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Preparation, characterization and application of nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] as a novel magnetically recoverable catalyst for the synthesis of pyrimido[4,5-*b*]quinolines

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6-Amino-1,3-dimethyluracil
Multi-component reaction
Solvent-free

ABSTRACT

A novel organic-inorganic hybrid magnetic nanomaterial namely nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] (nano-[FSRN][H_2PO_4]) has been prepared, and characterized by FT-IR, EDS, FE-SEM, VSM, XRD and TGA analyses. Afterward, an important class of uracil-bearing heterocycles namely pyrimido[4,5-*b*]quinolines has been synthesized through the one-pot multi-component reaction of 6-amino-1,3-dimethyluracil with arylaldehydes and dimedone using nano-[FSRN][H_2PO_4] as a dual-functional catalyst under solvent-free conditions. High yields, short reaction times, magnetic recoverability of the catalyst, no need to column chromatography for purification of the products and good compliance with green chemistry protocols are some advantages of the work.

1. Introduction

In recent years, many research groups have been focused on preparation and application of hybrid magnetic nanomaterials (organic-inorganic or inorganic-inorganic) in different scientific, pharmaceutical and industrial fields, because these materials possess many unique properties, e.g. chemical inertness, non-toxicity, proper thermal stability, aptitude to design (and functionalize) for different uses, environmentally-friendly nature, high surface-to-volume ratios, effectuality, and easy separation by an external magnet [1–17]. Some usages of these nanomaterials consist of degradation of organic pollutants [1], biofuel production [2], control of enzyme function [3], bioanalysis [4], application in energy storage paper supercapacitors [5], magnetic resonance imaging (MRI) [6], energy storage and conversion [7], drug delivery [8], and catalysis in organic transformation [9–17].

The benefits and high importance of multi-component reactions [18–20] and solvent-free conditions [21,22] have been well mentioned in the literature.

The heterocycles bearing uracil, pyrimidine, pyrimido-quinoline and quinoline scaffolds are of great importance in medicinal chemistry. The uracil and pyrimidine-containing ones have shown anticancer [23], antifungal [24], and antiviral [25] activities. The compounds having pyrimido-quinoline moiety have been utilized as antimalarial [26], anti-inflammatory [27], and anticancer [28] agents. Furthermore, several heterocycles, which have been applied as antihistaminic [29], and anti-inflammatory [30] have quinoline scaffold in their structure.

A practical method for synthesis of pyrimido[4,5-*b*]quinolines, as a class of heterocycles bearing uracil, pyrimidine, pyrimido-quinoline and quinoline scaffolds, is the one-pot multi-component reaction of 6-amino-1,3-dimethyluracil with arylaldehydes and dimedone; some catalysts have been reported for this reaction in the literature [31–38]. It is noteworthy that the production of pyrimido[4,5-*b*]quinolines by this method has not been comprehensively studied in the literature. So, introducing new efficacious catalysts to promote the reaction of 6-amino-1,3-dimethyluracil, arylaldehydes and dimedone is highly desirable.

Considering the above-mentioned issues on hybrid magnetic

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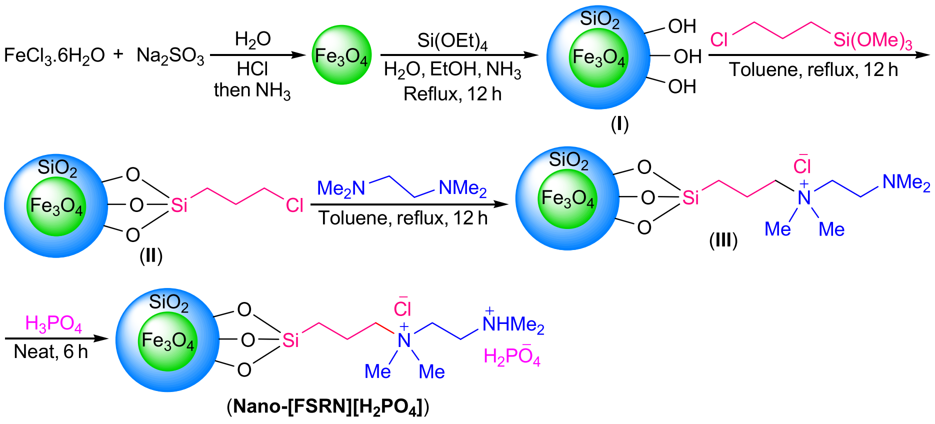


Scheme 1. The synthesis of nano-[FSRN][H_2PO_4].

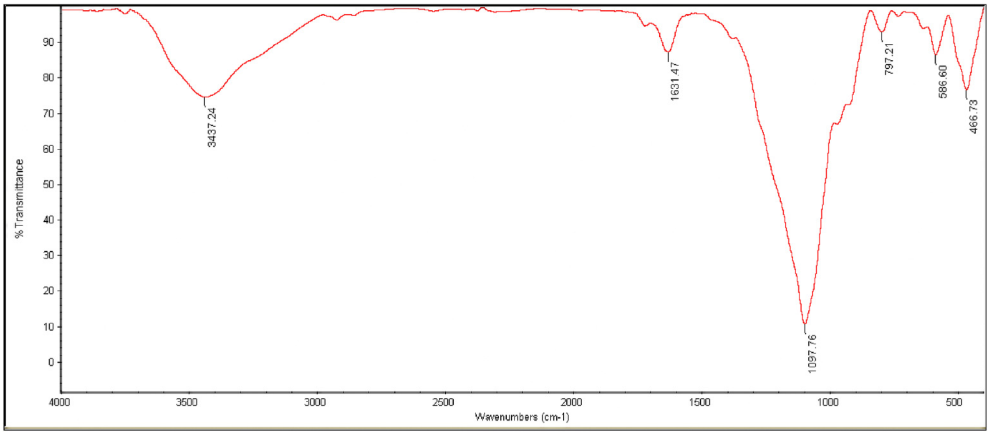


Fig. 1. The FT-IR spectrum of nano-[FSRN][H_2PO_4].

Table 1
The FT-IR results of nano-[FSRN][H_2PO_4].

Peak (cm^{-1})	Bond or functional group
467	Rocking of Si—O
587	Fe—O
797	Symmetric stretching vibrations of Si—O—Si
1098	Asymmetric stretching vibrations of Si—O—Si
~2927	Stretching vibration of C—H
2700—3730	Stretching of OH groups of dihydrogen phosphate and OH groups on silica surface

nanomaterials, multi-component reactions, solvent-free conditions and pyrimido[4,5-*b*]quinolines, we have prepared a novel organic-inorganic hybrid magnetic nanomaterial entitled nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] (nano-[FSRN][H_2PO_4]), and characterized it by FT-IR, EDS (energy-dispersive X-ray spectroscopy), FE-SEM (field emission scanning electron microscopy), VSM (vibrating sample magnetometry), XRD (X-ray diffraction) and TGA (thermogravimetry analysis) analyses. Afterward, we have utilized nano-[FSRN][H_2PO_4] as an effective, dual-functional and magnetically recoverable catalyst for the synthesis of pyrimido[4,5-*b*]quinolines through the one-pot multi-component reaction of 6-amino-1,3-dimethyluracil, arylaldehydes and dimedone under solvent-free conditions.

2. Experimental section

2.1. Materials and apparatus

The used reactants and solvents were purchased from Merck or Fluka Chemical Companies. Progress of the reactions was monitored by thin-layer chromatography (TLC) using silica gel SIL G/UV 254 plates. Melting points were measured using a Buchi B-545 apparatus in open capillary tubes. FT-IR spectra were recorded by a Shimadzu IR-60 instrument. ^1H and ^{13}C NMR spectra were run on a Bruker Avance DPX FT-NMR spectrometer. EDS was carried out by SAMx-EDS (France system). The morphologies and sizes of the particles were characterized by FE-SEM, model MIRA3TESCAN-XMU. VSM was performed using a MDK (Meghnatis Daghigh Kavir) apparatus (Iran). XRD analysis was achieved using Cu Kα

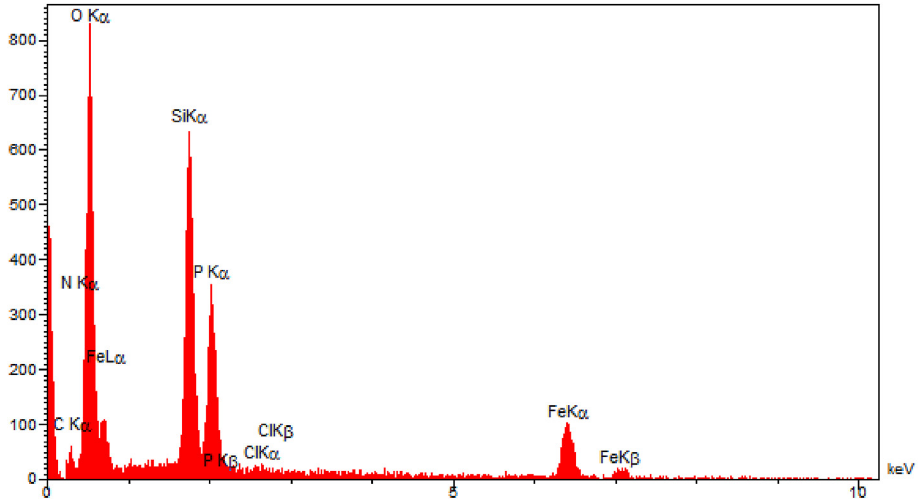


Fig. 2. The EDS spectrum of the nanomagnetic catalyst.

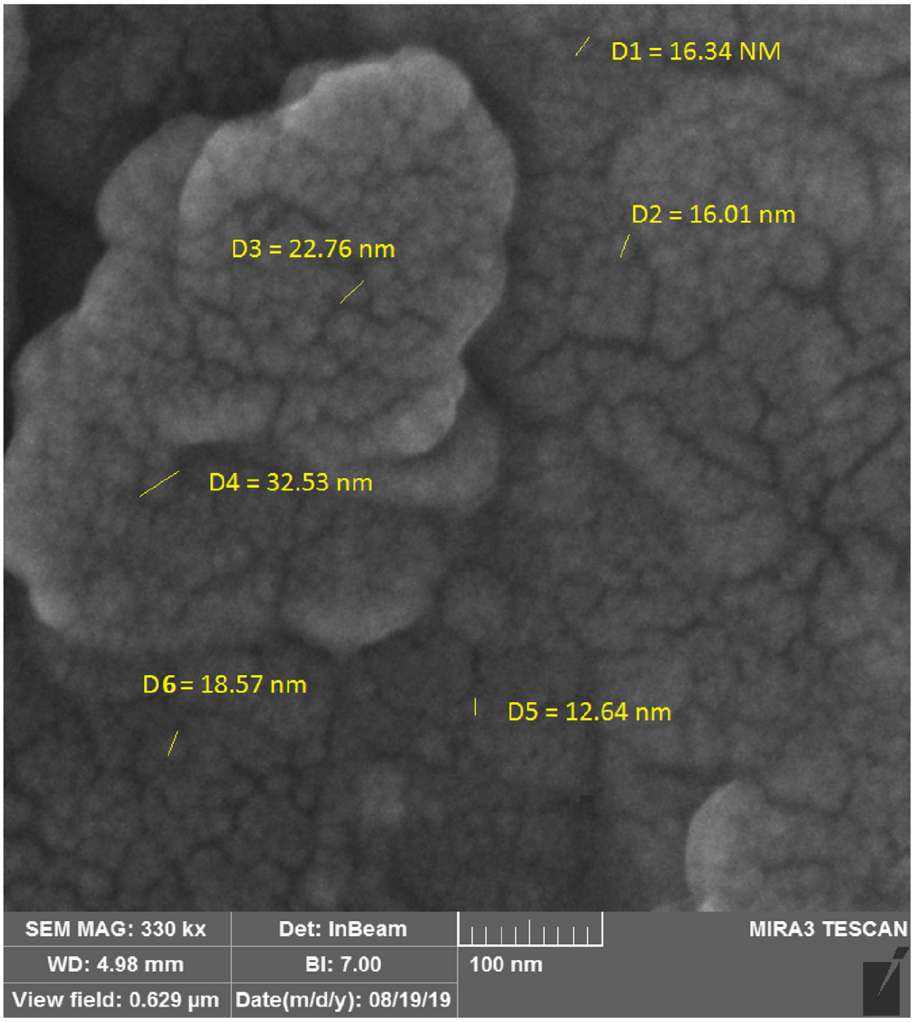


Fig. 3. The FE-SEM micrograph of nano-[FSRN][H_2PO_4].

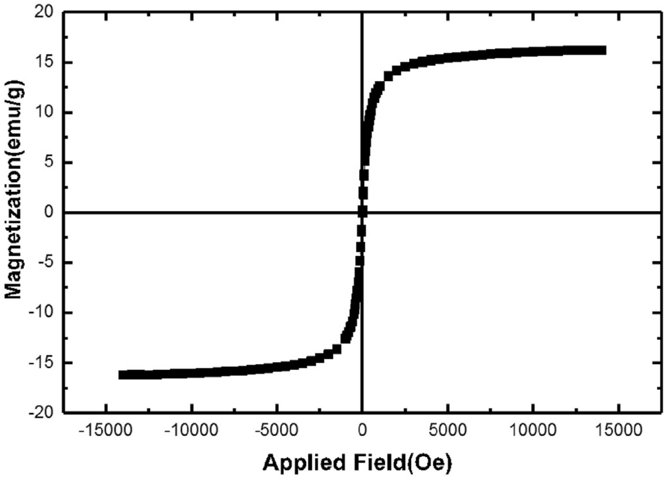


Fig. 4. The VSM curve of nano-[FSRN][H_2PO_4].

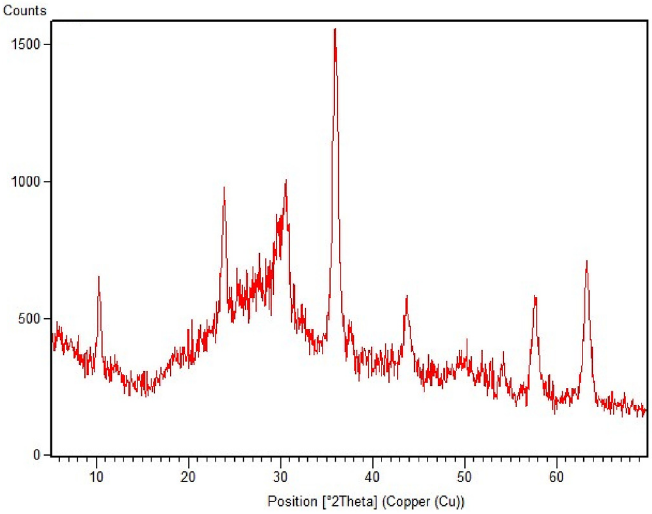


Fig. 5. The XRD diagram of the hybrid nanomaterial.

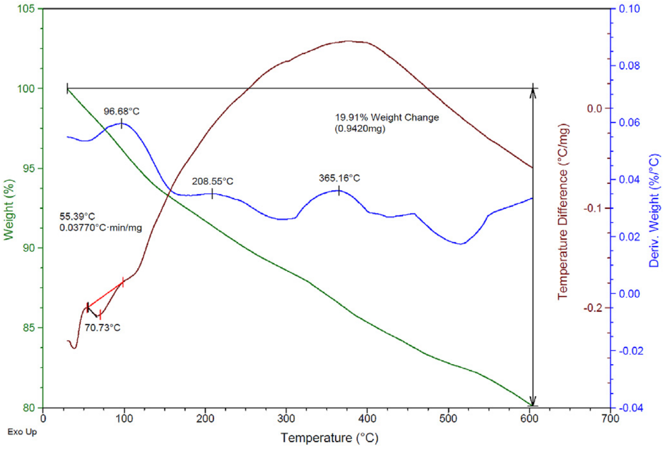


Fig. 6. The TG, DTG and DTA curves of nano-[FSRN][H_2PO_4].

radiation (λ = 1.5408, model: X'Pert PRO MPD, PANalytical, the Netherlands). TGA was performed by Bahr STA 504 (Germany) instrument, at 25–600 °C, with temperature increase rate of 10 °C.min^{-1} in argon atmosphere.

2.2. Production of nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] (nano-[FSRN][H_2PO_4])

Nano-Fe_3O_4 was prepared according to a reported method [39,40]. A mixture of nano-Fe_3O_4 (0.50 g), $Si(OEt)_4$ (1.5 ml), H_2O (10 ml), EtOH (40 ml) and ammonia (1.5 ml) was refluxed for 12 h to give **I**. Then, a mixture of **I** and (3-chloropropyl)trimethoxysilane (0.92 ml, 5 mmol) in dry toluene (40 ml) was refluxed under nitrogen gas for 12 h; the resulting mixture was centrifuged, decanted, washed twice by dry toluene and anhydrous Et_2O, and dried under vacuum at 90 °C to give **II** [40,41]. *N,N,N′,N′*-Tetramethylethylenediamine (0.75 ml, 5 mmol) was added to **II** in toluene (30 ml), and the resulting mixture was refluxed for 12 h. The obtained solid was separated by centrifuging and decanting, and washed by toluene and dried under vacuum at 90 °C to furnish **III**. Finally, H_3PO_4 (0.26 ml, 5 mmol) was added gradually to **III** at room temperature, stirred for 5 h at the same temperature and 1 h at 60 °C, and dried under vacuum at 90 °C to afford nano-[FSRN][H_2PO_4].

2.3. General procedure for the synthesis of pyrimido[4,5-b]quinolines

A mixture of 6-amino-1,3-dimethyluracil (0.155 g, 1 mmol), aldehyde (1 mmol), dimedone (0.140 g, 1 mmol) and nano-[FSRN][H_2PO_4] (0.080 g) was stirred vigorously by a small rod at 120 °C till the starting materials were consumed (as monitored by TLC). Then, the reaction mixture was cooled to room temperature, EtOAc (40 ml) was added, stirred for 2 min under reflux conditions, and the catalyst was separated magnetically (washed by EtOAc, and dried). EtOAc of the retained solution was evaporated, and the residue was recrystallized from EtOH (95%) to give the pure product.

Note: Selected spectral data and original spectrums of the synthesized pyrimido[4,5-*b*]quinolines have been presented in supplementary data.

3. Results and discussion

3.1. The catalyst characterization

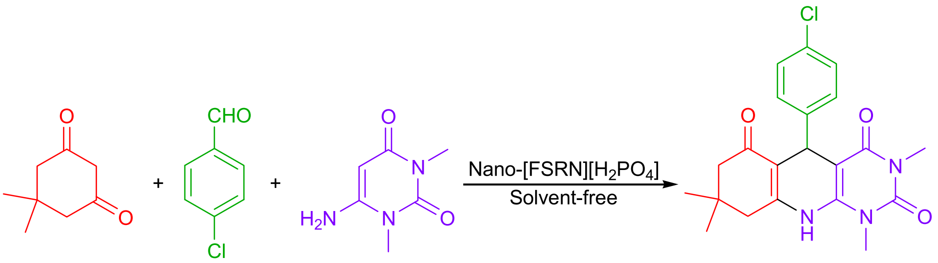
The novel organic-inorganic hybrid magnetic nanomaterial, i.e. nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] (nano-[FSRN][H_2PO_4]), was synthesized according to Scheme 1, and characterized by FT-IR, EDS, FE-SEM, VSM, XRD and TGA methods.

The peaks related to the expected bonds and functional groups in the structure of nano-[FSRN][H_2PO_4] were observed in the FT-IR spectrum (Fig. 1). The obtained data are summarized in Table 1; the literature confirmed these interpretations [40].

The EDS spectrum showed the presence of silicon, iron, oxygen, carbon, nitrogen, chlorine and phosphorous elements in the structure of nano-[FSRN][H_2PO_4] (as expected) (Fig. 2). No extra peak related to any impurity was seen in the spectrum.

FE-SEM was used for determination of size and morphology of the catalyst particles (Fig. 3). The micrograph showed that the particles are in nano-size (below 100 nm) with different crystalline shapes and also amorphous form [42].

Magnetic measurement of nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] was achieved using a vibrating sample magnetometer at room temperature; the respective curve is illustrated in Fig. 4. According to the VSM results, saturation magnetization of the catalyst



Scheme 2. The chosen reaction for finding the best conditions.

Table 2
Effect of the catalyst amount and temperature on the model reaction (Scheme 2).

Entry	The catalyst amount (g)	Temp. (°C)	Time (min)	Yield (%)
1	–	120	60	27
2	0.048	120	40	75
3	0.060	120	20	87
4	0.080	120	10	96[a]
5	0.085	120	10	96[a]
6	0.080	115	20	91
7	0.080	125	10	96[a]

[a] The reaction was almost completed.

was 16.17 emu.g^{-1}; however, saturation magnetization of the Fe_3O_4 (which has been prepared by the used method in this research) has been reported 52 emu.g^{-1} [40]. The silica coating on the Fe_3O_4 nanoparticles and the organic moieties immobilized on the silica surface caused the decrement in saturation magnetization. Nevertheless, appropriate magnetization of the catalyst was observed, and it could be easily isolated from the reaction mixture by an external magnet.

The XRD pattern of nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] was studied in a domain of $2\theta \approx$ 5-70° (Fig. 5). In the diagram, some sharp diffraction lines (at $2\theta \approx$ 10.2, 23.9, 30.5, 36.0, 43.8, 52.0, 54.2, 57.8, 63.3°) and two broad peaks (at $2\theta \approx$ 16.0–34.0° and 47.4–51.2°) were seen. These results verified that the nanoparticles are in both crystalline and amorphous forms (the literature confirmed this topic) [42]; this subject was also observed in the FE-SEM images (Fig. 3).

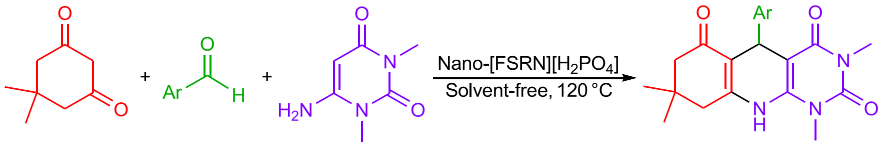
In another study, thermal stability of the catalyst was investigated by thermogravimetry (TG), derivative thermogravimetry (DTG) and differential thermal analysis (DTA); the respective curves are displayed in Fig. 6. As it can be seen in the Fig., weight losses of nano-[FSRN][H_2PO_4] happened in three steps: (i) below 145 °C, which can be pertained to evaporation of the adsorbed solvents (or water) on the silica surface, (ii) about 145–325 °C, the reason for this weight loss is decomposition of the organic moieties anchored to the silica surface, and (iii) about 325–600 °C, the condensation of the silanol groups caused this weigh loss. The literature data confirmed these explanations [42].

3.2. Application of nano-[FSRN][H_2PO_4] as catalyst for the production of pyrimido[4,5-b]quinolines

To find most suitable catalyst amount and the reaction temperature, the condensation of 6-amino-1,3-dimethyluracil (1 mmol), 4-chlorobenzaldehyde (1 mmol) and dimedone (1 mmol) was studied in the presence of different amounts of nano-[FSRN][H_2PO_4] (0.048–0.085 g) at a range of 115–125 °C in solvent-free conditions (Scheme 2); the results are summarized in Table 2. The obtained results showed that the most appropriate catalyst amount and temperature were 0.080 g and 120 °C, respectively (Table 2, entry 4). The reaction was also examined in the absence of nano-[FSRN][H_2PO_4] in solvent-free conditions at 120 °C in which the product was obtained in 27% after 60 min (Table 2, entry 1). Increment of the temperature up to 125 °C and the catalyst amount up to 0.085 g had no significant effect on the reaction results (Table 2, entries 5 and 7).

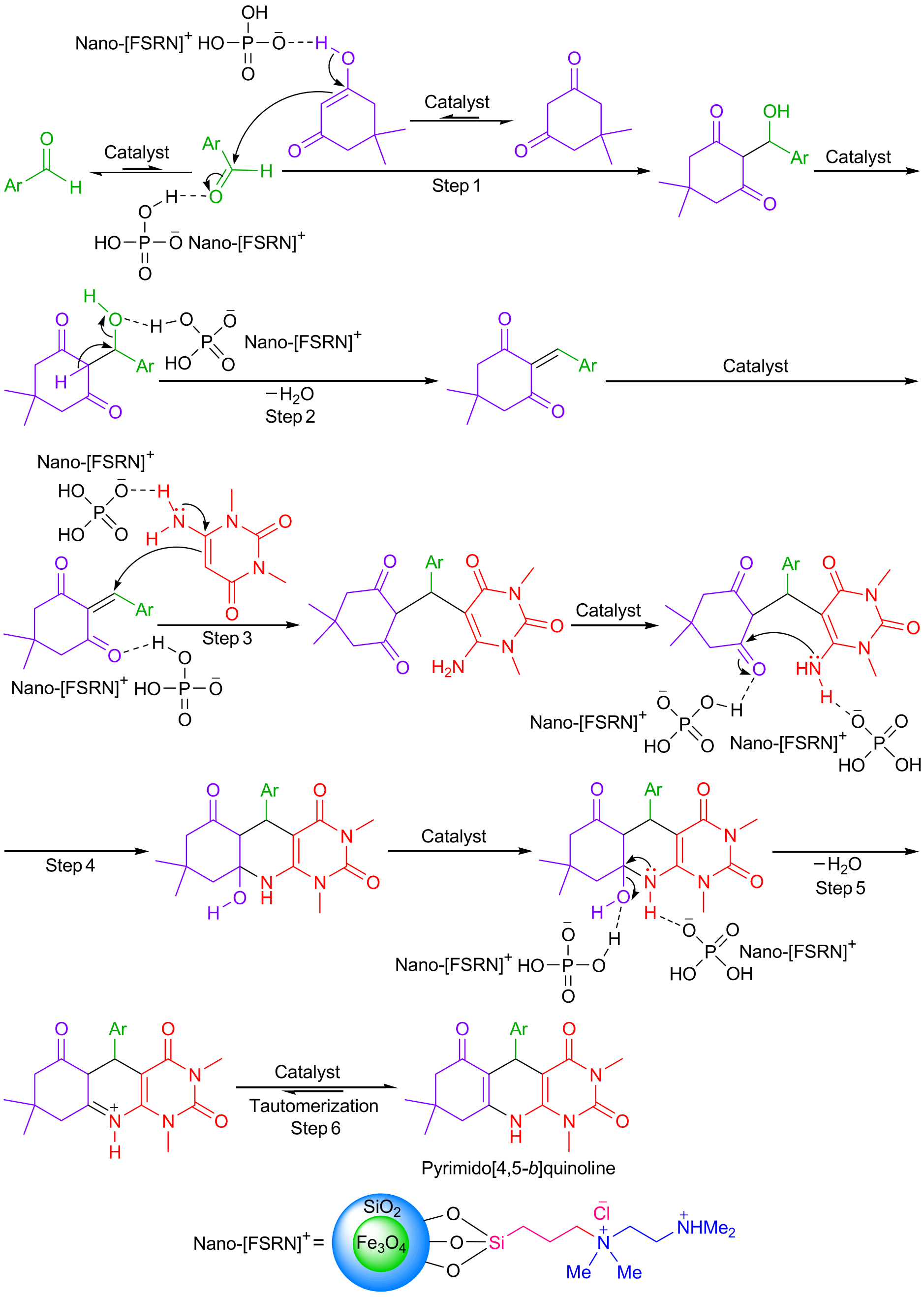
After finding the most suitable reaction conditions, miscellaneous derivatives of pyrimido[4,5-*b*]quinolines were prepared *via* reacting 6-amino-1,3-dimethyluracil with various arylaldehydes and dimedone; the results are shown in Table 3. High yields of the products were synthesized in short times in the case of all

Table 3
The preparation of pyrimido[4,5-*b*]quinolines using nano-[FSRN][H_2PO_4].



Compd. No.	Ar	Time (min)	Yield[a] (%)	M.p. (°C), Found (reported)
1	C_6H_5	10	96	270-272 (268–270) [33]
2	4-$Me_2NC_6H_4$	20	90	253-255 (this work)
3	4-$MeOC_6H_4$	10	95	304-306 (>300) [37]
4	4-MeC_6H_4	10	94	305-308 (>300) [32]
5	4-HOC_6H_4	30	79	321-323 (>300) [31]
6	3-$O_2NC_6H_4$	20	87	222-224 (220–223) [33]
7	2-$O_2NC_6H_4$	10	93	279-280 (281–285) [32]
8	4-ClC_6H_4	10	96	296-297 (292–294) [35]
9	2,4-$Cl_2C_6H_3$	20	84	>300 (>300) [35]
10	3-BrC_6H_4	10	91	285-287 (281–283) [38]

[a] Isolated yield.



Scheme 3. The proposed reaction mechanism.

aldehydes, including benzaldehyde and arylaldehydes bearing electron-donating, electron-withdrawing and halogen substituents on ortho, meta or para positions. Considering the obtained results, it can be said that nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] was a highly effective and general catalyst for the reaction.

The anion of nano-[FSRN][H_2PO_4] has two acidic and one basic sites; the hydrogen of OH groups are acidic, and the negative oxygen is basic (weak); hence, it can act as a dual-functional catalyst, and especially accelerate the organic transformations which require both acidic and basic catalysts together; for example, the production of pyrimido[4,5-*b*]quinoline derivatives. This subject has been clarified in the proposed mechanism (Scheme 3). As it is shown in Scheme 3, the acidic site catalyzes steps 1, 3 and 4 by activating the carbonyl groups to receive nucleophilic attacks; moreover, it catalyzes steps 2 and 5 *via* assistance to remove H_2O. The basic site also accelerates steps 1, 3 and 4 through activating the nucleophiles; it also helps removal of H_2O in step 5. Additionally, the nanomagnetic material catalyzes tautomerization (step 6). This mechanism is supported by the literature [32,34]. Discussions on dual-functionality of the catalysts, which possess both acidic and basic sites, have been mentioned in the literature [43].

Recoverability of nano-[FSRN][H_2PO_4] was studied on the reaction of 6-amino-1,3-dimethyluracil, 4-methylbenzaldehyde and dimedone; the catalyst was recovered by the procedure mentioned in the experimental procedure (section 2.3). It was successfully reused for 4 runs (the first run was performed using the fresh catalyst); nevertheless, the catalytic activity of nano-[FSRN][H_2PO_4] was slightly decreased during reusing (Fig. 7).

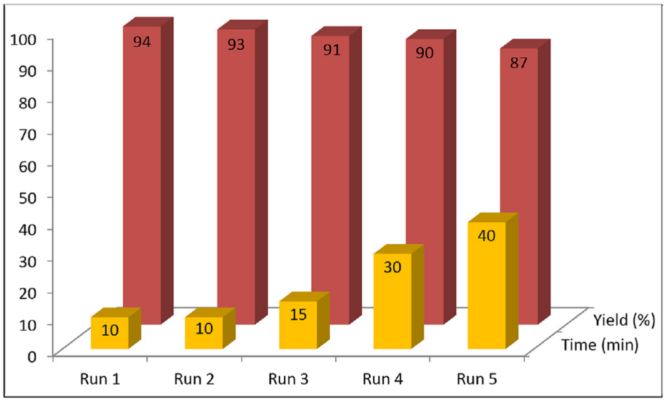


Fig. 7. The results of reusability of nano-[FSRN][H_2PO_4].

4. Conclusions

Briefly, a novel organic-inorganic hybrid nanomagnetic catalyst entitled nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] was introduced; it can promote the reactions which require acidic catalyst and the reactions which need acidic and basic catalysts simultaneously. In this research, a significance class of uracil-bearing heterocycles (i.e. pyrimido[4,5-*b*]quinolines) was prepared using nano-[FSRN][H_2PO_4]. This protocol has several advantages, e.g. efficacy, the synthesis of the products in high yields and short reaction times, usage of solvent-free conditions and multi-component reactions, recoverability of the nanocatalyst, easy workup, no need to column chromatography for purification of the products, and good compliance with green chemistry principles.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Abdolkarim Zare: Conceptualization, Methodology, Software, Writing - original draft, Writing - review & editing. **Nesa Lotfifar:** Investigation, Writing - original draft, Visualization. **Manije Dianat:** Investigation, Visualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2020.128030.

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