

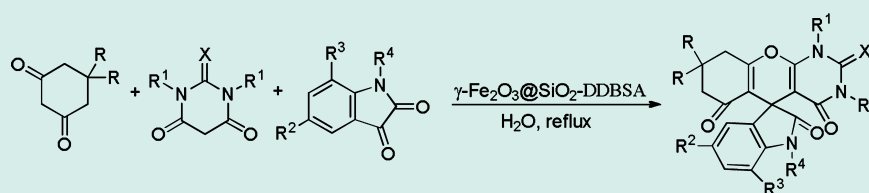
One-Pot, Three-Component Synthesis of a Library of Spirooxindole-Pyrimidines Catalyzed by Magnetic Nanoparticle Supported Dodecyl Benzenesulfonic Acid in Aqueous Media

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S Supporting Information



ABSTRACT: Dodecyl benzenesulfonic acid functionalized silica-coated magnetic nanoparticles ($\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$) were readily prepared and identified as an efficient catalyst for the synthesis of a library of spirooxindole-pyrimidine derivatives by three-component condensation reaction of barbituric acids, isatins and cyclohexane-1,3-diones. The aqueous reaction medium, easy recovery of the catalyst using an external magnet, and high yields make the protocol sustainable and economic.

KEYWORDS: one-pot synthesis, three-component reaction, spirooxindole-pyrimidine derivatives, functionalized silica-coated magnetic nanoparticles

INTRODUCTION

Currently, the development of new strategies for the recycling of catalysts has become an important research field for reasons of economic and environmental impact. Although catalysts immobilized on heterogeneous supports such as polystyrene and inorganic materials allow for recycling through filtration or centrifugation inevitably leads to the loss of the catalyst in the separation processes. To further address the issues of recyclability and reusability, magnetic nanoparticles (MNPs) have emerged as an attractive catalyst support because of their ability to be separated by magnetic fields. Moreover, magnetic nanoparticles have high surface area, low toxicity and price, remarkable chemical and mechanical stability. The surface of MNPs can be functionalized easily through appropriate surface modifications to enable the loading of a variety of desirable functionalities. Recently, MNPs have been successfully utilized to immobilize enzymes, transition metal catalysts and organo-catalysts.^{1–5} Meanwhile, multicomponent reactions (MCRs) have the great advantage of eliminating the isolation of unstable intermediates, and reducing the number of discrete chemical steps and waste products.⁶ On the other hand, spirooxindoles and pyrimidines are ubiquitous heterocyclic structural motifs present in a large number of natural and synthetic molecules with a wide range of utilities in medicinal chemistry.⁷ Thus, design of a recyclable catalytic system that promotes efficient one-pot synthesis of spirooxindole-pyrimidine derivatives is still highly desirable.

We have recently reported that magnetic Fe_3O_4 nanoparticles are excellent catalysts for the synthesis of quinoxalines⁸ and 2,3-dihydroquinazolin-4(1H)-ones.⁹ We have developed an efficient method for one-pot reductive amination of carbonyl compounds using NaBH_4 in the presence of a magnetically recoverable $\gamma\text{-Fe}_2\text{O}_3\text{@HAP-SO}_3\text{H}$.¹⁰ Immobilization of TfOH onto the silica-coated magnetic nanoparticles has also been successfully achieved.¹¹ In continuation with our interest in developing efficient and environmental benign synthetic methodologies,¹² we have prepared a new type of immobilized dodecyl benzenesulfonic acid (DDBSA) catalyst using magnetic nanoparticles ($\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$) and found that it is a highly active and recyclable catalyst for the synthesis of spirooxindole-pyrimidine derivatives by the three-component condensation reaction of cyclohexane-1,3-diones, barbituric acids and isatins or acenaphthylene-1,2-dione in refluxing water (Scheme 1).

RESULTS AND DISCUSSION

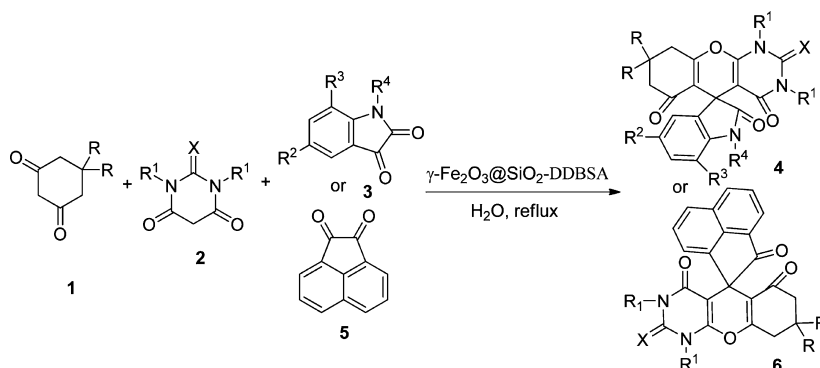
The MNP-supported DDBSA catalyst was prepared according to the procedure shown in Scheme 2. Coating of a layer of silica on the surface of $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles was achieved by sonication of $\gamma\text{-Fe}_2\text{O}_3$ suspension in an alkaline ethanol–water

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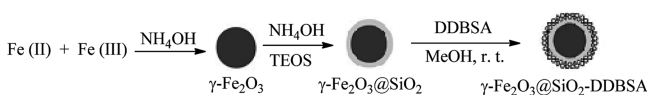
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Scheme 1. Synthesis of 8,9-Dihydrospiro[chromeno[2,3-d]pyrimidine-5,3'-indoline] and Spiro[acenaphthylene-1,5'-chromeno[2,3-d]pyrimidine] Derivatives



Scheme 2. Synthesis of $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$

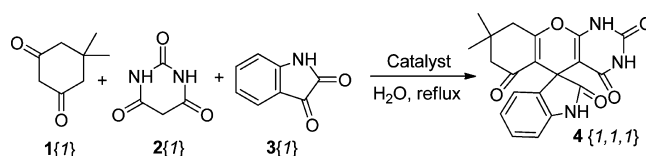


solution of tetraethyl orthosilicate (TEOS). Then, DDBSA was added to a suspension of $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$ in methanol, while dispersed by sonication. The mixture was concentrated and the residue was heated at 110 °C for 2 h under vacuum to obtain DDBSA-functionalized silica-coated magnetic nanoparticles [$\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$] (Scheme 2). The loading of DDBSA moiety on surface was determined by means of back-titration and pH analysis (0.25 mmol/g, 10 mg = 0.0025 mmol of DDBSA). The energy dispersive spectrum (EDS) indicated the presence of Fe, S, Si, O, and C. Scanning electron microscopy (SEM) revealed that the catalyst presented the uniform size of nanoparticles with average diameter around 50 nm. Transmission electron microscopy (TEM) further confirmed this catalyst was encapsulated by a thin silica layer. FT-IR spectra of $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$ displayed peaks that are characteristic of functionalized DDBSA group, which clearly differs from that of the unfunctionalized silica-coated nanomagnets ($\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$).¹³ The magnetic core was analyzed by XRD and the observed diffraction pattern agrees well with the JCPDS database for magnetite (see the Supporting Information, Figures 1–3).

The activity of the prepared catalyst as described above was next tested in the model reaction of 5,5-dimethylcyclohexane-1,3-dione **1**{1}, barbituric acid **2**{1}, and isatin **3**{1} in refluxing water. The reaction occurred smoothly in the presence of 15 mol % of $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$, affording a single product in 95% yield (Table 1, entry 15). Although $\gamma\text{-Fe}_2\text{O}_3\text{@HAP-SO}_3\text{H}$ is well-known to be a good catalyst for some organic reactions,^{10,14} its catalytic activity for this reaction was lower than $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$ (Table 1, entry 13). Other catalysts including acetic acid, trifluoromethanesulfonic acid, silicotungstic acid, $\text{HClO}_4/\text{SiO}_2$, LiCl and cerium ammonium nitrate were less effective (Table 1, entries 2–7). Notably, only a trace amount of the target product was observed when the reaction was performed in the absence of the catalyst (Table 1, entry 1).

The efficiency of the supported catalyst was found to be affected by the nature of the solvent and the quantity of the catalyst used in the reaction. After solvent screening, water proved to be the best choice for this transformation. The reaction was also monitored with different catalyst loading and

Table 1. Influence of Different Catalysts on the Reaction of 5,5-Dimethylcyclohexane-1,3-dione, Barbituric Acid, and Isatin^a



entry	catalyst (15 mol %)	time (h)	yield (%) ^b
1	no	10	trace
2	acetic acid	10	15
3	trifluoromethanesulfonic acid	10	25
4	silicotungstic acid	10	51
5	$\text{HClO}_4/\text{SiO}_2$	10	40
6	LiCl	10	13
7	cerium ammonium nitrate	10	28
8	nano Fe_3O_4	10	trace
9	nano $\gamma\text{-Fe}_2\text{O}_3$	10	trace
10	nano $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2$	10	trace
11	nano $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-HClO}_4$	10	30
12	nano $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-HBF}_4$	10	20
13	nano $\gamma\text{-Fe}_2\text{O}_3\text{@HAP-SO}_3\text{H}$	10	25
14	nano $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-H}_3\text{PW}_{12}\text{O}_{40}$	10	35
15	nano $\gamma\text{-Fe}_2\text{O}_3\text{@SiO}_2\text{-DDBSA}$	3	95

^aExperimental conditions: 5,5-dimethyl-cyclohexane-dione (1 mmol), barbituric acid (1 mmol), isatin (1 mmol), catalyst (15 mmol %), and H_2O (5 mL). ^bIsolated yields.

the results showed that 15 mol % of catalyst was the best choice for the completing the reaction. At a lower catalyst loading the reaction took longer and was not completed.

With the optimal conditions, we embarked on an investigation of the substrate scope of this new multi-component domino process with two cyclohexane-1,3-diones, three barbituric acids, and ten isatins (Figure 1 and Scheme 1). The results are summarized in Table 3. Various isatins reacted efficiently with dimedone and barbituric acids to afford the desired 8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraones (**4**) in high yields (Table 3, entries 1–16). Variation of the electronic properties of the substituents at either C5 of isatins was tolerable with high yields ranging from 88% to 95%. Furthermore, the nitrogen protected isatin substrates were suitable for the reaction, but no reaction was observed with more sterically demanding substrates, such as 4-bromoisatin. When malonyl urea was replaced by thiobarbituric acid, 2-thioxo-2,3,8,9-tetrahydrospiro[chromeno-

Table 2. Optimization of Reaction Conditions^a

entry	catalyst loading (mol %)	solvent	temperature (°C)	time (h)	yield (%) ^b
1	15	CH ₂ Cl ₂	reflux	10	20
2	15	THF	reflux	10	30
3	15	CH ₃ CN	reflux	10	32
4	15	MeOH	reflux	10	40
5	15	EtOH	reflux	10	51
6	15	DMF	reflux	10	35
7	15	Toluene	reflux	10	20
8	15	DMSO	100	10	36
9	5	H ₂ O	reflux	6	70
10	10	H ₂ O	reflux	4	83
11	15	H ₂ O	reflux	3	95
12	20	H ₂ O	reflux	3	95

^aExperimental conditions: 5,5-dimethyl-cyclohexane-dione (1 mmol), barbituric acid (1 mmol), isatin (1 mmol), and solvent (5 mL).

^bIsolated yields.

[2,3-*d*]pyrimidine-5,3'-indoline]-2',4,6(1*H*,7*H*)triones were also obtained in high yields (Table 3, entries 29–40). In addition, the model reaction was carried out in a scale of 50 mmol. As expected, the reaction proceeded nicely to afford the desired product in 92% yield in 3.5 h.

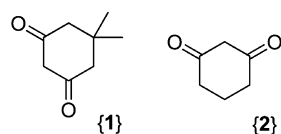
To further expand the potential of this approach as a tool for the construction of spirooxindole-pyrimidines, we investigated the reaction of acenaphthylene-1,2-dione (5), barbituric acids, and cyclohexane-1,3-diones. As shown in Table 3, all the

examined substrates gave the corresponding spiro[acenaphthylene-1,5'-chromeno[2,3-*d*]pyrimidine] derivatives (6) in high yields under the same reaction conditions. Unfortunately, although we screened a lot of conditions, acyclic 1,3-diones such as acetylacetone and dibenzoylmethane failed to give the desired spirooxindole-pyrimidines.

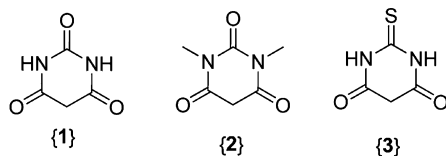
The structures of the prepared 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4,6(1*H*,3*H*,7*H*)-tetraones (4) and spiro[acenaphthylene-1,5'-chromeno[2,3-*d*]pyrimidine] derivatives (6) were characterized by spectroscopic methods. In cases of compounds 4 and 6, the products were obtained as 1:1 mixtures of diastereomers. In addition, the structure of product 4{2,2,5} was further confirmed by single crystal X-ray (see the Supporting Information, Figure 4).

Although the exact mechanism for this three-component reaction has not been established at present, a plausible mechanism for the formation of 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline] derivatives (4) (Scheme 3) is presented on the basis of the analysis of similar multi-component reaction of isatin.⁷ First, reaction of dimedone 1{1} with isatin 3{1} to yield intermediate I, which reacted further with barbituric acid 2{1} to form intermediate III, followed by cyclization to afford 4{1,1,1} and water. Alternatively, the intermediate III may be produced by addition of dimedone 1{1} to intermediate II derived from the reaction between isatin 3{1} and barbituric acid 2{1}. Attempts to isolate intermediate I and II did not successful due to they are too reactive. The intermediate I was quickly converted into 3',3',6',6'-tetramethyl-3',4',6',7'-tetrahydrospiro[indoline-3,9'-

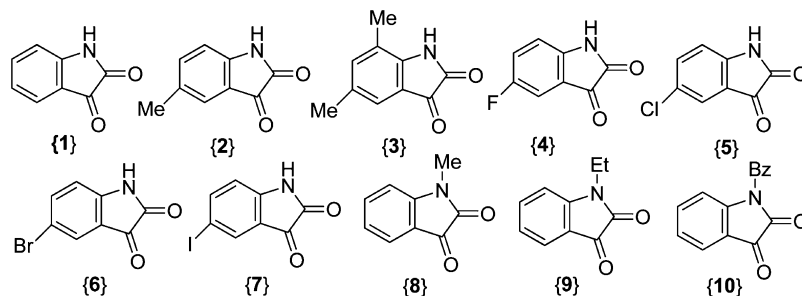
Cyclohexane-1,3-diones 1:



Barbituric acids 2:



Isatins 3:



Acenaphthylene-1,2-dione 5:

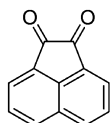


Figure 1. Diversity of reagents.

Table 3. One-Pot Synthesis of 8,9-Dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline] Derivatives 4 and Spiro[acenaphthylene-1,5'-chromeno[2,3-*d*]pyrimidine] Derivatives 6

entry	product	time (h)	yield (%) ^a	mp (°C)	
				found	reported
1	4{1,1,1}	3.0	95	>300	>300 ^{7e}
2	4{1,1,2}	5.5	93	292–293	290 ^{7e}
3	4{1,1,3}	6.0	92	>300	
4	4{1,1,4}	1.0	95	>300	
5	4{1,1,5}	2.0	95	>300	
6	4{1,1,6}	2.5	94	>300	>300 ^{7e}
7	4{1,1,7}	4.0	93	>300	
8	4{1,1,8}	3.0	95	>300	>300 ^{7e}
9	4{1,1,9}	3.0	93	250–251	253–255 ^{7k}
10	4{1,1,10}	3.0	90	256–257	258–259 ^{7k}
11	4{1,2,1}	3.5	95	>300	>300 ^{7e}
12	4{1,2,2}	3.5	94	>300	
13	4{1,2,4}	1.5	95	>300	
14	4{1,2,5}	2.5	95	>300	
15	4{1,2,6}	3.0	95	>300	
16	4{1,2,8}	3.5	90	250–251	250 ^{7e}
17	4{2,1,1}	3.0	93	>300	>300 ^{7e}
18	4{2,1,2}	6.0	88	>300	
19	4{2,1,4}	1.0	94	>300	
20	4{2,1,5}	2.0	93	>300	
21	4{2,1,6}	2.5	93	243–244	242–245 ^{7k}
22	4{2,1,8}	3.5	94	>300	>300 ^{7e}
23	4{2,2,1}	3.5	92	>300	
24	4{2,2,2}	5.5	85	>300	
25	4{2,2,4}	1.5	94	>300	
26	4{2,2,5}	2.5	93	>300	
27	4{2,2,6}	3.0	93	288–289	285 ^{7e}
28	4{2,2,8}	3.5	90	292–293	290 ^{7e}
29	4{1,3,1}	4.0	95	>300	
30	4{1,3,2}	6.0	94	>300	
31	4{1,3,4}	2.0	93	>300	
32	4{1,3,5}	3.0	95	>300	
33	4{1,3,6}	3.5	93	282–283	280 ^{7e}
34	4{1,3,8}	4.0	93	>300	>300 ^{7e}
35	4{2,3,1}	4.0	92	>300	>300 ^{7e}
36	4{2,3,2}	6.0	88	>300	
37	4{2,3,4}	2.0	91	>300	
38	4{2,3,5}	2.0	93	>300	
39	4{2,3,6}	3.5	93	>300	>300 ^{7e}
40	4{2,3,8}	4.0	88	>300	
41	6{1,1,5}	3.0	94	>300	>300 ^{7e}
42	6{1,2,5}	3.0	91	>300	
43	6{1,3,5}	3.5	93	291–293	292–294 ^{7e}
44	6{2,1,5}	3.5	93	>300	
45	6{2,2,5}	3.5	91	>300	
46	6{2,3,5}	4.0	92	>300	

^aIsolated yield.

xanthene]-1',2,8'(2*H*,5'*H*)-trione (**7**)¹⁵ through reaction further with another molecule of dimedone. The intermediate **II** was converted into 5,5'-(2-oxoindoline-3,3'-diyl)bis(pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**8**)¹⁶ with another molecule of barbituric acid. It is a pity that our results can not distinguish between these two mechanisms at this time.

The recyclability of magnetic γ -Fe₂O₃@SiO₂-DDBSA was examined using the model reaction of 5,5-dimethyl-cyclo-

hexanedione, barbituric acid and isatine. After each run, THF was added to dissolve the product, and the catalyst was separated by attaching an external magnet onto the reaction vessel. After a simple wash by THF and subsequent vacuum removal of residual solvent, the catalyst was reused for next run. To our delight, the catalyst was highly reusable under the investigated conditions, preserving almost unaltered its initial catalytic activity after six uses (see the Supporting Information, Figure 5). No quantifiable amount of leached Fe was detected in the filtrates as determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES). Furthermore, the TEM images of the catalyst after six recycles did not show any significant change in the shape and size of catalyst particles, proving its robustness.

CONCLUSIONS

In summary, we have developed an efficient one-pot, three-component reaction of barbituric acids, isatins, and cyclohexane-1,3-diones for the direct construction of a library of spirooxindole-pyrimidine derivatives catalyzed by nano magnetically silica-supported dodecyl benzenesulfonic acid in water. Product separation and catalyst recycling are easily accomplished with the assistance of the external magnet. The catalyst can be recycled at least six times.

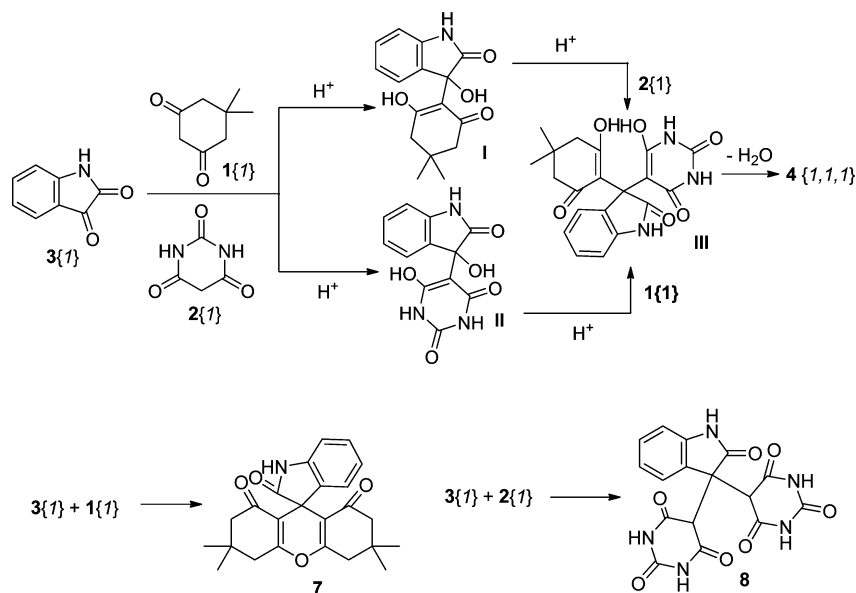
EXPERIMENTAL PROCEDURES

General. All solvents and chemicals were obtained commercially and were used as received. Sonication was performed in a KQ-250E ultrasonic clearer with a frequency of 40 kHz and a nominal power 250 W. X-ray diffraction analysis was carried out using a PANalytical X'Pert Pro X-ray diffractometer. Surface morphology and particle size were studied using a Hitachi S-4800 SEM instrument. Transmission electron microscope (TEM) observation was performed using Hitachi H-7650 microscope at 80 KV. Elemental compositions were determined with a Hitachi S-4800 scanning electron microscope equipped with an INCA 350 energy dispersive spectrometer (SEM-EDS) presenting a 133 eV resolution at 5.9 keV. Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were recorded using a Bruker-TENSOR 27 spectrometer instrument. NMR spectra were taken with a Bruker DRX-500 spectrometer at 500 MHz (¹H) and 125 MHz (¹³C) using DMSO-*d*₆ as the solvent with TMS as internal standard. Elemental analyses were obtained on a Vario EL III CHNOS elemental analyzer.

Preparation of Dodecyl Benzenesulfonic Acid-Functionalized Silica-Coated Magnetic Nanoparticles. The γ -Fe₂O₃ was prepared by a chemical coprecipitation technique of ferric and ferrous ions in an alkaline solution according to the literature procedures.¹⁷ Coating of a layer of silica on the surface of the γ -Fe₂O₃ was achieved by premixing (ultrasonic) a dispersion of the purified γ -Fe₂O₃ nanoparticles (8.5% w/w) with ethanol (80 mL) for 1 h at 40 °C. A concentrated ammonia solution (1.5 mL) was added and the resulting mixture stirred at 40 °C for 30 min. Subsequently, tetraethyl orthosilicate (TEOS, 1.0 mL) was charged to the reaction vessel and the mixture continuously stirred at 40 °C for 24 h. The silica-coated NPs were collected using a permanent magnet, followed by washing three times with ethanol, diethyl ether, and drying at 100 °C in a vacuum for 24 h.

To a suspension of γ -Fe₂O₃@SiO₂ (10.0 g) in 250 mL of dry methanol, dodecyl benzenesulfonic acid (DDBSA, 0.82 g, 2.5

Scheme 3. Proposed Mechanism for the Synthesis of Compound 4{1,1,1}



mmol) was added. The mixture was sonicated for 60 min at room temperature. The methanol was removed under reduced pressure and the residue was dried at 110 °C for 2 h to afford γ -Fe₂O₃@SiO₂-DDBSA (0.25 mmol/g, 10 mg = 0.0025 mmol of DDBSA) as a yellow powder.

Typical Procedure for Synthesis of 8,8-Dimethyl-8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3'-indoline]-2,2',4,6(1H,3H,7H)-tetraone 4 {1,1,1}. A mixture of 5,5-dimethyl-cyclohexane-dione 1{1} (0.14 g, 1 mmol), barbituric acid 2{1} (0.13 g, 1 mmol), isatine 3{1} (0.15 g, 1 mmol), and γ -Fe₂O₃@SiO₂-DDBSA (0.6 g) in refluxing water (5 mL) was stirred for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, γ -Fe₂O₃@SiO₂-DDBSA could be placed on the side wall of the reaction vessel with the aid of an external magnet, and water was removed from the mixture to leave a residue (including the product and catalyst). Then, the product was dissolved in THF and the catalyst easily separated from the product by attaching an external magnet onto the reaction vessel, followed by decantation of the product solution. This solution was concentrated to generate the crude product. The crude product was purified by column chromatography on silica gel using CH₂Cl₂/CH₃OH as the eluent.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of catalyst and product, and the crystal structure of product 4{2,2,5}. Copies of ¹H NMR and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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