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Synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates using nano-$ZnZr_4(PO_4)_6$ as an efficient catalyst

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ABSTRACT

Nanocrystalline $ZnZr_4(PO_4)_6$ ceramics as an efficient catalyst have been used for the preparation of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*]pyrazole-3-carboxylates by the four-component reaction of dimethylacetylenedicarboxylate, hydrazinehydrate, malononitrile and aromatic aldehydes in water at room temperature. In this research, Nano-$ZnZr_4(PO_4)_6$ coordinates with the active groups (particular C=O, C≡N and active H), thus increasing the activity of the groups. Also, this nanoscale heterogeneous catalysts present higher surface areas, which are mainly responsible for their catalytic activity. These surface atoms behave as the centers where the chemical reactions could be catalytically activated. The key advantages of this process are high yields, shorter reaction times, reusability of the catalyst, easy work-up, milder reaction conditions and being environmentally benign.

Keywords: *Nano-$ZnZr_4(PO_4)_6$, Catalytic activity, Pyrano[2,3-c]pyrazole, One-pot, Multicomponent reaction.*

1. Introduction

Pyranopyrazoles represent a common scaffold in numerous bioactive compounds and have a number of pharmacological properties. The synthesis of pyranopyrazoles is an interesting challenge because compounds with these scaffolds were reported to possess a multiplicity of pharmacological properties such as being used as an anticancer [1], analgesic [2], anti-inflammatory [3], Chk1 inhibitors [4], and having molluscicidal activities [5]. Pyrano[2,3-*c*]pyrazole is isomeric with pyrano[4,3-*c*]pyrazole, pyrano[3,2-*c*] pyrazole and pyrano[3,4-*c*]pyrazole. Practically, the construction of pyrano[2,3-*c*]pyrazole structures has been established through different approaches to reaction and cyclization: two-component, three-component and four-component reactions [6]. The synthesis of highly functionalized bioactive heterocycles from readily available starting materials using one-pot multicomponent domino reactions has gained considerable interest both from synthetic and medicinal chemists. Therefore, looking for efficient and concise methods for the synthesis of pyranopyrazoles is considered very important. Multicomponent reactions supply a convenient method for the synthesis of various compounds with pharmaceutical and biological activities. Many MCRs (multicomponent reactions) show advantages in atomic economy, energy saving, simplified steps, avoidance of time consuming expensive purification and efficient use of resources [7-11]. The eco-compatibility and utilization of MCRs are enhanced when the multicomponent strategy is applied in conjugation with a heterogeneous catalyst and a green solvent. The use of water as a green solvent for organic synthesis has recently attracted considerable attention. Organic reactions carried out in water, without the use of any hazardous and flammable organic solvents, are one of the current challenges particularly in our environmentally conscious society and in recent years. Thus, studies have focused on discovery new water-compatible and reusable catalysts [12].

The chemical synthesis productivity can be increased by nano sized catalysts due to the small size and high surface to volume ratios. Separation of the catalyst and

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the final product from the reaction mixture is one of the most vital aspects of synthetic protocols. Nanoparticles decrease reaction times, impart greater selectivity and can be easily recovered from the reaction mixture by simple filtration [13-17]. $MZr_4(PO_4)_6$ structure ceramics have been interesting because of their unique properties and potential applications in diverse fields [18-19].

Recently, γ-alumina [20], piperidine [21], imidazole [22], glycine [23] and *L*-Proline [24] were reported for the synthesis of pyrano[2,3-*c*] pyrazole derivatives. Many methods for the synthesis of pyrano[2,3-*c*] pyrazoles are known, but some of these methods have certain drawbacks, including long reaction times, use of toxic and non-reusable catalysts, and need for specific conditions. Herein, we report the use of nano-$ZnZr_4(PO_4)_6$ as an efficient and reusable catalyst for the preparation of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-*c*] pyrazole-3-carboxylates by the four-component reaction of dimethylacetylene dicarboxylate, hydrazinehydrate, malononitrile, and aromatic aldehydes in water at room temperature (Scheme 1).

2. Experimental

2.1. General

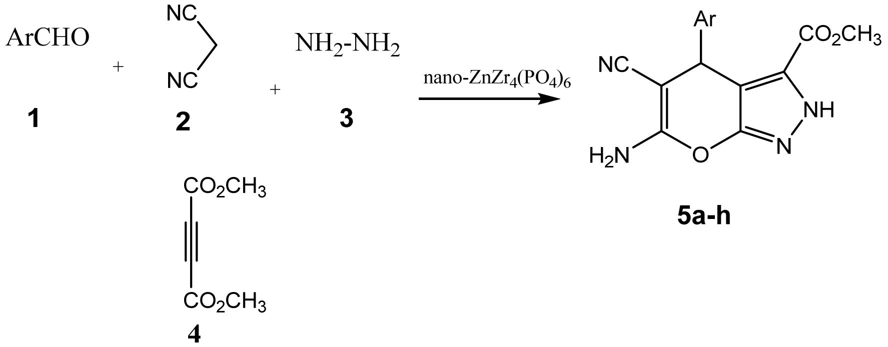
All organic materials were purchased commercially from Sigma–Aldrich and Merck and were used without further purification. A multiwave ultrasonic generator (Sonicator 3200; Bandelin, MS 73, Germany), equipped with a converter/transducer and titanium oscillator (horn), 12.5mm in diameter, operating at 20 kHz with a maximum power output of 200 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. All melting points were uncorrected and were determined in capillary tube on 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-d_6 as solvent and TMS as internal standard. CHN compositions were measured by Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatizedZr Kα radiation (λ= 1.5406 Å). In order to investigate the particle size and morphology of the synthesis structures nano-$ZnZr_4(PO_4)_6$, FE-SEM images of the products were visualized by a HITACHI S4160 Field Emission Scanning Electron Microscope.

2.2. Preparation of nano-$ZnZr_4(PO_4)_6$

$ZrOCl_2$ was used as zirconium source. Firstly, 1 mmol of $ZrOCl_2.8H_2O$ and 1 mmol of $Zn(NO_3)_2{\cdot}6H_2O$ were added in 15 mL of $HO(CH_2)_2OH$ and sonicated at 30 W power to complete dissolution. Afterward 0.8 ml H_3PO_4 (85%), 4 mmol of NH_4Cl and 1.4 mL of CH_3NH_2 water solution (25.0-30.0%) were added consecutively and sonicated for 30 min. Then, the reaction mixture was transferred into a Teflon-lined autoclave under autogenous pressure at 200ºC for 5 days. When the reaction was completed, dispersed precipitate was obtained. The solid was filtered and washed with distilled water and ethanol several times. Subsequently, the product was dried at 50ºC for 5 h and calcined at 700ºC for 2 h. Afterward, the solid was added in 20 mL of DMF and sonicated at 95 W power for 2 h. Finally, the resulting product was filtered, washed with distilled water and absolute ethanol and was dried at 150 ºC for 2 h in vacuum to afford pure nano-$ZnZr_4(PO_4)_6$ ceramics.

2.3. General procedure for the preparation of methyl 6- amino-5- cyano-4- aryl-2,4- dihydropyrano [2,3-c] pyrazole-3-carboxylates

A mixture of malononitrile (1 mmol), aldehydes (1 mmol) hydrazine hydrate (1 mmol), dimethyl acetylenedicarboxylate (1 mmol) and 0.40 mol % nano-$ZnZr_4(PO_4)_6$ in H_2O (5 mL) was stirred at room temperature for the specific time.



Scheme.1 Synthesis of pyrano[2,3-c]pyrazoles using nano-$ZnZr_4(PO_4)_6$.

The reaction was monitored by TLC. After cooling, the precipitated solid was filtered and washed with H_2O. The product was dissolved in hot CH_3OH and the catalyst was filtered. After cooling, the crude products were precipitated. The precipitate was washed with methanol to afford the pure product and was dried well under vacuum pump. The structures of the products were fully established on the basis of their ^1H NMR, ^{13}C NMR and FT-IR spectra (**See Supplementary data**).

3. Results and Discussion

Fig.1 shows the XRD spectra of nano-$ZnZr_4(PO_4)_6$. The particle size diameter (D) of the nano-$ZnZr_4(PO_4)_6$ has been calculated by the Debye–Scherrer equation ($D = K\lambda/\beta \cos \theta$), where β FWHM (full-width at half-maximum or half-width) is in radian and θ is the position of the maximum of the diffraction peak. K is the so-called shape factor, which usually takes a value of about 0.9, and λ is the X-ray wavelength.. According to the Debye–Scherrer equation, the average particle sizes of the as-synthesized nano-$ZnZr_4(PO_4)_6$ were calculated and the results show that nano-$ZnZr_4(PO_4)_6$ was obtained with an average diameter of 70-75 nm as confirmed by XRD analysis.

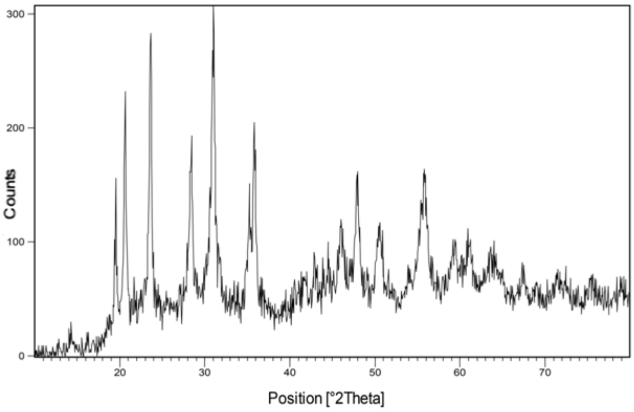


Fig. 1. The XRD pattern of nano-$ZnZr_4(PO_4)_6$.

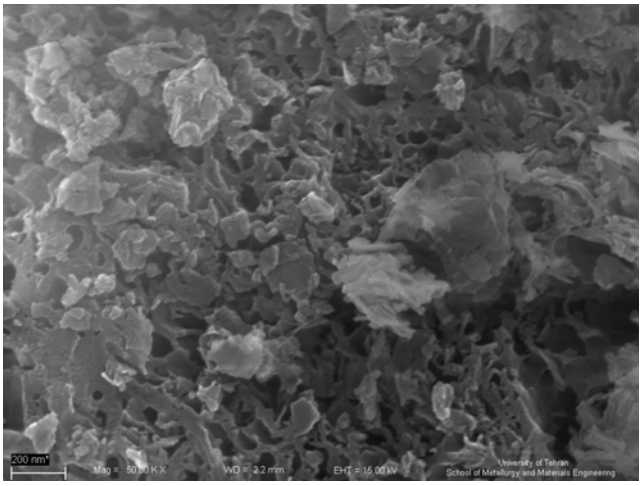


Fig. 2. FE-SEM images of nano-$ZnZr_4(PO_4)_6$.

In order to investigate the morphology and particle size of nano-$ZnZr_4(PO_4)_6$, FE-SEM image of nano-$ZnZr_4(PO_4)_6$ was presented in Fig. 2. The FE-SEM image shows particles with diameters in the range of nanometers. As shown in Fig. 3, the EDS analysis was carried out for nano-$ZnZr_4(PO_4)_6$. The EDS spectrum shows only Zn, Zr, P and O elements for $ZnZr_4(PO_4)_6$, which supports XRD results.

In order to optimize the reaction conditions for the synthesis of pyrano[2,3-*c*]pyrazoles, the reaction 4-nitrobenzaldehyde with dimethyl acetylene dicarboxylate, hydrazine and malononitrile was used as a model reaction at room temperature. Several reactions were scrutinized using different solvents, such as ethanol, acetonitrile, water and dichloromethane. In the presence of water the products were obtained in high yield. The model reaction was considered in presence of different catalysts. The best result was obtained in using nano-$ZnZr_4(PO_4)_6$. To optimize the catalyst quantity, the reaction was carried out with different quantities of the nano-$ZnZr_4(PO_4)_6$ and 0.40 % mol of nano-$ZnZr_4(PO_4)_6$ was found to be optimal (Table 1).

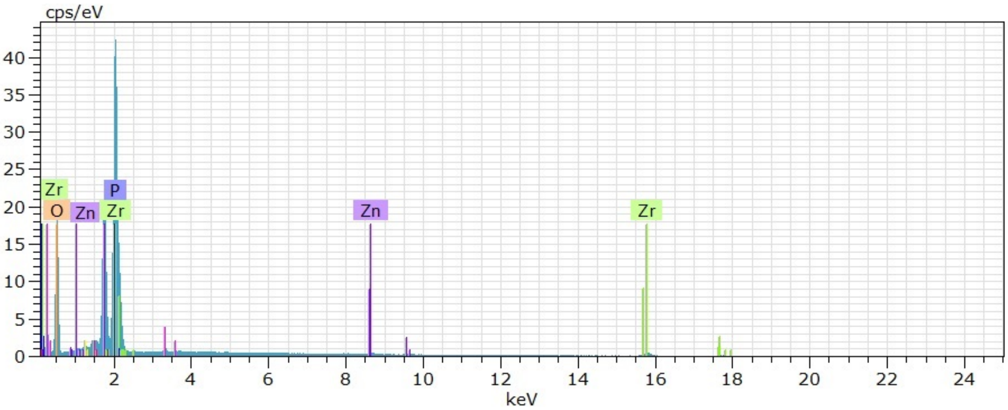


Fig. 3. EDS analysis of nano-$ZnZr_4(PO_4)_6$.

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

Entry	Solvent	Catalyst	mol (%)	Time (min)	Yield (%) [b]
1	CH_2Cl_2	$InCl_3$	2	80	25
2	CH_3CN	Et_3N	20	70	37
3	EtOH	ZnO	5	60	48
4	EtOH	CaO	5	60	44
5	H_2O	ZrO_2	8	70	50
6	H_2O	NiO	2	60	42
7	CH_3CN	ZnS	4	55	45
8	H_2O	SnO	3	65	40
9	CH_3CN	nano-$ZnZr_4(PO_4)_6$	0.60	40	65
10	EtOH	nano-$ZnZr_4(PO_4)_6$	0.40	30	76
11	H_2O	nano-$ZnZr_4(PO_4)_6$	0.20	30	86
12	**H_2O**	**nano-$ZnZr_4(PO_4)_6$**	**0.40**	**30**	**93**
13	H_2O	nano-$ZnZr_4(PO_4)_6$	0.60	30	93

[a]Reaction conditions: hydrazine (1 mmol), malononitrile (1 mmol) dimethyl acetylenedicarboxylate (1mmol) and 4-nitrobenzaldehyde (1 mmol).

[b]Isolated yields.

As expected, the increased surface area due to small particle size increased reactivity of the catalyst. This factor is responsible for the accessibility of the substrate molecules on the catalyst surface. The catalyst was recovered from the reaction mixture either by filtration or centrifugation; it was washed successively with methanol and water. The catalyst recycling has been checked for the synthesis of pyrano[2,3-*c*]pyrazoles.

Fig. 4 shows that the catalyst could be reused up to nine runs without considerable loss of activity. High catalytic activity and ease recovery of the reaction mixture through filtration or centrifugation methods, and several reuse times without significant losses in performance are additional eco-friendly attributes of this catalytic system.

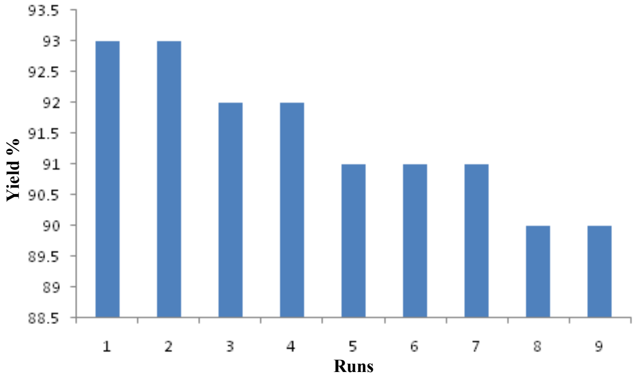


Fig. 4. Reusability of nano-$ZnZr_4(PO_4)_6$.

Investigations of the reaction scope revealed that various aromatic aldehydes (bearing electron-withdrawing and electron-donating groups) can be utilized in this protocol (Table 2). It was shown that aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron releasing groups. Meanwhile, it has been observed that better yields are obtained with substrates having electron-withdrawing groups. 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.

A plausible mechanism for the preparation of methyl 6- amino-5- cyano-4- aryl-2,4- dihydropyrano [2,3-*c*] pyrazole-3-carboxylates using nano-$ZnZr_4(PO_4)_6$ is shown in Scheme 2. Firstly, we assumed that the reaction occurs *via* a knoevenagel condensation between malononitril and aldehyde to form the intermediate **I** and meanwhile formation of pyrazole derivative **II** by reaction of hydrazine hydrate and dimethylacetylenedicarboxylate. Finally, Michael addition of **I**, **II**, was followed by cyclization and tautomerization. Nano-$ZnZr_4(PO_4)_6$ coordinate with the active groups (particular C=O, C≡N and active H), thus increasing the activity of the groups. Theoretically, nanoscale heterogeneous catalysts should present higher surface areas which are mainly responsible for their catalytic activity. These surface atoms behave as the centers where the chemical reactions could be catalytically activated.

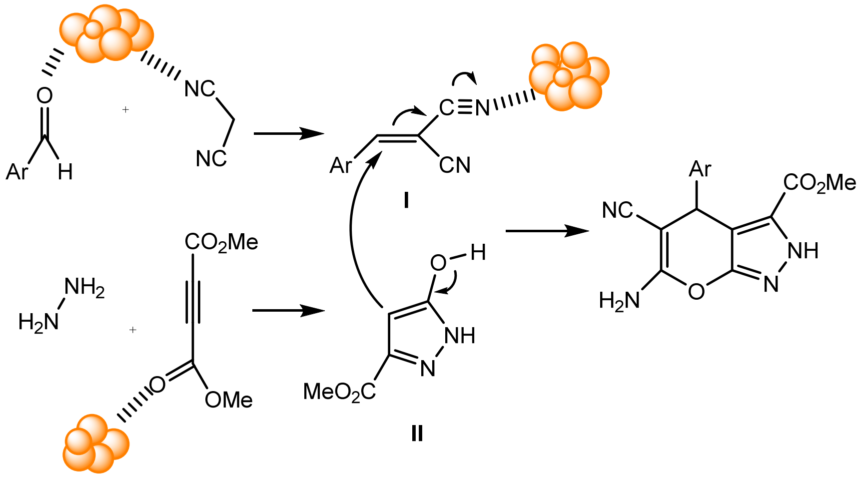
Table 2. Synthesis of pyrano[2,3-*c*]pyrazole-3-carboxylates by nano-$ZnZr_4(PO_4)_6$.[a]

Entry	Ar	Product	Time (min)	Yield (%) [b]	m.p.(°C)	
					Found	Reported[c]
1	4-NO_2-C_6H_5	**5a**	30	93	242-243	244-245
2	2-F- C_6H_5	**5b**	33	90	248-250	-----
3	4-OMe- C_6H_5	**5c**	36	86	238-240	-----
4	4-Me-C_6H_5	**5d**	35	89	242-244	-----
5	3-NO_2- C_6H_5	**5e**	32	90	234-235	236-237
6	C_6H_5	**5f**	33	87	231-232	231-232
7	2,3-OMe-C_6H_3	**5g**	42	83	239-241	-----
8	2-OMe- C_6H_5	**5h**	38	84	210-212	212-214
9	2-Me- C_6H_5	**5i**	40	86	237-239	239-240
10	3-OMe- C_6H_5	**5j**	36	85	205-207	208-210

[a] All the reactions were carried out in water.

[b] Isolated yields.

[c] All from ref. [25].



Scheme 2. Schematic mechanism for the catalytic activity of nano-$ZnZr_4(PO_4)_6$ in the synthesis of titled compound (**5a-h**).

4. Conclusion

In conclusion, we have developed a straightforward and efficient approach for the synthesis of methyl 6- amino-5- cyano-4- aryl-2,4- dihydropyrano [2,3-c] pyrazole-3-carboxylates by a simple one pot four-component condensation reaction of dimethyl acetylenedicarboxylate, hydrazine hydrate, malono nitrile and aldehydes using nano-$ZnZr_4(PO_4)_6$ in aqueous medium. The attractive feature of this protocol are the simple procedure, reusability of the catalyst, easy workup and the use of water as a solvent that is considered to be relatively environmentally benign.

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