A novel water-tolerant organosulfonic acid-functionalized silica-coated magnetic nanoparticles as a hydrophobic, recyclable and magnetically separable catalyst for the solvent-free Biginelli reaction

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Abstract:

Two novel and environmentally benign organosulfonic acid-functionalized silica-coated magnetic nanoparticle catalysts **1a** ($Fe_3O_4@SiO_2@Et-PhSO_3H$) and **1b** ($Fe_3O_4@SiO_2@Me\&Et-PhSO_3H$) have been prepared and their hydrophobicity and acidity were investigated, and tested for the three-component Biginelli reaction of benzaldehyde, methylacetoacetate, and urea under solvent-free conditions. The catalyst **1b** which was more hydrophobic, showed higher catalytic activity and was characterized extensively by fourier transform infrared spectroscopy (FT-IR), transmission electron microscopy (TEM), elemental analysis, water adsorption-desorption analysis, vibrating sample magnetometer (VSM) and acid/base titration. This catalyst was used in the reactions of a series of aldehydes, β-keto esters, and urea/thiourea. The catalyst was easily separated by an external magnet and the recovered catalyst was reused in four cycles without significant loss of activity. This green and reusable catalyst accompanied by simple experimental procedure and product isolation could be considered as an alternative protocol which will hopefully develop a clean and eco-friendly strategy for the synthesis of 3,4-dihydropyrimidin-2-ones/thiones (DHPMs) derivatives.

Keywords:

Hydrophobicity; Heterogeneous catalysis; Biginelli reaction; Magnetic core-shell nanoparticles; water toleration

1. Introduction

During the last two decades, with the development of nanotechnology, numerous nanomaterials have been designed and created. Amongst them, hybrid organic-inorganic materials based on $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticles as a special immobilizing carrier of the catalyst active sites have shown a significant contribution to the current researches. This is due to their inherent properties such as biocompatibility, easy renewability and recovery by magnetic separation, thermal stability against degradation, large surface area and higher loading of active sites. The aforementioned advantages of $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticles compared to the other heterogeneous catalysts have brought new opportunities for the design and synthesis of novel solid catalysts [1]. Although many investigations have been conducted on synthesis and characterization of acidic magnetic nanoparticles [2,3], no attention has been paid to combining hydrophobicity with acidity of materials for providing bifunctional $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticles containing both sulfonic acid and terminal organic groups protruding on the silica surface of nanocomposites. Introduction of sulfonic acid and organic groups into $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticles is interesting since the combination of both functionalities (acidic and hydrophobic) allows creation of a less polar organic environment with a relatively high acid strength for acid catalysed reactions [4]. In many acid catalysed reactions by solid acids [2,3,5], the water produced as a by-product of the reaction is co-adsorbed near the acidic sites and the surface of the catalyst. Therefore, the co-adsorbed water poisons the surface and active sites of the catalyst and reduces the performance of the catalyst.

As part of our efforts in exploring novel catalysts in organic transformations with green approach [6], we have designed, prepared and characterized two novel water-tolerant and sulfonic acid organic-inorganic hybrid interphase catalysts based on $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticles: $Fe_3O_4@SiO_2@Et-PhSO_3H$ (**1a**, Scheme 1) and $Fe_3O_4@SiO_2@Me\&Et-PhSO_3H$ (**1b**, Scheme 1); also, the acidity, hydrophobicity and utility of these catalysts in the Biginelli reaction were investigated under solvent-free conditions.

The utilization of multi-component reactions (MCRs) to synthesize novel chemicals, drug-like scaffold and natural product compounds has pervaded in organic transformations [7,8]. This is due to the fact that products can be prepared directly in a single step and diversity can be achieved simply by varying the reaction substrates [9]. The Biginelli reaction involving a three-component condensation of *β*-dicarbonyl compounds with aldehydes and urea or thiourea under

strongly acidic conditions is ranked as one of the most recognized and widely employed MCRs for the preparation of 3,4-dihydropyrimidin-2-ones/thiones (DHPMs) [10]. DHPMs exhibit a wide variety of biological and pharmacological activities such as antibacterial, antihypertensive, antivirial, α_{1a} adrenoceptor-selective antagonist and calcium channel blockers [11]. Some marine natural products containing the dihydropyrimidinone-5-carboxylate units such as batzelladine alkaloids have been found to be potent HIV (gp-120-CD4) inhibitors [11]. In addition, Monastrol and (R)-Mon-97 (Fig. 1) show promising anticancer activities and are thus considered as lead molecules for the development of new anticancer drugs [11]. Since the Biginelli reports many
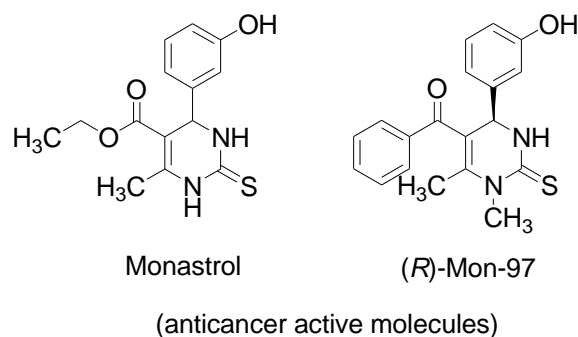

Monastrol   (R)-Mon-97

(anticancer active molecules)

Fig. 1 Biologically active DHPMs.

acid-catalyzed procedures have been introduced for this significant multicomponent reaction.[12] However, most of these reported methods require a high loading of expensive and non-recoverable catalysts and prolonged reaction times.

Avoiding the use of harmful organic solvent is one of the most fundamental strategies in green chemistry. For this reason, there have been several attempts in the literature to find alternative and environmentally benign synthetic routes for organic transformations. In this regards, the solvent-free condition and the use of water as solvent have received considerable attention and proved to be promising alternatives in the Biginelli reaction due to their environmentally friendly and green nature [12,13]. Among other possibilities, our purpose is the development of simple and eco-friendly conditions accompanied by an efficient, reusable and water tolerant catalyst.

2. Experimental Section

All chemicals were purchased from Merck and Aldrich Chemical Companies. Melting points were determined on a Büchi melting point B-540 apparatus. NMR spectra were recorded at 400

(^{1}H) and 100.6 (^{13}C) MHz, respectively, on a commercial Bruker instrument (DMX-400 MHz) instrument using DMSO-d_6 as solvent. IR spectra were recorded using KBr discs on an ABB Bomem Model FTLA 2000 spectrophotometer. The magnetic measurement of samples were carried out in a vibrating sample magnetometer (VSM) (4 inch, Daghigh Meghnatis Kashan Co., Kashan, Iran) at room temperature. Transmission electron microscope, TEM (Philips CM-10) was also used to obtain TEM images. Elemental analyses for C, H and S were performed using a Heraeus CHN-O Rapid analyzer (see ESI).

2.1. Preparation of Fe$_3$O$_4$@SiO$_2$

The synthesis of Fe$_3$O$_4$@SiO$_2$ was achieved using the procedure described by Luo and co-workers [14] This procedure involved a synthetic strategy based on the hydrolysis and condensation of tetraethoxysilane (TEOS) on the surface of Fe$_3$O$_4$ magnetic nanoparticles. In a typical preparation procedure, ferric chloride hexahydrate FeCl$_3$.6H$_2$O (11.0 g, 40.7 mmol) and ferrous chloride tetrahydrate FeCl$_2$.4H$_2$O (4.0 g, 20.1 mmol) were dissolved in deionized water (250 mL) under nitrogen atmosphere with mechanical stirrer at 85 °C. The pH value of the solution was adjusted to 9-11 using aqueous NH$_3$ (25 %). After continuous stirring for 4 h, the magnetite precipitates were washed with distilled water until the pH value descended to 7.0. The black precipitate (Fe$_3$O$_4$) was collected with a permanent magnet at the bottom of the reaction flask. The silica coated core–shell magnetic nanoparticles (Fe$_3$O$_4$/SiO$_2$ MNPs) were prepared by an ultrasonic pre-mixing of a dispersion of the above black precipitate (2.0 g) with ethanol (400 mL) for approximately 30 min at room temperature. Then, aqueous NH$_3$ (25 %, 12 mL) and TEOS (4.0 mL) were slowly added successively. The resulting solution was mechanically stirred continuously for 24 h, after which the black precipitate product (Fe$_3$O$_4$@SiO$_2$) was collected by magnetic separation and washed with ethanol (3 × 15 mL) and dried under vacuum overnight at room temperature (Scheme 1).

2.2. Preparation of *1a*

The surface functionalization of the silica coated magnetic nanoparticles with sulfonyl groups was carried out by adding 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane (CSPETS, 0.4 g, 1.23 mmol) to dry toluene (35 mL) containing silica-coated magnetic nanoparticles (1.0 g). The resulting mixture was stirred for 24 h and then washed with toluene (2 × 15 mL) and distilled

water. Finally, the solid was suspended in H_2SO_4 (1M) solution for 2 h, washed several times with water and dried at room temperature under vacuum overnight to give the corresponding **1a** (Scheme 1).

2.3. Preparation of *1b*

This procedure involved a synthetic strategy based on the co-condensation of 2-(4-chlorosulfonylphenyl)ethyltrimet-hoxysilane (CSPETS) and trimethoxymethylsilane (TMMS) on the silica coated magnetic nanoparticles. In a typical preparation procedure, 2-(4-chlorosulfonylphenyl)- ethyltrimethoxysilane (CSPETS, 0.2 g, 0.615 mmol) and trimethoxymethylsilane (TMMS, 0.2 g, 1.468 mmol) were added to dry toluene (35 mL) containing silica-coated magnetic nanoparticles (1.0 g). The resulting mixture was stirred for 24 h and then washed with toluene (2 × 15 mL) and distilled water. Finally, the solid was suspended in H_2SO_4 (1 M) solution for 2 h, washed several times with water and dried at room temperature under vacuum overnight to give the corresponding **1b** (Scheme 1).

2.4. Acidity of the *1a* and *1b*

The concentration of sulfonic acid groups was quantitatively estimated by ion-exchange *p*H analysis. The catalyst (50 mg) was added to an aqueous solution of NaCl (1 M, 25 mL), and the resulting mixture was stirred for 3 days, after which reverse titration by NaOH (0.05 M) was carried out on the above obtained solutions. The acid amount of **1a** and **1b** was determined to be 2.22 and 0.70 mmol g^{-1}, respectively.

2.5. General procedure for the one-pot preparation of 3,4-dihydropyrimidin-2-ones/thiones

A mixture of aldehyde (2 mmol), methyl acetoacetate (2 mmol), urea/thiourea (2.4 mmol) and catalyst **1b** (7.1 mg, 0.5 mol %)(in the case of thiourea, 1 mol % of the catalyst was used) was stirred at 100 °C for an appropriate time under solvent-free condition (Table 4). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with water (3 × 10 mL). Finally, the mixture was dissolved in hot EtOH and the catalyst was separated by magnetic decatation. The crude product was either recrystallized from EtOH or subjected to preparative thin layer chromatography (silica gel) for further purification.
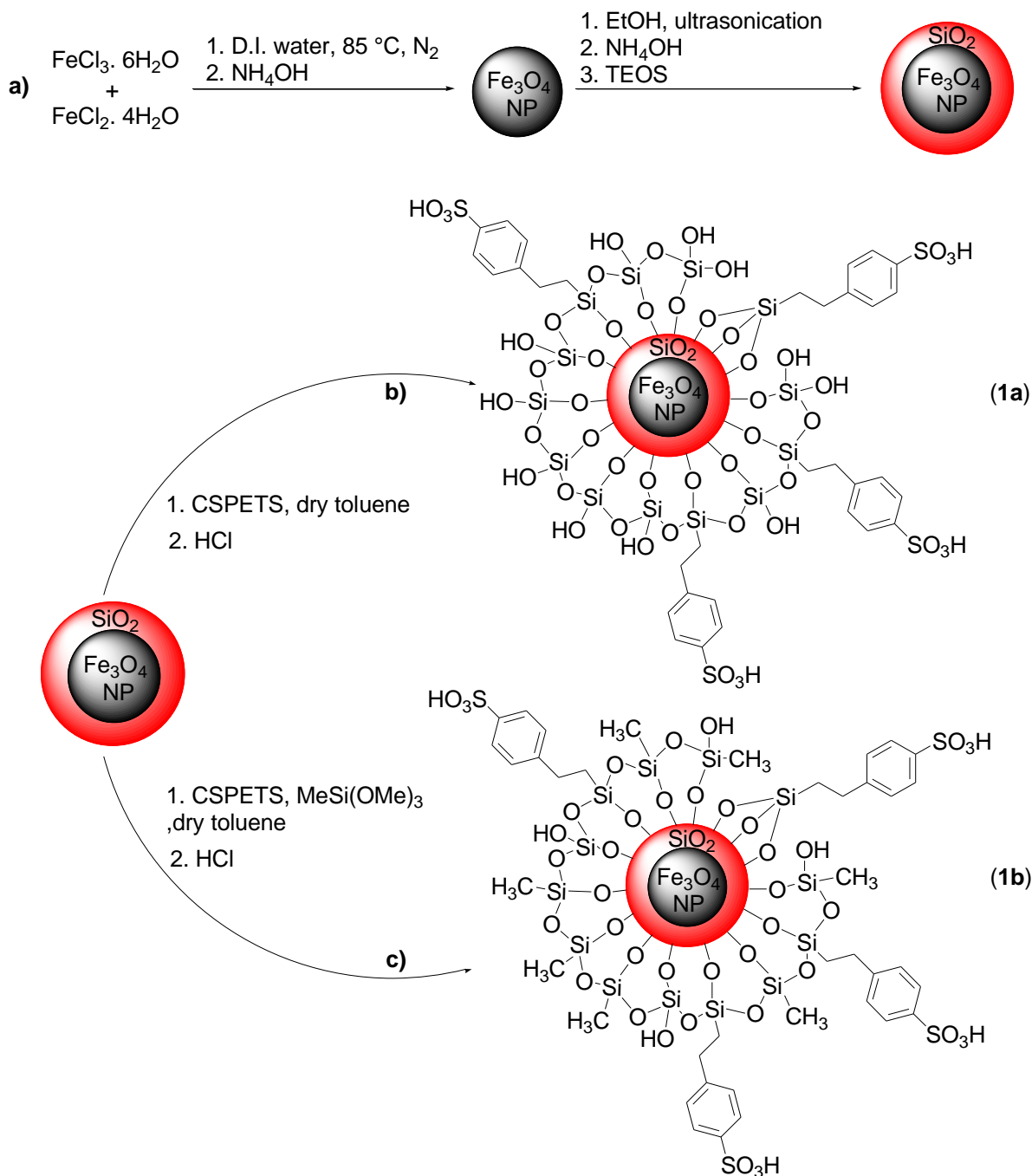
Scheme 1 Preparation routes of (a) Fe_3O_4 and $Fe_3O_4@SiO_2$, (b) $Fe_3O_4@SiO_2@Et-PhSO_3H$ (**1a**) and (c) $Fe_3O_4@SiO_2@Me\&Et-PhSO_3H$ (**1b**) core-shell magnetic nanoparticles.

3. Results and Discussion

A variety of parameters such as the polarity of reactants and products, hydrophobic-hydrophilic balance on catalyst's surface and the acidity of catalysts have considerable effect on the reaction

rate of the Biginelli reaction. The presence of water molecules as the reaction by-product in a non-polar reaction medium with hydrophilic active sites on catalyst's surface is likely to hinder the progress of the reaction. Solid acids are subjected to poisoning with water in the reactions in which this polar molecule is involved [15]. Further research was addressed to design, synthesis and catalytic application of surface modified–SO₃H solid materials in order to optimize the performance of catalysts [5]. As far as we know, there is not any report about surface hydrophobicity on sulfonic acid functionalized core-shell magnetic nanoparticles.

To test the catalytic capability of **1a** and **1b**, the Biginelli reaction of methyl acetoacetate (2.0 mmol), benzaldehyde (2.0 mmol), and urea (2.4 mmol) in the presence of the above catalysts (0.5 mol%) were investigated at 100 °C. To our delight, **1b** appeared to be much more active than **1a**, affording 90% yield of the desired DHPM in 120 min, while **1a** gave 83% yield of the product in 160 min (Scheme 2).

These results show that **1b** has a superior hydrophobic-hydrophilic and acidity balance in the Biginelli reaction; moreover, this catalyst (**1b**) with a moderate density of –SO₃H sites is shown as an interesting water-tolerant acid catalyst with higher activity to check this reaction. The greater reactivity of **1b** with respect to **1a** is probably due to a synergistic effect between sufficient hydrophobicity and acidity of siliceous network which in turn results in the following items:

   i) Remarkable shielding effect against polar molecules, accessibility of the active sites and easier diffusion of organic reactants within the network resulting from the presence of organic methyl groups in the surface of the **1b**.

   ii) Mild acidic conditions opting for the preparation of DHPMs.
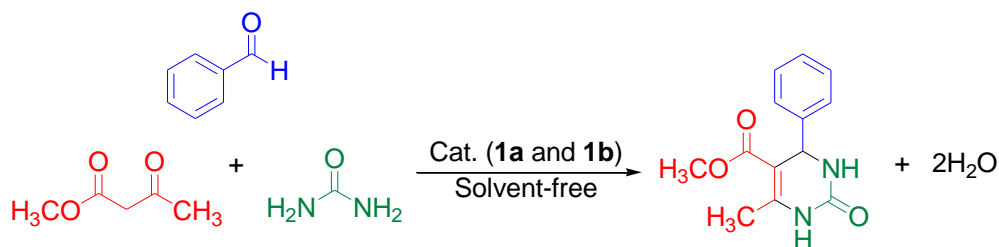
Scheme 2 Synthesis of methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate using **1a** and **1b**.

We have postulated that the formation of water as a by-product in the Biginelli reaction with either urea or thiourea inhibited the Biginelli reaction. As a result, the Biginelli reaction is not efficiently performed by **1a** catalyst because of the hydrophilicity of the surface and high acidity of the catalyst which in turn would lead to an enriched water concentration near the active sites during the reaction.

To confirm this hypothesis, superior stability and activity of the catalyst **1b** over the catalyst **1a**, water adsorption-desorption isotherms of catalysts **1a** and **1b** in the gas phase were measured (Figure 2). As can be seen in Figure 2, the surface of catalyst **1a** is more hydrophilic than catalyst **1b**. Therefore, it is readily poisoned with water molecules, which shows **1a** is not a suitable catalyst for the reactions accompanied with water as a by-product.

3.1. Characterization

The textural properties of the functionalized organic-inorganic hybrid catalysts synthesized for the current work were determined by vibrating sample magnetometer (VSM) and transmission electron microscopy (TEM). The surface area and surface sorption of the catalysts, **1a** and **1b** were determined by water adsorption-desorption analysis that are summarized in Table 1. The respective chemical compositions were determined by elemental analysis (carbon and sulfur content measurement) (Table 1).

The corresponding structural parameters such as surface area, and total pore volumes were calculated with the Brunauer–Emmet–Teller (BET) method (Table 1). BET surface area measurements indicated that, compared to **1a**, the surface area of **1b** was significantly decreased from 122.3 m^2g^{-1} to 95.8 m^2g^{-1} which was attributed to the surface modification in **1a** with the trimethoxymethylsilane (TMMS) precursor. In other words, the reduction of the surface area verifies that the loading of hydrophobic methyl regulator groups has been successful.

Table 1. Physicochemical and textural properties of sulfonic acid based magnetic nanoparticles.

Entry	Catalyst	S_{BET}[a]	V_p[b]	C (%)[c]	S (%)[c]	Proton content[d]
1	**1a**	122.36	0.10	6.60	2.18	2.22
2	**1b**	95.81	0.06	3.17	0.70	0.72

[a] BET surface area (m^2g^{-1}). [b] Total pore volume (cm^3g^{-1}). [c] Carbon and sulfur content measured by elemental analysis (w%). [d] Determined by reverse titration after ion-exchange (mmol H^+ g^{-1}) (see ESI).
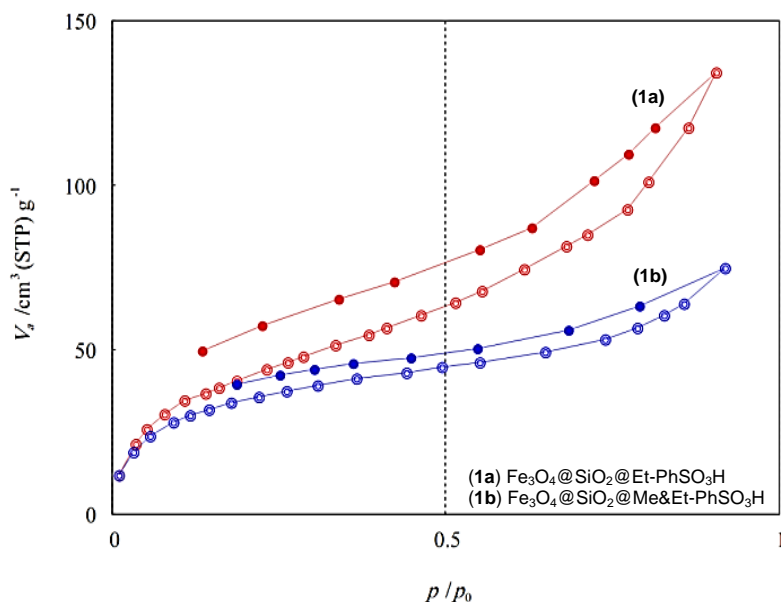
Fig. 2 Water adsorption-desorption isotherms of solid acid catalysts **1a** and **1b**.

In order to investigate the crystalline nature and morphological features of **1b**, transmission electron microscopy (TEM) was carried out. In this case, the TEM image provide more accurate information on the particle size and morphology of MNPs, therefore, these image was investigated. TEM observations clearly reveal the core-shell structure of the nanoparticles. Due to different electron density, this image display a dark nano-Fe_3O_4 core about 17 nm in diameter surrounded by a grey silica shell about 7 nm thick, and the average catalyst particles size is about 24 nm in diameter (Fig. 3).

The magnetic properties of the **1b** were evaluated at room temperature and the VSM magnetization curve of magnetic nanoparticles after functionalization, exhibit their superparamagnetic characteristics (Fig. 4a). The strong magnetization of the nanoparticles was also tested by simple attraction with an external magnet (Fig. 4b).

Also, FT-IR spectroscopy was employed to verify the synthesized blank Fe_3O_4 MNPs, $Fe_3O_4@SiO_2$ core-shell MNPs and the other core-shell surface modification samples (Fig. 5). FT-IR spectra of the bare magnetic Fe_3O_4 nanoparticles displayed a characteristic band at about 590 cm^{-1} (Fig. 5a). The unique O−Si−O absorption band of the silica shell in the $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticles appeared as a strong band at 1094 cm^{-1} (Fig. 5b), indicating that silica-coating was successful on the Fe_3O_4 magnetite surface. The presence of the anchored
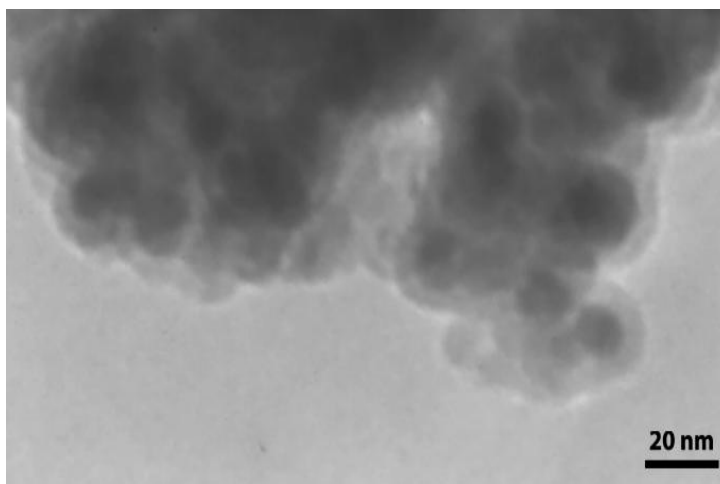
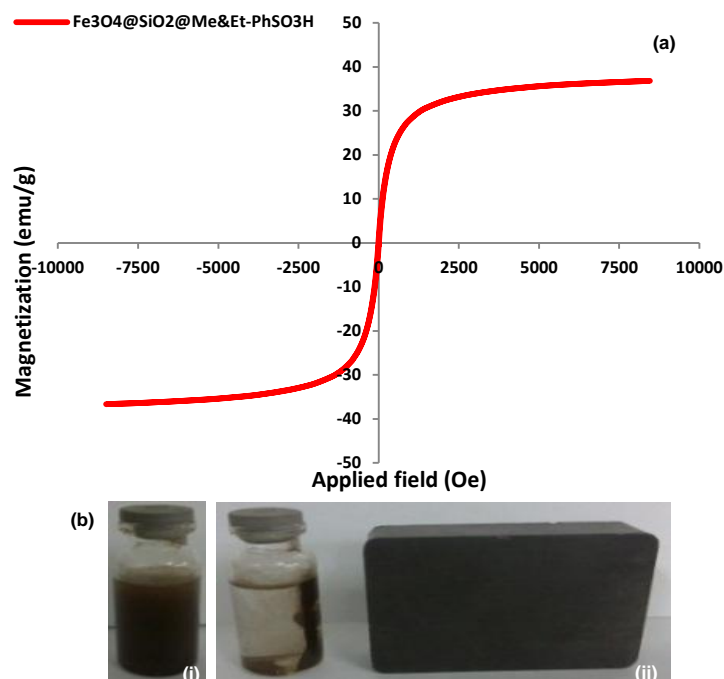**Fig. 3** TEM image of the **1b** magnetic core-shell nanoparticles.

Fig. 4 (a) Magnetization (M) as a function of field (H) for **1b**. (b) The picture displays the catalyst **1b** was dispersed in liquid (i) and captured by the outer magnet (ii).

alkyl groups is confirmed by the aliphatic weak C–H stretching vibrations appearing at 2922 in **1b** and 2926 cm^{-1} in **1a**. The increase in the intensity and broadening of the band at 3000–3500

cm^{-1} in the samples suggests that there are more OH groups on the magnetic nanoparticle surface after the modification and sulfonation.Thus the above results indicate that the functional groups were successfully grafted onto the surface of the magnetic $Fe_3O_4@SiO_2$ nanoparticles.

2. The Biginelli reaction

For this study, we initiated our investigation of the Biginelli reaction between benzaldehyde (2 mmol), methyl acetoacetate (2 mmol), and urea (2.4 mmol) as a model reaction under neat conditions and the role of various catalyst loadings, and temperatures was screened using **1b** as a heterogeneous catalyst (Table 2).

In order to find the best reaction conditions, we first examined the effect of temperature with constant loading of the catalyst (1 mol%). It was found that the yield of the desired 3,4-dihydropyrimidin-2-one was raised at higher temperature in shorter reaction times (Table 2, entries 1-3). Also, reducing the amount of the catalyst did not have any significant impact on the product yields at 90 °C (Table 2, entries 4 and 5). We also examined the effect of temperatures > 90 °C and lower loadings of the catalyst on the reaction (Table 2, entry 6-8). It gave the expected product in a good yield. It was concluded that solvent-free conditions at 100 °C in the presence of 0.5 mol% of the catalyst **1b** is the optimized condition for this three-component reaction (Table 2, entry 6).
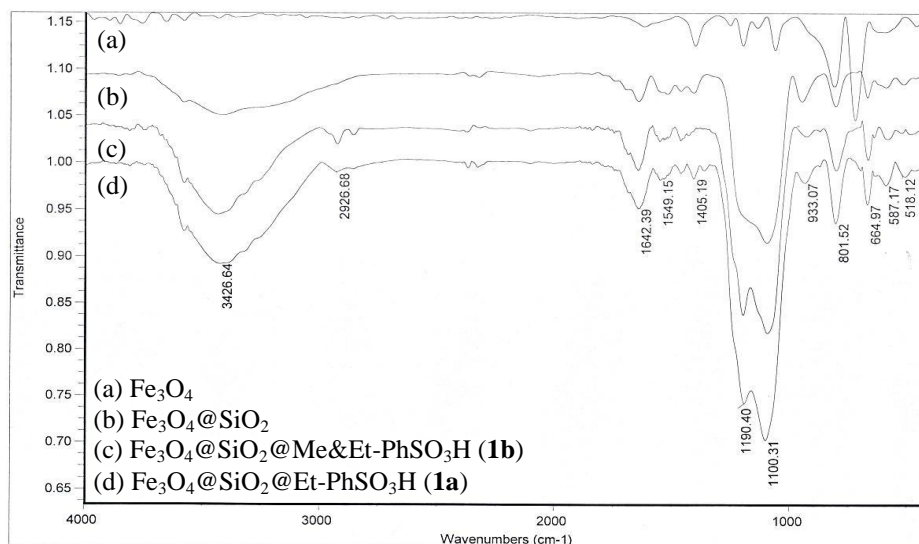

Fig. 5 FT-IR spectra for (a) Fe_3O_4 nanoparticles, (b) Fe_3O_4/SiO_2, (c) **1b**, and (d) **1a**.

Since thiopyrimidinones are important pharmacophores with regard to biological activity, our next objective was to develop an efficient procedure for their synthesis using thiourea as one of the reactants (Table 3). The aforementioned optimized conditions were not successful for the case of thiourea; therefore, the reaction was optimized with higher concentration of the catalyst (1 mol%, Table 3, entry 3).

With the optimized reaction conditions in hand, the generality of the procedure for the synthesis of the Biginelli reaction adducts was investigated with various aldehydes and urea/thiourea and a library of substituted DHPMs was obtained in high to excellent yields in appropriate times under solvent-free conditions (Table 4). Both electron-withdrawing as well as electron-donating substituents on the aldehyde aryl ring were tolerated and, in turn reacted with methyl acetoacetate and urea/thiourea under the optimized conditions.

Meta- and para-fluoro and meta-bromobenzaldehydes successfully produced the desired products in similarly excellent yields (Table 4, entries 2-4) indicating that the position of the electron-withdrawing substituent had no significant effect on the yield.

Table 2. Effects of reaction temperature and mol% of **1b** on the Biginelli reaction with urea.[a]

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield of **2a** (%)[b]
1	1	50	8	44
2	1	70	5	85
3	1	90	2	93
4	0.7	90	2.8	92
5	0.5	90	4.75	88
6	**0.5**	**100**	**2**	**90**
7	0.5	110	1.7	91
8	0.3	110	3.6	89

[a] Reaction conditions: benzaldehyde (2 mmol), methyl acetoacetate (2 mmol), urea (2.4 mmol). [b] Yields refer to the isolated pure products.

A similar behavior was observed with electron-releasing groups, meta-methyl (Table 4, entry 5), para-isopropyl (Table 4, entry 6), meta- and para-hydroxy (Table 4, entries 7 and 8) and para-methoxy (Table 4, entry 9) benzaldehydes produced the expected DHPMs in high to excellent yields. Also, bulky aromatic 1-naphthaldehyde showed a remarkable performance (Table 4, entries 10).

Table 3. Effects of reaction temperature and mol% of **1b** on the Biginelli reaction with urea.[a]

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield of **3a** (%)[b]
1	0.5	100	8.5	81
2	0.7	100	8	88
3	**1**	**100**	**8**	**91**
4	1.3	100	7	94

[a] Reaction conditions: benzaldehyde (2 mmol), methyl acetoacetate (2 mmol), thiourea (2.4 mmol). [b] Yields refer to the isolated pure products.

Furthermore, under similar reaction conditions, 3-phenylpropionaldehyde, a model for aliphatic and enolizable aldehyde, gave the corresponding DHPM in high yield (Table 4, entry 11). Then, we replaced urea with thiourea and were pleased to find that this three-component reaction was also catalyzed by **1b** in excellent yields (Table 4, entries 12-14).

Table 4. Synthesis of various substituted DHPM derivatives by using **1b**[a]
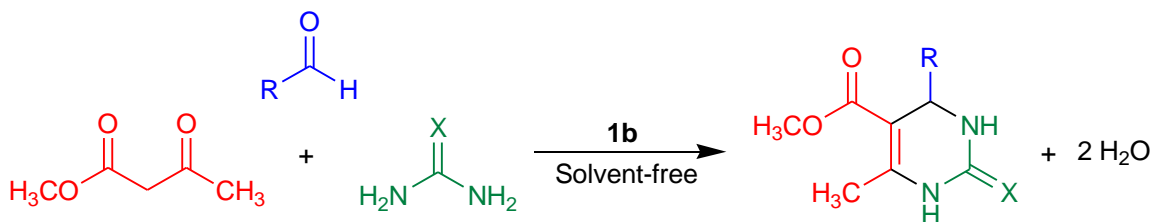
Entry	Aldehyde	X	Time (h)	Yield (%)[b]	Product[c]	TON
1	benzaldehyde	O	2	90	**2a**	180

2	3-fluorobenzaldehyde	O	1.9	92	**2b**	184
3	4-fluorobenzaldehyde	O	2	90	**2c**	180
4	3-bromobenzaldehyde	O	2.17	91	**2d**	182
5	3-methylbenzaldehyde	O	2.3	93	**2e**	186
6	4-isopropylbenzaldehyde	O	2.5	91	**2f**	182
7	3-hydroxybenzaldehyde	O	2.3	86	**2g**	172
8	4-hydroxybenzaldehyde	O	2.3	88	**2h**	176
9	4-methoxybenzaldehyde	O	2.5	89	**2i**	178
10	1-naphtaldehyde	O	1.8	93	**2j**	186
11	3-phenylpropionaldehyde	O	3.7	89	**2l**	178
12[d]	benzaldehyde	S	8	91	**3a**	91
13[d]	3-fluorobenzaldehyde	S	8	91	**3b**	91
14[d]	4-fluorobenzaldehyde	S	8.17	92	**3c**	92

a) Reaction conditions: aldehyde (2 mmol), methyl acetoacetate (2 mmol), urea or thiourea (2.4 mmol) and **1b** (0.5 mol%) at 100 °C. [b] Yields refer to the isolated pure products based on aldehydes. [c] All compounds were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy. [d] Reaction was carried out using 1 mol% of **1b**.

3.3. Reusability of *1b*

The recovery of **1b** (0.5 mol%) in the Biginelli reaction of benzaldehyde (2 mmol) with methyl acetoacetate (2 mmol) and urea (2.4 mmol) under solvent-free condition for 2 h at 100 °C was tested. The catalyst was easily recovered from the reaction mixture by external magnet, washed with water and ethanol and finally dried at 110 °C for 1 h prior to the next run. During the recycling experiment with fresh reactants, under the same reaction conditions, no considerable change in the activity of the catalyst was observed for at least 4 consecutive runs which clearly demonstrate the stability of the catalyst for these conditions in the Biginelli reaction (Fig. 6). It is very important to note that for the reactions in which water participates as a by-product, only a few solid acids show acceptable performance and stability [6,16].
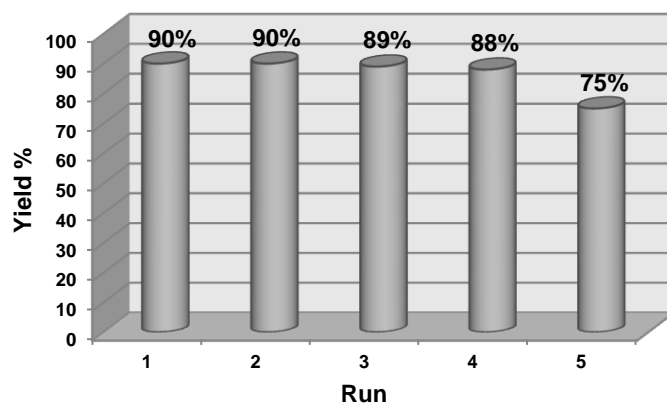
Fig. 6 Recyclability of **1b** for the Biginelli reaction of benzaldehyde, methyl acetoacetate and urea.

4. Conclusions

In summary, in this paper we designed, prepared and characterized two novel water-tolerant, sulfonic acid organic-inorganic hybrid interphase catalysts based $Fe_3O_4@SiO_2$ core-shell magnetic nanoparticle with dual functionality combining the hydrophobicity and acidity properties and studied these properties of the catalysts in the direct transformation of a library of substrates to DHPM derivatives. It has been shown that the catalyst **1b** is more reactive than **1a**. This remarkable reactivity improvement of **1b** in the Biginelli reaction is due to its hydrophobic nature of their surface area framework and shielding effect of the methyl groups bounded to this surface for sulfonic acid centers besides the moderate acid strength of these active sites. In other words, a synergistic effect between the hydrophobicity and acidity caused remarkable reactivity for **1b** catalyst.

Acknowledgements

References

[1] a) S. Shylesh, V. Schnemann and W. R. Thiel, *Angew. Chem. Int. Ed.,* 2010, **49**, 3428. b) V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara and J. M. Basset, *Chem. Rev.,* 2011, **111**, 3036. c) A. H. Lu, E. L. Salabas and F. Schuth, *Angew. Chem. Int. Ed.*, 2007, **46**, 1222.

[2] J. Mondal, T. Sen and A. Bhaumik, *Dalton Trans.*, 2012, **41**, 6173.

[3] a) Y. H. Liu, J. Deng, J. W. Gao and Z. H. Zhang, *Adv. Synth. Catal.*, 2012, **354**, 441. b) Q. Zhang, H. Su, J. Luo and Y. We, *Green Chem.*, 2012, **14**, 201. c) N. Koukabi, E. Kolvari, M. A. Zolfigol, A. Khazaei, B. S. Shaghasemi and B. Fasahati, *Adv. Synth. Catal.*, 2012, **354**, 2001. d) M. Z. Kassaee, H. Masrouri and F. Movahedi, *Appl. Catal. A: Gen.*, 2011, **395**, 28.

[4] Q. Yang, M. P. Kapoor and S. Inagaki, *J. Am. Chem. Soc.*, 2002, **124**, 9694.

[5] a) Q. Yanga, M. P. Kapoor, S. Inagaki, N. Shirokurac , J. N. Kondoc and K. Domenb, *J. Mol. Catal. A: Chem.*, 2005, **230**, 85. b) J. Liu, J. Yang, C. M. Li and Q. Yang, *J. Porous Mat.*, 2009, **16**, 273. c) M. Rat, M. H. Zahedi-Niaki, S. Kaliaguine and T. O. Do, *Micropor. Mesopor. Mater.*, 2008, **112**, 26. d) Q. Yang, J. Liu, M. P. Kapoor, S. Inagaki and C. Li, *J. Catal.*, 2004, **228**, 265. e) X. Yuan, H. I. Lee, J. W. Kim, J. E. Tie and J. M. Kim, *Chem. Lett.* 2003, **32**, 650. f) B. Sow, S. Hamoudi, M. H. Zahedi-Niaki and S. Kaliaguine, *Micropor. Mesopor. Mater.*, 2005, **79**, 129. g) J. A. Melero, L. F. Bautista, G. Morales, J. Iglesias and D. Briones, *Energ. Fuels*, 2009, **23**, 539.

[6] a) M. Navidi, B. Movassagh and S. Rayati, *Appl. Catal. A: Gen.*, 2013, **452**, 24. b) B. Karimi, H. M. Mirzaei and A. Mobaraki, *Catal. Sci. Technol.*, 2012, **2**, 828. c) B. Karimi, D. Zareyee, *Org. Lett.*, 2008, **10**, 3989; B. Karimi, D. Zareyee, *J. Mater. Chem.*, 2009, **19**, 8665. d) B. Karimi, M. Vafaeezadeh, *Chem. Commun.*, 2012, **48**, 3327. e) B. Karimi, M. Khalkhali, *J. Mol. Catal. A: Chem.*, 2007, **271**, 75. f) B. Karimi, E. Farhangi, *Chem.-Eur. J.*, 2011, **17**, 6056. g) B. Karimi, E. Farhangi, *Adv. Synth. Catal.*, 2013, **355**, 508.

[7] B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439.

[8] Z. D. Aron and L. E. Overman, *Chem. Commun.*, 2004, 253.

[9] J. E. B. Houck, A. Younai and J. T. Shaw, *Curr. Opin. Chem. Biol.*, 2010, **14**, 371.

[10] P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360.

[11] a) G. C. Rovnyak, K. S. Atwal, A. Hedeberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwart and M. F. Malley, *J. Med. Chem.*, 1992, **35**, 3254. b) V. Kettmann, J. Drimal and J. Svetlik, *Pharmazie*, 1996, **51**, 747. c) C. O. Kappe, *Molecules*, 1998, **3**, 1; B. Jauk, T. Pernat and C. O. Kappe, *Molecules*, 2000, **5**, 227. d) L. E. Overman, M. H. Rabinowitz and P. A. Renhowe, *J. Am. Chem. Soc.*, 1995, **117**, 2657. e) I. Garcia-Saez, S. De-Bonis, R. Lopez, F. Trucco, B. Rousseau, P. Thuery and F. Kozielski, *J. Biol. Chem.*, 2007, **282**, 9740.

[12] a) Z. J. Quan, Y. X. Da, Z. Zhang and X. C. Wang, *Catal. Commun.*, 2009, **10**, 1146. b) S. Gore, S. Baskaran and B. Koenig, *Green Chem.*, 2011, **13**, 1009. c) J. P. Wan and Y. J. Pan, *Chem. Commun.*, 2009, 2768. d) H. Murata, H. Ishitani and M. Iwamoto, *Org. Biomol. Chem.*, 2010, **8**, 1202. e) R. Gupta, S. Paul and R. Gupta, *J. Mol. Catal. A: Chem.*, 2007, **266**, 50. f) Z. J. Quan, Y. X. Da, Z. Zhang and X. C. Wang, *Catal. Commun.*, 2009, **10**, 1146. g) H. Murata, H. Ishitani and M. Iwamoto, *Org. Biomol. Chem.*, 2010, **8**, 1202.

[13] a) V. R. Choudhary, V. H. Tillu, V. S. Narkhede, H. B. Borate and R. D. Wakharkar, *Catal. Commun.*, 2003, **4**, 449. b) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol and P. Machado, *Chem. Rev.*, 2009, **109**, 4140. c) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725.

[14] Q. Zhang, H. Su, J. Luo and Y. Wei, *Green Chem.*, 2012, **14**, 201.

[15] a) I. K. Mbaraka, D. R. Radu, V. S. Y. Lin and B. H. Shanks, *J. Catal.*, 2003, **219**, 329. b) I. K. Mbaraka and B. H. Shanks, *J. Catal.*, 2005, **229**, 365.

[16] T. Okuhara, *Chem. Rev.*, 2002, **102**, 3641.