

Unexpected side reactions of imidazolium-based ionic liquids in the base-catalysed Baylis–Hillman reaction†

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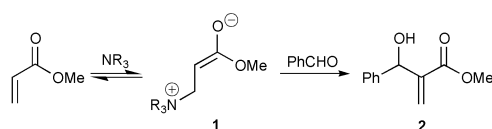
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Low yields are obtained when the Baylis–Hillman reaction is conducted in the presence of an imidazolium-based ionic liquid due to direct addition of the deprotonated imidazolium salt to the aldehyde. Ionic liquids are evidently not inert.

Since the pioneering work of Seddon, ionic liquids have emerged as a new class of stable, inert organic solvents with unique properties which can provide considerable benefit in synthesis.¹ The immiscibility of ionic liquids with a number of organic solvents and their zero vapour pressure aid their recyclability. Their high polarity and ability to solubilise both inorganic and organic materials can result in enhanced rates of chemical processes and can provide higher/different selectivities compared to conventional solvents. Thus, as a result of their ‘green’ credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in synthesis. They have been employed under acidic, basic and neutral conditions and their stability under different conditions has usually been assumed.

We have been interested in enhancing rates of Baylis–Hillman reactions² and some time ago considered the use of ionic liquids as we believed that their high polarity would provide a higher equilibrium concentration of the zwitterionic intermediate **1** and thereby lead to higher rates (Scheme 1). However, whilst a moderate increase in rate was indeed observed, yields were lower than in the absence of the ionic liquid and so we decided not to publish our results.³ We were therefore surprised to read a recent report by Afonso on the beneficial properties of employing imidazolium salts in Baylis–Hillman reactions.⁴ As a result of this publication we decided to carry out a more detailed study of our initial reactions and now report the finding that imidazolium salts are not inert, but that under mild basic conditions they are deprotonated to give reactive nucleophiles, which consume the aldehyde leading to lower yields. Indeed, the ease of deprotonation of this class of ionic liquids and subsequent reaction with electrophiles seems to have been overlooked by a considerable section of the chemistry community. We not only address the problems associated with the use of ionic liquids in the Baylis–Hillman reaction, but also provide corrections and explanations of Afonso’s results and other literature examples where imidazolium salts have been employed under basic conditions.

Initial test reactions between benzaldehyde and methyl acrylate catalysed by 3-hydroxyquinuclidine (3-HQD) showed that ionic liquids seemed to increase the reaction rate. An idea of relative rate was determined by ¹H NMR integration of the



Scheme 1 Baylis–Hillman Reaction.

† Electronic supplementary information (ESI) available: NMR data; details of conditions employed by Afonso and integrations and calculations. See <http://www.rsc.org/suppdata/cc/b2/b203079a/>

Table 1 Conversion and yield of Baylis–Hillman reaction (Scheme 1)^a

Entry	BMIM Cl	3-HQD	Conversion ^b after 4 h	Yield ^c after 4 h
1	—	0.1 eq.	12 ^d	12 ^d
2	0.5 eq.	0.1 eq.	69	25
3	0.5 eq.	0.2 eq.	85	36
4	0.5 eq.	0.5 eq.	86	37

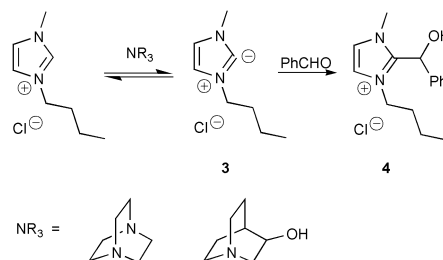
^a Conditions: Benzaldehyde (1.0 eq.), methyl acrylate (1.2 eq.), 3-hydroxyquinuclidine (3-HQD, 0.1, 0.2 and 0.5 eq.) and butylmethylimidazolium chloride (BMIM Cl, 0.5 eq.). ^b Conversion [BH-Product / (BH-Product + Benzaldehyde)] was measured by ¹H NMR spectroscopy. ^c Yields were calculated by ¹H NMR using Baylis–Hillman product signals relative to 3-HQD (used as internal standard). ^d Measured after 6 h.

Baylis–Hillman adduct relative to starting materials after 4 h (Table 1).

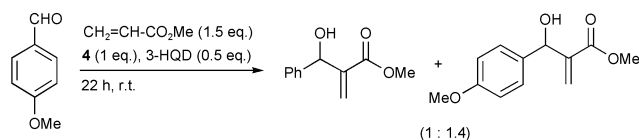
However, in analysing the NMR data we found that benzaldehyde was consumed at a much faster rate than consumption of methyl acrylate. Indeed, after 4 h using 0.5 equivalents of butylmethylimidazolium chloride,⁵ whilst benzaldehyde had been mostly consumed, large amounts of the methyl acrylate were unconverted (entry 3). We therefore conducted control experiments in which various combinations of different reactants were combined and discovered that benzaldehyde actually reacted with the ionic liquid in the presence of the mild base (3-HQD) to yield adduct **4** (Scheme 2).⁶ The reaction could be conducted using either DABCO or 3-hydroxyquinuclidine which were both equally effective. This showed that imidazolium-based ionic liquids are not inert solvents under mildly basic conditions.

In contrast to our studies, Afonso employed GC to integrate the Baylis–Hillman adduct *relative to benzaldehyde only* to obtain rate data and from this analysis concluded that the ionic liquid led to faster reactions. They assumed that all of the benzaldehyde was being converted to the Baylis–Hillman product, but this is clearly incorrect as it ignores the very significant side reaction involving the ionic liquid which consumes benzaldehyde. In fact, the isolated yields of the Baylis–Hillman adduct reported by Afonso were all rather low which is in keeping with our own observations.

As further transformations of the modified ionic liquid **4** did not occur, this substrate was tested as a potential promoter of the Baylis–Hillman reaction. However, during the course of the reaction, some of the original unsubstituted ionic liquid could be detected. Of course this reverse process also provided additional benzaldehyde which complicated our evaluation of the reaction



Scheme 2 Reaction of ionic liquid with benzaldehyde.



Scheme 3 Baylis–Hillman reaction in presence of modified ionic liquid **4**.

rate. However, the reverse process has even more sinister consequences to the recyclability of the ionic liquid. If the ionic liquid from one run of a Baylis–Hillman reaction is then employed again in a different Baylis–Hillman reaction a mixture of products would be obtained. This was tested and was indeed observed (Scheme 3). This clearly limits the reusability of the ionic liquid.

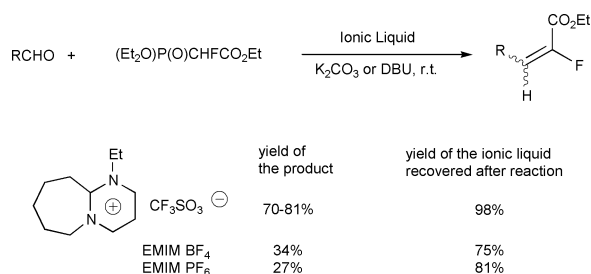
Afonso reported that the ionic liquid could be reused 4 times in the same Baylis–Hillman reaction and observed an increase in yield with each recycle. This surprising observation was not commented on but now is simple to understand. The ionic liquid reacts with benzaldehyde but as more of it is converted with each recycle, less benzaldehyde is consumed in this side reaction and so more benzaldehyde is available for the normal Baylis–Hillman reaction.

Imidazolium salts have a pK_a of around 24 in DMSO⁷ and so it is perhaps surprising that they can react with aldehydes under such mild basic conditions (the pK_a of DABCO is 8.7⁸). When the conjugate base is used as a carbene ligand for ruthenium (the Arduengo ligand) strong bases *e.g.* KO^tBu are commonly employed.⁹ Ionic liquids have been employed in palladium catalysed Heck reactions and it has been suggested that using imidazolium salts, the transformations could occur *via* Pd–carbene complexes; the carbene being derived from deprotonation of the imidazolium salt by a weak base.¹⁰ In such reactions, only a very small amount of the ionic liquid is converted into the carbene and so the transformation, if it occurs, usually goes unnoticed. Imidazolium salts have been reacted with benzaldehyde in the presence of strong base (NaH typically) and then a second electrophile.¹¹

The initial addition of the carbene to the aldehyde is similar to the initial addition of a thiazolium salt to benzaldehyde in the benzoin reaction.¹² However, evidently, imidazolium salts cannot function in the same way as thiazolium salts as the reaction stops at the adduct **4**.¹³ Oxazolium salts have also been studied as analogues of thiazolium salts and they behave in the same way as the imidazolium salts towards base and benzaldehyde.¹⁴

The literature examples illustrate that in general, strong bases have been employed to deprotonate imidazolium salts for subsequent use in synthesis. We have found that mild bases with pK_a 's as low as 8–9 are strong enough to generate the corresponding carbene.

Ionic liquids have been employed in the Horner–Wadsworth–Emmons reactions (Scheme 4) and interestingly low yields were obtained with ethylmethylimidazolium-based ionic liquids (27–34%) but much higher yields were obtained with DBU–Et salt.¹⁵ From our results it is highly likely that the low yields with ethylmethylimidazolium-based ionic liquids were due to the side reaction presented in Scheme 2.



Scheme 4 Horner–Wadsworth–Emmons reaction in ionic liquids published by Kitazume.

Finally, a Knoevenagel reaction has been conducted in hexylmethylimidazolium hexafluorophosphate. In this case malononitrile and benzaldehyde were employed together with glycine as a very weak base. Only one example was provided and it may be that other combinations of substrates lead to the problem side reaction highlighted above.¹⁶

In conclusion, the use of butylmethylimidazolium ionic liquids for the Baylis–Hillman reaction is not recommended due to low yields resulting from direct addition of the deprotonated butylmethylimidazolium to the aldehyde. This side reaction dominates even if 50 mol% ionic liquids are employed. This works highlights the need for caution when considering the use of ionic liquids under basic conditions as they are very readily deprotonated to give species capable of reacting with electrophiles.

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Notes and references

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- Other imidazolium salts behaved similarly, such as BMIM PF₆, EMIM OTf, EMIM Cl, EMIM PF₆ and EMIM BF₄ (using 3-HQD or DABCO as base). We have repeated Afonso's work and his results are reproducible: he obtained a 65% isolated yield and we obtained a 70% NMR yield for the reaction between benzaldehyde, methyl acrylate, DABCO and BMIM PF₆ (see supplementary material†). The main difference is that he did not observe the side reaction between the ionic liquid and the aldehyde which in the above case consumed 22% of the benzaldehyde.
- The modified ionic liquid **4** has been characterised (see supplementary material†) and peaks containing this species are observed in the crude NMR of the Baylis–Hillman reaction (again see supplementary material†). However, in the crude NMR we also observed an additional set of minor signals, which may belong to the parent ionic liquid indicating that further transformations are occurring.
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