

One-pot preparation of β -amido ketones and esters in four-component condensation reaction using ferric hydrogensulfate as effective and reusable catalyst

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Abstract

A new one-pot and efficient four-component condensation of benzaldehyde derivatives, enolizable ketones, acetyl chloride and acetonitrile or benzonitrile in the presence of ferric hydrogensulfate as an inexpensive and effective catalyst for the synthesis of β -amido ketones and esters is described. The present methodology offers several advantages, such as good yields, short reaction times and a recyclable catalyst with a very easy work up.

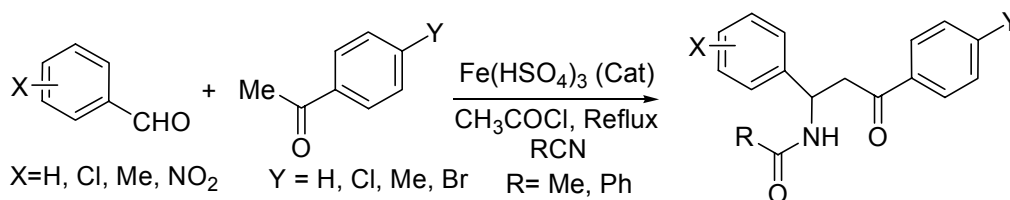
Keywords: Multi-component reaction, ferric hydrogensulfate, heterogeneous catalyst, β -amido ketone

Introduction

Multi-component reactions (MCRs) are important for the achievement of high levels of brevity and diversity. They allow more than two simple and flexible building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle.¹ MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis.^{1,2} Due to their inherent simple experimental procedures and their one-pot character, they are perfectly suited for automated synthesis. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency.¹⁻⁸

Amido- or amino ketone derivatives are important for their biological, pharmaceutical properties,^{9,10} and in the preparation of antibiotic drugs such as nikomycine or neopolyoxines.^{11,12} The common procedure for the synthesis of these class compounds is the Dakin-West reaction¹³⁻¹⁵ which involves the condensation of α -amino acids with acetic anhydride in the presence of suitable base,³⁻¹⁶ these reaction produce α -acetamido ketones

through an intermediate azalactone.¹⁶ Recently, other synthetic methods have been used for the formation of β -amido ketones through the multi-component condensation of aryl aldehydes, enolizable ketones and acetyl chlorides in acetonitrile in the presence of Lewis or Brønsted acid catalysts such as CoCl_2 ,^{17,18} montmorillonite K-10 clay,¹⁹ silica sulfuric acid,²⁰ BiCl_3 generated from BiOCl ,²¹ $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$,²² heteropoly acid,²³ sulfuric acid absorbed on silica gel,²⁴ $\text{Sc}(\text{OTf})_3$,²⁵ $\text{Cu}(\text{OTf})_2$,²⁵ silica supported $\text{H}_3\text{PW}_{12}\text{O}_{40}$,²⁶ $\text{K}_5\text{CoW}_{12}\text{O}_{40} \cdot 3\text{H}_2\text{O}$,²⁷ $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,²⁸ ZnO ,²⁹ Amberlyst-15,³⁰ iodine³¹ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$.³² Ferric salts have applied for the formation of carbon-nitrogen and carbon-oxygen bonds in organic synthesis.³³⁻³⁷ Ferric hydrogensulfate gained much interest in the Friedel-Crafts acylation of alkoxy benzenes by aliphatic anhydrides,³⁸ but there are a few reports on the application of this inorganic acidic salt in the literature.³⁸ Ferric hydrogensulfate as a recyclable solid Brønsted acid catalyst is safe, easy to handle, environmentally benign and presents fewer disposal problems. This catalyst was prepared from the reaction of anhydrous ferric chloride (1 mmol) with concentrated sulfuric acid (3 mmol).³⁸ This salt is stable and non-hygroscopic solid material, insoluble in most organic solvents. Herein, we wish to describe a new, simple, mild and effective procedure for the one-pot synthesis of β -amido ketones via a four-component condensation reaction between aldehydes, enolizable ketones, acetyl chloride and acetonitrile or benzonitrile in the presence of ferric hydrogensulfate as catalyst (Scheme 1). The MCRs for the preparation of β -amido ketones were carried out under reflux condition at 80 °C.



Scheme 1

Results and Discussion

First, we optimized the amount of ferric hydrogensulfate as catalyst in the reaction between benzaldehyde, acetophenone, acetyl chloride and acetonitrile (Table 1). The amount of ferric hydrogensulfate was chosen to be 25 mol%.

Table 1. Preparation of *N*-(3-oxo-1,3-diphenylpropyl) acetamide from the reaction of benzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile using variety amount of $\text{Fe}(\text{HSO}_4)_3$ under reflux condition at 80 °C

Entry	$\text{Fe}(\text{HSO}_4)_3$ (mol%)	Time (min)	Yield ^a %
1	10	120	79
2	15	80	82
3	20	65	85
4	25	50	93
5	50	30	90

^aIsolated yield.

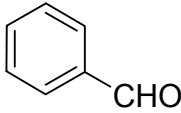
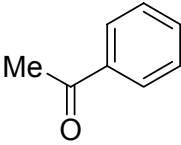
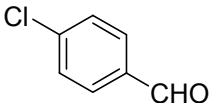
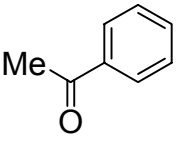
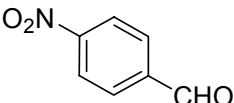
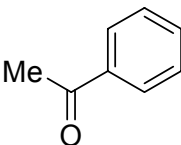
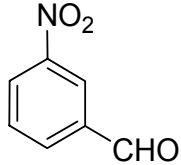
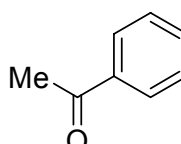
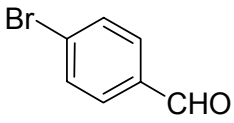
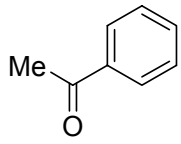
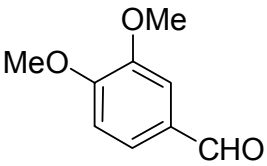
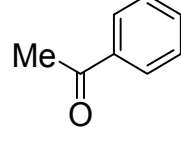
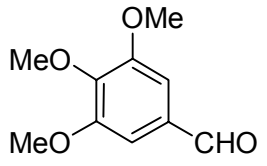
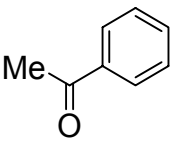
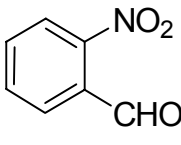
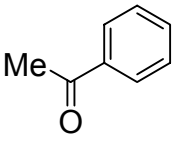
Thus, we continued preparation of β -amido ketones in an optimum model experiment: Aldehydes (1 equiv), enolizable ketone (1 equiv), acetyl chloride (1 mL), acetonitrile, reactant as well as solvent (2 mL) or benzonitrile (3equiv) in the presence of ferric hydrogensulfate (25 mol%) (Table 2).

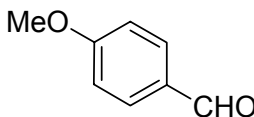
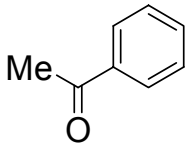
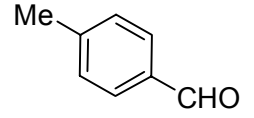
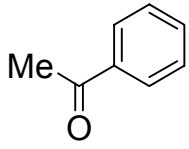
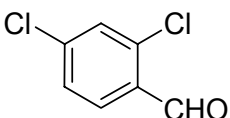
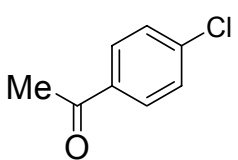
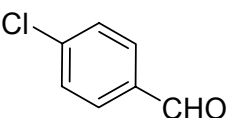
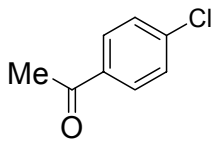
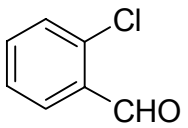
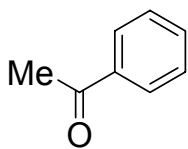
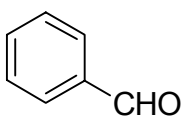
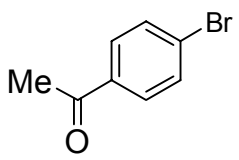
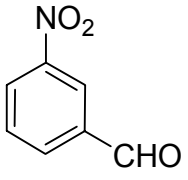
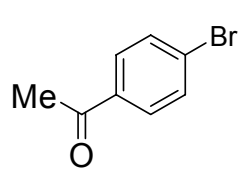
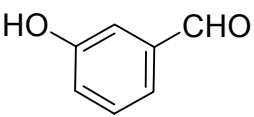
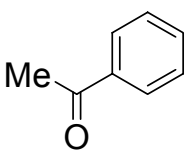
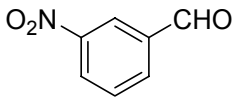
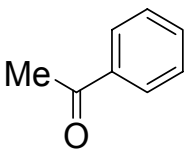
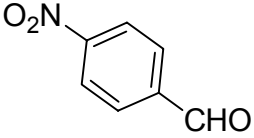
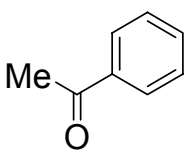
As shown in Table 2, aromatic aldehydes and acetophenone derivatives with both electron-withdrawing and electron-donating substituents afforded to the corresponding β -amido ketones without the formation of any side products, in high to excellent yields at reflux conditions (Table 2, Entries 1–16). Phenolic –OH groups under present reaction conditions were converted to acetate (–OAc) groups (Table 2, Entry 16).

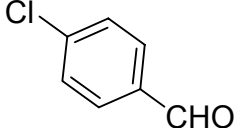
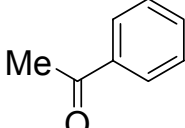
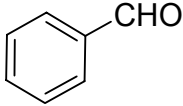
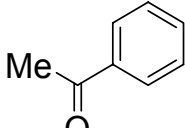
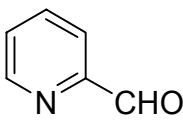
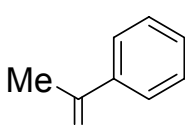
Under the optimized reaction conditions, by using benzonitrile in place of acetonitrile, aldehydes were transformed to their corresponding β -benzamido ketones in high yield (Table 2, Entries 17-20).

Interestingly, during the course of our study, we have noticed that when the 2-pyridinecarbaldehyde is treated with acetophenone under the same experimental conditions, the reaction was stopped and the catalyst was destroyed and loss its activity. We also added pyridine to the standard of reaction conditions (benzaldehyde/acetophenone/acetyl chloride/acetonitrile/catalyst), after a few minutes, pyridine destroys the catalyst and inhibit the preparation of *N*-(3-oxo-1,3-diphenyl-propyl)-acetamide (Table 2, Entry 21).

Table 2. Preparation of β -amido ketones from aldehydes and enolizable ketones in the presence of acetyl chloride and acetonitrile or benzonitrile catalyzed using ferric hydrogensulfate under reflux conditions

Entry	Aldehyde	Ketone	Time (min)	m.p. ($^{\circ}$ C) [Lit. m.p.]	Yield (%) ^a	Ref. ^b
1			50	102-104 [101-103]	93	19-32
2			90	149-152 [146-148]	94	17, 20-27, 29-32
3			120	138-141 [154-155]	85	18-22, 24, 29-32
4			120	127-129 [139-140]	90	19-22, 24,26, 27,29, 31
5			95	148-150 [148-150]	90	27,28, 32
6			55	118-120 [118-119]	86	28,32
7			55	168-169 [159-161]	87	27,28, 32
8			130	190-191 [186-188]	92	27,28, 31,32

9			65	127-130 [115-117]	90	18, 25-28, 31
10			60	112-115 [110-111]	86	27,28, 31
11			95	163-165 [156-158]	94	27,29
12			85	142-145 [143-145]	89	26, 28,29
13			75	134-136 [149-151]	89	19,23, 26-28, 31
14			65	99-101 [98-100]	88	23,26, 28,31
15			110	114-117 [115-118]	85	23, 26,28
16			65	115-117 [114-115]	87	19,22
17			150	191-193 [194-195]	78 ^c	22
18			150	139-142 [142-144]	75 ^c	31,32

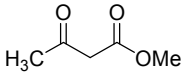
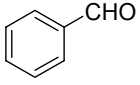
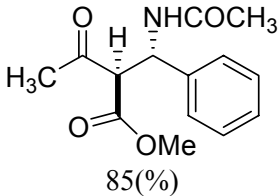
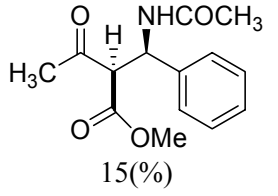
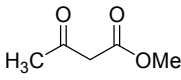
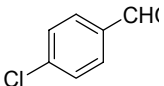
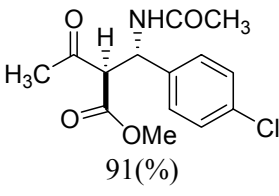
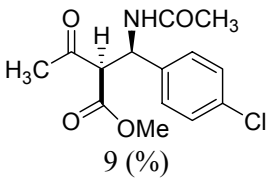
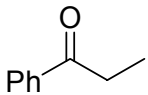
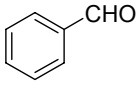
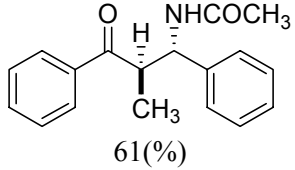
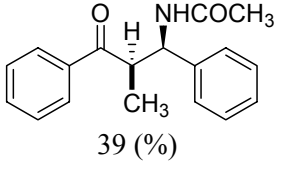
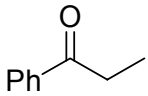
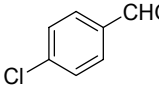
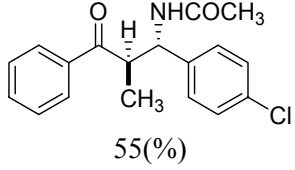
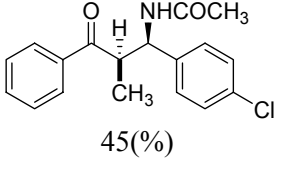
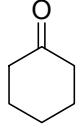
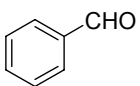
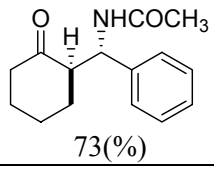
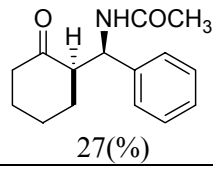
19			150	178-181 [180-182]	77 ^c	32
20			120	150-153 [153-154]	79 ^c	32
21			120	-	-	-

^aYields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.¹⁷⁻³² ^bThe references of known products in the literature. ^cUsing PhCN (~ 3equiv) in CH₂Cl₂ (5 mL).

We also studied the multi-component reaction of aromatic aldehydes, other enolizable ketones (propiophenone, methyl acetoacetate and cyclohexanone) and acetonitrile in the presence of acetyl chloride and Fe(HSO₄)₃ as catalyst. In all cases, mixtures of syn and anti diastereomers were obtained, whilst the diastereoselectivity depended upon the nature of the reactants. The amount of these syn and anti products was determined by ¹HNMR spectra, the coupling constant between H-2 and H-3 is 6-9Hz for an anti isomer, while 2-5 Hz for a syn isomer [17-19]. As it was shown in table 3, an anti diastereomer was found to be major product. Methyl acetoacetate afforded the corresponding β-acetamido esters in good yields with high diastereoselectivity. The anti/syn ratio was determined from ¹HNMR spectrum of crude reaction mixture.

In a typical experiment, after a period of time that the reaction was completed, the mixture was filtered and heterogeneous catalyst was recovered. Then, the residue solution was poured into the cooled water until solid crude product was formed. In every experiment whole of the ferric hydrogensulfate was easily recovered from the reaction mixture. The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus the recovery and reusability of ferric hydrogensulfate was investigated. The separated catalyst can be reused after washing with CHCl₃ and drying at 100 °C. The reusability of the catalyst was checked by the reaction of benzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile using 25 mol% of Fe(HSO₄)₃ under reflux condition at 80 °C. The results indicate that the catalyst can be used five times without any loss of its activity (Table 4).

Table 3. Preparation of β -acetamido ketoesters and β -acetamido ketones in the presence of $\text{Fe}(\text{HSO}_4)_3$

Entry	Enolizable ketones	Aldehydes	Time(min) / Yield ^a (%)	Products ^b	
				Anti	Syn
1			90 / 86	 85(%)	 15(%)
2			100 / 84	 91(%)	 9(%)
3			75 / 88	 61(%)	 39(%)
4			80 / 85	 55(%)	 45(%)
5			110 / 86	 73(%)	 27(%)

^aYields are reported after aqueous work-up. ^bRatio obtained from ¹H NMR of the crude reaction mixture; All syn and anti diastereomers have been reported previously in the literatures^{17, 19, 22, 25, 27, 28 and 32} thus we compared ¹NMR spectra with authentic samples.

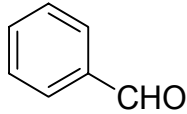
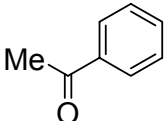
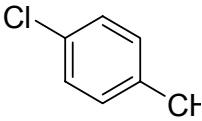
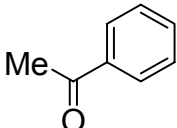
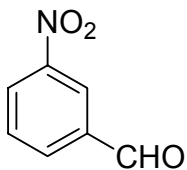
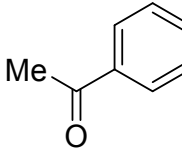
Table 4. Recyclability of the catalyst in the reaction of benzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile using 25 mol% of $\text{Fe}(\text{HSO}_4)_3$ under reflux condition at 80 °C

Run no.	Yield (%)
1	93
2	90
3	89
4	90
5	89

To show the merit of the present work in comparison with reported results in the literature, we compared results of ferric hydrogensulfate with BiOCl ,²¹ $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$,²² $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,²⁸ ZnO ²⁹ and I_2 ³¹ in the synthesis of β -acetamido ketone derivatives. As shown in Table 5, ferric hydrogensulfate can act as effective catalyst with respect to reaction times, yields and the obtained products.

In summary, we have demonstrated a new and important catalytic activity of ferric hydrogensulfate as an inexpensive, commercially available, reusable and non-corrosive catalyst for the synthesis of β -amido ketones in high to excellent yields under almost mild reaction conditions. The simple experimental procedure combined with the easy work-up and high to excellent yields of products are strong features of the presented method.

Table 5. Comparison result of ferric hydrogensulfate with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,²⁸ BiOCl ,²¹ $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$,²² ZnO ²⁹ and I_2 ³¹ in the synthesis of β -acetamido ketone

Entry	Aldehyde	Ketone	Catalyst	Molar ratio of aldehyde / ketone / (catalyst mol%)	Time	Yield%
1			$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	1/1/ (10 mol %)	7 h	96
			BiOCl	1/1/ (20 mol %)	7 h	92
			$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$	1/1/ (20 mol %)	5 h	90
			ZnO	1/1/ (50 mol %)	6 h	90
			I_2	1/1/ (10 mol %)	4.5 h	85
			$\text{Fe}(\text{HSO}_4)_3$	1/1/ (25 mol %)	50 min	93
2			$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	1/1/ (10 mol %)	6 h	98
			BiOCl	1/1/ (20 mol %)	10 h	80
			$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$	1/1/ (20 mol %)	8 h	91
			ZnO	1/1/ (50 mol %)	5.5 h	92
			I_2	1/1/ (10 mol %)	4.5 h	85
			$\text{Fe}(\text{HSO}_4)_3$	1/1/ (25 mol %)	90 min	94
3			$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	1/1/ (10 mol %)	10 h	90
			BiOCl	1/1/ (20 mol %)	8 h	91
			$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$	1/1/ (20 mol %)	6 h	92
			ZnO	1/1/ (50 mol %)	5 h	90
			I_2	1/1/ (10 mol %)	4 h	85
			$\text{Fe}(\text{HSO}_4)_3$	1/1/ (25 mol %)	120 min	90

Experimental Section

General Procedures. All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, ^1H NMR spectra). The NMR spectra were recorded on a Bruker Avance DEX 500 and 300 MHz instrument. The spectra were measured in CDCl_3 relative to TMS (0.00 ppm). IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. TLC was performed on Silica-gel polygram SIL G/UV 254 plates.

Preparation of ferric hydrogensulfate

A 50 mL suction flask was equipped with a dropping funnel. The gas outlet was connected to a vacuum system through an alkaline solution trap. Anhydrous ferric chloride (10 mmol) was charged into the flask and concentrated sulfuric acid 98% (30 mmol) was added dropwise over a period of 30 min at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 30 min at 100 °C, while the residual HCl was eliminated by suction. Finally, a pale-brown solid $\text{Fe}(\text{HSO}_4)_3$ was obtained.³⁶

Catalyst characterization

This paper report catalyst characterization of $\text{Fe}(\text{HSO}_4)_3$ for the first time.

X-Ray diffraction (XRD)

Powder X-Ray Diffraction (XRD) measurements were performed using D8 Advance diffract meter made by a Bruker axs company in Germany. Scans were taken with a 2θ step size of 0.02 and a counting time of 1.0s using $\text{CuK}\alpha$ radiation source generated at 40KV and 30mA. Specimens for XRD were prepared by compaction in to a glass-backed aluminium sample holder. Data was collected over a 2θ range from 4° to 70° and phases were identified by matching experimental patterns to entries in the Diffract^{plus} version 6.0 indexing soft ware. The catalyst which was prepared characterized by XRD and pattern is presented in figure 1. As it was shown in the figure 1, the actual phases for this catalyst was identified under the specified preparation conditions were $\text{Fe}(\text{HSO}_4)_3$ (tetragonal) and $\text{Fe}_2(\text{SO}_4)_3$ (monoclinic) that the $\text{Fe}_2(\text{SO}_4)_3$ (monoclinic) phase is highly selective for producing of product.

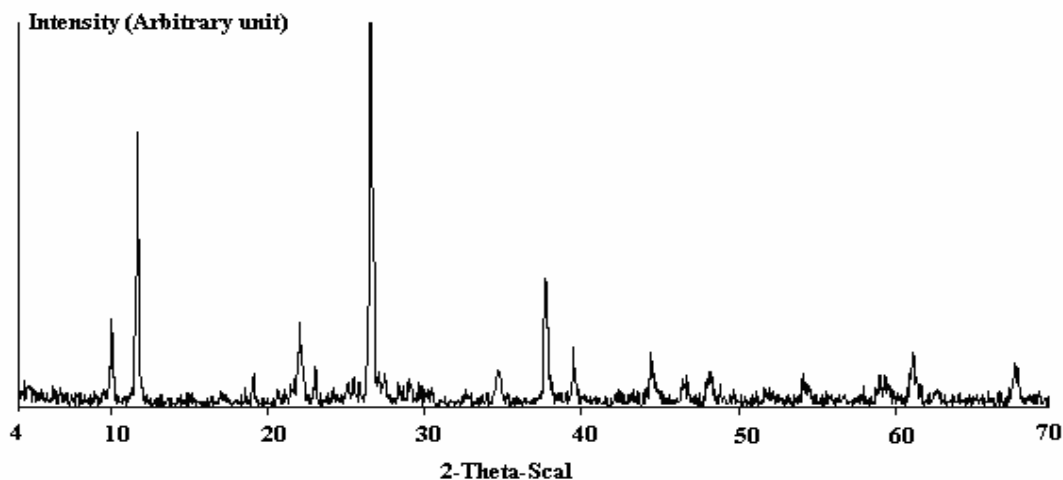


Figure 1

Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC)

The weight change of catalyst precursors were measured using a TGA/DSC simultaneous thermal analyzer apparatus of Rheometric Scientific Company (STA 1500+ Model) under a flow of dry air. The sample weight was chosen 25 mg and the temperature was raised from room

temperature to 500 °C using a linear programmer at a heating rate of 10 °C/min. The TGA and DSC curves for the catalyst are illustrated in figure 2. The weight losses found from TGA measurements agree fairly well with those expected for the decomposition of $\text{Fe}(\text{HSO}_4)_3$, to different oxides of iron and sulphate. The thermo gravimetric curve of catalyst showed two-stage decomposition which considered to be due to removal of physical absorbed water (80-120 °C) or basic $\text{Fe}(\text{HSO}_4)_3$ (140-330 °C), respectively. DSC measurement was performed in order to provide further evidence for the presence of the various species and evaluates their thermal behaviour. It shown in figure 2, the endothermic peak at lower temperature represents the removal of the physically adsorbed water from the material, while the endothermic peak at higher temperature represents solely the decomposition of the $\text{Fe}(\text{HSO}_4)_3$ to different oxides of iron and sulfate.

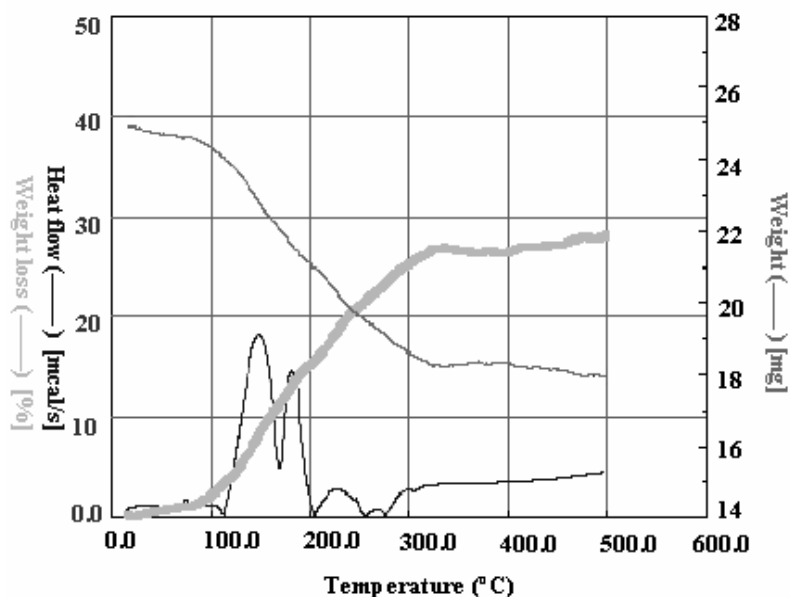


Figure 2

Specific surface area, total pore volume and pore size

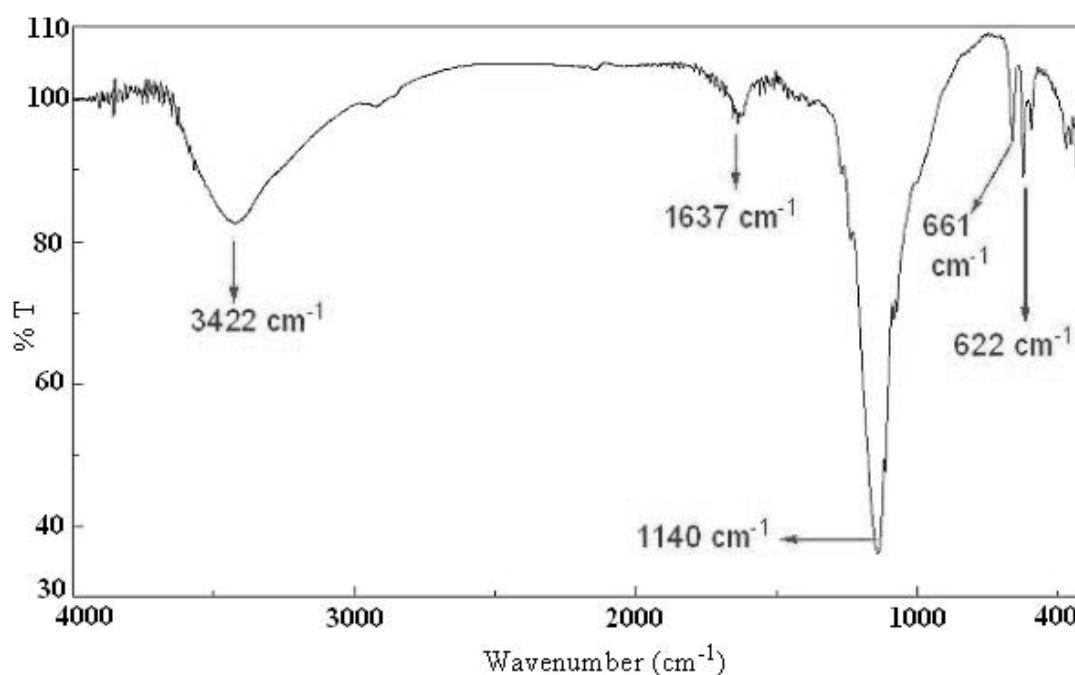
Brunauer- Emmett-Teller surface area BET measurements and the pore size in catalyst were conducted using a micro metrics adsorption equipment (Quantachrome instrument, model Nova 2000, USA) determining nitrogen (99.99% purity) as the analysis gas and the catalyst samples were slowly heated to 120 °C for 3h under nitrogen atmospheric. The BET specific surface area measurements of different precursors and catalysts were evacuated at -196 °C for 300 minutes. Characterization of catalyst was carried out using BET measurements and the BET specific surface area, total pore volume and average pore diameter are presented in Table 6. Results were shown that the catalyst have a good specific surface area and high pore volume, this might be a reason for high catalytic performance of catalyst.

Table 6. Specific surface area, total pore volume and pore size of the ferric hydrogensulfate

Catalyst	Parameters		
	Specific surface area	Pore volume	Pore size diameter
Fe(HSO ₄) ₃	71.44 m ² /g	12.7 cc/g	22.4 Å ^o

FT-IR spectrum of Fe(HSO₄)₃

The FT-IR spectrum of the catalyst was shown in figure 3. The catalyst is solid and solid state IR spectrum was recorded using the KBr disk technique. The spectrum shows a broad OH stretching absorption around 3500 and 3100 cm⁻¹. For sulfuric acid functional group in Fe(HSO₄)₃, the FT-IR absorption of the O=S=O stretching modes lies in 1140 cm⁻¹, and that of the S–O stretching mode lies in 600–700 cm⁻¹.

**Figure 3****Typical Experimental procedure for the one-pot preparation of *N*-(3-Oxo-1,3-diphenylpropyl) acetamide (Table 2, Entry 1)**

A solution of the benzaldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (1 mL) and acetonitrile (2 mL) or benzonitrile (3 mmol) in the presence of ferric hydrogensulfate (25 mol%) was heated at 80 °C under reflux conditions. The reaction mixture was stirred for the appropriate time (Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was filtered and the heterogeneous catalyst was recovered. Then, the residue solution was poured into 50 mL ice-water. The solid was separated and dissolved in

dichloromethane (5 mL). Silica-gel (2 g) was added to the solution. Evaporation of the solvent afforded a presorbed material, which was purified by column chromatography [Petroleum ether (60-80 °C)/ ethyl acetate (9/1)]. Eluent solvent was evaporated under reduced pressure gave the desired pure N-(3-Oxo-1,3-diphenylpropyl) acetamide in 93% yield. White crystals, m.p.: [102-104 °C]; ¹H NMR (CDCl₃, 300 MHz): δ= 2.03 (s, 3H), 3.45 (dd, *J* = 6.0 and 16.9 Hz, 1H), 3.77 (dd, *J* = 5.2 and 16.9 Hz, 1H), 5.58 (dd, *J* = 5.6 and 13.1 Hz, 1H), 6.90 (d, *J* = 6.3 Hz, 1H), 7.24-7.60 (m, 8H), 7.91 (d, *J* = 7.5 Hz, 2H) ppm; IR (KBr, cm⁻¹): 3286, 3091, 1693, 1650, 1556, 1273, 1066, 753, 691.

The spectral data of some representative β-acetamido ketones are given below:

N-[3-Phenyl-1-(4-chlorophenyl)-3-oxopropyl] acetamide (Table 2, Entry 2). [m.p.: 149-152 °C]; ¹H NMR (CDCl₃, 300 MHz): δ= 2.14 (s, 3H), 3.49 (dd, *J* = 7.1 and 13.9 Hz, 1H), 3.82 (dd, *J* = 7.1 and 14.5 Hz, 1H), 5.56 (s, 1H), 7.258-7.585 (m, 8H), 7.91 (d, *J* = 7.3 Hz, 2H) ppm; IR (KBr, cm⁻¹): 3481, 3291, 3081, 1689, 1652, 1599, 1553, 1492, 1449, 1375, 1354, 1295, 1229, 1092, 758, 692.

N-[3-Phenyl-1-(4-nitrophenyl)-3-oxopropyl] acetamide (Table 2, Entry 3). [m.p.: 138-141 °C]; ¹H NMR (CDCl₃, 300 MHz): δ= 2.10 (s, 3H), 3.52 (s, 1H), 3.82 (s, 1H), 5.71 (s, 1H), 7.04 (s, 1H), 7.16-8.15 (m, 9H) ppm; IR (KBr, cm⁻¹): 3291, 3076, 1689, 1653, 1601, 1517, 1351, 1233, 1017, 858, 752, 686.

N-[3-Phenyl-1-(3-nitrophenyl)-3-oxopropyl] acetamide (Table 2, Entry 4). [m.p.: 127-129 °C]; ¹H NMR (CDCl₃, 500 MHz): δ= 2.06 (s, 3H), 3.51 (dd, *J* = 5.6 and 17.5 Hz, 1H), 3.79 (dd, *J* = 5.3 and 17.5 Hz, 1H), 5.69 (dd, *J* = 5.4 and 13.6 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.44-7.49 (m, 3H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 1H), 8.23 (s, 1H) ppm; IR (KBr, cm⁻¹): 3291, 3076, 1689, 1653, 1517, 1351, 752, 694.

N-[3-Phenyl-1-(4-bromophenyl)-3-oxopropyl] acetamide (Table 2, Entry 5). [m.p.: 148-150 °C]; ¹H NMR (CDCl₃, 300 MHz): δ= 2.02 (s, 3H), 3.40 (dd, 1H, *J* = 6.0, 17.2 Hz), 3.72 (dd, 1H, *J* = 5.2, 16.8 Hz), 5.49-5.51 (m, 1H), 6.73 (d, 1H, *J* = 6.8), 7.19 (d, 2H, *J* = 8.4 Hz), 7.40 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 2H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 7.2 Hz), 7.87 (d, 2H, *J* = 7.2 Hz) ppm; ¹³C NMR (CDCl₃): 23.7, 42.9, 49.4, 128.3, 128.4, 129.0, 131.9, 134.0, 136.2, 140.2, 166.5, 196.5; IR (KBr, cm⁻¹): 3285, 2923, 1684, 1651, 1550, 1374, 1292, 1006, 757

N-[3-Phenyl-1-(3,4-dimethoxyphenyl)-3-oxopropyl] acetamide (Table 2, Entry 6). [m.p.: 118-120 °C]; ¹H NMR (CDCl₃, 300 MHz): δ= 2.01 (s, 3H), 3.39 (dd, 1H, *J* = 6.4, 16.8 Hz), 3.72 (dd, 1H, *J* = 5.2, 16.4 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 5.45-5.50 (m, 1H), 6.58 (d, 1H, *J* = 8.0 Hz), 6.76 (d, 1H, *J* = 8.0 Hz), 6.83 (sd, 2H, *J* = 8.0 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.89 (d, 2H, *J* = 7.2 Hz); ppm; ¹³C NMR (CDCl₃): 23.7, 43.4, 50.1, 56.1, 110.5, 111.3, 118.3, 128.3, 128.9, 133.6, 133.7, 149.2, 169.6, 199.0; IR (KBr, cm⁻¹): 3247, 3076, 2917, 2846, 1681, 1637, 1519, 1462, 1253, 1026, 751.

N-[3-Phenyl-1-(3,4,5-trimethoxyphenyl)-3-oxopropyl] acetamide (Table 2, Entry 7). [m.p.: 168-169 °C]; ¹H NMR (CDCl₃, 300 MHz): δ= 2.01 (s, 3H), 3.37 (dd, 1H, *J* = 6.0, 16.8 Hz), 3.69 (dd, 1H, *J* = 5.2, 16.8 Hz), 3.76 (s, 3H), 3.78 (s, 6H), 5.44 (q, 1H, *J* = 7.6 Hz), 6.52 (s, 2H), 6.67 (d, 1H, *J* = 7.6 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.55 (t, 1H, *J* = 7.2 Hz), 7.88 (d, 2H, *J* = 8.0 Hz) ppm;

^{13}C NMR (CDCl_3): 23.7, 43.4, 50.7, 56.3, 60.9, 103.9, 128.3, 128.9, 133.8, 136.8, 136.9, 153.5, 156.2, 169.5, 199.4; IR (KBr, cm^{-1}): 3276, 2928, 1688, 1648, 1592, 1458, 1339, 1246, 1001, 754 ***N*-[3-Phenyl-1-(2-nitrophenyl)-3-oxopropyl] acetamide (Table 2, Entry 8)**. [m.p. 190-191°C]; ^1H NMR (CDCl_3 , 300 MHz): δ =2.00 (s, 3 H), 3.63 (dd, 1H, J =5.6, 16.8 Hz), 3.71 (dd, 1H, J =6.4, 17.2 Hz), 5.93-5.97 (m, 1H), 7.07 (d, 1H, J =5.6 Hz), 7.39 (t, 1H, J =8.0 Hz), 7.46 (t, 2H, J =8.0 Hz), 7.57 (t, 2H, J =7.6 Hz), 7.71 (d, 1H, J =8.0 Hz), 7.92 (d, 2H, J =7.2 Hz), 7.94 (d, 1H, J =6.8) ppm; ^{13}C NMR (CDCl_3): 23.5, 42.4, 47.7, 125.3, 128.5, 128.6, 129.0, 130.1, 133.7, 134.1, 136.5, 137.1, 148.7, 169.5, 198.5; (KBr, cm^{-1}): 3326, 2379, 1686, 1651, 1544, 1517, 1357, 1337, 1059, 682.

***N*-[3-Phenyl-1-(4-methoxyphenyl)-3-oxopropyl] acetamide (Table 2, Entry 9)**. [m.p.: 127-130 °C]; ^1H NMR (CDCl_3 , 300 MHz): δ = 2.00 (s, 3H), 3.31–3.39 (dd, 1 H, J = 5.95, 16.59 Hz), 3.64–3.71 (dd, 1 H, J = 5.28, 16.57 Hz), 3.84 (s, 3 H), 5.53 (m, 1 H), 6.86 (br s, 1 H), 6.89 (br d, 2 H, J = 8.82 Hz), 7.18–7.34 (m, 5 H), 7.88 (br d, 2 H, J = 8.81 Hz) ppm; ^{13}C NMR (CDCl_3): δ = 23.37, 42.76, 50.02, 55.46, 113.80, 126.41, 127.30, 128.55, 129.66, 130.45, 141.07, 163.77, 169.49, 197.08 ppm; IR (KBr, cm^{-1}): 3270, 1675, 1640, 1598, 1570, 1525, 1420, 1365, 1250, 1205, 1170, 1020, 990, 830, 800, 700.

***N*-[3-Phenyl-1-(4-methylphenyl)-3-oxopropyl] acetamide (Table 2, Entry 10)**. [m.p.: 112-115 °C]; ^1H NMR (CDCl_3 , 300 MHz): δ = 2.13 (s, 3H), 2.30 (s, 3H), 3.47 (dd, J = 6.1 and 17.1 Hz, 1H), 3.79 (dd, J = 5.9 and 17.1 Hz, 1H), 5.57 (d, J = 6.7 Hz, 1H), 6.68 (br, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 7.1 Hz, 2H), 7.40 (d, J = 7.2 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.65 (d, J = 7.1 Hz, 2H) ppm; IR (KBr, cm^{-1}): 3276, 3091, 1684, 1651, 1608, 1560, 1409, 1298, 1201, 1163, 999, 812, 703.

***N*-[3-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-oxopropyl] acetamide (Table 2, entry 11)**. [mp: 163-165 °C]; ^1H NMR (CDCl_3 , 300 MHz) d 2.08 (s, 3H), 3.42 (dd, J =5.4 and 17.2 Hz, 1H), 3.77 (dd, J =6.0 and 17.2 Hz, 1H), 5.79 (dd, J =5.8 and 13.5 Hz, 1H), 7.22 (dd, J = 2.0 and 8.4Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.41-7.47(m, 4H), 7.84(d, 8.5 Hz 2H) ppm; IR (KBr, cm^{-1}) 3285, 3130, 2985, 1682, 1650, 1586, 1547, 1469, 1399, 1093, 990, 815.

***N*-(3-Oxo-1,3-di(4-chlorophenylpropyl) acetamide (Table 2, Entry 12)**. [m.p.: 142-145 °C]; ^1H NMR (CDCl_3 , 300 MHz): δ = 2.08 (s, 3H), 3.40 (dd, J = 7.3 and 10.9 Hz, 1H), 3.82 (dd, J = 7.3 and 10.9 Hz, 1H), 5.57 (m, 1H), 7.32 (s, 1H), 7.47 (d, J = 9.1 Hz, 4H), 7.90 (d, J = 9.1 Hz, 4H) ppm; ^{13}C NMR (CDCl_3): δ = 23.5, 43.6, 49.9, 128.4, 129.3, 129.5, 129.9, 133.8, 135.1, 139.7, 140.6, 170.5, 197.3 ppm; IR (KBr, cm^{-1}) 3264, 3056, 1670, 1635, 1584, 1292, 1088, 885, 825.

***N*-[3-(Phenyl)-1-(3-acetoxyphenyl)-3-oxopropyl] acetamide (Table 2, Entry 16)**. [m.p.: 115–117 °C]; ^1H NMR (500 MHz, CDCl_3): δ = 1.99 (s, 3H), 2.26 (s, 3H), 3.39–3.45 (dd, J = 5.8, 17.0 Hz, 1H), 3.68–3.74 (dd, J = 5.6, 17.2 Hz, 1H), 5.53–5.58 (m, 1H), 6.73–6.75 (d, J = 8.4 Hz, 1H), 6.95–6.98 (dd, J = 2.2, 7.8 Hz, 1H), 7.08–7.09 (t, J = 2.0 Hz, 1H), 7.17–7.19 (d, J = 8.0 Hz, 1H), 7.27–7.31 (t, J = 7.8 Hz, 1H), 7.42–7.46 (m, 2H), 7.53–7.57 (m, 1H), 7.88–7.89 (d, J = 7.6 Hz, 2H). ^{13}C NMR (CDCl_3): 21.3, 23.6, 43.2, 49.7, 120.1, 120.9, 124.2, 128.3, 128.9, 129.8, 133.79, 136.8, 143.0, 151.1, 169.5, 169.7, 198.5 ppm; IR (KBr, cm^{-1}): 3281, 3096, 1768, 1686, 1653, 1602, 1558, 1511, 1366, 1304, 1279, 1029, 909, 741.

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References

1. Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley, 2005.
2. Beck, B.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1701.
3. Nishiyama, Y.; Katahira, C.; Sonoda, N. *Tetrahedron Lett.* **2004**, *45*, 8539.
4. Portlock, D. E.; Naskar, D.; West, L.; Ostaszewski, R.; Chen, J. J. *Tetrahedron Lett.* **2003**, *44*, 5121.
5. Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239.
6. Ugi, I.; Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647.
7. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587.
8. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575.
9. Casimir, J. R.; Turetta, C.; Ettouati, L.; Paris, J. *Tetrahedron Lett.* **1995**, *36*, 4797.
10. Godfrey, A. G.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R.; Mitchell, D. *J. Org. Chem.* **2003**, *68*, 2623.
11. Dähn, U.; Hagenmaier, H.; Höhne, H.; König, W. A.; Wolf, G.; Zähler, H. *Arch. Microbiol.* **1976**, *107*, 143.
12. Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709.
13. Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91.
14. Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 745.
15. Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 757.
16. Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 91.
17. Mukhopadhyay, M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083.
18. Bhatia, B.; Reddy, M. M.; Iqbal, J. *J. Chem. Soc. Chem. Commun.* **1994**, 713.
19. Bahulayan, D.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 5735.
20. Khodaei, M. M.; Khosropour, A. R.; Fattahpour, P. *Tetrahedron Lett.* **2005**, *46*, 2105.
21. Ghosh, R.; Maity, S.; Chakraborty, A. *Synlett* **2005**, 115.
22. Ghosh, R.; Maity, S.; Chakraborty, A.; Chakraborty, S.; Mukherjee, A. K. *Tetrahedron* **2006**, *62*, 4059.
23. Rafiee, E.; Tork, F.; Joshaghani, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1221.
24. Yakaiah, T.; Reddy, V. G.; Lingaiah, B. P. V.; Narsaiah, B.; Shanthan Rao, P. *Synth. Commun.* **2005**, *35*, 1307.
25. Pandey, G.; Singh, R. P.; Garg, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 2137.
26. Rafiee, E.; Shahbazi, F.; Joshaghani, M.; Tork, F. *J. Mol. Catal. A: Chem.* **2005**, *242*, 129.

27. Nagarapu, L.; Kantevari, S.; Cheemalapati, V. N.; Apuri, S.; Kumari, V. *J. Mol. Catal. A: Chem.* **2007**, *264*, 22.
28. Khan, A. T.; Choudhury, L. H.; Parvin, T.; Asif Ali, M. *Tetrahedron Lett.* **2006**, *47*, 8137.
29. Maghsoodlou, M. T.; Hassankhani, A.; Shaterian, H. R.; Habibi-Khorasania, S. M.; Mosaddegh, E. *Tetrahedron Lett.* **2007**, *48*, 1729.
30. Das, B.; Reddy, K. R. *Helv. Chim. Acta* **2006**, *89*, 3109.
31. Das, B.; Reddy, K. R.; Ramu, R.; Thirupathi, P.; Ravikanth, B. *Synlett* **2006**, 1756.
32. Khan, A.; Parvin, T.; Choudhury, L. H. *Tetrahedron* **2007**, *63*, 5593
33. Iranpoor, N.; Salehi, P. *Synthesis* **1994**, 1152.
34. Salehi, P.; Iranpoor, N.; Kargar Behbahani, F. *Tetrahedron* **1998**, *54*, 943.
35. Khodaei, M. M.; Meybodi, F. A.; Rezaei, N.; Salehi, P. *Synth. Commun.* **2001**, *31*, 2047.
36. Salehi, P.; Irandoost, M.; Seddighi, B.; Kargar Behbahani, F.; Tahmasebi, D. P. *Synth. Commun.* **2000**, *30*, 1743.
37. Salehi, P.; Seddighi, B.; Irandoost, M.; Kargar Behbahani, F.; Tahmasebi, D. P. *Synth. Commun.* **2000**, *30*, 2967.
38. Salehi, P.; Khodaei, M. M.; Zolfigol, M. A.; Zeinoldini, S. *Synth. Commun.* **2003**, *33*, 1367.