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Aza-Michael addition of aliphatic or aromatic amines to α,β-unsaturated compounds catalyzed by a DBU-derived ionic liquid under solvent-free conditions

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ABSTRACT

A task-specific ionic liquid, 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate has been successfully used as a catalyst for aza-conjugate addition of aliphatic or aromatic amines to various electron deficient alkenes under solvent-free conditions and at room temperature. The catalyst can be reused for six times without noticeable loss of activity.

Carbon–nitrogen bond forming reaction is one of the most important methodologies in synthetic organic chemistry for preparation of β-aminocarbonyl compounds, which not only constitute components of biologically active natural products but also serve as key intermediates for the synthesis of β-aminoalcohols, β-lactams, and β-amino acids.[1] Mannich reaction of enolates with imines provides a classic route for the construction of β-amino carbonyl compounds.[2] However, this type of reaction often requires harsh reaction conditions and long reaction times. In contrast to the Mannich reaction, the aza-Michael addition of amines to electron-deficient alkenes has attracted considerable attention as an alternative protocol for C–N bond formation due to its atom economy and operational simplicity. Most aza-Michael reactions are usually carried out under a strong base or acid, which would lead to by-products or undesired harmful residues. Thus, milder Lewis acidic catalysts such as $LiClO_4$,[3a] $Yb(OTf_3)$,[3b,c] $Bi(NO_3)_3$,[3d] $FeCl_3{\cdot}6H_2O$,[3e] $CeCl_3{\cdot}7H_2O$,[3f] $InCl_3$,[3g] SmI_2,[3h] and $Cu(OTf)_2$[3i] were employed in the Michael protocol. Recently, some novel reagents that are used as a catalyst or promoter in conjugate addition have also been reported, including β-cyclodextrin,[4a] bromodimethylsulfonium bromide,[4b] boric acid in water,[4c] $ZrOCl_2{\cdot}8H_2O$ on montmorillonite K10,[4d] imidazolium-based polymer supported CuI,[4e] KF/Al_2O_3,[4f] and $[HP(HNCH_2CH_2)_3N]NO_3$[4g]. However, many of the above methods suffered from some drawbacks, such as the requirement for a large excess of reagents, substrate-selective for some catalysts, and the involvement of some toxic solvents such as 1,2-dichloroethane or acetonitrile. Ionic liquids[5] as catalysts or/and medium in reactions have been widely used in organic transformations due to their advantages such as good solvating ability, negligible vapor pressure, variable polarity and ease of work-up. However, the related report about basic ionic liquid as catalyst as well as reaction medium for organic condensation is relatively rare[6] and in most cases, large amount of ionic liquid was required as reaction solvent. Considering the relatively high cost of ionic liquid, the development of a novel, efficient, and basic ionic liquid used in catalytic amount loading for aza-conjugate reaction is highly desirable.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be far superior to other tertiary amines and its nucleophilic nature as well as its utility in organic synthesis has also been investigated over the past decades.[7] Recently, Kim et al. have successfully introduced DBU as promoter for aza-Michael addition.[8] However, this procedure suffered from hardly recyclability and unpleasant flavor of DBU, which went against the promising viewpoint of green chemistry in modern chemical research. Thus, considering both DBU's excellent catalytic properties and advantages of ionic liquids, we developed a new basic task-specified ionic liquid, 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate ([DBU][Ac]) through

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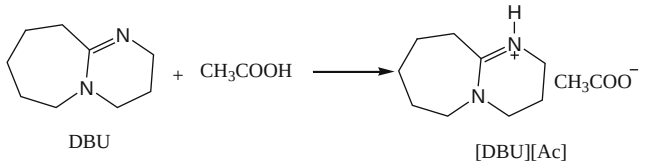


Scheme 1. Synthesis of ionic liquid [DBU][Ac].

the neutralization reaction of DBU and acetic acid (Scheme 1).[9] The DBU salt is the ionic liquid with weakly basicity at room temperature. The main aim of the work was to examine if the solventless addition of amines to electron-deficient olefins can proceed smoothly with [DBU][Ac] as catalyst.

For the comparison with DBU as promoter for aza-Michael addition reported by Kim et al.,[8] 50 mol % of the ionic liquid [DBU][Ac] was employed for the model reaction between dibenzylamine and methyl acrylate in acetonitrile at ambient temperature. The reaction catalyzed by [DBU][Ac] is slightly faster than that promoted by its parent base DBU (Table 1, entries 1 and 2), indicating the rationality of [DBU][Ac] as catalyst for the reaction. Other solvents such as methanol, toluene, and dichloromethane were also tested and they were all effective reaction mediums for the model reaction (entries 3–5). However, because of the toxicity of organic solvents and our pursuit for the establishment of the environmentally benign process for organic transformations, we attempted to conduct the reaction of dibenzylamine and methyl acrylate under solvent-free conditions and to our delight, the comparable yield (96%) was obtained within 4.5 h (entry 6). Thus, we chose solvent-free conditions for further studies. When the amount of catalyst [DBU][Ac] was reduced to 0.3 equiv, almost no decrease in the yield was observed (entry 7). However, the yields decreased obviously when the amount was further reduced to 0.01 equiv (entries 8 and 9). As a result, we adopted 0.3 equiv of [DBU][Ac] under solvent-free conditions at room temperature for the following examinations.

With the efficient catalytic system in hand, we investigated the suitability of a wide range of nitrogen nucleophiles for the [DBU][Ac]-catalyzed aza-Michael reactions using methyl acrylate as the substrate. The aliphatic secondary amines such as morpholine, piperidine, 1-methylpiperazine, 1-ethylpiperazine and pyrazole all underwent conjugate reactions with methyl acrylate favorably, and excellent yields of Michael adducts were obtained at ambient temperature under solvent-free conditions within short reaction times (Table 2, entries 1–4). Like dibenzylamine, morpholine, piperidine and pyarzole in the presence of ionic liquid [DBU][Ac] reacted faster and afforded higher or comparable yields compared with those mediated by DBU (entries 1, 4, and 5). It is of interest to note that when imidazole as a Michael donor was treated with methyl acrylate, imidazole disappeared in 2 h and no Michael product was detected. Judging from the disappearance of OCH_3 group in the ^1H NMR spectrum of the product, acylation product was formed instead, which may provide a possible method for acylation reaction of Michael acceptors (entry 7). However, 2-isopropylimidazole could react with methyl acrylate and 93% of Michael adduct was provided in 10 h (entry 6). It is suggested that steric bulkiness of reagent can assist in the formation of Michael adduct and is detrimental to acylation process. Benzylamine was also treated with methyl acrylate and 20% yield of di-substituted product was formed which was the same with the result catalyzed by DBU[8] (entry 8).

Having obtained satisfactory results with methyl acrylate, we then studied the solvent-free reaction of morpholine with other α,β-unsaturated compounds under the same conditions. Other various vinyl esters, acrylonitrile, and acrylamide were effective substrates to give the desired products in good to excellent yields (Table 2, entries 9–11, 13–14). Among the acrylate esters, the increasing chain of acrylates would lead to decreased reactivity (entries 9 and 10), as the result reported by Lin et al.[6c] α-Methyl-substituted ester and β-phenyl-substituted ester, ethyl cinnamate were also tested as acceptors, respectively, and were found that the former gave the rational yield smoothly and the latter exhibited relatively inert reaction activity due to the strong steric hindrance of phenyl group at β-position (entries 11 and 12).

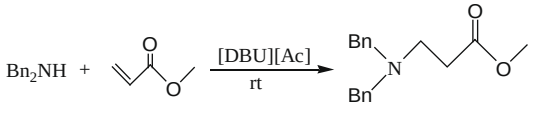
Relatively few reports about aza-Michael reaction involving aromatic amines were published due to the weak nucleophilicities of arylamines.[3a,4d,11] Thus, the task-specific ionic liquid [DBU][Ac] was used as a promoter for conjugate addition of aromatic amines to Michael acceptors under mild conditions. Cyclic ketones such as 2-cyclohexen-1-one and 2-cyclopenten-1-one were found to be suitable substrates to react smoothly with various aromatic amines and good to excellent yields were obtained (Table 3, entries 1–4). However, using [bmim]OH as catalyst, the reaction of *p*-toluidine with 2-cyclohexen-1-one gave lower yield than that catalyzed by [DBU][Ac] , even though the reaction time was prolonged to 24 h (entry 3). Chalcone was also treated as an acceptor to react with aromatic amines to afford good yields (entries 5 and 6), while no reaction occurred in the presence of [bmim]OH.[11] In addition, reaction of methyl acrylate with *p*-methoxyaniline proceeded efficiently with moderate heating (entry 7). All cases shown in Table 3 clearly indicate that the ionic liquid [DBU][Ac] has the excellent catalytic activity for the aza-Michael addition with aromatic amines as Michael donors.

In order to demonstrate the industrial applicability of this methodology, the solvent-free aza-Michael condensation of piperidine and methyl acrylate was carried out on a larger scale (100 mmol). The reaction was completed in 2 h. An excellent yield of 94% was obtained. On the same scale, the recyclability of the catalytic system was investigated using the same reaction as the model reaction. Upon the completion of the reaction, the product was isolated by vacuum distillation, while the residue ionic liquid was dried to remove water at 60 °C under vacuum for 5 h. The recovered ionic liquid was reused in subsequent reactions. As shown in Figure 1, the ionic liquid [DBU][Ac] could be recycled six times without considerable decrease of activity, and the used ionic liquid remained intact (^1H NMR).

Although [DBU][Ac] has weaker basicity than DBU, its catalytic property for aza-Michael reaction is better than that for DBU. The reason, we speculated, is that amines exhibited higher nucleophilicity in the presence of ionic liquids than in organic solvents.[12,6c] The reason for the better performance of [DBU][Ac] in conjugate

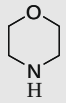
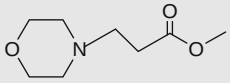
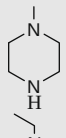
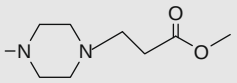
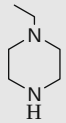
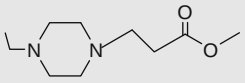
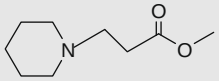
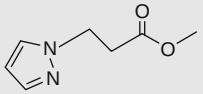
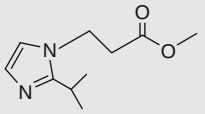
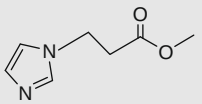
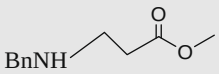
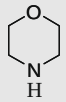
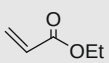
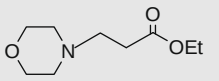
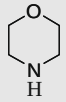
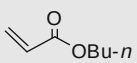
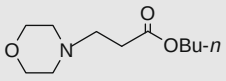
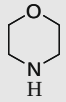
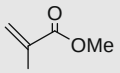
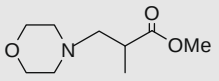
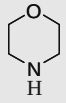
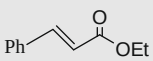
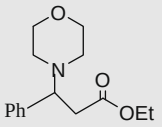
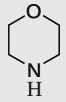
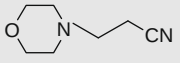
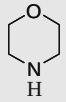
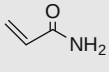
Table 1
Solvent-free conjugate addition of dibenzylamine (1 mmol) to methyl acrylate (1.3 mmol)

Entry	Solvent	Catalyst amount (mmol)	Time (h)	Yield[a] (%)
1[b]	Acetonitrile	0.5	6	95
2	Acetonitrile	0.5	5	94
3	Methanol	0.5	5	86
4	Toluene	0.5	5	89
5	Dichloromethane	0.5	5	90
6	Solvent-free	0.5	4.5	96
7	Solvent-free	0.3	4.5	95
8	Solvent-free	0.1	4.5	72
9	Solvent-free	0.01	4.5	43



[a] Isolated yields.
[b] Ref. 8: using DBU as catalyst.

Table 2
Results of aza-Michael addition of various amines to electron-deficit alkenes using [DBU][Ac] as catalyst under solvent-free conditions[a]

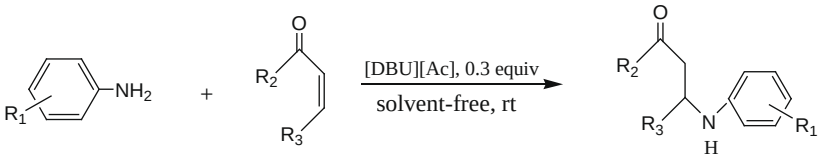
Entry[10]	Nitrogen nucleophile	Michael acceptor	Reaction time/Ref. 8 (h)	Product	Yield[b]/Ref. 8 (%)
1			1.5/4		93/90
2			1.5		90
3			1.5		87
4			1.5/4		92/88
5			5/14		93/95
6			10		93
7			2/14		0/95
8	$BnNH_2$		3/3		80/75
9			3		90
10			5		93
11			4		90
12			15		65
13			3		88
14			3		93

[a] Reactions were carried out on 1.0 mmol scale of substrate with 1.3 equiv of α,β-unsaturated compounds in the presence of 0.3 equiv ionic liquid at room temperature.
[b] Yields of isolated products.

reaction with aromatic amines than that catalyzed by imidazolium ionic liquid [bmim]OH is not very clear, which needs further detailed study.

In conclusion, we have developed a mild, simple, and efficient methodology using a new basic ionic liquid [DBU][Ac] as a catalyst for the conjugate addition of various aliphatic or aromatic amines

Table 3
[DBU][Ac] catalyzed aza-Michael reactions of various aromatic amines with α,β-unsaturated compounds at room temperature[a]



Entry	R_1	R_2	R_3	Time (h)	Yield[b] (%)
1	H	$-(CH_2)_3-$		5	89
2	4-Cl	$-(CH_2)_3-$		6	90
3	4-Me	$-(CH_2)_3-$		5/24[d]	85/71[d]
4[c]	2-Cl	$-(CH_2)_2-$		8	73
5[e]	4-MeO	Ph	Ph	8	88
6[e]	4-Cl	Ph	Ph	12	75
7[c]	4-MeO	MeO	H	6	80

[a] Reaction conditions: aromatic amines (1 mmol), Michael acceptors (1.5 mmol), 0.3 mol % [DBU][Ac], neat conditions, rt.
[b] GC yield for comparing with Ref. 11.
[c] Reactions at 60 °C.
[d] Results obtained in Ref. 11.
[e] 1.0 Equiv of [DBU][Ac] required for dissolving chalcone and aromatic amines.

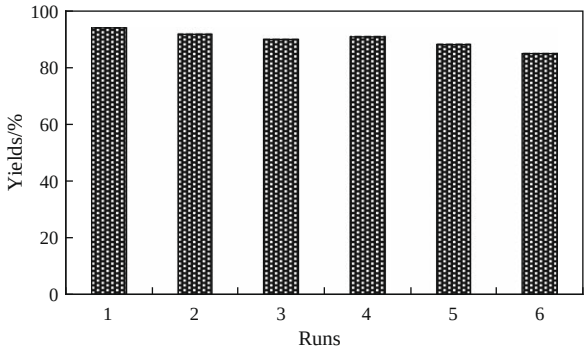


Figure 1. Reuse of ionic liquid for aza-Michael reaction between piperidine (100 mmol) and methyl acrylate under solvent-free conditions.

to a variety of structurally diverse α,β-unsaturated compounds. The reactions were conducted at room temperature under solvent-free conditions and in most cases, good to excellent yields of the desired 1,4-adducts were obtained. Also, the protocol could be scaled up to 100 mmol and proceeded smoothly showing the potential for industrial application. Upon completion of the reaction, the catalyst [DBU][Ac] could be recovered by drying under vacuum at 60 °C for 5 h and reused for six times without significant loss of the activity. The applicability of the task-specific ionic liquid [DBU][Ac] in other fields of organic transformation is underway in our laboratory.

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9. *General procedure for preparation of ionic liquid [DBU][Ac]*: To a 50 mL three-necked flask was added 6 mmol of DBU. Acetic acid (6 mmol) was then added dropwise at the temperature of ⩽5 °C cooled by ice bath. After dropwise addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 24 h. The oil residue was dried in vacuo at 60 °C for 24 h to afford [DBU][Ac] as a light yellow, viscous liquid. ^{1}H NMR (400 MHz, D_2O)

(ppm): 3.50–3.48 (m, 2H, 9-H), 3.44–3.41 (m, 2H, 11-H), 3.23–3.20 (m, 2H, 2-H), 2.75–2.72 (m, 2H, 6-H), 1.89–1.83 (m, 2H, 10-H), 1.68–1.51 (m, 6H, 3-H, 4-H, 5-H), 1.63 (s, 3H, CH_3); ^{13}C NMR (100 MHz, D_2O) (ppm): 174.4, 165.2, 53.1, 47.9, 37.8, 31.2, 28.6, 26.5, 25.1, 24.0, 19.5. Anal. Calcd for [DBU][Ac]: C, 62.10; H, 9.55; N, 13.11; O, 15.24. Found: C, 62.23; H, 9.50; N, 13.20; O, 15.07.

10. *General procedure for aza-Michael reaction of aliphatic amines with α,β-unsaturated compounds*: To a mixture of the aliphatic amine (1 mmol) and Michael acceptor (1.3 mmol) in 10 mL flask equipped with a magnetic stirrer was added ionic liquid [DBU][Ac] (0.3 equiv). The reaction mixture was stirred at ambient temperature for several hours until the disappearance of starting material monitored by TLC. Upon completion of the reaction, the mixture was extracted with ethyl acetate for several times. The combined organic phase was concentrated through vacuum evaporation and the resulting crude product was purified by silica column chromatography to give the desired product. These products are in good agreement with spectra data of literatures. The ionic liquid [DBU][Ac] after extraction was dried in vacuo at 60 °C for 5 h. The recovered ionic liquid was then reused in subsequent reactions.
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