

# Acylation of alcohols and amines with carboxylic acids: a first report catalyzed by iron(III) oxide-containing activated carbon<sup>☆</sup>

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## Abstract

An efficient and selective acylation of alcohols and amines employing carboxylic acids as acylating agents is realized through the metal oxide containing activated carbon catalyst achieved by carbonization of organic ion-exchangers after incorporation of Fe<sup>3+</sup>-ions with exchangeable cations present in resin for the first time.

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## 1. Introduction

Amides and organic esters represent an important family of intermediates widely employed in the synthesis of industrial chemicals, drugs, cosmetics and food additives. Acylation of alcohols and amines are usually performed employing acid anhydrides or acyl chlorides in the presence of stoichiometric amounts of amine bases, such as tertiary amines [1], 4-(dimethylamino)pyridine or 4-pyrrolidinopyridine [2] and tributylphosphine [3], etc. to afford excellent yields. On the other hand, protic and Lewis acids, such as *p*-toluenesulfonic acid [4], scandium trifluoromethanesulfonate [5], trimethylsilyl trifluoromethanesulfonate [6], zinc chloride [7] and cobalt chloride [8] are well

known to catalyze the acylation reaction using acetic anhydride as an acetylating agent. The above options employing acetic anhydride as acetylating agent and soluble bases or acids as reagents or catalysts presents insurmountable problems in the recovery of the catalyst and by-products achieve less than 50% atom economy in the consumption of acetic anhydride by utilizing only the acetyl group. The Cp<sub>2</sub>Sm(thf)<sub>2</sub> [9], tetrabutyl ammonium salt [10] and vinyl carboxylate [11] have proved to be the best catalysts for the acylation of amines with esters. Recently, research has been directed to overcome the above problems which culminated in the development of insoluble solid acids, such as montmorillonite K10 and KSF [12], molecular sieves and soluble Sc/La triflates [13] as catalysts. Previous reports using clay catalysts still utilize acetic anhydride as an acetylating agent, while the metal triflates are soluble and difficult to recover and reuse in the process although acetic acid is used as the acetylating agent. Therefore, there is a need

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to develop a reusable and economic solid acid catalyst for acylation using carboxylic acids as acylating agents to achieve high atom economy.

In continuation of our ongoing research program [14], herein, we report an efficient and selective acylation of alcohols and amines employing carboxylic acids as acylating agents realized through the metal oxide-containing activated carbon catalyst achieved by carbonization of organic ion-exchangers after incorporation of  $\text{Fe}^{3+}$ -ions with exchangeable cations present in resin for the first time.

## 2. Experimental

### 2.1. Preparation of the catalyst

Iron(III) oxide-containing activated carbon [FeAC] catalyst [15] was prepared by using column method. Amberlyst IRC-50 (DVB/methacrylic acid) resin (20 g) was loaded in a column and washed with 100 ml of distilled water.  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (25 g) dissolved in 100 ml water (1 M solution) and passed through the resin in a column manner over a period of 2 h, then washed with water and dried at  $100^\circ\text{C}$  over night. The dried resin was pyrolyzed at  $700^\circ\text{C}$  over a period of 4 h in an inert atmosphere to get FeAC catalyst and was stored in a desiccator.

### 2.2. Characterization of the catalyst

FeAC catalyst was characterized by using XRD, BET, scanning electron microscopy (SEM), TGA/DTA and CHNS-analysis and the metal ( $\text{Fe}^{3+}$ ) content was analyzed according to Vogel procedure and found to be 5.42% (by weight).

Acidity of the FeAC catalyst was estimated by the temperature-programmed-desorption of ammonia gas ( $\text{NH}_3$ -TPD) analysis and was found to be 0.0130 mmol/g catalyst. Specific surface areas of the Amberlyst IRC-50 (DVB/methacrylic acid) resin and FeAC catalyst are calculated from BET nitrogen isotherms determined at  $-196^\circ\text{C}$  (micrometrics ASAP 2000) on samples degassed at  $250^\circ\text{C}$  for 12 h before the experiment are found to be 222 and  $257\text{ m}^2/\text{g}$ , respectively.

The TGA/SDTA thermograms of the Amberlyst IRC-50 (DVB/methacrylic acid) resin and FeAC

catalyst further confirms the formation of activated carbon. The thermogram of Amberlyst IRC-50 shows that the main component flashes off between 200 and  $500^\circ\text{C}$  even under nitrogen atmosphere and the remaining carbon black decomposes further at higher temperatures. On the other hand, the thermogram of FeAC catalyst shows that except for an initial weight loss of 9.0% due to loss of the moisture it is stable between 100 and  $600^\circ\text{C}$ .

Morphology of Amberlyst IRC-50 (DVB/methacrylic acid) resin and FeAC catalyst as studied by SEM equipped with energy dispersive X-ray analysis (EDAX) shows, Amberlyst IRC-50 has perfect spherical shape, whereas in FeAC catalyst it ruptures and appears crystalline. This result provides a direct evidence for the formation of activated carbon catalyst.

The X-ray diffractogram of FeAC catalyst has similar characteristic d-spacing values, which resembles the iron(III) oxide diffractogram (ASTM number 32-469). The elemental composition, mainly the carbon to hydrogen atom ratio (C/H), for the Amberlyst IRC-50 (DVB/methacrylic acid) resin and FeAC catalyst are 1:1 and 18.4:1, respectively. The increase in carbon content further indicates the formation of the active carbon catalyst.

### 2.3. Materials and methods

All the starting materials were purchased from Aldrich,  $\text{Fe}_2\text{O}_3$  was purchased from SD Chemicals (India) and used without any further purification.

Elemental analysis by CHNS analysis was carried out on a Vario EL, Elementar, Germany. TGA/DTA measurements were carried out on Mettler Toledo—TGA/SDTA/851<sup>®</sup> system. XRD measurements were carried out on Siemens D 5000 diffractometer using Graphite filtered  $\text{Cu K}\alpha$ -radiation. Specific surface areas were calculated from BET nitrogen isotherms determined at  $-196^\circ\text{C}$  (Micrometrics ASAP 2000) on samples degassed at  $250^\circ\text{C}$  for 12 h before the experiment. SEM was performed with samples mounted on aluminum stubs using double adhesive tape coated with gold in Hitachi HUS-5 GB vacuum coater and scanned in Hitachi S-520 SEM. The products of the reactions were characterized by NMR and mass spectroscopic methods. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on Gemini Varian (200 MHz) NMR spectrometer, using TMS

as an internal standard. Mass spectroscopic analysis was performed at an ionization potential of 70 eV (scanned on VG 70-70H (micro mass)) spectrometer.

#### 2.4. Typical experimental procedure

1-Phenylethanol (0.61 g, 5 mmol) and glacial acetic acid (3.0 g, 50 mmol) corresponding to 1:10 molar ratio were refluxed under stirring in the presence of FeAC catalyst (200 mg). After completion of the reaction as monitored by TLC or GC, the reaction mixture was filtered and the catalyst was washed with ethyl acetate (2 × 10 ml). Ethyl acetate is used to extract the product and to wash off the product adhered on the surface of the catalyst. The combined filtrate fractions are washed with saturated sodium bicarbonate and brine, dried on anhydrous magnesium sulfate and concentrated under reduced pressure to obtain pure product. Yield, 0.81 g, 98%; the catalyst was dried in an oven at 120 °C for 1 h and reused.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.5–0.6 (d, 3H), 2.1 (s, 3H), 5.8–5.95 (q, 1H), 7.25–7.4 (m, 5H); EI mass: (*m/z*) = 164 (M<sup>+</sup>).

### 3. Results and discussion

This present methodology illustrates a simple acylation process and has wider applicability, extending the scope to alcohols and amines, such as benzylic, primary, secondary aromatic, allylic, and cyclic alcohols and benzylic, cyclic, primary and secondary amines, respectively (Tables 1 and 2). Exclusive formation of acylated products in quantitative yields with all the substrates used in this process is a significant achievement. It is very interesting to note that even at elevated temperatures no olefin, ether or polymeric products were found in the acylation of alcohols and amines coaxed with carboxylic acids. These results indicate that the process of acylation affords excellent possible atom economy when accounted with respect to substrate, product, acylating reagent and the catalyst.

The acetylation of cyclohexanol (Table 1, entry 8) in the presence of FeAC catalyst is much faster than the Amberlyst-15 solid acid and homogeneous catalyst, dodecatungstophosphoric acid [16]. Exclusive formation of cinnamyl acetate is achieved in the acylation of cinnamyl alcohol in the present liquid phase reaction

without any other side products (entry 4). Phenolic hydroxyl group reaction could not be acylated under similar conditions. This inertness has been exploited to selective acylation of alcoholic hydroxyl in phenols (Table 1, entry 3). Chiral menthol is acylated without any racemization (entry 9 [ $[\alpha]_D^{20}$  –98° (*c* = 1 in EtOH; lit. value –96° *c* = 1 in ethanol)). However, the acylation of tertiary alcohol afforded different products.

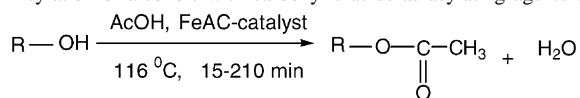
The selectivity towards the acetylation of primary and secondary alcohols with acetic acid is found to be similar (entries 1a and 2), but with propionic and butyric acids, corresponding acylated products are obtained in faster rate as shown in the case of 1-phenylethanol (Table 1, entries 1b and c).

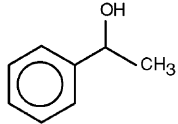
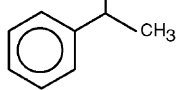
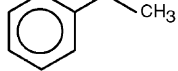
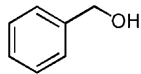
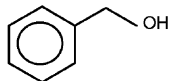
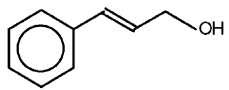
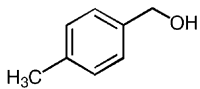
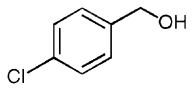
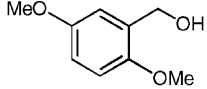
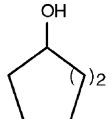
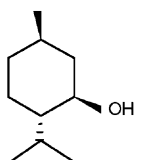
A number of primary and secondary amines belonging to the class of aromatic, cyclic and benzylic compounds (Table 2) have been selectively acetylated in the presence of FeAC catalyst using acetic acid as acetylating agent to the corresponding amides in excellent yields. The rate of the acylation of anilines is almost irrespective of the nature of the substituent presents either electronic withdrawing or donating groups (entries 2–8) except in the case of *p*-bromoaniline (entry 3). Acylation of phenolic hydroxyl could not be facilitated under similar condition. The inertness has been exploited to selective acetylation of *p*-aminophenol to corresponding *N*-acetyl derivative (entry 6). The selective acetylation achieved even in the presence of excess of the acetic acid is very significant which is in sharp contrast to the results obtained in the acetylation of 2-aminophenol using acetic anhydride wherein both hydroxyl and the amine groups are acetylated in the presence of excess acetylating agent [17]. Among the prepared compounds, *N*-acetyl-*p*-aminophenol (APAP), commonly known as acetaminophenol or paracetamol, is known for non-prescription analgesic and anti-pyretic agent. It's medicinal use is very well known, having properties similar to aspirin and also it is a major component in over 200 drug formulations.

The α-naphthyl amine is acetylated selectively with quantitative yields in the presence of the catalyst (entry 9), while major unidentified by-products are formed, when the reaction was conducted in the absence of the catalyst. The acylation of the chiral amine, (D)-(+)-α-methyl benzylamine afforded corresponding *N*-acetylated product in quantitative yields without any racemisation (Table 2 entry 10;

Table 1

Acylation of alcohols with carboxylic acids as acylating agents catalyzed by FeAC-catalyst

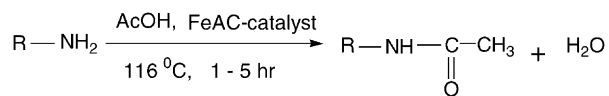


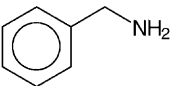
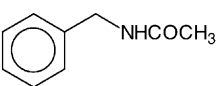
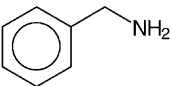
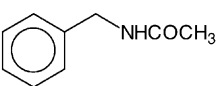
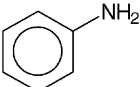
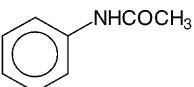
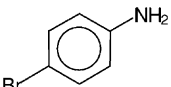
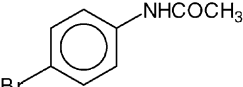
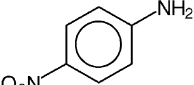
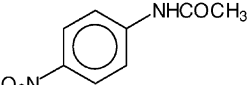
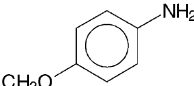
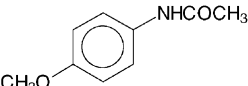
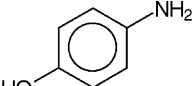
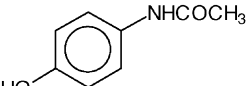
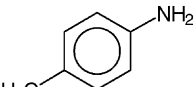
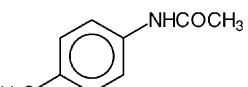
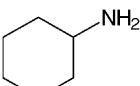
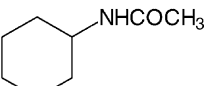
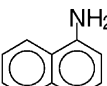
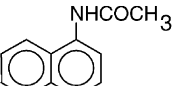
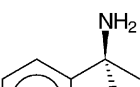
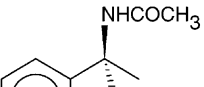
Entry	Alcohol <sup>a</sup>	Acid	Temperature (°C)	Time (h)	Yields <sup>b</sup> (%)
1a		Acetic	116	2.0	98
1b		Propionic	120	1.0	98
1c		Butyric	120	1.5	95
2		Acetic	116	2.0	99 <5 <sup>c</sup> <5 <sup>d</sup>
3		Acetic	116	3.0	98
4		Acetic	116	0.25	98 97 <sup>e</sup>
5		Acetic	116	2.0	98
6		Acetic	116	3.0	97
7		Acetic	116	2.0	98
8		Acetic	116	0.5	97
9		Acetic	116	3.5	99 98 <sup>e</sup>

<sup>a</sup> Alcohol: acid molar ratio is 1:10.<sup>b</sup> Isolated yields.<sup>c</sup> Activated carbon catalyzed reaction (without metal oxide).<sup>d</sup> Fe<sub>2</sub>O<sub>3</sub> catalyzed reaction.<sup>e</sup> Isolated yield after 5th re-cycle.

Table 2

N-acetylation of amines using acetic acid as acetylating agent catalyzed by FeAC catalyst



Entry	Amine <sup>a</sup> (substrate)	Reaction time <sup>b</sup> (h)	Product <sup>c</sup>	Yields <sup>d</sup> (%)
1a		2.0		99
1b		3.0		<5 <sup>e</sup>
2		1.0		98
3		1.0		96
4		3.0		97
5		2.5		99
6		3.0		98
7		3.5		97
8		3.0		98
9		5.0		99
10		0.75		98

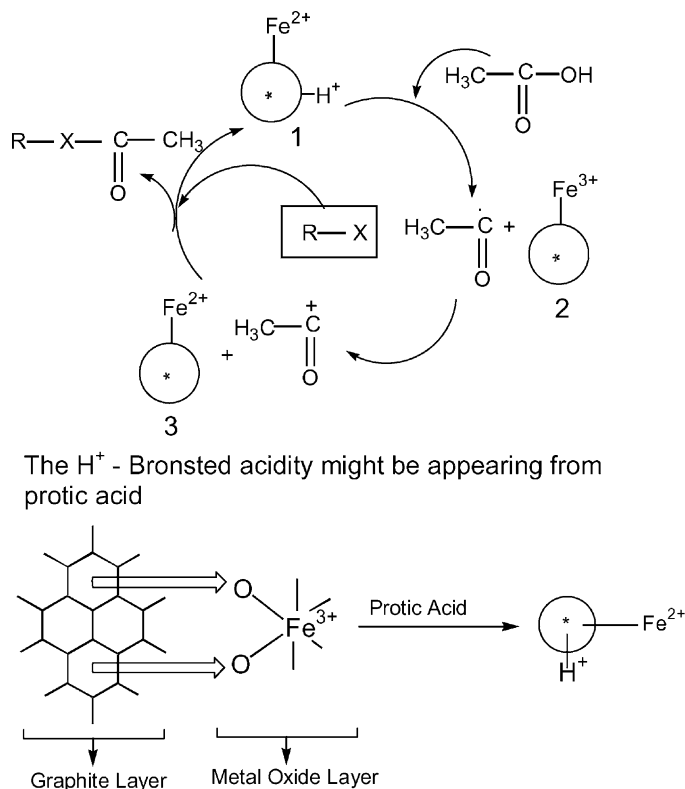
<sup>a</sup> Amine and acetic acid molar ratio was 1:10.<sup>b</sup> Where acetic acid reflux temperature was maintained.<sup>c</sup> All products were identified by their <sup>1</sup>H NMR and mass spectroscopy and/or comparison of their b.p. or m.p. with authentic samples.<sup>d</sup> Isolated yield.<sup>e</sup> In absence of FeAC catalyst.

$[\alpha]_D^{20}$  166° ( $c = 1$  in EtOH; lit. value 168.1,  $c = 1$  in ethanol)). In order to demonstrate the reusability of the FeAC catalyst, it was found to be consistent in selectivity and activity for five cycles (Table 1, entries 4 and 9).

### 3.1. Mechanism

Acylation of amines and alcohols generally proceeds via free radical mechanism which involves the formation of acyl carbonium ion (2) and the efficiency of the generation of this ion is very important. The plausible mechanism is described schematically in Scheme 1. Our new catalyst preparation method led to uniform distribution of iron(III) oxide particles on activated carbon matrix, which gives an active iron oxide layer covered on the carbon or graphite surface. The generation of the acyl carbonium-ion in the presence of protic solvents can be achieved via interaction of surface crystalline sites or defects, which are located in oxide layer.

The Bronsted acidity of the crystalline sites of surface oxide will be changed via interaction of de-localized electron density of the graphitic as well as metal oxide layers; therefore, their reactivity will also change. Initially, the active catalyst,  $Fe^{2+}$ -ion containing crystalline sites are formed (1) by the reduction of  $Fe^{3+}$ -ions on surface layer of iron(III) oxide covered the activated carbon, presumably with the amine or alcohol, because neither pure activated carbon nor pure iron(III) oxide catalyze these processes, the interaction between graphitic and metal oxide layers in activated carbon–iron(III) oxide composite is the key-step in the formation of catalytically active species. The generation of carbonium free radical (2) is likely to be facilitated by  $Fe^{2+}$ -ion containing lattice points on iron(III) oxide covered activated carbon (1), which in turn reduced to give carbonium ion and  $Fe^{2+}$ -lattice points containing iron(III) oxide covered activated carbon (3). The carbocation finally reacts with alcohol/amine to give the corresponding product with the regeneration of the FeAC catalyst.



Scheme 1.

#### 4. Conclusions

We have demonstrated highly efficient and selective acylation procedure for various functionalized primary and secondary alcohols and amines using acetic, propionic and butyric acids as acylating agents instead of acid anhydrides in presence of catalytic amount iron(III) oxide-containing activated carbon [FeAC] catalyst 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 of the catalyst, high atom economy and the mild reaction conditions. The present heterogeneous catalytic system may be a potential candidates not only for laboratory practice but also for commercial applications and offers an environmentally safer alternative to the existing processes.

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