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FULL PAPER

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4-(4-Propylpiperazine-1-yl)butane-1-sulfonic acid-modified silica-coated magnetic nanoparticles: A novel and recyclable catalyst for the synthesis of 5-arylidinebarbituric acids and pyrano[2,3-*d*]pyrimidinedione derivatives in aqueous media

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A mild, simple and efficient procedure for the preparation of barbituric acid and pyrano[2,3-*d*]pyrimidine derivatives in aqueous media is described using 4-(4-propylpiperazine-1-yl)butane-1-sulfonic acid-modified silica-coated magnetic nanoparticles as a novel and reusable catalyst. The catalyst was easily isolated from the reaction mixture by magnetic decantation using an external magnet and reused at least eight times without significant degradation in activity.

KEYWORDS
aqueous media, barbituric acid, heterogeneous catalyst, magnetite nanoparticles, pyrano[2,3-*d*]pyrimidines

1 | INTRODUCTION

5-Arylidinebarbituric acids and pyrano[2,3-*d*]pyrimidinedione derivatives are important classes of heterocyclic compounds which have attracted great interest due to their widespread biological and pharmacological properties, such as antitumour,[1] cardiotonic,[2] antibronchitic,[3] antimalarial,[4] antihypertensive,[5] analgesic[6] and antiviral[7] properties. A variety of catalysts and reagents have been used to facilitate the synthesis of 5-arylidinebarbituric acids including CuO-NPs,[8] $BiCl_3$,[9] $[DABCO](SO_3H)_2Cl_2$,[10] $Ce_1Mg_xZr_{1-x}O_2$ (CMZO),[11] BF_3/nano-g-Al_2O_3,[12] $CoFe_2O_4$,[13] $SiO_2 \cdot 12WO_3 \cdot 24H_2O$,[14] NH_2SO_3H[15] and $K_2NiP_2O_7$.[16] Pyrano[2,3-*d*]pyrimidinedione derivatives have also been prepared in the presence of various catalysts, such as Zn[L-proline]$_2$,[17] DAHP,[18] SBA-Pr-SO_3H,[19] L-proline,[20] $[BMIm]BF_4$,[21] *N*-methylmorpholine,[22] 1,4-dioxane,[23] $H_{14}[NaP_5W_{30}O_{110}]$,[24] dibutylamine (DBA)[25] and $[KAl(SO_4)_2]$.[26] Although some of these methods are effective, most of them suffer from drawbacks such as harsh reaction conditions, use of harmful organic solvents, long reaction times, tedious work-up procedures, expensive and moisture-sensitive reagents, strongly acidic conditions, unsatisfactory yields, non-recoverability of the catalyst and environmental pollution. Hence, finding newer and more efficient methods for the synthesis of these types of compounds is still important.

Reactions in aqueous media have many advantages such as high polarity that causes immiscibility with most organic compounds, simple work-up and environmental friendliness. Also, reactions in aqueous media are cheaper to operate and particularly important in industry.

Magnetic nanoparticles (MNPs) play a basic role in modern sciences and technologies due to their wide range of applications in various fields such as magnetic resonance imaging,[27] hyperthermia,[28] fluid transport,[29] drug delivery,[30] environmental remediation[31] and heterogeneous catalysis.[32]

Fe_3O_4 MNPs have superparamagnetic properties. These magnetic nanomaterials have gained significant popularity as heterogeneous supports for various catalytic species due to their easy preparation, good stability, ease of surface modification, high dispersibility, low toxicity, high surface area and easy recovery from solution using an external magnet.

In order to limit the aggregation of Fe_3O_4 nanoparticles, their surface is usually modified with silica layer, because the surface of silanol groups can easily react with various organic and inorganic materials to achieve specific purposes particularly in the field of catalysis.[33]

The use of recyclable solid acids in organic reactions is often considered for pursuing the principles of green chemistry. Nanostructured solid acids exhibit high activity and selectivity. Also, MNPs are unique due to their thermal stability, easy recovery by magnetic separation and higher catalytic activity.[34] Thus the combination of the advantageous of homogeneous protic acids and solid properties using silica-coated Fe_3O_4 nanoparticles is a useful and attractive way to prepare efficient catalytic systems.

2 | EXPERIMENTAL

2.1 | Chemicals

All chemicals, including iron(II) chloride tetrahydrate (99%), iron(III) chloride hexahydrate (98%) and aldehyde derivatives, were purchased from Merck or Fluka and were used without further purification. Water and other solvents were distilled before use. Yields refer to isolated products. The products were characterized by their physical constants, comparison with authentic samples and using Fourier transform infrared (FT-IR), ^{1}H NMR and ^{13}C NMR spectroscopies. Purity determination of substrates and reaction monitoring were accomplished by TLC using silica-gel Polygram SILG/UV 254 plates.

The FT-IR spectra were obtained with a VERTEX 70 (Bruker, Germany). Thermogravimetric analysis (TGA) was performed with a TG/DTA6300 (All-Nanotechnology Company, Japan). Samples were heated from 25 to 700°C at 10°C min^{-1} under nitrogen atmosphere. Scanning election microscopy (SEM) images were obtained with a Philips XL30. Wide-angle X-ray diffraction (XRD) measurements were performed at room temperature with a Siemens D-500 X-ray diffractometer (Germany), using Ni-filtered Co Kα radiation (λ = 0.15418 nm). The chemical composition was obtained using energy-dispersive X-ray (EDX) analysis (ESEM, Philips XL30).

2.2 | Catalyst Preparation

2.2.1 | Preparation of 4-(4-propylpiperazine-1-yl)butane-1-sulfonic acid-modified silica-coated MNPs (Fe_3O_4@SiO_2-Propyl-pip-$SO_3H.HSO_4$)[35]

Magnetite (Fe_3O_4) nanoparticles of approximately 9–11 nm in size were synthesized using a reported chemical co-precipitation technique.[36] The thus prepared Fe_3O_4 MNPs (4 g) were dispersed in a mixture of deionized water (48 ml) and ethanol (180 ml) by ultrasonication for 30 min. Subsequently, $NH_3{\cdot}H_2O$ (4.0 ml, 25%) and tetraethyl orthosilicate (TEOS; 2.4 ml) were charged to the reaction dish. After stirring at room temperature for 12 h, the silica-coated nanoparticles (Fe_3O_4@SiO_2) were collected using a permanent magnet followed by washing three times with ethanol and diethyl ether and dried at 40°C in vacuum for 24 h.

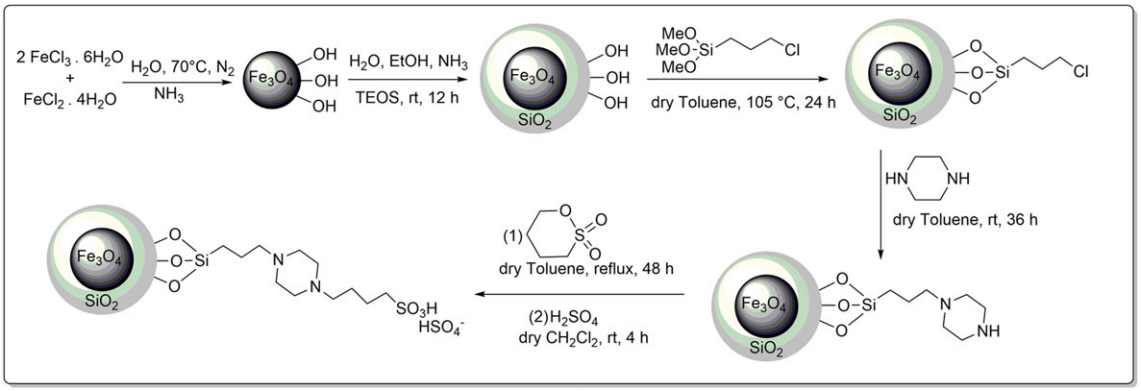
Then the obtained brown precipitate (3.0 g) in dry toluene (40 ml) was sonicated for 30 min. After this time, 3-chloropropyltrimethoxysilane (1.0 ml) was added to the dispersed Fe_3O_4@SiO_2 in toluene and slowly heated to 105°C. The reaction mixture was stirred at this temperature for 24 h. The residue was separated using an external magnet and washed three times with diethyl ether and dichloromethane and dried at 40°C in vacuum for 24 h. After this step, piperazine (2.83 g) was added to a magnetically stirred mixture of the prepared Fe_3O_4@SiO_2-Propyl-Cl (2.78 g) in dry toluene (40 ml), and the mixture was stirred at room temperature for 36 h. The resulting solid material was separated using an external magnet, washed with diethyl ether and dichloromethane, and dried at 40°C in vacuum to afford Fe_3O_4@SiO_2-Propyl-Pip MNPs.

In continuation, the sulfonation of the obtained MNPs was executed using the reaction of Fe_3O_4@SiO_2-Propyl-Pip MNPs with 1,4-butanesultone. For this purpose, Fe_3O_4@SiO_2-Propyl-Pip MNPs (0.5 g) and 1,4-butanesultone (1.2 ml) were suspended in dry toluene (40 ml) and the colloidal solution was refluxed for 48 h, followed by introduction with one equivalent of H_2SO_4 (0.62 ml) to yield the magnetically retrievable reagent (Fe_3O_4@SiO_2-Propyl-Pip-$SO_3H.HSO_4$) and the separation was repeated as in previous steps (Scheme 1).

2.3 | Catalytic Activity

2.3.1 | General procedure for preparation of 5-arylidinebarbituric acids

Aromatic aldehyde (1.0 mmol), barbituric acid (1.0 mmol) and Fe_3O_4@SiO_2-Propyl-Pip-$SO_3H.HSO_4$ (25 mg) in water (10 ml) were stirred at 60°C for the appropriate time. After evaporation of the solvent, the product was



SCHEME 1 Synthesis of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4

dissolved in warm ethanol. The catalyst was then separated using an external magnet from the aqueous ethanol. The obtained products were characterized using FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopies and by comparison of their melting points with reported ones.

2.3.2 | General procedure for preparation of pyrano[2,3-*d*]pyrimidinedione derivatives

A mixture of the aromatic aldehyde (1.0 mmol), barbituric acid (1.0 mmol), ethyl cyanoacetate (1.0 mmol) and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 (30 mg) in water (10 ml) was stirred at 80°C for the appropriate time. After completion of the reaction, the catalyst was collected using an external magnet and the product was purified by recrystallization from aqueous ethanol. The obtained products were characterized using FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopies and by comparison of their melting points with reported ones.

2.4 | Spectroscopic data

2.4.1 | 5-(4-Chlorobenzylidene)barbituric acid

FT-IR (KBr, ν_{max}, cm^{-1}): 3404, 3213, 2970, 1755, 1703, 1570. ^{1}H NMR (DMSO, δ, ppm): 7.53 (d, 2H, Ar—H), 8.08 (dd, 2H, Ar—H), 8.25 (s, 1H, HC═C), 11.25 (s, 1H, NH), 11.40 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ, ppm): 117.46, 127.70, 128.29 (2C), 133.25, 133.50 (2C), 148.70, 150.16, 165.10 (2C). EI-MS: m/z 250 (M^+).

2.4.2 | 5-(2-Chlorobenzylidene)barbituric acid

FT-IR (KBr, ν_{max}, cm^{-1}): 3462, 3121, 2981, 1754, 1569, 1454, 1079, 910, 782. ^{1}HNMR ($CDCl_3$, δ, ppm): 7.36 (t, 1H, H—Ar), 7.47 (t, 1H, H—Ar), 7.53 (d, 1H, H—Ar), 7.73 (d, 1H, Ar—H), 8.29 (s, 1H, HC═C), 11.25 (s, 1H, NH), 11.47 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ, ppm):121.76, 126.29, 128.29, 131.88, 132.25, 133.15, 146.70, 150.16, 160.85, 162.60 (2C). EI-MS: m/z 250 (M^+).

2.4.3 | 5-(4-Hydroxybenzylidene) barbituric acid

FT-IR (KBr, ν_{max}, cm^{-1}): 3420, 3216, 2970, 1755, 1703, 1570. ^{1}H NMR (DMSO, δ, ppm): 6.86 (d, 2H, Ar—H), 8.31 (dd, 2H, Ar—H), 8.24 (s, 1H, HC═C), 10.68 (s, 1H, OH), 11.13 (s, 1H, NH), 11.25 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ, ppm): 115.60 (2C), 118.76, 128.70, 148.80 (2C), 150.20, 152.32, 157.65, 165.10 (2C). EI-MS: m/z 232 (M^+).

2.4.4 | 7-Amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidine-6-carbonitrile

FT-IR (KBr, ν_{max}, cm^{-1}): 3319, 3282, 3145, 3063, 2215, 1743, 1668. ^{1}H NMR (DMSO, δ, ppm): 3.81 (s, 3H, OCH_3), 4.16 (s, 1H, CH), 6.80–6.89 (m, 4H, Ar—H and NH_2), 7.14 (d, J = 7.5 Hz, 2H, Ar—H), 10.80 (s, 1H, NH), 10.98 (s, 1H, NH). ^{13}C NMR (DMSO, δ, ppm): 53.46, 57.46, 58.66, 93.41, 113.14, 123.56, 129.50, 130.34, 151.36, 151.97, 155.61, 159.11, 161.99. MS: m/z 313.01 (M^+).

2.4.5 | Ethyl 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate

FT-IR (KBr, ν_{max}, cm^{-1}): 3311, 3188, 3091, 2228, 1690, 1648, 1543. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 1.17 (t, J = 7.1 Hz, 3H, CH_3), 3.8 (s, 1H, CH), 4.11 (q, J = 7.0 Hz, 2H, CH_2), 7.28 (m, 2H, H—Ar), 7.38 (m, 2H, H—Ar), 7.75 (s, 2H, NH_2), 10.99 (s, 1H, NH), 11.55 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, δ, ppm): 27.09, 39.5,

67.1, 78.3, 83.3, 128.8 (2C), 129.9 (2C), 130.5, 139.2, 150.1, 155.4, 155.8, 159.7, 160.9. MS: (M^+) *m/z* 313, 278, 188, 153, 111, 77, 57, 43.

2.4.6 | Ethyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate

FT-IR (KBr, ν_{max}, cm^{-1}): 3413, 3278, 2239, 2165, 1695, 1662, 1543. ^1H NMR (400 MHz, DMSO, δ, ppm): 1.29 (t, J = 7.2 Hz, 3H, CH_3), 3.32 (s, 3H, OCH_3), 3.71 (s, 1H, CH), 4.41 (q, J = 7.1 Hz, 2H, CH_2), 6.93 (m, 2H, H—Ar), 7.65 (m, 2H, H—Ar), 7.09 (s, 2H, NH_2), 10.03 (s, 1H, NH), 11.09 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, δ, ppm): 23.03, 37.2, 55.8, 62.02, 75.6, 78.9, 114.2, 130.1, 134.1, 143.9, 150.5, 157.2, 162.4, 165.2, 167.3. EI-MS: *m/z* = 89 (M^+), 269, 232, 221, 201, 176, 149, 110.

3 | RESULTS AND DISCUSSION

In recent years, the introduction of new catalysts for the promotion of organic reactions has become an important part of our ongoing research programme.[35,37–44] Herein and in continuation of these studies, we report the use of our novel magnetic Fe_3O_4-based nanoreagent formulated as Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4[35] as a catalyst in the preparation of 5-arylidinebarbituric acids and pyrano[2,3-*d*]pyrimidinedione derivatives.

3.1 | Catalyst Characterization

3.1.1 | FT-IR analysis

FT-IR spectra of Fe_3O_4, Fe_3O_4@SiO_2, Fe_3O_4@SiO_2-Propyl-Pip and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 are compared in Fig. 1. These spectra show broad bands at around 550–650 cm^{-1}, which are attributed to Fe—O vibrations. In the spectra of Fe_3O_4@SiO_2, Fe_3O_4@SiO_2-Propyl-Pip and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4, the strong band observed at around 1000–1200 cm^{-1} can be due to Si—O—Si stretching modes of the silica shell. In the case of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4, the strong bands at 1150 and 1432 cm^{-1} are related to the stretching modes of the S═O bonds and the broad band around 1100 cm^{-1} is assigned to other stretching modes of S═O which is overlapped with the stretching modes of Si—O. In this spectrum the bands corresponding to S—O stretching modes of sulfonic acid functional group lie at around 804 and 875 cm^{-1}. This comparison confirms the probable preparation of the catalyst.

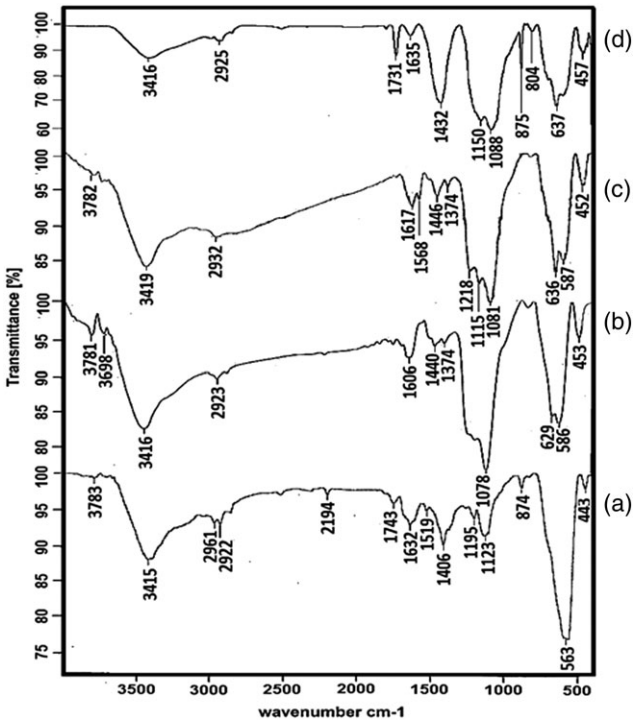


FIGURE 1 FT-IR spectra of Fe_3O_4 (a), Fe_3O_4@SiO_2 (b), Fe_3O_4@SiO_2-Propyl-Pip (c) and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 (d)

3.1.2 | Powder XRD

The XRD pattern of Fe_3O_4 clearly matches with the literature data from JCPDS 79-0419. Notably, the same peaks were also observed in the XRD pattern of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4, with slight changes in the nature of the peaks, which could be due to the presence of sulfonic acid functionality on the surface of the prepared reagent (Fig. 2).

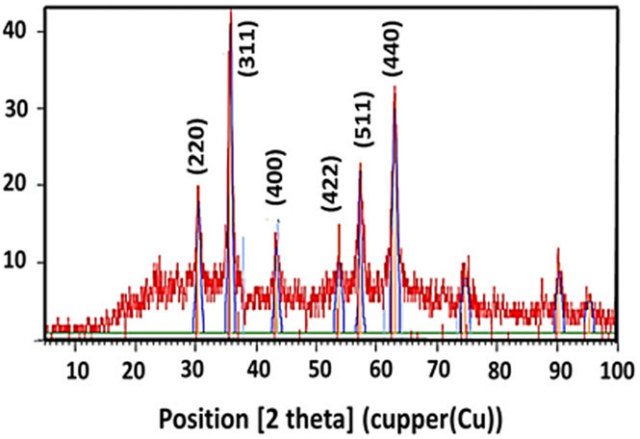


FIGURE 2 XRD pattern of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4

3.1.3 | Thermal analysis

The thermal stability of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 was investigated using TGA (Fig. 3). The loss of the adsorbed water on the support and silane groups resulted in initial weight loss of 0.87% up to 120°C. Another peak appears in the range from 120 to 200°C due to decomposition of the sulfonic acid group and formation of sulfur dioxide. According to TGA, the amount of sulfonic acid functionality on Fe_3O_4 is evaluated to be 0.18%. The curve also shows a steady weight loss in the range from 200 to 600°C, which could be ascribed to the loss of covalently attached organic moiety. The amount of organic moiety was found to be about 8.68% against total solid catalyst.

3.1.4 | SEM analysis

The samples of Fe_3O_4 and nano-sized Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 were analysed using SEM for determination of particle shape, surface morphology and size distribution (Fig. 4). The SEM images of Fe_3O_4 and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 samples show that these particles are roughly spherical in shape, and the average size is about 10–15 and 65–75 nm, respectively. An increase of the average size of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 is in agreement with its preparation.

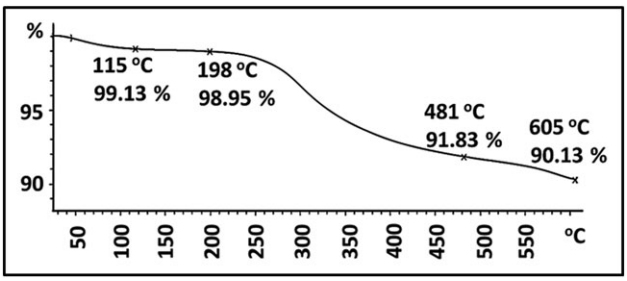


FIGURE 3 TGA curve of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4

3.1.5 | EDX analysis

The EDX spectrum of the Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 sample is shown in Fig. 5 Which clearly show the presence of N, C and S elements in the Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 catalyst. Moreover, the presence of Si, O and Fe signals indicates the wrapping of SiO_2 on the Fe_3O_4 particles, and the considerable intensity of the Si peak indicates that the Fe_3O_4 nanoparticles were trapped by SiO_2. According to the above analysis, it can be concluded that Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 had been successfully synthesized.

3.2 | Application of Fe_3O_4@SiO_2-Propyl-pip-SO_3H.HSO_4

After successful use of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in the synthesis of 1-(benzothiazolylamino) phenylmethyl-2-naphthols, we were interested in investigating the applicability of this reagent in the promotion of the synthesis of 5-arylidinebarbituric acids and pyrano[2,3-*d*]pyrimidinedione derivatives in aqueous media.

At first and in order to optimize the reaction conditions, the reaction of 4-chlorobenzaldehyde and

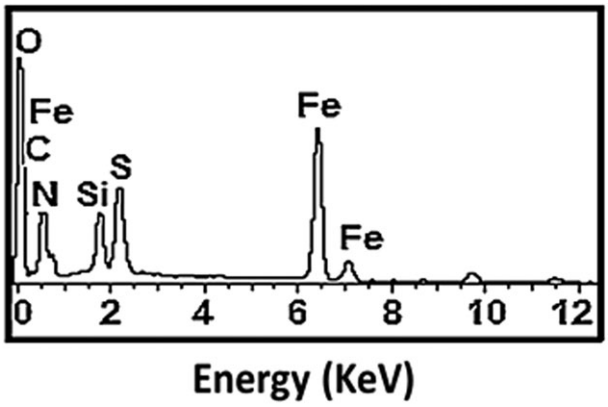


FIGURE 5 EDX spectrum of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4

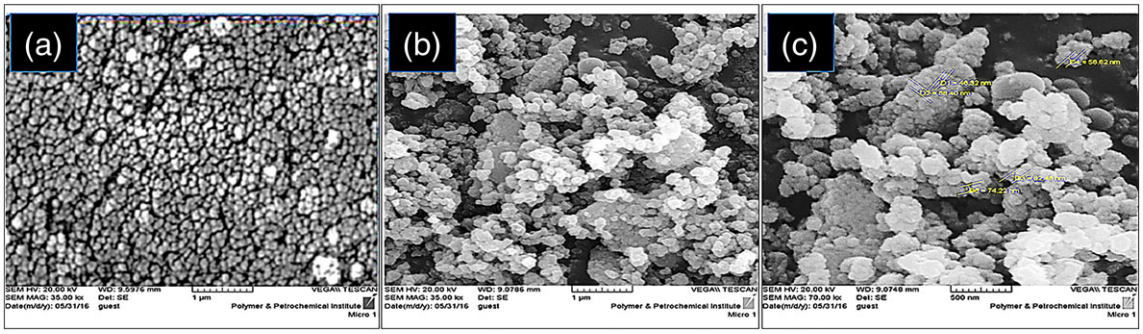
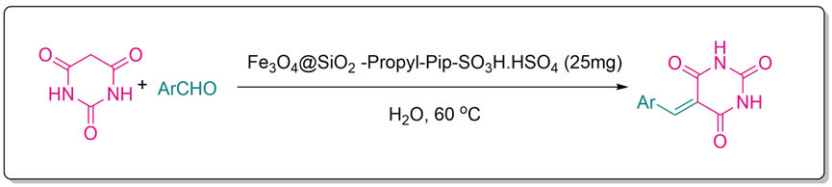


FIGURE 4 SEM micrographs of Fe_3O_4 (1 μm) (a), Fe_3O_4@SiO_2-Propyl-Pip-SO_3H (1 μm) (b) and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 (500 nm) (c)

TABLE 1 Optimization of reaction conditions for synthesis of 5-arylidinebarbituric acid derivatives using Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4[a]

Entry	Catalyst (mg)	Solvent	Temp. (°C)	Time (min)	Conversion (%)
1	25	H_2O	r.t.	60	100
2	25	H_2O	60	10	100
3	25	H_2O	80	10	100
4	15	H_2O	60	30	80
5	35	H_2O	60	5	100
6	25	H_2O–EtOH	60	40	100
7	25	EtOH	60	90	50
8	25	—	60	90	20
9	25	CH_2Cl_2	60	90	20
10	25	CH_3CN	60	90	20

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol), barbituric acid (1 mmol) and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 under various conditions.



SCHEME 2 Synthesis of 5-arylidinebarbituric acid derivatives catalysed by Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4

TABLE 2 Preparation of 5-arylidinebarbituric acid derivatives catalysed by Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4[a]

Entry	Aldehyde	Time (min)	Yield (%)[b]	M.p. (°C)	
				Found	Reported
1	C_6H_4CHO	12	89	248–250	255–256[10]
2	4-ClC_6H_4CHO	10	95	298–300	298.5[45]
3	2-ClC_6H_4CHO	15	89	261–263	268[15]
4	4-BrC_6H_4CHO	10	88	290–292	292–293[45]
5	4-$NO_2C_6H_4CHO$	15	93	273–274	268–270[46]
6	3-$NO_2C_6H_4CHO$	20	88	229–232	231–233[13]
7	2-$NO_2C_6H_4CHO$	25	88	273–275	274–276[10]
8	4-OHC_6H_4CHO	12	92	>300	>300[45]
9	2-OHC_6H_4CHO	12	94	252–254	249–250[13]
10	4-$MeOC_6H_4CHO$	20	95	297–300	306–308[47]
11	2-$MeOC_6H_4CHO$	22	89	265–267	268–269[8]
12	3-$CH_3C_6H_4CHO$	20	90	213–215	210–214[8]
13	C_6H_5CH&dbond;CHCHO	20	85	270–273	268[45]
14	4-$NMe_2C_6H_4CHO$	25	85	280–281	281–282[47]
15	2-Naphthaldehyde	30	92	266 (dec.)	266 (dec.)[45]
16	4-$CHOC_6H_4CHO$	40	91	>300	>300[10]
17	3-$CHOC_6H_4CHO$	45	90	>300	>300[10]

[a]Reaction conditions: aldehyde (1 mmol), barbituric acid (1 mmol) and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 (25 mg) in H_2O at 60°C.

[b]Isolated yields.

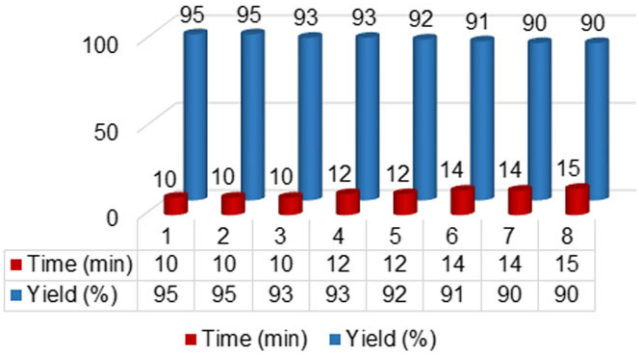


FIGURE 6 Reusability of fe3o4@sio2-propyl-pip-so3h.hso4 in the reaction of 4-chlorobenzaldehyde with barbituric acid

barbituric acid was selected as a model reaction and the effects of various conditions including amount of catalyst and temperature were explored (Table 1). For choosing the reaction media, various solvents such as EtOH, H_2O, CH_2Cl_2 and CH_3CN and also solvent-free conditions were used for this reaction. The best result was obtained using 25 mg of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 when the reaction is proceeded in water at 60°C (Scheme 2). It is important to note that using smaller amounts of the catalyst led to the product in longer times.

After optimization of the reaction conditions and in order to establish the effectiveness and the applicability of the method, the protocol was explored for a variety of

TABLE 3 Comparison of performance of various catalysts and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in synthesis of 5-(4-chlorobenzylidene) pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (Table 2, entry 2)

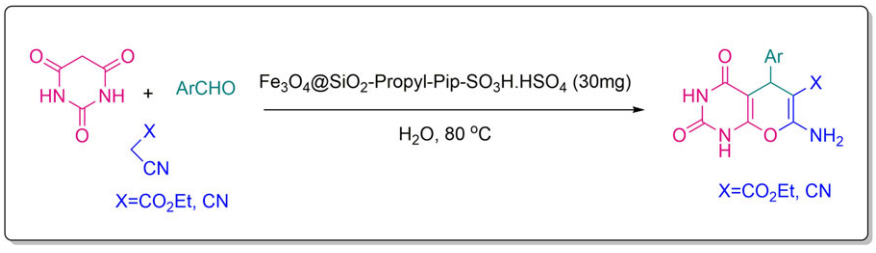
Entry	Catalyst/conditions	Time (min)	Yield (%)[a]	Ref.
1	1-*n*-Butyl-3-methylimmidazoliumtetrafluoroborate ([bmim]BF_4)/grinding	120	77	[45]
2	Aminosulfonic acid/grinding	180	96	[15]
3	PVP-Ni nanoparticles/ethylene glycol, 50°C	5	93	[47]
4	NaPTSA/solvent free, r.t.	4	92	[48]
5	CMZO/solvent free, microwave	3	94	[11]
6	$CoFe_2O_4$ nanoparticles/water–ethanol, r.t.	2	91	[13]
7	Copper oxide nanoparticles/solvent-free, r.t.	12	98	[8]
8	Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4/H_2O, 60°C	10	95	This work

[a]Isolated yields.

TABLE 4 Optimization of reaction conditions for synthesis of pyrano[2,3-*d*]pyrimidine derivatives using Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4[a]

Entry	Catalyst (mg)	Solvent	Temp. (°C)	Time (min)	Conversion (%)
1	20	H_2O	80	20	80
2	30	H_2O	80	20	100
3	40	H_2O	80	15	100
4	30	H_2O	Reflux	10	100
5	30	H_2O–EtOH	80	60	80
6	30	H_2O	r.t.	60	20
7	30	EtOH	r.t.	60	20
8	30	EtOH	80	60	20

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol), barbituric acid (1 mmol), malononitrile (1 mmol) and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 under various conditions.



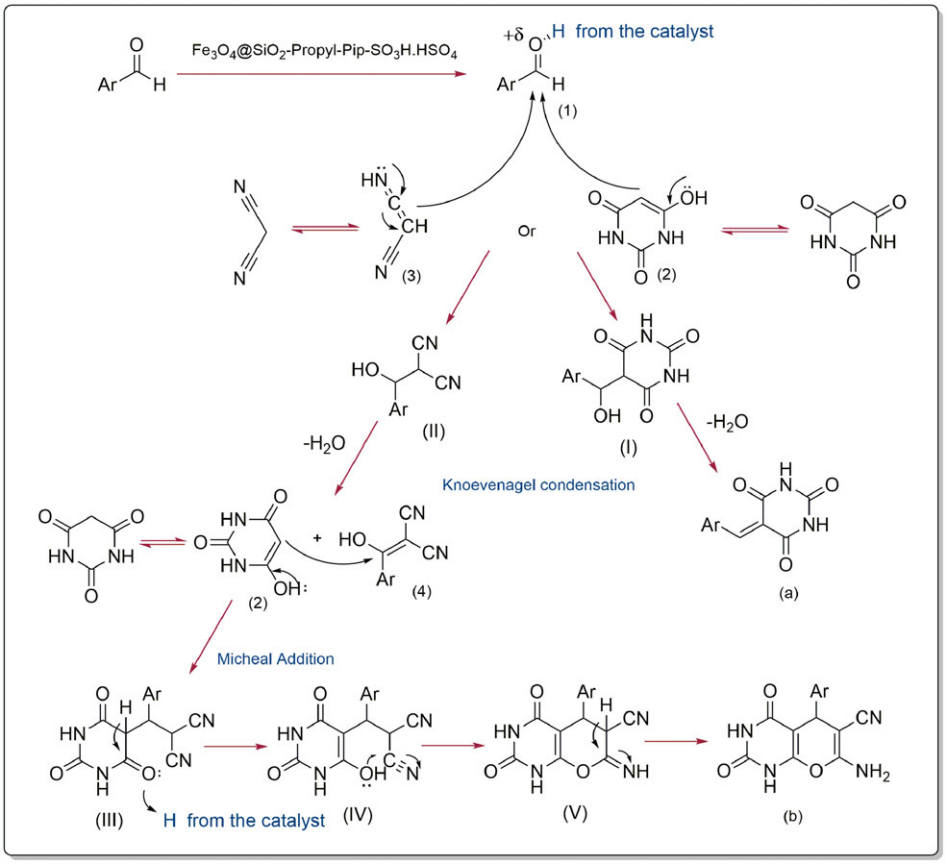
SCHEME 3 Synthesis of pyrano[2,3-*d*] pyrimidinone derivatives catalysed by Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4

TABLE 5 Preparation of pyrano[2,3-*d*]pyrimidine derivatives catalysed by Fe_3O_4@SiO_2-Propyl-Pip-$SO_3H.HSO_4$[a]

Entry	Aldehyde	X	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported
1	C_6H_4CHO	CN	15	90	219–220	221–224[49]
2	4-ClC_6H_4CHO	CN	20	95	240–242	246[50]
3	2-ClC_6H_4CHO	CN	25	92	210–212	211–212[51]
4	4-BrC_6H_4CHO	CN	15	90	227–230	230–231[18]
5	4-$NO_2C_6H_4CHO$	CN	20	97	240–243	238–240[25]
6	3-$NO_2C_6H_4CHO$	CN	15	90	265–268	267–269[42]
7	4-$MeOC_6H_4CHO$	CN	30	90	268–270	266–270[10]
8	4-OHC_6H_4CHO	CN	30	87	>300	>300[49]
9	4-$CHOC_6H_4CHO$	CN	25	90	>300	>300[52]
10	C_6H_4CHO	CO_2Et	50	85	202–204	206–210[25]
11	4-ClC_6H_4CHO	CO_2Et	60	90	>300	>300[53]
12	4-$NO_2C_6H_4CHO$	CO_2Et	60	85	286–289	289–293[25]
13	3-$NO_2C_6H_4CHO$	CO_2Et	70	80	245–248	265[17]
14	4-$MeOC_6H_4CHO$	CO_2Et	90	95	293–295	297–298[53]
15	4-MeC_6H_4CHO	CO_2Et	90	85	230–233	225[17]

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol), barbituric acid (1 mmol), malononitrile (1 mmol) and Fe_3O_4@SiO_2-Propyl-Pip-$SO_3H.HSO_4$ (30 mg) in H_2O at 80°C.

[b]Isolated yields.



SCHEME 4 Proposed mechanism of studied reactions in the presence of Fe_3O_4@SiO_2-Propyl-Pip-$SO_3H.HSO_4$

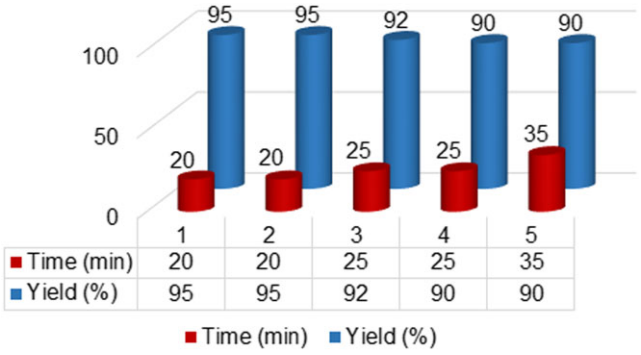


FIGURE 7 Reusability of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in the reaction of 4-chlorobenzaldehyde, barbituric acid and malononitrile

simple readily available substrates under the optimal conditions. It was observed that under the optimized conditions, a wide range of aromatic aldehydes containing electron-withdrawing as well as electron-donating groups such as Cl, Br, CH_3, OCH_3, Et, NO_2 and OH in the *ortho*, *meta* and *para* positions of the benzaldehyde ring in reaction with barbituric acid were easily converted to the corresponding products in short reaction times with high isolated yields (Table 2).

The recyclability of the catalyst was examined in the synthesis of 5-arylidinebarbituric acid derivatives. When the reaction was completed, the catalyst was separated using an external magnet, washed with ethanol and diethyl ether, dried and reused for the same reaction. This process was carried out over eight runs and each time the product was obtained with the least change in the reaction time and yield. The results are shown in Fig. 6.

Table 3 compares our results with the results reported using various other catalysts in the synthesis of 5-(4-chlorobenzylidene)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (Table 2, entry 2). This comparison demonstrates the favourable catalytic activity of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 compared to the other catalysts presented in Table 3.

After the successful application of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in the preparation of 5-arylidinebarbituric acid derivatives, we attempted to study the applicability of this catalyst in the promotion of the synthesis of pyrano[2,3-*d*]pyrimidinone derivatives by studying the reaction of 4-chlorobenzaldehyde, barbituric acid and malononitrile in the presence of this reagent. The obtained results (Table 4) indicated the suitable conditions for the synthesis of pyrano[2,3-*d*]pyrimidinones in the presence of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4, as shown in Scheme 3. After optimization studies and to determine the efficiency of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in the preparation of pyrano[2,3-*d*]pyrimidine derivatives, various aromatic aldehydes were subjected to the same reaction under the optimal conditions. The obtained results showed that these conversions occurred with excellent yields in very short times (Table 5).

The proposed mechanism for the synthesis of 5-arylidinebarbituric acids and pyrano[2,3-*d*]pyrimidinone derivatives in the presence of the catalyst is shown in Scheme 4. According to this mechanism, the aldehyde is activated by the proton from Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4. Then, the activated aldehyde (1) is attacked by activated barbituric acid (2) through a Knoevenagel reaction to generate intermediate (I) and, with loss of a

TABLE 6 Comparison of performance of various catalysts and Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in the synthesis of pyrano[2,3-*d*]pyrimidine derivatives

Entry	Catalyst/conditions	Time (min)	Yield (%)[a]	Ref.
1	Zn[L-proline]$_2$/EtOH, reflux	30–720	80–92	[17]
2	DBA/(H_2O, EtOH), reflux	43–129	83–94	[25]
3	$H_{14}[NaP_5W_{30}O_{110}]$/EtOH, reflux	30–60	85–90	[24]
4	DAHP/EtOH, r.t.	120	71–81	[18]
5	$[KAl(SO_4)_2]$/H_2O, 80°C	40–50	80–90	[26]
6	SBA-Pr-SO_3H/solvent-free, 140°C	5–45	30–90	[19]
7	Al-HMS-20/EtOH, r.t.	720	84–95	[49]
8	[BMIm]BF_4/90°C	180–300	82–95	[21]
9	1,4-Dioxane/H_2O, reflux	1–2	60–70	[23]
10	Fe_3O_4@SiO_2@formamidinesulfinic acid/H_2O, 80°C	360	73–91	[50]
11	Fe_3O_4@MCM-41@Zr-piperazine-MNPs/(H_2O, EtOH), 80°C	6–35	59–92	[54]
12	Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4/H_2O, 80°C	15–90	90–98	This work

[a]Isolated yields.

molecule of water, 5-arylidinebarbituric acid derivatives (a) are achieved (Table 2, entries 1–17).

For the three-component reaction, the activated aldehyde (1) is attacked by activated malononitrile (3) through a Knoevenagel reaction to generate intermediate (II) and, with loss of a molecule of water, cyanoolefin (4) is achieved. In continuation, a Michael addition occurs between (4) and (2) to generate intermediate (III). Then a hydrogen shift happens and the Michael adduct tautomerizes in the presence of acidic catalyst to generate intermediate (IV). Afterwards, it cyclizes to give intermediate (V) which is tautomerized to afford the pyrano[2,3-*d*]pyrimidinone derivatives (b) (Table 5, entries 1–15).

The recoverability of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 was measured in the synthesis of pyrano[2,3-*d*]pyrimidine derivatives under the optimized reaction conditions. This procedure was repeated five times and each time the product was obtained using the recovered catalyst with the least change in the reaction time and yield (Fig. 7). In order to show the unique catalytic behaviour of Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 in this reaction, we have compared our results with the results reported using other catalysts in the synthesis of pyrano[2,3-*d*]pyrimidinone derivatives. As is evident from Table 6, Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 is the most effective catalyst for this purpose.

4 | CONCLUSIONS

We have developed a simple and effective method for the synthesis of biologically and pharmacologically active 5-arylidinebarbituric acids and pyrano[2,3-*d*]pyrimidinone derivatives using Fe_3O_4@SiO_2-Propyl-Pip-SO_3H.HSO_4 as a heterogeneous magnetic nanocatalyst in appropriate times with excellent yields. This catalytic system offers advantages such as mild reaction conditions, short reaction times, high yields of products, easy catalyst preparation and simple separation and recovery of the catalyst from the reaction mixture using an external magnet, making it a useful and attractive process for the preparation of these compounds.

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