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ORIGINAL PAPER

Microwave-assisted synthesis of pyrido-dipyrimidines using magnetically $CuFe_2O_4$ nanoparticles as an efficient, reusable, and powerful catalyst in water

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Abstract An efficient and direct procedure for the synthesis of pyrido[2,3-d:6,5-d′]dipyrimidine derivatives has been described under microwave-assisted conditions. The reaction of 2-thiobarbituric acid with aromatic aldehydes and ammonium acetate catalyzed by $CuFe_2O_4$ nanoparticles was resulted in the formation of pyrido[2,3-d:6,5 d′] dipyrimidine derivatives. The corresponding products have been obtained in excellent isolated yields with high purity, in short reaction times and easy workup.

Keywords Multicomponent reactions · Magnetic nanoparticles · Microwave · Pyrido-dipyrimidines

Introduction

Organic compounds containing pyrido-pyrimidine scaffold as a core unit are important targets and have received more attention due to their wide range of biological and pharmaceutical features as well as the presence of this framework in a number of natural products [1, 2]. For example, piromidic acid (I) as an antibacterial drug and piritrexim isethionate (II) with antineoplastic drug are shown in Fig. 1 [3]. A great number of compounds that carry pyrido[2,3-d] pyrimidine moieties are reported to have significant properties such as antihypertensive [4], anti-inflammatory [5], antileishmanial [6], antibacterial [7], antifolate [8], analgesic [9], antimicrobial [10], anticonvulsants [11], anti-HIV [12], tuberculostatic [13], antiallergic [14], potassium sparing [15], antitumor [16], tyrosine kinase inhibitors [17], dihydrofolate reductase (DHFR) inhibitory activity [18], calcium channel antagonists [19], fibroblast growth factor receptor (FGFR3) [20].

Nowadays, the employment of novel adapted tools and techniques considering operational, economic, and environmental benefits over traditional methods have been increasingly recognized in organic, combinatorial, and medicinal chemistry mainly the synthesis of complicated molecules obtained in a very fast, efficient, and timesaving manner. For the utility of microwave energy in these slight cases, using microwaves as a valuable and powerful technology has become a major motivation for both industry and academia [21–23]. Replacing the oil bath with a microwave reactor and opening a new window in microwave-assisted organic synthesis (MAOS) lead to perform the reactions in dramatically shortened time as well as increasing yields in the much cleaned simple condition reactions [24]. Moreover, this method improves the bond forming efficiency. For these reasons, many organic reactions have been reported under microwave activation [25–27].

Nanocatalysis is essential for chemistry, material science, and nanoscience [1–4]. Due to extremely small size, the large ratio of surface to volume, many noble metal nanoparticles have been used as catalysts in various chemical reactions [28]. To allow for facile and simple recovery and recycling of catalyst, magnetic nanoparticles are attractive catalysts since they can be separated from the reaction medium after magnetization by an external magnet and are cost-effective. These heterogeneous magnetic nanoparticles catalysts can achieve many of the goals of green chemistry [28–30].

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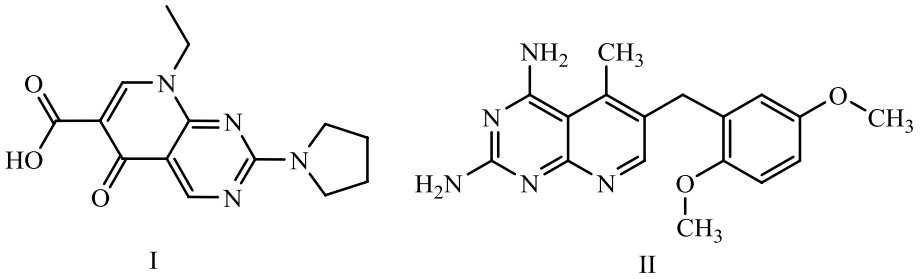


Fig. 1 Drug structures of some known pyrido[2,3-d]pyrimidines

In this research, we report greener route for one-pot, four-component synthesis of pyrido [2,3-d]pyrimidine derivatives via a water-mediated and $CuFe_2O_4$ nanoparticles as a reusable catalyst under microwave-assisted procedures. This method is simple, efficient, and fast with excellent yields.

Experimental

Chemicals and apparatus

Chemicals were purchased from the Merck and Fluka Chemical Companies in high purity. All of the materials were of commercial reagent grade. The aniline derivatives and salicylaldehyde were purified by standard procedures, and their purity determined by thin-layer chromatography (TLC). IR spectra were obtained as KBr pellets on a PerkinElmer 781 spectrophotometer and on an impact 400 Nicolet FT–IR spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded in DMSO-d_6 solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. Melting points were obtained with a Yanagimoto micro melting point apparatus are uncorrected. Mass spectra were recorded on an Agilent technology HP 5973 Network Mass Selective Detector mass spectrometer operating at an ionization potential of 70 eV. FESEM analysis was carried out using a Jeol SEM instrument (model-VEGA/TESCAN). The XRD patterns were recorded on an X-ray diffractometer (Bruker, D8 ADV ANCE, Germany). The XRD patterns were recorded on an X-ray diffractometer (Bruker, D8 ADV ANCE, Germany). The magnetic property of the catalyst was studied by vibrating sample magnetometer (VSM, Meghnatis Daghigh Kavir Company, Iran). The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company). The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

Typical experimental procedure for the preparation of magnetic nanocatalyst

$CuFe_2O_4$ nanoparticles were prepared by coprecipitation of $Cu(NO_3)_2{\cdot}3H_2O$ and $FeCl_3{\cdot}9H_2O$ in water in the presence of sodium hydroxide. Briefly, to a solution of $FeCl_3{\cdot}9H_2O$ (0.05 mol) and $Cu(NO_3)_2{\cdot}3H_2O$ (0.025 mol) in 100 mL of distilled water, 75 mL of NaOH 4 M was added at room temperature over a period of 10 min to form the reddish black precipitate. Then the reaction mixture was warmed to 90 °C and stirred. After 2 h, it was cooled to room temperature and the formed magnetic particles were separated by a magnetic separator. The catalyst was washed with distilled water and kept in air oven overnight at 80 °C. Then the catalyst was ground in a mortar–pestle and kept in a furnace at 800 °C at a heating rate of (2 °C/min) and cooled to 100 °C at (5 °C/min) in the air [31].

General procedure for the synthesis of 2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d′] dipyrimidine-4,6(1H,5H)-dione

A mixture of an aldehyde (0.25 mmol), 2-thiobarbituric acid (0.5 mmol), ammonium acetate (0.3 mmol), and $CuFe_2O_4$ (10 mol%), with distilled H_2O, in an open tall beaker was irradiated inside microwave oven at 100 W for an appropriate time (monitored by TLC). After completion of the reaction, for removing the catalyst, the hot solution was filtrated with external magnetic for several times. The solvent was evaporated, and the precipitate was washed from ethanol and hot water to afford the pure product.

5-Phenyl-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido [2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Cream powder; M.P: 211 °C Lit. [32] ($M.P_{rep}$: 238 °C decompose). IR (KBr) (ν_{max}/cm^{-1}): 3452 (NH), 3054 (C–H, sp^2 stretch), 2898 (C–H, sp^3), 1637 (C=O), 1440, 1559 (C=C, Ar). ^{1}H NMR (DMSO-d_6, 400 MHz) (ppm): 5.93 (*s*, 1H), 6.98–6.99 (*d*, 2H, $J = 6.0$ Hz), 7.05 (*s*, 1H), 7.15 (*s*, 2H), 7.60 (*s*, 1H), 7.91 (*s*, 1H), 11.33–12 (*s*, 3H).

5-(4-Nitrophenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Light brown powder; M.P: 330 °C Lit. [33] ($M.P_{rep}$: 269 °C decompose). IR (KBr) (ν_{max}/cm^{-1}): 3447 (NH), 3175 (C–H, sp^2 stretch), 1602 (C=O), 1432, 1509 (C=C, Ar). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.04 (*s*, 1H), 6.93 (*s*, 1H), 7.06 (*s*, 1H), 7.19 (*s*, 1H), 7.23–7.25 (*d*, 2H, $J = 8.4$ Hz), 8.04–8.28 (*d*, 2H, $J = 8.8$ Hz), 11.62 (*s*, 2H), 11.75–11.97 (*s*, 2H), 17.1(*s*, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 31.61, 95.68, 123.57, 128.26145.71, 152.56, 163.17, 164,173.5.

5-(2-Nitrophenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Yellow powder; M.P: 230 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3447 (NH), 3175 (C–H, sp^2 stretch), 1602 (C=O), 1432, 1509 (C=C, Ar). ^1H NMR (DMSO-d6, 400 MHz) δ (ppm): 6.09–6.21 (*s*, 1H), 6.93 (*s*, 1H), 7.06 (*s*, 1H), 7.19 (*s*, 1H), 7.30–7.32 (*m*, 1H), 7.45 (*m*, 1H), 7.49–7.51 (*d*, 2H), 11.57–11.99 (*s*, 5H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 29.15, 95.22, 124.05, 127.11, 129.79, 131.58, 136.07, 150.17, 163.19, 173.49. Anal. Calcd for $C_{15}H_{10}N_6O_4S_2$: C, 44.77; H, 2.50; N, 20.88, %; Found C, 44.81; H, 2.53; N, 20.91 %.

5-(4-Chloro-3-nitrophenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Yellow powder; M.P: 249 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3450 (NH), 3090 (C–H, sp^2 stretch), 1615 (C=O), 1434, 1542 (C=C, Ar). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 5.98 (*s*, 1H), 6.92 (*s*, 1H), 7.05 (*s*, 1H), 7.14–7.18 (*m*, 1H), 7.28–7.30(*m*, 1H), 7.53–7.56 (*m*, 2H), 11.63–11.70 (*m*, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 30.87, 95.31, 121.91, 123.78, 131.41, 132.75, 145.28, 147.76, 163.14, 163.94, 173.56. EI–MS (70 eV) m/z: 43(85.88), 69 (100), 116 (42.61), 144 (96.27), 311(85.72), 431 (3.071), 436 (0.30).

5-(3-Methoxyphenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Yellow powder; M.P: 242 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3591, 3447 (NH), 3166 (C–H, sp^2 stretch), 2922 (C–H, sp^3), 1632 (C=O), 1437, 1536 (C=C, Ar). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 3.63 (*s*, 3H), 5.91–5.97 (*s*, 1H), 6.49–6.52 (*s*, 1H), 6.56–6.57 (*m*, 1H), 6.62–6.64 (*m*, 1H), 6.93 (*s*, 1H),7.06 (*s*, 2H), 7.19–7.23 (*s*, 1H), 11.56–11.73 (*m*, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 30.89, 55.24, 96.21, 109.8, 113.61, 119.62, 129.09, 145.24, 159.42, 173.22. Anal. Calcd for $C_{16}H_{15}N_5O_3S_2$: C, 49.34; H, 3.88; N, 17.98 %; Found C, 49.38; H, 3.90; N, 18.02 %.

5-(Pyridine-2-yl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Red powder; M.P: 280 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3398 (NH), 3210 (C–H, sp^2 stretch), 2881 (C–H, sp^3), 1605 (C=O), 1455, 1533 (C=C, Ar). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.20 (*s*, 1H), 7.83 (*s*, 1H), 8.42 (*m*, 1H), 8.6 (*m*, 1H), 11.84 (*s*, 4H), 14–16 (*s*, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 32.03, 92.94, 124.86, 126.21, 141.98, 146.83, 158.93, 163.41, 174.28. EI–MS (70 eV) m/z: 51 (8.31), 77 (23.27), 124 (37.53), 126 (4.96), 228 (100), 352 (3.91), 358 (0.06).

5-(2-Fluorophenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

White powder; M.P: 240 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3432 (NH), 3108 (C–H, sp^2 stretch), 1623, 1687 (C=O), 1433, 1544 (C=C, Ar). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.01 (*s*, 1H), 6.91–7 (*m*, 3H), 7.08–7.12 (*m*, 4H), 11.49–11.75 (*m*, 4H), 17 (*s*, 1H).^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 26.88, 95.44, 115.26, 123.60, 127.55, 130.05, 130.44, 159.60, 162.03, 163.32, 173.24. Anal. Calcd for $C_{15}H_{12}FN_5O_2S_2$: C, 47.74; H, 3.20; N, 18.56, %; Found C, 47.76; H, 3.24; N, 18.60 %.

5,5′-(1,4-Phenylene)bis(2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione)

Red powder; M.P: 300 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3428 (NH), 3200 (C–H, sp^2 stretch), 2923 (C–H, sp^3), 1623 (C=O), 1434, 1535 (C=C, Ar).^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 5.59 (*s*, 2H), 7.22 (*m*, 2H), 7.46 (*m*, 1H), 7.51 (*m*, 2H), 7.86–7.91 (*m*, 4H), 7.98 (*m*, 2H), 11.61 (*s*, 1H), 12.09 (*s*, 1H), 12.40 (*s*, 2H), 13.41 (*s*, 2H).^{13}C NMR(DMSO-d_6, 100 MHz) δ (ppm): 30.89, 96.45, 115.36, 126.27, 163.06, 164.09, 173.46. EI–MS (70 eV) m/z: 135 (55.28), 264 (35.19), 289 (27.58), 637 (1.06), 636 (0.55).

5-(2-Hydroxynaphthalen-1-yl)2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Light brown powder; M.P: 308 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3530 (NH), 3069 (C–H, sp^2 stretch), 2892 (C–H, sp^3), 1680 (C=O), 1450, 1562 (C=C, Ar). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 5.85 (*s*, 1H), 6.75 (*s*, 1H), 6.94 (*m*, 1H), 7.07 (*s*, 1H), 7.19 (*m*, 1H), 11.40 (*s*, 2H), 11.56 (*s*, 2H), 17.1 (*s*, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 24.82, 91.66, 97.56, 115.48, 116.86, 123.45, 125.47, 127.62, 129.25, 131.29, 147.83, 154.56, 161.67, 173.72. Anal. Calcd for $C_{19}H_{13}FN_5O_3S_2$: C, 53.89; H, 3.09; N, 16.54,%; Found C, 53.92; H, 3.12; N, 16.56 %.

5-(4-Chloro)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido [2,3-d:6,5-d]dipyrimidine-4,6(1H,5H)-dione

Yellow powder; M.P: 257 °C decompose. IR (KBr) (ν_{max}/cm^{-1}): 3433 (NH), 3130 (C–H, sp^2 stretch), 1626 (C=O), 1434, 1534 (C=C, Ar). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 5.91 (*s*, 1H), 6.93–6.98 (*d*, 2H), 7.06 (*s*, 1H), 7.19 (*s*, 1H), 11.67 (*s*, 5H). ^{13}C NMR (DMSO-d6, 100 MHz) δ (ppm): 31.24, 93.17, 119.40, 122.08, 130.15, 133.85, 136.56, 144.09, 162.94, 165.23, 175.52. Anal. Calcd for $C_{15}H_{10}ClN_5O_2S_2$: C, 45.98; H, 2.57; N, 17.87, %; Found C, 46.01; H, 2.60; N, 17.92 %.

Results and discussion

The search for new highly effective synthetic methods and the use environmental friendly techniques in the reaction is important strategies directed toward the development of science and technology. Due to MAOS advantages, this is considered as a valuable and powerful technology. Many factors are important in the MAOS, such as solvent composition, time, and power of microwave oven. In the present study, in order to find the suitable condition for synthesis of pyrido[2,3-d]pyrimidine under microwave-assisted conditions. Because of more advantages of magnetic nanoparticles and our current success for synthesis of heterocyclic compound under $CuFe_2O_4$ [34], firstly, we examined model reaction of 4-chlorobenzaldehyde, 2-thiobarbituric acid and ammonium acetate with 1:2:1 mol ratio (Scheme 1) in the presence of a catalytic amount of $CuFe_2O_4$ in water under the lowest power in our microwave oven (100 w). $CuFe_2O_4$ nanoparticles with its structure are the good acidic catalyst and suitable for Hantzsch reaction. The excellent result (98 %) of product and short reaction time (1 min) confirms this suggestion.

The effect of the catalytic amount of $CuFe_2O_4$ on the synthesis of 5-(4-chloro)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d′]dipyrimidine-4,6(1H,5H)-dione (4f) is presented in Table 1. As it can be seen, the best amount of catalyst in this reaction is 10 mol %.

Table 1 Different amounts of the $CuFe_2O_4$ nanoparticles as catalyst in model reaction

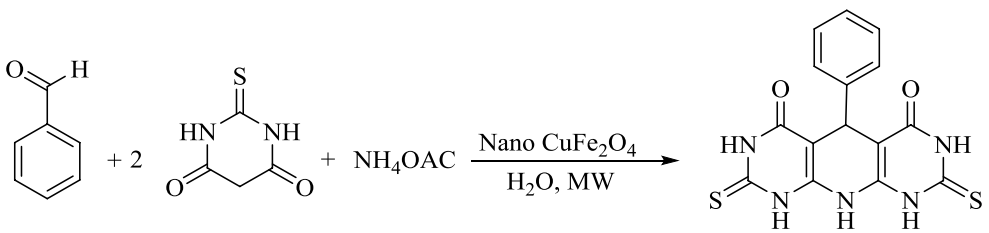
Entry	$CuFe_2O_4$ (mol%)	Time (min)	Yield[a] (%)b
1	5	10	87
2	10	10	98
3	15	10	90

[a] Reaction conditions: 4-chlorobenzaldehyde (0. 25 mmol), 2-thiobarbituric acid (0.5 mmol), ammonium acetate (0. 3 mmol), H_2O (5 mL), catalyst (10 mol%), power (100w)

Table 2 Power optimization for the synthesis of **4f**

Entry	Power (W)	Time (min)	Yield[a] (%)b
1	100	1	98
2	180	10	55
3	300	10	40
4	450	10	10

[a] Reaction conditions: 4-chlorobenzaldehyde (0. 25 mmol), 2-thiobarbituric acid (0.5 mmol), ammonium acetate (0. 3 mmol), H_2O (5 mL), catalyst (10 mol%)



Scheme 1 Reaction leading to the synthesis of novel pyrido[2,3-d]pyrimidine derivatives

Table 3 Comparison of the reported conditions used for the synthesis of pyrido[2,3-d:6,5-d']dipyrimidine with the present method

Entry	Catalyst	Time (min)	Condition	Yield[e] (%)[b]/Ref.
1	$CuFe_2O_4$ NPs[a]	1	MW	98/this work
2	*p*-TSA[b]	4 h	Δ	81/[35]
3	Al_2O_3 (solid phase)[c]	6 h	MW/800 w	86/[36]
4	Al_2O_3 (liquid phase)[c]	48 h	Δ	68/[36]
5	No catalyst[d]	15 h	Δ	80/[37]
6	No catalyst[b]	12 h	Δ	<40/[35]

[a] Reaction conditions: 4-chlorobenzaldehyde (0.25 mmol), 2-thiobarbituric acid (0.5 mmol), ammonium acetate (0.3 mmol), H_2O (5 mL), catalyst (12 mol%)

[b] Reaction conditions: 4-chlorobenzaldehyde, 1,3-dimethyl-6-aminouracil, barbituric acid 1:1:1, H_2O (5 mL)

[c] Reaction conditions: 4-chlorobenzaldehyde, 2-thiobarbituric acid, ammonium acetate 1:2:1

[d] Reaction conditions: 4-chlorobenzaldehyde, barbituric acid, ammonium acetate 1:2:1, H_2O:EtOH (4:1)

[e] Approximate yields

Finally, to optimize the power microwave oven in reaction, the same reaction was carried out at power ranging from 100 to 450 W. The yield of product **4f** was decreased, and the reaction time was extended when the power was increased from 100 to 450 W. The yield was leveled off when the power was further increased to 450 w. Therefore, the power of 100 W was chosen for all further microwave-assisted reactions (Table 2, entries 1–4).

To show the merit of this method, a comparison of this condition with very few reported methods in the formation of pyrido[2,3-d] pyrimidine is presented in Table 3.

Encouraged by this success, we extended the reaction of a 2-thiobarbituric acid with a range of other aromatic aldehydes and ammonium acetate under similar conditions. All results that are shown in Table 3 are stable solids and the structures of which were determined by IR, Mass, 1H and 13C NMR spectroscopy. Indeed, the spectral data were in good consistent with the structure of an unprecedented product (Scheme 2).

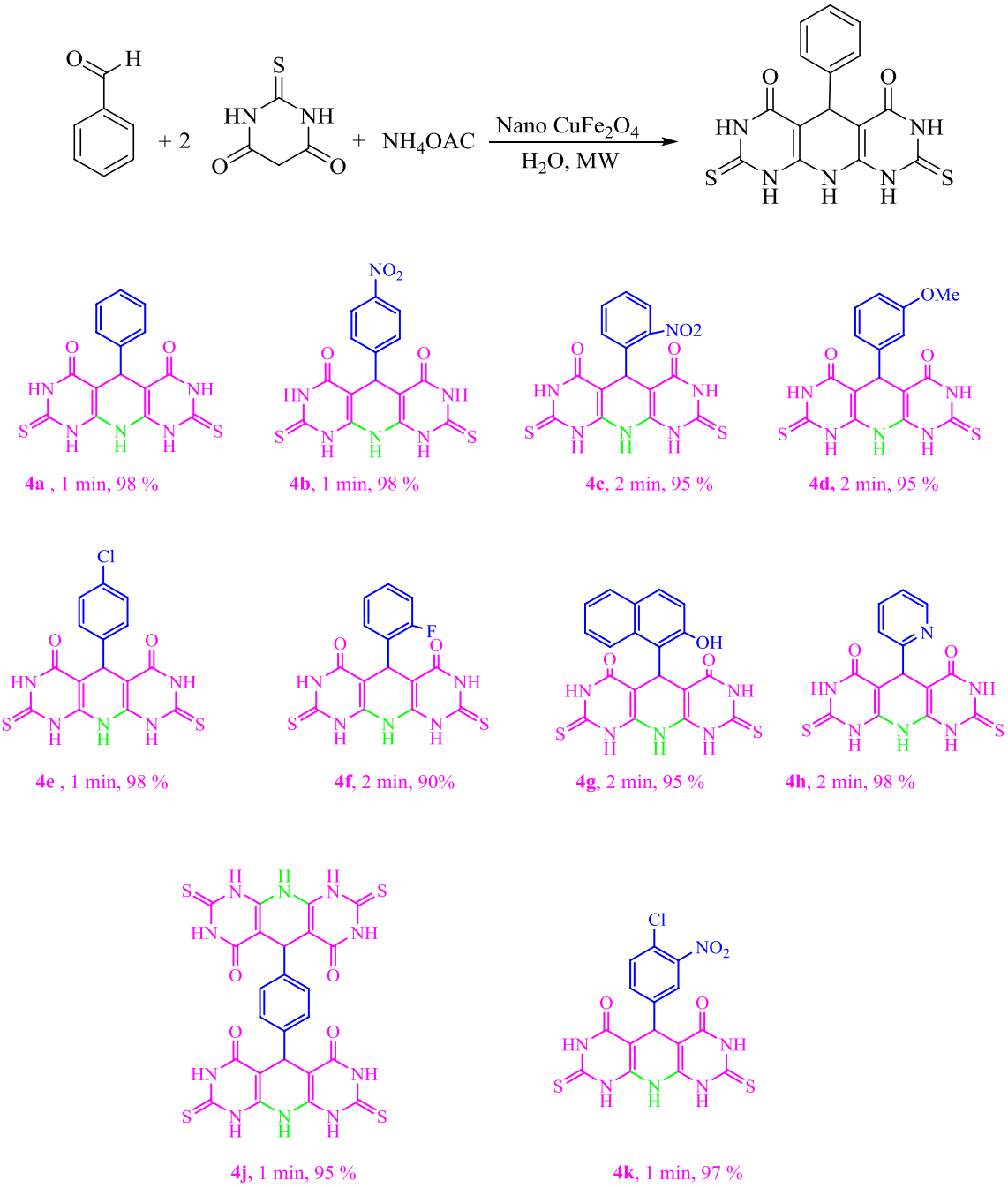
For the investigation of the reaction mechanism, addition of 2-thiobarbituric acid to active benzaldehyde leads to heterodiene **1**. This step was regarded as a fast Knoevenagel condensation reaction. On the other hand, when 2-thiobarbituric acid and ammonium acetate were irradiated, the intermediate **2** was formed. The reaction can mechanistically be considered to proceed through the intermediate **3** formed by Michael-type addition of the heterodiene **1** with intermediate **2**. Then, the intermediate **3** was converted to corresponding products by cyclization and dehydration. As shown in Scheme 3, the $CuFe_2O_4$ as Lewis acid increases the electrophilic character of the starting materials and stabilizes the intermediates through coordinating lone electron pairs of oxygen atom.

Characterization of $CuFe_2O_4$ nanospheres

The manganese ferrite nanoparticles were prepared by coprecipitation of Cu $(NO_3)_2$ and $FeCl_3$ in basic solution at 95 °C using the previously reported method. The synthesized $CuFe_2O_4$ was characterized by X-ray diffraction (XRD), field-emission scanning electron microscope (FESEM). Figure 2 presents the XRD diffraction patterns of the prepared $CuFe_2O_4$ nanoparticles. The position and relative intensities of all the peaks correspond well to the standard XRD pattern of $CuFe_2O_4$ (JCPDS card No. 34-0425) and indicating retention of the crystalline spinel structure. Also, according to Fig. 3, the FESEM images of fresh copper ferrite nanoparticles exhibited the morphology with an average particle size 45-50 nm in diameter.

The magnetization curve for $CuFe_2O_4$ nanoparticles is shown in Fig. 4. It is of great importance that a catalyst should possess sufficient magnetic and superparamagnetic properties for its practical application. Magnetic hysteresis measurements on $CuFe_2O_4$ were taken in an applied magnetic field at room temperature, with the field sweeping from -10000 to +10,000 Oersted. As shown in Fig. 4, the hysteresis loop for the sample was completely reversible confirming its superparamagnetic nature. The catalyst showed high permeability in magnetization and high reversibility in the hysteresis loop (Fig. 4).

Due to importance of recovery and reuse of catalysts in green chemistry, that is highly preferred for a greener process, after having demonstrated the effectiveness of $CuFe_2O_4$ as a catalyst, its reusability was investigated by the reaction of 4-chlorobenzaldehyde, 2-thiobarbituric acid, and ammonium acetate under optimized conditions. After the completion of the reaction monitored by TLC, the solution was filtrated and nanoparticles washed with acetone and EtOH several times. Then washed with distilled water and dried in an oven at 70 °C overnight. The recycled catalyst was used in subsequent reactions. The procedure was repeated, and the results indicated that in four consecutive runs, as shown in Fig. 5. The recovered catalyst was added to the reaction mixture under the same conditions for three cycles without a significant loss of yield and catalytic activity.



Scheme 2 Structure of pyrido[2,3-d:6,5-d′]dipyrimidine derivatives under microwave irradiation

Conclusions

In this paper, we have described a successful, efficient, and convenient strategy for the synthesis of pyrido-dipyrimidine derivatives in one-pot, four-component condensation reactions of benzaldehyde, 2-thiobarbituric acid, and ammonium acetate by using a powerful and green catalyst in water under microwave irradiation. The green solvent and catalyst, mild conditions, environmental acceptability and recyclability of the magnetic

Scheme 3 Proposed mechanism for the formation of **4a**

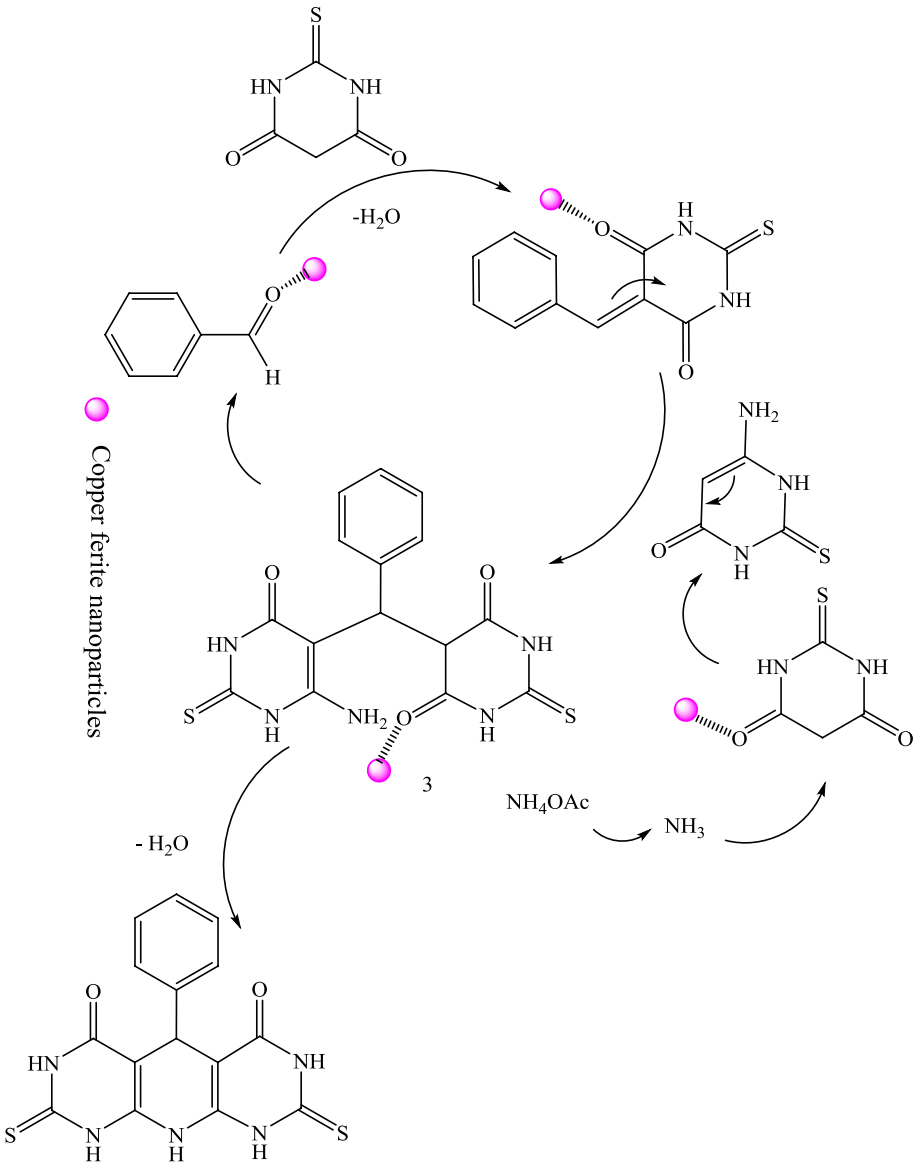
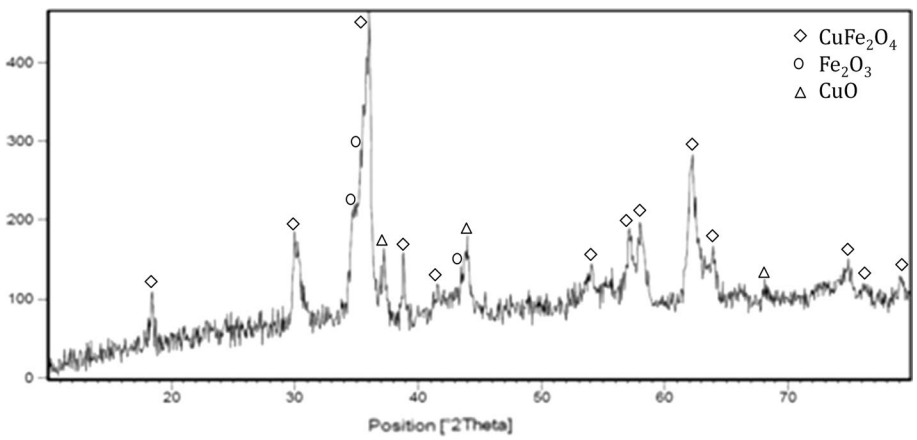


Fig. 2 X-ray diffraction patterns of calcinated $CuFe_2O_4$



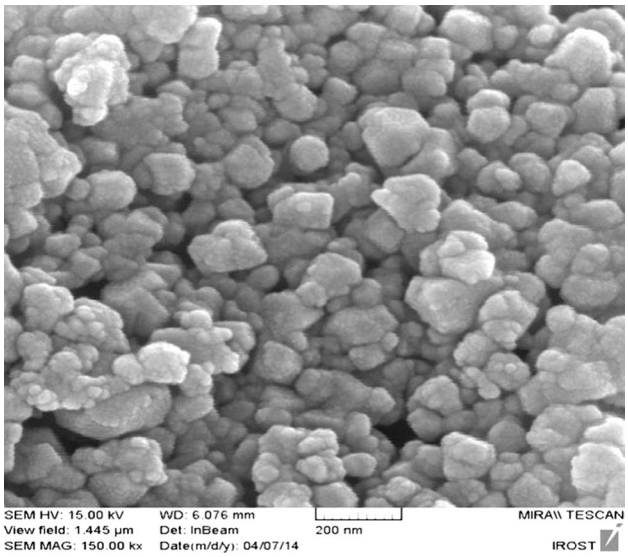


Fig. 3 FESEM image of nano-$CuFe_2O_4$

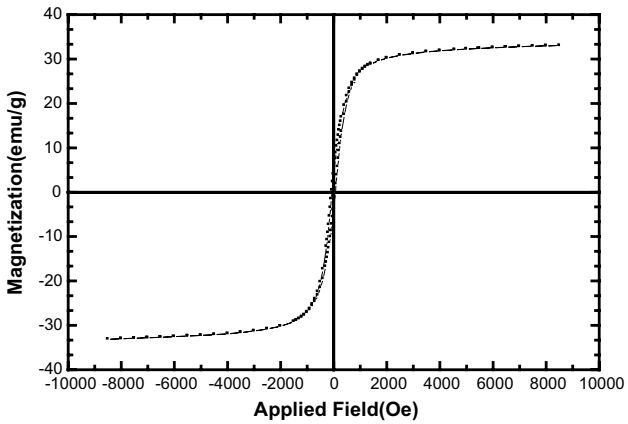


Fig. 4 Vibrating sample magnetometer curve of synthesized $CuFe_2O_4$ nanoparticles

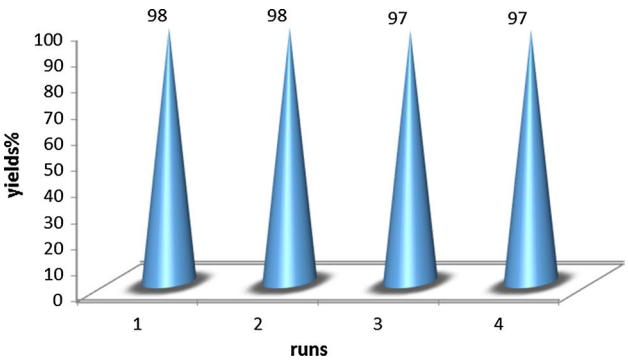


Fig. 5 Catalyst recyclability study on the synthesis of 5-(4-chloro)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d′]dipyrimidine-4,6(1H,5H)-dione

catalyst, convenient and simple workup, high to excellent product yields, and short reaction times are the notable features of this research.

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