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# $ZrP_2O_7$ NPs: A recyclable, efficient heterogeneous catalyst for the synthesis of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives *via* a multi-component reaction

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ABSTRACT

$ZrP_2O_7$ nanoparticles (NPs) as an efficient catalyst have been used for the preparation of 1,6-diamino-2- oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives *via* one-pot coupling of hydrazine hydrate, ethyl cyanoacetate, malononitrile and aromatic aldehydes under reflux conditions in ethanol. Using this method we obtained low reaction times, easy isolation of the targeted molecules, excellent yields.

***Keywords**: $ZrP_2O_7$ nanoparticles; Multi-component; N-amino-2-pyridones; One-pot; 1,2-Dihydropyridines.*

## 1. Introduction

Syntheses of heterocyclic compounds have become a significant area of research in organic chemistry. The improvement of new efficient methods to synthesis N-heterocycles with structural variety is one major class of modern synthetic organic chemists [1-3]. Among a large diversity of heterocyclic compounds, 2-pyridone derivatives are valuable building blocks in natural products synthesis and pharmaceuticals [4]. The synthesis of 2-pyridone is an interesting challenge because compounds with these scaffolds were reported to possess a multiplicity of pharmacological properties such as antibacterial [5], antifungal [6], antitumor [7-8], served as cardiotonic agents [9], psychotherapeutic agents [10], and potential HIC-1 specific transcriptase inhibitors [11] activities. Furthermore, 3,5-dicyanopyridine derivatives demonstrated remarkable anticancer activity against most of the tested subpanel tumor cell lines [12]. Synthesis of bioactive compounds should be facile, flexible, rapid and worthwhile in organic synthesis. Therefore, looking for efficient and concise methods for the synthesis of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydro pyridine-3,5-dicarbonitrile derivatives is hot topic of organic chemistry.

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Multi-component reactions have become increasingly popular as tools for the preparation of heterocyclic compounds. Multi-component reactions (MCRs) are very flexible, atom economic in nature, convergent, simple and are usually considered for the development of environmentally benign synthetic methods [13-18]. Thus, multi-component reactions (MCRs) play considerable roles in the organic and medicinal synthesis.

Heterogeneous catalysts have been proven to be effective for a large number of organic reactions. They decrease reaction times, impart greater selectivity and they can be easily recovered from the reaction mixture by simple filtration [19-24]. Nanoparticles as heterogeneous catalysts have received considerable attraction in organic reactions [25-26]. Zirconium pyrophosphate ($ZrP_2O_7$) is one of the greatly studied materials due to their useful contribution in various fields of applications. Pyrophosphate compounds, which contain zirconium, can reveal intensive luminescence at room temperature [27].

A few catalysts such as magnesium oxide (MgO) as a highly effective heterogeneous base catalyst, and by using bismuth (III) nitrate pentahydrate as an effective Lewis acid catalyst [28] and piperidine [29] have been used for synthesis of *N*-amino-2-pyridones. These procedures used 2-cyanoacetohydrazide as starting materials for the synthesis of *N*-amino-2-pyridones.

We report herein the synthesis of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives using a four component one pot coupling of hydrazine hydrate, ethyl cyanoacetate, malononitrile and aromatic aldehydes under reflux conditions in ethanol in the presence of $ZrP_2O_7$ nanoparticles (Scheme 1).

## 2. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. The reaction was monitored by TLC using 0.2 mm Merck silica gel 60 F254 pre-coated plates, which were visualized with UV light. Melting points were measured on an Electrothermal 9200 apparatus. The IR spectra were recorded on FT-IR Magna 550 apparatus using KBr discs. The $^1$HNMR and $^{13}$CNMR spectra were determined on a Bruker Avance DRX-400 MHz instrument using TMS as the internal standard. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Microscopic morphology of products was visualized by SEM (LEO 1455VP). Transmission electron microscopy (TEM) images were obtained on a Philips EM208 transmission electron microscope with an accelerating voltage of 100 kV. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ= 1.5406 Å).

### *2.1. Preparation of $ZrP_2O_7$ nanoparticles*

$ZrP_2O_7$ nanoparticle was prepared according to the procedure reported in the literature [30]. The catalyst was prepared *via* sonochemical method (worked at 20 kHz frequency and 80 W powers). $ZrOCl_2$ 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 drop wise in 20 min and the mixture was sonicated until the precipitation of solids was finished. 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.

### *2.2. General procedure for the preparation of N-Amino-2-pyridone derivatives:*

A mixture of hydrazine hydrate **1** (2 mmol), ethyl cyanoacetate **2** (2 mmol), malononitrile **3** (2 mmol), aromatic aldehydes **4** (2 mmol) and 8 mol% of $ZrP_2O_7$ NPs in ethanol (5 mL) was refluxed with stirring for the specific time (Table 2). The reaction was monitored by TLC. After cooling, the reaction mixture was dissolved in acetone and the mixture stirred for 2 min. The suspended solution was filtered and the heterogeneous catalyst was recovered. The acetone was evaporated and the solid separated out was filtered and recrystallized with ethanol to get pure product. The structures of the products were fully established on the basis of their $^1$H NMR, $^{13}$C NMR and FT-IR spectra.

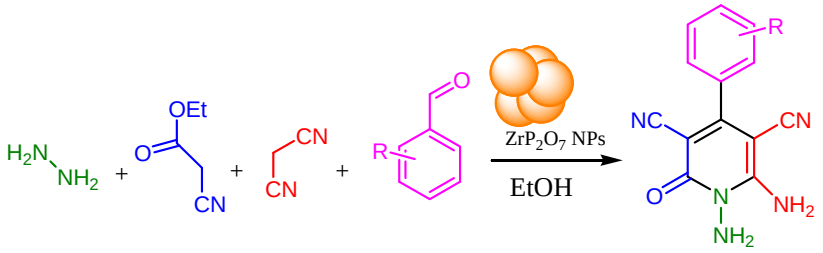
*Selected spectral data*

*1,6- Diamino-4- (4-methylphenyl)-2- oxo-1,2- dihydro pyridine-3,5-dicarbonitrile (**5a**):*

White crystals. m.p.: 238-240 °C, IR (KBr): $\bar{\nu}$ = 3402, 3452 ($NH_2$), 3304, 3334 ($NH_2$), 2217, 2220 (CN), 1640 (C=O), 1602 (C=C) cm$^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 2.27 (s, 3H, $CH_3$), 5.64 (s, 2H, $NH_2$), 7.32 (d, 2H, *J*= 8Hz, $CH_{Ar}$), 7.35 (d, 2H, *J*= 8Hz, $CH_{Ar}$), 8.47 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100MHz, DMSO-$d_6$): δ= 159.49, 159.03, 156.20, 140.55, 131.14, 128.43, 127.05, 116.12, 115.41, 86.77, 74.33, 20.99 ppm. Anal. Calcd. for $C_{14}H_{11}N_5O$: C 63.39, H 4.18, N 26.40; Found: C 63.14, H 4.29, N 26.25, MS (EI): *m/z*= 265, 228, 157, 126, 63, 50.

*1,6- Diamino-4- (4-chlorophenyl)-2- oxo-1,2- dihydro pyridine-3,5-dicarbonitrile (**5b**):*

White crystals. m.p.= 243 °C-245 °C, IR (KBr): $\bar{\nu}$ = 3392, 3416 ($NH_2$), 3294, 3306 ($NH_2$), 2215 (CN), 1670 (C=O), 1608 (C=C) cm$^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 5.66 (s, 2H, $NH_2$), 7.51 (d, 2H, *J* = 8Hz, $CH_{Ar}$), 7.61 (d, 2H, *J* = 8Hz, $CH_{Ar}$), 8.53 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100MHz, DMSO-$d_6$): δ= 159.20, 158.51, 156.63, 135.10, 133.23, 130.11, 128.73, 116.52, 115.31, 86.64, 74.64 ppm. Anal. Calcd. for $C_{13}H_8N_5OCl$: C 54.65, H 2.82, N 24.51; Found: C 54.31, H 2.93, N 24.22. MS (EI): *m/z*= 285 (is due to the $^{35}$Cl) and 287 (is due to the $^{37}$Cl), 241, 205, 161, 126, 75, 43.




1 2 3 4 5

**Scheme 1**. Synthesis of *N*-amino-2-pyridone derivatives in the presence of $ZrP_2O_7$ NPs.

*1,6- Diamino-4- (4-nitrophenyl)-2- oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (**5c**):*

Yellow crystals. m.p.= 226-228 °C, IR (KBr): $\bar{\nu}$ = 3284, 3392 ($NH_2$), 3314, 3324 ($NH_2$), 2219, 2224 (CN), 1672 (C=O), 1628 (C=C) $cm^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 5.69 (s, 2H, $NH_2$), 7.79 (d, 2H, *J*= 8.8Hz, $CH_{Ar}$), 8.37 (d, 2H, *J*= 8.8Hz, $CH_{Ar}$), 8.85 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): δ= 158.73, 157.34, 156.62, 148.77, 140.94, 129.36, 123.99, 115.70, 115.10, 86.12, 74.21 ppm. Anal. Calcd. for $C_{13}H_8N_6O_3$: C 52.71, H 2.72, N 28.37; Found: C 52.69, H 2.81, N 28.32. MS (EI): *m/z*= 296, 268, 196, 126, 98, 50.

*1,6- Diamino-4- (4-methoxyphenyl)-2- oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (**5d**):*

Cream crystals. m.p.= 222-224 °C, IR (KBr, ): $\bar{\nu}$ = 3456, 3398 ($NH_2$), 3270, 3222 ($NH_2$), 2215, 2124 (CN), 1662 (C=O), 1640 (C=C) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ= 3.82 (s, 3H, $OCH_3$), 5.63 (s, 2H, $NH_2$), 7.07 (d, 2H, *J*= 7.6Hz, $CH_{Ar}$), 7.43 (d, 2H, *J*= 7.6Hz, $CH_{Ar}$), 8.42 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): δ= 160.08, 159.23, 159.29, 156.64, 129.87, 126.46, 116.69, 115.77, 113.93, 87.24, 74.26, 56.22 ppm. Anal. Calcd. for $C_{14}H_{11}N_5O_2$: C 59.78, H 3.94, N 24.89; Found: C 59.72, H 3.98, N 24.79. MS (EI): *m/z*= 281, 218, 161, 113, 75, 63.

*1,6- Diamino-4- (2-fluorophenyl)-2- oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (**5e**):*

Brown crystals. m.p.= 249-251 °C, IR (KBr): $\bar{\nu}$ = 3446, 3404 ($NH_2$), 3244, 3284 ($NH_2$), 2219 (CN), 1650 (C=O), 1632 (C=C) $cm^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 5.66 (s, 2H, $NH_2$), 7.38 (d, 1H, *J*= 7.2 Hz, $CH_{Ar}$), 7.43 (d, 1H, *J*= 7.2 Hz, $CH_{Ar}$), 7.49 (t, 1H, *J*= 8.4 Hz, $CH_{Ar}$), 7.58 (t, 1H, *J*= 7.2 Hz, $CH_{Ar}$), 8.61 (s, 2H, $NH_2$) ppm. $^{13}$CNMR(100 MHz, DMSO-$d_6$): δ= 159.48, 157.04, 154.53, 133.12, 130.74, 125.42, 122.80, 116.72, 116.52, 116.30, 115.42, 87.77, 75.44 ppm. Anal. Calcd. for $C_{13}H_8N_5OF$: C 57.99, H 2.99, N 26.01; Found: C 57.86, H 3.05, N 25.98, MS (EI): *m/z*= 269, 223, 160, 143, 131, 63,43.

*1,6- Diamino-4- (2-nitrophenyl)-2- oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (**5f**):*

Yellow crystals. m.p.= 234-236 °C, IR (KBr): $\bar{\nu}$ = 3446, 3343 ($NH_2$), 3343, 3280 ($NH_2$), 2219 (CN), 1660 (C=O), 1592 (C=C) $cm^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 5.68 (s, 2H, $NH_2$), 7.67 (m, 4H, $CH_{Ar}$), 8.94 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): δ= 160.20, 159.53, 157.63, 135.10, 134.23, 131.13, 130.10, 128.83, 116.54, 116.31, 115.20, 86.64, 74.94 ppm. Anal. Calcd. for $C_{13}H_8N_6O_3$: C 52.71, H 2.72, N 28.37; Found: C 52.76, H 2.68, N 28.28, MS (EI): *m/z*= 296, 281, 252, 216, 110, 54.

*1,6- Diamino-4- (4-Bromophenyl)-2- oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (**5g**):*

Brown crystals. m.p.= 234-236 °C, IR (KBr): $\bar{\nu}$ = 3382, 3416 ($NH_2$), 3290, 3308 ($NH_2$), 2216 (CN), 1668 (C=O), 1608 (C=C) $cm^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 5.64 (s, 2H, $NH_2$), 7.50-8.49 (m, 4H, $CH_{Ar}$), 8.52 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): δ= 159.10, 158.40, 156.59, 135.20, 133.22, 130.01, 128.73, 116.52, 115.28, 86.64, 74.3 ppm. Anal. Calcd. for $C_{13}H_8N_5OBr$: C 47.29, H 2.44, N 21.21; Found: C 47.19, H 2.38, N 21.29, MS (EI): *m/z*= 329 (is due to $^{79}$Br) and 331 (is due to $^{81}$Br), 285, 233, 205, 165, 126, 75, 43.

*1,6-Diamino-4-phenyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (5h):*

White crystals. m.p.= 237-239 °C, IR (KBr): $\bar{\nu}$ = 3446, 3350 ($NH_2$), 3246, 3317 ($NH_2$), 2220 (CN), 1642 (C=O), 1600 (C=C) $cm^{-1}$. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 5.66 (s, 2H, $NH_2$), 7.48-7.56 (m, 5H, $CH_{Ar}$), 8.47 (s, 2H, $NH_2$) ppm. $^{13}$CNMR (100 MHz, DMSO-$d_6$): δ= 159.5, 159.1, 156.5, 134.6, 130.1, 128.5, 127.9, 116.3, 115.3, 86.4, 74.2 ppm. Anal. Calcd. for $C_{13}H_9N_5O$: C 62.15, H 3.61, N 27.87; Found: C 62.19, H 3.52, N 27.90, MS (EI): *m/z*= 251, 239, 160, 121, 75, 43.

## 3. Results and Discussion

The XRD pattern of the $ZrP_2O_7$ nanoparticles was shown in Fig. 1. The crystallite size diameter (D) of the $ZrP_2O_7$ nanoparticles has been calculated by Debye–Scherrer equation. Crystallite size of $ZrP_2O_7$ has been found to be 11 nm. The pattern agrees well with the reported pattern for $ZrP_2O_7$ nanoparticles (JCPDS No.49-1079). The SEM image shows particles with diameters in the range of nanometers (Fig. 2).

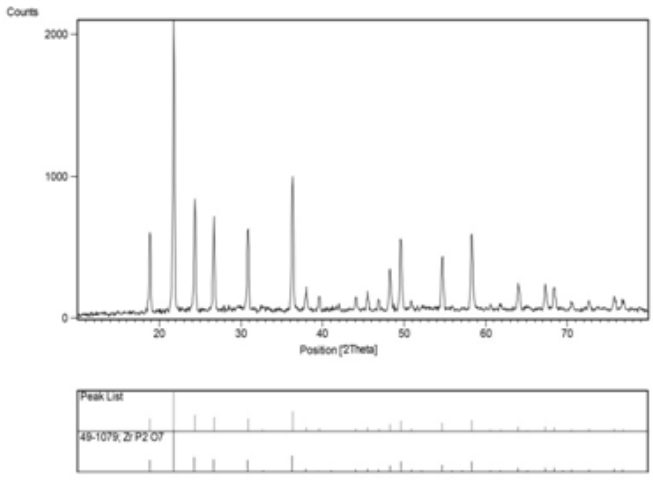



**Fig 1.** XRD of $ZrP_2O_7$ NPs.

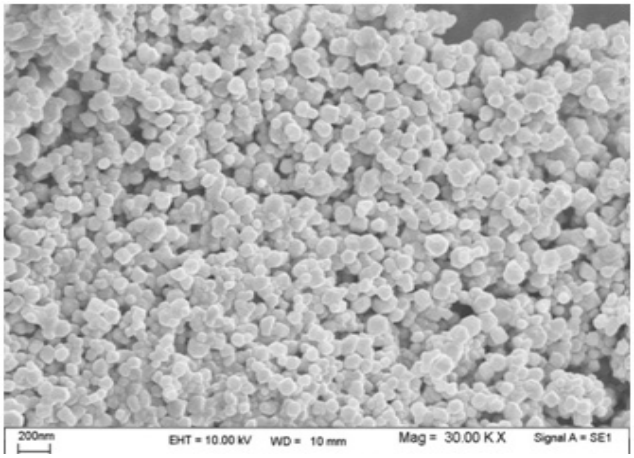



**Fig 2.** SEM images of $ZrP_2O_7$ NPs.

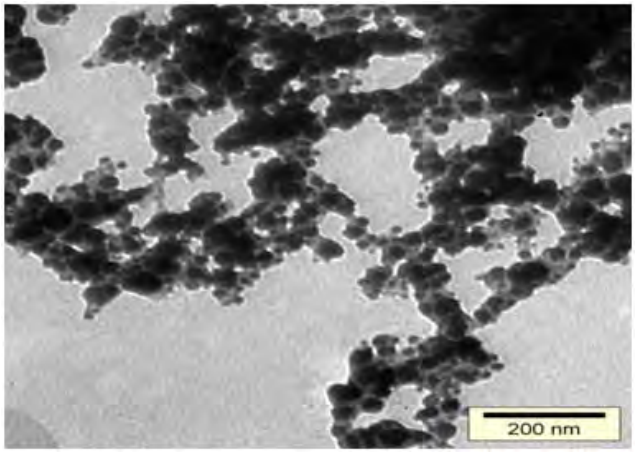



**Fig 3.** TEM of $ZrP_2O_7$ NPs.

The increased surface area due to small particle size increased reactivity. This factor is responsible for the accessibility of the substrate molecules on the catalyst surface.

The structural composition and characterization of the nano $ZrP_2O_7$ was further ascertained by TEM (Fig. 3).

Initially, we focused on systematic evaluation of different catalysts for the model reaction of 4-chlorobenzaldehyde, malononitrile, ethyl cyanoacetate and hydrazine under reflux conditions in ethanol (Table 1). The ZrP2O7 nanoparticle catalyst shows a crucial role in the achiever of the response. In the absence of $ZrP_2O_7$ nanoparticles, the product was obtained in very low yield after prolonged reaction time. When 4, 8 and 12 mol % of catalyst were used, the yields were 82 %, 85% and 85% respectively. Therefore, 8 mol % of $ZrP_2O_7$ NPs were expedient and excessive amount of $ZrP_2O_7$ nanoparticles did not increase the yields significantly. 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. So, we were encouraged to use $ZrP_2O_7$ NPs in the following optimization of the reaction conditions. Under the optimized set of controlled under reflux conditions in ethanol, a number of aromatic aldehydes were allowed to undergo multicomponent reaction with malononitrile, hydrazine hydrate and ethyl cyanoacetate in the presence of $ZrP_2O_7$ nanoparticles generating *N*-amino-2-pyridone derivatives in good yields (Table 2).

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

| Entry | Catalyst | Mol% | Time (min) | Yield%[b] |
|---|---|---|---|---|
| 1 | $SnCl_2$ | 10 | 85 | 30 |
| 2 | Nano $ZrO_2$ | 10 | 80 | 48 |
| 3 | NiO | 10 | 100 | 37 |
| 4 | $KZr_2(PO_4)_3$ | 10 | 60 | 55 |
| 5 | $ZrOCl_2.8H_2O$ | 8 | 90 | 40 |
| 6 | MgO | 20 | 60 | 78 [28] |
| 7 | $H_2SO_4$ | 3 | 90 | 35 |
| 8 | $H_3PO_4$ | 3 | 100 | 30 |
| 9 | $Na_3PO_4$ | 7 | 120 | 26 |
| 10 | $ZrP_2O_7$ NPs | 4 | 40 | 82 |
| 11 | $ZrP_2O_7$ NPs | 8 | 40 | 85 |
| 12 | $ZrP_2O_7$ NPs | 12 | 40 | 85 |

[a]Reaction conditions: Hydrazine hydrate (2 mmol), ethyl cyanoacetate (2 mmol), malononitrile (2 mmol), 4-Chlorobenzaldehyde (2 mmol) under reflux conditions in ethanol.

[b]Isolated yield.

**Table 2.** Synthesis of *N*-amino-2-pyridones using $ZrP_2O_7$ NPs under reflux conditions in ethanol.[a]

| Entry | Aldehydes | Product | Time (min) | Yield (%)[b] | m.p. (°C) | Ref. |
|---|---|---|---|---|---|---|
| 1 | 4-Me-$C_6H_4$ | 5a | 25 | 85 | 238-240 | [28] |
| 2 | 4-Cl-$C_6H_4$ | 5b | 22 | 91 | 242-243 | [28] |
| 3 | 4-$NO_2$-$C_6H_4$ | 5c | 22 | 91 | 226-228 | [28] |
| 4 | 4-OMe-$C_6H_4$ | 5d | 35 | 84 | 222-224 | [28] |
| 5 | 2-F-$C_6H_4$ | 5e | 24 | 86 | 249-251 | - |
| 6 | 2-$NO_2$-$C_6H_4$ | 5f | 20 | 85 | 234-236 | - |
| 7 | 4-Br-$C_6H_4$ | 5g | 22 | 92 | 235-237 | - |
| 8 | $C_6H_5$ | 5h | 23 | 83 | 237-238 | [28] |

[a]Reaction conditions: Hydrazine hydrate (2 mmol), ethyl cyanoacetate (2 mmol), malononitrile (2 mmol), 4-Chlorobenzaldehyde (2 mmol) under reflux conditions in ethanol with $ZrP_2O_7$ NPs.
[b]Isolated yield.

The results were excellent in yields using aromatic aldehydes, either bearing electron-withdrawing or electron-donating substituents under the same reaction condition. The method tolerates key functional groups such as halides, nitro and methoxy (Table 2, entries 2,3,4,5, 6, 7, …), and besides the para and meta positions on the aromatic ring of aldehydes.

In addition, we examined aliphatic aldehydes such as n-hexanal instead of benzaldehydes in the reaction, but we could not find significant amount of the title product from aliphatic aldehydes. The results showed that $ZrP_2O_7$ nanoparticles are a constant catalyst in reaction media and were used several times without significant loss of catalytic activity (Table 3). In the recycling procedure of $ZrP_2O_7$ NPs, after cooling, the reaction mixture was dissolved in acetone and the mixture stirred for 2 min. The solution was filtered and the heterogeneous catalyst was recovered. The recovered $ZrP_2O_7$ NPs was washed with ethanol and dried at 70◦C for 2 h.

## 4. Conclusions

In summary, we have developed the synthesis of N-amino-2-pyridone derivatives catalyzed by $ZrP_2O_7$ nanoparticles as the catalyst under reflux conditions in ethanol. These heterocyclic N-amino-2-pyridones compounds will provide promising candidates for chemical biology and drug discovery. Present method tolerates most of the substrates, and the catalyst can be recycled and reused at least five times without significant loss of activity. The advantages of this method are the use of an efficient catalyst, low reaction times, easy separation of products, excellent yields and the use of ethanol as a solvent that is considered to be relatively environmentally benign.

**Table 3.** Recycling of $ZrP_2O_7$ nanoparticles as catalyst.

| Run | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Yield (%)[a] | 97 | 96 | 93 | 89 | 85 |

[a]Isolated yield.

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