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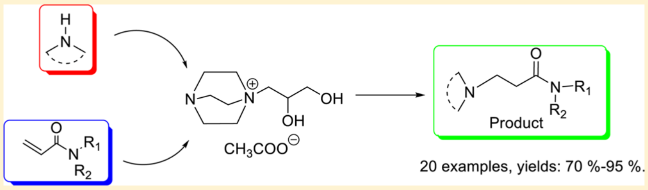
DABCO-Based Ionic Liquids: Recyclable Catalysts for Aza-Michael Addition of α,β-Unsaturated Amides under Solvent-Free Conditions

Anguo Ying,*,[†] Zhifeng Li,[‡] Jianguo Yang,[†] Shuo Liu,[‡] Songlin Xu,*,[‡] Hua Yan,[†] and Chenglin Wu[†]

[†]School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, People's Republic of China
[‡]School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

Ⓢ *Supporting Information*

ABSTRACT: An array of novel 1,4-diazobicyclo[2.2.2]octane (DABCO) based ionic liquids were developed and used as recyclable catalysts for the aza-Michael addition at room temperature without any organic solvent. [DABCO−PDO][OAc] was found to be the most efficient catalyst, and the amount of catalyst was only 10 mol %. Various amines reacted with a wide range of α,β-unsaturated amides, smoothly affording target products in good to excellent yields within hours. Moreover, the catalyst could be reused up to eight times, still maintaining a high catalytic activity. Finally, a plausible mechanism was proposed. FTIR and computational chemistry were used to verify the catalytic mechanism.



INTRODUCTION

The Michael addition reaction plays an important role in organic synthesis as a most pivotal method to form carbon−carbon and carbon−heteroatom bonds owing to its atom-economy and efficiency.[1] Additionally, many addition products such as β-amino, β-thio, and β-oxy ketone functionalities are important pharmaceutical intermediates that can be converted into a range of biologically active compounds by further manipulation.[2] Furthermore, the so-called aza-Michael addition is the most important path to β-amino carbonyl derivatives.[3] Traditionally, the Michael addition reaction is catalyzed by quantitative amount of strong bases in conventional organic solvents, which often leads to undesirable side reactions and is incompatible with green chemistry.[4] With the growing awareness in environmental protection, the chemical industry and research are under increasing pressure to develop new greener and more efficient alternatives to the traditional processes. Thus, a number of milder reagents such as $FeCl_3$/Montmorillonite K10,[5] KF/Al_2O_3,[6]imidazolium-based polymer supported CuI,[7] β-cyclodextrin,[8] PEG,[9] and enzymes[10] have been developed for the Michael addition over the past few years. Despite some success achieved, many of these reaction systems suffer from the disadvantages of longer reaction time, harsh reaction conditions, excess catalyst, and so on.

Over the past decades, room-temperature ionic liquids (RTILs) have been extensively studied and successfully applied in many areas such as organic chemistry,[11] electrochemistry,[12] materials chemistry,[13] chemical separations,[14] to name just a few. RTILs reveal unique physical and chemical properties, for instance, low melting point, negligible vapor pressure, excellent solvating ability, and ease of recyclability.[15] There have been many successful reports that employ RTILs as green solvents, as well as catalysts or promoters in organic synthesis reactions like Mannich reaction,[16] Friedel−Crafts reaction,[17] Knoevenagel condensation,[18] Henry reactions[19] and so on. Moreover, RTILs can be tailor-made for special purposes by modifying distinct cations and anions, which gain them more potential.[20] Similarly, the use of RTILs, including [Hmim]OTs,[21] [NMP]H_2PO_4,[22] [DBU][Ac],[23] [bmim]OH,[24] and [bmim][Sac],[25] in the Michael addition also made remarkable achievements.

To our knowledge, the relatively active Michael acceptors such as α,β-unsaturated aldehydes, α,β-unsaturated ketones, α,β-unsaturated esters, nitroalkanes, have been extensively studied with significant progress.[26] Despite significant importance of α,β-unsaturated amides adduct in biological and pharmacological activities, the researches of employing α,β-unsaturated amides as Michael acceptors are rare. Meaningly, researches on Michael addition of α,β-unsaturated amides are valuable and imminent. In continuation of our research program to develop green and efficient methodology in organic synthesis,[27] herein we report the synthesis of a class of novel RTILs based on 1,4-diazobicyclo [2.2.2] octane (DABCO) and 3-chloro-1,2-propanediol[28] and their applications as recyclable and efficient catalysts for aza-Michael addition of α,β-unsaturated amides.

RESULTS AND DISCUSSION

Four kinds of DABCO-based RTILs were synthesized (Scheme 1). As a prelude of this research, the catalytic activity of the RTILs was evaluated by aza-Michael addition of 4-methylpiperidine to acrylamide and the results are presented in Table 1. Notably, the aza-Michael addition could not proceed at all in the absence of any catalyst even the time was prolonged to 6 h. DABCO, the raw material for preparation of RTILs, was also introduced into the evaluation and 65% yield was obtained in

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Scheme 1. Synthesis of the [DABCO−PDO][X] Ionic Liquids

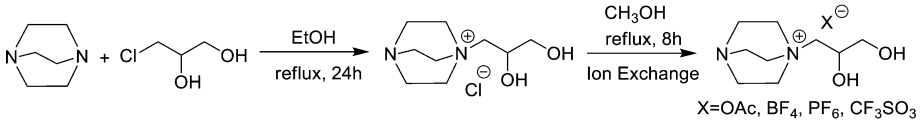
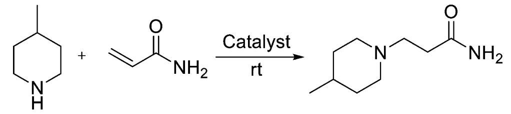


Table 1. Screening the Catalytic Activity of RTILs on the Aza-Michael Addition of 4-Methylpiperidine to Acrylamide[a]



entry	catalyst	time (h)	yield[b] (%)
1	blank	6	trace
2	DABCO	4	65
3	[DABCO−PDO][OAc]	1	95
4	[DABCO−PDO][BF_4]	1.5	86
5	[DABCO−PDO][PF_6]	1.5	91
6	[DABCO−PDO][CF_3SO_3]	1.5	88

[a] Reaction conditions: 4-methylpiperidine (5.0 mmol), acrylamide (5.0 mmol), catalyst (15 mol %), room temperature, solvent free. [b] Isolated yield.

4h, which proving the DABCO is not an efficient catalyst for the reaction. In contrast, the DABCO-based RTILs exhibited excellent catalytic performance giving the desired product in good to excellent yields within shorter times. The anion of RTILs had a certain impact on the catalytic performance, and the [DABCO−PDO][OAc] showed a higher catalytic effect than others with a higher yield and a shorter time. Thus, [DABCO−PDO][OAc] was used for further investigation.

It should be noted that the amount of catalyst in a reaction system greatly affects its practical use. Subsequently, the amount of ionic liquid required to promote the completion of the reaction was evaluated. As indicated in Figure 1, the yield of the product was just 60% in the presence of 1 mol % [DABCO−PDO][OAc], and the yield sharply increased to 95% with 10 mol % catalyst present. However, further increasing the amount of [DABCO−PDO][OAc] would not improve the yield. Therefore, from an economic standpoint, 10 mol % was the optimal amount for the reaction.

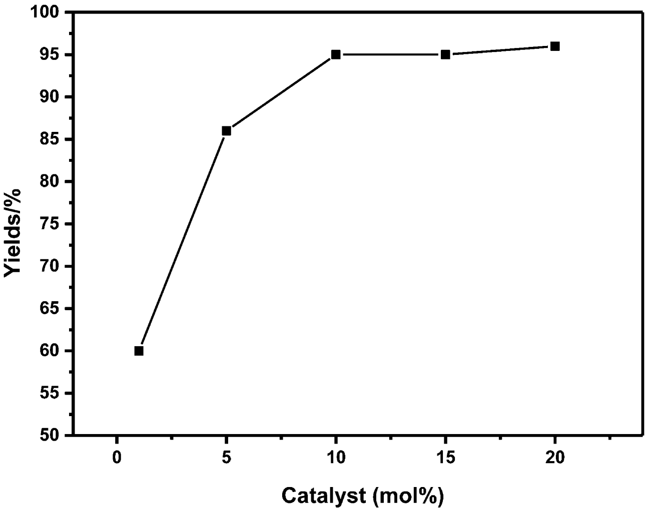


Figure 1. Influence of the catalyst amount on the reaction. Reaction conditions: 4-methylpiperidine (5.0 mmol), acrylamide (5.0 mmol), [DABCO−PDO][OAc], 1 h, room temperature, solvent free.

The influences of the solvent on the aza-Michael addition of 4-methylpiperidine to acrylamide were also carried out. As indicated in Table 2, all tested solvents were effective reaction mediums for the model reaction. However, after the addition of solvent, neither the yield nor the reaction time was improved significantly. From the perspective of our pursuit of establishing the environmentally benign process, solvent-free conditions were the best choice. Therefore, an optimum combination for the aza-Michael addition of 4-methylpiperidine to acrylamide is using 10 mol % of [DABCO−PDO][OAc] under solvent-free conditions.

Table 2. Influence of the solvent on the aza-Michael addition of 4-methylpiperidine to acrylamide[a]

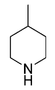
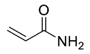
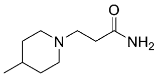
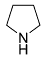
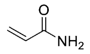
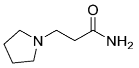
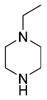
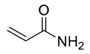
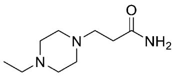
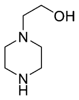
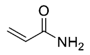
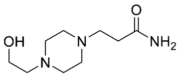
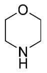
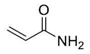
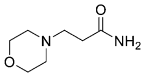
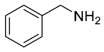
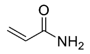
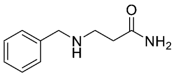
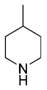
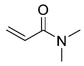
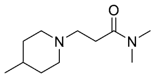
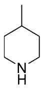
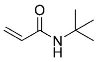
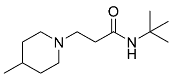
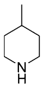
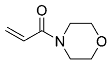
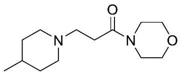
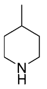
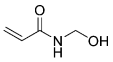
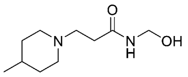
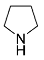
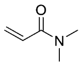
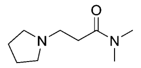
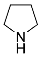
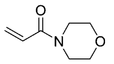
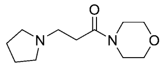
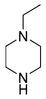
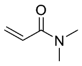
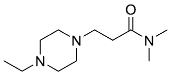
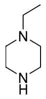
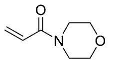
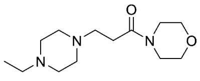
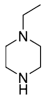
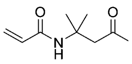
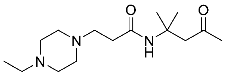
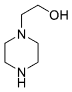
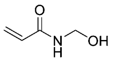
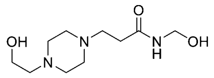
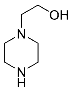
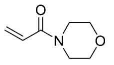
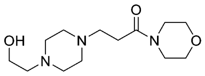
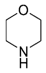
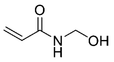
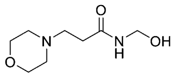
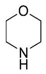
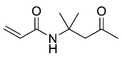
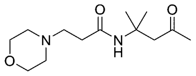
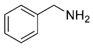
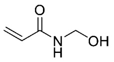
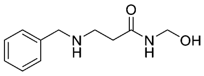
entry	solvent	time (h)	yield[b] (%)
1	CH_3OH	1	94
2	EtOH	1	96
3	CH_3CN	1.5	95
4	toluene	1.5	91
5	CH_2Cl_2	1	91
6	solvent free	1	95

[a] Reaction conditions: 4-methylpiperidine (5.0 mmol), acrylamide (5.0 mmol), [DABCO−PDO][OAc] (10 mol %), room temperature, solvent. [b] Isolated yield.

With an optimized set of conditions in hand, we then decoded the scope and applicability of this strategy for other structurally diverse substrates, and the results were summarized in Table 3. First, aza-Michael addition of acrylamide with different amines was examined (Table 3, entries 1−6). As shown, the reaction of various amines and acrylamide proceeded smoothly to afford the target product in good to excellent yields. It was found that the secondary amines such as 4-methylpiperidine, pyrrolidine, 1-ethylpiperazine, 2-(piperazin-1-yl)ethanol, and morpholine were efficient Michael donors, and the yield was no less than 90% in 1−2 h, while the primary amine (phenylmethanamine) could not react very well and only gave 78% yield even when the time was prolonged to 3 h.

Encouraged by these satisfying results, aza-Michael addition of various amines and a wide range of α,β-unsaturated amides were performed (Table 3, entries 7−20). It has been observed that the steric hindrance has a certain influence on the reaction. That is to say, for an identified amine, the larger the substituent on N position of α,β-unsaturated amides is, the lower the reaction rate and yield are (Table 3, entries 1 and 7−9). To our pleasure, *N,N*-dimethylacrylamide, *N-tert*-butylacrylamide, 1-morpholinoprop-2-en-1-one, *N*-(hydroxymethyl)acrylamide, and *N*-(2-methyl-4-oxopentan-2-yl)acrylamide are also efficient Michael acceptors to give the corresponding products in 70%−91% yields (Table 3, entries 7−20). It is worth mentioning that the complex *N*-(2-methyl-4-oxopentan-2-yl)acrylamide also reacted with 1-ethylpiperazine and morpholine successfully (Table 3, entries 15 and 19). Unfortunately, when reaction of

Table 3. Aza-Michael Addition of Various Amines with a Wide Range of α,β-Unsaturated Amides Catalyzed by [DABCO−PDO][OAc][a]

Entry	Amine	α,β-Unsaturated amide	Product[b]	Time(h)	Yield(%)[c]
1				1	95
2				1	95
3				1	91
4				2	90
5				2	90
6				3	78
7				1.5	91
8				3	88
9				1.5	90
10				1	93
11				2.5	91
12				2	90
13				1	90
14				2.5	79
15				3	87
16				2.5	88
17				2.5	87
18				2	90
19				4	75
20				4.5	70

[a] Reaction conditions: amine (5.0 mmol), α,β-unsaturated amide (5.0 mmol), [DABCO−PDO][OAc](10 mol %), room temperature, solvent free. [b] Products were ascertained by NMR spectroscopy and elemental analysis. [c] Isolated yield.

methacrylamide with morpholine was attempted, the reaction could not proceed at all owing to the electronic effect of substituted methyl in the olefin fraction of methacrylamide.

It is universally acknowledged that the reusability of a catalyst system is the key factor to determine whether it has potential application in industry or not. The model reaction of 4-methylpiperidine and acrylamide was chosen to investigate the reusability of [DABCO−PDO][OAc]. Upon completion of the reaction, the reaction solution was extracted by several cycles of ethyl acetate and purified by flash chromatography. The residual ionic liquid was dried under vacuum and reused for subsequent reactions without further processing. The results presented in Figure 2 demonstrated that [DABCO−PDO][OAc] could be reused up to 8 times while still maintaining a high catalytic activity, and the mass loss is small.

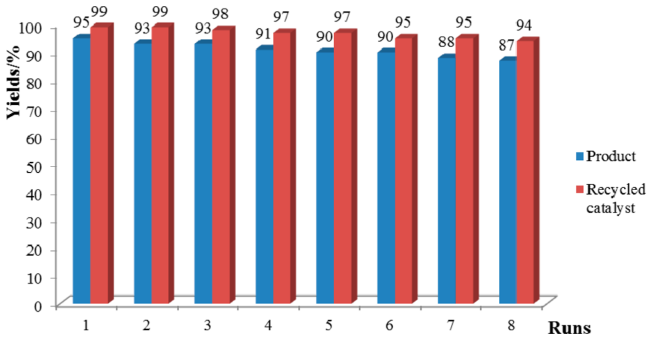
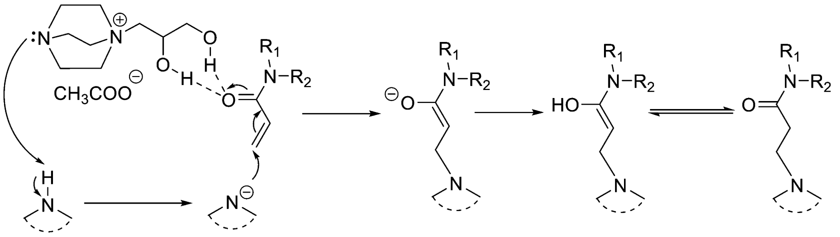


Figure 2. Recyclability of [DABCO−PDO][OAc]. All yields of recycled catalyst are calculated based on the original mass of [DABCO−PDO][OAc]. Reaction conditions: 4-methylpiperidine (5.0 mmol), acrylamide (5.0 mmol), [DABCO−PDO][OAc](10 mol %), 1 h, room temperature, solvent free.

A plausible mechanism for the aza-Michael addition of amines with α,β-unsaturated amides catalyzed by [DABCO−PDO][OAc] was depicted in Scheme 2. A dual catalytic role was held in this catalytic system. On one hand, the lone pair electrons of N atom of the IL could deprotonate hydrogen atom of amines enhancing nucleophilicity of amines. On the other hand, the hydroxyl groups of the ionic liquids and the carbonyl group of α,β-unsaturated amides could form hydrogen-bonding interactions making α,β-unsaturated amides more

Scheme 2. Plausible Mechanism for the Aza-Michael Addition of Amines with α,β-Unsatuated Amides Catalyzed by [DABCO−PDO][OAc]



vulnerable to be attacked by amines. From the plausible mechanism, it is suggested that the alkalinity of catalyst is in favor of the proceeding of reaction. The impact of catalyst anions on the catalytic performances is interpreted based on this point. Among the corresponding acids of different anions, CH_3COOH is the weakest acid, while HBF_4, HPF_6, and CF_3SO_3H are well-known strong acids. Consequently, [DABCO−PDO][OAc] prepared from the conjugated base of CH_3COOH shows the strongest alkalinity. In conclusion, [DABCO−PDO][OAc] exhibits a excellent catalytic activity.

To verify this plausible mechanism, the FTIR comparison of the acrylamide and acrylamide−[DABCO−PDO][OAc] mixture was commenced, and the results are shown in Figure 3. It was found that the infrared absorption of carbonyl in acrylamide is at 1675 cm^{-1}, while it is at 1575 cm^{-1} in mixture. The offset of 100 cm^{-1} indicates the existence of hydrogen bonds.

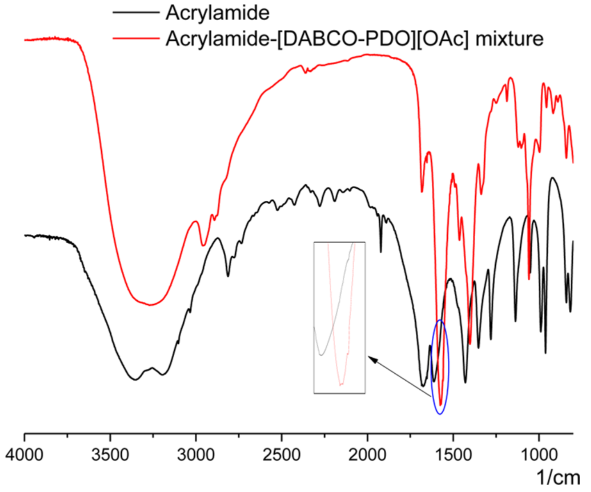


Figure 3. FTIR comparison of acrylamide and acrylamide−[DABCO−PDO][OAc] mixture.

Additionally, a technique of computational chemistry was introduced to calculate the charge of atom by Gaussian 03 employing the B3LYP/3-21G-optimized geometry. The charges of DABCO−PDO, acrylamide and acrylamide−[DABCO−PDO][OAc] mixture were calculated, respectively, and the results are given in Figure 4. The detailed comparison of acrylamide and acrylamide−[DABCO−PDO][OAc] mixture is summarized in Table 4. The charge of C_1 in acrylamide is −0.369 while the mixture provided the charge of −0.346 for C_1, which intimates there are hydrogen-bonding interactions between the hydroxyl groups of catalyst with the carbonyl group of acrylamide. To sum up, the catalytic mechanism has certain rationality.

■ CONCLUSIONS

In summary, an array of novel DABCO-based ionic liquids were developed and used as efficient and recyclable catalysts for the aza-Michael addition of various amines and a wide range of α,β-unsaturated amides under solvent-free conditions. [DABCO−PDO][OAc] was found to be the most efficient catalyst. Furthermore, the amount of catalyst was only 10 mol %. The reactions proceed smoothly affording target products in good to excellent yields within hours. Additionally, the catalyst could be reused up to eight times, still maintaining a high catalytic activity. The methodology thus represents a practical and green catalyst to the aza-Michael addition reactions.

■ EXPERIMENTAL SECTION

Preparation of RTILs [DABCO−PDO][X]. To a mixture of 1,4-diazobicyclo[2.2.2]octane (DABCO) (11.2 g, 100 mmol) in ethanol (50 mL) was added 3-chloro-1,2-propanediol (8.4 mL, 100 mmol), and the solution was refluxed for 24 h. The solvent was removed by rotatory evaporation under reduced pressure, and the intermediate was obtained without any purification. After that, the ion-exchange reagent ($KOAc/NaBF_4/KPF_6/CF_3SO_3K$) (20 mmol) was added to a solution of the intermediate (4.45g, 20 mmol) in methanol (20 mL). The mixture was refluxed for 8 h and evaporated under reduced pressure to give the corresponding RTILs.

NMR spectral and elemental analysis data of [DABCO−PDO][X]:

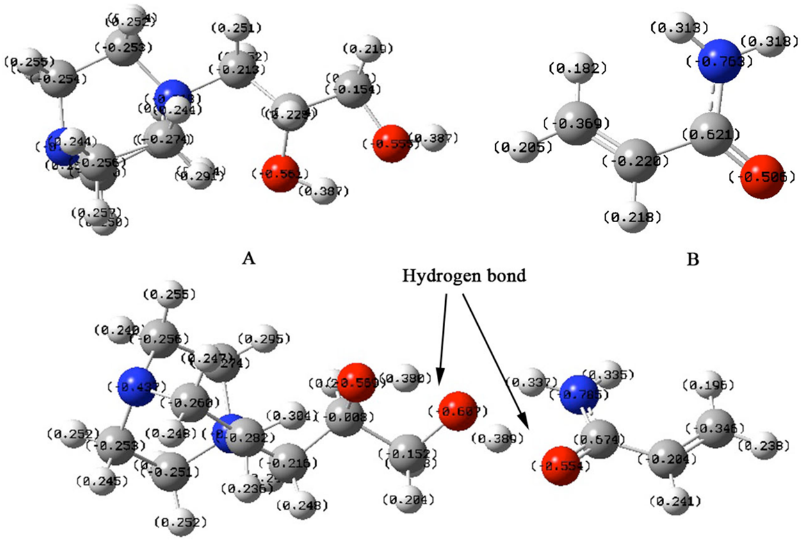
[DABCO−PDO][OAc]. ^{1}H NMR (400 MHz, DMSO): δ 4.01−4.11 (m, 2H), 3.14−3.49 (m, 12H), 2.99−3.01 (m, 5H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ 175.7, 67.8, 65.6, 64.5, 53.1, 45.2, 25.5. Anal. Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.37; O, 25.98. Found: C, 53.56; H, 9.10; N, 11.29; O, 26.05.

[DABCO−PDO][BF$_4$]. ^{1}H NMR (400 MHz, DMSO): δ 3.92−4.08 (m, 2H), 3.17−3.42 (m, 12H), 3.00−3.15 (m, 5H). ^{13}C NMR (100 MHz, DMSO): δ 67.5, 65.6, 64.2, 53.2, 49.1. Anal. Calcd for $C_9H_{19}BF_4N_2O_2$: C, 39.44; H, 6.99; B, 3.94; F, 27.73; N, 10.22; O, 11.68. Found: C, 39.39; H, 7.08; B, 3.93; F, 27.70; N, 10.19; O, 11.71.

[DABCO−PDO][PF$_6$]. ^{1}H NMR (400 MHz, DMSO): δ 3.93−4.10 (m, 2H), 3.16−3.43 (m, 12H), 3.00−3.03 (m, 5H). ^{13}C NMR (100 MHz, DMSO): δ 67.6, 65.1, 64.3, 53.3, 49.0. Anal. Calcd for $C_9H_{19}F_6N_2O_2P$: C, 32.54; H, 5.76; F, 34.31; N, 8.43; O, 9.63; P, 9.32. Found: C, 32.49; H, 5.80; F, 34.30; N, 8.44; O, 9.67; P, 9.30.

[DABCO−PDO][CF$_3$SO$_3$]. ^{1}H NMR (400 MHz, DMSO): δ 3.91−4.10 (m, 2H), 3.14−3.43 (m, 12H), 3.00−3.06 (m, 5H). ^{13}C NMR (100 MHz, DMSO): δ 122.7, 67.5, 65.7, 64.2, 53.3, 49.0. Anal. Calcd for $C_{10}H_{19}F_3N_2O_5S$: C, 35.71; H, 5.69; F, 16.95; N, 8.33; O, 23.79; S, 9.53. Found: C, 35.65; H, 5.79; F, 16.93; N, 8.29; O, 23.82; S, 9.52.

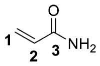
Typical Experimental Procedure for Aza-Michael Addition Reaction Catalyzed by [DABCO−PDO][OAc]. A mixture of mines (5.0 mmol), α,β-unsaturated amides (5.0 mmol), and [DABCO−PDO][OAc] (10 mol %) was stirred at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate. The resulting crude product was purified by column chromatography using methanol/ethyl acetate as the eluent. The resulting products were characterized by ^{1}H NMR and ^{13}C NMR. The residual ionic liquid was dried under vacuum and reused for subsequent reactions without further processing.



C

Figure 4. Charges of DABCO−PDO (**A**), acrylamide (**B**), and acrylamide−[DABCO−PDO][OAc] mixtures (**C**).

Table 4. Charge of Acrylamide and Acrylamide−[DABCO−PDO][OAc] Mixtures

Structure	Atom	Charge	
		acrylamide	mixture
	C_1	-0.369	-0.346
	C_2	-0.220	-0.204
	C_3	0.621	0.674
	O	-0.506	-0.554

NMR spectral and elemental analysis data of products:

3-(4-methylpiperidin-1-yl)propanamide (Table 3, Entry 1). 808 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 5.80 (s, 1H), 3.42 (d, 2H, *J* = 12.0 Hz), 2.72 (t, 2H, *J* = 6.4 Hz), 2.49 (d, 2H, *J* = 6.4 Hz), 2.17 (m, 2H), 1.69 (d, 2H, *J* = 13.2 Hz), 1.30 (s, 1H), 1.27 (d, 2H, *J* = 9.6 Hz), 0.94 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2, 72.4, 61.6, 53.8, 53.1, 33.6, 31.9, 30.3, 21.5. Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45; O, 9.40. Found: C, 63.38; H, 10.77; N, 16.36; O, 9.49.

3-(Pyrrolidin-1-yl)propanamide (Table 3, Entry 2). 675 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 6.07 (s, 1H), 2.72−2.75 (m, 2H), 2.54−2.57 (m, 4H), 2.38−2.41 (m, 2H), 1.75−1.78 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.4, 57.7, 53.4, 51.5, 33.1, 23.3, 18.3. Anal. Calcd for $C_7H_{14}N_2O$: C, 59.12; H, 9.92; N, 19.70; O, 11.25. Found: C, 59.01; H, 10.00; N, 19.66; O, 11.33.

3-(4-Ethylpiperazin-1-yl)propanamide (Table 3, Entry 3). 843 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (s, 1H), 5.62 (s, 1H), 2.63−2.66 (m, 3H), 2.46 (s, 4H), 2.40−2.46 (m, 5H), 2.18−2.26 (m, 2H), 1.10 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1, 53.8,52.8, 52.5, 52.2, 32.0, 11.9. Anal. Calcd for $C_9H_{19}N_3O$: C, 58.35; H, 10.34; N, 22.68; O, 8.64. Found: C, 58.30; H, 10.40; N, 22.63; O, 8.67.

3-(4-(2-Hydroxyethyl)piperazin-1-yl)propanamide (Table 3, Entry 4). 842 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.58−3.61 (m, 2H), 3.38 (s, 2H), 2.98 (s, 2H), 2.90 (s, 2H), 2.68−2.72 (m, 2H), 2.47−2.53 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 59.5, 57.8, 53.9, 53.0, 52.7, 37.2, 35.4, 30.8. Anal. Calcd for $C_9H_{19}N_3O_2$: C, 53.71; H, 9.52; N, 20.88; O, 15.90. Found: C, 53.62; H, 9.59; N, 20.85; O, 15.94.

3-Morpholinopropanamide (Table 3, Entry 5). 712 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85−7.86 (m, 1H), 6.07−6.08 (m, 1H), 3.73 (s, 4H), 2.40−2.66 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 66.7, 54.1, 52.8, 31.6. Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.15; H, 8.92; N, 17.71; O, 20.23. Found: C, 53.07; H, 9.01; N, 17.63; O, 20.29.

3-(Benzylamino)propanamide (Table 3, Entry 6). 695 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (s, 1H), 7.23−7.35 (m, 4H), 6.25 (s, 1H), 3.80 (s, 4H), 2.86−2.93 (m, 2H), 2.41 (t, 2H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2, 138.5, 128.6, 128.4, 127.4, 53.3, 44.6, 34.9. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72; O, 8.98. Found: C, 67.30; H, 7.98; N, 15.70; O, 9.02.

N,N-Dimethyl-3-(4-methylpiperidin-1-yl)propanamide (Table 3, Entry 7). 902 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (d, 1H, *J* = 4.8 Hz), 3.60 (d, 1H, *J* = 4.8 Hz), 3.05 (d, 2H, *J* = 11.6 Hz), 3.00 (s, 3H), 2.92 (s, 3H), 2.85−2.89 (m, 2H), 2.66 (d, 2H, *J* = 8.0 Hz), 2.17−2.23 (m, 2H), 1.96 (s, 1H), 1.66 (d, 2H, *J* = 11.6 Hz), 0.92 (d, 3H, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 72.5, 61.6, 53.6, 53.4, 37.2, 35.4, 32.9, 30.1, 30.0, 21.5. Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.13; O, 8.07. Found: C, 66.53; H, 11.24; N, 14.10; O, 8.13.

N-tert-Butyl-3-(4-methylpiperidin-1-yl)propanamide (Table 3, Entry 8). 995 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (s, 1H), 2.91 (d, 2H, *J* = 11.6 Hz), 2.55 (t, 2H, *J* = 6.0 Hz), 2.27 (t, 2H, *J* = 6.0 Hz), 2.18 (s, 1H), 1.94−2.00 (m, 2H), 1.69 (d, 2H, *J* = 12.8 Hz), 1.34 (s, 9H), 1.12−1.22 (m, 2H), 0.94 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.0, 54.4, 53.1, 50.3, 34.5, 33.2, 30.7, 28.9, 21.8. Anal. Calcd for $C_{13}H_{26}N_2O$: C, 68.98; H, 11.58; N, 12.38; O, 7.07. Found: C, 68.87; H, 11.66; N, 12.30; O, 7.17

3-(4-Methylpiperidin-1-yl)-1-morpholinopropan-1-one (Table 3, Entry 9). 1081 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (d, 1H, *J* = 2.8 Hz), 3.65 (d, 4H, *J* = 3.6 Hz), 3.59 (s, 3H), 3.47 (s, 2H), 3.01 (d, 2H, *J* = 11.6 Hz), 2.83 (t, 2H, *J* = 7.6 Hz), 2.64 (t, 2H, *J* = 7.6 Hz), 2.15 (t, 2H, *J* = 7.6 Hz), 1.96 (s, 1H), 1.65 (d, 2H, *J* = 12.8 Hz), 0.92 (d, 3H, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 72.5, 66.8, 66.6, 61.6, 53.7, 53.6, 45.9, 41.9, 33.2, 30.2, 30.0, 21.5. Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66; O, 13.31. Found: C, 64.91; H, 10.12; N, 11.63; O, 13.34.

N-(Hydroxymethyl)-3-(4-methylpiperidin-1-yl)propanamide (Table 3, Entry 10). 931 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (s, 1H), 4.69 (d, 1H, *J* = 6.0 Hz), 3.70 (d, 1H, *J* = 3.2 Hz), 3.58 (d, 1H, *J* = 3.2 Hz), 3.09 (d, 2H, *J* = 11.6 Hz), 2.82 (s, 2H), 2.52(s, 2H), 2.19−2.24 (m, 2H), 1.96 (s, 1H), 1.68 (d, 2H, *J* = 13.2 Hz), 1.44 (s, 1H), 1.30−1.43 (m, 2H), 0.92 (q, 3H, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 72.4, 63.7, 61.4, 53.4, 53.0, 33.3, 32.9, 31.9, 29.9, 21.4. Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99; O, 15.98. Found: C, C, 59.88; H, 10.17; N, 13.94; O, 16.01.

N,N-Dimethyl-3-(pyrrolidin-1-yl)propanamide (Table 3, Entry 11). 774 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.96 (s, 3H), 2.91 (s, 1H), 2.89 (s, 1H), 2.87 (s, 3H), 2.66−2.69 (m, 4H), 2.59 (t, 2H, *J* = 8.0 Hz), 1.77−1.81 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 72.5, 61.5, 53.7, 51.4, 37.2, 35.3, 31.7, 23.3. Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45; O, 9.40. Found: C, 63.41; H, 10.71; N, 16.42; O, 9.46.

1-Morpholino-3-(pyrrolidin-1-yl)propan-1-one (Table 3, Entry 12). 955 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.57−3.68 (m, 8H), 3.46 (d, 2H, J = 4.8 Hz), 2.57−2.65 (m, 6H), 1.80 (t, 4H, J = 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 66.7, 66.6, 53.9, 51.5, 45.9, 41.0, 31.9, 23.4. Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20; O, 15.07. Found: C, 62.14; H, 9.59; N, 13.13; O, 15.14.

3-(4-Ethylpiperazin-1-yl)-N,N-dimethylpropanamide (Table 3, Entry 13). 960 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.04 (s, 2H), 2.91 (s, 3H), 2.82 (s, 3H), 2.63−2.67 (m, 2H), 2.49 (s, 4H), 2.44 (d, 4H, J = 8.4 Hz), 2.37 (d, 2H, J = 7.2 Hz), 0.99 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 72.5, 61.3, 53.6, 52.4, 52.0, 51.9, 37.1, 35.3, 30.5, 11.4. Anal. Calcd for $C_{11}H_{23}N_3O$: C, 61.93; H, 10.87; N, 19.70; O, 7.50. Found: C, 61.85; H, 10.97; N, 19.62; O, 7.56.

3-(4-Ethylpiperazin-1-yl)-1-morpholinopropan-1-one (Table 3, Entry 14). 1008 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49−3.55 (m, 6H), 3.36 (s, 2H), 2.63 (d, 2H, J = 8.0 Hz), 2.33−2.46 (m, 12H), 0.98 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 66.7, 66.5, 53.8, 52.7, 52.2, 52.0, 45.9, 41.8, 30.4, 11.6. Anal. Calcd for $C_{13}H_{25}N_3O_2$: C, 61.15; H, 9.87; N, 16.46; O, 12.53. Found: C, 61.04; H, 9.94; N, 16.43; O, 12.59.

3-(4-Ethylpiperazin-1-yl)-N-(2-methyl-4-oxopentan-2-yl)-propanamide (Table 3, Entry 15). 1232 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 3.68 (t, 1H, J = 4.4 Hz), 3.55 (t, 1H, J = 4.4 Hz), 2.96 (s, 2H), 2.65−2.75 (m, 2H), 2.53 (t, 4H, J=6.0 Hz), 2.37−2.43 (m, 4H), 2.14 (t, 2H, J=6.0 Hz), 2.04 (s, 3H), 1.31 (s, 6H), 1.05 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.6, 172.0, 72.5, 61.4, 53.7, 52.7, 52.2, 52.0, 51.2, 50.5, 32.7, 31.5, 27.8, 11.8. Anal. Calcd for $C_{15}H_{29}N_3O_2$: C, 63.57; H, 10.31; N, 14.83; O, 11.29. Found: C, 63.47; H, 10.41; N, 14.79; O, 11.43.

3-(4-(2-Hydroxyethyl)piperazin-1-yl)-N-(hydroxymethyl)-propanamide (Table 3, Entry 16). 956 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (s, 1H), 4.72 (d, 1H, J = 6.4 Hz), 3.71 (d, 2H, J = 6.4 Hz), 3.63 (d, 2H, J = 5.2 Hz), 3.05 (s, 4H), 2.66 (s, 2H), 2.55−2.59 (m, 6H), 2.41 (t, 2H, J = 6.4 Hz), 1.24 (t, 2H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.2, 72.4, 64.1, 59.3, 58.3, 57.8, 53.5, 52.8, 52.4, 32.2. Anal. Calcd for $C_{10}H_{21}N_3O_3$: C, 51.93; H, 9.15; N, 18.17; O, 20.75. Found: C, 51.85; H, 9.24; N, 18.11; O, 20.80.

3-(4-(2-Hydroxyethyl)piperazin-1-yl)-1-morpholinopropan-1-one (Table 3, Entry 17). 1119 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69−3.71 (m, 1H), 3.61−3.68 (m, 4H), 3.60 (s, 1H), 3.55−3.58 (m, 3H), 3.44 (t, 4H, J = 4.4 Hz), 2.68−2.72 (m,2H), 2.51−2.54 (t, 8H, J = 4.4 Hz), 2.49 (t, 2H, J = 4.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 72.4, 66.8, 66.6, 61.5, 59.5, 57.8, 53.8, 53.0, 52.7, 45.9, 41.9, 30.5. Anal. Calcd for $C_{13}H_{25}N_3O_3$: C, 57.54; H, 9.29; N, 15.49; O, 17.69. Found: C, 57.47; H, 9.38; N, 15.42; O, 17.73.

N-(Hydroxymethyl)-3-morpholinopropanamide (Table 3, Entry 18). 847 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 4.69−4.71 (m, 2H), 3.69−3.71 (m, 4H), 2.62 (d, 2H, J = 6.4 Hz), 2.49 (s, 4H), 2.41 (d, 2H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 66.6, 63.7, 54.1, 53.0, 32.2. Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.88; O, 25.50. Found: C, 50.94; H, 8.68; N, 14.83; O, 25.55.

N-(2-Methyl-4-oxopentan-2-yl)-3-morpholinopropanamide (Table 3, Entry 19). 961 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (s, 1H), 3.74 (t, 4H, J = 4.8 Hz), 3.00 (s, 2H), 2.58 (t, 2H, J = 6.0 Hz), 2.53 (s, 4H), 2.26 (t, 2H, J = 6.0 Hz), 2.08 (s, 3H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.5, 171.8, 66.9, 54.3, 52.7, 51.2, 50.4, 32.5, 31.5, 27.8. Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93; O, 18.72. Found: C, 60.79; H, 9.53; N, 10.85; O, 18.83.

3-(Benzylamino)-N-(hydroxymethyl)propanamide (Table 3, Entry 20). 729 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22−7.34 (m, 5H), 4.02 (s, 2H), 3.71 (s, 2H), 2.92 (s, 2H), 2.46 (d, 2H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 137.3, 128.8, 128.5, 127.6, 63.4, 57.1, 47.7, 29.5. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45; O, 15.37. Found: C, 63.37; H, 7.82; N, 13.39; O, 15.42.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all four novel ionic liquids and all conjugated adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Tel/Fax: 86-576-88660359. E-mail: yinganguo@163.com, agying@tzc.edu.cn.
*E-mail: slxu@tju.edu.cn.

Notes

The authors declare no competing financial interest.

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