Novel Stereocontrolled Glycosidations of 2-Deoxyglucopyranosyl Fluoride Using a Heterogeneous Solid Acid, Sulfated Zirconia (SO_4/ZrO_2)

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Received 23 March 1999

Abstract: Novel stereocontrolled glycosidations of a 2-deoxy-α-D-glucopyranosyl fluoride using a heterogeneous and environmentally friendly solid acid, sulfated zirconia (SO_4/ZrO_2), have been developed. The glycosidations of the perbenzylated 2-deoxy-α-D-glucopyranosyl fluoride **1** and various alcohols using SO_4/ZrO_2 in CH_3CN at 25 °C for 1 h predominantly gave the corresponding 2-deoxy-α-D-glucopyranosides. On the other hand, the corresponding 2-deoxy-β-D-glucopyranosides were selectively obtained by the glycosidations of **1** and various alcohols employing SO_4/ZrO_2 in the presence of molecular sieves 5A in Et_2O at 0 °C for 1 h.

Key words: glycosidation, carbohydrate, 2-deoxy sugar, solid acid, sulfated zirconia

Highly effective, simple and environmentally acceptable glycosidations have attracted considerable attention in current synthetic organic chemistry related to both biomolecules and functional materials.[1] Some of the challenges for the greening of synthetic chemistry in the field of glycosidations may include the use of a heterogeneous and reusable solid acid as the activator.[2] On the other hand, deoxy sugars frequently appear in the glycosidic components of the bioactive substances.[3] Among them, 2-deoxyglycoside is one of the most common and important, and found in many biologically attractive natural products such as aureolic acids, anthracyclines, angucyclines, avermectins, ethythromycins, concanamycins, and recently discovered enediynes.[3] However, the direct stereocontrolled glycosidation of a 2-deoxy sugar, especially β-stereoselective glycosidation, is difficult due to the lack of stereodirecting anchimeric assistance from the C-2 position and the low stability of the glycosidic bond of a 2-deoxyglycoside under acidic conditions due to the lack of an electron-withdrawing C-2 substituent.[1c] Therefore, the development of direct stereocontrolled glycosidations of 2-deoxy sugar in an environmentally benign manner is of particular interest. In this communication, we wish to report the novel and direct stereocontrolled glycosidations of the totally benzylated 2-deoxy-α-D-glucopyranosyl fluoride and alcohols using a heterogeneous and environmentally friendly solid acid, sulfated zirconia (SO_4/ZrO_2),[4-6] for the selective syntheses of both the 2-deoxy-α- and β-D-glucopyranosides (Figure 1).

We recently announced novel stereocontrolled glycosidations of an α-D-mannopyranosyl fluoride and alcohols using SO_4/ZrO_2.[2f] Therefore, based on these results, we first examined the glycosidations of the totally benzylated 2-deoxy-α-glucopyranosyl fluoride (**1**)[7] and cyclohexylmethanol (**2**) using SO_4/ZrO_2 with or without molecular sieves 5A (MS 5A) under several conditions. These results are summarized in Table 1. It was found that the glycosidation of **1** and **2** using 5 wt% of SO_4/ZrO_2[8] in CH_3CN at 25 °C for 1 h smoothly proceeded to afford the corresponding 2-deoxyglucopyranoside in high yield with high α-stereoselectivity (entry 2 in Table 1). Moreover, the stereoselectivity of the glycosidation was dramatically changed by the solvent, and the corresponding 2-deoxy-β-glucopyranoside was predominantly produced when Et_2O was used as the solvent.[2f] Furthermore, it was found that the β-stereoselectivity was highly dependent on the reaction temperature and the amount of MS 5A; the use of 500 wt% of MS 5A as an additive along with 100 wt% of SO_4/ZrO_2 in Et_2O at 0 °C led to the highest chemical yield and stereoselectivity for the 2-deoxy-β-glucopyranoside (entry 7 in Table 1). Thus, the glycosidation of **1** and **2** using 5 wt% of SO_4/ZrO_2 in CH_3CN at 25 °C for 1 h predomi-

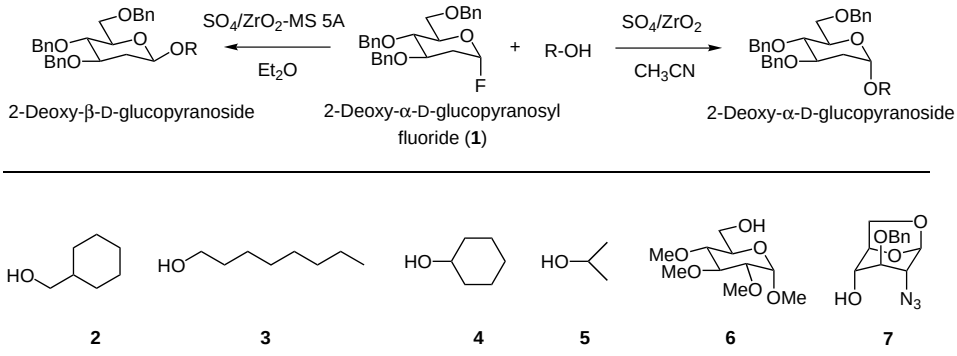

Figure 1

nantly gave the corresponding 2-deoxy-α-glucopyranoside, while the glycosidation employing 100 wt% of the same activator in the presence of 5 times the amount of MS 5A in Et_2O at 0 °C for 1 h afforded the corresponding 2-deoxy-β-glucopyranoside in high yield with high stereoselectivity. These optimized conditions for selectively obtaining both the 2-deoxy α- and β-glycosides including the reaction temperature and time, and the ratio of SO_4/ZrO_2 and MS 5A significantly differed from those for the previously reported stereocontrolled mannosylations[2f] probably due to the higher reactivity of the 2-deoxyglycosyl donor compared to that of the mannosyl donor.

Table 1. Glycosidations of **1** and **2** by SO_4/ZrO_2 under several conditions[a]

1 + **2** $\xrightarrow[1\text{ h}]{SO_4/ZrO_2}$ 2-Deoxy glucopyranosides

Entry	Solvent	Wt% of SO_4/ZO_2	Wt% of MS 5A	Temp. (°C)	Yield (%)[b]	α/β Ratio[c]
1	CH_3CN	5	0	45	74	85 : 15
2	CH_3CN	5	0	25	98	88 : 12
3	Et_2O	100	100	25	90	50 : 50
4	Et_2O	100	100	0	98	24 : 76
5	Et_2O	100	200	0	97	25 : 75
6	Et_2O	100	300	0	98	21 : 79
7	Et_2O	100	500	0	98	19 : 81
8	Et_2O	100	1000	0	96	18 : 82

[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 ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers.

To enhance the synthetic utility of this novel and environmentally benign reaction, the glycosidations using other primary and secondary alcohols **3**-**7** were next examined. Based on the results summarized in Table 2, all the glycosidations of **1** and **3**-**7** using 5 wt% of SO_4/ZrO_2 in CH_3CN at 25 °C for 1 h, as well as that of **2**, effectively proceeded to afford the corresponding 2-deoxy-α-glucopyranosides in high yields with high stereoselectivities.

On the other hand, the stereoselective syntheses of the corresponding 2-deoxy-β-glucopyranosides by the present glycosidation are outlined in Table 3. Although only entry 6 using **7** as the alcohol showed moderate yield and stereoselectivity, the other 2-deoxy-β-glucopyranosides were obtained in high yield with good to high stereoselectivities by the glycosidations of **1** and **3**-**6** as well as that of **2**.

General experimental protocols for the preparations of the 2-deoxy-α- and β-glucopyranosides:[9] 2-Deoxy-α-glucopyranosides: To a stirred solution of the glycosyl fluoride **1** (0.5 mmol) and an alcohol (1.0 mmol) in dry CH_3CN (5.0 ml) was added SO_4/ZrO_2 (5 wt% to the glycosyl donor **1**). After stirring for 1 h at 25 °C, the mixture

Table 2. α-Stereoselective glycosidations of **1** and several alcohols[a]

1 + **2**–**7** $\xrightarrow[CH_3CN,\ 25\ °C,\ 1\ h]{SO_4/ZrO_2\ (5\ wt\%)}$ 2-Deoxy glucopyranosides

Entry	Alcohol	Yield (%)[b]	α/β Ratio[c]
1	**2**	98	88 : 12
2	**3**	92	84 : 16
3	**4**	92	83 : 17
4	**5**	97	82 : 18
5	**6**	90	82 : 18
6	**7**	80	80 : 20

[a] All reactions were carried out by use of 2.0 equiv. of the alcohol to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers.

Table 3. β-Stereoselective glycosidations of **1** and several alcohols[a]

1 + **2**–**7** $\xrightarrow[Et_2O,\ 0\ °C,\ 1\ h]{SO_4/ZrO_2\ (100\ wt\%),\ MS\ 5A\ (500\ wt\%)}$ 2-Deoxy glucopyranosides

Entry	Alcohol	Yield (%)[b]	α/β Ratio[c]
1	**2**	98	19 : 81
2	**3**	96	15 : 85
3	**4**	97	20 : 80
4	**5**	99	19 : 81
5	**6**	85	27 : 73
6	**7**	56	33 : 67

[a] All reactions were carried out by use of 2.0 equiv. of the alcohol to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers.

was filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the 2-deoxyglucopyranosides which predominantly contained the α-anomer. 2-Deoxy-β-glucopyranosides: To a stirred solution of **1** (0.5 mmol) and an alcohol (1.0 mmol) in dry Et_2O (5.0 ml) were added powdered MS 5A (500 wt% to **1**) and SO_4/ZrO_2 (100 wt% to **1**). After stirring for 1 h at 0 °C, a similar workup and purification as that mentioned above gave the 2-deoxyglucopyranosides which selectively included the β-anomer.

In conclusion, we have presented the novel and stereocontrolled glycosidations of a 2-deoxy sugar and alcohols using an environmentally acceptable solid acid, SO_4/ZrO_2. Moreover, the results including the simple protocol, high yield and stereoselectivity should find wide application in the synthesis of biologically important natural products which possess a 2-deoxy sugar as a glycosidic component. Further studies along this line are currently underway.

Acknowledgement

Financial support by Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Science, Sports and Culture is gratefully acknowledged.

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(8) SO_4/ZrO_2 was purchased from Wako Pure Chemical Industries, Ltd. and dried at 200 °C/1 mmHg for 12 h before using.

(9) All 2-deoxyglucopyranosides 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_2-2 in the ^{1}H-NMR analyses.

Article Identifier:
1437-2096,E;1999,0,06,0813,0815,ftx,en;Y07099ST.pdf