Highly α-Selective Synthesis of Disaccharide Using Glycosyl Bromide by the Promotion of Phosphine Oxide

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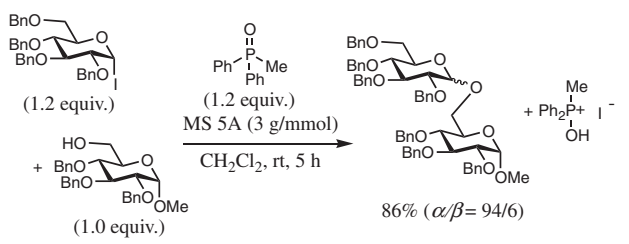
A simple and practical method for the glycosylation of several acceptors with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl bromide was established by the promotion of phosphine oxide. The corresponding disaccharides were obtained in high yields with extremely high α-selectivities under almost neutral condition.

There have been reported a number of stereoselective glycosylation methods for the syntheses of various glycosides and oligosaccharides.[1] A synthesis of 1,2-*cis*-glycoside, however, is known as a more difficult one in comparison with that of 1,2-*trans*-glycoside since the neighboring effect by the acyl group at 2 position in the former case is not useless, and also the S_N2 reaction to β-glycosyl bromide in that synthesis is not successfully carried out because of the anomeric effect to cause the β-glycosyl bromide to be unstable.[2] Lemieux and co-workers reported that more reactive β-glycosyl bromide could easily be formed by the in situ anomerization from α-glycosyl bromide which reacted with acceptors in the presence of tetraethylammonium bromide to afford α-glycopyranosides.[3] However, this method was not so useful as expected when glucose was used as a donor while it worked well with galactose or fucose as donors.[2]

Recently, highly α-selective glycosylation using glycosyl diphenylphosphinite and iodomethane was reported and dipheylmethylphosphine oxide was shown to promote the glycosylation of methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl iodide to afford the corresponding α-disaccharide stereoselectively.[4] It is remarkable that the diphenylmethylphosphine oxide worked as a nucleophile to attack glycosyl iodide to form a reactive intermediate, phosphonium salt, which in turn formed α-glycosyl linkage by the subsequent reaction with a glycosyl acceptor (Scheme 1). Then, the additives to form disaccharides with α-selectivities were studied, in order to perform the glycosylation reaction between several acceptors and glycosyl bromide, a more stable halo-sugar than glycosyl iodide.

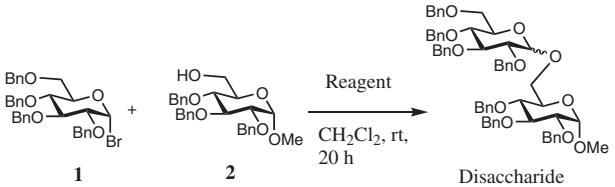


Scheme 1. Glycosylation of methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl iodide promoted by diphenylmethylphosphine oxide.

In this communication, we would like to report on highly α-selective glycosylation of several acceptors with glycosyl bromide using phosphine oxide as a promoter.

In the first place, glycosylations of acceptor **2** were tried with glycosyl bromide **1** which was prepared by Gillard's procedure[5] in the presence of several promoters in dichloromethane at room temperature (Table 1). It was then promoted effectively by using such phosphine oxides as diphenylmethylphosphine oxide, tributylphosphine oxide and triphenylphosphine oxide to afford **3** in good yields with high stereoselectivities (Table 1, Entries 1–4). While the yields and stereoselectivities of those promoted by triphenylphosphine sulfide or triphenyl phosphate remained low (Table 1, Entries 5,6), phosphoric acid triamide derivatives promoted the reactions effectively to give the corresponding disaccharides in highly α-selective manner (Table 1, Entries 7–

Table 1. Glycosylations of acceptor **2**, methyl 2,3,4-tribenzyl-glucopyranoside, with glycosyl bromide **1** in the presence of various reagents



1 **2** Disaccharide

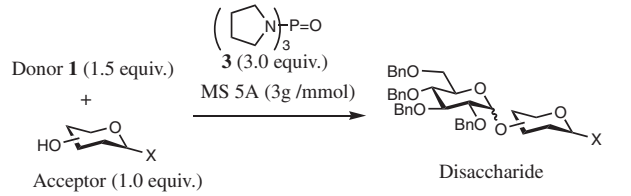
Entry	**1** /equiv.	Reagent[b]	Yield /%	α/β[a]
1	1.0	$Ph_2P(=O)Me$	72	94/6
2	1.2	$Ph_2P(=O)Me$	86	94/6
3	1.2	$Bu_3P=O$	86	94/6
4	1.2	$Ph_3P=O$	84	94/5
5	1.2	$Ph_3P=S$	10	80/20
6	1.2	$(PhO)_3P=O$	6	75/25
7	1.0	$(Me_2N)_3P=O$	74	94/6
8	1.2	$(Me_2N)_3P=O$	89	94/6
9	1.2		64	93/7
10	1.2		**92**	**94/6**
11	1.5	[c]	**quant.**	**96/4**
12	1.2	Et_4NBr / $(i\text{-}Pr)_2NEt$	84	90/10

[a] The α/β ratios were determined by HPLC analysis (Shodex SIL-5B, *n*-hexane/ethyl acetate = 4/1). [b] The same equivalent to **1** was used. [c] 3.0 equivalent of reagent was used.

10). Finally, it was found that tri(1-pyrrolidino)phosphine oxide[6] was the best promoter that afforded **3** in 92% yield (Table 1, Entry 10, $\alpha/\beta = 94/6$). The stereoselectivity of **3** rose effectively along with the increase of the amount of reagent (Table 1, Entry 11, $\alpha/\beta = 96/4$) while the α-selectivity of the glycosylation forming the same disaccharide remained low in Lemieux's procedure (Table 1, Entry 12, $\alpha/\beta = 90/10$).

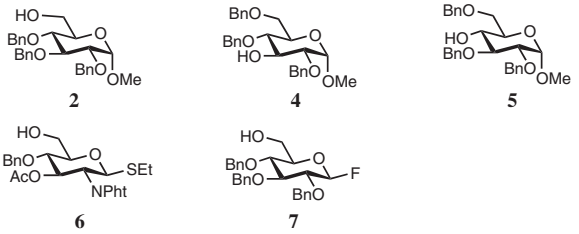
Next, glycosylations of various acceptors with glycosyl bromide **1** using tri(1-pyrrolidino)phosphine oxide were tried (Table 2). Each reaction efficiently proceeded in dichloromethane at room temperature to afford the corresponding disaccharides in good to high yields with high α-selectivities even when acid-labile glycosyl fluoride was used as an acceptor (Table 2, Condition a). When the reactions were carried out at reflux temperature in chloroform, the reaction rates rose higher while stereoselectivities lowered a little (Table 2, Condition b).

Table 2. Glycosylation of various acceptors with donor **1** by the promotion of tri(1-pyrrolidino)phosphine oxide



Entry	Acceptor	Condition[a]	Time/h	Yield/%(α/β)
1	**2**	a	20	95 (96/4)[b]
2	**2**	b	3	94 (95/5)[b]
3	**4**	a	72	91 (97/3)[b]
4	**4**	b	5	83 (96/4)[b]
5	**5**[d]	a	96	83 (98/2)[b]
6	**5**[d]	b	5	66 (96/4)[b]
7	**6**	a	40	88 (95/5)[b]
8	**6**	b	3	87 (92/8)[b]
9	**7**	a	24	88 (95/5)[c]
10	**7**	b	3	76 (93/7)[c]

[a] Condition a: CH_2Cl_2, rt; b: $CHCl_3$, reflux. [b] The α/β ratios were determined by HPLC analysis (In Entries 1-4 and 7,8; Shodex SIL-5B, *n*-hexane/ethyl acetate = 4/1, in Entry 5,6; YMC J'sphere M80, methanol/H_2O = 20/1). [c] The α/β ratios were determined by isolated yields of both isomers [d] 3.0 equiv. of **1** was used.



The present reaction is assumed to proceed via the reactive intermediates, glycosyl phosphonium bromides, which are rapidly formed from the corresponding glycosyl bromides and phosphine oxides. Glycosyl acceptors in turn react dominantly with highly reactive β-intermediate to afford α-disaccharide while the less-reactive α-intermediate is easily epimerized to more reactive β-one. In addition, hydrogen bromide, a coproduct, is rapidly neutralized by phosphine oxide to form a $(C_4H_8N)_3P{=}O{\cdot}HBr$ adduct.[7] Therefore, the present glycosylation proceeds smoothly under nearly neutral condition.

The typical experimental procedure is as follows: to a stirred suspension of MS5A (240 mg), **1** (0.0725 g, 0.120 mmol) and **2** (0.0371 g, 0.0799 mmol) in CH_2Cl_2 was added tri(1-pyrrolidino)phosphine oxide (0.0553 mL, 0.241 mmol) at room temperature. After stirring for 20 h, the reaction mixture was diluted with EtOAc and filtered through Celite. After having been dried over $MgSO_4$, filtered and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **3** (0.0750 g, 95%, $\alpha/\beta = 96/4$).

Thus, the glycosylation using glycosyl bromide was quite successfully carried out by the promotion of phosphine oxide to afford α-disaccharides in high yields with high α-selectivities.

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