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# Clay catalyzed chemoselective Michael type addition of aliphatic amines to α,β-ethylenic compounds

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Dedicated to the warm memory of Ms Sarah His of Senlis, France

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**Abstract**—Application of acidic clays as heterogeneous catalysts for the Michael type addition reaction of aliphatic amines to α,β-ethylenic compounds is presented. Aromatic amines do not participate in this transformation. 

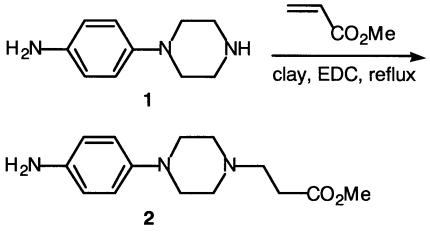
The scope of heterogeneous catalytic organic transformations is rapidly growing due to their well-documented advantages over homogeneous catalytic systems. Clays have emerged as ideal acidic heterogeneous catalysts as they are available in nature and are thus inexpensive. These clays have Brønsted as well as Lewis acidic sites[1] and thus increase their utility in both types of catalytic applications. The positive features of clays also include high stability, ease of handling and regeneration, lack of corrosiveness and other environmental hazards. In recent years, we[2] and others[1,3] have developed several new applications of clays in heterogeneous catalytic reactions.

One of the simple approaches towards β-amino derivatives such as β-aminoesters is via the Lewis acid-mediated addition of amines to α,β-ethylenic compounds.[4] Although, in some cases reaction occurs with no special activation,[5] in others stronger reaction conditions are required.[6]

A new catalytic system utilizing indium trichloride has been recently reported by Loh and Wei[7] for the addition of amines to α,β-ethylenic compounds. This catalyst is not selective and works equally well with aliphatic as well as aromatic amines. This encouraged us to investigate the reaction with clay catalysts and we wish to present our findings in this paper. To the best of our knowledge, the report by Laszlo[1b] with transition metal doped catalysts is the only reference available in the literature for the heterogeneous version of this reaction.

Effectiveness of clays to catalyze this conversion was tested for the reaction of morpholine and acrylonitrile. To our satisfaction, the addition product was obtained in high yield in a very short reaction time. Different aliphatic amines and α,β-ethylenic compounds were studied as substrates for this transformation which were catalyzed equally well with either kaolinitic clay[8] or commercially available Montmorillonite K10[9] and the results are presented in Table 1.

Several aromatic amines such as *p*-chloroaniline, *p*-nitroaniline, *p*-anisidine, *p*-toluidine, *o*-aminophenol and *o*-aminothiophenol were subjected for this reaction with clay as catalyst and methylacrylate or acrylonitrile as the Michael acceptors. In most of the cases, aromatic amine remained unchanged or in some cases, only a small amount of product of single addition was detected. This was further established by the following two experiments (Eq. (1)). A diamine **1** with aromatic and aliphatic amino groups incorporated in the same molecule was exposed to an excess of methylacrylate in refluxing dichloroethane. Careful analysis of the single product **2** revealed the inertness of aromatic amino group while the aliphatic one underwent the addition reaction.




(1)

Another control experiment was performed with an equal mixture of *p*-anisidine **3** and morpholine with excess of acrylonitrile under the same catalytic conditions (Eq. (2)).

*Keywords*: heterogeneous catalyst; Michael addition reaction; amines; α,β-ethylenic compounds.

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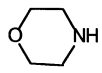
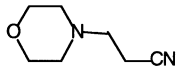
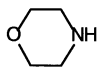
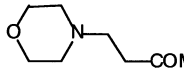
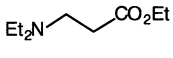
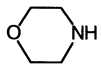
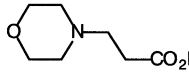
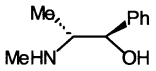
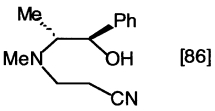
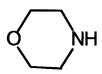
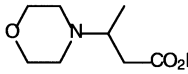
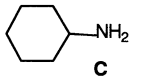
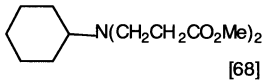
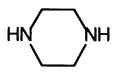
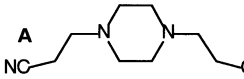
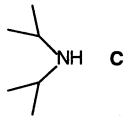
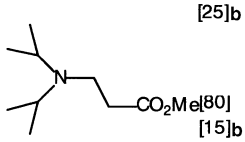
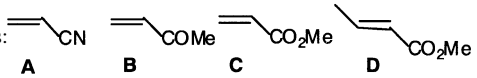
**Table 1.** Clay catalyzed reaction of amines with α,β-ethylenic compounds

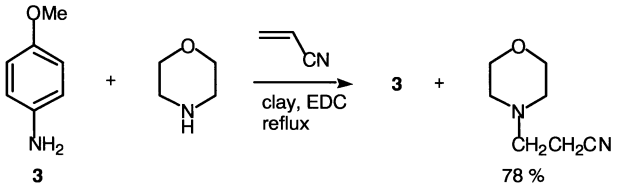
| Entry | Reagents | Product (% yield)[a] | Entry | Reagents | Product (% yield)[a] |
|---|---|---|---|---|---|
| 1. |  A |  [82] | 6. | $HO(CH_2)_3NH_2$ A | $HO(CH_2)_3N(CH_2CH_2CN)_2$ [85] |
| 2. |  B |  [88] | 7. | $Et_2NH$ E |  [83] |
| 3. |  C |  [91] | 8. |  A |  [86] |
| 4. |  D |  [90] [38]b | 9. |  C |  [68] [25]b |
| 5. |  A |  [76] | 10. |  C |  [80] [15]b |

Ethylenic components:  A B C D E All the reactions were performed in refluxing 1,2-dichloroethane (EDC) as solvent for 3 h (ent. 1–4, 6 and 7) and for 6 h (ent. 5, 8–10) with 2.0 equiv. (ent. 1–4, 7 and 8) and 3.5 equiv. ethylenic component (ent. 5, 6 and 9).

[a] Isolated yield. All the compounds were characterized by usual spectral and analytical methods.

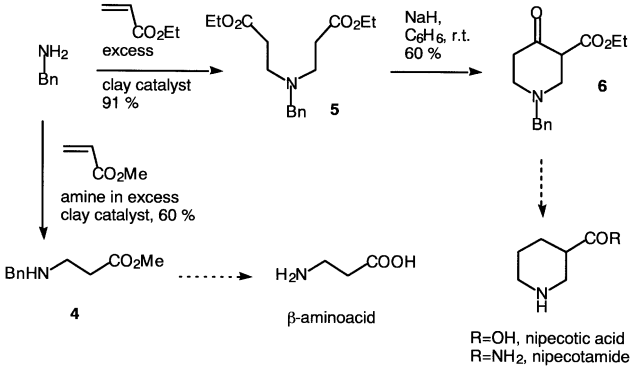
[b] Without catalyst.

As expected, the former remained unaffected while the latter furnished the addition product in high yield. These experiments clearly show that the Lewis acidity of clays is suitable only to activate aliphatic amines for the addition towards α,β-ethylenic compounds and failed for less nucleophilic aromatic amines. We feel that this selectivity could be useful to discriminate the two types of amines for synthetic applications.




(2)

Reaction of benzylamine and acrylates was separately investigated to establish conditions for selective preparation of mono and bis-addition products. Reaction of methylacrylate with excess of benzylamine in the presence of clay furnished **4** as a single product due to mono addition reaction, albeit in moderate yield (Eq. 3). The reaction of benzylamine with excess of ethylacrylate in presence of clay gave product **5** of bis-addition in excellent yield. Compound **5** was subjected to Dieckmann cyclization with sodium hydride to give ethyl-*N*-benzyl-4-oxo-3-piperidinecarboxylate **5** in moderate yield. While compound **4** is a direct precursor of β-aminoacids, **6** is used as starting material for the synthesis of numerous heterocyclic compounds,[10] and derivatives of nipecotic acids. Nipecotic acid derivatives have received importance as they are γ-aminobutyric acid (GABA) uptake inhibitors[11] and many new analogues are being prepared recently.[12]




(3)

Thus, we present here, a practical and selective clay catalyzed Michael type addition reaction of aliphatic amines towards α,β-ethylenic compounds.

## 1. Experimental

### 1.1. General

Melting points were recorded on electrothermal melting point apparatus and are uncorrected. The NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on Bruker WM 200 NMR spectrometer ($^1$H NMR at 200 MHz and $^{13}$C NMR at 50 MHz). Mass spectra were recorded on Finnigan MAT 1020B GC–MS (EI)

instrument. The FT-IR spectra were recorded on an ATI-Mattson Res. Series 1 spectrometer and Microanalyses were performed on a Carlo–Erba instrument. Reagent grade fine chemicals such as all amines, α,β-ethylenic compounds and solvents were used without further purification.

**1.1.1. 3-Morpholin-4-yl-propionitrile (Table 1, entry 1).** A mixture of morpholine (200 mg, 2.3 mmol), acrylonitrile (244 mg, 4.6 mmol) and kaolinetic clay (20 mg, 10%, w/w) in dry 1,2-dichloroethane (5 mL) is refluxed for 3 h under Ar. After the reaction (monitored by TLC), the catalyst was separated and the crude product was purified by column chromatography on silica gel (~10% EtOAc in light petroleum ether) to get pure product as yellow oil (264 mg, 82%).

Similar experimental procedure is followed for other examples and the chemical yields of isolated products are indicated in Table 1. Compounds from entries 1–4 were fully characterized and their analytical data were in accordance with the reported values.[13]

**1.1.2. 3-[4-(2-Cyanoethyl)-piperazine-1-yl]-propionitrile (Table 1, entry 5).** White solid. (mp 62–63°C). $^1$H NMR $\delta$ 2.45–2.55 (m, 12H), 2.69 (m, 4H) $\nu$ 3373, 2937, 2816, 2241 cm$^{-1}$. Mass (*m*/*z*) 192(25), 152(100), 138(10), 109(80), 97(30), 83(40), 70(75), 56(60). Microanalysis for $C_{10}H_{16}N_4$, Calcd: C, 62.50; H, 8.30; N, 29.16; found: C, 62.27; H, 8.59; N, 29.43%.

**1.1.3. 3-[(2-Cyanoethyl)-(3-hydroxypropyl)-amino]-propionitrile (Table 1, entry 6).** Yellow oil. $^1$H NMR $\delta$ 1.68 (m, 2H), 2.49 (t, *J*=7.1 Hz, 4H), 2.66 (t, *J*=7.3 Hz, 2H), 2.84 (t, *J*=7.3 Hz, 4H), 3.73 (t, *J*=6.9 Hz, 2H). $\nu$ 3425, 3260, 2928, 2853, 2249, 1638, 1400, 1051 cm$^{-1}$. Mass (*m*/*z*) 181(10), 141(30), 136(50), 117(60), 97(100), 90(25), 83(30), 71(15), 54(40). Microanalysis for $C_9H_{15}N_3O$, Calcd: C, 59.66; H, 8.28; N, 23.20; found: C, 59.50; H, 8.50; N, 23.40%.

**1.1.4. Ethyl(3-diethylamino)-propionate (Table 1, entry 7).** White semisolid. $^1$H NMR $\delta$ 0.99 (t, *J*=7.3 Hz, 6H), 1.21 (t, *J*=7.8 Hz, 3H), 2.37– 2.53 (m, 6H), 2.76 (t, *J*=7.3 Hz, 2H), 4.06 (q, *J*=7.5 Hz, 2H). $\nu$ 3405, 2912, 2833, 1732, 1425, 1265, 1110 cm$^{-1}$. Mass (*m*/*z*) 173(8), 158(16), 144(10), 106(10), 86(100), 72(20), 57(50). Microanalysis for $C_9H_{19}NO_2$, Calcd: C, 62.43; H, 10.98; N, 8.09; found: C, 62.10; H, 11.00; N, 8.11%.

**1.1.5. 3-[(2-Hydroxy-1(*R*)-methyl-2(S)-phenyl-ethyl)-methylamino]-propionitrile (Table 1, entry 8).** Colorless thick oil. $^1$H NMR $\delta$ 0.95 (d, *J*=6.8 Hz, 3H), 2.33 (s, 3H), 2.42 (t, *J*=6.8 Hz, 2H), 2.71–2.90 (m, 4H), 4.81 (d, *J*= 4.4 Hz, 1H), 7.20–7.40 (m, 5H). $\nu$ 3401, 2963, 2920, 2802, 2238, 1374, 1038, 696 cm$^{-1}$. Mass (*m*/*z*) 218(8). 148(2), 117(10), 111(100), 105(10), 77(15), 68(25). Microanalysis for $C_{13}H_{18}N_2O$, Calcd: C, 71.56; H, 8.26; N, 12.84; found: C, 71.48; H, 7.90; N, 12.92%.

**1.1.6. Methyl-3-[cyclohexyl-(2-methoxycarbonyl-ethyl)-amino]-propionate (Table 1, entry 9).** Yellow oil. $^1$H NMR $\delta$ 1.10–1.30 (m, 2H), 1.60–1.90 (m, 8H), 2.40–2.60 (m, 5H), 2.90 (t, *J*=6.8 Hz, 4H), 3.68 (s, 6H). $\nu$ 1745, 1150, 880 cm$^{-1}$. Mass (*m*/*z*) 271(5), 250(10), 228(25), 207(20), 198(40), 171(15), 142(30), 128(100), 98(50). Microanalysis for $C_{14}H_{25}NO_4$, Calcd: C, 61.99; H, 9.22; N, 5.16; found: C, 62.11; H, 9.50; N, 5.40%.

**1.1.7. Methyl-(3-diisopropylamino)-propionate (Table 1, entry 10).** White semisolid. $^1$H NMR $\delta$ 0.86 (d, *J*=6.4 Hz, 12H), 2.28 (t, *J*=7.5 Hz, 2H), 2.63 (t, *J*=5.9 Hz, 2H), 2.68 (hept, *J*=6.6 Hz, 2H), 3.49 (s, 3H). $\nu$ 2935, 2810, 1725, 1345, 1181, 980, 847 cm$^{-1}$. Mass (*m*/*z*) 187(10), 172(50), 158(8), 130(12), 114(60), 98(70), 70(72), 56(100). Microanalysis for $C_{10}H_{21}NO_2$, Calcd: C, 64.17; H, 11.23; N, 7.48; found: C, 64.30; H, 11.50; N, 7.80%.

**1.1.8. Methyl-{3-[4-(4-aminophenyl)piperazine-1yl]}-propionate (2): Eq. 1.** Red oil. $^1$H NMR $\delta$ 2.53 (t, *J*=7.3 Hz, 2H), 2.62 (t, *J*=5.1 Hz, 4H), 2.74 (t, 7.3, 2H), 3.04 (t, *J*=5.1 Hz, 4H), 3.31 (brs, 2H), 3.69 (s, 3H), 6.61 (d, *J*=8.8 Hz, 2H), 6.77 (d, *J*=8.8 Hz, 2H). $\nu$ 3373, 3017, 2950, 2824, 1731, 1513, 1261, 1215, 666 cm$^{-1}$. Mass (*m*/*z*) 263(100), 248(10), 190(25), 176(12), 147(15), 120(90), 106(20), 70(80), 56(85). Microanalysis for $C_{14}H_{21}N_3O_2$, Calcd: C, 63.88; H, 7.98; N, 15.96; found: C, 64.00; H, 7.91; N, 15.85%.

**1.1.9. Methly-(3-benzylamino)-propionate (4): Eq. 3.** Pale yellow oil. $^1$H NMR $\delta$ 2.64 (t, *J*=6.3 Hz, 2H), 2.95 (t, *J*=6.8 Hz, 2H), 3.40 (brs, 1H), 3.7 (s, 3H), 3.88 (s, 2H), 7.2–7.4 (m, 5H). $\nu$ 3217, 2921, 2861, 1742, 1550, 1417, 1325, 1260, 1207, 649 cm$^{-1}$. Mass (*m*/*z*) 193(7), 175(12), 160(5), 120(10), 91(100), 77(5), 65(20), 56(5). Microanalysis for $C_{11}H_{15}NO_2$, Calcd: C, 68.39; H, 7.77; N, 7.25; found: C, 68.45; H, 7.95; N, 7.43%.

**1.1.10. Ethyl-{3-[benzyl-(2-ethoxycarbonyl-ethyl)-amino]-propionate (5): Eq. 3.** Colorless oil. $^1$H NMR $\delta$ 1.20 (t, *J*=7.3 Hz, 6H), 2.47 (t, *J*=7.3 Hz, 4H), 2.82 (t, *J*=7.3 Hz, 4H), 3.60 (2H, s), 4.13 (quart, *J*=7.3 Hz, 4H), 7.1–7.4 (m, 5H). $\nu$ 3020, 2922, 2860, 1738, 1510, 1403, 1308, 1243, 1207, 1107, 752 cm$^{-1}$. Mass (*m*/*z*) 307(8), 278(7), 230(5), 220(100), 206(30), 190(5), 170(6), 146(7), 132(7), 118(10), 105(6), 91(75), 77(4), 65(5). Microanalysis for $C_{17}H_{25}NO_4$, Calcd: C, 66.45; H, 8.14; N, 4.56; found: C, 66.20; H, 8.41; N, 4.66%.

**1.1.11. Ethyl-(1-benzyl-4-oxo-3-piperidine)carboxylate**[13] **(6).** A solution of diester **5** (1 g; 3.26 mmol) in of anhydrous benzene (7 mL) was slowly added, under nitrogen atmosphere, to a suspension of oil free sodium hydride (0.194 g; 8.14 mmol) in anhydrous benzene (9 mL). Few drops of absolute ethanol were added to initiate the reaction, which was then refluxed for 3.5 h. At the completion of reaction (TLC), glacial acetic acid (1 mL) was added followed by water (3 mL) at room temperature. Reaction mixture was stirred for 30 min. The organic layer separated, dried and concentrated in vacuum to get 0.507 g (60%) of red oil as a pure compound.

$^1$H NMR $\delta$ 1.29 (t, *J*=7.3 Hz, 3H), 2.41 (t, *J*=7.3 Hz, 2H), 2.62 (t, *J*=7.3 Hz, 2H), 2.81 (t, *J*=7.3 Hz, 1H), 3.10 (d, *J*= 7.3 Hz, 2H), 3.66 (s, 2H), 4.20 (quartet, *J*=7.2 Hz, 2H). $\nu$ 2914, 1730, 1694, 1637, 1520, 1326, 1217, 1113, 740 cm$^{-1}$. Mass (*m*/*z*) 261(20), 232(10), 214(60), 188(50), 170(10), 146(5), 132(5), 124(35), 96(7), 91(100), 77(5), 65(7).

Microanalysis for $C_{15}H_{19}NO_3$, Calcd: C, 68.96; H, 7.28; N, 5.36; found: C, 69.11; H, 7.34; N, 5.56%.

## Acknowledgements

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