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ZrP_2O_7 nanoparticles as a robust and efficient catalyst for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones under microwave irradiation

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ABSTRACT

ZrP_2O_7 nanoparticles have been used as an efficient catalyst for the preparation of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones by a simple one-pot four-component reaction of phenyl hydrazines, ethyl acetoacetate ,β-naphthol and benzaldehydes under microwave irradiation in good to excellent yields. When the reaction was carried out using $ZrOCl_2.8H_2O$, ZrO_2 and ZrP_2O_7 NPs as the catalyst, the product were obtained in moderate to good yield. The highest yield 92% was reached when the reaction was performed with 0.6 mol% of catalyst loading. Atom economy, green reaction, short reaction times, easy isolation of the targeted molecules, recovery and reusability of the catalyst are some of the important features of this protocol.

Keywords: *ZrP_2O_7 nanoparticles, Pyrazolones, Microwave, Reusable catalyst.*

1. Introduction

The pyrazolone ring system is a structural component of a large number of biologically active compounds. The pyrazolone derivatives are acknowledged to possess a wide range of bioactivities and exhibit important biological properties such as inhibitory potential of Mycobacterium tuberculosis (MTB) [1], analgesic agents [2], anti-inflammatory and antipyretic [3] antimicrobial [4], antibacterial against *Escherichia coli* [5]. Moreau and et. al. have reported the approach to identification of the first micromolar inhibitors of WaaC and the preliminary SAR generated from family of pyrazolones identified by virtual screening [6]. Therefore, the development of new, rapid and clean synthetic paths towards focused libraries of such compounds is of great importance to both medicinal and synthetic chemists. Undoubtedly, the synthesis of pyrazolones through multicomponent reactions (MCR) has been paid much absorption due to excellent synthetic efficiency, inherent atom economy, procedural simplicity, and environmental friendliness. Multicomponent reactions are used to generate the target products in a single operation which reduce reaction times and energy [7-14]. In recent years, the use of heterogeneous catalysts has provided remarkable advantages in multicomponent reactions, such as shorter time, saving energy, facile catalyst separation and recycling. These advances have opened the door for the design of new nanocatalysts for particular applications in synthetic chemistry. The catalytic activity is usually increased with decreasing size of nanoparticles. However, when the size of active site is decreased to nanoscale dimensions, the surface free energy is increased considerably [15-19]. Recently, Zirconium pyrophosphate (ZrP_2O_7) was used as an appropriate catalyst in the synthesis of tetra-hydropyridines [20] and dehydrogenation of *n*-butane [21]. We report herein a simple and facile procedure for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones through one-pot four-component reaction of phenyl hydrazines, ethyl acetoacetate, aldehydes and *β*-naphthol catalyzed by ZrP_2O_7 NPs under microwave irradiation (Scheme 1). Recently, the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones has been reported using MCRs in the presence of *p*-TSA [22], and CuI nanoparticles [23].

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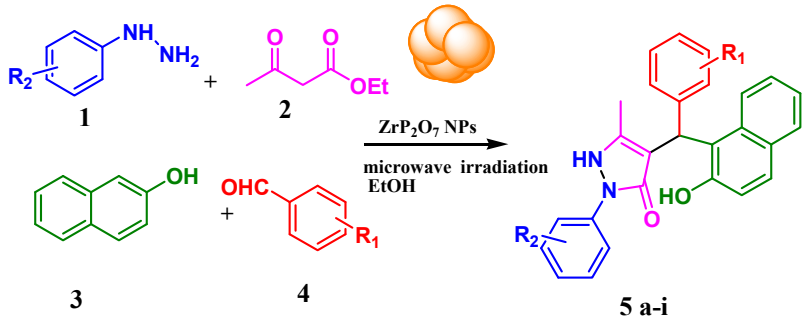


Scheme 1. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones.

2. Experimental

2.1. General

All the chemicals reagents used in our experiments were analytical grade and were used as received without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 200 W, was used for the ultra-sonic irradiation. The ultrasonic generator automatically adjusted the power level.^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the presence of tetramethylsilane as internal standard. The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Melting points were determined on Electro thermal 9200, and are not corrected. Microscopic morphology of products was visualized by SEM (LEO 1455VP). Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert company with mono chromatized Cu Karadiation (λ= 1.5406 Å). Microwave irradiation was carried out using a Litres Solo Microwave Oven ME3410W apparatus.

2.2. Preparation of ZrP_2O_7 nanoparticles

ZrP_2O_7 nanoparticle was prepared according to the procedure reported in the literature [20]. The catalyst was prepared *via* sonochemical method (worked at 20 kHz frequency and 80 W power). $ZrOCl_2$ was used as the zirconium source. Firstly the stoichiometric amount of $ZrOCl_2/8H_2O$ was added in 20 mL of distilled water and sonicated to completely dissolution. Afterward H_3PO_4 (85%) was added dropwise in 20 min and the mixture was sonicated. When the reaction was completed, 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.

2.3. General procedure for the preparation of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones:(5a-i)

A solution of phenylhydrazine (1 mmol) ethyl acetoacetate (1 mmol) and ZrP_2O_7 nanoparticles (.4 mol%) in ethanol (4 ml) was stirred at room temperature for 10 min. Then aromatic aldehyde (1 mmol), β-naphthol (1 mmol) were added to mixture under microwave irradiation at 300 W for the appropriate times (monitored by TLC). After completed reaction the residue was dissolved in hot ethanol and then filtered until heterogeneous catalyst was recovered. The ethanol was evaporated and the solid separated out was filtered and structures of the products were fully established on the basis of their ^{1}HNMR, ^{13}CNMR and FTIR spectra (See supplementary data).

2.4. Large-scale synthesis of selected compounds

A mixture of phenylhydrazine (10 mmol) ethyl acetoacetate (10 mmol) and ZrP_2O_7 nanoparticles (4 mol%) in ethanol (40 ml) was stirred at room temperature for 15 min. Then aromatic aldehydes (10 mmol), β-naphthol (10 mmol) were added to mixture under microwave irradiation at 400W for the appropriate times (monitored by TLC). After completed reaction the solid was filtered off and the residue was dissolved in hot ethanol and then filtered until heterogeneous catalyst was recovered. The ethanol was evaporated and the solid separated out was filtered. The results are summarized in Table 4.

3. Results and Discussion

The X-ray diffraction (XRD) pattern of the ZrP_2O_7 NPs is shown in Fig. 1. The average NP size was estimated from the full-width half-maximum of the peaks with use of the Debye–Sherrer equation. All reflection peaks can be readily indexed to pure cubic crystal phase of nano crystalline zirconium pyrophosphate. Also no specific peaks due to any impurities were observed. The pattern agrees well with the reported pattern for zirconium pyrophosphate (JCPDS No. 49-1079). The morphology and particle size of ZrP_2O_7

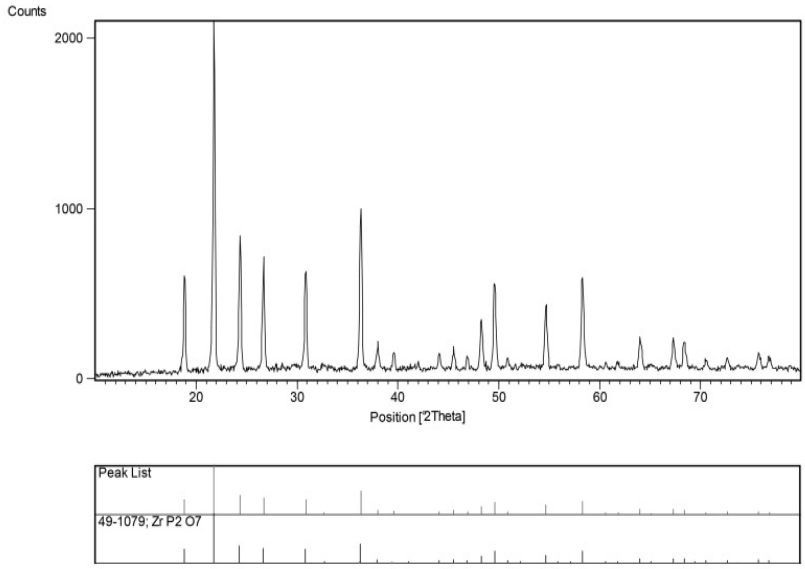


Fig. 1. The XRD pattern of ZrP_2O_7 NPs.

NPs was investigated by scanning electron microscopy (SEM) as shown in Fig. 2. The SEM image shows particles with diameters in the range of nanometers. The results show that ZrP_2O_7NPs were obtained with an average diameter of 11 nm as confirmed by the XRD analysis.

Initially, we focused on the systematic evaluation of different catalysts in the reaction of phenyl hydrazine, ethyl acetoacetate, β-naphthol and 4-nitrobenz-aldehyde. The ZrP_2O_7 nanoparticle catalyst shows a significant role in the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones. In the absence of ZrP_2O_7 nanoparticles, the product was obtained in very low yield after prolonged reaction time. When 0.2, 0.4, and 0.6 mol% of ZrP_2O_7 nanoparticles were used, the yields were 85, 92, and 92% respectively. Therefore, performing the reaction with a higher catalyst loading (0.6 mol %) had no significant effect on yield.

The model reactions were carried out in the presence of various catalysts, such as NiO, CuO, H_2SO_4, CAN, Alum, ZrO_2 and ZrP_2O_7 NPs. When the reaction was carried out using $ZrOCl_2.8H_2O$, ZrO_2 and ZrP_2O_7 NPs as the catalyst, the product could be obtained in moderate to good yield. The high catalytic activity of ZrP_2O_7 in comparison to other catalysts may be related to higher surface area available for greater adsorption of the reactants on its surface. The catalyst showed best activity in ethanol compared to other organic solvents such as CH_3CN, and H_2O (Table 1).

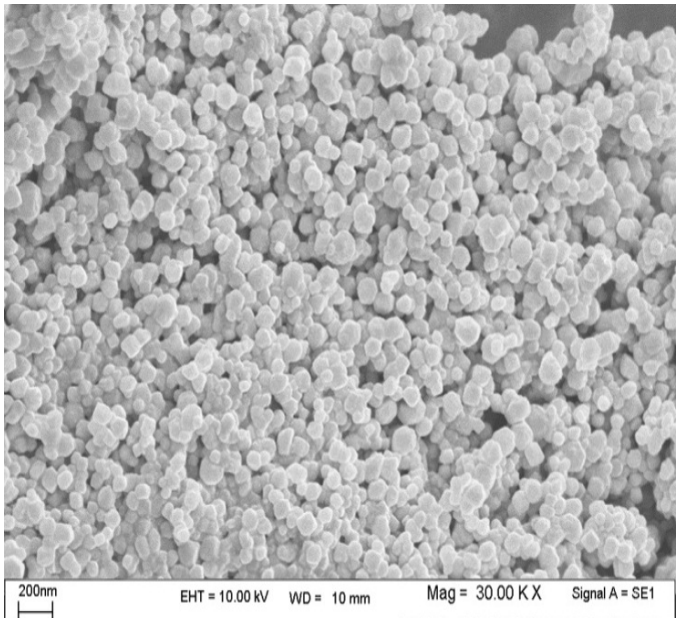


Fig. 2. SEM images of ZrP_2O_7 NPs.

Table 1. Optimization of reaction condition using different catalysts[a,b].

Entry	Solvent	Catalyst (mol)%	Time (min)	Yield[c](%)
1	H_2O	NiO (5)	80	33
2	EtOH	CuO (5)	80	29
3	H_2O	H_2SO_4(2)	82	35
4	CH_3CN	CAN(4)	75	31
5	H_2O	Alum(10)	80	41
6	CH_3CN	K10 clay(2)	80	45
7	H_2O	ZrO_2(4)	68	50
8	EtOH	$ZrOCl_2.8H_2O$ (2)	60	55
9	EtOH	ZrO_2 (6)	60	60
10	EtOH	ZrP_2O_7 (2)	55	66
11	H_2O	ZrP_2O_7 NPs (0.4)	45	70
12	CH_3CN	ZrP_2O_7 NPs (0.4)	40	75
13	EtOH	ZrP_2O_7 NPs (0.2)	35	85
14	**EtOH**	**ZrP_2O_7NPs (0.4)**	**25**	**92**
15	EtOH	ZrP_2O_7 NPs (0.6)	25	92

[a]Phenyl hydrazine, ethyl acetoacetate , β-naphthol and 4-nitrobenzaldehyde.
[b]Under microwave irradiation (300 W).
[c]Isolated yield.

In this research, microwave irradiation is used as a green technique for preparation of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones. In order to investigate the effect of intensity of microwave power on reaction, the reaction was also performed at different powers of the microwave irradiation (Table 2). When the power was 300 W, the yield of **5f** was 92%.

Almost all reactions worked well with a variety of aromatic aldehydes and the desired compounds were obtained in good to high yields (Table 3).

Table 2. Different powers for the synthesis of **5f** in ethanol using ZrP_2O_7 NPs.

Entry	Power	Time (min)	Yield[a](%)
1	200 W	33	81
2	**300 W**	**25**	**92**
3	400 W	22	88
4	500 W	22	85

[a]Isolated yield.

Table 3. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones using ZrP_2O_7 NPs[a].

Entry	Product	R_1	R_2	Time (min)	Yield(%)[b]	m.p.(°C)		Ref
						Found	Reported	
1	**5a**	H	H	35	86	204-206	205-206	[23]
2	**5b**	4-OMe	H	45	82	180-181	180-181	[23]
3	**5c**	4-NO_2	4-Cl	30	86	181-182	183-184	[23]
4	**5d**	4-Br	4-Cl	37	83	155-156	157-158	[23]
5	**5e**	4-Cl	H	32	90	172-174	176	[22]
6	**5f**	4-NO_2	H	25	92	207-209	207	[22]
7	**5g**	4-Me	H	40	83	178-180	179	[22]
8	**5h**	4-Cl	4-Cl	35	83	152-154	153	[22]
9	**5i**	4-isopropyl	H	42	82	184-186	-	-

[a]Under microwave irradiation (300 W).
[b]Isolated yield.

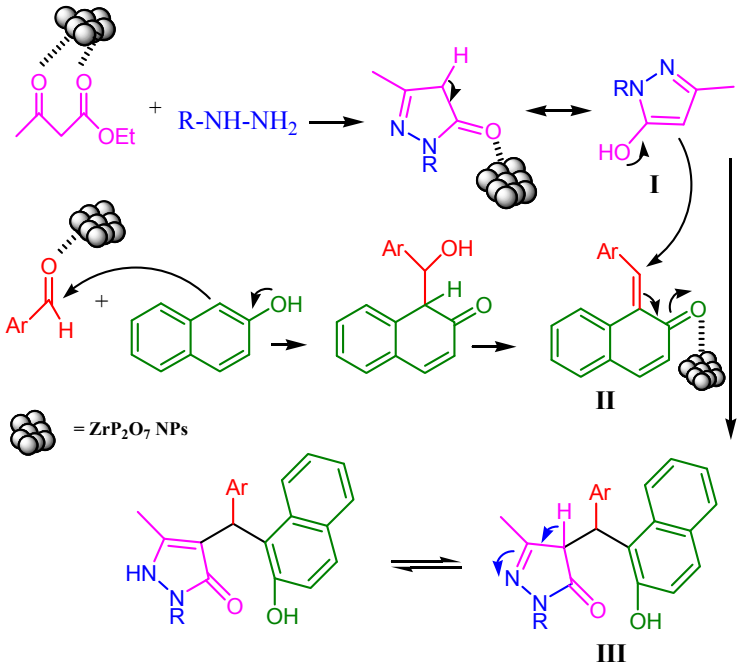
All the reactions reached completion within 25-45 min. As represented in Table 3, all aldehydes gave the expected products at high yields, either bearing electron-withdrawing groups or electron-donating groups.

A proposed mechanism for this four-component reaction was outlined in Scheme 2. The first step of this reaction can be visualized by activation of ethyl acetoacetate with nano ZrP_2O_7, following by nucleophilic attack of phenylhydrazine to give intermediate **I.** Meanwhile, β-naphthol undergoes condensation with aldehyde in presence of nano ZrP_2O_7 to afford α, β-unsaturated carbonyl compound (intermediate **II)**. Michael addition reaction between compounds **I** and **II** gives intermediate **III** following by tautomerization to afford the titled product.

All products were well characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. In ^{1}H NMR spectra in DMSO-d_6 showed a singlet around δ= 10.50 -11 corresponding to an OH group and a signal around δ= 7.00-7.50 corresponding to an NH.

To study the applicability of this method in larger scale synthesis, we performed selected reactions at 10 mmol scale. As can be seen, the reactions at large scale gave the product with a gradual decreasing of reaction yield (Table 4).

The recovered catalyst from the experiment was washed by chloroform and hot ethanol (3×5 mL). Then, it was dried in 100°C and used in the synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones. The catalyst was reused for five times. The reusability of nano-ZrP_2O_7 catalyst was examined for the synthesis of **5e** and it was found that product yields decreased to a small extent on each reuse (run 1, 90%; run 2, 89%; run 3, 89%; run 4, 87%; run 5, 86%) (Fig 3).



Scheme 2. Possible mechanism for the formation of pyrazolones in the presence of ZrP_2O_7 nanoparticles.

Table 4. The large-scale synthesis of some2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones using ZrP_2O_7 NPs.

Entry	product	R_1	R_2	Time (min)	Yield[b](%)
1	5a	H	H	45	81
2	5c	4-NO_2	4-Cl	35	79
3	5f	4-NO_2	H	30	85
4	5g	4-Me	H	48	75
5	5i	4-isopropyl	H	50	74

[a]Under microwave irradiation (400 W).

[b]Isolated yield.

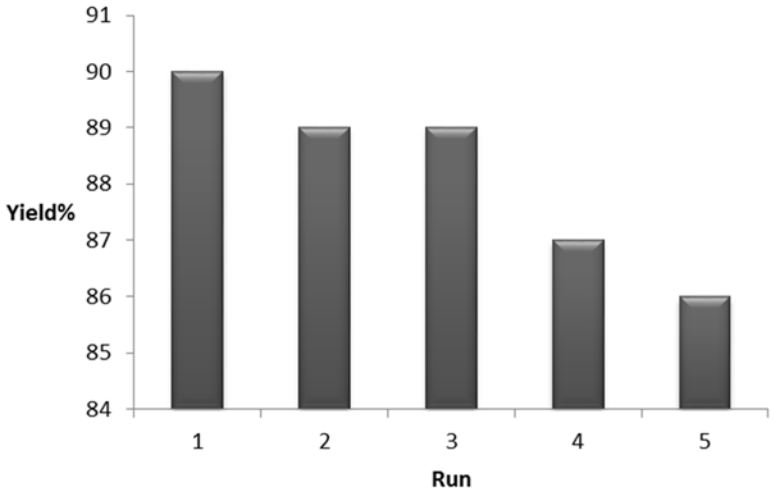


Fig. 3. Recoverability of the ZrP_2O_7 nanoparticles for synthesis **5e.**

4. Conclusions

In conclusion, we have developed a straightforward and efficient approach to synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones by a simple one-pot four-component reaction of phenyl hydrazines, ethyl acetoacetate , β-naphthol and benzaldehydes in the presence of ZrP_2O_7 nanoparticles as catalyst under microwave irradiation. This 'green' procedure can synthesize new substituted pyrazolone scaffolds. The advantages offered by this method include, easy workup, the employment of a cost-effective catalyst, short reaction times, excellent yields and use of microwave irradiation.

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