

Efficient and eco-friendly process for the synthesis of *N*-substituted 4-methylene-2-oxazolidinones in ionic liquids

Qinghua Zhang, Feng Shi, Yanlong Gu, Jing Yang and Youquan Deng*

Centre for Green Chemistry and Catalysis, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China

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Abstract—The carbonylation of amines with propargylic alcohol using CO₂ as carbonyl source to yield *N*-substituted 4-methylene-2-oxazolidinones could efficiently proceed in ionic liquids, and various 4-methylene oxazolidinones with high yields could be obtained under relatively mild conditions. This result showed that ionic liquid might be an effective catalyst and reaction medium for the activation of CO₂, which also offered a new way to the chemical fixation of CO₂.

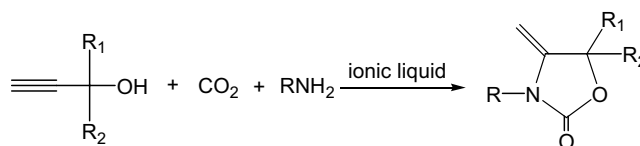
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1. Introduction

Oxazolidinones are an important class of heterocyclic compounds, which have been found to have a large range of applications as intermediates in organic synthesis.¹ Because they often show good antibacterial properties, these heterocyclic compounds are also widely used in pharmaceutical chemistry.² The conventional methods for the synthesis of oxazolidinones involve the reactions of amino alcohols with several different reagents such as phosgene,³ urea,⁴ dialkyl carbonate,⁵ isocyanates,⁶ or a mixture of carbon monoxide and oxygen,⁷ etc. From an environmental viewpoint, one-step synthesis of oxazolidinones using CO₂ as carbonyl source was highly desirable since CO₂ is a renewable, abundant and a nontoxic source of functional carbon units. Jean et al. reported that the synthesis of 4-methylene-2-oxazolidinones from primary amine, propargylic alcohol, and CO₂ could be effectively catalyzed by tertiary phosphines.⁸ However, the usage of large amounts of toxic tertiary phosphines made this process non-eco-friendly. These heterocyclic compounds could also be prepared directly from propargylic amine, alcohol, and CO₂ in the presence of noble metal catalyst,⁹ and good yield of the desired product could be obtained when appropriate solvents, such as toluene, were used. More recently, Kawanami et al. have also

reported the synthesis of oxazolidinones from CO₂ and aziridine in ionic liquids using I₂ as catalyst.¹⁰

In recent years, room temperature ionic liquids (RTILs) have received more and more attention as a new kind of possible ‘green’ solvent and catalyst media.¹¹ In comparison with conventional organic solvents currently being used in the industry, RTILs have several benefits, for example, they are nonvolatile, reusable, designable, thermally stable, and nonflammable, etc. Based on these outstanding characteristics, the potential industrial applications of RTILs in organic synthesis, gas separations, liquid–liquid extractions, electrochemical studies, and catalytic reactions, have been extensively studied.^{12–16} In our previously reported work, ionic liquids have been found to be efficient catalysts and reaction media for the activation of CO₂,¹⁷ and the synthesis of disubstituted ureas from aliphatic amines and CO₂ could be efficiently carried out.¹⁸ Herein, we wish to report that this method can be adapted for the one-step synthesis of *N*-substituted 4-methylene-2-oxazolidinones in the presence of propargylic alcohol (Scheme 1).



Scheme 1. Synthetic route for *N*-substituted 4-methylene-2-oxazolidinones.

Keywords: Ionic liquid; Carbon dioxide; Carbonylation; Catalysis; Amine.

*Corresponding author. Tel./fax: +86 931 4968116; e-mail: yqeng@lzb.ac.cn

2. Results and discussion

The results for synthesis of *N*-substituted 4-methylene-2-oxazolidinones derivatives from aliphatic amines, 2-methyl-3-butyn-2-ol and CO₂ are shown in Table 1. Under the given reaction conditions, the reaction between cyclohexyl amine and 2-methyl-3-butyn-2-ol hardly occurred if dimethyl sulfoxide and toluene were used as solvents (entries 1–3), and 44.1–91.6% yields could be obtained in the presence of ionic liquids (entries 4–10). As the results showed, the type of cations and anions of ionic liquids have strong impact on the forma-

tion of *N*-substituted 4-methylene-2-oxazolidinones derivatives. For ionic liquids containing BMIm⁺ cation, the best result was achieved in the presence of BMImBF₄ with 81.4% yield. The application of ionic liquid with PF₆[−] anion gave a relatively poor result, 44.1% yield, which may be related to the instability of anion PF₆[−] under the reaction conditions. The effects of ionic liquids containing different cations were further investigated. As it is shown in entries 6–8, the catalytic activity was gradually improved along with the increasing of the carbon number of alkyl chain and 91.6% yield was achieved when ionic liquid DMImBF₄ was used.

Table 1. The carbonylation of amines with 2-methyl-3-butyn-2-ol in different ionic liquids

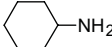
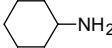
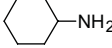
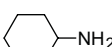
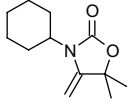
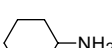
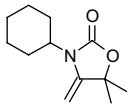
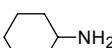
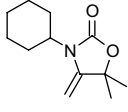
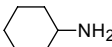
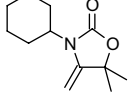
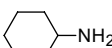
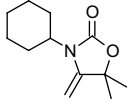
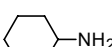
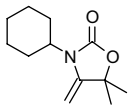
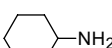
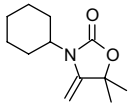
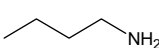
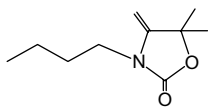
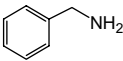
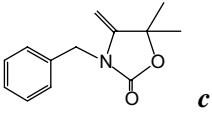
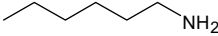
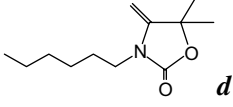
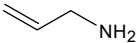
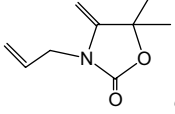
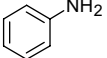
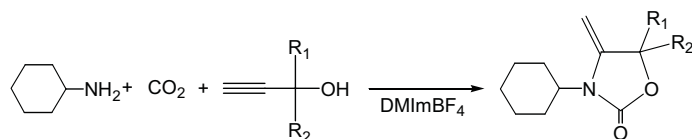
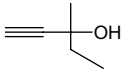
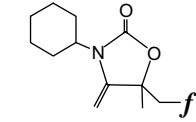
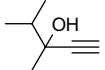
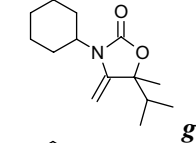
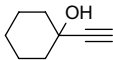
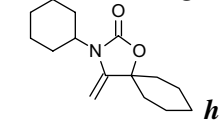
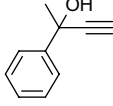
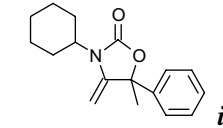
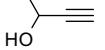
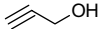
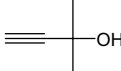
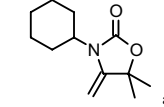
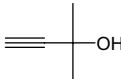
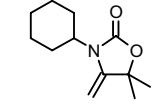
$\text{CH}_3\text{C}\equiv\text{CC}(\text{CH}_3)_2\text{OH} + \text{CO}_2 + \text{RNH}_2 \xrightarrow{\text{ionic liquid}} \text{R-N} \begin{array}{c} \diagup \text{C}(\text{CH}_3)=\text{C}(\text{CH}_3) \diagdown \\ \diagup \text{O} \diagdown \\ \text{O} \end{array}$				
Entry	Amines	Solvents	Products	Yield (%)
1		—	—	—
2		DMSO	—	—
3		Toluene	—	—
4		BMImCl	 a	48.6
5		BMImBr	 a	51.8
6		BMIMBF ₄	 a	81.4
7		BMIMPF ₆	 a	44.1
8		EMImBF ₄	 a	72.1
9		HMImBF ₄	 a	85.4
10		DMImBF ₄	 a	91.6
11		DMImBF ₄	 b	84.4

Table 1 (continued)

Entry	Amines	Solvents	Products	Yield (%)
12		DMImBF ₄	 c	95.3
13		DMImBF ₄	 d	82.7
14		DMImBF ₄	 e	77.9
15		DMImBF ₄	—	—

Reaction conditions: amine 10 mmol, 2-methyl-3-butyn-2-ol 10 mmol, ionic liquid 3 mL, CO₂ 5 MPa, 120 °C, 10 h.

Table 2. The carbonylation of cyclohexyl amine with different propargylic alcohol^a

Entry	Alcohols	Solvent	Product	Yield (%)
1		DMImBF ₄	 f	52.9
2		DMImBF ₄	 g	51.3
3		DMImBF ₄	 h	87.3
4		DMImBF ₄	 i	88.6
5		DMImBF ₄	—	—
6		DMImBF ₄	—	—
7 ^b		DMImBF ₄	 a	83.3
8 ^c		DMImBF ₄		77.5

^a Reaction conditions: cyclohexyl amine 10 mmol, 2-methyl-3-butyn-2-ol 10 mmol, ionic liquid 3 mL, CO₂ 5 MPa, 120 °C, 10 h.

^b Reused in the second time.

^c Reused in the third time.

The carbonylation reactions of 2-methyl-3-butyn-2-ol with various amines were further carried out in ionic liquid DMIImBF₄ (entries 11–15). It could be found that aliphatic amines could efficiently react with 2-methyl-3-butyn-2-ol, and high yields (77.9–95.3%) could be achieved when *n*-butylamine, *n*-hexylamine, benzylamine, and allylamine were employed as substrates, respectively. Unfortunately, the reaction hardly occurred for aromatic amines, for example, aniline, under the same reaction conditions, which may be attributed to the weak nucleophilic ability of the aromatic amines (entry 15).

The activity of ionic liquid DMIImBF₄ for reactions of cyclohexyl amine with different propargylic alcohols was further investigated (Table 2). Several results with moderate to high yields were obtained for four tertiary propargylic alcohols (entries 1–4). 88.6% yield could be achieved when 1-ethynyl-1-cyclohexanol was employed while only 51.3% yield could be obtained for 3,4-dimethyl-1-pentyn-3-ol. However, no desired products were detected when the reaction between cyclohexyl amine with secondary or primary propargylic alcohols were investigated, which indicated that such reaction seems to be specific only for tertiary alcohols (entries 5–6). Finally, the reusability of ionic liquid was conducted for the synthesis of 4-methylene-2-oxazolidinones (**a**) because of its high activity and 83.3% and 77.5% yield maintained, respectively, when it was reused at the second and third time (entry 7–8).

3. Conclusions

In conclusion, RTILs could be effective catalysts and reaction media for the activation of CO₂ to yield *N*-substituted 4-methylene-2-oxazolidinones from amines and propargylic alcohol with high yields under relatively mild conditions. Further investigation about the reaction mechanism and optimization of the ionic liquid as reaction medium with catalytic function is now underway.

4. Experimental

All reagents were of AR grade and used without further purification. Following ionic liquids were used in these reactions: BMIImCl (BMIIm = 1-butyl-3-methyl imidazole); BMIImBr; BMIImBF₄; BMIImPF₆; EMIImBF₄ (EMIIm = 1-ethyl-3-methyl imidazole); HMIImBF₄ (HMIIm = 1-hexyl-3-methyl imidazole); DMIImBF₄ (DMIIm = 1-decyl-3-methyl imidazole). All ionic liquids used in this work were synthesized according to previous papers¹⁹ and were dried in vacuo at 90 °C before use.

4.1. General procedure

All reactions were conducted in a 90 mL autoclave with a glass tube inside equipped with magnetic stirring. In each reaction, 2 mL ionic liquid, 10 mmol of amines, and 10 mmol of propargylic alcohol were introduced in turn without any additional organic solvent. The

reactor was flushed with CO₂, and then it was pressurized with the gas to 5 MPa. The reaction mixture was then magnetically stirred at 120 °C for 10 h. After reaction, the reaction vessel was cooled to room temperature and the resulting mixture was extracted with diethyl ether (4 mL × 3). Then, the combined organic phase was evaporated and dried in vacuum to afford the primary product. A pure product was obtained by further recrystallization of the primary product with a solution containing water and ethanol. Quantitative analysis was conducted with an Agilent 6820 GC (FID detector) and qualitative analyses were conducted with a HP 6890/5973 GC–MS. ¹H NMR spectrometer was recorded on an AV400 Bruker spectrometer operating at 400 MHz. Chemical shifts were reported in parts per million (ppm δ) and referenced to TMS. Infrared spectra were recorded as a thin film on sodium bromide and absorptions were reported in wavenumbers (cm^{−1}). All UV–vis spectra of products were recorded from an Agilent B453 spectrophotometer using anhydrous methanol as solvent. Melting points are uncorrected.²⁰

Acknowledgements

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20. Spectral data for selected products: compound (**a**): white solid, mp 55–56 °C, δ_{H} (400; CCl_3D) 1.10–1.17 (1H, m), 1.26–1.37 (2H, m), 1.42 (6H, s), 1.61–1.64 (3H, d, $J = 9.6$ Hz), 1.76–1.79 (2H, d, $J = 10.4$ Hz), 1.95–2.02 (2H, m), 3.54 (1H, m), 4.16 (1H, d, $J = 2.8$ Hz) and 4.34 (1H, d, $J = 2.8$ Hz) ν/cm^{-1} 1753 (C=O); $\lambda_{\text{max}}/\text{nm}$ 222, GC–MS: $m/z = 209$ (M^+), 194, 128, 112, 96, 84, 67, 55, 41; compound (**f**): white solid, mp 62–63 °C, δ_{H} (400; CCl_3D) 0.76 (3H, t, $J = 7.4$ Hz), 1.14 (1H, m), 1.29 (2H, m), 1.37 (3H, s), 1.62–1.78 (7H, m), 1.91–2.03 (2H, m), 3.57 (1H, m), 4.11 (1H, d, $J = 2.4$ Hz) and 4.40 (1H, d, $J = 2.8$ Hz) ν/cm^{-1} 1752 (C=O); $\lambda_{\text{max}}/\text{nm}$ 223, GC–MS: $m/z = 223$ (M^+), 194, 164, 142, 113, 98, 82, 67, 55, 41; compound (**g**): white solid, mp 99–101 °C; δ_{H} (400; CCl_3D) 0.88–1.96 (20H, m), 2.07 (1H, t, $J = 11.0$ Hz), 3.94 (1H, d, $J = 2.8$ Hz) and 4.25 (1H, d, $J = 2.4$ Hz) ν/cm^{-1} 1762 (C=O); $\lambda_{\text{max}}/\text{nm}$ 224, GC–MS: $m/z = 237$ (M^+), 195, 194, 178, 156, 113, 112, 83, 67, 55, 41; $\text{C}_{14}\text{H}_{23}\text{NO}_2$ (237.341): Calcd: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.64; H, 9.91; N, 5.99.