



Solvent-free, one-pot, four-component synthesis of 2H indazolo[2,1-b]phthalazine-triones catalyzed by Isatin-SO₃H coated on amino propyl modified magnetic nanoparticles (MnFe₂O₄@APTES@isatin-SO₃H) as a recyclable magnetic nanoparticle

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Abstract

The study involved the application of isatin-SO₃H coated on aminopropyl-modified magnetic nanoparticles (MnFe₂O₄@APTES@isatin-SO₃H) as a reusable nanocatalyst for the synthesis of 2H-indazolo[2,1-b] phthalazine triones. The comprehensive characterization techniques employed, including FT-IR, SEM, TEM, XRD, confirm the structural and functional integrity of the nanocatalyst. It exhibited excellent performance in a one-pot, four-component synthesis under solvent-free conditions at 80 °C. The method offered advantages such as short reaction time, high yields, and straightforward purification. Additionally, the magnetic properties of the nanoparticles allow for straightforward recovery using an external magnet, enabling multiple reuse cycles without significant loss in catalytic performance. This feature is crucial for sustainable practices in chemical synthesis, making the MnFe₂O₄@APTES@isatin-SO₃H nanocatalyst a promising candidate for future applications in organic synthesis.

Keywords: “aminopropyl, magnetic nanocatalyst, one-pot, four-component, solvent-free conditions”

Introduction

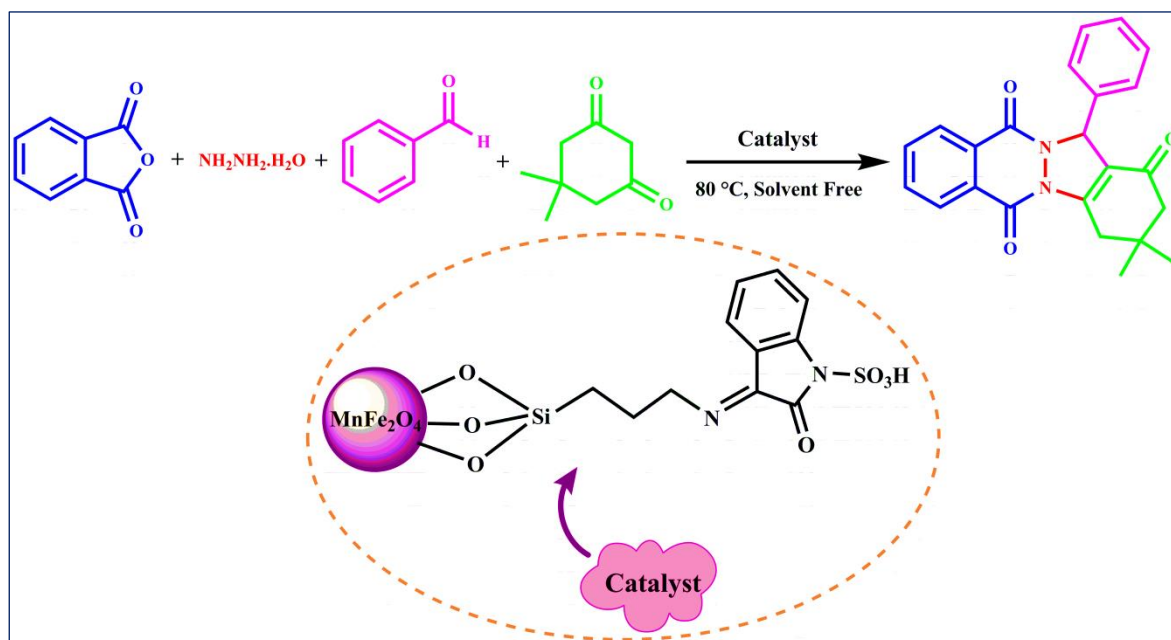
In recent times, there has been a significant emphasis in the field of chemistry on the development of environmentally friendly catalysts and methods for use in synthetic organic materials and industrial applications. [1]. Over the last few decades, a growing research interest has been directed towards preparing and applying highly efficient and recyclable catalysts in modern synthetic processes [2,3]. Magnetic MnFe₂O₄ nanoparticles have emerged as privileged support for the immobilization of various functional groups such as phosphorous, nitrogen, and organic moieties owing to the presence of high-density hydroxyl groups on their surface, high surface area, high stability, facile magnetic separation, environmental benignity, and high loading capacity [4-11]. Magnetic nanoparticles (MNPs) can be regarded as a promising field in various biological, medical, and industrial applications, such as solar water,[12] solar cells,[13] semiconductors,[14] data storage,[15] magnetic fluids,[16] magneto -thermal therapy,[17,18] magnetic resonance imaging,[19] biomolecular sensors,[20,21]and drug delivery[22,23]. One of the most applicable capabilities of nanoparticles in organic chemistry is the catalyst role with high surface-to-volume ratios and their surface atoms which are very active and selective [24]. These nanocatalysts can play two different roles as the sites of catalysis and support for catalytic processes [25]. Nowadays, nanomagnetic core-shell catalysts are excellent supports for various catalysts [26].

(3-Aminopropyl)triethoxysilane (APTES) is characterized by a single terminal amine group and three ethoxy groups connected to each silicon atom, serving as a crucial interface between organic and inorganic materials in the field of chemistry [27]. APTES holds significant importance in the synthesis of materials and is widely utilized as a silanization agent for modifying metal oxide nanoparticle (MONP) surfaces [28]. The introduction of amine (NH₂) enhances their dispersibility and anti-bacterial properties. The APTES-MONPs have various direct applications in electrochemical sensors, catalysts, and Pickering emulsions [29]. APTES modification links numerous organic, inorganic, or biochemical attachments essential to drug delivery, contaminants removal, catalyst immobilization, and medical imaging. The applications of silanes can be categorized based on their grafting functionality on inorganic surfaces [30] or their ability to provide integrity when used as top-coating polymers to resist coating rupture and disbanding. [31,32].

Solvent-free organic reactions have gained significant attention due to concerns about the environmental impact of organic solvents. Meanwhile, the construction of structurally diverse and complex molecules from simple and readily available starting materials while combining economic aspects with environmental ones is especially important in modern synthetic organic and medicinal chemistry. Multicomponent reactions (MCRs) involving domino processes have emerged as powerful tools to reach this near-ideal goal. Such transformations reduce the consumption of catalyst, solvent, time, labor, and energy, thereby minimizing waste compared to the corresponding series of individual reactions.[33,34] One of these MCRs is the preparation of indazolo[2,1-b]phthalazine-trione derivatives. These compounds have been shown to possess a broad spectrum of biological activities.[35] They have proved to be promising luminescence materials and fluorescence probes.[36]

The importance of MCRs has been recognized in various research fields including medicinal chemistry, combinatorial chemistry, diversity-oriented synthesis (DOS), and simple reaction design [37]. Furthermore, the use of one-pot multicomponent reactions with a recoverable nanomagnetic core-shell catalyst can be considered as part of green chemistry.

In recent years, the synthesis of nitrogen-containing heterocyclic compounds has gained attention due to their wide distribution and increasing use in biologically active pharmaceuticals, agrochemicals, and functional materials [38]. Among many heterocyclic compounds, heterocycles containing phthalazine moieties have received considerable attention because they show some pharmacological and biological activities and clinical applications [39]. These compounds are particularly noteworthy due to their bridgehead hydrazine content and their potential for cardiotonic [40], anticancer [41], anticonvulsant [42], anti-inflammatory [43], antifungal [44], hypolipidemic [45], and vasorelaxant activities [46], as well as unique electrical and optical properties [47]. Although a variety of different catalysts have been used for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones, Despite being effective, some of these methods can be limited by the requirement for harsh and strongly acidic conditions, the use of transition metal as a catalyst, extended reaction times, unsatisfactory yields of the products, or require additional instruments such as ultrasound.[48] Therefore, developing more efficient, cheaper, and more easily recovered catalysts for this four-component reaction remains highly desirable. Considering the above subjects and in continuation of our efforts toward the design of magnetic nanocatalysts[49] and sustainable synthesis development,[50] we use from Isatin-SO₃H coated on aminopropyl modified magnetic nanoparticles (MnFe₂O₄@APTES@isatin-SO₃H) as a magnetic nanoparticle for preparation indazolo[2,1-b]phthalazine-triones by one-pot, four-component condensation reaction of hydrazinium hydroxide, phthalic anhydride, dimedone, and aromatic aldehydes in the presence of an acid-base bifunctional reusable catalyst at 80 °C under solvent-free conditions (Scheme 1).



Scheme 1. One-pot four-component synthesis of 2H-indazolo[2,1 b]phthalazine-triones catalyzed by MnFe₂O₄@APTES@isatin-SO₃H

Experimental

General

All reagents and solvents used in the study were commercially purchased and did not undergo any additional purification. Fourier transform infrared (FT-IR) spectroscopy was conducted using a Nicolet Magna-400 spectrometer with KBr pellets. ¹H NMR data were collected in DMSO-d₆ using a Bruker DRX-400 spectrometer and tetramethylsilane as the internal reference. XRD patterns were recorded using a Philips diffractometer with monochromatized Cu K radiation. The morphology of the nanoparticles was analyzed using field emission scanning electron microscopy (FE-SEM) with model MIRA3. The microscopic morphology of the nanoparticles was observed using a Philips transmission electron microscope (TEM) operating at 100 Kv. The Yanagimoto micro melting point device was employed to measure the melting points without any correction. To monitor the reaction and determine substrate purity, thin-layer chromatography (TLC) was carried out on silica-gel polygram SILG/UV 254 plates provided by the Merck Company.

Synthesis of catalyst

Preparation of modified MnFe₂O₄ nanoparticles

After 30 min of nitrogen gas bubbling in 200 mL of purified, deoxygenated water, 5 g of Mn(NO₃)₂·4H₂O and 14 g of Fe(NO₃)₃·6H₂O were dissolved in ultrapure water with vigorous mechanical stirring. The aforementioned mixture was then stirred while 2.0 M NaOH solution was added dropwise until the pH reached 11. After that, the mixture was heated to 100 °C and maintained there for 2 h. In an external magnetic field, a black precipitate was gathered and then cleaned with ultrapure water. To get rid of the contaminants connected with the operations (such as OH⁻, NO₃⁻, and Na⁺), this washing was done three times. After freeze-drying, pure MnFe₂O₄ nanoparticles were finally produced.

Preparation of modified MnFe₂O₄@APTES nanoparticles

MnFe₂O₄ (3 g) was dispersed in 40 ml ethanol and 30 min was sonicated. Then, 3-aminopropyltriethoxysilane (5 ml, 21.36 mmol) was added to the suspended solid nanoparticles under mechanical stirring, and the reaction mixture were refluxed under nitrogen for 8 hr [30]. Amino propyl modified magnetic nanoparticles (MnFe₂O₄@APTES) was filtered, washed twice with EtOH and dried in vacuum at 50 °C.

Preparation of modified MnFe₂O₄@APTES@isatin nanoparticles

Isatin (10 mmol, 1.76 g) in 50 ml of ethanol was added to the MnFe₂O₄@APTES (3 g) and the mixture was refluxed for 8 hr at 80 °C. The resulting solid was filtered, washed and dried in a same procedure to create the nano-MnFe₂O₄@APTES@isatin.

Preparation of modified MnFe₂O₄@APTES@isatin-SO₃H nanoparticles

In the fourth step, chloro sulfuric acid (1.16 ml, 10 mmol) was added drop wise to a mixture of nano-MnFe₂O₄@APTES@isatin in dry dichloromethane (10 ml) and the reaction mixture was stirred for 6 hr. Finally, the nano-MnFe₂O₄@APTES@isatin-SO₃H as a brown solid was obtained after filtering, washing and drying

General procedure for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones

Aldehyde (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and MnFe₂O₄@APTES@isatin-SO₃H (0.005 mol, 10 mg) were added to a mixture of hydrazinium hydroxide (1.2 mmol) and phthalic anhydride (1 mmol). The reaction mixture was heated at 80 °C. After the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and ethyl acetate (5 ml) was added. The catalyst was separated by an external magnet, washed with ethyl acetate, dried, and re-used under the same reaction conditions for a consecutive run. Evaporation of the filtrate's solvent under reduced pressure gave the crude product. The pure product was obtained by recrystallizing from a mixture of ethanol and water.

Selected spectral data

3,3-dimethyl-13-phenyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7a). yellow powder. Mp 205-207 °C; IR (KBr): 2959, 2886, 1668, 1469, 1415, 1380, 1310, 1268, 1152, 1086, 1022, 970, 839, 785, 701, 619; ¹H NMR (400 MHz, CDCl₃) δ: 1.23 (6H, s, 2Me), 2.35 (2H, s, CH₂C), 3.24–3.47 (2H, AB system, J = 18.8 Hz, CH₂H_bCO), 6.47 (1H, s, CHN), 7.31–8.76 (9H, m, ArH).

13-(4-methoxyphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7b). yellow powder. Mp 216-218 °C; IR (KBr): 2955, 2836, 1661, 1403, 1363, 1311, 1270, 700; ¹H NMR (400 MHz, CDCl₃) δ: 1.23 (6H, s, 2Me), 2.36 (2H, s, CH₂C), 3.23–3.46 (2H, AB system, J = 19.2 Hz, CH₂H_bCO), 3.78 (3H, s, OMe), 6.44 (1H, s, CHN), 6.86–8.37 (8H, m, ArH).

13-(2-chlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7c). yellow powder. Mp 267-269 °C; IR (KBr): 2956, 2856, 1660, 1455, 1362, 1310, 1273, 730; ¹H NMR (400 MHz, CDCl₃) d: 1.23 (6H, s, 2Me), 2.34 (2H, s, CH₂C), 3.26–3.42 (2H, AB system, J = 19.0 Hz, CH_aH_bCO), 6.73 (1H, s, CHN), 7.26–8.38 (8H, m, ArH).

13-(3-chlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7d). white powder. Mp 203-205 °C; IR (KBr): 2953, 2850, 1658, 1466, 1362, 1307, 1267, 722; ¹H NMR (400 MHz, CDCl₃) d: 1.21 (6H, s, 2Me), 2.33 (2H, s, CH₂C), 3.21–3.40 (2H, AB system, J = 19.1 Hz, CH_aH_bCO), 6.45 (1H, s, CHN), 7.24–8.37 (8H, m, ArH).

13-(4-chlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7e). white powder. Mp 261-263 °C; IR (KBr): 2960, 2866, 1665, 1459, 1361, 1313, 1265, 709; ¹H NMR (400 MHz, CDCl₃) d: 1.23 (6H, s, 2Me), 2.35 (2H, s, CH₂C), 3.20–3.43 (2H, AB system, J = 18.8 Hz, CH_aH_bCO), 6.46 (1H, s, CHN), 7.29–8.36 (8H, m, ArH).

13-(2,4-dichlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7f). yellow powder. Mp 221-223 °C; IR (KBr): 2967, 2863, 1664, 1473, 1369, 1318, 1254, 708; ¹H NMR (400 MHz, CDCl₃) d: 1.22 (6H, s, 2Me), 2.33 (2H, s, CH₂C), 3.23–3.43 (2H, AB system, J = 19.2 Hz, CH_aH_bCO), 6.64 (1H, s, CHN), 7.26–8.41 (7H, m, ArH).

3,3-dimethyl-13-(2-nitrophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7g). yellow powder. Mp 235-237 °C; IR (KBr): 2930, 2831, 1659, 1625, 1515, 1371, 1311, 1170, 1103, 864, 698; ¹H NMR (400 MHz, CDCl₃) d: 1.22 (6H, s, 2Me), 2.38 (2H, s, CH₂C), 3.30–3.44 (2H, AB system, J = 19.2 Hz, CH_aH_bCO), 6.51 (1H, s, CHN), 7.63–8.41 (8H, m, ArH).

3,3-dimethyl-13-(3-nitrophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7h). yellow powder. Mp 274-276 °C; IR (KBr): 2928, 2841, 1661, 1622, 1516, 1375, 1314, 1144, 1105, 860, 699; ¹H NMR (400 MHz, CDCl₃) d: 1.23 (6H, s, 2Me), 2.36 (2H, s, CH₂C), 3.28–3.45 (2H, AB system, J = 19.1 Hz, CH_aH_bCO), 6.53 (1H, s, CHN), 7.56–8.39 (8H, m, ArH).

3,3-dimethyl-13-(4-nitrophenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7i). yellow powder. Mp 220-222 °C; IR (KBr): 2970, 2863, 1696, 1618, 1525, 1369, 1310, 1143, 1106, 859, 703; ¹H NMR (400 MHz, CDCl₃) d: 1.24 (6H, s, 2Me), 2.26 (2H, s, CH₂C), 3.23–3.44 (2H, AB system, J = 19.2 Hz, CH_aH_bCO), 6.55 (1H, s, CHN), 7.61–8.39 (8H, m, ArH).

3,3-dimethyl-13-o-tolyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7j). yellow powder. Mp 230-232 °C; IR (KBr): 2988, 2863, 1662, 1653, 1604, 1590, 1487, 1083, 831, 778, 675, 496; ¹H NMR (400 MHz, CDCl₃) d: 1.19 (6H, s, 2Me), 2.23 (3H, s, Me), 2.27 (2H, s, CH₂C), 3.19–3.39 (2H, AB system, J = 18.8 Hz, CH_aH_bCO), 6.38 (1H, s, CHN), 7.10–8.33 (8H, m, ArH).

3,3-dimethyl-13-p-tolyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7k). yellow powder. Mp 227-229 °C; IR (KBr): 2993, 2853, 1669, 1649, 1607, 1596, 1489, 1079, 830, 777, 673, 494; ¹H NMR (400 MHz, CDCl₃) d: 1.18 (6H, s, 2Me), 2.22 (3H, s, Me), 2.28 (2H, s, CH₂C), 3.20–3.36 (2H, AB system, J = 18.9 Hz, CH_aH_bCO), 6.39 (1H, s, CHN), 7.07–8.29 (8H, m, ArH).

13-(4-bromophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (7l). white powder. Mp 266-268 °C; IR (KBr): 2973, 2855, 1654, 1631, 1575, 1479, 1309, 1270; ¹H NMR (400 MHz, CDCl₃) d: 1.23 (6H, s, 2Me), 2.34 (2H, s, CH₂C), 3.26–3.42 (2H, AB system, J = 19.0 Hz, CH_aH_bCO), 6.43 (1H, s, CHN), 7.28–8.33 (8H, m, ArH).

Results and discussion

Structural analysis of the MnFe₂O₄@COF-SO₃H nanocatalyst

At first, the synthesis of manganese ferrites (MnFe₂O₄) nanoparticles consisted of combining Fe(III) salt and Mn(II) salt in an alkaline solution, leading to the precipitation of spinel ferrite, MnFe₂O₄, from the solution. Following this, 3-aminopropyltriethoxysilane was added to the suspended solid nanoparticles. In the third stage, Isatin was employed to form the nano-MnFe₂O₄@APTES@isatin. Lastly, chlorosulfonic acid was utilized for sulfonating the MnFe₂O₄@APTES@isatin.

The FT-IR spectra of nano-MnFe₂O₄@APTES@isatin-SO₃H MNPs are displayed in Figure 1, showing two distinct vibration bands at approximately 577 and 481 cm⁻¹, corresponding to the Fe–O and Mn–O vibrational modes in manganese ferrite, respectively. This confirms the formation of a single-phase MnFe₂O₄. In nano-

MnFe₂O₄@APTES@isatin, the absorption peaks at 1555 and 1677 cm⁻¹ were assigned to the C=N and C=O stretching vibrations, respectively. The broad peak observed at 2800-3590 cm⁻¹ is attributed to the stretching vibration of C-H, O-H, and N-H functional groups. Following the aciditation process by chlorosulfonic acid, the adsorption peak in the range of 1025-1190 cm⁻¹ is related to the O=S=O asymmetric and symmetric stretching modes as shown in Figure 1.

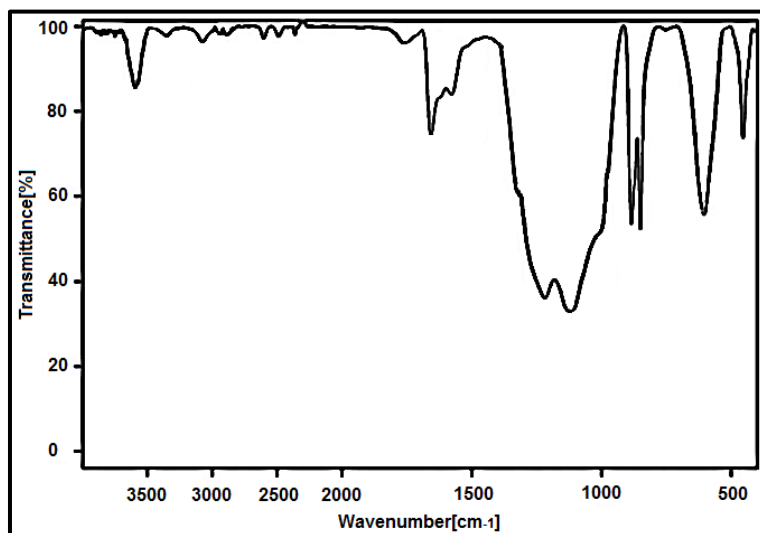


Figure (1) FT-IR spectra of nano-MnFe₂O₄@APTES@isatin-SO₃H

The composition of the nano-MnFe₂O₄@APTES@isatin-SO₃H MNPs was illustrated using x-ray diffraction patterns. The XRD pattern of the nano-MnFe₂O₄@APTES@isatin-SO₃H MNPs was examined within the 10–80° range (Figure 2). Figure 2 displays that the XRD patterns of the produced particles exhibit six distinct peaks at (2θ = 18.49°, 29.68°, 34.99°, 42.61°, 56.19° and 61.72°) by standard JCPDS (No. 01-074-2403), which correspond to specific lattice planes, confirming the phase purity of MnFe₂O₄. No impurity peaks were observed. The broad peaks between 2θ values of 20°–30° in this pattern indicate the amorphous nature of the organic compound.

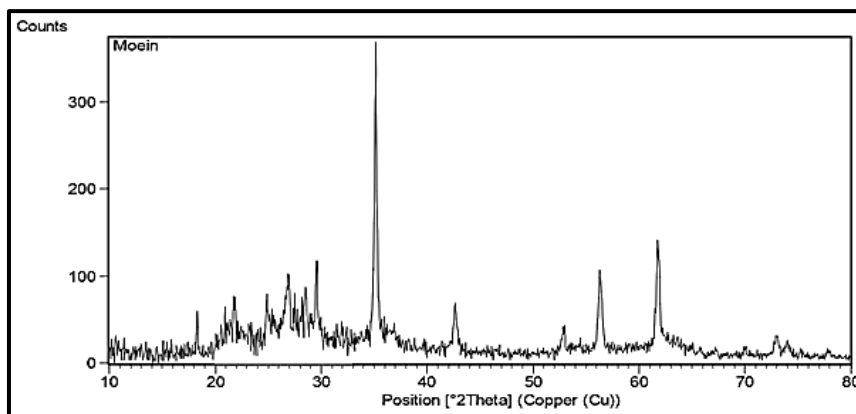


Figure (2) XRD patterns of nano-MnFe₂O₄@APTES@isatin-SO₃H

To get additional insight into the shapes particle sizes and morphology of the nano-MnFe₂O₄@APTES@isatin-SO₃H MNPs, scanning electron microscopy (SEM) was used (Figure 3a,b). As depicted in Figure 3, particles have a nearly spherical shape. It is evident from the images that both MnFe₂O₄ (Figure 3a) and MnFe₂O₄@APTES@isatin-SO₃H (Figure 3b) possess nano-sized structures, with average sizes of approximately 23 nm and 37 nm, respectively. To further examine the catalyst's morphology, a TEM analysis was conducted (Figure 4). The TEM images of the catalyst under investigation indicate a nearly uniform distribution.

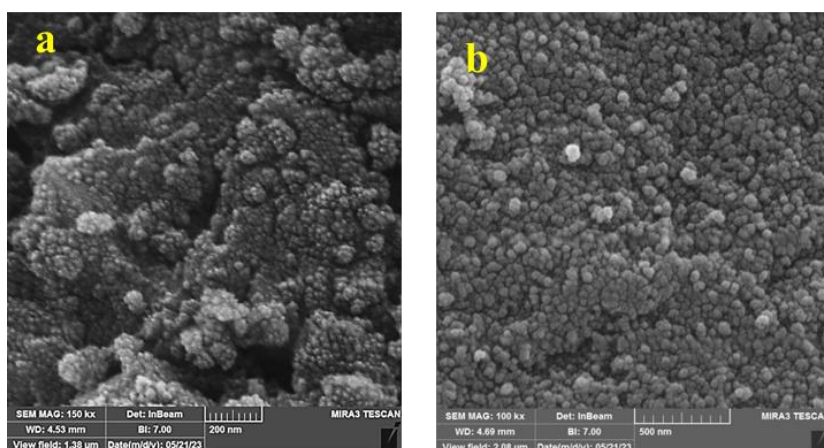


Figure (3) The FESEM images of (a) MnFe_2O_4 , (b) $\text{MnFe}_2\text{O}_4@\text{APTES}@\text{isatin-SO}_3\text{H}$

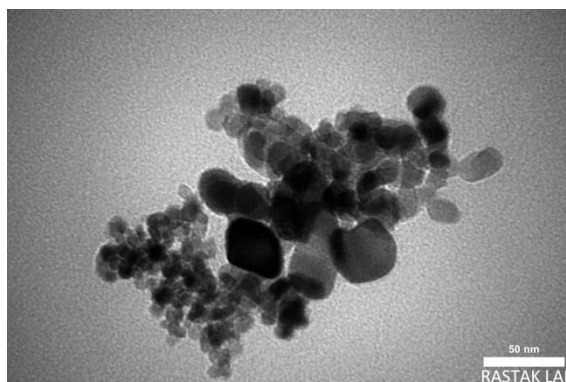


Figure (4) Transmission electron microscopy (TEM) of nano- $\text{MnFe}_2\text{O}_4@\text{APTES}@\text{isatin-SO}_3\text{H}$ MNPs

Initially the reaction between benzaldehyde (1 mmol), dimedone (1 mmol), hydrazinium hydroxide (1.2 mmol), and phthalic anhydride (1 mmol) as the model reaction was examined in the presence of 15 mg of $\text{MnFe}_2\text{O}_4@\text{APTES}@\text{isatin-SO}_3\text{H}$ catalyst in various solvents and under neat conditions (Table 1). When the reaction was performed solvent-free, the progress of the reaction was higher in comparison with solvent conditions (Table 1, entry 7). Therefore, the solvent-free condition was used for the synthesis of phthalazine derivatives. Then, the model reaction was examined in the presence of various amounts of the catalyst (Table 1, entries 9–11). As it was shown in Table 1, the best result was obtained when we carried out the model reaction in the presence of 15 mg of catalyst. This condensation was carried out with low amounts of $\text{MnFe}_2\text{O}_4@\text{APTES}@\text{isatin-SO}_3\text{H}$ of 5 and 10 mg, and the corresponding products were obtained in 65 and 82 % yield, respectively (Table 1, entries 9, 10). The use of a higher amount of catalyst did not improve the yield (Table 1, entry 11). The results show clearly that a catalyst is effective for this transformation and in the absence of it, the reaction did not take place even after a higher reaction time (Table 1, entry 8). The effect of temperature was also studied by carrying out the model reaction in the presence of a catalyst (15 mg) under solvent-free conditions (room temperature, 50, 60, 80, and 90 °C) and the best results were obtained at 80 °C (Table 1, entries 7, 12–15).

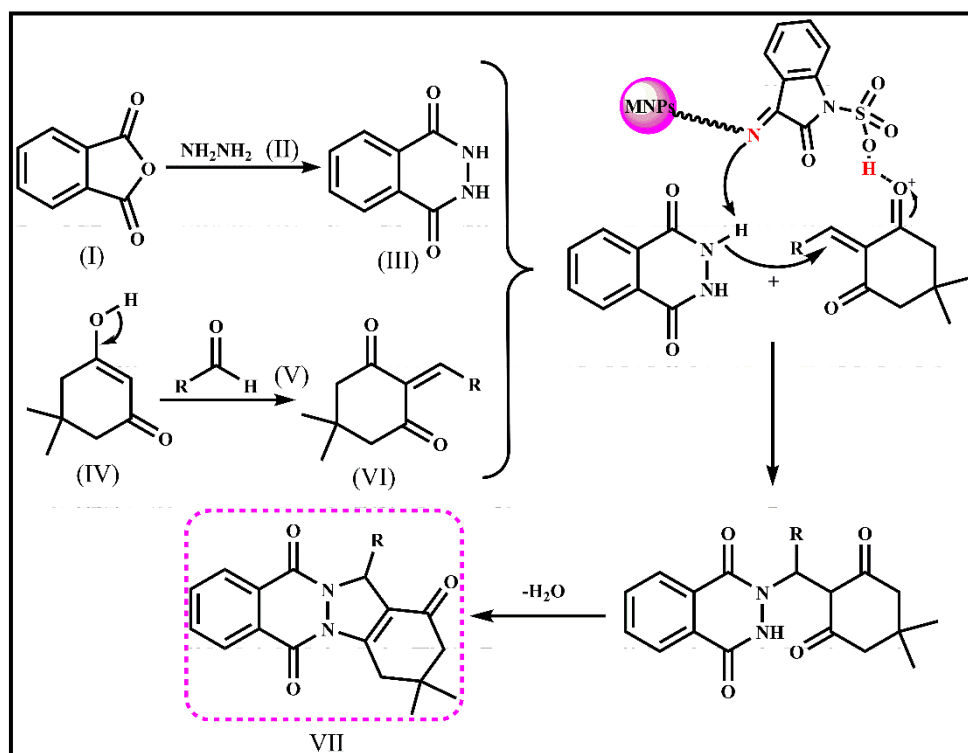
Table 1- Optimization of the amount of catalyst, solvent, and temperature in a one-pot, four component synthesis of the model reaction

Entry	Catalyst amount (mg)	Solvent	Condition	Time (min)	Yield (%) ^a
1	15	H ₂ O	Reflux	70	45
2	15	EtOH	Reflux	40	68
3	15	EtOH-H ₂ O	Reflux	40	60
4	15	CH ₃ CN	Reflux	70	47
5	15	CH ₂ Cl ₂	Reflux	70	52
6	15	CHCl ₃	Reflux	70	50
7	15	Solvent-Free	80 °C	5	96
8	None	Solvent-Free	80 °C	110	-
9	5	Solvent-Free	80 °C	90	65
10	10	Solvent-Free	80 °C	15	82
11	20	Solvent-Free	80 °C	15	90
12	15	Solvent-Free	r.t.	70	48
13	15	Solvent-Free	50 °C	10	69
14	15	Solvent-Free	60 °C	10	74
15	15	Solvent-Free	90 °C	5	95

Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), hydrazinium hydroxide (1.2 mmol), phthalic anhydride (1 mmol), MnFe₂O₄@APTES@isatin-SO₃H catalyst and solvent (3 mL)

^a Isolated yield

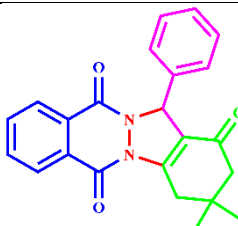
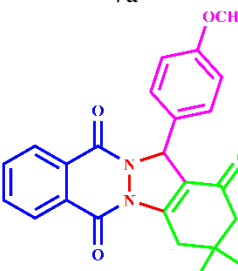
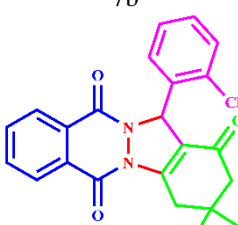
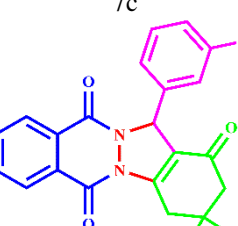
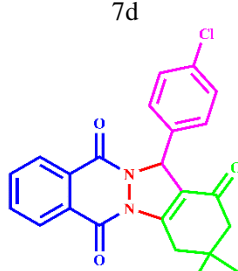
We suggest a mechanism for this reaction in which the MnFe₂O₄@APTES@isatin-SO₃H is an acid-base catalyst, as shown in Scheme 2. The mechanism contains two steps: initial formation of the phthalhydrazide (III) by nucleophilic addition of hydrazinium hydroxide (II) to phthalic anhydride (I) followed by dehydration occurs. The second step involves the initial formation of heterodiene (VI) by standard Knoevenagel condensation of dimedone (V) and aldehyde (IV). In the next step, the cooperation of the acid and basic sites of this catalyst leads to the Michael-type addition of formed phthalhydrazide to intermediate VI. Finally, cyclocondensation and dehydration of these intermediates occur to provide the corresponding products (VII).

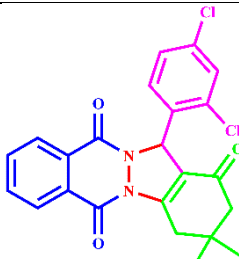
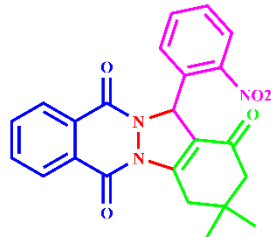
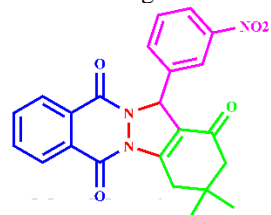
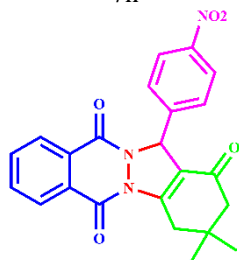
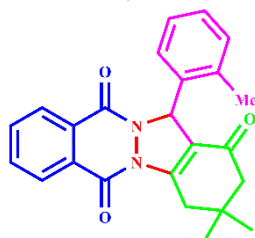
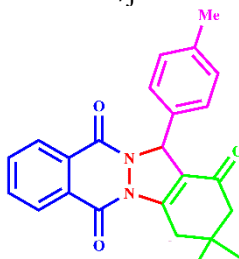


Scheme (2) Proposed mechanism for synthesis of 2H-indazolo[2,1-b]phthalazine-triones with MnFe₂O₄@APTES@isatin-SO₃H as catalyst

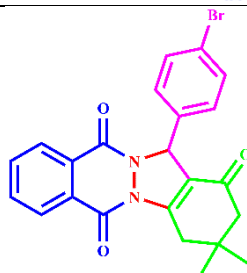
With the optimized conditions in hand, we proceeded to evaluate the scope of this method using a variety of different aromatic aldehydes in the presence of the synthesized catalyst. Notably, a variety of different aromatic aldehydes, including ortho-, meta-, and para-substituted aryl aldehydes, all reacted smoothly under the optimized reaction conditions to give the corresponding products in good to excellent yields. As shown in Table 4, the aldehydes bearing both electron-donating and electron-withdrawing groups participated in the condensation reaction with equal efficiency. Thus, the nature and position of the substituents on the aromatic ring had no discernible impact on the success of the reaction.

Table 2- Synthesis of indazolophthalazinetrione derivatives (7a–l) catalyzed with MnFe₂O₄@APTES@isatin-SO₃H at 80 °C under solvent-free conditions

Entry	Aldehyde	Product	Time (min)	Yield ^a (%)
1	C ₆ H ₅	 7a	5	96
2	4-OMeC ₆ H ₄	 7b	10	91
3	2-Cl C ₆ H ₄	 7c	4	96
4	3-ClC ₆ H ₄	 7d	5	95
5	4-ClC ₆ H ₄	 7e	4	97

6	$2,4\text{-Cl}_2\text{C}_6\text{H}_3$		4	97
		7f		
7	$2\text{-NO}_2\text{C}_6\text{H}_4$		4	90
		7g		
8	$3\text{-NO}_2\text{C}_6\text{H}_4$		6	92
		7h		
9	$4\text{-NO}_2\text{C}_6\text{H}_4$		5	97
		7i		
10	$2\text{-MeC}_6\text{H}_4$		10	88
		7j		
11	$4\text{-MeC}_6\text{H}_4$		10	85
		7k		

12

4-BrC₆H₄

7

95

71

^a Isolated yield

Conclusions

In summary, we have developed and characterized MnFe₂O₄@APTES@isatin-SO₃H as a highly effective and reusable heterogeneous magnetic nanocatalyst. In this paper, we addressed this challenge by examining the role of the silane primer APTES, commonly used as an adherent agent for inorganic/organic bonding. The nanoparticles were examined as a proficient heterogeneous Lewis acid catalyst for the eco-friendly synthesis of 2H-indazolo[1,2-b]phthalazine-triones through a one-pot, four-component condensation reaction under solvent-free conditions at 80 °C. The notable advantages of this synthetic approach encompass its high efficiency, wide applicability, favorable to excellent product yields, short reaction duration, simplicity, low reaction temperature, ease of product extraction, environmentally friendly reaction profile, avoidance of harmful catalysts and solvents, and adherence to the principles of green chemistry. These features render it a valuable and appealing technique for synthesizing 2H-indazolo[2,1-b]phthalazine-triones. Furthermore, the effortless retrieval and reusability of the catalyst position this method as an economically and environmentally preferable option for chemical industries. Additionally, the catalyst can be efficiently reclaimed using a permanent magnet and utilized for at least seven cycles without significant loss in activity.

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