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Novel Efficient Procedure for the Conjugate Addition of Amines to Electron Deficient Alkenes[1]

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Abstract—The novel efficient procedure has been developed for the conjugate addition of amines to electron deficient alkenes using the novel SO_3H functionalized ionic liquid as catalyst. The results showed that the novel catalyst owned high activities for the reactions with excellent yields within several minutes. Various amines and electron deficient alkenes were successfully transformed to the corresponding products in the catalytic system. Operational simplicity, without need of any solvent, low cost of the catalyst used, room temperature, high yields, reusability, excellent chemoselectivity and wide applicability are the key features of this methodology.

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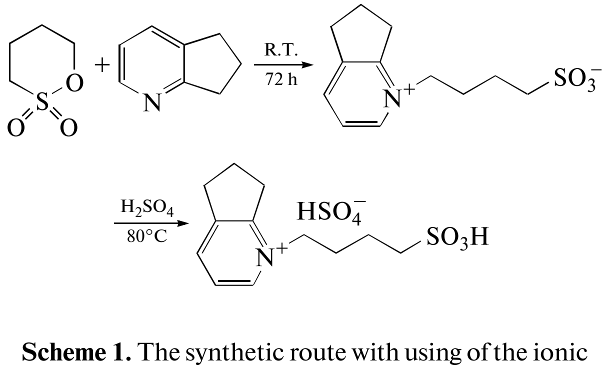
The addition of nitrogen compounds across multiple carbon–carbon bonds is an unsolved synthetically important problem for both basic research and chemical industry [1]. An alternative method for preparing these compounds is via Michael addition. It is a straightforward approach for the synthesis of substituted amines and their derivatives with 100% atom efficiency and without any byproduct formation [2]. Although a number of alternative procedures have been reported recently using a variety of reagents such as Pd compounds [3], $InCl_3$ [4], $CeCl_3$ [5], $Yb(OTf)_3$ [6], $Bi(NO_3)_3$ [7], $Bi(OTf)_3$ [8], $Cu(OAc)_2$ [9], $LiClO_4$ [10], clay [11], silica gel [12], SmI_2 [13], $FeCl_3$ [14], $CrCl_3$ [15], $SnCl_4$ [16], et al. Many suffer from the limitations such as the requirement for a large excess of reagents, long reaction time, harsh reaction conditions and involvement of toxic solvents such as acetonitrile or 1,2-dichloroethane. Hence, the development of less expensive, simpler, "greener" procedures for the reactions is still highly desirable. Aiming to these advantages, we developed a novel solvent-free protocol for the conjugate addition of amines to electron deficient alkenes at room temperature (R.T.) using the ionic liquid as catalyst (Scheme 1). The results showed that the catalyst was very efficient for the reactions with high yields.

EXPERIMENTAL

All organic reagents were commercial products of the highest purity available (>98%) and used for the reaction without further purification. Cyclohexamine, cyclopenta[b]pyridine, 1,4-butane sulfonate, acrylonitrile, butyl acrylate, methyl acrylate, mefhylamine, ethylamine, morpholine were purchased from Shanghai Chemicals Co.

Synthesis of the Catalyst

Preparations of zwitterions. Cyclopenta[b]pyridine and equimolar 1,4-butane sulfonate were mixed together and stirred magnetically for 72 h at 25°C. Then, a white solid zwitterion was formed and washed repeatedly with ether. After dried in vacuum (110°C, 0.01 Torr), the white solid zwitterion was obtained in high yield (>95%) and sufficient purity as assessed by a Varian DRX-400 NMR spectroscopy. Spectroscopic data of NMR ^1H (400 MHz, D_2O, TMS) for the zwitterions: $\delta = 1.693$ (m, 2H), 1.962 (m, 2H), 2.178 (m, 2H), 2.820 (t, $J = 7.8$ Hz, 2H), 3.041 (t, $J = 7.6$ Hz, 2H), 3.243 (t, $J = 7.8$ Hz, 2H), 4.381 (t, $J = 7.6$ Hz,



Scheme 1. The synthetic route with using of the ionic liquid.

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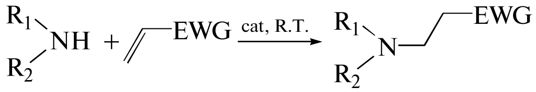
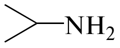
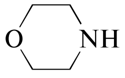
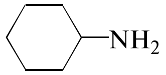
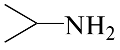
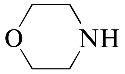
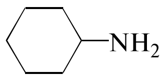
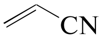
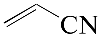
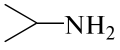
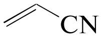
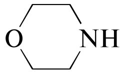
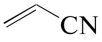
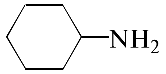
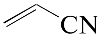
The conjugate additions of various amines with alkenes



Entry	Amines	Alkenes	Reaction time, min	Yield, %
1	$-NH_2$		5	99
2			10	98
3			10	97
4			15	96
5			25	94
6	$-NH_2$		7	99
7			15	96
8			20	96
9			25	94
10			35	92
11	$-NH_2$		4	99
12			5	98
13			15	97
14			20	95
15			25	95

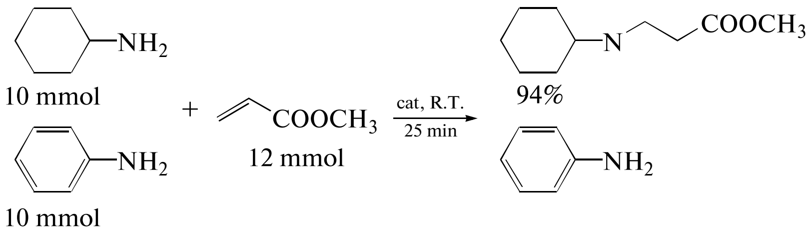
The reaction conditions: amine 20 mmol, alkenes 24 mmol, catalyst 50 mg, R.T. (25°C). The yield was estimated by GC analysis.

2H), 7.598 (t, $J = 7.0$ Hz, 1H), 8.110 (d, 1H), 8.337 (d, 1H).

Preparation of the novel strong Brønsted acidic ionic liquid. A stoichiometric amount of sulfuric acid was added to the above obtained zwitterion and the mixture was stirred at 80°C for 6 h to form the ionic liquid. The ionic liquid phase was then washed repeatedly with toluene and ether to remove non-ionic residues, and dried in vacuum (110°C, 0.01 Torr). The product was formed quantitatively and in high purity as assessed by mass balance and NMR ^{1}H spectroscopies. NMR ^{1}H (400 MHz, D_2O, TMS): $\delta =$ 1.781 (m, 2H), 2.043 (m, 2H), 2.258 (m, 2H), 2.896 (t, $J = 7.6$ Hz, 2H), 3.121 (t, $J = 7.6$ Hz, 2H), 3.325 (t, $J = 7.6$ Hz, 2H), 4.463 (t, $J = 7.6$ Hz, 2H), 7.678 (t, $J = 7.0$ Hz, 1H), 8.189 (d, 1H), 8.420 (d, 1H).

Conjugate Addition of Amines to Electron Deficient Alkenes

Typical procedure for the conjugate addition of amines was the next. A mixture of amine (20 mmol), alkene (24 mmol) and the catalyst (50 mg) was stirred at room temperature for the certain time as shown below. The process of the reaction was monitored by GC analysis. The reaction mixture was extracted with ethyl acetate (2 × 20 ml) and the combined extract was dried over anhydrous Na_2SO_4 and evaporated to leave a crude product, which was separated by column chromatography using neutral alumina as stationary phase and petroleum ether/ethyl acetate mixture (95 : 5) as eluent to give the corresponding product.

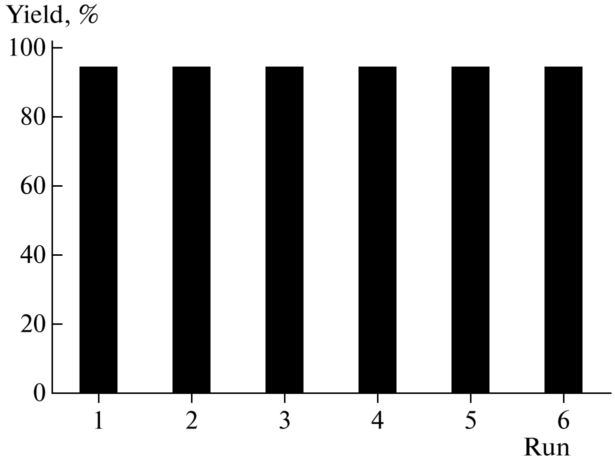


Scheme 2. The chemoselectivity of the catalyst.

RESULTS AND DISCUSSION

Catalytic Procedure for the Conjugate Addition

The conjugate additions of various amines with alkenes under solvent-free conditions were investigated first (table). The results showed that the reactions underwent smoothly at room temperature just within several minutes. The methylamine showed extremely high activity for all kinds of electron deficient alkenes with almost complete conversion within 5 min (entries 1, 6, 11). The yields slightly dropped with the increasing carbon atomicity of the amines because of the steric hindrance (entries 2, 3, 7, 8, 12, 13). The primary amines underwent the single substitution reaction under the reaction condition. These results indicated the usefulness of the novel catalyst for the reactions and the reaction conditions are mild and not sufficient enough to cause double substitution reaction. The multusubstitution reactions could also be activated when more alkenes and high temperature applied, then the double substituted products were obtained with high yields. As to the alkenes, the reactivity was affected by the electronic withdrawing groups (EWG) and the steric hindrance also had the certain effect on the reaction.



The reuse of the catalyst.

The Reuse of the Catalyst

One property of the catalyst is the heterogeneous catalytic process. Thus, recovery of the catalyst is very convenient. After reactions, the reaction mixture was extracted with ethyl acetate (2 × 20 ml) and the lower phase, the ionic liquid, could be reused without any disposal. The recovered activities were investigated through the reaction of cyclohexamine and methyl acrylate carefully (figure). The yield remained unchanged even after the catalyst had been recycled for six times.

The Chemoselectivity of the Catalyst

It is noteworthy that aromatic amines could not be transformed to the corresponding products under the same reaction conditions (Scheme 2). This result indicated that the present protocol could be applicable to the chemoselective addition of aliphatic amines in the presence of aromatic amines.

In conclusion, a novel efficient procedure has been developed for the conjugate addition of amines to electron deficient alkenes. Operational simplicity, without need of any solvent, low cost of the catalyst used, high yields, excellent chemoselectivity, wide applicability are the key features of this methodology.

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