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A multi-component reaction for direct access to 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)-3-carboxylates using nano-$NiZr_4(PO_4)_6$ in water

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Abstract. An efficient synthesis of 4,4′-(phenylmethylene)bis(*1H*-pyrazol-5-ol)-3-carboxylates is achieved by one-pot pseudo five-component reaction of phenylhydrazine, acetylenedicarboxylates, and aromatic aldehydes in the presence of nano-$NiZr_4(PO_4)_6$ at 60°C in water. Nano-$NiZr_4(PO_4)_6$ has been characterized by powder X-Ray Diffraction (XRD) and Scanning Electronic Microscopy (SEM). Use of simple and readily available starting materials, excellent yields in short time, reusability of the catalyst, little catalyst loading, and simple operational procedures are some of the important features of this protocol.

1. Introduction

Pyrazoles constitute a significant family of heterocyclic compounds for their potential pharmaceutical applications such as anti-cancer [1], antidepressants [2], antiviral [3], anti-inflammatory [4], anti-malarial [5], antibacterial [6], and antiallergic [7] activities. Efficient creation of complex molecules of chemical and biological importance is a challenging issue and has gained substantial interest in recent years [8-9]. Among numerous synthetic methods, the multicomponent reactions (MCRs) are valuable for the expedient creation of chemical libraries of drug-like compounds with high levels of molecular complexity [10,11]. Therefore, the development of new MCR-based methodologies can be regarded as one of the most important facets of organic chemistry [12]. The synthesis of 1-phenyl-1*H*-pyrazol-5-ols has been reported using MCR in the presence of $Ce(SO_4)_2.4H_2O$ [13], silica-bonded S-sulfonic acid [14], 1,3,5-tris(hydrogensulfato) benzene [15], 1-sulfopyridinium chloride [16], acetic acid [17], and nano-CeO_2 [18]. Some of these methods have certain disadvantages, including long reaction times, use of toxic and non-reusable catalyst, and operation under specific conditions [19,20]. The possibility of accomplishing multicomponent reactions in aqueous media with a heterogeneous catalyst could expand their efficiency from cost-effectiveness and environmental points of view [21,22]. Water has emerged as a versatile solvent in organic reactions as it is an eco-friendly, safe, cheap, nontoxic, and economical reaction medium [23]. $MZr_4(PO_4)_6$ structure ceramics have drawn much interest because of their unique properties and potential applications in diverse fields [24,25]. Accordingly, we used nano-$NiZr_4(PO_4)_6$ for the synthesis of pyrazole derivatives. Ideally, nanoscale heterogeneous catalysts should present higher surface areas, which are chiefly responsible for their catalytic activity [26,27].

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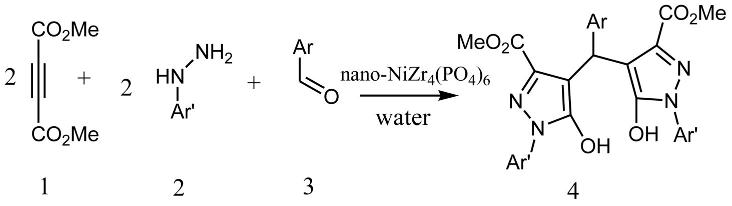


Scheme 1. One-pot synthesis of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)-3-carboxylates using nano-$NiZr_4(PO_4)_6$.

The use of highly efficient, economic, and recoverable catalysts with low or zero toxicity is essential from the green chemistry perspective [28-30]. Herein, we wish to report a highly efficient procedure for the preparation of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)3-car boxylates using nano-$NiZr_4(PO_4)_6$ in water (Scheme 1).

2. Experimental

2.1. Chemicals and instruments

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), 12.5 mm 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 determined in capillary tube on Boetius melting point microscope. FT-IR spectra were recorded with KBr pellets using a 550 Nicolet Magna-IR spectrometer. 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 analyser. Powder X-Ray Diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Zr Kα radiation (λ = 1.5406 Å). In order to investigate particle size and morphology of the nano-$NiZr_4(PO_4)_6$ synthesis structures, FE-SEM images of the products were visualized by a HITACHI S4160 Field Emission Scanning Electron Microscope.

2.2. Preparation of nano-$NiZr_4(PO_4)_6$

$ZrOCl_2$ was used as zirconium source. First, 1 mmol of $ZrOCl_2.8H_2O$ and 1 mmol of $Ni(NO_3)_2.2H_2O$ were added to 15 mL of $HO(CH_2)_2OH$ and sonicated at 30 W power for complete dissolution. Afterwards, 0.8 ml of 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 200°C for 5 days. When the reaction was completed, dispersed precipitate was obtained. The solid was filtered and washed with distilled water and ethanol for several times. Subsequently, the product was dried at 50°C for 5 h and calcined at 700°C for 2 h. Afterwards, the solid was added to 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 dried at 150°C for 2 h in vacuum to afford pure nano $NiZr_4(PO_4)_6$ ceramics.

2.3. General procedure for the preparation of 4,4′-(phenylmethylene)bis(1H-pyrazol-5-ol)3-carboxylates

Dimethyl acetylenedicarboxylate (2 mmol), phenylhydrazine (2 mmol), and nano $NiZr_4(PO_4)_6$ ceramics (0.4 mol%) as catalyst in H_2O were mixed and then stirred at room temperature for 5 min. Then, the aromatic aldehyde (1 mmol) was added into the mixture. The new mixture was stirred at 60°C for appropriate time. Then, it was allowed to cool down to room temperature. The formed precipitate was isolated by filtration. 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 EtOH to afford the pure product and then dried well under vacuum pump.

2.4. Physical and spectroscopic data

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-pheny l-1H-pyrazol-4-yl) (4-nitrophenyl) methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4a):
Golden powder; m.p. 215-216°C. – IR (KBr): ν = 3432.46, 3073.25, 2954.07, 1731.85, 1600.24, 1515.65, 1443.52, 1344.65, 1213.56, 1113.29, 842.25 cm^{-1}. – ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.85 (s, 6H, $2OCH_3$), 4.83 (2OH exchanged with water of DMSO-d_6), 6.92 (s, 1H, CH), 7.29-7.43 (t, J = 7.6 Hz, 6H, H-Ar), 7.52 (d, J = 8 Hz, 2H, H-Ar), 7.77-7.86 (m, 4H, H-Ar), 8.14 (d, J = 7.6 Hz, 2H, H-Ar). – Analysis for $C_{29}H_{23}N_5O_8$: calcd. C 61.16, H 4.07, N 12.30; found: C 61.17, H 4.12, N 12.43.

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(4-chlorophenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4b):
White powder; m.p. 223-225°C. – IR (KBr): ν = 3429.06, 3068.75, 2952.83, 1718.92, 1599,48, 1492.72 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.94

(s, 6H, 2OCH$_3$), 6.17 (s, 1H, CH), 7.23-7.26 (m, 2H, H-Ar), 7.29-7.32 (m, 2H, H-Ar), 7.35-7.40 (m, 2H, H-Ar), 7.46-7.50 (m, 4H, H-Ar), 7.84-7.90 (m, 4H, H-Ar), 10.59 (2OH). – Analysis for $C_{29}H_{23}ClN_4O_6$: calcd. C 62.31, H 4.15, N 10.02; found: C 62.22, H 4.15,N 9.87.

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(2,3-dichlorophenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4c):
White powder; m.p. 204-205°C. – IR (KBr): ν = 3443.18, 2925.75, 1725.23, 1593.02, 1499.96, 1208.67, 1112.19 cm^{-1}. – ^{1}HNMR (400 MHz, DMSO-d_6): δ (ppm) = 3.76 (s, 6H, 2OCH$_3$), 4.65 (2OH exchanged with water of DMSO-d_6), 6.73 (s, 1H, CH), 7.12-7.75 (m, 13 H, H-Ar). – ^{13}CNMR (100MHz, DMSO-d_6): δ (ppm) = 31.15, 52.06, 105.24, 122.43, 122.65, 126.87, 127.03, 129.14, 129.28, 129.55, 131.56, 131.97, 133.84, 138.34, 157.22, 162.84. – Analysis for $C_{29}H_{22}Cl_2N_4O_6$: calcd. C 58.70, H 3.74, N 9.44; found: C 58.63, H 3.80, N 9.51.

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(2-methylphenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4d):
Green powder; m.p. 186-187°C. – IR (KBr): ν = 3429.95, 3027.76, 2954.75, 1722.54, 1600.25, 1494.42, 1122.14, 863.26, 762.83 cm^{-1}. – ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.20 (s, 3H, CH$_3$), 3.88 (s, 6H, 2OCH$_3$), 4.86 (2OH exchanged with water of DMSO-d_6), 6.75 (s, 1H, CH), 6.93-7.76 (m,14H, Ar-H). – ^{13}CNMR (100MHz, DMSO-d_6): δ (ppm) = 31.04, 31.95, 52.32, 107.96, 122.83, 123.34, 124.85, 126.97, 127.47, 128.32, 128.45, 129.35, 137.43, 137.52, 138.56, 142.68, 162.45. – Analysis for $C_{30}H_{26}N_4O_6$: calcd. C 66.91, H 4.87, N 10.40; found: C 66.98, H 4.96, N 10.38.

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(phenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4e):
Brown powder; m.p. 285-286°C. – IR (KBr): ν = 3427.77, 2954.15, 1707.87, 1599.75, 1575.03, 759.86, 697.47 cm^{-1}. – ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.36 (s, 6H, 2OCH$_3$), 3.78 (2OH, exchanged with water of DMSO-d_6), 6.67 (s, CH, 1H), 7.08-7.93 (m, 15H, Ar-H). – ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 32.25, 51.48, 105.36, 121.28, 125.32, 125.67, 128.02, 128.99, 130.54, 137.30, 139.78, 140.22, 158.50, 164.30. – Analysis for $C_{29}H_{24}N_4O_6$: calcd. C 66.41, H 4.61, N 10.68; found: C 66.46, H 4.72, N 10.58.

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(2-chlorophenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4f):
White powder; m.p. 269-271°C. – IR (KBr): ν = 3420.06, 2957.63, 1723.62, 1595.90, 1552.35, 1207.73, 1131.42, 765.35 cm^{-1}. – ^{1}HNMR (400 MHz, DMSO-d_6): δ (ppm) = 3.75 (s, 6H, 2OCH$_3$), 4.65 (2OH exchanged with water of DMSO-d_6), 7.36 (s, 1H, CH), 7.51-7.55 (m, 6H, Ar-H), 7.77-7.80 (m, 8H, Ar-H). – ^{13}C NMR(100MHz,DMSO-d_6): δ (ppm) = 31.14, 51.67, 102.05, 122.58, 122.82, 127.35, 127.84, 129.38, 129.56, 131.46, 131.92, 133.20, 138.77, 141.06, 151.93, 162.94. – Analysis for $C_{29}H_{23}ClN_4O_6$: calcd. C 62.31, H 4.15, N 10.02; found: C 62.25, H 4.18, N 10.08.

Methyl 4-((3-(methoxycarbonyl)-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)(4-methylphenyl)methyl)-5-hydroxy-1-phenyl-1H-pyrazole-3-carboxylate (4g):
Green powder; m.p. 197-199°C. – IR (KBr): ν = 3432.33, 3063.25, 2952.85, 1729.78, 1602.72, 1506.93, 1447.84, 1207.55, 1122.83 cm^{-1}. – ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.17 (s, 3H, CH$_3$), 3.74 (s, 6H, 2OCH$_3$), 4.35 (2OH exchanged with water of DMSO-d_6), 6.68 (s, 1H, CH), 6.75-7.76 (m, 14H, Ar-H). – ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) = 29.3, 31.5, 51.68, 113.85, 122.83, 123.37, 124.86, 125.63, 126.95, 127.44, 128.43, 129.35, 138.52, 142.64, 162.43. – Analysis for $C_{30}H_{26}N_4O_6$: calcd. C 66.91, H 4.87, N 10.40; found: C 66.97, H 4.95, N, 10.34.

3. Results and discussion

The XRD patterns for nano-$NiZr_4(PO_4)_6$ nanoparticles are shown in Figure 1. The pattern agrees well with the reported pattern for nano-$NiZr_4(PO_4)_6$ nanoparticles (JCPDS No. 45-0013). The morphology and particle size of nano-$NiZr_4(PO_4)_6$ were investigated by Scanning Electron Microscopy (SEM) as shown in Figure 2. The SEM images show particles with diameters in the range of nanometers.

To begin this study, we chose phenylhydrazine (2 mmol), dimethyl acetylenedicarboxylate (2 mmol), and 4-nitrobenzaldehyde (1 mmol) as the standard substrates to search for suitable reaction conditions. Various solvents including DMF, water, CH$_3$CN, EtOH, and CHCl$_3$ were optimized (Table 1).

After systematic screening was made, we found

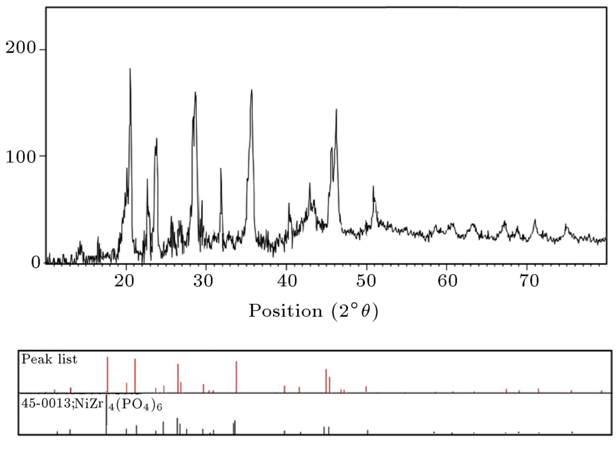


Figure 1. The XRD pattern of nano-$NiZr_4(PO_4)_6$.

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

Entry	**Conditions**	**Catalyst (mol%)**	**Time (min)**	**Yield (%)**[b]
1	$CHCl_3$	ZnO (3)	100	17
2	EtOH (reflux)	MgO (4)	50	32
3	H2O (60°C)	NiO (3)	65	41
4	EtOH (reflux)	CuO (4)	40	28
5	H_2O (60°C)	SnO (3)	55	31
6	H_2O (60°C)	ZnO (3)	38	52
7	CH_3CN (reflux)	ZnO (3)	45	40
8	H_2O (60°C)	$ZnAl_2O_4$ NPs (1.5)	25	65
9	CH_3CN (reflux)	nano-$NiZr_4(PO_4)_6$ (0.4)	25	63
10	EtOH (reflux)	nano-$NiZr_4(PO_4)_6$ (0.4)	20	75
11	H_2O (60°C)	nano-$NiZr_4(PO_4)_6$ (0.2)	15	87
12	H_2O (60°C)	nano-$NiZr_4(PO_4)_6$ (0.4)	15	94
13	H_2O (60°C)	nano-$NiZr_4(PO_4)_6$ (0.6)	15	94
14	H_2O (35°C)	nano-$NiZr_4(PO_4)_6$ (0.4)	20	77
15	H_2O (50°C)	nano-$NiZr_4(PO_4)_6$ (0.4)	15	86
16	H_2O (75°C)	nano-$NiZr_4(PO_4)_6$ (0.4)	15	94

[a] Phenylhydrazine (2 mmol), acetylenedicarboxylates (2 mmol), and 4-nitrobenz-aldehyde (1 mmol).

[b] Isolated yield.

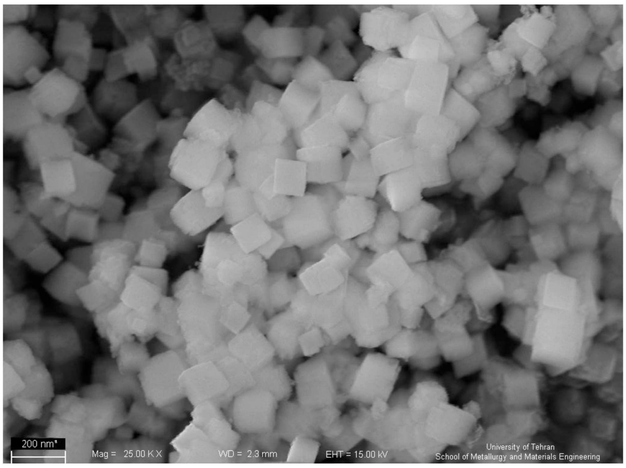


Figure 2. SEM image of nano-$NiZr_4(PO_4)_6$.

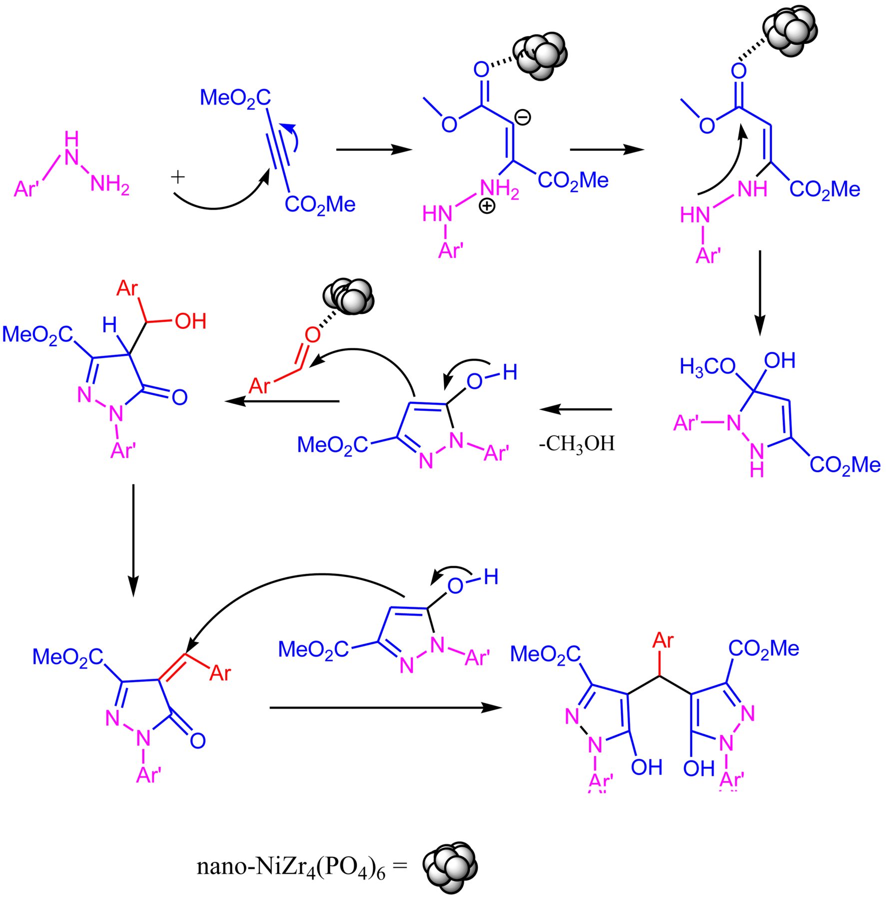
that, in the presence of nano-$NiZr_4(PO_4)_6$, substrates were transformed into the desired product in an excellent yield. When 0.2, 0.4, and 0.6 mol% of nano-$NiZr_4(PO_4)_6$ were used, the yields were 87, 94, and 94%, respectively. Therefore, performing the reaction with a higher catalyst loading (0.6 mol%) had no significant effect on yield. In this reaction, the use of polar solvents favoured the reaction mechanism. The catalyst showed best activity in water compared with other organic solvents such as EtOH, CH_3CN, and $CHCl_3$. Water with a dielectric constant of about 80 carried out reactions in good to excellent yields. Also, the activity and stability of the nano-$NiZr_4(PO_4)_6$ in water were maximal compared with other solvents for the synthesis of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)3-carboxylates. With these optimized conditions in hand, we examined the scope of this multicomponent reaction by using various easily available aldehydes (Table 2).

The mechanism of these domino reactions is presented in Scheme 2. This proposed mechanism is supported by the literature [14,15].

In the recycling procedure of nano-$NiZr_4(PO_4)_6$, the product was dissolved in hot CH_3OH and the catalyst was filtered. The solution was filtered and the heterogeneous catalyst was recovered. The recovered nano-$NiZr_4(PO_4)_6$ was washed 4 to 6 times with chloroform and ethyl acetate, and dried at 90°C for 5 h. We investigated recycling of the nano-$NiZr_4(PO_4)_6$ as catalyst for the synthesis of **4a**. The results showed that nano-$NiZr_4(PO_4)_6$ could be reused several times with a slightly decreased activity (run 1, 94%; run 2, 94%, run 3, 93%; run 4, 93%; run 5, 92%; run 6, 92%; run 7, 91%; run 8, 91%; and run 9, 90%).

4. Conclusions

We described an efficient one-pot synthesis of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)-3-carboxylates by the pseudo five-component reaction of phenylhydrazine, acetylenedicarboxylates, and aromatic aldehydes in the presence of nano-$NiZr_4(PO_4)_6$ at 60°C in water. The advantages offered by this method include short reaction time, simple procedure, high atom econ-



Scheme 2. Possible mechanism for the synthesis of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)3-carboxylates in the presence of nano-$NiZr_4(PO_4)_6$.

Table 2. Synthesis of 4,4′-(phenylmethylene)bis(1*H*-pyrazol-5-ol)3-carboxylates using nano-$NiZr_4(PO_4)_6$ at 60°C in water.

Entry	Aldehyde (Ar)	Product	Time (min)	Yield^a (%)	M.p. (°C)	M.p. (°C) [ref.]
1	4-NO_2-C_6H_4	**4a**	15	94	217-218	216-217 [14]
2	4-Cl- C_6H_4	**4b**	16	90	226-228	226-228 [15]
3	2,3-Cl- C_6H_3	**4c**	17	88	204-205	–
4	2-Me- C_6H_4	**4d**	23	86	186-187	–
5	C_6H_5	**4e**	20	88	285-286	287-289 [15]
6	2-Cl-C_6H_4	**4f**	20	87	269-271	267-269 [15]
7	4-Me- C_6H_4	**4g**	23	85	197-199	195-197 [15]
8	3-Br-C_6H_4	**4h**	20	86	255-257	–
9	2-Br-C_6H_4	**4i**	17	88	235-237	–
10	4-OMe-C_6H_4	**4j**	25	82	215-217	–
11	2,3- OMe-C_6H_3	**4k**	28	80	204-206	–

^{a}Isolated yield.

omy, excellent yields, use of no toxic organic solvent, and the employment of a cost-effective catalyst.

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