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PAPER

Manganese ferrite nanoparticles catalyzed tandem and green synthesis of spirooxindoles

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An environmentally benign and efficient method for the synthesis of spirooxindoles has been developed via a one-pot and three-component reaction of isatins, malononitrile, and anilinolactones in the presence of catalytic amount of manganese ferrite nanoparticles in PEG-400, as a nontoxic, green, and reusable solvent. The significant advantages of this protocol are; the use of magnetically recoverable and reusable catalyst, high to excellent product yields, operational simplicity and the use of PEG-400 as an environment-friendly solvent.

Introduction

Multicomponent reactions (MCRs) are special types of synthetically important organic reactions in which three or more different starting materials come together in a single reaction vessel to produce a final product containing diverse substituents from all the reactants.[1] Such strategies are excellent tools in modern organic synthesis and medicinal chemistry due to the product diversity, operational simplicity, reduction in reaction steps and work-ups, less time and energy consumption and a high degree of atom economy.[2,3] In the last decade, with increasing environmental concerns, the design of new MCRs with eco-friendly, green procedures has drawn significant attention, especially in the fields of drug discovery, organic synthesis, and material science.[4,5] The use of polyethylene glycol (PEG), as a green solvent for organic synthesis has attracted extensive attention recently, due to its many pros such as; water solubility, thermal stability over a wide range of temperatures, recoverability, non-volatility, non-explosiveness, commercial availability, and low toxicity.[6] A number of organic reactions have been reported using PEG as a solvent medium or support for various organic transformations.[7-9] Therefore, additional MCRs has become a critical and demanding research area in organic chemistry for the synthesis of molecular complexity and heterocyclic compounds such as spirooxindoles.[10,11.]

Notes and references
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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

Spirooxindole cores are an important constituent in many natural and synthetic biologically active compounds, as well as in many drug molecules,[12] in which an indole system is joined to varied heterocyclic motifs at the C-3 position through a spiro carbon atom. Molecules containing the spirooxindole moiety are widely found in a number of natural products such as Spirotryprostatin A, Horsfiline, and Elacomine (Figure 1).[13] These natural products have been shown to possess a variety of important biological activities such as; anti-tumor,[14] anti-tuberculosis,[15] anti-microbial,[16] anti-mycobacterium,[17] anti-fungus,[18] anti-malaria,[19] and anti-oxidation.[20] Consequently, looking for efficient, new and concise synthetic methods to prepare spirooxindole fused heterocycles is a major challenge and a popular field in chemistry [21-23] In recent years several methods using a variety of reagents and catalysts have been reported for the promoting preparation of spirooxindoles. One of an interesting catalysts for the synthesis of spiirooxindole derivatives is magnetic nanoparticles.[24, 25]

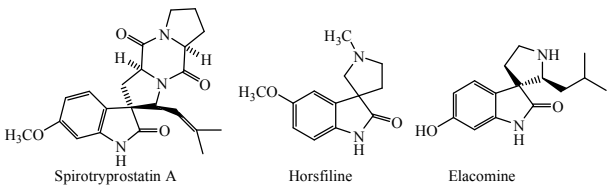

Figure 1. Selected spirooxindole natural products

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Magnetic nanoparticles are a group of nanostructured materials of considerable interest, largely due to their advanced technological and medical applications, envisioned or realized.[26,27] In recent years they have emerged as a suitable group of heterogeneous catalysts because of their extremely small size, large surface to volume ratio, and because they can achieve many of the goals of green chemistry. Magnetic nanoparticles open up new opportunities to come up with an amazing and efficient system to facilitate catalyst recovery in organic reactions, because the magnetic nature of these particles allows for simple recovery and recycling of the catalysts by an external magnet, and magnetic separation is an attractive alternative to filtration or centrifugation as it prevents the loss of catalyst and increases reusability.[28,29]

In this research we report an environmentally benign synthetic method to uncover a green protocol for one-pot three-component synthesis of 2-amino-2',5-dioxo-1-phenyl-5,7-dihydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,3'-indoline]-3-carbonitrile derivatives. This reaction was carried out by using manganese ferrite nanoparticles as an efficient, reusable, and recoverable catalyst in PEG-400, as a safe, inexpensive, reusable, and biodegradable polymeric solvent.

Experimental

The chemicals used in this work were obtained from Fluka and Merck and were used without purification. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO–d_6 solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (Cu K, radiation, k = 0.154056 nm), at a scanning speed of 2°/min from 10° to 100° /(2θ). Scanning electron microscope (SEM) was performed on a FEI Quanta 200 SEM operated at a 20 kV accelerating voltage. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

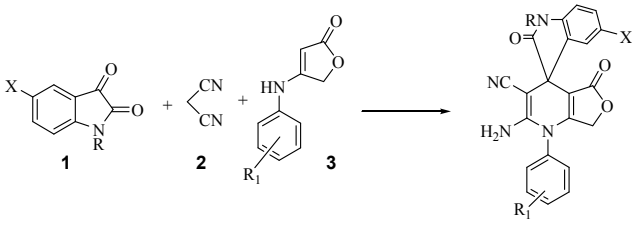
Typical experimental procedure for the preparation of catalyst

$MnFe_2O_4$ nanoparticles have been prepared following the reported standard protocol by co-precipitation of $MnCl_2$ and $FeCl_3$ in water in the presence of sodium hydroxide. Briefly, $MnCl_2{\cdot}4H_2O$ and $FeCl_3{\cdot}6H_2O$ were taken in molar ratio of Mn^{2+}: Fe^{3+}= 1:2 to prepare 0.3 mol·L^{-1} metal ion solution of 100 mL containing 0.1 mol·L^{-1} Mn^{2+} and 0.2 mol·L^{-1} Fe^{3+}. Then, it was slowly dropped into 100 mL NaOH solution of 3 mol·L^{-1} at the preheated temperature of 95°C. After aging for 2 h with continuous stirring, the mixture was filtered, washed and dried at 60°C for 12 h. [30]

Typical procedure for the preparation of 2-amino-2',5-dioxo-1-p-tolyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3'-indoline]-3-carbonitrile (5b): A mixture of isatin **1a** (1 mmol), malononitrile **2** (1 mmol), 4-(4-methylphenylamino) furan-2(3*H*)-one **3b** (1 mmol), and $MnFe_2O_4$ (5 mol%) were taken in PEG-400 (1 mL). The resulting mixture was stirred at 90°C for an appropriate time. After completion of the reaction as indicated by TLC, the mixture was magnetically concentrated with the aid of an external magnet to separate the catalyst. The separated catalyst washed with acetone several times followed by EtOH, then dried under vacuum and reutilized four times for the same reaction. After separation of the catalyst, H_2O (10 ml) was added to the reaction mixture and was shaken for a few minutes to dissolve PEG and precipitate the product. The crude product (insoluble in water) was filtered and re-crystallized by ethanol for more purification. The desired pure product was identified as white powder (Yield: 83%). mp>300°C. IR (KBr) (ν_{max}/ cm^{-1}): 3454, 2185, 1721, 1682. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.37 (3H, s, CH_3), 4.47-4.64 (2H, m, OCH_2) 5.99 (2H, s, NH_2), 6.82-7.44 (8H, m, ArH), 10.48 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 21.2, 48.2, 60.0, 66.1, 99.0, 109.8, 119.5, 122.5, 125.3, 128.9, 129.3, 131.2, 131.7, 134.3, 140.3, 141.8, 152.8, 159.6, 170.1, 178.0. Anal. Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58%;. Found C,68.69; H, 4.24; N, 14.53%. MS: *m/z* 384.

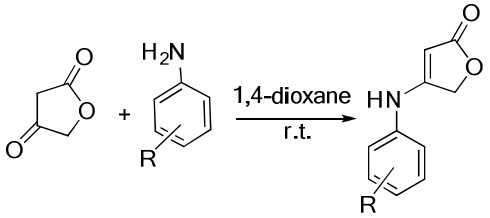
Results and discussion

Due to the unique properties of spirooxindole compounds and in continuation of our research for the efficient preparation of spirooxindole heterocycles [31-33] via a simple and environmentally benign synthetic method, a three component synthesis was planned based on foreseeing a one-pot reaction among isatins **1**, malononitrile **2**, and anilinolactones **3** for the synthesis of spirooxindoles (Scheme 1).



Scheme 1 One-pot synthesis of spirooxindoles.

Anilinolactones are versatile synthetic intermediates in organic synthesis that combine the nucleophilicity of an enamine and the electrophilicity of an enone. They are commonly applied in the preparation of heterocyclic compounds. [34,35] As shown in Scheme 2, when tetronic acid was reacted with an equimolar amount of various anilines in 1,4-dioxane at room temperature, the corresponding products were obtained in excellent yields and purity. [36]



Scheme 2. Synthetic rout of anilinolactones.

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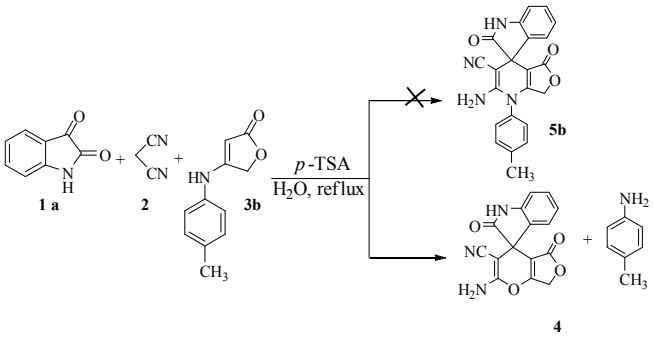
Recent studies on the preparation of spirooxindoles revealed that one of the usual conditions for their synthesis uses water as a solvent in the presence of p-toluenesulfonic acid (*p*-TSA) as an economical, non-toxic catalyst under reflux conditions. [37-40] Hence, the reaction of isatin **1a**, malononitrile **2**, and 4-(4-methylphenylamino) furan-2(3*H*)-one **3b** in a 1:1:1 molar ratio as a model substrate was refluxed for 8 hr in water with p-TSA (20%). After completion and work-up of the reaction a powdery product was obtained and purified.



Scheme 3. The reaction leading to the synthesis of spirooxindoles.

Product structure was characterized based on Mass, ^{1}H NMR, and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of product (as shown in Figure 2), the signal at δ= 10.70 ppm indicates the presence of –NH proton of oxindole ring (D_2O exchangeable), the NH_2 protons resonated at δ= 7.70 ppm with two integral values (exchangeable with D_2O), the aromatic protons exhibited multiplets in the region δ= 6.85–7.26 ppm with four integral values, the signals around δ= 5.06-5.21 ppm with two integral values are assigned to the protons of OCH_2 of tetronic acid. The ^{13}C NMR spectrum showed 15 distinct signals; also the mass spectrum of product displayed the molecular ion peak at *m/z*: 295. Surprisingly, the reaction did not proceed according to expectation and spectral data were inconsistent with the expected structure **5b**. Indeed, the data were in good agreement with the structure of an unprecedented product, and showed the structure of the unexpected product **4**. Also, the structure of the identity of the obtained product was confirmed by comparing its melting point with that of this previously. [41]

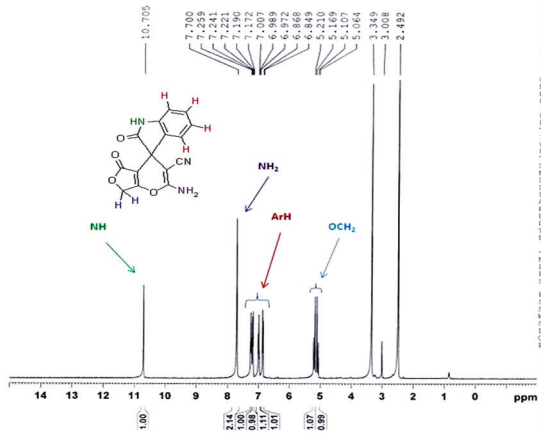
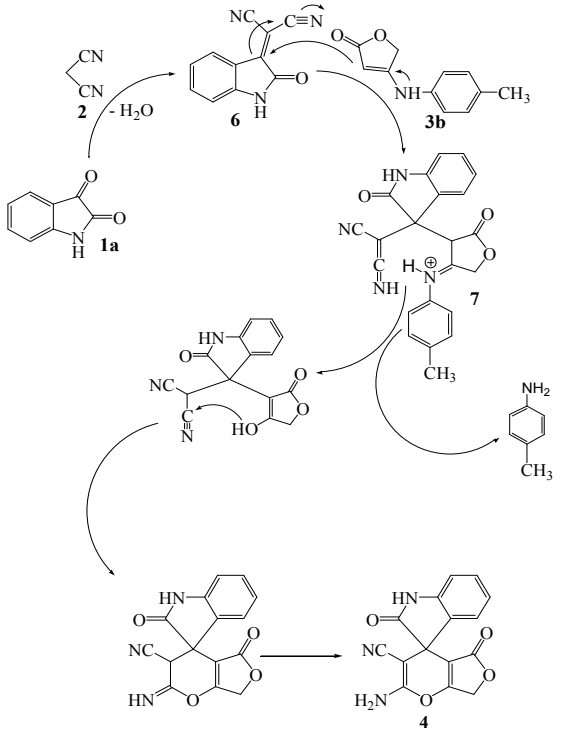


Figure 2. The ^{1}H NMR spectrum of 2-amino-2',5-dioxo-5,7-dihydrospiro[furo[3,4-*b*]pyran-4,3'-indoline]-3-carbonitrile **4**

Although the detailed mechanism of the above reaction has not yet been clarified, we proposed the possible pathway to form the spiro product **4** *via* domino reactions. As shown in Scheme 4, compound **4** could be synthesized *via* sequential condensation, addition, hydrolysis, cyclization and tautomerization. The reaction may proceed in a stepwise manner, in which the isatin **1a** can be firstly condensed with malononitrile **3** to afford isatylidene malononitrile **6** in the presence of *p*-TSA in water. This step was regarded as a fast Knoevenagel condensation reaction. Then, compound **6** is attacked by a Michael type addition with 4-(4-methylphenylamino) furan-2(3*H*)-one **3b** to produce the intermediate **7**. We suspect in the presence of *p*-TSA as a Bronsted acid and water, the iminium group in the intermediate **7**, was hydrolyzed followed by an intramolecular cyclization and tautomerizationto afford product **4** (Scheme 4). In the proposed mechanism, *p*-TSA may be able to catalyze the reaction steps due to its acidic nature.



Scheme 4. Proposed mechanism for the formation of compound **4**

In order to produce the expected product **5**, we continued to explore different catalysts and media on the model reaction (Scheme 5). The results are summarized in Table 1. As shown in this table, when we tested on the model reaction in PEG 400 or in ionic liquids (IL) with magnetic nanoparticles as the catalyst, the product **5b** was obtained (Table 1, entries 10-14). PEG-400 in the presence of $MnFe_2O_4$ as the catalyst proved to be the best system tested based on its reaction rate as well as yield while under other conditions as seen in Table 1, compound **4** was produced.

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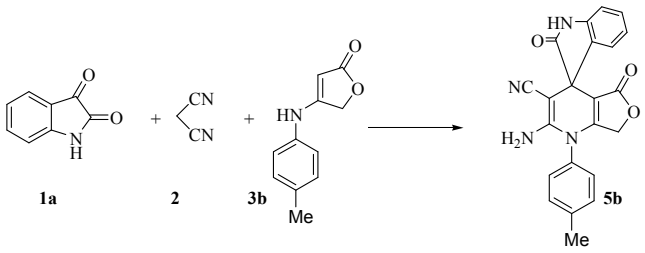

Scheme 5. Model reaction for the synthesis of 2-Amino-2',5-dioxo-1-*p*-tolyl-5,7-dihydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,3'-indoline]-3 carbonitrile **5b.**

Table 1. Screening on the various reaction conditions for the synthesis of **5b**

Entry	Medium	Catalyst	Product	Time (h)	Yield (%)[b]
1	H_2O(90°C)	*p*-TSA	**4**	8	75
2	H_2O(90°C)	Alum	**4**	12	68
3	EtOH(70°C)	*p*-TSA	**4**	12	69
4	CH_3CN(70°C)	*p*-TSA	**4**	12	48
5	[Bmim]Br(90°C)	*p*-TSA	**4**	4	70
6	[Bmim]PF_6(90°C)	*p*-TSA	**4**	4	73
7	PEG-400(100°C)	*p*-TSA	**4**	6	62
8	PEG-400(100°C)	CH_3COOH	**4**	6	51
9	PEG-400(100°C)	Nano $MnFe_2O_4$	**5b**	6	83
10	PEG-400(100°C)	Nano $CuFe_2O_4$	**5b**	6	70
11	PEG-400(100°C)	Nano Fe_3O_4	**5b**	8	46
12	[Bmim]PF_6(90°C)	Nano $MnFe_2O_4$	**5b**	8	54
13	[Bmim]PF_6(90°C)	Nano $CuFe_2O_4$	**5b**	8	51
14	PEG-400(100°C)	-	-	6	-
15	H_2O(90°C)	-	-	12	-
16	[Bmim]PF_6(90°C)	-	-	-	

[a]Reaction conditions isatin **1a** (1 mmol), malononitrile **2** (1 mmol), 4-(4 methylphenylamino) furan-2(3*H*)-one **3b** (1 mmol).

[b]Isolated yields.

Characterization of the catalyst

The manganese ferrite nanoparticles were prepared by co-precipitation of $MnCl_2$ and $FeCl_3$ in basic solution at 95°C using the previous reported method. The synthesized $MnFe_2O_4$ was characterized by X-ray diffraction (XRD), scanning electron microscope (SEM), and vibrating sample magnetometer (VSM). The position and relative intensities of all peaks were confirmed as well as with standard XRD pattern of $MnFe_2O_4$ (JCPDS card No. 73-1964). The calcined manganese ferrite at 800°C present a particle size of 33 nm, calculated from the broadening of the peak at $2\Theta = 35.31$ using the Scherer equation (Figure 3). The SEM image revealed that manganese ferrite nanoparticles have a mean diameter of about 30-35 nm (Figure 4). The magnetization curve for $MnFe_2O_4$ nanoparticles is shown in Figure 5. It is of great importance that a catalyst should possess sufficient magnetic and super paramagnetic properties for its practical application. Magnetic hysteresis measurements on $MnFe_2O_4$ were conducted in an applied magnetic field at room temperature, with the field sweeping from -10000 to +10000 Oersted. As shown in Figure 5, the hysteresis loop for the sample was completely reversible confirming its super paramagnetic nature. The catalyst showed high permeability in magnetization and high reversibility in the hysteresis loop.

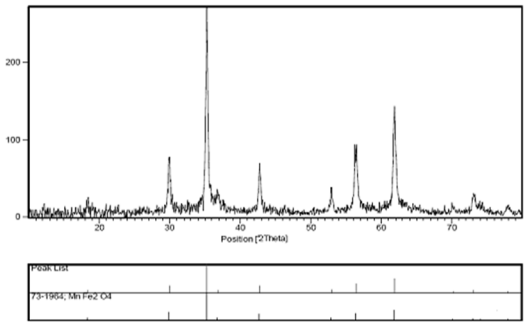

Figure 3. The X-ray diffraction patterns of calcinated $MnFe_2O_4$.

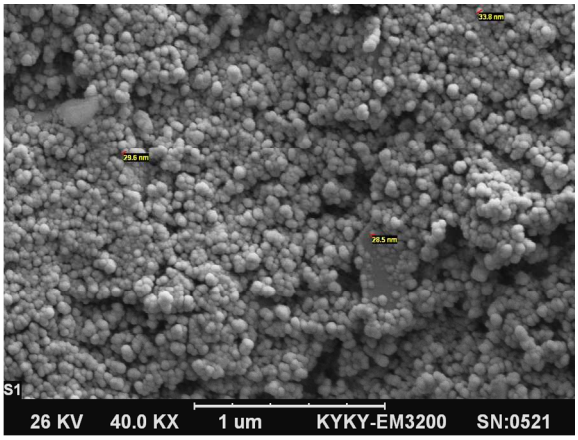

Figure 4. The SEM image of $MnFe_2O_4$ before the reaction

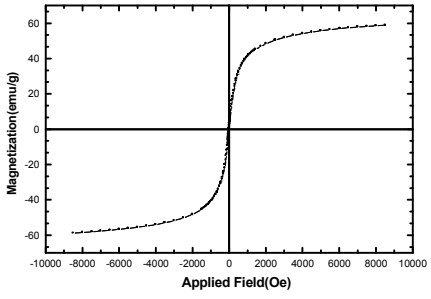

Figure 5. The vibrating sample magnetometer curve of synthesized$MnFe_2O_4$ nanoparticles.

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In the next step, in order to optimize the more suitable reaction conditions, we evaluated the amount of catalyst required, and the effect of temperature for this transformation. Our optimization studies revealed that when the model reaction was carried out in the presence of 2 mol% of catalyst, 62% yield is obtained. It was found that catalyst loadings above 5 mol% did not improve the reaction rate of yield. Thus 5 mol% of catalyst was chosen as the maximum quantity of the catalyst for the reaction (Table 2, Entry 2). Also, the effect of temperature was studied by carrying out the model reaction in PEG-400 at different temperatures in the presence of 5 mol% of catalyst. As shown in Table 2, when the reaction temperature was 25°C or 40°C (Table 2, Entries 5, 6), the reaction was proceeded, but the obtained yield remained low even after longer reaction time until 24 hr. However, at elevated temperature (40–90°C) using PEG-400 gave better results in terms of yield and reaction time. It was realized that when temperature increased up further to 110°C (Table 2, Entry 8), there was no significant improvement of the rate as well as yield of the reaction. Thus, the temperature of 90°C was found to be the most suitable reaction temperature for an optimum yield of desired product (Table 2, Entry 2).

Table 2 Evaluation of different amounts of the MnFe2O4 nanoparticles as catalyst and effect of temperature on the model reactiona.

Entry	Catalyst (mol%)	Temperature/°	Time (h)	Yield (%)[b]
1	2	90	8	62
2	5	90	6	83
3	10	90	8	83
4	20	90	8	84
5	5	25	24	<50
6	5	40	24	<50
7	5	70	10	72
8	5	110	6	83

[a]Reaction conditions: isatin **1a** (1 mmol), malononitrile **2** (1 mmol), 4-(4 methylphenylamino) furan-2(3*H*)-one **3b** (1 mmol), PEG-400 (1 mL)

[b]Isolated yields.

Most remarkably, we were also able to recycle the catalyst for five times with almost the same catalytic activity as illustrated in Figure 5. The catalyst was recovered in excellent yield (96–98%) after each of the new set of reaction. Isatin, malononitrile, and 4-(4-methylphenylamino) furan-2(3*H*)-one were also employed as the reactants of the model reaction for the reusability study of the catalyst at 90°C in PEG-400. In this procedure, after completion of the reaction, the catalyst could be magnetically recovered by an external magnetic field and the retained catalyst was washed with acetone to remove the residual product. After being dried, catalyst was subjected to other reaction runs. After separation of the catalyst, water (10 ml) was added to the reaction mixture and was shaken for a few minutes to dissolve PEG and precipitated the product. The crude product (insoluble in water) was filtered and washed with ethanol for further purification. The procedure was repeated and the results indicated that in five consecutive runs. The isolated yields were remained similar with no detectable loss (Figure 6).

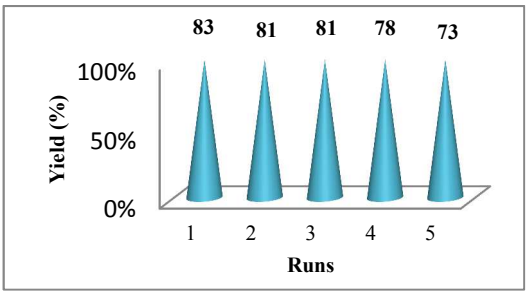

Figure 6. Catalyst recyclability study on the synthesis of 2-amino-2',5-dioxo-1-*p*-tolyl-5,7-dihydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,3'-indoline]-3-carbonitrile **5b**

Finally, we examined the recyclability of the PEG after the extraction of the product. In order to prove that the use of polyethylene glycol as environmentally benign solvent is also practical; it must be conveniently recycled with minimum loss and decomposition. In this procedure, after completion of the reaction, the crude product (insoluble in water) was filtered and recrystallized from ethanol for further purification. In order to recover the PEG, H_2O was evaporated under reduced pressure, and the result was washed with diethyl ether, and dried under reduced pressure. The recycled PEG does not change in its reactivity but approximately 5% weight loss of PEG was observed from cycle to cycle (Table 3).

Table 3. Evaluation of different amounts of the $MnFe_2O_4$ nanoparticles as catalyst and effect of temperature on the model reactiona.

No. of cycles	Fresh	Run 1	Run 2	Run 3
Product yield (%)[b]	83	82	80	80
Time (h)	6	6	6	6

[a]Reaction conditions: Isatin **1a** (1 mmol), malononitrile **2** (1 mmol), 4-(4 methylphenylamino) furan-2(3H)-one **3a** (1 mmol), $MnFe_2O_4$ (5 mol%), PEG-400 (1 mL), 90°C.
[b]Isolated

We have not established an exact mechanism for the formation of **5b**, however, a reasonable possibility based on literatures [42, 43] is shown in Scheme 6. Compound **5b** could be synthesized via sequential condensation, addition, cyclization and tautomerization. The process represents a typical domino reaction in which the activated isatin **1**, may be firstly condensed with malononitrile **2** to afford isatylidene malononitrile 6 in the presence of manganese ferrite nanoparticles as a catalyst in PEG-400. This step was regarded as a fast Knoevenagel condensation. Then, compound **6** is attacked by Michael addition of 4-(4-methylphenylamino) furan-2(3H)-one **3b** to give the intermediate **7**, followed by intra-molecular cyclization and tautomerization to afford the target product 5b. The manganese ferrite nanoparticles as a Lewis acid probably can catalyze the reaction steps.

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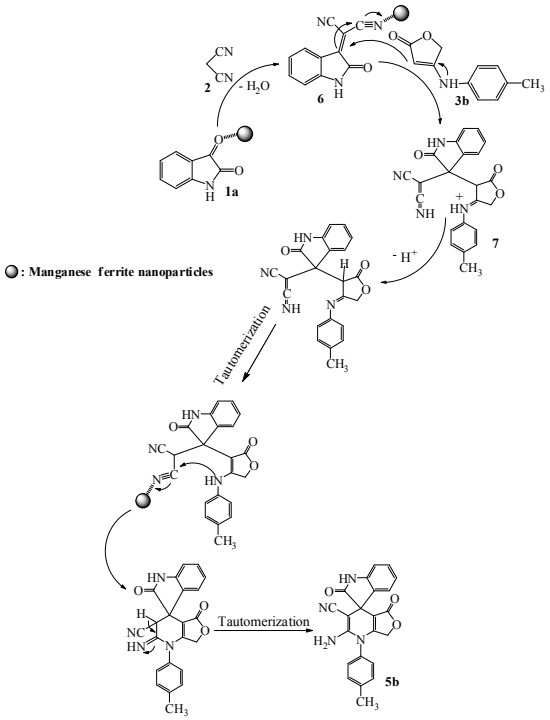
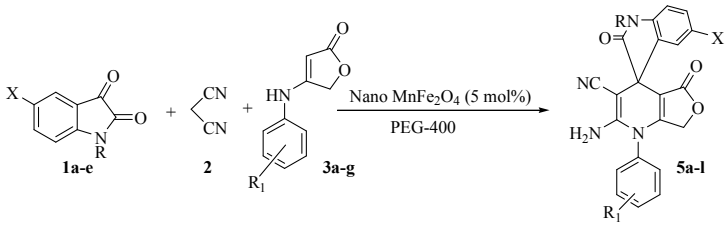


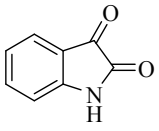
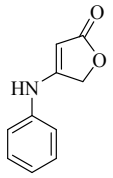
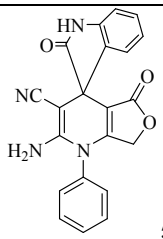
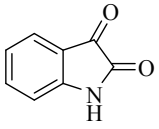
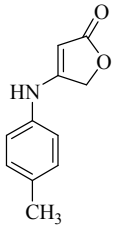
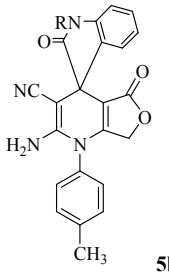
Scheme 6. Proposed mechanism for the synthesis of **5b.**

In order to generalize the optimum conditions and check the feasibility of this protocol, different derivatives of 2-amino-2',5 dioxo-1-phenyl-5,7-dihydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,3' indoline]-3-carbonitrile **5a-l** were prepared from the one-pot reaction mixture of isatins **1a-e**, malononitrile **2**, and anilinolactones **3a-g** in the presence of a catalytic amount of $MnFe_2O_4$ (5 mol%) in PEG-400 at 90°C. The results are summarized in Table 4. Compounds **5a–l** are stable solids and the structures of which were determined by IR, Mass, ^1H and ^{13}C NMR spectroscopy, and elemental analysis.

To determine the percent leaching of the manganese ferrite nanoparticles, the model reaction was carried out in the presence of catalyst for 1h, and at that point the catalyst was separated by external magnet. The residue was then allowed to react, but no significant progress was observed after 24h. Also, it was determined the amount of Fe and Mn metals in product **4a** as a model reaction by atomic absorption in that the quantity of the residue of Fe and Mn metals was not detectable.

Table 4. Synthesis of spiro-furo-pyridine-indoline-carbonitrile via one-pot three component reaction catalyzed by manganese ferrite nanoparticles in PEG-400[a]



Entry	Isatin 1	Anilinolactone 3	Product 5	Time (h)	Yield(%)[b]
1			 **5a**	5	79
2			 **5b**	5	83

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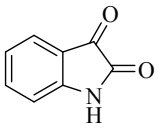
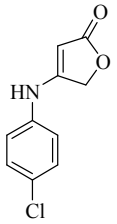
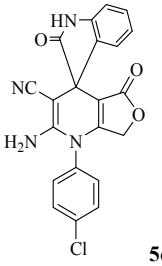
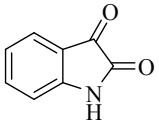
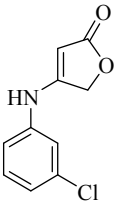
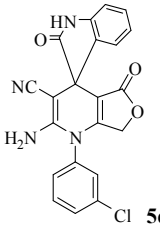
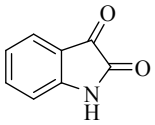
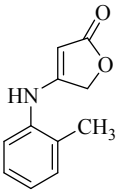
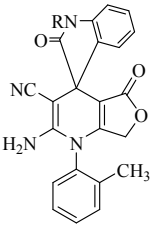
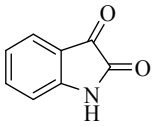
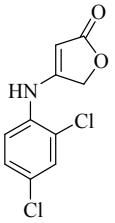
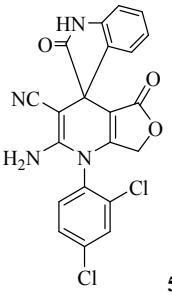
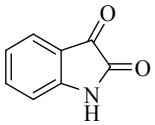
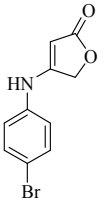
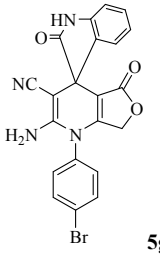
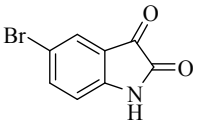
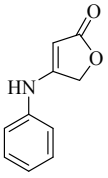
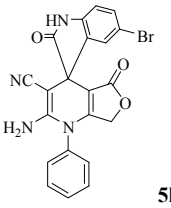
3			 **5c**	5	80
4			 **5d**	5	77
5			 **5e**	5	80
6			 **5f**	5	79
7			 **5g**	5	75
8			 **5h**	4	73

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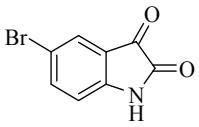
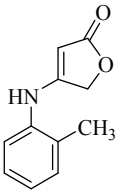
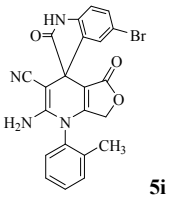
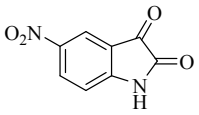
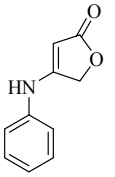
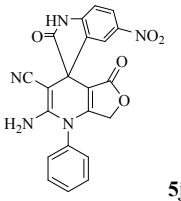
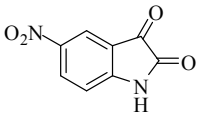
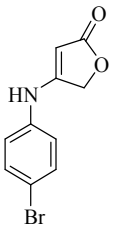
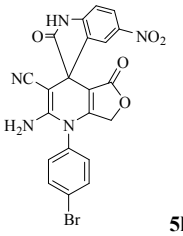
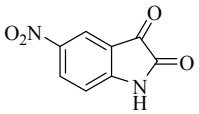
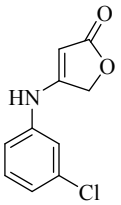
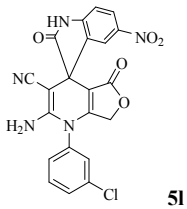
9			 **5i**	4	76
10			 **5j**	3	81
11			 **5k**	3	84
12			 **5l**	3	75

[a]Reaction conditions: isatin **1a-e** (1 mmol), malononitrile **2** (1 mmol), anilinolactones **3a-g** (1 mmol), $MnFe_2O_4$ (5 mol%), PEG-400 (1 mL), 90°C.
[b]Isolated yields.

Conclusions

In conclusion, we have developed an efficient and more environmentally friendly protocol for the one-pot synthesis of spirooxindoles via a three-component condensation reaction of isatins, malononitrile, and anilinolactones by using manganese ferrite nanoparticles as a powerful catalyst in PEG-400. The notable features of this procedure are mild and green reaction conditions, convenient workup, recyclability and reusability of the magnetic catalyst, high to excellent product yields, and recyclability of PEG.

Acknowledgements

This study is part of Zahra Rashid Ph. D thesis entitled: "Synthesis, modification and functionalization of magnetic nanoparticles for catalytic application in the synthesis of heterocyclic compounds and biomedical applications" which has been conducted in the Nanobiotechnology Research Center, Avicenna Research Institute. And also, we are thankful from University of Kashan for supporting this work by grant number 159148/15.

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