Tetrahedron Letters 51 (2010) 6294–6297

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel glycosylation of inactive glycosyl donors using an ionic liquid containing a protic acid under reduced pressure conditions

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ARTICLE INFO

Article history:
Received 23 August 2010
Revised 16 September 2010
Accepted 22 September 2010
Available online 29 September 2010

Keywords:
Glycosylation
Ionic liquids
Green chemistry
Inactive sugar
Reduced pressure

ABSTRACT

The glycosylation of inactive glycosyl donors, such as methyl glycosides and 1-hydroxy sugars with nearly stoichiometric amounts of various alcohols (1.1 equiv) in an ionic liquid containing a protic acid (acid-IL) under reduced pressure conditions proceeded effectively to give the corresponding glycosides in good to high yields. Furthermore, the acid-IL could be reused for additional glycosylations without the loss of efficiency.

Carbohydrates in living cells play important roles in many biological events including inflammation, cell adhesion, signal transduction, etc. Furthermore, many carbohydrates are found in various functional materials, such as biodegradable surfactants. Development of a practical and environmentally benign glycosylation reaction, which is one of the most important and fundamental transformations of carbohydrates, is therefore now becoming increasingly important and urgently needed both in the laboratory and in the industry.[1] Greener processes[2] for glycosylation may include the use of environmentally benign catalysts and solvents, both of which could be reused. Recently, ionic liquids[3,4] (ILs) have attracted growing interest as one of the most promising environmentally benign reaction media owing to their many unique properties including non-volatility, reusability, designability, and immiscibility with certain organic solvents and/or water. In this context, several greener O- and C-glycosylation reactions using ILs have been demonstrated by us[5] and other groups.[6] In these studies, the reusability of the ionic liquids as greener solvents for the glycosylation reactions was well demonstrated.

From an economical point of view, the glycosylation of inactive glycosyl donors, such as methyl glycosides[7] and 1-hydroxy sugars,[8] which are readily available from naturally occurring carbohydrates, has recently gained much attention as it can reduce the number of synthetic steps. Glycosylations using these inactive glycosyl donors are generally ineffective, however, because production of methanol or water during the reaction leads to competition with the glycosyl acceptors, and thus a large excess of the glycosyl acceptors is consequently required to obtain a high yield of the desired glycosylation product (glycoside). While our research was in progress, Auge and Sizun[9] reported the glycosylation of unprotected and non-activated monosaccharides using ionic liquids containing catalytic amounts of Lewis acids at atmospheric pressure. In their study, however, except for in a few cases, a large excess of the acceptor was used in these reactions. To overcome this general problem, we focused on the important non-volatile[5c,d] characteristics of ILs. We anticipated that the glycosylation reaction under reduced pressure conditions would be an effective means of selectively removing the water or methanol from the reaction mixture.[10] Herein we report the glycosylation of inactive glycosyl donors with nearly equimolar amounts of glycosyl acceptors utilizing ILs containing catalytic amounts of a protic acid under reduced pressure conditions and the significant effect of this approach on the glycosylation reaction.

Methyl glycoside **1** was selected as the initial inactive glycosyl donor, with 6-*O*-Bn-hexanediol (**2**) as the glycosyl acceptor. Three ionic liquids each containing a protic acid with an anion in common with the ionic liquid (acid-IL), such as 1-*n*-hexyl-3-methylimidazolium tetrafluoroborate (C_6mim[BF_4]) with HBF_4, 1-*n*-hexyl-3-methylimidazolium trifluoromethanesulfonate (C_6mim[OTf]) with HOTf, and 1-*n*-hexyl-3-methylimidazolium trifluoromethanesulfonimide (C_6mim[NTf_2]) with $HNTf_2$, were chosen as the reaction media.[5] We then examined the glycosylation of **1** with **2** (1.1 equiv) using the three acid-ILs (0.2 M for **1**) at 80 °C for 30 min under reduced pressure conditions (4.0 mmHg). These results are summarized in Table 1. It was found that the glycosylation of **1** with **2** (1.1 equiv)

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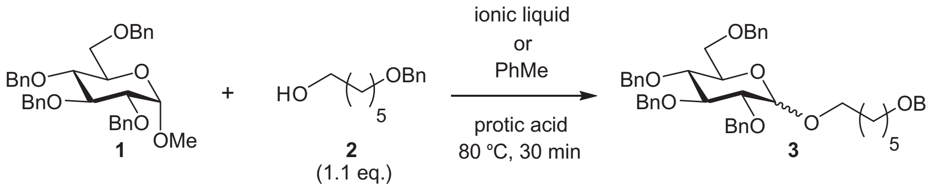
doi:10.1016/j.tetlet.2010.09.108

Table 1
Glycosylation of **1** with **2** using acid-ILs under reduced pressure conditions



Entry	Ionic liquid (0.2 M for **1**)	Protic acid (equiv to IL)	Pressure (mmHg)	Yield (%)	α/β ratio[a]
1	$C_6mim[NTf_2]$	$HNTf_2$ (0.05)	4	35	63/37
2	$C_6mim[OTf]$	HOTf (0.2)	4	41	65/35
3	$C_6mim[BF_4]$	HBF_4 (0.3)	4	59	60/40
4	$C_6mim[BF_4]$	HBF_4 (0.3)	760	30	66/34
5	PhMe	HBF_4 (0.3)	760	34	60/40

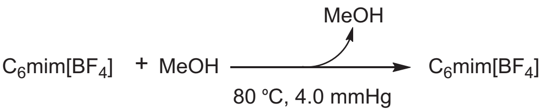
[a] α/β ratios were determined by HPLC analysis (column, CrestPak C18S®, 4.6 × 150 mm; eluent, 12% H_2O in MeOH; flow rate, 0.5 mL/min, 40 °C; detection, UV 250 nm).

in $C_6mim[BF_4]$ containing HBF_4 (0.3 equiv) under reduced pressure conditions proceeded smoothly to give the corresponding glycoside **3**[11] in 59% yield (25% of **1** was recovered), while the other ionic liquids containing a protic acid were less effective than $C_6mim[BF_4]$/HBF_4 (entries 1–3).

Next, in order to confirm the effects of both ionic liquid and reduced pressure on this glycosylation, we performed the reaction under atmospheric pressure (760 mmHg) in toluene, which is a conventional organic solvent for glycosylations, and in $C_6mim[BF_4]$. It was found that in both cases the chemical yields of the glycosylation at 760 mmHg were much lower than that of the reaction using $C_6mim[BF_4]$ at 4.0 mmHg (entries 3–5). These results clearly indicated that reduced pressure was effective for the glycosylation of methyl glycoside **1** with just slightly over an equimolar amount of glycosyl acceptors. In addition, we confirmed that 1.5 M methanol was removed from the $C_6mim[BF_4]$ after only 1 min of decompression at 80 °C, as shown in Table 2 (entries 1 and 2).

We further examined the glycosylation of 1-hydroxy sugar **4** with **2** (1.1 equiv) using the above three acid-ILs under reduced pressure conditions (Table 3, entries 1–3). In the glycosylation of **4**, although the $C_6mim[BF_4]$/HBF_4 system provided the glycoside **3** in good yield, $C_6mim[NTf_2]$/$HNTf_2$ (0.1 equiv) at 70 °C and 4.0 mmHg gave the best result, with **3** obtained in 82% yield (entry 3). In addition, it was found that the chemical yields of the glycosylations at 70 °C and 760 mmHg using toluene/$HNTf_2$ or $C_6mim[NTf_2]$/$HNTf_2$ were lower than that of the reaction using $C_6mim[NTf_2]$/$HNTf_2$ at 4.0 mmHg (entries 3–5). These results also showed that the use of the reduced pressure conditions was effective for the direct glycosylation of inactive glycosyl donors such as 1-hydroxy sugars. Furthermore, we measured the removal rate of 1.5 M water from $C_6mim[NTf_2]$ under reduced pressure conditions at 70 °C, as shown in Table 4. It was found that although a trace amount of water remained after 1 min of decompression at 70 °C and 4 mmHg, the water was completely removed from the mixture after 5 min of decompression (Table 4, entries 1 and 2).

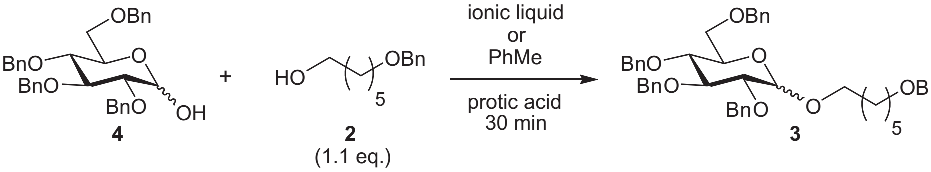
Table 2
The removal rate of methanol from an ionic liquid under reduced pressure conditions



Entry	Time (min)	Remaining MeOH[a] (%)
1	0	100
2	1	0

[a] The quantity was determined by ^1H NMR analysis.

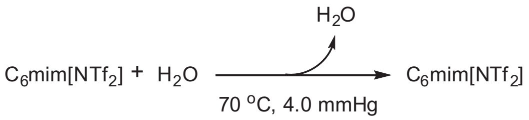
Table 3
Glycosylation of **4** with **2** using acid-ILs under reduced pressure conditions



Entry	Ionic liquid (0.2 M for **4**)	Protic acid (equiv to IL)	Pressure (mmHg)	Temp (°C)	Yield (%)/α/β[a]
1	$C_6mim[OTf]$	HOTf (0.1)	4	80	27 (67/33)
2	$C_6mim[BF_4]$	HBF_4 (0.3)	4	80	62 (68/32)
3	$C_6mim[NTf_2]$	$HNTf_2$ (0.1)	4	70	82 (65/35)
4	$C_6mim[NTf_2]$	$HNTf_2$ (0.1)	760	70	68 (53/47)
5	PhMe	$HNTf_2$ (0.1)	760	70	58 (62/38)

[a] α/β ratios were determined by HPLC analysis.

Table 4
The removal rate of water from an ionic liquid under reduced pressure conditions



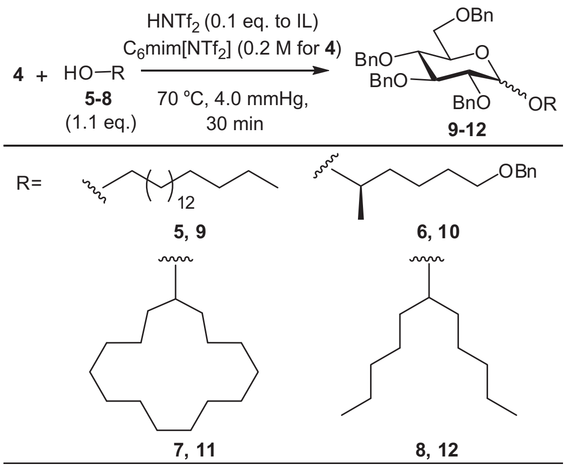
Entry	Time (min)	Remaining H_2O[a] (%)
1	0	100
2	5	0

[a] The quantity was determined by ^1H NMR analysis.

With these favorable results in hand, we next carried out the glycosylation of **4** with the alcohols **5**–**8** (1.1 equiv), including the poorly reactive secondary alcohols **6**, **7**, and **8**, to examine the scope and limitations of the reaction. These results are summarized in Table 5. It was found that the glycosylations of **4** with just slightly more than an equimolar amount (1.1 equiv) of these glycosyl acceptors proceeded smoothly in $C_6mim[NTf_2]/HNTf_2$ (0.1 equiv) at 70 °C and 4.0 mmHg for 30 min, as well as with **2**, to afford the corresponding glycosides **9**–**12** in good yields (entries 1–5). These results clearly indicated that the use of a non-volatile acid-IL under reduced pressure conditions provided significant advantages for the direct glycosylation of inactive glycosyl donors without the need for an excess quantity of glycosyl acceptor.

Finally, the reusability of the acid-IL $C_6mim[NTf_2]/HNTf_2$ for the glycosylation of **4** with **2** under reduced pressure conditions was investigated. First, we attempted to reuse the recovered $C_6mim[NTf_2]/HNTf_2$ after extraction of the products from the reaction mixture with a 5:1 mixture of hexane and EtOAc followed by drying. It was found, however, that the chemical yield gradually decreased as the recycle number increased (∼15% decrease for each reaction Table 6, entries 1–3) due to loss of the protic acid $HNTf_2$ during the glycosylation reaction at 70 °C and 4.0 mmHg for 30 min. Therefore, we next examined the reuse of the acid-IL after addition of $HNTf_2$ (0.05 equiv) to the recovered solvent. It was found that the efficiency of $C_6mim[NTf_2]/HNTf_2$ thus recovered was identical with that of the freshly prepared system and could be reused for the glycosylation under reduced pressure conditions without any loss in efficiency (entry 4).

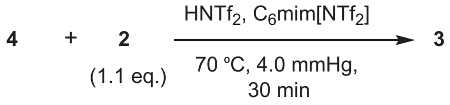
Table 5
Glycosylation of **4** with glycosyl acceptors **5**–**8** using $C_6mim[NTf_2]/HNTf_2$ under reduced pressure conditions



Entry	Acceptor	Product	Yield (%)	α/β ratio[a]
1	**2**	**3**	82	65/35
2	**5**	**9**	73	60/40
3	**6**	**10**	70	65/35
4	**7**	**11**	65	63/37
5	**8**	**12**	57	65/35

[a] α/β ratios were determined based on isolated yields of both isomers.

Table 6
Recycling of $C_6mim[NTf_2]$ for the glycosylation of **4** with **2** under reduced pressure conditions



Entry		Additive/$HNTf_2$ (equiv)	Yield (%) of **3**	α/β ratio[a]
1	1st run	—	82	65/35
2	1st reuse	0	69	52/48
3	2nd reuse	0	52	46/54
4	3rd reuse	0.05	84	68/32

[a] α/β ratios were determined by HPLC analysis.

In conclusion, we have developed a novel O-glycosylation of inactive glycosyl donors under reduced pressure conditions using a reusable ionic liquid containing a protic acid without the need for excess amounts of glycosyl acceptors. Furthermore, the effect of the reduced pressure conditions on the efficiency of the glycosylation was clearly demonstrated. Although this method presented herein is still not applicable for glycosylations using volatile glycosyl acceptors, and the stereoselectivity is not satisfactory, the results achieved with this simple and environmentally benign protocol should open a novel green process and find wide application in the synthesis of biomolecules and functional materials containing carbohydrate structures. Further studies along this line are currently in progress.

Acknowledgments

This research was supported by the High-Tech Research Center Project for Private Universities: Matching Fund Subsidy, 2006–2011, from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT).

Supplementary data

Supplementary data (experimental procedures and characterization of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.108.

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