

RESEARCH PAPER

Synthesis of pyrimidines using nano-NiZr₄(PO₄)₆ as a retrievable and robust heterogeneous catalyst

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ABSTRACT

Nano-NiZr₄(PO₄)₆ has been used as an effective and retrievable heterogeneous catalyst for the synthesis of pyrimidines through the reaction of benzaldehydes, guanidine hydrochloride and malononitrile under reflux conditions in ethanol. Experimental simplicity, wide range of products, excellent yields in short reaction times, reusability of the catalyst and low catalyst loading are some of the substantial features of this procedure. The best results were gained in EtOH and we found the convincing results for the synthesis of pyrimidines in the presence of nano-NiZr₄(PO₄)₆ (3 mg) under reflux conditions. The present catalytic method could be extended to a wide diversity of substrates for the synthesis of a variety-oriented library of pyrimidines.

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INTRODUCTION

Pyrimidines show antihypertensive [1], antimicrobial [2,3], antitumor [4], antimalarial [5], antioxidant [6] protein Kinase inhibitors [7] and antagonists of GPR40 activities [8]. Therefore, the development of beneficial ways for the preparation of pyrimidines is of great interest. A number of ways have been employed for the synthesis of pyrimidines in the presence of catalysts such as sodium acetate [9], Bi(NO₃)₃·5H₂O [10], NaOH [11,12] CuO microspheres [13] and K₂CO₃ [14]. Each of these procedures may have its own advantages but also suffer from such apparent drawbacks as prolonged reaction times, complicated work-up, non-reusable catalyst, low yield and hazardous reaction conditions. Despite the availability of these ways, there remains enough choice for a capable and reusable catalyst with high catalytic activity for the preparation of pyrimidines. Nanoparticles have emerged as a suitable group of heterogeneous catalysts owing

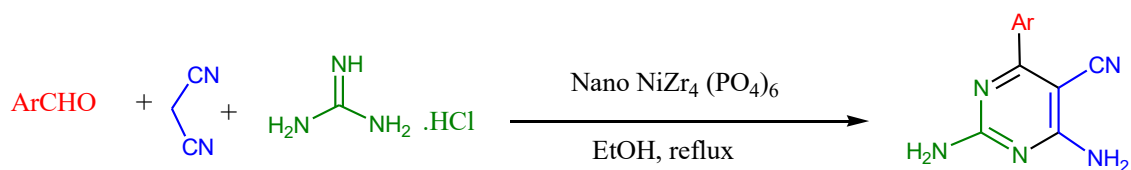
to their numerous applications in synthesis and catalysis [15,16]. Since, these nanoparticles are often recovered simply by easy workup, which prevents contamination of products, they may be considered as the promising safe, reusable, and greener catalysts compared to traditional catalysts [17,18]. MZr₄(PO₄)₆ nanoparticles as heterogeneous catalysts have been interested due to their unique properties and potential applications in diverse fields [19,20]. In this study, we report the use of nano-NiZr₄(PO₄)₆ as an effective catalyst for the preparation of pyrimidines by the reaction of benzaldehydes, malononitrile, and guanidine hydrochloride under reflux conditions in ethanol. (Scheme 1).

EXPERIMENTAL SECTION

Chemicals and apparatus

Reagent grade chemicals and solvents were purchased from Merck or Sigma-Aldrich. FT-IR spectra were recorded on FT-IR Magna 550 apparatus using the KBr plates. Powder

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Scheme 1. Synthesis of pyrimidines under reflux conditions using a nanocatalyst

X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Zr K α radiation ($\lambda = 1.5406 \text{ \AA}$). In order to study the size and morphology of the nano-NiZr₄(PO₄)₆ particles synthesised, FE-SEM images of the products were visualized by a HITACHI S4160 Field Emission Scanning Electron Microscope. The magnetic measurement of samples was performed by a vibrating sample magnetometer (VSM) (Kashan Kavir; Iran).

Preparation of nano NiZr₄(PO₄)₆

At first, 1 mmol of ZrOCl₂.8H₂O and 1 mmol of Ni(NO₃)₂.2H₂O were added in 15 mL of HO(CH₂)₂OH and sonicated at 30 W power to be completely dissolved. Afterward, 0.8 mL H₃PO₄ (85%), 4 mmol of NH₄Cl, and 1.4 mL of CH₃NH₂ 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 autogenously 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 several times. Subsequently product was dried at 50 °C for 5 h and calcinated at 700 °C for 2 h. Then, the solid was added in 20 mL of DMF and sonicated at 50 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-NiZr₄(PO₄)₆ ceramics.

General procedure for the preparation of 2,4-diamino-6-aryl-5-pyrimidinecarbonitrile (4a-h)

A mixture of benzaldehydes (1 mmol), malononitrile (1 mmol), guanidine hydrochloride (1 mmol), and nano-NiZr₄(PO₄)₆ (3 mg) were stirred in 10 mL ethanol under reflux condition. The reaction was monitored by TLC. After completion of the reaction, the solution was filtered and the heterogeneous catalyst was recovered. The solvent was evaporated and the solid obtained recrystallized from ethanol to afford the pyrimidines.

2,4-diamino-6-phenylpyrimidine-5-carbonitrile (4a): M. p. 236-238 °C; FT-IR (KBr): 3401, 3356 (NH₂), 2225 (CN) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.71-7.83 (4H, 2NH₂), 7.91-7.99 (3H, m, ArH), 8.32-8.38 (2H, m, ArH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 79.08, 117.84, 128.02, 128.04, 130.12, 137.04, 162.88, 164.92, 169.30; Analysis for C₁₁H₉N₅: calcd. C 62.55, H 4.29, N 33.16; found C 62.45, H 4.24, N 33.12.

2,4-diamino-6-(4-chlorophenyl)pyrimidine-5-carbonitrile (4b): M. p. 266-268 °C; FT-IR (KBr): 3436, 3165 (NH₂), 2194 (CN), 1628, 1695, 1523 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 7.64-7.69 (4H, 2 NH₂), 7.98-8.01 (2H, m, ArH), 8.45 (2H, m, ArH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 76.36, 118.25, 128.74, 130.46, 135.52, 136.30, 163.38, 165.47, 168.65; Analysis for C₁₁H₈ClN₅: calcd. C 53.78, H 3.28, N 28.51; found C 53.68, H 3.22, N 28.42.

RESULTS AND DISCUSSION

The XRD patterns of nano-NiZr₄(PO₄)₆ nanoparticles are shown in Fig. 1. The pattern agrees well with the reported pattern for nano-NiZr₄(PO₄)₆ nanoparticles (JCPDS No. 45-0013). The morphology and particle size of nano-NiZr₄(PO₄)₆ were studied by scanning electron microscopy (SEM) as shown in Fig. 2. The SEM images show particles with diameters in the range of nanometers.

The elemental compositions of the nanocatalyst were investigated by energy dispersive spectroscopy (EDS). EDS confirmed the presence of Ni, Zr, P and O in the compound (Fig. 3).

The magnetic properties of nano-NiZr₄(PO₄)₆ were determined using a vibrating sample magnetometer (VSM) (Fig. 4). The amount of saturation-magnetization for nano-NiZr₄(PO₄)₆ is ~ 0.03 emug⁻¹.

In order to determine the size distribution of nanoparticles, DLS (dynamic light scattering) graph of the nanoparticles are shown in Fig. 5. This size distribution is centered at a value of 138.2 nm.

Fig. 6 displays a FT-IR spectrum of nano-

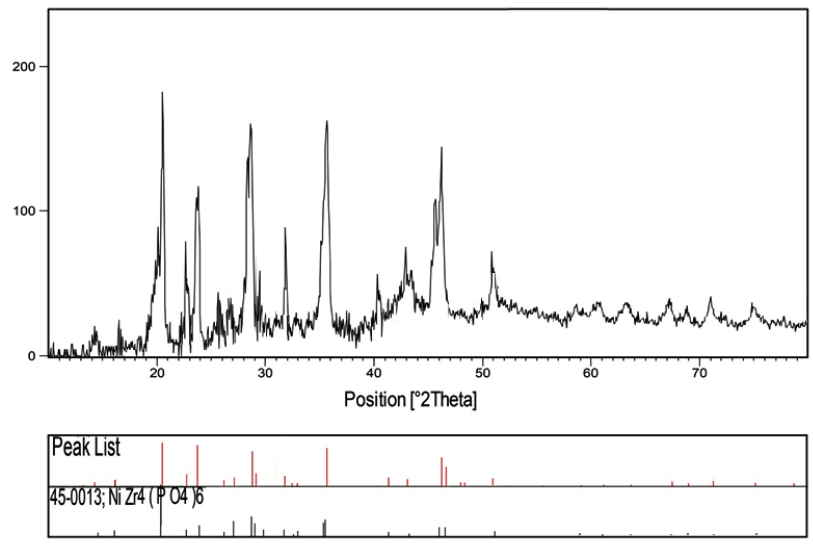


Fig. 1. XRD pattern of nano-NiZr₄(PO₄)₆

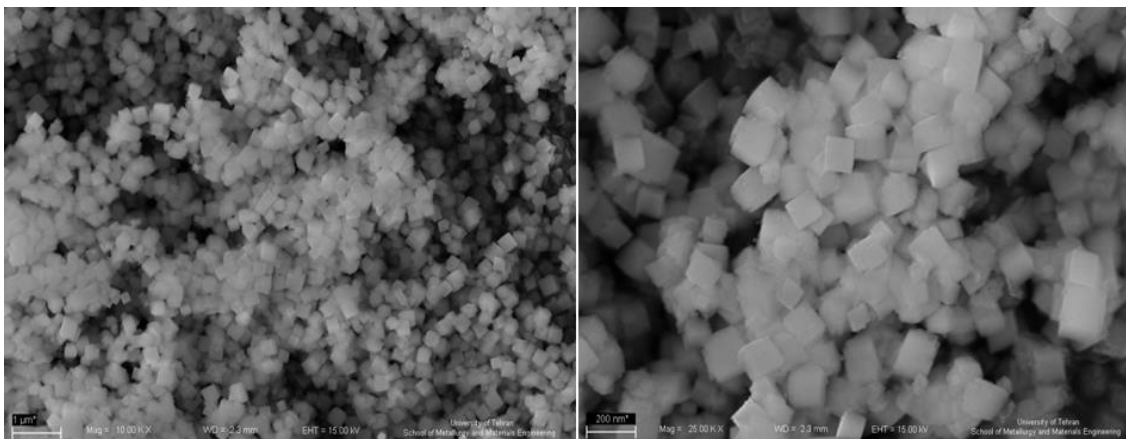


Fig .2. FE-SEM images of nano-NiZr₄(PO₄)₆

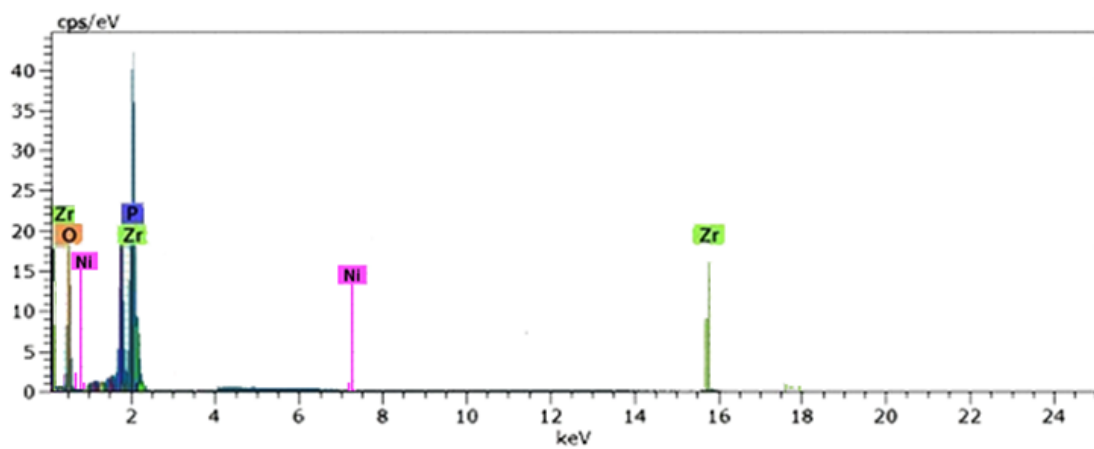


Fig. 3. EDS of nano-NiZr₄(PO₄)₆

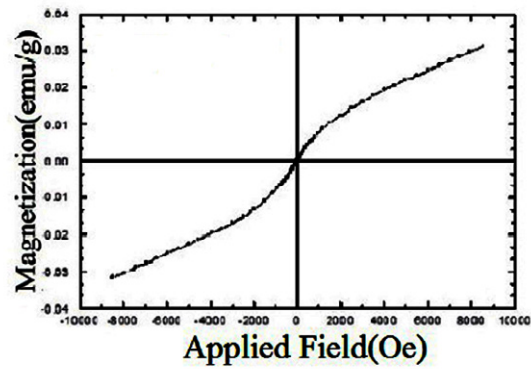


Fig. 4. The VSM curve of nano-NiZr₄(PO₄)₆

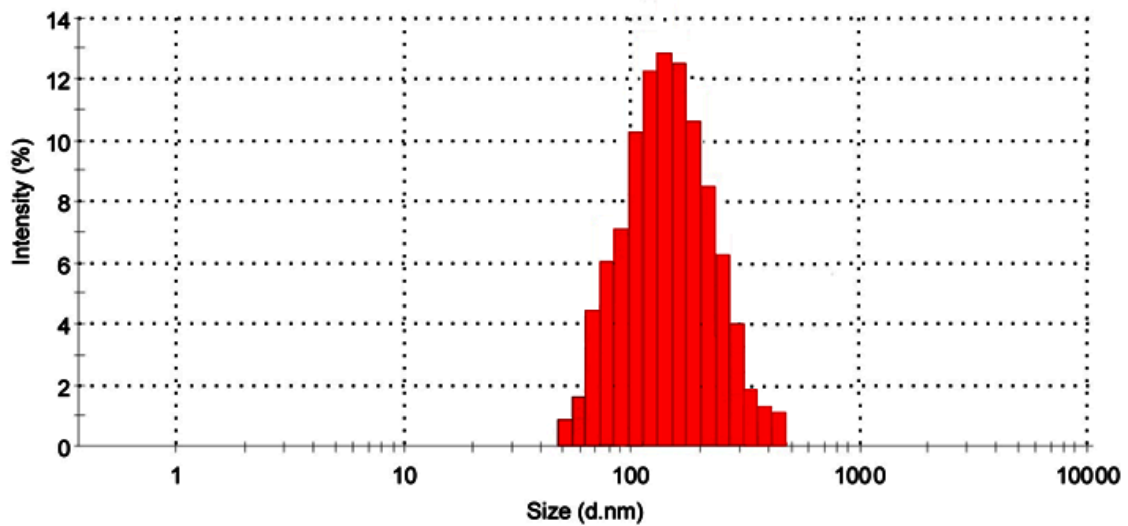


Fig. 5. DLS of nano-NiZr₄(PO₄)₆

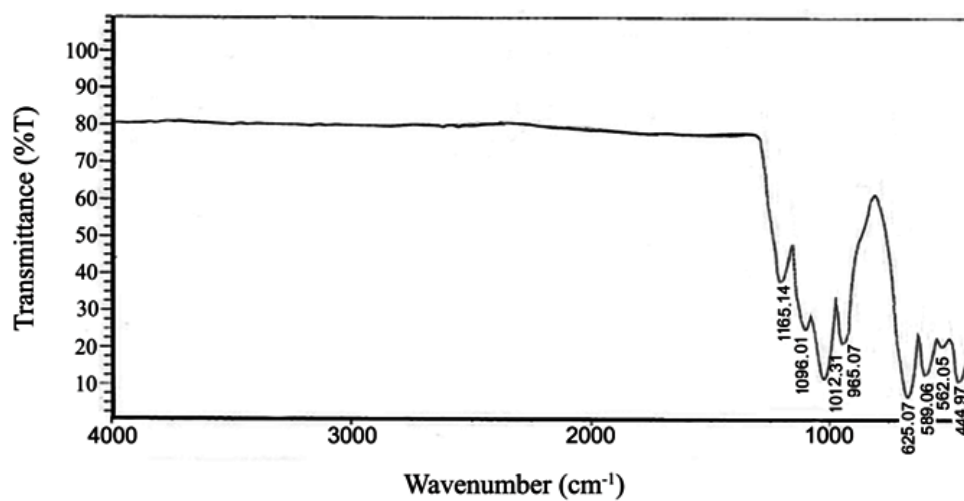


Fig. 6. FT-IR spectrum of nano-NiZr₄(PO₄)₆

Table 1. Synthesis of 2,4-diamino-6-phenylpyrimidine-5-carbonitrile (4a) under different conditions ^a

Entry	Solvent (reflux)	Catalyst (amount)	Time (min)	Yield% ^b
1	EtOH	No catalyst	400	<10
2	EtOH	Na ₂ CO ₃ (5 mol%)	300	25
3	EtOH	Et ₃ N (10 mol%)	300	38
4	EtOH	nano-NiO (5 mg)	200	48
5	EtOH	nano-ZrO ₂ (5 mg)	150	54
6	H ₂ O	nano-NiZr ₄ (PO ₄) ₆ (4 mg)	100	58
7	DMF	nano-NiZr ₄ (PO ₄) ₆ (4 mg)	80	64
8	CH ₃ CN	nano-NiZr ₄ (PO ₄) ₆ (4 mg)	70	80
9	CH ₃ OH	nano-NiZr ₄ (PO ₄) ₆ (4 mg)	60	85
10	EtOH	nano-NiZr ₄ (PO ₄) ₆ (2 mg)	60	88
11	EtOH	nano-NiZr ₄ (PO ₄) ₆ (3 mg)	60	92
12	EtOH	nano-NiZr ₄ (PO ₄) ₆ (4 mg)	60	92

^abenzaldehyde (1 mmol), malononitrile (1 mmol), guanidine hydrochloride (1mmol)^b Isolated yield;Table 2. Synthesis of pyrimidines using nano-NiZr₄(PO₄)₆ (3 mg)

Entry	Product	Ar	Time (min)	Yield ^a (%)
1	4a	C ₆ H ₅	60	92
2	4b	4-Cl-C ₆ H ₄	50	95
3	4c	4-Br-C ₆ H ₄	50	95
4	4d	4-OMe-C ₆ H ₄	80	84
5	4e	4-Me-C ₆ H ₄	80	85
6	4f	2,6-di-Cl-C ₆ H ₄	50	95
7	4g	2-Cl-C ₆ H ₄	50	93
8	4h	3-Me-C ₆ H ₄	80	89

^a Isolated yield;

NiZr₄(PO₄)₆. The bands at 1012, 1096, and 1165 cm⁻¹ correspond to asymmetric stretching P–O vibrations in PO₄ tetrahedron (ν₃); the band at 965 cm⁻¹ is due to symmetric stretching vibrations (ν₁). Three bands of asymmetric bending vibrations (ν₄) occur at 562, 589, and 625 cm⁻¹. The symmetric bending vibration (ν₂) is responsible for the absorption band at ~445 cm⁻¹ [21,22].

Initially, we focused on evaluation of diverse catalysts in the reaction of benzaldehyde, malononitrile, guanidine hydrochloride as a pattern reaction. Yields were determined by Na₂CO₃, Et₃N, nano-NiO, nano-ZrO₂, and nano-NiZr₄(PO₄)₆ (Table 1). The best results were gained in EtOH and we found the convincing results for the synthesis of pyrimidines in the presence of nano-NiZr₄(PO₄)₆ (3 mg) under reflux conditions. The use of polar solvents with moderate dielectric constant favours

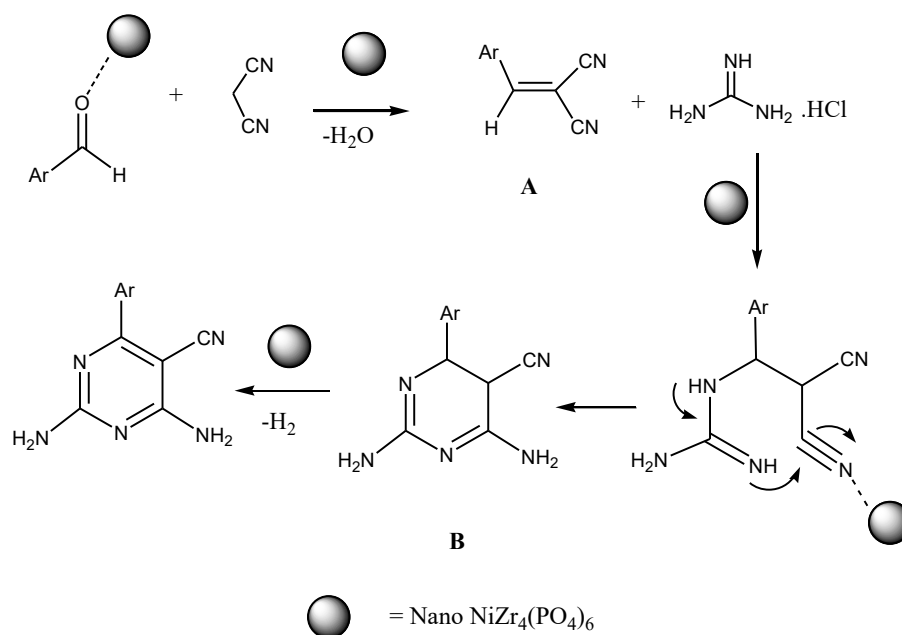
the condensation reactions. A series of aromatic aldehydes were studied under optimum conditions (Table 2). The results were good in yields using aromatic aldehydes, either bearing electron-withdrawing substituents or electron-donating substituents.

To compare the efficiency of nano-NiZr₄(PO₄)₆ with the reported catalysts for the synthesis of pyrimidines, we have tabulated the results in Table 3. As Table 3 indicates, nano-NiZr₄(PO₄)₆ is superior with respect to the reported catalysts in terms of reaction time, yield and conditions. Atom economy, reusable catalyst, low catalyst loading, applicability to a wide range of substrates and high yields of products are some of the notable features of this protocol.

The reusability of the nano NiZr₄(PO₄)₆ was examined for the model reaction and it was found that

Table 3. Comparison of catalytic activity of nano-NiZr₄(PO₄)₆ with other reported catalysts

Entry	catalyst	Time (min)	Yield, ^a %	[Ref]
1	Sodium acetate (20 mol%)	300	78	[9]
2	Potassium carbonate (10 mol%)	180	75	[14]
3	Sodium hydroxide (20 mol%)	60	88	[11]
4	nano-NiZr ₄ (PO ₄) ₆ (3 mg)	60	92	This work

^a Isolated yieldScheme 2. Possible mechanism for the synthesis of pyrimidines using nano-NiZr₄(PO₄)₆

product yields decreased to a small extent on each reuse (run 1, 92%; run 2, 92%; run 3, 91%; run 4, 91%; run 5, 90%, run 6, 90%). After completion of the reaction, the solution was filtered and the heterogeneous catalyst was recovered. The nanoparticles were then washed four times with dichloromethane and dried at room temperature for 24 h.

A plausible mechanism for the preparation of pyrimidines using nano-NiZr₄(PO₄)₆ is indicated in Scheme 2. Firstly, the reaction occurs by formation of the cyano olefin **A** from the condensation of malononitrile and aryl aldehyde. The second step is followed by Michael addition, cycloaddition, isomerization, and aromatization to afford the pyrimidines. Nano-NiZr₄(PO₄)₆ activate the C=O and C≡N groups for better reaction with nucleophiles. Unit cell representation of crystal structure of MZr₄(PO₄)₆ has been reported in the literature [23-24].

CONCLUSION

We have reported an efficient method for the synthesis of pyrimidines using nano-NiZr₄(PO₄)₆ as a robust and retrievable heterogeneous catalyst under reflux conditions in ethanol. The catalyst has been characterized by XRD, SEM, EDS, VSM, DLS and FT-IR. The advantages of this method include the reusability of the catalyst, low catalyst loading, high to excellent product yields, short reaction times and easy separation of products.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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