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Synthesis of 2,4-diamino-6-aryl-5-pyrimidinecarbonitrile promoted by amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles under conventional heating, microwave and ultrasound irradiations

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Abstract: Amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles have been used as an efficient catalyst for the preparation of 2,4-diamino-6-arylpyrimidine-5-carbonitrile derivatives by the one-pot reaction of aromatic aldehydes, malononitrile, and guanidine hydrochloride under conventional heating, microwave, and ultrasound irradiations. This method provides several advantages including mild reaction conditions, the reusability of the catalyst and low catalyst loading, and the use of microwave and ultrasonic irradiation as a valuable and powerful tool.

Keywords: $CoFe_2O_4$@SiO_2; heterogeneous catalyst; microwave; pyrimidine; ultrasound irradiation.

1 Introduction

Pyrimidines are one of the biologically substantial scaffolds due to their wide range of biological and pharmaceutical properties such as antihypertensive [1], antimicrobial [2, 3], antitumor [4], antimalarial [5], antioxidant [6], protein kinase inhibitors [7], and antagonists of GPR40 [8]. Therefore, the development of efficient methods for the synthesis of pyrimidines is of great interest. A number of methods have been developed for the synthesis of pyrimidines in the presence of catalysts such as sodium acetate [9], $Bi(NO_3)_3 \cdot 5H_2O$ [10], NaOH [11, 12], CuO microspheres [13], and K_2CO_3 [14]. Despite the availability of these methods, there remains enough scope for the use of an efficient and reusable catalyst with high catalytic activity for the preparation of pyrimidines. The completion of the reactions under conventional heating conditions requires several hours and the yields are low. The main concern for the improvement of high-throughput procedures is the rate of the applied reactions. In this regard, the application of microwave and ultrasound irradiations has been proven to be very beneficial. Microwave and ultrasound irradiations are used for a variety of organic syntheses due to short reaction times, easy workup, and excellent yields [15–18]. The practical rate acceleration upon microwave irradiation is owing to material-wave interactions leading to thermal and specific effects. The reaction is heated from the inside because the microwave energy is transferred immediately to the reagents. The solid catalysts absorb the microwave energy; consequently, they can serve as an internal heat source for the reactions [19, 20]. Ultrasound irradiation has been developed to hasten the chemical reactions proceeding through the formation, growth, and implosive collapse of bubbles in a liquid. Collapsing bubbles generate high temperatures and pressures [21, 22]. Compared with conventional heating, which creates thermal energy in the macro system, ultrasound irradiation is able to activate numerous reactions by the activation energy in microenvironments [23, 24]. In this study, we report the use of amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles as an efficient catalyst for the preparation of 2,4-diamino-6-arylpyrimidine-5-carbonitrile derivatives by the one-pot reaction of aromatic aldehydes, malononitrile, and guanidine hydrochloride under conventional heating, microwave, and ultrasound irradiations (Scheme 1).

2 Results and discussion

Initially, we focused on the systematic evaluation of different catalysts in the reaction of benzaldehyde, malononitrile, and guanidine hydrochloride as a model reaction. Yields were determined in the presence of Et_3N, Na_2CO_3, nano-CuI, nano-Fe_3O_4, nano-$CoFe_2O_4$, nano-$CoFe_2O_4$@SiO_2, and amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles, and the results are shown in Table 1. When the reaction was carried out using amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles as the catalyst, the products were obtained in good to high yields. In this research, microwave and ultrasound irradiations are used as green and complementary techniques for the preparation of pyrimidines. When the catalysis was performed under

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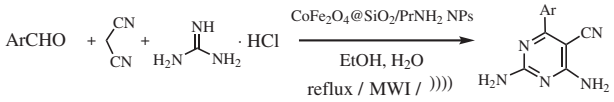


Scheme 1: Three-component reaction of aldehydes, malononitrile, and guanidine hydrochloride under conventional heating, microwave, and ultrasound irradiations.

microwave and ultrasound irradiations, the reaction rate increased considerably. The best results were obtained under ultrasound irradiation (40 W) in ethanol–water (3:7) and it was found that the reaction gave satisfying results in the presence of amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles at 8 mg, which gave excellent yields of products (Table 1). Longer reaction times were required under conventional heating and assistance of microwave and ultrasound irradiation improved the yields of the reactions and shortened the reaction times. The amount of used catalyst in the ultrasound method was lower than that on microwave irradiation because, in the latter, the catalyst acts as an internal heat source. The possible explanation for the positive association of irradiation is that the ultrasonic irradiation could increase the number of active cavitation bubbles and the size of the individual bubbles, both of which are predictable resulting in higher maximum collapse temperature and accelerated respective reaction. With the optimal conditions in hand, we turned to explore the efficacy of the catalyst using different aromatic aldehydes and the results are summarized in Table 2. Aromatic aldehydes with electron-withdrawing

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

Entry	Solvent	Conditions	Catalyst	Amount	Time (min)	Yield (%)[b]
1	H_2O	Reflux	Et_3N	10 mol%	300	38
2	EtOH	Reflux	Et_3N	10 mol%	300	30
3	EtOH	Reflux	Na_2CO_3	5 mol%	300	25
4	EtOH–H_2O (3:7)	Reflux	Nano-CuI	25 mg	180	48
5	EtOH–H_2O (3:7)	Reflux	Nano-Fe_3O_4	25 mg	180	51
6	EtOH–H_2O (3:7)	Reflux	Nano-$CoFe_2O_4$	25 mg	150	62
7	EtOH–H_2O (3:7)	Reflux	Nano-$CoFe_2O_4$@SiO_2	25 mg	150	64
8	EtOH–H_2O (3:7)	Reflux	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	20 mg	90	79
9	EtOH–H_2O (3:7)	Reflux	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	25 mg	90	82
10	EtOH–H_2O (3:7)	Reflux	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	30 mg	90	82
11	EtOH–H_2O (3:7)	MWI (400 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	10 mg	15	83
12	EtOH–H_2O (3:7)	MWI (400 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	15 mg	15	86
13	EtOH–H_2O (3:7)	MWI (400 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	20 mg	15	86
14	EtOH–H_2O (3:7)	MWI (300 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	20 mg	15	78
15	EtOH–H_2O (3:7)	MWI (500 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	20 mg	15	85
16	EtOH–H_2O (3:7)	US (40 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	6 mg	10	89
17	EtOH–H_2O (3:7)	US (40 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	8 mg	10	92
18	EtOH–H_2O (3:7)	US (40 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	10 mg	10	92
19	EtOH–H_2O (3:7)	US (30 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	10 mg	10	84
20	EtOH–H_2O (3:7)	US (50 W)	Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	10 mg	10	92

[a]Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and guanidine hydrochloride (1 mmol); [b]isolated yield.

Table 2: Synthesis of 5-pyrimidinecarbonitriles **4a–4h** using nano-$CoFe_2O_4$@SiO_2/$PrNH_2$.

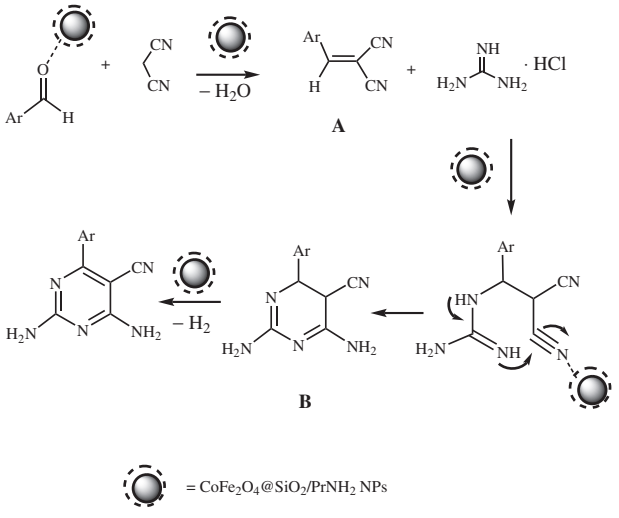
Entry	Product	Ar	Time (min) MWI[a]	Yield (%) MWI	Time (min) US[b]	Yield (%) US[c]	m. p. (°C)	m. p. (°C) [L]
1	**4a**	C_6H_5	15	86	10	92	237–239	237–239 [25, 26]
2	**4b**	4-Cl-C_6H_4	15	90	10	96	265–267	265–266 [25, 26]
3	**4c**	4-Br-C_6H_4	15	90	10	96	260–262	260–262 [25, 26]
4	**4d**	4-OMe-C_6H_4	20	81	15	87	236–238	236–238 [25, 26]
5	**4e**	4-Me-C_6H_4	20	83	15	89	255–257	255–257 [25, 26]
6	**4f**	2,6-Cl_2-C_6H_3	15	88	10	94	275–276	–
7	**4g**	2-Cl-C_6H_4	15	87	10	93	232–235	–
8	**4h**	3-Me-C_6H_4	15	84	10	90	225–227	–

[a]Microwave irradiations (400 W) and 15 mg of catalyst; [b]ultrasound irradiations (40 W), and 8 mg of catalyst; [c]isolated yield.

groups reacted faster than those with electron-donating groups. It has been observed that better yields are achieved with substrates having electron-withdrawing groups.

A mechanism for the reaction is outlined in Scheme 2. The reaction occurs through initial formation of the cyano olefin **A** from the condensation of malononitrile and aryl aldehyde, which is itself activated by the catalyst through hydrogen bonding. The second step is followed by Michael addition, cycloaddition, isomerization, and aromatization to afford the 5-pyrimidinecarbonitriles. The amino groups distributed on the surface of $CoFe_2O_4$@SiO_2 activate the C=O and C≡N groups for better reaction with nucleophiles through hydrogen bonding [27, 28].

We also investigated the recycling of amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles as a nanomagnetic catalyst; its reusability was achieved by the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), guanidine hydrochloride (1 mmol), and 8 mg of nano-$CoFe_2O_4$@SiO_2-$PrNH_2$ under ultrasound irradiations (40 W). In the recycling procedure for the catalyst, after completion of the reaction, 5 mL of ethanol was added and magnet was introduced into the mixture in the form of a magnetic stirrer bar and the catalyst was separated magnetically. The catalyst was washed with water and acetone, dried in an oven at 70°C for 150 min, and used directly with new substrates under the same conditions and without further purification. The results showed that the catalyst had been reused in model reactions for five reaction cycles. It was found that the 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%).



Scheme 2: Proposed mechanism for the formation of 5-pyrimidinecarbonitriles.

3 Conclusions

In conclusion, we have developed a simple and highly efficient procedure for the synthesis of 2,4-diamino-6-aryl-5-pyrimidinecarbonitriles using amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles as efficient catalyst under microwave and ultrasound irradiations. The remarkable advantages of this methodology are its easy work-up, short reaction times, use of a magnetically recoverable catalyst, high to excellent product yields, operational simplicity, little catalyst loading, and use of microwave irradiations and ultrasonic irradiation as a valuable and powerful technology.

4 Experimental section

All organic materials were purchased commercially from Sigma-Aldrich and Merck, and were used without further purification. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope. Fourier-transform infrared spectra were recorded with KBr pellets using a Magna-IR spectrometer 550 from Nicolet. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer with dimethyl sulfoxide (DMSO) as solvent and tetramethylsilane as internal standard. Powder X-ray diffraction was carried out on a Philips diffractometer from the X'pert Company. We used the Milestone microwave (Microwave Labstation, MLS GmbH, ATC-FO 300) for the syntheses. $CoFe_2O_4$@SiO_2-$PrNH_2$ nanoparticles were prepared according to the method reported in the literature with some modifications [24]. The microscopic morphology of the products was visualized using scanning electron microscope (MIRA3 TESCAN). The magnetic measurements of the samples were carried out in a vibrating sample magnetometer (Meghnatis Daghigh Kavir Co., Kashan Kavir, Iran) at room temperature in an applied magnetic field sweeping between ±10 kOe (1 kOe = 7.96×10^4 A m^{-1}). The synthesis and characterization of the $CoFe_2O_4$@SiO_2-$PrNH_2$ nanoparticles are described in the Supporting Information, which is available online. Spectral data were consistent with the literature values [25, 26].

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

A mixture of aldehydes (1 mmol), malononitrile (1 mmol), guanidine hydrochloride (1 mmol), solvent EtOH–H_2O

(3:7), and amino-functionalized $CoFe_2O_4@SiO_2$ nanoparticles nano-($CoFe_2O_4@SiO_2$-$PrNH_2$) was subjected under conventional heating, microwave, and ultrasound irradiations. The reaction was monitored using thin layer chromatography. After completion of the reaction, the catalyst was separated magnetically. The precipitate was filtered and recrystallized with *n*-hexane-ethyl acetate to obtain the pure products.

4.2 Spectral data

4.2.1 2,4-Diamino-6-phenylpyrimidine-5-carbonitrile (4a)

M. p. 237–239°C. – IR (KBr): $\overline{\nu}$ = 3400, 3359 (NH_2), 2223 (CN) cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 7.70–7.82 (4H, 2NH_2), 7.93–7.98 (3H, m, ArH), 8.30–8.37 (2H, m, ArH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm) = 79.09, 117.85, 128.03, 128.05, 130.13, 137.03, 162.87, 164.91, 169.33. – Analysis for $C_{11}H_9N_5$: calcd. C 62.55, H 4.29, N 33.16; found C 62.43, H 4.22, N 33.10.

4.2.2 2,4-Diamino-6-(4-chlorophenyl)pyrimidine-5-carbonitrile (4b)

M. p. 265–267°C. – IR (KBr): $\overline{\nu}$ = 3436, 3163 (NH_2), 2196 (CN), 1627, 1697, 1521 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 7.65 (4H, 2 NH_2), 7.98 (2H, m, ArH), 8.45 (2H, m, ArH). – ^{13}C NMR(100 MHz, [D_6]DMSO): δ (ppm) = 76.35, 118.23, 128.76, 130.47, 135.51, 136.32, 163.39, 165.49, 168.66. – Analysis for $C_{11}H_8ClN_5$: calcd. C 53.78, H 3.28, N 28.51; found C 53.65, H 3.20, N 28.45.

4.2.3 2,4-Diamino-6-(4-bromophenyl)pyrimidine-5-carbonitrile (4c)

M. p. 260–262°C. – IR (KBr): $\overline{\nu}$ = 3421, 3299 (NH_2), 2188 (CN), 1637, 1601, 1489 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 6.85–6.92 (4H, 2 NH_2), 7.02–7.04 (2 H, J = 8 Hz, ArH), 7.09–7.11 (2 H, J = 8 Hz, ArH). – ^{13}C NMR(100 MHz, [D_6]DMSO): δ (ppm) = 76.12, 118.39, 128.70, 130.40, 135.59, 136.22, 163.17, 165.32, 168.52. – Analysis for $C_{11}H_8BrN_5$: calcd. C 45.54, H 2.78, N 24.14; found: C 45.45, H 2.65, N 24.04.

4.2.4 2,4-Diamino-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (4d)

M. p. 236–238°C. – IR (KBr): $\overline{\nu}$ = 3388, 3323, 3285, 3206 (NH_2), 2200 (CN), 1645, 1480 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 3.59 (3H, s, OCH_3), 7.59–7.62 (4H, 2 NH_2), 7.30 (2 H, m, ArH), 8.35 (2H, m, ArH). – ^{13}C NMR (100 MHz, [D_6] DMSO): δ (ppm) = 54.31, 79.18, 113.45, 117.92, 125.67, 128.12, 160.21, 164.91, 167.40, 169.33. – Analysis for $C_{12}H_{11}N_5O$: calcd. C 59.74, H 4.60, N 29.03; found C 59.65, H 4.45, N 28.95.

4.2.5 2,4-Diamino-6-*p*-tolylpyrimidine-5-carbonitrile (4e)

M. p. 255–257°C, IR (KBr): $\overline{\nu}$ = 3428, 3323, 3214 (NH_2), 2192 (CN), 1639, 1601, 1510 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 2.09 (3H, s, CH_3), 7.51–7.62 (4H, 2 NH_2), 7.94–7.98 (2H, m, ArH), 8.02–8.07 (2H, m, ArH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm) = 21.93, 80.73, 118.57, 128.59, 130.62, 134.80, 140.53, 163.45, 165.56, 169.67. – Analysis for $C_{12}H_{11}N_5$: calcd. C 63.99, H 4.92, N 31.09, found C 63.85, H 4.83, N 31.15.

4.2.6 2,4-Diamino-6-(2,6-dichlorophenyl)pyrimidine-5-carbonitrile (4f)

M. p. 275–276°C, IR (KBr): $\overline{\nu}$ = 3408, 3349, 3307 (NH_2), 2188 (CN), 1643, 1619 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 6.85–6.90 (4H, 2 NH_2), 7.05–7.09 (3H, m, ArH); ^{13}C NMR(100 MHz, [D_6]DMSO): δ (ppm) = 77.02, 118.17, 127.32, 128.54, 130.21, 133.43, 163.39, 167.38, 168.55. – Analysis for $C_{11}H_7Cl_2N_5$: calcd. C 47.17, H 2.52, N 25.00; found C 47.08, H 2.45, N 24.85.

4.2.7 2,4-Diamino-6-(2-chlorophenyl)pyrimidine-5-carbonitrile (4g)

M. p. 232–235°C, IR (KBr): $\overline{\nu}$ = 3477, 3314, 3234 (NH_2), 2192 (CN), 1692, 1580 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 6.38–6.42 (4H, 2 NH_2), 7.51 (2H, m, ArH), 7.61 (2H, m, ArH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm) = 78.43, 117.83, 127.58, 128.47, 128.92, 129.92, 130.63, 133.20, 164.70, 166.74, 169.46. – Analysis for $C_{11}H_8ClN_5$: calcd. C 53.78, H 3.28, N 28.51, found C 53.62, H 3.17, N 28.42.

4.2.8 2,4-Diamino-6-(3-methylphenyl)pyrimidine-5-carbonitrile (4h)

M. p. 225–227°C. – IR (KBr): $\overline{\nu}$ = 3450, 3350 (NH_2), 2196 (CN), 1695, 1569 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 2.37 (3H, s, CH_3), 7.09–7.15 (4H, 2 NH_2), 7.35–7.37 (2H, d, J = 8 Hz), 7.78–7.80 (2H, d, J = 8 Hz). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm) = 23.84, 78.52, 117.85, 124.47, 129.20, 129.34, 131.22, 134.61, 137.53, 164.34, 166.75, 168.42. – Analysis for $C_{12}H_{11}N_5$: calcd. C 63.99, H 4.92, N 31.09; found C 63.85, H 4.85, N 30.98.

5 Supporting information

Synthesis and characterization of the $CoFe_2O_4$@SiO_2-$PrNH_2$ nanoparticles and copies of the H NMR spectra of the products are given in the Supporting Information, which is available online (DOI: https://doi.org/10.1515/znb-2017-0114).

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Graphical abstract

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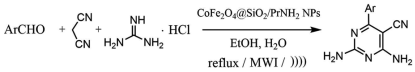
Synthesis of 2,4-diamino-6-aryl-5-pyrimidinecarbonitrile promoted by amino-functionalized $CoFe_2O_4$@SiO_2 nanoparticles under conventional heating, microwave and ultrasound irradiations



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