Neutral Ionic Liquid [hmim]Br as a Green Reagent and Solvent for the Mild and Efficient Dehydration of Benzyl Alcohols into (E)-Arylalkenes Under Microwave Irradiation^[‡]

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A mild and efficient, ionic-liquid-assisted, green protocol for the dehydration of benzyl alcohols into the corresponding (E)-arylalkenes under microwave irradiation has been developed. The method utilizes a neutral and recyclable ionic liquid (1-hexyl-3-methylimidazolium bromide) as a reagent and solvent to cleanly provide a wide range of olefins without the need of harsh and expensive Brønsted/Lewis acids. The method was extended to the efficient conversion of acetylated/benzoylated derivatives of benzyl alcohol into their corresponding (E)-arylalkenes. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

The dehydration of alcohols is a fundamental and extensively exploited transformation in organic synthesis due to the immense biological importance and synthetic utility of the ensuing alkenes.^[1] For instance, various methoxylated (E)-arylalkenes such as α -asarone are known to be active hypolipidemic agents besides possessing neuroleptic. antichloretic, antiplatelet and antifungal activities.^[1e,1i] In addition, a number of styrenes and polycyclic arylalkenes have been recognized as important synthons for various bioactive stilbenes as well as commercial anti-inflammatory agents through Heck and hydroformylation approaches, respectively.^[1f,1j,1d] The usual protocols for accomplishing the above dehydration employ various reagents like mineral acids, PTSA and oxalic acid.^[1a,1b,1c,1g] However, a majority of the above protocols are limited by their incompatibility with substrates possessing acid-sensitive functional groups and a propensity for undesired side reactions.^[1g] Accordingly, there has been a growing impetus to develop new protocols for the dehydration of alcohols under neutral conditions employing a variety of reagents including DMSO,^[2a,2b] triphenylbismuth dibromide-iodine,^[2c] PPh₃,^[2d] ZnCl₂^[2e] and metal triflates.^[2f] Recently, molecular iodine has also been reported to catalyze the dehydration of various alcohols.^[3] In addition, the dehydration of alcohols has also been attempted with several other dehydrating agents like phos-

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phorus pentachloride, phosphorus pentoxide, copper sulfate/toluene, titania catalyst at elevated temperatures, silica gel/copper sulfate and activated silica gel under solvent-free conditions.^[4] In spite of the availability of the dehydrating agents described above, a majority of these protocols continue to be afflicted with perennial limitations like the lack of generality, the formation of side products, the employment of expensive, moisture-sensitive and toxic catalysts, long reaction times and the harshness of Bronsted/Lewis acids, which not only precludes their use with substrates possessing sensitive functional groups but also leads to environmental harm. In particular, the controlled dehydration of benzyl alcohols into the corresponding olefins including the immensely important (*E*)-arylalkene derivatives^[1e,i] has</sup> remained a difficult proposition due to the preponderant tendency of the incipient benzylic carbocation to participate in competing side reactions leading to the formation of several side products^[5] including a dimer.^[5b,5d,5e] Recently, a notable report described a pseudourea-mediated dehydration of benzylic alcohols, in which the pseudourea was formed in situ. However, the protocol involved long reaction times and hazardous metal salts.^[6] In addition, a number of the protocols described above result in the formation of unwanted, toxic, cis isomers, which in turn, require tedious chromatographic separation owing to the similar $R_{\rm f}$ values of the *cis* and *trans* isomers.^[7]

The dehydration of benzyl alcohols through their prior derivatisation into benzoylated/acetylated counterparts also constitutes a useful strategy in the multistep synthesis of complex natural products.^[8] However, such transformations are often carried out with harsh bases, which preclude their usage in cases of substrates containing sensitive functional groups.^[8]



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The conventional Lewis/Bronsted catalysts are often toxic, corrosive and difficult to separate/recover from products, despite their high catalytic activity. A currently rapidly developing area in organic synthesis concerns the design and usage of catalysts that not only possess high activity and selectivity but are simultaneously benign to the environment and easily recoverable. In this context, ionic liquids have recently attracted considerable interest due to their several inherent virtues like low vapour pressure, easy recyclability and high thermal stability.^[9] In addition, there have been some interesting reports wherein the peculiar ability of neutral ionic liquids to effectively promote conventional acid/base-catalyzed reactions has come to the fore.^[10] Although a few recent reports have also disclosed the ionic-liquid-promoted dehydration of alcohols, the protocols were either limited to a single substrate like fructose^[11] or required the indispensable presence of an adjacent cyclopropyl moiety.[12]

In view of these concerns, we herein report that a neutral and recyclable ionic liquid efficiently acts as a green reagent and solvent for the dehydration of a diverse range of benzyl alcohols into the corresponding (E)-arylalkenes under microwave irradiation.

Results and Discussion

In continuation of our ongoing efforts toward the development of clean synthetic methodologies^[13] for the preparation of various bioactive compounds, we became interested in developing a mild, efficient and environmentally friendly alternative for the dehydration of benzyl alcohols in lieu of the prevalent harsh protocols.^[14] It has been widely recognized that the dehydration of benzyl alcohols is generally plagued by the extreme susceptibility of the product alkenes to further polymerization reactions, leading to the formation of several side products and tedious purification steps.^[15] We have also recently reported a silica-gel-supported, solvent-free protocol for the dehydration of substituted benzyl alcohols into the corresponding arylalkenes. However, the method was limited by moderate yields of the arylalkenes.^[4g] In view of the remarkable ability of ionic liquids to efficiently promote a wide range of conventional acid/base-catalyzed reactions,^[10] we became interested in exploring ionic liquids as green reagents and solvents for the dehydration of various benzyl alcohols. Initially, 4methoxyphenylpropan-1-ol (1a) was heated with commercially available ionic liquid 1-butyl-3-methylimidazolium chloride under microwave irradiation for 8 min, and the corresponding (E)-4-methoxyphenylpropene (1b) was obtained in 72% yield along with some side products and unreacted 1a. Encouraged by the above success, we employed various modifications in the reaction conditions, such as prolonged reaction time and increased reaction temperature, to further increase the reaction performance, but to no avail. Consequently, we shifted our attention to evaluate the dependence of the above reaction on the composition of the ionic liquid. A range of ionic liquids (Table 1) were investigated for their effects on the dehydration of **1a**. It is evident from Table 1 that the nature of the alkyl chain and anion in the ionic liquid play a crucial role in the efficient dehydration of benzyl alcohols. Thus, 1-butyl-3-methylimidazolium hexafluorophosphate and 1-butyl-3-methylimidazolium tetrafluoroborate (Table 1, Entries 2 and 3) provided a comparatively inferior yield of 1b along with some side products. However, 1-butyl-3-methylimidazolium bromide (Table 1, Entry 4) enhanced the yield of 1b to 78%. The best reaction performance was delivered by 1-hexyl-3methylimidazolium bromide (Table 1, Entry 5), which provided the product (1b) in 87% yield (100% conversion) after 7 min of microwave irradiation (Scheme 1). The favourable dependence of the reaction on the presence of the more lipophilic hexyl side chain, which allowed for easier aqueous extraction and isolation of the products with improved yield, has been observed previously.^[16] It was interesting to observe that no reaction occurred when only 1-methylimidazole (Table 1, Entry 6) was used as the solvent for the dehydration of 1a, while the treatment of 1a with the wellknown dehydrating agent PTSA/toluene^[1h] (Table 1, Entry 7) under microwave irradiation resulted in a comparatively



Scheme 1. Dehydration of benzyl alcohols and their acetylated/benzoylated derivatives.

Table 1. Effect of different ionic liquids on the dehydration of 1a under microwave irradiation.^[a]



[a] CEM monomode microwave. Reaction conditions: 1.7 mmol of **1a**, 1 mL of ionic liquid, 150 W, 140 °C. [b] 1 mL of 1-methylimidazole was used in place of the ionic liquid. [c] 0.15 mmol of p-toluenesulfonic acid, 4 mL of toluene. [d] Isolated yield of **1b** after column chromatography.



lower yield of **1b** (46%) along with side products. Surprisingly, the imidazolium-based ionic liquid incorporating the PTSA moiety (Table 1, Entry 8) provided **1b** in an improved yield (68%) with less side product formation, thus emphas-

izing the peculiar role of the ionic liquid in efficient dehydrations. Similarly, the basic ionic liquid [bmim]OH (Table 1, Entry 9) provided the expected **1b** in only 55% yield. In order to evaluate the role of the microwave irradia-

Table 2. Dehydration of benzyl alcohols and their derivatives into corresponding (E)-arylalkenes with 1-hexyl-3-methylimidazolium bromide under microwave.^[a]



[a] CEM monomode microwave. Reaction conditions: 1.7 mmol of substrate 1a-25a, ionic liquid (1 mL), 150 W, 140 °C. [b] Based on NMR spectroscopy. [c] Not detected.

tion, the dehydration of 1a with 1-hexyl-3-methylimidazolium bromide was carried out under conventional heating at 140 °C for 2 h, and 1b was isolated in 74% yield. In addition, the same reaction at room temperature required prolonged stirring (18 h) to give the expected 1b in 81% yield.

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We subsequently extended the developed method to the dehydration of a range of substituted benzyl alcohols (Table 2) to rapidly provide the expected products within 6-12 min. We generally observed that the product yields were higher with substrates having a methoxy substitution on the aromatic ring. The various structurally diverse alcohols underwent smooth dehydration in good to excellent yields. We note that the developed method was also suitable for the efficient dehydration of polycyclic aromatic benzyl alcohols (Table 2, Entries 5-7, 11, and 14) into the corresponding olefins, which are important synthons for the synthesis of various commercial anti-inflammatory agents.^[1d] In addition, the hindered tertiary alcohols (Table 2, Entries 20-21) also underwent clean dehydration under the developed reaction conditions. The efficient and neutral nature of this dehydration protocol further prompted us to extend it to the conversion of acetylated/benzoylated derivatives of benzyl alcohols into their respective alkenes, due to their immense utility in complex, natural-product synthesis. Consequently, acetylated (Table 2, Entries 16-18) and benzoylated (Table 2, Entry 19) derivatives of benzyl alcohols were reacted under similar reaction conditions, and the corresponding (E)-arylalkenes were obtained in good yields (80-85%). Our protocol compares very favourably with conventional protocols for the dehydration of acetylated/benzoylated derivatives of benzyl alcohols into their respective alkenes, which involve strong acids and the prolonged heating of substrates at elevated temperatures.^[17]

In the case of the unsymmetrical dialkyl alcohol (Table 2, Entry 20), a mixture of two alkenes was obtained in a 4:1 ratio, wherein the major product was obtained as per Zaitzev's rule. Similarly, the α , β -unsaturated alcohol (Table 2, Entry 15) was converted into its corresponding butadiene in 74% yield. However, the β -alcohol (Table 2, Entry 22) provided the corresponding alkene in lower yield (22%), while no reaction occurred with the γ -alcohol (Table 2, Entry 24). Thus, the method showed selective dehydration of activated benzyl alcohols over β - and γ alcohols.

The method developed herein allows the dehydration of benzyl alcohols under neutral conditions, which not only augments its compatibility with acid-sensitive functional groups but also minimizes the formation of unwanted side products. Although there is a previous report disclosing the DMSO-mediated^[2a,2b] dehydration of benzylic alcohols under neutral conditions, that methodology was limited by low to moderate yields and difficulty in removing DMSO from the organic products.^[10a]

Mechanistically, the ionic-liquid-promoted dehydration may occur through an initial polarization of the C–O bond of the carbinol by the imidazolium cation of the ionic liquid.^[12] Subsequently, an efficient absorption of microwave radiation by the carbinol-ionic-liquid intermediate could result in the elimination of water to provide the arylalkene (Figure 1).



Figure 1. Proposed mechanism of ionic-liquid-assisted dehydration.

In order to check the recyclability of the ionic liquid, after completion of the reaction, the product **1b** was extracted with ethyl ether, and the remaining ionic liquid was reused as such for subsequent cycles. A 5–6% loss in activity was observed after three cycles. We note that prior lyophilisation of the ionic liquid for 30 min allowed it to be efficiently used for five cycles without any loss of activity.

Conclusions

In conclusion, a mild and efficient protocol for the dehydration of various benzyl alcohols and their acetylated/benzoylated counterparts into the corresponding (*E*)-arylalkenes with a recyclable ionic liquid as a reagent and solvent under microwave irradiation was developed. The method allowed hitherto tedious dehydrations to be performed under mild and neutral conditions without any additional harsh Brønsted/Lewis acids, which not only enhances its compatibility with substrates possessing acid-sensitive functional groups but also augments its eco-friendly nature. The remarkable selectivity of the developed method towards the dehydration of activated benzyl alcohols over β - and γ alcohols provides a convenient chemo-selective tool for intricate, multistep, natural-product synthesis.

Experimental Section

General: All the substrates were either obtained from commercial sources (Merck or Acros) or synthesized from the corresponding benzaldehydes/Grignard reagents^[4g] or by the reduction of the corresponding acetophenones.^[1h] The ionic liquids were obtained either commercially (Merck or Alfa Aesar) or synthesized ([hmim]-Br) according to the reported method.^[97] The purity of the ionic liquids was verified by NMR before use. ¹H (300 MHz) and ¹³C (75.4 MHz) NMR spectra were recorded with a Bruker Avance-300



spectrometer. A CEM Discover[®] focused microwave oven (2450 MHz, 300 W) was used.

General Procedure for the Dehydration of Benzyl Alcohols under Focused Microwave Irradiation. Representative Procedure for the Dehydration of 4-Methoxyphenylpropan-1-ol (1a): A mixture of 4-methoxyphenylpropan-1-ol (1a) (283 mg, 1.7 mmol) and ionic liquid [hmim]Br (1 mL) was irradiated for 7 min in a 100 mL round-bottomed flask in a focused microwave system (150 W, 140 °C) fitted with a reflux condenser. After completion of the reaction, the mixture was cooled and extracted with ethyl ether (3×10 mL), and the ionic liquid was recovered as a residue to be used in the next cycle. The combined organic layers were washed with water, dried and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (60–120 mesh size) with a 1:20 mixture of ethyl acetate and hexane to give 1b (220 mg, 87%) as a colourless liquid, whose spectroscopic data agreed well with the reported values.^[186]

This procedure was used for the dehydration of all the benzyl alcohols (Entries 2a–25a, Table 2) into their corresponding aryl-alkenes, whose spectroscopic data agreed well with the reported values.^[18]

General Procedure for the Dehydration of 4-Methoxyphenylpropan-1-ol (1a) under Conventional Heating: A mixture of 1a (283 mg, 1.7 mmol) and ionic liquid [hmim]Br (1 mL) was heated in a 100 mL round-bottomed flask in an oil bath at 140 °C for 2 h. After the completion of the reaction, the mixture was worked up as described above to give the pure product 1b (187 mg, 74%) as a colourless liquid, whose spectroscopic data agreed well with the reported values.^[18f]

Supporting Information (see also the footnote on the first page of this article): Experimental details, compounds characterization data and NMR spectra of some representatives (*E*)-arylalkenes.

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