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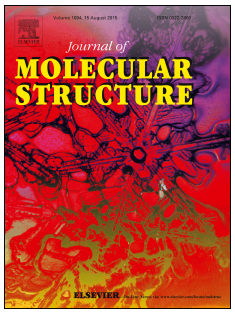

MIL-53(Fe): Introduction of a new catalyst for the synthesis of Pyrimido[4,5-*d*]pyrimidine derivatives under solvent-free conditions

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MIL-53(Fe): Introduction of a New Catalyst for the Synthesis of Pyrimido[4,5-*d*]pyrimidine Derivatives Under Solvent-free Conditions

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Abstract— In this study, the efficiency of MIL-53(Fe) metal-organic framework (MOF) the one-pot, three-component reaction of isothiocyanate, aromatic aldehydes and 6-aminouracil and/or *N*,*N*-dimethyl-6-aminouracil to form pyrimido[4,5-*d*]pyrimidine derivatives is investigated. Using this method all reactions are performed at 110 ^{o}C under solvent-free conditions with good to excellent product yields during acceptable reaction times. The other important merit of this method is simple recovery of MIL-53(Fe) through filtration which makes it reusable for further cycles without considerable decrease in its activity. The method is demonstrated to be a truly green process with sustainability and economics.

Keywords: Pyrimido[4,5-*d*]pyrimidine, Metal-Organic Framework, MIL-53(Fe), Heterocyclic, Solvent-free.

1. Introduction

Nowadays, the requirements of green chemistry principles encourage the chemical community to search for more environmentally sustainable methods for chemical syntheses. In this regard the development of new heterogeneous recyclable catalysts and the use of less toxic materials as solvents and reagents are two important challenges.

Porous metal-organic frameworks (MOFs) are an intriguing class of porous crystalline networks synthesized by assembling inorganic vertices with organic struts [1]. Over the past few decades and because of their various attractive applications in catalysis [2], selective gas adsorption and separation [3], and drug delivery [4-6], MOFs have received great attention. In particular, due to the important properties such as: high surface area, structural flexibility, porosity, and chemical tenability, MOFs are considered as promising materials for applications in heterogeneous catalysis. For these reasons, the synthesis and design of different kinds of metal-organic frameworks (MOFs) became necessary to achieve more knowledge about their structural diversity and investigate their various properties.

A solvent-free or solid state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other matrices. Thermal process or irradiation with ultraviolet, microwave or ultrasound can be employed to bring about these types of reactions. Solvent-free reactions obviously reduce pollution, and bring down handling costs via simplification of experimental procedure, work-up technique and saving in labour. These would be especially important during industrial production [7, 8].

Heterocyclic chemistry is currently experiencing a renaissance because of the interest in heterocyclic scaffolds as templates for combinatorial chemistry [9]. As heteroaromatic compounds are present in many natural products [10], and are constituents of numerous therapeutic agents [11], they represent ideal drug-like structures for the elaboration of an increase in molecular diversity. Pyrimido[4,5-*d*]pyrimidines constitute a class of heterocyclic compounds showing a wide spectrum of biological properties including antimicrobial [12], antioxidant [13], antihypertensive [14], antiallergic [15], and anticancer [16] activities. Many methods and catalysts have been developed for the preparation of pyrimido[4,5-*d*]pyrimidines [17-19]. Although these methods are useful, some of them are accompanied with

disadvantages including long reaction times, harsh reaction conditions, slow yields and use of toxic and non-reusable catalysts. Therefore, introduction of new catalysts to promote the synthesis of these types of compounds, which may solve all or some of the above mentioned disadvantages is still a demand.

2. Results and discussion

Because of the very important characteristics of metal organic-inorganic frame works (MOFs), as mentioned in previously, and as a part of our current studies on the development of new pathways in heterocyclic synthesis [20, 21], herein, we report a simple, rapid and one-pot procedure for the regioselective synthesis of pyrimido[4,5-*d*]pyrimidines with high yields and purity assisted by MIL-53(Fe) as a green, efficient and recyclable promoter (Scheme 1).

2.1. Structure and morphology of the MIL-53(Fe)

MIL-53(Fe) was obtained according to the method reported in the literature (Scheme 2) [20a, 22]. The structure of MIL-53(Fe), used in this study, is shown in Fig. 1. The structure of this catalyst was determined using SEM and XRD (Figs. S1, S2) (see Supplementary Information). The figures indicate that the catalyst consists of pure phases and no characteristic peaks are observed determining impurities. To confirm the composition, MIL-53(Fe) has also been characterized by energy-dispersive X-ray spectroscopy (EDX). As shown in Figure S3 (see Supplementary Information), the synthesized MIL-53(Fe) catalyst contains only iron, nitrogen, carbon and oxygen elements. FT-IR spectrum of MIL-53(Fe) is shown in Figure S4 (see Supplementary Information). IR spectrum showed the characteristic peaks of aromatic rings at 731 cm^{-1}, COO^- (1396 cm^{-1} and 1540 cm^{-1}), C=O (1685 cm^{-1}) and Fe-O vibrational peak located at 559 cm^{-1} which demonstrate the formation of the Fe-oxo band between the Fe(III) and carboxylic group of terephthalic acid. The thermo gravimetric analysis (TGA) of MIL-53(Fe) shows mass loss of organic materials as they decompose upon heating (Figure S5) (see Supplementary Information).

2.2. Catalytic activity of MIL-53(Fe) in the synthesis of pyrimido[4,5-d]pyrimidines

In order to determine the catalytic ability of MIL-53(Fe), its promoting effect is studied in the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives. First of all, to optimize the reaction temperature, the reaction of isothiocyanate, benzaldehyde and 6-aminouracil to form corresponding pyrimido[4,5-*d*]pyrimidine derivative was studied under solvent-free conditions in the presence of 0.005 g MIL-53(Fe) at different temperatures. The results are summarized in Table 1. Accordingly, the reaction proceeded in the highest yield at 110 ^oC.

The effect of amount of the catalyst on the conversion and rate of the reaction was studied with varying amounts of MIL-53(Fe) at 110 ^oC under solvent-free conditions (Table 2). It was found that 0.005 g of MIL-53(Fe) was sufficient to smoothly carry out this reaction. An increase in the amount of MIL-53(Fe) to more than 0.005 g showed no substantial improvement in yield, whereas it was reduced by decreasing the amount of MIL-53(Fe) to 0.004 g.

The results obtained from the optimization studies encouraged us to investigate the promoting effect of MIL-53(Fe) in the synthesis of pyrimido[4,5-*d*]pyrimidines drived from different types of aromatic aldehydes. As shown in Table 3, a variety of aromatic aldehydes

containing electron-withdrawing or electron-donating substituents in reaction with isothiocyanate and 6-aminouracil were successfully converted to the desired products in good to high yields with high purity using this method. When *N*,*N*-dimethyl-6-aminouracil was used instead of 6-aminouracil, the same reactions were also performed efficiently producing the corresponding products in high yields during acceptable reaction times.

The structures of the compounds including **4a–4m** were deduced from their elemental analyses and also their IR, ^{1}H NMR, and ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. Among the obtained products the compounds **4b**-**4k** have been previously reported in the literatures [18, 19].

Reusability is an important feature of a catalyst to make it suitable to be used in organic transformations by researchers. Hence, the reusability of MIL-53(Fe) was checked in the synthesis of 5,6-diphenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (Table 3, entry 1). After filtration and washing with CH_2Cl_2 the catalyst was dried at room temperature for 24 h and used for the next catalytic cycle. The results showed that this catalyst can be reused three times without significant loss of activity.

A comparison of the efficiency of this method with selected previous methods is summarized in Table 4. Which indicate the superiority of this method to the previously reported methods in terms of yields and reaction times.

A tentative mechanism for the formation of **4a** is shown in Scheme 3 [17]. Primarily, the intermediate **A** is formed in situ via the reaction of 6-aminouracil **1** with phenylisothiocyanate **2**. Then, the nucleophilic attack of the intermediate **A** to aldehyde **3** in the presence of the catalyst gives the intermediate **B** which upon cyclization and dehydration affords the desired product **4a**.

In summary, we have reported a simple, environmentally benign, and efficient synthetic method for the preparation of pyrimido[4,5-*d*]pyrimidines derivatives using MIL-53(Fe) under solvent-free conditions. The notable features of this procedure are the use of a cheap, easy to handle, and reusable catalyst, high yields, short reaction times and solvent-free conditions, which make it a useful and attractive process for pyrimido[4,5-*d*]pyrimidines synthesis.

3. Experimental

3.1. Materials

All chemicals were obtained from Fluka or Merck and were used without further purification. All the materials were of commercial reagent grade and were used without further purification. The IR spectra were recorded on a Perkin Elmer 781 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker 300 MHz spectrometer with DMSO-d_6 as the solvent using TMS as an internal standard. All melting points are uncorrected and were determined in a capillary tube using a Boetius melting point microscope. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer.

3.2. Synthesis of MIL-53(Fe)

MIL-53(Fe) was synthesized according to the method reported in the literature with some modifications [20a, 22]. In a typical catalyst preparation, $FeCl_3$ (5 mmol, 1.35g) and 1,4-benzenedicarboxylates acid (5 mmol, 0.83g) were added to 25 mL, *N*,*N*-dimethylformanide (DMF) and sonicated for 10 minutes. The solution was transferred and sealed in a teflon-lined autoclave, and kept at 150^{o}C for 15h. A light brown powder was collected by filtration and washed three times with 100 mL of fresh DMF. After wards, the MIL-53(Fe) was kept under

stirring in methanol for three days. Finally, the solid powder was heated at 150 ^{o}C overnight to remove guest molecules (H_2O, DMF, and methanol).

3.3. General procedure for the synthesis of pyrimido[4,5-d]pyrimidine derivatives 4a–4m

A mixture of isothiocyanate (1 mmol), aromatic aldehyde (1 mmol) and 6-aminouracil or *N*,*N*-dimethyl-6-aminouracil (1 mmol) and MIL-53(Fe) (0.005 g) was heated at 110 ^{o}C under solvent-free conditions for the appropriate time (Table 3). After completion of the reaction as indicated by TLC (ethyl acetate: *n*-hexane, 1:3), the reaction mixture was cool to room temperature and CH_2Cl_2 was added. The catalyst was separated by simple filtration [20a]. The solvent was evaporated and the residue was recrystallized from ethanol to afford the pure product.

All products gave satisfactory spectral data in accordance with the assigned structures. The spectral data of the new products are as follow:

5,6-Diphenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (4a)

White solid, m.p. 290-292°C.^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.24 (s, 1H, CH), 6.93-7.03 (m, 3H, ArH), 7.24-7.30 (t, 2H, ArH), 7.47-7.59 (m, 4H, ArH, NH), 7.81-7.84 (d, 2H, ArH), 9.97 (s, 1H, NH), 11.13 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 78.556, 90.100, 115.060, 121.584, 129.068, 129.291, 129.405, 129.546, 130.253, 130.909, 137.363, 147.076, 157.617, 162.067, 162.197. FT-IR (KBr) v: 3490, 1699, 1618 cm^{-1}. MS (EI) (m/z): 350.08 (M^+). Anal. Calcd. for: $C_{18}H_{14}N_4O_2S$ (Mr= 350.40): C 61.70, H 4.03, N 15.99. Found: C 61.79, H 4.00, N 15.94.

5-(4-Nitrophenyl)-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (4l)

White solid; m.p. 255-257°C.^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.32 (s, 1H, CH), 6.97-7.34 (m, 6H, ArH, NH), 8.09-8.12 (d, 2H, ArH), 8.32-8.36 (d, 2H, ArH), 10.39 (s, 1H, NH), 11.26 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 77.038, 90.089, 112.570, 119.115, 121.687, 127.086, 127.158, 135.476, 144.819, 146.987, 155.115, 157.414, 159.554. FT-IR (KBr) v: 3494, 1697, 1622 cm^{-1}. MS (EI) (m/z): 395.07 (M^+). Anal. Calcd. for: $C_{18}H_{13}N_5O_4S$ (Mr= 395.39): C 54.68, H 3.31, N 17.71. Found: C 54.58, H 3.33, N 17.76.

5-(4-Hydroxyphenyl)-6-phenyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (4m)

White solid; m.p. 283-285°C.^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.19 (s, 1H, CH), 7.18-7.31 (m, 5H, ArH), 7.51-7.62 (m, 3H, ArH), 7.83-7.86 (t, 2H, ArH), 9.58 (s, 1H, OH), 10.38 (s, 1H, NH), 11.90 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 77.554, 89.384, 112.477, 118.878, 121.825, 125.257, 126.138, 126.448, 126.627, 127.047, 130.732, 140.481, 148.495, 151.901, 155.386. FT-IR (KBr) v: 3497, 1691, 1626 cm^{-1}. MS (EI) (m/z): 366.08 (M^+). Anal. Calcd. for: $C_{18}H_{14}N_4O_3S$ (Mr= 366.40): C 59.01, H 3.85, N 15.29. Found: C 58.92, H 3.89, N 15.37.

Acknowledgments

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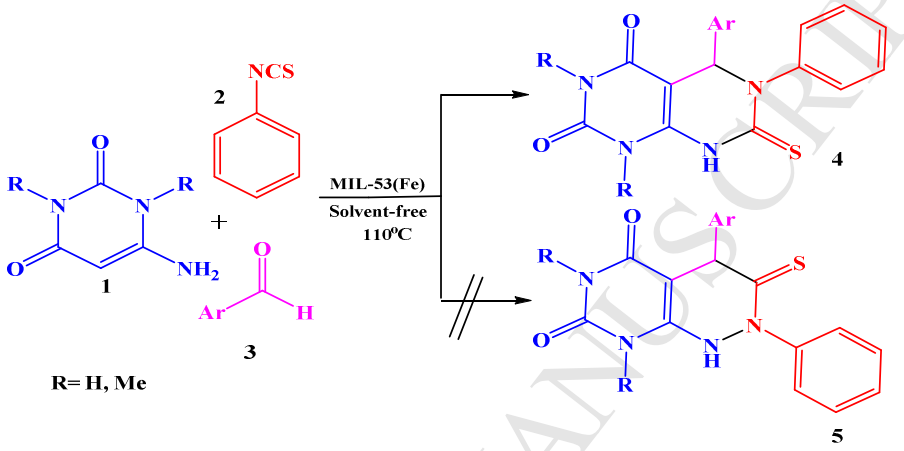
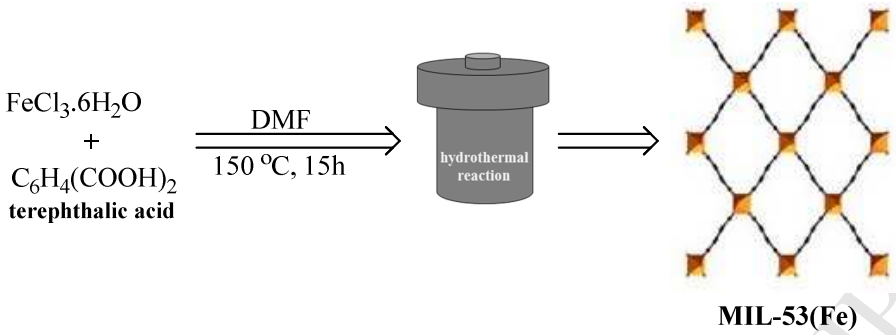


Scheme 1. Synthesis of pyrimido[4,5-*d*]pyrimidines.



Scheme 2. Preparation process of MIL-53(Fe).

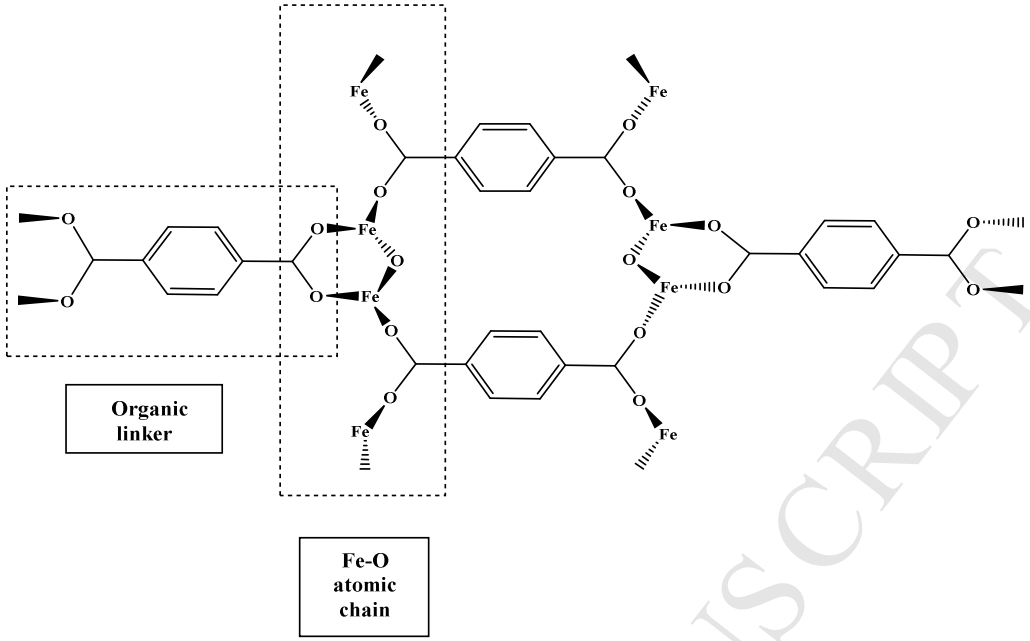


Figure 1. Structure MIL-53(Fe) metal–organic framework.

Table 1. Optimization of temperature in the synthesis of pyrimido[4,5-*d*]pyrimidine derivative of benzaldehyde.[a]

Entry	Temperature (◦C)	Time (min.)	Yield (%)[b]
1	60	90	45
2	70	80	51
3	80	60	73
4	90	20	82
5	100	20	90
6	110	20	98
7	120	20	98

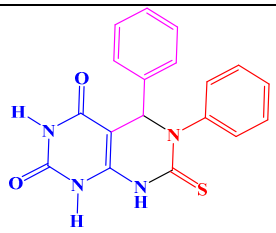
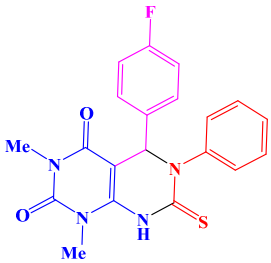
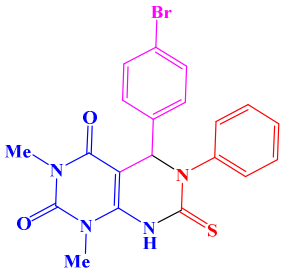
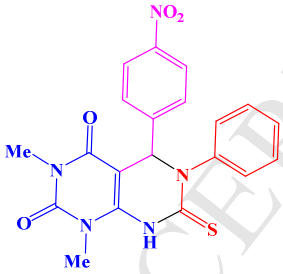
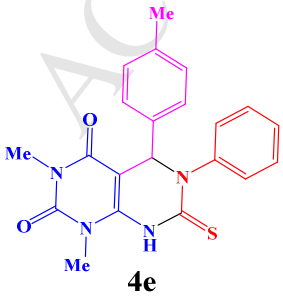
[a]Reaction conditions: isothiocyanate (1 mmol), benzaldehyde (1 mmol) and 6-aminouracil (1 mmol), MIL-53(Fe) (0.005 g), solvent-free.
[b]Isolated yield.

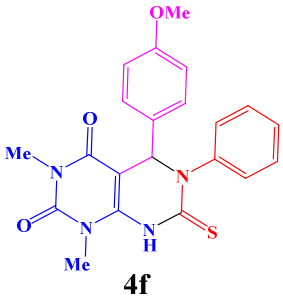
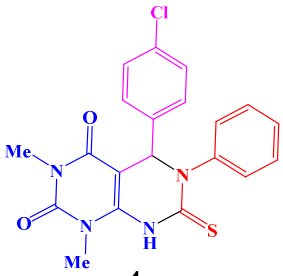
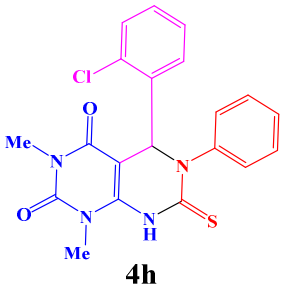
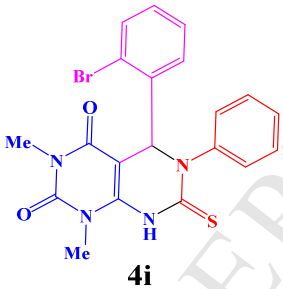
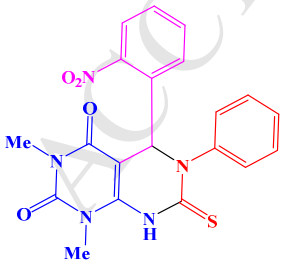
Table 2. The effect of the amounts of the catalyst in the synthesis of pyrimido[4,5-*d*]pyrimidine derivative of benzaldehyde. [a]

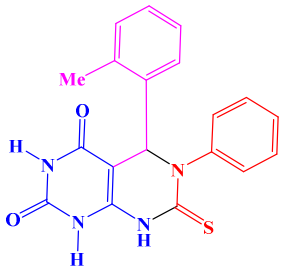
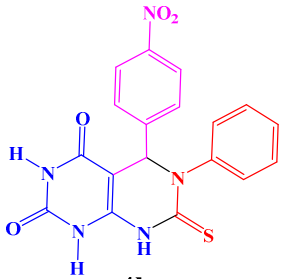
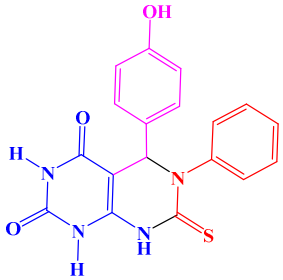
Entry	MIL-53(Fe) (g)	Time (min.)	Yield (%)[b]
1	None	100	10
2	0.001	80	49
4	0.002	20	66
5	0.003	20	80
6	0.004	20	84
7	0.005	20	98
8	0.006	20	97

[a]Reaction conditions: isothiocyanate (1 mmol), benzaldehyde (1 mmol) and 6-aminouracil (1 mmol), solvent-free, 110 ^{o}C.
[b]Isolated yield.

Table 3. Synthesis of pyrimido[4,5-*d*]pyrimidines in the presence of MIL-53(Fe).

Entry	Product	Yield (%)[a]	M.P.(°C)	Lit. M.P.(°C)
1	 **4a**	98	290-292	------[b, c]
2	 **4b**	92	265-267	264-266[18]
3	 **4c**	97	278-280	283-284[18]
4	 **4d**	98	275-277	283-284[18]
5	 **4e**	89	268-271	268–271[18]

6	 **4f**	95	274-276	272-274[18]
7	 **4g**	93	276-278	274-275[19]
8	 **4h**	86	274-276	273-276[18]
9	 **4i**	91	261-263	259-261[18]
10	 **4j**	96	285-287	282-283[18]

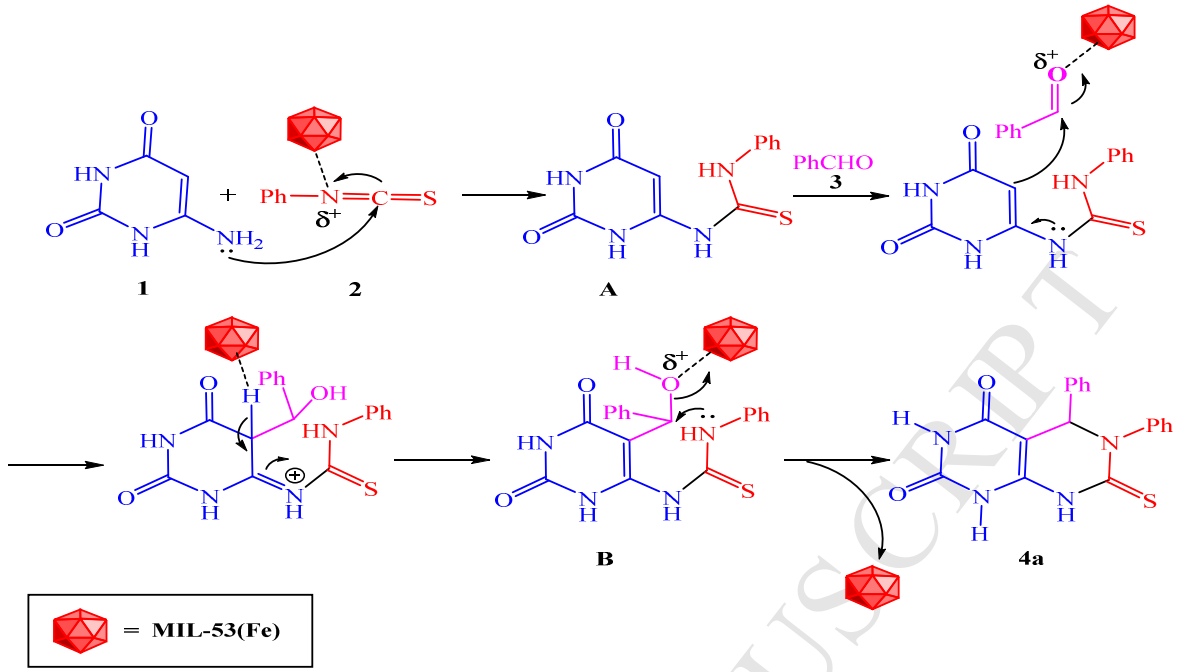
11	 **4k**	88	271-273	270-272[18]
12	 **4l**	97	255-257	------[b]
13	 **4m**	94	283-285	------[b]

[a] Yield obtained after 20-25 min.
[b] New compound.
[c] **4a**, yield 98% in the presence of MIL-53(Fe) for the first run, 97% in the second run, and 95% in the third run using the recycled catalyst.

Table 4. MIL-53(Fe) catalyzed the synthesis of pyrimido[4,5-*d*]pyrimidine **4d** in comparison with other reagents reported in the literature. [a]

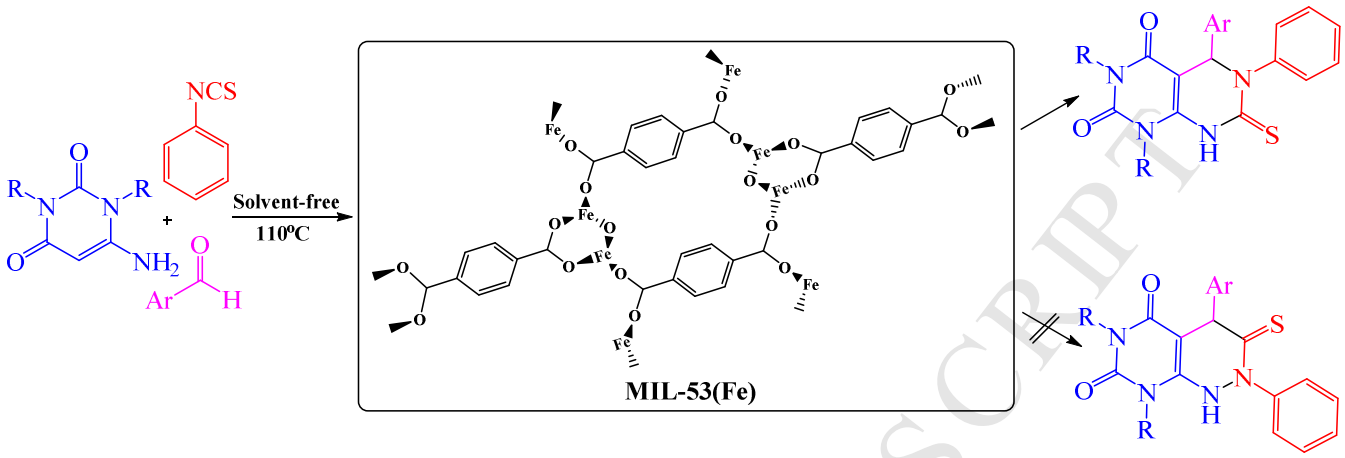
Entry	Catalyst	Conditions	Time/ Yield (%)	References
1	*p*-TSA	Water/ reflux	1 h/ 67	17
2	Fe_3O_4@SiO_2@Propyl-ANDSA	Water/ reflux	60 min./ 98	18
3	PEG–SO_3H	Water/ 70°C	60 min./ 90	19
4	MIL-53(Fe)	Solvent-free/ 110°C	20 min./ 98	This work

[a] Based on the three-component reaction of 4-nitrobenzaldehyde; *N*,*N*-dimethyl-6-aminouracil and phenylisothiocyanate.



Scheme 3. The proposed mechanism for the synthesis of **4a** catalyzed by MIL-53(Fe).

Graphical abstract



Research Highlights

- The MIL-53(Fe) were characterized by spectroscopic analysis including EDX, SEM, TGA, XRD and FT-IR analysis.
- The attractive features of this process are high yields, short reaction times, simple workup and environmentally benign procedure.
- MIL-53(Fe) as an efficient and green catalyst for the multicomponent synthesis of pyrimido[4,5-*d*]pyrimidines.
- The catalyst can be recovered several cycles without any loss of catalytic activity.
- Synthesis and characterization of new derivatives.