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Fe₃O₄ magnetic nanoparticles as efficient and recyclable catalysts for preparation of 3-azaaryl-3-hydroxyindolin-2-ones under ultrasound irradiation

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Abstract : Fe₃O₄ magnetic nanoparticles were synthesized via chemical precipitation method and used as an efficient and recyclable catalyst in ultrasound-assisted sp³ C-H functionalization of 2-methylpyridines. Good yields of 3-substituted-3-hydroxyindolin-2-ones were obtained via reaction of 2-methylpyridines and isatins

under mild conditions. The catalyst, retained activity for five runs. © Global Scientific Inc.

Keywords : Fe₃O₄; Magnetic nanoparticles; Ultrasound irradiation; Isatin; 3-hydroxyindolin-2-ones.

INTRODUCTION

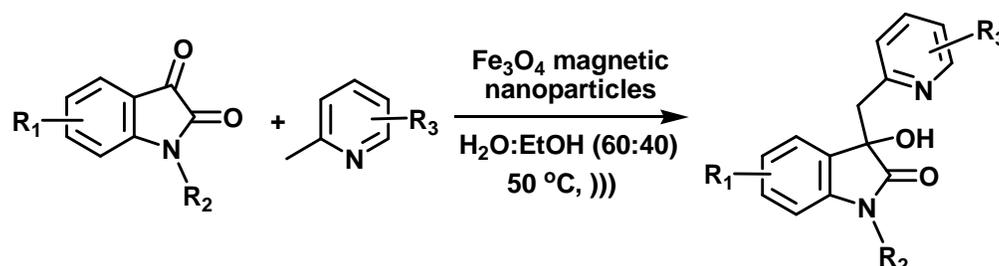
In the last decade, the use of nano-sized magnetic particles in the manufacture of fine chemicals has attracted increasing attention, owing to the special features such as unique electrical and magnetic properties, selectivity, stability and above all, reusability, which are most sought after in green chemistry, drug delivery and biosensors^[1-11]. Specially, Fe₃O₄ magnetic nanoparticles have attracted great attention in recent years because of their inherent properties such as ease of recovery by using an external magnetic field, high surface areas, low toxicity and moisture insensitivity^[12-15]. On the other hand, Oxindoles are well known amongst different isatin derivatives and are useful as

antibacterial, anti-inflammatory and laxative agents^[16,17]. Such heterocyclic compounds were recently isolated from plants and marine animals, for example, the alkaloid convolutamydine A from the marine bryozoan *Amathia convolute*^[18]. To date, most attention has been focused on the direct addition of nucleophiles to isatins to construct, for example, 3-aryl^[19], 3-alkyl^[20] or 3-indolyl^[21] substituted 3-hydroxyindolin-2-ones. Recently, 3-azaarene-substituted 3-hydroxyindolin-2-ones have attracted attention as a new motif. A literature survey showed that the reported methods on the synthesis of 3-azaaryl-3-hydroxyindolin-2-ones from the reaction of 2-methylpyridines and isatins, are associated with serious drawbacks such as long reaction times^[22-24], use of toxic solvents^[22,24], need of special

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apparatus^[25], high load of catalysts^[22,23] and environmental concerns related to catalyst waste^[22,23]. Our interest in the study of oxindole type molecules^[21,26], prompted us to investigate the reaction of 2-methylpyridines and isatins under catalysis of Fe_3O_4

magnetic nanoparticles, as a heterogeneous recyclable catalyst. Our successful experiences in the application of sonic waves in heterogeneous catalytic systems^[27,28], also, prompted us to take advantage of ultrasound irradiation in this reaction (Scheme 1).



Scheme 1 : Ultrasound-assisted reaction of 2-methylpyridines and isatins under catalysis of Fe_3O_4 magnetic nanoparticles

MATERIALS AND METHOD

General

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^1H NMR spectra were obtained on a Bruker DRX-400 Avance spectrometer and ^{13}C NMR spectra were obtained on a Bruker DRX-100 Avance spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra were expressed in ppm downfield from tetramethylsilane. Melting points were measured on a Büchi Melting Point B-540 instrument and are uncorrected. Elemental analyses were made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. X-ray powder diffraction (XRD) measurements were performed using a Philips diffractometer with mono chromatized $\text{Cu } k_\alpha$ radiation. The morphology of synthesized samples was characterized with a scanning electron microscope (SEM) from Philips Company (XL30 ESEM). Ultrasonication was performed in a TECNO-GAZ Tecna 3 ultrasonic cleaner with a frequency of 50-60 KHz and a normal power of 250 W. The reaction flask was located in the water bath of the ultrasonic cleaner. Analytical GLC evaluations of product mixtures were carried out on a Varian CP-3800 chromatograph (using a split/splitless injector, CP Sil 8CB column, FID assembly).

Materials

Fe_3O_4 magnetite nanoparticles were synthesized with higher efficiency by using a five-necked reactor. A

stock solution of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10.4 g), $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (4.0 g) and HCl (1.7 mL, 12 mol L^{-1}) in 50 mL of deionized water which was degassed with nitrogen gas for 20 min before use, added dropwise (by using a dropping funnel connected to one neck) into 500 mL of degassed NaOH solution (1.5 mol L^{-1}) at 80 °C during 30 min. Central neck was connected to a home-made condenser allowing circulation of cold water to prevent vaporization of solution. A glassware stirrer rotating at 1000 rpm, was passed through the condenser and central neck. Third neck was used to sparge nitrogen gas during the synthesis. The other necks were used for temperature monitoring and sampling. After completion, the obtained Fe_3O_4 nanoparticles were separated from the reaction medium by a magnetic field (1.4 T strength), and washed with 500 mL deionized water four times. The obtained nanoparticles were characterized by using XRD, SEM and TEM. Figure 1 shows the XRD pattern of the synthesized nanoparticles, which matched well with library patterns (JCPDS No. 19-629), indicating that the sample has a cubic crystal system. No specific reflection due to any impurities was observed and the broad peaks indicated the nano size of the particles, with an average crystallite size of about 35 nm (calculated by Debye-Scherrer equation, $D = K\lambda / \beta \cos\theta$, where β is full-width at half-maximum in radians, θ is the position of the maximum diffraction peak, K is the so-called shape factor, which usually takes a value of about 0.9, and λ is the X-ray wavelength ($\lambda = 1.5406 \text{ \AA}$ for Cu $K\alpha$)).

SEM and TEM images of the prepared nanoparticles were obtained as shown in Figure 2.

Fe_3O_4 surface morphology analysis by SEM demonstrated the agglomeration of many ultrafine particles,

which their diameter ranged from 10 to 40 nm as it is obvious from TEM.

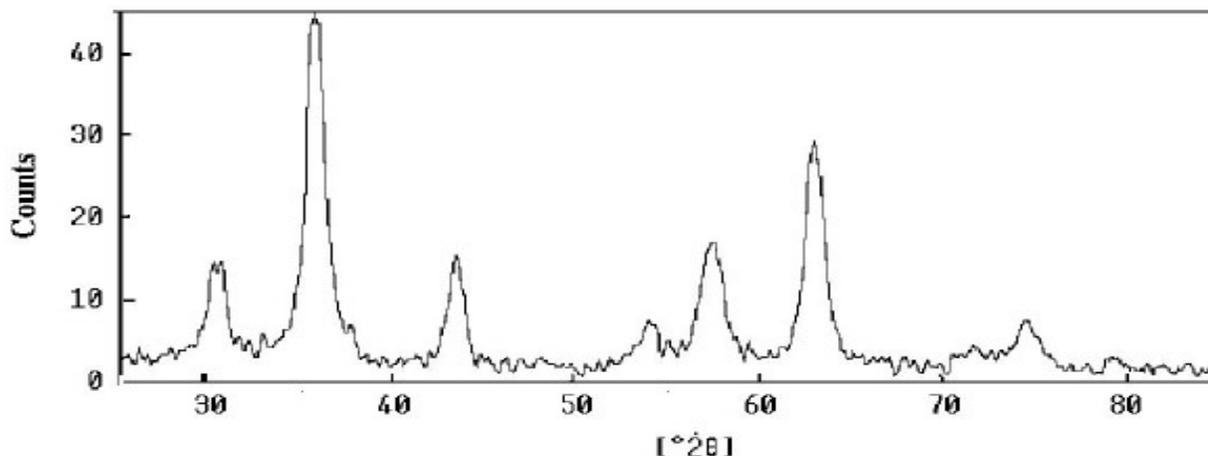


Figure 1 : XRD pattern of synthesized Fe_3O_4 magnetic nanoparticles

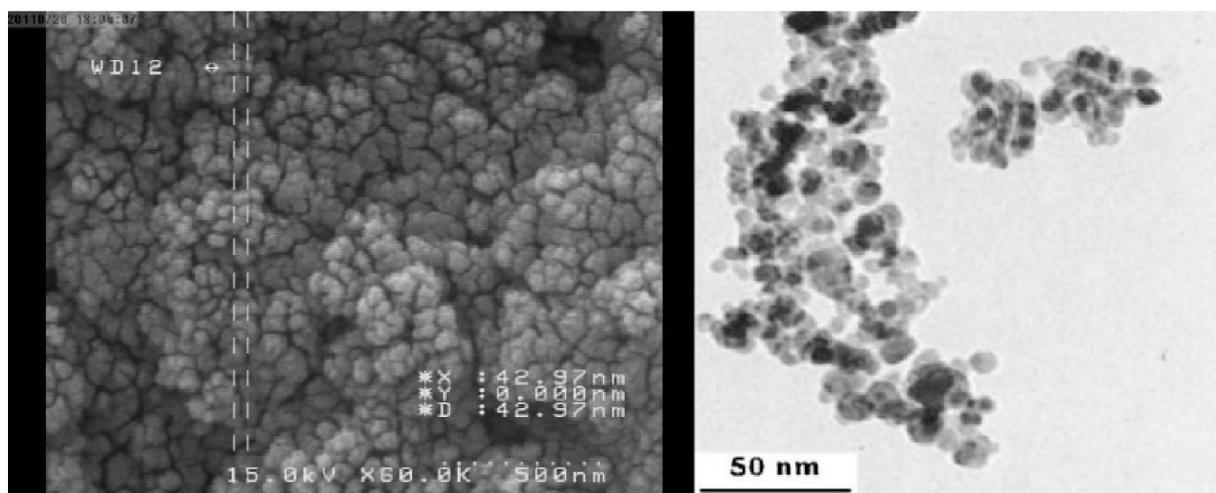


Figure 2 : SEM (left) and TEM (right) images of synthesized Fe_3O_4 magnetic nanoparticles

General procedure for the synthesis of 3-azaaryl-3-hydroxyindolin-2-ones

Isatin (1.0 mmol), 2-methylpyridine (1.0 mmol) and Fe_3O_4 magnetic nanoparticles (300 mg), were added to 10 mL of a 60:40 mixture of H_2O : Ethanol and the reaction mixture was irradiated at 50 °C for the appropriate time (TABLE 3). After completion of the reaction, the mixture was cooled in an ice bath and then filtered and washed with cold ethanol to separate the precipitated product. The obtained solid was then dissolved in ethyl acetate and the catalyst was recovered by a magnetic field of 1.4 T. Recrystallization from ethyl acetate provided the pure products and the recovered catalyst was washed with acetone and reused for successive cycles.

Selected spectroscopic data

3-hydroxy-1-methyl-3-(pyridin-2-ylmethyl)indolin-2-one, **3b**

Pale Yellow solid, m.p. 136 °C; IR (KBr): ν (cm^{-1}); 601, 752, 1092, 1470, 1610, 1715, 2963, 3353. ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 3.08 (d, J = 14.8 Hz, 1H), 3.18 (s, 3H), 3.33 (d, J = 14.8 Hz, 1H), 6.77–6.84 (m, 2H), 6.94 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.25 (m, 2H), 7.52 (s, 1H), 7.65 (t, J = 7.8 Hz, 1H), 8.59 (d, J = 4.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3 , 25 °C): δ = 26.21, 42.60, 76.22, 108.24, 122.32, 122.69, 123.90, 124.61, 129.38, 131.01, 137.10, 140.33, 143.00, 148.20, 157.72 ppm. Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$: C, 70.85; H, 5.55; N, 11.02. found: C, 70.88; H, 5.54; N, 11.02.

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DISCUSSION AND CONCLUSIONS

In order to optimize the reaction conditions, 2-methylpyridine and isatin were selected as model substrates and progress of the reaction was monitored by GLC technique. To examine the influence of the cata-

lyst type and loading, the reaction was carried out in different catalysts and loadings. Decrease in the corresponding 2-methylpyridine peak areas was selected as a measure of reaction progress. Also, the peak of ethanol was used as internal standard. The results are summarized in TABLE 1.

TABLE 1 : Effect of different catalysts and loadings on the reaction of 2-methylpyridine and isatin

Entry ^a	Reaction time, min	2-methylpyridine consumption, %	Catalyst Type	Catalyst Loading
1	15	10	Fe ₃ O ₄ nanoparticles	300 mg
2	30	42	"	"
3	60	77	"	"
4	90	80	"	"
5	90	<5	Commercial magnetite granules	"
6	60	35	FeCl ₃ ·6H ₂ O	5 mol%
7	60	<5	FeCl ₂ ·4H ₂ O	"

^aThe reaction was carried out according to general experimental procedure.

Based on these data, 300 mg of Fe₃O₄ nanoparticles per mmole of 2-methylpyridine was selected as the optimized catalyst concentration. Commercial magnetite granules, on the other hand, were not as satisfying (entry 5). Higher activity of Fe₃O₄ nanoparticles may be attributable to the larger surface area of these particles. Considering a Lewis acid role for the catalyst, led to a comparison between Fe⁺³ and Fe⁺² ions in a homogeneous system. Fe⁺³ resulted in a moderate consumption of 2-methylpyridine, while Fe⁺² failed in this reaction (entries 6, 7). Hence, higher efficiency of Fe₃O₄ nanoparticles against homogeneous Fe⁺³ ions may be related to the Fe⁺³ species of the crystal structure and their oxide counterparts.

In order to confirm heterogeneity of the catalyst, the reaction of 2-methylpyridine and isatin was interrupted half way of the reaction. The catalyst was removed by a magnetic field of 1.4 T and the reaction continued without catalyst. GLC analysis showed 35% of 2-methylpyridine consumption before interruption (30 min), and an additional 5% consumption of 2-methylpyridine after 6 h. This result showed that no considerable leaching of cations was occurred during the reaction. Solvent screening experiments showed that the yields were solvent dependent (TABLE 2). A mixture of H₂O: Ethanol (60:40) was used as the best solvent. Large excess of water may have a dual role. First, it helps precipitation of the products and results in an

easy work-up procedure and catalyst recycling (see experimental), which minimizes organic solvent waste. Second, it may prevent dehydration of the product and subsequent attack of a second nucleophile to form 3,32-di(pyridin-2-ylmethyl)indolin-2-one.

TABLE 2 : Effect of solvents on the yield of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-one

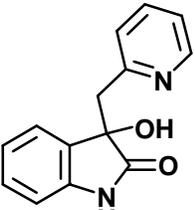
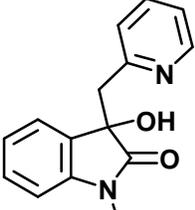
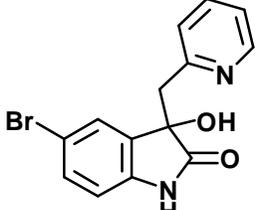
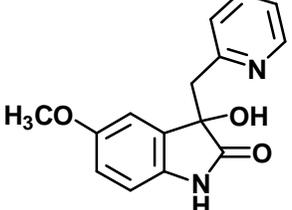
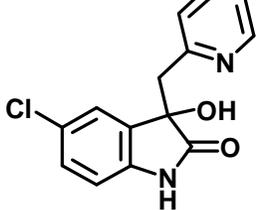
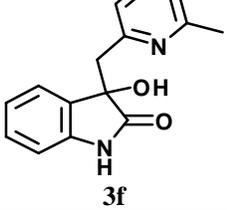
Entry ^a	Solvent	Reaction time, min	Yield ^b %
1	1,4-dioxane	60	55
2	THF	"	38
3	Toluene	"	32
4	Ethanol	"	63
5	H ₂ O: Ethanol (60:40)	"	75

^aThe reaction was carried out according to general experimental procedure; ^bIsolated yields.

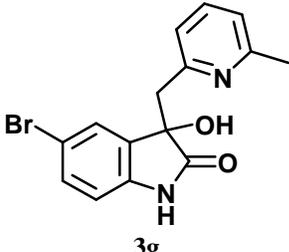
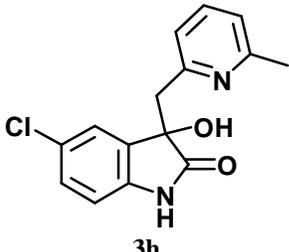
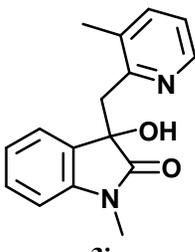
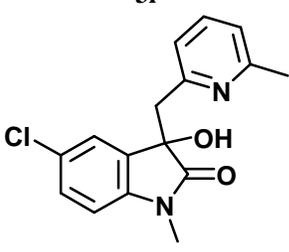
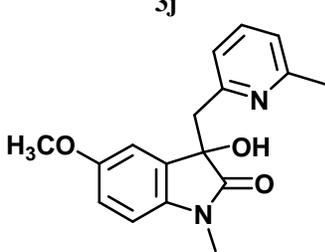
With the optimized conditions in hand (Scheme 1), various substrates were used and indicated the generality and scope of the reaction. Typical results are shown in TABLE 3. In all cases, the products were insoluble in the reaction media and a simple work-up provided spectroscopically pure products.

As it is evident from these data, isatins bearing electron releasing substituents resulted in higher yields and shorter reaction times. Specially, substituents on the 5-position of the isatin ring system, have a more dramatic effect (entries b-e). All of the reactions were also, conducted in the absence of ultrasound irradiation. In this

TABLE 3 : Ultrasound-assisted synthesis of 3-azaaryl-3-hydroxyindolin-2-ones catalyzed by Fe₃O₄ magnetic nanoparticles

Entry ^a	R ₁ , R ₂ , R ₃	Product	Reaction time, min	Yield (%) ^{b,c}	
				Ultrasound irradiated	Mechanically stirred
a	H, H, H	 3a	60	75	68
b	H, methyl, H	 3b	45	78	62
c	5-bromo, H, H	 3c	30	92	79
d	5-methoxy, H, H	 3d	30	85	77
e	5-chloro, H, H	 3e	60	73	63
f	H, H, 6-methyl	 3f	75	73	65

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Entry ^a	R ₁ , R ₂ , R ₃	Product	Reaction time, min	Yield (%) ^{b,c}	
				Ultrasound irradiated	Mechanically stirred
g	5-bromo, H, 6-methyl		60	88	70
h	5-chloro, H, 6-methyl		90	72	60
i	H, methyl, 3-methyl		75	68	62
j	5-chloro, methyl, 6-methyl		75	64	58
k	5-methoxy, methyl, 6-methyl		55	70	66

^aAll products were characterized by ¹H NMR, ¹³C NMR and IR data; ^bIsolated yields; ^cIdentified by comparison with authentic samples^[22-25].

case, vigorous mechanical stirring of the reaction mixture, provided slightly lower yields of the products. These results revealed the potential application of ultrasound irradiation in promotion of this reaction. Ultrasound irradiation in fact, is known to generate extremely fine emulsions to enhance mass transfer^[29].

In order to evaluate reusability of the catalyst, the reaction of 2-methylpyridine and isatin was carried out in the presence of the recycled catalyst in successive runs. From reaction run 1 to 5, the yields were 75%, 75%, 73%, 69% and 56%, respectively. Therefore after five runs, 19% decrease in the efficiency of catalyst

was observed.

In brief, a combination of Fe₃O₄ magnetic nanoparticles and ultrasound irradiation was found to be an effective catalytic system for preparation of 3-azaaryl-3-hydroxyindolin-2-ones. Highlights of the present work are: higher yields, easy work-up, use of nontoxic solvents and milder reaction conditions.

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