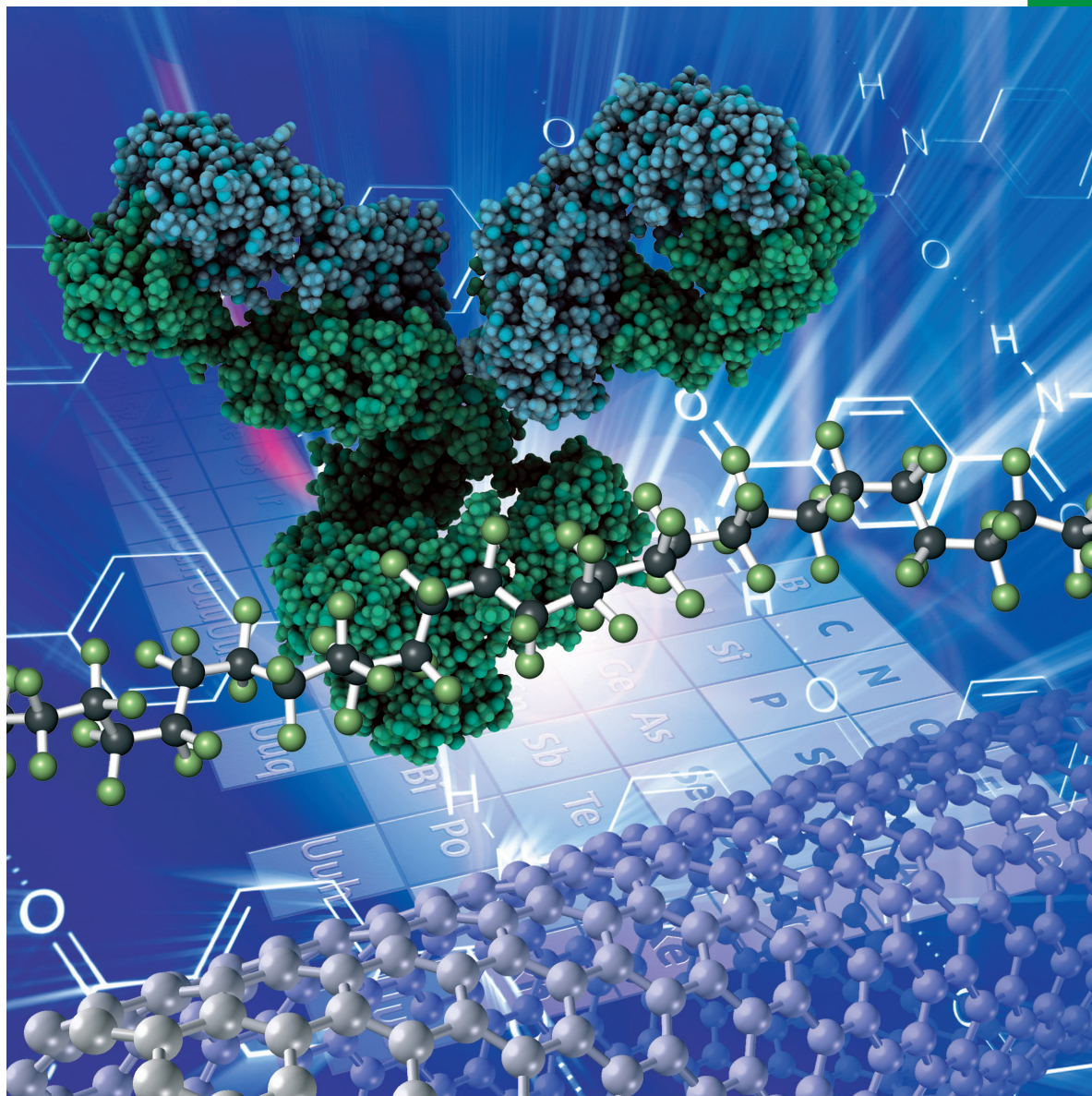


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Catalysis

Role of Anion and Cation in the 1-Methyl-3-butyl Imidazolium Ionic Liquids BMImX: The Knoevenagel Condensation

Fabiana Pandolfi, Marta Feroci, and Isabella Chiarotto*^[a]

This paper is dedicated to Prof. Achille Inesi, on the occasion of his 77th birthday.

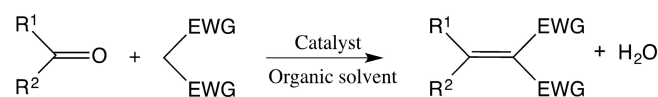
1-Methyl-3-butylimidazolium ionic liquids BMImX (X anions: Ac^- , HCO_3^- , Cl^- , BF_4^- , PF_6^- , I^- , CF_3CO_2^- , $(\text{CF}_3\text{SO}_2)_2\text{N}^-$, CF_3SO_3^-) were used as catalysts in the Knoevenagel condensation reaction. The catalytic activity was compared with that of the inorganic salts NaAc, NaHCO_3 , NaCl. Whereas it is quite important to select suitable cation and anion depending on the purpose, the basicity of the anion X^- and the ability of the counter-ion BMIm^+ to avoid the ion pairing with anion X^- was investigated. 1-Methyl-3-butyl imidazolium acetate [BMImAc] and 1-methyl-3-butyl imidazolium hydrogen carbonate

[BMImHCO₃] show the most significant catalytic power and their catalytic effect was studied on a wide range of aromatic, heteroaromatic or aliphatic aldehydes or ketones with active methylene compounds. The corresponding substituted alkenes were obtained in excellent yields (up to 98%) in the absence of any solvent at room temperature within short times. The interesting feature of this study includes explanation on role of the cation BMIm^+ as proton donor (versus anions Ac^- or HCO_3^-), in ion pair formation (with anion X^-) and activator of the aldehyde structure.

Introduction

Ionic liquids (ILs) could be regarded as a class of salts, resulting from the association of a large organic cation with a weakly coordinating inorganic anion, that melt around 100 °C or below.^[1] Owing to their peculiar singular physico-chemical properties (melting point, chemical and thermal stability, negligible vapour pressure, conductivity, solvating power etc.) ILs are frequently utilized in different fields: green solvent in organic synthesis, chemistry, electrochemistry, biochemistry, chemical engineering, new materials etc.^[2] Imidazolium based ionic liquids are probably the most popular class of ILs. They are marked by a complex and intriguing reactivity related, *inter alia*, to the scaffold of the cation and the nature of the anion. The acidity of the imidazolium cation BMIm^+ ($\text{pK}_a=22$ in DMSO^[3]) and the possible basicity of its counter ion (Ac^- , $\text{pK}_a=4.76$ in H_2O , 12.6 in DMSO;^[4] HCO_3^- , $\text{pK}_a=6.36$ in H_2O , 10.25 in DMSO^[4]) are reported by many authors. The mutual interactions between BMIM^+ and X^- were recently analysed.^[5] The formation of a new C–C bond could be a serious hindrance (and an intriguing challenge) in a procedure of organic synthesis. The Knoevenagel condensation between activated methylene compounds and aldehydes is a versatile reaction for

the formation of C–C bond through losing a molecule of water. In the classical procedure the condensation is performed in organic solvent in the presence of bases (Scheme 1).^[6]



Scheme 1. Classical procedure of condensation in organic solvent

Owing to its very frequent utilization in organic synthesis, the Knoevenagel reaction has spurred a continuous investigation aimed to find new, more efficient and green catalysts. Accordingly, the Knoevenagel reaction can be performed using bases,^[7] Lewis acids,^[8] amino acids,^[9] organometallic compounds,^[10] enzymes,^[11] InCl_3 in the presence of acetic anhydride etc.^[12] The procedures can be carried out in the presence of water or organic solvents or in the absence of any solvent. Homogeneous and heterogeneous catalysts were reported. Many authors emphasize that the Knoevenagel reaction could be effectively catalysed by suitable ionic liquids.^[13]

Thus it is interesting:

- to verify the possible utilization of 1-methyl-3-butylimidazolium ionic liquids BMImX (anion $\text{X}^- = \text{Ac}^-$, HCO_3^- , Cl^- , BF_4^- , PF_6^- , I^- , CF_3CO_2^- , $(\text{CF}_3\text{SO}_2)_2\text{N}^-$, CF_3SO_3^-), particularly the effect of

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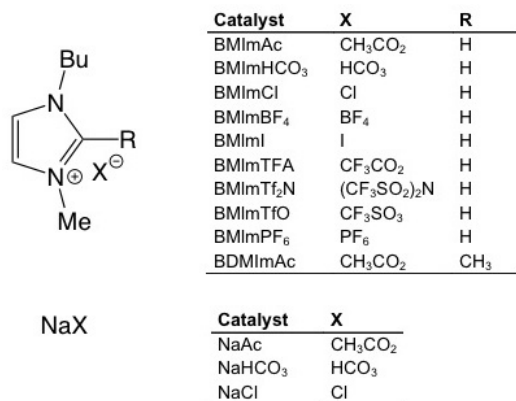


Figure 1. 1-Methyl-3-butylimidazolium ionic liquids BMImX and inorganic salts NaX used as catalysts in the Knoevenagel reaction.

BMImHCO₃ currently not yet considered by other authors, compared to inorganic salts NaX as catalysts in the Knoevenagel reaction (Figure 1).

- to evaluate the peculiar role played by the anion X⁻ and the one of the cations BMIm⁺ and Na⁺.

Results and Discussion

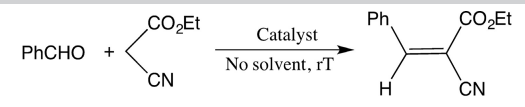
The use of ionic liquids BMImX and other inorganic salts in the Knoevenagel condensation results very interesting to compare the behaviour and the role of the anion and cation. We initially verified the possible catalytic activity of ionic liquids BMImX (Figure 1) with C–H acid CN(CH₂)CO₂Et **2a** and benzaldehyde PhCHO **1a** chosen as substrate samples. The effect of the presence in the reaction mixture of the imidazolium ionic liquids BMImX was then compared with the one of the inorganic salts NaAc, NaHCO₃ and NaCl (Figure 1). The presence and the nature of the solvent, the molar ratio substrates/catalyst (i.e. the catalytic or stoichiometric quantity of ionic liquid) and the value of the temperature could affect the efficiency of the reaction. Accordingly, to have comparable results, any evaluation of the efficiency of the catalyst was carried out at room temperature, in the absence of any solvent and using catalytic quantity of ionic liquid (% ≤ 10).

A mixture of PhCHO **1a** (1.0 mmol) and CN(CH₂)CO₂Et **2a** (1.0 mmol), and catalyst (added at a prefixed concentration, see Table 1) was stirred at room temperature. The stirring was stopped after different prefixed values of the reaction time.

We can note that:

- In the absence of catalyst (stirring time 24 h, rt), the analysis of the final mixture shows the total absence of the Knoevenagel adduct **3aa** (Table 1, entry 1).
- In the presence of BMImAc, the efficiency of the procedure is affected by the concentration of BMImAc and by the stirring time. Selecting a stirring time of 24 h, the yield of the Knoevenagel adduct **3aa** increases on increasing the concentration of BMImAc (Table 1, entries 2–6).

Table 1. Knoevenagel condensation of benzaldehyde PhCHO with ethyl cyanoacetate. Effect of nature and concentration (%) of catalysts (imidazolium based ionic liquids BMImX or inorganic salt) and of the stirring time.^[a]



Entry	1a Catalyst	2a Catalyst (%)	Reaction time (h)	3aa Yields of 3aa (%) ^[b]
1	-	-	24	-
2	BMImAc	3	24	39
3	BMImAc	4	24	55
4	BMImAc	5	24	63
5	BMImAc	7	24	80
6	BMImAc	10	24	98
7	BMImAc	10	1.5	95
8	BMImAc	10	0.5	93
9	BMImHCO ₃	10	1.0	90
10	BMImHCO ₃	10	24	95
11	BMImCl	10	24	15
12	BMImBF ₄	10	24	-
13	BMImPF ₆	10	24	-
14	BMImI	10	24	20
15	BMImTFA	10	24	50
16	BMImTf ₂ N	10	24	-
17	BMImTfO	10	24	-
18	NaAc	10	24	25
15	NaAc	10	1.5	-
16	NaHCO ₃	10	24	50
17	NaHCO ₃	10	1.5	-
18	NaCl	10	24	3
19	NaCl	10	1.5	-
20	BDMImAc	10	0.5	98
21	BDMImAc	10	1.5	98

[a] A mixture of PhCHO **1a** (1.0 mmol) and CN(CH₂)CO₂Et **2a** (1.0 mmol), and catalyst was stirred at room temperature. [b] Isolated yield.

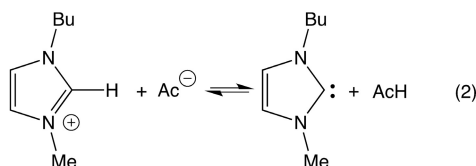
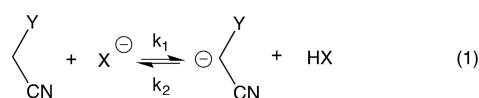
- Selecting a concentration of BMImAc of 10%, the yield of **3aa** increases on increasing of the stirring time (Table 1, entries 6–8).
- The catalytic ability of BMImHCO₃ is comparable with the one of BMImAc (Table 1, entries 9, 10).
- On the contrary, using the imidazolium ionic liquid BMImCl or BMImI, the yield of the Knoevenagel adduct **3aa** decreases significantly (Table 1, entries 11 and 14), while the lower basicity of trifluoroacetate anion (in comparison to acetate anion) leads to lower yields (Table 1, entry 6 vs 15). No adduct **3aa** was obtained using ionic liquids BMImBF₄ and BMImPF₆ as well as BMImTf₂N and BMImTfO (Table 1, entries 12, 13, 16, 17).

Finally, we investigated the possible utilization as catalyst of inorganic salts NaAc, NaHCO₃ and NaCl to compare the ion pairing ability of cation Na⁺, versus BMIm⁺, over the anions. In all cases, established a stirring time of 1.5 h, no adduct **3aa** was obtained (Table 1, entries 15, 17, 19). Instead, selecting a stirring time of 24 h, the adduct **3aa** was obtained according to the yields 25% (NaAc), 50% (NaHCO₃) and 3% (NaCl) (Table 1, entries 14, 16, 18).

The considerable catalytic activity of BMImAc and BMImHCO₃, compared with that of BMImCl, BMImBF₄ and BMImPF₆, suggests that in the imidazolium based ionic liquids the role of

the anion is very important. The catalytic activity of BMImAc and BMImHCO₃ must be related chiefly to the anion basicity. Concerning this, we should keep in mind that the basicity of the anions Ac⁻ and HCO₃⁻ is not negligible (pK_a = 12.6 and 10.25 respectively in DMSO. These values are only indicative, as our reaction is carried out under solventless conditions).^[4] The efficiency of a catalytic process is evaluable, *ceteris paribus*, both by the final yield of the isolated product and by the reaction times. In our reaction conditions, the limited catalytic activity of NaAc and NaHCO₃ (low yields and long reaction times), with respect to BMImAc and BMImHCO₃, suggests that the ion pairing ability of the cation Na⁺ is remarkable with respect to the one of the large organic cation with low charge density BMIm⁺. The base catalysed Knoevenagel reaction is triggered by the deprotonation of the C–H acid yielding the related carbanion, followed by the attack of the carbanion to the scaffold of benzaldehyde.

The catalytic activity of BMImAc or BMImHCO₃, in the Knoevenagel condensation suggests the presence of a proton exchange equilibrium between anions Ac⁻ or HCO₃⁻ and CN(CH₂)Y (Scheme 2, eq. 1). The anion Ac⁻ (as well as HCO₃⁻) is



Scheme 2. A proton exchange equilibrium between anions and CN(CH₂)Y (eq. 1) and cation BMIm (eq. 2).

basic enough to establish a significant equilibrium of proton exchange with the C–H acids CNCH₂Y **2a** and **2b**.^[4] The anions Ac⁻ (pK_a = 12.6 in DMSO) and HCO₃⁻ (pK_a = 10.25 in DMSO) are thus able to promote an operative endogenous proton exchange equilibrium with C–H acids CN(CH₂)CO₂Et (pK_a = 13.1 in DMSO) and CH₂(CN)₂ (pK_a = 16.4 in DMSO), yielding the related carbanions CN(CH⁻)CO₂Et and CH⁻(CN)₂. These active methylene compounds start the catalytic cycle via a nucleophilic addition to the carbonyl group of the aldehyde or ketone scaffold. Accordingly, the endogenous equilibrium of proton exchange could be regarded as a source of the carbanions CN(CH⁻)CO₂Et and CH⁻(CN)₂ able to provide the catalytic cycle.

The efficiency of the Ac⁻ anion as catalyst in the Knoevenagel reaction is affected by the thermodynamics of the equilibrium (1) (affected by the values of the pK_a of Ac⁻ and CN(CH₂)CO₂Et) as well as by the related kinetic values of k₁ and k₂ (Scheme 2).^[4] The different ion pairing ability (versus the counter-ion Ac⁻) of cations Na⁺ and BMIm⁺ could significantly modify the kinetics of the equilibrium of the proton exchange,

affecting the reaction times. The cation BMIm⁺ shows a lower ion pairing ability than Na⁺ versus the anion X⁻, rendering it more reactive. Moreover, it cannot be excluded a role of the BMIm⁺ cation as hydrogen bond donor activating the carbonyl moiety.^[13c] The utilization as catalysts of BMImAc or BMImHCO₃ ensures the best results as regard the yield and the reaction time. Both these salts are marked by anion and cation able to carry out the catalytic process.

On the contrary, the utilization as catalyst of NaAc, NaHCO₃, BMImCl or NaCl involves a significant decrease of the yields and longer reaction times.

The investigation of the Knoevenagel condensation catalysed by the ionic liquid BMImHCO₃ and involving the C–H acids CN(CH₂)CO₂Et **2a** and CH₂(CN)₂ **2b** was extended to different aromatic (Table 2, entries 1–7, 12–17), heteroaromatic (Table 2, entries 10, 11, 19), aliphatic (Table 2, entries 8, 18) aldehydes and ketones (Table 2, entry 9). The corresponding substituted alkenes were obtained, in any case, in elevated yields (> 90%), in short stirring times, in the absence of any solvent using an equimolar mixture of C–H acid and aldehydic or ketonic substrate at room temperature.

Last, we must keep in mind that the anion Ac⁻ (as well as HCO₃⁻) could be involved, in theory, in an equilibrium of proton exchange with the cation BMIm⁺ beyond that with the C–H acid present (i.e. CN(CH₂)CO₂Et or CH₂(CN)₂) (Scheme 2, eq. 1 and 2, respectively).

Nevertheless, the exogenous proton exchange equilibrium (1) is the only equilibrium of proton exchange operative involving Ac⁻ at T < 60 °C (Scheme 2, eq. 1).^[5]

In fact, the effectiveness of an equilibrium of the endogenous proton exchange between BMIm⁺ and Ac⁻, in pure BMImAc or in organic solvent at T < 60 °C, was definitively ruled out by us via electrochemical analysis that revealed that this equilibrium is operative at T > 60 °C.^[13]

As a consequence, in the Knoevenagel mixture selected by us, the cation BMIm⁺ behaves as a better counter ion of reactive anions Ac⁻ and HCO₃⁻ as it shows a lower ion pairing ability than Na⁺ and possibly enhances the reaction rate due to its hydrogen bond donor ability. As regards this last question, we compared the catalytic activity of the ionic liquid BMImAc with the one of BDMImAc (i.e. an imidazolium cation with a methyl group in the C2-position, thus having a noteworthy minor hydrogen bond donor ability). We verified that although the catalytic activity of BMImAc and BDMImAc are comparable (Table 1, entry 21 vs. 7), the lack of an acidic hydrogen atom in C-2 position renders BDMImAc a more efficient catalyst in shorter times (Table 1, entry 20 vs 8).^[14]

Conclusions

A comparison between the behaviour of ionic liquids BMImX (X = Ac⁻, HCO₃⁻, Cl⁻, BF₄⁻, PF₆⁻, I⁻, CF₃CO₂⁻, (CF₃SO₂)₂N⁻, CF₃SO₃⁻) as catalysts in the Knoevenagel reaction with the one of inorganic salts (NaAc, NaHCO₃, NaCl), allows to clarify the role of the anion X⁻ and of the imidazolium cation BMIm⁺ (pK_a = 22 in DMSO) in this important base catalysed organic reaction. The utilization of the ionic liquid BMImAc and BMImHCO₃ (concen-

Table 2. Knoevenagel condensation catalysed by BMImHCO₃^[a]

Entry	1	2	3	Time (min)	Yield % ^[b]
1		2a		60	90
2		2a		90	91
3		2a		90	95
4		2a		5	98
5		2a		10	98
6		2a		5	96
7		2a		10	96
8		2a		30	95
9		2a		30	95
10		2a		30	95
11		2a		10	95
12	1e	2b		5	95
13	1d	2b		5	96
14	1b	2b		30	97
15		2b		30	98
16	1a	2b		30	95
17	1g	2b		5	96
18	1h	2b		30	96

Table 2. continued

Entry	1	2	3	Time (min)	Yield % ^[b]
19	1l	2b		30	97
20	1b	2c		5	98

[a] A mixture of carbonyl compound (1.0 mmol), activated methylene compound (1.0 mmol) and catalyst (10 mol %) was stirred at room temperature in a 5-mL vial. [b] Isolated yield.

tration $\leq 10\%$) in different Knoevenagel mixtures (aromatic, heteroaromatic, or aliphatic aldehydes or ketones with different active methylene compounds) allows to obtain the condensation products in very elevated yields ($> 95\%$) and in short reaction times at room temperature in the absence of any solvent. The catalytic power of the ionic liquids is affected by the basicity of X⁻ and by the ability of the large counter ion BMIm⁺ to avoid the formation of ion pair. Accordingly, the catalytic power of BMImAc and BMImHCO₃ is considerable; on the contrary, the one of NaX is minor or quite trifling.

The exogenous equilibrium of proton exchange between the anions Ac⁻ and HCO₃⁻ and the cation BMIm⁺ is not competitive with the endogenous proton exchange. Nevertheless, the formation of a hydrogen bond between BMIm⁺ and aldehyde cannot be ruled out.

Supporting information summary

Experimental procedure and all spectroscopic data are provided in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: BMIm Hydrogen Carbonate • Catalyst • Ionic liquids • Knoevenagel condensation • Solvent free

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- [14] As further confirmation it was verified the activity of tetrabutylammonium acetate as catalyst in 10% amount that resulted operative after 1.5 h producing 91% yield.

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