

RESEARCH PAPER

Fe₃O₄ magnetic nanoparticles (MNPs) as an effective catalyst for synthesis of indole derivatives

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ABSTRACT

The principal aim of this research is the application of Fe₃O₄ (MNPs) in the synthesis of some indole derivatives. Fe₃O₄ MNPs were prepared by Co-Precipitation method from the reaction of FeCl₂.4H₂O and FeCl₃.6H₂O in ammonia solution. Morphology and structure of Fe₃O₄ MNPs were determined by FT-IR, X-Ray diffraction (XRD), transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Fe₃O₄ (MNPs) has been used as a highly efficient catalyst for the synthesis of some Indole derivatives like 6H-Indole [2,3-b] quinoxaline, 3-methyl-6H-Indole [2,3-b] quinoxaline and (z)-3-(pyridine-2-yl-imino)-Indole-2-one. The reaction was carried out using various amounts of Fe₃O₄ nanoparticles in various solvents and solvent-free conditions. The optimum amount of nano-Fe₃O₄ was 5 mol% in THF under reflux conditions. The structures of indole derivatives were further established by NMR, and FT-IR spectra. In view of excellent catalytic capacity, the exceedingly simple workup procedure, environmentally friendly reaction and good yield, Fe₃O₄ (MNPs) was proved to be the good catalyst for this reaction.

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INTRODUCTION

Fe₃O₄ Magnetite Nanoparticles (MNPs) have attracted a great deal of attention over the past decade due to their pharmaceutical activities, properties and applications in ferrofluids, magnetic media, biomedicine, and catalytic activities [1-4]. They have been used as an excellent heterogeneous catalyst for the synthesis of organic compounds [5-7], because of their large surface area, simple handling, recoverable from the reaction mixture using an external magnetic field, oxidative stability, and high catalytic activities [8-10]. Fe₃O₄ MNPs have been prepared using various methods, including thermal decomposition [11-12], co-precipitation [13, 14], hydrothermal synthesis, microemulsion, and ultrasound irradiation [15]. The most commonly used methods are thermal decomposition [16] and co-precipitation [17, 18].

In co-precipitation method, Fe₃O₄ MNPs have been synthesized using Fe²⁺ and Fe³⁺ ions in alkaline solutions, under an inert (N₂ or Ar) atmosphere.

Indole derivatives, a nonpolar purine analog [19] are well known because of their chemical properties and pharmaceutical activities such as, antifungal [20, 21], anticancer [22, 23], anti-inflammatory [24, 25], antibacterial [26], and antimicrobial activities [27]. They are present in some important heterocyclic compounds and biochemical molecules such as dacinostat, tryptophan, semaxanib, serotonin, ziprasidone, and melatonin [28, 29]. Isatin (1H-indole-2, 3-dione) has also been known for several years as an intermediate for the synthesis of a large variety of heterocyclic compounds [30, 31]. The substitution at the 3 and 2 positions of the isatin ring can take place by connecting an additional heterocyclic ring

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[32, 33]. Due to the descriptions presented above, in this project, we have tried to use Fe₃O₄ MNPs as a heterogeneous catalyst for the synthesis of some indole derivatives in good yields and under mild reaction conditions.

EXPERIMENT

Materials preparation

All solvents were purified and dried using established procedures. TLC silica gel 60, and aluminum sheets were purchased from Merck. The NMR spectra were recorded on Bruker XL 500 (500 MHz) instruments, FT-IR measurements were recorded on a Shimadzu 8400s spectrometer with KBr plates. Melting points were determined on an Electrothermal 9100 without further corrections. The sizes of MNPs were evaluated using a transmission electron microscope (TEM, 150 kV, and Philips-CM 10).

Preparation of Fe₃O₄ MNPs

The MNPs were prepared according to a previously reported procedure [36]. Typically, FeCl₃·6H₂O (0.02 mol) and FeCl₂·4H₂O (0.01 mol) were dissolved in distilled water (100 ml) in a three-necked round-bottom flask (250 ml). The resulting transparent solution was heated at 90 °C with rapid mechanical stirring under N₂ atmosphere for 1h. A solution of concentrated aqueous ammonia (10 ml, 25 wt %) was then added to the solution in a dropwise manner over a 30 min period using a dropping funnel. The reaction mixture was then

cooled to room temperature and the resulting magnetic particles collected with an external magnet and rinsed thoroughly with distilled water.

General Procedure for Synthesis of indole derivatives using Fe₃O₄ magnetic nanoparticles

Isatin (1mmol) was reacted with an amine (1mmol) in the presence of Fe₃O₄ magnetic nanoparticles (5 mol%) in THF (5 ml) under reflux condition. The progress of the reaction was monitored by TLC using *n*-hexane: ethyl acetate (4:1) and detected by UV lamp (254 & 366 nm). At the end of the reaction, the catalyst was recovered by an external magnet, washed with EtOH, dried at 60°C for 1h and reused four times for the same reaction. The residue of the reaction mixture was evaporated, and the crude product was purified by short-column chromatography on silica gel (*n*-hexane: EtOAc / 4:1). The products were identified by comparison of their ¹H-NMR, FT-IR spectra and physical data with those of authentic samples.

6*H*-Indole [2,3-*b*] quinoxaline (1)

Yellow powder, Yield 85 %, m.p> 300 °C. FT-IR(KBr, ν_{\max} cm⁻¹): 3433(N-H), 3022(C-H), 1562(C=N), 1525(C=C), 1216(C-N), 774 (C-N), ¹H-NMR(400MHz, DMSO-d₆): δ H(ppm) 8.65 (br, 1H, NH), 8.51 (d, *J*= 8, 1H, ArH), 8.35 (d.d, *J*= 7.2, *J*=1.2, 1H, ArH), 8.12 (d.d, *J*= 8.4, *J*=0.8, 1H, ArH), 7.76-7.84 (m, 1H, ArH), 7.73-7.76 (m, 1H, ArH), 7.68-7.72 (m, 1H, ArH), 7.55 (d, *J*= 8.4, 1H, ArH), 7.39-7.43 (m, 1H, ArH).

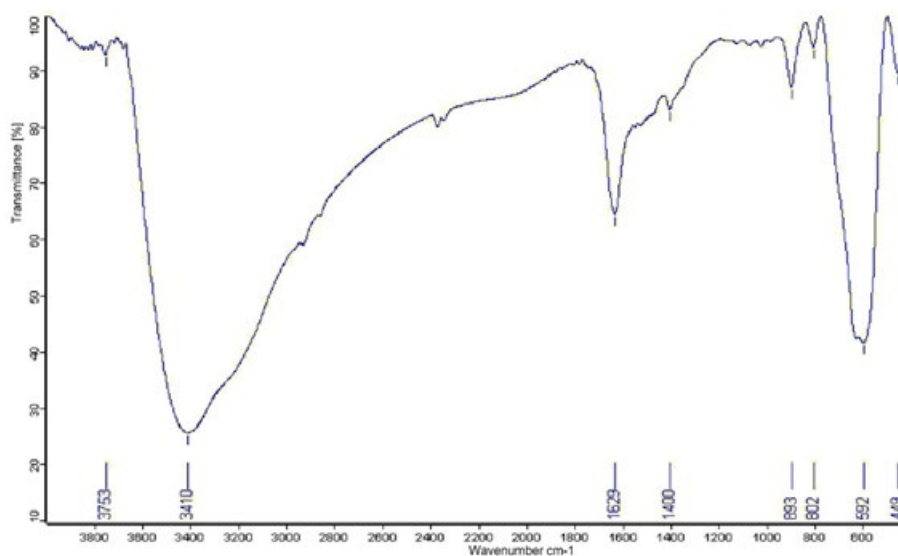


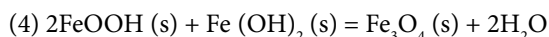
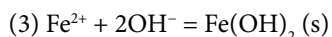
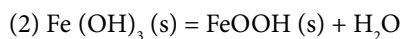
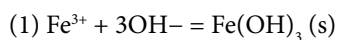
Fig. 1: FT-IR spectra of Fe₃O₄ magnetic nanoparticles

3-methyl-6H-Indole [2,3-b]- quinoxaline (2)

Yellow powder, Yield 80 %, m.p> 300 °C. ¹H-NMR(400MHz, DMSO-d6): δ H(ppm) 8.65 (br. 2H, NH), 8.47 (d.d, J= 8.4, J=1.2, 2H, ArH), 8.22 (d, J= 8.4, 2H, ArH), 8.11 (s, 1H, ArH), 8.10 (d, J= 8.4, 2H, ArH), 7.88 (s, 1H, ArH), 7.62-7.69 (m, 3H, ArH), 7.55-7.58 (m, 3H, ArH), 7.39-7.44 (m, 2H, ArH), 2.66 (s, 3H, -CH₃), 2.66 (s, 3H, -CH₃).

RESULTS AND DISCUSSIONS

In this study, application of Fe₃O₄ MNPs in the synthesis of some isatin derivatives was investigated. Fe₃O₄ MNPs were prepared by Co-Precipitation method from the reaction of FeCl₂.4H₂O and FeCl₃.6H₂O in ammonia solution. The proposed mechanism of Fe₃O₄ MNPs preparation is as followed: [34, 14]



The FT-IR spectra of prepared Fe₃O₄ nanoparticles are shown in Fig. 1.

These spectra show that the data are the same as reported in the literature [35, 36]. A strong peak at around 592 cm⁻¹ can be attributed to the Fe-O-Fe stretching vibration. The broad band at around 3400 cm⁻¹ is due to the adsorbed water and OH groups.

XRD patterns of Fe₃O₄ MNPs are shown in Fig. 2.

XRD measurement was used to characterize the crystalline structure and average size of nanoparticles. As shown in Fig. 2, XRD pattern of Fe₃O₄ MNPs shows nine high intense peaks in the whole spectrum of 2θ values ranging from 20° to 80°. They are consistent with the standard pattern for JCPDS Card No. (79 - 0417) [37] confirming that Fe₃O₄ nanoparticles have been formed. The broad

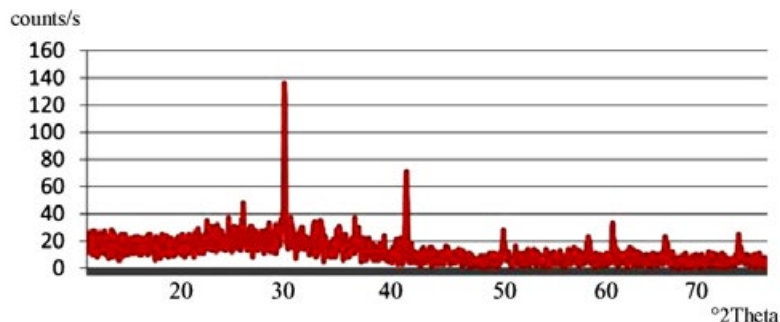


Fig. 2: XRD patterns of Fe₃O₄ magnetic nanoparticles

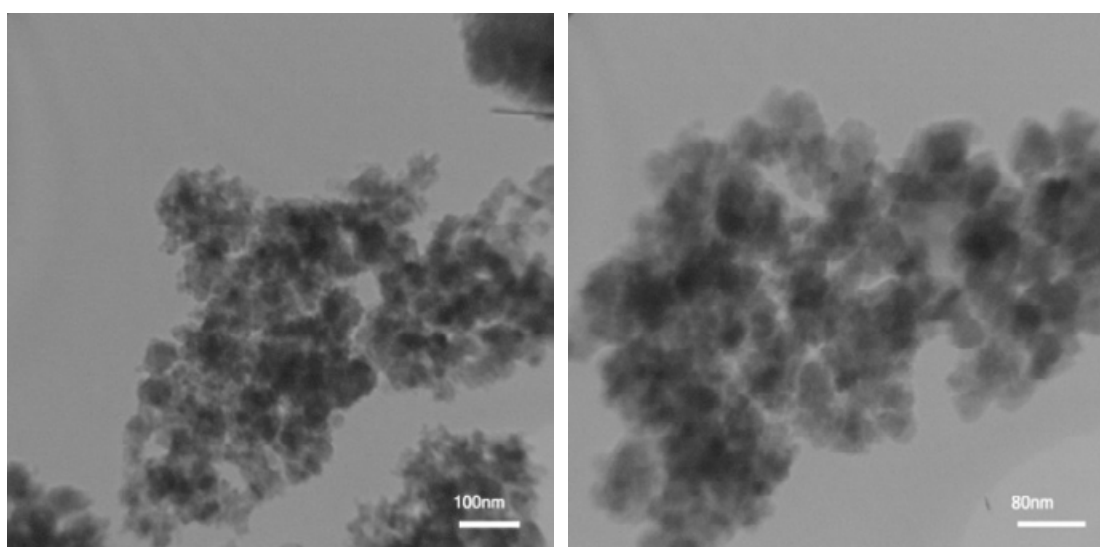


Fig. 3: TEM images of Fe₃O₄ MNPs

X-ray diffraction peaks around their bases indicate that the Fe₃O₄ magnetic particles are in nano sizes. The average diameter which can be evaluated from Debye–Scherrer equation [38, 39] ($D=K\lambda/\beta\cos\theta$, where K is constant, λ is X-ray wavelength and β is the peak width at half maximum) was obtained about 13 nm.

TEM (Fig. 3) investigation shows the average diameter of 10-60 nm for the Fe₃O₄ MNPs. SEM image (Fig. 4) shows spherical shape of particles.

The model reaction of isatin and

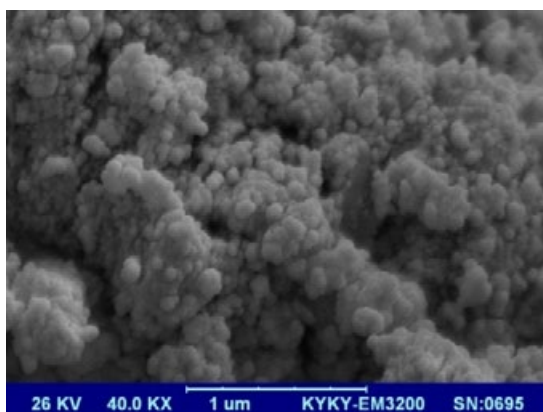


Fig. 4: SEM images of Fe₃O₄ MNPs

o-phenylenediamine was carried out using various amounts of Fe₃O₄ nanoparticles in various solvents and solvent-free conditions. The optimum amount of nano-Fe₃O₄ was 5 mol% as shown in Table 1. Increasing the amount of catalyst does not improve the yield of the product any further, whereas decreasing the amount of catalyst leads to decrease in the product (Table 1).

It was found that in the absence of Fe₃O₄ magnetic nanoparticles, the yield of the product on TLC plate is not good even after 2 h of the reaction (Table 1, Entry 16). The best results were obtained with 5 mol% of Fe₃O₄ magnetic nanoparticles in THF under reflux conditions (Table 1, Entry 4).

To evaluate the scope and limitations of this methodology, we extended our studies to include a variety of structurally different amines with isatin. The results are summarized in Table 2 (Table 2, entries 1–6). The reactions proceeded almost smoothly within 1-2 h, to provide the corresponding indole derivatives in good yields.


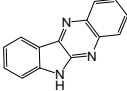
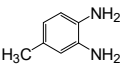
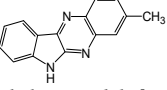

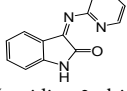
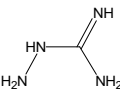
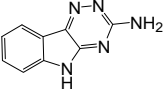
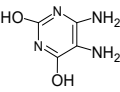
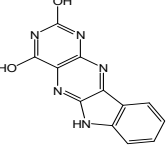

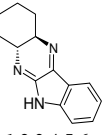
A plausible mechanism for the reaction is envisaged in (Scheme 1). Carbonyl group is first activated by MNPs (Fe³⁺), and then the amine nitrogen attacks to positive center to afford imine intermediate [36].

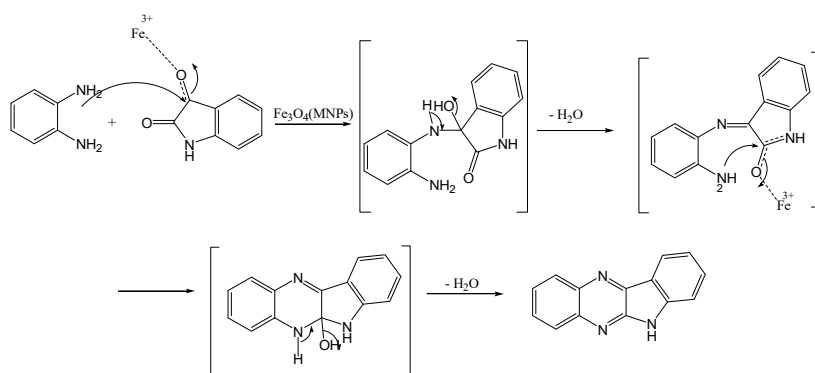
Table 1: Reaction of isatin (1mmol) and *o*-phenylenediamine (1 mmol) under different conditions

Entry	Solvent	Catalyst	Catalyst (mol%)	Time	Yield ^a (%)
1	THF	-	-	2h	48
2	THF	Fe ₃ O ₄ MNPs	3	2h	60
3	THF	Fe ₃ O ₄ MNPs	4	2h	76
4	THF	Fe ₃ O ₄ MNPs	5	1h	85
5	THF	Fe ₃ O ₄ MNPs	10	1h	84
6	CH ₃ CN	-	-	2h	30
7	CH ₃ CN	Fe ₃ O ₄ MNPs	3	1h	35
8	CH ₃ CN	Fe ₃ O ₄ MNPs	4	1h	62
9	CH ₃ CN	Fe ₃ O ₄ MNPs	5	1h	79
10	CH ₃ CN	Fe ₃ O ₄ MNPs	10	1h	79
11	<i>n</i> -Hexane	-	-	2h	trace
12	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	3	2h	23
13	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	4	2h	41
14	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	5	2h	60
15	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	10	2h	62
16	EtOH	-	-	2h	58
17	EtOH	Fe ₃ O ₄ MNPs	3	2h	61
18	EtOH	Fe ₃ O ₄ MNPs	4	2h	72
19	EtOH	Fe ₃ O ₄ MNPs	5	2h	78
20	EtOH	Fe ₃ O ₄ MNPs	10	2h	79
21	Solvent-free	-	-	2h	55
22	Solvent-free	Fe ₃ O ₄ MNPs	3	2h	62
23	Solvent-free	Fe ₃ O ₄ MNPs	4	2h	67
24	Solvent-free	Fe ₃ O ₄ MNPs	5	2h	68
25	Solvent-free	Fe ₃ O ₄ MNPs	10	2h	67

^a Isolate Yield.

Table 2: Synthesis of indole derivatives using Fe₃O₄ MNPs.

Entry	Amine	Product	Reaction time (min) in THF	Yield (mol %)	Ref.
1		 6H-Indolo [2,3-b] quinoxaline (1)	40	85	-
2		 3-methyl-6H-Indolo [2,3-b]-quinoxaline (2)	60	80	-
3		 (z)-3-(pyridine-2-yl-imino)-Indole-2-one (3)	70	85	[40]
4		 9H- 1,3,4,9-tetraaza-fluorene-2-ylamine (4)	90	75	[41]
5		 10H-1,3-dihydroxypyrimidino[4,5:2',3']pyrazino[2,3-b]indole (5)	90	71	[42]
6		 1,2,3,4,5,6-hexahydroquinoxalino[3,2-b]-3H-Indole (6)	60	80	[43]



Scheme 1: Plausible mechanism for the synthesis of 6H-Indolo[2,3-b]quinoxaline

Table 3: Recycling of the Fe₃O₄ MNPs catalyst.

Number of cycles	Yield ^a (%)
1	85
2	85
3	82
4	78

^a Isolated yield after chromatographyTable 4: Comparison of the efficacy of Fe₃O₄ MNPs with some of those reported in the literature

Compounds	Catalyst	Time	Yield	Ref.
3	acetic acid	3h	-	[40]
3	Fe ₃ O ₄ MNPs	70 min	85	This work
4	NaOH	2 h	-	[41]
4	Fe ₃ O ₄ MNPs	90 min	75	This work
5	Triethylamine/EtOH	5 h	81	[42]
5	Fe ₃ O ₄ MNPs	90min	71	This work
6	glacial acetic acid	6 h	85	[43]
6	Fe ₃ O ₄ MNPs	60 min	80	This work

The catalyst was simply recovered by external magnetic field, washed with ethanol, and dried at 60 °C for 1 h. The recovered catalyst was then added to a fresh reaction mixture under the same conditions and reused 4 times without significant loss of activity (Table 3). Further recycling of the nanocatalyst led to a gradual loss of the catalyst during the recovering and washing stages.

A comparison of the efficacy of Fe₃O₄ MNPs catalyst with other catalysts reported in the literature is presented in Table 4. In addition, to achieve the general advantages attributed to the inherent magnetic property of nanocatalysts, Fe₃O₄ MNPs exhibited exceptionally high catalytic activity compared to the other catalysts, to yield the desired products in shorter reaction times and under milder reaction conditions.

CONCLUSION

In summary, indole derivatives were synthesized with the reaction of isatin and amines using Fe₃O₄ MNPs as an inexpensive and reusable catalyst in THF. The reactions were carried out in short reaction time and smooth reaction conditions and the corresponding products were obtained in good to excellent yields. Separation of the catalyst and products after proceeding was much easier than that in usual methods. It represents a straightforward protocol for the eco-friendly and efficient synthesis of indole derivatives.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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