yb(OTf)₃ and B(OCH₂CH=CH₂)₃ was investigated. Various amounts of Yb(OTf)₃ were used in the reaction with equimolar amounts of **1** and B(OCH₂CH=CH₂)₃ in CH₂Cl₂. The reaction using 0.5 molar equivalents of Yb(OTf)₃ gave the allyl glucoside in as good yield as the reaction using 1 molar equivalent of Yb(OTf)₃. Various amounts of B(OCH₂CH=CH₂)₃ were added to the reaction using equimolar amounts of **1** and Yb(OTf)₃. The reaction using less than 0.6 molar equivalents of B(OCH₂CH=CH₂)₃ reduced the yields of the allyl glucoside. This result showed that two of

Table 2. Effect of the molar ratio among **1**, Yb(OTf)₃ and B(OCH₂CH=CH₂)₃

Entry	mol% of Yb(OTf) ₃	mol% of B(OAll) ₃	Yield(%)
1	100	100	86
2	50	100	90
3	30	100	65
4	10	100	16
5	100	60	82
6	100	40	71
7	100	30	55
8	50	60	85

the three allyloxy groups of B(OCH₂CH=CH₂)₃ could have the potential to react. Based on these results, we examined the reaction using 0.5 molar equivalents of Yb(OTf)₃ and 0.6 molar equivalents of B(OCH₂CH=CH₂)₃ toward **1**, and found that this reaction condition also afforded the allyl glucoside in good yield. These results are shown in Table 2.

Table 3. Synthesis of allyl glycosides from glycosyl acetates

Entry	Glycosyl Acetate	Yield(%)	α/β
1	1	85 ^{a)}	6/5
2		75 ^{a)}	3/2
3		76 ^{a)}	α
4		60 ^{b)}	2/3
5		83 ^{b)}	5/1
6		72 ^{b)}	α

a) Molar ratio ; glycosyl acetate:Yb(OTf)₃:B(OCH₂CH=CH₂)₃=1:0.5:0.6
 b) Molar ratio ; glycosyl acetate:Yb(OTf)₃:B(OCH₂CH=CH₂)₃=1:1:1

We applied this reaction to the synthesis of allyl glycosides from several 1-*O*-acetyl glycopyranoses. As the glycosyl acetates, 2,3,4,6-tetra-*O*-benzyl-**D**-galactopyranosyl acetate (**2**), 2,3,4,6-tetra-*O*-benzyl-**D**-mannopyranosyl acetate (**3**), 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-**D**-glucopyranosyl acetate (**5**), 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-**D**-mannopyranosyl acetate (**6**), and 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-**D**-glucopyranosyl acetate (**4**) were used. The reactions of these glycosyl acetates with B(OCH₂CH=CH₂)₃ using Yb(OTf)₃ in CH₂Cl₂ at room temperature gave the corresponding allyl glycopyranosides in good yields, respectively. These results are shown in Table 3.

Allyl glycosides are widely used in synthetic carbohydrate chemistry, and several methods to synthesize them based on the reaction of glycosyl acetates with allyl alcohol in the presence of some activators have already been reported.⁸ While these methods usually use a large excess of the allyl alcohol and activators, and in some cases, the benzyl group at the C-3 position and the acetyl group at the C-2 position were removed,^{9,10} our method reported here did not require using a large excess of B(OCH₂CH=CH₂)₃ and Yb(OTf)₃ and did not give any unprotected compounds at all.

As mentioned above, we found that several trialkyl borates worked as highly reactive glycosyl acceptors of the glycosyl acetates and developed a convenient synthetic method of allyl glycosides using B(OCH₂CH=CH₂)₃ which is relatively stable in air and commercially available.

ACKNOWLEDGEMENT

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11. A typical experimental procedure is as follows: A 0.2 M (1 M=1 mol·dm⁻³) CH₂Cl₂ solution of B(OCH₂CH=CH₂)₃ (1 mL, 0.2 mmol) was added to a solution of compound (**1**) (0.2 mmol) and

Yb(OTf)₃ (0.2 mmol) in CH₂Cl₂ (4 mL) at rt. The resulting mixture was stirred overnight. The reaction was then quenched by addition of sat. NaHCO₃ solution (5 mL). The reaction mixture was extracted with CHCl₃, and the organic layer was washed with water and sat. NaCl solution. After the organic layer was dried over Na₂SO₄, the solvent was evaporated under reduced pressure. The crude product was purified by a preparative silica gel TLC (ethyl acetate/hexane) to give the corresponding alkyl glycosides.