An efficient synthesis of pyrimido[4,5-*b*]quinoline and indenopyrido[2,3-*d*]pyrimidine derivatives in the presence of Fe_3O_4@nano-cellulose/Sb(V) as bio-based magnetic nano-catalyst

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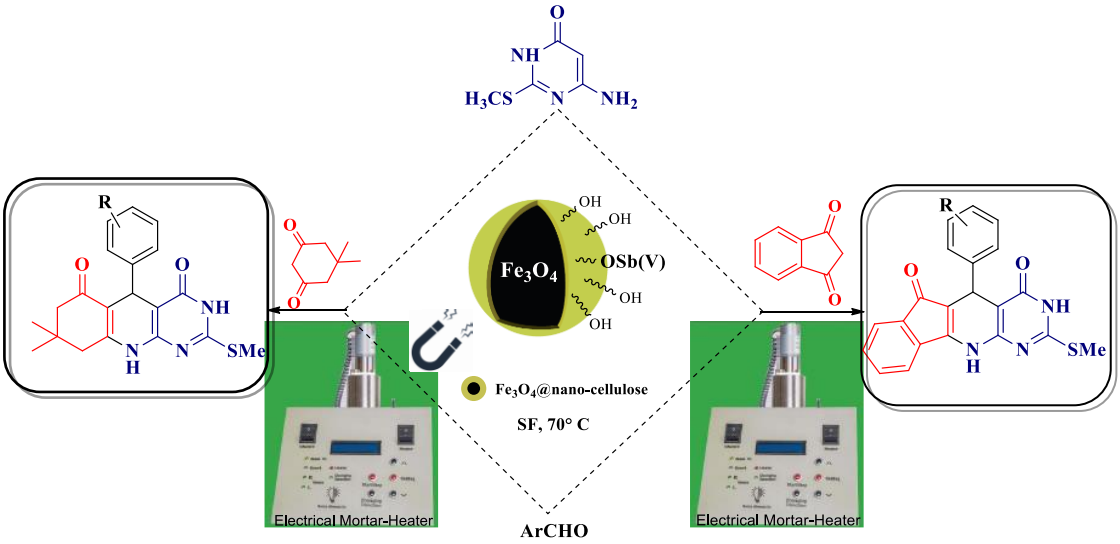
Graphical abstract



Abstract. In this study, an eco-friendly approach has been introduced for the synthesis of pyrimido[4,5-*b*]quinolones and indenopyrido[2,3-*d*]pyrimidines. This synthesis was done *via* a three component coupling of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, 1,3-indanedione/dimedone and aromatic aldehydes using Fe_3O_4@nano-cellulose/Sb(V) as catalyst under solvent-free condition at 70 °C by electrical mortar-heater. The catalyst was separated from the reaction mixture by an external magnet and reused for subsequent

reactions. The present procedure offers many advantages such as high yield, easy work-up, simple isolation of catalyst by external magnet and high reusability of the it. The structure of the obtained pyrimido[4,5-*b*]quinolones and indenopyrido[2,3-*d*]pyrimidines products were studied by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic data.

KEYWORDS

Fe_3O_4@nano-cellulose/Sb(V); Bio-based catalyst; Pyrimido[4,5-*b*]quinoline, Indenopyrido[2,3-*d*]pyrimidine; Solvent-free; Multi component reaction

1. Introduction

Indenopyrido[2,3-*d*]pyrimidine (IPP) and pyrimido[4,5-*b*]quinolone (PQ) exhibit pharmacologic properties and are used in medicinal chemistry. Some of the pharmacological activities of these compounds are anticancer agents inhibiting tyrosine kinases [1-3], antitumor [4, 5], antihistaminic [6], anti-inflammatory [7], antibacterial [8-12]. Therefore, these heterocyclic compounds are highly regarded in research.

Numerous methods and various catalysts such as *p*-TSA [13], acetic acid [14], $InCl_3$ [15], 1,2- dimethyl-*N*-butanesulfonic acid imidazolium hydrogen sulfate ((DMBSI)HSO_4) [16], nano-Fe_3O_4@SiO_2-SO_3H [17], ethylene glycol under sonication condition [18], Fe_3O_4@urea/HITh-SO_3H MNPs [19], $CoFe_2O_4$@SiO_2@$Si(CH_2)_3NHCOOCH_2COOH$ [20], [H_2-DABCO][ClO_4]$_2$ [21], nano-[Fe_3O_4@-SiO_2@R-$NHMe_2$][H_2PO_4] [22], SBA-15/$PrN(CH_2PO_3H_2)_2$ [23], En/MIL-100(Cr) [24] and Fe_3O_4@NCs/Cu(II) [25] have been reported for the synthesis of IPP and PQ. Since the last few decades, green chemistry have been gaining much attention for chemists. Therefore, the preparation of environmentally friendly catalysts is still considered as an interesting challenge.

Previously, we have synthesized and characterized Fe_3O_4@nano-cellulose/Sb(V) (FNC-Sb(V)) as a new magnetic and bio-based nano-catalyst [26]. In this work, we wish to report efficient and ecofriendly procedure for the synthesis of IPP and PQ derivatives *via* one-pot three component condensation of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (AMP), 1,3 indanedione/dimedone and various aldehydes in the presence of FNC-Sb(V).

2. Experimental

2. 1. Materials and methods

All solvents and chemical materials were prepared from Merck, Aldrich, and Fluka chemical companies. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was applied to record the ^{1}H-NMR and ^{13}C-NMR spectra. Melting points were achieved by a Buchi melting point B-540 B. V. CHI apparatus. Electrical mortar-heater which was used for grinding of reaction mixture at 70 °C, purchased from Borna-Kherad Co., Iran, Yazd.

2. 2. Synthesis of AMP

In step one, in a 100 ml round bottom vessel, 0.3 g of sodium metal was added in 20 ml of dry ethanol, then 1 g of thiourea and 1.38 ml of ethylcyanoacetate were charged to it. The resulting solution was refluxed for 4 hours. The obtained residue was dissolved in 30 ml of water and gradually added NaOH (0.5 M) to obtain neutral pH. At this stage, the substance 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one was synthesized.

In step two, a mixture of 0.5 g of 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one, 0.14 g NaOH, 35 mL of dry methanol and 0.2 ml of methyliodide was heated under reflux condition. Then, obtained product AMP, was washed with water and dried at 110 °C.

2. 3. General procedure for synthesis of PQ and IPP derivatives

A mixture of AMP (0.156 g), indanedione/dimedone (0.146/0.140 g), aldehyde (0.106 g) and FNC-Sb(V) (0.03 g) was grinded by an electrical mortar-heater at 70 °C. The progress of reaction was monitored by TLC (*n*-Hexan:EtOAc, 8:2). After completion of reaction, 5 ml of ethanol was added to the reaction mixture and the catalyst was separated by an external magnet. By cooling of the mixture, the product was appeared as solid which crystallized from EtOH:H_2O (1:1).

3. Results and discussion

In this work, an efficient and environmentally benign protocol was developed for the synthesis of PQ and IPP derivatives using three-component reaction of AMP, 1,3 indanedione/dimedone and various aromatic aldehydes in the presence of FNC-Sb(V). The steps of the synthesis of FNC-Sb(V) catalyst are shown in scheme 1. The resulted catalyst was characterized by FT-IR, XRD, VSM, EDS, and TGA.

x

Scheme 1

AMP as a very expensive substrate for preparation of PQ and IPP was synthesized in two stage (Scheme 2).

Scheme 2.

To investigate the catalytic activity of FNC-Sb(V), the reaction of AMP (0.156 g), dimedone (0.140 g) and 4-chlorobenzaldehyde (0.28 g) was performed as a model reaction under various conditions (Table 1). According to the results, the best condition is using 0.03 g of the FNC-Sb(V) under solvent-free condition at 70 °C by using electrical mortar-heater (Table 1, entry 8). In a reaction, without catalyst, a low yield of the product was achieved after a long reaction time (Table 1, entry 13), indicating the high efficiency of catalyst for this reaction.

Table 1

According to the results of the model reaction, we have decided to synthesis of PQ and IPP derivatives which the results are shown in Table 2. The aromatic aldehydes with electron-withdrawing groups are more active than others. The structure of products were characterized by their melting points and spectral analysis such as FTIR and NMR.

Table 2

In order to examine the reusability of FNC-Sb (V), it was separated by an external magnet, washed with chloroform and dried at room temperature. The separated FNC-Sb (V) was reused four times without considerable decrease of catalytic activity (Figure 1). The slight decrease in the catalytic activity may be due to obstruction of the active sites of the catalyst or partial secretion of antimony from it.

Figure 1

The catalytic activity of FNC-Sb (V) in model reaction was compared with other reported catalysts (Table 3). According to obtained data, using FNC-Sb (V) was caused reaction promotion in shorter reaction time with higher yields.

Table 3

The proposed mechanism for the synthesis of PQ **(4)** was shown in scheme 3. The Lewis acid moiety of catalyst, (Sb(V)), increases the electrophilic activity of carbonyl group in aldehyde and dimedone. In an acceptable mechanism, it is assumed that the reaction may continue at first through the Knoevenagel condensation between aldehydes and dimedone to form intermediate **I**. Next, Michael addition of AMP to intermediate **I** affords **II**. Intermediate **II** converts to **III** after tautomerization. Then, intermediate **III** converts *via* cyclization to product **4**.

Scheme 3.

4. Conclusion

In summary, we have introduced a simple multi-component procedure for the facile synthesis of PQ and IPP derivatives using FNC-Sb(V) as a bio-based magnetic nano-catalyst with high efficiency. The PQ and IPP derivatives were prepared *via* one-pot three-component reaction of AMP, 1,3-indanedione/dimedone and various aldehydes under solvent-free condition at 70 °C by electrical mortar-heater. This protocol include many advantages such as high atom-economy, mild reaction conditions and use of inexpensive reusable heterogeneous catalyst.

Acknowledgements

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Captions

Scheme 1. Preparation of FNC-Sb(V)

Scheme 2. Synthesis of AMP

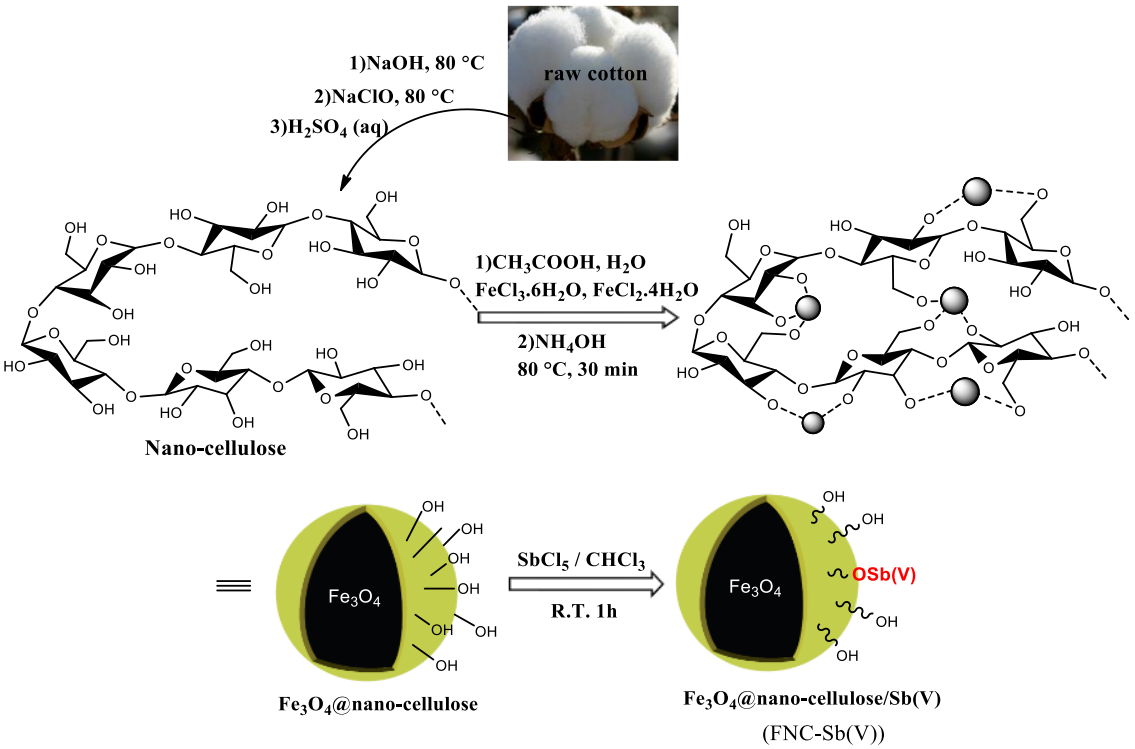
Scheme 3. Proposed mechanism for the synthesis of PQ derivatives

Table 1. The reaction of AMP (1 mmol), dimedone (1 mmol) and 4-chlorobenzaldehyde (1 mmol) under various conditions.

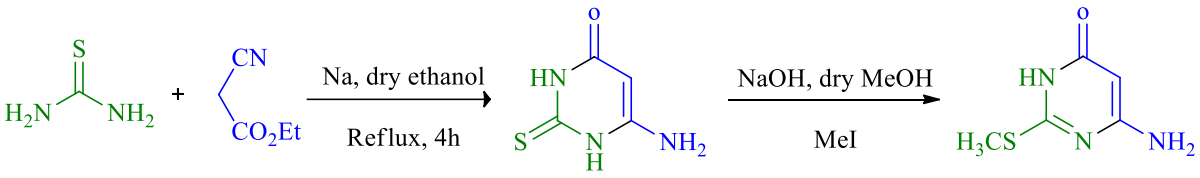
Table 2. Synthesis of PQ and IPP derivatives **(4a-m)** in the presence of FNC-Sb(V) under solvent-free condition at 70 °C in electrical mortar-heater.

Table 3. Comparison catalytic performances of FNC-Sb(V) versus some other catalysts for the synthesis of PQ

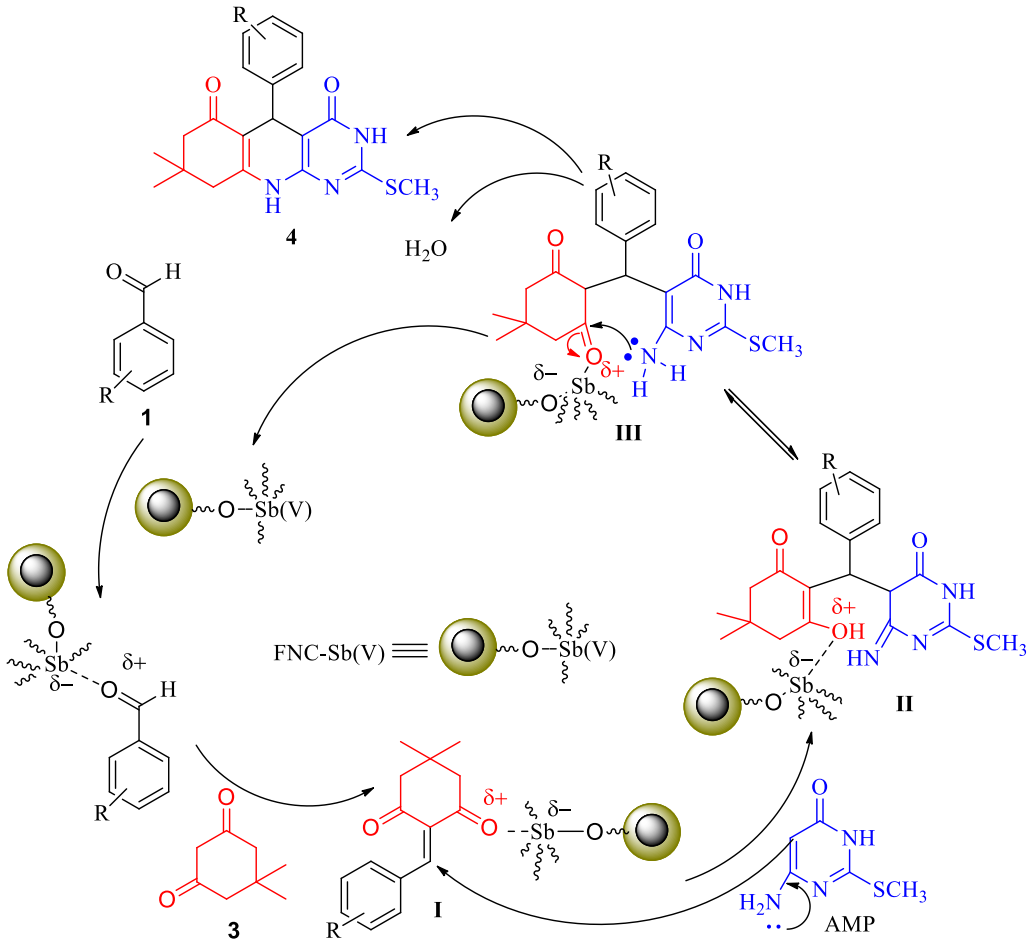
Figure 1. Catalyst reusability experiments



Scheme 1.



Scheme 2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SCH3
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δ–
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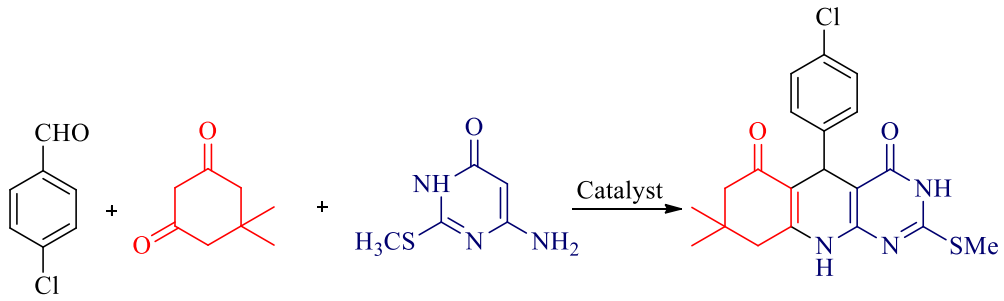
H
III
O–Sb(V)
FNC-Sb(V)
δ+
OH
HN
δ–
II
δ+
δ–
I
3
H2N
AMP

Scheme 3.

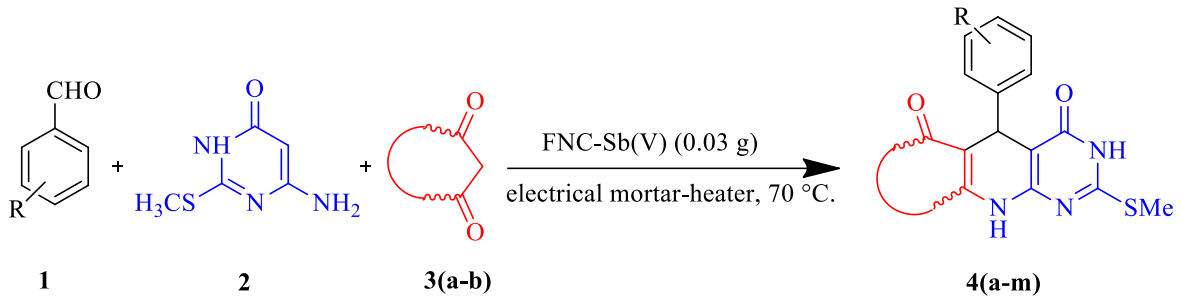
Table 1. The reaction of AMP (1 mmol), dimedone (1 mmol) and 4-chlorobenzaldehyde (1 mmol) under various conditions.



Entry	solvent	Catalyst (g)[a]	condition	Time (min)	Yield (%)[b]
1	H_2O	0.03	reflux	18	73
2	C_2H_5OH	0.03	reflux	12	80
3	CH_3OH	0.03	reflux	20	69
4	CH_3CN	0.03	reflux	20	72
5	C_2H_5OH	-	r.t.[c]	30	25
6	-	0.03	90 °C [d]	6	93
7	-	0.03	80 °C [d]	6	98
8	**-**	**0.03**	**70 °C [d]**	**6**	**98**
9	-	0.03	60 °C [d]	6	82
10	-	0.03	50 °C [d]	6	75
11	-	0.02	70 °C[d]	6	94
12	-	0.04	70 °C [d]	6	98
13	-	-	70 °C [d]	50	47

[a] FNC-Sb(V), [b] Isolated yield, [c] Room temperature, [d] Electrical mortar-heater

Table 2. Synthesis of PQ and IPP derivatives **(4a-m)** in the presence of FNC-Sb(V) under solvent-free condition at 70 °C in electrical mortar-heater.



1 **2** **3(a-b)** **4(a-m)**

Entry	R	3	Product	Time (min)	Yield (%)	M.P. °C [Ref.]
		a or b				Found
1	4-Cl-	a	4a	6	98	>300[17]
2	4-NO_2-	a	4b	4	98	>300[27]
3	H-	a	4c	6	94	>300[27]
4	2,4-$(OMe)_2$-	a	4d	6	95	>300[27]
5	3-NO_2-	a	4e	5	98	>300[27]
6	2,4-$(Cl)_2$-	a	4f	4	92	>300[27]
7	4-OMe-	a	4g	5	92	>300[17]
8	3,4-$(OH)_2$-	a	4h	5	95	>300[27]
9	4-OMe-	b	4i	6	90	>300[27]
10	4-Cl-	b	4j	7	98	>300[27]
11	2,4-$(Cl)_2$-	b	4k	5	92	>300[27]
12	4-Me-	b	4l	6	80	>300[27]
13	4-OH-3-OMe-	b	4m	6	89	>300[27]

[a]dimidone [b]1,3-indanedione

Table 3. Comparison catalytic performances of FNC-Sb(V) versus some other catalysts for the synthesis of PQ

Entry	solvent	catalyst	Tem. (°C)	Time (min)	Yield(%)[d]	[Ref.]
1	H_2O:EtOH	SBA-Pr-SO_3H [a]	90	60	85	[28]
2	H_2O	$InCl_3$	90	60	91	[15]
3	H_2O	P-TSA [b]	90	150	89	[13]
4	H_2O	Fe_3O_4@Cellulose-SO_3H	80	20	90	[29]
5	H_2O	Fe_3O_4@SiO_2-SO_3H	70	25	92	[17]
6	H_2O	[Bmim]Br[c]	95	210	90	[30]
7	-	Fe_3O_4@NCs[e]	70	24	51	-
8	-	FNC-Sb(V)	**70** [f]	**6**	**98**	**[This work]**

[a]Sulfonic acid functionalized SBA-15, [b]*p*-Toluenesulfonic acid (PTSA), [c] Ionic liquid 1-*n*-butyl-3-methylimidazolium bromide, [d]Isolated yield, [e]Fe_3O_4@Nano-cellulose, [f] By Electrical Mortar-Heater

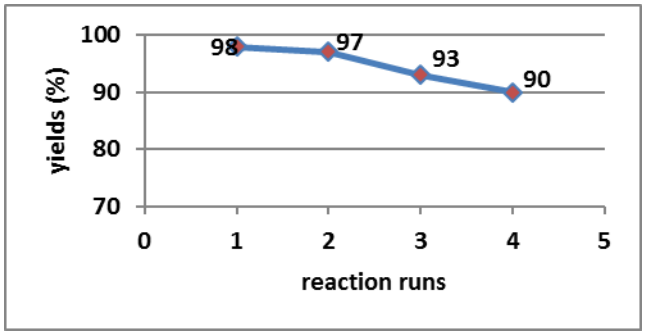


Figure 1.