Highly α-Selective Glycosylation with Glycosyl Acetate via Glycosyl Phosphonium Iodide

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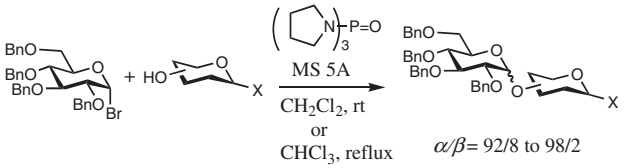
Mild and highly α-selective glycosylations of several acceptors with glycosyl phosphonium iodide, a glycosyl donor readily generated in situ from glycosyl acetate, proceeded smoothly to afford the corresponding disaccharides in high yields.

The in-situ anomerization procedure using glycosyl halide and tetraalkyl ammonium halide has been applied to the highly α-selective synthesis of complex oligosaccharides composed of D-glucose, D-galactose, and D-fucose derivatives.[1,2] The above glycosyl halide is generally prepared from glycosyl acetate and trialkylsilyl halides but is unstable for the isolation.[3,4] To isolate glycosyl bromide is a necessary process because undesired reverse reaction to form glycosyl acetate takes place when the above mixture was used in the next glycosylation reaction.[4,5] Thus, the one-pot synthesis of α-glycoside via the in-situ anomerization procedure starting from glycosyl acetate is considered difficult.

Recently, a highly α-selective glycosylation using glycosyl phosphonium bromide, a glycosyl donor generated from glycosyl bromide and phosphine oxide, was reported from our laboratory (Scheme 1).[6] Even though, the donor employed in the above glycosylation reacted efficiently to afford the corresponding disaccharides in high yields with high selectivities, the glycosyl bromide is unstable and needed to use the freshly prepared bromide. Then, the one-pot glycosylation of several accepters using glycosyl acetate and iodotrimethylsilane in the presence of phosphine oxide was tried. The reaction proceeded via glycosyl phosphonium iodide which was formed by the reaction of glycosyl iodide and phosphine oxide.

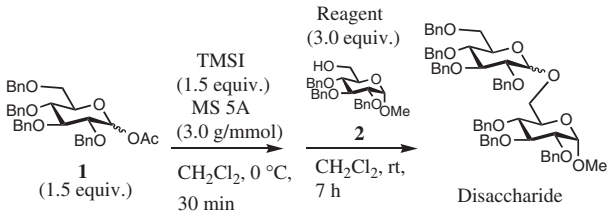


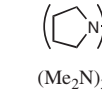
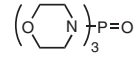
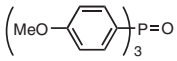
Scheme 1. Glycosylation of several acceptors with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl bromide promoted by tri(1-pyrrolidino)phosphine oxide.

In this communication, we would like to report on highly α-selective glycosylation of several acceptors with glycosyl acetate under mild conditions by the promotion of iodotrimethylsilane and phosphine oxide in combination.

In the first place, glycosylations of acceptor **2** with glycosyl iodide generated from glycosyl acetate and iodotrimethylsilane in the presence of several promoters were tried in dichloromethane at room temperature (Table 1). When phosphoric acid triamide derivatives were used,[7] the desired disaccharides were obtained in moderate yields with high stereoselectivities (Table 1, Entries 1–3). When trialkylphosphine oxides were used, on the other hand, they worked effectively to give the corresponding disaccharides in highly α-selective manner (Table 1, Entries 6–9) while yields and stereoselectivities of those promoted by triphenylphosphine sulfide and phenyl diphenylphosphinite, respectively, remained low (Table 1, Entries 4–5). It is thus noted that the triphenylphosphine oxide promoted the glycosylation excellently to give the corresponding disaccharide in high yield with high selectivity (Table 1, Entry 9). In the absence of phosphine oxide, however, the stereoselectivity was not controlled (Table 1, Entry 10). In the case of using tetrabutylammonium iodide as a promoter in the presence of *N*,*N*-diisopropylethylamine, it gave a starting material, glycosyl acetate **1**, by the reverse reaction between glycosyl iodide and trimethylsilyl acetate (Table 1, Entry 11). It is remarkable that such a reverse reaction

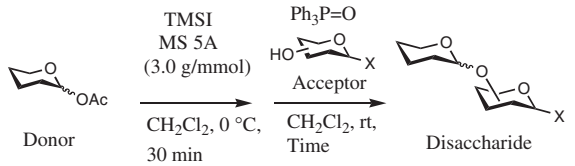
Table 1. Glycosylations of acceptor **2**, methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside, with glycosyl acetate **1** via glycosyl phosphonium iodide using various reagents



Entry	Reagent[a]	Yield /%	α/β[b]
1		61	94.1/5.9
2	$(Me_2N)_3P{=}O$	69	94.3/5.7
3		61	95.9/4.1
4	$Ph_3P{=}S$	58	71.2/28.8
5	$Ph_2P(=O)OPh$	56	95.2/4.8
6	$n\text{-}Bu_3P{=}O$	72	95.0/5.0
7	$Ph_2P(=O)Me$	73	95.4/4.6
8		69	94.8/5.2
9	$Ph_3P{=}O$	**89**	**96.1/3.9**
10	———	59	68.4/31.6
11	$n\text{-}Bu_4NI$ / $(i\text{-}Pr)_2NEt$	19[c]	91.6/8.4

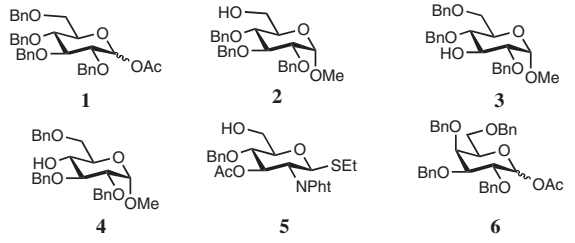
[a]The same equivalent to **1** was used. [b]The α/β ratios were determined by HPLC analysis. [c]Quantitative amount of 1 was recovered.

Table 2. Glycosylation of various acceptors with donor **1** or **6** via glycosyl phosphonium iodide using TMSI and $Ph_3P{=}O$



Entry	Donor	Acceptor	Condition[a]	Time /h	Yield /%(α/β)[b]
1	**1**	**2**	a	7	89 (96.1/3.9)
2		**3**	b	24	91 (97.4/2.6)
3		**4**	b	34	80 (98.9/1.1)
4		**5**	a	21	85 (94.9/5.1)
5	**6**	**2**	a	7	93 (96.6/3.4)
6		**3**	a	34	94 (93.1/6.9)
7		**4**	b	34	91 (96.3/3.7)

[a]Condition a: **1** or **6** (1.5 equiv.), $Ph_3P{=}O$ (3.0 equiv.), TMSI (1.5 equiv.); b: **1** or **6** (3.0 equiv.), $Ph_3P{=}O$ (6.0 equiv.), TMSI (3.0 equiv.). [b]The α/β ratios were determined by HPLC analysis (In Entries 1, 2, 4 and 5, Shodex SIL-5B, *n*-hexane/ethyl acetate = 4/1; in Entry 3, YMC J'sphere M80, methanol/H_2O = 20/1; in Entry 6, GL Science Intersil SIL, *n*-hexane/ethyl acetate = 4/1; in Entry 7, DAICEL CHIRALCEL OD–H, *n*-hexane/isopropanol = 10/1).



had never taken place when phosphine oxides was used as a promoter. The details of this effect are now under investigation.

Next, glycosylations of the acceptors with glucosyl acetate or galactosyl acetate using iodotrimethylsilane and triphenylphosphine oxide were tried (Table 2). Each reaction efficiently proceeded in dichloromethane at room temperature and afforded the corresponding disaccharides in high yields with high α-selectivities, as expected.

The present reaction is assumed to proceed via the reactive intermediates, glycosyl phosphonium iodides, which were formed from the corresponding glycosyl iodides and phosphine oxides.[8] Glycosyl acceptors should in turn react dominantly with highly-reactive β-intermediate to afford α-disaccharide while less-reactive α-intermediate epimerizes to the above more reactive β-one and it affords the above mentioned glycoside. In addition, hydrogen iodide, a co-product, is rapidly neutralized by phosphine oxide to form a $Ph_3P{=}O$–HI adduct,[9] so that the present glycosylation proceeds smoothly under nearly-neutral condition.

The typical experimental procedure is as follows: to a stirred suspension of MS5A (240 mg) and **1** (0.0693 g, 0.119 mmol) in CH_2Cl_2 was added iodotrimethylsilane (17.1 μL, 0.120 mmol) at 0 °C. After stirring for 30 min, $Ph_3P{=}O$ (0.0668 g, 0.240 mmol) and **2** (0.0369 g, 0.0794 mmol) were successively added. The reaction mixture was diluted with EtOAc, after additional 7 h stirring at room temperature. After filtered through Celite and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **3** (0.0694 g, 89%, α/β = 96.1/3.9).

Thus, the glycosylations using glycosyl phosphonium iodide generated from the corresponding glycosyl acetate, i.e., a glycosyl donor which is easy both to access and to handle, proceeded successfully in CH_2Cl_2 at room temperature. It is noteworthy that glycosyl phosphonium iodide did not react with trimethylsilyl acetate, a co-product formed in the formation of the iodide, therefore, the present one-pot glycosylation proceeds effectively.

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References and Notes

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5 For example, one-pot glycosylation of **2** using 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl bromide prepared from the corresponding acetate and bromotrimethylsilane in the presence of tetraethylammonium bromide and *N*,*N*-diisopropylethylamine afforded glycosyl acetate as a main product.

6 T. Mukaiyama and Y. Kobashi, *Chem. Lett.*, **33**, 10 (2004).

7 They were shown as the best promoters in the reactions using glycosyl bromide (cf. Ref. 4).

8 The glycosyl phosphonium iodide was not detected by ^1H NMR study on the reaction of glycosyl iodide and triphenylphosphine oxide in $CDCl_3$. This result indicates that very small amounts of glycosyl phosphonium iodide exist in equilibrium to a mixture of glycosyl iodide and phosphine oxide.

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