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A novel greener glycosidation using an acid-ionic liquid containing a protic acid

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Abstract—The glycosidations of glucopyranosyl diethyl phosphite and alcohols using an ionic liquid, 1-*n*-hexyl-3-methylimidazolium trifluoromethanesulfonimidide (C_6 mim[NTf₂]) containing a protic acid, trifluoromethanesulfonimide (HNTf₂), as a novel solvent-catalyst system, effectively proceeded under mild conditions to give the corresponding glycosides in good to high yields. Furthermore, this acid–ionic liquid combination could be reused many times for the glycosidations without any loss in efficiency. © 2003 Elsevier Ltd. All rights reserved.

Carbohydrates are a naturally abundant and recyclable feedstock. Accordingly, carbohydrates are expected to be one of the most promising natural resources instead of fossil fuels in the coming generation. On the other hand, many carbohydrates, namely glycosubstances, are found in biologically important molecules such as glycoproteins, glycolipids and antibiotics. Furthermore, glycosubstances also appear as new functional materials such as biodegradable surfactants. Therefore, carbohydrates continue to be the central focus of research in chemistry, biology and material science.¹ In this context, 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.² Furthermore, the establishment of 'Green Carbohydrate Chemistry' would be of significant importance as a major branch of Green Chemistry.³ The greening of chemistry in the field of glycosidation may include the use of environmentally benign catalysts and solvents, both of which could be reused.³ Recently, ionic liquids have been described as one of the most promising environmentally benign reaction media.⁴ They have several benefits compared to conventional organic solvents. For example, they are non-volatile, immiscible with some organic solvents, reusable, designable, etc. However, glycosidation using an ionic

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liquid has never been reported so far. Herein, we report, to the best of our knowledge, the first glycosidation using an ionic liquid as an environmentally benign reaction solvent (Fig. 1).

In this study, we selected a glycosyl phosphite⁵⁻⁹ as the glycosyl donor because glycosyl phosphite is effectively activated by both weak Lewis and protic acids. 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. Furthermore, since both miscibility with water and the hygroscopic nature of the ionic liquids decreases markedly with increasing alkyl chain length of the cation moiety,¹⁰ 1-*n*-hexyl substituted imidazolium cation was



Figure 1.

Keywords: glycosidation; ionic liquid; protic acid; diethyl phosphite; green chemistry.

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

used. In addition, a protic acid possessing a common anion with the ionic liquid was employed as the reaction promoter.¹¹ Thus, we first examined the glycosidations of the glucopyranosyl diethyl phosphite (1) $(\alpha/\beta = 10/1)$ and cyclohexylmethanol (2) (2.0 equiv. to 1) using several ionic liquids (0.1 M for 1) containing protic acids (1 mol% to ionic liquid), such as 1-*n*-hexyl-3-methylimidazolium tetrafluoroborate $(C_6 mim[BF_4])$ with HBF₄, 1-*n*-hexyl-3-methylimidazolium trifluoromethanesulfonate (C6mim[OTf]) with HOTf and 1-n-hexyl-3-methylimidazolium trifluoromethanesulfonimidide (C_6 mim[NTf₂]) with HNTf₂, at 25°C for 1 h. Based on the results summarized in Table 1, these glycosidations proceeded smoothly to give the corresponding glycoside 8 in good to high yields (entries 1-3in Table 1). These results clearly indicated, for the first time, that an acid-ionic liquid, namely, an ionic liquid containing a catalytic amount of protic acid was effective as a solvent-catalyst system for chemical glycosidation. Among the examined acid-ionic liquids, $C_6 mim[NTf_2]$ containing HNTf_2 showed a better result compared to the others with respect to both the chemical yield and stereoselectivity (entry 3 in Table 1). Our attention next turned to the effect of the amount of the protic acid, HNTf₂, in the ionic liquid, C₆mim[NTf₂]. It was confirmed that when the reaction was performed using 1 mol% HNTf₂ to C₆mim[NTf₂], the highest chemical yield was obtained (entries 3-6 in Table 1). Thus, the glycosidation of 1 and 2 using $HNTf_2$ (1) mol% to $C_6 \min[PF_6]$ in $C_6 \min[PF_6]$ (0.1 M for 1) effectively proceeded under mild conditions (25°C, 1 h) to give **8** in 91% yield with good β -stereoselectivity.¹²

At this stage, we compared the chemical yield and the stereoselectivity of the glycosidation using the acidionic liquid with those using conventional organic solvents. Thus, the glycosidations using HNTf₂ as a protic acid in Et₂O, PhMe, MeCN and CH₂Cl₂ were examined. From the results summarized in Table 2, the chemical yield of the glycosidation using $C_6 mim[NTf_2]$ was higher than those using the examined organic solvents. Furthermore, the stereoselectivity of the glycosidation using $C_6 \min[NTf_2]$ was higher than those using Et₂O and PhMe and compared with those in MeCN and CH₂Cl₂. However, MeCN and CH₂Cl₂ had to be dried using suitable dehydrating agents and be distilled under anhydrous conditions. In contrast, it was confirmed that the drying of the non-volatile ionic liquid, $C_6 mim[NTf_2]$, under reduced pressure (25°C/1 mmHg) was sufficient for the present glycosidation. These results clearly demonstrated that the use of the ionic liquid, $C_6 \min[NTf_2]$, is more effective than those of the conventional organic solvents in several aspects.

Furthermore, we examined the effect of the purity of the ionic liquid on this glycosidation. Generally, one of the major impurities of ionic liquids is considered to be the halide impurity.^{4d} Therefore, the effect of the addition of C_6 mimCl, which was a material used to prepare C_6 mim[NTf₂], to the acid–ionic liquid was tested as

Table 2. Glycosidations of 1 and 2 using HNTf₂ in ionic liquid and organic solvents

	0Bn 1	2 ionic liquid 25 °C, 1 h	B	
Entry	Solvent	Yield (%)	α/β ratio	
1	Et ₂ O	84	32/68	
2	PhMe	84	25/75	
3	MeCN	85	19/81	
4	CH ₂ Cl ₂	89	16/84	
5	C ₆ mim[NTf ₂]	91	18/82	

HNT fp

BnO

Table 3. Glycosidations of 1 and 2 using $C_6mim[NTf_2]$ containing HNTf₂ and C_6mimCl



Table 4. Recycling of $C_6 mim[NTf_2]$ with HNTf₂ in the glycosidations of 1 and 2



Entry	Reaction cycle	Yield (%)	α/β ratio
1	0	91	18/82
2	1	87	18/82
3	2	89	19/81
4	3	89	18/82
5	4	90	18/82
6	5	89	17/83

Table 5. Glycosidations of 1 and several alcohols 2-7 using C₆mim[NTf₂] with HNTf₂

BnO BnO BnO	OBn OP(OEt) ₂ +	HNTf ₂ C ₆ mim[NTf ₂] R−OH → 2-7 25 °C, 1 h	BnO BnO BnO OBn R 8-13
Entry	Alcohol	Yield (%)	α/β ratio
1	2	91	18/82
2	3	99	17/83
3	4	99	25/75
4	5	88	20/80
5	6	84	23/77
6	7	63	57/43

shown in Table 3. It was found that the addition of only 5 mol% C_6 mimCl significantly decreased the chemical yield due to the basicity^{4,13} of C_6 mimCl (entry 4 in Table 3). These results strongly suggested that free of Cl⁻ was very important for the glycosidation.

Next, we tested the acid-ionic liquid recycling. After the extraction of the products with a mixture of 5:1 hexane-ethyl acetate, drying at 25° C/1 mmHg for 12 h, the recovered C₆mim[NTf₂] containing HNTf₂ was reused many times (at least five times) without any loss in efficiency to provide the same yields and stereoselectivities as described in Table 4. It was noted that the homogeneous protic acid, $HNTf_2$, was recovered in the ionic liquid, $C_6mim[NTf_2]$, and no further addition of $HNTf_2$ was needed to repeatedly perform the glycosidation. Furthermore, the organic solvent used for the extraction could also be reused.

With these new and 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 summarized in Table 5. It was found that although only when the reaction was performed using the low reactive sugar derivative alcohol 7, the chemical yield was moderate (entry 6 in Table 5), the other alcohols 3-6 were effectively coupled with 1 in $C_6 mim[NTf_2]$ with HNTf₂ at 25°C for 1 h, as well as 2, to afford the corresponding glycosides in good to high yields with good β -stereoselectivities (entries 1–5 in Table 5). It was confirmed that $C_6 \min[NTf_2]$ had a suitable ability to dissolve the glycosyl donor and acceptors. Unfortunately, the β -stereoselectivity is slightly lower than those of the conventional glycosidation methods using 1.5^{-9} Since the configuration at the anomeric position of the isolated glycoside was not epimerized under the present glycosidation conditions, the predominant β -stereoselectivity must arise from kinetic control.

In conclusion, we have developed a novel glycosidation using an ionic liquid containing a protic acid. Moreover, the results including the simple and environmentally benign protocol¹⁴ and the good yield and stereoselectivity should find wide application in the synthesis of biomolecules and functional materials containing carbohydrate(s). Further studies along this line are currently in progress.

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- 14. Typical procedure: To a mixture of the glucopyranosyl diethyl phosphite 1 (0.1 mmol) and alcohol (0.2 mmol) was added $C_6mim[NTf_2]$ (1.0 M for 1) containing HNTf₂ (1 mol% to $C_6mim[NTf_2]$). After stirring for 1 h at 25°C, the mixture was extracted with a mixture of 5:1 hexaneethyl acetate and the combined extracts were concentrated in vacuo. Purification of the residue by flash column chromatography gave the glucopyranosides. All glucopyranosides were fully characterized by spectroscopic means and found identical with the authentic samples, and the α/β ratios were determined by HPLC analysis.