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Fe_3O_4@nano-cellulose/Ti(IV): An efficient and natural-based magnetic nano-catalyst for the synthesis of functionalized pyrimido [4,5-*b*] quinolines in aqueous media

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KEYWORDS
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6-amino-2-(methylthio)pyrimidin-4(3*H*)-one;
Fe_3O_4@NCs/Ti(IV);
Nano-cellulose;
Natural based catalyst;
Magnetic catalyst.

Abstract. A simple, efficient, and high-yielding one-pot protocol for the synthesis of pyrimido [4,5-*b*] quinoline derivatives was developed in this study. Pyrimido [4,5-*b*] quinolines were synthesized by three-component reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, dimedone, and various substituted aldehydes using Fe_3O_4@NCs/Ti(IV) as a magnetic natural-based catalyst in water at 70°C. Several advantages of this protocol are good yield, short reaction time, easy work-up, recyclability, and the environmentally-friendliness of the catalyst. 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one as an important substrate was synthesized, purified, identified, and then applied to the synthesis of pyrimido [4,5-*b*] quinolines. The structures of the products were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra.

1. Introduction

Considering the green chemistry aspects, biopolymers like cellulose, as one of the most important biopolymers, have received growing attention as a non-toxic, hydrophile, renewable, and biocompatible polymer with a large surface area [1–3]. Recently, Magnetic Nanoparticles (MNPs) have appeared as an excellent type of catalyst support because of their good stability, easy synthesis and functionalization, high surface area, easy separation by magnetic forces, and low toxicity and price [4]. Other important features of these magnetic catalysts are high catalytic activity, high degree of chemical stability in various organic and inorganic solvents, reusability, and benign character in the context of green chemistry [5–7]. Fe_3O_4 nanoparticles are coated with various materials such as surfactants [8], polymers [9], silica [10], biopolymers like cellulose [11,12], and chitosan [13] to form a core-shell structure. Thus, one of the main purposes of the present work is to prepare nano-cellulose by sulfuric acid hydrolysis of cotton and use it for the synthesis of Fe_3O_4@nano-cellulose/Ti(IV), abbreviated as Fe_3O_4@NCs/Ti(IV) (Scheme 1) [11].

Multicomponent Reactions (MCRs) have emerged as a powerful synthetic tool for the preparation of biologically active compounds [14]. Pyridopyrimidines and pyrimidoquinoline are important classes of hetero-

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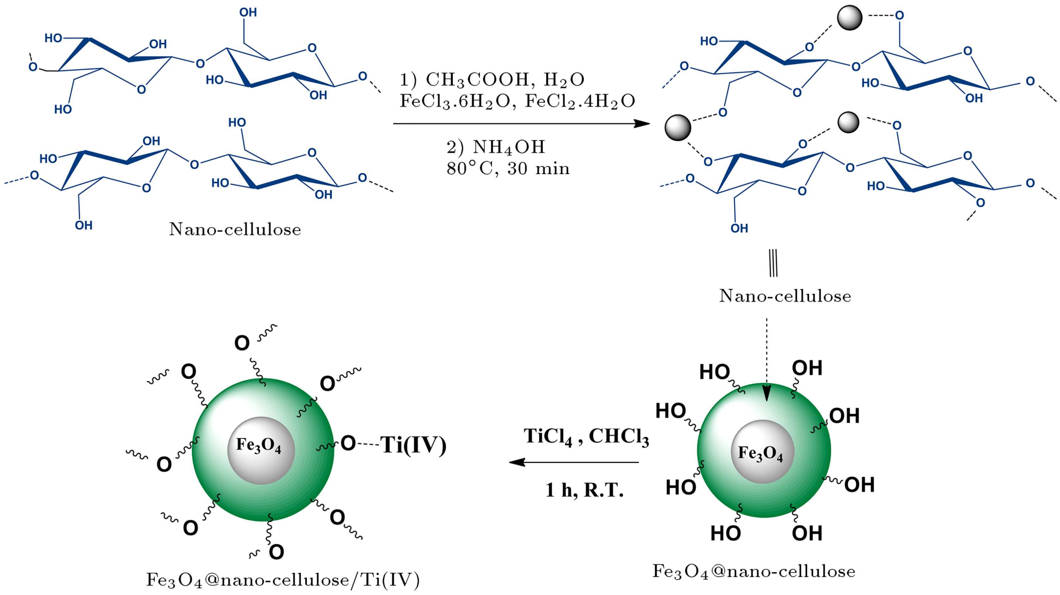


Scheme 1. Synthesis protocol for Fe_3O_4@NCs/Ti(IV).

cycles that are found in a wide variety of biologically active products. Several multi-component reactions have been reported for the synthesis of pyridopyrimidines and pyrimidoquinoline [15–18]. A number of pharmacological activities are antiviral [19], antitumor [20], antifolate [21], antihistaminic [22], anti-inflammatory [23], antibacterial [24], and antioxidant [25]. Thier structural moiety is present in ramastine (anti-allergic) [26], pirenperone (tranquilizer) [27], anticonvulsive [28], antipyretic [29], and cardiotonic [30]. Pyrimido [4,5-*b*] quinoline has been reported in this work by the cyclization of 6-amino-2(methylthio)pyrimidin-4(3*H*)-one, dimedone, and various aldehydes.

Previously, uracil derivatives with cyclic 1,3-diketones and the aromatic aldehydes have been catalyzed by several techniques such as reflux in ethanol [31], and various catalysts such as 1,3-disulfonic acid imidazolium hydrogen sulfate ([dsim]HSO_4) [32], Fe_3O_4NPs-cell [17], $RuCl_3.xH_2O$ [33], DMF/MW [34], piperidine/reflux [35], and sulfonic acid supported on hydroxyapatite-encapsulated-γ-Fe_2O_3 ([γ-Fe_2O_3@HAp-SO_3H]) have been used [18]. Some of these methods have limitations such as the need for drastic conditions, longer reaction times, expensive reagents, strongly acidic conditions, high temperature, and use of organic solvents, which have environmental limitations. Further to our research on the application of solid acids to organic synthesis [36–42], Fe_3O_4@NCs/Ti(IV) as an efficient, natural based, inexpensive, eco-friendly, and reusable magnetic nanocatalyst was used in this work for one-pot synthesis of pyrimido [4,5-*b*] quinolone *via* a three-component reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, dimedone, and various aromatic aldehydes in water at 70°C.

2. Experimental section

2.1. Materials and methods

All compounds were purchased from Merck chemical company. Nano-cellulose and Fe_3O_4@NCs were synthesized *via* our previously reported methods [11]. 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one was synthesized in our laboratory. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{13}C NMR and ^{1}H NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus.

2.2. Preparation of Fe_3O_4@NCs/Ti(IV)

In a well-ventilated system, $TiCl_4$ (5 ml) was added dropwise to the mixture of Fe_3O_4@NCs (0.5 g) in chloroform (20 ml). The mixture was stirred for one hour at room temperature. The resulting suspension was filtered, washed with chloroform, and dried at room temperature. The final weight of obtained Fe_3O_4@NCs/Ti(IV) is 0.64 g.

2.3. General procedure for synthesis of pyrimido [4,5-b] quinoline derivatives

A mixture of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (1 mmol), aldehyde (1 mmol), dimedone (1 mmol) was heated at 70°C in the presence of Fe_3O_4@NCs/Ti(IV) (0.02 g) in water. Following the completion of the reaction (monitored by TLC, EtOAc:petroleum ether 8:4), the catalyst was separated by an external magnet and reused for the next experiment. Then, the reaction mixture was concentrated and cooled. The obtained solid was filtered off and recrystallized from EtOH: H_2O (1:1) to furnish the desired pure product. The recovered catalyst was washed 3 times with ethanol, and then dried and reused for subsequent runs under the same reaction conditions.

3. Results and discussion

3.1. Characterization of Fe_3O_4@NCs/Ti(IV)

Fe_3O_4@NCs/Ti(IV) is characterized by Fourier Transform Infrared (FT-IR) spectroscopy, Field Emission Scanning Electron Microscopy (FESEM), X-Ray Diffraction (XRD), Vibrating Sample Magnetometry (VSM), and Thermo-Gravimetric Analysis (TGA).

The FT-IR spectra of (a) nano-cellulose, (b) Fe_3O_4@NCs, and (c) Fe_3O_4@NCs/Ti(IV) are shown in Figure 1. The FT-IR spectrum of nano-cellulose shows a broad band at 3337 cm^{-1} which corresponds to the stretching vibrations of OH groups. The absorption bands around 1055 and 1108 cm^{-1} display the stretching vibrations of the C-O bonds. For Fe_3O_4@NCs, cellulose absorptions appear in addition to the stretching vibrations of Fe-O groups at 586 and 634 cm^{-1}, indicating that the magnetic Fe_3O_4 NPs are coated by nano-cellulose. The FT-IR spectrum of Fe_3O_4@NCs/(IV) shows a characteristic peak at 794 cm^{-1} corresponding to C-O-Ti stretching according to the IR spectrum of $Ti(OBu)_4$. The peak at 406 cm^{-1} corresponds to O-Ti-O bending vibrations. The stretching vibrations of O-H bonds are observed at 3376 cm^{-1}. The band 1585 cm^{-1} might be due to the H-O-H bending vibration of adsorbed water. In comparison with Fe_3O_4@NCs, bonding Ti to the cellulosic shell shifts Fe-O stretching vibrations to lower wave number (from 586 and 634 cm^{-1} to 558 and 606 cm^{-1}, respectively).

The particle sizes of nano-cellulose and Fe_3O_4@NCs/Ti(IV) were investigated by FESEM in which their dimensions were achieved below 50 nm (Figure 2).

The structure and phase purity of Fe_3O_4, Fe_3O_4@NCs, and Fe_3O_4@NCs/Ti(IV) are studied by means of high angle XRD analysis (Figure 3). The bare Fe_3O_4 shows diffraction peaks at 2θ = 30.4358°, 35.8507°, 43.4470°, 53.9461°, 57.4597°, and 63.0368°with FWHM equal to 0.4723, 0.4723, 0.4723, 0.7872, 0.6298, and 0.6298, respectively, which are quite consistent with the cubic spinel structure of pure Fe_3O_4 described in the literature (Figure 3(a)). The same peaks were also observed in the Fe_3O_4@NCs XRD pattern, indicating retention of the crystalline spinel ferrite core structure during the cellulose-coating process. Moreover, a diffraction peak at 2θ =23.0444 appeared in the Fe_3O_4@NCs MNPs, which could be related to the cellulose coating of Fe_3O_4 NPs (Figure 3(b)). The XRD pattern of Fe_3O_4@NCs/TiCl shows an amorphous structure (Figure 3(c)). The weak diffraction peaks at 2θ = 29.9870°, 35.6108°, 46.5512°, and 56.0212° correspond to Fe_3O_4 cores (Figure 3(c)). Other peaks at around $2\theta = 21° - 23°$ reveal the existence of cellulose and bonding of Ti to cellulosic shell.

To investigate the magnetic property of catalyst, magnetic measurements were carried out using a Vibrating Sample Magnetometer (VSM) in an applied magnetic field at 300 K. As shown in Figure 4, no hysteresis loop and no remanence could be detected and, also, the coercivity value was zero for all samples, suggesting typical superparamagnetic property at room temperature. The saturation magnetization (Ms) values of Fe_3O_4, Fe_3O_4@NCs, and Fe_3O_4@NCs/Ti(IV) are 49.177, 33.057, and 6.062 emu/g, respectively.

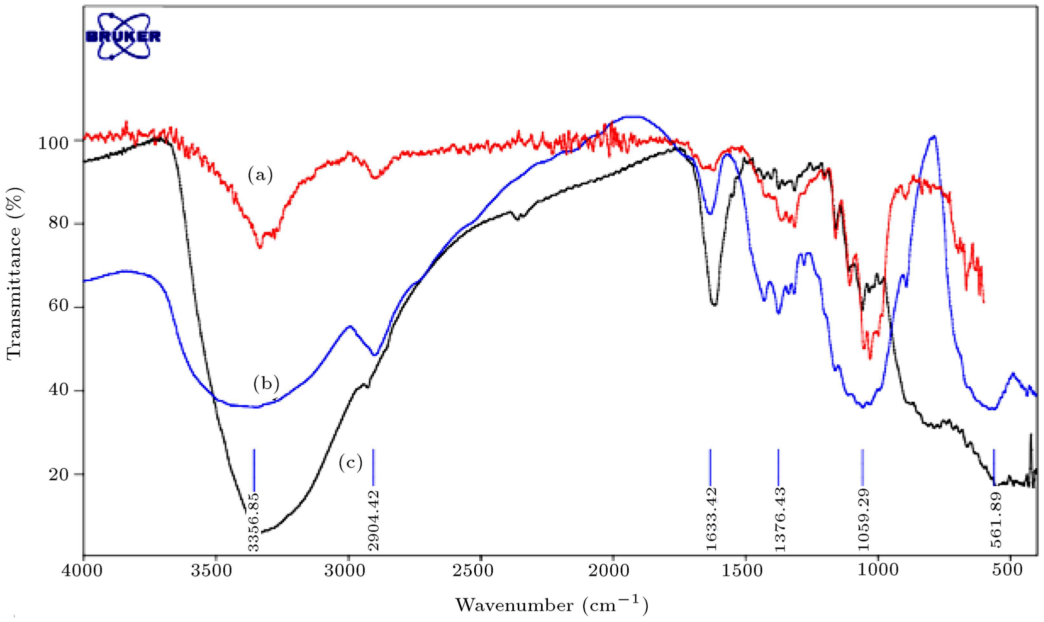


Figure 1. FT-IR spectra of (a) nano-cellulose, (b) Fe_3O_4@NCs, and (c) Fe_3O_4@NCs/Ti(IV).

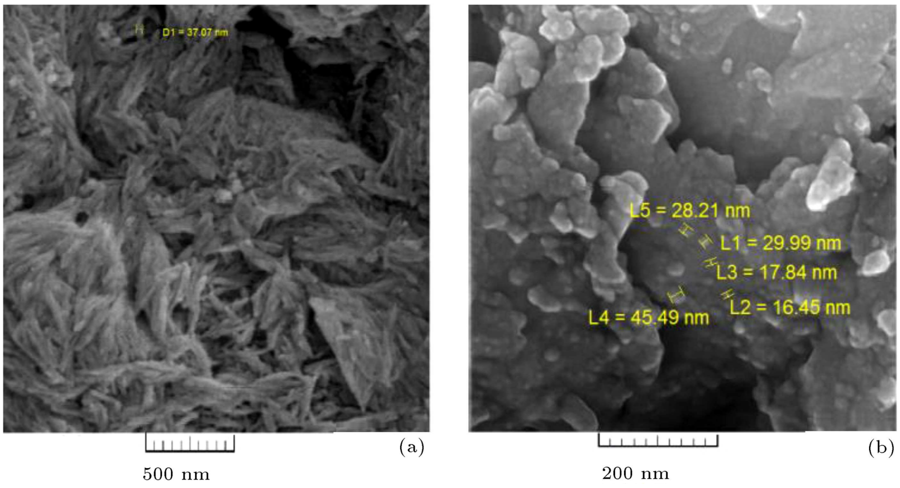


Figure 2. FESEM image of (a) nano-cellulose and (b) Fe_3O_4@NCs/Ti(IV).

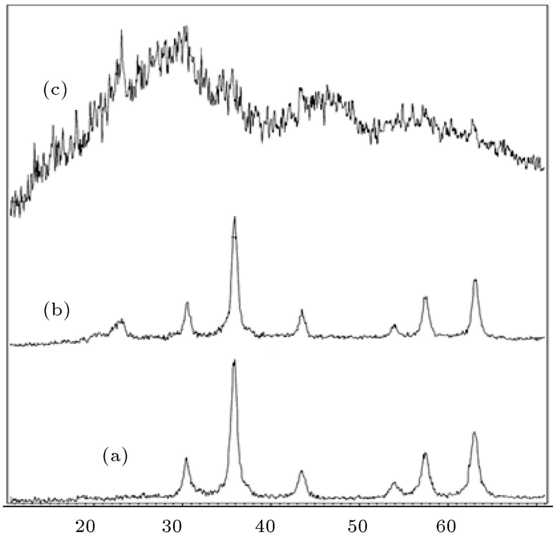


Figure 3. XRD patterns of (a) Fe_3O_4, (b) Fe_3O_4@NCs, and (c) Fe_3O_4@NCs/Ti(IV).

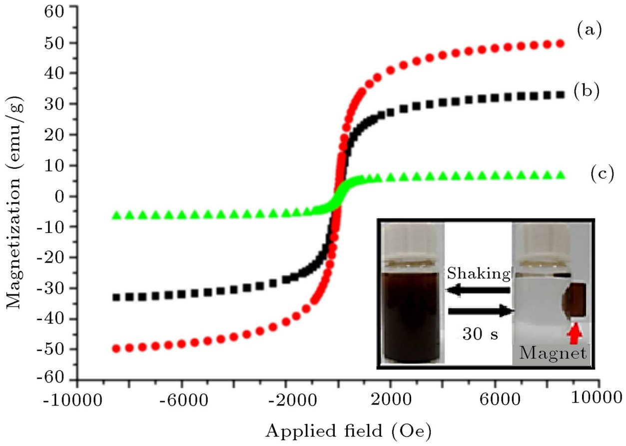


Figure 4. Magnetization loops of (a) Fe_3O_4, (b) Fe_3O_4@NCs, and (c) Fe_3O_4@NCs/Ti(IV).

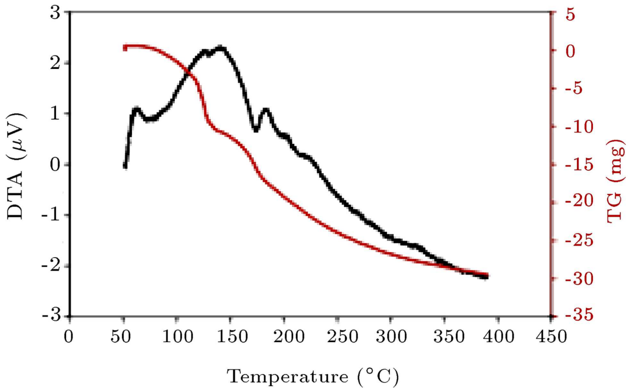


Figure 5. Thermal gravimetric analysis pattern of Fe_3O_4@NCs/Ti(IV).

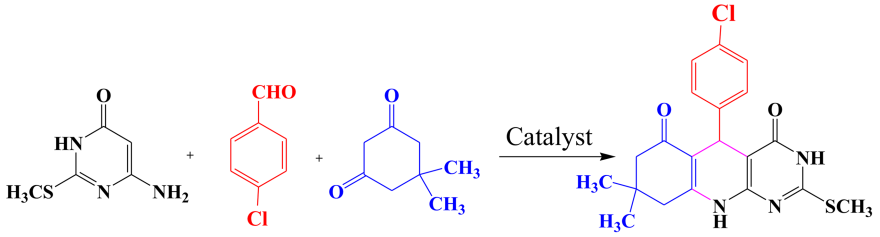
These results indicate that magnetization of Fe_3O_4 decreased considerably by coating it with nano-cellulose and bonding $TiCl_4$ to OH groups of nano-cellulose. Even with the reduction of the saturation magnetization, the catalyst can still be efficiently separated from solution with a permanent magnet (as shown in the inset of Figure 4).

The thermal stability of Fe_3O_4@NCs/Ti(IV) was investigated by Thermo-Gravimetric Analysis (TGA) in the temperature range of 50–372°C (Figure 5). The TGA curve illustrates four mass-loss steps. Firstly, minor weight loss (2.14%) from 50 to 100°C resulted from the removal of catalyst moisture.

3.2. Catalyst efficiency for synthesis of pyrimido [4,5-b]quinoline derivatives

After characterization of Fe_3O_4@NCs/Ti(IV), the activity of the catalyst was evaluated for the synthesis of pyrimido [4,5-*b*]quinoline derivatives. For optimization of the reaction conditions, the reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, dimedone, and 4-chlorobenzaldehyde as a model reaction was investigated (Table 1). As shown in Table 1, entry 13, it

Table 1. The reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, dimedone, and 4-chlorobenzaldehyde in the presence of Fe_3O_4@NCs/Ti(IV) under various conditions.[a]



Entry	Solvent	Catalyst (g)	Condition	Time (min)	Yield (%)[b]
1	—	—	70°C	45	40
2	-	Fe_3O_4@NCs	70°C	30	47
3	C_2H_5OH	-	R. T.	35	30
4	C_2H_5OH	Catalyst (0.03)[c]	R. T.	15	80
5	C_2H_5OH	Catalyst (0.03)c	60°C	6	92
6	H_2O	Catalyst (0.03)[c]	60°C	6	93
7	H_2O	Catalyst (0.03)[c]	R. T.	15	84
8	-	Catalyst (0.03)[c]	R. T.	15	82
9	-	Catalyst (0.03)[c]	60°C	8	91
10	H_2O	Catalyst (0.05)[c]	70°C	4	94
11	H_2O	Catalyst (0.04)[c]	70°C	4	96
12	H_2O	Catalyst (0.03)[c]	70°C	4	96
13	H_2O	Catalyst (0.02)[c]	70°C	4	97
14	H_2O	Catalyst (0.03), 2th run[c]	70°C	4	94
15	H_2O	Catalyst (0.03), 3rd run[c]	70°C	4	89
16	H_2O	Catalyst (0.03), 4th run[c]	70°C	4	81

a: The amount ratio of 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one (mmol), dimedone (mmol), and 4-chlorobenzaldehyde (mmol) are equal to 1 : 1 : 1; b: Isolated yield; c: Fe_3O_4@ NCs/Ti(IV).

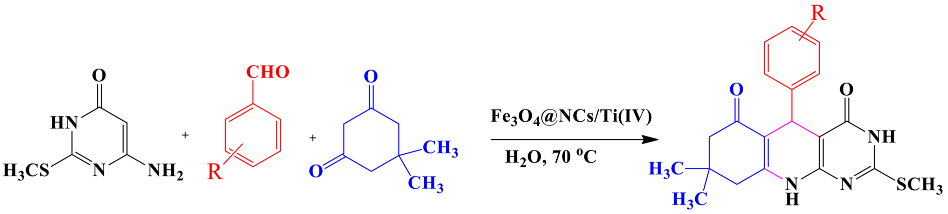
Table 2. Comparative study of the present method and some other reported methods for synthesis of pyrimido [4,5-*b*] quinoline derivatives.

Entry	Solvent	Catalyst	Temperature (°C)	Time (min)	Yield (%)[a]
1	C_2H_5OH	-	Reflux	30	78 (31)
2	C_2H_5OH	[dsim]HSO_4[b]	70	15	91 (32)
3	H_2O	Fe_3O_4NPs-cell	Reflux	2 h	86 (17)
4	H_2O	$RuCl_3.xH_2O$	85	30	95 (33)
5	C_2H_5OH	[γ -Fe_2O_3@HAp-SO_3H][c]	60	4	94 (18)
6	C_2H_5OH	Piperidine	Reflux	30	80 (35)
7	H_2O	Fe_3O_4@NCs/Ti(IV) (0.03 g)	70	4	97 (This work)

a: Isolated yield; b: 1,3-disulfonic acid imidazolium hydrogen sulfate; c: sulfonic acid supported on hydroxyapatite-encapsulated-γ -Fe_2O_3.

was found that using 0.02 g of Fe_3O_4@NCs/Ti(IV) in water as a reaction solvent at 70°C was the optimal reaction condition. In order to compare the efficiency of the present nano-catalyst with those of other catalysts, the model reaction was also performed using the reported catalysts for the synthesis of pyrimido [4,5-*b*]quinoline derivatives. As Table 2 indicates, in comparison with other catalysts, we have observed good and high yields of products under green conditions using Fe_3O_4@NCs/Ti(IV). Finally, the above optimized reaction conditions were explored for the synthesis of pyrimido [4,5-*b*]quinoline derivatives and

Table 3. Synthesis of pyrimido [4,5-*b*] quinoline derivatives (4a-o) in the presence of Fe_3O_4@NCs/Ti(IV) in water as solvent at 70°C.[a]



Entry	R	Product	Time (min)	Yield (%)[b]	M.P. °C (ref.)
1	4-MeO-	4a	6	95	> 300 [31]
2	2,4-$(MeO)_2$-	4b	5	96	> 300
3	2,4-$(Cl)_2$-	4c	5	96	> 300
4	4-NO_2-	4d	4	94	> 300 [31]
5	H-	4e	6	92	> 300 [31]
6	4-OH-3-MeO-	4f	7	95	> 300
7	4-CO_2Me-	4g	6	89	> 300
8	3,4,5-F-	4h	5	91	> 300
9	3-Br-	4i	4	94	> 300
10	4-Me-	4j	5	85	> 300
11	4-Cl-	4k	4	97	> 300 [31]
12	3-NO_2-	4l	5	95	> 300
13	3,4-OH-	4m	6	96	> 300
14	4-Br-	4n	5	95	> 300
15	4-CO_2H-	4o	6	93	> 300

a: I (mmol) : II (mmol) : III (mmol) : Fe_3O_4@NCs/Ti(IV) is equal to 1 : 1 : 1 : 0.02; b: Isolated yield.

the results are summarized in Table 3. The reusability of the catalyst was also investigated in the model reaction. The magnetic nature of the catalyst allowed its facile recovery by simple separation by an external magnet, washing with ethanol and drying at room temperature to provide an opportunity for recycling experiments. The separated nano-catalyst was reused three times in the above-mentioned reaction for the synthesis of 4k without considerable loss of its catalytic activity (Table 1). Partial loss of activity may be due to active sites blockage of the catalyst and/or partial leaching of Ti(IV) from the catalyst.

Aromatic aldehydes containing electron-donating groups or electron-withdrawing groups were employed and reacted to give the corresponding products 4a-o in high yield under the present reaction conditions. The suggested mechanism for the synthesis of pyrimido [4,5-*b*]quinoline (VII) was shown in Scheme 2. The carbonyl oxygen of aldehyde coordinates with the Lewis acid moiety, thus increasing the electrophilicity of the carbonyl carbon and making it possible to carry out the reaction in a short time. In a plausible mechanism, it is assumed that the reaction may proceed initially through the Knoevenagel condensation between aldehydes and dimedone to form intermediate 1. Next, Michael addition of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one to intermediate 1 affords 2. Intermediate 2 converts into 3 after tautomerization. Then, intermediate 3 converts *via* cyclization to the product. The structures of the products 4a-o were studied by their melting point, IR and ^{1}H, and ^{13}C NMR spectra.

4. Conclusion

This study developed a facile and green one-pot three-component reaction for the synthesis of pyrimido[4,5-*b*]quinoline derivatives using Fe_3O_4@NCs/Ti(IV) as a highly efficient, magnetite recoverable, eco-friendly, inexpensive and novel bio-based heterogeneous catalyst. This protocol includes some important advantages such as mild reaction conditions, short reaction time, excellent yields, easy work-up procedure, product purity, magnetic separation, and reusability of nanocatalyst.

Acknowledgments

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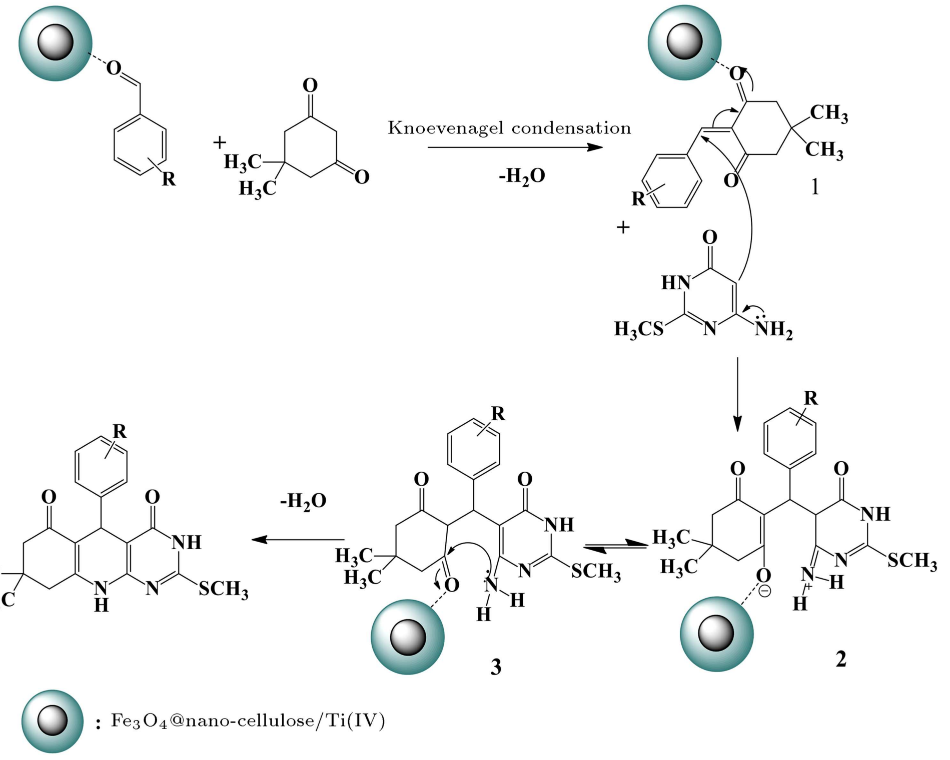

Scheme 2. Proposed mechanism for the synthesis of pyrimido [4,5-*b*]quinoline derivatives 4a-o.

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