Dialkyl Imidazolium Benzoates – Room Temperature Ionic Liquids Useful in the Peracetylation and Perbenzoylation of Simple and Sulfated Saccharides

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Dedicated to the late Professor Raymond Lemieux to recognize his remarkable contributions to the field of carbohydrate chemistry.

Abstract: Dialkyl imidazolium benzoates, room temperature ionic liquids including 1-ethyl-3-methyl imidazolium benzoate, 1-butyl-3-methyl imidazolium benzoate and 1-hexyl-3-methyl imidazolium benzoate were used in the peracetylation and perbenzoylation of several simple and sulfated carbohydrates. Organic solvents and catalysts were not required in the syntheses and these ionic liquids gave excellent yields in short reaction times.

Key words: carbohydrates, sulfated sugars, acylation, ionic liquids, microwave

Glycosaminoglycans (GAGs), a family of structurally complex, highly sulfated, polydisperse, linear polysaccharides are of particular interest to our laboratory as they display a wide array of important biological properties.[1] Simple sulfated monosaccharides have proven useful in developing new GAG chemistry.[2] Peracetylation and perbenzoylation play vital roles in protection strategies, separation and characterization of carbohydrates. Acetic anhydride is the most widely used reagent for peracetylation and benzoyl chloride, well-known for its corrosiveness and pungent smell, for benzoylation of carbohydrates. Pyridine, toxic and odoriferous, is widely used as solvent/catalyst in these reactions. DMAP and sodium acetate are other common acetylation catalysts,[3] as are the Lewis acids, $TaCl_5$ and $TaCl_5$-silica gel[4] and boron trifloride.[5]

Room Temperature Ionic Liquids (RTILs) are liquids at room temperature composed entirely of ions. RTILs are fast becoming an alternative for environmentally harmful, volatile, organic solvents. RTILs are finding a place in modern chemistry due to their desirable properties, including almost no vapor pressure, making RTILs non-volatile, odorless, recyclable, non-flammable and thermally stable. RTILs can dissolve many complex polar molecules, and while their high viscosity can be an advantage in coating materials,[6] it can complicate their use as reaction solvents. Their use with polar reactants can avoid the processes of solvolysis and solvation, which often complicate reactions in which aqueous and organic solvents are used. The hazardous flammable nature and toxicity of many organic solvents have also resulted in environmental concerns motivating the development of these alternate environmentally 'greener' solvents. Many reviews on RTILs and their uses in modern chemistry have appeared recently in the literature.[7,8] Dicyanamide ionic liquids ([bmIm][dca] and [emIm][dca]) had also been recently demonstrated to afford clean and mild method for *O*-acetylation of simple saccharides.[9] For these reasons, we decided to investigate the use of RTILs in the peracetylation and perbenzoylation of the simple, underivatized and sulfated monosaccharides.

1-Ethyl-3-methyl imidazolium benzoate [emIm][ba] was first reported[10] in 1994 as an ionic liquid useful in electrochemistry. In this communication, we introduce [emIm][ba], 1-butyl-3-methyl imidazolium benzoate [bmIm][ba] and 1-hexyl-3-methyl imidazolium benzoate [hmIm][ba] (Figure 1) as good solvent/catalysts in the peracylation of simple and sulfated carbohydrates.

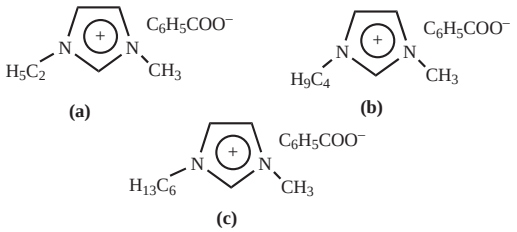

Figure 1 (a) 1-Ethyl-3-methyl imidazolium benzoate, (b) 1-butyl-3-methyl imidazolium benzoate and (c) 1-hexyl-3-methyl imidazolium benzoate.

Since many of the RTILs used in this study are commercially unavailable, conventional methods relying on using silver oxide[10,11] were first used for their preparation. While this approach afforded reasonable yields, a silver colloid contaminated all the RTILs synthesized by this method. A recently developed approach using microwave irradiation[12] was next investigated, which yielded clean [emIm][ba], [bmIm][ba] and [hmIm][ba] without the required use of any metal. In a typical reaction procedure (Equation 1), a household microwave was used to heat 1-ethyl-3-methyl imidazolium chloride (1 mmol) mixed

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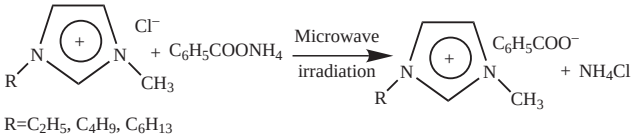
with ammonium benzoate (1 mmol). The contents were microwaved in a test tube for 45 s with 20 s of intermittent mixing (20 s + 10 s + 20 s + 10 s + 5 s) on a vortex stirrer. The by-product, ammonium chloride, precipitated on the sides of the test tube resulting in the easy recovery of a clear solution of [emIm][ba]. The RTIL was dried under vacuum at 70 ºC prior to being used in acylation reactions. The purity of the RTIL was confirmed by using ^{1}H NMR.[13] The yields obtained in the synthesis of the three RTILs are given in Table 1.



Equation 1 Synthesis of RTILs [emIm][ba], [bmIm][ba] and [hmIm][ba].

Table 1 Synthesis of RTILs Using Microwave Energy

RTIL	Starting material	Yield (%)
[emIm][ba]	[emIm][Cl], ammonium benzoate	87
[bmIm][ba]	[bmIm][Cl], ammonium benzoate	86
[hmIm][ba]	[hmIm][Cl], ammonium benzoate	87

Peracetylation of various simple saccharides including β-D-glucose, α-D-glucose, D-mannose (α, β mixture), and D-galactose (α, β mixture), and sulfated saccharides, phenyl 4-*O*-sulfo-β-D-glucopyranoside (**1**) and phenyl 6-*O*-sulfo-β-D-glucopyranoside (**2**), was achieved using [emIm][ba] as a solvent/catalyst. It is important to note that acetic anhydride and RTIL act as co-solvents in these reactions. Various dialkyl imidazolium benzoate ionic liquids (Figure 1) were found to give good to excellent isolated yields in short reaction times (Table 2). The conversions were quantitative in most cases based on the disappearance of the starting material by TLC.

The sugar reactants were not completely soluble in the [emIm][ba], [bmIm][ba] and [hmIm][ba] RTILs. Despite the biphasic nature of the reactions, acetylation took less than 24 h for completion. No organic solvents were required for any of the reactions, and only a stoichiometric amount of acetic anhydride was required for complete reaction. The anomeric ratio of products, corresponding to reaction selectivity, was determined by using ^{1}H NMR.

The recovered yields of peracetylation products varied. For both β-D-glucose (Equation 2) and α-D-glucose, the yield was quantitative, but was found to decrease to 78% and 71% for mannose and galactose, respectively. In the cases of α-D-glucose and -D-glucose, the selectivity was found to favor the β-product, but in the cases of D-mannose (α, β mixture) and D-galactose (α, β mixture), the α-product was favored. The higher yields for the pure anomeric forms might result from their increased crystallinity.

Peracetylation of β-D-glucose was next attempted by using commercially available RTILs, 1-butyl-3-methylimidazolium hexafluorophosphate [bmIm][PF_6] and 1-butyl-3-methyl imidazolium tetrafluoroborate [bmIm][BF_4]. In both cases, no product was observed and only starting material was recovered after 24 h. The basic nature of the benzoate ions in the RTILs shown in Figure 1 apparently represents an important catalytic component in these acylation reactions.

The peracetylation yield was found to decrease significantly with the increase in the alkyl chain length of the imidazole moiety (Table 1, entries 1, 7 and 8). In addition, the reaction time also increases with the increased alkyl chain length in the imidazole component of the ionic liquid, from 4 h to 5 h to 7 h, when using [emIm][ba], [bmIm][ba] and [hmIm][ba], respectively. This might result from the increased viscosity of the ionic liquids containing longer chain lengths in the alkyl groups of the imidazole moiety. Reaction selectivity was also altered with a change in the alkyl chain length. For both [emIm][ba] and [bmIm][ba], the selectivity completely favored the β-anomer, but for [hmIm][ba], α-anomeric product was also formed.

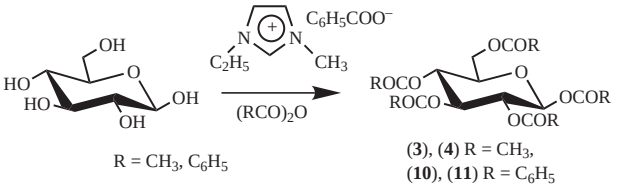
The sodium salts of sulfated sugars are insoluble in most organic solvents and are difficult to peracetylate.[14] Currently only water and formamide can serve as solvents for these sulfated carbohydrates.[15] The sodium salts of both **1** and **2** were found to be soluble in [emIm][ba] facilitating their peracetylation. This property of benzoate RTILs to dissolve sulfated sugars makes these solvents potentially very important for future use in the chemical modification of GAGs. By using [emIm][ba] as a solvent/catalyst, phenyl 2,3,4-tri-*O*-acetyl-4- and 6-*O*-sulfo-β-D-glucopyranoside (**8**) and (**9**) could be easily obtained in high yield.

Dialkyl imidazolium benzoate RTILs were also found to be effective solvents for perbenzoylation of simple saccharides (Table 3). Initial studies using benzoyl chloride failed to afford the desired product. In subsequent studies, benzoic anhydride was used to afford completely benzoylated products **10**–**12**. Recovered yields of perbenzoylated products, ranging from 53% to 55%, were obtained using [emIm][ba]. In contrast to the peracetylation reactions, β-D-glucose, and D-mannose (α, β mixture) favored α-products while α-D-glucose favored β-products.

Following each reaction, RTILs were recovered by filtration and subsequent evaporation of the permeate. The purities of the recovered RTILs were assessed by ^{1}H NMR. In the acetylation reactions, the acetate product formed could replace the benzoate ion in the ionic liquid destabilizing it and further complicating its recovery. Destabilization of the RTIL might also result from the use of water to recover product.

While the eventual purpose of using the RTILs is to eliminate the use of volatile organic solvents, it is important to understand the stability of RTILs when mixed with various organic solvents. The stability of [emIm][ba] was examined when combined with various organic solvents

including, acetone, acetonitrile, methanol, chloroform and ethyl acetate. ^{1}H NMR spectra of RTIL taken before and after washing with these solvents revealed the loss of a portion of its anionic component, benzoate. [EmIm][ba] was only found to be stable when washed with anhydrous diethyl ether. Additional efforts are currently underway to improve the recovery and recycling of these ionic liquids.



Equation 2 Peracylation of β-D-glucose in 1-ethyl-3-methyl imidazolium benzoate.

In a typical acetylation reaction procedure (Equation 2), acetic anhydride (5.33 mmol) was added to a suspension of β-D-glucose (1.08 mmol) and [emIm][ba] (2.16 mmol). The reaction mixture was stirred at room temperature until the completion of the reaction, monitored by the disappearance of the starting materials on TLC. Water was then added to the reaction mixture to precipitate the product, which was recovered by filtration and purified by silica gel chromatography (petroleum ether:ethyl acetate, 9:1 → 3:1) to afford **3** (416mg, 100%). The purity of the final product was confirmed by ^{1}H NMR.

The phenyl 4-*O*-sulfo--D-glucopyranoside (**1**) and phenyl 6-*O*-sulfo-β-D-glucopyranoside (**2**) were synthesized from phenyl β-D-glucopyranoside (200 mg, 0.78 mmol) by selective 6-silylation with *tert*-butyldimethylsilyl chloride (180 mg, 1.17 mmol) in pyridine (4 mL). After 40 min, acetic anhydride (450 μL, 4.77 mmol) was added and the reaction mixture was stirred overnight at room temperature, concentrated and co-evaporated with toluene. The peracetylated 6-silylated derivative (302 mg, 78%), obtained by recrystallization (petroleum ether:ethyl acetate), was treated with trifluoroacetic acid (500 μL) for 5 minutes. The solution was co-evaporated with water to give an inseparable mixture of 4- and 6-hydroxyl derivatives (227 mg, 98%). Sulfonation using sulfur trioxide–trimethylamine complex (238 mg, 1.71 mmol) in DMF at 50 °C overnight afforded the 4- and 6-*O*- sulfo derivatives that were purified by silica gel chromatography (ethyl acetate/methanol/water, 10:2:1 + triethylamine 0.5%). De-acetylation of both the 4- and 6-*O*-sulfo derivatives (500 mg, 1.08 mmol) was carried out with catalytic sodium methoxide in methanol (5 mL). After 4 hours, neutralization with Amberlite IR-120H$^+$, concentration and purification by silica gel chromatography (ethyl acetate/methanol/water 16:2:1) followed by ion-exchange chromatography on Sephadex C-25 (Na$^+$) (methanol/water 1:1) afforded as sodium salts the 6-*O*-sulfo (198 mg, 54%) and the 4-*O*-sulfo compounds (96 mg, 27%).

A representative peracetylation procedure for the sulfated sugars (Equation 3) involved the addition of acetic anhydride (0.77 mmol) to a suspension of **1** (0.26 mmol) and [emIm][ba] (1.34 mmol). The reaction was followed by TLC until the starting material disappeared. Water was added to extract the peracetylated product from the reaction and was evaporated to recover the product, which was purified by silica gel chromatography (ethyl acetate/methanol/water 6:2:1) to afford **8** (46mg, 74%). The structure of the final product was confirmed by both ^{1}H NMR[16] and mass spectroscopy.[17]

In a representative perbenzoylation reaction procedure (Equation 2), β-D-glucose (0.34 mmol) was added to a suspension of benzoic anhydride (1.70 mmol) in [emIm][ba] (1.35 mmol). In this case additional [emIm][ba] was required (because benzoic anhydride is a solid in contrast to liquid acetic anhydride). The reaction was followed until completion as determined by the disappearance of the starting material using TLC. The prod-

Table 2 Peracetylation of Various Unsubstituted and Sulfated Saccharides in RTILs at Room Temperature

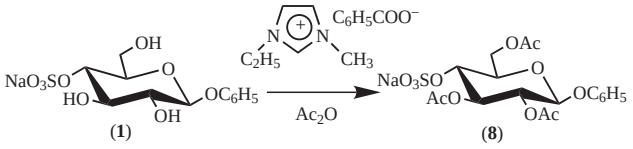
Entry	Compound	Ac_2O (equiv)	Solvent (equiv)	Time (h)	Products	Yield (%)	Anomeric ratio (α:β)[a]
1	β-D-glucose	5	[emIm][ba](2)	4.0	**3**	100	0:1
2	α-D-glucose	5	[emIm][ba](2)	4.0	**3**, **4**	100	2:1
3	D-mannose (α:β = 1:0.5)	5	[emIm][ba](2)	3.0	**5**	78	1:0
4	D-galactose (α:β = 1:2)	5	[emIm][ba](2)	4.5	**6**, **7**	71	1:1
5	phenyl-4-*O*-sulfo-β-D-glucopyranose (**1**)	3	[emIm][ba](2)	2.0	**8**	74	0:1
6	phenyl-6-*O*-sulfo-β-D-glucopyranose (**2**)	3	[emIm][ba](4.4)	1.0	**9**	73	0:1
7	β-D-glucose	5	[bmIm][ba](2)	5.0	**3**	82	0:1
8	β-D-glucose	5	[hmIm][ba](2)	7.0	**3**, **4**	68	1:0.2
9	β-D-glucose	5	[bmIm][PF_6](2)	24.0	–	0	–
10	β-D-glucose	5	[bmIm][BF_4](2)	24.0	–	0	–

[a] The anomeric ratio of the starting materials was determined by using ^{1}H NMR in D_2O immediately after dissolution.

Table 3 Preliminary Results of Perbenzoylation of Simple Saccharides

Entry	Compound	$(PhCO)_2O$ (equiv)	Solvent (equiv)	Time (h)	Products	Yield (%)	Anomeric ratio (α:β)
1	β-D-glucose	5	[emIm][ba](4)	5.5	**10**, **11**	55	1:1.2
2	α-D-glucose	5	[emIm][ba](4)	5.0	**10**, **11**	54	1:0.8
3	D-mannose (α:β = 1:0.5)	5	[emIm][ba](4)	6.0	**12**	53	1:0

uct was precipitated by adding water, recovered by filtration, and purified by silica gel chromatography (petroleum ether: ethyl acetate 9:1 → 3:1) to afford an inseparable mixture of **10** and **11** (213mg, 55%). The identity and purity were confirmed by ^{1}H NMR.[16]



Equation 3 Peracetylation of phenyl-4-*O*-sulfo-β-D-glucopyranose (**1**) using 1-ethyl-3-methyl imidazolium benzoate.

In summary, acetylation and benzoylation of unsubstituted and sulfated monosaccharides have been successfully accomplished in RTILs. While some α, β selectivity was observed, at present we are unable to explain this selectivity.

Future studies will examine these issues as well as extend the application of these reactions to other sulfated reactants such as GAGs and GAG-derived oligosaccharides.

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(13) NMR data: **[emIm][ba]**: ^{1}H NMR (DMSO, 400 MHz) δ 1.39 (3 H, t, CH_3), 3.84 (3 H, s, CH_3), 4.16 (2 H, q, CH_2), 7.44 (2 H, m, Ph), 7.54 (1 H, m, Ph), 7.70 (1 H, t, *J* = 1.7 Hz, Im), 7.79 (1 H, t, *J* = 1.8 Hz, Im), 7.92 (2 H, m, Ph), 9.25 (1 H, s, Im). **[bmIm][ba]**: ^{1}H NMR (DMSO, 400 MHz) δ 0.91 (3 H, t, CH_3), 1.28 (2 H, m, CH_2), 1.78 (2 H, m, CH_2), 3.88 (3 H, s, CH_3), 4.20 (2 H, t, CH_2), 7.49 (2 H, m, Ph), 7.60 (1 H, m, Ph), 7.77 (1 H, t, *J* = 1.7 Hz, Im), 7.84 (1 H, t, *J* = 1.7 Hz, Im), 7.96 (2 H, m, Ph), 9.36 (1 H, s, Im). **[hmIm][ba]**: ^{1}H NMR (DMSO, 400MHz) δ 0.84 (3 H, t, CH_3), 1.24 (6 H, m, 3 CH_2), 1.76 (2 H, m, CH_2), 3.84 (3 H, s, CH_3), 4.14 (2 H, t, CH_2), 7.16 (1 H, t, *J* = 1.7 Hz, Im), 7.47 (2 H, m, Ph), 7.59 (1 H, m, Ph), 7.87 (1H, t, *J* = 1.8 Hz, Im), 7.93 (2 H, m, Ph), 9.24 (1 H, s, Im)..
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(16) NMR data: Compound (**1**): ^{1}H NMR (D_2O, 400 MHz) δ 3.58 (1 H, dd, *J* = 7.8 Hz, 9.2 Hz, H-2), 3.62 (1 H, ddd, *J* = 2.1 Hz, 5.6 Hz, 9.8 Hz, H-5), 3.80 (2 H, m, H-3, H-6b), 3.95 (1 H, dd, *J* = 2.1 Hz, 12.5 Hz, H-6a), 4.24 (1 H, dd, *J* = 9.0 Hz, 9.8 Hz, H-4), 4.97 (1 H, d, *J* = 7.9 Hz, H-1), 7.01–7.32 (5 H, m, Ph). Compound (**2**): ^{1}H NMR (D_2O, 400 MHz) δ 3.43–3.51 (3 H, m, H-2, H-3, H-4), 3.69 (1 H, ddd, *J* = 2.0 Hz, 5.8 Hz, 7.6 Hz, H-5), 4.18 (1 H, dd, *J* = 5.8 Hz, 11.0 Hz, H-6b), 4.39 (1 H, dd, *J* = 2.0 Hz, 11.0 Hz, H-6a), 4.91 (1 H, d, *J* = 7.4 Hz, H-1), 7.00–7.32 (5 H, m, Ph). Compound (**8**): ^{1}H NMR (D_2O, 400 MHz) δ 2.04 (3 H, s, OAc), 2.05 (3 H, s, OAc), 2.06 (3 H, s, OAc), 4.98 (1 H, ddd, *J* = 2.5 Hz, 6.6 Hz, 9.7 Hz, H-5), 4.37 (1 H, dd, *J* = 6.6 Hz, 12.2 Hz, H-6b), 4.42–4.49 (2 H, m, H-4, H-6a), 5.14 (1 H, dd, *J* = 8.0 Hz, 9.7 Hz, H-2), 5.27 (1 H, d, *J* = 8.0 Hz, H-1), 5.38 (1 H, t, *J* = 9.7 Hz, H-3), 7.00–7.32 (5 H, m, Ph). Compound (**9**): ^{1}H NMR (D_2O, 400 MHz) δ 2.03 (3 H, s, OAc), 2.08 (3 H, s, OAc), 2.09 (3 H, s, OAc), 4.09–4.21 (3 H, m, H-5, H-6a, H-6b), 5.12 (1 H, t, *J* = 9.5 Hz, H-4), 5.21 (1 H, dd, *J* = 8.0 Hz, 9.5 Hz, H-2), 5.33 (1 H, d, *J* = 8.0 Hz, H-1), 5.42 (1 H, t, *J* = 9.5 Hz, H-3), 7.05–7.36 (5 H, m, Ph). Compounds (**10**) and (**11**): ^{1}H NMR (D_2O, 400 MHz) δ 4.39–4.69 (5.25 H, m, H-5α,β, H-6aα,β, H-6bα,β), 5.69 (1 H, dd, *J* = 3.7 Hz, 10.3 Hz, H-2α), 5.80–5.90 (2.5 H, m, H-4α, H-2β, H-4β), 6.05 (0.75 H, t, *J* = 9.4 Hz, H-3β), 6.30 (0.75 H, d, *J* = 7.9 Hz, H-1β), 6.33 (1 H, t, *J* = 10.0 Hz, H-3α), 6.85 (1 H, d, *J* = 3.7 Hz, H-1α), 8.18–7.27 (25 H, m, Ar).
(17) MS (ESI): 461 [M + H^+].