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# Knoevenagel condensation catalyzed by novel Nmm-based ionic

liquids in water

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**ABSTRACT:** A series of novel *N*-methyl morpholine (Nmm) based ionic liquids with 1,2-propanediol group were synthesized and used as catalysts for Knoevenagel condensation at room temperature in water. Under the effect of the catalyst, various aldehydes or aliphatic ketones could react with a wide range of activated methylene compounds well, including malononitrile, alkyl cyanoacetate, cyanoacetamide,  $\beta$ -diketone, barbituric acid, 2-arylacetonitrile and thiazolidinedione. Furthermore, most of the products could be separated just by filtrating and washing with water. Additionally, the catalyst is recyclable and applicable for the large-scale synthesis.

#### INTRODUCTION

Ionic liquids (ILs) were introduced as environmentally benign reaction media and widely applied in the field of organic synthesis,<sup>1,2</sup> electrochemistry<sup>3</sup> and materials chemistry,<sup>4,5</sup> as a alternative procedure to avoid the use of harmful organic reagents and solvents. In recent years, many functional ILs have also been synthesized and developed further as catalysts, playing a remarkable role in various reactions like Knoevenagel condensation,<sup>6</sup> Henry reaction,<sup>7</sup> Mannich reaction,<sup>8</sup> Friedel-Crafts alkylation.<sup>9</sup> Meanwhile it has been found that cations and anions of ILs have synergetic effect in catalyzing these organic reactions.<sup>10,11</sup> Therefore, It is necessary to explore well-designed, cheap and easily available IL catalysts for organic synthesis.

Knoevenagel condensation between activated methylene compounds and aldehydes is one of the most important carbon-carbon double bond forming reactions, through losing a molecule of  $H_2O$  in the presence of catalysts such as solid bases,<sup>12,13</sup> amino acids,<sup>14,15</sup> lewis acids,<sup>16,17</sup> organometallic compounds.<sup>18,19</sup> The reaction usually takes long time to perform in organic solvent under heating or other special conditions.

"the best solvent is no solvent and if a solvent is needed it should preferably be water" stated by R. A. Sheldon.<sup>20</sup> Water represents a green solvent because it is cheap, readily available, non-flammable and non-toxic. However, Knoevenagel dehydration condensation in water is still a fundamental challenge because the large excess of water pushes the equilibrium in favor of the hydrated compounds.<sup>21</sup> A few examples of this reaction, conducted in water, were reported by employing a wide array of catalysts such as KI<sub>3</sub>,<sup>22</sup> ionic liquids,<sup>6,23</sup> organometallic cage<sup>24</sup> and calcium vanadate apatite.<sup>25</sup> In most cases, the range of activated methylene compounds was limited to malononitrile and alkyl cyanoacetate, and the range of carbonyl compounds was limited to aromatic aldehydes in water. Up to now, the poor tolerance

for substrates is still the main hurdle with the Knoevenagel condensation in water, and there is a need to improve the reaction based on green and sustainable chemistry.

In this manuscript, a serial of basic ionic liquids based on *N*-methyl morpholine (Nmm) and 3-chloro-1,2-propanediol were synthesized as catalysts in Knoevenagel condensation. These catalysts are compatible with various carbonyl compounds including aromatic/aliphatic/heterocyclic/ $\alpha$ , $\beta$ -unsaturated aldehydes and aliphatic ketones, meanwhile they are also tolerant of various activated methylene compounds such as malononitrile, alkyl cyanoacetate, cyanoacetamide,  $\beta$ -diketone, barbituric acid, 2arylnitrile and thiazolidinedione. Most of the products could be obtained at room temperature in water with excellent yield and selectivity, and the separation is simple just by filtrating and washing with water when the products are solid. Moreover, the catalysts are recyclable and applicable for the largescale synthesis. Additionally, as far as I know the application of morpholine-based ionic liquids in Knoevenagel condensation has not been reported before.

#### **RESULTS AND DISCUSSION**

Five new Nmm-based ionic liquids were synthesized (Scheme 1); the preparation of [Nmm-PDO][OH], [Nmm-PDO][OAc], [Nmm-PDO][BF<sub>4</sub>], [Nmm-PDO][Gly] and [Nbmm][OAc] were described in detail in the Supplementary Material.



Scheme 1. Synthesis of the [Nmm-PDO][X] and [Nbmm][OAc] Ionic Liquids

At first, the condensation of benzaldehyde with malononitrile was chosen as the model reaction to

optimize conditions including catalysts, reaction time and catalyst dosage. As shown in Table 1, Five Nmm-based IL catalysts were tested by using water as the solvent at room temperature for 7 min (Table 1, entries 1-4), and [Nmm-PDO][OAc] showed the highest activity (entry 2). The reaction could not be carried out successfully in the absence of IL catalysts, even reaction time was prolonged to 10 h (entry 6). For comparison, we used [Nbmm][OAc] as the catalyst, and the target product **3a** was only obtained in 66% yield (entry 5); although the anion is also the acetate ion in [Nmm-PDO][OAc], the yield of 3a was 99% while using [Nmm-PDO][OAc] as the catalyst (entry 2); the results implied hydrogen bonding interaction existed between the carbonyl group of the aldehyde and the hydroxyl groups in the cation of [Nmm-PDO][OAc], and the hydrogen bonding interaction increased the electrophilicity of the carbon atom in the carbonyl group (see reaction mechanism in Scheme 2). When reacted under solvent-free condition, the reaction mixture precipitated as soon as the catalyst was added, and it could not be stirred so well that the yield is not so high (entry 7). When using water as solvent, product 3a solidified and dissolved out of the reaction solution in several minutes (entry 2); and the pure product was isolated just by filtrating and washing with water. We also investigated the effect of catalyst dosage on the model reaction. When decreasing the dosage of the catalyst [Nmm-PDO][OAc], product 3a could be generated in high yield as well, but more time needed to complete the reaction (entry 8-10); even we reduced the amount of [Nmm-PDO][OAc] to 0.2 mol%, 3a was also provided with 73 % yield after 24 h.

Table 1. Knoevenagel condensation of benzaldehyde (1a) with malononitrile (2a) catalyzed by Nmm-base ionic liquids: Optimization of conditions.<sup>*a*</sup>

	СНО	+ ( CN	Catalyst r.t.		
	1a 2a		За		
Entry	Cat.		Slovent	Time(min)	Yield <sup>b</sup> (%)
1	[Nmm-PDO][	OH]	H <sub>2</sub> O	7	97
2	[Nmm-PDO][OAc]		$H_2O$	7	99
3	[Nmm-PDO][	BF <sub>4</sub> ]	H <sub>2</sub> O	7	73

4	[Nmm-PDO][Gly]	$H_2O$	7	90	
5	[Nbmm][OAc]	$H_2O$	7	66	
6	Catalyst free	$H_2O$	600	trace	
7	[Nmm-PDO][OAc]	neat	20	82	
$8^{\rm c}$	[Nmm-PDO][OAc]	$H_2O$	35	96	
9 <sup>d</sup>	[Nmm-PDO][OAc]	$H_2O$	90	95	
$10^{\rm e}$	[Nmm-PDO][OAc]	$H_2O$	1440	73	

<sup>*a*</sup> Reaction conditions: benzaldehyde (0.5 mmol, 51 μL), malononitrile (0.5 mmol, 33 mg), catalyst (10 mol%), solvent (1 mL), room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Catalyst 5 mol%. <sup>d</sup> Catalyst 1 mol%. <sup>e</sup> Catalyst 0.2 mol%.

The scope of Nmm-based ionic liquid-catalyzed Knoevenagel condensation was investigated under the optimized condition (10 mol% [Nmm-PDO][OAc] as the catalyst, water as solvent, room temperature); and most of the substrates could provide good to excellent yields as shown in Table 2. Under the optimized condition, aromatic/aliphatic/heteroaryl/ $\alpha$ , $\beta$ -unsaturated aldehydes as well as aliphatic ketones were completely tolerated in this reaction. Compared to various aldehydes, the condensations of aliphatic ketone with activated methylene compound need more time (entries 16-17, 24), because steric hindrance by the substrates could decrease the reaction rate. Moreover the reaction rate of aliphatic aldehydes were slower than aromatic aldehydes (entry 15). Furthermore, the position of the substituents on the aryl group (*ortho* vs *meta* vs *para*) affected the yield of **3**, and the *para*substituted substrates with least steric hindrance gave higher yields (compare entries 4-8).

we also extended the scope of substrates from malononitrile to a wide range of activated methylene compounds, including alkyl cyanoacetates, cyanoacetamide,  $\beta$ -diketone, benzothiazole-2-acetonitrile, barbituric acid, 2,4-thiazolidinedione. Compared to malononitrile, other activated methylene compounds needed more time to perform the Knoevenagel condensation with aldehydes or aliphatic ketones (Table 2, entries 18-37). Because the methylene group of malononitrile is more activated than other activated methylene compounds due to the stronger electron-withdrawing ability of the CN group. When we used water as solvent, 2,4-thiazolidinedione did not work under standard condition; this result caused by poor solubility of 2,4-thiazolidinedione in water possibly; fortunately, it also afforded the corresponding target compounds in the excellent yields when [Nmm-PDO][Gly] was used as the catalyst and the

temperature was raised to 60 °C under solvent-free condition (entries 36-37). To sum up, the Nmmbased ionic liquid-catalyzed Knoevenagel condensation above could tolerate various aromatic aldehydes, aliphatic ketones and diversified activated methylene compounds including alkyl cyanoacetates, cyanoacetamide,  $\beta$ -diketone, benzothiazole-2-acetonitrile, 2,4-thiazolidinedione, barbituric acid. In addition, compared with the reported melting point and NMR data, the reaction is highly stereoseletive when using Nmm-based ionic liquids as catalysts; the structure of new compounds **3u**, **3v**, **3a'** was also confirmed by X-ray crystallography (Figure S1-S3 in Supporting Information).

$ \begin{array}{c} R^{1} = 0 + H_{H} = WG^{1} \\ R^{2} + H_{H} = WG^{2} \end{array} \xrightarrow{ [MML-PDO][OAc] (10mol%)} R^{1} = EWG^{1} \\ R^{2} = EWG^{2} \end{array} $					
	1	2	3		
Entry	1	2	3	t/min	Yield <sup>b</sup> /%
1	CHO 1a	NC_CN 2a	CN CN 3a	7	99
2	H <sub>3</sub> C Tho	2a	H <sub>3</sub> C CN Sb	8	98
3	HO CHO	2a	HO 3c	8	99
4	H <sub>3</sub> CO <sup>CHO</sup> 1d	2a	H <sub>3</sub> CO 3d	8	99
5	OCH <sub>3</sub> CHO 1e	2a	OCH <sub>3</sub> CN CN 3e	10	92

Table 2. Knoevenagel condensations catalyzed by [MML-PDO][OAc]<sup>a</sup>





8



9

<sup>a</sup> Reaction conditions: carbonyl compound (0.5 mmol), activated methylene compound (0.5 mmol), catalyst [Nmm-PDO][OAc] (10 mol%), water (1 mL), room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Catalyst [Nmm-PDO][Gly] (10 mol%). <sup>d</sup> Solvent-free at 60 <sup>o</sup>C

The model reaction of benzaldehyde with malononitrile was chosen to examin the catalyst's recyclability and applicability in the large-scale synthesis. After completion of the reaction, product **3a** was filtered from the reaction mixture, the residual water solution of ionic liquid was evaporated under vacuum and reused for six runs without further processing; the result showed that the catalyst still maintaining a high catalytic activity even in the sixth run (See supporting information, Table S1). In addition, the scaled-up experiment was performed on a one-mol scale, and 143 g of **3a** were prepared in 93 % yield. This result demonstrated that the catalyst [Nmm-PDO][OAc] was efficient for large-scale production as well.

A possible mechanism for the [Nmm-PDO][OAc] catalyzed Knoevenagel condensation is proposed in Scheme 2 according to the results above (herein, reaction of benzaldehyde **1a** with ethyl cyanoacetate **2c** is chosen as the example). At first, the acetate anion of the IL removes a proton ( $H^+$ ) from the methylene of ethyl cyanoacetates to form carbanion **A**. At the same time, the hydroxyl groups of the IL and the carbonyl group of benzaldehyde can form hydrogen-bonding interactions which making benzaldehyde more vulnerable by **A**.<sup>23</sup> Then **A** attack on the electron-deficient carbonyl carbon of benzaldehyde leading to the Knoevenagel product **3y** via the intermediates **B** and **C**.

Scheme 2. Possible Mechanism for the Knoevenagel condensations catalyzed by [MML-PDO][OAc] between methyl cyanoacetate and benzaldehyde



To verify the proposed mechanism, we compared the FTIR spectrum of benzaldehyde with benzaldehyde-[Nmm-PDO][OAc] mixture, and the results were shown in Figure 1. It was found that the absorption peak of carbonyl group in benzaldehyde was at 1703 cm<sup>-1</sup>, while it was red-shifted to 1573 cm<sup>-1</sup> in mixture. Furthermore, we also compared the <sup>13</sup>C NMR spectrum of benzaldehyde with benzaldehyde-[Nmm-PDO][OAc] mixture (Figure S4,S5 in the ESI); the chemical shift of carbonyl group in benzaldehyde was 193.13, while it was 193.37 in mixture. These results implied the existence of the hydrogen bonding interactions between the carbonyl group of the aldehyde and the hydroxyl groups in [Nmm-PDO][OAc]. In addition, to verify the synergistic action of acetate anion and hydroxyl groups in the [Nmm-PDO][OAc], the catalyst of [Nmm-PDO][OAc] was replaced with alcohol-NaOAc binary system or NaOAc; and alcohol-NaOAc binary system showed higher catalytic activity than NaOAc under standard conditions; this result indicated the synergistic action of acetate anion and hydroxyl groups was exist in the catalytic system.



Figure 1. FTIR comparison of benzaldehyde and benzaldehyde-[Nmm-PDO][OH] mixture

Additionally, Thermal gravimetric analysis (TGA) of the [Nmm-PDO][OAc] and [Nmm-PDO][Gly] were also studied at the range of 25-600 °C, with a temperature ramp rate of 10 °C/min under nitrogen atmosphere (Figure S6,S7). As TG and DTG diagram indicates, [Nmm-PDO][OAc] showed a stable structure up to 197 °C (initial thermal-decomposition temperature), and [Nmm-PDO][Gly] up to 195 °C.

#### CONCLUSION

We have developed readily available and eco-friendly Nmm-based ILs as the efficient and recyclable catalysts for the Knoevenagel condensations of various aldehydes, aliphatic ketones with a wide range of activated methylene compounds. All the substrates containing activated methylene group except thiazolidinedione were performed well at room temperature in water, including malononitrile, alkyl cyanoacetates, cyanoacetamide,  $\beta$ -diketone, barbituric acid and benzothiazole-2-acetonitrile. And the thiazolidinedione could also afford the corresponding products when using [Nmm-PDO][Gly] as the catalyst at 60 °C under solvent-free condition. Additionally, the catalyst is recyclable and applicable for

the large-scale synthesis. All the results thus represent a practical and green catalyst for the Knoevenagel condensations in water.

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#### A. SUPPLEMENTARY DATA

The supplementary material contains general experimental procedures, characterization data, and <sup>1</sup>H, <sup>13</sup>C NMR spectra of these synthesized compounds. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org

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(1) The Knoevenagel condensations catalyzed by the novel Nmm-based ionic liquids show higher tolerance for diverse substrates.

(2) The purification is easy and applicable for the large-scale synthesis.

(3) The catalyst is recyclable.