

A recyclable protocol for aza-Michael addition of amines to α,β -unsaturated compounds using Cu-Al hydrotalcite

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Abstract

Aza-Michael adducts are obtained in very good yields by the conjugate addition of amines to α,β -unsaturated compounds using Cu-Al-CO₃ hydrotalcite catalyst. The catalyst is used for four cycles with consistent activity and selectivity.

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1. Introduction

The conjugate addition of amines to α,β -unsaturated compounds to form β -amino carbonyl compounds constitutes a key reaction in the synthesis of various complex natural products, antibiotics, β -amino alcohols and chiral auxiliaries [1,2]. Consequently, a large number of methods have been reported for the 1,4-addition of amines to electron-deficient olefins through the activation of amines by stoichiometric or catalytic Lewis acids such as La(OTf)₃ [3], AlCl₃, HgCl₂, TiCl₄ [4], InCl₃ [5], CeCl₃·7H₂O·NaI [6], Yb(OTf)₃ [7], FeCl₃·6H₂O, Co(OAc)₂ [8], Bi(NO₃)₃ [9], Bi(OTf)₃ [10], Ni(ClO₄)₂·6H₂O [11], LiClO₄ [12] and copper salts [13]. However, many of these methods often involve the use of strong acid catalysts, demanding aqueous workup for the catalyst separation, non-recyclability, difficulty in disposal and polymerization of the product. In contrast, there are only few reports on addition of amines to α,β -unsaturated compounds activated by heterogeneous catalysts, transition metal doped montmorillonite and kaolinite clays [4,14]. More recently, a green approach in ionic liquids has been devel-

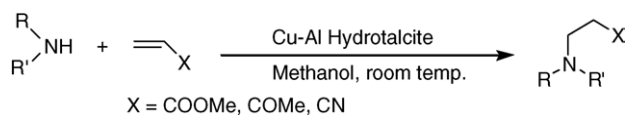
oped for the conjugate addition of amines to α,β -unsaturated compounds [15,16]. Although the recent advances made this route attractive, the development of simple, convenient, and environmentally benign recyclable approaches are highly desirable.

Layered double hydroxides (LDHs) or hydrotalcite like compounds (HTs) have recently received much attention in view of their potential usefulness as adsorbents, anion exchangers and most importantly as basic catalysts [17]. The structure of hydrotalcite consists of brucite [Mg(OH)₂] type octahedral layers in which a part of the M(II) cations are isomorphously substituted by M(III) cations. The excess positive charge of the octahedral layers resulting from this substitution is compensated by interstitial layers built of anions and crystal water. These LDHs consist of alternating cationic M(II)_(1-x)M(III)_x(OH)₂^{x+} and anionic Aⁿ⁻·zH₂O layers, where M(II) is a divalent cation such as Mg, Cu, Ni, Co, Mn, Zn; M(III) is a trivalent cation such as Al, Fe, Cr, Ru, V, In, Ga; Aⁿ⁻ denotes exchangeable anions [18] such as OH⁻, Cl⁻, CO₃²⁻, NO₃⁻, SO₄²⁻ and the value of the *x* is in the range from 0.1 to 0.33. As a part of our research program aimed at developing the synthetic utility of solid catalysts in fine chemical synthesis, herein we report Cu-Al hydrotalcite (cat. 1) catalyzed conjugate addition of amines to α,β -unsaturated compounds to afford aza-Michael adducts in very good yields at room temperature (Scheme 1).

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Scheme 1.

2. Experimental

$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, KF, KO^tBu , NaOH, Na_2CO_3 , methyl acrylate (MA), acrylonitrile (AN) and methyl vinyl ketone (MVK) and amines were purchased from Aldrich or Fluka and used without further purification. 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. Commercial MgO was purchased from s.d.fine-chem Ltd., India. Nano-MgO was purchased from NanoScale Materials Inc., Manhattan, USA. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

2.1. Preparation of the catalysts

2.1.1. Synthesis of Cu-Al hydrotalcite catalyst

Cu-Al hydrotalcite (Cu/Al, 3:1) was prepared as follows [19]. A mixture of solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (32.92 g, 0.1404 mol) and $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (16.88 g, 0.045 mol) in deionised and decarbonated water (140 mL) and the aqueous solutions of sodium hydroxide (13.124 g, 0.328 mol) and sodium carbonate (8.9252 g, 0.0842 mol) in deionised and decarbonated water (140 mL) were added simultaneously drop-wise from the respective burettes into the round bottomed flask. The pH of the reaction mixture was maintained constantly (8–9) by the continuous addition of base solution. The resulting slurry was aged at 65 °C for 30 min. The solid product was isolated by filtration, washed thoroughly with deionised and decarbonated water, and dried at under vacuum. The weight of the catalyst obtained was 17.6 g. The copper content in the catalyst was found to be 6.91 mmol/g. The catalyst was characterized by XRD and it is similar to that reported earlier [19].

2.1.2. Synthesis of various hydrotalcites

Mg-Al- NO_3 HT, calcined Mg-Al- NO_3 HT, Mg-Al-OH (rehydrated) HT, Mg-Al-F HT and Mg-Al- O^tBu HT catalysts were prepared according to our previously reported procedures [18b].

2.2. Typical experimental procedure for the conjugate addition of amines to α,β -unsaturated compounds

In a typical procedure, methyl acrylate (1.2 mmol), dibutyl amine (1.0 mmol) and cat. **1** (0.05 g) were taken in methanol (5 mL) and stirred at room temperature for the appropriate time (Tables 1 and 2). After completion of the

Table 1

Aza-Michael reaction between dibutylamine and methyl acrylate using various solid catalysts^a

Entry	Catalyst	Time (h)	Yield (%) ^b
1	Mg-Al- NO_3 Hydrotalcite	6.0	52
2	Calcined Mg-Al- NO_3 Hydrotalcite	6.0	60
3	Mg-Al-OH (rehydrated) Hydrotalcite	6.0	68
4	Mg-Al-F Hydrotalcite	6.0	66
5	Mg-Al- O^tBu Hydrotalcite	6.0	70
6	Cu-Al Hydrotalcite (cat. 1)	3.0	90
7	MgO (commercial)	6.0	70
8	MgO (nano)	6.0	75
9	None	6.0	38

^a Reaction conditions: dibutyl amine (1.0 mmol), methyl acrylate (1.2 mmol), catalyst (0.05 g), and methanol (5 mL) at room temperature.

^b Yield after column chromatography.



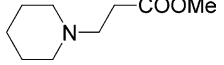


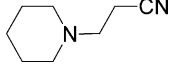

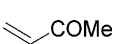
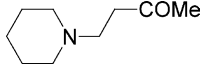
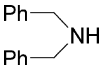

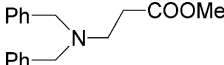
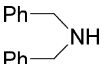

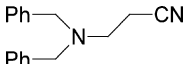
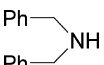
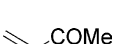
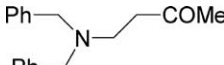


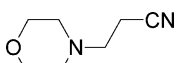

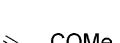
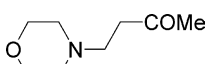
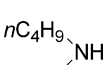

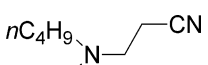
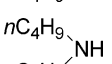
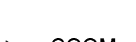
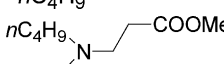
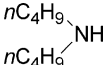
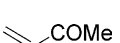
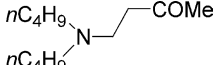
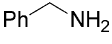
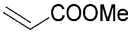
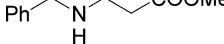
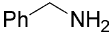
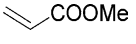

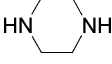

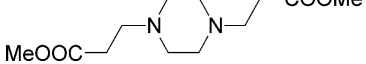
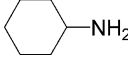

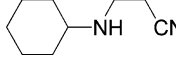
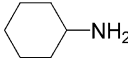

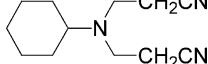
reaction, monitored by TLC, the reaction mixture was filtered and washed with ethyl acetate (3 mL \times 5 mL). The combined ethyl acetate extracts were concentrated in vacuo, and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate/*n*-hexane to afford the pure methyl 3-(dibutylamino)propanoate [6]. ¹H NMR (200 MHz, CDCl_3) δ 2.50 (*t*, *J* = 7.30 Hz, 2H); 2.80 (*t*, *J* = 6.92 Hz, 2H); 3.57 (*s*, 4H); 3.61 (*s*, 3H); 7.22–7.35 (*m*, 10H). IR (KBr, cm^{-1}) 3026, 1732, 1494, 1428; MS (EI) *m/z* 283 (M^+), 210, 91, 77. Anal. calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_2$; C: 76.29; H: 7.47; N: 4.94; found C: 76.40; H: 7.42; N: 4.72. All other products gave satisfactory NMR and mass spectral data [7,14].

3. Results and discussion

The results of the conjugate addition of dibutyl amine with methyl acrylate in methanol as a solvent at room temperature with different heterogeneous catalysts are summarized in Table 1. The data in Table 1 show that the Cu-Al HT (Table 1, entry 6) catalyst is more active than the other catalysts, Mg-Al- NO_3 HT (Table 1, entry 1), calcined Mg-Al- NO_3 HT (Table 1, entry 2), Mg-Al-OH (rehydrated) HT (Table 1, entry 3), Mg-Al-F HT (Table 1, entry 4), Mg-Al- O^tBu HT (Table 1, entry 5). Commercial MgO (Table 1, entry 7) and nano-MgO (Table 1, entry 8) catalysts displayed moderate activity. A control experiment was conducted in the absence of catalyst and it was observed that addition of dibutyl amine to methyl acrylate (Table 1, entry 9) resulted in the formation of desired product in low yields (ca. 38%) under similar reaction conditions.

Various cyclic and acyclic aliphatic amines including morpholine underwent 1,4-addition with a range of α,β -unsaturated compounds to afford the corresponding aza-Michael adducts (Table 2). The reaction proceeded smoothly within 3–5 h for all substrates. There is no reaction when aromatic amines such as aniline, *p*-chloroaniline are treated with the Michael acceptor, methyl acrylate. The inertness of aromatic amines is exemplified by taking an equimolar mix-

Table 2
Aza-Michael reaction using Cu-Al hydrotalcite^a

Entry	Amine	Acceptor	Time (h)	Product	Yield (%) ^b
1			3.0		90
2			3.5		88
3			4.0		84
4			5.0		75
5			5.5		80
6			5.0		75
7			4.0		86
8			2.5		80
9			5.0		88
10			3.0		90
			3.0		89 ^c
11			5.0		88
12			5.5		78 ^d
13			5.5		80 ^e
14			5.0		90 ^e
15			5.0		70 ^d
16			5.0		70 ^e

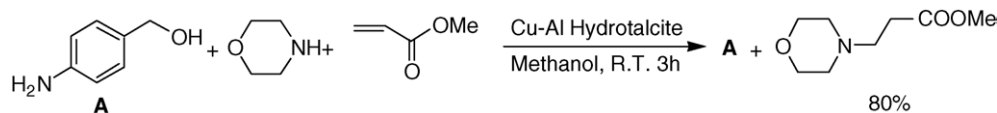
^a Reaction conditions are exemplified in the general reaction procedure.

^b Isolated yield after silica gel chromatography.

^c Isolated yield after fourth cycle.

^d Five to nine percent of bis-adducts were formed.

^e 2.4 equivalents of acceptor used.



Scheme 2.

ture of *p*-aminobenzyl alcohol and morpholine with methyl acrylate as the Michael acceptor under similar reaction conditions using Cu-Al hydrotalcite (cat. **1**). As expected, aliphatic amine gave addition product in good yield (Scheme 2). This clearly shows that cat. **1** is suitable to activate the aliphatic amines only and fails in the case of aromatic amines for the aza-Michael addition reaction.

The reaction of cyclic amines such as piperidine with methyl acrylate (MA), acrylonitrile (AN) and methyl vinyl ketone (MVK) gave 90, 88 and 84% yields, respectively, in 3–4 h (Table 2, entries 1–3). Sterically hindered amine, for example dibenzylamine (Table 2, entries 4–6) with MA, AN and MVK offered 1,4-addition products in 75–80% yields in 5–5.5 h. Other amines like morpholine (Table 2, entries 7 and 8), dibutyl amine (Table 2, entries 9–11) and cyclohexyl amine (Table 2, entry 15) were reacted in equal ease with MA, AN and MVK and gave 70–88% yields in 2.5–5 h. However, benzylamine with MA gave mono-addition product as major in 78% yield along with 5–9% bis-adduct (Table 2, entry 12). No byproducts resulting from 1,2-addition were observed. The use of excess Michael acceptor gave bis-adducts as a sole product in good yields (Table 2 and entries 13, 14 and 16).

The Cu-Al hydrotalcite (cat. **1**) was removed after the reaction by filtration, washed with methanol and dried under vacuo. The recovered catalyst is reused several times without loss of activity (Table 2, entry 10). The leaching of the metal after the first cycle was determined by Atomic Absorption Spectrometer and it is negligible (0.059%).

4. Conclusions

In summary, we have described a simple, convenient, and efficient protocol for the 1,4-conjugate addition of amines to α,β -unsaturated compounds using Cu-Al hydrotalcite catalyst at room temperature in very good yields. The Cu-Al hydrotalcite shows enhanced activity over the other solid catalysts tested and reused for several cycles with consistent activity and selectivity.

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