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## The Knoevenagel condensation catalysed by ionic liquids: a mass spectrometric insight into the reaction mechanism

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The creation of carbon-carbon bonds is still a highly required topic in organic chemistry for the capacity to give a wide variety of new products of industrial value. Accordingly, the Knoevenagel condensation between activated methylene compounds and aldehydes is one of the most known carbon coupling reactions. In this work, the catalytic activity of imidazolium-based ionic liquids (1-butyl-3-methylimidazolium acetate, 1-butyl-3-methylimidazolium chloride, 1-methyl-3-carboxymethylimidazolium chloride) was studied under solvent-free conditions and compared with that of sodium salts (sodium chloride, sodium acetate). Mass spectrometric techniques were used to monitor the formation of the reaction products and to detect the key intermediates of the process. Based on the catalyst employed different reaction mechanisms were highlighted, thus laying the foundation for the design of more specific and efficient catalysts.

## Introduction

lonic liquids (ILs) represent a fascinating class of stable compounds that, contrary to the electrically neutral liquids, are predominantly made of ions and typically consist of large organic cations combined with inorganic or organic anions.<sup>1,2</sup> The high designability, as well as the opportunity to recycle them after each reactive cycle, have made ILs efficient catalysts and green reaction media in the place of common volatile solvents.<sup>3,4</sup> Interestingly, the incorporation of a functional group into either the anion or cation scaffold allowed to enhance specific properties and favour their task-specific uses for catalytic applications.<sup>5</sup> Among them, imidazolium-based ILs are known to be efficient precursors of *N*-heterocyclic carbenes (NHCs) arising from the chemically or electrochemically induced C2-H deprotonation. Once generated, NHCs can act as basic or nucleophilic catalysts in a variety of chemical reactions.<sup>6</sup>

The formation of carbon-carbon bonds is still highly exploited in synthetic chemistry to obtain a wide variety of new products of industrial and pharmaceutical value. The Knoevenagel condensation between activated methylene compounds and aromatic aldehydes represents an important reaction to obtain this type of bonds.<sup>7</sup> Knoevenagel reactions are typically performed with nitrogen-based catalysts, categorized as tertiary, secondary, primary amines, and ammonium salts. Among those, also imidazole-based ionic liquids are widely used as efficient catalysts.<sup>8</sup>

A flourishing debate is still open on the mechanism of this reaction since two main reaction pathways have been proposed. The first one, known as the Knoevenagel

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mechanism,<sup>7a</sup> assumes that the catalyst combines with the aldehyde forming a Schiff base; the second one is the basecatalysed alternative proposed by Hann and Lapworth<sup>9</sup> according to which the catalyst removes a proton from the methylene activated compound giving rise to a carbanion that easily adds to the aldehyde. Therefore, based on the catalyst employed, the same condensation product can be obtained through different intermediates, thus creating new research opportunities to design specific catalysts.

Gas-phase studies performed by means of mass spectrometry (MS) offer the unique chance to intercept short-lived species, such as the transient intermediates of a chemical transformation. To this end, mass spectrometric techniques are often coupled with atmospheric pressure ionization sources (API), such as electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) sources, which gently transfer ionic species to the gas-phase environment to elucidate their functions at a specific reaction stage.<sup>10</sup> The most relevant aspect of mass spectrometry consists in investigating intrinsic properties of charged species, including their structure and reactivity, in the absence of solvent molecules and counterions, commonly affecting the substrate reactivity. The possibility to assess ionic compounds in their isolated state or specifically design a micro-solvated environment provides energetic, mechanistic, and kinetic information of catalytic reactions at a strictly molecular level.<sup>11</sup> With this regard, MS techniques were deeply exploited to investigate fundamental thermochemical properties of ionic liquids and carbenic derivatives, such as proton affinity and gas-phase basicity/acidity,<sup>12</sup> ion-pair evaporation<sup>13</sup> and clusters speciation.<sup>14</sup> The effective strategy to insert a "silent" charge tag into the cation scaffold succeeded in "fishing" out from the solution charged *N*-heterocyclic carbenes and highlight their structure, intrinsic reactivity, and catalytic activity.<sup>15</sup> Besides, the higher sensitivity and selectivity of MS compared to other spectroscopic methods allows one to monitor the reaction progress over time by simultaneously sampling from the reaction mixture a low amount of structurally similar reactants,

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<sup>†</sup> Electronic supplementary information (ESI†) available: NMR spectra of synthesized samples and APCI and ESI mass spectra. See DOI: 10.1039/x0xx00000x

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## intermediates, and products without problems of band overlapping. Accordingly, the Knoevenagel condensation was first studied by atmospheric pressure ionization MS in 1999 in the presence of piperidine catalyst, thus isolating and characterizing a Schiff base intermediate consistent with the mechanism proposed by Knoevenagel.<sup>16</sup>

Based on our interest in ionic liquids<sup>17</sup> and the use of mass spectrometry to investigate reaction mechanisms in the gasphase environment,<sup>18</sup> we have studied the catalytic behaviour of different imidazolium-based ILs in the Knoevenagel condensation compared to that of common organic and inorganic salts showing different basic properties.

## **Results and discussion**

The mechanistic details of the Knoevenagel condensation were investigated by mass spectrometry in the presence of different catalysts, imidazolium-based ILs (1-butyl-3-methylimidazolium acetate, 1-butyl-3-methylimidazolium chloride, 1-methyl-3-carboxymethylimidazolium chloride) and sodium salts (NaCl, NaAc, Ac<sup>-</sup> = acetate), listed in Table 1. Thus, we have i) monitored over time the formation of the reaction products, ii) intercepted the key intermediates of the process and iii) elucidated the overall reaction mechanism for each catalyst employed.

## The reaction products

p-Anisaldehyde 1 was used as a model substrate with the methylene-activated compounds 2a-b and the reaction mixture was stirred at room temperature under solvent-free conditions for 24 hours. The typical products of condensation between ethyl cyanoacetate 2a and aldehydes or ketones in the presence of bases, i.e. ammonium acetate, as catalysts are  $\alpha,\beta$ -unsaturated cyanoacetates. Malononitrile 2b is one of the most reactive compounds in the Knoevenagel condensation as the reaction can proceed to the product without catalyst, albeit very slowly.^19

The imidazolium-based ionic liquids are probably the most popular class of ILs and are marked by a complex and intriguing reactivity related, inter alia, to the scaffold of the cation and the nature of the anion. The mutual interactions between BMIM<sup>+</sup> and X<sup>-</sup> have been analysed.<sup>20</sup> The progress of the Knoevenagel reaction, the interactions between the catalyst and the reactants, and the action of the imidazolium ionic liquids BMImX (X = Cl<sup>-</sup>, Ac<sup>-</sup>) were compared with those of the sodium salts NaCl, NaAc, and with the task-specific ionic liquid 1-methyl-3-carboxymethylimidazolium chloride (MAICI) which is known to have high thermal stability<sup>21</sup> and nearly universal solubility. <sup>22</sup> The synthetic yields of the product (3a-b) and their comparison with the yields obtained in the previous work <sup>8a</sup> are reported in Table 2. A different reactivity was observed in the presence of ethyl cyanoacetate 2a or malononitrile 2b depending on the catalyst employed. Excellent yields of 3b were

R	Catalyst	-R	X
-N	BMImAc	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	CH₃COO <sup>-</sup>
	BMImCl	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	Cl⁻
-N(+ ^	MAICI	-CH₂COOH	Cl⁻
CH <sub>3</sub>			
	Catalyst	X	
NaX	NaAc	CH₃COO <sup>-</sup>	
	NaCl	Cl-	

always obtained by using **2b** (Table 2, entries 6-9) except when NaCl was used (Table 2, entry 10). On the contrary, only the ionic liquid BMImAc efficiently catalysed the reaction of *p*anisaldehyde **1** with **2a** (Table 2, entry 1) leading to a final yield of product **3a** comparable to that obtained by using **2b** and ionic liquid catalysts or NaAc (Table 2, entries 6-9). The use of MAICI with the less acidic methylene-activated compound **2a** has a negative effect, being the presence of carboxylic group detrimental for the catalytic system, and very small amount of product was observed (Table 2, entry 3).

Table 2. Synthetic yields (%) of the Knoevenagel condensation between p-anisaldehyde 1 (0.5 mmol) and C-H acids 2a-b (0.5 mmol) in the presence of catalyst (10 mol %) after 24 hours.



Entry	Catalyst	2	Yield of 3 (%)	Reference
1	BMImAc	2a	98	[8a]
2	BMImCl	2a	25	[8a]
3	MAICI	2a	1 <sup>§</sup>	This work
4	NaAc	2a	25	[8a]
5	NaCl	2a	3	[8a]
6	BMImAc	2b	99	This work
7	BMImCl	2b	94	This work
8	MAICI	2b	91	This work
9	NaAc	2b	98	This work
10	NaCl	2b	43	This work

<sup>§</sup> very low yield of **3** was also obtained carrying out the reaction with BMImCl and acetic acid 1:1 molar ratio

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In order to follow the progress of the reaction in the presence of the most promising catalysts, the formation of the condensation product was monitored over time under APCI mass spectrometric conditions. This approach ensures the ionization of low-polar compounds such as the products 3a-b that were detected as radical molecular anions  $M^{-}$  (m/z 3a = 231; 3b = 184) resulting from the capture of thermal electrons, commonly present in the corona discharge.<sup>23</sup> First of all, the 10 structure of these species was confirmed by subjecting them to 11 sequential collision-induced dissociation reactions (MS<sup>n</sup>). As 12 displayed in Scheme S1 (see the ESI<sup>+</sup>), the ions at m/z 231 and 13 184 showed the same fragmentation patterns of the 14 corresponding isolated Knoevenagel products, previously 15 characterized by NMR-spectroscopy,<sup>8a</sup> and some diagnostic 16 daughter ions reported for similar methoxy-functionalized 17 compounds analysed under negative collision-induced 18 dissociation (CID) conditions.24 19

The variation of the product intensities was then evaluated over time and reported as a percentage of the total ion current (TIC). Figure 1a shows that the BMImAc-catalysed condensation giving rise to the product 3a is complete after only 2 hours since no further increase of the product intensity was observed after this period of time. When the BMIm<sup>+</sup> was replaced by sodium cation, the reaction rate leading to 3a dramatically decreases (Figure 1b), according to the low amount of product isolated after 24 hours (Table 2, entry 4).

Interestingly, with the malononitrile 2b, the formation of product **3b** occurred in less than 30 minutes by using BMImAc catalyst (Figure 2a), whereas at least 2 hours were required to obtain high yields of product 3b when the acetate was replaced by the chloride anion (Figure 2b). A reaction time of ca. 4 hours was instead necessary in the presence of the N-acid substituent of the MAI cation or by using the NaAc catalyst in which sodium has replaced the BMIm cation of the BMImAc catalyst (Figures 2c and d). Hence, it clearly appears that a crucial role is played by both cation and anion in the catalytic mechanism.



Figure 1. Plot of the relative intensities versus time for the Knoevenagel product 3a in the presence of the most efficient catalysts: a) BMImAc and b) NaAc



Figure 2. Plot of the relative intensities versus time for the Knoevenagel product 3b in the presence of the most efficient catalysts: a) BMImAc, b) BMImCl, c) MAICl and d) NaAc.

Therefore, BMImAc resulted to be the most efficient catalyst leading to a prompt formation of the final products 3a-b and significantly reducing the total reaction time compared to all other catalysts employed.

#### The reaction intermediates

In order to outline the mechanistic picture of the Knoevenagel condensation catalysed by ionic liquids and sodium salts, the key intermediates of the process were intercepted and characterized by mass spectrometry.

Since no ionic intermediates were detected under APCI conditions, the reaction mixtures were analysed by ESI mass spectrometry. In the early stages of the reaction, two negativecharged ions were regularly detected for all the catalysts employed except for BMImAc, as shown in Figure 3 in which the BMImCl system was chosen as a representative example for all the catalysts employed. The deprotonated reagents 2a or 2b are listed as  $\mathbf{r}_{a-b}$  (m/z = 112 and 65) and two ions at m/z = 248 and 201 are assigned to the intermediate  $i_{la-b}$ . These species are consistent with the negative-charged adduct between the deprotonated C-H acids  $\mathbf{r}_a$  or  $\mathbf{r}_b$  and the *p*-anisaldehyde **1**. Interestingly,  $\mathbf{i}_{la-b}$  were not detected with the most efficient BMImAc catalyst. Only in the chloride-based systems (BMImCl, MAICI, and NaCI) the protonated form of the intermediates ila-b, named  $i_{IIa-b}$ , was intercepted as a Cl<sup>-</sup> adduct (Figure 3, m/z = 284/6 and 237/9), as confirmed by the characteristic isotopic pattern of the chlorine atom. Since the ions  $i_{la-b}$  can formally correspond either to a covalent intermediate or to a labile

#### **Journal Name**



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**Figure 3.** ESI-(-) mass spectra of a 1:1 a) *p*-anisaldehyde/**2a** and b) *p*-anisaldehyde/**2b** reaction mixture stirred for 4 hours and 20 minutes, respectively, in the presence of 10 mol % of BMImCl catalyst. The ion at m/z 151 (\*) corresponds to the acid derivative of the *p*-anisaldehyde resulting from its facile air oxidation.

adduct between the two substrates **1** and **2a-b**, CID experiments were carried out to characterize these charged species. Accordingly, the main fragmentation channel observed consists in the loss of a water molecule leading to the daughter ions at m/z 230 and 183, respectively (Figures 4a and 4b), whereas the loss of the *p*-anisaldehyde **1** as a neutral counterpart (C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>), giving rise to the deprotonated **2a-b** at m/z 112 and 65, only represents a minor channel. This result points to the formation of a covalent-bonded species that is prone to dehydrate leading to the condensation product rather than back-dissociate and release the two reagents.

Likewise, the intermediate  $i_{IIb}$  fragments by the loss of a water molecule giving rise to the chloride-attached Knoevenagel product **3b** at *m*/*z* 219 (Figure 5b and Scheme S2, ESI<sup>+</sup>). Alternatively, the release of an HCl moiety from both i<sub>lla-b</sub> parent species regenerates the aldol intermediates  $i_{la-b}$  at m/z 248 and 201 (Figure 5a and 5b), the structures of which were probed by their MS<sup>n</sup> fragmentation patterns (Figures 5a and 5b, insets). Interestingly, the fragment ion at m/z 169 in Figure 5b was also reported in the CID mass spectrum of the radical anion at m/z184 (Scheme S1, ESI<sup>+</sup>), suggesting that i<sub>II</sub> can easily rearrange to form the condensation product. This fragmentation pattern was further confirmed by dissociating the corresponding <sup>37</sup>Cl isotope-containing species (Figure S2, ESI<sup>+</sup>). For each catalyst employed, the relative intensities of the diagnostic peaks r<sub>a</sub> and  $i_{la}$  were compared, highlighting that the  $i_l/r$  intensity ratio (1%) is much lower when the synthetic yield of the final products 3a is higher (Table 3). Without the intent to provide a quantitative estimate, the highest  $i_l/r$  ratio (2.67) was found in the presence of the least efficient MAICI catalyst (Table 3, entry 5). This result agrees with the notion that an efficient catalyst acts by driving



**Figure 4.** ESI-(-) CID mass spectra of the intermediates a)  $i_{la}$  at m/z 248 and b)  $i_{lb}$  at m/z 201 respectively isolated from a 1:1 *p*-anisaldehyde/**2a** and a 1:1 *p*-anisaldehyde/**2b** reaction mixture in the presence of 10% BMImCl catalyst.



**Figure 5.** ESI-(-) CID mass spectra of the <sup>35</sup>Cl isotope-containing intermediates a) **i**<sub>IIa</sub> at m/z 284 and b) **i**<sub>IIb</sub> at m/z 237 respectively isolated from a 1:1 *p*-anisaldehyde/**2a** and a 1:1 *p*-anisaldehyde/**2b** reaction mixture in the presence of 10% BMImCl catalyst. In the inset: ESI-(-) CID mass spectrum of the daughter ions at a) m/z 248 and b) 201 respectively isolated from the sequence  $284 \rightarrow 248$  and  $237 \rightarrow 201$ , arising from the fragmentation of the intermediate **i**<sub>IIa-b</sub>.

#### Journal Name

**Table 3.** Relative intensity ratios (1%) of the negative-charged intermediate  $i_{1a}$  versus  $r_a$  compared to the synthetic yields of product **3a** obtained after 24 hours.



1	BMImAc	_	_	98[04]
2	NaAc	4 h	0.550	25 <sup>[8a]</sup>
3	BMImCl	4 h	0.838	25 <sup>[8a]</sup>
4	NaCl	4 h	2.42	3 <sup>[8a]</sup>
5	MAICI	4 h	2.67	1



the formation of the final product and preventing the significant build-up of the intermediate  $i_{la}$ . Accordingly, in the high yield systems employing malononitrile **2b** as a reagent,  $i_{lb}$  was detected only at early reaction times.

When the most efficient catalyst was used, the ionic liquid BMImAc, the negative-charged intermediate **i**<sub>1</sub> was not found even at short reaction times (Table 3, entry 1), although the condensation product was isolated in 95% yield after only 1.5 hours of reaction.<sup>8a</sup> It follows that the ionic liquid BMImAc could efficiently catalyse the Knoevenagel condensation passing through different intermediates.

Since in the negative ion mode no intermediates were detected, the catalytic mechanism of the BMImAc was elucidated by monitoring the reaction between 1 and 2a-b in the ESI positive ion mode. A similar analysis was also performed in the presence of the BMImCl catalyst which shares with BMImAc the same organic cation. For the sake of conciseness, we display the data corresponding to the reaction of malononitrile reagent 2b, as comparable results were obtained by using the ethyl cyanoacetate substrate 2a (see Figure S4 in the ESI<sup>+</sup>). The mass spectrum of the reaction mixture, reported in Figure 6a, is dominated by the ionic species at m/z 139, corresponding to the BMIm cation, also detected when BMImCl was used as a reaction catalyst (Figure 6b). A second peak at m/z 275 is instead characteristic of only the BMImAc system since similar ions were not identified by using BMImCl. Again, this species can correspond either to a hydrogen-bonded adduct between the aldehyde 1 and the BMIm cation or to a protonated covalent intermediate, as shown in Figure 6a. The first hypothesis was excluded since a labile species at m/z 275 should also be detected in the BMImCl system. Therefore, we considered the possible formation of a covalent intermediate between the BMIm-derived carbene and the *p*-anisaldehyde. Many papers report the use of the imidazolium acetates in organocatalytic reactions (i.e., catalysed by NHC), and for this particular employment they were appointed as "organocatalytic ionic liquids".17 Thus, it has been postulated that sufficiently basic

Figure 6. ESI-(+) mass spectra of a 1:1 *p*-anisaldehyde and **2b** reaction mixture in the presence of a) BMImAc and b) BMImCl catalyst.

anions of imidazolium-based ionic liquids, such as acetate, can promote the cation-anion proton transfer, speaking in favour of the spontaneous formation of *N*-heterocyclic carbenes in ionic liquids.<sup>25</sup> Nevertheless, the presence of carbenes in imidazolium acetate ionic liquids have never been directly probed by spectroscopic techniques, thus pointing to a very low concentration in solution.<sup>26</sup> In the presence of *p*-anisaldehyde, the cation-anion proton transfer equilibrium can be shifted towards the generation of carbene, therefore allowing the formation of the transient adduct between aldehyde and carbene intercepted by MS. This result, as well as the isolation in the neat BMImAc of a positively charged hydrogen-bonded adduct between the BMIm cation and the corresponding carbene (Figure S3, ESI<sup>+</sup>), provides an indirect mass spectrometric evidence on this debate, in support of the spontaneous formation of carbene from imidazolium-based ionic liquids with basic anions. Accordingly, the ionic intermediate at m/z 275 was characterized by CID experiments and the formation of a daughter ion at m/z 201 is consistent with concerted dehydration (-H<sub>2</sub>O) and cleavage of the imidazolium side chain (-C<sub>4</sub>H<sub>8</sub>), both indicative of a covalent species (Figure 7a). The dehydration reaction, typically involving hydroxyl groups, also represents a direct fragmentation channel leading to the daughter ion at m/z 257 that is structurally consistent with a carbocation species (inset of Figure 7a and Scheme S3a, ESI<sup>+</sup>). This result was confirmed by comparing the CID mass spectrum of the ion at m/z 275 with that of the covalent adduct between 1-butyl-3-methyl-imidazolydene and cyclohexane carboxaldehyde (Figure 7b and Scheme S3b, ESI<sup>+</sup>), first isolated and characterized by NMR in 2010.<sup>27</sup> However, the concomitant presence with the covalent-bonded adduct of a loosely-bonded ionic population at m/z 275 cannot be excluded, in the light of the intense daughter ion at *m*/z 139 which

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**Figure 7.** ESI-(+) CID mass spectra of the ions at a) m/z 275 and b) m/z 251 isolated from a 1:1 a) *p*-anisaldehyde/**2b** and b) cyclohexane carboxaldehyde/**2b** reaction mixture in the presence of 10% BMImAc catalyst.

corresponds to the BMIm cation. Nevertheless, it is also conceivable that the covalent-bonded population is consumed in the reaction and therefore does not accumulate.

#### The reaction mechanism

According to the mass spectrometric results collected in this work, two different reaction mechanisms for the Knoevenagel condensation were highlighted, depending on the catalysts employed. As previously described, in the presence of the BMImCl and MAICl ionic liquids and the sodium salts NaAc and NaCl, the reaction proceeds through the formation of the intermediate  $i_l$  (Table 4). This species can be assigned to the negative-charged aldol of the base-catalysed<sup>39</sup>/mechanism postulated by Hann and Lapworth.<sup>9</sup> According to this pathway, chloride or acetate anions can act as a base removing a proton from the methylene compounds **2a-b** to form the resonance-stabilized anion at m/z 112 or 65 ( $r_{a-b}$ ). The activated reagent adds to the carbonyl group of the aldehyde leading to the  $i_{la-b}$  intermediates at m/z 248 and 201, respectively. After that, the transient species  $i_{lla-b}$  can release a water molecule giving rise to

the Knoevenagel product and return the catalyst (Scheme 1). Although the reaction is triggered by the chloride or acetate anions, the role of the BMIm and MAI cations in the catalysis is worthy of note. As previously reported,<sup>8a</sup> large organic cations with low charge density, such as BMIm and MAI, show a lower ion-pairing ability than small inorganic cation (e.g. Na<sup>+</sup>) versus the chloride anion, rendering it more reactive. Besides, the BMIm and MAI cations can behave as hydrogen bond donors, activating the carbonyl moiety of the aldehyde towards the nucleophilic attack of the C-H acids, once deprotonated by the ionic liquid counter-anion (Scheme 2).<sup>8e</sup>

This reaction seems to occur through a concerted mechanism since no positive-charged adduct between BMIm or MAI cation and *p*-anisaldehyde **1** was intercepted by analysing the corresponding reaction mixtures over time. The important role played by the cation in the catalysis is also confirmed by the synthetic yields of the reaction reported in Table 2. Accordingly, the yield of **3a** switches from 3% when NaCl was employed as a catalyst to 25% when sodium is replaced by BMIm cation (Table 2, entries 2 and 5).

Similar results were obtained for product **3b** with a synthetic yield that switches from 43% in the presence of NaCl to 94% by using BMImCl catalyst (Table 2, entries 7 and 10). The different reaction outcomes found by using ethyl cyanoacetate **2a** or malononitrile **2b** are predominantly ascribed to the different acidity of the two methylene substrates, depending on the chemical features of its electron-withdrawing groups (pKa  $CH_2(CN)_2 = 11^{28}$  and pKa  $CH_2(CN)CO_2Et = 12^{29}$ ). Interestingly,

Table 4. Key intermediates and different reaction mechanisms for the Knoevenagel condensation catalysed by ionic liquids and sodium salts.

Catalyst	X	İı	İnhc	X <sup>-</sup> -catalysed	NHC-catalysed
		CH <sub>3</sub> O	CH <sub>3</sub> O <sup>OH</sup> Bu H <sub>1</sub> O <sup>H</sup> Me		
		Y= CO <sub>2</sub> Et; CN			
BMImAc	CH <sub>3</sub> COO <sup>−</sup>	X	+		$\checkmark$
BMImCl	Cl⁻	+	X	$\checkmark$	
MAICI	Cl⁻	+	X	$\checkmark$	
NaAc	CH₃COO <sup>-</sup>	+	X	$\checkmark$	
NaCl	Cl⁻	+	X	$\checkmark$	

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**Scheme 1.** Base-catalysed mechanism proposed for the formation of the Knoevenagel product in the reactions catalysed by the ionic liquids BMImCl, MAICl, and sodium salts NaCl, NaAc. X<sup>-</sup> stands for Cl<sup>-</sup> or Ac<sup>-</sup>.

only the yield of the ethyl cyanoacetate-derived product **3a** was dramatically low in the presence of MAICI catalyst in which the cation bears an acidic group in the *N*1- chain (Table 2, entry 3). The MAICI catalyst, with the acidic function, seems to hinder the reaction progress, preventing the formation of the product. In fact, poor yields were obtained by carrying out the reaction with BMImCl as the catalyst with an equal amount of acetic acid (see note in Table 2). This result underlines the importance of designing tailored ionic liquids to improve their effectiveness as catalysts.



Scheme 2. Schematic representation of the imidazolium cation (R: -  $(CH_2)_3CH_3$  or  $-CH_2COOH$ ) activating the *p*-anisaldehyde by increasing the polarisation of the carbonyl moiety through the formation of a hydrogen bond with the C2-H, and the counter ion CI<sup>-</sup> deprotonating the methylene compound (Y:  $-CO_2Et$  or -CN).

Hence, we can conclude that the outcome of the Knoevenagel condensation following the base-catalysed 1678chahls7594is affected by i) the basicity of the anionic catalyst, ii) the acidity of the methylene compound and iii) the chemical features of the counter-cation of the catalyst. Passing to the BMImAccatalysed condensation, four experimental results account for a reaction mechanism different from that observed for the chloride-based ionic liquids and the sodium salts: i) the high yield of the Knoevenagel product 3a comparable to that of product **3b**, obtained from the more reactive C-H acid **2b**; ii) the formation of product **3b** occurring in the range of few minutes only by using BMImAc catalyst; iii) the absence of the negativecharged intermediates i<sub>la-b</sub> and iv) the interception of a carbenealdehyde adduct in the positive ion mode. Based on this evidence, BMImAc can catalyse the reaction through a Knoevenagel-like mechanism according to which the catalyst combines with the aldehyde leading to a positive-charged addition intermediate<sup>30</sup> before the intervention of the methylene-derived carbanion.7a In this specific case, the formation of the final product would be mediated by the 1butyl-3-methyl-imidazolydene playing a nucleophilic attack on the *p*-anisaldehyde **1** (Scheme 3).



**Scheme 3.** Proposed NHC-mediated mechanism for the Knoevenagel condensation in the presence of BMImAc catalyst.

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59 60 The *N*-heterocyclic carbenes can indeed act as a nucleophile by adding to the carbonyl group of the aldehyde, leading to a zwitterionic adduct that rearranges into the so-called Breslow intermediate.<sup>31</sup> The protonation of these species before the Breslow rearrangement forms a transient benzylic alcohol intermediate that was recognized by different authors in NHC- or base-catalysed reactions.<sup>32,33</sup>

#### Experimental

Reagents (*p*-anisaldehyde 98%, ethyl cyanoacetate  $\geq$ 98%, malononitrile  $\geq$ 99%), catalysts (1-butyl-3-methylimidazolium acetate  $\geq$ 98%, 1-butyl-3-methylimidazolium chloride  $\geq$ 99%, sodium acetate  $\geq$ 99%) and all solvents were purchased from Sigma-Aldrich Ltd and used without further purification. The acidic ionic liquid 1-methyl-3-carboxymethylimidazolium chloride (MAICI) was synthesized according to the literature procedure.<sup>34</sup> The Knoevenagel condensation was carried out at room temperature under solvent-free conditions. The detailed synthetic procedure and all spectroscopic data are provided in the Supplementary Information. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature using a Bruker AC 200 spectrometer with CDCl<sub>3</sub> as internal standard.

The Knoevenagel condensation was monitored over time by electrospray ionization and atmospheric pressure chemical ionization mass spectrometry (ESI-MS and APCI-MS) in positive and negative ion mode. A mixture of *p*-anisaldehyde (0.5 mmol), activated methylene compound (0.5 mmol) and a 10% amount of catalyst was stirred at room temperature in a 1.5 mL tube for 24 hours under solvent-free conditions. At prefixed time intervals, 1.0  $\mu\text{L}$  of the reaction mixture was sampled from the vessel, diluted to a 1.0 x  $10^{-4}$  M concentration with H<sub>2</sub>O/CH<sub>3</sub>CN (1:10 V/V), and analysed in an LTQ-XL linear ion-trap (Thermo Fisher Scientific). Sample solutions were infused into the ion source of the instrument and the ionization method was chosen based on the chemical properties of the compounds we intended to track. Polar reagents and reaction intermediates were analysed by ESI, whereas non-polar Knoevenagel products were detected under APCI conditions.

Typical experimental parameters were as follows: flow rate 10  $\mu$ L/min, source voltage 2-4 kV, capillary temperature 275°C for the ESI source; flow rate 20  $\mu$ L/min, discharge current 3-5  $\mu$ A, capillary 275°C and vaporizer temperature 25 °C for the APCI source. Nitrogen was used in both cases as sheath and auxiliary gas at a flow rate of 11 and 2 arbitrary units (a. u.  $\approx$  0.37 L/min), respectively. Other source parameters, such as capillary and tube lens voltages, were adjusted in a low range value to ensure the soft ionization of the species present in the reaction mixture. Full scan mass spectra were recorded in the range of 50-500 *m/z* by using the Xcalibur 2.0.6 software supplied with the instrument and the progress of the reaction were evaluated by correlating the reagent and product ion intensities as a percentage of the total ion current (TIC) to the reaction time. All the ionic species involved in the condensation, including the

putative intermediates, were characterized by collision induced dissociation (CID) experiments performed by the reasing 500 energy of mass-selected ions in the presence of helium as collision gas (pressure of ca.  $3 \times 10^{-3}$  Torr). Depending on the species of interest, normalized collision energies ranging between 20% and 40% were typically applied, and an activation time of 30 ms was used. Ions were isolated with a window of 1 m/z and the Q value was optimized to ensure stable trapping fields for all the ionic species under investigation.

## Conclusions

A mass spectrometric study of the Knoevenagel condensation using different catalysts was described. In the presence of chloride-based ionic liquids (BMImCl, MAICl) and sodium salts (NaCl, NaAc), the reaction proceeds through a base-catalysed pathway, as demonstrated by the isolation of a diagnostic negatively charged aldol intermediate. Hence, the insertion of an acidic group on the lateral chain of the MAI cation drastically reduced the yields of the reaction between the aldehyde and less acidic methylene activated reagents.

On the contrary, in the presence of BMImAc catalyst, the acidbase equilibrium between the BMIm cation and the Ac<sup>-</sup> anion gives rise to a catalytic amount of the corresponding NHC that triggers the reaction by adding to the aldehydic reagent. The reaction then proceeds through a Knoevenagel-like mechanism. Excellent yields of the product were thus obtained regardless of the pK<sub>a</sub> of the methylene substrate. As a result, the request for task-specific catalysts needs precise knowledge of the reaction mechanisms, and such detailed information can be obtained by the interception and the characterization of the elusive intermediates of the process under investigation. The use of mass spectrometry has again proved to be a promising approach to meet the demands of organic synthesis and improve the design of suitable catalytic systems.

## **Author Contributions**

I.C., C.S., A.T. conceived the idea and wrote the manuscript. All authors have contributed to and approved the manuscript.

## **Conflicts of interest**

There are no conflicts of interest to declare.

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