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Halodehydroxylation of alcohols to yield benzylic and alkyl halides in ionic liquids

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Abstract

Background: Alcohols are widely used, and sometimes renewable, reagents but the hydroxyl moiety is a relatively poor leaving group under mild conditions. Direct nucleophilic substitution of alcohols is a desirable reaction for synthetic and process chemists.

Results: Synthesis of twelve alkyl and benzyl halides was achieved in [Bmim]PF₆ (Bmim = 1-butyl-3-methylimidazolium) from their parent alcohols using ammonium halides as the halogenating agents. Trends in reactivity based on the alcohol and halide were discovered. Mechanistic evidence suggests that the reaction proceeds via S_N2 substitution of the hydroxyl group, which is activated via hydrogen-bonding with the acidic proton of the imidazolium cation. Also, for benzyl substrates, equilibria involving formation of dibenzyl ether complicate the reactions and reduce optimum yields.

Conclusions: Ammonium halides are useful, solid and relatively safe reagents for the conversion of some primary alcohols to organohalides in ionic liquids (yields up to 81 %). Indanol under the same conditions yields biindenylidene (GC yield 63 %).

Keywords: Halogenation, Ionic liquid, Catalysis, Substitution, Solid acid, Microwave, Dehydration

Background

Alcohols are widely encountered chemicals and are useful intermediates in modern organic synthesis due to their ability to be transformed into a wide range of products. Furthermore, many renewable feedstocks contain hydroxyl moieties. Unfortunately, hydroxyl groups are not favourable leaving groups under mild conditions. This usually means, for nucleophilic substitution reactions, that the alcohol must be activated and subsequently displaced in order to produce the desired product. This sort of procedure violates the principles of green chemistry as the activation step can be considered unnecessary derivatization. Therefore, direct nucleophilic substitution of alcohols is desired and is one of the key green chemistry research areas previously identified by pharmaceutical manufacturers [1]. Catalytic methods for these reactions remain relatively underexplored and were the focus of a recent review [2].

In particular, halogenation of alcohols is a useful reaction as alcohol-starting materials are cheap and large varieties are commercially available. Many procedures are known that convert alcohols to halides however, they can involve harsh conditions and hazardous chemicals. For example, the chlorination of alcohols is traditionally performed using HCl gas or thionyl chloride, both of which are hazardous to human health and often produce many side reactions. Although improvements have been made upon these halogenation reactions, further green methodology is desired. On a laboratory scale, ammonium halide salts (NH₄X) are solid reagents, which means they are easy to handle and measure.

Discovering a mild, neutral, highly selective and environmentally friendly system for catalytic dehydroxy-halogenation is desirable but it is not a trivial task. Compromises in the journey towards an ideal sustainable process have to be made. This is exhibited by some of the trends found in the literature regarding chlorination of alcohols. Some reports involve the use of triphenylphosphine (PPh₃) as a superstoichiometric additive in dehydroxychlorination reactions [3, 4]. Although these

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systems use mild conditions (often performed at room temperature with neutral chlorinating agents), exhibit high selectivity, and possess a large and diverse substrate scope, a large amount of PPh_3 oxide is formed in the reaction, which causes purification to be troublesome. An interesting reagent that has been researched in dehydroxychlorination reactions is 2,4,6-trichloro-1,3,5-triazine (TCT), which is generally considered non-toxic. Systems involving this reagent, in combination with either DMSO or DMF, give very good yields in short reaction times with no heating required [5, 6]. A drawback with these systems is that only two chlorine atoms of TCT are used in the reaction, and therefore atom efficiency is compromised. Another type of chlorination system involves the use of silicon-based chlorinating agents in the presence of Group 13 chlorides (e.g. InCl_3) as catalysts [7, 8].

Recently reported methodologies concerning bromination and iodination of alcohols are similar in substance to the reports of chlorination processes; some are truly 'green' systems whereas others would not be suitable for scale-up [9–12]. One particular system produces alkyl iodides starting from the corresponding ketone with the use of a ruthenium-based catalyst that is active towards both reduction and halogenation [11]. This system appears to be extremely useful as it can be used for a number of substrates and uses a mild iodinating agent, NaI . However, while crucial to organic synthesis, precious metal catalysis is often not economically feasible on a large scale.

Solvents are required in most organic synthetic processes to produce homogeneous mixtures, provide a means for energy and mass transfer, stabilize transition states, and/or provide a means for separation and purification of products [12]. In the substitution reactions described above, dipolar aprotic solvents (e.g. DMF, DMSO) are often required to dissolve ionic reagents and stabilize intermediates. Ionic liquids are one class of alternative reaction media, which are suitable replacements for such solvents [13]. The field of catalytic reactions performed in ionic liquids has been reviewed extensively and the sheer volume of transformations performed with ionic liquids is outstanding [14–16]. In surveying these reactions, an interesting observation is warranted. Depending on its properties, an ionic liquid can be used as an 'innocent' solvent, a ligand precursor, a co-catalyst, or even the catalyst itself. Ionic liquids have been used as "reagent-solvents" in bromination and iodination of alcohols, where the active nucleophile originates as the anion of the ionic liquid [17–19]. These systems have commonly been used with long-chain alcohols [19], which have previously been problematic to halogenate due to their poor solubility in most solvents. The greenness of these systems is enhanced as the ionic liquid

can be regenerated and reused a number of times simply by stirring, with a NaX salt ($\text{X} = \text{Br}, \text{I}$), at an elevated temperature over a short period of time [19]. This allows a number of reactions to be performed in the same solvent, which is generally unheard of in reactions involving traditional organic solvents.

The research presented in the current article arose from earlier findings in our group [20]. Upon investigating microwave-assisted catalytic dehydrative etherification of benzyl alcohols in ionic liquids, attempts were made to observe the affect of pH on the reaction. Upon addition of a stoichiometric amount of NH_4Cl to reactions containing benzyl alcohol as the substrate, the major product obtained was benzyl chloride. As this reaction was peripheral to the original study, no further investigation was performed at that time regarding the conditions and scope of this reaction. As mentioned above, the halogenation of alcohols under relatively mild conditions is an important synthetic transformation and the development of greener methods of performing these reactions is desired. Therefore, it was deemed worthwhile to perform further studies of this halogenation process. The goals of this study commence with the optimization of the chlorination process described above. Attempts were made to observe the affects of different ionic liquids, reaction time and temperature on the chlorination process. Using the optimized conditions as a starting point, reactions were performed on benzyl alcohol using different ammonium salts (NH_4F , NH_4Br and NH_4I) to observe if halogenation could be performed using these reagents. A summary of optimization parameters is shown in Fig. 1.

Results and discussion

Further to our initially reported study [20], we discovered that palladium was not an essential component in the catalytic system for chlorinating benzyl alcohol. Therefore, a number of reaction variables (time, temperature and nature of the ionic liquid) were optimized for the non-metal catalyzed reaction of benzyl alcohol with NH_4Cl to yield benzyl chloride. Reaction conditions (MW time and temperature) were optimized for the conversion of benzyl alcohol to benzyl chloride in $[\text{Bmim}]\text{PF}_6$ (Figs. 2, 3). At 150°C , after the optimum reaction time of 17 min, an NMR yield of 68 % was obtained. There is a distinct

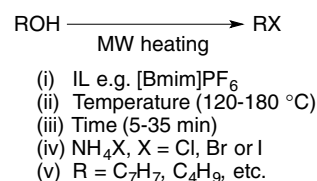


Fig. 1 Parameters to be considered in optimizing catalytic halodehydroxylation of alcohols in ionic liquids

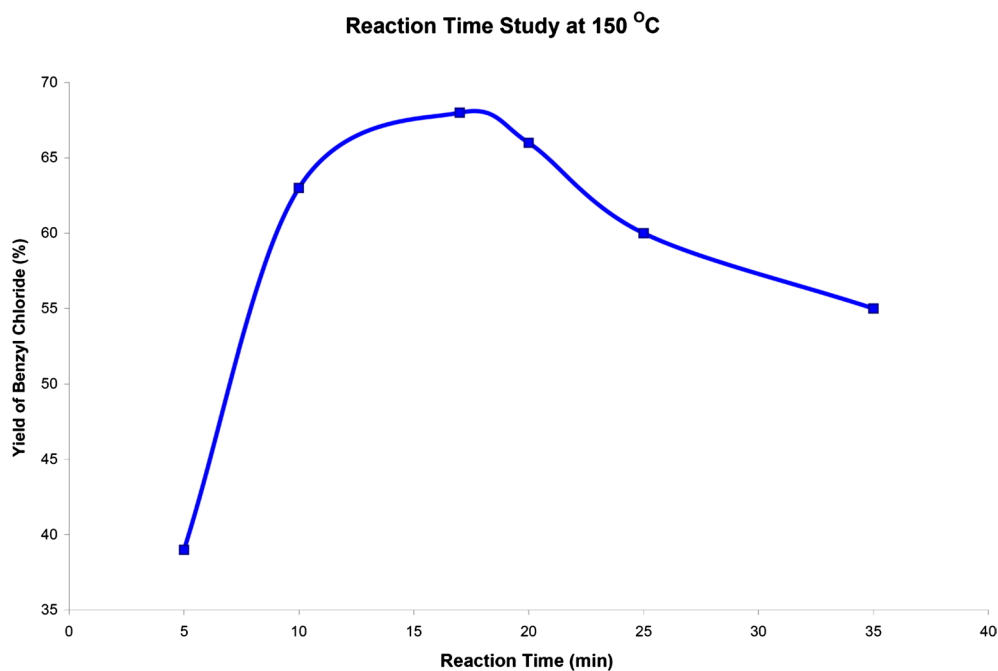


Fig. 2 Reaction time study of the imidazolium catalyzed transformation of benzyl alcohol to benzyl chloride. ([Bmim]PF₆, 150 °C, 17 min, 68 %)

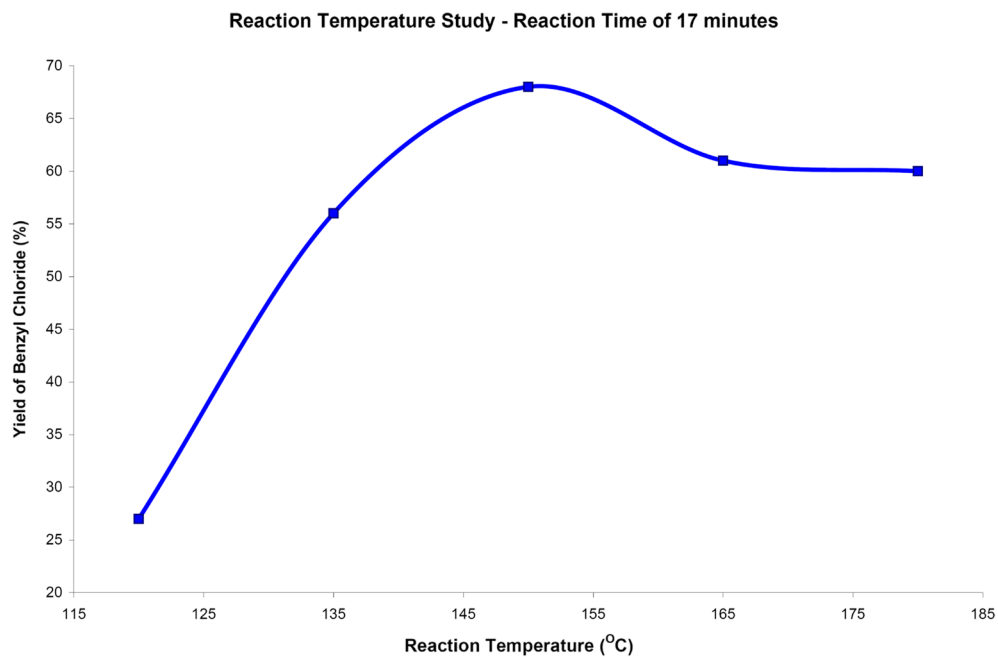


Fig. 3 Reaction temperature study of the imidazolium catalyzed transformation of benzyl alcohol to benzyl chloride. ([Bmim]PF₆, 150 °C, 17 min, 68 %)

rise to a maximum yield followed by a decrease in yield with longer reaction times. Similar decreases in yield are observed when reactions are performed at higher

temperatures. The decrease in yields is a result of by-product formation such as dibenzylether [20]. Products and unreacted starting materials could be isolated from

the reaction mixture via vacuum distillation, using apparatus described elsewhere [21]. Purified products could then be isolated via flash chromatography or fractional reduced pressure distillation. Isolated yields (when determined) were not significantly different to those obtained via GC or NMR analyses.

The effect the ionic liquid had on this reaction was investigated while all other variables were kept constant (Table 1). [Bmim]PF₆ was the most suitable solvent for this reaction. The reaction does not occur in hydrophilic ionic liquids, e.g. [Bmim]BF₄, nor the conventional hydrophilic solvent DMF. This is not unexpected because dehydration reactions can be enhanced in hydrophobic reaction media. The reaction was also performed in two other hydrophobic ionic liquids: [P₆₆₆₁₄]DBS and [BMmim]PF₆. This shows that the hydrophobicity of the solvent is not the only requirement and that the cation plays a critical role in the reaction outcome. An interesting inference can be made by comparing the results for [Bmim]PF₆ and [BMmim]PF₆ (68 % for [Bmim]PF₆, 18 % for [BMmim]PF₆). The only difference between these two ionic liquids is the identity of the substituent on the carbon between the nitrogens of the cation (Fig. 4): [Bmim]PF₆ contains an acidic proton

whereas [BMmim]PF₆ bears a methyl group at this position. This observation leads to a hypothesis that the acidic proton of [Bmim]PF₆ is playing a significant role in the production of benzyl chloride. Another interesting conclusion that can be drawn via comparison of the results for [Bmim]PF₆ and [BMmim]PF₆ is that HF, potentially produced via hydrolytic decomposition of the PF₆[−] anion, is not playing a major role in the production of benzyl chloride. Since the hydrolytic instability of PF₆[−] should be independent of the nature of the imidazolium cation. If HF was the active catalyst, it would be expected that both [Bmim]PF₆ and [BMmim]PF₆ would give very similar results in the chlorination of benzyl chloride. Based on the nature of the imidazolium systems, it was hypothesized that either one of two species was acting as the catalyst: an acidic species or a N-heterocyclic carbene (NHC) generated from the deprotonation of [Bmim]PF₆ (Fig. 5). It was predicted that if the catalyst was acidic, addition of base would hinder the reaction whereas if the catalyst was an NHC, addition of base would improve the yield. Therefore, a reaction was performed where the optimized reaction conditions were used and KOH (potassium hydroxide) was added. It was found that under these conditions, no benzyl chloride was produced, suggesting that the active catalyst is an acidic species.

Table 1 Reaction screening: effect of reaction medium, halogenating agent and alcohol on dehydroxyhalogenation reactions

Alcohol	Solvent	Halide	Yield (%)
BnOH	[Bmim]PF ₆	Cl	68 (65)
BnOH	[BMmim]PF ₆	Cl	18
BnOH	[Bmim]BF ₄	Cl	0
BnOH	[Bmim]Cl	Cl	0
BnOH	[P ₆₆₆₁₄]DBS	Cl	5
BnOH	DMF	Cl	0
BnOH	[Bmim]PF ₆	Br	50
BnOH	[Bmim]PF ₆	I	72
<i>p</i> -Cl-BnOH	[Bmim]PF ₆	Cl	81 (77)
<i>p</i> -Br-BnOH	[Bmim]PF ₆	Cl	65
<i>p</i> -NO ₂ -BnOH	[Bmim]PF ₆	Cl	58
<i>p</i> -CH ₃ -BnOH	[Bmim]PF ₆	Cl	46 ^a
<i>p</i> -OH-BnOH	[Bmim]PF ₆	Cl	0
<i>p</i> -CH ₃ O-BnOH	[Bmim]PF ₆	Cl	0
<i>n</i> -BuOH	[Bmim]PF ₆	F	0
<i>n</i> -BuOH	[Bmim]PF ₆	Cl	51 (51)
<i>n</i> -BuOH	[Bmim]PF ₆	Br	65 (62)
<i>n</i> -BuOH	[Bmim]PF ₆	I	82
citronellol	[Bmim]PF ₆	Cl	50

Conditions (unless otherwise stated): MW, 150 °C, 15 min. Yield reported obtained via NMR analyses. Value in parentheses is isolated yield

^a T = 125 °C

Mechanistic and equilibrium considerations

In this particular system, there are three acidic species that could be proposed as catalysts in this reaction: NH₄⁺, HF and the acidic proton of [Bmim]PF₆. As [Bmim]Cl could also be used as the chlorinating reagent, one can conclude that NH₄⁺ is not the major catalyst as the reaction proceeds even when NH₄⁺ is not present. Also, we have already hypothesized that HF is not the catalytic species, as significantly different results were obtained when [Bmim]PF₆ and [BMmim]PF₆ were used, which should produce the same amount of HF if anion decomposition was occurring. Therefore, we propose that the major catalytic species in the presented reaction system is the acidic proton of [Bmim]PF₆. The involvement of this proton is supported by the large decrease in yield (from 68 to 18 %) when [BMmim]PF₆, which does not contain this acidic proton, is used as the solvent instead of [Bmim]PF₆ in the chlorination of benzyl alcohol. The proposal that this acidic proton is involved is based on precedent seen in the literature. Despite having a relatively high pK_a of 21–24 [22], this proton has been observed to participate in a number of interactions. In one particular case, where Michael addition reactions were studied, results obtained suggested that the acidic

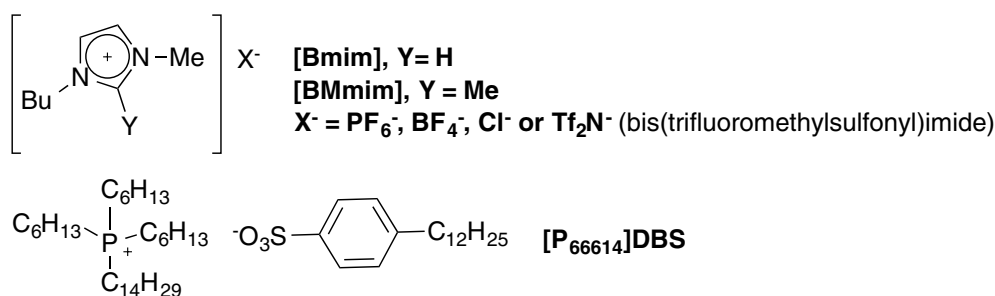


Fig. 4 Ionic liquids screened for suitability in the conversion of benzyl alcohol to benzyl chloride

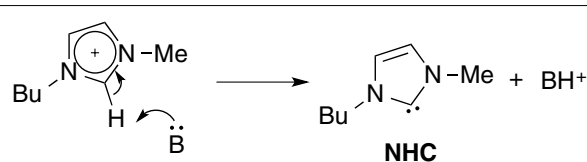


Fig. 5 Formation of NHC from [Bmim]⁺ in the presence of base (B)

proton of [Bmim]PF₆ formed a hydrogen bond with a basic catalyst, resulting in a decrease of activity [23].

In nucleophilic substitution reactions, there are two general mechanisms: S_N1 and S_N2. For S_N1 reactions, the leaving group (in this case -OH) is ejected, forming a carbocation intermediate, which is attacked by the nucleophile. In general, S_N1 reactions are favored by good leaving groups and highly branched systems that can form a stable carbocation intermediate (e.g. 3° alkyl reagents). For S_N2 reactions, an incoming nucleophile attacks from the backside of the substrate and ejects the leaving group. S_N2 reactions are favored by good nucleophiles and unhindered C-X bonds such as primary alcohols. In order to determine whether an S_N1 or S_N2 process dominates, competition studies were performed. Reaction of one equiv. NH₄Cl with one equiv. of both benzyl alcohol and 1-phenyl ethanol was performed. This afforded benzyl chloride in yields identical to those performed in the absence of 1-phenyl ethanol. Under the reaction conditions explored, there was no evidence of 1-phenyl ethanol reacting. This lack of reactivity suggests that the reaction does not proceed in an S_N1 fashion, as the more stable carbocation should afford higher yields of 1-phenyl-chloroethane than benzyl chloride.

The proposed mechanism for the conversion of benzyl alcohol to benzyl chloride for the reaction system used in this study is presented in Fig. 6. As described in the background section, hydroxyl moieties are very poor leaving groups and usually require activation of some sort in order to be displaced by a nucleophile. This is usually done by protonating the oxygen of the hydroxyl group

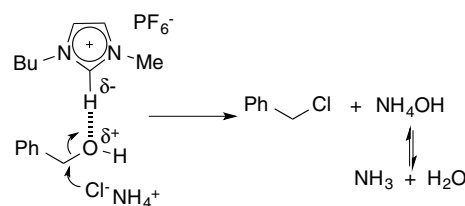


Fig. 6 Schematic representation of alcohol activation via hydrogen-bonding with an imidazolium cation

with acid, producing an excellent leaving group. In the proposed mechanism (Fig. 6), we suggest that the activation of the alcohol occurs through hydrogen-bonding of the acidic proton of the imidazolium cation with the oxygen of the alcohol, causing the alcohol to bear a slight positive charge. This causes the alcohol to be activated and subsequently displaced by the chloride nucleophile in a S_N2 fashion.

The examination of this proposed mechanism allows for rationalization of some of the previously described results. For the reaction performed in the phosphonium based ionic liquid, [P₆₆₆₁₄]DBS, a very low yield of product was observed. Since this ionic liquid does not contain an acidic site similar to [Bmim]PF₆, without this acidic site, activation of the alcohol could not be achieved, leading to very poor conversions.

In our previous studies involving dehydration reactions of benzyl alcohols [20, 21], equilibria between the alcohol and product were observed. In the studies herein varying quantities of dibenzyl ether co-product were noted. This led to problems in obtaining better yields of benzyl chloride with longer reaction times. To investigate the role of dibenzyl ether in these halogenation processes, a reaction was attempted, using the optimized conditions (17 min, 150 °C, [Bmim]PF₆) where dibenzyl ether and a molar equivalent of water was reacted in the presence of NH₄Cl instead of benzyl alcohol (Fig. 7). From this reaction, it was found that after the reaction,

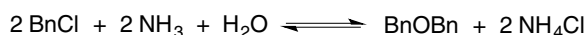


Fig. 7 Observed equilibrium between benzyl chloride and dibenzyl ether in the presence of water and ammonium chloride

both benzyl chloride and dibenzyl ether were present. This result indicates that an equilibrium does indeed exist between the two compounds, and explains the observed time dependence on the yield of benzyl chloride. As the reaction proceeds and water is produced, the yield of benzyl chloride decreases as the yield of dibenzyl ether increases.

Since benzyl chloride is the desired product in the reactions that have been presented thus far, it would be desirable to control the selectivity of these reactions and improve the yield of benzyl chloride. In the dehydration reaction of benzyl alcohol to produce dibenzyl ether, water is produced as a by-product. However, based on the mechanism proposed in Fig. 6 for the formation of benzyl chloride from benzyl alcohol, hydroxide is formally produced as a by-product. While the majority of the hydroxide produced may undergo rapid proton transfer with NH_4^+ to produce H_2O , the highly ionic nature of the solvent may allow a substantial amount of the hydroxide to exist as a charged species in solution. Based on this argument, we hypothesized that the presence of a small amount of water added to the reaction mixture would hinder the production of dibenzyl ether more than it would suppress the production of benzyl chloride. In order to investigate this prediction, the best yielding reaction presented above (68 % yield of benzyl chloride) was attempted in the presence of a half molar equivalent of water with respect to benzyl alcohol to see what effect this had on the yield. It was found that this reaction yielded 75 % benzyl chloride, improving the yield slightly from what was previously observed. This result is in agreement with the rationale presented above. However, the amount of water added needs to be carefully controlled. When three molar equivalents of H_2O are added, only a 39 % yield of benzyl chloride was obtained. Nevertheless, these findings show that dehydroxylation reactions need to be explored carefully in terms of the water content of the reaction medium and methods for removing water to enhance yields.

In summary, it has been discovered that an equilibrium exists between benzyl chloride and dibenzyl ether in the reactions that have been studied and that some control over this equilibrium can be acquired with the addition of a small amount of water to the reaction mixture. However, in order to improve the yield of benzyl chloride, it is necessary to gain further control of the production of dibenzyl ether, either through an additive or catalytic species.

Extension of this reaction to bromide, iodide and other alcohols

Using the optimized reaction conditions for the conversion of benzyl alcohol to benzyl chloride, attempts were made to halogenate benzyl alcohol with NH_4Br and NH_4I . The results for these reactions are summarized in Table 1. The yield of benzyl iodide is quite similar to the yield of benzyl chloride under the same conditions (72 versus 68 %), but the yield of benzyl bromide (50 %) is significantly lower. Based on the proposed mechanism, it would be expected that the best nucleophile, iodide, would give the best yield followed by bromide and chloride. Since dibenzyl ether was also observed as a product in the reactions involving NH_4Br and NH_4I , it is expected that similar equilibria exist in these halogenation reactions, as was the case for the chlorination reaction. Therefore, these yields are not completely comparable as the time and temperature dependence of the bromination and iodination reactions have not been fully investigated. Fluorination of benzyl alcohol was attempted with NH_4F using a number of reaction conditions (80–180 °C, 15–40 min). For all of these reactions, it was not possible to identify any fluorinated product, although all of the starting material had reacted, in most cases. This result is not surprising based on the properties of the fluoride anion, which is a poor nucleophile but extremely basic and rarely reacts neatly in nucleophilic displacement reactions.

Using the optimized conditions for the chlorination of benzyl alcohol, attempts were made to halogenate a variety of other alcohols. These included substituted benzyl alcohols, both functionalized and non-functionalized aliphatic alcohols, and a secondary alcohol. The results of these studies are discussed below.

The first group of alcohols that were studied were *para*-substituted benzyl alcohols, to investigate the effect substituents had on the yield of the chlorination reactions. The results obtained are shown in Table 1. Products were identified via ^1H NMR spectra of known compounds in combination with GC–MS analysis of the reaction mixtures. Isolated yields for some products are also reported. From these results, a number of interesting observations are made. Firstly, it is obvious that the yield of the chlorinated product is very much dependent on the substituent at the *para*-position of the aromatic ring. This is opposite to what was observed in the etherification reactions of benzyl alcohols, using a similar reaction system [20], where it was found that the substituent at the *para*-position had little effect on the yield of the etherification product. For the chlorination reactions, in comparison to when $\text{Y} = \text{H}$, it is seen that when $\text{Y} = \text{Cl}$, the yield of the chlorinated benzyl alcohol is improved whereas when $\text{Y} = \text{Br}$, NO_2 or CH_3 , the yield decreases. These trends

can be rationalized using a number of arguments. When $Y = \text{CH}_3$ and the reaction is attempted at 150°C , a large number of by-products were observed from the GC–MS analysis making calculation of the yield of the chlorinated product difficult. However, by lowering the temperature to 125°C , better control of the reaction was obtained and a 46 % yield of 4-methylbenzyl chloride could be determined. This suggests that at higher temperatures the chlorinated product is generated but reacts further to give the observed side-products (incl. aryl-substituted methanes). This can be rationalized by considering that with an electron-donating group in the *para*-position, such as CH_3 , the benzylic carbocation that could be generated in the reaction mixture would react to give high mass by-products (e.g. di(*p*-tolyl)methane). For $Y = \text{Br}$ and Cl , one would expect similar yields. This is not the case as when $Y = \text{Br}$, the yield obtained was 65 % whereas when $Y = \text{Cl}$ the yield was 81 %. In the case when $Y = \text{Br}$ or Cl , the corresponding etherification product is also obtained in a significant amount. As was explored to a certain extent above (Fig. 7), an equilibrium exists between the chlorinated product and the etherification product that is highly dependent upon reaction time. It is predicted that this equilibrium is also dependent upon electronic properties of the aromatic ring system, which is based upon the nature of the substituents. Therefore, it is possible that for $Y = \text{Br}$ and Cl , the reaction conditions used did not optimize the yield of the chlorinated product. For the reaction involving 4-nitrobenzyl alcohol ($Y = \text{NO}_2$), a number of interesting observations were made. From the GC–MS analysis, it is shown that the only product obtained was 4-nitrobenzyl chloride, along with unreacted starting material. This was the only benzyl alcohol substrate that did not produce any ether by-product, which is consistent with the results obtained previously [20]. These observations suggest that the nitro group extensively modulates the reactivity of the alcohol and may give rise to some information regarding the mechanism of the etherification reactions. In comparison to the reaction of benzyl alcohol under identical conditions, it is observed that the nitro-substituted benzyl alcohol produces a slightly lower yield of the desired product (58 versus 68 %). This result is not surprising and can be rationalized using the finer details of the proposed

mechanism of these reactions (Fig. 6). In this mechanism, a slight positive charge is generated, suggesting that a build-up of positive charge in the transition state will also be observed. In the presence of an electron-withdrawing group, such as NO_2 , this positively charged species would be destabilized, increasing the energy of the transition state and slowing the transformation of the alcohol to the chloride. No yield of chlorinated product was obtained for $Y = \text{OH}$ and OCH_3 . Upon attempting to analyze the products of these reactions, it was found that the reaction mixtures were uncharacteristically viscous and a product had formed that did not dissolve in organic solvents (ether, acetone and hydrocarbons). These observations suggested that some sort of polymeric product formed in these reactions, as proposed in Fig. 8. This also implies that the methoxy group of 4-methoxybenzyl alcohol undergoes hydrolysis under these reaction conditions, producing the phenoxide which could further react in a similar way as 4-hydroxybenzyl alcohol to give a polymeric product. These results show that unfortunately this method is not applicable to all types of benzylic alcohols.

In order to investigate substrate scope, chlorination was attempted using 2-phenylethanol as the substrate. Using the optimum reaction conditions for chlorination of benzyl alcohol, 2-phenylethyl chloride was obtained in 60 % yield. From the GC–MS analysis, it was observed that only a very small amount of the etherification product was obtained and that no other by-products were produced. This result suggests that benzyl alcohols are much more reactive in this system, leading to unwanted side-products. Interestingly, the chlorination of this substrate was studied with an indium-catalysed system that used chlorodimethylsilane as the chlorinating agent, and although this system was successful in chlorinating a wide range of alcohols, no yield was obtained for this particular substrate [8]. This result was rationalized with the prediction that a carbocation intermediate was being formed and since 2-phenylethanol is a primary alcohol, a primary carbocation would have to be formed, which is unflavored [8]. The fact that the system presented herein is effective in the transformation of a primary alcohol to a primary chloride further supports the $\text{S}_{\text{N}}2$ -like mechanism described above.

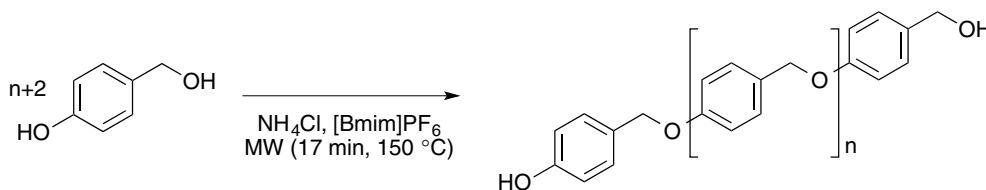


Fig. 8 Postulated reaction from attempted chlorination of 4-hydroxybenzyl alcohol

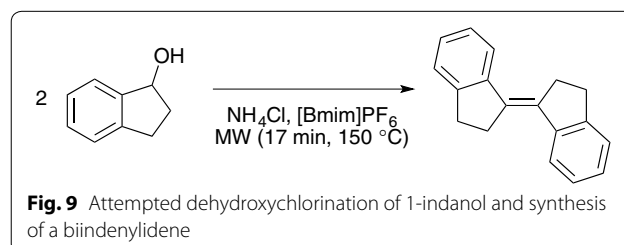
With the discovery that this chlorination system was effective in the chlorination of 2-phenylethanol, investigations were performed to see if this system could be expanded to simple aliphatic alcohols. Since it is known that the [Bmim]⁺ cation interacts favorably with aromatic systems [24], the halogenation of 1-butanol (Table 1) was investigated to see if the presence of the aromatic ring was required for the halogenation to occur. The yield of the butyl halide increases with increasing nucleophilicity of the anion reacted (best yield obtained with NH₄I). This is the trend expected when studying substitution reactions that follow S_N2 mechanisms. This mechanism is also supported by the observation that no 2-butyl halides or rearrangement products were obtained based on analysis of the ¹H NMR spectra for the reactions involving 1-butanol. One would expect that if a S_N1 mechanism existed in these reactions, rearrangement products would be observed, as is the case with the indium-catalysed system [8]. As well, it should be noted that no ether by-products were observed in these reactions, suggesting that etherification under these reaction conditions is limited primarily to compounds containing aromatic groups. Given the selectivity of these reactions, ionic liquid recycling studies were performed for the n-butanol to 1-chlorobutane process. The reaction was performed (150 °C, 17 min) and after completion, the product could be isolated via distillation. The diluted ionic liquid phase containing some unreacted alcohol was dried over anhydrous sodium sulfate, decanted, concentrated and then successfully re-used for the same reaction four times. Yields obtained were 50–57 % (based on the amount of alcohol added before each reaction).

Although it was observed that halogenation could be performed on aliphatic alcohols, the effect of functional groups on the halogenation process had not yet been determined. For this study, the renewable alcohol citronellol was chosen (Table 1) as it contains a double bond that could be reactive under the acidic conditions contained in this chlorination system. As before, the optimized conditions obtained from the study of benzyl alcohol were used. From the GC–MS analysis of this reaction, it was found that the desired chlorinated product was obtained as the major product. A number of other by-products were obtained in small amounts such as the terminal alkene generated from an elimination reaction involving either the hydroxyl of the starting material or the generated chloride. This suggests that for the most part, the double bond functionality of citronellol is insensitive to the reaction conditions and similar compounds could be halogenated. However, if more acid-sensitive functional groups were present in the starting material, such as terminal alkenes or esters, it is predicted

these groups would not be able to withstand the conditions of this halogenation system.

Based on the S_N2-like mechanism proposed, it would be expected that the halogenation of secondary and tertiary alcohols using this system would be more difficult than benzylic and primary alcohols due to steric hindrance. This hypothesis was investigated by analyzing the reaction of 1-indanol (Fig. 9), a secondary alcohol, under the optimum conditions for halogenation of benzyl alcohol. Analysis of the reaction by ¹H NMR and GC–MS led to a very interesting discovery. From the GC trace, only one major product was observed. The mass spectrum of this compound shows that the molecular ion has *m/z* 232.2, which corresponds to the alkene-bound dimer shown in Fig. 9. This type of product had not been seen in any of the other previous halogenation reactions performed and is highly unusual. The product was isolated (63 % yield) via flash chromatography and characterized via NMR spectroscopy, and high resolution mass spectrometry, which confirmed the identity of the product as spectra were in agreement with literature data [25]. Further investigation of this reaction would be worthwhile to see if it could be expanded for use with other secondary alcohols. If expansion were possible, this system could pose as an alternative to the McMurry reaction.

Overall, it has been shown that NH₄X (X = Cl, Br, I) in [Bmim]PF₆ under microwave irradiation can be used to halogenate a number of alcohols. Fluorination was not possible under the conditions explored. With respect to *para*-substituted benzyl alcohols, the halogenation process is highly dependent upon the nature of the substituent. For aliphatic alcohols, the results obtained support a S_N2 mechanism, as the yield is directly correlated to the nucleophilicity of the anion used and no rearrangement products are observed. It has also been shown that it is possible to chlorinate unsaturated aliphatic alcohols. However, it is predicted that this system would not be suitable to halogenate alcohols containing acid-sensitive functional groups. For 1-indanol, a secondary alcohol, an unusual coupled product was obtained upon attempting chlorination. Therefore, further investigation into the reactivity of secondary and tertiary alcohols in this reaction system may be warranted.



Experimental

Chemicals and instrumentation

[Bmim]Cl, [Bmim]Br, [Bmim]Tf₂N, [Bmim]BF₄ and [Bmim]PF₆ were prepared according to literature procedures [26–28]. [BMmim]PF₆ (BMmim, 1-butyl-2,3-dimethylimidazolium) was purchased from Alfa Aesar, while [P₆₆₆₁₄]DBS was received as a gift from Cytec Inc. Benzyl alcohol was distilled under vacuum and stored under a blanket of nitrogen in contact with 4 Å activated molecular sieves. Butanol was distilled from sodium hydroxide (NaOH) and stored, with 4 Å molecular sieves, under nitrogen. All other reagents were purchased from either Alfa Aesar or Sigma Aldrich and used without further purification.

A Biotage microwave reactor was used to run the experiments under microwave (MW) irradiation. The ‘very high’ absorption level setting was used each time to ensure controlled heating of the reaction. ¹H NMR spectra were acquired on a Bruker AVANCE 500 MHz spectrometer with TMS as the internal standard. GC–MS spectra were recorded on an Agilent 7890A GC system coupled with an Agilent 5975C MS detector that was equipped with a capillary column DB-5 (column length: 30.0 m and column diameter: 0.25 mm). All ¹H NMR experiments were performed with acetone-*d*₆ as the solvent, except when [P₆₆₆₁₄]DBS was used, in which case the ¹H NMR experiments were performed in chloroform-*d*. In all cases, samples were injected into the GC–MS instrument with use of diethyl ether as the solvent. All yields were determined by ¹H NMR with use of acetophenone as the internal standard and reported in reference to the limiting reagent. Products could be isolated via vacuum distillation or flash chromatography.

General procedure for dehydroxyhalogenation reactions

Ammonium salt (1.10 mmol), alcohol (1.10 mmol), and ionic liquid (0.50 g) were placed in a 2 mL microwave vial equipped with a stir-bar. The vial was sealed under nitrogen and the reaction mixture was stirred at room temperature for 15 min to ensure homogeneity. The reaction was then subjected to microwave irradiation for a set period of time at a pre-selected temperature, both of which are noted in the results section above. Upon cooling, a sample of known mass was taken from the reaction mixture, added to a known amount of acetophenone (internal standard) and dissolved in acetone-*d*₆ to be analyzed by ¹H NMR. For analysis by GC–MS, a 0.1 g sample of the reaction mixture was extracted with 2.5 mL of dry diethyl ether. For product isolation, the ionic liquid was extracted with 3 × 5 mL diethyl ether. The combined extracts were concentrated and flash chromatography was performed using a

Biotage Isolera system to separate any unreacted alcohol and ether by-products from the desired halogenated product.

Ionic liquid recycling was performed as follows. Ammonium chloride (4.40 mmol), *n*-butanol (4.40 mmol), and [Bmim]PF₆ (2.00 g) were placed in a microwave vial. The mixture was microwave-heated to 150 °C for 17 min whilst stirring. Upon cooling, the vial was transferred to a distillation apparatus and the chlorobutane isolated [21]. The ionic liquid phase was then treated as follows prior to re-use. The contents of the microwave vial were dissolved in anhydrous acetone (10 mL) and dried over anhydrous sodium sulfate. The mixture was decanted and the acetone removed under vacuum. The resulting ionic liquid was then re-used. Yields of chlorobutane were 51, 57, 56, 54, and 52 % (based on the amount of alcohol added before each reaction).

Conclusions

Further investigation of catalytic chlorodehydroxylation of benzyl alcohol in ionic liquids led to a number of interesting observations. Firstly, although it was initially thought that this transformation was palladium-catalysed [20], it has been proven that this transformation is acid-catalysed and that the presence of palladium has a negative effect on the yield of the desired product. As well, when benzyl alcohols, with the exception of 4-nitrobenzyl alcohol, are employed in this reaction system, an equilibrium exists between the chlorinated product and the corresponding ether that is highly dependent upon reaction temperature, time and substituent. Furthermore, based on experimentally obtained data, it appears that the dehydroxyhalogenation reaction proceeds through a S_N2 mechanism and that the acidic proton of [Bmim]PF₆ plays a crucial role in this process. It has also been shown that this reaction system can be expanded for use with other ammonium halide salts, with the exception of NH₄F, and both functionalized and non-functionalized primary alcohols. However, when 1-indanol, a secondary alcohol, was used, no chlorinated product was observed and an interesting biindenylidene product was formed in moderate yields. It is known that biindenylidenes have interesting photochromic properties [1, 29–31]. Overall, NH₄X (X = Cl, Br, I) in [Bmim]PF₆ under microwave irradiation is a safe, green method of transforming several alcohols into the corresponding halides.

Abbreviations

[Bmim]: 1-butyl-3-methylimidazolium; [BMmim]: 1-butyl-2,3-dimethylimidazolium; [P₆₆₆₁₄]: trihexyl-tetradecylphosphonium; DBS: dodecylbenzenesulfonate; PPh₃: triphenylphosphine; TCT: 2,4,6-trichloro-1,3,5-triazine; DMF: *N,N*′-dimethylformamide; DMSO: dimethylsulfoxide; GC–MS: gas chromatography-mass spectrometry; OAc: acetate; TMS: tetramethylsilane; MW: microwave.

Authors' contributions

CP performed the majority (80 %) of reactions and analyses with the remaining portion performed by HK (20 %). FK conceived of the study, and participated in its design and coordination and wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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