

One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones (Thiones) Promoted by Nano-BF₃.SiO₂

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3,4-Dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thione were synthesized under solvent free condition in the presence of nano-silica supported boron trifluoride (nano-BF₃.SiO₂). The reactions were carried out at 80 °C for 15 min under solvent free condition. This methods have some advantages such as good to excellent yield, mild reaction condition, ease of operation and workup, short reaction time and high product purity.

Keywords: Nano-BF₃.SiO₂, Biginelli reaction, Aldehyde, 3,4-Dihydropyrimidin-2(1H)-ones, 3,4-Dihydropyrimidin-2(1H)-thiones

INTRODUCTION

4-Dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones were synthesized *via* Biginelli procedure. This protocol is an acid catalyzed three component reaction between an aldehyde, β -ketoester or β -diketone and urea or thiourea. Some Biginelli products have potential pharmaceutical applications such as antiviral, antitumor, antibacterial, anti-inflammatory and antihypertensive. Meanwhile, dihydropyrimidones are calcium channel blockers, antihypertensive agents, alpha-1a-antagonists, and neuropeptide Y (NPY) antagonists [1]. The most important examples are batzelladine alkaloids, which are potent HIV group-120-CD₄ inhibitors [2]. Many catalysts such as H₃PMo₁₂O₄₀ [3], 12-tungstophosphoric acid [4], chloroacetic acid [5], CuI [6], Fe(CF₃CO₂)₃ [7], NaHSO₄.SiO₂ [8], Trichloroisocyanuric acid [9], ZrCl₄ [10], NH₂SO₃H [11], Y(NO₃)₃.6H₂O [12], have been applied in Biginelli reaction.

Organic reactions under solvent free condition are of interest from both industrial and academic viewpoints. Meanwhile, the BF₃.SiO₂ [13-14] is a bench-top catalyst which is reusable, cheap, readily available, eco-friendly, versatile and efficient for promotion of many acid catalyzed organic reactions. These catalysts do not need special precautions for preparation, handling or storage, and they can be stored at ambient temperature for months without losing their catalytic activity.

In this work, we have investigated the application of nano-BF₃.SiO₂ for synthesis of Biginelli-type compounds.

EXPERIMENTAL

General

The materials were purchased from Sigma-Aldrich and Merck and were used without any additional purification. Products were characterized by FT-IR, ¹H NMR and comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55

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spectrometer. A Bruker (DRX-500 Avanes) NMR was used to record the ^1H NMR spectra. Nano $\text{BF}_3\cdot\text{SiO}_2$ was synthesized according to literature [13]. The SEM of nano particles determined with VEGA/TESCAN scanning electron microscope.

Preparation of Nano $\text{BF}_3\cdot\text{SiO}_2$ and $\text{BF}_3\cdot\text{SiO}_2$

0.37 g of BF_3 (0.7 ml of $\text{BF}_3\cdot\text{Et}_2\text{O}$) was added dropwise to a mixture of 0.63 g of silicagel or nano-silicagel and 5 ml of chloroform. The mixture was stirred for 1 h at room temperature. The resulted suspension was filtered. The obtained solid was washed with chloroform and dried at room temperature.

Typical Procedures for Preparation of 3,4-Dihydropyrimidinones/thiones in the Presence of 37% Nano- $\text{BF}_3\cdot\text{SiO}_2$

A mixture of aldehyde (2 mmol), ethyl acetoacetate or acetylacetone (2 mmol), urea or thiourea (2.5 mmol) and 37% nano- $\text{BF}_3\cdot\text{SiO}_2$ (0.05 g) was heated with stirring at $80\text{ }^\circ\text{C}$ for 15 min. After completion of reaction, the product was dissolved to methanol and filtered to recover the catalyst. The solvent was evaporated and the crude product recrystallized from 85% ethanol.

RESULTS AND DISCUSSION

The dimensions of nanoparticles were observed with SEM. The size of commercial silica gel and synthesized nano $\text{BF}_3\cdot\text{SiO}_2$ are about 14-24 nm and 47-71 nm (Fig. 1), respectively.

For identification of the structure of $\text{BF}_3\cdot\text{SiO}_2$, we studied IR spectra of $\text{BF}_3\cdot\text{OEt}_2$, $\text{BF}_3\cdot\text{SiO}_2$, and SiO_2 (Fig. 2). In all of these spectra, OH stretching band is observed and strong intermolecular hydrogen bonding occurs in the hydroxyl groups. Therefore, the resulting O-H absorption is very broad. The moisture in BF_3 causes the presence of OH stretching bond in its infrared spectrum. Comparison of the infrared spectra of $\text{BF}_3\cdot\text{SiO}_2$ and SiO_2 show that, in both of them, the absorption bands for Si-OH and Si-O-Si are appeared in $\sim 800\text{ cm}^{-1}$ and $\sim 1100\text{ cm}^{-1}$, respectively. In BF_3/SiO_2 spectrum, the absorption of B-F band is observed in 700 and 900 cm^{-1} . In IR spectrum of $\text{BF}_3\cdot\text{SiO}_2$, the B-O, Si-OH and Si-O-Si are observed in 1520 , 800 and 1100 cm^{-1} , respectively. Comparison of the infrared spectra of different percentage of $\text{BF}_3\cdot\text{SiO}_2$ shows that with increasing of percentage of BF_3 , the intensity of B-O band in 1520 cm^{-1} is increased. Based on these results, we suggest the following structure for $\text{BF}_3\cdot\text{SiO}_2$ (Scheme 1).

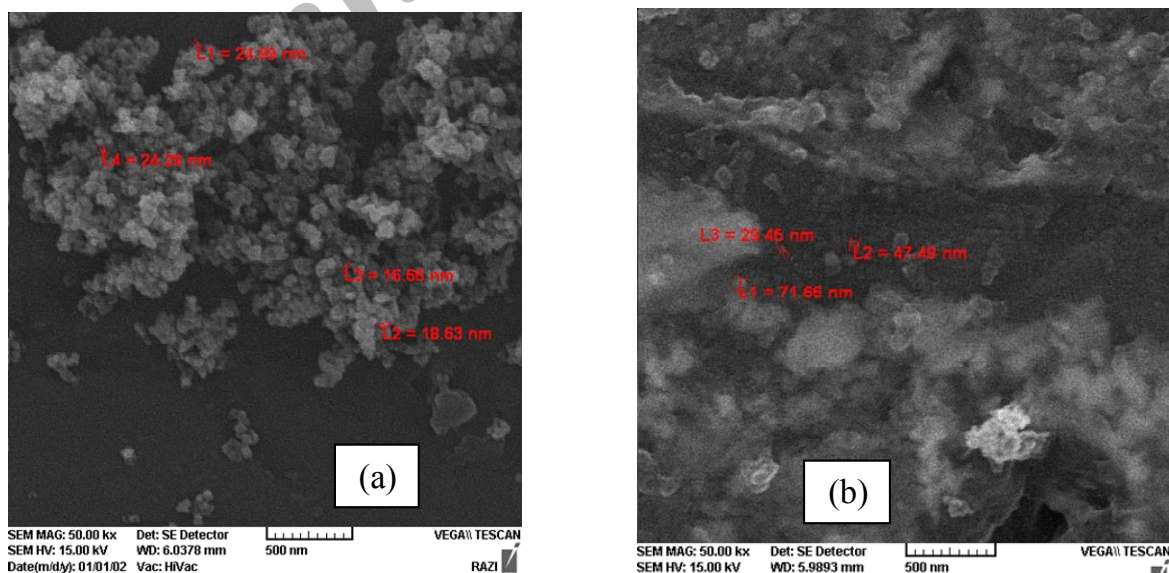


Fig. 1. SEM photograph of (a) nano- SiO_2 and (b) nano- $\text{BF}_3\cdot\text{SiO}_2$.

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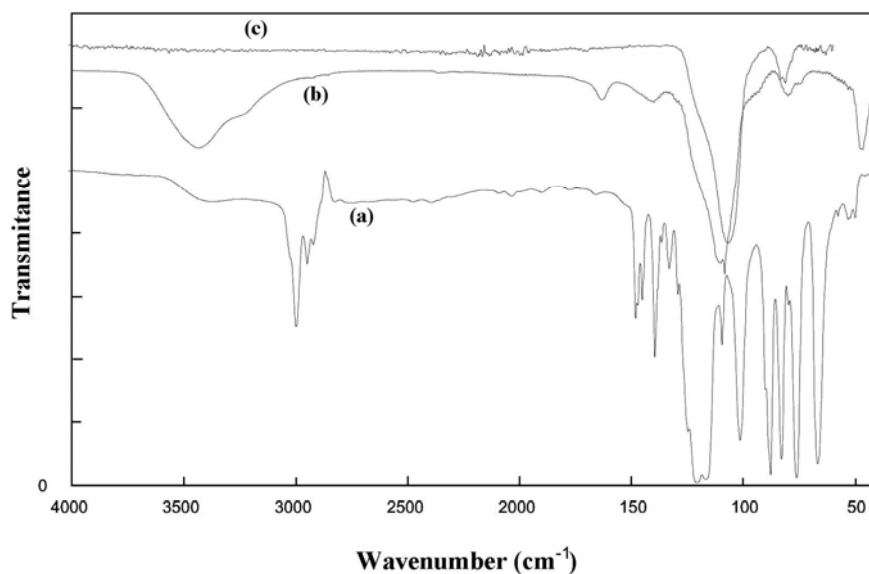
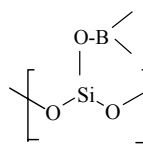
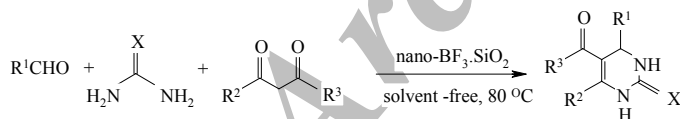


Fig. 2. FT-IR spectrum of: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, (b) $\text{BF}_3 \cdot \text{SiO}_2$, (c) SiO_2 .



Scheme 1



Scheme 2

In the next steps, we investigated the application of nano- $\text{BF}_3 \cdot \text{SiO}_2$ for synthesis of Biginelli-type compounds. The reactions were carried out in stirring at 80 °C under solvent free conditions (Scheme 2).

Initially, we examined the synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one using 4-Methylbenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2.5 mmol) and $\text{BF}_3 \cdot \text{SiO}_2$ as the catalyst under

various conditions (Table 1). We have found that the best conditions are using 37% $\text{BF}_3 \cdot \text{SiO}_2$ (0.3 g) under solvent-free conditions at 80 °C (Table 1, entry 3). We have repeated the above mentioned reaction with 37% nano- $\text{BF}_3 \cdot \text{SiO}_2$ and found that the activity of 37% nano- $\text{BF}_3 \cdot \text{SiO}_2$ is six times and 0.05 g of it is necessary. To examine the reusability of nano- $\text{BF}_3 \cdot \text{SiO}_2$ under solvent free condition, after each run, the product was dissolved to CHCl_3 and filtered. The catalyst residue was washed with acetone and reused. Treatment with acetone removes the tar from the catalyst surface more efficiently (Table 1, entries 14 and 15). The catalyst was reusable although a gradual decline was observed in its activity.

Next, the synthesis of various Biginelli type products were studied and summarized in Table 2. In all cases, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1H)-ones/thiones in moderate to good yields. In summary, we have described nano-silica supported boron trifluoride (nano- $\text{BF}_3 \cdot \text{SiO}_2$) is an efficient, eco-friendly catalyst for synthesis of Biginelli-type compounds under solvent-free conditions. Most of the products are known and were characterized by FT-IR and ^1H NMR and through comparison of their physical properties with those reported in the literature.

In conclusion, nano- $\text{BF}_3 \cdot \text{SiO}_2$ has been applied for the

Table 1. Synthesis of 5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one under Various Conditions

Entry	Catalyst (g)	Solvent	Conditions	Time (min)	Yield (%) ^a	Ref.
1	28% BF ₃ .SiO ₂ (0.3)	-	80 °C	15	52	-
2	33% BF ₃ .SiO ₂ (0.3)	-	80 °C	15	66	-
3	37% BF ₃ .SiO ₂ (0.3)	-	80 °C	15	90	-
4	45% BF ₃ .SiO ₂ (0.3)	-	80 °C	15	92	-
5	37% BF ₃ .SiO ₂ (0.3)	-	80 °C	15	67	-
6	37% BF ₃ .SiO ₂ (0.3)	-	80 °C	15	93	-
7	37% BF ₃ .SiO ₂ (0.3)	-	r.t.	15	42	-
8	37% BF ₃ .SiO ₂ (0.3)	-	Reflux	15	72	-
9	37% BF ₃ .SiO ₂ (0.3)	EtOH	r.t.	30	42	-
10	37% BF ₃ .SiO ₂ (0.3)	EtOH	Reflux	30	66	-
11	37% BF ₃ .SiO ₂ (0.3)	CHCl ₃	r.t.	30	48	-
12	45% BF ₃ .SiO ₂ (0.3)	CHCl ₃	Reflux	30	62	-
13	37% Nano-BF ₃ .SiO ₂ (0.05)	H ₂ O	60 °C	270	63	-
14	37% Nano-BF ₃ .SiO ₂ (0.3), 2 nd run	-	80 °C	15	88	-
15	37% Nano-BF ₃ .SiO ₂ (0.3), 3 rd run	-	80 °C	15	85	-
16	H ₃ PMo ₁₂ O ₄₀ (2 mol%)	HOAc	Reflux	240	75	[3]
17	12-Tungstophosphoric acid (2 mol%)	HOAc	Reflux	360	70	[4]
18	Chloroacetic acid (10 mol%)	-	90 °C	180	86	[5]
19	CuI (15 mol%)	-	90 °C	25	87	[6]
20	Fe(CF ₃ CO ₂) ₃ (5 mol%)	-	70 °C	20	95	[7]
21	NaHSO ₄ .SiO ₂ (10 mol%)	CH ₃ CN	Reflux	120	88	[8]
22	Trichloroisocyanuric acid (15 mol%)	EtOH	Reflux	720	92	[9]
23	ZrCl ₄ (10 mol%)	EtOH	Reflux	240	88	[10]
24	NH ₂ SO ₃ H (75 mol%)	EtOH	Ultrasound	40	87	[11]
25	Y(NO ₃) ₃ .6H ₂ O (5 mol%)	-	70 °C	45	80	[12]

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Table 2. Synthesis of Dihydropyrimidinones/thiones in the Presence of 37% Nano-BF₃.SiO₂

Entry	R ¹	R ²	R ³	X	Yield (%) ^a	Yield (%) ^b	M.p. (°C)	Ref.
1	2-NO ₂ -C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	92	93	216-218	[4]
2	4-NO ₂ -C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	93	92	212-213	[3]
3	4-Cl-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	91	92	213-214	[4]
4	4-MeO-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	89	88	203-204	[5]
5	3-MeO-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	87	89	220-221	[17]
6	4-Me-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	O	92	93	215-216	[3]
7	Ph	CH ₃	OCH ₂ CH ₃	O	91	90	206-207	[3]
8	2-Furyl	CH ₃	OCH ₂ CH ₃	O	86	85	201-202	[4]
9	Isopropyl	CH ₃	OCH ₂ CH ₃	O	87	88	200-201	[5]
10	C ₆ H ₄ -CH ₂ CH ₂ -	CH ₃	OCH ₂ CH ₃	O	86	85	156-157	-
11	C ₆ H ₄ -C=C-	CH ₃	OCH ₂ CH ₃	O	81	80	229-230	[6]
12	Ph	CH ₃	CH ₃	O	93	92	232-235	[7]
13	4-Cl-C ₆ H ₄	CH ₃	CH ₃	O	93	90	212-213	[16]
14	Ph	CH ₃	OCH ₂ CH ₃	S	92	91	192-194	[3]
15	4-Cl-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	S	90	92	176-177	[5]
16	2-Cl-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	S	89	90	219-221	[15]
17	4-MeO-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	S	91	93	141-143	[4]
18	4-Me-C ₆ H ₄	CH ₃	OCH ₂ CH ₃	S	92	91	191-193	[5]
19	Ph	CH ₃	CH ₃	S	94	95	214-215	[7]
20	4-Cl-C ₆ H ₄	CH ₃	CH ₃	S	93	92	208-209	[15]
21	2-Cl-C ₆ H ₄	CH ₃	CH ₃	S	94	93	173-175	[15]
22	4-MeO-C ₆ H ₄	CH ₃	CH ₃	S	88	87	161-163	[15]
23	Ph	Ph	OCH ₂ CH ₃	S	90	92	183-185	[15]
24	4-MeO-C ₆ H ₄	Ph	OCH ₂ CH ₃	S	87	88	151-152	[15]
25	2-Cl-5- NO ₂ -C ₆ H ₄	Ph	OCH ₂ CH ₃	S	90	91	238-239	[15]

^aA mixture of aldehyde (2 mmol):urea/thiourea (2.5 mmol):ethylacetoacetate (acetylacetone) (2 mmol) and 0.3 g of 37% BF₃.SiO₂ was stirred at 80 °C in solvent free condition. ^bA mixture of aldehyde (2 mmol):urea/thiourea (2.5 mmol):ethylacetoacetate (acetylacetone) (2 mmol) and 0.05g of 37% nano-BF₃.SiO₂ was stirred at 80 °C in solvent free condition.

preparation of 3,4-dihydropyrimidinones/thiones of aldehydes, ethyl acetoacetate or acetylacetone and urea or thiourea in a simple and straightforward protocol. Short reaction times, high yields, simplicity of operation, easy work-up are some advantages of this method.

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