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SYNTHESIS OF ALKYL GLYCOSIDES USING TRIALKYL BORATES

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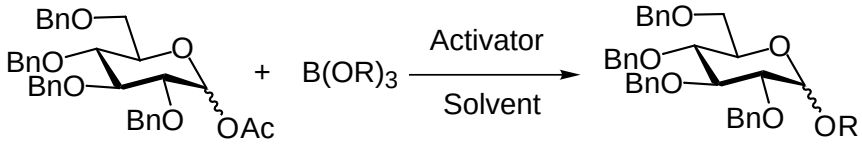
Abstract-Some trialkyl borates worked as highly reactive glycosyl acceptors of glycosyl acetates. Several allyl glycosides were obtained in good yields by the reaction of glycosyl acetates with triallyl borate using ytterbium(III) trifluoromethanesulfonate as the activator.

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 (BF_3•OEt_2) in the presence of ytterbium(III) trifluoromethanesulfonate ($Yb(OTf)_3$).[4] This reactivity enhancement was caused by the formation of a BF_3-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 ($B(OR)_3$) as new glycosyl acceptors.

We investigated the reaction of **1** with triallyl borate ($B(OCH_2CH=CH_2)_3$)[5] as one of the trialkyl borates. The reaction using $Yb(OTf)_3$ in dichloromethane (CH_2Cl_2) gave the expected corresponding allyl glucoside in 86% yield, and this result showed that $B(OCH_2CH=CH_2)_3$ worked as the highly reactive glycosyl acceptor of **1**.[6] Furthermore, the reaction between **1** and $B(OCH_2CH=CH_2)_3$ was examined in detail. The reaction using tin(II) trifluoromethanesulfonate ($Sn(OTf)_2$) 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 ($Cp_2Zr(OTf)_2$•THF) were also effective for this reaction. On the other hand, the reactions using zinc trifluoromethanesulfonate ($Zn(OTf)_2$) and halide salts such as BF_3•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 Yb $(OTf)_3$ 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 CH_2Cl_2 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 CH_2Cl_2 also afforded the corresponding methyl and phenyl glucosides in 98 and 68% yields, respectively. These results are summarized in Table 1.



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_2Cl_2	86	6/5
2		BF_3•OEt_2	CH_2Cl_2	44	2/3
3		$TiCl_4$	CH_2Cl_2	none	
4		$SnCl_4$	CH_2Cl_2	21	N.d.
5		$TrtClO_4$	CH_2Cl_2	70	4/1
6		$Cp_2Zr(OTf)_2$•THF	CH_2Cl_2	70	1/1
7		$Zn(OTf)_2$	CH_2Cl_2	trace	
8		$Mg(OTf)_2$	CH_2Cl_2	62	3/2
9		$Sn(OTf)_2$	CH_2Cl_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_2Cl_2	98	3/2
14	Ph	$Yb(OTf)_3$	CH_2Cl_2	63	3/1

a) Molar ratio; **1**: Activator: $B(OR)_3$ =1:1:1. N.d.=Not determined.

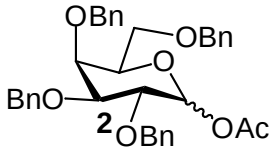
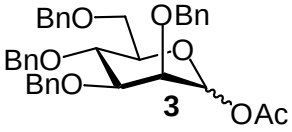
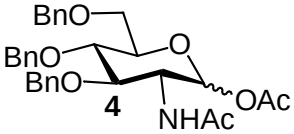
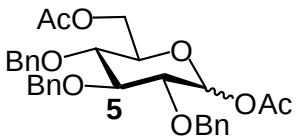
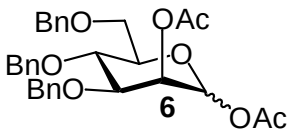
The effect of the molar ratio among **1**, $Yb(OTf)_3$ and $B(OCH_2CH{=}CH_2)_3$ was investigated. Various amounts of $Yb(OTf)_3$ were used in the reaction with equimolar amounts of **1** and $B(OCH_2CH{=}CH_2)_3$ in CH_2Cl_2. The reaction using 0.5 molar equivalents of $Yb(OTf)_3$ gave the allyl glucoside in as good yield as the reaction using 1 molar equivalent of $Yb(OTf)_3$. Various amounts of $B(OCH_2CH{=}CH_2)_3$ were added to the reaction using equimolar amounts of **1** and $Yb(OTf)_3$. The reaction using less than 0.6 molar equivalents of $B(OCH_2CH{=}CH_2)_3$ 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 $B(OCH_2CH=CH_2)_3$

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 $B(OCH_2CH=CH_2)_3$ 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 $B(OCH_2CH=CH_2)_3$ 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:$Yb(OTf)_3$:$B(OCH_2CH=CH_2)_3$=1:0.5:0.6
b) Molar ratio ; glycosyl acetate:$Yb(OTf)_3$:$B(OCH_2CH=CH_2)_3$=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 $B(OCH_2CH=CH_2)_3$ using $Yb(OTf)_3$ in CH_2Cl_2 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 $B(OCH_2CH=CH_2)_3$ 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 $B(OCH_2CH=CH_2)_3$ which is relatively stable in air and commercially available.

ACKNOWLEDGEMENT

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5. $B(OCH_2CH=CH_2)_3$ was prepared by the reaction of allyl alcohol with $B(OH)_3$ in the presence of CaH_2 as mentioned in the following references: T. E. Cole, R. Quintanilla, and S. Rodewald, *Synth. React. Inorg. Met. -Org. Chem.*, **1990**, 20, 55. $B(OCH_2CH=CH_2)_3$ is also commercially available from Gelest, Inc. (Azuma Co., Ltd.) and Sigma-Aldrich Japan Co., Ltd.
6. The following paper also suggested an enhancement in the reactivity of the alcohol by the formation of a boron-alkoxide: K. Toshima, H. Nagai, Y. Ushiki, and S. Matsumura, *Synlett*, **1998**, 1007.
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9. T. Takano, F. Nakatsubo, and K. Murakami, *Carbohydr. Res*., **1990**, 203, 341.
10. M.-Z. Liu, H.-N. Fan, Z.-W. Guo, and Y.-Z. Hui, *Carbohydr. Res*., **1996**, 290, 233.
11. A typical experimental procedure is as follows: A 0.2 M (1 M=1 mol•dm^{-3}) CH_2Cl_2 solution of $B(OCH_2CH=CH_2)_3$ (1 mL, 0.2 mmol) was added to a solution of compound (**1**) (0.2 mmol) and

$Yb(OTf)_3$ (0.2 mmol) in CH_2Cl_2 (4 mL) at rt. The resulting mixture was stirred overnight. The reaction was then quenched by addition of sat. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with $CHCl_3$, and the organic layer was washed with water and sat. NaCl solution. After the organic layer was dried over Na_2SO_4, 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.