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FULL PAPER

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Nicotine-based ionic liquid supported on magnetic nanoparticles: An efficient and recyclable catalyst for selective one-pot synthesis of *mono*- and *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles

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In this study, an acidic nicotine-based ionic liquid supported on magnetic nanoparticles ([NicTC]HSO_4@MNPs) was synthesized and characterized by different techniques. The activity of this catalyst was evaluated in a multi-component reaction of 2-aminobenzothiazole, aldehydes/dialdehydes and β-ketoesters/1,3-diketones to afford a series of novel *mono*- and *bis*-4*H*-pyrimido[2,1-*b*]benzothiazole derivatives. In addition, mild reaction conditions, high yields, excellent selectivity as well as easy recovery and reusability of the catalyst, make this method an economic and environmentally-benign process.

KEYWORDS

4*H* -Pyrimido[2,1-*b*]benzothiazoles, fused heterocyclic compounds, nicotine-based ionic liquid, selective synthesis, solvent-free conditions

1 | INTRODUCTION

Pyrimido[2,1-*b*]benzothiazoles are an important class of fused nitrogen heterocycles, which has been found in the manufacture of natural molecules and drug molecules with various biological activities.[1–4] Furthermore, these compounds act as chemosensitizers in chemotherapy and neuroprotectant-cerebral anti-ischemic agents.[5] Up to now, several methods have been described for the synthesis of simple derivatives of these heterocycles.[6] Although the reported methods are more or less useful, but in some cases, high loading non-reusable catalysts and high temperatures are required for successful transformation. On the other hand, the synthesis of *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles has not been reported so far. Consequently, introduction of an efficient and environmentally-friendly protocol for the synthesis of complex derivatives of pyrimido[2,1-*b*]benzothiazole is still required.

In recent years, ionic liquids (ILs) have attracted a considerable attention in catalytic systems because they can dissolve a wide variety of organic, organometallic, and inorganic compounds.[7] In addition, they have low vapor pressure, low melting point and relatively thermal stability.[8] Despite these advantages, their high viscosity, difficulties in recovery and reusability limit their practical applications in chemical processes.[9] Moreover, the toxicity of some ILs renders their utilization in biological systems such as microorganisms[10] and human cell line.[11] To overcome these problems, they can be prepared from biocompatible materials or immobilized on solid supports to obtain heterogeneous catalysts. In this respect, nicotine as a biocompatible material and as an efficient alternative

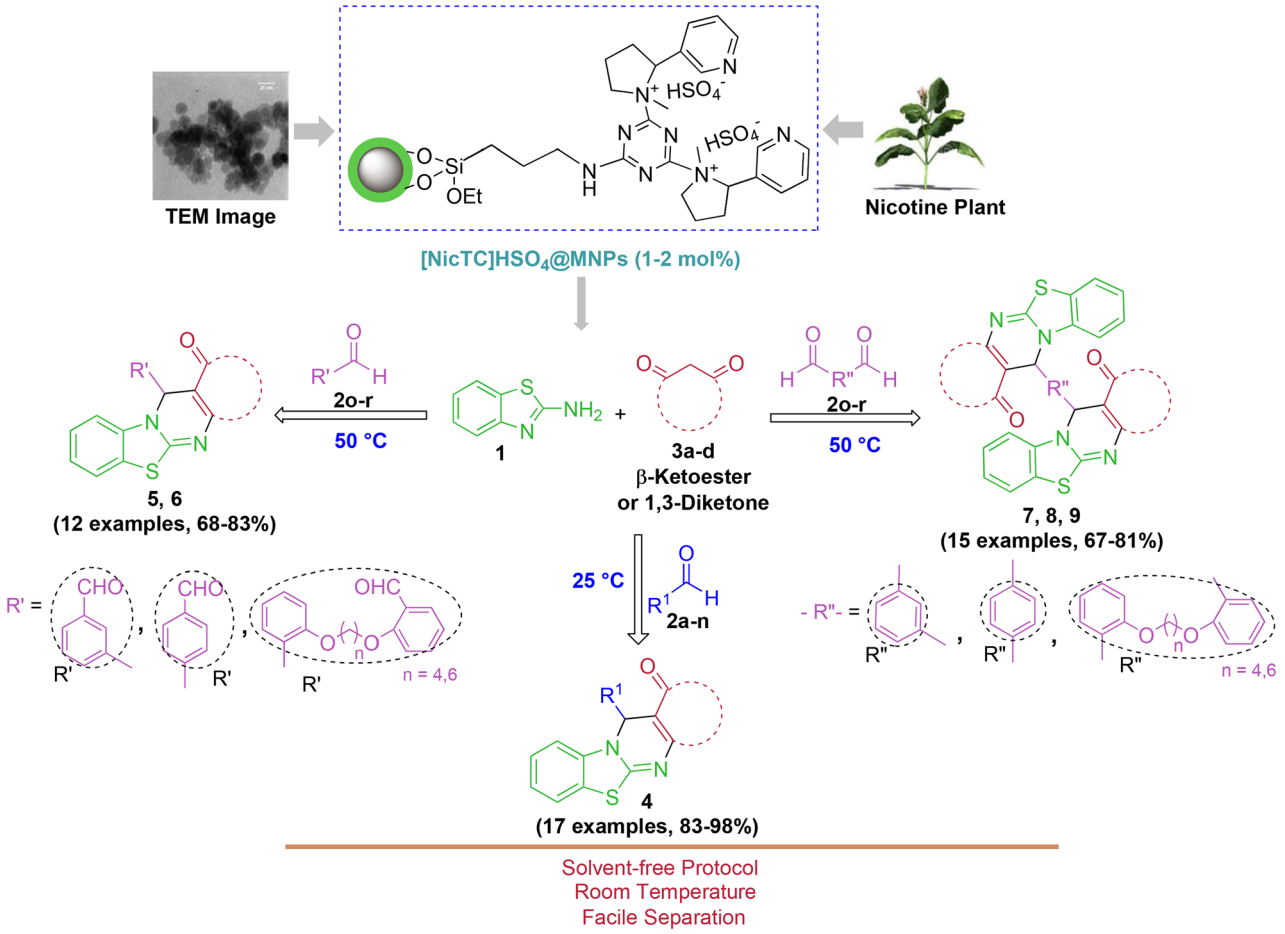
for hazardous pyridine, has been recently applied for production of ionic liquids.[12] Among the solid supports, magnetic nanoparticles (MNPs) are of practical importance because of their unique features including providing greater accessibility of active sites, easy synthesis and functionalization, good stability and facile separation by applying an external magnet.[13–15] Also, these nanoparticles have been used in many fields such as magnetic recording devices, targeted drug delivery, biomedicine, biosensors, magnetic fluids, bioprobes and catalysis.[16] According to the above mentioned advantages of nicotine and MNPs, the application of nicotine-based ionic liquid supported on magnetic nanoparticles as catalyst provides an environmentally benign process.

In continuation of our interest relating to the introduction of valuable catalytic systems,[17] we report an acidic nicotine-based ionic liquid supported on magnetic nanoparticles ([NicTC]HSO_4@MNPs) as a reusable heterogeneous catalyst for the efficient synthesis of novel *mono-* and *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles under solvent-free conditions (Scheme 1).

2 | EXPERIMENTAL

2.1 | General

The chemicals were purchased from Fluka and Merck chemical companies. 2,2′-(hexane-1,6-diylbis (oxy)) dibenzaldehyde **2q** and 2,2′-(butane-1,4-diylbis (oxy)) dibenzaldehyde **2r** were prepared according to the previously reported method.[18] Melting points were determined with a Stuart Scientific SMP2 apparatus. FT-IR spectra were recorded on a Nicolet-Impact 400D spectrophotometer. ^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer using DMSO-d_6 solvent. Elemental analysis was performed on a LECO, CHNS-932 analyzer. Thermogravimetric and derivative thermogravimetric analysis (TGA/DTG) were evaluated on a Perkin-Elmer STA 6000 instrument under argon flow at a uniform heating rate of 20 °C min^{-1} in the range 30–600 °C. Magnetic measurements were carried out with a vibrating sample magnetometer (Meghnatis Daghigh Kavir Co.) at room temperature. The scanning electron microscope



SCHEME 1 Synthesis of mono- and bis-4H-pyrimido[2,1-*b*]benzothiazoles catalyzed by [NicTC]HSO_4@MNPs

(SEM) measurement was carried out on a Hitachi S-4700 field emission scanning electron microscope. The transmission electron microscopy (TEM) was carried out on a Philips CM10 instrument operating at 100 kV. X-ray diffraction patterns were obtained with a Bruker XRD D8 Advance instrument with Co Kα radiation at 40 kV.

2.2 | Preparation of nicotine-based ionic liquid supported on magnetic nanoparticles ([NicTC]HSO_4@MNPs, scheme 2)

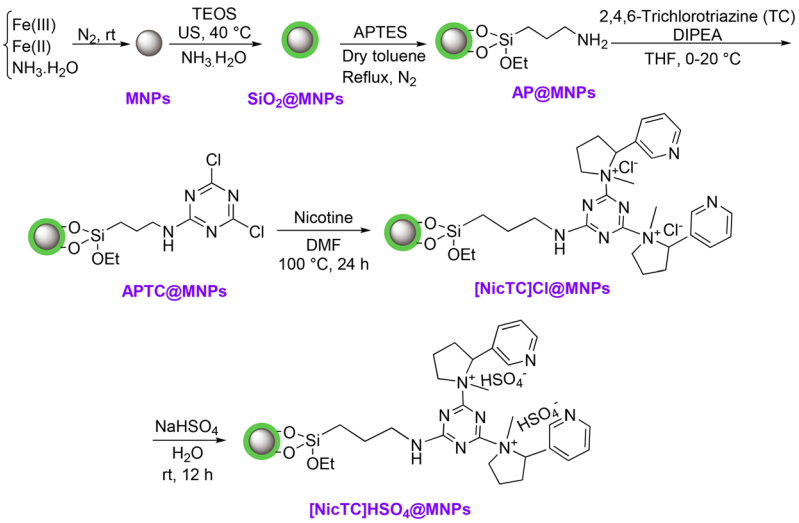
The magnetic nanoparticles (MNPs) and silica coated magnetic nanoparticles (SiO_2@MNPs) were prepared according to the previously reported method.[19] Then, a mixture of 3-aminopropyltriethoxysilane (APTES, 6 ml) and dispersed SiO_2@MNPs (2 g) in dry toluene (40 ml) was refluxed under nitrogen atmosphere for 24 h. The resulting AP@MNPs were separated by an external magnet, washed with diethyl ether and dried under vacuum. Subsequently, the dispersed AP@MNPs (2 g) were reacted with 1.85 g trichlorotriazine (TC) and 1.7 ml diisopropylethylamine (DIPEA) in 10 ml dry THF at 0–20 °C.[20] The solid material was magnetically separated, washed with hot THF and then dried under vacuum to provide APTC@MNPs. After that, the dispersed APTC@MNPs (2 g) in 20 ml DMF was reacted with nicotine (5.4 g) at 100 °C for 24 h. The solid material was magnetically separated, washed with DMF and ethanol and then dried to produce [NicTC]Cl@MNPs. Finally, a mixture of [NicTC]Cl@MNPs (1.85 g) and sodium hydrogen sulfate (9.25 g) was stirred in water (30 ml) at room temperature for 12 h. The solid material was magnetically separated, washed with water and ethanol and dried in a vacuum oven at 80 °C to produce the desired nicotine-based ionic liquid supported on magnetic nanoparticles ([NicTC]HSO_4@MNPs).

2.3 | General procedure for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles catalyzed by [NicTC]HSO_4@MNPs

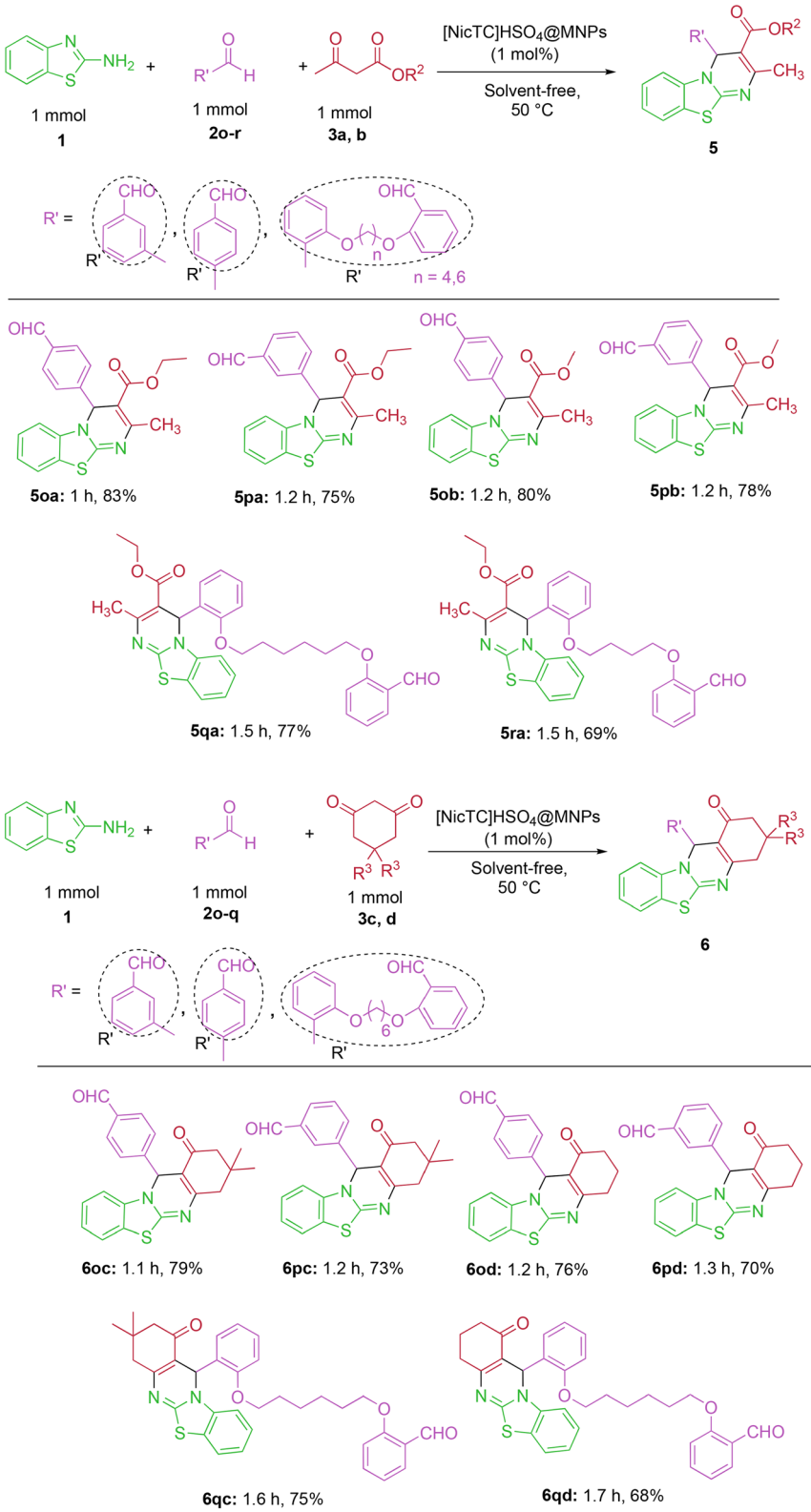
A mixture of 2-aminobenzothiazole **1** (1 mmol), aryl aldehyde **2** (1 mmol), and β-ketoester/1,3-diketone **3** (1 mmol) and [NicTC]HSO_4@MNPs catalyst (25 mg, 1 mol% HSO_4^-) was stirred at room temperature for the appropriate time stated in Table 3. The reaction progress was monitored by TLC (eluent: petroleum ether/EtOAc, 4:1). After completion of the reaction, hot ethanol (5 ml) was added and the catalyst was simply separated using an external magnet and then washed with hot ethanol (5 ml). The organic residue was cooled to room temperature, filtered, washed with EtOH for several times and dried under vacuum to provide the pure desired products in 83–98% yields (Table 3).

2.4 | General procedure for the selective synthesis of *mono*- and *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles from dialdehydes catalyzed by [NicTC]HSO_4@MNPs

For the synthesis of *mono*- derivatives, a mixture of 2-aminobenzothiazole (1 mmol), dialdehyde (1 mmol), β-ketoester/1,3-diketone (1 mmol) and [NicTC]HSO_4@MNPs (25 mg, 1 mol% HSO_4^-) was stirred at 50 °C under solvent-free conditions for the suitable time presented in Schemes 3 and 4. After completion of the reaction as monitored by TLC (eluent: petroleum ether/EtOAc, 4:1),



SCHEME 2 The schematic procedure for the preparation of [NicTC]HSO_4@MNPs catalyst



SCHEME 3 Selective synthesis of mono-4H-pyrimido[2,1-*b*]benzothiazoles from β-ketoesters catalyzed by [NicTC]HSO_4@MNPs

SCHEME 4 Selective synthesis of mono-4H-pyrimido[2,1-*b*]benzothiazoles from 1,3-diketones catalyzed by [NicTC]HSO_4@MNPs

the crude product was purified according to the above mentioned procedure to provide pure *mono*-4*H*-pyrimido[2,1-*b*]benzothiazole derivatives in 68–83% yields.

For the synthesis of symmetric *bis*-4*H*-pyrimido[2,1-*b*] benzothiazoles, the reaction between 2-aminobenzothiazole (1 mmol), dialdehyde (0.5 mmol) and β-ketoester/1,3-diketones (1 mmol) was carried out in the presence of [NicTC]HSO_4@MNPs (50 mg, 2 mol% HSO_4^-) at 50 °C for 1.4–2 h. The workup was performed according to the procedure above mentioned and purification of the crude product by silica gel column

chromatography (eluent: petroleum ether/EtOAc, 4:1) provided the pure symmetric *bis*- derivatives in 69–81% yields (Schemes 5, 6).

For the synthesis of unsymmetric *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles, a mixture of 2-aminobenzothiazole (1 mmol), dialdehyde (0.5 mmol), 0.5 mmol of each of two different 1,3-dicarbonyl compounds and [NicTC]HSO_4@MNPs (50 mg, 2 mol% HSO_4^-) was stirred at 50 °C for 1.4–1.5 h. At the end of the reaction which was monitored by TLC (eluent: petroleum ether/EtOAc, 4:1), the workup and purification of the crude product was performed according to the above mentioned procedure to produce the pure unsymmetric *bis*-derivatives in 67–70% yields (Scheme 7).

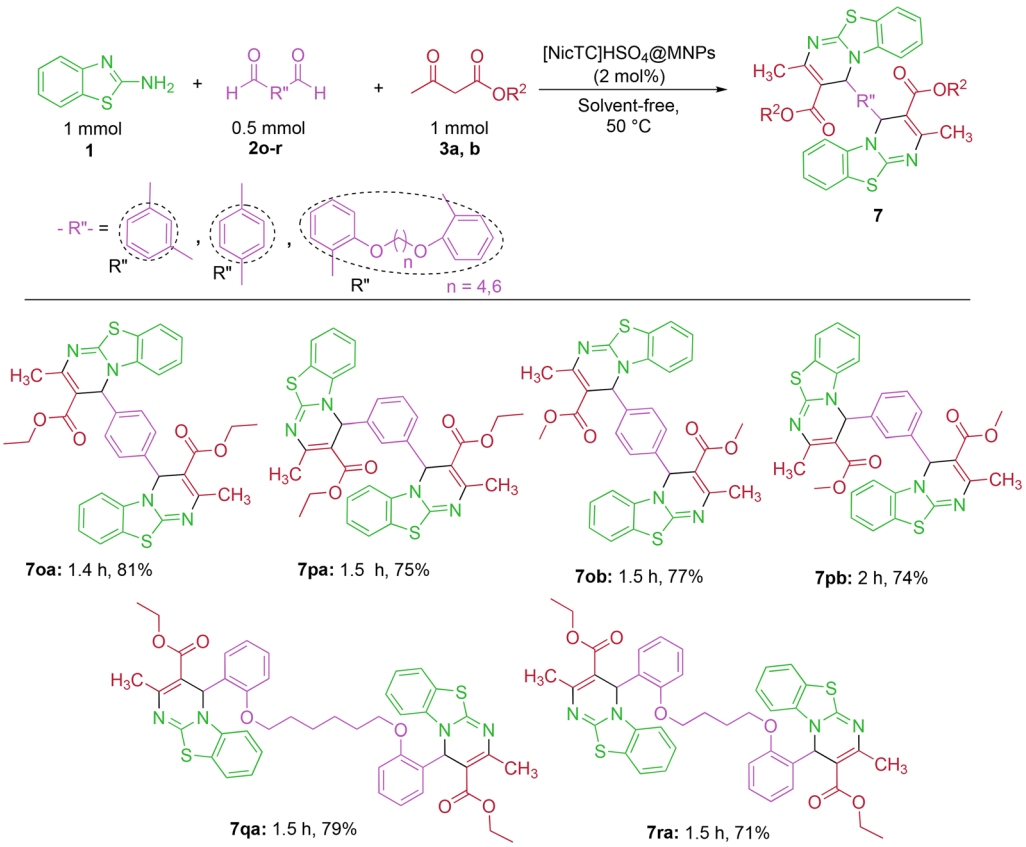
3 | RESULTS AND DISCUSSION

3.1 | Preparation and characterization of nicotine-based ionic liquid supported on magnetic nanoparticles ([NicTC]HSO_4@MNPs)

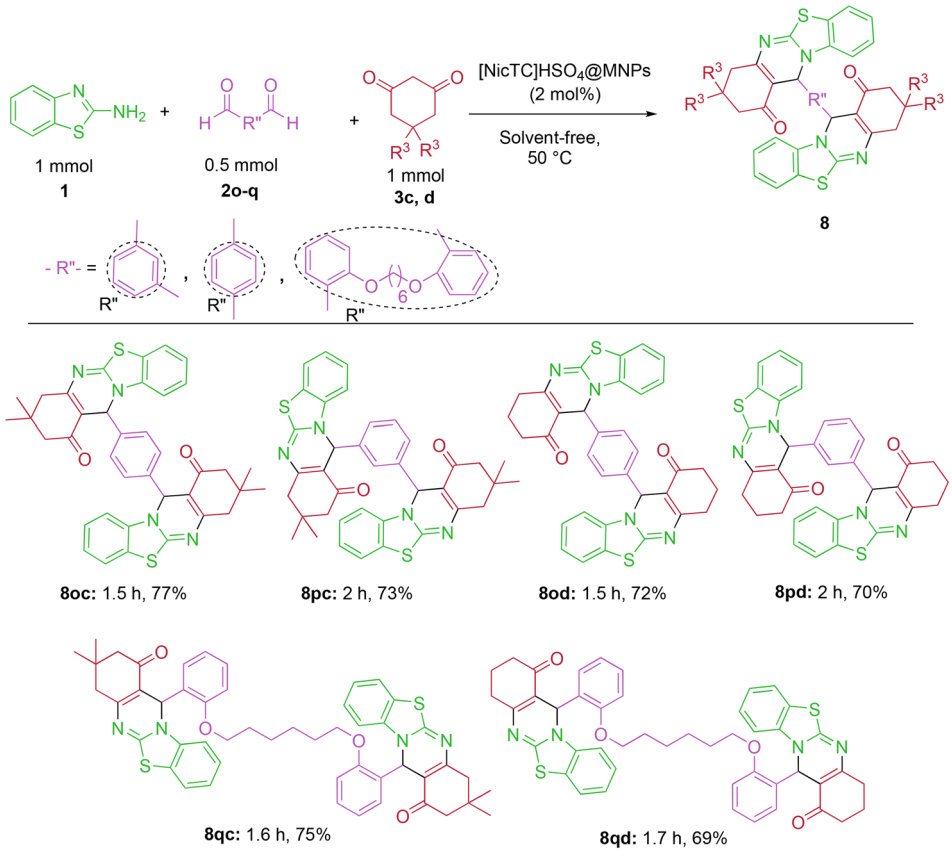
Recently, we reported a new nicotine-based organocatalyst supported on silica nanoparticles (Fe (III)-NicTC@nSiO_2) for the synthesis of 1,5-benzodiazepines.[12g] Regarding our previous research, herein, the synthesis of an acidic nicotine-based ionic liquid stabilized on magnetic nanoparticles ([NicTC]HSO_4@MNPs) was investigated (Scheme 2).

In brief, magnetic nanoparticles (MNPs) were prepared via the coprecipitation method and preserved with a layer of silica (SiO_2@MNPs).[21] Treatment of SiO_2@MNPs with 3-aminopropyltriethoxysilane (APTES) under inert conditions produced AP@MNPs. In the following, the amino group of AP@MNPs was reacted with trichlorotriazine (TC) in the presence of diisopropylethylamine (DIPEA) in anhydrous THF at 0–20 °C to provide APTC@MNPs.[20] Then, the active chlorine groups were substituted with nicotine in DMF at 100 °C to produce [NicTC]Cl@MNPs. Finally, the target acidic catalyst, [NicTC]HSO_4@MNPs was prepared by adding $NaHSO_4$ to [NicTC]Cl@MNPs in water. The synthesized [NicTC]HSO_4@MNPs was characterized using different techniques, including FT-IR, VSM, TEM, SEM, EDX, TG/DTG, XRD and elemental analysis.

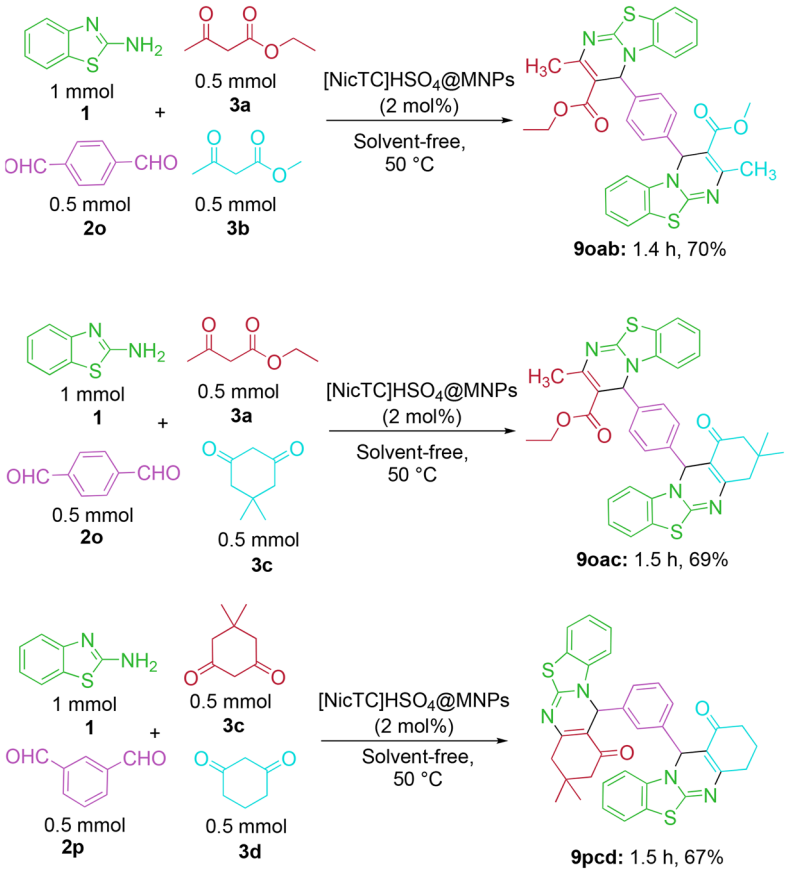
The FT-IR spectra of MNPs, SiO_2@MNPs, APTC@MNPs and [NicTC]HSO_4@MNPs are presented in Figure 1. The characteristic bands at 560 and 465 cm^{-1}, attributed to the symmetric and asymmetric



SCHEME 5 Selective synthesis of symmetric *bis*-4H-pyrimido[2,1-*b*]benzothiazoles from β-ketoesters catalyzed by [NicTC]HSO_4@MNPs



SCHEME 6 Selective synthesis of symmetric *bis*-4H-pyrimido[2,1-*b*] benzothiazoles from 1,3-diketones catalyzed by [NicTC]HSO_4@MNPs



SCHEME 7 Selective synthesis of unsymmetric bis-4H-pyrimido[2,1-*b*]benzothiazoles catalyzed by [NicTC]HSO_4@MNPs

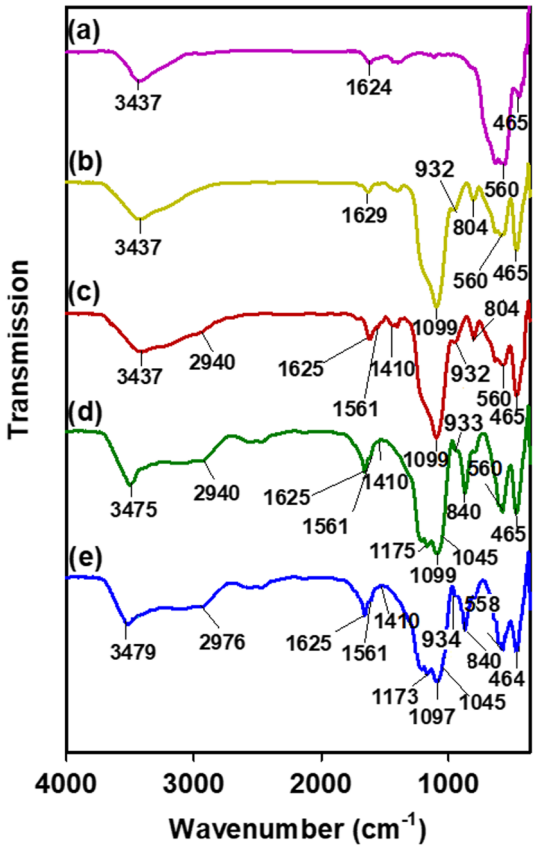


FIGURE 1 FT-IR spectra of: (a) MNPs, (b) SiO_2@MNPs, (c) APTC@MNPs, (d) [NicTC]HSO_4@MNPs and (e) the 5-times reused catalyst

Fe–O vibrations (Figure 1a), confirm the existence of Fe_3O_4 component in all samples. Also, all these samples show a broad band centered around 3437 cm^{-1} that is assigned to the OH group. The spectrum of the SiO_2@MNPs (Figure 1b) exhibits the characteristic bands at about 1099, 932 and 804 cm^{-1}, which are attributed to the stretching vibrations of Si–O–Si, Si–OH and Si–O–Fe, respectively. In the FT-IR spectra of APTC@MNPs and [NicTC]HSO_4@MNPs (Figures 1c and 1d), the typical bands observed at about 2940 cm^{-1} (C–H), 1625 cm^{-1} (C=N), 1561 cm^{-1} (C=C) and 1410 cm^{-1} (C–H). In addition, the bands at 1175 and 1045 cm^{-1} in the spectrum of [NicTC]HSO_4@MNPs (Figure 1d) correspond to the vibrations of S=O group. These results confirm that IL has been successfully supported on the surface of SiO_2@MNPs.

Due to importance of easy recovery of the catalyst by an external magnet, the magnetic property of [NicTC]HSO_4@MNPs was also evaluated (Figure 2). The saturation magnetization (Ms) values of MNPs, SiO_2@MNPs and [NicTC]HSO_4@MNPs catalyst were obtained to be 69.40, 38.96 and 19.52 emu g^{-1}, respectively. Although, the superparamagnetic characteristic of the prepared

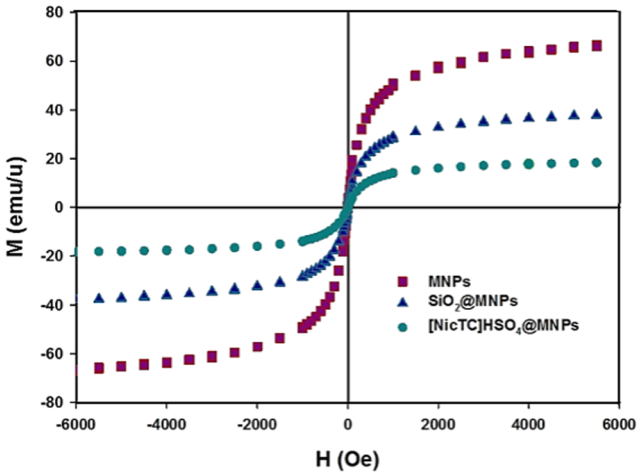


FIGURE 2 Magnetization curves for MNPs, SiO_2@MNPs and [NicTC]HSO_4@MNPs

catalyst is smaller than that of the bulk magnetic sample, but it is enough for easy separation of the catalyst from the reaction mixture by an external magnet.

The morphology of the surface of [NicTC]HSO_4@MNPs catalyst was investigated by SEM, SEM–EDX and TEM spectroscopies. As shown in Figure 3, the presence of all expected elements C, N, S, O, Si and Fe in the EDX analysis of [NicTC]HSO_4@MNPs is indicative of successful functionalization of MNPs by covalent attachment of nicotine ionic liquid. The TEM image of the catalyst revealed dark spherical morphology with an average diameter of 12–15 nm.

The TG/DTG analysis of the synthesized catalyst is presented in Figure 4. As shown, [NicTC]HSO_4@MNPs are thermally stable up to 400–500 °C, and above this temperature the process of decomposition proceeds relatively fast, in which the organic construction was omitted from the catalyst. This high thermal stability provides the excellent activity of the catalyst without any considerable leak of the active species. The total weight loss was 19.60%.

The X-ray diffraction patterns of MNPs, SiO_2@MNPs, APTC@MNPs, [NicTC]Cl@MNPs and [NicTC]HSO_4@MNPs show the same typical peak positions and relative intensities (Figure 5). The peaks at 30.44°, 36.08°, 43.67°, 53.24°, 57.68° and 63.32° correspond to the (220), (311), (400), (422), (511) and (440) reflections, respectively, of the crystalline structure of the standard naked MNPs sample (JCPDS 19–0629). A broad peak at 2θ = 15.16°-28.68° is attributed to the amorphous silica shell surrounding of the MNPs core.[22] As can be seen, the phase composition of MNPs remains intact after coating the nanoparticles with silica.

According to the elemental analysis of the [NicTC]HSO_4@MNPs catalyst (C = 7.15, H = 1.86, N = 2.29 and

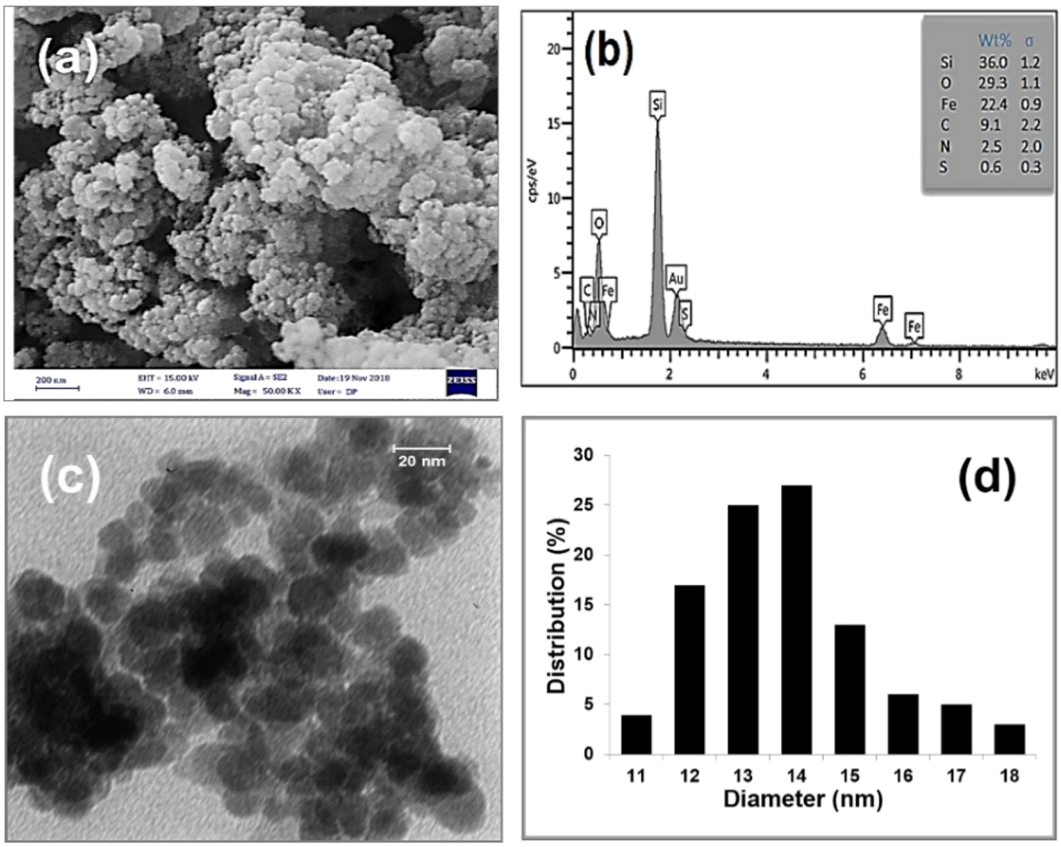


FIGURE 3 FE-SEM images of: (a) [NicTC]HSOa@MNPs, (b) SEM–EDX spectrum of [NicTC]HSO_4@MNPs, (c) TEM image of [SiAPTANic]HSO_4@MNPs and (d) particle size distribution for [NicTC]HSO_4@MNPs catalyst

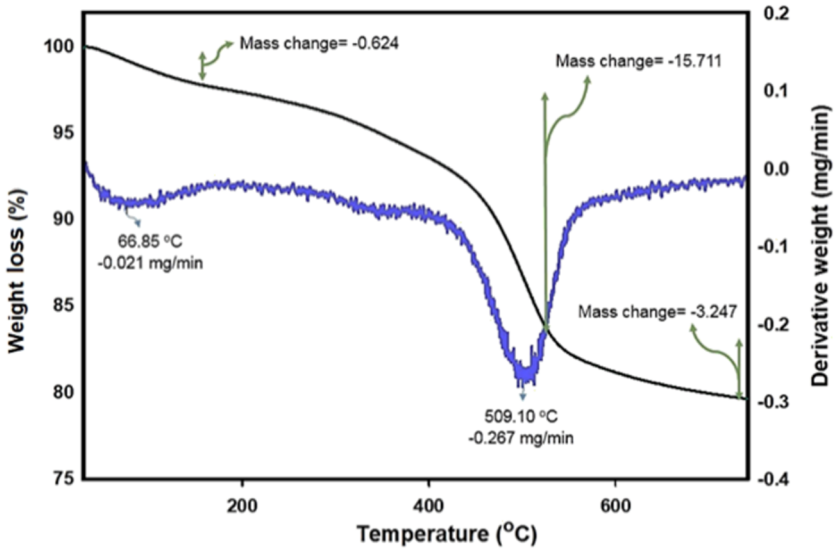


FIGURE 4 TGA/DTG analysis of [NicTC]HSO_4@MNPs catalyst

S = 1.04), the amount of organic layer supported on the magnetic nanoparticles was 0.4 mmol/g of the catalyst (based on nitrogen content). Furthermore, the acidity of the [NicTC]HSO_4@MNPs catalyst, determined by potentiometric titration (NaOH 0.01 N), showed that the acidic sites on the magnetic nanoparticles was 0.4 mmol/g of catalyst.

3.2 | Optimization of the reaction conditions for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives

For optimization of the reaction conditions, the present study was initiated with 2-aminobenzothiazole **1** (1 mmol), 4-nitrobenzaldehyde **2a** (1 mmol) and ethyl acetoacetate

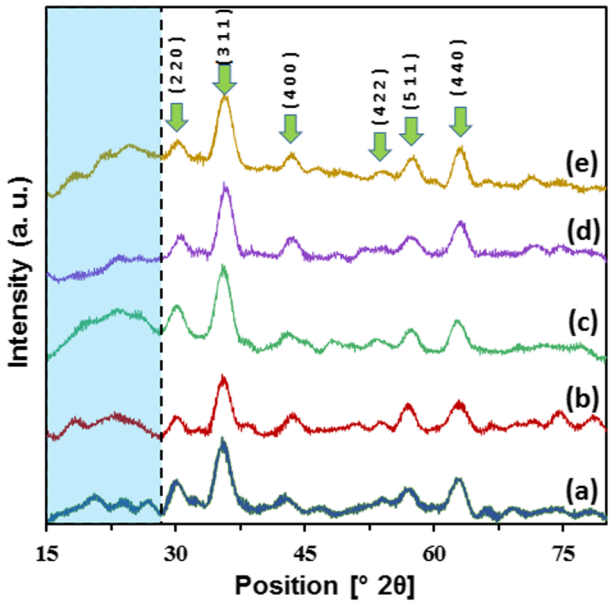


FIGURE 5 X-ray diffraction patterns of: (a) MNPs1, (b) SiO_2@MNPs, (c) APTC@MNPs, (d) [NicTC]Cl@MNPs and (e) [NicTC]HSO_4@MNPs

3a (1 mmol) as the model substrates at room temperature under solvent-free conditions. The results are summarized in Table 1. No reaction was observed in the absence of the catalyst even after 7 h (Table 1, entry 1). Then, the reaction was carried out in the presence of 2 mol% of different catalysts such as $SnCl_2{\cdot}2H_2O$, $FeCl_3$, $BiCl_3$, Bi$(OTf)_3$, $H_3PW_{12}O_{40}$, [Hmim]HSO_4 and $NaHSO_4$ at room temperature under solvent-free conditions and the target compound **4aa** was obtained in 14–69% yields (Table 1, entries 2–8). Surprisingly, application of [NicTC]HSO_4@MNPs catalyst (Table 1, entry 9), not only enhanced the reaction rate but also provided an excellent yield of the product **4aa** (20 min, 98%). Furthermore, the reaction was performed with 0.5 mol% and 1 mol% of the catalyst and the yields were found to be 65% and 98%, respectively (Table 1, entries 10, 11). In addition, the model reaction was performed in various solvents such as CH_3CN, EtOH, $CHCl_3$, CH_2Cl_2 and *n*-hexane instead of solvent-free conditions (Table 1, entries 12–16). As can be seen, the desired product was obtained in low yield (10–68%). Accordingly, the solvent-free conditions was regarded as the best conditions for this reaction. To compare the efficiency of [NicTC]HSO_4@MNPs catalyst with those of MNPs, SiO_2@MNPs, APTC@MNPs and [NicTC]Cl@MNPs, the model reaction was also carried out in the presence of these reagents. As shown in Table 2, MNPs and SiO_2@MNPs were not effective in this reaction but in the presence of APTC@MNPs and [NicTC]Cl@MNPs, the desired product was obtained in only 15% and 28% yields, respectively. Consequently, 1 mol% [NicTC]

TABLE 1 Optimization of reaction conditions for synthesis of **4aa**[a]

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[c]
1	-	-	7	-
2	$SnCl_2{\cdot}2H_2O$ (2)	-	3	27
3	$FeCl_3$ (2)	-	3	15
4	$BiCl_3$ (2)	-	3	14
5	Bi$(OTf)_3$ (2)	-	3	20
6	$H_3PW_{12}O_{40}$ (2)	-	3	32
7	[Hmim]HSO_4 (2)	-	3	69
8	$NaHSO_4$ (2)	-	3	38
9[b]	[NicTC]HSO_4@MNPs (2)	-	20 min	98
10[b]	[NicTC]HSO_4@MNPs (1)	-	20 min	98
11[b]	[NicTC]HSO_4@MNPs (0.5)	-	3	65
12	[NicTC]HSO_4@MNPs (1)	CH_3CN	3	63
13	[NicTC]HSO_4@MNPs (1)	EtOH	3	68
14	[NicTC]HSO_4@MNPs (1)	CH_3Cl	3	58
15	[NicTC]HSO_4@MNPs (1)	CH_2Cl_2	3	30
16	[NicTC]HSO_4@MNPs (1)	*n*-hexane	3	10

[a]Reaction conditions: 2-aminobenzothiazole **1** (1 mmol), 4-nitrobenzaldehyde **2a** (1 mmol), ethyl acetoacetate **3a** (1 mmol) and catalyst at room temperature under solvent-free conditions or in the presence of different solvents.
[b]According to CHNS analysis of [NicTC]HSO_4@MNPs: 50 mg (2 mol% HSO_4^-), 25 mg (1 mol% HSO_4^-) and 12.5 mg (0.5 mol% HSO_4^-).
[c]Isolated yield.

TABLE 2 Comparison of the activity of [NicTC]HSO_4@MNPs with those of other reagents in the synthesis of **4aa**[a]

Entry	Catalyst (mg)	Time (h)	Yield (%)[b]
1	MNPs (25)	3	-
2	SiO_2@MNPs (25)	3	-
3	APTC@MNPs (25)	3	15
4	[NicTC]Cl@MNPs (25)	3	28
5	[NicTC]HSO_4@MNPs (25)	20 min	98

[a]Reaction conditions: 2-aminobenzothiazole **1** (1 mmol), 4-nitrobenzaldehyde **2a** (1 mmol), ethyl acetoacetate **3a** (1 mmol) and catalyst at room temperature under solvent-free conditions.
[b]Isolated yield.

HSO_4@MNPs under solvent-free conditions at room temperature was found to be optimum to give the best yield of the desired product **4aa**.

3.3 | Synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles

Next, we examined the scope and generality of this procedure for the synthesis of different 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives under the optimized conditions. As shown in Table 3, the one-pot three-component reaction of 2-aminobenzothiazole **1** with different aryl aldehydes **2** bearing either electron-withdrawing or electron-donating groups and β-ketoesters **3** (e.g. ethyl acetoacetate and methyl acetoacetate**)** proceeded smoothly to generate the desired 4*H*-pyrimido[2,1-*b*]benzothiazoles in excellent yields (Table 3, entries 1–4, 10, 11). The α,β-unsaturated aldehydes such as cinnamaldehyde, and heterocyclic aldehydes such as 6-chloro-4-oxo-4*H*-chromene-3-carbaldehyde, 5-methylfurfural, and 2-thiophenecarbaldehyde as well as polycyclic aldehydes such as naphthalene-2-carbaldehyde also participated effectively in this reaction to produce the respective pyrimido[2,1-*b*]benzothiazoles in high yields (Table 3, entries 5–9). In addition, when cyclic 1,3-diketones such as dimedone **3c** and 1,3-cyclohexanedione **3d** were applied instead of β-ketoesters in the aforesaid multi-component reaction, they transformed successfully to the respective products in high yields (Table 3, entries 12–17). In general, the reactions were very fast and completed within 20–50 min and the product yields were 83–98%.

3.4 | Selective synthesis of *mono*- and *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles

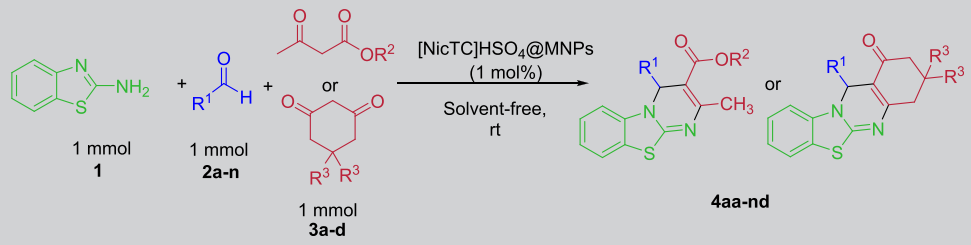
By obtaining worthy results as above mentioned, we then tried the synthesis of pyrimido[2,1-b]benzothiazoles by using substrates containing two formyl groups such as terephthaldialdehyde **2o**, isophthaldialdehyde **2p**, 2,2′-(hexane-1,6-diylbis (oxy))dibenzaldehyde **2q** and 2,2′-(butane-1,4-diylbis (oxy))dibenzaldehyde **2r**. As revealed in Schemes 3 and 4, when 2-aminobenzothiazole was reacted with dialdehydes and β-ketoesters/1,3-diketones in a 1:1:1 molar ratio under the optimized conditions, only one formyl group participated selectively to produce *mono*-4*H*-pyrimido[2,1-*b*]benzothiazoles in 68–83% yields. It is worth noting that such transformation is precious since the remaining free formyl group could be used for the production of other important organic compounds. Whereas, the reaction of 2-aminobenzothiazole with dialdehydes and β-ketoesters/1,3-diketones with a 2:1:2 molar ratio proceeded efficiently in the presence of 2 mol% of catalyst at 50 °C under solvent-free conditions to produce the corresponding symmetric *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles in 69–81% yields (Schemes 5, 6).

The further superior aspect of this catalytic method could be found in the synthesis of various unsymmetric *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles (Scheme 7). In this respect, the multi-component reaction between 2-aminobenzothiazole (1 mmol), dialdehydes (1 mmol) and 1 mmol of each of two different 1,3-dicarbonyl compounds resulted in novel unsymmetric *bis*-4*H*-pyrimido[2,1-*b*]benzothiazoles in 67–70% yields (Scheme 7). It is important to note that the single-step selective synthesis of *mono*-pyrimido[2,1-*b*]benzothiazoles, symmetric and unsymmetric *bis*-pyrimido[2,1-*b*]benzothiazoles is reported for the first time which could be considered as the most attractive and fascinating aspect of this catalytic system (Scheme 3–7). All products were identified by their melting points, spectral data and elemntal analysis (Supporting Information).

3.5 | Reaction mechanism

Based on the experimental results, a mechanistic pathway for synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole **4aa** is described in Scheme 8. First, activation of the carbonyl group of aldehyde by the [NicTC]HSO_4@MNPs catalyst gives intermediate **A** which upon the Knoevenagel condensation with enol form of ethyl acetoacetate **3a** provides **B**. Then, Michael type addition of 2-aminobenzothiazole **1** to intermediate **B** in the presence of the catalyst results in iminium ion **C** which upon proton transfer produces intermediate **D**. Next, the intermediate **D** undergoes intramolecular cyclization in the presence of the catalyst to afford **E**. Afterward, the intermediate **E** is converted to the related intermediate **F** via anomeric based oxidation.[23] In order to confirm this goal, the model reaction was also performed under argon atmosphere and the desired product was obtained in

TABLE 3 [NicTC]HSO_4@MNPs-catalyzed multi-component synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles[a]



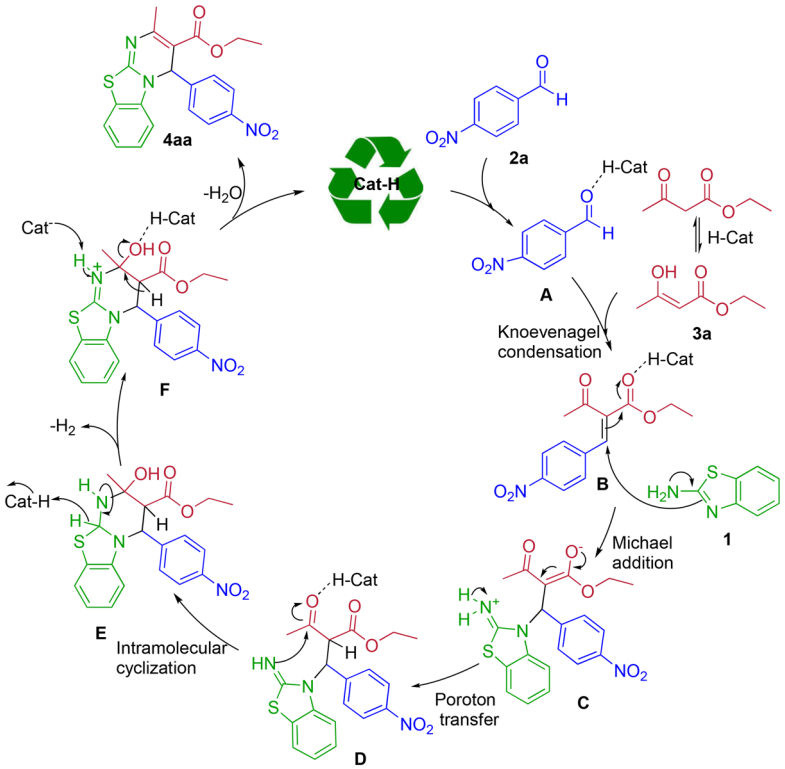
Entry	R^1	β-ketoester (1,3-diketone)	Product	Time (min)	Yield (%)[b]	Ref.
1	4-$NO_2C_6H_4$		4aa	20	98	[6g]
2	2,4-$(Cl)_2C_6H_3$		**4ba**	30	97	[6g]
3	3-$NO_2C_6H_4$		**4ca**	25	92	[6h]
4	4-CH $(CH_3)_2C_6H_4$	**3a**	**4da**	40	90	-
5	Cinnamyl		**4ea**	50	88	-
6	6-Chloro-4-oxo-4*H*-chromen-3-yl		**4fa**	50	83	-
7	5-Methylfuran-2-yl		**4ga**	50	85	-
8	Naphthalene-2-yl		**4 ha**	40	90	-
9	Thiophen-2-yl		4ib	45	86	-
10	4-$PhCH_2OC_6H_4$		**4jb**	50	89	-
11	3-$MeOC_6H_4$	**3b**	**4 kb**	30	95	-
12	4-BrC_6H_4		4lc	35	96	[6e]
13	3-$MeOC_6H_4$		**4ic**	40	90	-
14	4-C $(CH_3)_3C_6H_4$	**3c**	**4mc**	40	88	-
15	4-$PhCH_2OC_6H_4$		**4jc**	50	83	-
16	3-$MeOC_6H_4$		4id	40	91	-
17	4-PhC_6H_4	**3d**	**4nd**	45	89	-

[a]Reaction conditions: 2-aminobenzothiazole **1** (1 mmol), aldehyde **2** (1 mmol), β-ketoester/1,3-diketone **3** (1 mmol) and [NicTC]HSO_4@MNPs (1 mol%) at room temperature under solvent-free conditions.
[b]Isolated yield.

comparable yield. Finally, elimination of water from **F** produces the desired products **4aa** and releases the catalyst which can be used in the next catalytic cycle.

3.6 | Reusability of [NicTC]HSO_4@MNPs

Due to the superparamagnetic properties and a good saturation magnetization value (19.52 emu.g^{-1}), [NicTC]HSO_4@MNPs catalyst displayed excellent reusability in the synthesis of **4aa** by the reaction of 2-aminobenzothiazole **1**, 4-nitrobenzaldehyde **2a** and ethyl acetoacetate **3a**. At the end of the reaction, the mixture was diluted with hot ethanol and the catalyst was simply separated with an external magnet. The separated catalyst was washed with hot ethanol, dried and then reused in successive cycles. As shown in Figure 6, the catalyst can be reused at least five times without any significant loss of its efficiency and activity. On the other hand, comparison of the FT-IR spectra of the fresh and reused



SCHEME 8 Proposed mechanism for the synthesis of **4aa**

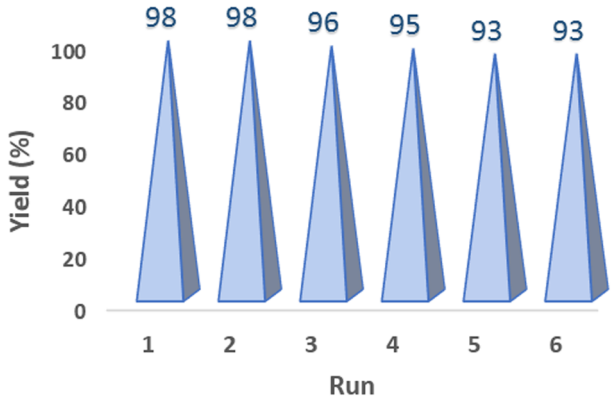


FIGURE 6 Recovery and reuse of the catalyst for the synthesis of **4aa**

catalyst showed no obvious change in the structure of the catalyst and its characteristic bands, indicating that the catalyst is stable under the reaction conditions. (Figure 1e).

4 | CONCLUSION

In summary, we have developed [NicTC]HSO_4@MNPs as a novel and efficient catalyst for the preparation of a series of 4*H*-pyrimido[2,1-*b*]benzothiazole via a one-pot multi-component reaction of 2-aminobenzothiazole, aldehydes and β-ketoesters/1,3-diketones at room temperature under solvent-free conditions. Also, selective synthesis of *mono*-4*H*-pyrimido[2,1-*b*]benzothiazoles and symmetric as well as unsymmetric *bis*-4*H*-pyrimido[2,1-*b*] benzothiazoles from dialdehydes which is reported for the first time, can be considered as one of the outstanding features of this catalytic method. Furthermore, short reaction times, high yields, easy work-up, prevention of poisonous organic solvents as well as feasibility of recovery and reuse of the catalyst make this method an economic and environmentally-benign process for the formation of such a fine heterocycles.

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REFERENCES

[1] a)G. P. Ellis, *Chemistry of Heterocyclic Compounds: Synthesis of Fused Heterocycles*, Vol. 47, John Wiley & Sons, Ltd., New York **2008**. b)M. T. Gabr, N. S. El-Gohary, E. R. El-Bendary, M. M. El-Kerdawy, *Eur. J. Med. Chem.* **2014**, *85*, 576.

c)A. M. Youssef, E. Noaman, *Arzneim.-Forsch./Drug Res.* **2007**, *57*, 547.

[2] a)P. K. Sahu, P. K. Sahu, S. K. Gupta, D. Thavaselvamd, D. D. Agarwal, *Eur. J. Med. Chem.* **2012**, *54*, 366. b)S. Maddila, S. Gorle, N. Seshadri, P. Lavanya, S. B. Jonnalagadda, *Arab. J. Chem.* **2016**, *9*, 681. c)L. Racane, V. Tralic-Kulenovic, S. K. Pavelic, I. Ratkaj, P. Peixoto, R. Nhili, S. Depauw, M. P. Hildebrand, M. H. David-Cordonnier, K. Pavelic, G. Karminski-Zamola, *J. Med. Chem.* **2010**, *53*, 2418.

[3] a)Q. Chao, K. G. Sprankle, R. M. Grotzfeld, A. G. Lai, T. A. Carter, A. M. Velasco, R. N. Gunawardane, M. D. Cramer, M. F. Gardner, J. James, P. P. Zarrinkar, H. K. Patel, S. S. Bhagwat, *J. Med. Chem.* **2009**, *52*, 7808. b) P. K. Sharma, M. Kumar, V. Mohan, *Res. Chem. Intermed.* **2010**, *36*, 985.

[4] a)H. P. Singh, C. S. Sharma, C. P. Gautam, *Middle-East J. Sci. Res.* **2009**, *4*, 203. b)H. S. Hilal, M. S. Ali-Shtayeh, R. Arafat, T. Al-Tel, W. Voelter, A. Barakat, *Eur. J. Med. Chem.* **2006**, *41*, 1017.

[5] a)R. G. Bretzel, C. C. Bollen, E. Maeser, K. F. Federlin, *Am. J. Kidney Dis.* **1993**, *21*, 53. b)V. Klusa, *Drugs Future* **1995**, *20*, 135. c)R. Boer, V. Gekeler, *Drugs Future* **1995**, *20*, 499.

[6] a)L. Nagarapu, H. K. Gaikwad, J. D. Palem, R. Venkatesh, R. Bantu, B. Sridhar, *Synth. Commun.* **2013**, *43*, 93. b) P. K. Sahu, P. K. Sahu, S. K. Gupta, D. D. Agarwal, *Ind. Eng. Chem. Res.* **2014**, *53*, 2085. c)P. K. Sahu, P. K. Sahu, Y. Sharma, D. D. Agarwal, *J. Heterocyclic Chem.* **2014**, *51*, 1193. d) M. M. Heravi, E. Hashemi, Y. S. Beheshtiha, K. Kamjou, M. Toolabi, N. Hosseintash, *J. Mol. Catal. A: Chem.* **2014**, *392*, 173. e)A. B. Atar, Y. S. Jeong, Y. T. Jeong, *Tetrahedron* **2014**, *70*, 5207. f)A. Shaabani, A. Rahmati, S. Naderi, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5553. g)M. Koura, S. Paula, J. H. Clarkb, V. K. Guptac, R. Kant, *J. Mol. Catal. A: Chem.* **2016**, *411*, 299. h)N. Safajoo, B. B. F. Mirjalili, A. Bamoniri, *RSC Adv.* **2019**, *9*, 1278.

[7] a)J. W. Lee, J. Y. Shin, Y. S. Chun, H. B. Jang, C. E. Song, S. G. Lee, *Acc. Chem. Res.* **2010**, *43*, 985. b)D. Betz, P. Altmann, M. Cokoja, W. A. Herrmann, F. E. Kühn, *Coord. Chem. Rev.* **2011**, *255*, 1518. c)J. M. Gomes, S. S. Silva, R. L. Reis, *Chem. Soc. Rev.* **2019**, *48*, 4317. d)N. Kaur, *Synth. Commun.* **2019**, *49*, 1679.

[8] a)L. C. Henderson, D. J. Eyckens, *Front. Chem.* **2019**, *7*, 263. b) T. Welton, *Biophys. Rev.* **2018**, *10*, 691.

[9] S. Sahoo, P. Kumar, F. Lefebvre, S. B. Halligudi, *Appl. Catal. A. Gen.* **2009**, *354*, 17.

[10] a)K. M. Docherty, M. V. Joyce, K. J. Kulacki, C. F. Kulpa, *Green Chem.* **2010**, *12*, 701. b)D. Zhao, Y. Liao, Z. Zhang, *Clean* **2007**, *35*, 42.

[11] X. Wang, C. A. Ohlin, Q. Lu, Z. Fei, J. Hub, P. J. Dyson, *Green Chem.* **2007**, *9*, 1191.

[12] a)Z. P. Visak, S. L. Yague, J. N. C. Lopes, L. P. N. Rebelo, *J. Phys. Chem. B* **2007**, *111*, 79347. b)T. Heckel, A. Winkel, R. Wilhelm, *Tetrahedron: Asymmetry* **2013**, *24*, 1127. c) F. Tamaddon, D. Azadi, *J. Mol. Liq.* **2018**, *249*, 789. d) S. T. Handy, *Chem. – Eur. J.* **2003**, *9*, 2938. e)C. H. Richardson, H. H. Shepard, *J. Agric. Res.* **1930**, *40*, 1007. f)A. A. Hullio, G. M. Mastoi, *Iranian J. Catal.* **2012**, *2*, 165. g)M. Moeini, M. Nasr-Esfahani, I. Mohammadpoor-Baltork, M. Moghadam, S. Tangestaninejad, V. Mirkhani, *Catal. Lett.* **2019**, *12*, 353.

[13] a)J. Miao, H. Wan, G. Guan, *Catal. Commun.* **2011**, *12*, 353. b) N. Azgomi, M. Okhtary, *J. Mol. Catal. A: Chem.* **2015**, *398*, 58. c)X. Zheng, S. Luo, L. Zhang, J. P. Cheng, X. Zheng, *Green Chem.* **2009**, *11*, 455. d)R. Ghorbani-Vaghei, N. Sarmast, *Appl. Organomet. Chem.* **2018**, *32*, 4003. e)S. Moradi, M. A. Zolfigol, M. Zarei, D. A. Alonso, A. Khoshnood, A. Tajally, *Appl. Organomet. Chem.* **2018**, *32*, 4043. f)M. Pourghasemi-Lati, F. Shirini, M. Alinia-Asli, M. A. Rezvani, *Appl. Organomet. Chem.* **2018**, *32*, 4605.

[14] a)M. Nasrollahzadeh, Z. Issaabadia, S. M. Sajadi, *RSC Adv.* **2018**, *8*, 27631. b)A. Taher, J.-B. Kim, J.-Y. Jung, W.-S. Ahn, M.-J. Jin, *Synlett* **2009**, *15*, 2477. c)Y. Gu, C. Ogawa, J. Kobayashi, Y. Mori, S. Kobayashi, Y. Gu, *Angew. Chem. Int. Ed.* **2006**, *45*, 7217. d)S. Minakata, M. Komatsu, *Chem. Rev.* **2008**, *109*, 711. e)K. Wu, D. Su, J. Liu, R. Saha, J. P. Wang, *Nanotechnology* **2019**, *30*, 502003. f)S. Gul, S. B. Khan, I. U. Rehman, M. A. Khan, M. I. Khan, *Front. Mater.* **2019**, *6*, 179.

[15] a)Q. Zhang, H. Su, J. Luo, Y. Wei, *Green Chem.* **2012**, *14*, 201. b)A. Ying, H. Hou, S. Liu, G. Chen, J. Yang, S. Xu, *ACS Sustainable Chem. Eng.* **2016**, *4*, 625. c)H. T. Nguyen, N.-P. T. Le, D.-K. N. Chau, P. H. Tran, *RSC Adv.* **2018**, *8*, 35681. d)P. H. Li, B. L. Li, H. C. Hu, X. N. Zhao, Z. H. Zhang, *Catal. Commun.* **2014**, *46*, 118. e)J. Isaad, A. El Achari, *J. Mol. Struct.* **2018**, *1154*, 557. f)J. Isaad, *RSC Adv.* **2014**, *4*, 49333. g)J. Deng, L.-P. Mo, F.-Y. Zhao, Z. H. Zhang, S.-X. Liu, *ACS Comb. Sci.* **2012**, *14*, 335. h)I. D. Hierro, Y. Pérez, M. Fajardo, *Mol. Catal.* **2018**, *450*, 112.

[16] a)L. H. Reddy, J. L. Arias, J. Nicolas, P. Couvreur, *Chem. Rev.* **2012**, *112*, 5818. b)S. Laurent, D. Forge, M. Port, A. Roch, C. Robic, L. Vander Elst, R. N. Muller, *Chem. Rev.* **2008**, *108*, 2064. c)M. Zhang, Y. H. Liu, Z. R. Shang, H. C. Hu, Z. H. Zhang, *Catal. Commun.* **2017**, *88*, 39. d)M. N. Chen, L. P. Mo, Z. S. Cui, Z. H. Zhang, *Curr. Opin. Green Sustain. Chem.* **2019**, *15*, 27. e)M. Zhang, P. Liu, Y. H. Liu, Z. R. Shang, H. C. Hu, Z. H. Zhang, *RSC Adv.* **2016**, *6*, 106160. f)X. N. Zhao, H. C. Hu, F. J. Zhang, Z. H. Zhang, *Appl. Catal. A. Gen.* **2014**, *482*, 258.

[17] a)B. Asadi, I. Mohammadpoor-Baltork, S. Tangestaninejad, M. Moghadam, V. Mirkhani, A. Landarani-Isfahani, *New J. Chem.* **2016**, *40*, 6171. b)M. Azizi, M. Nasr-Esfahani, I. Mohammadpoor-Baltork, M. Moghadam, V. Mirkhani, S. Tangestaninejad, R. Kia, *J. Org. Chem.* **2018**, *83*, 14743. c) F. Rahmani, I. Mohammadpoor-Baltork, A. R. Khosropour, M. Moghadam, S. Tangestaninejad, V. Mirkhani, *Tetrahedron Lett.* **2016**, *57*, 2294. d)E. Estakhri, M. Nasr-Esfahani, I. Mohammadpoor-Baltork, S. Tangestaninejad, M. Moghadam, V. Mirkhani, *Appl. Organomet. Chem.* **2017**, *31*, 3799.

[18] C. R. Matos, F. S. Miranda, J. W. D. M. Carneiro, C. B. Pinheiro, C. M. Ronconi, *Phys. Chem. Chem. Phys.* **2013**, *15*, 13013.

[19] F. Rastegari, I. Mohammadpoor-Baltork, A. R. Khosropour, S. Tangestaninejad, V. Mirkhani, M. Moghadam, *RSC Adv.* **2015**, *5*, 15274.

[20] M. Ghotbinejad, A. R. Khosropour, I. Mohammadpoor-Baltork, M. Moghadam, S. Tangestaninejad, V. Mirkhani, *J. Mol. Catal. A: Chem.* **2014**, *385*, 78.

[21] a)A. Bee, R. Massart, S. Neveu, *J. Magn. Magn. Mater.* **1995**, *149*, 6. b)V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara, J. M. Basset, *Chem. Rev.* **2011**, *111*, 3036. c) L. Wu, A. Mendoza-Garcia, Q. Li, S. Sun, *Chem. Rev.* **2016**, *116*, 10473. d)M. Shokouhimehr, Y. Piao, J. Kim, Y. Jang, T. Hyeon, *Angew. Chem. Int. Ed.* **2007**, *46*, 7039.

[22] H.-J. Xu, X. Wan, Y.-Y. Shen, S. Xu, Y.-S. Feng, *Org. Lett.* **2012**, *14*, 1210.

[23] a)M. A. Zolfigol, A. Khazaei, S. Alaie, S. Baghery, F. Maleki, Y. Bayatb, A. Asgari, *RSC Adv.* **2016**, *6*, 58667. b) M. A. Zolfigol, F. Karimi, M. Yarie, M. Torabi, *Appl. Organomet. Chem.* **2018**, *32*, 4063.

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