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[bmim][OTf]: a versatile room temperature glycosylation promoter

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ABSTRACT

[bmim][OTf] is a versatile, ionic liquid promoter for the room temperature glycosylation of both thiophenyl and trichloroacetimidate glycoside donors; the conditions are mild, with no requirement for molecular sieves, and are compatible with a wide range of donors and protecting groups.

Glycosidic bond formation is a crucial step in oligosaccharide synthesis but despite many efforts, there is still a need to identify a general, mild and convenient glycosylation promoter.

Anomeric trichloroacetimidates and thioglycosides are among the most effective and commonly used glycosyl donors in the chemical synthesis of oligosaccharides. Trichloroacetimidates are activated by strong Lewis acids such as TMSOTf,[1] boron trifluoride etherate[2] and lithium triflate[3] among others. Thioglycosides, which are convenient and attractive building blocks due to their stability, accessibility and compatibility,[4] are activated by *N*-iodosuccinimide/TMSOTf or trifluoromethanesulfonic acid (TfOH) combinations,[5] dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate,[6] methylsulfenyl triflate,[7] benzeneselenyl triflate,[8] iodonium dicollidine perchlorate[9] and benzenesulfinyl piperidine/triflic anhydride.[10] Although these promoters are convenient for the assembly of oligosaccharides, there are several drawbacks—typically low temperature and molecular sieves are required—and other problems, mainly due to side reactions with by-products resulting from the promoters.[11]

These issues, in conjunction with our interest in developing new approaches that would allow automated oligosaccharide synthesis, encouraged our search for a new promoter that satisfied several criteria: mild enough to be used at room temperature and tolerant of a wide range of saccharide donors and acceptors, compatible with various protecting groups and recyclable. Herein, we report the identification and mode of activation of a versatile ionic liquid, 1-butyl-3-methylimidazolium triflate ([bmim][OTf], **1a**) (Fig. 1), as a co-solvent and glycosylation promoter for activated thioglycoside and trichloroacetimidate donors. This promoter is used at room temperature without requirement for molecular sieves and is recyclable.

Ionic liquids (ILs) are a class of solvents which have attracted growing interest due to their unique physical and chemical properties.[12,13] ILs consist of poorly coordinating ion pairs and are typically considered polar. Furthermore, their physical and chemical properties can be tuned by altering the cation or the anion. There are currently many applications of ILs as solvents in chemistry, with some able to act as recyclable catalysts as well as reaction media in organic reactions.[12–14]

More recently, examples of base-catalysed reactions involving ILs have been described in oligosaccharide synthesis.[15–18] Interestingly, the use of **1a** as a catalyst for Mannich-type reactions had previously been reported.[19] Furthermore, NMR studies by Rencurosi et al.[20] on protected glucoside α- and β-trichloroacetimidates have suggested that triflate-based ionic liquids participate in glycosylation reactions in combination with a Lewis acid catalyst, by formation of a transient α-glycosyl triflate that yields predominantly β-glycoside products.[17] This is in agreement with Toshima's observations in terms of selectivity.[18]

Herein, we report the ability of [bmim][OTf] **1a** to act as a room temperature glycosylation promoter and co-solvent towards a range of donors and acceptors (Fig. 1).

In our initial studies, peracetylated galactose trichloroacetimidate **2**[21] was used as a model donor in combination with a series of acceptors **9a–e** to yield a series of corresponding glycoside products **10a–e** (Fig. 2). In general, reactions proceeded smoothly at room temperature with the expected α/β-selectivities and in good yields; in some cases, yields exceeded those of reactions performed with TMSOTf at −40 °C (Table 1, entries 1–8). Having demonstrated that **1a** catalyses the glycosylation of **2**, trichloroacetimidate donors **3a**,[2] **4a**[22] and **4b**[23] were prepared and reacted with commercially available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **9c** (Table 1, entries 9–14). Trichloroacetimidate **4b** gave disaccharide **13b** in 78% yield, which represents a slight increase when compared to the same reaction in the presence of a Lewis acid (Table 1, entries 13 and 14). Peracetylated glycoside donors are considered to be electronically deactivated species (disarmed) and in general, require a more potent activator. In the case of the less activated peracetylated donors **3a** and **4a**, the addition of a catalytic amount of triflic acid for efficient activation was required (see entries 10 and 12, Table 1, respectively).

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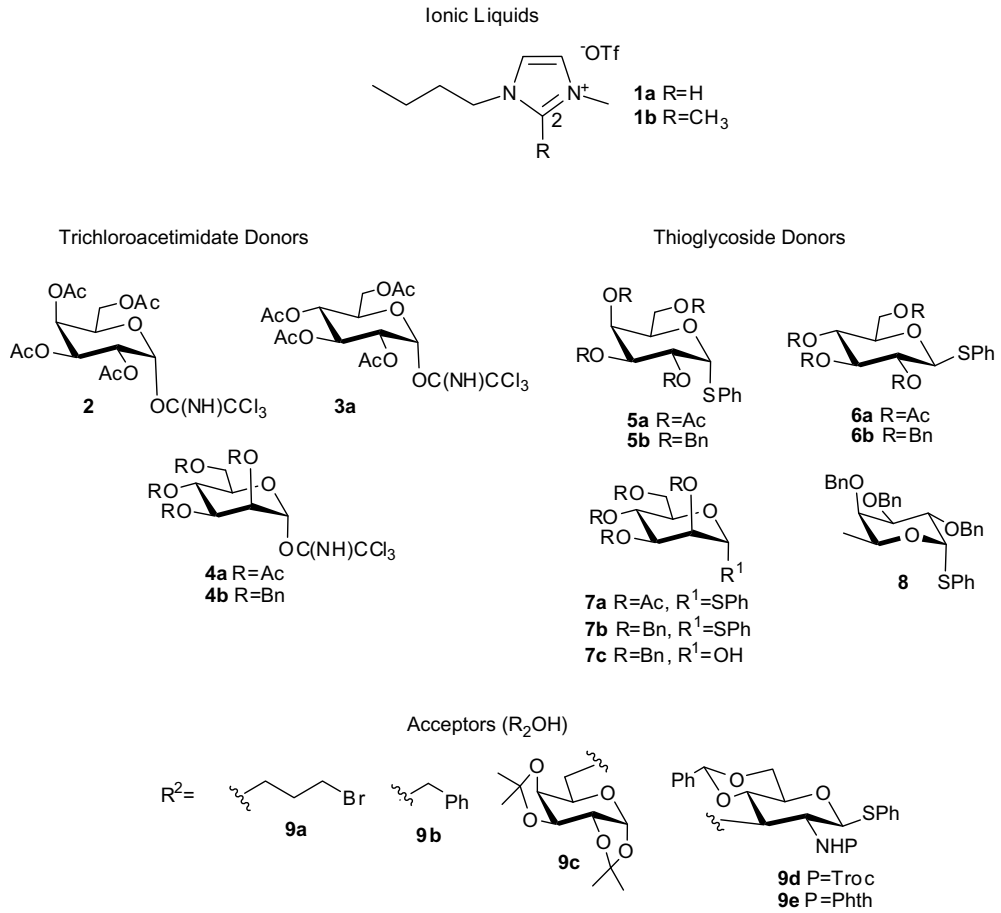


Figure 1. Ionic liquids, trichloroacetimidate and thioglycoside donors used in this study.

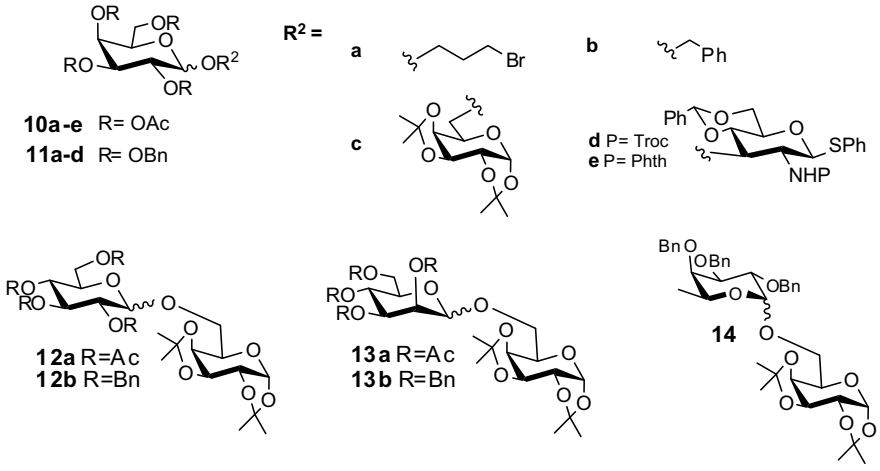
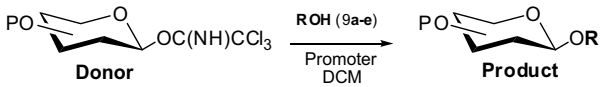


Figure 2. Structures of glycoside products **10**–**14**.

Interestingly, donors **3a** and **4a** are stable in CH_2Cl_2 solution with IL **1a** as co-solvent and did not hydrolyse to the corresponding hemiacetals, when exposed to air and/or heat. To assess the stability of **4a** in $CDCl_3$ and [bmim][OTf] **1a** (10% v/v), ^1H NMR spectra were recorded over seven days followed by heating the sample to 50 °C; no degradation of **4a** was observed. This stability may be due to the reported ability of ILs to act as 'liquid molecular sieves'.[24] That imidate **2**, which is also a deactivated glycoside donor, could be activated with [bmim][OTf] **1a** without a requirement for TMSOTf, can be explained by the higher reactivity profile of **2** as a glycosyl donor in comparison with the corresponding glucose and mannose thioglycosides.[25]

Encouraged by these results, we decided to extend the methodology to thiophenyl glycosides, another commonly used class of glycosyl donor. Activated phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside **5b**[26] was used as a model donor with alcohols 9a–c as acceptors (Table 2). Glycosylation reactions were extremely clean, and were complete within a few hours at RT and

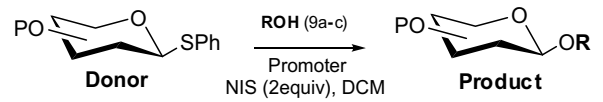
Table 1
Summary of the glycosylation reactions with trichloroacetimidate donors[a]



Entry	Donor	Acceptor	Promoter	Product	Yield (%)	α/β ratio[b]
1	**2**	**9a**	TMSOTf	**10a**	70	Only β
2	**2**	**9a**	**1a**	**10a**	78	Only β
3	**2**	**9b**	TMSOTf	**10b**	77	Only β
4	**2**	**9b**	**1a**	**10b**	75	Only β
5	**2**	**9c**	**1a**	**10c**	69	Only β
6	**2**	**9d**	**1a**	**10d**	78	Only β
7	**2**	**9e**	TMSOTf	**10e**	70	Only β
8	**2**	**9e**	**1a**	**10e**	80	Only β
9	**3a**	**9c**	TMSOTf	**12a**	75	Only β
10	**3a**	**9c**	**1a**, TMSOTf	**12a**	85	Only β
11	**4a**	**9c**	TMSOTf	**13a**	70	Only α
12	**4a**	**9c**	**1a**, TMSOTf	**13a**	77	Only α
13	**4b**	**9c**	TMSOTf	**13b**	65	3/2
14	**4b**	**9c**	**1a**	**13b**	78	5/1

[a] All reactions were performed in DCM in the presence of TMSOTf (0.2 equiv) at −40 °C or with **1a** (10% v/v) at room temperature (rt) or with **1a** (10% v/v) and TMSOTf at rt as promoter.
[b] Determined by NMR spectroscopy (^{1}H and HMQC data).

Table 2
Summary of the glycosylation reactions[a] with thioglycoside donors



Entry	Donor	Acceptor	Promoter	Product	Yield (%)	α/β ratio[b]
1	**5a**	**9c**	TMSOTf	**10c**	83	Only β
2	**5a**	**9c**	**1a**, TMSOTf	**10c**	95	Only β
3	**5b**	**9a**	TMSOTf	**11a**	96	>99 β
4	**5b**	**9a**	**1a**	**11a**	92	>99 β
5	**5b**	**9b**	TMSOTf	**11b**	83	2/8
6	**5b**	**9b**	**1a**	**11b**	86	2.5/7.5
7	**5b**	**9c**	TMSOTf	**11c**	82	0.2/1
8	**5b**	**9c**	**1a**	**11c**	83	0.7/1
9	**6a**	**9c**	TMSOTf	**12a**	70	Only β
10	**6a**	**9c**	**1a**, TMSOTf	**12a**	80	Only β
11	**6b**	**9c**	TMSOTf	**12b**	75	0.02/1
12	**6b**	**9c**	**1a**	**12b**	85	0.7/1
13	**7a**	**9c**	TMSOTf	**13a**	70	Only α
14	**7a**	**9c**	**1a**, TMSOTf	**13a**	80	Only α
15	**7b**	**9c**	TMSOTf	**13b**	75	1/1.3
16	**7b**	**9c**	**1a**	**13b**	87	1.5/1
17	**8**	**9c**	TMSOTf	**14**	75	1/1
18	**8**	**9c**	**1a**	**14**	70	0.9/1
19	**6a**, **6b**	**9c**	**1a**	**12b**	71	0.7/1

[a] All reactions were performed in DCM, in the presence of NIS (2 equiv) and TMSOTf (0.2 equiv) at −40 °C or with **1a** (10% v/v) at room temperature (rt) or with **1a** (10% v/v) and TMSOTf at rt as promoter.
[b] Determined by NMR spectroscopy (^{1}H and HMQC data).

proceeded in excellent yields (Table 2, entries 3–8). In order to explore the scope of this process, a series of thioglycoside donors **5a**,[27] **6a**,[28] **6b**,[27] **7a**,[29] **7b**[29] and **8**[30] were utilised and glycosylations with acceptor **9c** were performed under the same conditions; see Table 2 for details.

In general, conversion yields were excellent for activated donors, and comparable or in some cases exceeding those achieved in reactions where TMSOTf was used at −40 °C as the activator. Interestingly, an increase in α-selectivity was observed using [bmim][OTf] **1a** (Table 2, see entries 7 and 8, 11 and 12, 15 and 16), when glycosylation reactions were performed with activated glycosides where non-participating groups at C-2 were present.

Glycosylation yields for deactivated sugar glycosides are typically lower in comparison to the corresponding electronically activated (armed) glycosides.[31] Although [bmim][OTf] did not efficiently activate donors **5a**, **6a** and **7a** and the reactions proceeded very slowly, the addition of 0.2 mol % TfOH provided the desired glycosides in excellent yields (Table 2, entries 2, 10 and 14) with the added advantages that these reactions take place at room temperature in a matter of hours, do not produce significant amounts of side products and these glycosylations do not require the use of molecular sieves.

In order to understand the role of IL **1a** in the mechanism of thioglycoside activation, a model reaction with donor **7a** in the presence of *N*-iodosuccinimide (NIS), [bmim][OTf] **1a** and CD_2Cl_2 was followed by ^{1}H NMR and ^{19}F NMR spectroscopy at room temperature and spectra were recorded at regular time intervals until completion of the reaction (Fig. 3). It is important to note that the CD_2Cl_2 used contains traces of water, thus when thiophenyl mannoside derivative **7b** is activated, the hydrolysed hemiacetal product **7c** will be produced.

This experiment showed that **7b** (H-1, doublet at 5.59 ppm, J = 1.74 Hz) was converted within 3 h to the corresponding hemiacetal **7c** (H-1′, doublet at 5.13 ppm, J = 1.92 Hz, observed $[M+Na]^+$ = 563.3)[32] (Fig. 3). Additionally, the appearance of characteristic resonances corresponding to *N*-iodosuccinimide (singlet at 2.87 ppm) which yields electrophilic I^+ and succinimide (singlet at 2.67 ppm), typically catalysed by acid,[33] were also detected over the course of the reaction (Fig. 2, Supplementary data). The signals corresponding to [bmim][OTf] **1a** remained constant throughout the reaction in both the ^{1}H NMR spectra (singlet at 8.99 ppm (1H), multiplet at 1.85 ppm (2H), multiplet at 1.35 ppm (2H) and a triplet at 0.96 ppm (3H)) and in the ^{19}F NMR spectra (singlet at 77.21 ppm, see Fig. 3, Supplementary data). In order to establish if H-2 of the imidazolium moiety was involved in the reaction, 1-butyl-2,3-dimethylimidazolium triflate **1b** was prepared and its ability to promote glycosylation was tested. If the IL is acting as an acid and the formation of the iodonium ion, substituting H-2 for CH_3 should suppress the reaction. Using donor **5b** in combination with acceptor **9c** and with **1b** as the IL component, the desired disaccharide **11c** was obtained in good yield, suggesting that the imidazolium ring does not participate directly in the activation of NIS. Furthermore, no TfOH was detected in the ^{1}H or ^{19}F NMR spectra associated with **1a**, however, when K_2CO_3 (20 mol %) was added to this control reaction, the formation of **11c** was completely suppressed.

These results imply that the counterion of [bmim][OTf] **1a** is critical for catalysing the formation of the iodonium ion and we suggest that slowly released TfOH is the catalyst. To identify the source of H^+, Karl Fisher titration experiments[34] were used to measure the water content of **1a**, which was found to be 0.58 ± 0.03% in weight, which is consistent with the water content of other ionic liquids of similar chemical nature.[35]

Another aspect we wanted to explore was the recyclability of the IL. Reactions were carried out using donors **4a** and **5b** with acceptor **9c**. After extraction of the products and reagents with a mixture of ether and hexanes, the IL could be reused up to three times without loss of activity (Table 1, Supplementary data).

In summary, we have shown that [bmim][OTf] **1a** in anhydrous dichloromethane serves as a room temperature selective glycosylation promoter for activated (armed) thiophenyl and trichloroacetimidate glycosyl donors, while the less active (disarmed) donors require the addition of catalytic triflic acid. The glycosylation conditions are mild and compatible with a range of hydroxyl protecting groups, such as acetates, benzyl ethers, acetals, and are also amenable to NH_2 masking strategies, that is, phthalimide (Phth) and trichloroethylcarbamate (Troc). Mechanistically, we suggest that **1a** works by slow release of triflic acid but **1a** also acts as a

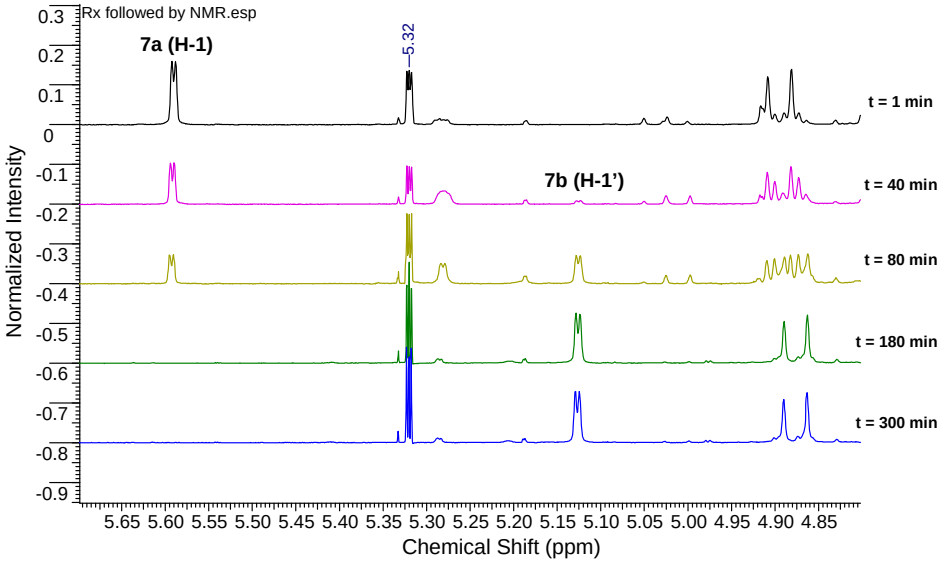


Figure 3. Partial ^{1}H NMR spectra of the IL catalysed glycosylation reaction collected over 300 min.

stabilizing agent with respect to hydrolysis, and reactions proceed cleanly and in good yields at room temperature and without the need of molecular sieves. When non-participating groups at C-2 were present, an increase in α selectivity was observed when compared with reactions carried out using TMSOTf at lower temperatures.

Moreover, the ability to recycle the IL is also very attractive in terms of green chemistry, since the amount of organic waste will be reduced. In addition, the use of an IL to promote glycosylation reactions at room temperature is amenable to automated synthesis protocols where low temperatures are not required.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.042.

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