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Ionic Liquid Attached to Colloidal Silica Nanoparticles as Catalyst for the Synthesis of Pyrimidines

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Abstract

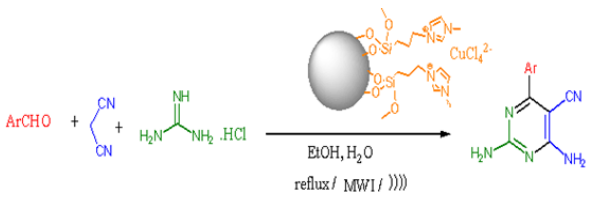
Bis (1(3-trimethoxysilylpropyl)-3-methyl-imidazolium) copper tetrachloride tethered to colloidal silica nanoparticles have been used as an efficient catalyst for the preparation of 2,4-diamino-6-arylpyrimidine-5-carbonitrile derivatives by the one-pot reaction of aromatic aldehydes, malononitrile, and guanidine hydrochloride under conventional heating, microwave and ultrasound irradiations. The catalyst was characterized by ^{1}H NMR spectroscopy, dynamic light scattering (DLS), scanning electron microscope (SEM), energy dispersive spectroscopy (EDS) and thermogravimetric analysis (TGA). The remarkable advantages of this methodology are easy work-up, short reaction times, high to excellent product yields, operational simplicity, low catalyst loading and use of ultrasonic irradiation as a valuable and powerful technology.

Keywords: *Pyrimidine, Heterogeneous catalyst, Ionic liquid, Colloidal silica nanoparticles, Microwave, Ultrasound irradiation.*

1. INRODUCTION

Pyrimidines constitute a significant family of heterocyclic compounds for their potential pharmaceutical applications including antihypertensive [1], antimicrobial [2,3], antitumor [4], antimalarial [5], antioxidant [6] protein Kinase inhibitors [7] and antagonists of GPR40 [8]. Therefore, the enlargement of beneficial ways for the preparation of pyrimidines is of great interest. A number of ways have been increased for the synthesis of pyrimidines in the presence of catalysts such as sodium acetate [9], $Bi(NO_3)_3.5H_2O$ [10], NaOH [11,12] CuO microspheres [13] and K_2CO_3 [14]. Despite the availability of these ways, there remains adequate scope for the use of an efficient procedure for the preparation of pyramidines. The completion of the reactions under conventional heating conditions requires several hours and the yields are low. The essential concern for the progression 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 diversity of organic syntheses owing to short reaction times, easy workup and excellent yields [15-18]. The practical rate acceleration upon microwave is owing to material–wave interactions leading to thermal effects. The reaction is heated from the inside since 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 derived by the form, growth, and implosive collapse of bubbles in a liquid. Collapsing of bubbles produce high temperatures and

pressures [21-22]. Compared to conventional heating which makes thermal energy in the macro system, ultrasound irradiation is able to activate numerous reactions by the activation energy in micro environment [23]. Multi-component reactions (MCRs) constitute a very powerful tool to synthesize various and complex heterocyclic compounds [24,25]. In this study, we report the use of bis (1(3-trimethoxysilylpropyl)-3-methyl-imidazolium) copper tetrachloride tethered to colloidal silica nanoparticles as an effective catalyst for the preparation of arylpyrimidines by the multi-component reaction of aromatic aldehydes, malononitrile and guanidine hydrochloride under different conditions (Scheme 1).



Scheme 1. *Synthesis of pyrimidines.*

2. EXPERIMENTAL

2.1. Materials and Apparatus

DLS was accomplished using a Malvern Zetasizer Nano-S. The thermogravimetric analysis (TGA) curves are recorded using a V5.1A DUPONT 2000. To study the morphology and particle size of NPs, FE-SEM analysis and EDS spectrum of the products was visualized by a Sigma ZEISS.

2.2. Preparation of Ionic Liquid/Nano-Colloidal Silica

0.098 mL of nano-colloidal silica (LUDOX SM colloidal silica 30 wt.% suspension in H_2O) was diluted in 3 mL of deionized water, and 0.0018 mol of 1-(3-trimethoxysilylpropyl)3-methylimidazolium chloride (IL) was added slowly with continuous stirring during 1 hour. Then, 150 mg of $CuCl_2.2H_2O$ was added and refluxed for 24 h. After 24 h, IL functionalized nano-silica was separated by centrifugation and rinsed with methanol for four times, then, IL/Cu^{2+}/SiO_2 was dried by lyophilization/freeze-drying. The purity of the resultant IL/Cu^{2+}/SiO_2 was confirmed using ^{1}H NMR spectrum. The Cu loading was estimated using XRF to be 4.7 wt%

2.3. General Procedure for the Preparation of Pyrimidines (4a-h)

A mixture of aldehydes (1 mmol), malononitrile (1 mmol), guanidine hydrochloride (1 mmol), solvent EtOH:H_2O (5:5) and nanocatalyst was subjected under different conditions. After supplementation of the reaction (TLC), ethyl acetate was added. The catalyst was insoluble in ethyl acetate and it could therefore be recycled by an easy filtration. The solvent was evaporated and the solid obtained recrystallized from ethanol to afford the pyrimidines.

2.4. Spectral Data

2,4-diamino-6-phenylpyrimidine-5-carbonitrile (**4a**): M. p. 237-239 °C. IR (KBr):

3401, 3358 (NH_2), 2225 (CN) cm^{-1}. ^{1}H NMR (400 MHz, [D_6]DMSO): δ (ppm): 7.71-7.83 (4H, $2NH_2$), 7.94-7.99 (3H, m, ArH), 8.31-8.38 (2H, m, ArH). ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm): 79.08, 117.84, 128.04, 128.06, 130.14, 137.04, 162.88, 164.92, 169.34. Analysis for $C_{11}H_9N_5$: calcd. C 62.55, H 4.29, N 33.16; found C 62.44, H 4.23, N 33.12.

2, 4- diamino – 6 - (4 – chloro phenyl) pyrimidine-5-carbonitrile (**4b**): M. p. 265-267 °C. IR (KBr):

3435, 3164 (NH_2), 2196 (CN), 1628, 1697, 1522 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]DMSO): δ (ppm): 7.65 (4H, 2 NH_2), 7.96 (2H, m, ArH), 8.45 (2H, m, ArH). ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm): 76.35, 118.23, 128.75, 130.48, 135.52, 136.33, 163.38, 165.46, 168.64. 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.

2,4-diamino-6-(4-bromophenyl) pyrimidine-5-carbonitrile (**4c**):

M. p. 260-262 °C. IR (KBr): 3422, 3299 (NH_2), 2187 (CN), 1636, 1601, 1484 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm): 6.84-6.91 (4H, 2 NH_2), 7.03-7.05 (2 H, J = 8 Hz, ArH), 7.08-7.12 (2 H, J = 8 Hz, ArH). ^{13}C NMR(100 MHz, [D_6]DMSO): δ (ppm): 76.13, 118.38, 128.72, 130.41, 135.59, 136.23, 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 45.46, H 2.64, N 24.05.

2,4-diamino-6-(4-methoxyphenyl) pyrimidine-5-carbonitrile (**4d**):

M. p. 236-238 °C. IR (KBr): 3387, 3324, 3283, 3205 (NH_2), 2201 (CN), 1646, 1482 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm): 3.59 (3H, s, OCH_3), 7.58-7.61 (4H, 2 NH_2), 7.32 (2 H, m, ArH), 8.34 (2H, m, ArH). ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm): 54.32, 79.19, 113.46, 117.93, 125.67, 128.13, 160.21, 164.92, 167.40, 169.33. Analysis for $C_{12}H_{11}N_5O$: calcd. C 59.74, H 4.60, N 29.03; found C 59.64, H 4.45, N 28.96.

2, 4- diamino -6 – *p* – tolyl pyrimidine -5 - carbonitrile (**4e**):

M. p. 255-257 °C, IR (KBr): 3425, 3324, 3216 (NH_2), 2193 (CN), 1638, 1601, 1512 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm): 2.08 (3H, s, CH_3), 7.52-7.63 (4H, 2 NH_2), 7.95-7.97 (2H, m, ArH), 8.03-8.08 (2H, m, ArH). ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm): 21.94, 80.73, 118.58, 128.58, 130.62, 134.82, 140.54, 163.46, 165.55, 169.69. 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.

2, 4 – diamino – 6 - (2, 6-dichlorophenyl) pyrimidine-5-carbonitrile (**4f**):

M. p. 275-276 °C, IR (KBr): 3405, 3348, 3306 (NH_2), 2184 (CN), 1644, 1618 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 6.85-6.92 (4 H, 2 NH_2), 7.06-7.10 (3H, m, ArH); ^{13}C NMR(100 MHz, [D_6]DMSO): δ (ppm): 77.03, 118.17, 127.34, 128.55, 130.21, 133.45, 163.39, 167.39, 168.55. Anal. for $C_{11}H_7Cl_2N_5$: calcd. C 47.17, H 2.52, N 25.00; found C 47.09, H 2.46, N 24.84.

2 , 4 – diamino – 6 - (2 - chlorophenyl) pyrimidine-5-carbonitrile (**4g**):

M. p. 232-235 °C, IR (KBr): 3478, 3315, 3236 (NH_2), 2193 (CN), 1694, 1581 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm): 6.38-6.43 (4H, 2 NH_2), 7.52 (2H, m, ArH), 7.61 (2H, m, ArH). ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm): 78.44, 117.85, 127.58, 128.48, 128.92, 129.93, 130.64, 133.20, 164.70, 166.75, 169.47. Anal. for $C_{11}H_8ClN_5$: calcd. C 53.78, H 3.28, N 28.51, found C 53.62, H 3.16, N 28.42.

2,4-diamino-6-(3-methylphenyl) pyrimidine-5-carbonitrile (**4h**):

M. p. 225-227 °C. IR (KBr): 3452, 3354 (NH_2), 2196 (CN), 1695, 1569 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ (ppm): 2.36 (3H, s, CH_3), 7.08-7.14 (4H, 2 NH_2), 7.36-7.38 (2H, d, J = 8 Hz), 7.79-7.81 (2H, d, J = 8 Hz). ^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm): 23.85, 78.53, 117.85, 124.48, 129.22, 129.34, 131.23, 134.61, 137.54, 164.34, 166.76, 168.43. Anal. for $C_{12}H_{11}N_5$: calcd. C 63.99, H 4.92, N 31.09; found C 63.83, H 4.86, N 30.94.

3. RESULTS AND DISCUSSION

3.1. Characterization of the Nanocatalyst

Figure 1a and 1b exhibit the ^1H NMR spectra for the 1(3-trimethoxy silylpropyl)3-methyl-imidazolium chloride and bis (1(3-trimethoxysilylpropyl) 3-methyl-imidazolium) copper tetrachloride tethered to silica nanoparticles in DMSO, respectively. The spectra of both materials are consistent with anticipated results for untethered and silica-tethered ionic liquids.

Figure 2 displays FESEM image of bis (1(3-trimethoxysilylpropyl)3-methylimidazolium) copper tetrachloride tethered to silica nanoparticles (IL/nano-colloidal silica). It is apperceived that the particles are aggregated and glued with very large and continuous aggregates observed.

To investigate the size distribution of nanoparticle [26, 27], dynamic light scattering were demonstrated in Figure 3. Size distribution is centered at 42.5 nm.

The elemental compositions of the nanoparticles were investigated by Energy Dispersive Spectroscopy. EDS corroborated the attendance of Si, O, N, C, Cl and Cu in the compound (Figure 4).

Thermogravimetric analysis studies the thermal properties of the ionic liquid of untethered to SiO_2 and silica-tethered ionic liquids. The curve displays a weight loss about 36.5% for ionic liquid@nano-colloidal silica from 230 to 540 ºC, resulting from the demolition of organic spacer annexed to the nanoparticles (Fig 5)

FT-IR of bis (1(3-trimethoxysilyl propyl)-3-methylimidazolium) copper tetrachloride tethered to colloidal silica nanoparticles is shown in Figure 6. The absorption peak at 3436 cm^{-1} related to the stretching vibrational absorptions of O-H. The bands at 467, 1078, 1636 and 3425 cm^{-1} are the characteristic absorptions of SiO_2, which indicates the evidence for the formation of a silica shell. The increase of the bands at 1572 cm^{-1} provides a direct indication of the existence of the N-H bending vibration.

3.2. Catalytic Behaviors of Nanoparticles for the Synthesis Pyrimidines

Initially, we concentrated on evaluation of diverse catalysts in the reaction of benzaldehyde, malononitrile, guanidine hydrochloride as a pattern reaction. Yields were determined by Na_2CO_3, Et_3N, nano-Fe_3O_4, nano-CuI, nano-CuO, nano-ZnO and ionic liquid@nano-colloidal silica and the results are shown in Table 1. When the reaction was performed by ionic liquid @nano-colloidal silica as the catalyst, the products were generated in good yields. In this research, microwave and ultrasound irradiations are utilized as green techniques for synthesis of pyrimidines. When the catalysis was carried out under microwave and ultrasound irradiations, the reaction rate rise extremely.

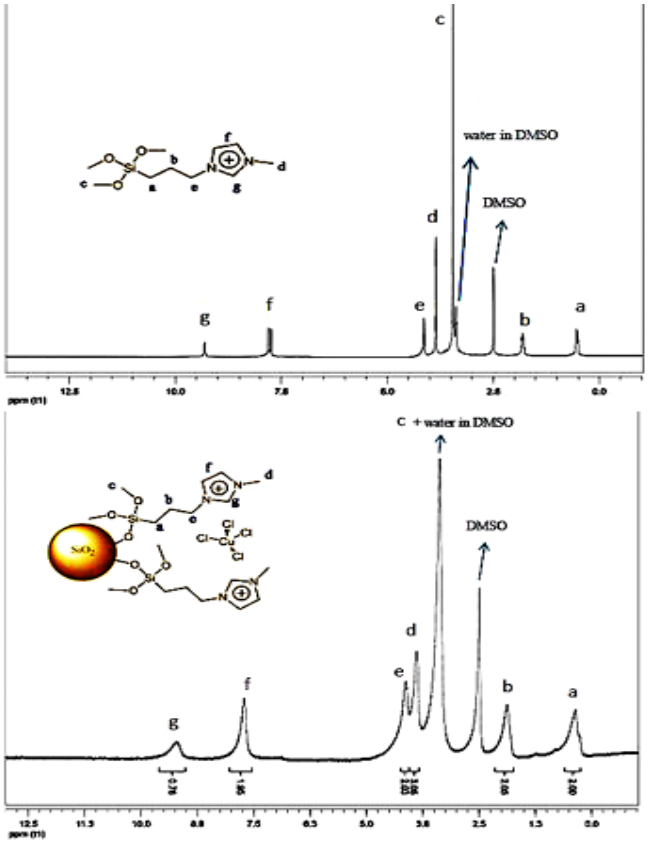


Figure 1. *(a) ^1H NMR spectrum of 1(3-trimethoxysilylpropyl)-3-methyl-imidazoli - um chloride and (b) bis (1(3-trimethoxysilylpropyl)-3-methyl-imidazoli - um) copper tetrachloride tethered to silica nanoparticles (nanocatalyst) in dimethyl sulfoxide (DMSO).*

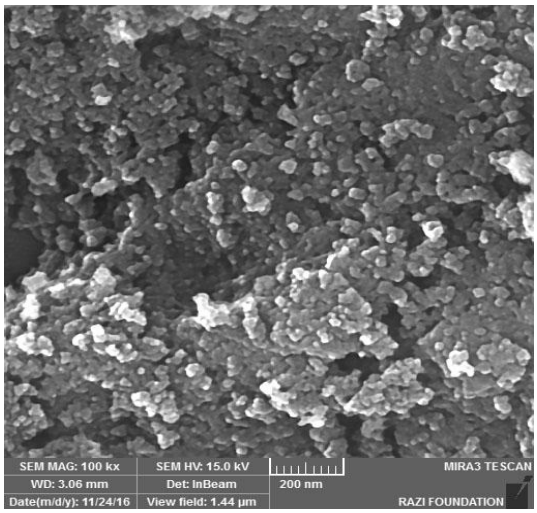


Figure 2. *FE-SEM image of nanocatalyst.*

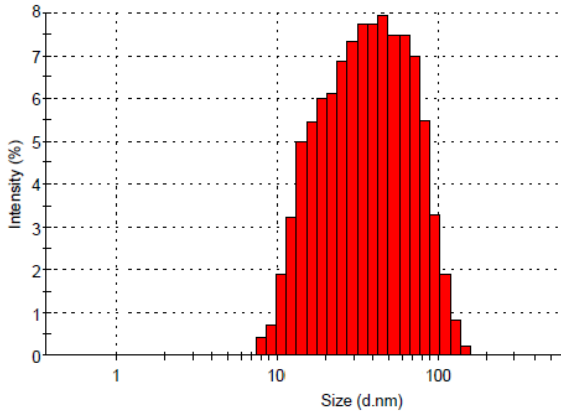


***Figure 3**. DLS of nanocatalyst.*

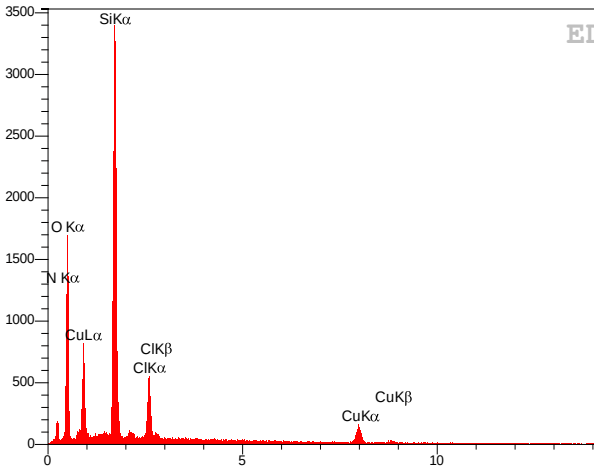


***Figure 4**. EDS of nanocatalyst.*

The best results were obtained under ultrasound irradiations (40 W) in ethanol: water (5:5) and found that the reaction gave satisfying results by of ionic liquid@ nanocolloidal silica at 8 mg which gave good yields of products (Table 1).

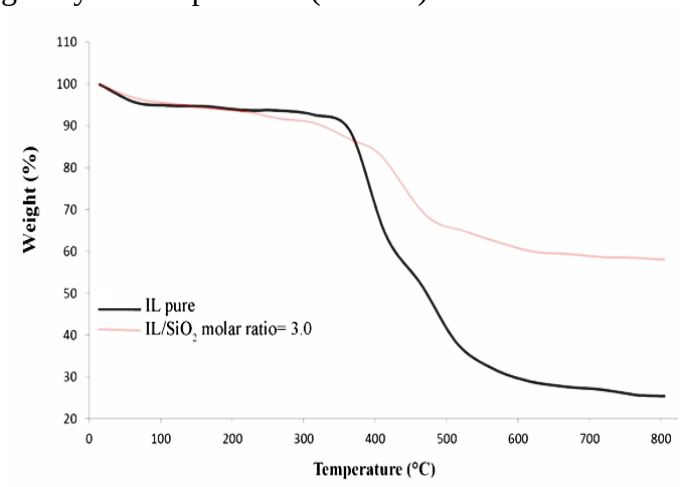


***Figure 5**. TGA of IL and nanocatalyst.*

We turned to explore the efficacy of the catalyst by different aromatic aldehydes and the results are summed up in Table 2. A mechanism for the reaction is outlined in Scheme 2. The reaction occurs *via* initial formation of the cyano olefin **A** from the condensation of malononitrile and aryl aldehyde, which is itself activated by the catalyst. The second step is followed by Michael addition, cycloaddition, isomerization, and aromatization to afford the 5-pyrimidinecarbonitriles. The catalyst activate the C=O and C≡N groups for better reaction with nucleophiles.

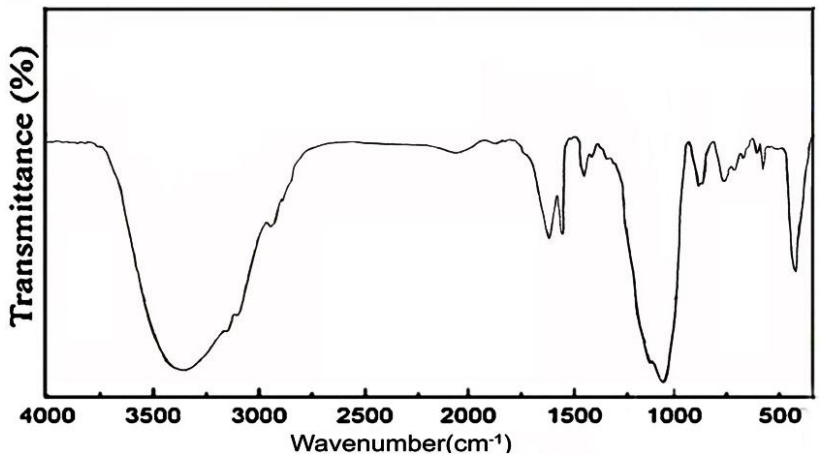
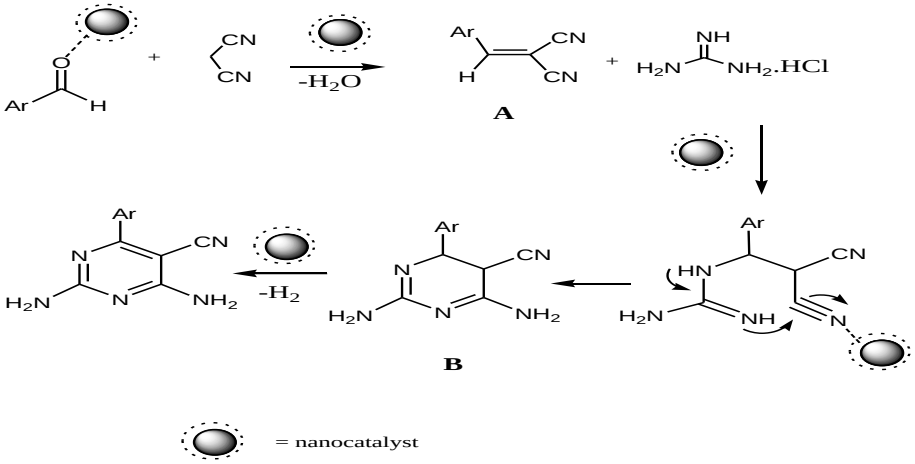


***Figure 6**. FT-IR of nanocatalyst.*



Scheme 2*. Formation mechanism of 5-pyrimidinecarbonitriles.*

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

Entry	Solvent	Conditions	Catalyst	amount	Time (min)	Yield%[d]
1	H_2O	reflux	Et_3N	10 mol%	300	38
2	EtOH	reflux	Na_2CO_3	5 mol%	300	25
3	EtOH:H_2O (5:5)	reflux	nano-CuI	10 mol%	180	48
4	EtOH:H_2O (5:5)	reflux	nano-Fe_3O_4	5 mol%	180	51
5	EtOH:H_2O (5:5)	reflux	nano-CuO	10 mol%	150	62
6	EtOH:H_2O (5:5)	reflux	nano-ZnO	7 mol%	150	64
7	EtOH:H_2O (5:5)	reflux	IL@ nano-colloidal silica	30 mg	90	80
8	EtOH:H_2O (5:5)	MWI [b](400 W)	IL@ nano-colloidal silica	10 mg	15	84
9	EtOH:H_2O (5:5)	MWI (400 W)	IL@ nano-colloidal silica	15 mg	15	87
10	EtOH:H_2O (5:5)	MWI (400 W)	IL@ nano-colloidal silica	20 mg	15	87
11	EtOH:H_2O (5:5)	MWI (300 W)	IL@ nano-colloidal silica	20 mg	15	79
12	EtOH:H_2O (5:5)	MWI (500 W)	IL@ nano-colloidal silica	20 mg	15	86
13	EtOH:H_2O (5:5)	US [c] (40 W)	IL@ nano-colloidal silica	6 mg	10	90
14	EtOH:H_2O (5:5)	US (40 W)	IL@ nano-colloidal silica	8 mg	10	93
15	EtOH:H_2O (5:5)	US (40 W)	IL@ nano-colloidal silica	10 mg	10	93
16	EtOH:H_2O (5:5)	US (30 W)	IL@ nano-colloidal silica	10 mg	10	85
17	EtOH:H_2O (5:5)	US (50 W)	IL@ nano-colloidal silica	10 mg	10	93
18	EtOH:H_2O (5:5)	MWI (500 W)	———	——	25	15

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and guanidine hydrochloride (1 mmol)
[b] MWI: Microwave irradiations [c] Ultrasound irradiations [d] Isolated yield

Table 2*. Synthesis of pyrimidines using IL@nano-colloidal silica.*

Entry	Product	Ar	Time (min) MWI[a]	Yield[c] % MWI	Time (min) US[b]	Yield[c] % US	m.p. (°C)	m.p. (°C) [lit.]
1	4a	C_6H_5	15	87	10	93	237-239	237-239 [28]
2	4b	4-Cl-C_6H_4	15	92	10	98	265-267	265-266 [28]
3	4c	4-Br-C_6H_4	15	92	10	98	260-262	260-262 [28]
4	4d	4-OMe-C_6H_4	20	81	15	88	236-238	236-238 [28]
5	4e	4-Me-C_6H_4	20	85	15	90	255-257	255-257 [28]
6	4f	2,6-di-Cl-C_6H_4	15	89	10	95	275-276	——
7	4g	2-Cl-C_6H_4	15	88	10	94	232-235	——
8	4h	3-Me- C_6H_4	15	85	10	91	225-227	——
9	4i	furan-2-carbaldehyde	15	87	10	92	218-220	——
10	4g	thiophene-2-carbaldehyde	15	86	10	90	222-224	——

[a] Microwave irradiations (400 W) and15 mg of catalyst [b] Ultrasound irradiations (40 W), and 8 mg of catalyst [c] Isolated yield

4. CONCLUSIONS

In conclusion, we have developed an effective way for the synthesis of pyrimidines using nanoparticles as excellent catalysts under different conditions. The advantages of this way are short reaction times, high to excellent product yields, operational simplicity, little catalyst loading and use of ultrasonic irradiations as a green technology.

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