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Note

Synthesis of benzylidenated hexopyranosides in ionic liquids

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Abstract—The synthesis of 4,6-*O*-benzylidenated monosaccharides and disaccharides has been studied using ionic liquids as a unique solvent alternative. An examination of several imidazolium ionic liquids indicates that the benzylidenation of hexopyranosides in 3-butyl-1-methylimidazolium tetrafluoroborate, [bmim]BF_4, gives the highest yields for most of the substrates, and that this solvent system could be readily recycled.

Keywords: Benzylidenation; Ionic liquid; [bmim]BF_4; [emim]BF_4; [bmim]PF_6; Glycosides

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Carbohydrates play an important role in a vast array of biological recognition processes and in many other important areas of nutrition and biomaterials.[1,2] The investigation of these properties is often dependent upon the synthesis of complex carbohydrates, and these synthons frequently rely on selective functionalization of hydroxyl groups.[3] A commonly employed methodology is the formation and derivatization of 4,6-*O*-benzylidenated monosaccharides.[4] In addition, the benzylidenation of monosaccharides has been reported to yield a novel organogelator that exhibited unique gelling properties with various solvents.[5–8]

In light of the versatility and application of benzylidenated carbohydrates, their synthesis remains a continuing point of interest. Methyl 4,6-*O*-benzylidene-D-hexopyranosides are commonly obtained by reacting the underivatized glycoside with benzaldehyde and an acid catalyst.[9] Alternatively, benzylidenation can be accomplished in high yield employing a benzylidene acetal, in the presence of a Lewis acid such as $ZnCl_2$, or via a Brønsted acid catalyst.[10–15] Recent studies have examined alternative methodologies, including the use of ultrasonics,[16] lanthanide cation-exchange resins,[17] tin(II) triflates,[18] and microwave[19] assisted benzylidenation of carbohydrates.

Studies by Harjani et al.[20] have highlighted the unique reactivity of benzaldehyde and substituted derivatives in ionic liquids suggesting an alternative methodology for benzylidenating carbohydrates. Ionic liquids are organic salts with melting points typically under 100 °C, often even lower than room temperature.[21] However, due to their ionic nature, these liquids exhibit no measurable vapor pressure, are nonflammable, possess unique chemical and thermal stability, and are water and air stable. These properties and their intrinsic recyclability have resulted in increasing application of ionic liquids in the Green Chemistry focus area.[22]

Ionic liquids have been shown to exhibit excellent solubilizing properties, facilitating a wide range of chemical reactions, including alkylations,[23] hydrogenations,[24] cycloadditions,[25] esterifications,[26] arylations,[27] cyclodimerizations[28] and Beckmann rearrangements.[29] Furthermore, since ionic liquids do not mix with a number of organic solvents, they provide a unique way to create valuable two-phase systems for separation and isolation of compounds.[30–32]

Since many traditional solvents and catalyst systems are incompatible with sugars, ionic liquids have been examined as an alternative reaction media for carrying out chemical reactions with carbohydrates.[33] These reports have highlighted the potential of ionic liquids to be used for mild acetylation of sugars[34] and glycosylation reactions. Sasaki et al. reported that the glycosidations by

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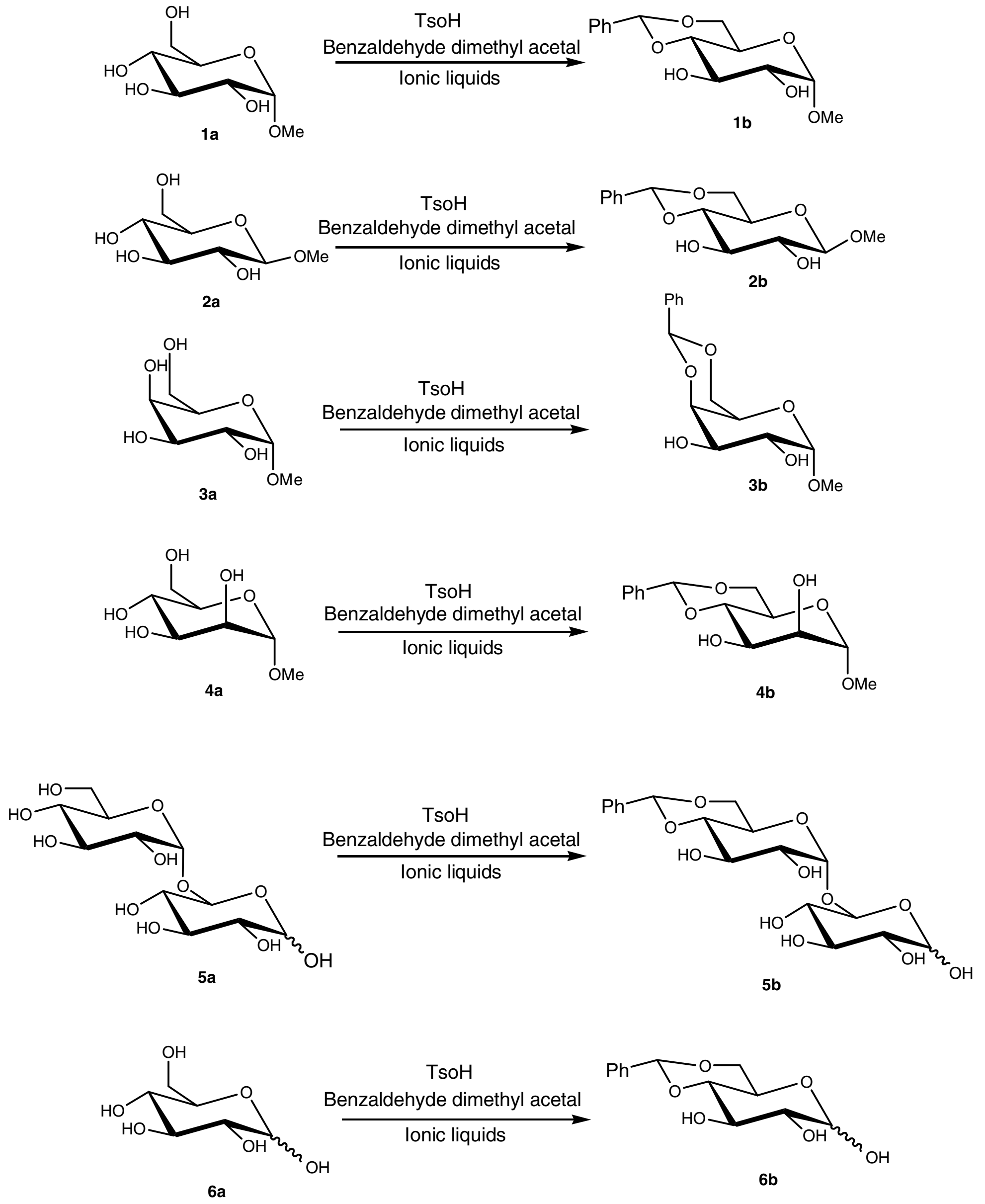
glucopyranosyl fluoride with assorted alcohols, using an ionic liquid and a protic acid catalyst, proceeded under mild conditions to afford the corresponding glycosides in good yields.[35] The reactivity of glycosyl trichloroacetimidates and diethyl phosphates with alcohols in the presence and absence of Lewis acids have been also recently reported with several ionic liquids.[36,37]

Selective enzymatic acylations of carbohydrates have been explored in both organic solvents and ionic liquids, and it was observed that the reactions in ionic liquids took place more rapidly and more selectively than those in conventional organic solvents.[38] A facile synthesis of 1,2-orthoesters of carbohydrates in [bmim]PF$_6$ has been described by Radhakrishnan et al. as a simpler and eco-friendly method.[39] The use of 1-butyl-3-methylimidazolium tetrafluoroborate as the reaction medium and iron(III) chloride hexahydrate as a catalyst has been employed for the efficient preparation of α,α′-bis(substituted benzylidene) cycloalkanones.[40] The intrinsic properties of the ionic liquids described above facilitate reaction work-up and recycling of the solvent.

The purpose of this investigation was to examine the potential of employing ionic liquids for the 4,6-*O*-benzylidenation of hexopyranosides. Herein, we report the results of benzylidenation of methyl glycosides **1a**–**4a** by employing several imidazolium ionic liquids (namely, [bmim]BF$_4$, [emim]BF$_4$, [bmim]PO$_4$, and [bmim]MeSO$_4$) as reaction media (Scheme 1). The yields of the corresponding benzylidenation products **1b**–**4b** results are summarized in Table 1.

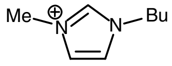


Scheme 1. Benzylidenation of **1a**–**6a** in various ionic liquids.

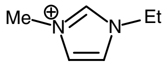
Table 1. Isolated yields for benzylidenation of **1a**–**5a** in various ionic liquids

Entry	**1b** (%)	**2b** (%)	**3b** (%)	**4b** (%)	**5b** (%)
[bmin]BF_4	99	74	92	88	61
[emin]BF_4	38	25	48	55	<5
[bmin]PF_6	<5	64	<5	17	<5
[bmin]$MeSO_4$	75	<5	<5	<5	<5

[bmim]:



[emim]:



Optimization studies indicated that optimal results required a twofold molar equivalent amount of benzaldehyde dimethyl acetal for the benzylidenations of the substrates studied. For the reaction solvent, we examined a series of imidazolium ionic liquids, which are liquids at room temperature, having low viscosity. Among the ionic liquids studied, [bmim]BF_4 exhibited optimal solubility for substrates **1a**–**5a** at 85 °C and gave the highest yields. The benzylidenation of **1a**–**4a** with benzaldehyde dimethyl acetal in [bmim]BF_4 gave **1b**–**4b** in high yields ranging from 74% to 99%, and gave **1b**–**4b** in reduced yields ranging from 25% to 55% when [emim]BF_4 was employed. There were no significant benzylidenated products in both [bmim]PF_6 and [bmim]SO_4, except that the benzylidenation of **2a** in [bmim]PF_6 gave **2b** in 64% yield, and benzylidenation of **1a** in [bmim]$MeSO_4$ gave **2b** in 75% yield, as shown in Table 1.

The solubilizing abilities of ionic liquids for polysaccharides have been reported by several authors.[41] As a preliminary study for benzylidinating oligo- and polysaccharides, we examined the benzylidenation of maltose. Treatment of **5a** gave a 61% yield of **5b** in [bmim]BF_4. There was no significant reaction with other imidazolium ionic liquids for the benzylidenation of maltose. Clearly, the structure of the ionic liquid affected the reactivity of the substrates, and BF_4^- is a better counter anion to facilitate the benzylidenation of the substrates than other anions. The benzylidenation of D-glucose (**6a**) in [bmim]BF_4 produced **6b** in 86% yield ($\alpha:\beta = 1:1$), higher than that obtained in routine solvents.[42] Indeed, in most cases, the optimal ionic liquid provided the desired 4,6-*O*-benzylidene in comparable or enhanced yields than have been reported for conventional organic solvents.[10–15,43]

In addition, we tested the recycling properties of ionic liquids employed in this study. In brief, upon completion of benzylidenation and extraction of the products, the ionic liquids were quantitatively recycled by washing with toluene, water, and then filtered through a pad of Celite. All volatiles were removed by evaporation and the residue was dried at 70 °C under reduced pressure. Following this procedure, with **1a**–**5a** the recovered ionic liquids were reused for the benzylidenation reaction at least five times without any loss in efficiency, providing the same yields as described above.

In summary, we have developed a novel benzylidenation methodology employing ionic liquids. Moreover, the results indicate that benzylidenation in an ionic liquid provides a good yield employing a recyclable, environmentally benign solvent.

1. Experimental

1.1. General methods

All starting materials and reagents were obtained from Aldrich or Fluka Chemical Company. TLC was performed on silica gel HF-254 and chromatography on silica gel 60-PF_{254} (EM SCIENCE). NMR spectra were recorded with a Bruker 400 DMX spectrometer in $CDCl_3$.

1.2. Benzylidenation procedure

The substrate (0.50 mmol) and benzaldehyde dimethyl acetal (1.00 mmol) were dissolved in ionic liquid (0.70–2.00 mL) together with PTSA·H_2O (1% molar ratio), subsequently, the mixture was heated up to 80 °C for 2 h. After cooling to room temperature, an excess amount of Na_2CO_3 was added and this mixture was extracted with EtOAc (3 × 5 mL), washed with brine, water and dried. Purification of the residue by column chromatography gave the benzylidenated carbohydrate.[†]

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[†] All compounds' spectra are consistent with reported values.

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