Collagen-Coated Superparamagnetic Iron Oxide Nanoparticles as a Sustainable Catalyst for Spirooxindole Synthesis

Shima Ghanbari

Iran University of Science and Technology

Maryam Esmkhani

Iran University of Science and Technology

Shahrzad Javanshir (✉ shjavan@iust.ac.ir)

Iran University of Science and Technology

Research Article

Keywords: catalysis, nanoparticles, catalytic properties

Posted Date: May 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-509159/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

In this work, a novel magnetic organic-inorganic hybrid catalyst was fabricated by encapsulating magnetite@silica ($\text{Fe}_3\text{O}_4@\text{SiO}_2$) nanoparticles with Isinglass protein collagen (IGPC) using epichlorohydrin (ECH) as crosslinking agent. Characterization studies of the prepared particles were accomplished by various analytical techniques specifically, Fourier transform infrared (FTIR) analysis, scanning electron microscopy (SEM), transmission electron microscopy (TEM), vibrating sample magnetometry (VSM), energy dispersive X-ray (EDX), X-ray diffraction (XRD), and Brunauer–Emmett–Teller (BET) analysis. The XRD results showed a crystalline and amorphous phase which contribute to magnetite and isinglass respectively. Moreover, the formation of the core/shell structure had been confirmed by TEM images. The synthesized $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ was applied as bifunctional heterogeneous catalyst in the synthesis of spirooxindole derivatives demonstrating excellent catalytic properties, stability and recyclability.

Introduction

Nowadays, the use of bifunctional catalysts has become a new field to promote chemical reactions in green, and environmentally friendly pathways and processes. In order to develop new approaches that are more respectful of the environment, catalyst development strategies are now oriented towards polymers of natural origin such as polysaccharides or proteins which come from renewable resources, often biocompatible and also more biodegradable than their synthetic counterparts. Bio-based heterogeneous catalysts, prepared from renewable natural polymers, have received significant attention in recent years due to their substantial advantages such as biodegradability, stability, and recyclability. The combination of nanoparticles and biodegradable polymers can result in nano-biocomposites, which have the potential for various catalytic and environmental applications¹⁻⁵.

Plentiful supports have been commonly used for the immobilization of natural polymers such as silica, resins, silica composites, and magnetic materials among others. Magnetic nanoparticles based on metals such as Cu, Co, Fe, and Ni provide a potent solid support system to immobilize proteins⁶⁻¹⁰, among them, magnetite nanoparticles (Fe_3O_4) have remarkable properties such as superparamagnetism, low toxicity, high specific surface area, biocompatibility and easy separation which makes them more interesting for researchers.

One of the most commonly used techniques for the immobilization of proteins is cross-linking. For collagen materials, many crosslinkers such as glutaraldehyde, isocyanates, glyoxal, and carbodiimides, were used¹¹.

Natural polymers such as polysaccharides (cellulose, chitosan, chitin, alginate, carrageenan, lignin, fucoidan, etc.) and proteins have been used as catalysts in chemical transformations¹²⁻¹⁸. Coating magnetic particles with natural polymers allows them to use their functional groups for promoting chemical reactions and also easy separation^{19,20}.

Based on our interest for turning agricultural and marine waste into value added materials, [21-23] we have used Isinglass (IG), a natural polymer derived from swim bladder of fish with high content of collagen protein, for encapsulating $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanoparticles using epichlorohydrin (ECH) as crosslinking agent. The prepared hybrid material named $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ was applied as bifunctional heterogeneous catalyst in the synthesis of spirooxindole derivatives. Such hybrid material based on natural polymer IG with both acidic and basic groups has been shown to be a very effective catalyst in a variety of chemical transformation, including the synthesis of, triazoles²⁴, 4H-pyran derivatives²⁵, and Suzuki coupling²⁶. IG contains many amino acids whom their properties and catalytic performances have been demonstrated for many years^{27,28}.

Defined as processes allowing at least three reagents to react in a single pot, all of which participate in the structure of the final product, multicomponent reactions make it possible to synthesize highly functionalized compounds. In addition, multicomponent reactions offer rapid access to a wide variety of potential active ingredients. In the same way that a 4-digit code offers 10,000 possibilities, the possible variations for each reagent give access to an impressive number of related compounds. Very useful in combinatorial chemistry, MCRs make it possible to constitute chemical libraries for high throughput screening in the pharmaceutical industry. Several evocative tags are commonly involved in MCRs such as the atomic economy, easy to implement, using very mild reaction conditions, and without recourse to toxic metals, these reactions represent a definite step forward to ideal synthesis^{29, 30}.

Heterocyclic compounds represent more than 90% of the active ingredients possessing a wide range of applications in pharmaceutical industry, veterinary medicine and phytochemistry³¹. Indoles, oxindoles, and spirooxindoles are important heterocyclic compounds, and ubiquitous motifs in naturally and unnaturally occurring biologically active pharmaceutical ingredients^{29, 30, 314}. Some biologically active indoles, oxindoles and spirooxindoles are presented in figure 1.

So far, various methods and catalysts have been used for the synthesis of these compounds, including the reaction between isatin, malononitrile and dimedone with different catalysts such as α -amylase³², $\text{CoFe}_2\text{O}_4@\text{SiO}_2@\text{SO}_3\text{H}$ ³³, $\text{MgO}@\text{PMO-IL}$ ³⁴, magnetic sulfonated chitosan³⁵, magnetic poly ethyleneimine³⁶, etc.

Here, we have developed a new collagen-coated superparamagnetic iron oxide nanoparticle as a sustainable bio-based catalyst for the direct synthesis of spirooxindole (Figure 2).

Results And Discussion

Synthesis pathway of $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ is illustrated in figure 2. Fe_3O_4 NPs were prepared by co-precipitation method by dissolving divalent and trivalent iron salts into distilled water, followed by precipitation with NH_4OH . Afterward, TEOS was hydrolyzed to form silica oligomers, which were coated on the surface of Fe_3O_4 nanoparticles to obtain $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanoparticles. Subsequently, ECH was cross-

linked on the surface of $\text{Fe}_3\text{O}_4/\text{SiO}_2$. $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ was obtained by nucleophilic addition of IG to as-prepared magnetic nanoparticles. (figure 2)

Characterization of the $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$

After preparation of the nanocatalyst, its composition, structure, morphology and textural properties was properly characterized by different methods and techniques. The FT-IR spectra of the $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$, $\text{Fe}_3\text{O}_4@\text{SiO}_2$, and Fe_3O_4 are compared in Figure S1 (see supporting information). The three curves show variation in the intensity of the bands in different regions. The FTIR spectrum of Fe_3O_4 indicates the characteristic band of Fe–O at 596 cm^{-1} . The peak identified at 3426 cm^{-1} which was assigned to the O–H stretching vibrations was shifted from 3426 to 3276 cm^{-1} in $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ with a net diminution of intensity indicating the involvement of isinglass in the synthesis of final composite. The characteristic bands appeared at 1400 , 1385 and 1220 cm^{-1} were attributed to C–O (carboxyl), C–OH (secondary) and C–O groups. Finally, this FT-IR spectrum can be clearly shown that the $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ was successfully prepared.

The morphology and the structure of the $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ was characterized by SEM and TEM analysis (figure 3a and b). The average particle size was estimated to be 58 nm . Moreover, the well-ordered structure of the catalyst and its almost uniform distribution are clearly observable (Fig. 3a). The core-shell structure of the magnetic particles was proofed with the black centres and the brightest areas as Fe_3O_4 cores and SiO_2 shells respectively. These images also approve that the particles are nanometric in size (Fig. 3b).

Furthermore, the presence of carbon, oxygen, nitrogen, iron and Si elements were confirmed by energy dispersive X-ray (EDX) analysis which was showed in Figure 4a and b.

The magnetic features of Fe_3O_4 , $\text{Fe}_3\text{O}_4@\text{SiO}_2$ and $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ were investigated using VSM analysis. Magnetic hysteresis loop measurements of $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ indicate that its saturation magnetization value ($17.162\text{ emus. g}^{-1}$) is less than Fe_3O_4 (63.9 emus. g^{-1}). This value demonstrated the incorporation of IG on the surface of Fe_3O_4 (Figure 5).

In addition, in XRD pattern (figure 6) the peaks in 35 , 57 , and 62 were assigned to the presence of Fe_3O_4 in structure. The broad peak at 10 - 20 attributed to the amorphous structure of isinglass. The patterns were compared in X'pert software and correspond with 00 - 001 - 1111 , 00 - 002 - 0459 reference card numbers. (The individual reference card numbers were collected from the X'pert HighScore Plus version 1.0d software developed by the PANalytical B.V.)

According to the results of BET analysis shown in figure S2 (see supporting information), the special surface area $8.6115\text{ m}^2\text{ g}^{-1}$ and the volume of P/P° is $0.298949197\text{ cm}^3\text{ g}^{-1}$. Also, the volume of the single-point adsorption cavity and the single-point cavity desorption volume is $0.051635\text{ cm}^3/\text{g}$ and $0.045370\text{ cm}^3/\text{g}$ respectively.

Investigation the catalytic activities of Fe₃O₄@SiO₂/ECH/IG for the synthesis of spirooxindole derivatives **4a-t**

The catalytic behavior of Fe₃O₄@SiO₂/ECH/IG was investigated for the synthesis of spirooxindole derivatives *via* a three- component reaction between CH-acids, malononitrile, and isatin derivatives under different conditions. To find the optimal reaction conditions, various factors such as catalyst loading, solvent, time and reaction temperature were scrutinized in a model reaction including dimedone (**1a**), malononitrile (**2a**), and isatin (**3a**) to estimate the proper catalytic loading and time (figure 7). Amid different solvents, the mixture of EtOH/H₂O (1:1) was completed in a shorter time and gave a better yield (Table S1).

For further optimization, the effect of temperature, type of catalyst, and the amount of catalyst were also investigated and tabulated in Table S2 and S3 (See supporting information).

The results revealed the high performance of Fe₃O₄@SiO₂/ECH/IG due to synergistic effects and improved number of active sites on surface. The highest conversion of 94% was attained at a catalyst loading of 10 mg and reaction temperature 60 °C.

To generalize the optimum conditions, different spirooxindole derivatives from **4a-t** were prepared through a one pot reaction of isatin derivatives **1**, malononitrile **2** and 1,3 dicarbonyl derivatives **3a-3e** in the presence of Fe₃O₄@SiO₂/ECH/IG. (figure 7). The results are summarized in table 1.

Table 1 Synthesis of spirooxindole derivatives in the presence of Fe₃O₄@SiO₂/ECH/IG

Entry	R ₁	R ₂	1,3-dicarbonyl compound	Time (min)	Yield (%)	m.p. °C (reported)	Product
1	H	H	3a	10	94	301-303 (302-306) ⁴⁰	4a
2	H	H	3b	10	88	282-284 (278-280) ⁴¹	4b
3	H	H	3c	20	81	267-268 (268-270) ⁴¹	4c
4	H	H	3d	15	85	230-232 (240-241) ³⁷²	4d
5	H	H	3e	25	80	301-303 (290-292) ²¹	4e
6	H	NO ₂	3a	10	89	>300 (302-304) ³⁸³	4f
7	H	NO ₂	3b	5	85	>300 (306-307) ³⁹⁴	4g
8	H	NO ₂	3c	5	93	286-288 (288-289) ⁴⁰⁵	4h
9	H	NO ₂	3d	10	98	240-242 (253-255) ⁴¹⁶	4i
10	H	NO ₂	3e	30	82	297-299 (294-296) ⁴²⁷	4j
11	H	Cl	3c	20	70	234-236 (240-242) ⁴³	4k
12	H	Cl	3e	30	79	>300 (300-302) ⁴³	4l
13	Bn	H	3a	10	86	284-286 (281-282) ⁴⁴	4m
14	Bn	H	3b	5	92	282-284 (282-284) ⁴⁵	4n
15	Bn	H	3e	30	88	273-275 (280-282) ⁴⁶	4o
16	Me	H	3a	10	80	260-262 (255-258) ⁴⁷	4p
17	Me	H	3b	10	83	244-246 (243-245) ⁴⁸	4q
18	Me	H	3c	35	94	279-281 (285-286) ⁴⁹	4r
19	Me	H	3d	15	92	274-276 (280-282) ⁵⁰	4s

20	Me	H	3e	30	83	281-283 (283-285) ⁵¹	4t
----	----	---	----	----	----	------------------------------------	----

*Reaction condition: Isatin 1 (1 mmol), 2 (1 mmol), 1,3-dicarbonyl 3 (1 mmol), 10 mg catalyst, and 3 ml solvent at 60 °C

Catalyst Recyclability

The easy separation of Fe₃O₄@SiO₂/ECH/IG heterogenous catalyst was mentioned further. In this regard, the recyclability of the nanocatalyst in the model reaction was investigated. At the end of the reaction, Fe₃O₄@SiO₂/ECH/IG was collected by an external magnetic field and washed with ethanol and water. The dried magnetic nanocatalyst was successively used for four times in the model reaction with a yield as 89%. According to the results displayed in Figure S3(see supporting information), there is no significant reduction in the catalytic efficiency of Fe₃O₄@SiO₂/ECH/IG. FTIR spectra of the recycled catalyst were recorded after multiple cycles and compared with the fresh catalyst (Figure S1). It is clear that the used catalyst has not endure any structural changes.

In order to demonstrate the efficacy of the prepared Fe₃O₄@SiO₂/ECH/IG catalyst, the catalytic activity in the preparation of spirooxindole derivatives was compared with the previous reports. It has several advantages over the reported studies which can be seen in table 2.

Table 2. Comparison of the present catalyst for the synthesis of spirooxindole derivatives with reported studies

Entry	Catalyst	Conditions	Time(min)	Yield(%)	References
1	[Bmim]OH	Solvent free/R.T.	600	98	52
2	Tris-hydroxymethyl aminomethane	Ethanol/R.T.	240	94	53
3	Trisodium citrate dihydrate	EtOH:Water/R.T.	120	96	54
4	Fe ₃ O ₄ @SiO ₂ /ECH/IG	EtOH:Water/60°C	10	94	This work

Experimental Section

Reagents and Apparatus

All reagents and materials were purchased from commercial sources and used without purification. All of them were analytical grade. The commercially swim bladders, isinglass, were purchased from grocery store. All methods were carried out in accordance with relevant guidelines and regulations. The known products were identified by comparison of their melting points. Melting points were determined in open capillaries using an Electrothermal 9100 instrument. Infrared (IR) spectra were acquired on a Shimadzu FT-IR-8400S spectrometer with spectroscopic grade KBr. The ¹HNMR (500 MHz) were obtained on a

Bruker Avance DPX-300 instrument. The spectra were obtained in DMSO-d₆ relative to TMS as internal standard. Scanning electron microscopy (SEM) was recorded on a VEG2/TESCAN 30kv with gold coating, and energy dispersive X-ray spectroscopy (EDX) was recorded on a VEG//TESCAN-XMU.

General procedure for the preparation of the Fe₃O₄ NPs

The superparamagnetic iron oxide nanoparticles (SPIONs) were synthesized using a co-precipitation method described before^{55,56}. In a brief, FeCl₃·6H₂O (1.215 g) and FeCl₂·4H₂O (0.637 g) (Fe²⁺/Fe³⁺ = 1:2) were dissolved in deionized water (20 mL) under an inert atmosphere to get a homogenous solution. Chemical precipitation was carried out by the slow addition of NaOH solution (25%), stirring vigorously at 80 °C for 60 min, until the pH= 10 was attained. The obtained magnetic particles were separated by an external magnetic field, washed three times with deionized water and ethanol (25 mL), and dried in a 65 °C oven for 24 h.

General procedure for the preparation of Fe₃O₄@SiO₂.

Initially, Fe₃O₄ (1 g) and DI water (50 mL) were for 30 min. Then, ammonia (5 ml) and 50 ml ethanol were added to the flask followed by adding 1.5 ml TEOS. The mixture was stirred for 24 h in room temperature. The prepared Fe₃O₄@SiO₂ was magnetically separated, washed sequentially with water and ethanol and dried in a vacuum oven at 50 °C.

General procedure for the preparation of Fe₃O₄@SiO₂/ECH

Fe₃O₄@SiO₂ (1g) was mixed with 1 ml ECH and 3 ml of ethanol and stirred for 5h at 60 °C. The resulted precipitate was then washed and dried in a vacuum oven at 50 °C.

General procedure for the preparation of Fe₃O₄@SiO₂/ECH/IG

0.1 g of the dried precipitate was dissolved in 20 ml ethanol and mixed with 0.2 g isinglass. The mixture was sonicated for 30 min and then stirred for 1 h. As before the obtained precipitate was washed and dried.

General experimental procedure for the synthesis of benzimidazoles derivatives catalysed by Fe₃O₄@SiO₂/ECH/IG

A mixture of isatin (1 mmol), malononitrile (1 mmol), various 1,3 dicarbonyls (1 mmol), and Fe₃O₄@SiO₂/ECH/IG (0.02 g) in EtOH/water (1:1) had been stirred for an appropriate period of time. After completion of the reaction as indicated by TLC, the reaction mixture had been dissolved in hot ethanol and the catalyst was recovered by external magnet, washed, dried and then reused in successive reaction. The reaction mixture had been recrystallized with ethanol to afford pure desired substituted benzimidazoles.

Conclusions

In summary, we devised a novel collagen-coated superparamagnetic organic-inorganic hybrid catalyst, Fe₃O₄@SiO₂/ECH/IG, which exhibited radically enhanced catalytic activity in the synthesis of a wide range of substituted spirooxindole derivatives through a one pot atom economical process. This bifunctional heterogeneous catalyst efficiency is achieved in several aspects, such as high product yields under mild conditions, stability, recyclability, and high reaction rate.

References

- 1 Zhao, Z.-S., Zhang, Y., Fang, T., Han, Z.-B. & Liang, F.-S. Chitosan-Coated Metal–Organic-Framework Nanoparticles as Catalysts for Tandem Deacetalization–Knoevenagel Condensation Reactions. *ACS Applied Nano Materials* **3**, 6316-6320 (2020).
- 2 Veisi, H., Ozturk, T., Karmakar, B., Tamoradi, T. & Hemmati, S. In situ decorated Pd NPs on chitosan-encapsulated Fe₃O₄/SiO₂-NH₂ as magnetic catalyst in Suzuki-Miyaura coupling and 4-nitrophenol reduction. *Carbohydrate polymers* **235**, 115966 (2020).
- 3 Amirnejat, S., Nosrati, A., Javanshir, S. & Naimi-Jamal, M. R. Superparamagnetic alginate-based nanocomposite modified by L-arginine: An eco-friendly bifunctional catalysts and an efficient antibacterial agent. *International journal of biological macromolecules* **152**, 834-845 (2020).
- 4 Ali, F., Khan, S. B., Shaheen, N. & Zhu, Y. Z. Eggshell membranes coated chitosan decorated with metal nanoparticles for the catalytic reduction of organic contaminants. *Carbohydrate Polymers*, 117681 (2021).
- 5 Zhou, Y., Shen, J., Bai, Y., Li, T. & Xue, G. Enhanced degradation of Acid Red 73 by using cellulose-based hydrogel coated Fe₃O₄ nanocomposite as a Fenton-like catalyst. *International journal of biological macromolecules* **152**, 242-249 (2020).
- 6 Ohata, J., Martin, S. C. & Ball, Z. T. Metal-Mediated Functionalization of Natural Peptides and Proteins: Panning for Bioconjugation Gold. *Angewandte Chemie International Edition* **58**, 6176-6199 (2019).
- 7 Li, X. *et al.* Highly active enzyme–metal nanohybrids synthesized in protein–polymer conjugates. *Nature Catalysis* **2**, 718-725 (2019).
- 8 Patel, S. K. *et al.* Synthesis of cross-linked protein-metal hybrid nanoflowers and its application in repeated batch decolorization of synthetic dyes. *Journal of hazardous materials* **347**, 442-450 (2018).
- 9 Patel, S. K., Otari, S. V., Kang, Y. C. & Lee, J.-K. Protein–inorganic hybrid system for efficient his-tagged enzymes immobilization and its application in L-xylulose production. *RSC advances* **7**, 3488-3494 (2017).

- 10 Li, C., Jiang, S., Zhao, X. & Liang, H. Co-immobilization of enzymes and magnetic nanoparticles by metal-nucleotide hydrogel nanofibers for improving stability and recycling. *Molecules* **22**, 179 (2017).
- 11 Mylkie, K., Nowak, P., Rybczynski, P. & Ziegler-Borowska, M. Polymer-Coated Magnetite Nanoparticles for Protein Immobilization. *Materials* **14**, 248 (2021).
- 12 Saneinezhad, S., Mohammadi, L., Zadsirjan, V., Bamoharram, F. F. & Heravi, M. M. Silver nanoparticles-decorated Preyssler functionalized cellulose biocomposite as a novel and efficient catalyst for the synthesis of 2-amino-4 H-pyrans and spirochromenes. *Scientific reports* **10**, 1-26 (2020).
- 13 Dolatkah, Z., Javanshir, S., Bazgir, A. & Hemmati, B. Palladium on magnetic Irish moss: A new nano-biocatalyst for suzuki type cross-coupling reactions. *Applied Organometallic Chemistry* **33**, e4859 (2019).
- 14 Liu, Y., Xu, H., Yu, H., Yang, H. & Chen, T. Synthesis of lignin-derived nitrogen-doped carbon as a novel catalyst for 4-NP reduction evaluation. *Scientific reports* **10**, 1-14 (2020).
- 15 Tan, J. M., Bullo, S., Fakurazi, S. & Hussein, M. Z. Preparation, characterisation and biological evaluation of biopolymer-coated multi-walled carbon nanotubes for sustained-delivery of silibinin. *Scientific Reports* **10**, 1-15 (2020).
- 16 Çalışkan, M. & Baran, T. Decorated palladium nanoparticles on chitosan/ δ -FeOOH microspheres: A highly active and recyclable catalyst for Suzuki coupling reaction and cyanation of aryl halides. *International Journal of Biological Macromolecules* (2021).
- 17 Nasrollahzadeh, M., Shafiei, N., Nezafat, Z., Bidgoli, N. S. S. & Soleimani, F. Recent progresses in the application of cellulose, starch, alginate, gum, pectin, chitin and chitosan based (nano) catalysts in sustainable and selective oxidation reactions: A review. *Carbohydrate Polymers*, 116353 (2020).
- 18 Banazadeh, M., Amirnejat, S. & Javanshir, S. Synthesis, Characterization, and Catalytic Properties of Magnetic Fe₃O₄@ FU: A Heterogeneous Nanostructured Mesoporous Bio-Based Catalyst for the Synthesis of Imidazole Derivatives. *Frontiers in chemistry* **8** (2020).
- 19 Veisi, H., Mohammadi, L., Hemmati, S., Tamoradi, T. & Mohammadi, P. In situ immobilized silver nanoparticles on rubia tinctorum extract-coated ultrasmall iron oxide nanoparticles: an efficient nanocatalyst with magnetic recyclability for synthesis of propargylamines by A₃ coupling reaction. *ACS omega* **4**, 13991-14003 (2019).
- 20 Rajabi-Moghaddam, H., Naimi-Jamal, M. & Tajbakhsh, M. Fabrication of copper (II)-coated magnetic core-shell nanoparticles Fe₃O₄@ SiO₂-2-aminobenzohydrazide and investigation of its catalytic application in the synthesis of 1, 2, 3-triazole compounds. *Scientific Reports* **11**, 1-14 (2021).
- 21 Javanshir, S., Pourshiri, N. S., Dolatkah, Z. & Farhadnia, M. Caspian Isinglass, a versatile and sustainable biocatalyst for domino synthesis of spirooxindoles and spiroacenaphthylenes in water.

Monatshefte für Chemie-Chemical Monthly **148**, 703-710 (2017).

- 22 Dekamin, M. G. *et al.* Sodium alginate: An efficient biopolymeric catalyst for green synthesis of 2-amino-4H-pyran derivatives. *International journal of biological macromolecules* **87**, 172-179 (2016).
- 23 Hemmati, B., Javanshir, S. & Dolatkah, Z. Hybrid magnetic Irish moss/Fe₃O₄ as a nano-biocatalyst for synthesis of imidazopyrimidine derivatives. *RSC advances* **6**, 50431-50436 (2016).
- 24 Dolatkah, Z., Javanshir, S., Bazgir, A. & Mohammadkhani, A. Magnetic Isinglass a Nano-Bio Support for Copper Immobilization: Cu-IG@ Fe₃O₄ a Heterogeneous Catalyst for Triazoles Synthesis. *ChemistrySelect* **3**, 5486-5493 (2018).
- 25 Pourian, E., Javanshir, S., Dolatkah, Z., Molaei, S. & Maleki, A. Ultrasonic-assisted preparation, characterization, and use of novel biocompatible core/shell Fe₃O₄@ GA@ isinglass in the synthesis of 1, 4-dihydropyridine and 4 H-pyran derivatives. *ACS omega* **3**, 5012-5020 (2018).
- 26 Dolatkah, Z., Javanshir, S. & Bazgir, A. Isinglass-palladium as collagen peptide-metal complex: a highly efficient heterogeneous biocatalyst for Suzuki cross-coupling reaction in water. *Journal of the Iranian Chemical Society* **16**, 1473-1481 (2019).
- 27 Burate, P. A., Javle, B. R., Desale, P. H. & Kinage, A. K. Amino acid amide based ionic liquid as an efficient organo-catalyst for solvent-free Knoevenagel condensation at room temperature. *Catalysis Letters* **149**, 2368-2375 (2019).
- 28 Wang, J. *et al.* Efficient conversion of N-acetyl-d-glucosamine into nitrogen-containing compound 3-acetamido-5-acetyl-furan using amino acid ionic liquid as the recyclable catalyst. *Science of The Total Environment* **710**, 136293 (2020).
- 29 Demurtas, M. *et al.* Indole derivatives as multifunctional drugs: Synthesis and evaluation of antioxidant, photoprotective and antiproliferative activity of indole hydrazones. *Bioorganic chemistry* **85**, 568-576 (2019).
- 30 Nájera, C. & Sansano, J. M. Synthesis of pyrrolizidines and indolizidines by multicomponent 1, 3-dipolar cycloaddition of azomethine ylides. *Pure and Applied Chemistry* **91**, 575-596 (2019).
- 31 Karimi, A. R. & Sedaghatpour, F. Novel mono-and bis (spiro-2-amino-4H-pyrans): alum-catalyzed reaction of 4-hydroxycoumarin and malononitrile with isatins, quinones, or ninhydrin. *Synthesis* **2010**, 1731-1735 (2010).
- 32 He, T., Zeng, Q.-Q., Yang, D.-C., He, Y.-H. & Guan, Z. Biocatalytic one-pot three-component synthesis of 3, 3'-disubstituted oxindoles and spirooxindole pyrans using α -amylase from hog pancreas. *RSC Advances* **5**, 37843-37852 (2015).

- 33 Zamani-Ranjbar-Garmroodi, B., Nasser, M. A., Allahresani, A. & Hemmat, K. Application of immobilized sulfonic acid on the cobalt ferrite magnetic nanocatalyst (CoFe₂O₄@ SiO₂/SO₃H) in the synthesis of spirooxindoles. *Research on Chemical Intermediates* **45**, 5665-5680 (2019).
- 34 Baharfar, R., Zareyee, D. & Allahgholipour, S. L. Synthesis and characterization of MgO nanoparticles supported on ionic liquid-based periodic mesoporous organosilica (MgO@ PMO-IL) as a highly efficient and reusable nanocatalyst for the synthesis of novel spirooxindole-furan derivatives. *Applied Organometallic Chemistry* **33**, e4805 (2019).
- 35 Naeimi, H. & Lahouti, S. Sulfonated chitosan encapsulated magnetically Fe₃O₄ nanoparticles as effective and reusable catalyst for ultrasound-promoted rapid, three-component synthesis of spiro-4H-pyrans. *Journal of the Iranian Chemical Society* **15**, 2017-2031 (2018).
- 36 Khoobi, M. *et al.* Polyethyleneimine-modified superparamagnetic Fe₃O₄ nanoparticles: An efficient, reusable and water tolerance nanocatalyst. *Journal of Magnetism and Magnetic Materials* **375**, 217-226 (2015).
- 37 Jamatia, R., Gupta, A. & Pal, A. K. Nano-FGT: a green and sustainable catalyst for the synthesis of spirooxindoles in aqueous medium. *RSC advances* **6**, 20994-21000 (2016).
- 38 Elinson, M. N., Ryzhkov, F. V., Zaimovskaya, T. A. & Egorov, M. P. Solvent-free multicomponent assembling of isatins, malononitrile, and dimedone: fast and efficient way to functionalized spirooxindole system. *Monatshefte für Chemie-Chemical Monthly* **147**, 755-760 (2016).
- 39 Mamaghani, M., Tabatabaeian, K., Pourshiva, M. & Nia, R. H. Rapid and efficient synthesis of spiro-oxindoles using Fe³⁺-montmorillonite under ultrasonic irradiation. *Journal of Chemical Research* **39**, 314-317 (2015).
- 40 Keshavarz, M. Ion-pair immobilization of l-proline anion onto cationic polymer support and a study of its catalytic activity for one-pot synthesis of spiroindolones. *Journal of the Iranian Chemical Society* **13**, 553-561 (2016).
- 41 Baharfar, R. & Azimi, R. Immobilization of 1, 4-diazabicyclo [2.2. 2] Octane (DABCO) over mesoporous silica SBA-15: an efficient approach for the synthesis of functionalized spirochromenes. *Synthetic Communications* **44**, 89-100 (2014).
- 42 Goli-Jolodar, O., Shirini, F. & Seddighi, M. Introduction of a novel basic ionic liquid containing dual basic functional groups for the efficient synthesis of spiro-4H-pyrans. *Journal of Molecular Liquids* **224**, 1092-1101 (2016).
- 43 Mohamadpour, F., Maghsoodlou, M. T., Lashkari, M., Heydari, R. & Hazeri, N. Synthesis of Quinolines, Spiro [4 H-pyran-oxindoles] and Xanthenes Under Solvent-Free Conditions. *Organic Preparations and Procedures International* **51**, 456-476 (2019).

- 44 Nagaraju, S., Paplal, B., Sathish, K., Giri, S. & Kashinath, D. Synthesis of functionalized chromene and spirochromenes using l-proline-melamine as highly efficient and recyclable homogeneous catalyst at room temperature. *Tetrahedron letters* **58**, 4200-4204 (2017).
- 45 Moradi, L., Ataei, Z. & Zahraei, Z. Convenient synthesis of spirooxindoles using SnO₂ nanoparticles as effective reusable catalyst at room temperature and study of their in vitro antimicrobial activity. *Journal of the Iranian Chemical Society* **16**, 1273-1281 (2019).
- 46 Wagh, Y. B., Padvi, S. A., Mahulikar, P. P. & Dalal, D. S. CsF promoted rapid synthesis of spirooxindole-pyran annulated heterocycles at room temperature in ethanol. *Journal of Heterocyclic Chemistry* **57**, 1101-1110 (2020).
- 47 Chandam, D. R., Mulik, A. G., Patil, D. R. & Deshmukh, M. B. Oxalic acid dihydrate: proline as a new recyclable designer solvent: a sustainable, green avenue for the synthesis of spirooxindole. *Research on Chemical Intermediates* **42**, 1411-1423 (2016).
- 48 Wang, G. D., Zhang, X. N. & Zhang, Z. H. One-Pot Three-Component Synthesis of Spirooxindoles Catalyzed by Hexamethylenetetramine in Water. *Journal of Heterocyclic Chemistry* **50**, 61-65 (2013).
- 49 Meshram, H. M., Kumar, D. A., Prasad, B. R. V. & Goud, P. R. Efficient and convenient polyethylene glycol (PEG)-mediated synthesis of spiro-oxindoles. *Helvetica Chimica Acta* **93**, 648 (2010).
- 50 Baghernejad, M., Khodabakhshi, S. & Tajik, S. Isatin-based three-component synthesis of new spirooxindoles using magnetic nano-sized copper ferrite. *New Journal of Chemistry* **40**, 2704-2709 (2016).
- 51 Kidwai, M., Jahan, A. & Mishra, N. K. Gold (III) chloride (HAuCl₄· 3H₂O) in PEG: A new and efficient catalytic system for the synthesis of functionalized spirochromenes. *Applied Catalysis A: General* **425**, 35-43 (2012).
- 52 Padvi, S. A., Tayade, Y. A., Wagh, Y. B. & Dalal, D. S. [bmim] OH: An efficient catalyst for the synthesis of mono and bis spirooxindole derivatives in ethanol at room temperature. *Chinese Chemical Letters* **27**, 714-720 (2016).
- 53 Khot, S. S., Anbhule, P. V., Desai, U. V. & Wadgaonkar, P. P. Tris-hydroxymethylaminomethane (THAM): an efficient organocatalyst in diversity-oriented and environmentally benign synthesis of spirochromenes. *Comptes Rendus Chimie* **21**, 814-821 (2018).
- 54 Brahmachari, G. & Banerjee, B. Facile and Chemically Sustainable One-Pot Synthesis of a Wide Array of Fused O-and N-Heterocycles Catalyzed by Trisodium Citrate Dihydrate under Ambient Conditions. *Asian Journal of Organic Chemistry* **5**, 271-286 (2016).
- 55 Dangolani, S. K., Panahi, F., Nourisefat, M. & Khalafi-Nezhad, A. 4-Dialkylaminopyridine modified magnetic nanoparticles: as an efficient nano-organocatalyst for one-pot synthesis of 2-amino-4 H-

chromene-3-carbonitrile derivatives in water. *RSC advances* **6**, 92316-92324 (2016).

56 Mohammadfam, Y., Heris, S. Z. & Khazini, L. Experimental Investigation of Fe₃O₄/hydraulic oil magnetic nanofluids rheological properties and performance in the presence of magnetic field. *Tribology International* **142**, 105995 (2020).

Figures

Figure 1

Some biologically active oxindoles and spirooxindoles

Figure 2

Schematic representation of the catalyst synthesis procedures.

Figure 3

a) SEM images of Fe_3O_4 , $\text{Fe}_3\text{O}_4@\text{SiO}_2$ and $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ and b) TEM images of $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$

Figure 4

Energy dispersive X-ray analysis (EDX) of Fe₃O₄@SiO₂/ECH/IG and b) elemental mapping of C (red); N (blue), O (green), Fe (violet), Si (orange) and Cl (pink) atoms for Fe₃O₄@SiO₂/ECH/IG.

Figure 5

VSM analysis of the prepared $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$.

Figure 6

XRD pattern of $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$.

Figure 7

Schematic representation of the $\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{ECH}/\text{IG}$ and its catalytic activity in the one-pot synthesis of spirooxindole derivatives (4a-t) through multicomponent reaction (MCR) strategy.

Figure 8

Proposed catalytic mechanism of Fe₃O₄@SiO₂/ECH/IG.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarymaterial.docx](#)