[bmim][OTf] as co-solvent/promoter in room temperature reactivity-based one-pot glycosylation reactions†

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[bmim][OTf] can promote regio- and chemo-selective glycosylation reactions at room temperature. Furthermore, the applicability to ambient three-component reactivity-based one-pot glycosylation reactions is demonstrated for the synthesis of several trisaccharides.

Since the emergence of glycobiology, there has been considerable interest in understanding glycan diversity and function. Carbohydrates are sophisticated carriers of biomolecular information involved in a myriad of biological processes.[1] Despite the many synthetic efforts,[2] there is still a need for the development of reliable methods that are applicable to both laboratory and industrial scale preparation.

Herein, we describe the investigation and use of [bmim][OTf] **1** as a mild room temperature promoter in combination with *N*-iodosuccinimide (NIS) in chemo- and regio-selective glycosylation reactions and the application to three-component one-pot oligosaccharide synthesis.

Typically, oligosaccharide synthesis entails sequential addition of monosaccharides to a growing oligosaccharide chain, where each addition involves laborious protecting group manipulations and purification procedures. A very attractive alternative to traditional approaches is the commonly known "one-pot glycosylation", which facilitates that multiple glycosylation steps can be performed in a single reaction vessel.[3] Many of these one-pot convergent approaches are based on the selective activation of one glycosyl donor leaving group (LG) over another. The concept was initially exemplified by Fraser-Reid's armed–disarmed methodology[4] and although this approach has been successfully utilised by others,[5] most strategies require exquisite control of reaction temperatures to avoid side reactions. Orthogonal, chemo- and stereo-selective glycosylation approaches are an essential feature of one-pot strategies, since the most reactive saccharide derivative first acts as the glycosyl donor and the resulting product is immediately ready to act as a glycosyl donor in the next coupling step.

Room temperature ionic liquids (RTILs) have recently emerged as a new class of solvent for a broad range of synthetic applications.[6] The high polarity of RTILs can provide strong accelerating effects to reactions involving cationic intermediates and in particular they have been shown to exhibit excellent solubilising properties and have been used to facilitate a wide range of chemical transformations, including acetylation, *ortho*-esterification, benzylidenation and glycosylation reactions of carbohydrates.[7–9] As part of our programme to develop new methods and strategies for oligosaccharide synthesis, we became interested in the application of ionic liquids for glycosylation reactions. We have recently reported the use of **1** as a mild and versatile ionic liquid (IL) recyclable solvent/promoter of room temperature glycosylation reactions using trichloroacetimidate and thiophenyl glycoside donors.[8] The conditions are mild, and compatible with a range of hydroxyl and amine protecting groups and we further demonstrated the importance of the IL counter ion component to promote glycosylation reactions.[9] We also showed that the reaction of 'armed' glycoside donor **2a** with model acceptor **3** in the presence of NIS and **1** as promoter and co-solvent gave disaccharide product **4a** in good yields (70%, 0.7/1 (α/β)), while 'disarmed' donor **2b** could not be activated by these mild conditions and required the presence of catalytic Lewis acid.[8]

The application of room temperature regio- and chemoselective glycosylation strategies involving ILs could not only simplify carbohydrate synthesis but also lead to its automation. To that end, we focused on the development of a reactivity-based one-pot strategy for oligosaccharide synthesis at ambient temperature. Initial experiments were aimed at further examining the versatility and selectivity of IL promoter **1** towards the choice of protecting groups in the glycoside donor. To explore the reactivity boundaries of differently protected thioglycosides with **1** as promoter, a series of glucose based thioglycoside donors **2c**,[10] **2d**,[11] **2e**,[12] **2f**, **2g**[13] and **2h** possessing different reactivity profiles[5] were prepared in good yields and their couplings with commercial 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3** as model acceptor in presence of **1** and NIS were monitored. (Table 1) Thus, activation of **2d** and **2e** proceeded smoothly, and as a result products **4d** (60%, β) and **4e** (83%, 0.95/1 (α/β)) were isolated from each glycosylation reaction. (Table 1, entries 4 and 5) When the same reaction conditions were applied to the reaction of less active thioglycoside **2c**, **2f**, **2g** or **2h** no product formation was detected after 2 h. It is expected that acyl substituents have a disarming effect on thioglycosides, hence the stability of **2c–2g** under the mild reaction conditions. Furthermore, as Fraser-Reid has shown,[7] 4,6-*O*-benzylidene-protected pyranosyl systems, such as **2g** and **2h**, are also less active glycosyl donors than their 4,6-di-*O*-benzyl congeners, because the formation of oxycarbenium cations is disfavoured, due to the greater strain the conformational deformation imposes on the *trans*-fused bicyclic nucleus. To further probe that the activation with **1** at

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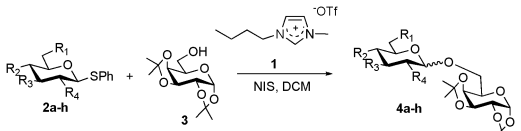
Table 1 Comparative reactivity of the differently protected thioglycosides **2a–g** in the presence of IL **1**



2a, 4a R_1=R_2=R_3=R_4=OBn
2b, 4b R_1=R_2=R_3=R_4=OAc
2c, 4c R_1=R_2=R_3=R_4=OBz
2d, 4d R_1=R_2=R_3=OBn, R_4=OAc
2e, 4e R_1=OAc, R_2=R_3=R_4=OBn
2f, 4f R_1=R_2=OAc, R_3=R_4=OBn
2g, 4g R_1=R_2=OCHPh, R_3=R_4=OBn
2h, 4h R_1=R_2=OCHPh, R_3=OAc, R_4=NHTroc

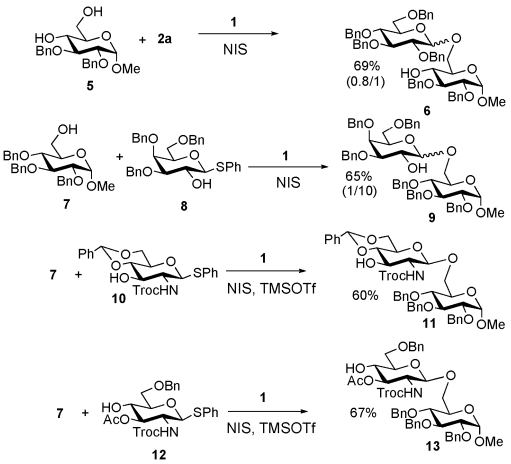
Entry[a]	Donor	Product	Yield (%)	α/β ratio[b]
1	**2a**	**4a**	70	0.7/1
2	**2b**	s.m.	—	—
3	**2c**	s.m.	—	—
4	**2d**	**4d**	60	Only β
5	**2e**	**4e**	83	0.95/1
6	**2f**	s.m.	—	—
7	**2g**	s.m.	—	—
8	**2h**	s.m.	—	—
9	**2a**, **2b**	**4a**, **2b**	68, 92	0.7/1 (**4a**)
10	**2e**, **2h**	**4e**, **2h**	80, 94	0.95/1 (**4e**)

[a] All reactions at room temperature. [b] Determined by NMR spectroscopy (^{1}H and HMQC data). s.m. recovered starting material.

room temperature could discern between armed and disarmed glycosides in a one-pot environment, chemoselective one-pot competition reactions whereby reactive donor (**2a** or **2e**), unreactive donor (**2b** or **2h**, respectively) and acceptor **3** were subjected to the same glycosylation conditions at room temperature as before in the presence of NIS and **1** (10% v/v). (Table 1, entries 9 and 10) In every case, only the products derived from the "armed" donors were detected with almost complete recovery of the "disarmed" thioglycosides. As a result, disaccharide **4a** (68%, 0.7/1 (α/β)) or **4e** (80%, 0.95/1 (α/β)) was obtained along with unreacted thiophenyl **2b** (92%) or **2h** (94%) after column chromatography.

Regioselective glycosylation strategies are particularly important for the assembly of branched oligosaccharides. With the aim of exemplifying that regioselective coupling reactions with donors and acceptors both containing a free hydroxyl group could be carried out at room temperature in the presence of IL **1**, partially protected glycoside acceptors **5**[14] and **7**[15] and donors **8**,[16] **10**[17] and **12** were prepared. (Scheme 1) Regioselective glycosylation of 4,6-diol **5** with armed donor **2a**, at room temperature with **1** as promoter yielded exclusively (1–6)-linked disaccharide **6** in 69% yield (0.8/1 (α/β)). Reaction of glycoside acceptor **7** with thioglycoside **8**, which contains a free OH at C-2, gave disaccharide **9** in 65% yield (1/10 (α/β)). In the case of disarmed derivatives **10** or **12**, the addition of TMSOTf (0.8 equiv.) to the room temperature reaction mixture containing **1** and NIS was required, and disaccharides **11** and **13** were obtained in yields of 60% and 67% respectively. In all cases, no self glycosylation products were detected under the mild conditions of the reaction albeit the reactions were carried out at room temperature.

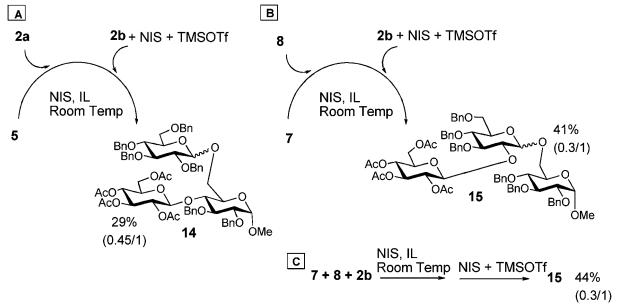
Having found an IL based promoter that allows for selective activation at room temperature of "armed" thioglycosides in the presence of "disarmed" donors and that can be applied in



Scheme 1

regioselective glycosylation, it was decided to validate the methodology on three-component one-pot synthesis of trisaccharides **14** and **15**, as model systems, also at room temperature. (Scheme 2) *In situ* double differential glycosylation, as exemplified by Fraser-Reid using 2,6 and 3,6 diol acceptors in one-pot sequential glycosylation reactions, relies on the difference in reactivity between a primary and a secondary OH present in the same sugar moiety.[18] The strategy is very useful in terms of synthesizing branched oligosaccharides, thus, to test the feasibility of our approach, a step-wise component addition to generate branched trisaccharide **14** in one pot was first investigated. (Scheme 2A) Thus, perbenzylated glycoside donor **2a** (2 equiv.) was reacted with 4,6-diol **5** in the presence of NIS and **1**, resulting in the exclusive glycosylation of the more reactive 6-OH to give the intermediate disaccharide **6**, which was not isolated. Instead, peracetylated thioglycoside **2b** (3 equiv.), another 2 equivalents of NIS and TMSOTf (1 equiv.) were added to the reaction to glycosylate the remaining 4-OH to give, following purification, trisaccharide **14** in 29% yield (0.45/1 (α/β)). The synthesis of linear trisaccharide **15** in one pot was then attempted following the above step-wise addition. (Scheme 2B) Unlike traditional one-pot synthesis, our strategy entails the coupling of a selectively protected armed thioglycoside donor **8** containing a free secondary OH, which acts as donor in the first instance and becomes the acceptor in the second step. Thus, thioglycoside **8** (2 equiv.) was reacted with acceptor **7**, bearing a primary and therefore more reactive OH, in the presence of NIS and **1** to give selectively the 1–6-linked disaccharide **9**, with the 2-OH free for further coupling. Peracetylated thioglycoside **2b** (3 equiv.) was then added to intermediate **9** in the same pot followed by the addition of excess NIS (2 equiv.) and TMSOTf (1 equiv.) to give trisaccharide **15** in 41% yield after purification (0.3/1 (α/β)).

On the basis that IL **1** can selectively activate armed glycosides in the presence of deactivated donors, an alternative and more attractive one-pot strategy whereby all of the glycoside building blocks are combined at the start of the reaction, was attempted. (Scheme 2C) Thus, the reaction to form **15** was carried out with the three components, donors **8** and **2b** and acceptor **7**, mixed together in the presence of **1** and



Scheme 2

NIS. After 3 h at room temperature (to allow disaccharide **9** to form) excess NIS and TMSOTf were added to activate **2b**. Product **15** was isolated in 44% yield following purification on silica.

These experiments demonstrate the applicability of a mild promoter such as **1** for room temperature one-pot reactions where the reactivity of the building blocks can be tuned accordingly by choosing the right combination of protecting groups. It is important to note that although yields for the one-pot reactions are moderate, they correspond to the formation of two glycosidic bonds with no purification by column chromatography in between steps.

In conclusion, we have shown the versatility of IL **1** in combination with NIS to selectively promote at room temperature activated glycosyl donors in presence of less active glycosides. We have exemplified the usefulness of IL **1** in regio- and chemo-selective glycosylation reactions where both donor and acceptor bear a free OH of distinct reactivity. Furthermore, we have demonstrated that a mild promoter such as **1** can be used for room temperature reactivity-based one-pot reactions, whereby the building block reactivity is tuned by the choice of protecting groups. To the best of our knowledge, we have presented the first example of a one-pot glycosylation reaction where a partially protected 'armed' monosaccharide glycoside is used firstly as the glycosyl donor and the resulting product becomes the glycosyl acceptor in the following step, without any protecting group manipulations, in both a sequential synthetic approach and where all the components are mixed together in one vessel at the beginning of the synthesis. The recyclability properties of the IL promoter are also very attractive in terms of green chemistry and this combined with the ability of **1** to promote glycosylation reactions at room temperature makes this strategy convenient and cost effective for automated oligosaccharide synthetic protocols where no strict control of low temperatures will be required.

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