Iranian Journal of Catalysis 9(4), 2019, 321-328

IRANIAN JOURNAL OF CATALYSIS

Nano-BF_3/cellulose as a biodegradable novel catalyst for synthesis of highly functionalized tetrahydropyridines

Seyede Azita Fazeli-Attar, Bi Bi Fatemeh Mirjalili*

Department of Chemistry, College of Science, Yazd University, Yazd, P.O. Box. 89195-741, I. R. Iran.

Received 2 March 2018; received in revised form 14 September 2018; accepted 5 October 2018

ABSTRACT

Nano-cellulose with high amount of free OH groups could be used as supporting agents for boron trifluoride (BF_3). Nano-BF_3/cellulose is a solid acid and a biodegradable catalyst which was prepared via reaction of nano-cellulose and BF_3. The structure of this catalyst was studied by FT-IR, FESEM, TEM, XRD, EDS, TGA, XRF and BET. In this research, the synthesis of highly functionalized tetrahydropyridines has been developed via a five-component reaction of aldehyde, amine and ethyl acetoacetate using nano-BF_3/cellulose under solvent-free conditions. The structures of obtained products were identified by FTIR, ^{1}H NMR and ^{13}C NMR. Some advantages of this protocol are high to good yields, environmentally benign procedure, easy work-up of reaction and moderate reusability of the catalyst.

***Keywords**: Multicomponent reactions, Tetrahydropyridines, Nano-BF_3/cellulose, Solid acid.*

1. Introduction

Heterocycles are often found in bioactive molecules or drugs [1], so the synthesis of these compounds with high-yield is preferred. Multicomponent reactions (MCRs) are convergent reactions in which three or more components react to form a single product and they are often valuable synthetic methods for preparing these complex structures. MCRs have been considered more and more in recent years because of advantages over conventional linear syntheses, including environmentally friendly activities, lower costs, shorter reaction times, and high degrees of atom economy [2-5]. The synthesis of highly functionalized piperidines is a good example for application of MCRs.

Tetrahydropyridines (THPs) have been the subject of considerable synthetic efforts because of their potent pharmacological properties including antimalarial [6], and anticancer effects [7]. Droperidol [8], tazomeline [9] and GTS-21 [10] are known as THPs which have been used as drugs in the treatment of Alzheimer disease [11] (Fig. 1).

*Corresponding author.
E-mail address: fmirjalili@yazd.ac.ir (B.B.F. Mirjalili)

Recently, these compounds have been synthesized via reaction of *p*-substituted anilines, *p*-substituted aldehydes and alkyl acetoacetate by different catalysts including BDMS [12], L-proline/TFA [6], TBATB [13], I_2 [14], CAN [15], $ZrOCl_2.8H_2O$ [16], $ZrCl_4$ [7],

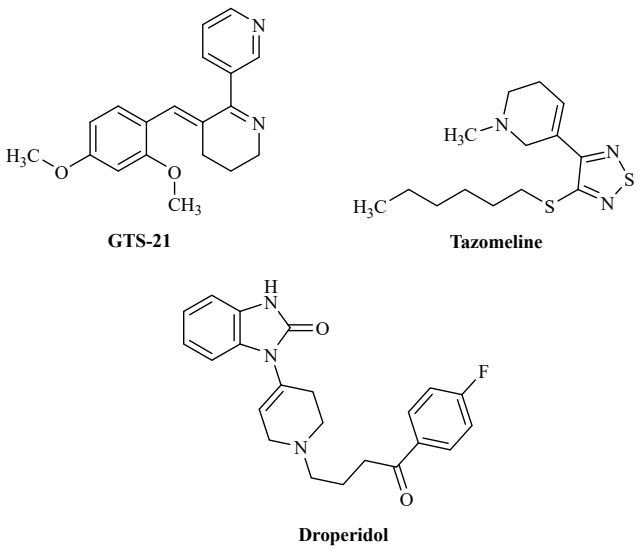


Fig. 1. Effective chemical structures in the treatment of Alzheimer disease.

p-TsOH·H_2O [17], $Fe(NO_3)_3.9H_2O$ [18], $FeCl_3/SiO_2$ [19], HOAc [20], $BF_3.SiO_2$ [21], amberlite IRA400-Cl resin/I_2/KI [22], $NiFe_2O_4@SiO_2$ [23], L-Proline nitrate [24], nano-silica sulfuric acid [25], Zn NPs [26], $TiCl_2.2H_2O$ [27] and chloroacetic acid [28].

Nowadays, chemists prefer to use natural catalysts [29] which can be decomposed in the environment. Cellulose as a biopolymer and biodegradable material can be used as a support in preparation of different catalysts. OH groups in cellulose have the ability to interact with Lewis acids and make solid acid catalysts to yield clean and efficient chemical reactions [30-32]. If we make this biopolymer in nano size, we will be able to increase its area and promote its characters. For this purpose, in this work cotton was chosen as a cheap and readily available source for synthesizing of nano-cellulose [33]. For removing substances (except cellulose) that are in cotton such as lignin, hemicellulose, wax and organic acids**,** it was treated with NaOH and then NaClO, respectively. Then, the obtained cellulose was treated with concentrated H_2SO_4 for partial hydrolysis of its acetal linkages to prepare nano-cellulose and increase the free OH groups. This nano-cellulose could be used as supporters for boron trifluoride (BF_3) and make a new, biodegradable, inexpensive and eco-friendly bio-catalyst. Therefore, nano-BF_3/cellulose was applied to synthesize alkyl-1-aryl-4-(arylamino)-2,6-di-aryl-1,2,5,6-tetrahydropyridine-3-carboxylates.

2. Experimental

2.1. General

All compounds were purchased from Merck, Aldrich and Fluka chemical companies and used without any additional purification. A refrigerated centrifuge (Appendorf Centrifuge 5417R) was used for preparation of nano-cellulose. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the ^1H NMR and ^{13}C NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. Powder X-ray diffraction (XRD) pattern was obtained by a Philips Xpert MPD diffractometer equipped with a Cu Ka anode (k = 1.54 Å) in the 2θ range from 10 to 80°. Field emission scanning electron microscopy (FESEM) was obtained on a Mira 3-XMU. Elemental analysis was done by Costech ECS 4010 CHNS-O analyzer. XRF analysis was done with BRUKER, S4 EXPLORER instrument and the thermal gravimetric analysis (TGA) was performed with "STA 504" instrument. Quantitative elemental information (EDS) of nano-BF_3/cellulose was measured by the EDS instrument, Phenom pro X.

2.2. Preparation of nano-cellulose from cotton

Cotton fibers were washed with distilled water several times and dried in an air-circulated oven at 100±2 °C until obtaining the constant weight. Then they were chopped to an approximate length of 5-10 mm. The fibers were then treated with a 17.5 w/v NaOH solution at 100 °C for 12 hours under mechanical stirring. This treatment allowed purifying of cellulose by removing other constituents such as lignin, hemicellulose, wax, organic acids and so on in the fibers. Subsequently, fibers were filtered and washed with distilled water until the alkali was completely eliminated. It was then bleached with 100 ml of 1:1 aqueous dilution of 3.5% w/v sodium hypochlorite at 80 °C for 3 hours under mechanical stirring. The resulting alpha cellulose was hydrolyzed partially using 65% sulfuric acid aqueous solution with a cotton-to-acid weight ratio of 1–10 at 45 °C. After 1 hour, the obtained suspension was diluted with water five-fold to stop the hydrolysis reaction. The suspension was centrifuged at 12,000 rpm to separate the nano-cellulose from acid solution. The washing with water and centrifuging was repeated four to five times to remove any remaining free acid. The yield of obtained nano-cellulose is 65% [33].

2.3. Preparation of nano-BF_3/cellulose

In a well-ventilated system, BF_3 (4 mL) was added drop wise to the mixture of nano-cellulose (1.6 g) in chloroform (10 mL). The mixture was stirred for one hour at room temperature. The resulted suspension was filtered, washed with chloroform and dried at room temperature.

2.4. General procedure for the synthesis of highly functionalized THPs.

A mixture of para-substituted anilines (2 mmol) and ethyl acetoacetate (1 mmol) was stirred at 85 °C for 30 min in the presence of nano-BF_3/cellulose (0.03 g). Then, the para-substituted benzaldehydes (2 mmol) was added and the heating was continued. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was dissolved in hot ethanol and filtered off for separation of catalyst. By adding water and sodium carbonate to filtrate, the product was appeared as a solid. For more purification of product, solid was recrystallized by ethanol.

3. Results and Discussion

For synthesis of nano-BF_3/cellulose as a new catalyst, $BF_3.OEt_2$ was added drop wise to an appropriate amount of nano-cellulose in chloroform as a solvent at room temperature.

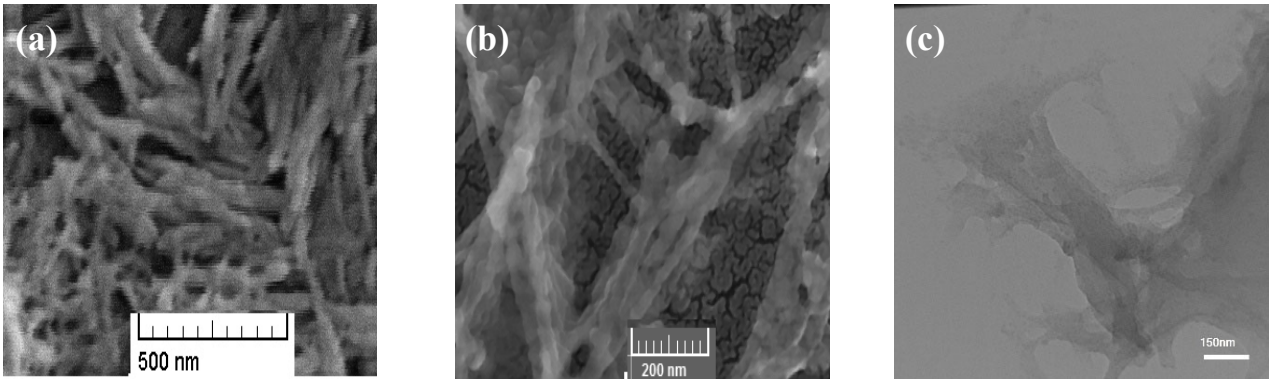


Fig. 2. FESEM image of (a) nano-cellulose and (b) nano-BF_3/cellulose, (c) TEM of nano-BF_3/cellulose.

After a while, the obtained solid was filtered and washed with chloroform for removal of any unreacted BF_3. In order to investigate the particle size and morphology of nano-cellulose and nano-BF_3/cellulose, FESEM and TEM images of their nanoparticles are presented in Fig. 2. These results showed that the dimension of catalyst was achieved below 25 nm.

The FT-IR spectra of $BF_3.OEt_2$, nano-cellulose and nano-BF_3/cellulose are compared in Fig. 3. In FT-IR spectrum of nano-BF_3/cellulose, the absorption band at 1315 cm^{-1} is assigned to the B-O stretching band.

Moreover, the X-ray diffraction (XRD) pattern of the BF_3/nano-cellulose nanoparticles was shown in Fig. 4. The values of 2θ and FWHM are shown in Table 1. According to XRD pattern, the three signals at 2θ = 14.97, 16.74 and 22.83, have FWHM = 1.1021, 0.3149, and 1.0234, respectively. The existence of cellulose and the signal in 2θ = 20.38 prove the bonding of B to the cellulose backbone. The particle size of catalyst calculated by Debye-Sherrer equation is 73 nm (2θ =14.97, FWHM=1.1021).

Existence of C, O and F in catalyst was proved by EDS analysis data (Fig. 5), because Boron (B) is not detectable by EDS. Therefore, the XRF analysis of nano-BF_3/cellulose was performed to determine its elemental component.

The XRF analysis of catalyst was done by comparison of its Kilo Counts per second (KCPS) with pure samples. In our catalyst, nano-BF_3/cellulose, the percentage of elements B and F were determined via the comparison of pure NaF and H_3BO_3 with KCPS as can be seen in table 1. The number of moles of B and F is equal to 0.12 mol and 0.02 mol, respectively, so, the ratio of B: F is 6:1.

The thermal gravimetric analysis (TG-DTA) pattern of BF_3/nano-cellulose was detected by heating from 50 °C to 800 °C (Fig. 6). This curve indicates three weight loss steps.

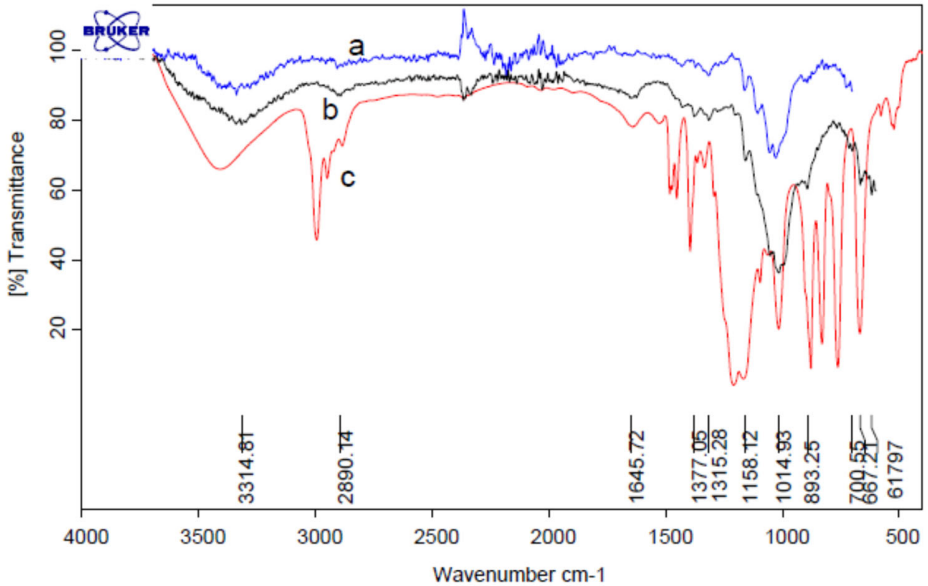


Fig. 3. FT-IR spectra of (a) nano-cellulose, (b) nano-BF_3/cellulose and (c) $BF_3.OEt_2$.

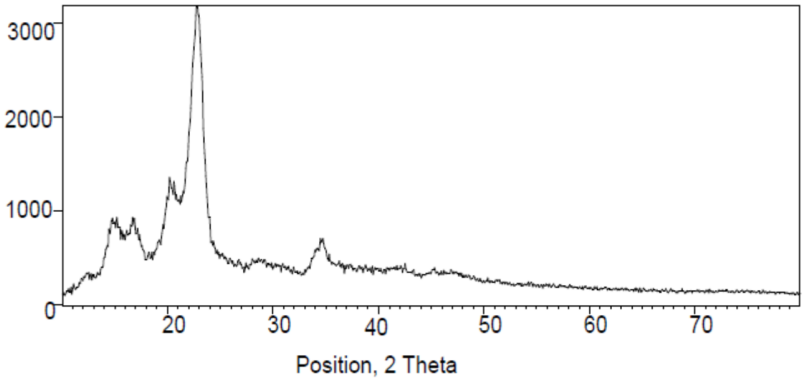


Fig. 4. XRD pattern of nano-BF_3/cellulose.

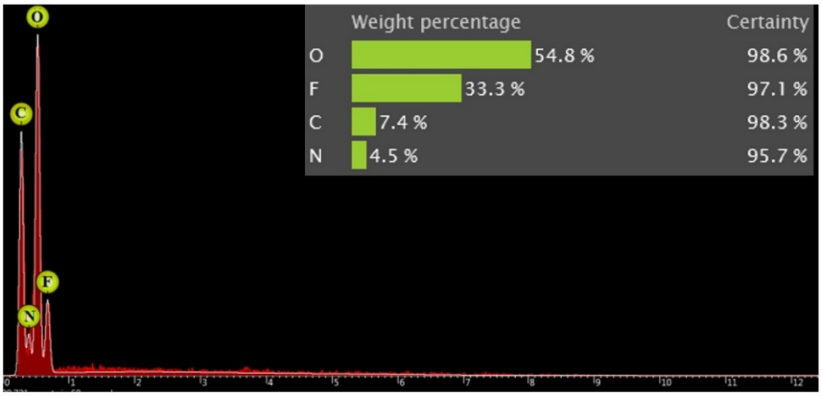


Fig. 5. EDS spectra of nano-BF_3/cellulose.

Table 1. XRF analysis of nano-BF_3/cellulose.

Sample	H_3BO_3	NaF	Catalyst	
KCPS	2.5	40.7	0.2	0.4
Amount of element (%)	17.74(B)	45(F)	1.42(B)	0.45(F)

First, there is a small weight loss (3.8%) in the temperatures from 50 to 100 °C, this is related to removal of the moisture of the catalyst. The next stage of weight loss (15.6 %) occurred in the temperature range 156–183°C. The main weight loss (23%) is observed in the range of 200–380 °C due to the decomposition of cellulose. The char yield of the catalyst in 814 °C is 27.4 % of original weight.

The specific surface area of catalyst was measured by BET theory. Single point surface area at $P/P_0 = 0.018778107$ is 0.0495 m^2/g and the BET surface area is 0.0268 m^2/g. The N_2 adsorption isotherm of catalyst at 77 K is depicted in Fig. 7.

According to the above-mentioned data, the proposed structure for BF_3/nano-cellulose has been showed in Fig. 8.

In this study, we decided to test nano-BF_3/cellulose as a novel catalyst for synthesis of highly functionalized tetrahydropyridines because of easy preparation, storing and using of this catalyst.

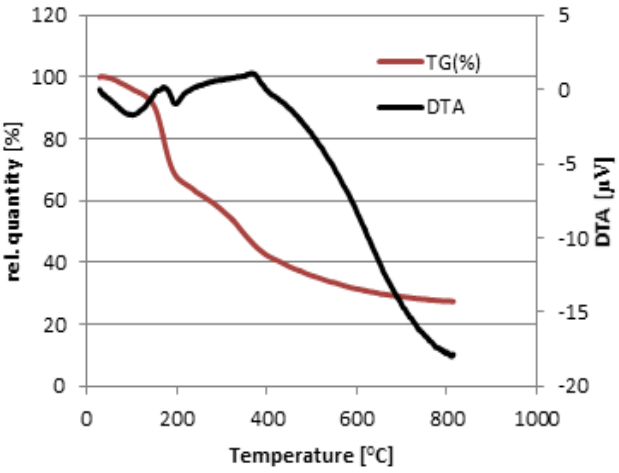


Fig. 6. Thermal gravimetric analysis (TG-DTG) pattern of nano-BF_3/cellulose.

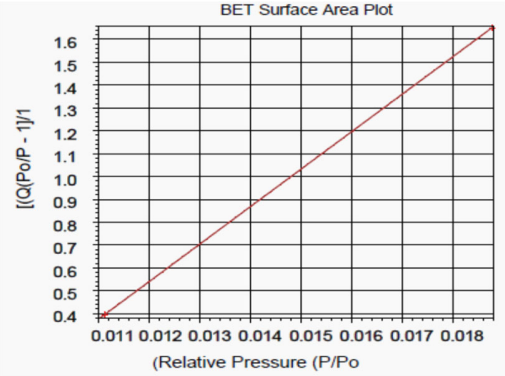


Fig. 7. N_2 adsorption isotherm on nano-BF_3/cellulose.

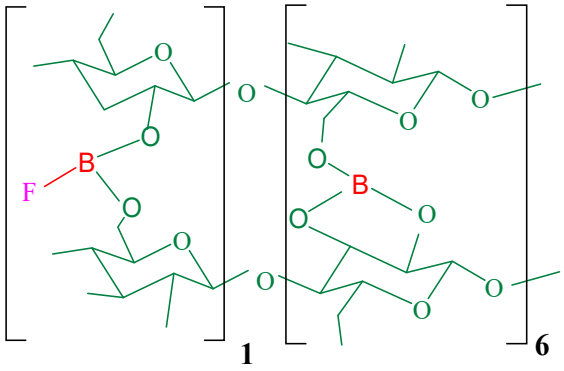
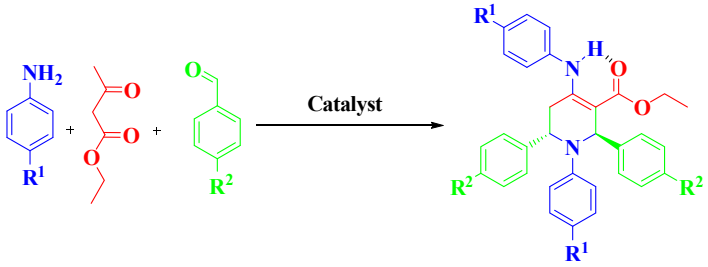


Fig. 8. Proposed structure of nano-BF_3/cellulose.

Table 2. Optimization of reaction conditions for the synthesis of highly substituted tetrahydropyridines.[a]



Entry	Catalyst	Solvent, Condition	Time(h)/ Yield (%)[b]	Ref.
1	nano-BF_3/cellulose (0.05 g)	S. F., 85 ºC	4/64	-
2	nano-BF_3/cellulose (0.05 g)	C_2H_5OH, R.T.	4/30	-
3	nano-BF_3/cellulose (0.05 g)	C_2H_5OH, 60 °C	4/25	-
4	nano-BF_3/cellulose (0.05 g)	C_2H_5OH, Reflux	4/27	-
5	nano-BF_3/cellulose (0.05 g)	H_2O, Reflux	4/5	-
6	nano-BF_3/cellulose (0.05 g)	C_2H_5OH/H_2O(1:1), Reflux	4/5	-
7	nano-BF_3/cellulose (0.05 g)	n-Hexane, Reflux	4/10	-
8	nano-BF_3/cellulose (0.02 g)	S. F., 85 °C	4/42	-
9	nano-BF_3/cellulose (0.03 g)	S. F., 85 °C	4/82	-
10	nano-BF_3/cellulose (0.04 g)	S. F., 85 °C	4/65	-
11	nano-BF_3/cellulose (0.03 g), 2nd run	S. F., 85 °C	4/75	-
12	nano-BF_3/cellulose (0.03 g), 3rd run	S. F., 85 °C	4/75	-
13	nano-BF_3/cellulose (0.03 g), 4th run	S. F., 85 °C	4/73	-
14	nano-BF_3/cellulose (0.03 g), 5th run	S. F., 85 °C	4/70	-
15	*p*-TsOH·H_2O (0.11 g)	EtOH, R.T.	12/88	[17]
16	$BF_3.SiO_2$ (15 mol %)[c]	MeOH, 65 °C	8/71	[21]
17	I_2/KI/AER-400 Cl(1.2 mmol)[d]	MeOH, R.T.	18/72	[22]
18	L-proline nitrate (10 mol %)	MeOH, R.T.	13/63	[24]
19	$TiCl_2.2H_2O$ (15 mol %)	EtOH, R.T.	3.5/89	[27]

[a]The amount ratio of benzaldehyde (mmol), 4-chloroaniline (mmol), ethyl acetoacetate (mmol) are equal to 2:2:1.
[b]Isolated yield.
[c]4-Methylbenzaldehyde, aniline and ethyl acetoacetate were used.
[d]Benzaldehyde, 4-bromoaniline and ethyl acetoacetate were used.

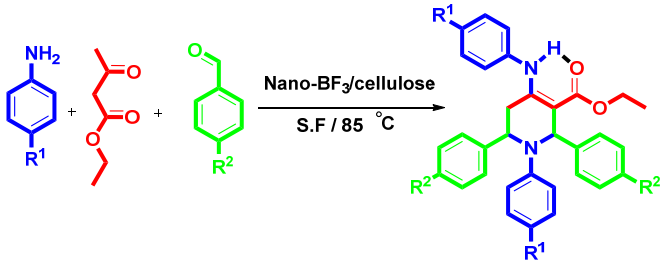
Initially, for evaluation of the catalytic activity of nano-BF_3/cellulose, the mixture of 4-chloroaniline, ethyl acetoacetate and benzaldehyde was chosen as the model reaction to synthesize tetrahydropyridine derivatives. This reaction was also chosen to optimize the amount of catalyst and the reaction condition. We have noted that 0.03 g of the catalyst is the best amount for the formation of product and solvent-free conditions were preferred rather than using different solvents because of easier work-up and more yields.

In order to investigate the reusability of the catalyst, after completion of the model reaction, the catalyst was isolated by adding ethanol to reaction mixture and then filtering. The recovered catalyst was washed with hot EtOH and then acetone, followed by drying at room temperature. It was observed that the recovered nanocatalyst could be used five times with only a slight decrease in its catalytic activity (Table 2, Entries 11 and 14). To indicate the worthiness of the present research, we compared this catalyst with some reported results (Table 2, Entries 15-19) showing nano-BF_3/cellulose is effective and environmentally friendly.

For scrutiny of this catalyst's efficiency, we have synthesized tetrahydropyridine derivatives via condensation of para-substituted anilines (2 mmol), ethyl acetoacetate (1 mmol) and para-substituted benzaldehydes (2 mmol) in the presence of BF_3/nano-celluose (0.03 g) under solvent-free conditions at 85°C (Table 3). All compounds were identified by physical and spectroscopic data.

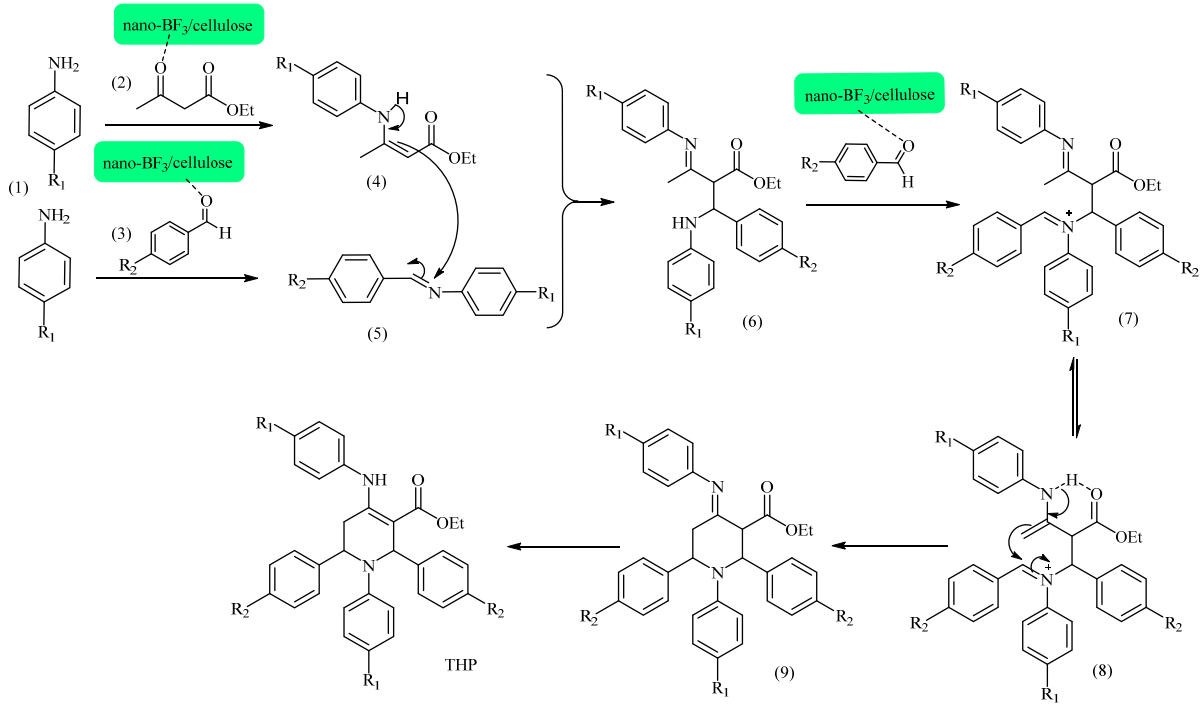
A mechanism for this multi component reaction is proposed in scheme 2. BF_3 in BF_3/nano-cellulose activates the C=O group in β-ketoester and aldehyde to promote the β-enaminone (4) or imine (5) formation. The intermolecular Mannich addition of the β-enaminone (4) to the imine (5) affords the intermediate (6). Subsequently, the reaction of activated aldehyde with the intermediate (6) proceeds to afford the intermediate (7) by the elimination of H_2O. Then, tautomerization of (7) generates intermediate (8), which immediately undergoes intramolecular Mannich-type reaction to give intermediate (9). Finally, the intermediate (9) tautomerizes to generate the desired THP derivative containing the conjugated ester group which attached to NH with hydrogen bonding.

Table 3. Synthesis of tetrahydropyridine derivatives in the presence of nano-BF_3/cellulose under solvent-free conditions.[a]



Entry	R^1/ R^2	Time(h)/Yield(%)[b]	m.p. (°C)	Ref.
1	H/Br	3/67	218-220	[34]
2	Me/H	5/79	193-194	[15]
3	Me/Br	3/85	215-217	[35]
4	Et/Cl	6/90	209-211	[35]
5	Cl/H	4/82	202-204	[14]
6	Cl/Cl	3.5/90	214-215	[16]
7	Br/Cl	3.5/88	193-195	[34]
8	Br/OMe	5/90	217-219	[22]
9	H/Me	3.5/81	228-230	[20]
10	H/Cl	3/70	202-204	[34]
11	Et/H	7/80	187-189	[35]
12	Et/Me	6/88	176-178	[35]
13	Br/ H	3/75	200-202	[15]

[a]Para-substituted anilines (2 mmol), ethyl acetoacetate (1 mmol) and para-substituted benzaldehydes(2 mmol) in the presence of nano-BF_3/cellulose (0.03 g) was used under solvent-free conditions at 85 °C.
[b]Isolated yield.



Scheme 1. A proposed mechanism for preparation of THP.

4. Conclusions

We have developed a multicomponent synthesis of highly functionalized tetrahydropyridines that was catalyzed with a biodegradable catalyst to generate moderate to good yields. Some advantages of this protocol are easy work-up, good yields, using environmentally friendly catalyst with medium reusability.

Acknowledgments

The Research Council of Yazd University was gratefully acknowledged for the financial support for this work.

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