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$CuFe_2O_4$ and ZrP_2O_7 nanoparticles as highly efficient catalysts for the one-pot synthesis of phthalazine derivatives under solvent-free conditions

J. Safaei-Ghomi[a,*], A. Hatami[a,b], H. Shahbazi-Alavi[a] and A. Ziarati[c]

a. *Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, P.O. Box 87317-51167, Kashan, Iran.*
b. *Phytochemistry Group, Barij Medicinal Plants Research Center, Kashan, P.O. Box 1178, Iran.*
c. *School of Chemistry, College of Science, University of Tehran, Tehran 14155-6455, Iran.*

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KEYWORDS
Pyrazolophthalazines; Indazolophthalazine; Solvent-free conditions; $CuFe_2O_4$ NPs; ZrP_2O_7 NPs.

Abstract. ZrP_2O_7 and $CuFe_2O_4$ nanoparticles as efficient and reusable heterogeneous catalysts have been used for the preparation of *2H*-indazolo[2,1-*b*]phthalazine-triones and *1H*-pyrazolo[1,2-*b*]phthalazine-diones, respectively, under solvent-free conditions in good to excellent yields and short reaction times.

1. Introduction

Compounds containing nitrogen moiety have attracted much attention due to participation in the structure of biological active molecules [1-4], among which pyrazole derivatives show important biological properties including anti-inflammatory [5]; antifungal activity against three phytopathogenic fungi, namely *Helminthosporium* species, *Fusarium oxysporum*, and *Alternaria alternata* [6]; anticancer [7]; nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the P236L mutant [8]; suppression of A549 lung cancer cell growth [9]; antibacterial (inhibitory activity against Escherichia coli FabH) [10], and antihypoglycemic activity [11] (Figure 1).

Some other examples of pyrazole derivatives such as celecoxib, SC-558, mefobutazone, and deracoxib have been reported as potent NSAIDs [12]. Phthalazines have been reported to possess a multiplicity of biological properties such as antimicrobial [13]; the most potent anticonvulsant activity and the highest protection index value [14]; antifungal activity against *C. albicans*, *C. tropicalis*, *C. krusei*, and *C. neoformans* [15]; anticancer [16]; cardiotonic [17]; inhibitory activity toward phosphodiesterase 5 (PDE5) and vasorelaxant activity [18]; and excellent reversible inhibition of HAV 3C proteinase with an IC50 value in the low micromolar range [19]. Pyrazolo[1,2-*b*]phthalazine-diones have been described as anti-inflammatory, analgesic, anti-hypoxic, and anti-pyretic agents [20] (Figure 2).

Meanwhile, 7-amino- 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives have proved to be promising luminescence materials and fluorescence probes [21]. Therefore, the development of simple strategies for the synthesis of 2*H*-indazolo[2,1-*b*]ph- thalazine-triones and pyrazolo[1,2-*b*]phthalazine-diones is an interesting challenge. Generally, research on the multi-component synthesis is still a significant issue in the fields of chemistry. Multi-Component Reactions (MCRs) are highly flexible, convergent, fruitful, and valuable for organic synthesis and they rapidly provide molecular complexity starting from simple substrates [22]. In addition, MCRs are environmentally friendly and play a

*. *Corresponding author. Tel.: +98 31 55912385; Fax: +98 31 55912397*
E-mail address: safaei@kashanu.ac.ir (J. Safaei-Ghomi)

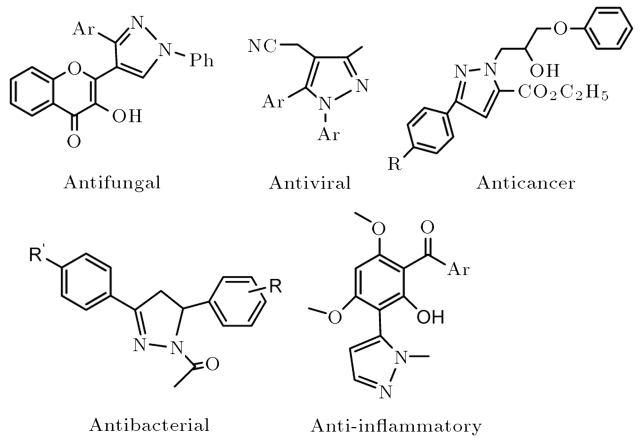


Figure 1. Biologically important pyrazoles.

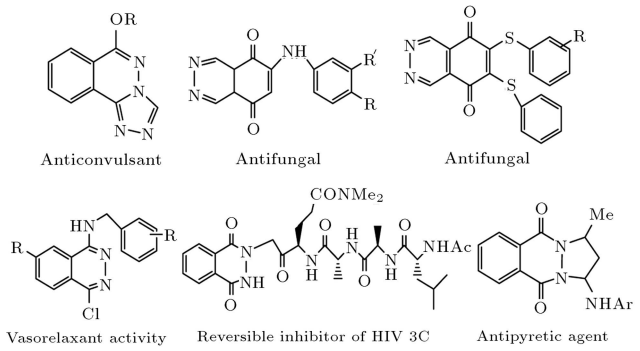


Figure 2. Some biological activities of phthalazines.

prominent role in green chemistry [23-24]. Green chemistry emphasizes the need for environmentally clean synthesis, which involves reduction or elimination of the use or generation of hazardous chemicals and simple separation with recovery and reuse of reagents [25-26]. Solvent-free organic synthesis is the best eco-friendly methodology to overcome the problems from the viewpoint of green chemistry. The advantages of solvent-free processes are reduced reaction times, minimization of environmental impact factor, decreased energy consumption, and easy workup [27-29].

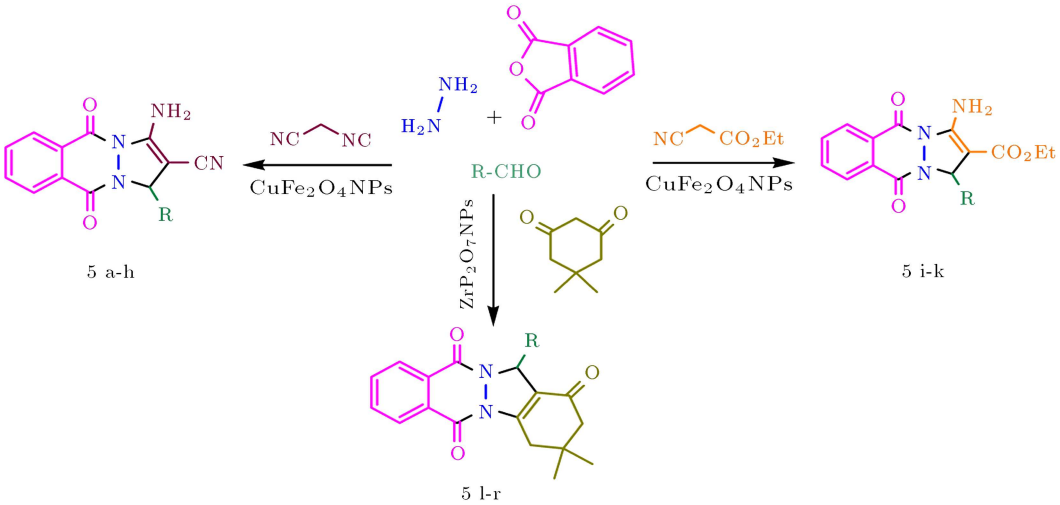
The combination of multi-component reaction with solvent-free conditions has been proven to be a valuable strategy in organic chemistry [30]. Similarly, nanoparticles have received considerable attention with the aim of finding significant applications in organic reactions. Nanoparticles reduce reaction times and they can be recovered from the reaction mixture using simple filtration [31-32]. Zirconium pyrophosphate (ZrP_2O_7) is one of the greatly studied materials due to its useful contribution to various fields of application [33]. Pyrophosphate compounds, which contain zirconium, can reveal intensive luminescence at room temperature [34-35]. Nanoparticles can be utilized as a suitable catalysts in organic reactions due to their high surface-to-volume ratio and coordinated parts, which provide a large number of active sites per unit area in comparison with other catalysts [36-38]. The improvement of a recyclable catalyst based on magnetic nanoparticles has received increasing interest as an emerging application in the heterogeneous catalyst field [39-40]. $CuFe_2O_4$ is widely used as a magnetic material and is one of the important ferrites [41-42]. Recently, $CuFe_2O_4$ nanoparticles have been used as a suitable catalyst in many reactions including synthesis of 1,4-disubstituted 1,2,3-triazoles [43], 5-substituted 1H-tetrazoles [44], diaryl/aryl alkyl sulphides [45], and Friedel-Crafts acylation [46].

A number of methods have been developed for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones and 1*H*-pyrazolo[1,2-*b*]phthalazine-diones. The synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives *via* the three-component coupling of aldehydes, malononitrile or ethyl cyanoacetate, and phthalhydrazide has been reported using MCRs in the presence of diverse catalysts such as PTSA/[Bmim]Br (100°C, 3 h) [47], nano-ZnO [48] [Bmim]OH/MW (100W, 45°C, 4-5 min) [49], 1,8-diazabicyclo[5,4,0]-undec-7-en-8-ium acetate (DBU[CH_3COO], solvent-free) [50], nano-CuI [51] $NiCl_2.6H_2O$ (ethanol/reflux) [52], and $InCl_3$ (solvent-free, 80°C) [53]. Recently, several methods have been reported for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones comprising the use of PTSA (solvent-free, 80°C) [54], H_2SO_4 [55], [Bmim]Br, (sonochemistry) [56], ceric ammonium nitrate (PEG-400) [57], and silica sulfuric acid [58]. We wish to report herein a highly efficient procedure for the preparation of 2*H*-indazolo[2,1-*b*]phthalazine-triones using ZrP_2O_7 nanoparticles and the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-diones using $CuFe_2O_4$ nanoparticles as efficient and reusable heterogeneous catalysts under solvent-free conditions in good to excellent yields (Scheme 1).

2. Experimental

2.1. Materials and apparatus

All the chemicals used were of research grade and were used without further purification. All melting points were uncorrected and determined in capillary tubes on a Boetius melting point microscope. FT-IR spectra were recorded with KBr pellets using a Magna-IR, spectrometer 550 Nicolet. NMR spectra were recorded on a Bruker 400 MHz spectrometer with DMSO and $CDCl_3$ as solvent and TMS as internal standard. Powder X-Ray Diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company. The magnetic properties of $CuFe_2O_4$ nanoparticles were measured with a vibrating sample magnetometer (VSM, PPMS-9T) at 300 K in Iran, Kashan University. In order to investigate the particle size and morphology of the synthetic structures of $CuFe_2O_4$ and ZrP_2O_7 nanoparticles, FE-SEM images of the products were



Scheme 1. Synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-diones and 2*H*-indazolo[2,1-*b*] phthalazine-triones catalyzed by $CuFe_2O_4$ nanaparticles and ZrP_2O_7 nanoparticles.

visualized by a HITACHI S4160 Field Emission Scanning Electron Microscope.

2.2. Preparation of ZrP_2O_7 nanoparticles

ZrP_2O_7 nanoparticle was prepared according to the procedure reported in the literature [59]. The catalyst was prepared *via* sonochemical method (worked at 20 kHz of frequency and 80 W of power). $ZrOCl_2$ was used as the zirconium source. Firstly, the stoichiometric amount of $ZrOCl_2/8H_2O$ was added to 20 ml of distilled water and sonicated to completely dissolve. Then, H_3PO_4 (85%) was added dropwise for over a course of 20 min and the mixture was sonicated until the precipitation of solids was finished. When the reaction was completed, a disperse white precipitate was obtained. The solid was filtered and washed with distilled water and ethanol several times. Subsequently, the catalyst was dried at 100°C for 8 h and calcined at 500°C for 1 h to obtain pure nano zirconium pyrophosphate. The characterizations of the nanoparticles can be found in [51,54].

2.3. Preparation of $CuFe_2O_4$ nanoparticles

The $CuFe_2O_4$ nanoparticles were prepared according to the procedure reported in the literature [60]. In a typical procedure, analytical grade Cu $(CH_3COO)_2.H_2O$, $Fe(NO_3)_3 9H_2O$, NaOH, and NaCl were mixed in a molar ratio (1:2:8:2) and ground together in an agate mortar for about 100 min. The reaction readily started during the mixing process, accompanied by release of heat. As the reaction proceeded, the mixture became mushy and underwent gradual changes in color from blue (1 min) to finally brown (10 min). This mixture was washed with deionized water for several times. After removal of sodium chloride by washing, the powders were dried at 80°C for 2 h. Then, the powders were calcined at 800°C for 2 h to obtain final powders.

2.4. General procedure for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones (5a-k)

Hydrazine monohydrate (1 mmol) and phthalic anhydride (1 mmol) were mixed at 70°C (5 min). Then, aromatic aldehydes (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol), and $CuFe_2O_4$ nanoparticles (7 mol%), as catalyst, were added and stirred at 90°C under solvent-free conditions for the stipulated times. The progress of the reaction was monitored by TLC. After cooling, 5 mL of ethanol was added to the reaction mixture and the catalyst $CuFe_2O_4$ was separated magnetically. The reaction mixture was filtered and the precipitate washed with ethanol to afford the pure product.

2.5. General procedure for the synthesis of 2H-indazolo [2,1-b]phthalazine-triones (5l-r)

Hydrazine monohydrate (1 mmol) and phthalic anhydride (1 mmol) were mixed at 70°C (5 min). Then, aromatic aldehydes (1 mmol), dimedone (1 mmol), and ZrP_2O_7 nanoparticles (10% mol), as catalyst, were added and stirred at 80°C under solvent-free conditions for the specific time. After cooling, the solid was filtered off and washed with ethyl acetate/n-hexane. The residue was dissolved in chloroform and then filtered until heterogeneous catalyst was recovered. The filtrate was evaporated to afford the pure product.

3. Results and discussion

The morphology and particle size distribution of ZrP_2O_7 nanoparticles were investigated by Scanning Electron Microscopy (SEM) and are illustrated in Figure 3(a). The SEM image shows particles with diameters in the range of nanometers. The XRD

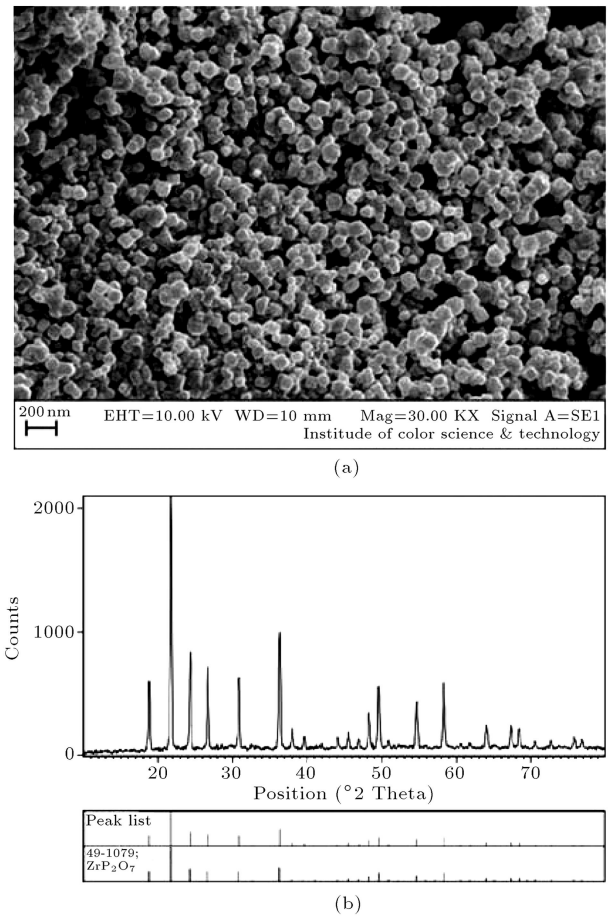


Figure 3. (a) SEM image of ZrP_2O_7 NPs. (b) XRD of ZrP_2O_7 NPs.

pattern of the ZrP_2O_7 nanoparticles is shown in Figure 3(b). The results show that ZrP_2O_7 nanoparticles were obtained with an average diameter of 11-16 nm, as confirmed by XRD analysis. The XRD data of ZrP_2O_7 nanoparticles are shown in Table 1. Based on Figure 3(b), the diffraction peaks observed can be indexed to pure cubic crystal of ZrP_2O_7 ($a = 8.2953$ Å, $b = 8.2953$ Å, $c = 8.2953$ Å) with space group of Pa-3. Also, no specific peaks due to any impurities were observed. The XRD pattern agrees well with the reported pattern for zirconium pyrophosphate (JCPDS No. 49-1079). For investigation of the influence of ultrasound irradiation in this reaction, the synthesis of nano ZrP_2O_7 was compared with techniques such as hydrothermal, solvothermal, and solid state methods [61-62]. As shown in Table 2, particle sizes of nano ZrP_2O_7 prepared *via* conventional methods were ranging from 200 nm to 1 μm. However, the size of ZrP_2O_7 nanoparticles prepared in the presence of ultrasound was reduced to 10 nm. This observation is described by the effect of sonication. It is known that size control must be done within a very short nucleation period and the final particle number does not change during the particle growth. When the solution, containing the precursor, is exposed to ultrasound irradiation, extremely high pressures and temperatures are produced during acoustic cavitation, providing the energy to generate ZrP_2O_7 nuclei. Also, the produced high temperature and the adsorbed bubbling on surface of the nuclei reduce the interfacial free energy between nuclei and solution, consequently, inhibiting the growth of particles [63-64]. The high surface area due to small particle size increases reactivity of particles. This factor is responsible for the upward accessibility of the substrate molecules on the catalyst surface [65].

Initially, we had explored and optimized different reaction parameters for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones by the four-component condensation reaction of phthalic anhydride, hydrazine monohydrate, 4-chlorobenzaldehyde, and dimedone as a model reaction. We observed the effect of different solvents on the progress of reaction. Under solvent-free conditions, we determined the best level for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones. The model reaction was considered in presence of different catalysts. Extraordinarily, the best result was obtained when using ZrP_2O_7 NPs. To optimize the catalyst quantity, the reaction was carried out with different quantities of ZrP_2O_7 NPs; 10 mol% of ZrP_2O_7 NPs was found to be optimal (Table 3).

Table 1. The XRD data of ZrP_2O_7 NPs.

Pos.[°2Th.]	19.0068	21.9236	24.5016	26.8305	31.0071	36.44 90	38.1238	39.7298	4 4.2683
FWHM [°2Th.]	0.6715	0.6124	0.6124	0.6715	0.6124	0.6124	0.6124	0.6715	0.6124
Pos.[°2Th.]	45.6542	47.0324	48.4037	49.7207	51.0344	54.8017	58.4135	60.7319	61.9827
FWHM [°2Th.]	0.6124	0.6124	0.6715	0.7305	0.6124	0.7305	0.7305	0.78 95	1.1438
Pos.[°2Th.]	64.1391	67.4234	68.5248	70.6656	72.7492	75.8722	76.8699	–	–
FWHM [°2Th.]	0.7895	0.7895	0.7895	0.7895	0.7895	0.6715	0.7233	–	–

Table 2. Comparison of ultrasonic method with other methods to prepare ZrP_2O_7.

Method	**Ultrasonic**	**Hydrothermal**	**Solvothermal with surfactant**	**Solvothermal without surfactant**	**Solid state reaction**
Particle size	10-30 nm	1000 nm	About 200 nm	About 20 μm	About 1 μm

Table 3. Optimization of the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione[a].

Entry	Solvent	Catalyst (mol%)	Yield (%)[b]
1	Solvent-free (80°C)	– –	Trace
2	H_2O (80°C)	MgO (10)	Trace
3	CH_3CN (reflux)	$AlCl_3$ (5)	25
4	CH_2Cl_2 (reflux)	$CuSO_4$ (10)	34
5	$CHCl_3$ (reflux)	ZrO_2 NPs (10)	49
6	EtOH (reflux)	TiO_2 (10)	33
7	EtOH (reflux)	ZrP_2O_7 NPs (10)	75
8	Solvent-free (80°C)	ZrO_2 NPs (15)	60
9	Solvent-free (80°C)	ZrP_2O_7 NPs (5)	82
10	**Solvent-free (80°C)**	**ZrP_2O_7 NPs (10)**	**91**
11	Solvent-free (80°C)	ZrP_2O_7 NPs (15)	91

[a] Phthalic anhydride (1 mmol), hydrazine monohydrate (1 mmol), 4-chlorobenzaldehyde (1 mmol), and dimedone (1 mmol).

[b] Isolated yield.

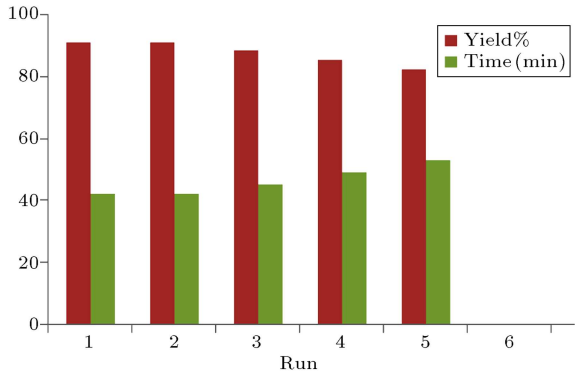
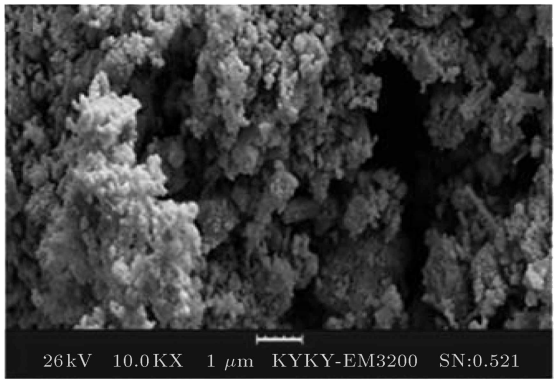


Figure 4. Recycling of ZrP_2O_7 NPs as catalyst for synthesis **5a**.

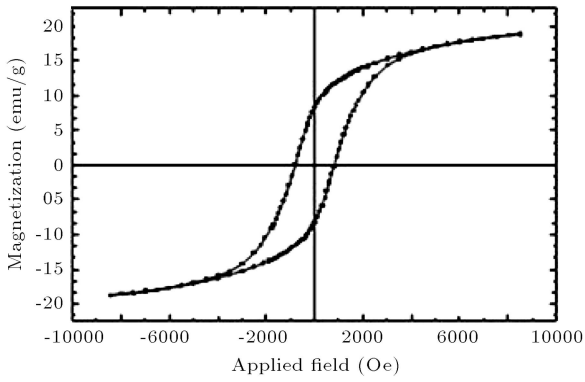
In the recycling procedure of ZrP_2O_7 NPs, chloroform was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by simple filtration. The recovered ZrP_2O_7 NPs was washed with ethanol and dried at 70°C for 2 h. The recycling ability of the catalyst was tested for five runs, providing almost similar yields of the desired product (Figure 4).

In order to study the morphology and particle size of $CuFe_2O_4$ nanoparticles, SEM image of $CuFe_2O_4$ nanoparticles is presented in Figure 5(a). These results show that $CuFe_2O_4$ NPs were gained with a particle size between 40 and 42 nm.

The magnetization curves of $CuFe_2O_4$ nanoparticles are shown in Figure 5(b). The $CuFe_2O_4$ nanoparticles also show ferromagnetic property as suggested by the field dependent magnetization study at 300 K. Ferromagnetic materials possess a permanent magnetic moment in the absence of an external field and a very large permanent magnetization. In ferromagnetic materials, this permanent magnetic moment is the result of the cooperative interaction of large numbers of



(a)



(b)

Figure 5. (a) SEM image of $CuFe_2O_4$ NPs. (b) VSM of $CuFe_2O_4$.

atomic spins in what are called domains, regions where all spins are aligned in the same direction.

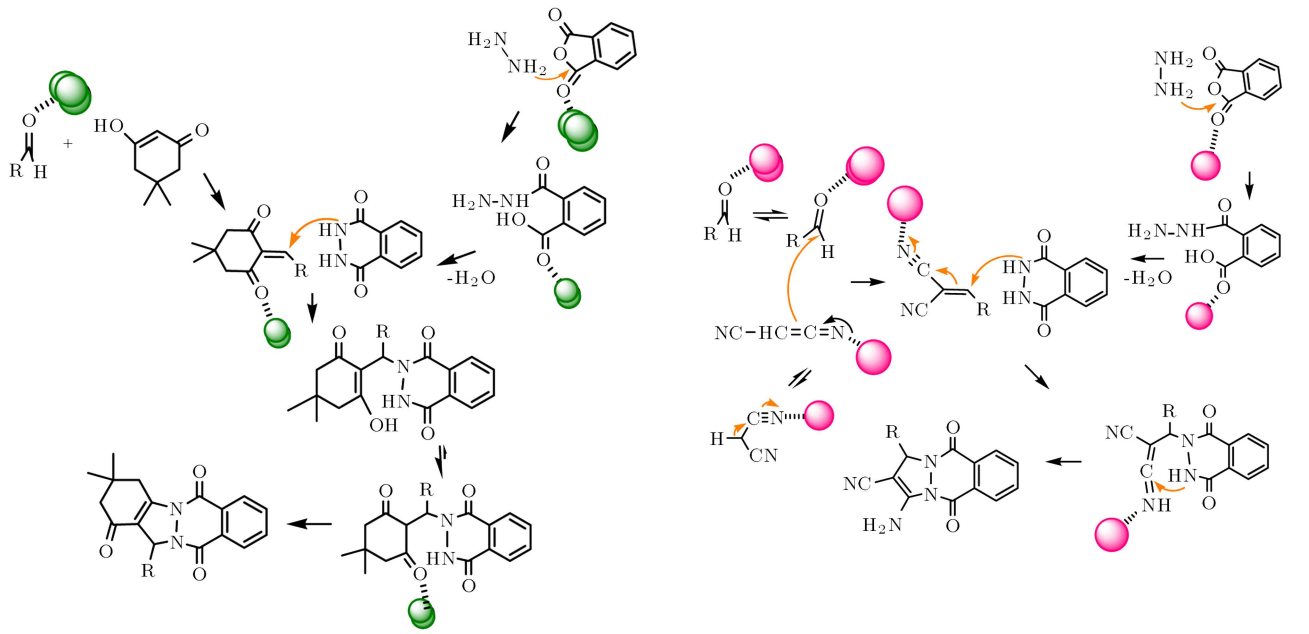
Meanwhile, we have presented an efficient method for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazinediones using $CuFe_2O_4$ nanoparticles. We carried out the reaction of phthalic anhydride, hydrazine monohydrate, benzaldehyde, and malononitrile or ethyl

cyanoacetate in the presence of different catalysts to screen a suitable catalyst for the systematic evaluation of the reaction condition. Also, the effect of the solvents on the reaction was investigated. The best results were obtained under solvent-free conditions and we found that the reaction gave satisfying result in the presence of $CuFe_2O_4$ nanoparticles. Next, we optimized the required amount of $CuFe_2O_4$ NPs; the optimum amount was found to be 7 mol% (Table 4). We also investigated recycling of the $CuFe_2O_4$ NPs as catalyst under solvent-free conditions. The $CuFe_2O_4$ NPs were separated by an external magnet for pursuant experiments to study their reusability. The results showed that $CuFe_2O_4$ NPs could be reused several times without noticeable loss of catalytic activity.

We next examined a wide variety of aromatic aldehydes, either bearing electron-withdrawing groups or electron-donating groups (Table 5).

In addition, we examined aliphatic aldehydes such as *n*-hexanal instead of benzaldehydes in the reaction, but we could not find considerable amount of the title product from aliphatic aldehydes. Subsequently, the scope of the reaction was also investigated with phthalic anhydride, hydrazine monohydrate, 4-chlorobenzaldehyde, and acyclic 1,3-diketones. This reaction could not be observed when the acyclic 1,3-diketones were used as a substrate.

The proposed mechanism for the preparation of 2*H*-indazolo[2,1-*b*]phthalazine-triones and 1*H*-pyrazolo[1,2-*b*]phthalazine-diones is shown in Scheme 2.



Scheme 2. (a) Proposed mechanism for the four-component reaction leading to compounds 5l-r. (b) Proposed reaction pathway for the synthesis of 5a-k by $CuFe_2O_4$ NPs.

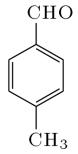
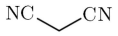
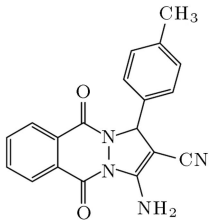
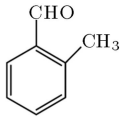
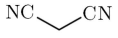
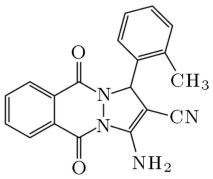
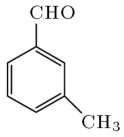
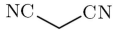
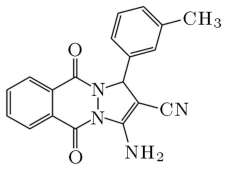
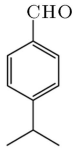
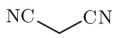
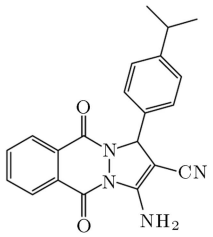
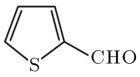
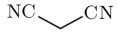
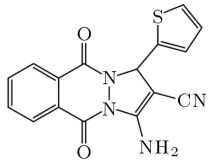
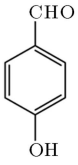
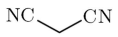
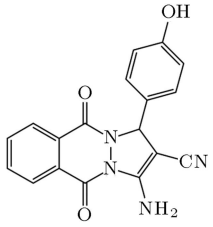
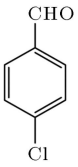
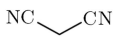
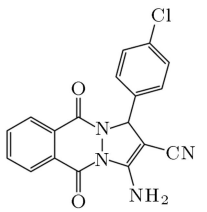
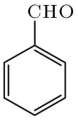
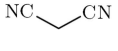
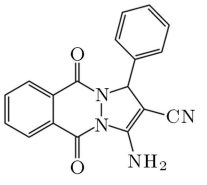
Table 4. Optimization of the synthesis of 1*H*-pyrazolo[1,2-*b*] phthalazine-diones[a].

Entry	Solvent	Catalyst (mol%)	Yield (%)[b]
1	Solvent-free (80°C)	– -	10
2	H_2O (80°C)	MgO (10)	27
3	CH_3CN (reflux)	$FeCl_3$ (10)	25
4	CH_2Cl_2 (reflux)	$GaCl_3$ (10)	33
5	$CHCl_3$ (reflux)	Et_3N (10)	40
6	EtOH (reflux)	CuCl (10)	43
7	EtOH (reflux)	$CuFe_2O_4$ NPs (10)	69
8	Solvent-free (80°C)	CuCl(15)	50
9	Solvent-free (80°C)	$CuFe_2O_4$ NPs (4)	80
10	**Solvent-free (80°C)**	**$CuFe_2O_4$ NPs (7)**	**91**
11	Solvent-free (80°C)	$CuFe_2O_4$ NPs (10)	90

[a] Phthalic anhydride (1 mmol), hydrazine monohydrate (1 mmol), 4-chlorobenzaldehyde (1 mmol), and dimedone (1 mmol);

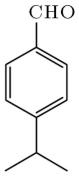
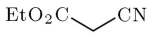
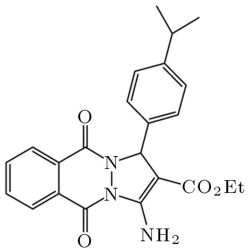
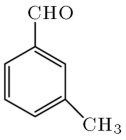
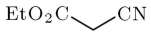
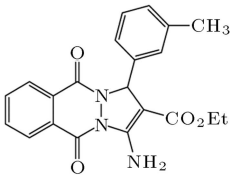
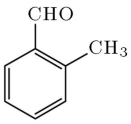
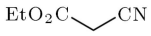
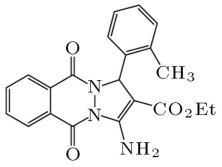
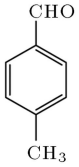
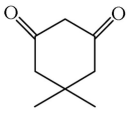
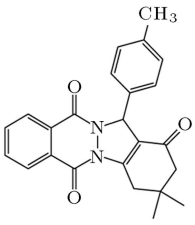
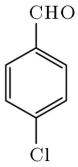
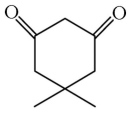
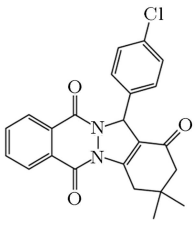
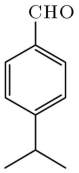
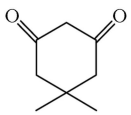
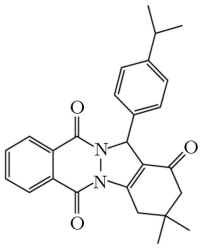
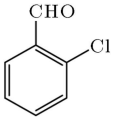
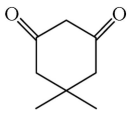
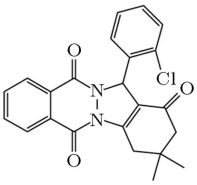
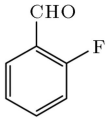
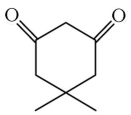
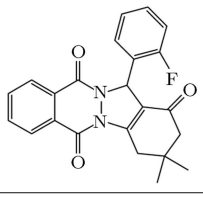
[b] Isolated yield.

Table 5. Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones and 2*H*-indazolo[2,1-*b*]phthalazine-triones.

Entry	Aldehyde	Compound 4	Product 5(a-r)	Time(min)	Yield (%)[a]
1				47	85
2				53	81
3				48	84
4				48	86
5				45	86
6				58	80
7				42	91
8				47	91

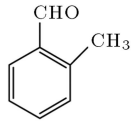
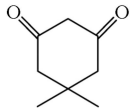
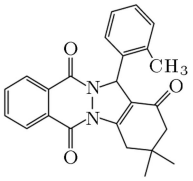
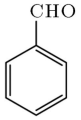
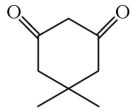
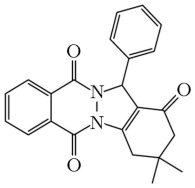
[a] Isolated yield.

Table 5. Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones and 2*H*-indazolo[2,1-*b*]phthalazine-triones (continued).

Entry	Aldehyde	Compound 4	Product 5(a-r)	Time(min)	Yield (%)[a]
9				49	87
10				53	85
11				54	83
12				40	83
13				31	91
14				38	85
15				33	88
16				33	86

[a] Isolated yield.

Table 5. Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones and 2*H*-indazolo[2,1-*b*]phthalazine-triones (continued).

Entry	Aldehyde	Compound 4	Product 5(a-r)	Time(min)	Yield (%)[a]
17				41	81
18				35	85

[a] Isolated yield.

Initially, we assumed that the reaction occurred via a Knoevenagel condensation of dimedone or malononitrile and aldehydes. Then, the subsequent Michael-type addition of the phthalhydrazide to the preliminary intermediate, followed by cyclization, afforded the titled products.

4. Conclusion

We have described an efficient and clean route for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones and 1*H*-pyrazolo[1,2-*b*]phthalazine-diones using heterogeneous catalysts under solvent-free conditions in good to excellent yields. The advantages offered by this method include easy workup, the employment of a cost-effective catalyst, short reaction times, using an eco-safe approach, and performing a one-pot reaction under solvent-free conditions that is considered relatively environmentally benign.

Acknowledgements

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Biographies

Javad Safaei-Ghomi received a BS degree in Chemistry from the University of Kashan, Kashan, Iran, in 1985, an MS degree in Organic Chemistry from the University of Mazandaran, Babolsar, Iran, in 1988, and a PhD degree in Organic Chemistry from the University of Wollongong, Australia, in 1995. He is currently Professor in the Department of Organic Chemistry at the University of Kashan, Iran. His research interests include asymmetric synthesis of amino acids, antioxidant and antibacterial activity of herbal extracts, using nanoparticles in multicomponent reactions, and new methods for functionalization of fullerene.

Alireza Hatami obtained his MS degree in Organic Chemistry from the University of Kashan, Iran, in 2008, on the study of Synthesis of 5-Phenyl-1,4-Benzodiazepine-2-one Derivatives. He graduated with PhD degree under the supervision of Professor Javad Safaei-Ghomi at the same university on the study of Multicomponent synthesis of furan-2(5H)-one, pyrazolophthalazine and indazolophthalazine derivatives using prepared zirconium phosphate-based nanocatalysts.

Hossein Shahbazi-Alavi obtained his MS degree in Organic Chemistry from the University of Kashan, Iran, in 2013, on the study of synthesis of phthalazine derivatives under solvent-free conditions. He is currently a PhD student under the supervision of Professor Javad Safaei-Ghomi at the same university.

Abolfazl Ziarati obtained his MS degree in Organic Chemistry from the University of Kashan, Iran, in 2012, on the study of synthesis of tetrahydropyridines under mild conditions. He is currently a PhD student in the Department of Chemistry at the University of Tehran, Iran. His research interests lie in nanoscience and nanotechnology, application of nanoparticles as catalyst in organic reactions.