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N-(2-pyridylmethyl)-*L*-histidine functionalized Fe_3O_4 magnetic nanoparticles as an efficient catalyst for synthesis of *β*-amino ketones

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Histidine.

Abstract. *N*-(2-pyridylmethyl)-*L*-histidine functionalized Fe_3O_4 magnetic nanoparticles (PMHis@Fe_3O_4 MNPs) efficiently catalyzed the three-component Mannich-type reaction of ketones, aromatic aldehydes, and anilines to synthesize *β*-amino ketones in good to high yields. Mannich adducts were obtained in moderate to high diastereoselectivity, favoring anti isomers. The imidazole moiety of PMHis residue on a catalyst plays an important role in the diastereoselectivity. PMHis@Fe_3O_4 MNPs were prepared by the simple coprecipitation from an aqueous solution of Fe^{2+} and Fe^{3+} ions using NH_4OH in the presence of *L*-histidine, followed by reductive amination with 2-pyridine carbaldehyde in the presence of $NaBH_4$. Obtained PMHis@Fe_3O_4 MNPs were characterized by FT-IR, XRD, VSM, BET, TGA, SEM, EDX, and TEM analyses.

1. Introduction

β-amino ketones and their derivatives are broadly found to be key structural units in many natural products and drugs [1–6] and are attractive targets for chemical synthesis because of their widespread utility as biologically active molecules such as antibacterial [7], anti-inflammatory [8], antifungal [9], antiviral [10], analgesic [11], and anticancer activities [12,13]. Consequently, the development of new synthetic approaches to *β*-amino ketones is of interest from synthetic and medicinal chemists' points of view. However, different reactions were reported to construct *β*-amino ketone derivatives including conjugate addition [14–16], oxidative ring-opening reaction of isoxazolidines [17], hydrogenation of enamino ketones obtained from *β*-diketones [18,19], electrophilic amination of cyclopropanols [20], and Mannich reaction as a classical method for preparing *β*-amino ketones and aldehydes [21–29].

Due to their easy preparation, functionalization, and separation using an external magnetic field and good dispersion in water and recoverability, the role of functionalized Fe_3O_4 magnetic nanoparticles in catalysis has received much attention [30–34]. Moreover, these nanoparticles have a wide range of applications in magnetic resonance imaging such as Magnetic Resonance Imaging (MRI) contrast agent [35], lithium-ion batteries [36], drug delivery [37], and dye adsorption [38]. Therefore, the development of new and simple methods for the preparation and functionalization of iron oxide magnetic nanoparticles is of interest. Re-

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cently, we have reported on pyridylmethylaminoacetic acid functionalized Fe_3O_4 magnetic nanoparticles as an efficient catalyst for the three-component synthesis of 2-aminochromene and 2-aminopyran derivatives [32]. Moreover, some immobilized complexes of W and V on Fe_3O_4 magnetic nanoparticles considered as catalysts for the oxidation of alcohols and sulfides were reported [30,31].

In this paper, *N*-(2-pyridylmethyl)-*L*-histidine functionalized Fe_3O_4 magnetic nanoparticles (PMHis @Fe_3O_4 MNPs) were prepared and used in a diastereoselective three-component Mannich-type reaction among anilines, aromatic aldehydes, and enolizable ketones.

2. Experimental

2.1. Material and methods

$FeCl_3{\cdot}6H_2O$, $FeCl_2{\cdot}4H_2O$, *L*-histidine, pyridine-2-carbaldehyde, cyclohexanone, benzaldehydes, anilines, acetophenone, and all other chemicals were purchased from Merck or Fluka and used without any further purification. FT-IR spectra were collected using a Win-Bomem, version 3.04 Galatic Industries Corporation, spectrometer. X-Ray Diffraction (XRD) patterns were measured using a Bruker D8 Advance with CuK (α) radiation ($\lambda = 0.15406$ nm) in the range of $4° < 2\theta < 70°$. NETZSDT TG 209 F1 Iris instrument was used for TGA analysis under N_2 flow. Scanning Electron Microscope (SEM) images along with Energy Dispersive X-ray (EDX) analysis and Transmission Electron Microscopy (TEM) were obtained using VWGA3 TESCAN (20.0 KV) and Philips CM120 microscopes, respectively. The magnetic properties were measured at room temperature with respect to a vibrating sample magnetometer from Meghnatis Daghigh Kavir Co. Kashan Kavir (VSM). Brunauer-Emmett-Teller (BET) analysis was carried out using a BELSORP Mini II analyzer.

2.2. Synthesis of PMHis@Fe_3O_4 MNPs

L-Histidine (3 mmol, 0.465 g) was added to a mixture of $FeCl_3{\cdot}6H_2O$ (2.4 mmol, 0.65 g) and $FeCl_2{\cdot}4H_2O$ (1.2 mmol, 0.24 g) in 20 mL of deionized water; then, pH was adjusted to 11 using NH_4OH solution and refluxed for 6 h under N_2 atmosphere. Obtained precipitate was separated using an external magnetic field, washed with deionized water, and dried in the oven at 60°C for 3 h; of note, it is denoted by His@Fe_3O_4 MNPs. Reductive amination was conducted by the dispersion of 0.1 g of His@Fe_3O_4 MNPs in EtOH (10 mL) using ultrasonic treatment for 30 min, followed by the addition of pyridine-2-carbaldehyde (4.5 mmol, 0.482 g) and, then, stirring at room temperature for 6 h. After cooling the mixture to $0 - 4$°C, a solution of $NaBH_4$ (4.5 mmol, 0.17 g) in 5 mL water was added and stirred for 3 h at the same temperature. The obtained PMHis@Fe_3O_4 MNPs were separated using an external magnetic field and thoroughly washed with deionized water and dried in the oven at 60°C for 24 h.

2.3. PMHis@Fe_3O_4 MNPs catalyzed Mannich reaction

To a mixture of ketone (1.5 mmol), aromatic aldehyde (0.5 mmol), and aniline (0.5 mmol) in water (1 mL), 20 mg of PMHis@Fe_3O_4 MNPs was added and stirred at room temperature for 18-24 h. After completing the reaction, monitored by TLC (eluent: petroleum ether/EtOAc: 7/3), 3 mL CH_2Cl_2 was added and the catalyst was separated by an external magnetic field. Then, the organic phase was separated and evaporated under vacuum. The obtained solid was washed with cold *n*-hexane to remove any remaining ketones. Any further purification was carried out by column chromatography on silica gel using petroleum ether/ethyl acetate.

Selected ^{1}H NMR spectral data of synthesized Mannich adducts are as follows:

2-(((4-Chlorophenyl)amino)(3-nitrophenyl)methyl)cyclohexanone:
(500 MHz, $CDCl_3$) δ = 8.20–8.55 (m, 1H, CH_{Ar}), 8.03–8.04 (m, 1H, CH_{Ar}), 7.72–7.75 (m, 1H, CH_{Ar}), 7.43–7.46 (t, J = 8 Hz, 1H, CH_{Ar}), 6.97 (d, J = 8.5 Hz, 2H, CH_{Ar}), 6.44 (d, J = 8.5 Hz, 2H, CH_{Ar}), 4.52–5.12 (br., 1H, NH), 4.84 (d, J = 4.5 Hz, 0.38H, CH–N, *syn*), 4.69 (d, J = 5.5 Hz, 0.62H, CH–N, *anti*), 2.82–2.90 (m, 1H, CH–CO), 2.30–2.39 (m, 2H, CH_2–CO), 1.59–2.03 (m, 6H, 3×CH_2) ppm.

2-((4-Chlorophenyl)((4-chlorophenyl)amino)methyl)cyclohexanone:
(500 MHz, $CDCl_3$) δ = 7.34 (d, J = 8.5 Hz, 2H, CH_{Ar}), 7.08 (d, J = 8.5 Hz, 2H, CH_{Ar}), 6.60 (d, J = 9.0 Hz, 2H, CH_{Ar}), 6.44 (d, J = 9.0 Hz, 2H, CH_{Ar}), 4.32–4.71 (br., 1H, NH), 4.71 (d, J = 4.5 Hz, 0.31H, CH–N, *syn*), 4.56 (d, J = 6.5 Hz, 0.69H, CH–N, *anti*), 2.88–2.91 (m, 1H, CH–CO), 2.38–2.45 (m, 2H, CH_2–CO), 1.54–2.03 (m, 6H, 3×CH_2) ppm.

2-((Phenylamino)(pyridin-2-yl)methyl)cyclohexanone:
(500 MHz, $CDCl_3$) δ = 8.53–8.54 (m, 1H, CH_{Py}), 4.57–7.61 (m, 1H, CH_{Py}), 7.49 (m, 1H, CH_{Py}), 7.10–7.15 (m, 3H, $CH_{Ar\&Py}$), 6.65–6.69 (m, 1H, CH_{Ar}), 6.61–6.63 (m, 2H, CH_{Ar}), 4.76–5.62 (br., 1H, NH), 4.98 (d, J = 6.0 Hz, 0.13H, CH–N, *syn*), 4.80 (d, J = 4.0 Hz, 0.87H, CH–N, *anti*), 3.33–3.37 (m, 1H, CH–CO), 2.33–2.36 (m, 2H, CH_2–CO), 1.59–2.13 (m, 6H, 3×CH_2) ppm.

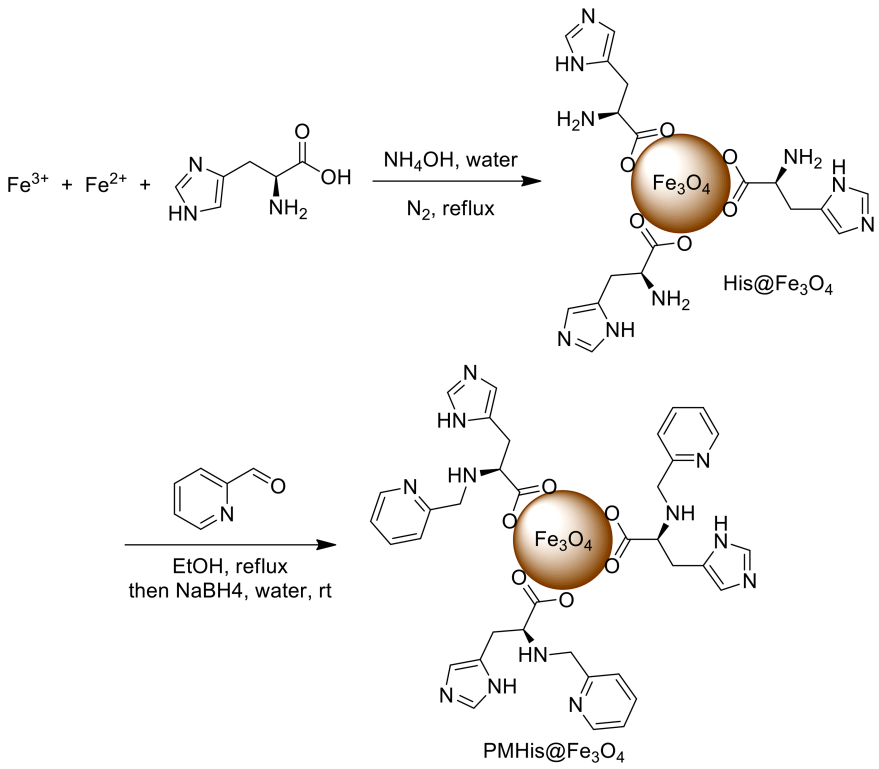
3. Results and discussion

3.1. Synthesis of PMHis@Fe_3O_4 MNPs

PMHis@Fe_3O_4 MNPs were prepared by the coprecipitation of Fe^{3+} and Fe^{2+} ions from alkaline solution in the presence of *L*-histidine that acted as size-controlled MNPs by coordinating Fe ions with carboxylate groups of *L*-histidines, affording *N*-(2-pyridylmethyl)-*L*-histidine anchored Fe_3O_4 MNPs (His@Fe_3O_4 MNPs). Subsequently, NH_2 moieties of anchored *L*-histidine were converted into secondary amine via reductive amination by being subjected to 2-pyridine carbaldehyde, followed by the reduction of in situ generated imine using $NaBH_4$, leading to 2-pyridylmethyl moieties on the nitrogen atom (Scheme 1).

3.2. Characterization of PMHis@Fe_3O_4 MNPs

FT-IR spectra of His@Fe_3O_4 MNPs show broad peaks at around 3420 and 3247 cm^{-1}, accounting for the stretching vibrations of N–H and O–H. Peaks at 2929 and 2856 cm^{-1} correspond to the asymmetric and symmetric vibrations of CH_2 moieties, respectively. The C=O stretching mod of carboxylate anions appears at 1637 cm^{-1}. Peaks at 1539 and 1101 cm^{-1} are associated with the scissoring vibration of primary NH_2 and stretching mods of C–N bonds, respectively. Vibrations of Fe–O appear at 586 and 879 cm^{-1}. In the FT-IR spectra of PMHis@Fe_3O_4 MNPs, due to the conversion of primary amine to the secondary amine group, the peak of the scissoring vibration of NH_2 at 1539 cm^{-1} disappears. The strong peak at 1442 cm^{-1} is related to the pyridine ring C=C vibrations. C–N bands appear at 1135 and 1012 cm^{-1}. The peak at 852 cm^{-1} corresponds to the wagging vibration of N–H bonds. The characteristic peak of Fe-O is also observed at 582 cm^{-1} (Figure 1(a)). The XRD pattern of the synthesized PMHis@Fe_3O_4 MNPs is shown in Figure 1(b), in which the observed peaks are in good agreement with the face-centered cubic Fe_3O_4, as previously reported [39]. Magnetic properties of His@Fe_3O_4 and PMHis@Fe_3O_4 MNPs were studied by VSM analysis, from which the superparamagnetic properties of the synthesized His@Fe_3O_4 and PMHis@Fe_3O_4 MNPs at room temperature with the saturation magnetization (Ms) values of 52 and 43 emu/g and no hysteresis loop ($Hc = 0$) were concluded, respectively (Figure 1(c). The lower saturation magnetization value of PMHis@Fe_3O_4 MNPs rather than His@Fe_3O_4 MNPs due to the shielding effect of organic residues indicated the successful modification and functionalization of His@Fe_3O_4 MNPs with 2-pyridine carbaldehyde. With this behavior, a simple and easy separation of PMHis@Fe_3O_4 MNPs catalyst from the reaction mixture using an external magnetite field can be guaranteed. In order to study the specific surface areas of the synthesized PMHis@Fe_3O_4 MNPs,



Scheme 1. Preparation of PMHis@Fe_3O_4 MNPs.

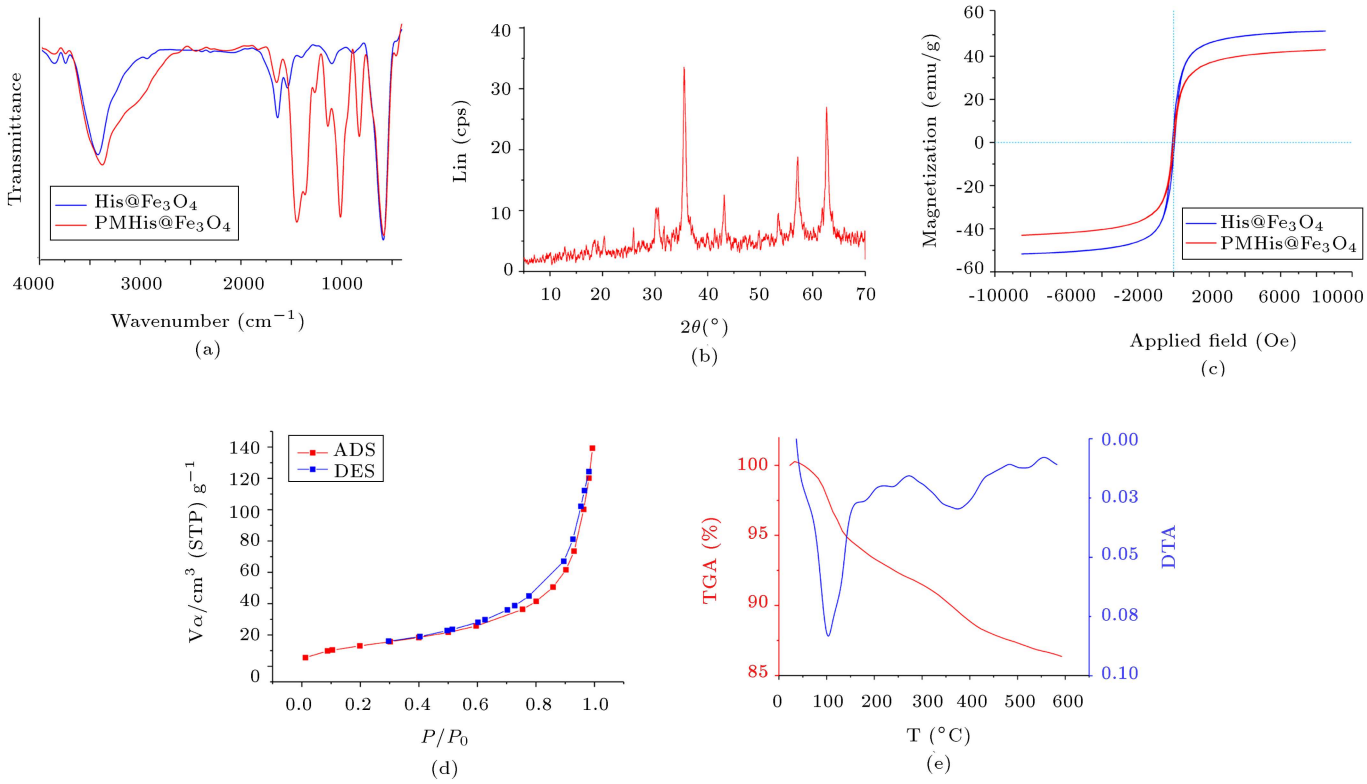


Figure 1. Ft-IR spectra (a), X-Ray Diffraction (XRD) pattern (b), VSM analysis (c), N_2 adsorption-desorption isotherm (d), and TGA (e) of PMHis@Fe_3O_4 MNPs.

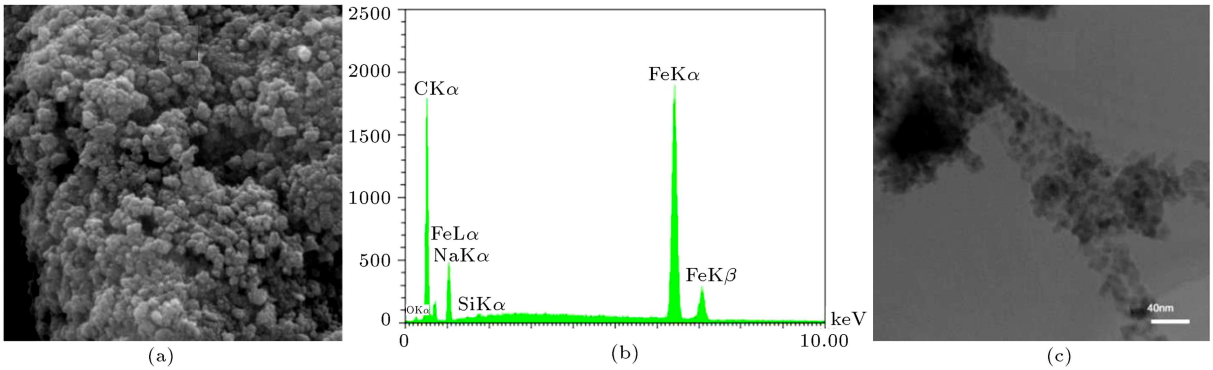


Figure 2. SEM image (a), EDX analysis (b), and TEM images (c) of PMH@Fe_3O_4 MNPs.

BET analysis was conducted by measuring the N_2 adsorption-desorption isotherm (Figure 1(d)). BET surface area, total pore volume, and average pore diameter were determined to be 50.964 m^2/g, 0.2072 cm^3/g, and 16.264 nm, respectively. The thermal behavior and stability of the synthesized PMHis@Fe_3O_4 MNPs were investigated by Thermo Gravimetric (TG) analysis. By heating a sample of PMHis@Fe_3O_4 MNPs under N_2 atmosphere at a rate of 10°C/min, two-step weight losses were shown: 4.9% at 95–130°C relating to the removal of adsorbed water molecules and 3.93% at around 262–432°C due to the decomposition of organic residue (Figure 1(e)).

The surface morphology of PMHis@Fe_3O_4 MNPs was studied by SEM images, in which the aggregated spherical Fe_3O_4 MNPs are shown (Figure 2(a)). In order to investigate the chemical composition of the prepared PMHis@Fe_3O_4 MNPs, EDX analysis was conducted, revealing that the sample was composed of Fe, O, and C elements that indicate the formation of iron oxide nanoparticles capped with organic molecules on the surface of nanoparticles. Because of the high intensities of O and Fe, the intensity of nitrogen atoms peak (ca. 0.392 keV) is too low to detect (Figure 2(b)). TEM images were used to study the shape and size of PMHis@Fe_3O_4 MNPs, indicating the formation of spherical nanoparticles with a diameter of 5–8 nm (Figure 2(c)).

3.3. Catalytic activity of PMHis@Fe_3O_4 MNPs

Then, the prepared PMHis@Fe_3O_4 MNPs (20 mg) were investigated as a catalyst in the Mannich reaction among cyclohexanone, aniline, and benzaldehyde. When the reaction was conducted under solvent-free conditions, a complex mixture including Mannich and aldol adducts was obtained (identified by NMR). Conducting reaction in water as a green solvent afforded the corresponding Mannich adduct in 63% yield at an 84/16 ratio of *anti/syn* isomers, along with the formation of aldol adduct as a minor byproduct. Aldol product is a major product when the reaction was conducted in EtOH. Water acts both as a green environment and brings the substrates closer to each other on the catalyst surface because of the hydrophobicity of the substrates. Increasing the amount of catalyst (50 mg) not only did not improve the yield of expected Mannich adduct, but also gave rise to an increase in the aldol adduct yield. However, during the lower reaction (less than 6 h), the aldol adduct was not detected, and Mannich product was also obtained in moderate yield. No Mannich adduct was obtained when the reaction was conducted using His@Fe_3O_4 MNPs (20 mg) as a catalyst.

Through the optimum conditions at hand, the Mannich-type reaction of cyclohexanone and anilines and aromatic aldehydes was conducted at room temperature for 18 h (Scheme 2). Different substituted anilines and aromatic aldehydes were tolerated under reaction conditions, leading to the corresponding Mannich products in 58–81% yields at an anti/syn ratio of 55/45–87/13 (Table 1). Characterized by the high reactivity of electron withdrawing substituted benzaldehydes, the stereoselectivity decreased due to the *anti/syn* ratio of 55/45 in the case of 4-nitrobenzaldehyde (Entries 4 and 11). However, 3-nitrobenzaldehyde produced higher stereoselectivity (62/38) (Entry 12). Heteroaromatic aldehydes including pyridine-2-carbaldehyde and furfural were also compatible with the reaction affording the corresponding Mannich adducts in 65–78% yields, with up to *anti/syn* ratio of 87/13 (Entries 6 and 7).

An ORTEP view of 2-[(2-chlorophenyl)(phenyl -amino)methyl]-cyclohexanone (Entry 3), obtained by the analysis of X-ray single-crystal structures, with atomic labeling is shown in Figure 3. The *anti*-stereochemistry shows the R, S relative configuration of the two stereocenters at 73.21 (15)°and −157.66 (12)° torsion angles of C6–C1–C7–N1 and C6–C1–C7–C8, respectively. The proposed reaction mechanism involves generating enamine via the reaction of cyclohexanone and secondary amine moiety of PMHis anchored on Fe_3O_4 MNPs, followed by the addition of enamine to imine, which is in situ formed by the reaction of benzaldehyde and aniline. The obtained stereoselectivity could be rationalized by the addition of enamine to the imine moiety via transition states **T.S.1** or **T.S.2**, in which two isomeric forms of imidazole played a critical role by forming H-bond with nitrogen of imine. When H-bond occurred by N-H adjacent to the substitution of imidazole ring (1-*H*-imidazo*L*-5-yl), a favorable transition state (**T.S.1**) was formed, in which *N*-aryl moiety was placed away

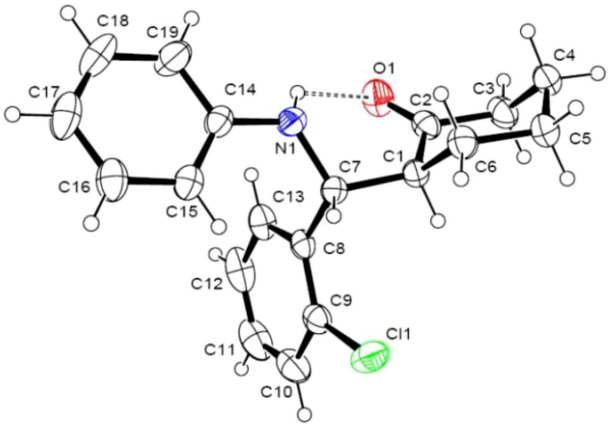
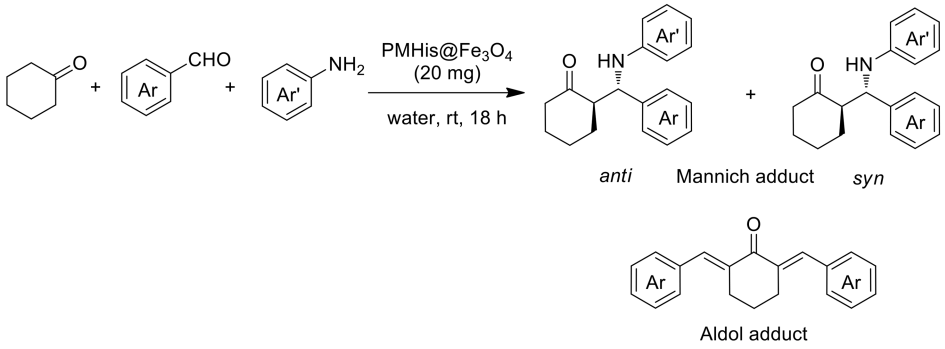
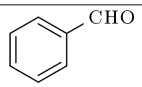
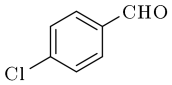
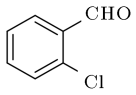
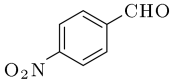
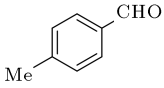
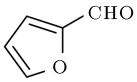
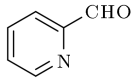
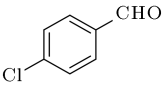
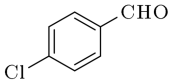
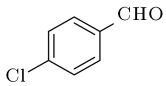
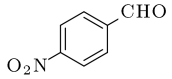
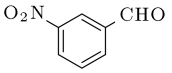


Figure 3. ORTEP representations (45% probability level) of the crystal structures of 2-[(2-chlorophenyl)(phenylamino)methyl]cyclohexanone (CCDC 923369).



Scheme 2. PMHis@Fe_3O_4 MNPs catalyzing the Mannich-type reaction of cyclohexanone.

Table 1. Scope of the PMHis@Fe_3O_4 MNPs that catalyzed Mannich-type reaction.[a]

Entry	ArCHO	Ar′NH_2	Yield (%)[b]	Anti/syn[c]
1		$C_6H_5NH_2$	63	84/16
2		$C_6H_5NH_2$	78	62/38
3		$C_6H_5NH_2$	80	86/14
4		$C_6H_5NH_2$	73	55/45
5		$C_6H_5NH_2$	58	72/28
6		$C_6H_5NH_2$	65	83/17
7		$C_6H_5NH_2$	78	87/13
8		4-$ClC_6H_4NH_2$	81	69/31
9		4-$BrC_6H_4NH_2$	79	69/31
10		3-$MeC_6H_4NH_2$	76	80/20
11		4-$ClC_6H_4NH_2$	80	55/45
12		4-$ClC_6H_4NH_2$	78	62/38

[a]Reaction conditions: aromatic aldehyde (0.5 mmol), aniline (0.5 mmol) and cyclohexanone (1.5 mmol), water (1 ml) rt, 18 h. [b]Yields of isolated products. [c]Determined by ^1H NMR.

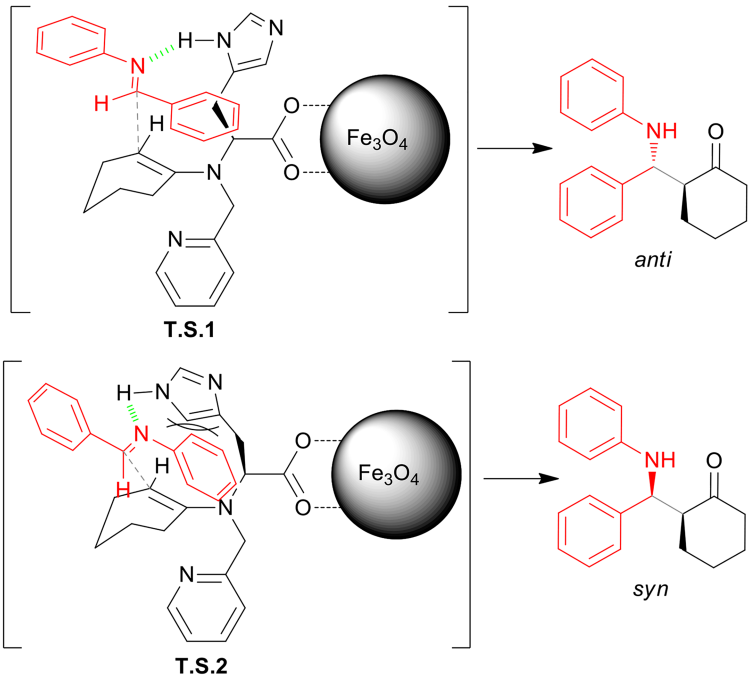
from the residue of the PMHis that led to the *anti*-Mannich adduct. The formation of the H-bond by N-H away from substitution in the imidazole ring (1-*H*-imidazo*L*-4-yl) led to unfavorable **T.S.2**, resulting in the formation of *syn* isomer (Scheme 3).

Moreover, this study investigated PMHis@Fe_3O_4 MNPs that catalyzed the three-component Mannich-type reaction of acetophenone and in-situ generated aldimines, leading to the corresponding β-amino ketones in 65–71% yields (Scheme 4).

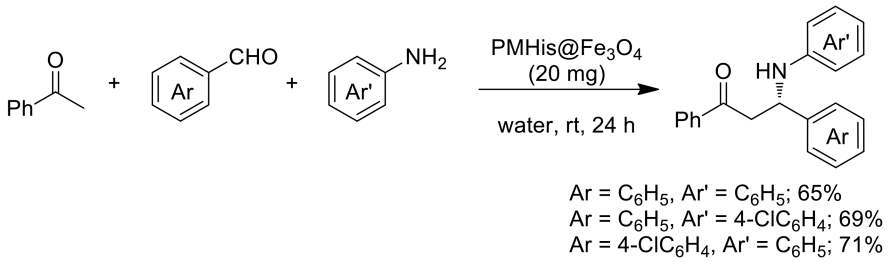
The recoverability of the PMHis@Fe_3O_4 MNP catalysts was investigated by the separation of the applied catalyst from the reaction medium after product extraction using an external magnetic field. After washing and drying, PMHis@Fe_3O_4 MNPs were subjected to fresh regents under the same reaction conditions, indicating no considerable decrease in the yield of the corresponding Mannich adduct for four runs (Figure 4).

4. Conclusions

In summary, PMHis@Fe_3O_4 MNPs were synthesized and characterized by FT-IR, XRD, VSM, BET, TGA, SEM, EDX, and TEM analyses. Functionalization of PMHis residue on the MNPs was confirmed by FT-IR, EDX, and TGA techniques. The crystalline phase of the MNPs was confirmed as Fe_3O_4 by XRD. VSM analysis revealed the superparamagnetic properties of the synthesized Fe_3O_4 MNPs. The catalytic activity



Scheme 3. Proposed transition states to form *anti* and *syn* Mannich adducts.



Scheme 4. PMHis@Fe_3O_4 MNPs catalyzing the Mannich-type reaction of acetophenone.

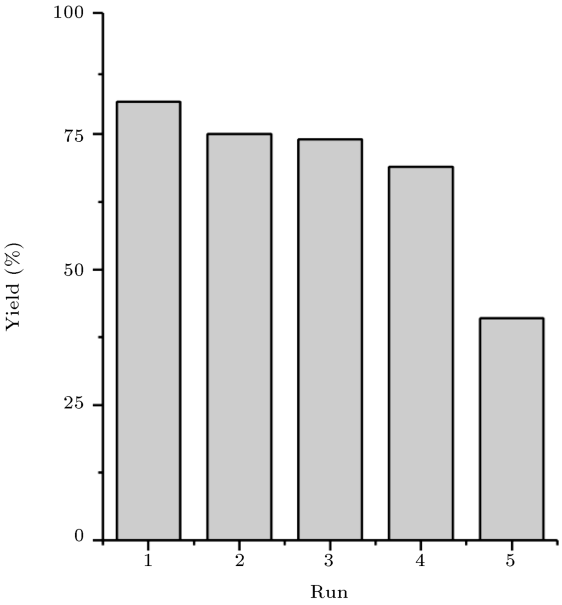


Figure 4. Recyclability of the PMHis@Fe_3O_4 MNPs catalyst in the Mannich-type reaction of 4-chlorobenzaldehyde, 4-chloroaniline, and cyclohexanone.

of the synthesized PMHis@Fe_3O_4 MNPs was investigated in the three-component Mannich-type reaction of ketones, aromatic aldehyde, and anilines, leading to β-amino ketones in good to high yields with moderate to good diastereoselectivity. The simple preparation of catalyst and reaction procedure, easy separation, and recoverability of the catalyst and the application of water as a reaction medium are some advantages of the proposed protocol.

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