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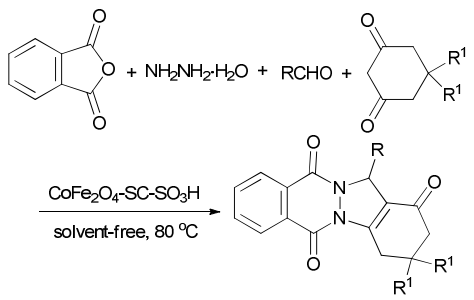
• **Graphical Abstract:**



A highly efficient and recyclable cobalt ferrite chitosan sulfonic acid magnetic nanoparticle for one-pot, four-component synthesis of 2H-indazolo[2,1-*b*]phthalazine-triones

Xiao-Na Zhao, Guo-Fei Hu, Meng Tang, Tai-Tai Shi, Xiao-Li Guo, Tao-Tao Li, Zhan-Hui Zhang*

A novel magnetical cobalt ferrite chitosan sulfonic acid ($CoFe_2O_4$-CS-SO_3H) was prepared and identified as an efficient catalyst for synthesis of 2*H*-indazolo[2,1-b]phthalazine-triones by one-pot, four-component reaction.

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A highly efficient and recyclable cobalt ferrite chitosan sulfonic acid magnetic nanoparticle for one-pot, four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

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Abstract

A highly efficient magnetic $CoFe_2O_4$ chitosan sulfonic acid nanoparticle ($CoFe_2O_4$-CS-SO_3H) was prepared and applied for one-pot, four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones by condensation of phthalic anhydride, hydrazinium hydroxide,1,3-cyclohexanedione and aldehydes under solvent-free conditions at 80 ºC. The magnetic nanocatalyst could be readily recovered by applying an external magnet and recycled for several times without significant loss of its catalytic activity.

Keywords:

Magnetic nanoparticle; Chitosan; Sulfonic acid; Heterogeneous catalyst; Multi-component reaction, 2*H*-indazolo[2,1-*b*]phthalazine-triones

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Introduction

Heterogeneous catalysts have gained much importance in recent years due to environmental and economic considerations. These heterogeneous catalysts are advantageous over homogeneous catalysts as they can be recovered from the reaction mixture through filtration or centrifugation and reused after activation, thereby making the process economically viable.[1] Compared to other supports such as silica, alumina, activated carbon, metal oxides, zeolites, clays, polymers, magnetic nanoparticles (MNPs) are arguably the most extensively investigated and emerged as excellent and ideal supports with significant industrial potential due to their extraordinary properties such as large specific surface area, readily disersed in reaction solution, and easy functionalization with various groups.[2] Their super-paramagnetic character makes them be effective and easily recovered from the reaction system using an external permanent magnet, which eliminates the necessity of tedious filtration, centrifugation or membrane separation steps and enhances the product purity. Thus, a wide range of the magnetically recyclable nanocatalysts with excellent catalytic activities have been developed and applied in versatile organic reactions.[3] Among the various MNPs as the core magnetic supports, cobalt ferrite is one of the most versatile magnetic materials as it has moderate saturation magnetization, high chemical stability and mechanical strength and can be prepared by simple methods.[4]

A wide range of organic reactions depend on the use of protic acids as catalysts. However, difficulties in the separation of the catalyst from the product and generation of enormous quantities of waste have been limited the applications of these liquid acids. There are many reports on the preparation and applications of solid-supported acid.[5] Recently, chitosan (CS) as one kind of the widely used bio-based polymers has been attarcing more and more attention.[6] It is natural, non-toxic, biodegradable, hydrophilic and reproducible molecule, and widely used in many industrial and manufacturing processes. Chitosan has also been used as effective catalyst in organic synthesis,

however, it can not be separated easily from water due to its low density.[7] It is the alkaline deacetylated product of chitin and comprises a great quantity of hydroxyl and amino groups, which make it be attached on magnetic nanoparticles ions through chelate mechanism without using any linkers.[8] Thus, combining the attractive properties of magnetic $CoFe_2O_4$ and chitosan, the development of novel, highly active and reusable immobilized catalysts by further functionalization is therefore an interesting challenge.

Due to growing concerns over the adverse influence of organic solvents on the environment, solvent-free organic reactions have also attracted tremendous attention. Meanwhile, the construction of structurally diverse and complex molecular 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.[9] 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 activites.[10] They have proved to be promising luminescence materials and fluorescence probes.[11] The synthesis of indazolo[2,1-*b*]phthalazine-triones can be carried out by three-component condensation of phthalhydrazide, dimedone, and aromatic aldehydes[12-18] or four-component reaction of phthalic anhydride, hydrazinium hydroxide, dimedone and aromatic aldehydes in the presence of various catalysts such as sulfuric acid-modified PEG-6000 (PEG-OSO_3H),[19] $Ce(SO_4)_2{\cdot}4H_2O$,[20] ZnO nanoparticles,[21] cellulose-SO_3H,[22] starch sulfate,[23] ionic liquid *N*,*N*,*N*,*N*-tetramethylguanidiniumacetate [TMG][Ac],[24] 1-butyl-3-methylimidazolium bromide ([Bmim]Br),[25] and 2-pyrrolidonium hydrogensulfate ([Hnhp][HSO_4]).[26] Despite being effective, some of these methods involve the use of transtition metal as catalyst, extended reaction times, unsatisfactory yields of the products, or require additional instruments such as ultra sound.

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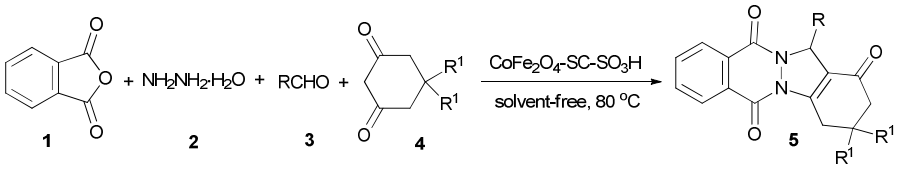
Therefore, the development of novel, more efficient, cheaper, and more easily recovered catalysts for this four-component reaction remains highly desirable.

Considering the above subjects and in continuation of our efforts toward the design of magnetic nanocatalysts[27] and sustainable synthesis development,[28] we wish to report here a new type of magnetic $CoFe_2O_4$ chitosan sulfonic acid nanoparticle ($CoFe_2O_4$-CS-SO_3H) as a powerful catalyst for the green and efficient synthesis of indazolo[2,1-*b*]phthalazine-triones by one-pot, four-component reaction of phthalic anhydride, hydrazinium hydroxide,1,3-cyclohexanedione and aldehydes (Scheme 1).



Scheme 1. One-pot four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

Results and discussion

Preparation and characterization of $CoFe_2O_4$-CS-SO_3H

The magnetic $CoFe_2O_4$ chitosan sulfonic acid nanoparticle ($CoFe_2O_4$-CS-SO_3H) was prepared by two steps as presented in Scheme 2. The first step is the preparation of magnetic $CoFe_2O_4$-chitosan nanopaticles by one-pot synthesis method. Chitosan was firstly dissolved in 3% acetic acid solution, then aqueous solution of $FeCl_3 \cdot 6H_2O$ and $CoCl_2 \cdot 6H_2O$ was added. The mixture was stirred strongly for 2 h, and then NaOH solution was added. The formed $CoFe_2O_4$ has weak interaction with amino and hydroxyl groups in chitosan. Then, the $CoFe_2O_4$-CS served as supported for the immobilization of SO_3H group by the reaction of amino and hydroxyl groups with chlorosulfonic acid in CH_2Cl_2 led to sulfonic acid-functionalized magnetic $CoFe_2O_4$ nanoparticles ($CoFe_2O_4$-CS-SO_3H). It was found that the content of sulfonic acid was 0.50 mmol/g determined by acid-base titration. Also, the pH of this solid acid (10 %, w/v) was measured using pH meter at 25 ºC. At first 0.5 g solid sulfonic acid was dispersed in 5 ml distilled water by ultrasonic bath for 1 h,

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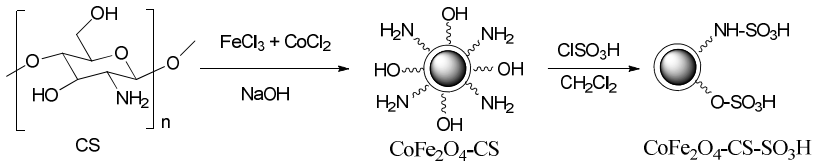
then measured and found to be 1.25.



Scheme 2. Synthesis of $CoFe_2O_4$-CS-SO_3H

XRD analysis. The XRD pattern of the sample is shown in Figure 1. As seen in Fig. 1, $CoFe_2O_4$-CS-SO_3H show typical characteristic peaks at the 2θ values of 18.2, 29.0, 35.5, 43.6, 57.7 and 61.7 with the corresponding reflection of (111), (220), (311), (400), (511) and (440) crystal planes. The observed diffraction peaks agree with the cubic structure of $CoFe_2O_4$ (JCPDS 221086),[4] suggesting that the coating process did not result in the phase change of $CoFe_2O_4$.

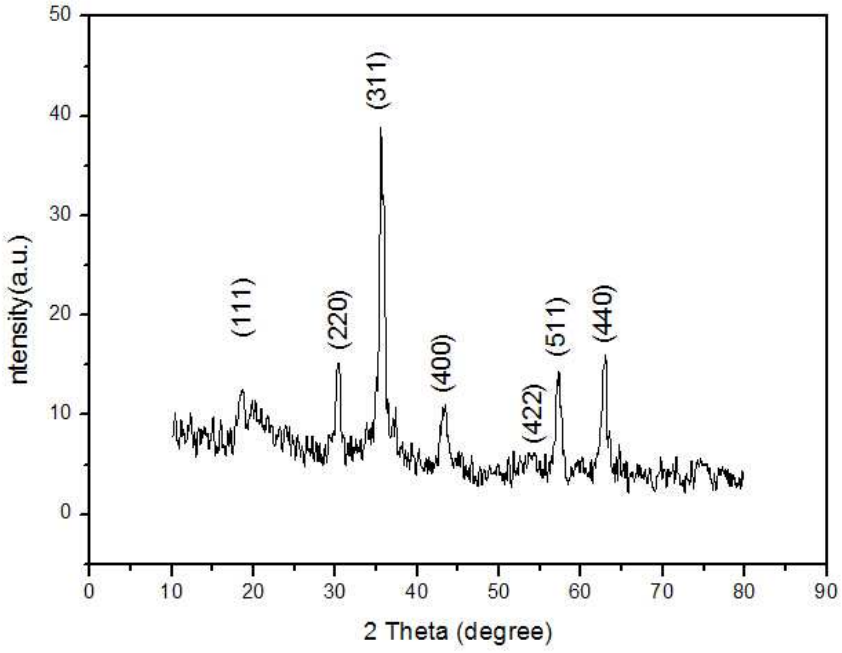


Fig. 1. XRD pattern of $CoFe_2O_4$-CS-SO_3H

TEM and EDX elemental analysis. The TEM images of the synthesized $CoFe_2O_4$-CS-SO_3H are shown in Figures 2. The images confirmed the formation of single-phase $CoFe_2O_4$ nanoparticles, with spherical morphology. The average nanopartical diameter of $CoFe_2O_4$-CS-SO_3H was estimated

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to be ca. 50-60 nm based on the TEM image, which is also in accordance with the result calculated by the Scherrer formula. The presence of C, O, Fe, Co and S atoms was observed in the EDX spectrum (Fig. 3).

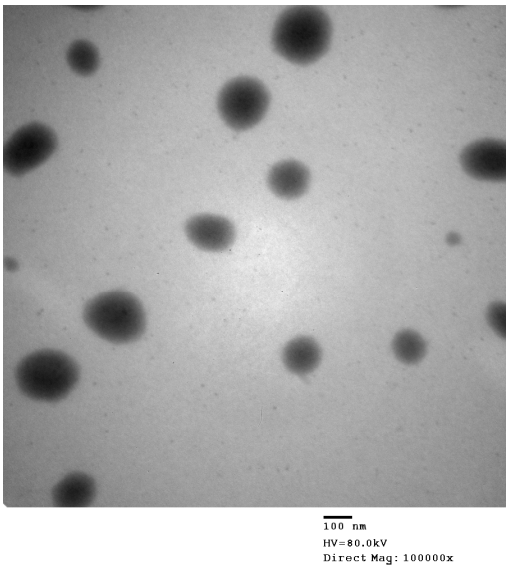

Fig. 2. TEM images of $CoFe_2O_4$-CS-SO_3H

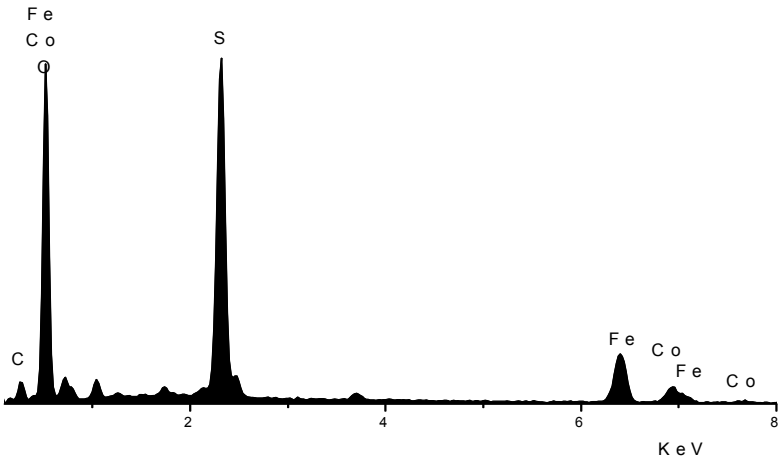

Fig. 3. EDS spectrum of $CoFe_2O_4$-CS-SO_3H

FT-IR analysis. Fig. 4 shows the Fourier transform infrared (FTIR) spectra of $CoFe_2O_4$ (a), $CoFe_2O_4$-CS (b) and $CoFe_2O_4$-CS-SO_3H (c). The Co–O and Fe–O stretching vibration near 593 cm^{-1} was observed in figure 4(a), (b) and (c). The significant features observed for figure 4(b) are

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the appearance of the peaks at 1074, 1300, 1606, 2891, 3427 cm^{-1} corresponding to C-OH, C-N, N-H, C-H, and OH stretching models of the chitosan molecules. The three new bands appered in figure 4(c) at 650, 1090 and 1160 cm^{-1} corresponding to the O=S=O asymmetic and symmetric stretching vibrations and S-O stretching vibration of the sulfonic acid groups.

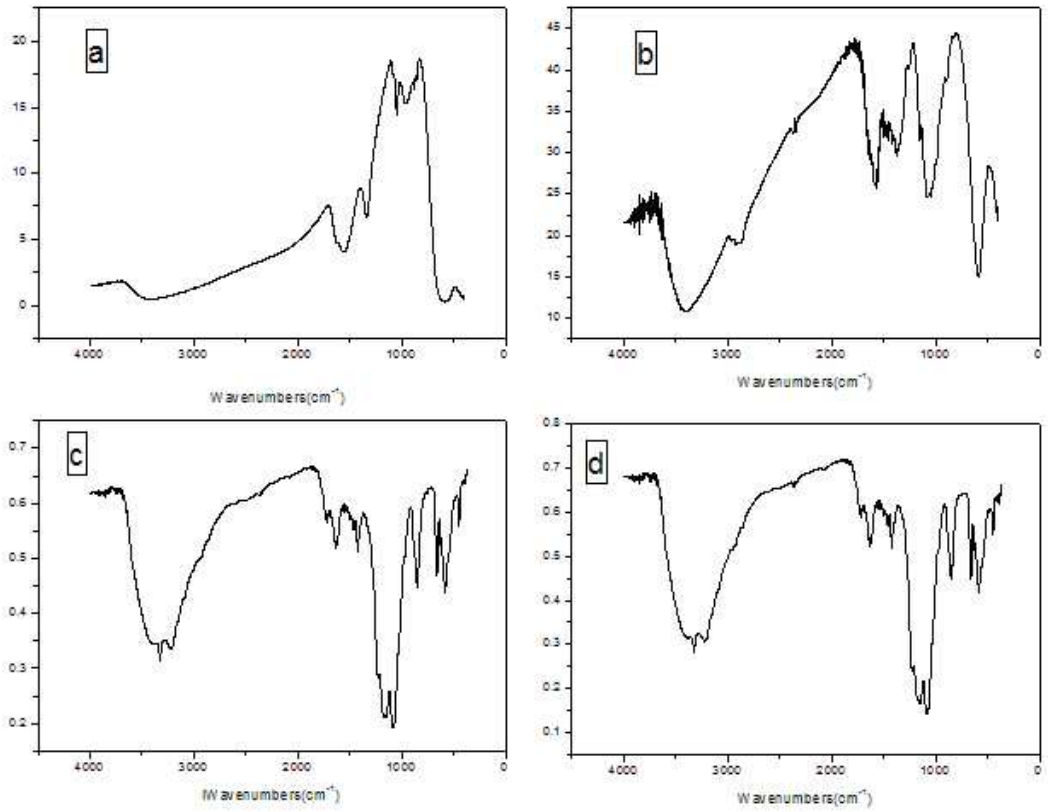

Fig. 4. FT-IR spectra of (a) $CoFe_2O_4$, (b) $CoFe_2O_4$-CS, and (c) fresh and (d) reused $CoFe_2O_4$-CS-SO_3H

The magnetic properties. The magnetic properties of the samples $CoFe_2O_4$ and $CoFe_2O_4$-CS-SO_3H were measured at room temperature using a vibrating sample magnetometery (VSM). As shown in Fig. 5, the value of magnetic saturation (Msat) for $CoFe_2O_4$-CS-SO_3H is about 41.5 emu g-1, which is lower than that of bare $CoFe_2O_4$ nanoparticles (ca. 49.6 emu g-1). The reason should be ascribed to the existence of CS-SO_3H hybrid material shells on $CoFe_2O_4$ cores. Even with this reduction in the saturation magnetization, the prepared catalyst could still be

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efficiently separated with the help of an external magnetic force.

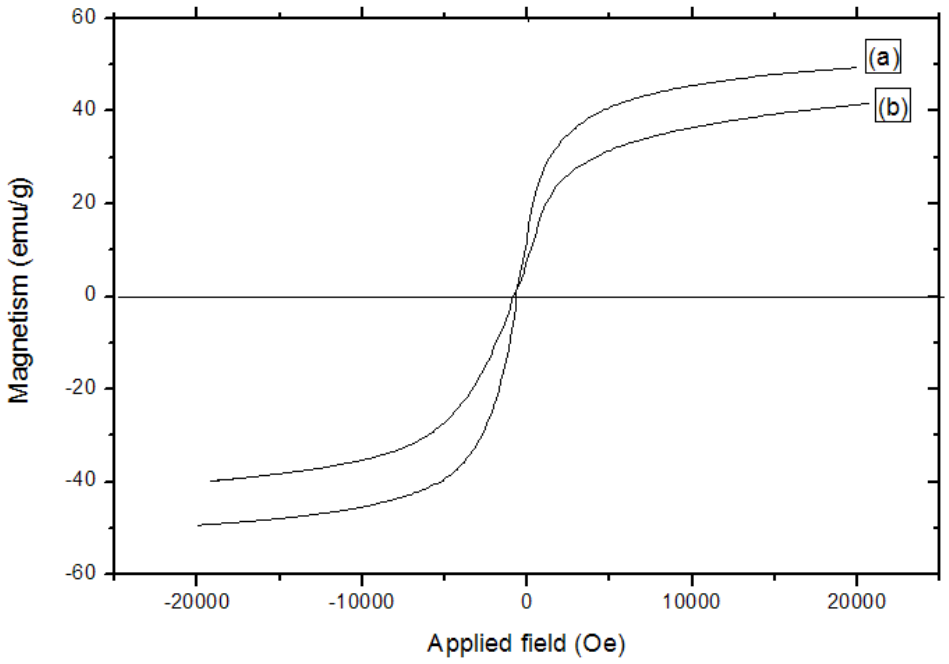


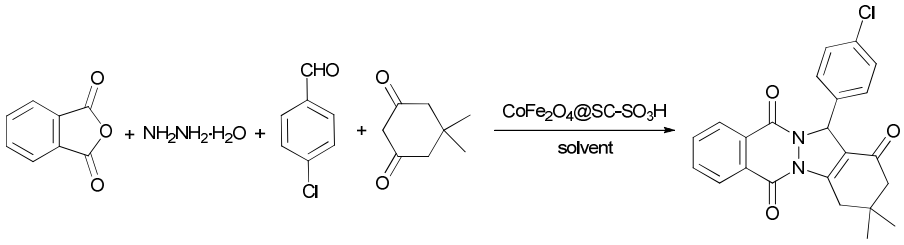
Fig. 5. Magnetization curves of $CoFe_2O_4$ (a) and $CoFe_2O_4$-CS-SO_3H (b)

Catalytic activity of $CoFe_2O_4$-SC-SO_3H

In order to evaluate the catalytic reactivity of $CoFe_2O_4$@SC-SO_3H, one-pot four-component reaction of phthalic anhydride, hydrazinium hydroxide, 5,5-dimethyl 1,3-cyclohexanedione and 4-chlorobenzaldehyde was chosen the model reaction for our investigation, and the results are displayed in Table 1. In the absence of the catalyst, only a trace amount of the desired product was observed even after 1 h (Table 1, entry 1), which domonstrated that catalyst plays an important role in this reaction. Several reaction conditions were tested in order to identify the optimized conditions. Firstly, the influence of different solvents on the reaction was examined, and a good yield was obtained with EtOH (Table 1, entry 5). Toluene, CH_3CN, AcOEt, H_2O, PEG 400, glycerol, [bmin]BF_4, and [bmin]PF_6 were found to be inferior. To our delight, when the reaction was carried

out under solvent-free condition at 80 ^{o}C, the yield could be improved to 95%. Other experinental parmeters such as temperature and amount of catalyst were also optimized. It was observed that only 5% yield of product was obtained at room temperature. The yield of the desired product was greatly improved with the increasing of temperature. The best yield was observed when the reaction was performed at 80 ^{o}C. Increasing or decreasing the temperature from 80 ^{o}C led to a decrease in the yield (Table 1, entries 13 and 15). With respect to the catalyst loading, 0.5 mol% (10 mg) was found to be optimal. When the loading of catalyst was lowered to 0.4 mol%, the reaction would proceed incompletely (Table 1, entry 17). Any further addition of catalyst had no positive effect on the overall yield of product. Therefore, on the basis of the above experiments, the most suitable reaction conditions for this one-pot process included $CoFe_2O_4$-SC-SO_3H (0.5 mol%, 10 mg) as the catalyst under solvent-free conditions at 80 ^{o}C (Table 1, entry 14).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Solvent	Temp. (^{o}C)	Time (min)	Yield (%)[b]
1	no	no	80	60	trace
2	0.5	Toluene	80	10	7
3	0.5	CH_3CN	reflux	10	33
4	0.5	AcOEt	reflux	10	29
5	0.5	EtOH	reflux	10	52
6	0.5	H_2O	80	10	10
7	0.5	PEG 400	80	10	18
8	0.5	Glycerol	80	10	21
9	0.5	[bmin]BF_4	80	10	31
10	0.5	[bmin]PF_6	80	10	19
11	0.5	no	25	10	6

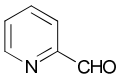
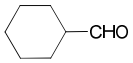
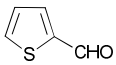
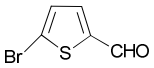
12	0.5	no	50	6	77
13	0.5	no	60	6	82
14	0.5	no	80	6	95
15	0.5	no	100	6	90
16	0.25	no	80	6	30
17	0.4	no	80	6	60
18	1.0	no	80	6	95

[a] Experimental conditions: phthalic anhydride (1 mmol), hydrazinium hydroxide (1.2 mmol), 4-chlorobenzaldehyde (1 mmol) and 5,5-dimethyl 1,3-cyclohexanedione (1 mmol), solvent (5 ml).
[b] Isolated yields.

After optimizing of the reaction conditions, the generality and scope of the reaction were investigated. As illustrated in Table 2, a variety of aromatic aldehydes bearing electron-rich and electron-poor groups at either *ortho*-, *meta*- or *para*-positions of the aromatic ring were smoothly converted into 2*H*-indazolo[2,1-*b*]phthalazine-triones in high to excellent yields. A wide range of synthetically useful functional groups including thioether, halide and trifluoromethyl groups remained intact during the present reaction conditions. In addition, the presence of three methoxy electron donating groups on the aromatic ring of the aldehyde performed well and afforded the desired product in 90% yield. Also, heterocyclic aromatic aldehyde such as picolinaldehyde also underwent efficient conversion into the targeted product in 86% yield. It should be noted that aliphatic aldehyde such as cyclohexanecarbaldehyde was also compatible under these reaction conditions and was successfully transformed into the desired products in 83% yield (entry 17). Replacement of 5,5-dimethyl 1,3-cyclohexanedione with 1,3-cyclohexanedion under identical conditions also produced the expected products in high yields (Table 2, entries 18-22).

Table 2 Four-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones catalyzed by $CoFe_2O_4$-CS-SO_3H[a]

Entry	Aldehydes	R	Product	Time (min)	Yield (%)[b]	MP (ºC)
1	PhCHO	Me	**5a**	7	90	209-210 (208-209)[18]
2	4-$OMeC_6H_4CHO$	Me	**5b**	6	92	219-220 (218-209)[18]

3	4-$O(CH_2)_2MeC_6H_4CHO$	Me	**5c**	7	91	159-160
4	4-$O(CH_2)_4MeC_6H_4CHO$	Me	**5d**	7	89	165-166
5	2,3,4-$(OMe)_3C_6H_2CHO$	Me	**5e**	8	90	184-185
6	4-MeC_6H_4CHO	Me	**5f**	6	93	229-230 (227-228)[18]
7	4-$SMeC_6H_4CHO$	Me	**5g**	6	91	230-231 (229-231)[14]
8	2-FC_6H_4CHO	Me	**5h**	7	86	271-222 (270-272)[15]
9	4-FC_6H_4CHO	Me	**5i**	6	89	221-222 (220-222)[18]
10	2-ClC_6H_4CHO	Me	**5j**	8	90	269-270 (268-270)[18]
11	3-ClC_6H_4CHO	Me	**5k**	7	91	206-207 (204-206)[18]
12	4-ClC_6H_4CHO	Me	**5l**	6	95	260-262 (262-264)[18]
13	3-$NO_2C_6H_4CHO$	Me	**5m**	6	89	271-272 (270-272)[18]
14	4-$NO_2C_6H_4CHO$	Me	**5n**	6	93	225-226 (222-225)[14]
15	4-$CF_3C_6H_4CHO$	Me	**5o**	6	93	217-218 (215-217)[25]
16		Me	**5p**	8	86	230-232 (229-231)[15]
17		Me	**5q**	10	83	220-222 (221-222)[18]
18	4-$OMeC_6H_4CHO$	H	**5r**	7	91	253-254 (254-255)[13]
19	4-MeC_6H_4CHO	H	**5s**	7	94	243-245 (244-246)[13]
20	4-ClC_6H_4CHO	H	**5t**	7	92	273-275 (272-273)[12]
21		H	**5u**	8	85	240-242
22		H	**5v**	8	88	206-208

[a] Reaction conditions: phthalic anhydride (1 mmol), hydrazinium hydroxide (1.1 mmol), aldehydes (1 mmol), $CoFe_2O_4$@CS-SO_3H (0.01 g), 80 °C.
[b] Isolated yield.

Recycling of the catalyst

The magnetic property of $CoFe_2O_4$@CS-SO_3H facilitates efficient recovery of the catalyst from the reaction mixture during work-up procedure. After completion of the reaction, ethyl acetate was added to the reaction mixture. The catalyst was separated by a strong external permanent magnet, washed with ethyl acetate to remove residual product, dried under vacuum, and reused directly for the next cycle. The catalyst was used over five runs, and no significant loss of catalytic activity was observed (Fig. 6). FT-IR images of fresh and recovered catalysts indicated that no significant change had occurred. This indicates that $CoFe_2O_4$@CS-SO_3H was very high chemical stable and can endure

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high temperature condition (Fig. 4).

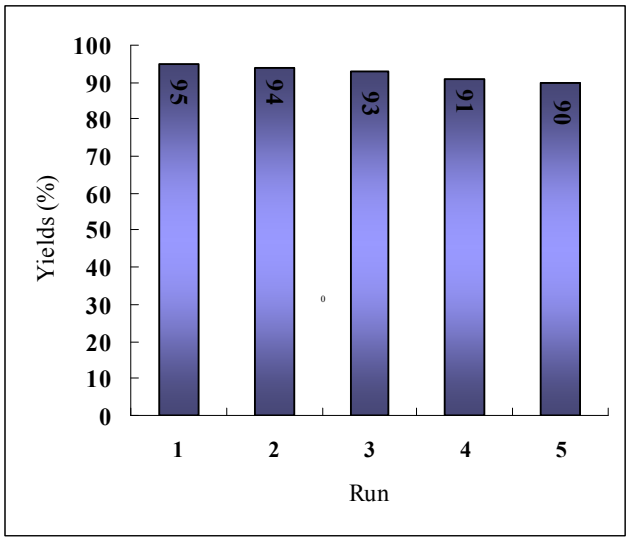

Fig. 6. The recycling of the catalyst

To compare the efficiency of our catalyst with some of the previously employed catalysts, we have tabulated the results of these catalysts for the synthesis of product **5a** in Table 3. As can be seen in Table 3, the results clearly indicated that our catalyst is an equally or more efficient catalyst for this four-compoent reaction.

Table 3 Comparison of our results with previously reported methods

Entry	Catalyst	Reaction conditions	Time (min)	Yield (%)
1	PEG-OSO_3H (8 mol%)	solvent-free, 80 ºC	13	87[19]
2	$Ce(SO_4)_2 \cdot 4H_2O$ (10 mol%)	solvent-free, 125 ºC	6	78[20]
3	ZnO (5 mol%)	solvent-free, 60 ºC	5	97[21]
4	cellulose-SO_3H (4 mol%)	solvent-free, 60 ºC	7	91[22]
5	starch sulfate (0.8 mol%)	solvent-free, 80 ºC	7	89[23]
6	[TMG][Ac] (10 mol%)	solvent-free, 80 ºC	15	92[24]
7	[Bmim]Br (0.5 g)	ultrasonic irradiation	10	93[25]
8	([Hnhp][HSO_4]) (5 mol%)	solvent-free, 80 ºC	7	88[26]
9	$CoFe_2O_4$-SC-SO_3H (0.5 mol%)	solvent-free, 80 ºC	7	90 (this work)

Conclusions

In summary, a nanosized magnetic $CoFe_2O_4$ chitosan sulfonic acid was prepared and characterized by XRD, TEM, SEM, EDX and IR spectroscopy. The catalyst showed highly activity for one-pot, atom-economical syhthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones by four-component reaction of phthalic anhydride, hydrazinium hydroxide,1,3-cyclohexanedione and aldehydes. This simple and environmentally benign catalysis proceeds under solvent-free conditions, requires short reaction times, and provides products in high to excellent yields. The catalyst could be readily recovered by applying an external magnet and recycled for several times without appreciable loss of its catalytic activity, which demonstrated the value of the present $CoFe_2O_4$-SC-SO_3H as a green heterogeneous catalyst with potential use for industrial applications.

Experimental

Materials and instruments

Chemicals were purchased from and used without further purification. The known products were characterized by comparision of their spectral and physical data with those reported in the literature. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 spectrometer in $CDCl_3$ solution with TMS as an internal standard. X-ray power diffraction (XRD) analysis was carried out on a PANalytical X'Pert Pro X-ray diffractometer. FT-IR spectra were obtained with potassium bromide pellets on potassium bromide pellets in the range 400-4000 cm^{-1} with a Bruker-TENSOR 27 spectrometer. Surface morphology and particle size were studied using a Hitachi S-4800 SEM instrument. Transmission electron microscope (TEM) images was obtained using Hitachi H-7650 microscope at 80 KV for characterization of the catalyst. 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. Elemental analyses were performed by using a Vario EL III CHNOS elemental analyzer.

Preparation of magnetic $CoFe_2O_4$ chitosan sulfonic acid nanoparticle ($CoFe_2O_4$-CS-SO_3H)

Chitosan coated $CoFe_2O_4$ nanoparticles ($CoFe_2O_4$-CS) were prepared as follow: 1.50 g of chitosan was dissolved in 3% acetic acid solution (100 ml) in a 500 ml three-necked flask equipped with a stirrer and dropping funnel. Then, the aqueous solution of 2.70 g of $FeCl_3 \cdot 6H_2O$ and 1.19 g of $CoCl_2 \cdot 6H_2O$ (50 ml) was slowly added into the mixture. The mixture was stirred strongly for 2 h, and then NaOH (3 mol/L) solution was added until the pH increased to 12. The reaction mixture was then continually stirred under refluxing condition for 1 h. After cooling the solution to room temperature, the chitosan coated $CoFe_2O_4$ NPs were collected using a permanent magnet and washed with water, ethanol, then dried under vacuum at 50 ^oC for 24 h.

$CoFe_2O_4$-CS-SO_3H was prepared by the reaction of $CoFe_2O_4$-CS and chlorosulfonic acid. Typically, a mixture of $CoFe_2O_4$-CS (1.2 g) was suspended in dichloromethane (5 mL) in a 100 mL round bottom flask equipped with a gas outlet tube and a dropping funnel containing a solution of chlorosulfonic acid (2 mL) in dichloromethane (15 mL). The chlorosulfonic acid solution was added drop-wise over a period of 30 min at 0 ^oC. After the addition was complete, the mixture was shaken for 1 h until all HCl was removed from reaction vessel. Then, the product was separated by magnetic decantation and washed with EtOH to remove unattached substrates. Finally, the obtained $CoFe_2O_4$-CS-SO_3H NPs were dried under vacuum at 80 ^oC for 24 h.

General procedure for synthesis of amides

Aldehyde (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and $CoFe_2O_4$-CS-SO_3H (0.005 mol, 10 mg) was added to a mixture of hydrazinium hydroxide (1.2 mmol) and phthalic anhydride (1 mmol). The reaction mixture was heated at 80 ^oC. After completion of 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 for a consecutive run under the same reaction conditions. Evaporation of the solvent of the filtrate under

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reduced pressure gave the crude product. The pure product was obtained by column chromatography on silica gel with hexane/ethyl acetate.

Some selected spectra data for non-reported products

*3,3-Dimethyl-13-(4-propoxy-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b]phthalazine-1,6,11-trione (**5c**)*. Yellow needles; IR (KBr): 2953, 1667, 1366, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, J = 7.0 Hz, 3H), d=1.23 (s, 3H), 1.25 (s, 3H), 1.73-1.79 (m, 2H), 2.37 (s, 2H), 3.26 and 3.44 (AB system, J_{AB} = 19.0 Hz, 2H), 3.92 (t, J = 6.5 Hz, 2H), 6.44 (s, 1H), 6.86 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.86-7.88 (m, 2H), 8.29-8.30 (m, 1H), 8.36-8.38 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125MHz) δ 14.0, 22.4, 28.2, 28.5, 28.7, 28.9, 34.7, 38.1, 51.0, 64.6, 67.9, 114.6, 118.6, 127.7, 127.9, 128.0, 128.5, 129.0, 129.2, 133.5, 134.5, 150.7, 154.3, 156.1, 159.4, 192.3 ppm. Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.28; H, 5.89; N, 6.70; ESI-MS: m/z = 431 $(M+1)^+$.

*3,3-Dimethyl-13-(4-pentyloxy-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b]phthalazine-1,6,11-trione (**5d**)*. Yellow needles; IR (KBr): 2961, 2363, 1659, 1358, 1312, 1250, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.02 (t, J = 7.5 Hz, 3H), d=1.23 (s, 3H), 1.25 (s, 3H), 1.27-1.30 (m, 2H), 1.76-1.81 (m, 2H), 2.20 (s, 2H), 2.37 (s, 2H), 3.26 and 3.44 (AB system, J_{AB} = 19.0 Hz, 2H), 3.89 (t, J = 6.5 Hz, 2H), 6.44 (s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.86-7.88 (m, 2H), 8.29-8.30 (m, 1H), 8.36-8.38 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125MHz) δ 10.5, 22.5, 28.3, 28.5, 28.7, 29.7, 30.9, 34.7, 38.1, 51.0, 53.8, 64.6, 69.4, 118.7, 127.7, 127.9, 128.1, 128.5, 129.0, 129.2, 129.8, 133.5, 134.5, 150.8, 154.3, 156.1, 159.4, 192.3 ppm. Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.53; H, 6.40; N, 5.92; ESI-MS: m/z = 459 $(M+1)^+$.

*3,3-Dimethyl-13-(2,3,4-trimethoxy-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b]phthalazine-1,6,11-trione (**5e**)*. Yellow needles; IR (KBr): 2967, 2654, 1665, 1364, 1285, 1098, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20 (s, 3H), 1.23 (s, 3H), 2.34 (d, J = 2.5 Hz, 2H), 3.26 and 3.42 (AB system, J_{AB} = 18.5 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.58 (s, 1H), 6.67 (d, J = 9.0 Hz, 1H),

7.08 (d, J = 8.5 Hz, 1H), 7.86-7.88 (m, 2H), 8.29-8.31 (m, 1H), 8.38-8.40 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125MHz) δ 28.4, 28.6, 30.9, 34.7, 38.1, 51.0, 55.8, 56.1, 60.6, 60.9, 62.0, 118.3, 127.6, 127.9, 129.0, 129.2, 133.4, 134.4, 142.1, 151.0, 152.0, 154.0, 154.1, 156.1, 157.2, 192.3 ppm. Anal. Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.51; H, 5.66; N, 6.07; ESI-MS: m/z = 463 $(M+1)^+$.

*3,3-Dimethyl-13-(4-methylsulfanyl-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b]phthalazine-1,6, 11-trione (**5g**)*. Yellow needles; IR (KBr): 2959, 2374, 1663, 1362, 1269, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 6H), 2.36 (s, 2H), 2.46 (s, 3H), 3.26 and 3.43 (AB system, J_{AB} = 19.0 Hz, 2H), 6.43 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.87-7.88 (m, 2H), 8.28-8.30 (m, 1H), 8.37-8.38 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.5, 28.3, 28.5, 28.7, 34.7, 38.1, 50.9, 64.6, 118.4, 126.6, 127.6, 127.7, 128.0, 129.0, 133.0, 133.6, 134.6, 136.0, 139.3, 151.0, 154.3, 156.0, 192.3 ppm. Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69. Found: C, 68.77; H, 5.51; N, 6.70; ESI-MS: m/z =419 $(M+1)^+$.

*13-Thiophen-2-yl-2,3,4,13-tetrahydro-indazolo[1,2-b]phthalazine-1,6,11-trione (**5u**)*. Yellow needles; IR (KBr): 3295, 1640, 1549, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.39-2.43 (m, 2H)), 2.59-2.70 (m, 2H), 3.39-3.46 (m, 1H)), 3.66-3.73 (m, 1H), 6.93 (s, 1H), 7.09 (d, J = 4.5 Hz, 1H), 7.34 (d, J = 5.0 Hz, 1H), 7.42 (d, J = 3.5 Hz, 2H), 7.94-8.00 (m, 2H), 8.42-8.46 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3, 24.5, 29.7, 30.9, 36.9, 59.5, 118.5, 125.9, 127.1, 127.8, 128.1, 128.2, 133.6, 134.6, 138.8, 153.0, 154.4, 156.1, 192.5 ppm. Anal. Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99. Found: C, 64.96; H, 3.90; N, 8.21; ESI-MS: m/z = 351 $(M+1)^+$.

*13-(5-Bromothiophen-2-yl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**5v**)*. Yellow needles; IR (KBr): 3448, 1661, 1359, 1260, 1142, 1108, 1001, 801, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29-2.34 (m, 2H), 2.52-2.61 (m, 2H), 3.28-3.35 (m, 1H), 3.56-3.62 (m, 1H), 6.73 (s, 1H), 6.94 (d, J = 3.5 Hz, 1H), 7.06 (d, J = 4.5 Hz, 1H), 7.86-7.92 (m, 2H), 8.34-8.37 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125MHz) δ 22.3, 24.5, 36.9, 59.5, 113.2, 117.7, 127.8, 128.2, 128.5, 128.8,

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128.9, 129.9, 133.8, 134.7, 140.1, 153.4, 154.4, 156.0, 192.4 ppm. Anal. Calcd for $C_{19}H_{13}BrN_2O_3S$: C, 53.16; H, 3.05; N, 6.53. Found: C, 52.98; H, 2.96; N, 6.72; ESI-MS: m/z = 430 $(M+1)^+$.

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