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FULL PAPER

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Green synthesis of new pyrimido[4,5-d]pyrimidine derivatives using 7-aminonaphthalene-1,3-disulfonic acid-functionalized magnetic Fe_3O_4@SiO_2 nanoparticles as catalyst

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Abstract

We, herein, describe a novel, simple, efficient and one-pot multi-component procedure for the synthesis of substituted pyrimido[4,5-d]pyrimidines via reaction of *N,N*-dimethyl-6-amino uracil, isothiocyanate and aromatic aldehydes promoted by 7-aminonaphthalene-1,3-disulfonic acid (ANDSA)-functionalized magnetic Fe_3O_4@SiO_2 in water as solvent and without using any other harmful organic reagents. Compared with other reactions, using these organic–inorganic hybrid heterogeneous catalysts can help us to achieve a green procedure, high catalytic activity, easy recovery with an external magnetic field, and short reaction times.

KEYWORDS

green chemistry, magnetic nanoparticles, *N,N*-dimethyl 6-amino uracil, phenylisothiocyanate, pyrimido[4,5-d]pyrimidine

1 | INTRODUCTION

In recent years, the use of hazardous solvents, expensive and toxic reagents, and formation of undesirable byproducts are some constraints for synthetic chemists.[1,2] Chemists use selective and environmentally friendly catalysts, such as porous solids, heterogeneous catalysts and nano-catalysts,[3,4] as well as non-toxic solvents that are directly related to the principles of green chemistry.

Nanoparticles due to their high surface area, high activity and selectivity, easy separation and isolation of products from the reaction mixture have been developed as suitable replacements for conventional heterogeneous catalysts.[5–8] The nano-sized particles increase the exposed surface area of the active component of the catalyst, so appending the contact between reactants and catalyst dramatically, and mimicking the homogeneous catalysts. Insolubility of nano-sized particles in reaction solvents like heterogeneous catalysts that cause their ease of separation from the reaction mixture makes the product isolation stage effortless. However, nano-sized particles like homogeneous catalysts enhance the contact between reactants and catalyst dramatically, and increase the exposed surface area of the active component of the catalyst. Also, chemical and physical properties of nano-catalysts like size, shape, composition and morphology can impress their activity and selectivity.[8]

Recently, supported magnetic metal nanoparticles have been introduced as a new class of nano-catalysts. Because of their high surface area, they generally display higher catalytic activity than traditional heterogeneous acid catalysts.[9,10]

One class of heterocyclic compounds known to display various pharmaceutical and biological activities is pyrimidines. Among them, the pyrido[2,3-d]pyrimidines and pyrimido[4,5-d]pyrimidines are an important class of

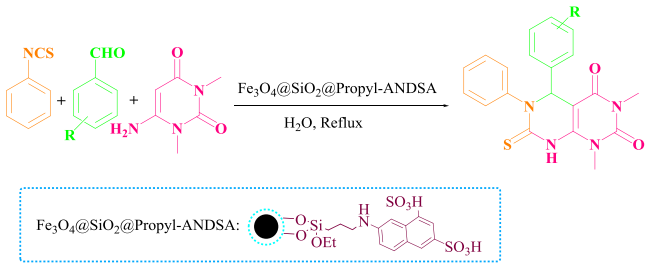
annulated uracil with biological significance, such as antiallergic, anticancer, antihypertensive, vasodilators and bronchodilators agents.[11] Moreover, various attempts that have been made towards the synthetic manipulation of uracil for the preparation of pyrimido[4,5-d]pyrimidine derivatives include three-component reactions,[12–15] as well as cycloaddition reactions.[16–19] Some of them use *p*-toluenesulfonic acid,[14] AcOH[13,16] and iodine[19] as catalysts. Few reported procedures[12,17,18] are solvent-free, while one of them[14] uses water as solvent. However, these methods require forcing conditions, long reaction times, high energy and complex synthetic pathways.[20] To overcome these difficulties, there is a need to develop more effective and sustainable chemical procedures for the synthesis of pyrimido[4,5-d]pyrimidines.

It is on this basis that we have recently introduced 7-aminonaphthalene-1,3-disulfonic acid-functionalized magnetic Fe_3O_4@SiO_2 nanoparticles (Fe_3O_4@SiO_2@Propyl-ANDSA) as an easily prepared and effective heterogeneous catalyst for the synthesis of polysubstituted pyrrolidinones.[21] Now, in this article, we have presented another important application of Fe_3O_4@SiO_2@Propyl-ANDSA as an efficient, mild, safe, non-toxic and magnetic powerful solid acid catalyst in three-component condensation of aldehydes, isothiocyanate and *N*,*N*-dimethyl 6-amino uracil in water leading to the formation of pyrimido[4,5-d]pyrimidine derivatives without requiring any hazardous solvent (Scheme 1).

2 | EXPERIMENTAL

2.1 | Chemicals and instruments

All commercial materials were purchased from Merck. ^{1}H NMR and ^{13}C NMR spectra were measured at Bruker BioSpin GmbH 400 MHz FT NMR spectrometers. Elemental analyses (C, H, N, S) were performed with Leco-932, and mass analysis was also performed on 5973 network mass-selective detector (70 eV). Fourier transform infrared (FT-IR) spectra were recorded on a PerkinElmer 10.02.00 FT spectrophotometer from KBr pellets. Melting points were measured on a BUCHI 510 apparatus in open capillary tubes.



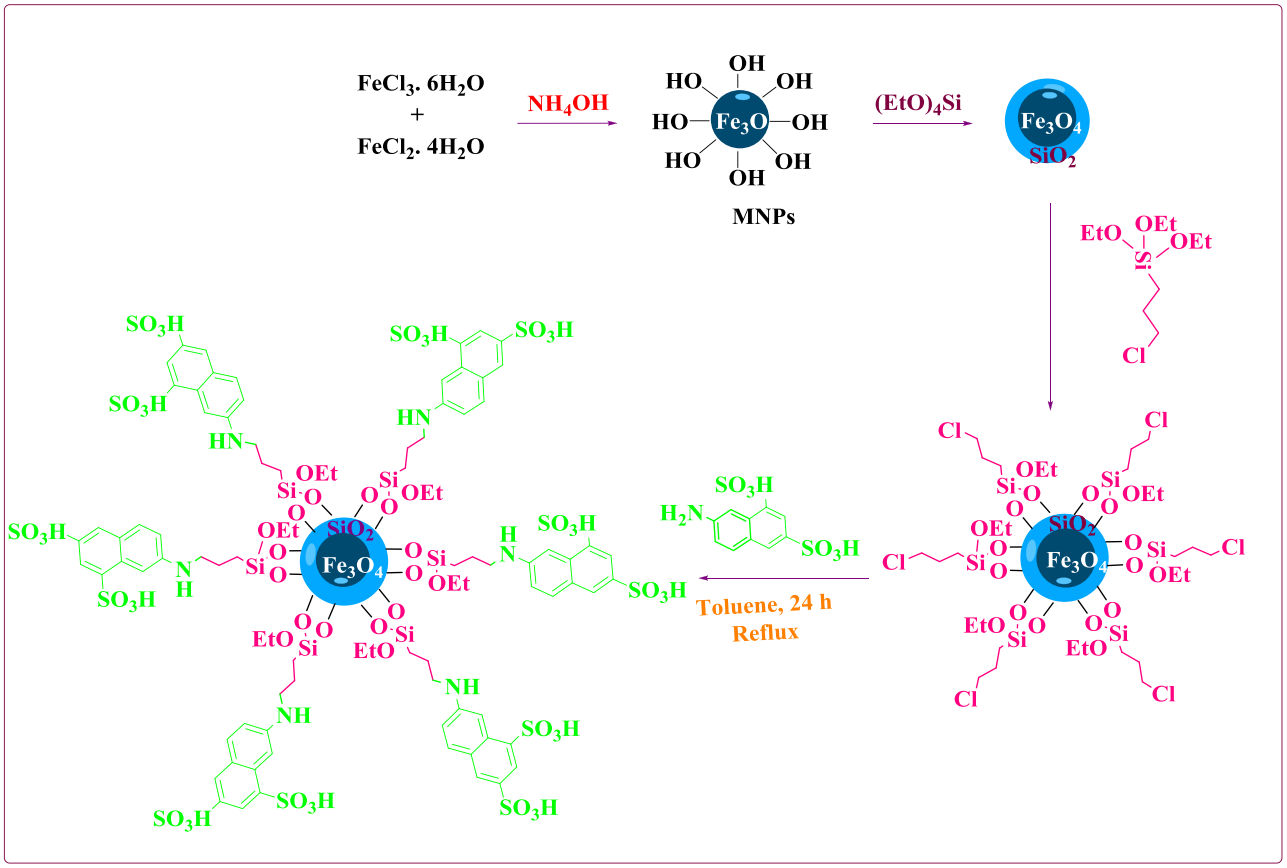
SCHEME 1 Fe_3O_4@SiO_2@Propyl-ANDSA catalyzed synthesis of pyrimido[4,5-d]pyrimidine

2.2 | Preparation of ANDSA-functionalized magnetic Fe_3O_4 nanoparticles (Fe_3O_4@SiO_2@Propyl-ANDSA)

The magnetic nanoparticles (Fe_3O_4) were synthesized according to Massart's method using $FeCl_3{\cdot}6H_2O$ and $FeCl_2{\cdot}4H_2O$. As illustrated in Scheme 2, preparation of catalyst followed with coating a layer of silica on the surface of the Fe_3O_4 nanoparticles and then functionalization of the iron oxide with two sulfonic acid groups was achieved by treatment with tetraethyl orthosilicate [$(EtO)_4Si$] and then with 3-chloropropyltriethoxysilane, followed by ANDSA (Scheme 2). Fe_3O_4@SiO_2@Propyl-ANDSA nanoparticles were characterized by FT-IR, scanning electron microscopy, transmission electron microscopy (TEM), thermo-gravimetric analysis (TGA), X-ray powder diffraction, X-ray photoelectron spectroscopy, energy-dispersive X-ray spectroscopy (EDX), vibrating sample magnetometer (VSM) and ion exchange pH-analysis.[21] In order to determine the amount of ANDSA loaded on the surface of fe3o4@sio2@Propyl, we measured the percentage of sulfur in Fe_3O_4@SiO_2@Propyl-ANDSA and Fe_3O_4@SiO_2@Propyl, with elemental analysis. Using the obtained data (Tables S1 and S2), the amount of ANDSA loaded on the Fe_3O_4@SiO_2@Propyl was calculated as 6.48%.

2.3 | General procedure for the synthesis of pyrimido[4,5-d]pyrimidine

In a 10-ml flask, a mixture of phenylisothiocyanate (1 mmol, 0.120 ml), aldehyde (1 mmol) and *N*,*N*-dimethyl-6-amino uracil (1 mmol, 0.155 g) in water (5 ml) was refluxed for an appropriate time in the presence of 0.05 g of Fe_3O_4@SiO_2@Propyl-ANDSA as catalyst. After completion of the reaction, the catalyst was separated by an external magnet, and the resulting precipitates were collected and washed with hot water (5 ml) and cold ethanol (10 ml). The crude product was purified by recrystallization from EtOH. The structures of all the products were established on the basis of their physical and spectral [FT-IR, ^{1}H NMR, ^{13}C NMR, CHNS and mass spectroscopy (MS)] data, and compared with those reported for known C_4, C_6, C_8, C_{13} and C_{15} products.



SCHEME 2 Stepwise synthesis pathway of Fe_3O_4@SiO_2@Propyl-ANDSA as a nano-magnetic core–shell supported solid acid catalyst

2.4 | 5-(2-Fluorophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 1)

Cream powder (80%); m.p.: 244–245 °C; [found: C, 59.73; H, 4.64; N, 14.47; S, 7.28. $C_{20}H_{17}FN_4O_2S$ requires: C, 60.59; H, 4.32; N, 14.13; S, 8.09%]; IR (KBr) (ν_{max}, cm^{-1}) 3207, 1698, 1591; δ_H (400 MHz, DMSO-d_6); 3.12 (s, 6H, $2CH_3$), 5.61 (s, 1H, CH), 6.96–7.44 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 27.9, 29.9, 31.2, 114.6, 114.8, 123.5, 127.1, 127.2, 127.3, 128.7, 129.8, 150.3, 153.5, 153.6, 159.4, 161.9. MS: m/z = 396 (M^+).

2.5 | 5-(4-Fluorophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 2)

Cream powder (90%); m.p.: 264–266 °C; [found: C, 60.73; H, 3.94; N, 14.89; S, 7.00. $C_{20}H_{17}FN_4O_2S$ requires: C, 60.59; H, 4.32; N, 14.13; S, 8.09%]; IR (KBr) (ν_{max}, cm^{-1}) 3363, 1702, 1680; δ_H (400 MHz, DMSO-d_6); 3.22 (s, 6H, $2CH_3$), 5.63 (s, 1H, CH), 7.07–7.51 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); δ 27.9, 29.9, 34.7, 85.7, 114.0, 114.2, 122.9, 128.2, 128.3, 135.4, 150.4, 153.9, 154.1, 158.9, 161.3, 162.7; MS: m/z = 396 (M^+).

2.6 | 5-(2-Chlorophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 3)

White powder (83%); m.p.: 273–276 °C; IR (KBr) (ν_{max}, cm^{-1}) 3447, 1693, 1655; [found: C, 57.54; H, 4.59; N, 13.18; S, 7.61. $C_{20}H_{17}ClN_4O_2S$ requires: C, 52.52; H, 3.75; N, 12.25; S, 7.01%; C, 58.15; H, 4.15; N, 13.57; S, 7.76%]; δ_H (400 MHz, DMSO-d_6); 3.15 (s, 6H, $2CH_3$), 5.53 (s, 1H, CH), 6.95–7.49 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 30.0, 34.6, 85.1, 86.4, 126.4, 127.1, 129.1, 129.3, 132.3, 138.3, 150.3, 154.0, 161.8, 162.9, 176.6; MS: m/z = 412 (M^+).

2.7 | 5-(2-Bromophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 4)

White solid (90%); m.p.: 259–261 °C; IR (KBr) (ν_{max}, cm^{-1}) 3369, 1697, 1679; [found: C, 52.22; H, 4.16; N, 12.54; S, 6.85. $C_{20}H_{17}BrN_4O_2S$ requires: C, 52.52; H, 3.75; N,

12.25; S, 7.01%]; δ_H (400 MHz, DMSO-d_6); 3.04 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 5.47 (s, 1H, CH), 7.08–7.48 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 28.1, 29.9, 36.7, 85.2, 86.4, 122.8, 126.9, 127.3, 129.2, 132.8, 139.9, 150.3, 154.0, 161.8, 162.9; MS: m/z = 457 (M^+).

2.8 | 5-(3-Bromophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 5)

White powder (87%); m.p.: 226–229 °C; IR (KBr) (ν_{max}, cm^{-1}) 3415, 1702, 1675; [found: C, 47.13; H, 4.46; N, 11.61; S, 6.43. $C_{20}H_{17}BrN_4O_2S$ requires: C, 52.52; H, 3.75; N, 12.25; S, 7.01%]; δ_H (400 MHz, DMSO-d_6); 3.23 (s, 6H, $2CH_3$), 5.67 (s, 1H, CH), 7.21–7.50 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 27.9, 29.9, 35.1, 55.9, 121.3, 125.7, 127.8, 129.1, 129.7, 142.8, 150.4. MS: m/z = 457 (M^+).

2.9 | 5-(4-Bromophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 6)

Light yellow powder (98%); m.p.: 283–284 °C (278–279 °C)[24d]; IR (KBr) (ν_{max}, cm^{-1}) 3368, 1699, 1691; δ_H (400 MHz, DMSO-d_6); 3.13 (s, 6H, $2CH_3$), 5.53 (s, 1H, CH), 7.04–7.35 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 27.9, 29.9, 34.9, 85.4, 117.8, 128.9, 129.0, 130.3, 139.2, 150.3, 154.3, 163.0; MS: m/z = 457 (M^+).

2.10 | 1,3-Dimethyl-5-(2-nitrophenyl)-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 7)

Light yellow powder (95%); m.p.: 282–283 °C; IR (KBr) (ν_{max}, cm^{-1}) 3436, 1693, 1655; [found: C, 55.88; H, 4.88; N, 16.47; S, 7.01. $C_{20}H_{17}N_5O_4S$ requires: C, 56.73; H, 4.05; N, 16.54; S, 7.57%]; δ_H (400 MHz, DMSO-d_6); 3.01 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 6.10 (s, 1H, CH), 7.20–7.58 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 28.2, 29.8, 32.1, 80.3, 83.6, 85.6, 123.4, 126.6, 128.6, 131.3, 133.3, 149.6, 150.2, 154.4, 158.3, 161.8, 163.3, 163.5. MS: m/z = 423 (M^+).

2.11 | 1,3-Dimethyl-5-(4-nitrophenyl)-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 8)

Light yellow powder (98%); m.p.: 283–284 °C (272–273 °C)[24d]; IR (KBr) (ν_{max}, cm^{-1}) 3339, 1695, 1668; δ_H (400 MHz, DMSO-d_6); 3.15 (s, 6H, $2CH_3$), 5.66 (s, 1H, CH), 7.40 (s, 7H, ArH), 8.06 (s, 3H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 28.0, 30.0, 35.8, 122.8, 127.9, 145.2, 148.8, 150.3. MS: m/z = 423 (M^+).

2.12 | 5-(2,3-Dichlorophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 9)

White powder (96%); m.p.: 275–278 °C; IR (KBr) (ν_{max}, cm^{-1}) 3373, 1697, 1662; [found: C, 52.98; H, 4.55; N, 12.83; S, 7.61. $C_{20}H_{16}Cl_2N_4O_2S$ requires: C, 53.70; H, 3.61; N, 12.52; S, 7.17%]; δ_H (400 MHz, DMSO-d_6); 3.03 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 5.55 (s, 1H, CH), 6.95 (m, 2H, ArH), 7.23 (m, 2H, ArH), 7.33 (m, 2H, ArH), 7.44 (m, 4H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 28.3, 30.1, 64.8, 85.1, 86.0, 127.1, 127.7, 127.8, 130.0, 131.5, 141.3, 150.2, 153.7, 154.1, 158.2, 161.8, 161.9, 162.9, 163.5; MS: m/z = 447 (M^+).

2.13 | 5-(2,4-Dichlorophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 10)

White powder (90%); m.p.: 265–268 °C; IR (KBr) (ν_{max}, cm^{-1}) 3352, 1702, 1680; [found: C, 53.34; H, 4.44; N, 11.89; S, 6.86. $C_{20}H_{16}Cl_2N_4O_2S$ requires: C, 53.70; H, 3.61; N, 12.52; S, 7.17%]; δ_H (400 MHz, DMSO-d_6); 3.03 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 5.49 (s, 1H, CH), 6.96 (m, 2H, ArH), 7.42 (m, 7H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 30.1, 34.3, 55.9, 104.1, 123.6, 126.4, 128.7, 130.4, 130.6, 131.0, 133.2, 137.6, 150.2, 153.6, 154.1, 188.8; MS: m/z = 447 (M^+).

2.14 | 5-(4-Chloro-3-nitrophenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 11)

White powder (95%); m.p.: 275–277 °C; IR (KBr) (ν_{max}, cm^{-1}) 3473, 1693, 1662; [found: C, 51.80; H, 4.07; N, 14.92; S, 6.65. $C_{20}H_{16}ClN_5O_4S$ requires: C, 52.46; H, 3.49; N, 15.30; S, 6.99%]; δ_H (400 MHz, DMSO-d_6); 3.15 (s, 6H, $2CH_3$), 5.62 (s, 1H, CH), 7.44–8.30 (m, 9H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 27.9, 29.9, 35.0, 79.1, 120.8, 123.4, 128.1, 130.3, 132.2, 136.6, 141.7, 147.7, 150.4; MS: m/z = 457 (M^+).

2.15 | 1,3-Dimethyl-6-phenyl-7-thioxo-5-(o-tolyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 12)

White powder (86%); m.p.: 270–272 °C.; IR (KBr) (ν_{max}, cm^{-1}) 3454, 1693, 1654; [found: C, 64.54; H, 5.59; N, 14.80; S, 8.07. $C_{21}H_{20}N_4O_2S$ requires: C, 64.27; H, 5.14; N, 14.28; S, 8.17%]; δ_H (400 MHz, DMSO-d_6); 2.00 (s, 3H, CH_3), 3.12 (s, 6H, $2CH_3$), 5.47 (s, 1H, CH), 7.03–7.45 (m, 10H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 19.6, 29.9, 34.3, 79.1, 86.3, 125.1, 125.2, 126.7, 130.2, 135.3, 138.8, 150.3, 153.7; MS: m/z = 392 (M^+).

2.16 | 1,3-Dimethyl-6-phenyl-7-thioxo-5-(p-tolyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 13)

White powder (80%); m.p.: 268–271 °C (271–272 °C)[24d]; IR (KBr) (ν_{max}, cm^{-1}) 3364, 1697, 1674; δ_H (400 MHz, DMSO-d_6); 2.25 (s, 3H, CH_3), 3.15 (s, 6H, $2CH_3$), 5.55 (s, 1H, CH), 6.99 (s, 6H, ArH), 7.44 (s, 4H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 20.4, 27.9, 29.9, 34.9, 86.1, 103.0, 126.4, 128.2, 133.5, 136.3, 150.4, 154.2, 162.5; MS: m/z = 392 (M^+).

2.17 | 4-(2-Methoxyphenyl)-6,8-dimethyl-3-phenyl-2-thioxo-2,3,4,8-tetrahydropyrido[2,3-d]pyrimidine-5,7(1*H*,6*H*)-dione (Table 2, Entry 14)

White powder (89%); m.p.: 239–241 °C; IR (KBr) (ν_{max}, cm^{-1}) 3405, 1689, 1672; [found: C, 59.73; H, 5.64; N, 13.47; S, 7.01. $C_{21}H_{20}N_4O_3S$ requires: C, 61.75; H, 4.94; N, 13.72; S, 7.85%]; δ_H (400 MHz, DMSO-d_6); 3.12 (s, 6H, $2CH_3$), 3.58 (s, 3H, OCH_3), 5.50 (s, 1H, CH), 6.85 (m, 3H, ArH), 7.09 (m, 7H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 29.8, 31.9, 55.5, 86.2, 110.7, 119.6, 126.5, 127.4, 128.4, 150.4, 153.3, 157.4, 162.4; MS: m/z = 408 (M^+).

2.18 | 5-(4-Methoxyphenyl)-1,3-dimethyl-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 15)

White powder (90%); m.p.: 272–274 °C (271–272 °C)[24d]; IR (KBr) (ν_{max}, cm^{-1}) 3353, 1694, 1680; δ_H (400 MHz, DMSO-d_6); 3.12 (s, 6H, $2CH_3$), 3.68 (s, 3H, OCH_3), 5.51 (s, 1H, CH), 6.73 (m, 2H, ArH), 6.96 (m, 3H, ArH), 7.40 (m, 5H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 27.9, 29.9, 34.5, 54.8, 85.9, 113.0, 127.4, 127.5, 131.1, 150.4, 154.0, 156.8, 162.6; MS: m/z = 408 (M^+).

2.19 | 1,3-Dimethyl-6-phenyl-7-thioxo-5-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 2, Entry 16)

White powder (80%); m.p.: 291–292 °C; IR (KBr) (ν_{max}, cm^{-1}) 3367, 1686, 1667; [found: C, 60.04; H, 5.63; N, 11.55; S, 6.32. $C_{23}H_{24}N_4O_5S$ requires: C, 58.96; H, 5.16; N, 11.96; S, 6.84%]; δ_H (400 MHz, DMSO-d_6); 3.15 (s, 6H, CH_3), 3.63 (s, 9H, $3OCH_3$), 5.54 (s, 1H, CH), 6.36 (s, 2H, ArH), 7.39 (s, 5H, ArH, NH); δ_C (400 MHz, DMSO-d_6); 28.0, 29.9, 35.3, 55.8, 59.9, 104.2, 135.2, 148.0, 150.4, 152.2, 154.0, 154.1, 154.2, 156.7, 161.3, 180.8; MS: m/z = 468 (M^+).

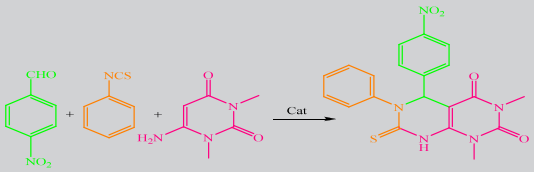
3 | RESULTS AND DISCUSSION

Sulfuric acid is a basic and efficacious catalyst for practical chemical processes, and is widely used in the generation of industrially important chemicals.[22] Sulfuric acid that functionalized silica-coated magnetite nanoparticles as recyclable strong solid acid catalysts opened up a new path to show an amazing and efficient system to simplify catalyst recovery in different organic reactions. This catalyst allows the mixture of well-known methods for catalyst heterogenization with techniques for magnetic separation.[10,23]

In order to evaluate the catalytic capability of the synthesized heterogeneous catalyst (Fe_3O_4@SiO_2@Propyl-ANDSA) in organic reactions, we chose to examine its activity in a one-pot reaction for the synthesis of pyrimido[4,5-d]pyrimidine. In order to establish the conditions of the involved reactions, we initially investigated the reaction between isothiocyanate, 4-nitrobenzaldehyde and *N*,*N*-dimethyl 6-amino uracil as the model reaction. The effects of different reaction parameters such as the catalyst loading, temperature and solvent were screened on the rates and yields of this model reaction. As summarized in Table 1, the best results were obtained for the model synthesis of 1,3-dimethyl-5-(4-nitrophenyl)-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione in terms of the reaction rate and yield when the reaction was carried out in reflux conditions in water using 0.05 g of the catalyst (Entry 14). A further decrease or increase in the amount of catalyst (Table 1, Entries 9–13 and 15, 16) did not improve the yield of the product.

In order to establish the important role of this catalyst, the reaction was repeated using 0.05 g of each one of Fe_3O_4 magnetic nanoparticles (MNPs) and ANDSA. It was suggested that the catalytically active site of Fe_3O_4 NPs is Fe^{3+} (as a Lewis acid) and of ANDSA is two -SO_3H groups (as acidic sites) that coordinate to the nitrogen group of

TABLE 1 Screening the reaction parameters for the synthesis of 1,3-dimethyl-5-(4-nitrophenyl)-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione[a]



Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	0.02	–	25	120	20
2	0.02	H_2O	25	120	38
3	0.02	EtOH	25	90	20
4	0.02	CH_3CN	25	90	25
5	0.02	–	50	100	43
6	0.02	H_2O	50	120	55
7	0.02	EtOH	50	90	30
8	0.02	CH_3CN	50	90	42
9	0.02	H_2O	reflux	120	70
10	0.02	EtOH	reflux	120	52
11	0.02	–	100	100	50
12	0.02	H_2O/EtOH	reflux	100	60
13	0.04	H_2O	reflux	100	85
14	0.05	H_2O	reflux	60	98
15	0.06	H_2O	reflux	60	98
16	0.07	H_2O	reflux	60	98
17	Fe_3O_4 (MNPs)	H_2O	reflux	300	30
18	ANDSA	H_2O	reflux	300	27
19	–	H_2O	reflux	300	–

[a]Conditions: phenylisothiocyanate (1 mmol), 4-nitrobenzaldehyde (1 mmol), *N*,*N*-dimethyl-6-amino uracil (1 mmol), solvent (5 ml).

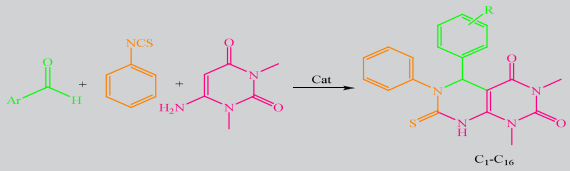
[b]Isolated pure yield.

phenylisothiocyanate and carbonyl group of the aldehyde. This interaction accelerates the conjugation and directs the additions of the nucleophiles to the corresponding substrates. When these catalysts were applied, the reaction yields obtained were only about 30% and 27%, respectively. In the absence of the catalyst under optimized conditions, a very low yield of the expected product was obtained after a long reaction time (Table 1, Entries 17–19). To evaluate the effects of temperature, we performed this reaction at various temperatures using Fe_3O_4@SiO_2@Propyl-ANDSA as the catalyst (Table 1, Entries 2, 6, 9). The results ascertain that reflux conditions (100 °C) appeared to be optimum.

The effect of the solvent on this reaction is another factor that was also investigated. As seen in Table 1, the best conditions along with higher yield were prepared by H_2O among different solvents (EtOH, CH_3CN, EtOH/H_2O and solvent-free conditions). In this reaction, the organic product, aldehyde and phenylisothiocyanate are hardly water soluble, whereas *N*,*N*-dimethyl 6-amino uracil is slightly soluble in hot water. This repulsive interaction between hydrophobic molecules and water leads to the formation of hydrophobic aggregates that allow reducing the contact surface between water and organic molecules. To maintain the network of hydrogen bonds (related to its high cohesive energy density), water swabs itself around these aggregates, thus acting as an internal pressure that speeded up reactions with negative activation volume.

Having optimized the conditions, we next examined the generality of these conditions to other substrates using varying electron-withdrawing and electron-donating aromatic aldehydes (Scheme 1). As shown in Table 2, generally, the aldehydes containing electron-withdrawing groups display higher reactivity in comparison to the

TABLE 2 Synthesis of pyrimido[4,5-d]pyrimidine using Fe_3O_4@SiO_2@Propyl-ANDSA as a heterogeneous catalyst[a]



Entry	r	Product	Time (min)	Yield (%)[b]	m.p. (°C)	
					Found	Reported
1	2-FC_6H_4	C_1	120	80	244–245	–
2	4-FC_6H_4	C_2	150	90	264–266	–
3	2-ClC_6H_4	C_3	180	83	273–276	–
4	2-BrC_6H_4	C_4	90	90	259–261	–
5	3-BrC_6H_4	C_5	180	87	226–229	–
6	4-BrC_6H_4	C_6	75	98	283–284	278–279[15]
7	2-$O_2NC_6H_4$	C_7	45	95	282–283	–
8	4-$O_2NC_6H_4$	C_8	60	98	283–284	272–273[15]
9	2,3-$Cl_2C_6H_3$	C_9	210	96	275–278	–
10	2,4-$Cl_2C_6H_3$	C_{10}	180	90	265–268	–
11	3-Cl,4-$O_2NC_6H_3$	C_{11}	90	95	275–277	–
12	2-MeC_6H_4	C_{12}	45	86	270–272	–
13	4-MeC_6H_4	C_{13}	20	80	268–271	271–272[15]
14	2-$OMeC_6H_4$	C_{14}	25	89	239–241	
15	4-$OMeC_6H_4$	C_{15}	30	90	272–274	271–272[15]
16	3,4,5-$(OMe)_3C_6H_2$	C_{16}	20	80	291–292	–

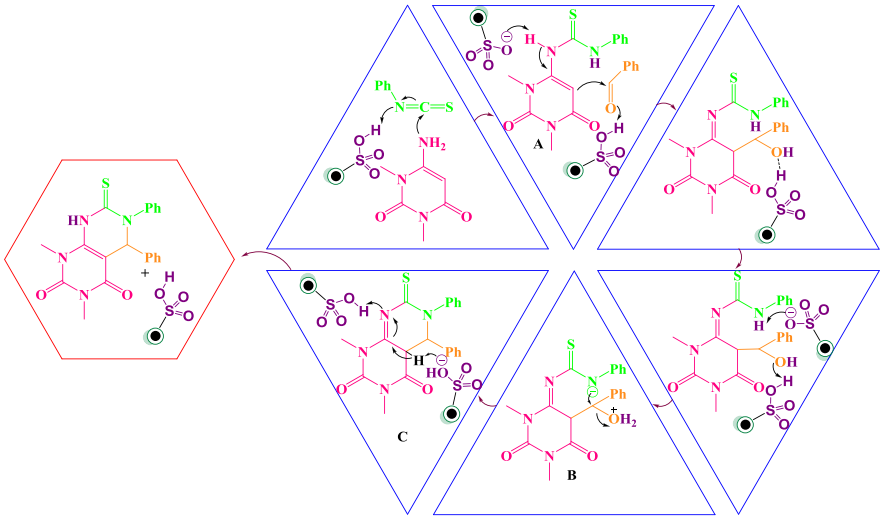
[a]Reaction conditions: phenylisothiocyanate (1 mmol), aldehyde (1 mmol), *N*,*N*-dimethyl-6-amino uracil (1 mmol) and Fe_3O_4@SiO_2@Propyl-ANDSA in water (5 ml) at reflux condition.

[b]Yield refer to the isolated pure products.

aldehydes carrying electron-releasing groups. As shown in Scheme 3, in the present of catalyst that activated the carbonyl group, nucleophilic attack of intermediate A to aldehyde occurred. The electron-withdrawing groups intensified the positive charge on carbon in carbonyl groups and caused higher reactivity of aldehydes containing electron-withdrawing groups in comparison with the aldehydes carrying electron-releasing groups. Moreover, in previous reports, only para- and ortho-substituted aldehydes undergo this reaction, but in this method we could react meta-substituted aldehydes and aldehydes with two substitutes. The results are summarized in Table 2. As indicated above, in all cases the reaction produces the products in good yields, and with the use of water as solvent it eliminates problems associated with solvent use, such as cost, safety and pollution. All products were characterized on the basis of their spectroscopic data, such as FT-IR, ^1H and ^{13}C NMR spectra, mass and CHNS.

A plausible mechanism to explain the three-component condensation reactions between phenylisothiocyanate, aldehyde and *N*,*N*-dimethyl-6-amino uracil based on previously reported reactions[14] is depicted in Scheme 3. Initially, the catalyst-accelerated condensation of *N*,*N*-dimethyl 6-amino uracil with phenylisothiocyanate was applied to produce the intermediate (A). Subsequently, in the presence of the catalyst, nucleophilic attack of intermediate A to aldehyde activated with MNPs produced intermediate B, which is followed by cyclization and loss of one molecular water to give intermediate C. Finally, the intermediate C is tautomerized using the MNP catalyst to produce the fully aromatized pyrimido[4,5-d]pyrimidine.

The ability to recycle, catalytic activity and reuse it was studied in the model one-pot three-component reaction between 4-nitrobenzaldehyde, phenylisothiocyanate and *N*,*N*-dimethyl-6-amino uracil in water and reflux condition using 0.05 g of the catalyst. At the end of the



SCHEME 3 Suggested mechanism for the synthesis of pyrimido[4,5-d] pyrimidines catalyzed by Fe_3O_4@SiO_2@Propyl-ANDSA MNPs

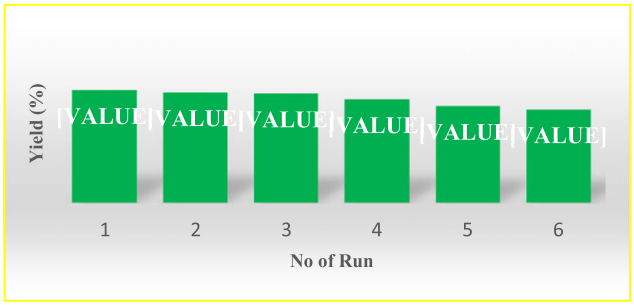


FIGURE 1 Recyclability test of Fe_3O_4@SiO_2@Propyl-ANDSA

reaction, the separated catalyst can be reused after being washed with warm EtOH and drying at 80 °C. Fe_3O_4@SiO_2@Propyl-ANDSA was used again for subsequent experiments under similar reaction conditions. Figure 1 illustrates that the catalyst could be reused for the next cycle without any notable loss of its activity. Yields of the product decreased only slightly after reusing the catalyst five times. Therefore, one possible reason for the decrease in the yield could be due to weight loss of the catalyst after each stage of retrieval. Another reason is infected and non-activated catalyst surface. The FT-IR analysis of Fe_3O_4@SiO_2@Propyl-ANDSA after the sixth run confirms the stability of the nano-catalyst during the recycling procedure (Figure S61). In addition, the TEM image of the catalyst after recycling did not show a considerable change in the morphology, which clearly indicated that Fe_3O_4@SiO_2@Propyl-ANDSA is recyclable and stable under the reaction conditions (Figure S62).

Furthermore, in order to show changes of the main elements on the surface of the catalyst before and after catalytic reaction, we used elemental analysis (CHNS). After catalytic reaction, the percentages of the main elements did not change significantly (Table S2), demonstrating the stability of the catalyst.

4 | CONCLUSION

In this paper, we have developed a green method for the synthesis of pyrimido[4,5-d]pyrimidine derivates via one-pot three-components reaction under reflux conditions in water and using Fe_3O_4@SiO_2@Propyl-ANDSA as an excellent heterogeneous nano-catalyst. High yield, a simple work-up procedure, ease of separation and recyclability of the magnetic catalyst, waste reduction, and generated products with meta as well as with two substitute aldehydes that have not yet been reported are some advantages of this method.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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