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Environmentally benign and stereoselective formation of β-*O*-glycosidic linkages using benzyl-protected glucopyranosyl phosphite and montmorillonite K-10

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Abstract—An environmentally benign and highly stereoselective β-glucopyranosylation without neighboring group participation has been developed employing benzyl-protected glucopyranosyl diethyl phosphite as a glycosyl donor and montmorillonite K-10 as an activator.

Carbohydrates are a naturally abundant and recyclable feedstock. On the other hand, a number of glycosides and oligosaccharides are found in many bioactive or functional molecules. One of the most important transformation reactions of carbohydrates is a chemical glycosidation,[1] which is very useful for preparing both natural and unnatural glycosides. Therefore, a highly effective, simple and environmentally benign glycosidation method is now urgently needed both in the laboratory and in industry. In this context, the greening of chemical glycosidation may include the use of a heterogeneous and reusable solid acid as an activator. In previous studies, we have demonstrated several stereoselective *O*-glycosidations using glycals,[2] glycosyl fluorides,[3] glycosyl sulfoxides[4] and 1-hydroxy sugars[5] as glycosyl donors and montmorillonite K-10, sulfated zirconia (SO_4/ZrO_2) or Nafion®-H as environmentally friendly promoters. Glycosyl phosphites have also attracted considerable attention as effective glycosyl donors,[6–10] and Wong[7c] and Hashimoto[9a] have independently announced the highly stereoselective 1,2-*trans*-β-glycosidation reactions of glycopyranosyl phosphites

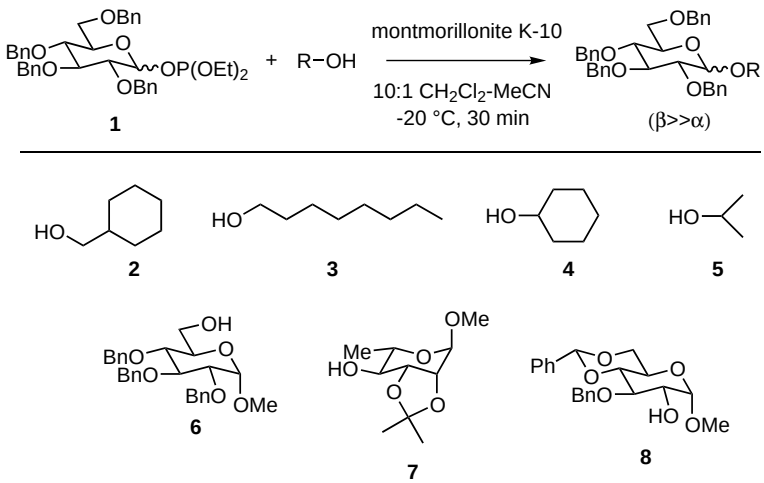

Figure 1.

Keywords: glycosidation; glycosyl phosphite; β-glucopyranoside; solid acid; montmorillonite K-10.

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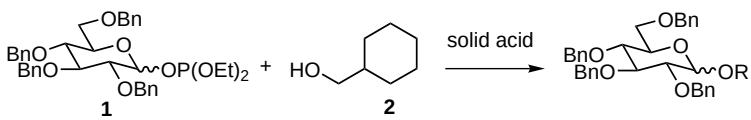
using a homogeneous promoter. In this letter, we disclose the novel and environmentally benign glycosidations of glucopyranosyl phosphite and alcohols using a heterogeneous and reusable solid acid, montmorillonite K-10, for the highly stereoselective synthesis of β-glucopyranosides with a non-participating group (Fig. 1). To the best of our knowledge, this is the first example of heterogeneous solid acid-mediated glycosidation of glycosyl phosphite.

In our first experiments, we examined the glycosidations of the totally benzylated glucopyranosyl diethyl phosphite **1** (α/β = 73/27) and cyclohexylmethanol (**2**) using several heterogeneous solid acids such as Nafion®-H,[11] sulfated zirconia (SO_4/ZrO_2)[12] and montmorillonite K-10.[13] These heterogeneous solid acids are well known as environmentally benign solid acids because they are easily handled due to their nonvolatile, noncorrosive and odorless properties, and they can be recovered from the reaction mixture by only filtration and then reused. These results are summarized in Table 1. It was found, for the first time, that the glucosyl phosphite **1** was effectively activated by these heterogeneous solid acids in CH_2Cl_2 under mild conditions and smoothly coupled with the alcohol **2** to give the corresponding glucopyranosides in high yield. Among them, montmorillonite K-10 was shown to be superior to the other solid acids with respect to both the chemical yield and unusual β-stereoselectivity.[14] Next our attention turned to the solvent effect on this glycosidation. Therefore, the glycosidations of **1** and **2** using montmorillonite K-10 in several solvents such as MeCN, PhMe and Et_2O were tested and compared to that in CH_2Cl_2. It was confirmed that the highest yield was obtained in CH_2Cl_2 while the highest β-stereoselectivity was observed in MeCN. In addition, the glycosidation effectively proceeded even at 0°C for 30 min in both cases. Furthermore, the addition of 100 wt% montmorillonite K-10 to the glycosyl donor **1** led to the best results and the use of a smaller or larger amount of montmorillonite K-10 was less effective in both cases. Therefore, we further examined the glycosidations of **1** and **2** using 100 wt% montmorillonite K-10 in mixed-solvents of CH_2Cl_2 and MeCN. After several attempts, we finally found that the glycosidation of **1** and **2** using 100 wt% montmorillonite K-10 in 10:1 CH_2Cl_2–MeCN at −20°C for 30 min was the best combination to afford the corresponding glucopyranosides in 94% yield with 6:94 α/β-stereoselectivity.

To enhance the synthetic utility of this novel glycosidation, the glycosidations using other primary and secondary alcohols **3**–**8** including sugar derivatives **6**–**8** were next examined. Based on the results summarized in Table 2, the glycosidations of **1** and **3**–**5** using 100 wt% montmorillonite K-10 in 10:1 CH_2Cl_2–MeCN at −20°C for 30 min, as well as that of **2**, effectively proceeded to give the corresponding β-glucopyranosides in high yields. When the sugar derivatives **6**–**8** were employed as the glycosyl acceptors, a longer reaction time (2 h) was required, and 3.0 equiv. of the glycosyl acceptor was needed in the case of the low reactive glycosyl acceptor such as **7** to obtain the good yields of the corresponding β-glucopyranosides. Since the configuration of the anomeric position was not

Table 1. Glycosidations of **1** and **2** by a solid acid under several conditions[a]



Entry	Solid acid (wt%)	Solvent (0.1 M)	Temp. (°C)	Time (h)	Yield (%)[b]	α/β ratio[c]
1	Nafion®-H (100)	CH_2Cl_2	25	15	83	28/72
2	SO_4/ZrO_2 (100)	CH_2Cl_2	25	15	73	55/45
3	K-10 (100)	CH_2Cl_2	25	15	90	27/73
4	K-10 (100)	Et_2O	25	15	62	56/44
5	K-10 (100)	MeCN	25	15	75	18/82
6	K-10 (100)	PhMe	25	15	80	26/74
7	K-10 (50)	CH_2Cl_2	0	0.5	89	23/77
8	K-10 (100)	CH_2Cl_2	0	0.5	93	23/77
9	K-10 (200)	CH_2Cl_2	0	0.5	92	24/76
10	K-10 (50)	MeCN	0	0.5	83	11/89
11	K-10 (100)	MeCN	0	0.5	86	11/89
12	K-10 (200)	MeCN	0	0.5	84	14/86
13	K-10 (100)	CH_2Cl_2–MeCN (5:1)[d]	−20	0.5	82	6/94
14	K-10 (100)	CH_2Cl_2–MeCN (10:1)[d]	−20	0.5	94	6/94
15	K-10 (100)	CH_2Cl_2–MeCN (15:1)[d]	−20	0.5	87	10/90

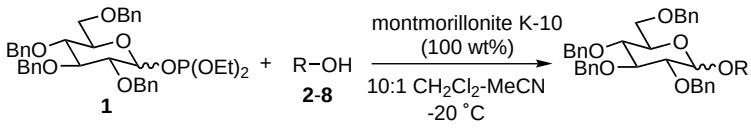
[a] All reactions were carried out by use of 2.0 equiv. of **2** to **1**.

[b] Isolated yields after purification by column chromatography.

[c] α:β Ratios were determined by HPLC analysis (column, CrestPak C18S®, 4.6×150 mm; eluent, 10% H_2O in MeCN; flow rate, 1.0 mL/min, 40°C; detection, UV 250 nm).

[d] 0.05 M solvent was used. K-10: montmorillonite K-10.

Table 2. Glycosidations of **1** and several alcohols **2–8** by montomorillonite K-10



Entry	Alcohol[a]	Time (h)	Yield (%)[b]	α/β Ratio[c]
1	**2**	0.5	94	6/94
2	**3**	0.5	88	6/94
3	**4**	0.5	88	7/93
4	**5**	0.5	86	8/92
5	**6**	2	77	7/93
6	**7**[d]	2	74	16/84
7	**8**	2	73	13/87

[a] All reactions were carried out by use of 2.0 equiv. of alcohol to **1**.
[b] Isolated yields after purification by column chromatography.
[c] α:β Ratios were determined by HPLC analysis (column, CrestPak C18S®, 4.6×150 mm; eluent, 10% H_2O in MeCN for entries 1–4, 6 and 7, 12.5% H_2O in MeCN for entry 5; flow rate, 1.0 mL/min, 40°C; detection, UV 250 nm).
[d] 3.0 equiv. of alcohol was used.

epimerized under the present glycosidation conditions, the predominant β-stereoselectivity must arise from kinetic control.

Finally, we tested the solid acid recycling. After filtration, washing with methanol and heating at 100°C/1 mmHg for 12 h, the montmorillonite K-10 was reused for at least three times and showed good to high yields and high stereoselectivities as described in Table 3.

The general experimental protocol:[15] To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl diethyl phosphite **1** (α/β = 73/27, 0.1 mmol) and an alcohol (0.2 mmol) in dry 10:1 CH_2Cl_2–MeCN (2 mL) was added montmorillonite K-10 (100 wt% to the glycosyl donor **1**). After stirring at −20°C for 30 min, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave the corresponding glucopyranosides which predominately contained the β-anomer.

In conclusion, we have presented the novel and highly stereoselective synthesis of β-glucopyranosides by the glycosidations of benzyl-protected glucopyranosyl diethyl phosphite and alcohols using a heterogeneous and environmentally acceptable solid acid, montmorillonite K-10. The results including the simple and environmentally friendly protocol, high yield and stereoselectivity should find widespread application for the synthesis of carbohydrate-containing bioactive or functional molecules.

Table 3. Recycling of montmorillonite K-10 in glycosidation of **1** and **2**

Recycling number	0	1st	2nd	3rd
Yield (%)	94	90	86	70
α/β ratio	6/94	5/95	5/95	7/93

Acknowledgements

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11. Nafion®-H was purchased from Aldrich Chemical Company, Inc. as Nafion® perfluorinated ion-exchange powder and dried at 25°C/1 mmHg for 2 h before using.
12. SO_4/ZrO_2 was purchased from Wako Pure Chemical Industries, Ltd. and dried at 200°C/1 mmHg for 12 h before using.
13. Montmorillonite K-10 was purchased from Aldrich Chemical Company, Inc. and dried at 200°C/1 mmHg for 12 h before using.
14. It is noteworthy that the tendency during the stereoselectivity of the present glycosidation is similar to those in Wong's, Watanabe's and Hashimoto's glycosidations, all of which use benzyl-protected glucopyranosyl phosphite and a homogeneous promoter, see: Refs. 7c, 8a and 9a.
15. All α- and β-glucopyranosides were purified by silica gel column chromatography and were fully characterized by spectroscopic means. The configurations of the anomeric centers were clearly confirmed by the coupling constants between H-1 and H-2 in the ^{1}H NMR analyses.