

SYNTHESIS AND CHARACTERIZATION OF Fe₃O₄@MELAMINE SULFONIC ACID NANOCOMPOSITE AS A NOVEL MAGNETICALLY RECYCLABLE NANO CATALYST IN ONE-POT PREPARATION OF 3, 4-DIHYDROPYRIMIDINONES/THIONES

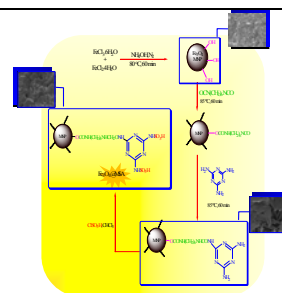
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Melamine sulfonic acid supported Fe₃O₄ magnetic nanocomposite, Fe₃O₄@MSA, has been prepared and successfully applied as a solid acid catalyst for one-pot three-component condensation reaction of aldehyde, β-ketoester and urea or thiourea under solvent free conditions. The nanocomposite has been characterized by FT-IR, TGA and SEM spectroscopies. The nanomagnetic catalyst could be readily separated via application of an external magnet, allowing straightforward recovery and reuse.



INTRODUCTION

Evolution of clean and environmentally benign chemical processes using less hazardous catalysts has become a primary goal in synthetic organic chemistry. In spite of the advantages of heterogenized catalysts, the tedious recycling of catalysts by filtration and the inevitable loss of some solid catalyst in the separation process, especially with air sensitive materials, are some of the drawbacks of the traditional procedures.¹ Therefore, there is more interest to introduce more efficient manners for catalyst recovery, especially from the standpoint of green chemistry.

Nowadays, surface functionalized iron oxide magnetic nanoparticles (MNPs) are a kind of novel functional materials, which have been widely used for the catalyst support.²⁻⁴ Good biocompatibility and biodegradability as well as basic magnetic

characteristics could be denoted for functional organic materials grafted to MNPs.⁵ Moreover, the catalytic performance of MNPs is enhanced, for the available surface area of the nonporous MNPs is external and the internal diffusion is practically avoided.

On the other hands, the catalytic one-pot three-component condensation reaction of an aldehyde, β-ketoester and urea for the construction of dihydropyrimidine frameworks has recently been the subject of numerous investigations.⁶⁻¹⁰ During the last decade, several improved variations of the original Biginelli multicomponent reaction have been developed and many 3, 4 Dihydropyrimidin-2(1H)-ones (DHPMs) synthesized to exhibit a spectrum of interesting pharmacological properties.¹¹⁻¹³ Although these methods have their own advantages, many of them suffer from one or more drawbacks such as harsh reaction conditions,

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prolonged time period, poor yields, use of hazardous and expensive catalysts, difficulty in workup and lack of reusability of the catalyst. Therefore a better catalyst that would be superior to the existing ones, especially with regard to recyclability, is still required.

By considering all the above-mentioned points and previously reports about successful application of heterogeneous magnetic solid acids in organic transformations,¹⁴⁻¹⁵ herein, for the first time, melamine sulfonic acid conjugated magnetite nanoparticles, $\text{Fe}_3\text{O}_4\text{@MSA}$, was successfully prepared and its performance as powerful magnetic solid acid catalyst for the synthesis of 3,4-dihydropyrimidinones/thione under solvent-free conditions was investigated. The magnetic nature of this composite allows a convenient method for removing and recycling of the supported catalyst by applying an external magnetic field, which may optimize operational cost and enhance product's purity.

RESULTS AND DISCUSSION

In this study, Fe_3O_4 nanoparticles with a size range of 48-64 nm (Fig 1) were firstly prepared by the modified controlled chemical coprecipitation method from the solution of ferrous/ferric mixed salt-solution in alkaline medium.

The magnetic nanoparticles prepared by this method had significant numbers of hydroxyl groups on the surface. For grafting melamine sulfonic acid onto the surface of the magnetite nanoparticles, first, the isocyanate groups were preliminarily bonded onto the surface by the

reaction of hydroxyl groups of magnetite with hexamethylene diisocyanate, HMDI. After removing of unreacted HMDI, melamine was reacted with modified magnetic nanoparticles. Ultimately, the reaction of amino groups of melamine with chlorosulfuric acid led to $\text{Fe}_3\text{O}_4\text{@MSA}$. The schematic diagram for the synthetic procedure is shown in Scheme 1.

Due to the paramagnetic nature of the nanoparticle core, nuclear magnetic resonance technique could not be used to confirm $\text{Fe}_3\text{O}_4\text{@MSA}$ synthesis. Instead, titration and FT-IR were used to characterize the composite structure. Sulfonic acid loading was calculated based on titration of the proton-exchanged brine solution and shown the loading of 5 mmol $\text{SO}_3\text{H g}^{-1}$ of catalyst.

Fig. 2 shows the FT-IR spectra of HMDI, melamine, MNPs and $\text{Fe}_3\text{O}_4\text{@MSA}$ in the 400–4000 cm^{-1} wave number range. The IR spectrum of the $\text{Fe}_3\text{O}_4\text{@MSA}$ shows characteristic adsorption bands at 3330 and 1630 cm^{-1} correspond to NH and C=O groups. The NHCO stretching was also observed at 1570 cm^{-1} . In addition, adsorption bands at 3474 and 3419 can be attributed to the NH and OH of NHSO_3H . It is worthy to note that disappearance of the isocyanate peak in the IR spectrum at about 2280 cm^{-1} was also observed. The FT-IR bands at low wavenumbers ($\leq 700\text{cm}^{-1}$) come from vibrations of Fe–O bonds of iron oxide, in which for the bulk Fe_3O_4 samples appear at 570 and 375 cm^{-1} but for Fe_3O_4 nanoparticles at 624 and 579 cm^{-1} as a blue shift, due to the size reduction. Thus, all the above results indicate that MSA has been grafted successfully on MNPs.

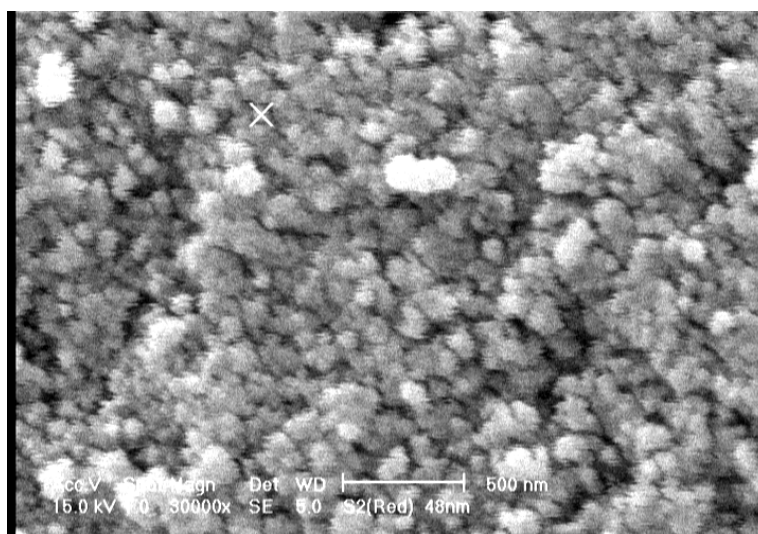
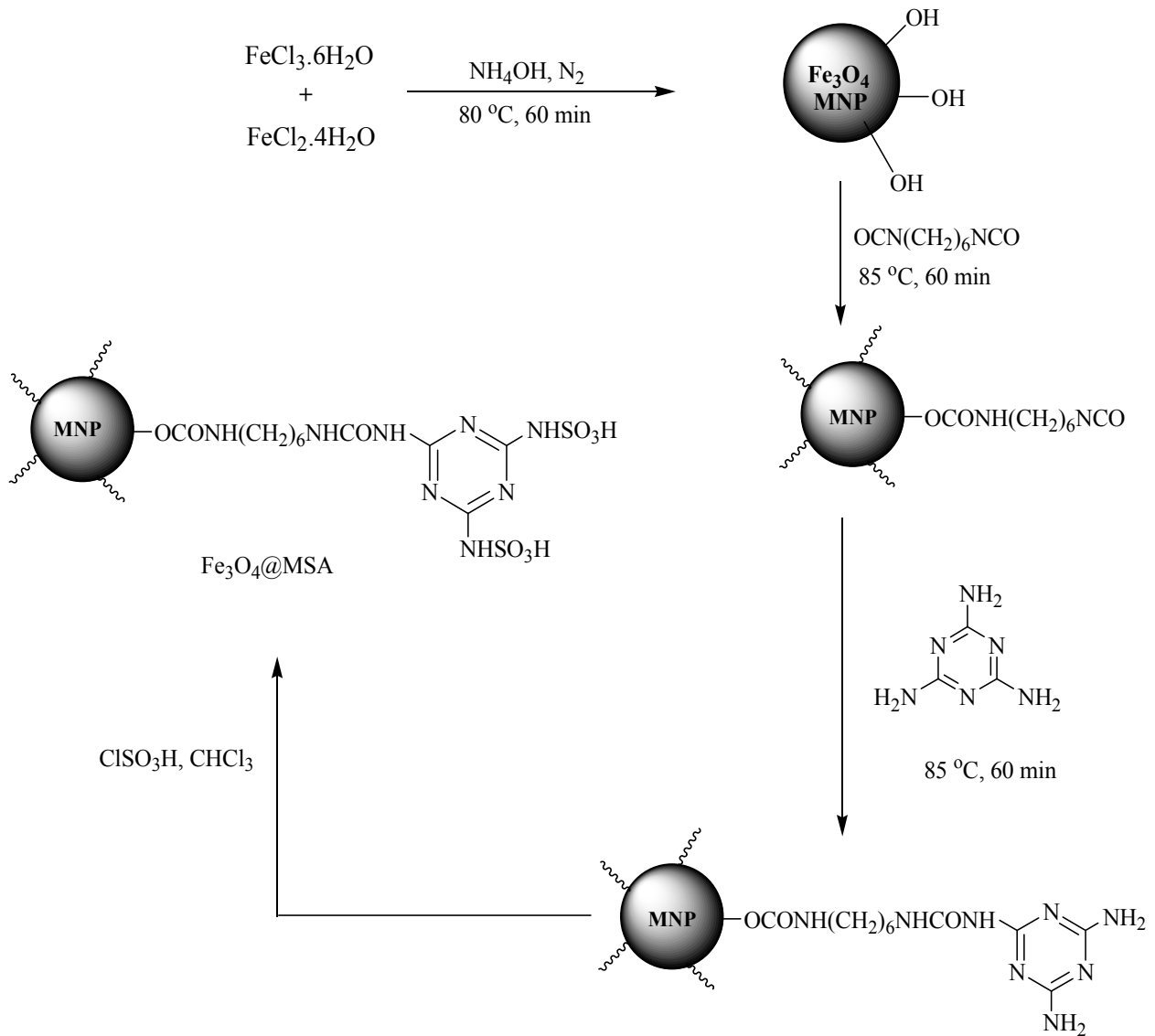


Fig. 1 – SEM image of Fe_3O_4 nanoparticles.



Scheme 1 – Synthesis of Melamine sulfonic acid conjugated magnetite nanoparticles ($\text{Fe}_3\text{O}_4@MSA$).

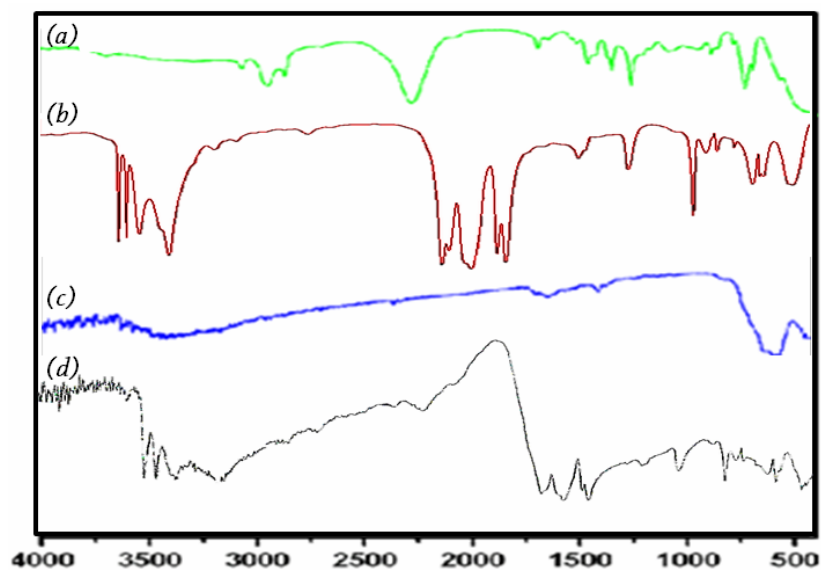


Fig. 2 – FT-IR spectra of (a) HMDI, (b) Melamine, (c) MNPs and (d) $\text{Fe}_3\text{O}_4@MSA$.

Fig. 3 shows the TGA analysis of $\text{Fe}_3\text{O}_4@\text{MSA}$. The thermogram exhibits a three-stage degradation pattern over the range of 30-500 °C. The first weight loss of 5% below 200 °C which might be due to the loss of residual water adhering to the sample surface. The second weight loss step of about 55% in the region of 220-300 °C was due to the cleavage of the urethane linkage, which is similar to conventional polyurethanes

which generally start to decompose around 200-220 °C.¹⁷ The last stage of degradation in the region of 380-490°C, probably, is due to thermal decomposition of melamine moieties.

The structural and morphological characterization of melamine conjugated Fe_3O_4 (Fig. 4) and $\text{Fe}_3\text{O}_4@\text{MSA}$ (Fig. 5) were performed by measuring SEM using a Philips XL30 scanning electron microscope.

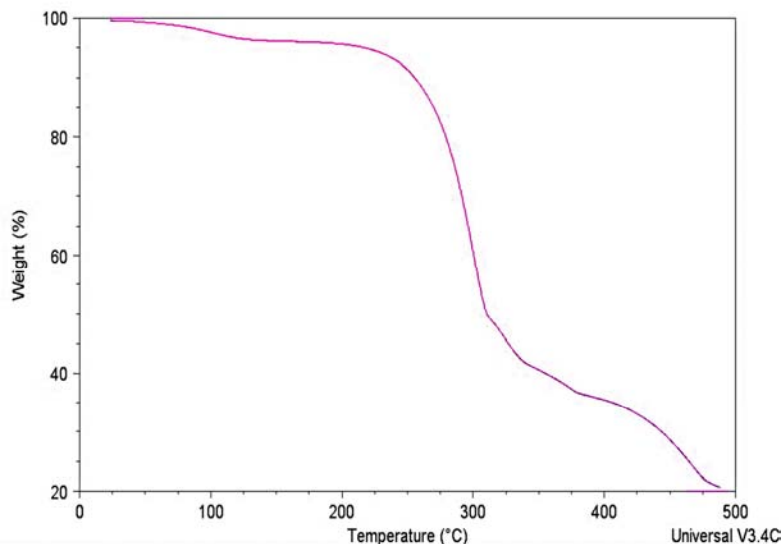


Fig. 3 – TGA Curve of $\text{Fe}_3\text{O}_4@\text{MSA}$.

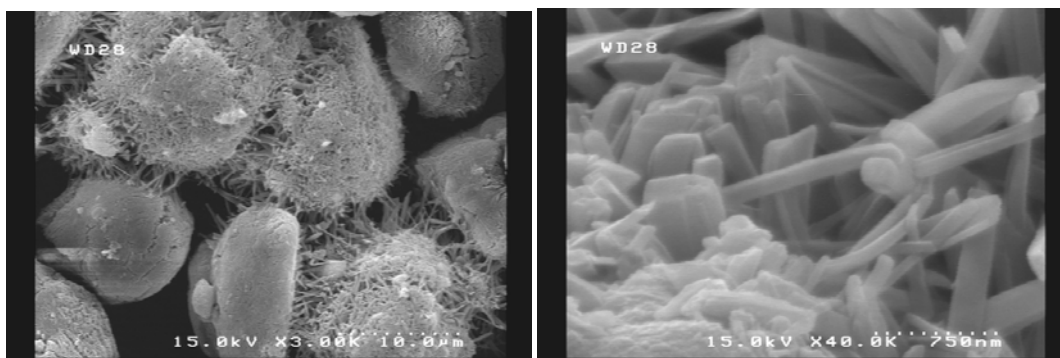


Fig. 4 – SEM images of melamine conjugated Fe_3O_4 nanoparticles.

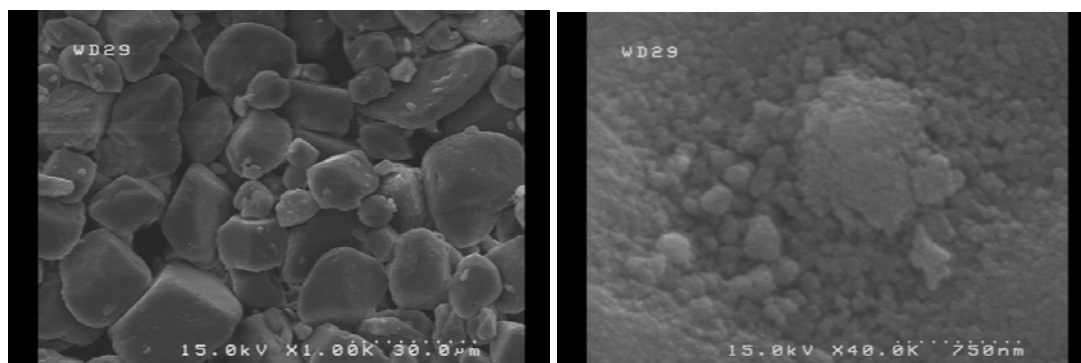


Fig. 5 – SEM images of $\text{Fe}_3\text{O}_4@\text{MSA}$.

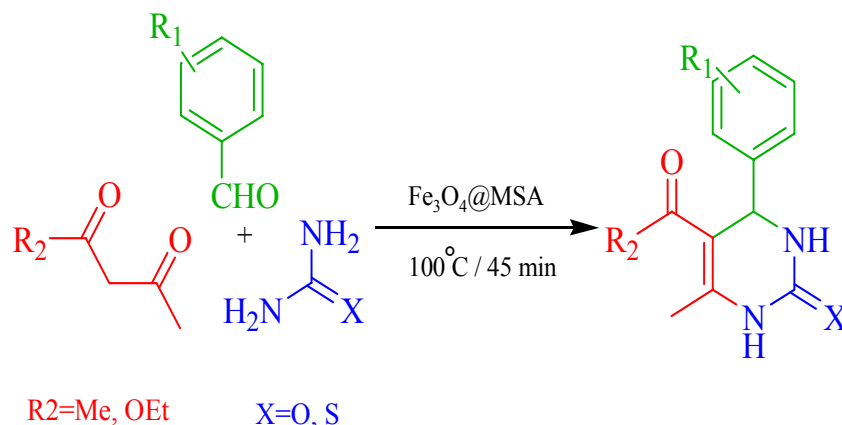
To evaluate the catalytic activity of $\text{Fe}_3\text{O}_4@\text{MSA}$ as nanomagnet heterogeneous solid acid catalyst in the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones (DHPMs) through multicomponent reaction (Scheme 2), a model three-component coupling reaction of benzaldehyde (1 mmol), ethylacetoacetate (1 mmol) and urea (1.5 mmol) was examined to determine whether the use of $\text{Fe}_3\text{O}_4@\text{MSA}$ was efficient and to investigate the optimized conditions.

After some experiments, it was found that for efficient coupling reaction presence of 0.1 g of catalyst under solvent free conditions at 100 °C is the best condition (45 min, 93%). Using lower amounts of catalyst resulted to corresponding DHPM in lower yield, while higher amounts of catalyst have no considerable effect on reaction time and yield. In order to show the role of the

catalyst, similar reaction in the absence of the catalyst was also examined. Under these conditions, the reactions led to the formation of the desired product in low yields after a long reaction time.

Subsequently, with optimal conditions in hand, 1:1:1.5 molar ratios of aldehyde, ethylacetoacetate and urea/thiourea and 0.1 g of $\text{Fe}_3\text{O}_4@\text{MSA}$ at 100°C under solvent-free conditions, the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of DHPMs having different steric and electronic properties (Table 1).

With this promising result in hand, to evaluate the generality and synthetic scope of this coupling protocol, this three-component condensation reaction was also preceded with acetyl acetone (Table 2).



Scheme 2 – Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones (DHPMs).

Table 1

The one-pot three-component condensation reaction of aldehyde, ethyl acetoacetate and urea or thiourea catalyzed by $\text{Fe}_3\text{O}_4@\text{MSA}$ under thermal solvent free conditions

NO.	Aldehyde	X	product	Yield (%)
1		O		93
2		O		94

Table 1 (continued)

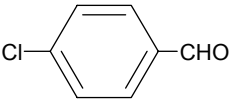
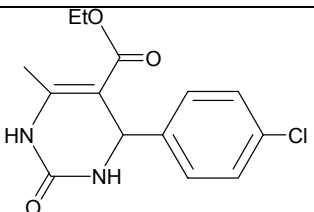
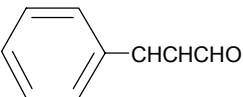
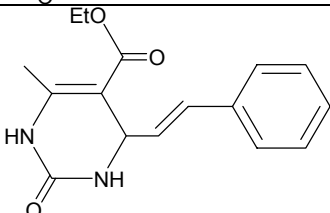
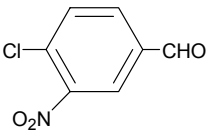
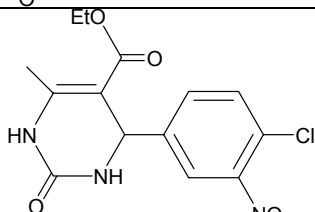
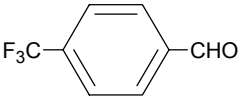
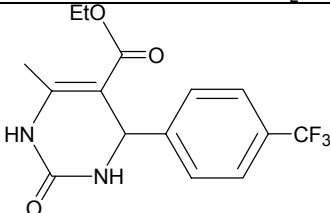

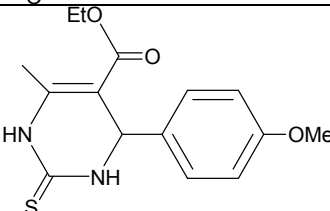

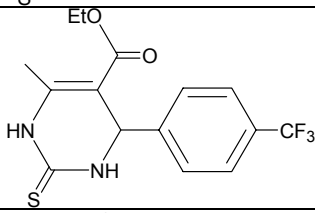
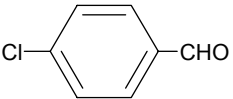
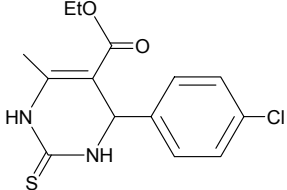
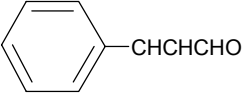
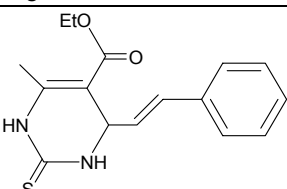
3		O		92
4		O		72
5		O		98
6		O		67
7		S		70
8		S		98
9		S		77
10		S		93

Table 2

The one-pot three-component condensation reaction of aldehyde, acetyl acetone and urea or thiourea catalyzed by $\text{Fe}_3\text{O}_4@\text{MSA}$ under thermal solvent free conditions


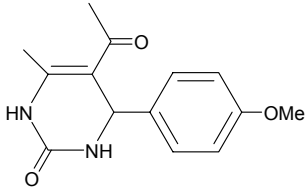

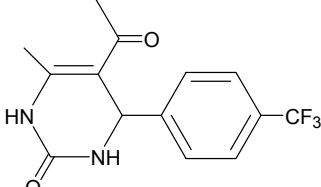
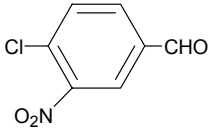
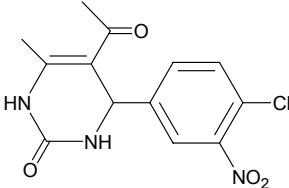
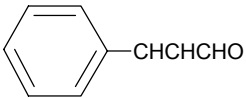
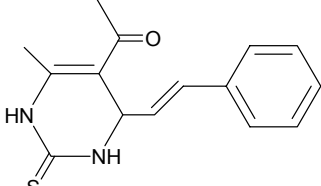
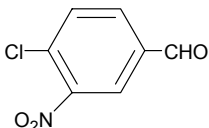
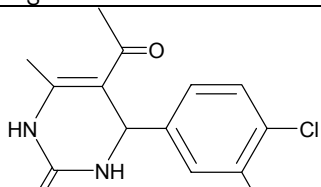

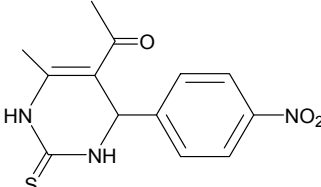
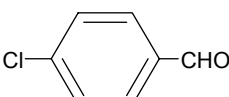
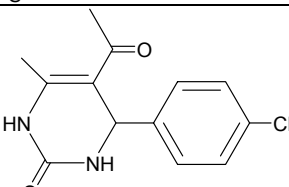
NO.	R ¹	X	product	Yield (%)
1		O		98
2		O		77
3		O		64
4		S		94
5		S		70
6		S		85
7		S		96

Table 3

Comparison of 5-ethoxycarbonyl-4-phenyl-6-methyl-3, 4 dihydropyrimidin-2(1H)-one synthesis with different catalysts

Entry	Catalyst	Catalyst loading (g or wt. %)	Molar ratio ^a	Conditions	Time (h)	Yield (%)	Ref
1	Fe ₃ O ₄ @MSA	0.1g	1:1:1.5	100 °C/ S.F ^b	0.75	93	This work
2	Yb(III)-resin	80%	1:1:1.5	120 °C/ S.F	48	80	[21]
3	Montmorillonite KSF	15%	1:1:1.5	100 °C/ S.F	48	77	[22]
4	Sulfated zirconia	15.15%	1:1:1.5	60 °C/ S.F	4	94	[23]
5	PS-PEG-SO ₃ H	0.3 g	1:1:1.2	80 °C/ Dioxane:-propanol	10	80	[24]
6	ZrOCl ₂ .8H ₂ O	10 mol%	1:1:1.3	ethanol/water	2	56	[25]
7	Silica-sulfuric acid	35%	1:1:1.5	Reflux /ethanol	6	91	[26]
8	H ₃ PMO ₁₂ O ₄₀	11%	1:1:1.5	Reflux/acetic acid	5	80	[27]
9	NaCl	0.07 g	1:1:1	Reflux/DMF	3	39	[9]
10	Envirocat EPZ10	10 mol%	1:1:1.5	Reflux /toluene	6	84	[28]
11	Zeolite [HY(Si/Al = 2.43, H ₅₆ (SiO ₂) ₁₃₆ (AlO ₂) ₅₆]	15%	1:0.8:1	Reflux /toluene	12	80	[29]
12	Zn(BF ₄) ₂ aq	0.6mol% aldehyde	1:1:1.2	R.T/ S.F	3	73	[30]

^a Molar ratio of benzaldehyde: ethyl acetoacetate: urea, ^b Solvent free

In order to show the merit of the presented protocol in DHPMs synthesis, we have compared the results obtained using Fe₃O₄@MSA with some of those reported in the literature (Table 3).

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. Products were characterized by comparison of their physical data, IR and 1H & 13C NMR spectra with known samples. The TGA curve of the melamine sulfonic acid conjugated Fe₃O₄ magnetic nanoparticles was recorded on a Bahr, SPA 503 at heating rates of 10 °C min⁻¹. The thermal behaviour was studied by heating 1–3 mg of samples in aluminium-cripped pans under nitrogen gas flow, over the temperature range of 25–700 °C.

Preparation of melamine sulfonic acid conjugated Fe₃O₄ magnetic nanoparticles (Fe₃O₄@MSA)

Preparation of Fe₃O₄@MSA involved four steps. First, superparamagnetic nanoparticles (MNPs) were prepared via improved chemical co-precipitation method.¹⁶ According to this method, FeCl₂.4H₂O (3.1736 g, 1.6 mmol) and FeCl₃.6H₂O (7.5684 g, 2.8 mmol) were dissolved in 320 mL of deionized water and the solution was stirred under N₂ at 80 °C for 1 h. 40 mL of NH₃.H₂O was injected into the reaction mixture rapidly, stirred under N₂ for another 1h and then cooled to room temperature. The precipitated particles were washed five times with hot water and separated by magnetic decantation. Finally, MNPs were dried under vacuum at 60 °C.

For introducing isocyanate groups onto the surface of the magnetic nanoparticles, MNPs-NCO, in the second step, the

MNP powder (0.232 g, 1mmol) was dispersed in dry CHCl₃ (10 mL) by sonication and hexamethylene diisocyanate (1.68 g, 10 mmol) in 20 mL of dry CHCl₃ was added dropwise to the mixture. After mechanically agitation for 1 h at 85 °C, the suspended substance was separated with external magnetic field. For removing unreacted hexamethylene diisocyanate, the settlement product was isolated with magnetic and decantation for 5 times. The precipitated product (MNPs-NCS) was used in the next step.

To graft melamine onto the surface of magnetic nanoparticles, synthesized (MNPs-NCO) was suspended in dry CHCl₃ (15 mL) and melamine (1.89 g, 15 mmol) was added to the mixture. After stirring the reaction mixture for 1 h at 85 °C, the precipitate was separated by magnetic decantation and washed with CHCl₃ several times.

Finally for preparation of Fe₃O₄@MSA, a suction flask (100 mL) was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. Melamine conjugated Fe₃O₄ magnetic nanoparticles (0.55 g) was added into the flask and dispersed by ultrasonic for 10 min in dry CHCl₃ (15 mL). Chlorosulfonic acid (0.1mL, 1.5 mmol) in CHCl₃ (20 mL) was added dropwise over a period of 10 min at room temperature, while the residual HCl was eliminated by suction. Then the Fe₃O₄@MSA was separated from the reaction mixture by a magnetic field and washed several times with dry CHCl₃. Fe₃O₄@MSA was dried under vacuum at 60 °C.

All the procedures that MNPs was involved in, were carried out under N₂ protection to avoid possible oxidation during reaction.

pH-analysis of Fe₃O₄@MSA

To an aqueous solution of NaCl (1 M, 25 mL) with an initial pH 5.9, the Fe₃O₄@MSA (100 mg) was added and the resulting mixture stirred for 24 h after which the pH of solution decreased to 1.7. This is equal to a loading 5 mmol/g

of SO₃H groups of acidic catalyst. Additionally, this result was confirmed by back-titration analysis of the catalyst.

Typical procedure for the preparation of 3, 4-dihydropyrimidin-2(1H)-ones/thiones

A mixture of aromatic aldehyde (1.0 mmol), ethyl acetoacetate or acetyl acetone (1.0 mmol), urea or thiourea (1.5 mmol), and Fe₃O₄@MSA (0.1 g) was heated at 100 °C for 45 min. After complete consumption of aromatic aldehyde as judged by TLC (using n-hexane – ethyl acetate as eluent), the mixture was washed with ice water to separate the excess of urea or thiourea. The crude product was dissolved in hot ethanol and the magnetic catalyst was concentrated on the sidewall of the reaction vessel using an external magnet. The hot solution was separated by decantation and allows reaching to room temperature. The crystalline isolated products gave satisfactory spectral data (¹H NMR and ¹³C NMR) and compared with those reported in literature.

CONCLUSIONS

In this research Fe₃O₄@MSA was successfully achieved by a multiple synthetic procedure which is confirmed with FT-IR, TGA, and SEM. The most interesting features of the present work include durability as well as efficient catalytic activity for one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via three-component coupling reactions of aromatic aldehydes, β-diketone and urea or thiourea under solvent free conditions at 100 °C. In contrast to the existing methods, this method offers several advantages including high yield, short reaction time, simple work-up procedure and ease of separation, as well as the ability to tolerate a variety of substitutions in the reagents.

REFERENCES

- L. Mamani, M. Sheykhani, A. Heydari, M. Faraji and Y. Yamini, *Appl. Catal. A-Gen.*, **2010**, *377*, 64-69.
- Y. Zhang, Y. Zhao and C. Xia, *J. Mol. Catal. A: Chem.*, **2009**, *306*, 107-112.
- D. Wu, X. Feng, M. Takase, M.C. Harberecht and K. Mullen, *Tetrahedron*, **2008**, *64*, 11379-11386.
- W. C. Lim and I. S. Lee, *Nano Today*, **2010**, *5*, 412-434.
- A. R. Kiasat and S. Nazari, *J. Incl. Phenom. Macrocycl. Chem.*, **2013**, *76(3)*, 363-368.
- M. Z. Kassaei, H. Masrouri and F. Movahedi, *Appl. Catal. A-Gen.*, **2011**, *395*, 28-33.
- R. Tayebee, B. Maleki and M. Ghadamgahi, *Chin. J. Catal.*, **2012**, *33*, 659-666.
- M. Nasr-Esfahani, S. J. Hoseini and F. Mohamadi, *Chin. J. Catal.*, **2011**, *32*, 1484-1489.
- M. A. Kolosov, D. V. Orlov, D. A. Beloborodov and V. V. Dotsenko, *Mol. Divers.*, **2009**, *13*, 5-25.
- M. Tajbakhsh, Y. Ranjbar, A. Masuodi and S. A. Khaksar, *Chin. J. Catal.*, **2012**, *33*, 1542-1545.
- D. Xu and H. Li, Y. Wang, *Tetrahedron*, **2012**, *68*, 7867-7872.
- V. M. Timoshenko, Y. M. Markitanov and Y. G. Shermolovich, *Tetrahedron Lett.*, **2011**, *52*, 6619-6622.
- M. M. Heravi, S. Asadi, and B. M. Lashkariani, *Mol. Divers.*, **2013**, *17*, 389-407
- D. Girija, H. S. Bhojya Naik, B. Vinay Kumar, C.N. Sudhamani and K. Harish, *Lett. Org. Chem.*, **2013**, *10*, 468-477.
- A. Mobinikhaledi, H. Moghanian and Z. Souiri, *Lett. Org. Chem.*, **2014**, *11*, 432-439.
- B. K. Singh, M. Mishra, N. Saxena, G. P. Yadav, P. R. Maulik, M. K.; Sahoo, R. L. Gaur, P. K. Murthy and R. P. Tripathi, *Eur. J. Med. Chem.*, **2008**, *43*, 2717-2723.
- C. S. Gill, B. A. Price and C. W. Jones, *J. Catal.*, **2007**, *251*, 145-152.
- T. Hara, T. Kaneta, K. Mori, T. Mitsudome, T. Mizugaki, K. Ebitani and K. Kaneda, *Green Chem.*, **2007**, *9*, 1246-1251.
- K. Can, M. Ozmen and M. Ersoz, *Colloids Surf. B*, **2009**, *71*, 154-159.
- A. R. Kiasat and S. Nazari, *J. Mol. Catal. A- Chem.*, **2012**, *365*, 80-86.
- A. Dondoni and A. Massi, *Tetrahedron Lett.*, **2001**, *42*, 7975-7978.
- F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, *Tetrahedron Lett.*, **1999**, *40*, 3465-3468.
- D. A. Beltran, L. L. Romero, V. H. L. Corona, E. G. Zamora and G. N. Silva, *Molecules*, **2006**, *11*, 731-738.
- Z. J. Quan, Y. X. Da, Z. Zhang and X. C. Wang, *Catal Commun.*, **2009**, *10*, 1146-1148.
- J. C. Rodriguez-Dominguez, D. Bernardi and G. Kirsch, *Tetrahedron Lett.*, **2007**, *48*, 5777-5780.
- P. Salehi, M. Dabiri, M. A. Zolfigol and M. A. Bodaghi Fard, *Tetrahedron Lett.*, **2003**, *44*, 2889-2891.
- M. M. Heravi, K. Bakhtiari and F. Bamoharram, *Catal Commun.*, **2006**, *7*, 373-376.
- K. Y. Lee and K. Y. Ko, *Bull. Korean Chem. Soc.*, **2004**, *25*, 1929-1931.
- V. Radha Rani, N. Srinivas, M. Radha Kishan, S. J. Kulkarni and K. V. Raghavan, *Green Chem.*, **2001**, *3*, 305-306.
- S. K. Kundu, A. Majee and A. Hajra, *Indian J. Chem. Sec. B*, **2009**, *48*, 408-412.

