Assessment of the suitability of imidazolium ionic liquids as reaction medium for base-catalysed reactions
Case of Knoevenagel and Claisen–Schmidt reactions

Pilar Formentín, Hermenegildo García*, Antonio Leyva

Instituto de Tecnología Química UPV-CSIC, Av. Los Naranjos s/n 46022, Valencia, Spain

Abstract

For the Knoevenagel condensation of benzaldehyde and malononitrile in 1-butyl-3-methylimidazolium hexafluorophosphate [(bmim)PF$_6$] to which alkali metal hydroxide in ethanol had been previously added, the product is formed with high selectivity and the ionic liquid could be reused for at least five runs without the need of additional base. Low to moderate mass balances were observed in the first runs until the ionic liquid becomes saturated and the mass balances become almost complete. For the Claisen–Schmidt condensation of acetophenone with benzaldehyde, besides the expected conjugated ketone formed with high selectivity, minor amounts of ethyl benzoate are also formed. Reuse of the ionic liquid require additional amounts of base. Acid–base titration shows that most of the base (up to 80%) may disappear by reaction with the ionic liquid in the absence of any reagent. Therefore, addition of extra amounts of base is necessary in order to achieve high substrate conversion in subsequent runs and the reactions become not catalytic. This raises the point that imidazolium ionic liquids are only suitable for a small range of base catalysed reactions, and that imidazolium liquids substituted at the 2-position will be more suited as medium for based-catalysed reactions.
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1. Introduction

The use of ionic liquids as reaction medium is a topic of much current interest in the context of environmentally friendly chemical reactions [1,2]. Most of the reports in this area have focused on Lewis acid or noble metal-catalysed reactions. In comparison, reports dealing with basic catalysis in ionic liquids are considerably more scarce although it is attracting growing interest [3–7]. At the present they are limited to *O*-alkylation of phenols, benzoin condensation and more recently to the Robinson annulation and Knoevenagel condensation. In the latter case, glycine or ethylammonium were used as bases and no data concerning the possibility of ionic liquid reuse was given. In fact, the major advantage of utilising ionic liquids as solvents would be their recycling and this point needs to be demonstrated for each reaction [8–10]. However, the possibility that ionic liquids having an imidazolium structure would not be stable in the presence of bases is also possible in view of the easy formation of imidazolidene carbenes [11,12] This instability against bases could invalidate imidazolium ionic liquids as a general medium to perform base-catalysed reactions. The present work addresses this issue.

Herein, we describe our results in two different hydroxide catalysed reactions, namely the Claisen–Schmidt and Knoevenagel condensation. For the present study, 1-butyl-3-methylimidazolium hexafluorophosphate [(bmim)PF$_6$] was selected as the ionic liquid of choice due their availability and the convenient viscosity at room temperature [2].

2. Experimental

Addition of the base to the [(bmim)PF$_6$] was accomplished by adding alkali metal hydroxide dissolved in the minimum amount of alcohol. The alcohol was used to facilitate the addition and solubilisation of the hydroxide and it was subsequently removed by heating at 50 °C under vacuum. For the amount of base and the volume of [(bmim)PF$_6$] used a clear ionic liquid was obtained after incorporation of the hydroxide.

2.1. Knoevenagel condensation

A solution of 7.2 mg KOH (0.2 mmol) in ethanol (0.2 ml) was added to 0.5 g [(bmim)PF$_6$]. The clear solution was out-gassed at 50 °C under vacuum for 12 h. To this basic solution, 10.6 mg benzaldehyde (0.1 mmol) and 6.6 mg malononitrile (0.1 mmol) were added. The reaction mixture was magnetically stirred at room temperature for 6 h at which time the viscous solution was submitted to continuous liquid–liquid extraction with ethyl ether until no further product recovery was obtained. The organic extracts were then concentrated in vacuum. The reaction mixture was analysed by GC (HP, 5% phenylmethyl silicone, 30 m) and GC-mass spectroscopy (HP 5644A, 5% phenylmethyl silicone, 25 m). After the ethyl ether extraction, the ionic liquid was submitted at 40 °C under reduced pressure for 12 h and a second run was performed under identical reaction conditions but without addition of any base. Five reuses were carried out.

2.2. Claisen–Schmidt condensation

An ethanolic solution (0.2 ml) with 8 mg NaOH (0.2 mmol) was added to 0.5 g [(bmim)PF$_6$]. After treatment of the ionic liquid under vacuum at 50 °C, 10.6 mg benzaldehyde (0.1 mmol) and acetophenone (12 mg, 0.1 mmol) or *ortho*-hydroxy acetophenone (13.6 mg, 0.1 mmol) were added. The reaction mixture was magnetically stirred at 40 °C (acetophenone) or 110 °C (*ortho*-hydroxyacetophenone) for 6 h. After this time, the mixture was exhaustively extracted with ethyl ether. The organic extracts were then concentrated in vacuum and the residue was analysed by GC and GC-mass spectroscopy as before. After ethyl ether extraction and vacuum treatment at 40 °C, the ionic liquid was reused under identical reaction conditions. This cycling of reaction/extraction was repeated with or without addition of extra amounts of NaOH (8 mg) in ethanol (see Tables 2 and 3 for conditions).

2.3. Acid–base titrations

NaOH (8 mg) was dissolved in 0.5 g of [(bmim)PF$_6$] by means of an intermediate ethanolic solution followed by subsequent evacuation at 50 °C under reduced pressure for 6 h, as previously described for the Knoevenagel and Claisen–Schmidt reactions. Then, the ionic liquid was maintained at room temperature or at 110 °C. Aliquots of 100 mg of the ionic liquid were periodically taken added to bidistilled water (5 ml) and the basic emulsion titrated using a 10^{-2} M HCl solution and phenolphthaleine as indicator.

3. Results

The Knoevenagel reaction of benzaldehyde (**1**) with malononitrile (**2**) was carried out in KOH dissolved in [(bmim)PF$_6$] at room temperature. The only product ob-
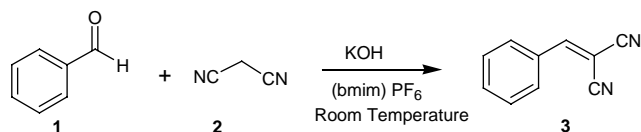
Scheme 1.

served was the corresponding β,β-dicyanostyrene (**3**), that can be recovered by liquid–liquid extraction using ethyl ether (Scheme 1). However, although the disappearance of benzaldehyde and malononitrile was almost complete the yield of the condensation product was low due to unsatisfactory mass balances. The problem of low mass balance is not attributable to a poorly performed extraction procedure since additional extraction did not lead to a significant increase of the mass balance. Furthermore, the mass balance improves remarkably (>70%) when the reaction is carried out under the same conditions but with two-fold the reagent concentration. Nevertheless the low mass balance, a second reuse was carried out. We reasoned that the amount of the reagents and product present in the ionic liquid and not recoverable by extraction will increase up to a moment in which the saturation of reactants and products will be reached. At this point essentially complete mass balance should be obtained. The important issue is to determine at this moment if the reaction is catalytic from the point of view of the base and solvent (no additional amounts of base needed), if the ionic liquid is reusable, and how high is the product selectivity at this stage.

In fact, a second reuse of the ionic liquid with the same quantities of benzaldehyde and malononitrile without addition of extra amounts of base also gives styrene (3) with almost complete selectivity and with mass balance much higher than in the first round. Mass balance after the third reuse becomes almost complete. At this moment the selectivity was also complete. Table 1 contains the results obtained for this reaction. However, after the third reuse a certain depletion of base was taken place since the reagent conversion was not complete. Nevertheless, the process can

Table 1

Results of the Knoevenagel condensation of benzaldehyde (0.1 mmol) with malononitrile (0.1 mmol) in [(bmim)PF$_6$] (0.5 ml), containing KOH (7.2 mg) at room temperature after 6 h reaction time

Run	MB (%)[a]	Conversion (%)[b]
1	29	96
2	74	94
3	92	93
4	97	57
5	98	60

[a] MB is mass balance defined as millimole of **1** or any product derived therefrom divided by initial benzaldehyde millimole in percentage. Dicyanostyrene was the only product observed with almost complete selectivity (>95%).

[b] Conversion indicates millimole initial of benzaldehyde minus millimole of benzaldehyde after 6 h of reaction time divided by the initial benzaldehyde millimole in percentage.

Table 2

Results of the Claisen–Schmidt condensation of acetophenone (0.1 mmol) with benzaldehyde (0.1 mmol) in [(bmim)PF$_6$] (0.5 ml), containing NaOH (8 mg) at 40 °C after 6 h reaction time

Run	MB(%)[a]	Conversion (%)[b]	Selectivity to **5** (%)[c]
1	56	99	75
2	81	26	99
3	>95	3	96
4[d]	95	85	73

[a] MB is mass balance defined as millimole of **1** or any product derived therefrom divided by initial benzaldehyde millimole in percentage. The MB of acetophenone was equal or higher than that of benzaldehyde.

[b] Conversion is initial millimole of benzaldehyde minus millimole of benzaldehyde after 6 h of reaction time divided by the initial benzaldehyde millimole in percentatge.

[c] The formation of ethyl benzoate amounts for the difference on selectivity up to 100%.

[d] After addition of an extra amount of NaOH (8 mg).

be considered catalytic since 0.5 mmol of reagents were converted with 0.13 mmol of base. Our experimental procedure of Knoevenagel reaction in ionic liquid contrasts with a recent report in which an extractable organic base (glycine) instead of hydroxide was used, and where the recycling was not possible [5].

The second base-catalysed reaction that was performed in [(bmim)PF$_6$] was the Claisen–Schmidt condensation of acetophenones with benzaldehyde. Firstly acetophenone (**4**) was reacted at 40 °C with benzaldehyde in the ionic liquid [(bmim)PF$_6$] to which sodium hydroxide dissolved in ethanolic solution was previously added (Scheme 2). Prior to the reaction, the ionic liquid was submitted to vacuum and heating to remove the ethanol excess. This point will become relevant when discussing the origin of by-products and the nature of the base. Besides the expected chalcone (**5**), other product identified as ethyl benzoate (**6**) was also formed. The results are summarised in Table 2. The time conversion plot for the reaction of benzaldehyde and acetophenone is shown in Fig. 1. As can be seen in this plot, chalcone and ethyl benzoate are both primary and stable products under
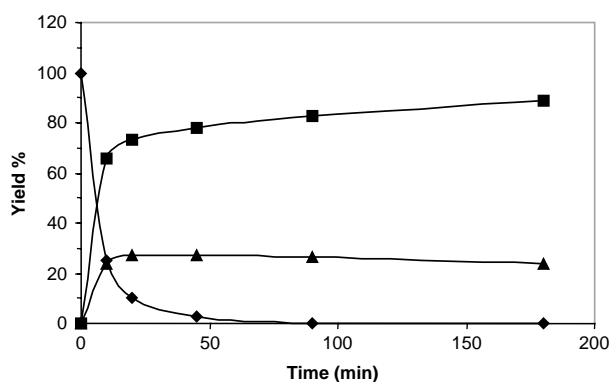

Fig. 1. Time conversion plot for the reaction of acetophenone (0.1 mmol) with benzaldehyde (0.1 mmol) in [(bmim)PF$_6$] (0.5 ml), containing NaOH (8 mg). Plots for compounds **1**, **5** and **6**, have been indicated with (◆) (■) and (▲), respectively.

the conditions studied. Also the mass balances in the first run were moderate and they were higher for acetophenone than for benzaldehyde. This seems to point to the formation of unrecoverable benzaldehyde derived products. The observation of ethyl benzoate as a by-product for benzaldehyde lends support to this rationalisation. To confirm that ethyl benzoate derives from benzaldehyde, a control reaction was carried out in which benzaldehyde in the absence of acetophenone was submitted to NaOH in [(bmim)PF$_6$] under the same reaction procedure. As anticipated formation of ethyl benzoate was observed as the only product. In addition, another control was performed in which oxygen was bubbled through the ionic melt containing benzaldehyde to determine if the aerobic oxidation of benzaldehyde to benzoic acid can take place. Benzaldehyde was recovered without any evidence for the formation of benzoic acid. Oxymetric titrations point that the oxygen solubility in [(bmim)PF$_6$] is very low [13].

In the second reuse, the mass balance was remarkably higher as expected and chalcone selectivity was almost complete. In the third reuse, mass balances were almost complete, but very low conversion was observed. Apparently, the base was completely consumed during the previous reactions. This base consumption does not fit with the simplest reaction mechanism of the Claisen–Schmidt in which only catalytic amounts of base should be required.

There are two possibilities to explain the depletion of sodium hydroxide, either by reaction with the ionic liquid or with benzaldehyde. The fact that N,N'-dialkylimidazolium reacts with bases to form imidazolidene carbenes is well documented in the literature [11,12]. Herein, we proceeded to perform an acid/base titration after addition of NaOH and ethanol evacuation. We measured that 40% of the added hydroxide disappears in the process. Further heating at 110 °C leaves only a residual concentration of 20% of the added base. These titrations clearly indicate that a significant amount of base is consumed by reaction with the ionic liquid, particularly at high temperatures. In addition, the nature of the residual base may not correspond necessarily to OH$^-$, but to other species (see Schemes 3 and 4). Thus, it appears that [(bmim)PF$_6$] can only be considered appropriate medium for those reactions requiring only catalytic amounts of base in which depletion of the base may not be so critical. This happens to be the case of the Knoevenagel condensation.

Furthermore, formation of ethyl benzoate should also consume two equivalents of base according to the mechanism proposed in Scheme 3. The fact that ethyl benzoate was not observed in the Knoevenagel condensation is most probably due to the milder conditions (room temperature versus 40 °C) required for the reaction of malononitrile with benzaldehyde. The possibility that the ethyl benzoate would arise from a Cannizzaro type disproportionation was disregarded based on the failure to detect of benzyl alcohol that should be the concurrent product for this type of disproportionation reaction.
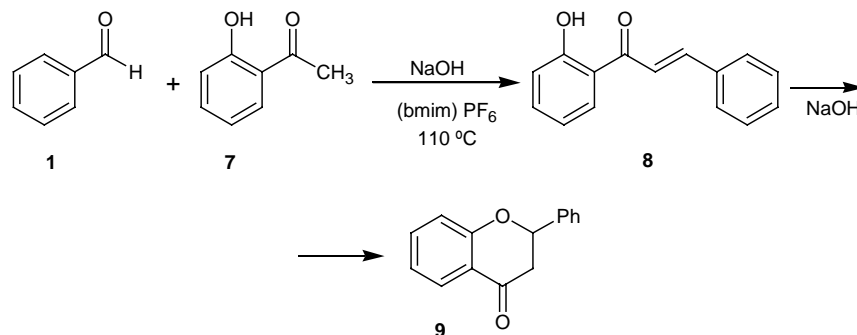
Scheme 2.

Scheme 3.

Scheme 4.
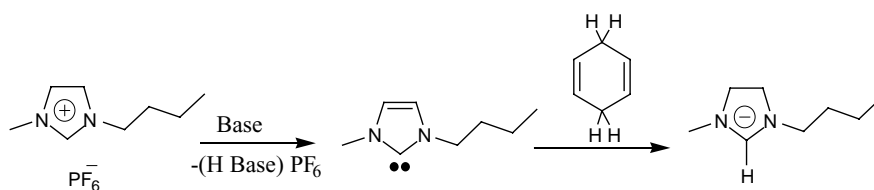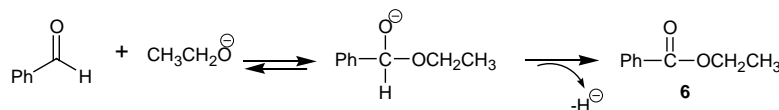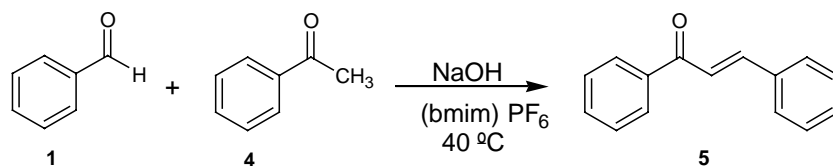
On the other hand, the formation of ethyl benzoate would require the presence of sodium ethoxide. It has to be remarked that before the Claisen–Schmidt condensation, the ionic liquid was submitted to outgassing to remove any remaining neutral ethanol. Then, the ethoxy group of ethyl benzoate cannot come from ethanol but more likely from sodium ethoxide. The actual hydride acceptor (in the second step of Scheme 3 an H$^-$ is lost) would be [(bmim)PF$_6$] or more likely the corresponding imidazolidene carbene derived from bmim by proton abstraction in agreement with the NaOH consumption in [(bmim)PF$_6$].

To provide some experimental support to the mechanistic proposal shown in Scheme 3, comparison of ^{1}H NMR of [(bmim)PF$_6$] in CDCl$_3$ before an after addition of NaOH was made. Fig. 2 shows the corresponding NMR in where the disappearance of the signal at 8.8 ppm characteristic of the H-2 can be clearly observed. This indicates that OH$^-$ is removing H-2, generating the corresponding carbene (Scheme 4). This observation is compatible with the consumption of NaOH determined by acid/base titration and with the acidity of the

hydrogen at the 2-position of imidazolium cations, that is known to undergo deuterium exchange in D$_2$O even at pH = 7 at room temperature [14]. On the other hand, the reaction of imidazolium with *tert*-butoxide is known to give imidazolidene carbenes in quantitative yields [11]. These carbenes can be used as ligands for organometallic complexes such as the Grubbs catalyst [15].

Even more, if when the carbene is generated, 1,4-cyclohexadiene is added then a new signal appears at 8.3 ppm (Fig. 2, spectrum c). This signal is different from the H-2 of the starting [(bmim)PF$_6$] and would indicate that hydride abstraction according to Scheme 4 is taking place. The ability of 1,4 cyclohexadiene as hydride donor is very well documented [16].

The third base catalysed reaction studied in [(bmim)PF$_6$] was the Claisen–Schmidt condensation *ortho*-hydroxyacetophenone (**7**) with benzaldehyde (**1**). In this case, the primary *o*-hydroxychalcone (**8**) can undergo a subsequent cyclisation to form the corresponding flavanone (**9**) (Scheme 5). For this Claisen–Schmidt condensation of
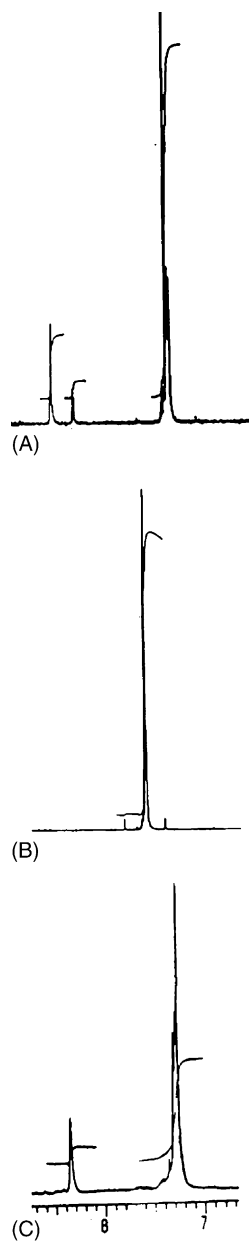

Scheme 5.

Fig. 2. Aromatic region of the ^{1}H NMR recorded for [(bmim)PF$_6$] in CDCl$_3$: (A) before addition NaOH; (B) after addition of an ethanolic solution of NaOH followed exhaustive outgassing and (C) sample b after addition of 1,4-cyclohexadiene.

Table 3
Results of the Claisen–Schmidt condensation of *o*-hydroxyacetophenone (0.1 mmol) with benzaldehyde (0.1 mmol) in [(bmim)PF$_6$] (0.5 ml), containing NaOH (8 mg) at 110 °C after 6 h reaction time

Run	MB (%)[a]	Conversion (%)[b]	Selectivity (%)[c]	
			8	**9**
1	10	95	79	16
2	37	66	77	23
3	>95	4	76	24
4[d]	73	76	75	25

[a] MB is mass balance defined as millimole of **1** or any product derived therefrom divided by initial benzaldehyde millimole in percentage. The MB of acetophenone was equal or higher than that of benzaldehyde.

[b] Conversion is millimole initial of benzaldehyde minus millimole of benzaldehyde after 6 h of reaction time divided by the initial benzaldehyde millimole in percentatge.

[c] The formation of ethyl benzoate amounts for the difference on selectivity up to 100%.

[d] After addition of an extra amount of NaOH (8 mg).

the mass balance. Noteworthy is the fact that the selectivity of chalcone versus flavone remains unaltered in the successive cycles. Concerning the origin of the poor mass balancing one possibility would be that the sodium salt of basic species are retained in the ionic liquid, making them unextractable in organic solvents. To check this possibility an experiment was carried out in where at the final time an aqueous HCl solution was added to the ionic liquid before extracting with ethyl ether. Under these conditions with prior neutralisation, the mass balance was somewhat higher (17%, compare with Table 3, entry 1), thus indicating that the low mass balance is due only in part to the presence of basic species in the ionic liquid. In this regard, the possibility that an interaction or a reversible chemical reaction between the imidazolidene carbene and the carbonyl reagents, as previously suggested [17], seems also reasonable to explain the low mass balances observed using ionic liquids in basic conditions.

In summary, it has been reported that the ionic liquid [(bmim)PF$_6$] can be as a suitable medium to perform base-catalysed reaction. The products can be recovered by simple extraction without the need of neutralisation and the ionic liquid reused in successive runs. However, caution should be exercised since two general problems can be encountered. The first one is base depletion by reaction with the relatively acidic H-2 of the imidazolium heterocycle. The second problem is the low mass balances at the initial runs, but eventually they go very high once the ionic liquid has been saturated. For some base-catalysed reactions that require only catalytic amounts of weak bases such as Knoevenagel condensation the reaction may not require the addition of extra amounts of base during the recycle. But, in general, additional amounts of base need to be added in the successive runs since imidazolium ion reacts with bases. One point that deserves further study is the exact nature of the bases present in the ionic liquid. Imidazolidene carbene together with ethoxide (when using ethanol as solvent for

ortho-hydroxyacetophenone, formation of ethyl benzoate was also observed. Ethyl benzoate should be formed by the same mechanism depicted in Scheme 3. However, for the reaction between **1** and **7,** the amount of ethyl benzoate (**6**) formed was very minor. Again the mass balances in the first run were very low and increased significantly in the second run, although the conversion decreased remarkably (Table 3). In fact, in the third run, the condensation takes place in a very minor extent in agreement with a considerable depletion in base observed previously. Addition of an extra amount of base to the ionic liquid in the forth run largely increases the conversion, while keeping very high

P. Formentín et al. / Journal of Molecular Catalysis A: Chemical 214 (2004) 137–142

the addition of base) seems to be involved from the data obtained. Furthermore, imidazolidene carbene can act as hydride acceptor. The problem of the base consumption by the ionic liquid and formation of imidazolidene formation could be possibly avoided if an imidazolium substituted at the 2-position is used for base catalysed reactions.

Acknowledgements

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