An efficient method for the synthesis of *N*-amino-2-pyridones using reusable catalyst ZnO nanoparticles

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A concise and highly efficient protocol for the synthesis of *N*-amino-2-pyridones has been developed by a four-component coupling of hydrazine hydrate, ethyl cyanoacetate, malononitrile and aromatic aldehydes in the presence of ZnO nanoparticles under mild conditions. The key advantages of this process are using an inexpensive and reusable catalyst, easy work-up and excellent yields.

Keywords: *N*-amino-2-pyridones, ZnO nanoparticles, one-pot, four-component reactions, 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile

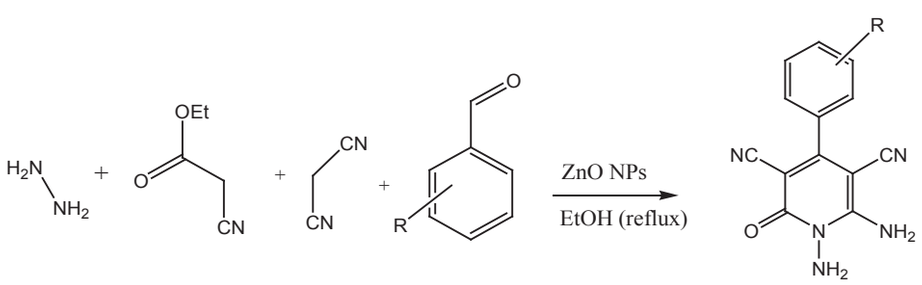
N-Amino-2-pyridones are an important class of heterocyclic compounds with a wide range of pronounced biological properties. Compounds containing the 2-pyridone moiety are utilised as antibacterial,[1] antifungal,[2] antitumor,[3,4] cardiotonic agents,[5] psychotherapeutic agents[6] and potential HIC-1 specific transcriptase inhibitors.[7] Among a large variety of *N*-amino-2-pyridone compounds, 3,5-Dicyano-1,2-dihydropyrid-2-ones have received much attention because of their presence in a broad spectrum of synthetic organic molecules with diverse biological and pharmacological activities.[8] 3,5-Dicyanopyridines contain an important privileged heterocyclic scaffold and have demonstrated significant anticancer activity.[9] Therefore, *N*-amino-2-pyridones serve as useful building blocks for the synthesis of complex and important organic molecules. Recently, fused heterobicyclic systems containing the 1,2,4-triazinopyridinone moiety have been synthesised by heterocyclisation of *N*-amino-2-pyridones with different reagents. 1,2,4-Triazinopyridinones have antifungal properties.[10] Meanwhile, reactions of some active carbonyl compounds with 4-aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile derivatives have been documented in recent years.[11] Therefore, looking for efficient and simple methods for the synthesis of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives is considered very important. Multi-component reactions (MCRs) serve as an attractive and efficient strategy for the synthesis of heterocycles. Consequently, synthetic organic chemists worldwide have been paid much attention to the use of MCRs to synthesise a wide range of compounds.[12–18]

Nanoparticles are highly active due to their high surface-to-volume ratio. They decrease reaction times, impart greater selectivity and they can be easily recovered from reaction mixtures by simple filtration.[19,20] Among various nanoparticles, ZnO nanoparticles have received considerable attention because of their remarkable properties in diverse fields.[21] Recently, ZnO nanoparticles were used as a useful catalyst in many reactions including the synthesis of β-phosphonomalonates,[22] polyfunctionalised pyridines[23] and 2,3-disubstituted quinololin-4(1H)-ones[24] and to provide easy access to fully decorated 4H-pyran scaffolds.[25]

A few catalysts such as magnesium oxide (MgO) as a highly effective heterogeneous base catalyst, bismuth(III) nitrate pentahydrate as an effective Lewis acid catalyst[26] and piperidine[27] have been used for the synthesis of *N*-amino-2-pyridones. We report here the synthesis of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives using a four-component one-pot protocol under mild conditions in the presence of ZnO nanoparticles (Scheme 1).

Results and discussion

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. From the results, it is obvious that ZnO nanoparticles are the best catalyst among those examined in Table 1. When 4, 8 and 12 mol% of ZnO nanoparticles were used, the yields were 84%, 92% and 92% respectively (Table 1). Therefore, 8 mol% of ZnO NPs were convenient and further excess did not increase the yields significantly. The reusability of the nano-ZnO catalyst was examined and it was found that product yields decreased to a small extent on each reuse (run 1, 92%; run 2, 90%; run 3, 89%; run 4, 87%; run 5, 85%). In



1 **2** **3** **4a–h** **5a–h**

Scheme 1

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Table 1 Optimisation of reaction conditions using different catalysts[a]

Entry	Catalyst/mol%	Time/min	Yield/%[b]
1	Nano-SiO_2 (10)	80	15
2	Al_2O_3 (10)	80	12
3	NiO (10)	100	37
4	Bulk ZnO (10)	60	55
5	ZnO NPs (4)	40	84
6	ZnO NPs (8)	40	92
7	ZnO NPs (12)	40	92

[a]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 ZnO NPs[a]

Product	Aldehyde (R)	Yield/%[b]
5a	4-Me	82
5b	4-Cl	92
5c	4-NO_2	92
5d	4-OMe	84
5e	2-F	88
5f	2-NO_2	91
5g	4-Br	90
5h	H	91

[a]Hydrazine hydrate (2 mmol), ethyl cyanoacetate (2 mmol), malononitrile (2 mmol), aldehyde (2 mmol) under reflux conditions in ethanol with ZnO NPs.
[b]Isolated yield.

the recycling procedure of ZnO NPs, hot acetone was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by filtration. The nanoparticles were then washed three to four times with dichloromethane and methanol and dried at 150 °C for 10 h.

Utilising the optimal reaction conditions, we next examined a wide variety of aldehydes, yields were excellent using aromatic aldehydes, either bearing electron-withdrawing substituents or electron-donating substituents (Table 2).

We found that aromatic aldehydes gave the desired products, but the aliphatic aldehydes such as hexanal did not react significantly. In the case of hexanal, all starting materials in the reaction were almost intact with formation of only a trace of product without any side-products after 220 min.

All products were characterised by IR, ^{1}H NMR and ^{13}C NMR.

Experimental

The products were isolated and characterised by physical and spectroscopic data. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer in the presence of TMS as internal standard. The IR spectra were recorded on an FTIR Magna 550 apparatus using KBr plates. Melting points were determined on an Electrothermal 9200 apparatus, and are not corrected. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyser. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatised Cu Kαradiation (λ = 1.5406 Å). Microscopic morphology of products was visualised by SEM (LEO 1455VP). The mass spectra were recorded on a Joel D-30 instrument at an ionisation potential of 70 eV. The compositional analysis was done by energy dispersive X-ray analysis (EDAX, Kevex, Delta Class I).

Synthesis of ZnO nanoparticles

Zinc oxide nanoparticles were prepared according to the procedure reported by Shen et *al*.[28] In a typical procedure, zinc acetate (9.10 g, 0.05 mol) and oxalic acid (5.4 g, 0.06 mol) were combined by grinding in an agate mortar for 1 h at room temperature. Afterwards, the formed ZnC_2O_4. $2H_2O$ nanoparticles were calcined at 450 °C in oven for 30 min to produce ZnO nanoparticles under thermal decomposition conditions. (See also Electron Supplementary Information.)

Synthesis of N-amino-2-pyridones (**5a**–**h**)*; general procedure*

A mixture of hydrazine hydrate, **1** (0.100 g, 2.0 mmol), ethyl cyanoacetate, **2** (0.226 g, 2.0 mmol), malononitrile, **3** (0.132 g, 2.0 mmol), aromatic aldehydes, **4** (2.0 mmol) and 8 mol% of ZnO 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 recrystallised from 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 FTIR spectra.

1,6-Diamino-4-(4-methylphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5a**): White crystals; yield: 82%; m.p. 238–240 °C (lit.[26] 238 °C). IR (KBr): ν_{max} 3402, 3452 (NH_2), 3304, 3334 (NH_2), 2217, 2220 (CN), 1640 (C=O), 1602 (C=C) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 5.64 (s, 2H, NH_2), 7.32 (d, 2H, J = 8 Hz, CH_{Ar}), 7.35 (d, 2H, J = 8 Hz, CH_{Ar}), 8.48 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6):δ 21.0, 74.3, 86.8, 115.4, 116.1, 127.0, 128.4, 131.1, 140.5, 156.2, 159.0, 159.5, 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, 26.35%. MS (EI): (*m/z*): 265 [M$^+$].

1,6-Diamino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5b**): White crystals; yield: 92%; m.p. 243–245 °C (lit.[26] 242–243 °C). IR (KBr): ν_{max} 3392, 3416 (NH_2), 3294, 3306 (NH_2), 2215 (CN), 1670 (C=O), 1608 (C=C) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.66 (s, 2H, NH_2), 7.51 (d, 2H, J = 8 Hz, CH_{Ar}), 7.62 (d, 2H, J = 8 Hz, CH_{Ar}), 8.53 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.6, 86.6, 115.3, 116.5, 128.7, 130.1, 133.2, 135.1, 156.6, 158.5, 159.2 ppm. Anal. calcd for $C_{13}H_8N_5OCl$: C, 54.65; H, 2.82; N, 24.51; found: C 54.61; H, 2.93; N, 24.42%. MS (EI): (*m/z*):285 [M$^+$,^{35}Cl] and 287 [M$^+$, ^{37}Cl].

1,6-Diamino-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyri-dine-3,5-dicarbonitrile (**5c**): Yellow crystals; yield: 92%; m.p. 226–228 °C (lit.[26]226–228 °C). IR (KBr): ν_{max} 3284, 3392 (NH_2), 3314, 3324 (NH_2), 2219, 2224 (CN), 1672 (C=O), 1628 (C=C) cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.70 (s, 2H, NH_2), 7.80 (d, 2H, J = 8.8 Hz, CH_{Ar}), 8.38 (d, 2H, J = 8.8 Hz, CH_{Ar}), 8.85 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.2, 86.1, 115.1, 115.7, 124.0, 129.4, 140.9, 148.8, 156.6, 157.3, 158.7 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 [M$^+$].

1,6-Diamino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5d**): Cream crystals; yield: 84%; m.p. 222–224 °C (lit.[26]222–224 °C), IR (KBr): ν_{max} 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 = 7.6 Hz, CH_{Ar}), 7.43 (d, 2H, J = 7.6 Hz, CH_{Ar}), 8.43 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.2, 74.3, 87.2, 113.9, 115.7, 116.7, 126.5, 129.9, 156.6, 159.3, 159.5, 160.1 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 [M$^+$].

1,6-Diamino-4-(2-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5e**): Brown crystals; yield: 88%; m.p. 249–251 °C, IR (KBr): ν_{max} 3446, 3404 (NH_2), 3244, 3284 (NH_2), 2219 (CN), 1650 (C=O), 1632 (C=C) cm^{-1}, ^{1}H NMR (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}), 8.62 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 75.4, 87.7, 115.4, 116.3, 116.5, 116.7, 122.8, 125.4, 130.7, 133.1, 154.5, 157.0, 159.5, 161.5 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 [M^+].

1,6-Diamino-4-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5f**): Yellow crystals; yield: 91%; m.p. 234–236 °C, IR (KBr): ν_{max} 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}C NMR (100 MHz, DMSO-d_6): δ 74.9, 86.6, 115.2, 116.3, 123.5, 128.8, 130.1, 131.2, 134.2, 135.1, 157.6, 159.5, 160.2 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 [M^+].

1,6-Diamino-4-(4-bromophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5g**): Brown crystals; yield: 90%; m.p. 234–236 °C, IR (KBr): ν_{max} 3382, 3416 (NH_2), 3290, 3308 (NH_2), 2216 (CN), 1668 (C=O), 1608 (C=C) cm^{-1}, ^{1}H NMR (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}C NMR (100 MHz, DMSO-d_6): δ 74.3, 86.6, 115.3, 116.5, 128.7, 130.0, 133.2, 135.2, 156.6, 158.4, 159.1 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 [M^+, ^{79}Br] and 331 [M^+, ^{81}Br].

1,6-Diamino-4-phenyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**5h**): White crystals; yield: 91%; m.p. 237–239 °C, IR (KBr): ν_{max} 3446, 3350 (NH_2), 3246, 3317 (NH_2), 2220 (CN), 1642 (C=O), 1600 (C=C) cm^{-1}, ^{1}H NMR (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}C NMR (100 MHz, DMSO-d_6): δ 74.2, 86.4, 115.3, 1116.3, 127.9, 128.5, 130.1, 134.6, 156.5, 159.1, 159.5 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 [M^+].

Electronic Supplementary Information

Some characteristics of the ZnO nanoparticles are described in the ESI available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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