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Synthesis and characterization of pyridine-4-carboxylic acid functionalized Fe₃O₄

nanoparticles as a magnetic catalyst for synthesis of tetrahydrobenzo[b]pyran derivatives

under solvent-free conditions

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Abstract

Pyridine-4-carboxylic acid (PYCA) functionalized Fe_3O_4 nanoparticles as an organic–inorganic hybrid heterogeneous catalyst was fabricated and characterized by FT-IR, XRD, TGA, TEM, SEM and VSM techniques. The catalytic activity of the magnetic catalyst was probed through one-pot synthesis of tetrahydrobenzo[*b*]pyran derivatives from three component reactions of aromatic aldehydes, malononitrile and dimedone under solvent-free conditions. Simple procedure, high yields, short reaction time and environmentally benign method are advantages of this protocol. The catalyst was readily separated using an external magnet and reusable without significant loss of its catalytic efficiency.

Keywords

Nanomagnetic catalyst, Pyridine-4-carboxylic acid, Tetrahydrobenzo[*b*]pyran, Aldehydes, Malononitrile, Dimedone

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Introduction

Environmentally benign, economical, practical and efficient processes for the catalyst separation and reuse have been increasingly important goals in the chemical community [1]. Magnetic nanoparticles are efficient, readily available, high-surface-area resulting in high catalyst loading capacity and outstanding stability heterogeneous supports for catalyst. They show identical and sometimes even higher activity than their corresponding homogeneous analogues [2-4]. Magnetic nanocatalysts can easily be separated and recycled from the products by an external magnet [5]. Surface functionalized iron oxide magnetic nanoparticles (MNPs) are a kind of novel functional materials, which have been widely used in biotechnology and catalysis [6-8]. Good biocompatibility and biodegradability as well as basic magnetic characteristics could be denoted for functional organic materials grafted to MNPs [9-11].

Multi-component reactions (MCRs) have proven to be a valuable asset in organic and medicinal chemistry [12-15]. Such protocols can use for drug design, and drug discovery because of their simplicity, efficiency, and high selectivity [16, 17]. MCRs can reduce the number of steps and present advantages, such as low energy consumption and little to no waste production, leading to desired environmentally friendly processes. Synthesis of bioactive and complex molecules should be facile, fast, and efficient with minimal workup in this methodology [16-18]. Compounds containing tetrahydrobenzo[*b*]pyran, has been of considerable interest to chemists because they may contribute to potential pharmacological activities [19], such as spasmolytic, diuretic, anti-coagulant, anti-cancer, antiancaphylactia activities [20-23]. However, some of the reported methods require prolonged reaction time, reagents in stoichiometric amounts and generate unsatisfactory yields of the products [24-29].

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In the present study, we present our results on the preparation and characterization of magnetic, pyridine-4-carboxylic acid (PYCA) functionalized Fe_3O_4 nanoparticles (Fe_3O_4 -PYCA) and its catalytic application for three-component synthesis of tetrahydrobenzo[*b*]pyran derivatives from aromatic aldehydes, malononitrile and dimedone under solvent-free conditions (Scheme 1).

Experimental

Chemicals and materials

Melting points were measured on an Electrothermal 9100 apparatus. The X-ray powder diffraction (XRD) of the catalyst was carried out on a Philips PW 1830 X-ray diffractometer with CuK α source (λ =1.5418 Å) in a range of Bragg's angle (10-80°) at room temperature. Scanning electron microscope (SEM) analyses were taken using VEGA//TESCAN KYKY-EM 3200 microscope (acceleration voltage 26 kV). Transmission electron microscopy (TEM) experiments were conducted on a Philips EM 208 electron microscope. Thermo gravimetric analysis (TGA) was recorded on a Stanton Red craft STA-780 (London, UK). NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ¹H, 100.6 MHz for ¹³C). The spectra were measured in DMSO-d₆ as solvent. IR spectra were recorded on an FT-IR Bruker vector 22 spectrophotometer. Magnetic measurements were performed using vibration sample magnetometer (VSM, MDK, and Model 7400) analysis.

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General Procedure

Preparation of the magnetic Fe₃O₄ nanoparticles (MNPs)

FeCl₃.6H₂O (4.865 g, 0.018 mol) and FeCl₂·4H₂O (1.789 g, 0.0089 mol) were added to 100 mL deionized water and sonicated until the salts dissolved completely. Then, 10 mL of 25% NH₄OH (10 mL) was added quickly into the reaction mixture in one portion under N₂ atmosphere at room temperature followed by stirring about 30 min with mechanical stirrer. The black precipitate was washed with doubly distilled water (five times).

Preparation of pyridine-4-carboxylic acid functionalizedFe₃O₄ nanoparticles(Fe₃O₄-PYCA)

The obtained MNPs powder (1 g) was dispersed in 150 mL water solution by sonication for 30 min, and then 0.010 mol (0.123 g) of PYCA was added to the above mixture which a black suspension was formed. This suspension was then refluxed at 100 $^{\circ}$ C for 6 h, with vigorous stirring. Fe₃O₄–PYCA nanoparticle was separated from the aqueous solution by magnetic decantation, washed with distilled water several times and then dried in an oven overnight (Scheme 2). Whole synthesis was done under N₂ atmosphere.

General procedure for the synthesis of tetrahydrobenzo[*b*]pyran derivatives under solventfree conditions

A mixture of aromatic aldehydes (1 mmol), malononitrile (1 mmol, 0.066 g) and dimedone (1 mmol, 0.140 g) and Fe₃O₄–PYCA nanoparticles (15 mol %) as a catalyst at 70 $^{\circ}$ C was stirred under solvent-free conditions for the 29-34 min. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to room temperature. Then, the reaction

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mixture was dissolved in dichloromethane (10 mL) and subsequent Fe_3O_4 -PYCA nanoparticle catalyst was separated by an external magnet at 5 min. The solution containing the product was evaporated and the residue solid was recrystallized using diethylether and the product obtained as a white powder. Finally, the isolated catalyst was washed several times with dried CH_2Cl_2 , dried under vacuum at 60 °C to give the pure Fe_3O_4 -PYCA nanoparticle catalyst.

Selected spectra for some known product are given below:

2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran (Table 2, entry 2) : white solid; mp =210-211 °C. IR (KBr): v_{max} = 3380 and 3182 (NH₂), 2189 (CN), 1676 (C=O), 1218 (C–O) cm⁻¹.; ¹H NMR (400.13 MHz, DMSO-d₆): δ = 0.92 and 1.03 (2s, 6H, 2CH₃), 2.12 and 2.30 (AB quartet, 2H, *J* = 16.0 Hz, CH₂), 2.52 (m, 2H, CH₂), 4.19 (s, 1H, CH), 7.07 (s, 2H, NH₂), 7.17 (d, 2H, *J* =8.4 Hz, 2CH_{arom}), 7.35 (d, 2H, *J* = 8.4 Hz, 2CH_{arom}); ¹³C NMR (100.6 MHz, DMSO-d₆): δ = 27.7, 29.2, 32.7, 36.2, 51.8, 58.9, 113.4, 121.4, 129.8, 130.7, 132.9, 144.7, 159.5, 163.8, 196.6.

2-Amino-3-cyano-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran (Table 2, entry 4) : white solid; mp =226-228 °C. IR (KBr): v_{max} = 3353 and 3213 (NH₂), 2231 (CN), 1655 (C=O), 1214 (C–O) cm⁻¹.; ¹H NMR (400.13 MHz, DMSO-d₆): δ = 0.95 and 1.03 (2s, 6H, 2CH₃), 2.10 and 2.25 (AB quartet, 2H, *J* = 8.1 Hz), 2.51 (m, 2H, CH₂), 4.29 (s, 1H), 7.14 (s, 2H, NH₂), 7.35 (d, 2H, *J* =8.1 Hz), 7.75 (d, 2H, *J* = 8.1 Hz, 2CH_{arom}); ¹³C NMR (100.6 MHz, DMSO d₆): δ = 27.7, 29.1, 32.5,36.6, 50.8, 58.2, 110.4, 112.5, 119.7, 120.3, 129.4, 133.1, 151.2, 159.3,163.8, 196.6.

2-Amino-3-cyano-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetra-hydrobenzo[*b*]pyran (Table 2, entry 6) : white solid; mp =213-214 °C. IR (KBr): v_{max} = 3426 and 3329 (NH₂), 2191

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(CN), 1677 (C=O), 1207 (C–O) cm⁻¹.; ¹H NMR (400.13 MHz, DMSO-d₆): $\delta = 0.91$ and 1.03 (2s, 6H, 2CH₃), 2.08 and 2.25 (AB quartet, 2H, J = 16.0 Hz), 2.26 (s, 3H, CH₃), 2.50 (s, 2H), 4.11 (s, 1H), 6.98 (s, 2H, NH₂), 7.01 (d, 2H, J = 8.0 Hz), 7.09 (d, 2H, J = 8.0 Hz, 2CH_{arom}); ¹³C NMR(100.6 MHz, DMSO-d₆): $\delta = 21.5$, 27.7, 29.3, 32.7, 36.1, 50.9, 59.4, 113.8,120.9, 127.8, 129.9, 136.6, 142.9, 159.7, 163.8, 196.9.

Results and discussion

Characterization of the prepared Fe₃O₄-PYCA nanoparticles

X-ray diffraction (XRD) analysis

Phase investigation of the supported catalyst was performed by XRD and result presented in Fig. 1. The result shown in Fig. 1 was fitted for observed six peaks with the following miller indices: (2 2 0), (3 1 1), (4 0 0), (4 2 2), (5 1 1), and (4 4 0). The XRD pattern indicates that Fe₃O₄–PYCA nanoparticles,is broadened owing to semicrystalline, indicating that the PYCA have been successfully supported on Fe₃O₄ nanoparticle. The average MNPs corediameter was calculated to be about 11 nm from the XRD results by Scherrer's equation, D = k λ/β cose, where k is a constant (generally considered as 0.94), λ is the wavelength of Cu Ka (1.54 °A), β is the corrected diffraction line full-width at half-maximum (FWHM), and θ is Bragg's angle [30-31] (figure 1).

Fourier transform infrared (FT-IR) analysis

The presence of the coating agents on the surface of the magnetite nanoparticles was also supported by the FT-IR spectroscopy analysis. The peaks around 2923 and 2853 cm⁻¹, for asymmetric and symmetric vibrations of C–H stretching can be obviously found. The adsorption

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peaks at 1629 and 1461 cm⁻¹ corresponds to the asymmetric and symmetric stretching vibration of COO (carboxylate group) of pyridine-4-carboxylate moiety. The characteristic absorbing peaks of Fe₃O₄ are appeared at 633 and 583 cm⁻¹, which can be ascribed to the vibrations of Fe– O group. Therefore, the obtained data from FT-IR spectroscopy can be confirmed the existence of the nonmagnetic particle and heterocyclic moiety in the structure of Fe₃O₄–PYCA nanoparticle (Figure 2).

Thermogravimetric analysis (TGA)

Thermal gravimetric analysis (TGA) and differential thermal gravimetric (DTG) were performed at the range of 25 to 900 °C under atmosphere N₂, to determine the loading of organic groups coated on the surface of the magnetite (Figure 3). TGA curve of the Fe₃O₄–PYCA nanoparticle shows the mass loss of the organic functional group as it decompose upon heating. The curve shows a weight loss about 3.53% from 900 °C, resulting from the decomposition of functional group grafting to the MNPs surface. The amount of adsorbed pyridine-4-carboxylic acid calculated by Eq. (1) is 0.4mmol g⁻¹.

Eq. (1): mmolpyridine-4-carboxylic acid= (weight loss / $100 \times Mw$ pyridine-4-carboxylic acid) × 1000 = 0.4mmol

TEM analysis

Morphology of synthesized of Fe_3O_4 –PYCA nanoparticles were investigated by TEM that shown in Figure 4. Particles are observed to have spherical morphology from Fig.4. Average particle size is estimated about 13 nm from the TEM micrographs, which is in a very good agreement with the crystallite size estimated from XRD at 11.5 nm. As shown in Fig. 4, a

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basically core–shell structure (dark colored core for Fe_3O_4 nanoparticles and light-colored shell for PYCA) was obtained. This is an indication of nearly single crystalline character of Fe_3O_4 – PYCA nanoparticles.

Scanning electron microscope (SEM)

Scanning electron microscopy (SEM) has been a primary tool for determining the size distribution, particle shape, surface morphology and fundamental physical properties. In Fig. 5, the SEM image of the Fe_3O_4 –PYCA nanoparticle is shown (Figure 5). The SEM image of Fe_3O_4 –PYCA showed a spherelike structure.

Vibrating sample magnetometer (VSM)

The room temperature magnetization curves proved that the Fe₃O₄–PYCA nanoparticle is super paramagnetic. Saturation magnetization of MNPs was 92.13 emu/g and saturation magnetization of Fe₃O₄–PYCA nanoparticles was 76.89 emu/g. Compared with the uncoated Fe₃O₄ nanoparticle, the saturation magnetization of the Fe₃O₄–PYCA nanoparticle obviously decreased because the diamagnetic contribution of the organic group resulted in a low mass fraction of the Fe₃O₄ magnetic substance. Even with this reduction in the saturation magnetization, the solid could still be efficiently separated from solution with a permanent magnet (Figure 6).

Catalytic application of Fe₃O₄–PYCA nanoparticles

First, to find optimization conditions, the reaction of benzaldehyde, malononitrile and dimedone in the presence of the Fe_3O_4 -PYCA nanoparticles as catalyst was selected as model

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reaction. The reaction was carried out with different amount of Fe_3O_4 –PYCA nanoparticles as catalyst (10, 15, 20 mol %) in different temperatures (25, 50, 70 °C).

The obtained results in Table 1 showed that an optimal condition was 15 mol % of Fe_3O_4 -PYCA nanoparticles at 70 °C (Table 1, entry 8). Next, various aromatic aldehydes were used in the reactions that led to the corresponding products in high to excellent yields (Table 2). As shown in Table 2, the reactions with the aromatic aldehydes including electron-donating or electron-withdrawing substituents afforded the desired products in high to excellent yields.

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According to the literature survey [36], the suggested mechanism for the formation of the products is shown in Scheme 3.

The recycling of the Fe_3O_4 -PYCA nanoparticles was studied using the model reaction (Experimental section). The recovered Catalyst was reused several runs without any loss of its activities (Fig. 7 and 8).

In order to show the accessibility of the present work, it was compared with several reported results in the literature in Table 3 [22, 34, 37, 38]. The results show that the reactions in the presence of Fe_3O_4 –PYCA nanoparticle were carried out in short times (29-34 min) relative to other catalysts with the similar yields (Table 3).

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Conclusions

We were synthesized Fe₃O₄–PYCA nanoparticle as an organic–inorganic hybrid heterogeneous catalyst and characterized by FT-IR, XRD, TGA, TEM, SEM and VSM techniques. Size evaluation via various techniques revealed size of Fe₃O₄–PYCA nano particles around 11–13 nm with nearly single crystalline character. The most interesting features of the present work include durability as well as efficient catalytic activity for synthesis of tetrahydrobenzo[*b*]pyran derivatives via the reaction of an aromatic aldehydes, malononitrile and dimedone under solvent free at 70 °C. The attractive features of this protocol are simple procedure, inexpensive work up, ease of handling, high yields of products and use of reusable nanocatalyst.

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Supplementary Material

Supplemental data for this article is available at the publisher's website.

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Table 1. Optimization conditions for reactions of benzaldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in the presence of different amount of Fe3O4–PYCA nanoparticles as catalyst in diffrent temperatures under solvent-free conditions

Entry	Amount of catalyst (mol %)	Temperature (°C)	Time (min)	Yield (%) ^a
1	10	25	100	
2	15	25	100	Trace
3	20	25	80	37
4	10	50	75	50
5	15	50	70	60
6	20	50	70	75
7	10	70	40	85
8	15	70	30	96
9	20	70	30	96

^aYields refer to isolated pure product

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Table 2. Three-component reactions of aromatic aldehydes (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in the presence of Fe3O4–PYCA nanoparticles as catalyst (15 mol %) as catalyst under solvent free at 70° C

Entr	Aldehyde	Product	Time	Yield	Melting Point (°C)	
у			(min)	(%)	Found	Reported [Rf]
1	C ₆ H ₅	Me Me O NH ₂	30	96	230-231	229–232 [32]
2	4-ClC ₆ H ₄	CI O Me Me Me NH ₂	30	96	210-211	208-210 [33]
3	4-NO ₂ C ₆ H ₄	Me Me O NH ₂	33	94	179-181	180–183 [34]
4	4-CNC ₆ H ₄	CN O Me Me Me O NH ₂	29	95	226-228	224-227 [35]
5	4-OHC ₆ H ₄	OH OH CN Me Me ONH ₂	34	91	215-216	213–215 [32]
6	4-MeC ₆ H ₄	Me O Me Me Me NH ₂	32	93	213-214	210-212 [33]

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7	4- OMeC ₆ H ₄	OMe OMe CN Me Me Me	34	92	200-202	198–200 [34]
8	2-ClC ₆ H ₄	Me Me O NH ₂	32	95	194-196	196–198 [32]
9	2- NO ₂ C ₆ H ₄	Me Me NH ₂	32	91	181-182	180–183 [35]

^aYields refer to the isolated pure products

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Table 3. Comparison the results of Fe_3O_4 –PYCA nanoparticle with other catalysts in the synthesis of tetrahydrobenzo[*b*]pyran derivatives

Entry	Catalyst	Conditions	Time	Yield (%) ^a
				[Ref]
1	starch solution (4ml)	50 °C	30 min	92 [33]
2	SO ₄ ²⁻ /MCM-41 (25 mg)	ethanol (4 mL) , reflux	50 min	86 [34]
3	Silica bonded S- sulfonic acid (0.1 g)	EtOH:H ₂ O (50:50 v/v), reflux	45 min	90 [37]
4	Pentaluoropropionic acid (PFPA) (35 mol %)	EtOH:H ₂ O (1: 1), R.T	80 min	90 [38]
5	Fe ₃ O ₄ –PYCA nanoparticle (15 mol %)	70 °C, solvent-free	30 min	96 (Present work)

^aYields refer to isolated pure products



Figure 1. XRD powder pattern of Fe₃O₄–PYCA nanoparticles

²⁰ ACCEPTED MANUSCRIPT



Figure 2. FT-IR spectra for Fe_3O_4 nanoparticles, pyridine-4-carboxylic acid and Fe_3O_4 -PYCA nanoparticles

²¹ ACCEPTED MANUSCRIPT



Figure 3. TGA thermograms of Fe₃O₄–PYCA nanoparticles

²² ACCEPTED MANUSCRIPT



Figure 4. TEM micrographs of Fe₃O₄–PYCA nanoparticles

²³ ACCEPTED MANUSCRIPT



Figure 5. The SEM images of Fe₃O₄–PYCA nanoparticles

²⁴ ACCEPTED MANUSCRIPT



Figure 6. Room temperature magnetization curves of Fe_3O_4 nanoparticle and Fe_3O_4 -PYCA nanoparticle

²⁵ ACCEPTED MANUSCRIPT



Figure 7. Image showing Fe₃O₄–PYCA nanoparticle was can be separated by applied magnetics field. A reaction mixture in the absence (left) and presence of a magnetic field (right)



Figure 8. The recycling of the Fe₃O₄–PYCA nanoparticles as catalyst

²⁷ ACCEPTED MANUSCRIPT



Scheme. 1. Synthesis of tetrahydrobenzo[*b*]pyran derivatives using pyridine-4-carboxylic acid functionalized Fe_3O_4 nanoparticles (Fe_3O_4 –PYCA) as a nanomagnetic catalyst

²⁸ ACCEPTED MANUSCRIPT



Scheme. 2. Preparation of Fe₃O₄–PYCA nanoparticles

²⁹ ACCEPTED MANUSCRIPT



Scheme 3. The suggested mechanism for the formation of the tetrahydrobenzo[*b*]pyran derivatives

³⁰ ACCEPTED MANUSCRIPT