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Acylation of amines with carboxylic acids: the atom economic protocol catalysed by Fe(III)-montmorillonite *

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An efficient and selective acylation of amines employing carboxylic acid as acylating agent was realised for the first time through tuning up of acidic sites of montmorillonite K10 achieved by incorporation of the right choice of exchangeable cations.

KEY WORDS: acylation; amine; carboxylic acid; acylating agent; atom economy; modified montmorillonite; reusable catalyst

1. Introduction

Amides represent an important class of chemicals that are especially used as intermediates for drugs and pharmaceuticals, azo and sulfur dyes, fine chemicals and as additive for hydrogen peroxide, photographic chemicals and as antioxidants [1]. Acylation of amines is usually performed using acid chlorides or anhydrides as an acylating agent in the presence of stoichiometric amounts of amine bases such as pyridine derivatives like 4-(dimethylamino)pyridine or 4-pyrrolidinopyridine [2,3], tertiary amines [3] and tributylphosphine [4], *etc.*, and Lewis acids such as lithium chloride [5], zinc chloride [6] and cobalt chloride [7] to afford good yields. The above option employing acetic anhydride as acetylating agent and soluble bases or acids as reagents or catalysts presents insurmountable problems in the recovery of large amounts of soluble bases or acids and achieves less than 50% atom economy in the consumption of acetic anhydride by utilizing only the acetyl group. These disadvantages have negative impact on eco-economic front, rendering these processes unviable both in terms of ecofriendliness and economy. $Cp_2Sm(thf)_2$ [8], tetrabutyl ammonium salt [9] and vinyl carboxylate [10] are the best catalysts for the acylation of amines with esters. Earlier, Li *et al.* reported the montmorillonite K-10 and KSF [11] catalysed acetylation of primary and secondary amines in the presence of acetic anhydride as the acetylating agent. The use of clays as solid acids has received considerable attention in nitration and tosylation reactions [12].

In our continued efforts to develop suitable solid acid montmorillonite clay catalysts for acylation reactions using acetic acid as an acylating agent, we have designed and prepared various solid acids which have an expandable layer lattice with magnetic field acidity (H_0) values between 1.5 and -3 and their acidities may be tuned further by metal ion exchange with the introduction of a large number of Lewis acidic sites. Recently, we have reported [13] an efficient catalyst for the selective acylation of alcohols with carboxylic acids as acylating agents. Herein, we report a simple, selective and environmentally acceptable synthesis of amides from amines *via* acylation using carboxylic acid as an acylating agent and modified montmorillonite clay as catalyst. The yields are quantitative and highly selective to achieve higher atom economy. There is no by-product formation except water (see scheme 1).

2. Experimental

2.1. Preparation of the catalysts

The metal-ion-exchanged montmorillonite clay catalysts were prepared adopting Lazlo *et al.*'s procedure [14], and dried in an oven at 250 °C overnight, prior to use in acylation of amines.

2.2. Characterisation

The metal content of each Fe^{3+}-, Zn^{2+}-, Cu^{2+}- and Al^{3+}-exchanged montmorillonite catalyst was analysed according to Vogel's procedure [15] and found to be 6.3, 1.79, 1.28 and 7.82%, respectively. It is known that, at low aqueous concentrations and at ordinary temperatures, the extent of exchange increases with increasing valency of the exchanging cation [16]. Therefore, the higher Fe^{3+} and Al^{3+} content is attributed to a higher exchange capacity of

$$\text{R–NH}_2 \xrightarrow[116\,^{\circ}\text{C},5\text{–}300\ \text{min}]{\text{AcOH, Fe}^{+}\text{-mont}} \text{R–NHAc} + \text{H}_2\text{O}$$

R = aliphatic acyclic, cyclic, heterocyclic and
aromatic amines

Scheme 1.

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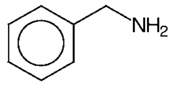
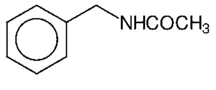
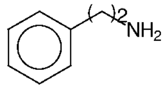
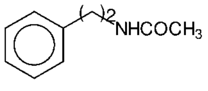
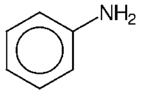
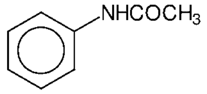
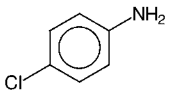
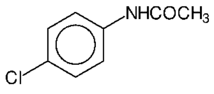
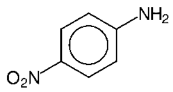
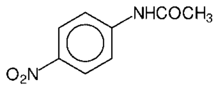
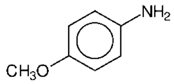
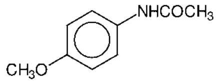
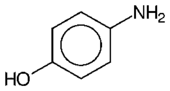
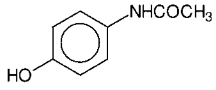
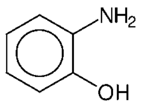
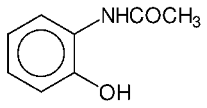
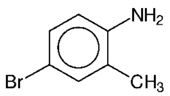
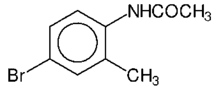
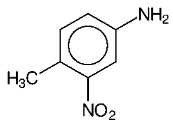
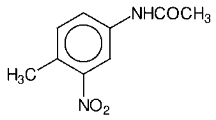
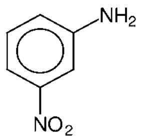
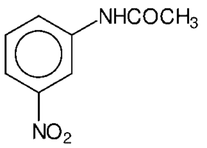
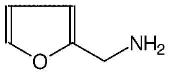
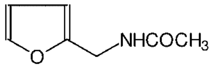
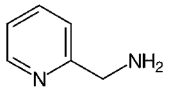
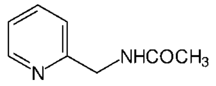
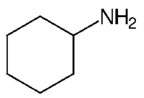
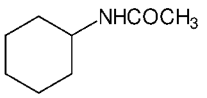
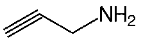
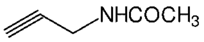
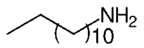
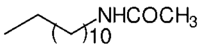
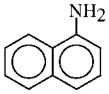
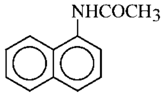
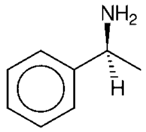
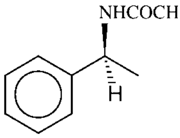
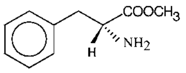
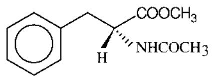
Table 1

N-acetylation of amines using acetic acid as acetylating agent.

Entry	Amine[a] (substrate)	Reaction time[d] (h)	Product[b]	Yield[c] (%)
1a		0.08		99
1b		0.08		< 5 [f]
2		1.0		98
3		3.0		98
4		3.0		99
5		3.0		97
6		2.5		99
7		3.0		98
8		3.0		99
9		3.0		97
10		3.0		98
11		6.0		98
12		2.5		97
13		3.5		95
14		3.0		97
15		4.0		72[e]
16		3.5		98
17		5.0		99
18		0.75		98
19		2.0		96

[a] Amine and acetic acid molar ratio was 1 : 10.

[b] All products were identified by ^{1}H NMR and mass spectroscopy and/or comparison of their bp or mp with authentic samples.

[c] Isolated yields.

[d] Where acetic acid reflux temperature was maintained.

[e] Confirmed by ^{1}H-NMR.

[f] In absence of catalyst.

the trivalent Fe^{3+} and Al^{3+} cations. The maximum acid strength for K10 montmorillonite with Hammett indicators in benzene is known ($-8.2 \geqslant H_0$) [17]. As it is difficult to judge colour changes of Hammett indicators for the coloured Fe^{3+}- and Cu^{2+}-montmorillonites, the acidity of the Fe^{3+}-, Zn^{2+}-, Cu^{2+}- and Al^{3+}-exchanged montmorillonites and montmorillonite K10 was estimated by the temperature-programmed desorption of ammonia gas (NH_3-TPD) analysis (table 3). Specific surface areas are calculated from BET nitrogen isotherms determined at −196 °C (Micrometrics ASAP 2000) on samples degassed at 250 °C for 12 h before the experiment (table 3).

The products of the reactions were characterised by NMR and mass-spectroscopic methods. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Gemini Varian (200 MHz) NMR spectrometer, using TMS as an internal standard. Mass-spectroscopic analysis was performed with a Micromass VG 7070H spectrometer.

3. Catalytic reactions

3.1. *Typical procedure*

In a typical experimental procedure, 0.60 g (5 mmol), (D)-(+)-α-methylbenzylamine and 3 g (50 mmol) glacial acetic acid were heated at reflux temperature 116 °C in a two-necked round-bottom flask (50 ml) in presence of 0.1 g of Fe^{3+}-montmorillonite clay catalyst. After completion of the reaction as monitored by TLC, ethyl acetate was added to the reaction mixture. It was filtered off the catalyst and the filtrate was concentrated on rotavapor to get the product (pale yellow to colorless liquid). The product was analysed by ^{1}H NMR and mass spectra. Yield: 0.80 g (98%), ^{1}H NMR: δ 7.3–7.4 (5 H, m), 5.6–5.8 (1 H, broad peak), 5.1–5.2 (1 H, q), 2.0 (3 H, s), 1.5 (3 H, d); MS: $m/z = 163\,(M^+)$.

3.2. Results and discussion

A number of primary and secondary amines belonging to the class of aliphatic cyclic and acyclic, heterocyclic and aromatic compounds (table 1) have been selectively acetylated to the corresponding amides in excellent yields in the presence of the Fe^{3+}-montmorillonite clay catalyst using the acetic acid as acetylating agent. The versatility of our catalytic system provides a wide range of intermediates for pharmaceuticals and fine chemicals. Among all the substrates, benzylamine reacts with acetic acid at a faster rate (entry 1a). In the absence of a catalyst, the acetylation of benzylamine yields less than 5% of acetylated product in similar reaction conditions (entry 1b). The rate of the acylation of anilines is almost irrespective of the nature of the substituent present, either electron withdrawing or donating groups (entries 3–11), except in the case of m-nitroaniline (entry 11). Acylation of phenolic hydroxyls could not be facilitated under similar conditions. The inertness has been exploited to selective acetylation of *para* and *ortho* amino phenols to corresponding N-acetyl derivatives (entries 7 and 8). The selective acetylation, achieved even in the presence of excess of acetic acid, is very significant which is in stark contrast to the results obtained in acetylation of 2-aminophenol using acetic anhydride wherein both hydroxyl and the amine groups are acetylated in the presence of excess acetylating agent [11]. N-acetyl-p-aminophenol (APAP), commonly known as acetaminophen or paracetamol, is known for non-prescription analgesic and anti-pyretic agent. Its medicinal use is very well known, having properties similar to aspirin and also it is a major component in over 200 drug formulations. Among the heterocyclic amines the reaction is relatively faster for furfurylamine when compared to 2-(2-aminoethyl)pyridine (entries 12 and 13). Furfurylamide is a very useful building block for the synthesis of natural products [18]. The acetylation of propargylamine leads to the corresponding amide (entry 15) with a selectivity close to 100% at 72% conversion. It is striking to note that no by-product is formed prompted by oligomerisation, polymerisation or rearrangement even at acetic acid reflux conditions. However, the reaction did not go further and the unconverted propargylamine was recovered as such. Acetylation of aliphatic fatty amines proceeds smoothly in the presence of acetic acid (entry 16). The α-naphthylamine is acetylated selectively with quantitative yields in the presence of the catalyst (entry 17), while major unidentified by-products are formed when the reaction was conducted in the absence of the catalyst. The acylation of the chiral amines, (L)-phenylalanine methyl ester and (D)-(+)-α-methylbenzylamine afforded the corresponding N-acetylated product in quantitative yields without any racemisation (entries 18 and 19).

Table 2
N-acylation of (D)-(+)-α-methylbenzylamine with various carboxylic acids.

Entry	Acid	Temp (°C)	Time (h)	Yield[a] (%)
1	Acetic[b]	116	0.75	98
2	Propionic	120	1.00	99
3	Butyric	120	0.75	98
4	Acetic[c]	116	6.00	52[c]

[a] Isolated yields; all the products have no change in optical purity.
[b] Catalyst recycled for the fifth time.
[c] In absence of catalyst.

In order to understand the effect acids of higher homologues the acylation of (D)-(+)-α-methylbenzylamine with various carboxylic acids was conducted. The reaction afforded quantitative yields with high selectivity (table 2). In a control reaction conducted in absence of the catalyst the yield of the acetylated product is only 52% for 6 h. In all the cases, there is no racemisation and the products are found to be optically pure. The selectivity and activity of Cu^{2+}- and Fe^{3+}-montmorillonite in the acetylation of (D)-(+)-α-methylbenzylamine is consistent for five cycles (table 2, entry 1). The efficacy of the catalyst is thus demonstrated as indicated in the runs conducted with or without catalysts. Moreover the clay catalyst will act as a by-functional catalyst wherein it serves as a molecular sieve to absorb water formed during the reaction to shift the equilibrium forward and force the reaction with

Table 3
N-acetylation of amines with acetic acid mediated by various metal-ion-exchanged montmorillonite clays.

Entry	Amine	Mont[a]	Total acidity (mmol/g-cat)	Surface area (m^2/g)	Metal content (mmol/0.1 g)	Time (min)	Yield[b] (%)
1	Benzylamine	Fe^{3+}-	1.029	248	0.075	5	99
		Cu^{2+}-	0.350	234	0.020	20	98
		Al^{3+}-	0.524	226	0.034	30	99
		Zn^{2+}-	0.547	228	0.027	30	99
		Mont-K10	0.047	240	–	40	98
2	(D)-(+)-α-methylbenzylamine	Fe^{3+}-				45	98
		Cu^{2+}-				50	97
		Al^{3+}-				60	98
		Zn^{2+}-				60	99
		Mont-K10				75	99

[a] M^{n+}-exchanged montmorillonite K10.
[b] Isolated product.

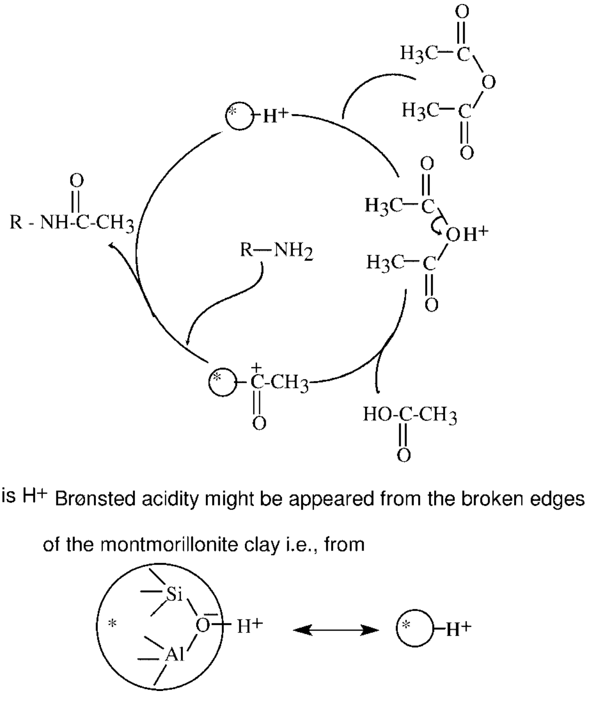
the solid acid possessing compatible acidic sites towards the formation of selective N-acylated product. These results indicate that a right admix of Brønsted and Lewis acidities is an essential requirement to trigger catalytic acylations of amines with carboxylic acid to afford optimum yields.

The acylation of amines is efficiently catalysed by acid-treated montmorillonites commercially known as K10 and KSF catalysts wherein the acetic anhydride is an acetylating agent to produce corresponding amides [11]. According to the reaction mechanism, it is well known that the acylation of amines using acetic anhydride as acylating agent proceeds through the generation of acylcarbonium ion from the acid anhydride by the Brønsted (H^+) acid, which in turn reacts with amine to give an amide followed by the re-generation of the Brønsted (H^+) acid to accomplish another cycle. In the acid-treated montmorillonite K10, the density of the Brønsted acidic sites increases because of increased number of broken edges resulting from the broken layers to favour the formation of amides through the well established mechanism as represented in scheme 2.

In the acylation of amines with a carboxylic acid as an acylating agent, the generation of an acylcarbonium ion from carboxylic acid is a difficult task which has been achieved *via* the evolution of compatible acidic sites of the montmorillonite. In search of a better catalyst for the selective acylation using carboxylic acid as acylating agent, we have used several metal-exchanged montmorillonite K10 samples. Introduction of metal through an ion-exchange process to montmorillonite K10 catalyst increases both the Lewis acidity and the Brønsted acidity to form the right admix of Brønsted and Lewis acid sites to coax the acylation of amines selectively. Brønsted acidity is generated from the interstitial cation–aqua complex of the metal ion as described. Thus, the interaction of water molecules formed during the reaction with metal–aqua complex enables the generation of hydronium ion (Brønsted acidity) and metal hydroxide as described in the reversible reaction [19,20]

$$M^+(H_2O)_n + H_2O \rightleftharpoons M^+(OH)(H_2O))_{n-1} + H_3^+O$$

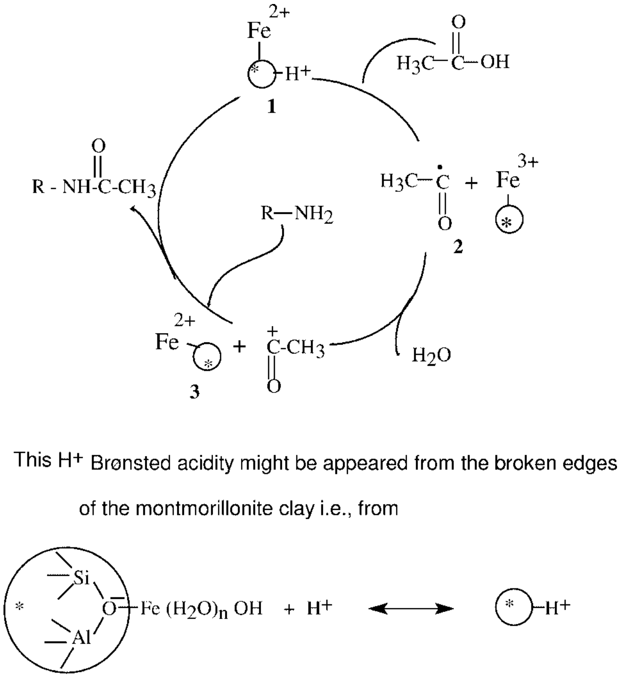
The consumption of Brønsted acid further shifts towards the right side to generate more of Brønsted acidity. Water as a by-product is formed during the reaction in a very minute amount (1 mmol/mmol of substrate) and this dilution is not expected to affect the acidity of the catalyst and thereby catalyst activity. Moreover, the clay catalyst which has a hydrophilic character, was pre-treated at 250 °C to remove mostly layered hydrated water present in the interlayers of the montmorillonite. However, the excess water present in the system could not affect the acidic sites as it forms binary mixture with acetic acid used as a solvent, apart from acting as acylating agent in the present reaction. Thus, the hydrated cations of montmorillonite are more reactive than their corresponding homogeneous analogues. Further, the cationic-aqua complexes present in interlayers which have an array of layered negative charges will not allow the cationic complex to go out of interlayers. The order of the activity in the acetylation reaction is Fe^{3+}-mont > Cu^{2+}-mont > Al^{3+}-mont $\geqslant$ Zn^{2+}-mont > K10-mont (table 3). Thus, the Fe^{3+}- and Cu^{2+}-montmorillonite are the most superior catalysts compared to other metal-ion-exchanged montmorillonites. The order of the activity could not be juxtaposed to the order of the acidity, as Cu^{2+}-montmorillonite displays poor acidity. It is thus unambiguously clear that not the acidity alone is responsible for the display of higher activity. The Fe^{3+} and Cu^{2+} ion have the lower redox potentials which can polarise the carboxylic acid more strongly than the other metals exchanged. As these redox-metal-exchanged montmorillonites displayed superior activity over aluminium and zinc, the mechanistic path is assumed to proceed *via* the free radical mechanism. The plausible mechanism involving a free radical is described in scheme 3. However, both the metals involve one electron redox reaction. Initially, the active catalyst, Fe^{2+}-montmorillonite (**1**) is formed by the reduction of Fe^{3+}-montmorillonite, presumably with the amine. The generation of a carbonium free radical (**2**) is likely facilitated by Fe^{2+}-montmorillonite (**1**) which in turn is oxidised to give carbonium ion and Fe^{3+}-montmorillonite (**3**). The carbocation finally reacts with amine to give amide with the simultaneous reformation of the catalyst and water.



This H+ Brønsted acidity might be appeared from the broken edges of the montmorillonite clay i.e., from

Scheme 2.

In conclusion, we have demonstrated the use of carboxylic acids as acylating agents instead of expensive acid anhydrides in presence of tuned-up montmorillonite clay catalysts to achieve optimum yields for the first time. In our methodology, notably the aspect of effluent treatments does not arise as water is the only by-product. The advantages include the operational simplicity, recyclability



This H^+ Brønsted acidity might be appeared from the broken edges of the montmorillonite clay i.e., from

Scheme 3.

of the catalyst, high atom economy and the mild reaction conditions. The present heterogeneous catalytic system may be a potential candidate not only for laboratory practice but also for commercial applications and offers an environmentally safer alternative to the existing processes.

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