ORIGINAL PAPER

Tannic Acid-Cu-modified Fe_3O_4@SiO_2 nanoparticles (Fe_3O_4@SiO_2@TA-Cu NPs): New recyclable magnetic catalyst for the three-component synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

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Abstract

An effectual encapsulation–functionalization procedure for preparing high-activity magnetic Fe_3O_4@SiO_2@Tannic Acid-Cu (Fe_3O_4@SiO_2@TA-Cu) nanocomposite was described. Tannic acid-Cu complexes were uniformly protected on the surface of Fe_3O_4@SiO_2 nanoparticles. The newly prepared catalyst was characterized by XRD, FT-IR, SEM, and EDX. The obtained nanocomposites showed excellent catalytic performance and good stability for the one-pot synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines via three-component condensations of aldehydes, malononitrile, and thiophenols in water. The catalyst was separated by a magnet and reused at least five times without remarkable degradation in the performance. The desired products were prepared in high yields by an easy workup procedure with this protocol.

Introduction

Substituted pyridines are significant heterocyclic compounds, which have gained much attention in medicinal chemistry due to their extensive biological and pharmaceutical activities [1, 2]. Among them, the pyridine derivatives of 2-amino-3,5-dicarbonitrile-6-thio-pyridines were reported to display many pharmaceutical properties and are effective as anti-hepatitis B virus [3], antibacterial [4], anti-prion [5], anticancer agents [6], and as potassium channel openers for treatment of urinary incontinence [7]. In addition, with some of these heterocycles, the new drugs for Parkinson's disease, hypoxia, asthma, epilepsy, and kidney [8] disease have developed. Several methods have been reported for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines. Recently, scientists have mainly applied the multi-component reactions (MCRs) as one of the most essential existing methods to synthesize 2-amino-3,5-dicarbonitrile-6-thio-pyridines via the cyclo-condensation of aldehyde, malononitrile, and thiol under various conditions.

Multicomponent reactions (MCRs) are effective in the synthesis of organic heterocyclics. Recently, the three MCRs have been interested since they provide high sustainability and eco-friendly conditions [9–11]. MCRs also have many advantages, such as simple purification, easy synthesis of compounds in one-pot, green conditions, high yields of products with heterogeneous catalysts, and the ease of workup [12–20].

Otherwise, the magnetic nanoparticles (MNPs), because of their essential properties such as practical reusability, simple preparation, high surface area, ease of functionalization, easy catalyst separation, and high loading capacity, has been extensively used as the heterogeneous catalysts for MCRs [21–24]. The combination of magnetic heterogeneous catalysts and MCRs is a new and helpful strategy for the synthesis of heterocycle systems [25].

The MCRs of aldehyde, malononitrile, and thiol for the synthesis of 2-amino-3, 5-dicarbonitrile- 6-thio-pyridines have been carried out under using various bases such as Et_3N, DABCO, *N,N*-DIPEA, piperidine, 2,4,6-collidine, DMAP, *N,N* dimethylaniline, *N,N*-diethylaniline [26], WEB [27], DBU [28], silica-bonded *N* propyldiethylenetriamine [29], macrocyclic Schiff base ligand [25], KOH [30], K_2CO_3 [31], Na_2SiO_3 [32], TBAB/Cs_2CO_3 [33], MgO [34], $ZrOCl_2$/$NaNH_2$ [35], TBAF [36], KF/Al_2O_3 [37], molecular sieves 4 Å [38], CaO NPs [39], CH_3COONa [40], 2-HEAA [41],

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[bmIm]OH [42], [bmim][Br] [43] and using a variety of Lewis acids such as $ZnCl_2$, $AlCl_3$, $FeCl_3$, I_2, Cu $(OTf)_3$, $InCl_3$, $BF_3.Et_2O$ [44], $Sc(OTf)_3$ [45], y-Fe_2O_3-2-HEAS [46], silica NPs [47], CuI NPs [48], boric acid [49], phosphotungstic acid/CTAB [50], Zn(II), and Cd(II) MOFs [51].

However, some of these reported methods contain some faults such as using toxic catalysts or solvents, difficult reaction conditions, the performance of the side reactions, and low yield of desired product despite the longer reaction time. So, it is significant to develop an improved method for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.

Following the above-mentioned significance, and the values of substituted pyridines as unique medicinal compounds, herein, we wish to report a novel, efficient, and green strategy for the synthesis of these classes of compounds. For this purpose, a new tannic acid-Cu modification process onto the surface of $Fe_3O_4@SiO_2$ nanospheres was developed for the catalytic application. Tannic acid-Cu coordination complexes were coated onto the surface of $Fe_3O_4@SiO_2$ nanospheres.

Immobilizing metal nanoparticles on magnetic substrates can improve their dispersity and magnetically separating the catalyst, thereby facilitating the recycling and reuse of it. But, to improve the comprehensive performance and the stability of magnetic substrates, magnetic substrates have been encapsulated through inorganic or organic layers or functionalized with active functional groups. A suitable substrate for this purpose is Tannic acid (TA) [52–54]. Tannic acid (TA) is a green and polyphenolic compound widely available in nature. The active phenolic hydroxyl groups dedicate TA with metal ion chelating ability [55, 56]. In this work, we fabricated the $Fe_3O_4@SiO_2@TA$-Cu nanoparticles as a new, facile, non-explosive, economic, green, and environmentally friendly catalyst with uniformly dispersed and easily recoverable NPs. The newly prepared catalyst was characterized by XRD, FT-IR, SEM, and EDX. The synthesized $Fe_3O_4@SiO_2@TA$-Cu nanoparticles were successfully used as a magnetically recyclable heterogeneous catalyst for the one-pot synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines via three-component condensations of benzaldehydes, malononitrile, and thiophenols in water.

Experimental

Materials and instrumentation

All reagents were bought from Merck Company and used without further purification. Fourier-transform infrared spectra (FT-IR) were recorded on an Avatar 370 FT-IR Thermal Nicolet spectrometer. XRD patterns were recorded by an X-ray diffractometer, model X'Pert Pro. Holland (Panalytical). Morphology of the nanocatalyst was observed by a Mira 3-XMU FE-SEM. The reaction products were purified by column chromatography. The purity determining of the product was checked by TLC on silica gel Polygram STL G/UV 254 plates. The melting point is determined with an Electro-Thermal Type 9200 melting point apparatus. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX-400 Fourier transformer spectrometer (Peoria, IL). Chemical shift values were brought in ppm at room temperature using $CDCl_3$ or DMSO-d6 as a solvent and reported in ppm downfield from TMS. The mass spectra were gained on a Varian Mat CH-7 instrument at 70 eV in electron impact (EI) mode.

Preparation of the silica-coated Fe_3O_4 magnetic nanoparticles ($Fe_3O_4@SiO_2$)

Fe_3O_4@Silica was prepared according to the reported procedure [57]. The mixture of the Fe_3O_4 nanoparticles (0.045 g) with distilled water (15 mL) and ethanol (100 mL) was dispersed under ultra-sonification for 30 min. Ammonium hydroxide 25% solution (2 mL) was added to the suspension under continuous stirring. After that, the tetraethylorthosilicate (TEOS, 0.1 mL) was added drop wise into the suspension. The stirring was continued at room temperature for 24 h to silica was formed on the surface of Fe_3O_4 nanoparticles by the hydrolysis and condensation of TEOS. The silica-coated Fe_3O_4 nanoparticles were separated from the mixture using an external magnet and washed with deionized water three times. It was then dried under vacuum at 80 °C overnight.

A typical procedure for the synthesis of Tannic Acid-Cu-modified $Fe_3O_4@SiO_2$ nanoparticles ($Fe_3O_4@SiO_2@TA$-Cu nanoparticles)

A solution of tannic acid (10 mL, 0.1 M) in EtOH was added to a suspension of the.

obtained $Fe_3O_4@SiO_2$ NPs in EtOH (0.2 gr) with a vigorous stirring. After 10 min, the copper acetate solution (10 mL, 0.1 M) in EtOH was added dropwise into the suspension of nanoparticles. The stirring was continued at room temperature for 4 h. After completion of the reaction, the nanoparticles were washed with deionized water several times and once with absolute ethanol. Then were separated from the mixture by an external magnet and finally dried in the oven at 60 °C for 6 h.

General procedure for the synthesis of 2-amino-3,5-dicarbonitrile-6- thio-pyridines in the presence of $Fe_3O_4@SiO_2@TA$-Cu nanoparticles

A mixture of benzaldehyde (1 mmol), malononitrile (2 mmol), thiophenol derivative (1 mmol) and H_2O (5 mL)

in the presence of the $Fe_3O_4@SiO_2@TA-Cu$ NPs (0.05 gr) was stirred at room temperature. After the completion of the reaction (The progress of the reaction was monitored by TLC, hexane/ethyl acetate), the magnetic catalyst was separated from the mixture using an external magnet and reused. The reaction mixture was filtered and the obtained solid washed with cold H_2O (2 × 10 mL). The collected product was poured by recrystallization in EtOH. The isolated compounds were characterized by their melting points, FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry (MS).

Spectral data for known 2-amino-3,5-dicarbonitrile-6-thio-pyridines

2-Amino-4-phenyl-6-(phenylthio) pyridine-3,5-dicarbonitrile (4a)

White solid; mp 218–220 °C; FT-IR (KBr, disk) ν: 3479, 3351, 3215, 3064, 2220, 1623, 1522, 1441,1263,1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.84 (br, 2H, NH$_2$), 7.62–7.59 (m, 7H, Ar), 7.53–7.50 (m, 3H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 166.64, 160.10, 159.14, 135.23, 134.50, 131.01, 130.18, 129.90, 129.15, 128.93, 127.65, 115.80, 115.52, 93.88, 88.00. MS, m/z (%): 328 [M$^+$].

2-Amino-6-(phenylthio)-4-(p-tolyl) pyridine-3,5-dicarbonitrile (4b)

Yellow solid, mp 213–215 °C; IR (KBr, disk) ν: 3473, 3325, 2213, 1622, 1542, 1258, 1020, 759 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.81 (br, 2H, NH$_2$), 7.64–7.60 (m, 2H, Ar), 7.52–7.49 (m, 3H, Ar), 7.45 (d, J = 7.6 Hz, 2H, Ar), 7.40 (d, J = 8.0 Hz, 2H, Ar), 2.40 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 166.01, 160.13, 159.22, 141.0, 135.57, 131.40, 130.24, 129.86, 129.60, 128.91, 127.62, 116.10, 115.65, 93.83, 87.40, 21.55; MS, m/z (%): 342 [M$^+$].

2-Amino-4-(4-chlorophenyl)-6-(phenylthio) pyridine-3,5-dicarbonitrile (4c)

Yellow solid, mp 220–222 °C; IR (KBr, disk) ν: 3465, 3340, 2214, 1625, 1580, 1546, 1295, 780, 741, 690 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.88 (br, 2H, NH$_2$), 7.66 (d, J = 8.4 Hz, 2H, Ar), 7.59 (d, J = 8.4 Hz, 4H, Ar), 7.54–7.51 (m, 3H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 166.71, 159.90, 158.0, 135.84, 135.32, 133.21, 130.90, 130.33, 130.01, 129.40, 127.50, 115.77, 115.31, 93.79, 87.60; MS, m/z (%): 362 [M$^+$].

2-Amino-4-(4-nitrophenyl)-6-(phenylthio) pyridine-3,5-dicarbonitrile (4d)

Yellow solid, m.p. 289–290 °C; IR (KBr, disk) ν: 3428, 3336, 3230, 2215, 1634, 1550, 1513, 1460, 1350, 1262, 780 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.50–7.58 (m, 5H, Ar), 7.84–7.95 (m, 4H, Ar, NH$_2$), 8.35–8.39 (m, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 87.40, 93.45, 115.05, 115.39, 124.32, 127.37, 129.95, 130.22, 131.09, 135.25, 140.66, 149.05, 157.16, 159.91, 167.0; MS, m/z (%): 373 [M$^+$].

2-Amino-4-(4-methoxyphenyl)-6-(phenylthio) pyridine-3,5-dicarbonitrile (4e)

Yellow solid, mp 240–242 °C, ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.78 (s, 2H, NH$_2$), 7.65–7.50 (m, 7H, Ar), 7.17–7014 (d, J = 9 Hz, 2H, Ar) 3.87 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 166.64, 161.35, 160.30, 158.81, 136.30, 130.75, 130.13, 129.93, 127.76, 126.30, 116.05, 115.79, 114.60, 93.91, 87.50, 55.85; MS, m/z (%): 358 [M$^+$];

2-Amino-4-(4-hydroxyphenyl)-6-(phenylthio) pyridine-3,5-dicarbonitrile (4f)

Yellow solid, mp 312–314 °C, IR (KBr, disk) ν: 3400, 3367, 3335, 3247, 3117, 2217, 1650, 1632, 1572, 1479, 1295 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 4.10 (br, 2H, NH$_2$), 7.29–7.45 (m, 9H, Ar), 10.05 (bs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 94.0, 96.92, 115.61, 116.05, 116.03, 124.55, 128.11, 129.89, 130.16, 130.85, 135.43, 158.90, 159.93, 162.05, 166.70; MS, m/z (%): 344 [M$^+$].

2-Amino-4-(4-(dimethylamino) phenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile (4 g).

Brown solid, mp 288–290 °C, IR (KBr, disk) ν: 3415, 3335, 3117, 2310, 1625, 1568, 1521, 1387, 1205, 820 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 3.1–3.33 (m, 6H, CH$_3$), 5.05 (bs, 2H, NH$_2$), 7.45–8.12 (m, 9H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 161.90, 160.10, 158.60, 155.14, 134.0, 119.22, 115.98, 115.91, 115.55, 115.0, 112.11, 69.26; MS, m/z (%): 371 [M$^+$].

2-Amino-6-(phenylthio)-4-(thiophen-2-yl) pyridine-3,5-dicarbonitrile (4 h)

Yellow solid, mp 248–250 °C, IR (KBr, disk) ν: 3488, 3345, 3221, 3075, 2215, 1735, 1650, 1625, 1548, 1401, 1256 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ:

7.25–7.55 (*m*, 7H, Ar), 7.95–7.98 (*m*, 1H, Ar) 8.61 (br, 2H, NH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 87.31, 115.60, 115.93, 127.56, 128.35, 129.91, 130.16, 131.28, 132.04, 133.25, 133.29, 135.28, 151.37, 160.25, 167.13; MS, *m/z (%)*: 334 [M$^+$].

2-Amino-6-((4-chlorophenyl) thio)-4-henylpyridine-3,5-dicarbonitrile (4i)

White solid; mp 225–227 °C IR (KBr, disk) ν: 3438 (NH), 3315 (NH), 2203 (CN), 1600, 1291, 780; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.93 (s, 2 H, NH$_2$), 7.69–7.59 (*m*, 9 H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 167.0, 160.15, 159.0, 137.21, 135.28, 134.35, 130.98, 129.95, 129.24, 128.90, 126.53, 115.72, 115.46, 93.73, 87.0; MS, *m/z (%)*: 362 [M$^+$].

2-Amino-4-phenyl-6-(p-tolylthio) pyridine-3,5-dicarbonitrile (4j)

Yellow solid; mp 238–240 °C; IR (KBr, disk) ν: 3467, 3348, 2219, 2195, 1625, 1522; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.26 (br, 2H, NH$_2$), 7.60–7.54 (*m*, 6H, Ar), 7.50–7.47 (*m*, 3H, Ar), 2.61 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 20.98, 87.22, 96.03, 114.81, 115.25, 124.55, 128.48, 129.91, 130.11, 131.0, 134.22, 135.69, 142.37, 158.21, 159.30, 169.59; MS, *m/z (%)*: 342 (M$^+$).

2-Amino-6-((4-methoxyphenyl) thio)-4-phenylpyridine-3,5-dicarbonitrile (4 k)

Yellow solid, mp 228–229 °C; IR (KBr, disk) ν: 3430, 3340, 2210, 1629, 1591, 1248, 1130, 833, 755 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 7.99 (br, 2H, NH$_2$), 7.59–7.54 (*m*, 5H, Ar), 7.50 (d, *J* = 8.6 Hz, 2H, Ar), 7.07 (d, *J* = 8.6 Hz, 2H, Ar), 3.83 (s, 3H, OCH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 54.0, 86.12, 95.11, 114.04, 114.30, 114.63, 124.78, 128.27,

130.05, 131.96, 136.71, 159.30, 162.37, 168.54, 184.0; MS, *m/z (%)*: 358 [M$^+$].

2-Amino-6-((2-aminophenyl) thio)-4-phenylpyridine-3,5-dicarbonitrile (4 l)

Yellow solid, mp 225–227 °C; IR (KBr, disk) ν: 3465, 3358, 2920, 2213, 1610, 1264, 1158, 750 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 6.65 (br, 2H, NH$_2$), 7.11–7.16 (*m*, 4H, Ar), 7.30–7.48 (*m*, 5H, Ar), 8.01(br, 2H, NH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ:

88.25, 95.66, 115.23, 118.68, 119.0, 120.84, 128.39, 129.03, 130.95, 131.54, 136.73, 148.53, 159.59, 168.0; MS, *m/z (%)*: 343 [M$^+$].

Results and discussion

Characterization of magnetic Fe$_3$O$_4$@SiO$_2$@TA-Cu nanocomposite

The construction process of the catalyst is schematically shown in scheme 1. The prepared Fe$_3$O$_4$ nanospheres were covered with SiO$_2$. The SiO$_2$ shell increased the chemical stability and acid resistance of the magnetic core. Then, Cu(OAc)$_2$ was added to the solution of TA. When Cu(OAc)$_2$ was added to the solution, Cu^{2+} was adsorbed onto the TA layer through static and coordination interactions. A uniform TA-Cu coordination-complex coating on the SiO$_2$ shell was formed.
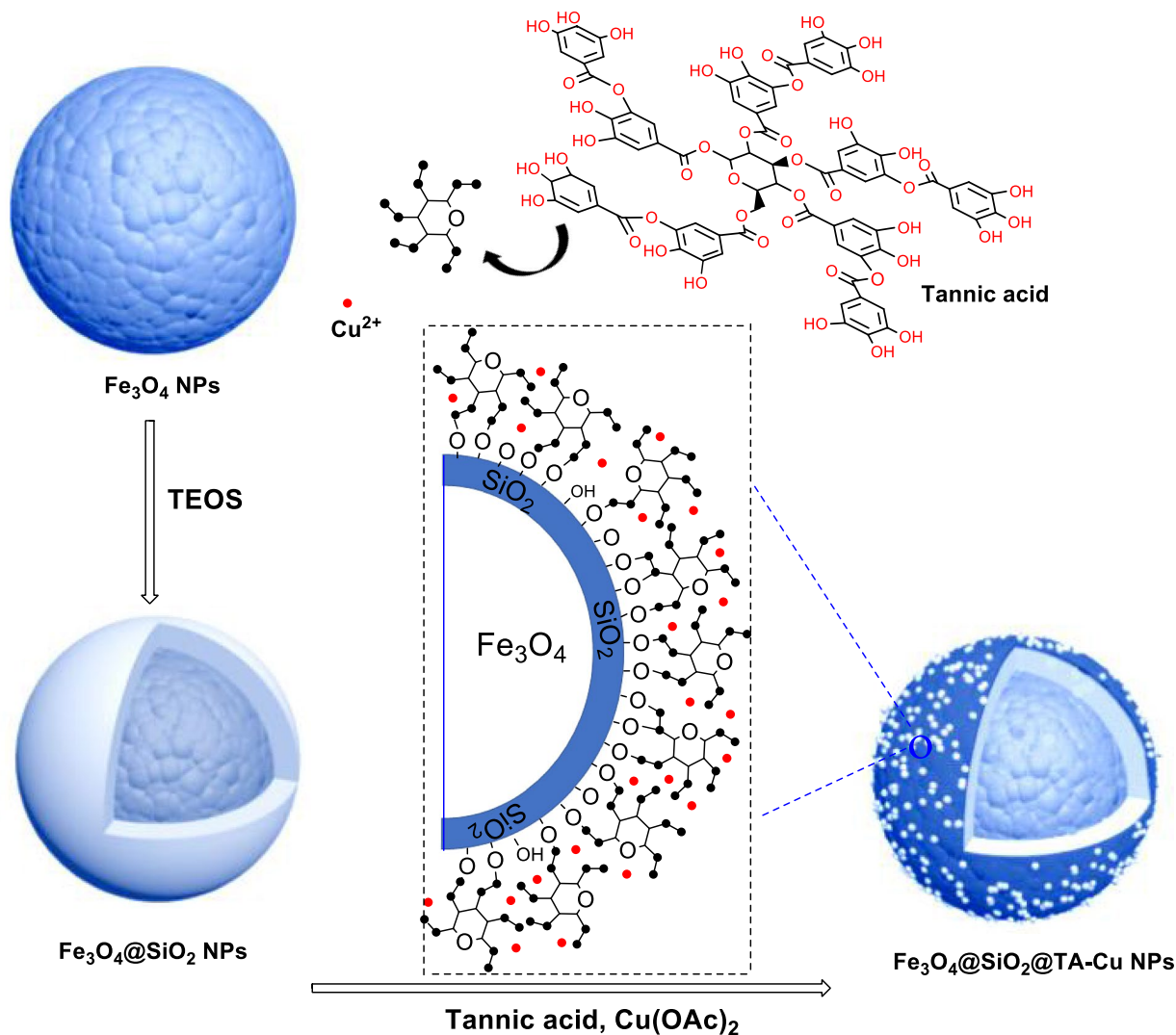
FT-IR analysis

Figure 1 presents the FT-IR spectra of Fe$_3$O$_4$, Fe$_3$O$_4$@SiO$_2$ and Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles. As shown in Fig. 1, for pure Fe$_3$O$_4$ (red color), the characteristic bands at 550 and 3358 cm^{-1} were belonged to the Fe–O bond and OH functional group [58, 59]. The FT-IR analysis of the Fe$_3$O$_4$@SiO$_2$ also demonstrates a peak at around 540 cm^{-1}, which is related to Fe–O vibration and the bands at approximately 1090, 800, and 470 cm^{-1} are from Si–O vibrations. In the case of Fe$_3$O$_4$@SiO$_2$@TA-Cu, new bands were observed in the range of 700 to 1700 cm^{-1}. The mentioned bands belonged to functional groups of tannic acid. Regarding TA-Cu and Fe$_3$O$_4$@SiO$_2$ interactions, it is expected to observe a shift in bands of TA functional groups. Accordingly, characteristic bands of pure tannic acid and corresponded bands were reported in Table 1 [60, 61]. From Fig. 1, the wide and strong band was observed, which centered at 3356 cm^{-1}, related to the overlapping of the OH functional group of TA and Fe$_3$O$_4$. The FT-IR analysis of the Fe$_3$O$_4$@SiO$_2$@TA-Cu also demonstrates the bands at approximately 1090 cm^{-1}, 800 cm^{-1}, and 470 cm^{-1} are from Si–O vibrations. In Table 1 the Comparison FT-IR position of TA and Fe$_3$O$_4$@SiO$_2$@TA-Cu was also demonstrated.

Additionally, the bands at 1612, 1067 cm^{-1} were attributed to the stretching and bending vibration of Cu–O [62].

XRD analysis

The XRD analysis was carried out to probe the structure of Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles (Fig. 2). In form recorded pattern, a lack of the characteristic peaks of pure Fe$_3$O$_4$ was found. This trend can be explained by complex formation. Indeed, the thin layer of the Cu-tannic acid complex was appropriately formed on the Fe$_3$O$_4$@SiO$_2$ surface.

Scheme 1 The schematic diagram for the synthesis of Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles The Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticle was described by FT-IR, FE-SEM, and EDX analysis
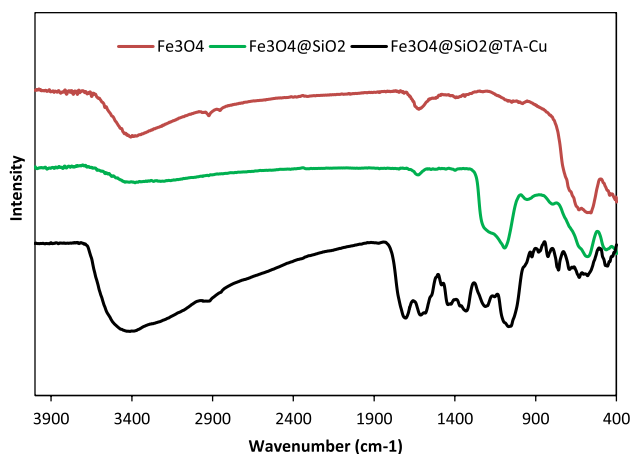
Fig. 1 FT-IR analysis of Fe$_3$O$_4$, Fe$_3$O$_4$@SiO$_2$ and Fe$_3$O$_4$@SiO$_2$@TA-Cu

Table 1 Comparison FT-IR position of TA and Fe$_3$O$_4$@SiO$_2$@TA-Cu

Assignment of bands	Frequencies for TA (cm^{-1})	Frequencies for Fe$_3$O$_4$@SiO$_2$@TA-Cu (cm^{-1})
OH Stretching vibration	3356	3411
-CH$_2$	2920	2913
C=O	1718	1704
C-C$_{aromatic}$ stretching vibration	1452	1442
C-O	1191	1210
C=C	754	758

The peak at 25° indicated the nature of Tannic acid [63]. Additionally, 39, 53.5, and 65° showed diffraction patterns that can related to the Fe$_3$O$_4$ and TA-Cu complex.

Fig. 2 The XRD pattern of Fe$_3$O$_4$@SiO$_2$@TA-Cu
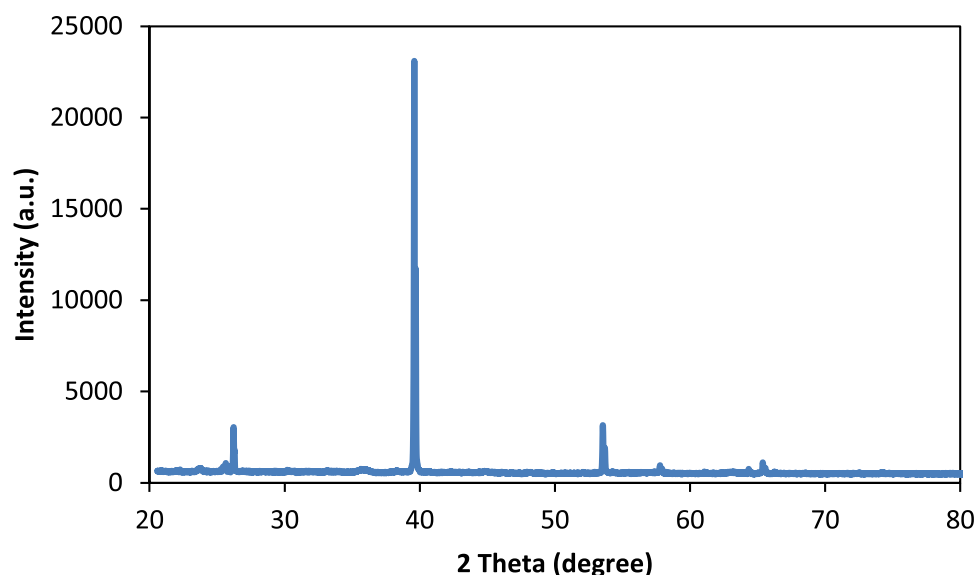
FE-SEM and EDS analysis

Figure 3 illustrates FE-SEM images and EDS spectra of Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles. The average size of coated particles was less than 100 nm and the spherical shape was changed due to complex coating. As can be seen, the characteristic peaks belonged to C, O, Fe, Si, and Cu elements which confirm the presence of Tannic acid and Cu on Fe$_3$O$_4$@SiO$_2$ nanoparticles.

Magnetic characterization

The magnetic characterization of Fe$_3$O$_4$@SiO$_2$ and Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles was studied by vibrating sample magnetometer (VSM). The curves of magnetization are shown in Figs. 4. The magnetic properties were analyzed by room temperature vibrant sample magnetometer (VSM) with an applied – 15 to 15 KOe field. These magnetic nanoparticles have a lot of attention. The prepared MNPs are separated from the reaction mixture by applying an outer magnet. Figure 4 demonstrates that the saturation magnetization of Fe$_3$O$_4$@SiO$_2$ and Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles were found 70 and 49 emu/g, respectively.
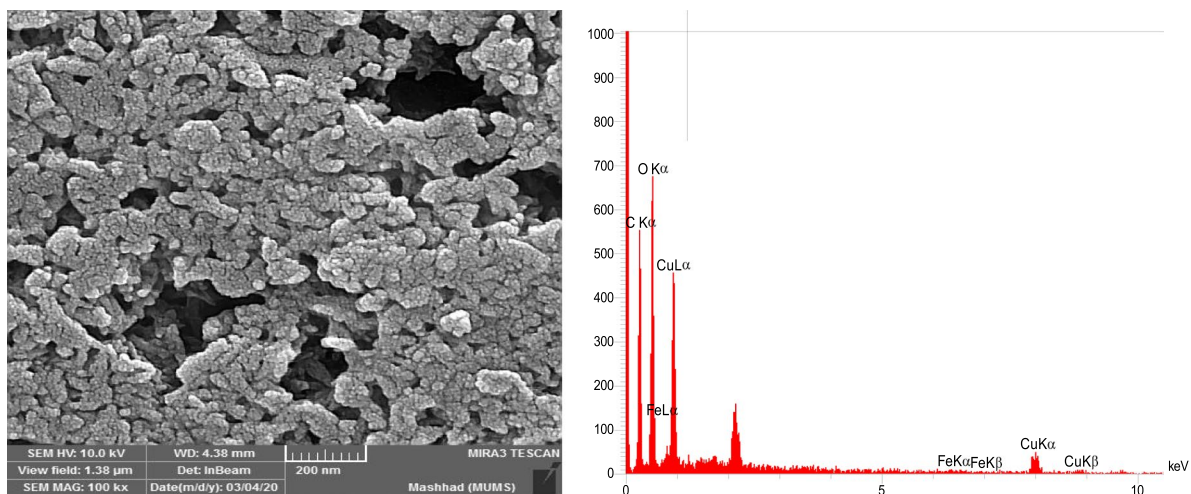
Fig. 3 FE-SEM and EDS analysis of Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles
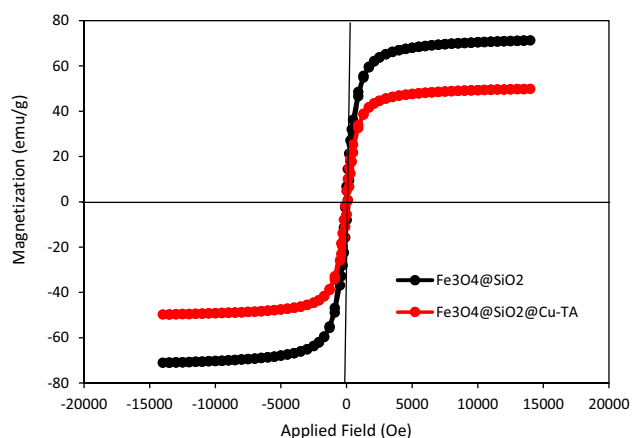
Fig. 4 The VSM magnetization curve of the $Fe_3O_4@SiO_2$ and $Fe_3O_4@SiO_2@TA$-Cu nanoparticles

The catalytic application of magnetic Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles for the synthesis of 2-amino-3,5-dicarbonitrile-6- thio-pyridines derivatives

After characterization of the $Fe_3O_4@SiO_2@TA$-Cu nanoparticles, we reported the synthesis of 2-amino-3,5-dicarbonitrile-6- thio-pyridines (4a-j) using a one-pot three-component reaction of benzaldehyde, malononitrile, and thiophenol in the presence of $Fe_3O_4@SiO_2@TA$-Cu nanoparticles at room temperature (Scheme 2).

At first, we optimized different reaction parameters for the synthesis of 2-amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (4a) as the model reaction (Table 2). The first screening was done under solvent-free conditions. In the presence of the catalyst, the product was obtained in

Scheme 2 The reaction of synthesis of 2-amino-3,5-dicarbonitrile-6- thio-pyridines (4a-l)
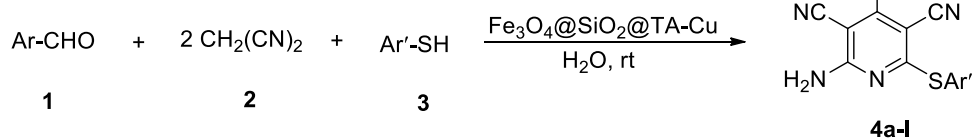
Table 2 The results of optimization experiments for the three-component reaction for the model reaction of benzaldehydes, malononitrile, and thiophenols at room temperature.
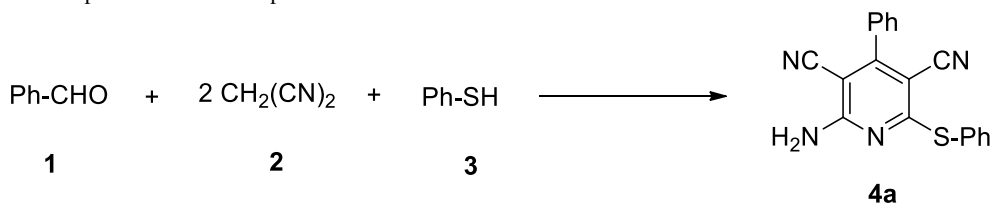
Entry	Catalyst	Amount of catalyst (gr)	Solvent	Time (min)	Yield
1[a]	$Fe_3O_4@SiO_2@TA$-Cu	0.05	–	30	40
2	–	–	H_2O	30	Trace
3	$Fe_3O_4@SiO_2@TA$-Cu	0.05	H_2O	7	95
4	$Fe_3O_4@SiO_2@TA$-Cu	0.05	Toluene	60	70
5	$Fe_3O_4@SiO_2@TA$-Cu	0.05	EtOH	60	75
6	$Fe_3O_4@SiO_2@TA$-Cu	0.05	DMF	60	Trace
7	$Fe_3O_4@SiO_2@TA$-Cu	0.05	CH_3CN	60	30
8	$Fe_3O_4@SiO_2@TA$-Cu	0.05	$CHCl_3$	60	40
9	$Fe_3O_4@SiO_2@TA$-Cu	0.03	H_2O	20	75
10	$Fe_3O_4@SiO_2@TA$-Cu	0.07	H_2O	20	95
11	$Fe_3O_4@SiO_2@TA$-Cu	0.1	H_2O	10	95
12[b]	$Fe_3O_4@SiO_2@TA$-Cu	0.05	H_2O	10	95
13	$Cu(OAc)_2$	0.05	H_2O	60	55
14	Fe_3O_4	0.05	H_2O	60	Trace
15	Tannic acid	0.05	H_2O	120	Trace

[a]At 100 °C temperature

[b]At reflux condition

only 40% yield (Table 2, entry 1). When the reaction was performed using H$_2$O as a solvent, in the absence of catalyst, the reaction did not proceed successfully even after a longer reaction time, in contrast, using the catalyst, the reaction times were decreased to 7 min and the desired product was obtained in excellent yields (Table 2, entries 2, 3). In continuation of our work, the catalytic activity of Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles in some solvents was also investigated (Table 2, entries 4–8). Among the solvents, the best result has been obtained in H$_2$O. The using solvent-free condition or solvents like toluene, EtOH, DMF, CH$_3$CN, and CHCl$_3$ gave a low yield of the product despite a longer time of reaction. Then, the condensation reaction occurred more successfully in the H$_2$O as a safe solvent. One important case of green chemistry is the replacing of hazardous solvents with relatively nontoxic solvents. This is a great advantage of this new catalytic system concerning green chemistry since no toxic solvent is required to synthesis of desired products. We also studied the effect of the amount of catalyst loading (Table 2, entries 3, 9–11). The formation of 2-amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (4a) was done with an amount of 0.03 g, 0.05 g, 0.07 g, and 0.1 g of the catalyst. It was obtained that the 0.05 g of the magnetic Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles was the optimal experimental amount (Table 2, entry 3). Increasing the amount of catalyst did not enhance the rate of reaction or the yield of the product (Table 2, entries 10, 11). In contrast, a lower amount of catalysts has decreased the yield of the product even after a longer reaction time (Table 2, entry 9). The effect of temperature on the reaction was also studied. It was found that at the high reaction temperature (at reflux condition, entry 12) the rate and yield of the reaction were not improved. To demonstrate the high catalytic effect of Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles, the synthesis of (4a) was also performed using Cu(OAc)$_2$, Fe$_3$O$_4$ NPs, and Tannic acid separately (Table 2, entries 13–15). As shown in Table 1, just 55% conversion was performed after 60 min in the presence of Cu(OAc)$_2$ (Table 2, entry 13). When the Fe$_3$O$_4$ NPs and Tannic acid were taken separately as the catalyst, they gave the product in trace yield (Table 2, entries 14, 15). Therefore, the Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles can be suggested as an efficient solid acid catalyst for the synthesis of 2-amino-3,5-dicarbonitrile-6- thio-pyridines.

In continuation, to study the general application of this procedure, the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines was investigated by various aldehydes and thiophenols under optimized reaction conditions (Table 3).

As is evident from the results shown in Table 3, this method is highly appropriate with many benzaldehydes with both an electron-donating and an electron-withdrawing group, such as chloro, nitro, methyl, methoxy, hydroxy, and N, N dimethylamine groups. All benzaldehyde derivatives gave the desired products in good to excellent yields

(Table 3, entries 1–8). Similarly, the substituents on thiophenol show the same effects on the reaction: Chloro, methyl, methoxy, and amino-substituted thiophenols produced the corresponding pyridine derivatives in good to excellent yields using this catalyst. (Table 3, entries 8–12). However, with aliphatic aldehydes and thiols, the reaction was not efficient. The structures of all the products were confirmed from their spectral (FT-IR, ^{1}H NMR, ^{13}C NMR, and MS) data.

Then, the resultant nanocomposites exhibited excellent catalytic performance and good stability for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines. The excellent adsorption of TA is mainly due to the presence of large number of functional groups via hydrogen bonding and π–π interaction. Then, tannic acid-metal with surface binding affinity could activate the reactant through the strong chelating interaction between reactant groups and Cu ions and improved the rate and yield of the products [52, 64, 65].

In continuation, we compared the reported methods with the other catalysts recently reported for synthesis tetrazole derivatives in the literature. As it is found (Table 4), despite the merits of most of the previously reported methods, the Fe$_3$O$_4$@SiO$_2$@TA-Cu NPs are the more efficient catalysts than many of the methods reported in the literature for this reaction.

The proposed mechanism for the preparation of 2-amino-3,5-dicarbonitrile-6- thio-pyridines is shown in Scheme 3. The first step of the mechanism involves the Knoevenagel condensation of an aldehyde with malononitrile to form the corresponding Knoevenagel product A. The reaction proceeds through the subsequent Michael-type addition of the second molecule of malononitrile to the Knoevenagel adduct A and thiolate addition to C≡N of the adduct and cyclization to produce dihydropyridine (B) [25, 29]. Aromatization of B under the reaction conditions gives desired pyridine derivatives. It is believed that the final step of the reaction mechanism for the synthesis of target molecules proceeded through vinylogous anomeric-based oxidation mechanism [66] (Scheme 3). In this mechanism, it is supposed that dual activation of aldehyde, malononitrile, and thiol by Fe$_3$O$_4$@SiO$_2$@TA-Cu has also taken place.

Recycling of catalyst

Metal–organic frameworks (MOFs), are a class of emerging catalysts with many promising characters. These new heterogeneous catalysts usually are very stable and may be easily recycled and reused after the application [51]. The other advantage of this heterogeneous catalyst is that it can easily be recovered by an external magnet and can be reused without significant loss of catalytic activities. As shown in Fig. 5, when the reaction of benzaldehyde (1a), malononitrile (2), and thiophenol (3a) was done as a model reaction,

Table 3 The screening results for the synthesis of 2-amino-3,5-dicarbonitrile-6- thio-pyridines using the magnetic Fe₃O₄@SiO₂@TA-Cu nanocatalyst[a]
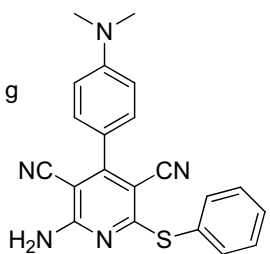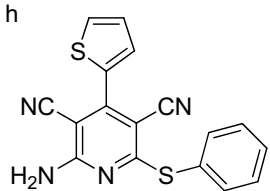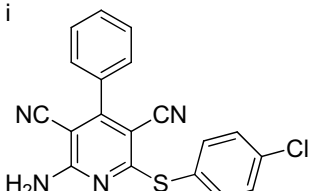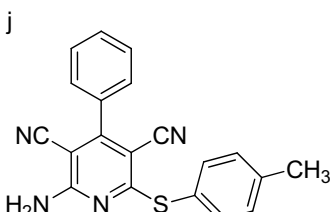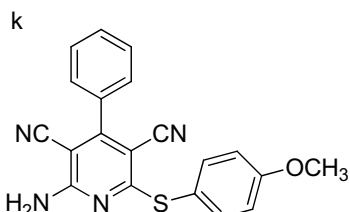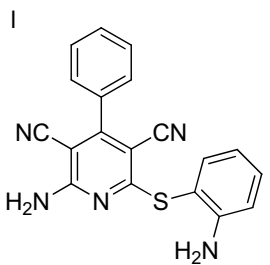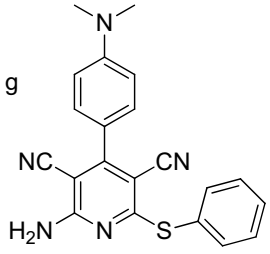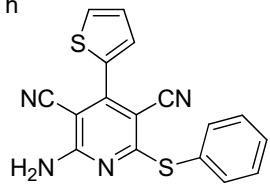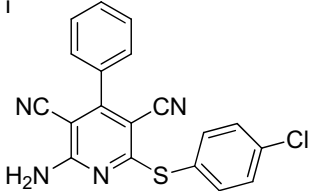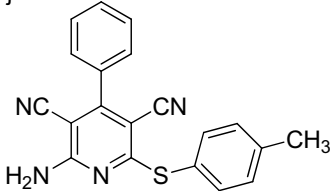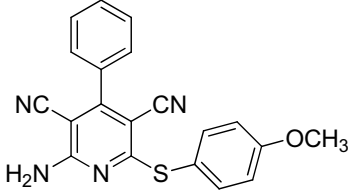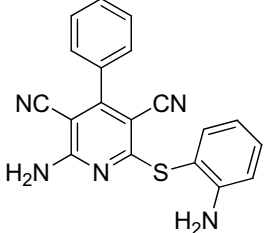
Entry	Product[b]	Time (min)	Isolated yield	Mp (°C)[reference]
1	g	7	95	218–220[40]
2	h	20	85	213–215[41]
3	i	7	90	220–222[41]
4	j	5	95	289–290[37]
5	k	20	80	240–242[40]
6	l	15	90	312–314[40]

Table 3 (continued)

Entry	Product[b]	Time (min)	Isolated yield	Mp (°C)[reference]
7	g	20	90	288–290[25]
8	h	15	88	248–250[25]
9	i	15	95	225–227[37]
10	j	10	85	238–240[41]
11	k	10	87	228–229[31]
12	l	15	90	225–227[36]

[a]Reaction conditions: benzaldehyde derivatives (1 mmol), malononitrile (2 mmol), and thiophenols derivatives (1 mmol), Fe_3O_4@SiO_2@TA-Cu NPs (0.05 gr), H_2O (5 cc), room temperature

[b]All obtained products are known compounds and were characterized based on spectral data (FT-IR, ^{1}H NMR, ^{13}C NMR, and MS) and were identified by comparing their melting points with authentic samples

Table 4 Comparison of various catalysts for the synthesis of 2-Amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (4a)

Entry	Catalyst/	Conditions (solvent, temperature, time)	Yield (%)
1	Fe3O4@ CoII(macrocyclic Schiff base ligand)[25]	Solvent-Free, 100 °C, 13 min	90
2	WEB[27]	EtOH, 65 °C, 20 min	90
3	DBU[28]	EtOH, 35 °C, 15 min	80
4	DABCO[26]	EtOH, reflux, 2.5 h	45
5	Zn(II) and Cd(II) MOFs[51]	Solvent-Free, 100 °C, 30 min	86
6	CuI NPs[48]	EtOH/H$_2$O, reflux, 100 min	90
7	[bmIm]OH[42]	EtOH, r.t, 1.1 h	92
8	silica NPs[47]	EtOH, reflux, 3 h	70
9	TBAB/Cs$_2$CO$_3$[33]	MeOH, r.t, 3 h	92
10[a]	silica-bonded *N* propyldiethylenetriamine[29]	EtOH, reflux, 40 min	88
11	CH$_3$COONa[40]	MeOH, microwave irradiation, 3 min	89
12	*y*-Fe$_2$O$_3$-2-HEAS[46]	Solvent-Free, 50 °C, 10 min	91
13	Na$_2$SiO$_3$[32]	EtOH, r.t, 60 min	78
14	Fe$_3$O$_4$@SiO$_2$@TA-Cu [present work]	H$_2$O, r.t, 7 min	95

[a]Conditions for the synthesis of 2-Amino-4-phenyl-6-*p*-tolylsulfanyl)-pyridine-3,5-dicarbonitrile

Scheme 3 The proposed mechanism for the preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridines by Fe$_3$O$_4$@SiO$_2$@TA-Cu NPs
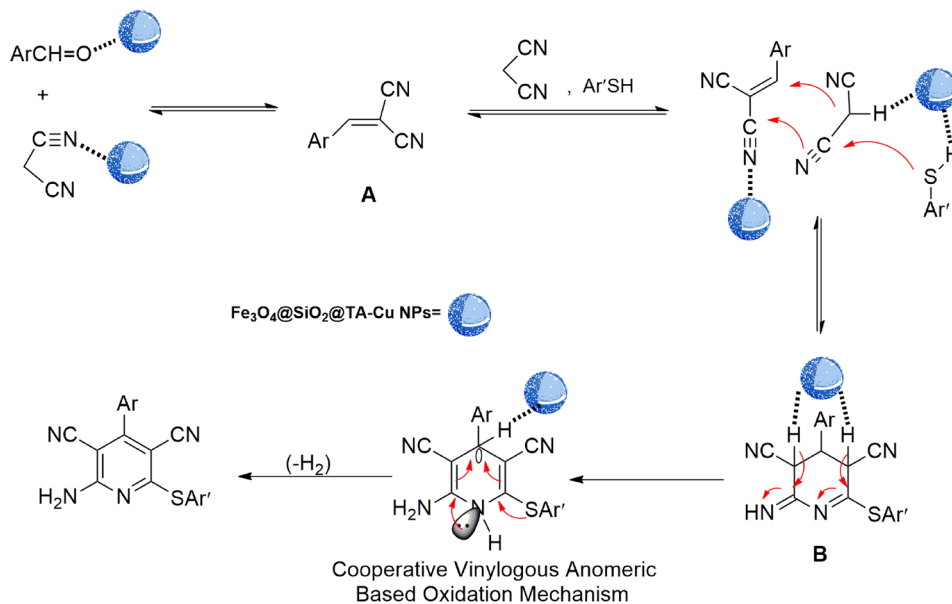

the Fe$_3$O$_4$@SiO$_2$@TA-Cu nanocatalyst reused for five cycles without almost considerable loss of the activity.

Conclusion

In summary, the surfaces of Fe3O4@SiO2 nanoparticles were successfully modified with a uniform thin layer of TA-Cu coordination complexes by a modification process for catalytic application. The results demonstrated that the Fe$_3$O$_4$@SiO$_2$@TA-Cu nanoparticles are efficient, and

recyclable catalysts for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines via three-component condensations of aldehydes, malononitrile, and thiophenols in water. This protocol provides several advantages such as the strong ability of catalyst to immobilize metal nanoparticles, high chemical stabilities of catalyst in the action mixture, high specific surface area of catalyst, uniformly dispersed and easily recoverable NPs, high yield of products, simple work up, simple separation of the magnetic catalyst, green method, avoiding hazardous organic solvent in the reaction environment.

Fig. 5 Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in the presence of reused $Fe_3O_4@SiO_2@TA$-Cu nanoparticles
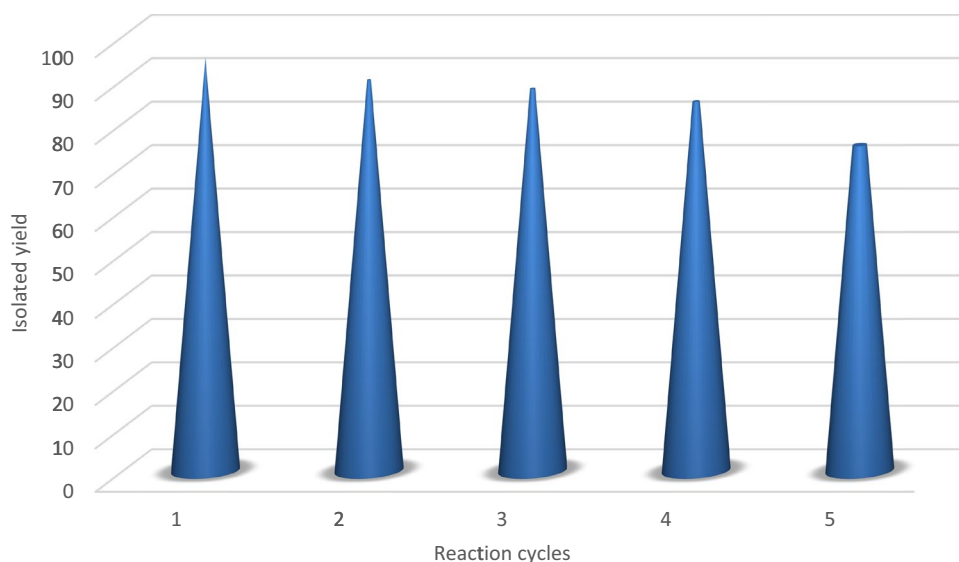
Declarations

Conflict of interest No potential conflict of interest was reported by the authors.

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