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Tetrahedron Letters 45 (2004) 7043–7047
Tetrahedron Letters

A novel glycosidation of glycosyl fluoride using a designed ionic liquid and its effect on the stereoselectivity

Kaname Sasaki, 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 29 June 2004; revised 26 July 2004; accepted 28 July 2004
Available online 13 August 2004

Abstract—The glycosidations of glucopyranosyl fluoride and alcohols using an ionic liquid containing a protic acid effectively proceeded under mild conditions to afford the corresponding glycosides in good to high yields. The stereoselectivity of the glycosidation was significantly affected by the ionic liquid solvent. 1-*n*-Hexyl-3-methylimidazolium trifluoromethanesulfonate (C_6mim[OTf]), containing a trifluoromethanesulfonate anion, and 1-(3-cyanopropyl)-3-methylimidazolium trifluoromethanesulfonimidide (CNC_3mim[NTf_2]), possessing a cyano group at the side chain of the imidazolium cation, gave the β-stereoselectivity.

The development of a practical and environmentally benign glycosidation, which is one of the most important and fundamental transformation reactions of carbohydrates, is now becoming more and more important, and urgently needed both in the laboratory and in industry.[1] The greening of chemistry[2] in the field of glycosidation reactions may include the use of an environmentally benign catalyst and solvent, both of which could be reused. Recently, ionic liquids have been described as one of the most promising environmentally benign reaction media.[3] In this context, we previously reported the glycosidation of glucopyranosyl phosphite using an ionic liquid containing a protic acid,[4] and the glycosidations of glycals and glycosyl trichloroacetimidates in ionic liquids were independently reported by Yadav et al.[5] and Poletti et al.,[6] respectively. In these studies, the recyclability of the ionic liquids as greener solvents for the glycosidation reactions was well demonstrated. Another more promising feature of ionic liquid is its designability. Through our previous study, we have expected that stereoselectivity of glycosidation would be strongly influenced by ionic liquid as a solvent because many glycosidation reactions involve a cationic species, namely, an oxonium intermediate, which could interact with an anion species. Therefore, if an oxonium intermediate could interact with an anion species contained in ionic liquid, stereoselective glycosidation induced by ionic liquid would be achieved. Although Poletti et al. showed that the stereoselectivity of a glycosidation using a glycosyl trichloroacetimidate was changed by the ionic liquid,[6] a systematic study related to the effect of the ionic liquid on the stereoselectivity of the glycosidation reaction has never been reported. Herein, we report the stereoselective glycosidation of glycosyl fluoride and alcohols controlled by a designed ionic liquid and its effect on the stereoselectivity (Fig. 1).

In this study, we selected a glycosyl fluoride[7] as the glycosyl donor because glycosyl fluoride is effectively activated by both Lewis and protic acids.[8] For the reaction solvent, we chose several ionic substances, which are liquids at room temperature, 25 °C, having a low viscosity, and have the ability to dissolve the glycosyl donor and several glycosyl acceptors as shown in Figure 1. Thus, we first examined the glycosidations of the glucopyranosyl fluoride **1β** (α/β = 1/>20) and cyclohexylmethanol (**2**) (2.0 equiv to **1**) using several ionic liquids (0.1 M for **1β**) containing a protic acid (3 mol% to ionic liquid (IL)) possessing a common anion with the ionic liquid, such as 1-*n*-hexyl-3-methylimidazolium tetrafluoroborate (C_6mim[BF_4]) with HBF_4, 1-*n*-hexyl-3-methylimidazolium trifluoromethanesulfonimidide (C_6mim[NTf_2]) with $HNTf_2$, 1-*n*-hexyl-3-methylimidazolium perchlorate (C_6mim[ClO_4]) with $HClO_4$ and

Keywords: Carbohydrate; Glycosidation; Glycosyl fluoride; Ionic liquid; Designability.
* Corresponding author. Tel./fax: +81 45 566 1576; e-mail: toshima@applc.keio.ac.jp

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doi:10.1016/j.tetlet.2004.07.128

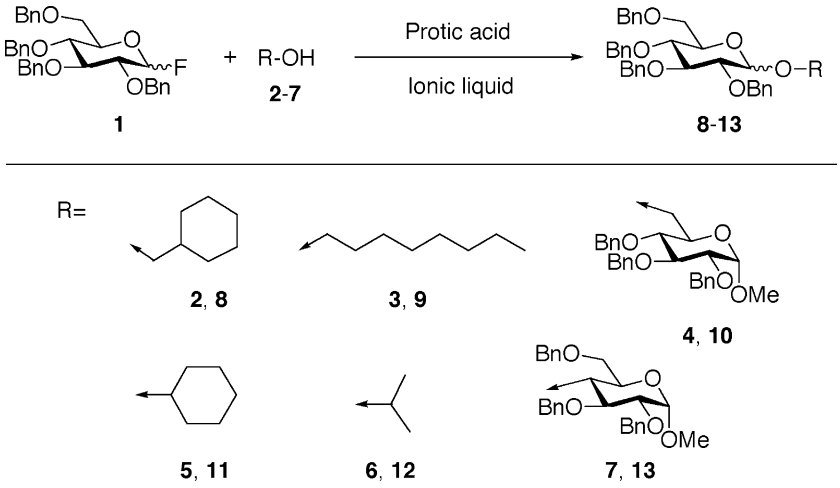
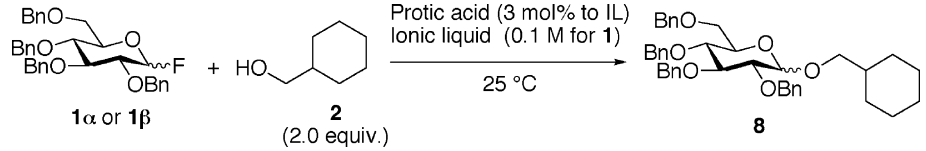


Figure 1. Glycosidations of glycosyl fluoride and alcohols using an acid–ionic liquid.

1-*n*-hexyl-3-methylimidazolium trifluoromethanesulfonate (C_6mim[OTf]) with HOTf at 25 °C. These results are summarized in Table 1. Although the glycosidation of **1** using C_6mim[BF_4] with HBF_4 needed a long reaction time and gave a moderate yield of the corresponding glycoside **8** (Table 1, entry 1), other glycosidations proceeded very smoothly to afford **8** in good to high yields (Table 1, entries 2–4). These results clearly indicated, for the first time, that the glycosyl fluoride was effectively activated by an acid–ionic liquid, namely, an ionic liquid containing a protic acid, and coupled with an alcohol. It was noteworthy that the stereoselectivity of the glycosidation was highly dependent on the catalyst–solvent system. Among the examined acid–ionic liquids, C_6mim[NTf_2] containing $HNTf_2$ provided the α-stereoselectivity with good yield (Table 1, entry 2), while C_6mim[OTf] with HOTf afforded the highest β-stereoselectivity with high yield (Table 1, entry 4). It was also confirmed that although the reactivity of **1β** was higher than that of the corresponding α-anomer **1α** (α/β = >20/1), the stereoselectivity of the glycosidation using **1β** was quite similar to that using **1α** (Table 1, entry 4 vs 5). These results clearly showed that the stereoselectivity of the glycosidation is highly independent of the configuration at the anomeric center of the glycosyl donor **1**, and this reaction proceeded via the S_N1 type pathway and involved a cationic species, that is, an oxonium intermediate. Furthermore, since no epimerization of the generated glycosidic bond occurred during the glycosidation reaction, the stereoselectivity of the glycosidation was due to kinetic control. Therefore, the α-stereoselectivity observed using C_6mim[NTf_2] containing $HNTf_2$ must result from the anomeric effect, while the β-stereoselectivity shown using C_6mim[ClO_4] with $HClO_4$ or C_6mim[OTf] with HOTf must arise from the α-oriented coordination of the perchlorate or trifluoromethanesulfonate anion with the oxonium intermediate.[9]

At this stage, we had a question as to which anion is a real factor to induce the unusual β-stereoselectivity without neighboring group participation, the anion from the ionic liquid or from the protic acid. To answer this question, we next examined the glycosidations of **1** and **2** using C_6mim[NTf_2] with HOTf and C_6mim[OTf] with $HNTf_2$, both of which contained a protic acid possessing a different anion from the ionic liquid (Table 1, entries 6 and 7). Comparing these results with those using

Table 1. Glycosidations of **1** and **2** in ionic liquids containing protic acids



Entry	Donor	Ionic liquid	Protic acid	Time/h	Yield/%[a]	α/β Ratio[b]
1	**1β**	C_6mim[BF_4]	HBF_4	24	41	47/53
2	**1β**	C_6mim[NTf_2]	$HNTf_2$	1	86	68/32
3	**1β**	C_6mim[ClO_4]	$HClO_4$	1	83	30/70
4	**1β**	C_6mim[OTf]	HOTf	1	89	24/76
5	**1α**	C_6mim[OTf]	HOTf	4	85	26/74
6	**1β**	C_6mim[NTf_2]	HOTf	1	82	52/48
7	**1β**	C_6mim[OTf]	$HNTf_2$	1	88	25/75

[a] Isolated yields after purification by column chromatography.
[b] 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).

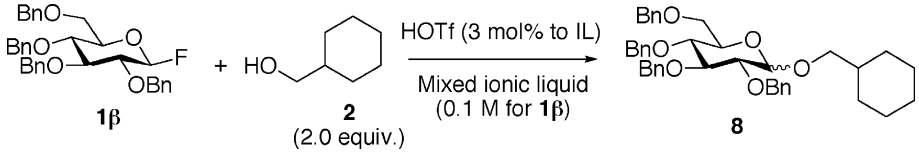
C_6mim[NTf_2] with $HNTf_2$ and C_6mim[OTf] with HOTf, it was made clear that the β-stereoselectivity was observed only when C_6mim[OTf] was used as the solvent. These results demonstrated that the stereoselectivity of the glycosidation was highly dependent on the ionic liquid, not the protic acid, and the β-stereoselectivity was induced by the α-coordination of the trifluoromethanesulfonate anion from the ionic liquid, C_6mim[OTf], with the oxonium intermediate.

With these new results in hand, we next attempted the glycosidation reaction at a lower temperature to further improve the β-stereoselectivity, because the α-triflate intermediate must be held more tightly at lower temperatures. However, C_6mim[OTf] itself is unfortunately a solid salt at 0 °C. Although 1-ethyl-3-methylimidazolium trifluoromethanesulfonate (C_2mim[OTf]), which possesses a shorter alkyl chain, has a lower melting point, it is much more hydroscopic than C_6mim[OTf]. Indeed, the chemical yield of the glycosidation of **1** and **2** using C_2mim[OTf] was lower than that employing C_6mim[OTf]. Therefore, the use of a mixture of C_6mim[OTf] and C_6mim[NTf_2] was attempted. From the results summarized in Table 2, it was found that although a longer reaction time (24 h) was required at 0 °C to obtain the high yield of the corresponding glycoside, the β-stereoselectivity increased as expected (Table 2, entries 7–12). Furthermore, the β-stereoselectivity gradually increased as the ratio of C_6mim[OTf] in the mixed ionic liquid increased. The same tendency was also observed at 25 °C (Table 2, entries 1–6). These results also showed that the trifluoromethanesulfonate anion competed with the trifluoromethanesulfonimide anion for the coordination with the oxonium cation generated from the glycosyl donor, and the β-stereoselectivity of the present glycosidation was induced by the trifluoromethanesulfonate anion from the ionic liquid, C_6mim[OTf]. Since the 8:2 (mol/mol) mixture of C_6mim[OTf] and C_6mim[NTf_2] became a solid (Table 2, entries 11 and 12), the highest β-stereoselectivity was obtained when the 7:3 (mol/mol) mixture was employed at 0 °C (Table 2, entry 10). Thus, the glycosidation of **1** and **2** in a 7:3 (mol/mol) mixture of C_6mim[OTf] and C_6mim[NTf_2] at 0 °C for 24 h gave the glycoside **8** in high yield (91%) with good β-stereoselectivity (α/β = 18/82).

Knowing these preferable results, we next carried out the glycosidations of **1** and several alcohols **3**–**7** including the sugar derivatives to examine the scope and limitations of the present glycosidation. These results are outlined in Table 3. It was found that other primary alcohols **3** and **4** were effectively coupled with **1**, as well as **2**, to afford the corresponding glycosides in high yields with good β-stereoselectivities (Table 3, entries 1–3). When the reactions were performed using the secondary alcohols **5** and **6**, satisfactory chemical yields and stereoselectivities were obtained at the higher temperature of 25 °C in C_6mim[OTf] as the sole solvent (Table 3, entries 4 and 5). Unfortunately, the low reactive secondary alcohol **7**, however, gave a poor result under similar reaction conditions (Table 3).

Our attention was next turned to the modification of the side chain of the imidazolium cation moiety of the ionic liquid, C_6mim[NTf_2]. Therefore, we newly designed and synthesized 1-(2-ethoxyethyl)-3-methylimidazolium trifluoromethanesulfonimidide ($EtOC_2$mim[NTf_2]) possessing an ether function and 1-(3-cyanopropyl)-3-methylimidazolium trifluoromethanesulfonimidide (CNC_3mim[NTf_2]) containing a cyano group.[10] The results of the glycosidations of **1** and **2** using a protic acid, $HNTf_2$, in these novel ionic liquids are described in Figure 2. When $EtOC_2$mim[NTf_2] was used as the solvent, unfortunately, no stereoselectivity was observed. However, in the case of CNC_3mim[NTf_2], β-stereoselectivity was induced. The chemical yield and stereoselectivity were very similar to those using C_6mim[OTf] under similar conditions. Compared the result when using C_6mim[NTf_2], the cyano group in CNC_3mim[NTf_2] significantly influenced the stereoselectivity of the glycosidation. These results strongly suggested that the cyano group[11] in the side chain of the imidazolium cation coordinated with the oxonium

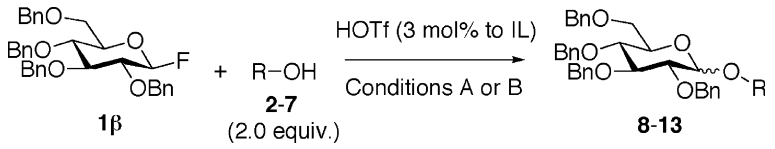
Table 2. Glycosidations of **1** and **2** in mixed ionic liquids



Entry	Ratio of mixed ionic liquid (C_6mim[NTf_2]/C_6mim[OTf])	25 °C, 1 h (Entries 1–6)		0 °C, 24 h (Entries 7–12)	
		Yield/%[b]	α/β Ratio[c]	Yield/%[b]	α/β Ratio[c]
1, 7	10/0	82	52/48	81	52/48
2, 8	7/3	90	39/61	90	24/76
3, 9	5/5	89	30/70	89	21/79
4, 10	3/7	89	27/73	91	18/82
5, 11[a]	2/8	93	25/75	—	—
6, 12[a]	0/10	89	24/76	—	—

[a] Isolated yields after purification by column chromatography.
[b] 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).
[c] The used ionic liquid is solid state at 0 °C.

Table 3. Glycosidations of **1** and several alcohols **2–7**



Entry	Alcohol	Conditions[a]	Product	Yield/%[b]	α/β Ratio[c]
1	**2**	A	**8**	91	18/82
2	**3**	A	**9**	95	20/80
3	**4**	A	**10**	99	13/87
4	**5**	B	**11**	91	29/71
5	**6**	B	**12**	77	28/72
6	**7**	B	**13**	54	42/58

[a] Conditions A: C_6mim[OTf]/C_6mim[NTf_2] = 7/3, 0 °C, 24 h. Conditions B: C_6mim[OTf], 25 °C, 1 h.
[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, 2, and 4–6, 12.5% H_2O in MeCN for entry 3; flow rate, 1.0 mL/min, 40 °C; detection, UV 250 nm).

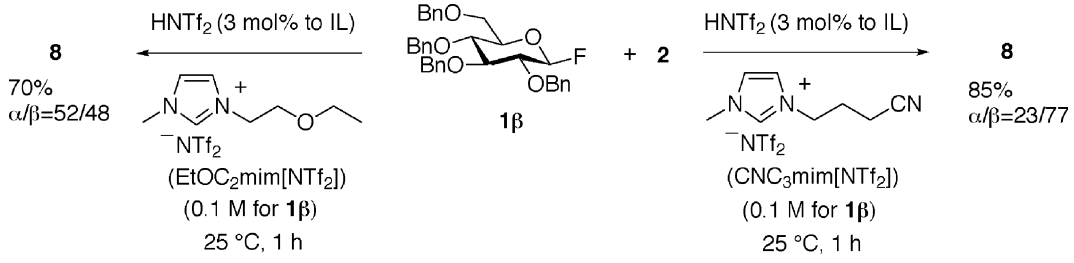


Figure 2. Glycosidations of **1β** and **2** using $EtOC_2$mim[NTf_2] and CNC_3mim[NTf_2].

intermediate more effectively than trifluoromethanesulfonimide anion. These results also indicated that the interaction between the oxonium intermediate and trifluoromethanesulfonimide anion was very weak and did not affect the stereoselectivity of the glycosidation.

In conclusion, we presented novel glycosidations of glucopyranosyl fluoride and alcohols using an ionic liquid containing a protic acid. Furthermore, although the stereoselectivity is still not very high, the effect of the ionic liquids on the stereoselectivity of the glycosidation was clearly demonstrated. These results should be instructive for further research that employs ionic liquids in stereoselective and environmentally benign glycosidation reactions. Further studies along this line are currently in progress.

Acknowledgements

This research was supported in part by Grant-in-Aid for the 21st Century COE program 'KEIO Life Conjugate Chemistry' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

1. (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212; (b) Sina, P. *Pure. Appl. Chem.* **1991**, *63*, 519; (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503; (d) Boons, B. G. *Tetrahedron* **1996**, *52*, 1095; (e) Davis, B. G. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 2137.
2. *Green Chemistry: Theory and Practice*; Anastas, P. T., Warner, J. C., Eds.; Oxford University Press: Great Britain, 1998.
3. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (c) Sheldon, R. *Chem. Commun.* **2001**, 2399; (d) *Ionic Liquid in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2002.
4. Sasaki, K.; Nagai, H.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2003**, *44*, 5605.
5. Yadav, J. S.; Reddy, B. V. S.; Reddy, J. S. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2390.
6. Poletti, L.; Rencurosi, A.; Lay, L.; Russo, G. *Synlett* **2003**, 2297.
7. For reviews on glycosyl fluoride, see: (a) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799; (b) Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15.
8. For glycosidations of glycosyl fluoride using protic acid, see: (a) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1998**, 643; (b) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1999**, 813–815; (c) Mukaiyama, T.; Jona, H.; Takeuchi, K. *Chem. Lett.* **2000**, 696; (d) Jona, H.; Takeuchi, K.; Mukaiyama, T. *Chem. Lett.* **2000**, 1278; (e) Jona, H.; Mandai, H.; Mukaiyama, T. *Chem. Lett.* **2001**, 426.
9. Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506.
10. The synthesis of newly designed ionic liquids will be reported elsewhere. CNC_3mim[NTf_2]: ^{1}H NMR (300 MHz, neat): δ 8.46 (1H, s, N–CH=N), 7.39 (1H, s, CH=C), 7.33 (1H, s, CH=C), 4.20 (2H, t, $J_{1,2}$ = 5.7 Hz, N–CH_2), 3.81 (3H, s, N–CH_3), 2.43 (2H, t, $J_{2,3}$ = 5.7 Hz, CH_2–CN), 2.17 (2H, tt, $J_{1,2} = J_{2,3}$ = 5.7 Hz, CH_2); ^{13}C

NMR (75 MHz, neat): δ 136.48, 124.22, 122.47, 120.21 (q, $J_{C,F}$ = 318.7 Hz), 119.33, 48.38, 36.05, 25.78, 13.81. $EtOC_2mim[NTf_2]$: ^1H NMR (300 MHz, neat): δ 7.68 (1H, s, N–CH=N), 6.60 (1H, s, CH=C), 6.51 (1H, s, CH=C), 3.43 (2H, t, $J_{1,2}$ = 4.2 Hz, N–CH_2), 3.02 (3H, s, N–CH_3), 2.87 (2H, t, $J_{1,2}$ = 4.2 Hz, CH_2–CH_2–O), 2.60 (2H, q, $J_{4,5}$ = 6.9 Hz, CH_2–CH_3), 0.21 (3H, q, $J_{4,5}$ = 6.9 Hz, CH_2–CH_3); ^{13}C NMR (75 MHz, neat): δ 136.44, 123.26, 122.90, 119.90 (q, $J_{C,F}$ = 318.5 Hz), 67.54, 66.18, 49.70, 35.66, 14.07.

11. Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379.