Pergamon

Tetrahedron Letters 41 (2000) 10233–10237

TETRAHEDRON LETTERS

A novel promoter, heteropoly acid, mediated chemo- and stereoselective sulfoxide glycosidation reactions

Hideyuki Nagai, Shuichi Matsumura and Kazunobu Toshima*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 7 September 2000; revised 4 October 2000; accepted 12 October 2000

Abstract

The chemo- and stereoselective glycosidations of sulfinylglycosides and alcohols using a heteropoly acid, $H_3PW_{12}O_{40}$, as a new promoter have been developed.

Keywords: sulfoxide glycosidation; sulfinylglycoside; heteropoly acid; α-mannopyranoside; 2-deoxy-α-glucopyranoside.

A chemo- and stereoselective chemical glycosidation method, which is synthetically very important for the preparation of natural and unnatural glycosides, is urgently needed both in the laboratory and in industry.[1] Among the glycosidation protocols recently developed,[1] the sulfoxide methodology (Kahne's methodology)[2] is particularly attractive especially for oligosaccharide synthesis since the sulfinylglycoside can be easily prepared from another glycosyl donor, thioglycoside,[1] and converted into the other glycosyl donor, sulfonylglycoside.[1c,3] Up to now, Tf_2O,[2] TfOH[4,5] and TMSOTf[6] have been used for the activation of the sulfinylglycoside. In this communication, we describe that novel use of a readily available, inexpensive, easily handling, noncorrosive, nonvolatile and odorless solid acid, heteropoly acid, is very effective for the chemo- and stereoselective sulfoxide glycosidation reaction (Fig. 1).

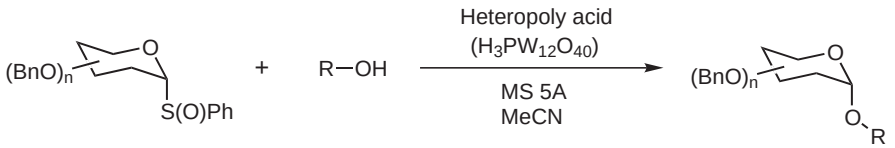


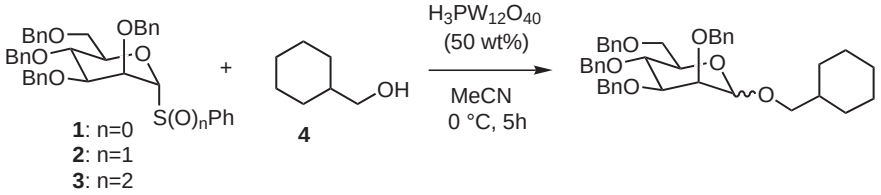
Figure 1.

* Corresponding author. Tel/fax: +81 45 566 1576; e-mail: toshima@applc.keio.ac.jp

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01821-9

In this study, we selected one of the heteropoly acids, $H_3PW_{12}O_{40}$,[7] which has high thermal and hydrolytic stabilities and a low oxidation potential.[8,9] We first examined the glycosidation of the thioglycoside **1**, the sulfinylglycoside **2**, and the sulfonylglycoside **3** with cyclohexylmethanol (**4**) using the heteropoly acid, $H_3PW_{12}O_{40}$, in MeCN. As the results show in Table 1, only the sulfinylglycoside **2** was smoothly activated and cross-coupled with **4** under mild conditions, while both the thioglycoside **1** and the sulfonylglycoside **3** were not reacted with **4** under similar conditions and recovered in almost quantitative yields. These results clearly indicated the high chemoselective activation of the sulfinylglycoside by the heteropoly acid, $H_3PW_{12}O_{40}$.

Table 1
Glycosidations of **1**–**3** with cyclohexylmethanol (**4**) using $H_3PW_{12}O_{40}$[a]



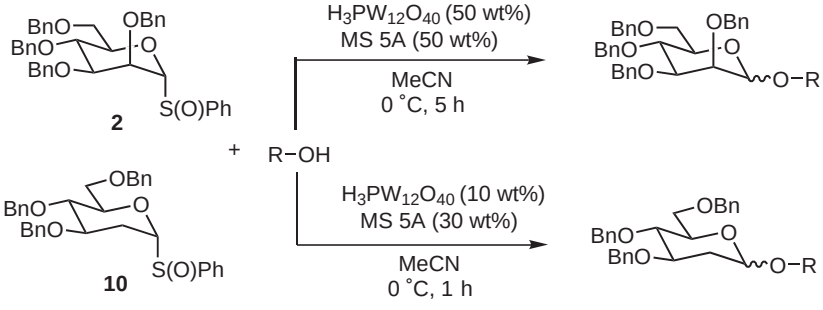
Entry	Glycosyl donor	Yield (%)[b]	α/β Ratio[c]
1	**1**	0	–
2	**2**	68	79/21
3	**3**	0	–

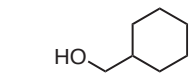
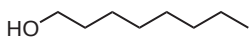
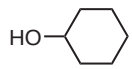
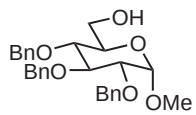
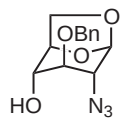
[a] All reactions were carried out by use of 1.2 equiv. of **4** to the glycosyl donor.
[b] Isolated yields after purification by column chromatography.
[c] α/β Ratios were determined by ^{1}H NMR (300 MHz) spectroscopy and/or isolation of pure isomers.

Our attention next turned to the effects of solvents and dehydrating agents in the glycosidation reaction. Therefore, we examined the glycosidations of **2** and **4** in several solvents such as CH_2Cl_2, PhMe, THF, Et_2O, $MeNO_2$ and MeCN. Among them, MeCN was shown to be superior to the other solvents with respect to the chemical yield and the α-stereoselectivity in the glycosidation. Furthermore, it was found that when MS 5A was used as the additive, the chemical yield and the α-stereoselectivity were significantly improved. Thus, the glycosidation of **2** and **4** using 50 wt% $H_3PW_{12}O_{40}$ in the presence of 50 wt% MS 5A in MeCN at 0°C for 5 h effectively proceeded to afford the corresponding mannopyranoside in high yield (84%) with excellent α-stereoselectivity (α/β = 98/2).

To enhance the synthetic utility of this novel and convenient glycosidation method, the glycosidation of **2** and other primary and secondary alcohols **5**–**9** were next examined. These results are summarized as entries 1–6 in Table 2. All the glycosidations of **2** with **5**–**9** using 50 wt% $H_3PW_{12}O_{40}$ in the presence of 50 wt% MS 5A in MeCN at 0°C for 5 h, as well as that of **4**, effectively proceeded to give the corresponding mannopyranosides in good to high yields with excellent α-stereoselectivities. The stereoselective synthesis of several 2-deoxy-α-glucopyranosides by the present glycosidation protocol is also outlined as entries 7–12 in Table 2. Thus, several 2-deoxyglucopyranosides were effectively obtained in good to high yields with good α-stereoselectivities by the glycosidation of the sulfinylglycoside **10** with the alcohols **4**–**9** using 10 wt% $H_3PW_{12}O_{40}$ in the presence of 30 wt% MS 5A in MeCN at 0°C for 1 h. These optimized

Table 2
Glycosidations of **2** and **10** with several alcohols using $H_3PW_{12}O_{40}$[a]



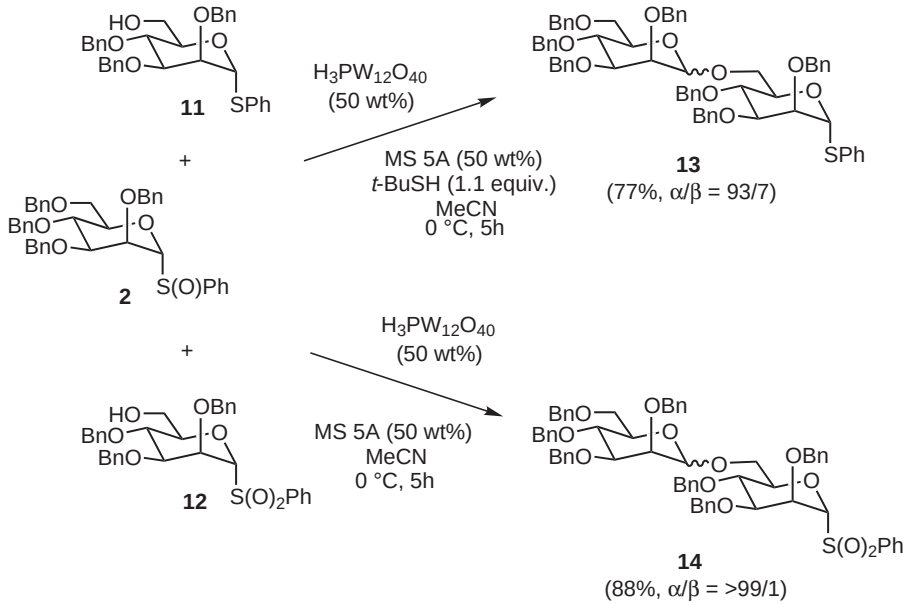
		2		10	
Entry	Alcohol	Yield (%)[b]	α/β Ratio[c]	Yield (%)[b]	α/β Ratio[c]
1, 7	 **4**	84	98/2	88	88/12
2, 8	 **5**	78	99/1	89	89/11
3, 9	 **6**	78	99/1	78	81/19
4, 10	 **7**	79	99/1	76	90/10
5, 11	 **8**	81	>99/1	80	91/19
6, 12	 **9**	75	>99/1	83	80/20

[a] All reactions were carried out by use of 1.2 equiv. of the alcohol to the glycosyl donor. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H-NMR (300 MHz) spectroscopy and / or isolation of pure isomers.

conditions for selectively obtaining the 2-deoxy-α-glucopyranosides including the reaction time and the amount and ratio of $H_3PW_{12}O_{40}$ and MS 5A differed from those for the α-stereoselective mannosylations of **2** probably due to the higher reactivity of the 2-deoxyglucosyl donor **10** compared to that of the mannosyl donor **2**. Since the configuration of the anomeric position was not isomerized by exposure of the isolated single β-anomer of the *O*-glycoside to the reaction

conditions, the predominant α-stereoselectivity observed in these glycosidations must arise from the kinetic anomeric effect.[10]

Finally, we examined the glycosidations of the sulfinylglycoside **2** with the thioglycoside **11** and sulfonylglycoside **12** (Scheme 1). When the sulfonylglycoside **12** was employed as a glycosyl acceptor, the glycosidation smoothly proceeded under the conditions similar to those for the alcohols **4**–**9** to give the disaccharide **14** in high yield with excellent α-stereoselectivity. On the other hand, in the glycosidation of **2** and **11**, the conditions needed the addition of an agent that scavenged phenylsulfenic acid (PhSOH),[4,5] a highly reactive byproduct that formed following activation of anomeric sulfoxide with a heteropoly acid. Thus, the effective glycosidation of **2** and **11** was realized using 50 wt% $H_3PW_{12}O_{40}$ in the presence of 50 wt% MS 5A and 1.1 equiv. of *t*-BuSH as a new scavenger of the phenylsulfenic acid in MeCN at 0°C for 5 h to furnish the disaccharide **13** in good yield with high α-stereoselectivity.



Scheme 1.

A typical experimental protocol:[11] to a stirred mixture of the sulfinylglycoside **2** (0.5 mmol), an alcohol (0.6 mmol) and MS 5A (50 wt% of the glycosyl donor **2**) in dry MeCN (5.0 ml) was added $H_3PW_{12}O_{40}$ (50 wt% of the glycosyl donor **2**). After stirring for 5 h at 0°C, the mixture was quenched with sat. $NaHCO_3$ (aq.) and then filtered to remove the MS 5A. The filtrate was extracted with EtOAc. The extract was washed with sat. NaCl (aq.), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography gave the corresponding *O*-mannopyranosides that exclusively contained the α anomer.

In conclusion, we have presented the chemo- and stereoselective glycosidations of sulfinylglycosides and alcohols using a readily available, inexpensive, easily handling, noncorrosive, nonvolatile and odorless heteropoly acid, $H_3PW_{12}O_{40}$. Moreover, the results including the convenient protocol, high yield and good stereoselectivity should find wide application in the synthesis of many types of *O*-glycosides, which are found in biomolecules and functional materials. Further studies along this line are currently underway.

Acknowledgements

This work was partially supported by the New Energy and Industrial Technology Development Organization (NEDO) and the Research Institute of Innovative Technology for the Earth (RITE).

References

1. For some reviews on *O*-glycosidations, see: (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212; (b) Sinaÿ, P. *Pure Appl. Chem.* **1991**, *63*, 519; (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503; (d) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095; (e) In *Preparative Carbohydrate Chemistry*, Hanessian, S., Ed.; Marcel Dekker: New York, 1977; Chapters 12–22.
2. Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
3. (a) Brown, D. S.; Ley, S. V.; Vile, S. *Tetrahedron Lett.* **1988**, *29*, 4873; (b) Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. *Tetrahedron* **1991**, *47*, 1329.
4. Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580.
5. Alonso, I.; Khiar, N.; Martin-Lomas, M. *Tetrahedron Lett.* **1996**, *37*, 1477.
6. Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015.
7. For recent reviews on heteropoly acids, see: (a) Kozhevnikov, I. V. *Chem. Rev.* **1988**, *98*, 171; (b) Mizuno, N.; Misono, M. *Chem. Rev.* **1988**, *98*, 199.
8. The heteropoly acid, $H_3PW_{12}O_{40}{\cdot}nH_2O$, was purchased from Aldrich Chemical Company, Inc. and dried at 200°C/1 mmHg for 14 h before using.
9. The studies on glycosidation using a heteropoly acid have been reported. (a) Kiromura, K.; Kitazawa, S.; Takata, Y.; Sakakibara, T. U.S. Patent 4,874,852, 1988; (b) Kitazawa, S.; Okumura, M.; Kinomura, K.; Sakakibara. T. *Chem. Lett.* **1990**, 1733; (c) Toshima, K.; Nagai, H.; Matsumura, S. *Synlett* **1999**, 1420.
10. (a) In *The anomeric Effect and Related Stereoelectron Effects at Oxgen*, Kirby, A. J., Ed.; Springer-Verlag: New York, 1983; (b) In *Stereoelectronic Effects in Organic Chemistry*, Deslongchmps, P., Ed.; Pergamon Press: Oxford, 1983.
11. All mannopyranosides and 2-deoxyglucopyranosides were purified by silica-gel column chromatography and were fully characterized by spectroscopic means. The anomeric configuration is assigned in each case with the aid of ^{1}H NMR analysis and confirmed by the comparison with the authentic samples, see; (a) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1998**, 643; (b) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1999**, 813.