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# Ionic liquid as catalytic and reusable media for cyanoethoxycarbonylation of aldehydes

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## 1. Introduction

lonic liquids (ILs) are of current interest as eco-friendly alternatives to the volatile organic solvents in organic synthesis and catalysis [1]. ILs are essentially made up of organic cations and inorganic anions [2–4] with unique chemical and physical properties such as negligible vapor pressure and decent solubility for organic, inorganic and organometallic compounds [5,6]. Notably, switching over to an ionic liquid from a traditional organic solvent often results in a significant improvement in reactivity and selectivity of a catalytic system [1]. ILs also have the ability to support homogeneous catalysts for their recyclability. Various ionic liquids are reported in the literature, however 1,3-dialkylimidazolium salts as room temperature ILs have emerged as leading media for various organic transformations [7–10].

Cyanohydrin esters are useful intermediates for pharmaceuticals, agrochemicals, and insecticides [11–15]. These cyanohydrin esters [16–26] can readily be synthesized by cyanocarbonylation of aldehydes in the presence of various catalysts [27–32]. However, invariably this reaction uses environmentally hazardous solvents and requires extreme reaction parameters such as prolonged reaction time, very low reaction temperatures, tedious product isolation and difficult catalyst recovery. In the quest of developing solvent-free and

## ABSTRACT

Various ionic liquids (**IL 1–9**) based on *N*-methyl *N'*-alkyl imidazolium salts were explored as catalytic media in cyanoethoxycarbonylation of various aldehydes. The study revealed that the alkyl chain length and counter ion of the ionic liquid are critical for the product yield. The highest product yield of cyanohydrin carbonate (up to 96%) was obtained with C<sub>5</sub> alkyl chain with Br<sup>-</sup> as counter ion (**IL 3**). On the other hand  $PF_6^-$  as counter ion failed to catalyze the cyanoethoxycarbonylation reaction.

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environmentally benign synthetic protocol, previously we have reported the synthesis of cyanosilylethers of aldehydes and ketones [33], aminonitriles [34],  $\beta$ -amino carbonyl compounds [35] under solvent-free condition. Herein we are reporting for the first time the use of ionic liquids as reusable catalyst as well as reaction media for cyanoethoxycarbonylation of aldehydes using ethylcyanoformate as a cyanide source.

# 2. Experimental

## 2.1. General information

NMR spectra were obtained with a Bruker F113V spectrometer (500 MHz and 125 MHz for <sup>1</sup>H and <sup>13</sup>C respectively) and are referenced internally with TMS. High-resolution mass spectra were obtained with a LC–MS (Q-TOF) LC (Waters), MS (Micromass) instruments. For the product purification flash chromatography was performed using silica gel 60–200 mesh purchased from s. d. Fine-Chemicals Limited, Mumbai (India). Shimadzu GC with CHORMATO-PAK (2 m, 4 mm) was used for the conversion of the substrates.

## 2.2. General procedure for the cyanoethoxycarbonylation

The cyanoethoxycarbonylation reaction was conducted in a 5 ml RBF sealed with a rubber septum. At first a mixture of 0.5 g of ionic liquids (**IL 1–9**) and an appropriate aldehyde (0.625 mmol) was stirred magnetically for 10 min. To this stirring solution,

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$$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ &$$

IL 5 : n=11:[C<sub>12</sub>mim]<sup>+</sup>Br<sup>-</sup>

Fig. 1. Structure of various ionic liquids.

ethylcyanoformate (1.2 mmol, 0.098 ml) was added through a syringe over a period of 5 min and the resulting reaction mass was further stirred for 2 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the product was extracted with *n*-hexane ( $3 \times 2$  ml) and purified by column chromatography (hexane:ethylacetate 90:10). The recovered ionic liquid was kept under vacuum for 8 h to remove volatiles and stored in a desiccator for its reuse in subsequent catalytic runs. Characterization data of some of the representative compounds are discussed below.

# 2.2.1. 2-Ethoxycarbonyl-2-hydroxy-2-phenyl-acetonitrile (2a)

Colorless liquid. <sup>1</sup>H NMR  $\delta$  = 1.32 (t, *J* = 7.5, 3H), 4.25–4.30 (m, 2H), 6.26 (s, 1H), 7.43–7.54 (m, 5H) ppm. <sup>13</sup>C NMR 14.21, 65.73, 66.48, 115.93, 127.99, 129.38, 130.74, 131.37, 153.53 ppm.

*2.2.2.* 2-*E*thoxycarbonyl-2-hydroxy-2-(2-methylphenyl)-acetonitrile (**2b**)

<sup>1</sup>H NMR  $\delta$  = 1.33 (t, *J* = 7.5, 3H), 2.44 (s, 3H), 4.25–4.31 (m, 2H), 6.38 (s, 1H), 7.23–7.37 (m, 3H), 7.55 (d, *J* = 8, 1H) ppm. <sup>13</sup>C NMR  $\delta$  = 14.27, 19.06, 64.72, 65.75, 115.83, 126.93, 128.75, 129.55, 130.83, 131.48, 136.90, 153.61 ppm.

2.2.3. 2-Ethoxycarbonyl- 2-hydroxy-2-(4-methylphenyl)-acetonitrile (2c)

<sup>1</sup>H NMR δ = 1.33 (t, *J* = 7, 3H), 2.38 (s, 3H), 4.28 (q, *J* = 7, 2H), 6.22 (s, 1H), 7.24–7.26 (m, 2H), 7.42–7.43 (m, 2H) ppm. <sup>13</sup>C NMR δ = 14.32, 21.53, 66.48, 65.73, 116.10, 128.12, 130.10, 141.14, 153.65 ppm.

2.2.4. 2-Ethoxycarbonyl-2-hydroxy-2-(3-methylphenyl)-acetonitrile (2d)

<sup>1</sup>H NMR  $\delta$  = 1.33 (t, *J* = 7, 3H), 2.38 (s, 3H), 4.24–4.30 (m, 2H), 6.22 (s, 1H), 7.26–7.34 (m, 4H) ppm. <sup>13</sup>C NMR  $\delta$  = 14.24, 21.24, 65.70, 66.53, 116.02, 125.09, 128.57, 129.26, 131.26, 131.51, 139.40, 153.57 ppm.

2.2.5. 2-Ethoxycarbonyl-2-hydroxy-2-(2-methoxylphenyl)-acetonitrile (**2e**)

<sup>1</sup>H NMR  $\delta$  = 1.32 (t, *J* = 7, 3H), 3.86 (s, 3H), 4.26–4.29 (m, 2H), 6.58 (s, 1H), 6.94(d, *J* = 8, 1H), 7.00–7.03 (m, 1H), 7.40–7.4(m, 1H), 7.55 (dd, *J* = 2, 6, 1H) ppm. <sup>13</sup>C NMR  $\delta$  = 14.28, 55.90, 61.85, 65.57, 111.25, 116.10, 119.60, 121.09, 128.09, 132.21, 153.66, 156.89 ppm.

2.2.6. 2-Ethoxycarbonyl-2-hydroxy-2-(4-bromophenyl)-acetonitrile (2h)

<sup>1</sup>H NMR  $\delta$  = 1.31 (t, *J* = 7, 3H), 4.22–4.30 (m, 2H), 6.20 (s, 1H), 7.40 (d, *J* = 8.5, 2H), 7.57 (d, *J* = 8.5, 2H) ppm. <sup>13</sup>C NMR  $\delta$  = 14.24, 65.78, 65.92, 115.52, 125.21, 129.60, 130.40, 132.63, 153.3 8 ppm.

2.2.7. 2-Ethoxycarbonyl-2-hydroxy-3-methyl-4-phenyl-but-3-enonitrile (2j)

<sup>1</sup>H NMR  $\delta$  = 1.37 (t, *J* = 7, 3H), 2.06 (s, 3H), 4.31 (q, *J* = 5, 2H), 5.79 (s, 1H), 6.85 (s, 1H), 7.29–7.39 (m, 5H) ppm. <sup>13</sup>C NMR  $\delta$  = 13.68, 65.10, 69.73, 114.84, 127.53, 127.94, 128.56, 133.02, 134.72, 153.02 ppm. Anal.

Calc. for  $C_{14}H_{15}NO_3$  C 68.56, H 6.16, N 5.71 found C 68.63, H 6.21, N 5.68 ppm.

2.2.8. 2-Ethoxycarbonyl-2-hydroxy-3,3-dimethylbutanenitrile (2k)

<sup>1</sup>H NMR  $\delta$  = 1.12 (s, 9H), 1.35 (t, *J* = 7, 3H), 4.25–4.31 (m, 2H), 4.92 (s, 1H) ppm. <sup>13</sup>C NMR  $\delta$  = 14.12, 25.10, 34.89, 65.37, 73.19, 115.96, 153.93 ppm. Anal. Calc. for C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub> C 58.36, H 8.16, N 7.56 found C 58.40, H 8.23, N 7.49.

2.2.9. 2-Ethoxycarbonyl-2-hydroxy-4-methylpentanenitrile (21)

<sup>1</sup>H NMR  $\delta$  = 0.99 (d, *J* = 5.5, 6H), 1.34 (t, *J* = 7, 3H), 1.80–1.91 (m, 3H), 4.25–4.30 (m, 2H), 5.23 (t, *J* = 7.5, 1H) ppm. <sup>13</sup>C NMR  $\delta$  = 14.11, 22.03, 22.15, 24.36, 40.85, 63.47, 65.37, 116.76, 153.62 ppm. Anal. Calc. for C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub> C 58.36, H 8.16, N 7.56 found C 58.31, H 8.18, N 7.52.

## 3. Result and discussion

A series of ionic liquids (**IL 1–9**) (Fig. 1) based on *N*-methyl *N'*alkyl imidazole having different alkyl chain lengths and counter ions was explored for their usefulness in cyanoethoxycarbonylation of benzaldehyde as a model substrate at room temperature and the results are presented in Table 1. Ionic liquids viz., 1-ethyl-3-methyl imidazolium bromide (IL 1), 1-dodecyl-3-methyl imidazolium bromide (IL 5) and 1-butyl-3-methyl imidazolium chloride (IL 6) were solid at room temperature; hence dry dichloromethane was used as co-solvent for carrying out cyanoethoxycarbonylation of benzaldehyde. These ILs in combination with dichloromethane gave 2ethoxycarbonyl-2-hydroxy-2-phenyl-acetonitrile in excellent yields (80-98%) in 4-12 h (entries 1, 5 and 6). Room temperature ILs viz., IL **2** and **IL 3** bearing  $C_4$  and  $C_5$  alkyl chain length with  $Br^-$  as counter ion (entries 2, 3) do not require the use of co-solvent to give the desired product in excellent yield (~98%) in 4 and 2 h respectively. Liquid **IL** with C<sub>7</sub> alkyl chain (**IL 4**) though gave high product yield (86%) but took 12 h reaction time (entry 4). These results led us to explore the role of counter anion with the **ILs** having alkyl chain C<sub>4</sub> and  $C_5$  where desired products were obtained in excellent yields. Besides, the results achieved with  $Cl^{-}$  as counter ion (entries 6 and 7) were as good as with  $Br^-$  ion. Ironically, when  $PF_6^-$  was used as counter ion there was no product formation even after 24 h (entries 8, 9). Surprisingly in the absence of any of the above **ILs** (entry 11) or in the presence of CH<sub>2</sub>Cl<sub>2</sub> (a commonly preferred solvent for this system, entry 12) there was no product formation in cyanoethoxycarbonylation

 Table 1

 Effect of carbon chain and counter ion on cyanoethoxycarbonylation of benzaldehyde.<sup>a</sup>

 CHO
 CN
 O

L

$\bigcirc$	+ NC 0	; RI	0,00
Entry	Ionic liquid	Time (h)	Conversion (%) <sup>b</sup>
1 <sup>c</sup>	<b>IL 1</b> ; $[C_2 mim]^+ Br^-$	4	93
2	<b>IL 2</b> ; $[C_4 mim]^+ Br^-$	4	98
3	<b>IL 3</b> ; [C <sub>5</sub> mim] <sup>+</sup> Br	2	>98
4	<b>IL 4</b> ; [C <sub>7</sub> mim] <sup>+</sup> Br <sup>-</sup>	12	86
5 <sup>c</sup>	<b>IL 5</b> ; [C <sub>12</sub> mim] <sup>+</sup> Br <sup>-</sup>	12	80
6 <sup>c</sup>	<b>IL 6</b> ; [C <sub>4</sub> mim] <sup>+</sup> Cl <sup>-</sup>	4	98
7	<b>IL 7</b> ; [C <sub>5</sub> mim] <sup>+</sup> Cl <sup>-</sup>	2.5	97
8	<b>IL 8</b> ; $[C_4 mim]^+ PF_6^-$	24	NR
9	<b>IL 9</b> ; $[C_5 mim]^+ PF_6^-$	24	NR
10 <sup>d</sup>	<b>IL 3</b> ; $[C_5 mim]^+ Br^-$	30	98
11	-	48	NR
12 <sup>e</sup>	-	48	NR

<sup>a</sup> 0.5 g ionic liquid (**IL 1–9**), benzaldehyde 63 μl, ethylcyanoformate 98 μl.

 $^{\rm b}\,$  Conversion determined by GC Analysis SHIMADZU GC-14B, CHORMATO-PAK (2 m, 4 mm) column.

<sup>c</sup> Using 0.5 ml CH<sub>2</sub>Cl<sub>2</sub>.

<sup>d</sup> 10 mol% ionic liquid with respect to the benzaldehyde.

<sup>e</sup> Reaction carried out in  $CH_2Cl_2$  as a solvent (1 ml).

0

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### Table 2 (continued)



<sup>a</sup> 0.5 g (2.3 mmol) of ionic liquid **IL 3**, 0.625 mmol of respective aldehyde and 1.2 mmol of ethylcynoformate were stirred for 2 h at room temperature.

<sup>b</sup> Conversion determined by SHIMADZU GC-14B, CHORMATO-PAK (2 m, 4 mm) column.

<sup>c</sup> Isolated yield.



Fig. 2. <sup>13</sup>C NMR spectrum of the mixture of ionic liquid **IL 3** and ethylcyanoformate (**ECF**) in CDCl<sub>3</sub> (only those peaks have been marked where changes were observed). Peaks marked with **A** and **B** belong to the starting material and intermediate species respectively.



Scheme 1. Proposed mechanism for cyanoethoxycarbonylation of benzaldehyde in IL 3.

of benzaldehyde. These results clearly demonstrate the role of ILs as catalyst as well as reaction media.

Among the various ILs used, IL 3 furnished best result in cyanoethoxycarbonylation of benzaldehyde, hence this ionic liquid was further employed as catalytic medium for the cyanoethoxycarbonylation of various aromatic and aliphatic aldehydes (Table 2). Excellent product yields (90-96%) achieved for all the aliphatic and aromatic substrates used in the present study suggest that this protocol is quite general in nature for cyanoethoxycarbonylation reaction.

It was rather intriguing to note that cyanoethoxycarbonylation of benzaldehyde proceeded smoothly in IL 2 and IL 3 but failed to proceed with IL 7 and IL 8. This led us to examine the role of counter ions in these ILs. It was clearly evident from the results that ILs with Br<sup>-</sup> and Cl<sup>-</sup> as counter ions worked well possibly due to the sufficient basic nature to polarize ethylcyanoformate (ECF), which is not the case with  $PF_6^-$  as counter ion. In order to capture an intermediate species during cyanoethoxycarbonylation reaction, we have taken equimolar quantity of ECF and IL 3 in CDCl<sub>3</sub> and recorded its <sup>13</sup>C NMR after 30 min (Fig. 2). The NMR spectrum clearly shows the presence of two sets of peaks for methylene and methyl carbons. While peaks marked with A in Fig. 2 belongs to ECF (compared with pure **ECF**) peaks marked with **B** are from the intermediate species **B** (Step 1, Scheme 1). Similarly along with CN from **ECF** (at  $\delta$ 109.26 ppm) peak for  $^{-}$ CN (at  $\delta$  111.45) possibly from intermediate B can also been seen. Based on these observations it can be deduced that a basic bromide ion polarize ECF and liberates <sup>-</sup>CN ion which attacks the carbonyl carbon of aldehyde (polarized by the electron deficient imidazole ring). Simultaneously, negatively charged oxygen of aldehyde attacks the acylbromide intermediate (formed in the



Fig. 3. Catalytic cycles with respect to % yield of the product formed in cyanoethoxycarbonylation of 2-MeO-benzaldehyde in ionic liquid (IL 3).

first step) to give the product (ethylcyanohydrin carbonate) and liberate the bromide ion (Step 2, Scheme 1). Since  $PF_6^-$  ion is not basic enough to produce such an intermediate species (**B**), it failed to catalyze the cyanation reaction. Further, chloride ion is also basic (though to a lesser extent than bromide), **ILs** having Cl<sup>-</sup> counter ion also show fairly good catalytic activity (Table 1, entries 6, 7).

The recyclability experiments were carried out in IL 3 as representative ionic liquid in the cyanoethoxycarbonylation of 2-MeObenzaldehyde as a representative substrate at room temperature. After completion of the catalytic reaction the products were extracted with *n*-hexane and purified by column chromatography. The recovered ionic liquid was dried in vacuum and was used as such for the subsequent catalytic runs. The catalytic system worked well up to eight catalytic runs (Fig. 3).

## 4. Conclusion

In conclusion we have developed a green and straightforward protocol for the synthesis of cyanohydrincarbonates of aldehydes using various ionic liquids as catalytic medium. Among all the ionic liquids used excellent product yield (up to 96%) was obtained with IL 3 in 2 h. Easy recyclability of ILs used in the present study with virtually no evaporational losses makes this protocol environmentally safe and scalable process for the synthesis of cyanohydrin carbonates of aldehydes.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.catcom.2010.04.005.

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