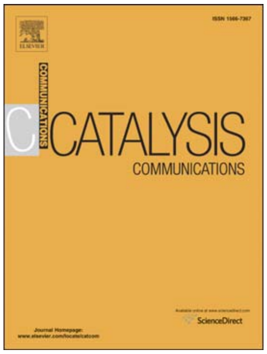

# Design, preparation and characterization of urea-functionalized $Fe_3O_4/SiO_2$ magnetic nanocatalyst and application for the one-pot multicomponent synthesis of substituted imidazole derivatives

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# Design, preparation and characterization of urea-functionalized $Fe_3O_4/SiO_2$ magnetic nanocatalyst and application for the one-pot multicomponent synthesis of substituted imidazole derivatives

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## Abstract

Novel urea-functionalized silica-based magnetite hybrid core-shell nanoparticles were prepared and characterized by Fourier transforms infrared spectroscopy (FT-IR), energy-dispersive X-ray spectroscopy (EDX), scanning electron microscopy (SEM), X-ray diffraction (XRD) and vibrating sample magnetometer (VSM) analyses. It was used as a highly efficient and recoverable heterogeneous nanocatalyst for the one-pot three-component condensation reaction between benzil or benzoin with various substituted aldehydes and ammonium acetate to afford the corresponding imidazoles under mild reaction conditions in high-to-quantitative yields. The catalyst was recycled at least five times without significant decrease in the catalytic activity.

**Keywords:** Heterogeneous nanocatalyst, $Fe_3O_4/SiO_2$, Imidazole, Benzil, Magnetite nanoparticles.

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## 1. Introduction

The use of environmentally benign, maintainable and efficiently reusable catalysts provides both economic and ecological advantages [1]. Recycling of homogeneous catalysts is thus a main issue in large-scale production of chemicals [2]. Recently, nanoparticles have appeared as efficient catalysts and supports for the immobilization of homogeneous catalysts [3-6]. High specific surface area of metallic nanoparticles provides more catalytically active sites are guaranteed.

Nanoparticle $Fe_3O_4$-supported catalysts can be simply separated from the reaction mixture by an external permanent magnet. This strategy is typically more effective than filtration or centrifugation that become annoying for such small nanoparticles [2, 7-9]. Pristine iron oxide magnetite nanoparticles (MNPs) will aggregate quickly into large bunch and therefor will lose their unique properties. It is needed to cover nanoparticles with organic component to prevent aggregation and thus retain their nano-scale properties [10]. The coating of iron oxides with silica to form core–shell structures is rather simple because of the presence of surface FeOH groups. Here, we report a versatile and useful preparation of recoverable $Fe_3O_4/SiO_2$-supported urea nanocatalyst through a covalent bond linkage.

Developing of new multicomponent reactions (MCRs) are an area of considerable interest due to the fact that the products are formed in a single step and also the variety could be achieved only by changing the reaction components [11-13]. Multi-substituted imidazoles are an important class of pharmaceutical compounds and play important roles in biochemical processes [14, 15]. Among these, the imidazole derivatives are well known to anti-inflammatory [16], anti-parasitic [17], antifungal [18], antiviral [19] and high cytotoxicity, which have indicated them as new candidates in cancer therapy [20].

Recently, the synthesis of 2,4,5-trisubstituted imidazoles has been performed by condensation of benzil and benzoin, aldehydes and ammonium acetate in the presence of $ZrCl_4$ [21], TBAB [22], DABCO [23], $Al_2O_3$ [24] and nano-crystalline magnesium oxide [25]. But, some of these synthetic methods are associated with one or more disadvantages such as using expensive reagents, long reaction times, complex work-up and purifications and generation of large amount of toxic wastes. Therefore, the development of simple, effective, high-yielding, and environmentally friendly approaches using new catalysts for the synthesis of highly substituted imidazoles is an important task for organic chemists.

In continuation of our research on the introduction of recoverable catalysts in organic synthesis [26-29], in current study, we disclose that MNPs-urea can be used as a novel magnetic nanocatalyst for the synthesis of substituted imidazoles.

To the best of our knowledge, this is the first report of design, preparation, and characterization $Fe_3O_4/SiO_2$/urea nanocomposite and its application as a heterogeneous catalyst in organic reactions.

## 2. Experimental section

### *2.1. General*

Analytical thin layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates using ethyl acetate and *n*-hexane as eluents. Melting points were determined in open capillaries using an Electrothermal 9100 instrument. Infrared (IR) spectra were acquired on a Shimadzu FT-IR-8400S spectrometer. $^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) spectra were recorded on a Bruker DRX-500

Avance spectrometers with $CDCl_3$ as solvent at ambient temperature and tetramethylsilane (TMS) as the internal standard. All chemical shifts are given relative to TMS. All yields refer to the isolated products. The X-ray powder diffraction (XRD) data were collected on an X'Pert MPD.Philips diffractometer with Cu radiation source ($\lambda$ = 1.54050˚A) at 40 Kv voltage and 40 mA current. Magnetic susceptibility measurements were carried out using a vibrating sample magnetometer (BHV-55, Riken, Japan) at room temperature. EDX spectra were recorded on Numerix DXP–X10P. SEM images were obtained on a KYKY EM-3200.

### *2.2. Preparation of the magnetic $Fe_3O_4$ nanoparticles (MNPs)*

Typically, iron (III) chloride hexahydrate (4.6 g, 0.017 mol) and iron (II) chloride tetrahydrate (2.2 g, 0.011 mol) were added to 100 mL deionized water and sonicated until the salts dissolved completely. Then, 10 mL of 25% aqueous ammonia was quickly added into the reaction mixture under $N_2$ atmosphere at room temperature followed by stirring about 30 min with mechanical stirrer. The precipitates were collected using an external magnet and washed distilled water.

### *2.3. Preparation of MNPs coated by silica (MNPs-$SiO_2$)*

Following the Stöber method with some modifications [30], the surface adapted MNPs (1 g) were dispersed in 50 mL of distilled water by the ultrasonic treatment for 20 min to form a Ferro fluid. Then, the consequence dispersion was centrifuged for 30 min and adjusted to 2.0 wt%. 2 mL of the Ferro fluid was first diluted with water (40 mL), the consequence suspension and 5 mL of $NH_3.H_2O$ were poured into 140 mL of ethanol with stirring at 40 °C. In conclusion, under continuous mechanical stirring, 1 mL of TEOS diluted in ethanol (20 mL) was drop wise added to this dispersion. The resulting dispersion was kept stirred mechanically for 14h at room temperature. The magnetic $Fe_3O_4/SiO_2$ nanoparticles were collected by magnetic separation and washed with ethanol and deionized water [31].

### 2.3. Preparation of MNPs-$SiO_2$ coated by (3-chloropropyl)-trimethoxysilane (MNPs-$SiO_2$-Cl)

Chloropropyl-modified silica-coated magnetic nanoparticles were prepared following the modified procedure of Zeng et al. [32]. In a typical route 1 mL (5 mmol) of (3-chloropropyl)-trimethoxysilane (CPTS) was dissolved in 100 mL of dried toluene, this mixture was added to 1 g of $Fe_3O_4/SiO_2$ and the solution was stirred for 18 h at 60 °C. The chloropropyl-functionalized solid ($Fe_3O_4/SiO_2$-Cl) was washed with toluene, separated by a magnet, and dried in vacuum.

### 2.4. Preparation of urea-functionalized magnetic $Fe_3O_4$ nanoparticles (MNPs-$SiO_2$-urea)

The prepared $Fe_3O_4/SiO_2$-Cl (1 g) and KI (1.66 g, 10 mmol) were added to a solution of urea (0.6 g, 10 mmol) and $K_2CO_3$ (1.38 g, 10 mmol) in acetonitrile (50 mL) in a round-bottom flask and the mixture was stirred under reflux condition for 8 h. The obtained solid was then magnetically collected from the solution and washed abundantly with water/ethanol followed by drying at 80 °C for 12 h.

### 2.5. General procedure for the preparation of 2,4,5-trisubstituted imidazole derivatives

MNPs-$SiO_2$-urea (0.0088 g) was added to a mixture of benzil or benzoin (1.0 mmol), various substituted aldehydes (1.0 mmol) and $NH_4OAc$ (4.0 mmol) in refluxing ethanol and stirred for appropriate times. The progress was monitored by TLC. After completion of the reaction the catalyst was separated by an external magnet and the simple product was isolated by filtration of the reaction mixture. Pure products were obtained via re-crystallization by EtOH.

## 3. Results and discussions

### *3.1. Characterization of MNPs-SiO$_2$-urea*

The process of the preparation urea-functionalized $Fe_3O_{4/}SiO_2$ nanoparticles is shown in Scheme 1.

**< Scheme 1>**

MNPs-urea was characterized using a variety of different techniques. The XRD pattern of MNPs-urea is shown in Fig. 1. The position and relative intensities of all peaks are in a good agreement with standard XRD pattern of $Fe_3O_4$ (JCPDS card No. 19-0629). The XRD patterns of the particles show six characteristic peaks, revealing a cubic iron oxide phrase ($2\theta$= 18.01°, 30.26°, 37.31°, 43.29°, 55.52°, 57.32°). It is implied that the resultant nanoparticles are pure $Fe_3O_4$ with a spinel structure and that the grafting process did not induce any phase change of $Fe_3O_4$.

**< Fig. 1>**

As illustrated in Fig. 2, the particle size was studied by scanning electron microscopy (SEM) and the identification of $Fe_3O_4/SiO_2$/urea was based on the analysis of SEM images. It was confirmed that the catalyst was made up of nanometer-sized particles less than 70 nm. Fig. 3 shows that the $Fe_3O_4/SiO_2$/urea nanoparticles have a core–shell structure and spherical morphology.

**<Fig. 2>**

To identify the elemental composition of MNPs-$SiO_2$/urea, an energy-dispersive X-ray spectroscopy (EDX) was obtained. As can be seen in Fig. 3, EDX pattern obviously approves the well-dispersion of $Fe_3O_4$ nanoparticles. Chemical characterization of the typical sample showed that it was composed of iron, silicon, oxygen and carbon elements.

**<Fig. 3>**

Fourier transform infrared (FT-IR) spectra of MNPs, urea and MNPs-$SiO_2$/urea were prepared (Please see the Supplementary data file). The peaks at 635 and 577 cm$^{-1}$ are assigned to the Fe$^{3+}$ O Fe$^{3+}$ and Fe$^{2+}$ O Fe$^{2+}$ symmetrical stretching vibrations, respectively. The covalent bond between silane and magnetite surface is underlined by the appearance of the band at 1097 cm$^{-1}$characteristic for Si–O groups. Absorption bands at 960 and 810 cm$^{-1}$ is associated to vibrating bands for Si–O–Si groups. These results indicate that $SiO_2$ layer is formed on the surfaces of $Fe_3O_4$. The presence of anchored propyl groups were confirmed by stretching vibrations appeared at about 2935, 2986 cm$^{-1}$ (C–H stretching vibrations) in the FT-IR spectrum. The signals appeared at 1530-1560 cm$^{-1}$ region can be assigned to the N-H bending and 1645 cm$^{-1}$ is attributed to C=O stretching of urea.

Magnetic measurements were registered by using vibrating sample magnetometer (VSM) at 300 K. The magnetization curves measured for $Fe_3O_4$ nanoparticles, $Fe_3O_4/SiO_2$ and $Fe_3O_4/SiO_2$/urea are compared in Fig. 4. As it was seen in Fig. 4 the values of the saturation magnetization were 50.5, 38.2 and 24.7 emu/g for $Fe_3O_4$ nanoparticles, $Fe_3O_4/SiO_2$ core-shell and $Fe_3O_4/SiO_2$/urea respectively in +8000 Oe. The reduction of the saturation magnetization proposes the formation of $Fe_3O_4/SiO_2$/urea. Even with this decreasing in the saturation magnetization, the catalyst still can be expertly separated simply from the solution by applying of an external magnetic force.

**<Fig. 4>**

### *3.2. Application of MNPs-urea for the synthesis of imidazole derivatives*

MNPs-urea was tested as basic magnetically separable heterogeneous nanocatalyst for the synthesis of the imidazole **(5a-t)** from reaction of benzil **1** or benzoin **2**, wide range of aromatic aldehyde **3** and ammonium acetate **4** under reflux ethanol at 80 °C (Scheme 2). After completion of the reaction, the catalyst was easily separated by a magnet and the solid product was purified by recrystallization from ethanol.

**<Scheme 2>**

To find the optimal reaction conditions, the one-pot three-component condensation reaction of benzoin (1 mmol), 4-chlorobenzaldehyde (1 mmol) and ammonium acetate (4 mmol) as an ammonia source was carried out under various reaction conditions. In the absence of any catalyst, the desired product **5b** was not obtained after 420 min in various solvents and conditions (Table 1, entries 1-7). Interestingly, the yield of the desired product **5b** was improved when amounts of catalyst were added to the reaction mixture (entries 8-14). The next optimization experiments were carried out for obtained the amount of catalyst required for this condensation. It was found that using 0.0088 g $Fe_3O_4/SiO_2$/urea in EtOH under reflux conditions is sufficient to push the reaction forward (entries 15-18). To illustrate the need of nano-$Fe_3O_4/SiO_2$/urea for these reactions, a model reaction was conducted with $Fe_3O_4$, urea and $Fe_3O_4/SiO_2$ (entries 19-22). These results suggest that $Fe_3O_4/SiO_2$/urea is more suitable for this reaction.

**<Table 1>**

In order to generalize the optimum conditions, different derivatives of imidazoles (**5a-t**) were prepared from the one-pot reaction mixture of aromatic aldehyde (**3a-t**), benzil **1** or benzoin **2** and ammonium acetate **4** under refluxing condition. The results are summarized in

Table 1S (Please see the Supplementary data file). It is obvious from Table 1S that when benzoin **2** is used instead of benzil **1**, the reaction time was increased. Aromatic and heteroaromatic aldehydes carrying both different electron-donating and electron-withdrawing groups were subjected to the condensation and in all cases the desired product was synthesized in high yields.

Also, the reusability of $Fe_3O_4/SiO_2$/urea for the MCR to afford **5b** was also investigated for at least five runs. The catalyst was then washed, air-dried and used directly without a considerable loss of catalytic activity. The results are summarized in Fig. 5.

**<Fig. 5>**

## 4. Conclusion

In summary, we have introduced a novel urea-functionalized heterogeneous magnetic nanocatalyst through a facile and simple procedure starting from commercially available raw materials. It was found that the magnetic nanocatalyst can be utilized as an efficient heterogeneous catalyst for the one-pot three-component condensation reaction of benzil or benzoin with various substituted aldehydes and ammonium acetate in refluxing ethanol in short reaction times and excellent yields under mild reaction conditions. The present reaction can be classified as a new protocol for the preparation of synthetically, biologically and pharmaceutically relevant imidazole derivatives. This procedure includes further important aspects like the easy workup procedure, reusability of the catalyst, high atom economy, excellent yields, and environmentally benign reaction conditions.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at www.elsevier.com.

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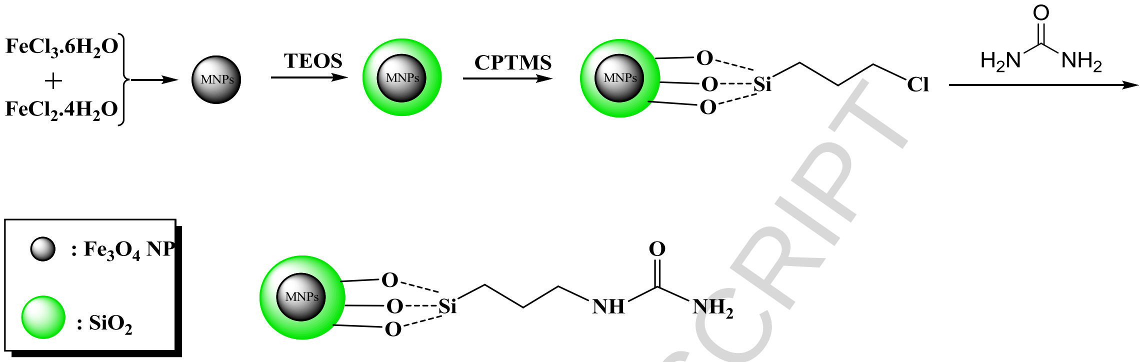


**Scheme 1.** Preparation of $Fe_3O_4/SiO_2$-urea nanoparticles.

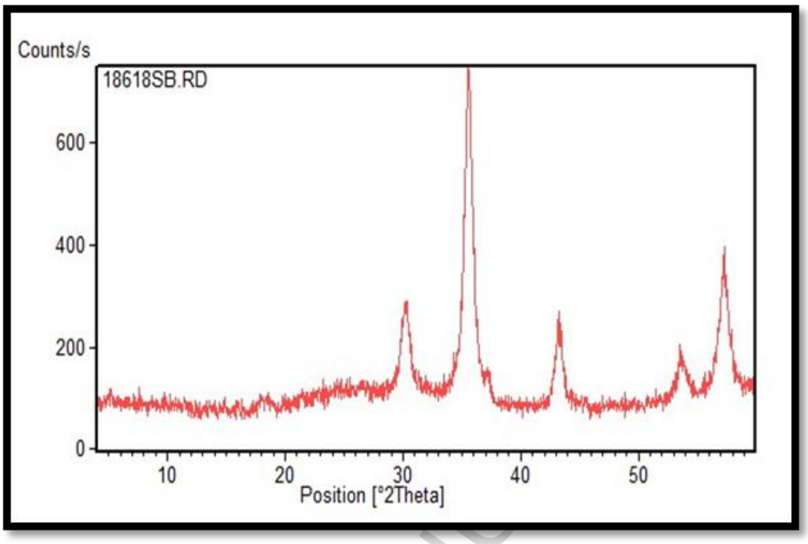


**Fig. 1**. XRD pattern the $Fe_3O_4/SiO_2$/urea.

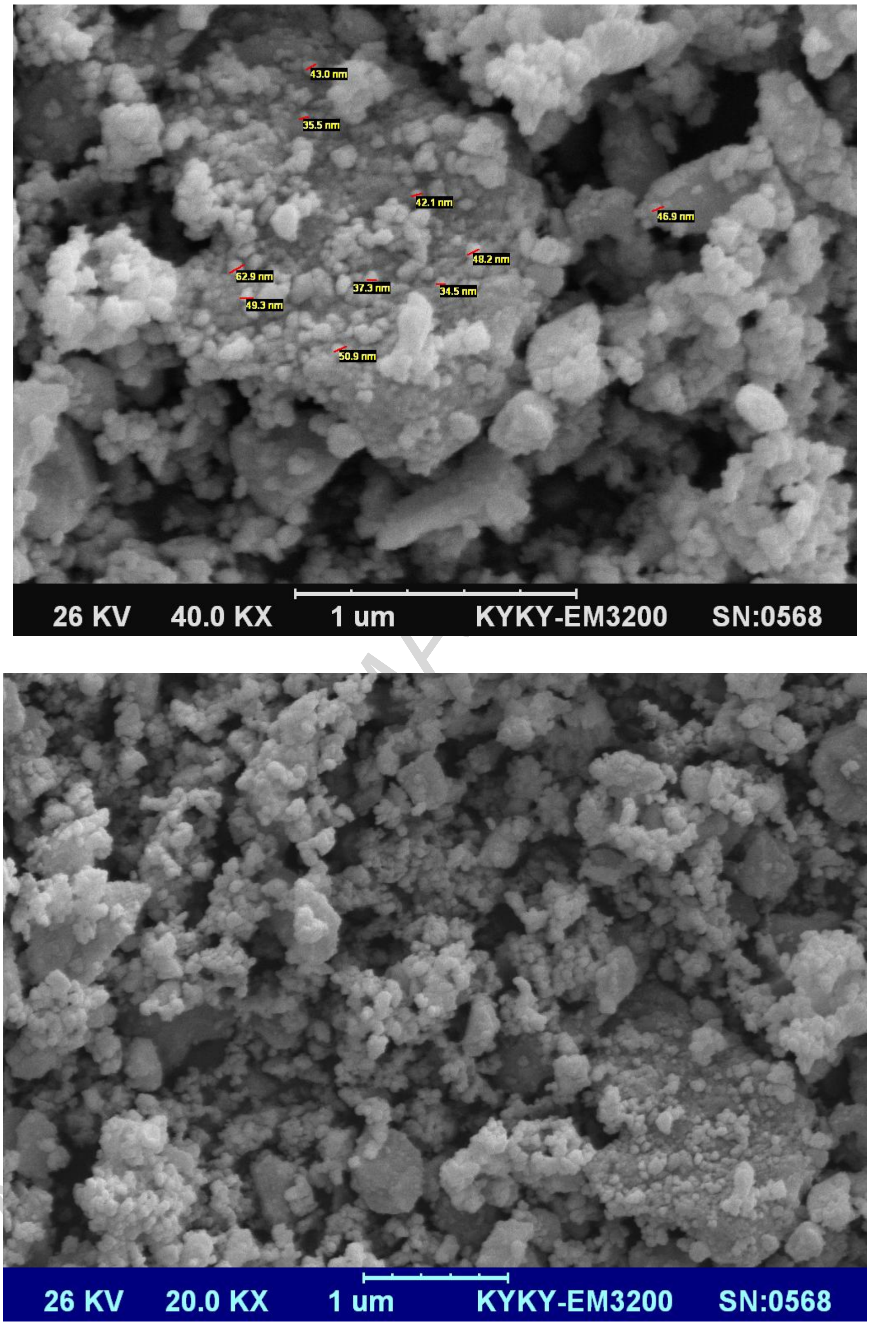


**Fig. 2**. SEM images of the $Fe_3O_4/SiO_2$/urea.

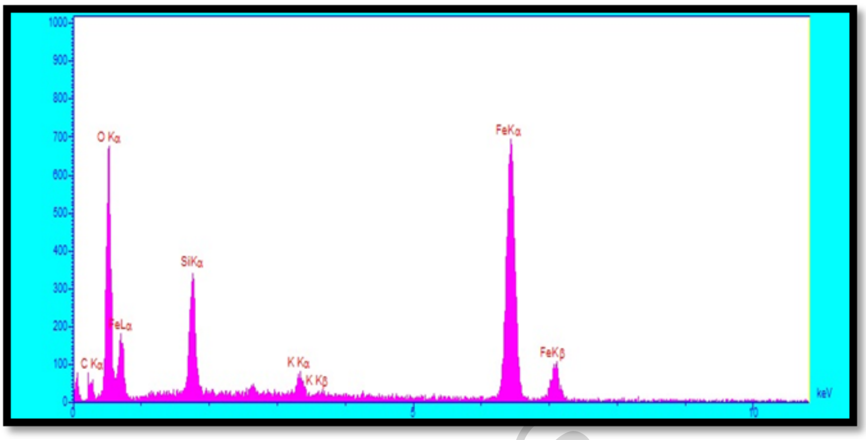


**Fig. 3**. EDX pattern of the $Fe_3O_4/SiO_2$/urea.

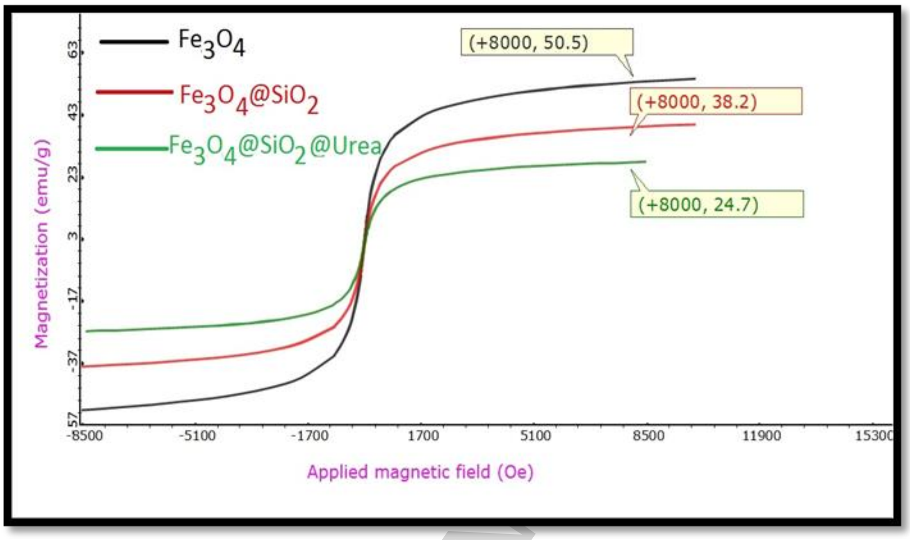
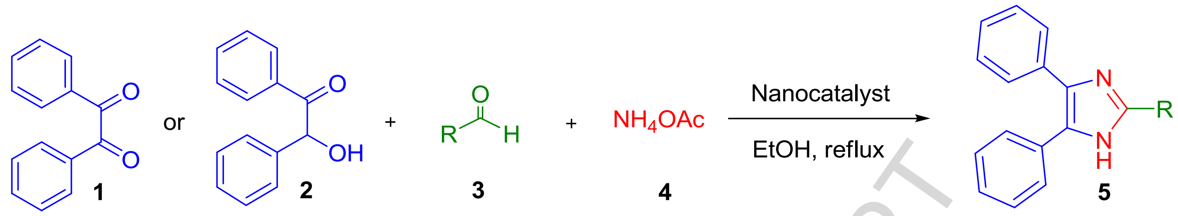
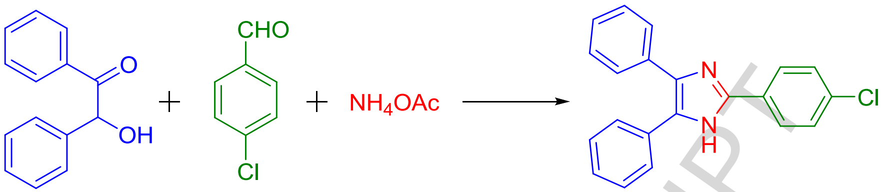


**Fig. 4**. VSM curve of the a) $Fe_3O_4$, b) $Fe_3O_4/SiO_2$, c) $Fe_3O_4/SiO_2$/urea.



**Scheme 2**. Three-component reaction of benzil or benzoin with aromatic aldehydes and ammonium acetate by $Fe_3O_4/SiO_2$/urea under refluxing conditions.

**Table 1.** Optimization of the three-component reaction of benzoin (**1**), *p*-chlorobenzaldehyde (**3b**) and ammonium acetate (**4**) under various conditions[a]



**2** **3b** **4** **5b**

| Entry | Catalyst | Catalyst loading (g) | Condition | Temperature (°C) | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | - | - | Solvent-free | r.t. | 420 | - |
| 2 | - | - | $H_2O$ | r.t. | 420 | - |
| 3 | - | - | EtOH | r.t. | 420 | Trace |
| 4 | - | - | EtOH | 50 | 420 | Trace |
| 5 | - | - | EtOH | Reflux | 420 | 20 |
| 6 | - | - | $H_2O$ | Reflux | 420 | Trace |
| 7 | - | - | Solvent-free | 50 | 420 | - |
| 8 | $Fe_3O_4/SiO_2$/urea | 0.0500 | EtOH | r.t. | 420 | 32 |
| 9 | $Fe_3O_4/SiO_2$/urea | 0.0500 | EtOH | 50 | 240 | 54 |
| 10 | $Fe_3O_4/SiO_2$/urea | 0.0500 | Solvent-free | 50 | 360 | 48 |
| 11 | $Fe_3O_4/SiO_2$/urea | 0.0500 | EtOH | Reflux | 120 | 80 |
| 12 | $Fe_3O_4/SiO_2$/urea | 0.0500 | $H_2O$ | Reflux | 120 | 28 |
| 13 | $Fe_3O_4/SiO_2$/urea | 0.0500 | $CH_3CN$ | Reflux | 120 | 42 |
| 14 | $Fe_3O_4/SiO_2$/urea | 0.0500 | THF | Reflux | 120 | 29 |
| 15 | $Fe_3O_4/SiO_2$/urea | 0.0017 | EtOH | Reflux | 150 | 70 |
| 16 | $Fe_3O_4/SiO_2$/urea | 0.0035 | EtOH | Reflux | 70 | 87 |
| 17 | $Fe_3O_4/SiO_2$/urea | 0.0088 | EtOH | Reflux | 50 | 95 |
| 18 | $Fe_3O_4/SiO_2$/urea | 0.0176 | EtOH | Reflux | 50 | 86 |
| 19 | $Fe_3O_4$ | 0.0500 | EtOH | Reflux | 120 | 55 |
| 20 | urea | 0.0500 | EtOH | Reflux | 120 | 36 |
| 21 | $Fe_3O_4/SiO_2$ | 0.0500 | EtOH | Reflux | 120 | 72 |
| 22 | $Fe_3O_4/SiO_2$ | 0.0088 | EtOH | Reflux | 50 | 46 |

[a] Reaction conditions: *p*-chlorobenzaldehyde (1 mmol), benzoin (1 mmol), ammonium acetate (4 mmol), solvent (2 mL) and required amount of the catalysts. [b] The yields refer to the isolated product **5b**.

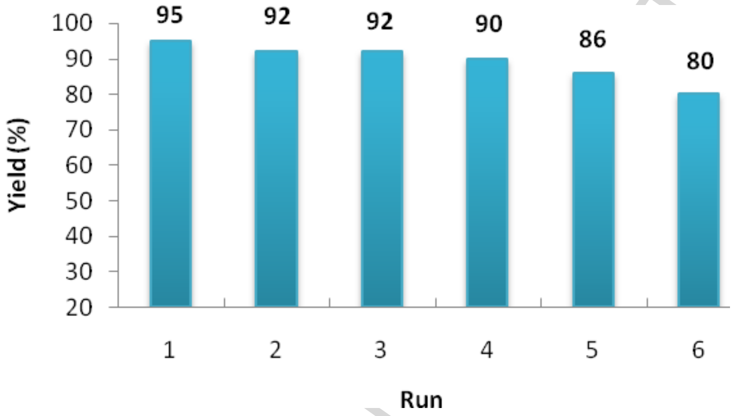


**Fig. 5.** Reusability of $Fe_3O_4/SiO_2$/urea for the synthesis of **5b**.

## Graphical Abstract

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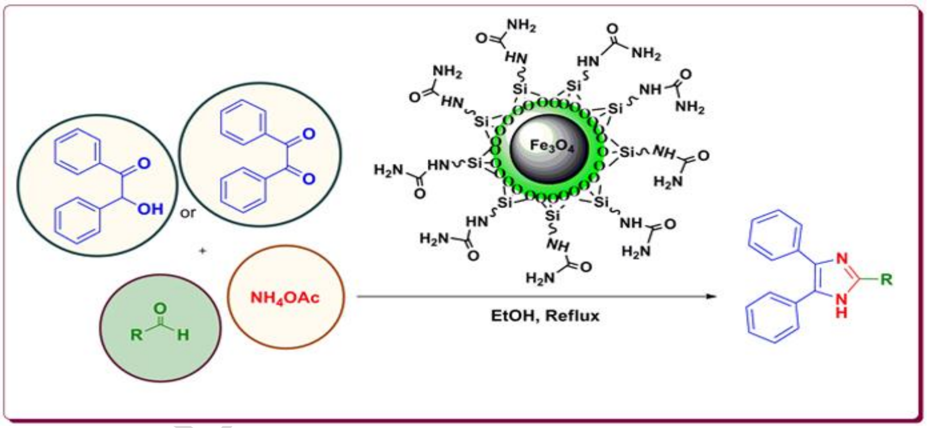
# Design, preparation and characterization of urea-functionalized $Fe_3O_4/SiO_2$ magnetic nanocatalyst and application for the one-pot multicomponent synthesis of substituted imidazole derivatives

Ali Maleki*, Zahra Alirezvani, Saeid Maleki



**Highlights**

- A new urea-functionalized silica-based magnetite hybrid core-shell structure was prepared.
- It showed excellent catalytic activity for the synthesis of substituted imidazoles.
- The heterogeneous nanocatalyst was simply separated from the reaction mixture.
- The catalyst was recycled several times without significant loss in catalytic activity.