

Sulfonated Magnetic Nanoparticles as Recyclable Catalyst for Facile One-Pot Green Synthesis of 3,4-Dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione Derivatives

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ABSTRACT: Sulfonated magnetic nanoparticles ($SO_3H-Fe_3O_4@SiO_2$ MNPs) have been explored as an efficient, cost-effective, and recyclable nanocatalyst for the facile synthesis of 3,4-dihydro-2H-indazolo[1,2-b]phthalazin-1,6,11(13H)-triones through a one-pot three-component reaction between aldehydes, dimedone, and phthalhydrazide under mild and green (solvent-free) conditions. Simple separation of the catalyst using an external magnet, efficient recyclability of the developed magnetic nanocatalyst up to five fresh runs without significant loss in its catalytic activity, excellent yields of the designed reactions (88 to 98%), low reaction times as well as solvent-free and facial reaction condition are some advantages of the present procedure that qualified the fabricated magnetic nanocatalyst for industrial applications.

KEYWORDS: Organic synthesis; Sulfonated magnetic nanoparticles; Nanocatalyst; Green chemistry; Recyclability.

INTRODUCTION

As a decisive fact, growth of mankind, society, and industrializations has led to increasing concerns on environmental issues in the past few decades. In this context, a great deal of concerns is related to chemical industries [1, 2]. So many strategies including, selected green media (e.g., water) or solvent-free procedures, eco-friendly reagents, ultrasound, or microwave-assisted techniques, as well as recyclable catalysts, have been introduced to solve this problem [3]. Among these, recyclable heterogeneous catalysts have attracted a great deal of interest due to their superior features including,

eco-friendly and economically viable organic transformations academically and industrially [3, 4].

In this context, metal oxide nanoparticles are of particular interest as heterogeneous catalysts due to their interesting structural properties as well as high catalytic activities. These nano-sized particles are easily dispersible in reaction mediums after proper surface modification [5-7]. In recent years, numerous approaches have been design and developed for the fabrication of heterogeneous supported nanocatalysts through immobilizing different homogeneous precursors on solid supports. The most

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important advantages of immobilized nanocatalysts over their non-supported counterparts can be listed as low/or non-toxic, air- and moisture-compatible, easily separable and recyclable [8-10]. Despite these advantages, such nanoparticles often suffer from the tedious task of recycling *via* expensive ultra-centrifugation, which limits their utility as catalysts. However, the issue of separation and reusability of these nanocatalysts has been solved using Magnetic Nanoparticles (MNPs) as excellent supports amenable to simple magnetic separation [11-15]. These NPs have been extensively used in various fields including, analytical and bioanalytical chemistry [16], cell separation [17], protein separation [18], drug delivery systems [19], magnetic resonance imaging (MRI) [20], and hyperthermia cancer treatment [21]. Moreover, MNPs are conveniently used as supports for immobilization of homogeneous catalysts and can be functionalized effectively through appropriate surface modifications [22-37]. Therefore, MNPs supported-catalytic systems can be considered as potential candidates mainly due to their high surface area, low cost, easy synthesis, and magnetic properties that lead to a facile separation through an external magnetic field [38-41]. Based on mentioned superior features, many MNPs-supported catalysts have been successfully utilized for catalyzing a broad series of chemical reactions such as oxidation [42], polymerization [43], and even enzymatic reactions [44]. In recent years, a variety of magnetic nano-oxides modified with different acidic moieties such as phosphotungstic ($H_3PW_{12}O_{40}$), Pressler-type heteropolyacid, sulfamic, and sulfonic acids have been synthesized and successfully employed to selectively catalyze various chemical reactions [45-49].

Heterocyclic compounds containing nitrogen elements are well-known compounds and many of them occur naturally. In general, these compounds constitute the largest portion of chemical entities, which provide useful scaffolds for many natural products, fine chemicals, and biologically active pharmaceuticals that are of vital importance to life [50-53]. Among these, phthalazine derivatives are important members of nitrogen-containing heterocyclic compounds with a bridgehead hydrazine unit, which possess multiple pharmacological properties including, anti-convulsant [54], vasorelaxant [55], and cardiotoxic [56] agents. Albeit, numerous approaches have been introduced so far for the synthesis of different

phthalazine derivatives [57-60], demands for development of more improved synthetic strategies for scaffold manipulation of *N*-heterocycles containing phthalazine moiety still exist due to their wide range of applications.

In continuation of our research interest for developing more benign and efficient heterogeneous nanocatalysts and their application for the synthesis of various heterocyclic compounds including, *2H*-indazolo[1,2-*b*]phthalazinetriones [48, 61, 62], herein, for the first time we investigated the catalytic capability of sulfonated magnetic nanoparticles ($SO_3H-Fe_3O_4@SiO_2$ MNPs) as a magnetically recoverable heterogeneous catalyst for the synthesis of *2H*-indazolo[1,2-*b*]phthalazine-1,6,11(*13H*)-trione derivatives. The effect of some parameters including, solvent, time, temperature, and amount of catalyst on the yield of reactions were also examined.

EXPERIMENTAL SECTION

Materials

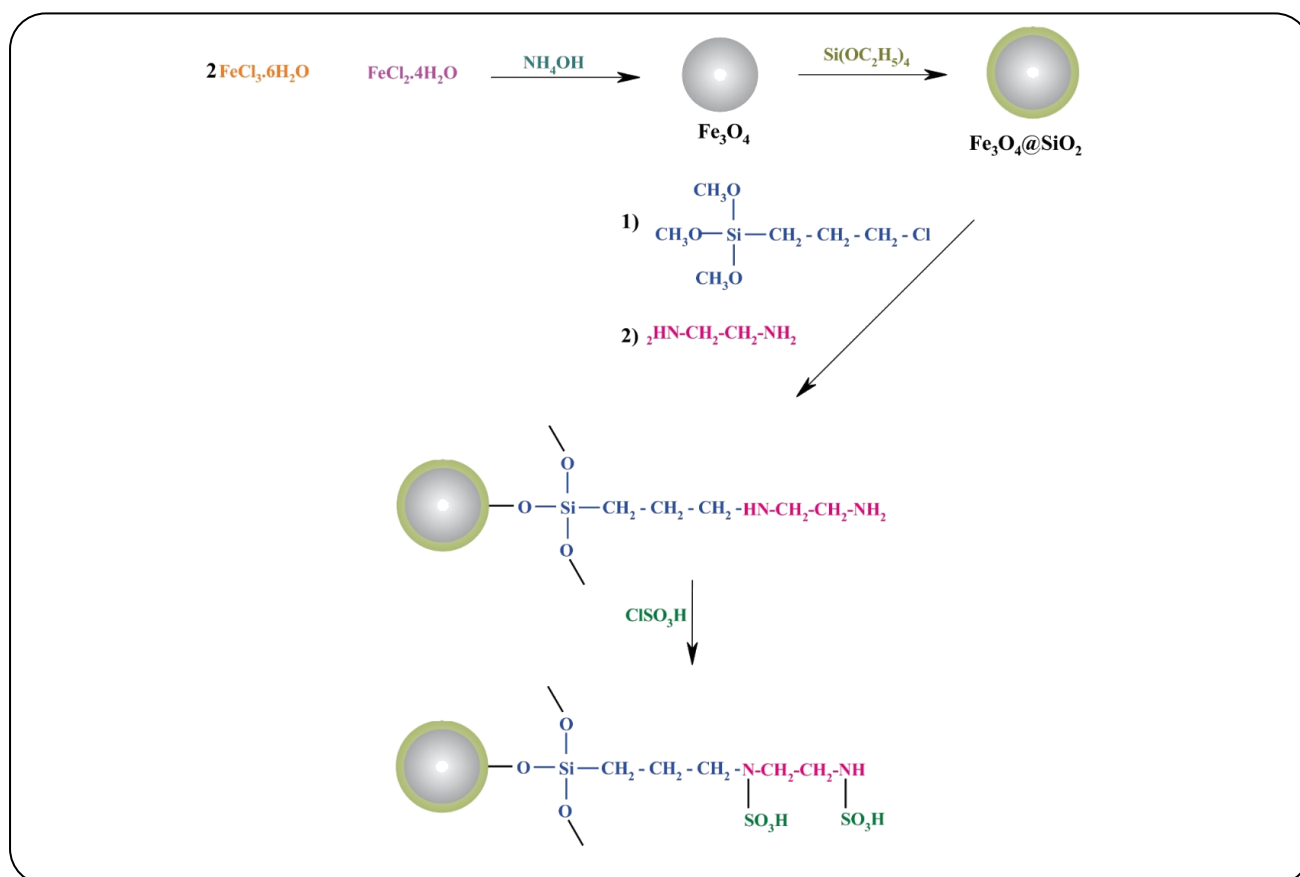
Chemicals used in this work were purchased from Fluka (Switzerland) or Merck (Darmstadt, Germany) chemical companies and used without purification.

Instrumentations

Fourier Transform InfraRed (FT-IR) spectra were recorded in KBr pellets on a Shimadzu 435-U-04 FTIR spectrometer (Kyoto, Japan). 1H NMR and ^{13}C NMR spectra were obtained using a Bruker instrument (Bruker, Ettlingen, Germany) in $DSMO-d_6$ or $CDCl_3$ as solvents and tetramethylsilane (TMS) as an internal standard. Mass Spectra (MS) were recorded with a FINNIGAN-MAT 8430 spectrometer (Bremen, Germany) operating at an ionization potential of 70 eV. Ultrasonication was performed in a 2200 ETH-SONICA ultrasound cleaner with a frequency of 45 kHz.

Synthesis of the catalyst ($SO_3H-Fe_3O_4@SiO_2$ MNPs)

The catalyst was synthesized according to our previously reported procedure and fully characterized by different analytical techniques [63]. In brief, a mixture of $FeCl_3 \cdot 6H_2O$ and $FeCl_2 \cdot 4H_2O$ were sonicated in a basic solution to produce Fe_3O_4 NPs. In the second step, a layer of SiO_2 was coated on the external surface of the Fe_3O_4 NPs in order to protect the Fe_3O_4 NPs from possible oxidation or aggregation. Subsequently, the fabricated



Scheme 1: Sequential synthesis of sulfonated magnetic nanoparticles ($\text{SO}_3\text{H}-\text{Fe}_3\text{O}_4@\text{SiO}_2$ MNPs).

$\text{Fe}_3\text{O}_4@\text{SiO}_2$ core-shell MNPs were treated with 3-chloropropyltrimethoxysilane to afford $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Cl}$ core-shell MNPs. In the following step, these MNPs were treated with ethylenediamine to produce aminated $\text{Fe}_3\text{O}_4@\text{SiO}_2$ MNPs. Eventually, sulfonation of both amine groups in the aminated $\text{Fe}_3\text{O}_4@\text{SiO}_2$ MNPs was carried out by reaction with chlorosulfonic acid under ultrasonication to yield the *N,N'*-disulfonated $\text{Fe}_3\text{O}_4@\text{SiO}_2$ MNPs (Scheme 1). The characterization of the catalyst was performed by different analytical techniques such as elemental analysis, FTIR, EDX, SEM, XRD, and XRF in our previous work [63].

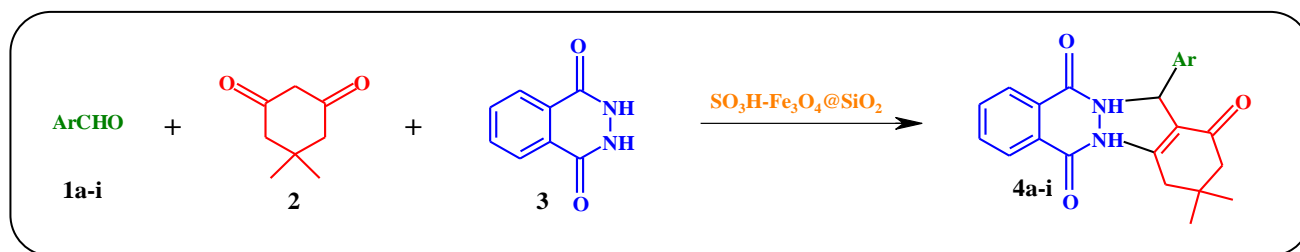
General procedure for the $\text{SO}_3\text{H}-\text{Fe}_3\text{O}_4@\text{SiO}_2$ MNPs-catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones (4*a-i*)

A 25-mL round-bottomed flask was charged with aromatic aldehyde **1** (1 mmol), dimedone (0.14 g, 1 mmol), phthalhydrazide (0.16 g, 1 mmol), and the nanocatalyst (0.03 g). The reaction mixture was stirred at 80 °C under

the solvent-free condition for an appropriate time until the reaction was completed as monitored by thin layer chromatography (TLC; Table 2). Then, the reaction mixture was cooled to room temperature, diluted with ethanol (10 mL) and stirred at room temperature for about 10 minutes. After separation of the catalyst using an external magnetic bar, the solvent (ethanol) was removed using a rotary evaporator under reduced pressure. The crude product was washed with water and recrystallized from ethyl acetate/*n*-hexane (1:3 v/v) to afford the pure product.

Selected data

3,4-Dihydro-3,3-dimethyl-13-(4-(prop-2-yn-1-yloxy)phenyl)-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione (**4h**)
 mp 222-226 °C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3279, 3042, 2956, 2125, 1655, 1629, 1603, 1511; ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ : 1.03 (s, 6H, 2Me), 2.17 (s, 2H, CH_2), 2.41 (t, 2H, $\text{C}\equiv\text{CH}$), 3.02-3.20 (m, 2H, CH_2CO), 4.67 (s, 2H, $\text{C}\equiv\text{CH}$), 6.15 (s, 1H, CH), 6.79-8.15 (m, 8H, H-Ar) ppm;



Scheme 2: Synthesis of 2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-triones **4a-i** catalyzed by $\text{SO}_3\text{H-Fe}_3\text{O}_4@\text{SiO}_2$ MNPs.

^{13}C NMR (62.9 MHz, CDCl_3) δ : 28.5, 28.6, 34.6, 38.0, 51.0, 55.7, 64.4, 75.6, 76.6, 77.0, 77.4, 78.4, 115.0, 118.4, 127.7, 127.9, 128.5, 128.9, 129.1, 129.3, 133.5, 134.5, 150.8, 154.3, 156.0, 157.8 ppm; MS (m/z): 426.5 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(2-(prop-2-yn-1-yloxy)phenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4i)

mp 233-236 °C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3316, 3033, 2958, 2137, 1655, 1622, 1602, 1493; ^1H NMR (300 MHz, CDCl_3) δ : 1.20-1.28 (s, 6H, Me), 2.20-2.34 (s, 2H, CH_2), 2.39-2.43 (t, 1H, $\text{C}\equiv\text{CH}$), 3.18-3.25 and 3.46-3.52 (dd, 2H, CH_2CO), 4.49-4.51 (s, 2H, CH_2CCH), 6.51 (s, 1H, CH), 6.80-8.36 (m, 8H, H-Ar) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ : 28.1, 29.0, 34.5, 38.1, 50.9, 55.9, 63.8, 75.7, 76.6, 77.0, 77.2, 77.8, 116.6, 121.8, 127.7, 128.0, 129.0, 129.3, 129.9, 131.5, 133.2, 134.1, 151.7, 154.1, 155.1, 156.0 ppm; MS (m/z): 426.5 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4f)

mp 228-230 °C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3036, 2957, 1658, 1623, 1611; ^1H NMR (90 MHz, CDCl_3) δ : 1.21 (s, 6H, 2Me), 2.29 (s, 3H, Me), 2.32 (s, 2H, CH_2CO), 3.31-3.36 (dd, 2H, CH_2), 6.41 (s, 1H, CH), 7.17-8.29 (m, 8H, H-Ar) ppm.

3,4-Dihydro-3,3-dimethyl-13-(4-Bromophenyl)-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (4g)

mp 266-268 °C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3075, 2957, 1688, 1654, 1623, 1604; ^1H NMR (90 MHz, CDCl_3) δ : 1.21 (s, 6H, 2Me), 2.33 (s, 2H, CH_2CO), 3.30-3.33 (dd, 2H, CH_2), 6.41 (s, 1H, CH), 7.33-8.30 (m, 8H, H-Ar) ppm.

RESULTS AND DISCUSSION

In order to explore the catalytic potential of $\text{SO}_3\text{H-Fe}_3\text{O}_4@\text{SiO}_2$ MNPs as a heterogeneous acidic

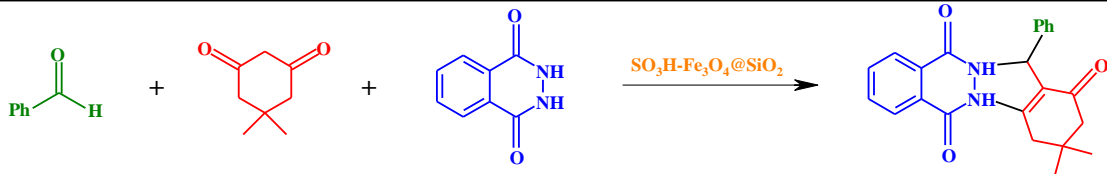
nanocatalyst in organic transformations, we decide to synthesize 3,4-dihydro-2H-indazolo[1,2-b]phthalazine-triones *via* one-pot three-component reactions between aldehydes, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and phthalhydrazide as shown in Scheme 2.

The catalytic activity of the $\text{SO}_3\text{H-Fe}_3\text{O}_4@\text{SiO}_2$ MNPs and optimization of the reaction condition

To optimize the reaction condition, we preliminarily carried out the reaction between benzaldehyde, dimedone, and phthalhydrazide as the model reaction. In addition, the effect of the reaction parameters such as catalyst loading, solvent (H_2O , EtOH, and CH_3CN), time, and temperature on the rate and yield of this model reaction was investigated. The experimental results summarized in Table 1, clearly indicated that the best results in terms of the reaction rates and yields are obtained when the reaction was carried out under solvent-free conditions at 60 °C using a small amount of catalyst (0.03 g) (entry 7). Also, it was noted that no further improvement in the yield occurs when the reaction was conducted at higher temperatures and prolonged reaction times (entries 8-11). Furthermore, increasing the amount of the catalyst to 0.05 g caused a considerable reduction of the reaction yield (entry 13). Moreover, the indispensable role of the catalyst in the reaction was approved by conducting the reaction in the absence of the catalyst which resulted in only a trace amount of the expected product (entry 14).

To extend the generality and scope of the reaction, we conducted the reaction with a diverse series of substituted aromatic aldehydes (**1a-i**) under the optimal conditions as discussed above (*i.e.* solvent-free, 60 °C, and catalyst loading of 0.03 g). According to the experimental results summarized in Table 2, the reactions generally proceeded almost fast and smoothly to furnish the respective products in excellent yields (88-98%) irrespective of

Table 1: Screening the reaction parameters for the model synthesis of 3,4-dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione.^a



Entry	Catalyst (g)	solvent	Temperature (°C)	Time (min)	Yield (%) ^b
1	0.01	no solvent	r.t.	80	38
2	0.01	H ₂ O	r.t.	80	15
3	0.01	EtOH	r.t.	80	32
4	0.01	CH ₃ CN	r.t.	80	12
5	0.01	EtOH	reflux	80	75
6	0.03	no solvent	40	100	87
7	0.03	no solvent	60	25	98
8	0.03	no solvent	80	25	98
9	0.03	no solvent	100	50	92
10	0.03	no solvent	80	50	98
11	0.03	no solvent	80	80	95
12	0.02	no solvent	60	60	90
13	0.05	no solvent	80	60	85
14	no catalyst	no solvent	80	120	trace

^a Condition: benzaldehyde (1 mmol), phthalhydrazide (1 mmol), dimedone (1 mmol), solvent (5 mL).

^b Isolated pure yield

the nature of the substituent groups attached to the aromatic rings.

It should be pointed out that using this procedure two new compounds (**4h** and **4i**) were synthesized and characterized by their physical properties and spectral data (FTIR, ¹H/¹³C NMR, and MS). All other products are known compounds and characterized by their physical properties and spectral data (FTIR and ¹H NMR), and compared with the reported data (Table 2).

The proposed catalytic reaction mechanism

A plausible mechanism to explain the formation of 3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-triones is shown in Scheme 3. It is likely that, initially, the dimedone in its enolized form undergoes

condensation with the catalyst-activated aldehyde followed by dehydration to produce the intermediate arylidene **A**. In the next step, the nucleophilic addition reaction of the phthalhydrazide with the intermediate **A** takes place under the catalytic effect

Regeneration and reusability of the catalyst

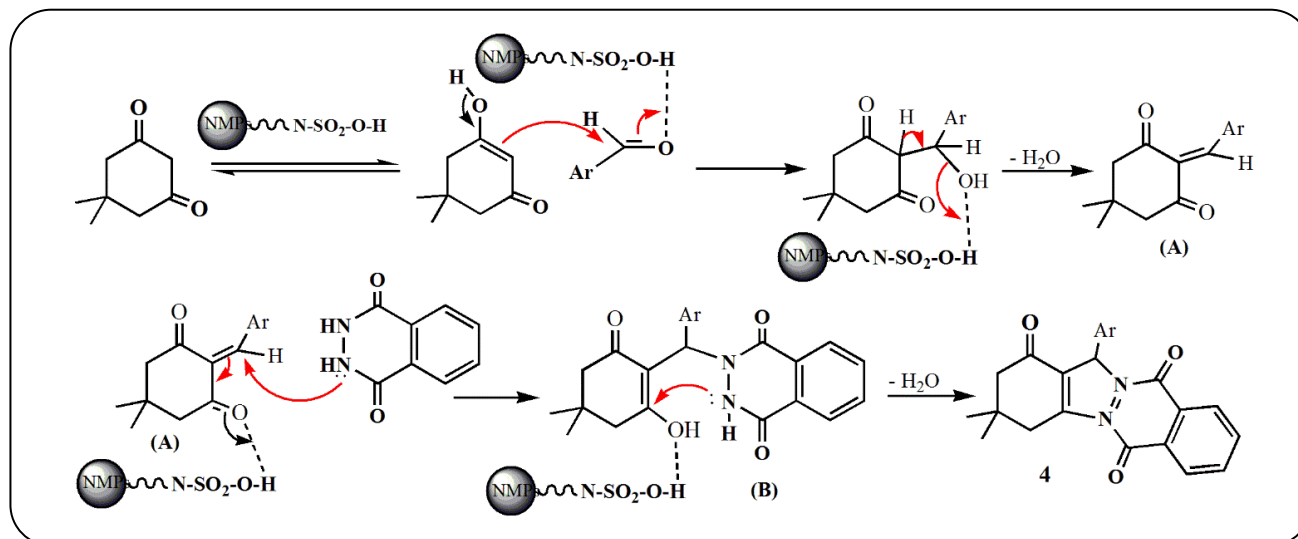
The regeneration and reuse of a catalyst are important from materials science, ecological, as well as economic point of views. The reusability of the SO₃H-Fe₃O₄@SiO₂ catalyst was examined for the model reaction between benzaldehyde, dimedone, and phthalhydrazide. The recycling process involved the isolation of the catalyst from the reaction mixture simply using an external magnetic bar followed by washing with ethanol

Table 2: Synthesis of 13-aryl-3,4-dihydro-3,3-dimethyl-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-triones catalyzed by $SO_3H-Fe_3O_4@SiO_2$ MNPs under solvent-free condition at 60 °C.^a

Entry	Ar	Product	Time (min)	Yield (%) ^b	Mp (°C)	
					Found	Reported
1	C ₆ H ₅	4a	25	98	202-205	204-206 [57]
2	2,4-(Cl) ₂ C ₆ H ₃	4b	30	90	219-222	219-221 [58]
3	4-ClC ₆ H ₄	4c	20	92	258-260	262-264 [57]
4	4-BrC ₆ H ₄	4d	25	92	266-268	265-267 [60]
5	4-MeC ₆ H ₄	4e	25	98	228-230	227-229 [57]
6	4-NO ₂ C ₆ H ₄	4f	20	96	214-216	217-219 [58]
7	3-BrC ₆ H ₄	4g	30	89	262-264	260-264 [60]
8 ^{new}	4-(HC≡C-CH ₂ O)C ₆ H ₄	4h	35	92	222-224	-
9 ^{new}	2-(HC≡C-CH ₂ O)C ₆ H ₄	4i	37	88	233-235	-

^a Condition: aldehyde 1 (1 mmol), dimedone 2 (1 mmol), phthalhydrazide 3 (1 mmol), catalyst (0.03 g), temperature 60 °C.

^b Isolated pure yield.



Scheme 3: The proposed mechanism for the synthesis of 3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-triones catalyzed by $SO_3H-Fe_3O_4@SiO_2$ MNPs.

and drying in reduced pressure at room temperature. As shown in Fig. 1, the recovered catalyst can be used for five consecutive fresh runs without any noticeable loss of the catalytic activity.

CONCLUSIONS

In summary, a simple procedure has been developed for the synthesis of 2H-Indazolo[1,2-b]phthalazine-1,6,11(13H)-triones via one-pot three-component reaction

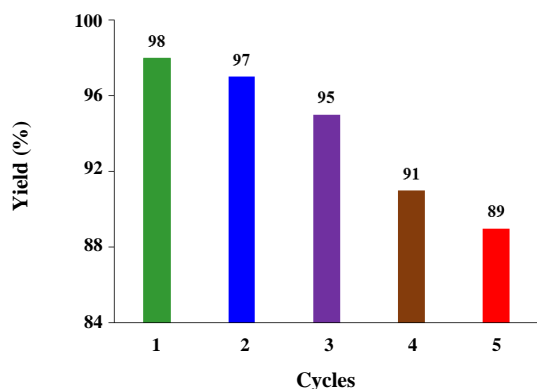


Fig. 1: Reusability of $\text{SO}_3\text{H-Fe}_3\text{O}_4@\text{SiO}_2$ nanocatalyst for the synthesis of 2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-triones.

between variously substituted aromatic aldehydes, phthalhydrazide, and dimedone under the green solvent-free condition in the presence of sulfonated magnetic nanoparticles ($\text{SO}_3\text{H-Fe}_3\text{O}_4@\text{SiO}_2$ MNPs) as an effective and magnetically recyclable nanocatalyst. The reactions proceed smoothly under facial condition including, solvent-free and mild reaction condition, as well as almost in short reaction times and easy experimental set-up. In addition, under this condition, the reactions lead to excellent yields (88 to 98%). As a result, the $\text{SO}_3\text{H-Fe}_3\text{O}_4@\text{SiO}_2$ MNP has high potential as a heterogeneous catalyst in organic synthesis mainly due to ease of synthesis, high stability and selectivity, easy separation from reaction mixtures using an external magnetic bar, and efficient recyclability and reusability.

Supporting Information

Supplementary data associated with this manuscript can be found in the online version at <http://www.ijcce.ac.ir>.

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Competing interests

The authors declare that they have no competing interests.

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