

Cu(acac)₂ immobilized in ionic liquids: A reusable catalytic system for the insertion of α -diazo compounds into N–H bonds of amines

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Abstract

Copper(II) acetylacetonate (Cu(acac)₂) immobilized in ionic liquids (ILs) catalyzes the insertion of α -diazoacetate into N–H bonds of amines to afford glycine esters in good yields under ambient conditions. The use of ionic liquid allows easy separation of the product and recycling of copper catalyst.

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1. Introduction

The catalytic insertion of α -diazo compounds into X–H (X=C, N, O, S) bonds is a very powerful tool for the construction of versatile building blocks used in the synthesis of α -amino acids, peptides and β -lactam antibiotics [1,2]. Intra and intermolecular N–H insertion reactions have received much attention in the last few decades [3].

Yates reported the first catalytic N–H insertion using copper bronze [4]. Saegusa et al. [5] and Nicoud and Kagan [6] employed CuCN catalyst for the insertion of diazo compounds into N–H bonds. Later Rh(OAc)₂ and its derivatives have emerged as powerful catalysts for the insertion reaction of diazo compounds into X–H bonds [7–9]. Simonneaux and co-workers reported this reaction using ruthenium complexes [10]. Recently, Morilla et al. rediscovered Cu(I) homoscorpionate complex for the reaction of different amines and diazo compounds under mild conditions [11]. Asymmetric version of this reaction using Cu(I) and Ag(I) carbenoids was also developed [12]. Very recently, Perez and co-workers reported the {[HC(3,5-Me₂pz)₃]Cu(NCMe)}BF₄ complex catalyzed trans-

fer of the :CHCO₂Et unit from ethyl diazoacetate to several saturated and unsaturated substrates with very high yields and under biphasic conditions using ionic liquid [bmim][PF₆] and hexane as the reaction medium [13].

Undoubtedly, ionic liquids (ILs) are acknowledged as eco-benevolent alternatives to the volatile organic solvents in view of their unique physical properties such as very low vapor pressure, wide liquid range, high thermal stability and possess highly conductive solvation ability for a variety of organic substrates and catalysts including Lewis acids and enzymes [14]. The utility of ionic liquids has been well demonstrated for various organic and bio-transformations [15]. Wang et al. demonstrated intramolecular N–H insertion using Cu(acac)₂ catalyst for the synthesis of 5,6-membered cyclic aza rings [16]. Very recently, C–H insertion of diazo compounds has been reported using rhodium acetate in ionic liquids or in water [17]. In continuation of our studies on ionic liquids as recyclable media for various organic transformations, and the use of (Cu(acac)₂) catalysts, [18] herein, we report the N–H insertion of diazo compounds using Cu(acac)₂ immobilized in ionic liquids at room temperature (Scheme 1) to give glycine esters in good yields.

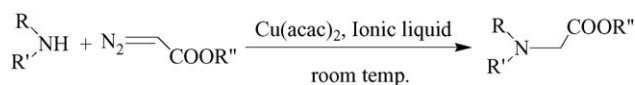
2. Experimental

1-Methyl imidazole, *n*-butyl bromide, NaBF₄, NaPF₆, ethyl diazoacetate and *tert* butyl diazoacetate were purchased from Aldrich or Fluka and used without further purification. Amines

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Scheme 1.

Table 1
Insertion of EDA into morpholine N–H bond using copper catalysts under different reaction conditions

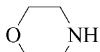
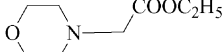
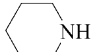
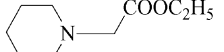
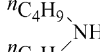
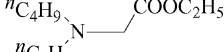
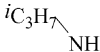
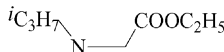
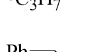
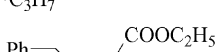
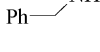
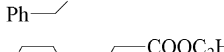
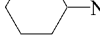
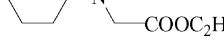
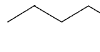
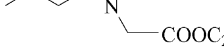
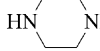
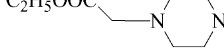
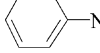
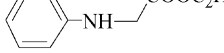
Entry	Copper salt	Solvent	Time (h)	Isolated yield (%)
1	Cu(acac) ₂	IL	1.5	90 ^a
2	CuCl	IL	1.5	60
3	CuCl	IL	1.5	50
4	Cu(acac) ₂	H ₂ O	1.5	50
5	Cu(acac) ₂	Toluene	1.5	40
6	–	IL	1.5	–

Reaction conditions: Morpholine (1 mmol), EDA (1 mmol), Cu catalyst (5 mol%), room temperature.

^a Using 1 mL of ionic liquid, [bmim][BF₄].

were purchased from S.D. Fine Chemicals Ltd., Mumbai. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F₂₅₄ plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

Table 2
Insertion of diazo acetate into N–H of amines using Cu(acac)₂ in [bmim][BF₄]

Entry	Amine	Time (h)	Product	Isolated yield (%)
1		1.5		90, 88 ^a , 85 ^b
2		2		88
3		3.5		84, 80 ^b
4		3.5		80
5		4		88
6		5		80 ^c
7		4		75 ^c
8		4.5		85 ^c
9		4		90
10		5		88 ^c , 80 ^{b,c}

2.1. Synthesis of ionic liquids

[bmim][BF₄] and [bmim][PF₆] were synthesized according to the procedures reported in the literature and the purity was confirmed by ¹H NMR and TGA-DTA analysis [19].

2.2. Typical procedure for the insertion of diazo compounds into amines

To a solution of Cu(acac)₂ (0.013 g, 5 mol%) in ionic liquid (1 mL) and morpholine (0.087 mL, 1 mmol), ethyl diazoacetate (0.105 mL, 1 mmol) was added drop-wise under nitrogen atmosphere within 15 min and stirred at room temperature for 1.5 h. After completion of the reaction, as monitored by TLC, the crude product was extracted with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was purified by column chromatography on silica gel with ethyl acetate: *n*-hexane (2:8) as eluent to afford pure ethyl-4-morpholinylacetate (0.155 g, 90% yield): ¹H NMR (200 MHz, CDCl₃) δ 4.19 (q, 2H, COOCH₂), 3.71 (t, 4H, CH₂), 3.14 (s, 2H, CH₂), 2.57 (t, 4H, CH₂), 1.29 (t, 3H, CH₃); MS (70 eV) *m/z* (%) 173 (M⁺, 25%), 144 (20%), 100 (100%). All other products gave satisfactory results in comparison with data in the literature [20]. The ionic liquid containing Cu(acac)₂ was dried under vacuum and preserved for the next run.

Table 2 (Continued)

Entry	Amine	Time (h)	Product	Isolated yield (%)
11		6		80 ^c
12		4.5		85 ^c
13		2		85 ^d , 80 ^b
14		4		80 ^d

Reaction conditions: Amine (1 mmol), EDA (1 mmol), Cu(acac)₂ (5 mol%), [bmim][BF₄], room temperature.

^a Using [bmim][PF₆].

^b Yield after fourth cycle.

^c 2 mmol EDA used.

^d 1 mmol *tert* butyl diazoacetate used as carbene source.

3. Results and discussion

Initially, the catalytic activity of different copper sources were examined using ethyl diazoacetate (EDA) as carbene source with morpholine and results are presented in Table 1. Among the various copper sources tested, CuCl, CuCl₂, displayed moderate activity compared to Cu(acac)₂ in ionic liquids (Table 1, entries 1–3), whereas the reaction with copper powder was rather sluggish with the formation of some unidentified products (Table 1, entry 4). To ascertain the superior performance of ionic liquids (ILs) over the other solvents, experiments were conducted using Cu(acac)₂ as the catalyst separately in water and toluene (Table 1, entries 5 and 6). It was observed that the reaction was significantly faster and efficient in ILs. However, there was no reaction in the absence of copper catalyst (Table 1, entry 7).

Under optimized conditions, a variety of amines including primary, secondary, aliphatic, aromatic, acyclic and cyclic amines underwent reaction with EDA in presence of 5 mol% Cu(acac)₂ in 1 mL of ionic liquid to give the corresponding N-substituted glycine ethyl esters in good yields (Table 2). Both [bmim][BF₄] and [bmim][PF₆] showed almost similar activities in the insertion of diazo compounds into N–H bonds of amines (Table 2, entry 1). Impressively, cyclic amines such as morpholine, piperidine were found to be more active and gave the corresponding products in high yields at a faster rate (Table 2, entries 1, 2 and 13). Bulky amines, dibutyl, diisopropyl and dibenzyl amines also afforded the products in good yields (Table 2, entries 3–5). In case of primary amines and piperazine, bis-insertion products were obtained in the presence of two equivalents of EDA (Table 2, entries 6–12). Interestingly, bulky glycine esters can also be synthesized in good yields by using the present protocol (Table 2, entries 13 and 14). Finally, upon completion of the reaction, the ionic liquid phase containing [bmim][BF₄] and Cu(acac)₂ was almost quantitatively recovered by simple extraction of the product with Et₂O. The recovered ionic liquid phase containing the catalyst was reused for several cycles with minimal loss of activity (Table 2, entries

1, 3 and 13). AAS analysis shows 0.15% of copper leaching into the solution after the first cycle and a total of 0.63% of copper leaching after the fourth cycle.

4. Conclusions

In conclusion, a simple, efficient and recyclable protocol for a facile N–H insertion of diazoacetate has been developed using Cu(acac)₂ immobilized in ionic liquids at room temperature.

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