# RSC Advances

## COMMUNICATION

# Efficient synthesis of 2-oxazolidinones from epoxides and carbamates catalyzed by amine-functionalized ionic liquids

Jianpeng Shang,[*a] Zuopeng Li,[a] Caina Su,[a] Yong Guo[a] and Youquan Deng[b]

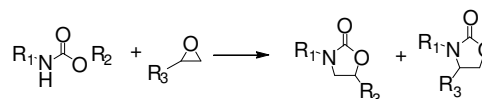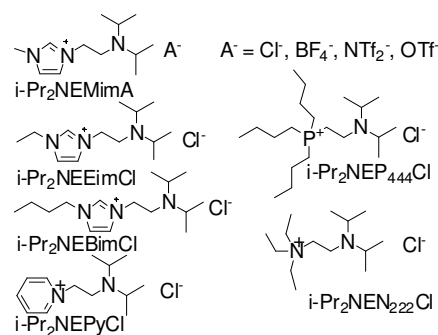**A series of amine-functionalized ionic liquids were prepared and their catalytic performance were tested in the synthesis 2-oxazodinones from epoxides and carbamates. Under optimized reaction conditions, good to excellent yields of various 2-oxazolidinones were achieved with different epoxides and carbamates. Moreoveer, the amine-functionalized ionic liquid catalyst could be easily recovered and reused without significantly loss in activity.**

2-oxazolidinones are important cyclic compounds in both fine chemicals and synthetic organic chemistry. They are widely used in the synthesis of pharmaceuticals, pesticides, cosmetics, and so on.[1-3] Since the 2-oxazolidinones preparation generally uses highly toxic phosgene,[4] and therefore involves environmental and safety problems, much efforts have been made to explore green alternative methods for 2-oxazolidinones synthesis. Several non-phosgene routes for 2-oxazolidinones synthesis have been developed: (1) oxidative carbonylation of β-aminoalcohols with CO and $O_2$, (2) carbonylation of β-aminoalcohols with organic carbonate, (3) cycloaddition of $CO_2$ with β-aminoalcohols or aziridines. Although the oxidative carbonylation of β-aminoalcohols catalyzed by transition metal is an efficient way to produce 2-oxazolidinones,[5-7] such route is not eco-friendly due to the potential explosion hazards and poisonous CO. As an alternative, organic carbonates were used for the synthesis 2-oxazolidinones.[8-10] It should be noted that the organic carbonates are mainly produced by phosgenation or oxidative carbonylation routes.[11, 12] Under these circumstances, the direct synthesis of 2-oxazolidiones from $CO_2$ and β-aminoalcohols[13-15] or aziridines[16-19] is preferable from environmental and economical viewpoints, however, some stoichiometrically consumed dehydrating reagents and high pressure or high temperature are required in most of these

works. Since epoxides are known to produce ring-opened addition products with nucleophilic reagents,[20] another non-phosgene route for 2-oxazolidinones synthesis is the reaction between epoxides and carbamates, and then intramolecular cyclization to give the expected 2-oxazolidinones,[21-23] scheme 1. Several alkaline agents,[23, 24] such as triethylamine, have been reported as catalysts for the 2-oxazolidinones synthesis from epoxides and carbamates. However, the volatility, separation and recovery problems of those catalysts are still maintained and accordingly limit their practical application.



**Scheme 1** Synthesis of 2-oxazolidinones from epoxides and carbamates



**Scheme 2** The structure and abbreviation of the amine-functionalized ionic liquids used in this study

Ionic liquids (ILs), defined as organic salts with melting points below 100 $^{o}$C, have attracted considerable attention as alternative reaction media and catalytic materials because of their peculiar physicochemical properties. Moreover, various functionalized ILs, incorporating different functional groups into the ILs structure, have been explored and used as solvents or catalysts in chemical processes.[25-27] Herein, in order to avoid the use of volatile organic amines, a series of amine-

a. Department of Chemistry and Environmental Engineering, Shanxi Datong University, Datong, 037009, China.
*Corresponding author: E-mail: nmsjp2006@126.com Fax: +86 352 7624721
b. Centre for Green Chemistry and Catalysis, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, China.

functionalized ILs (Scheme 2) were prepared and their catalytic performances for 2-oxazodinones synthesis from epoxides and carbamates were tested.
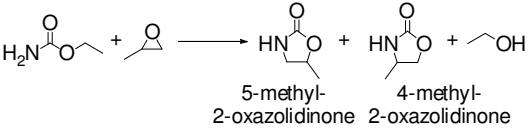
In our initial study, the reaction of propylene oxide (PO) and ethyl carbamate (EC) was chosen as the model reaction to explore the catalyst system, Table 1. Generally, the reaction was carried out at 140 $^{o}$C for 24h in the presence of 10 mol% catalyst. In the blank test (entry 1), the conversion of PO was only 12%, suggested that catalyst was essential for such reaction proceeded successfully. When the organic base triethylamine used as catalyst, the conversion of PO reached to 90%, entry 2. Owing to the volatility of organic amine and the high catalytic activity toward this reaction, some amine-functionalized ILs with different cations and anions were prepared and investigated in such reaction, entry 3-12. From the results, it could be found that both the cation and anion of the investigated ILs have strong impact on the catalytic activity, and the highest conversion of PO was achieved with i-Pr$_2$NEMimCl as catalyst (entry 3). The effects of the cation structure on the catalytic performance were tested using pyridinium-, quaternary ammonium-and quaternary phosphonate-based amine-functionalized ILs as catalysts (entries 4-6), the results showed that the catalytic efficiency decreased in the order of i-Pr$_2$NEMimCl > i-Pr$_2$NEP$_{444}$Cl > i-Pr$_2$NEN$_{222}$Cl > i-Pr$_2$NEPyCl. The effects of imidazolium based amine-functionalized ILs with different anions (Cl$^-$, BF$_4^-$, NTf$_2^-$, OTf$^-$) on the reaction was also investigated. The halide anion Cl$^-$ gave excellent result, Whereas, BF$_4^-$, NTf$_2^-$, OTf$^-$ were found to be inactive (entries 7-9). When the NaCl was used as catalyst (entry 10), the conversion of PO was only 12%, suggested that the single Cl$^-$ has no activity for this reaction and the high activity of the i-Pr$_2$NEMimCl may derived from the combination effects of amine group and Cl$^-$. Moreover, the alkyl length of the imidazolium cation has a weak effects on the reaction and the conversion of the PO decreased from 97% to 88% as alkyl chain length of the cation increased from C$_1$ to C$_4$ (entries 3, 11-12), probably duo to the alteration of the solubility of the ionic liquids in the reaction mixture. Furthermore, although the general solid base KF/Al$_2$O$_3$ was found to show some catalytic activity for this reaction (entry 13), the conversion of PO was lower than that of i-Pr$_2$NEMimCl used as catalyst, which suggested that the ionic environment supplied by ILs may be helpful for such reaction.

Subsequently, the influence of the reaction temperature on the reaction was investigated under identical reaction condition. As is easily seen, reaction temperature has a great influence on the reaction outcome with variation of reaction temperature from 120 to 140 $^{o}$C (entries 3, 14-15), the conversion of PO reached 97% as the reaction temperature was increased up to 140 $^{o}$C. Additionally, the conversion of PO was increased with increasing the reaction time and reached 97% after 24 h (entries 3, 16-18).

Notably, the 5-methyl-2-oxazolidinone was preferentially formed with high selectivity in all cases listed in Table 1. The major product corresponds to the nucleophilic ring opening of the PO at the less substitute site under basic conditions,[28] followed by intramolecular cyclization to produce the

corresponding 5-methyl-2-oxazolidinone. Moreover, the 4-methyl-2-oxazolidinone as byproduct was observed, which was formed duo to the nucleophilic ring opening of the PO at methyl substitute site.

**Table 1.** Synthesis of 5-methyl-2-oxazolidinone from PO and EC with different catalysts and reaction conditions[a]



5-methyl-2-oxazolidinone    4-methyl-2-oxazolidinone

| Entry | Catalyst (mol%) | T($^{o}$C) | T(h) | Conv. (%) | Sel. (%)[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | -- | 140 | 24 | 12 | 98 | 11 |
| 2 | Et$_3$N | 140 | 24 | 90 | 99 | 88 |
| 3 | i-Pr$_2$NEMimCl | 140 | 24 | 97 | 99 | 96 |
| 4 | i-Pr$_2$NEPyCl | 140 | 24 | 67 | 99 | 64 |
| 5 | i-Pr$_2$NEN$_{222}$Cl | 140 | 24 | 73 | 98 | 70 |
| 6 | i-Pr$_2$NEP$_{444}$Cl | 140 | 24 | 88 | 99 | 84 |
| 7 | i-Pr$_2$NEMimBF$_4$ | 140 | 24 | 0 | - | - |
| 8 | i-Pr$_2$NEMimNTf$_2$ | 140 | 24 | 0 | - | - |
| 9 | i-Pr$_2$NEMimOTf | 140 | 24 | 0 | - | - |
| 10 | NaCl | 140 | 24 | 12 | 98 | 10 |
| 11 | i-Pr$_2$NEEimCl | 140 | 24 | 88 | 98 | 85 |
| 12 | i-Pr$_2$NEBimCl | 140 | 24 | 88 | 98 | 85 |
| 13 | KF/Al$_2$O$_3$ | 140 | 24 | 72 | 99 | 70 |
| 14 | i-Pr$_2$NEMimCl | 120 | 24 | 57 | 98 | 54 |
| 15 | i-Pr$_2$NEMimCl | 130 | 24 | 78 | 98 | 75 |
| 16 | i-Pr$_2$NEMimCl | 140 | 8 | 80 | 99 | 78 |
| 17 | i-Pr$_2$NEMimCl | 140 | 15 | 91 | 98 | 88 |
| 18 | i-Pr$_2$NEMimCl | 140 | 20 | 95 | 98 | 92 |

[a] Reaction conditions: 10 mmol PO; 15 mmol EC; 1 mmol catalysts; 120-140 °C; 8-24 h. Conversions and selectivities were determined by gas chromatography.

[b] Selectivity of the 5-methyl-2-oxazolidinone.

[c] Isolated yield based on the charged PO.
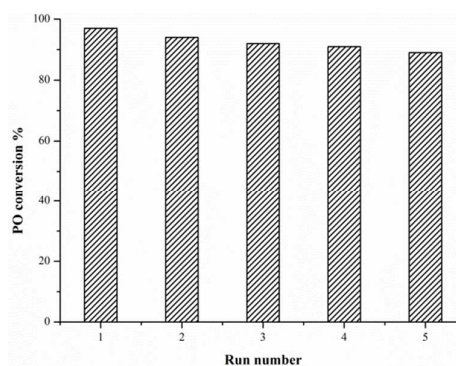


Fig.1 Recycling test of i-Pr$_2$NEMimCl. Reaction conditions: 10 mmol PO; 15 mmol EC; recovered i-Pr$_2$NEMimCl; 140 °C; 24 h.

The recycling performance of i-Pr$_2$NEMimCl was also investigated in the reaction of EC and PO, Fig.1. The results showed a slight decrease in the activity after each run, which could be ascribed to the fact that i-Pr$_2$NEMimCl was recovered only 95% of the charged amount after each run by extracted

with diethyl ether, suggesting that the i-Pr$_2$NEMimCl catalyst could be reused without significantly loss in activity.

**Table 2**. Synthesis of 2-oxazolidinones from various epoxides and EC[a]



| Entry | Epoxide | Major product | Conv. (%) | Sel. (%)[b] | Yield (%)[c] |
|-------|---------|---------------|-----------|-------------|--------------|
| 1 | | | 97 | 99 | 96 |
| 2 | | | 96 | 100 | 95 |
| 3 | | | 95 | 98 | 93 |
| 4 | | | 97 | 99 | 95 |
| 5 | | | 98 | 98 | 95 |
| 6 | | | 96 | 98 | 94 |
| 7 | | | 95 | 74 | 93 |
| 8 | | | 82 | 100 | 81 |

[a] Reaction conditions: 10 mmol epoxides; 15 mmol EC; 1 mmol catalysts; 140 °C; 24 h. Conversions and selectivities were determined by gas chromatography.

[b] Selectivity of the 5-substituted-2-oxazolidinone.

[c] Isolated yield based on the charged PO.

To demonstrate the utility and generality of this approach to formation 2-oxazolidinones, the reaction of EC with different epoxides were carried out under the optimized conditions, the results shown in Table 2. Excellent yields of the corresponding 2-oxazolidinones were obtained with terminal epoxides (entries 1–7), while the disubstituted epoxide, cyclohexene oxide (entry 8), gave lower activity towards the production of the corresponding 2-oxazolidinones, which might be due to the high hindrance of cyclohexene oxide. However, the selectivity of the 5-substituted-2-oxazolidinones for the styrene oxide (entry 7) was much lower than that of other epoxides, which might be ascribed to the conjugative effect derived from the benzene ring, which should favourably attack at the carbon atom at which phenyl substitute was connected to afford 4-substituted-2-oxazolidinones.[29]

Moreover, the reaction of PO and different carbamates with various substituents on nitrogen or oxygen atom were also

investigated, the results shown in Table 3. The carbamates with different alkyl or benzyl substituent on oxygen atom (entries 1-4) gave good to excellent yields of the corresponding 2-oxazolidinones, however, the much lower yield of the corresponding 2-oxazolidinones was obtained when the phenyl substituent on the oxygen atom (entry 5), which could be ascribed to the weaker leaving ability of the *phenoxy* than the alkoxy or benzyloxy during the intramolecular cyclization step. Additionally, the substituent on the nitrogen atom of carbamates gave lower yield of the corresponding 2-oxazolidinones, entries 6-7, which could be duo to the high hindrance of substituent on the nitrogen atom and unfavorable for the nucleophilic addition to the PO.

**Table 3**. Synthesis of 2-oxazolidinones from various carbamates and PO[a]



| Entry | carbamate | Major product | Conv. (%) | Yield (%)[b] |
|-------|-----------|---------------|-----------|--------------|
| 1 | | | 97 | 96 |
| 2 | | | 98 | 96 |
| 3 | | | 96 | 94 |
| 4 | | | 95 | 93 |
| 5 | | | 46 | 43 |
| 6 | | | 72 | 70 |
| 7 | | | 76 | 74 |

[a] Reaction conditions: 10 mmol PO; 15 mmol carbamates; 1 mmol catalysts; 140 °C; 24 h. Conversions were determined by gas chromatography.

[b] Isolated yield based on the charged PO.

Based on the reaction mechanism reported in the previous literature,[23] the 2-oxazolidinone was formed in two consecutive steps, scheme 3. The first is the formation of compound I by nucleophilic addition between epoxide and carbamate, followed by the formation of the 2-oxazolidinone II in the second step by intramolecular cyclization.
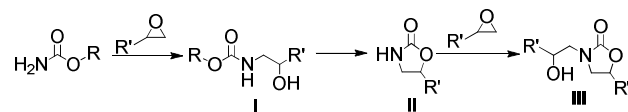


**Scheme 3** Illustration for the formation of hydroxyl functionalized 2-oxazolidinones

**COMMUNICATION**

It is worth to note that during the reaction processes, we never detected the presence of the compound I. This fact indicated that the rate-limiting step for the conversion of epoxide into 2-oxazolidinone is the ring-opening step of epoxide. Thus, we supposed that if the epoxide is in excess, the further ring opening of epoxide with the formed 2-oxazolidinone II could be occurred and generate the hydroxyl functionalized 2-oxazolidinone III which also represent an important class of compounds have wide utility in pharmaceutical chemistry. So, we carried out the reaction under the optimized condition with the mole ratio of EC：epoxide equal to 1:3. The results are shown in Table 4. It can be seen that excellent yields of hydroxyl functionalized 2-oxazolidinones were obtained with various epoxides.

Table 4. Hydroxyl functionalized 2-oxazolidinones synthesis from various epoxides and EC[a]



| Entry | carbamate | Major product | Conv. (%) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | | | 98 | 97 |
| 2 | | | 97 | 96 |
| 3 | | | 97 | 95 |
| 4 | | | 98 | 98 |
| 5 | | | 97 | 96 |
| 6 | | | 96 | 94 |

[a] Reaction conditions: 30 mmol epoxides; 10 mmol EC; 1 mmol catalysts; 140 °C; 24 h. Conversions were determined by gas chromatography.

[b] Isolated yield based on the charged EC.

## Conclusions

In conclusion, an amine-functionalized ILs catalyst was developed for the synthesis of 2-oxazolidinones from epoxides and carbamates. Under the optimized reaction conditions, good to excellent yields of various 2-oxazolidinones were obtained with different epoxides and carbamates. Meanwhile,

the hydroxyl functionalized 2-oxazolidinones were successfully synthesized when the epoxides were in excess.

## Notes and references

1   G. Zappia, E. Gacs-Baitz, G. Delle Monache, D. Misiti, L. Nevola and B. Botta, *Curr. Org. Chem.,* 2007, **4**, 81-135.
2   X. Dou, L. He and Z. Yang, *Synth. Commun.,* 2012*,* **42***,* 62-74.
3   T. A. Mukhtar and G. D. Wright, *Chem. Rev.*, 2005, **105**, 529-542.
4   S. Matsunaga, N. Kumagai, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 4712-4713.
5   B. Gabriele, G. Salerno, D. Brindisi, M. Costa and G. P.Chiusoli, *Org. Lett.*, 2000*,* **2**, 625-627.
6   J. Liu, X. Peng, J. Liu, S. Zheng, W. Sun and C. Xia, *Tetrahedron Lett.*, 2007, **48**, 929-932.
7   F. Li and C. Xia, *J. Catal.*, 2004, **227**, 542-546.
8   S. Pulla, V. Unnikrishnan, P. Ramidi, S. Z. Sullivan, A. Ghosh, J. L. Dallas and P. Munshi, *J. Mol. Catal. A: Chem.*, 2011, **338**, 33-43.
9   B. Wang, S. Yang, L. Min, Y. Gu, Y. Zhang, X. Wu, L. Zhang, E. H. M. Elageed, S. Wu, and G. Gao, *Adv. Synth. Catal.*, 2014, **356**, 3125-3134.
10  F. Li, H. Li, L. Wang, P. He and Y. Cao, *Catal. Sci. Technol.*, 2015, **5**, 1021-1034.
11  B. Schäffner, F. Schäffner, S. P. Verevkin and A. Börner, *Chem. Rev.*, 2010, **110**, 4554-4581.
12  S. A. Anderson and T. W. Root, *J. Mol. Catal. A: Chem.*, 2004, **220**, 247-255.
13  S. I. Fujita, H. Kanamaru, H. Senboku and M. Arai, *Int. J. Mol. Sci.*, 2006, **7**, 438-450.
14  K. I. Tominaga and Y. Sasaki, *Synlett*, 2002, **2**, 307-309.
15  R. Juárez, P.Concepción, A. Corma and H. García, *Chem. Commun.*, 2010, **46**, 4181-4183.
16  A. W. Miller and S. T. Nguyen, *Org. Lett.*, 2004, **6**, 2301-2304.
17  M. T. Hancock and A. R. Pinhas, *Tetrahedron Lett.*, 2003, **44**, 5457-5460.
18  Y. Wu, L. He, Y. Du, J. Wang, C. Miao and W. Li, *Tetrahedron*, 2009, **65**, 6204-6210.
19  R. A. Watile, D. B. Bagal, K. M. Deshmukh, K. P. Dhake and B. M. Bhanage, *J. Mol. Catal. A: Chem.*, 2011, **351**, 196-203.
20  S. Bonollo, F. Fringuelli, F. Pizzo and L. Vaccaro, *Synlett*, 2007, **17**, 2683-2686.
21  L. I. Kas'yan, V. A. Pal'chikov and Ya. S. Bondarenko, *Russ. J. Org. Chem.*, 2011, **47**, 797-841.
22  A. Cwik, A. Fuchs, Z. Hell, I. Bojtos, D. Halmai and P. Bombicz, *Org. Biomol. Chem.*, 2005, **3**, 967-969.
23  G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre and L. Sambri, *Org. Lett.*, 2005, **7**, 1983-1985.
24  Y. Iwakura and S. I. Izawa, *J. Org. Chem.,* 1964, **29**, 379-382.
25  R. D. Rogers and K. R. Seddon, *Science,* 2003, **302**, 792-793.
26  H. P. SteinrÜk and P. Wasserscheid, *Catal. Lett.*, 2015, **145**, 380-397.
27  Y. Gu and G. Li, *Adv. Synth. Catal.*, 2009, **351**, 817-847.
28  S. Bonollo, F. Fringuelli, F. Pizzo and L. Vaccaro, *Synlett*, 2007, **17**, 2683–2686.
29  S. Bonollo, D. Lanari and L. Vaccaro, *Eur. J. Org. Chem.*, 2011, **14**, 2587–2598.

The amine-functionalized ionic liquids can be an efficient catalyst for 2-oxazolidinones synthesis from epoxides and carbamates