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$SbCl_5.SiO_2$: an reusable lewis acid for one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones (thiones)

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Nano-$SbCl_5.SiO_2$ and $SbCl_5.SiO_2$ are bench-top catalysts which are reusable, readily available, 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 an ambient temperature for months without losing their catalytic activity. 4-dihydropyrimidin-2(1*H*)-ones(thiones) were synthesized in the presence of Nano-$SbCl_5.SiO_2$ or $SbCl_5.SiO_2$ as a reusable and efficient catalyst.

Keywords: $SbCl_5.SiO_2$; Biginelli reaction; aldehyde; 3,4-dihydropyrimidin-2(1*H*)-ones; 3,4 dihydropyrimidin-2(1*H*)-thiones

1. INTRODUCTION

4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidin-2(1*H*)-thiones were synthesized via Biginelli procedure. This protocol is an acid catalyzed three component reaction between 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-CD_4 inhibitors [2]. Many catalysts such as $H_3PMo_{12}O_{40}$ [3], 12-tungstophosphoric acid [4], $KAl(SO_4)_2.12H_2O.SiO_2$ [5], chloroacetic acid [6], $LaCl_3.7H_2O$ [7], KSF [8], $TaBr_5$ [9], T_3P [10], HBF_4 [11], and PPh_3 [12] have been applied in Biginelli reaction. Antimony pentachloride ($SbCl_5$), a thin, coloured and fuming liquid, is used in industry and organic synthesis. Since Antimony pentachloride is a liquid with a high specific gravity that fumes in air, it reacts with moisture to form HCl. The handling and the usability of $SbCl_5$ as a liquid form is laborious and the supported form is indeed preferable. It has been claimed that the supported $SbCl_5$ is a solid superacid. $SbCl_5$ is used extensively in organic synthesis as a Lewis acid for enhancing a variety of organic reactions such as the Friedel–Craft alkylation [13], electrophilic additions to alkenes and 1,3-dienes [14], and aromatization of enamines [15].

2. EXPERIMENTAL

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. The products were characterized by FT-IR, ^1H-NMR and by a comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-500 Avanes) NMR was used to record the ^1H NMR spectra. The SEM of nano particles was determined with a VEGA/TESCAN scanning electron microscope.

2.1. Preparation of silica-supported antimony pentachloride (50%$SbCl_5$.SiO_2)

In a beaker, to a mixture of 3 g of silica gel and 20 ml dichloromethane, 1.28 ml of $SbCl_5$ was added and stirred for 30 minutes. Then, the obtained suspension was filtered, washed with chloroform, and dried at room temperature.

2.2. Typical procedures for preparation of 3,4-dihydropyrimidinones/thiones in the presence of 50% nano- $SbCl_5$.SiO_2

A mixture of aldehyde (2 mmol), ethyl acetoacetate or acetylacetone (2 mmol), urea or thiourea (2 mmol), and 50% nano-$SbCl_5$.SiO_2 (0.04 g) was heated with stirring at 100 °C for 2-8 hours. After the completion of the reaction, the product was dissolved to chloroform and filtered to recover the catalyst. The solvent was evaporated and the crude product re-crystallized from ethanol.

3. RESULTS AND DISCUSSION

$SbCl_5$.SiO_2 and nano-$SbCl_5$.SiO_2 are bench-top catalysts which are reusable, readily available, 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 an ambient temperature for months without losing their catalytic activity.

For identification of the structure of $SbCl_5$.SiO_2, we studied the FT-IR spectra of $SbCl_5$, $SbCl_5$.SiO_2 and SiO_2 (Figure 1). In all of the spectra, an 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 $SbCl_5$ causes the presence of OH stretching bond in its infrared spectra. The infrared spectra of $SbCl_5$.SiO_2 and SiO_2 are similar. In both of them, the absorbtion band of Si-OH and Si-O-Si are appeared in ~800 cm^{-1} and ~1065 cm^{-1} respectively. In $SbCl_5$ spectrum, the absorbtion of Sb-Cl is observed in 1567 cm^{-1}. In the IR spectrum of $SbCl_5$.SiO_2, the Sb-Cl, Sb-O, Si-OH and Si-O-Si are observed in 1567, 560, 3340 and 1065 cm^{-1}, respectively [16-17]. Based on these results, we suggest the following structure for $SbCl_5$.SiO_2 (Scheme 1).

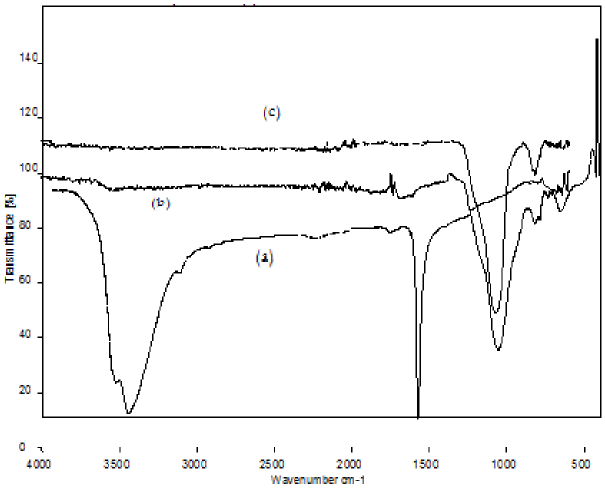
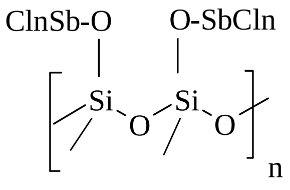


Fig. 1. FT-IR (ATR) spectrum of (a) $SbCl_5$, (b) $SbCl_5$.SiO_2 and (c) SiO_2.



Scheme 1

The dimensions of nanoparticles were observed with SEM. The articles sizes synthesized nano $SbCl_5.SiO_2$ are about 26-46 nm (figure 2).

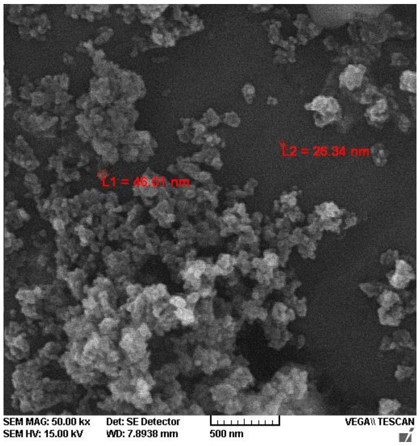
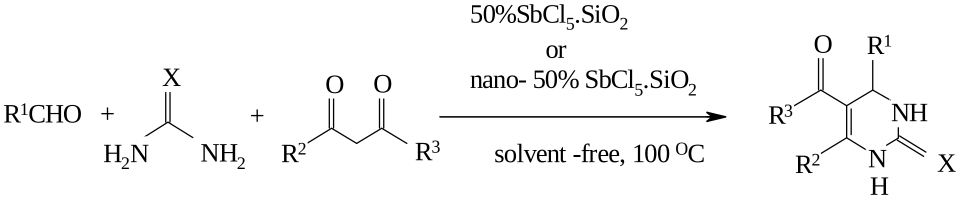


Fig. 2. SEM photograph of nano- $SbCl_5.SiO_2$.

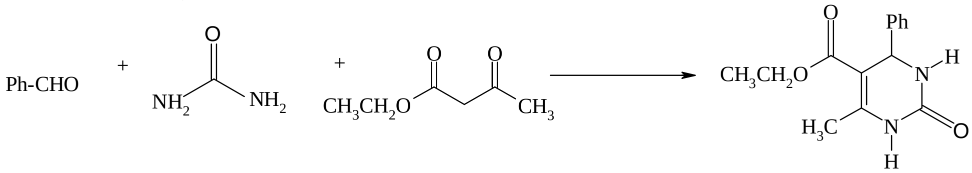
In this work, we have investigated the application of $SbCl_5.SiO_2$ and nano-$SbCl_5.SiO_2$ for synthesis of Biginelli-type compounds. The reaction was carried out in stirring at 100 °C under solvent-free conditions for 2-8 h. (Scheme 2).



Scheme 2.

Initially, we examined the synthesis of 5-ethoxycarbonyl-6-methyl-4-(phenyl)-3-4-dihydropyrimidin-2(1*H*)-one using benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1 mmol) and 50% $SbCl_5.SiO_2$ as the catalyst under various conditions (Table 1). We have found that the best conditions are using 50% $SbCl_5.SiO_2$ (0.02 g), or 50% Nano-$SbCl_5.SiO_2$ (0.007 g) under solvent-free conditions at 100 °C (Table 1, entries 5, 19). We repeated the above mentioned reaction with 50% nano-$SbCl_5.SiO_2$ and found that the activity of 50% nano-$SbCl_5.SiO_2$ is three times of its bulk form and 0.007 g of it is necessary. To examine the reusability of nano-$SbCl_5.SiO_2$ in solvent-free conditions, after each run, the product was dissolved to $CHCl_3$ and filtered. The catalyst residue was washed with hot chloroform (tree times), dried in an oven at 120 °C for 2 hours and reused. Treatment with hot chloroform removes the tar from the catalyst surface more efficiently (Table 1, entries 15-17). The catalyst was reusable although a gradual decline was observed in its activity.

Table 1. synthesis of 5-ethoxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1*H*)-one under various conditions**.**



Ent.	Catal.(g)	Solv.	Cond.	Sonication Power(W)	Time (h)	Yield (%)	Ref.
1	40% $SbCl_5.SiO_2$ (0.02)	S-F	100 °C	-	5:30	70	-
2	50% $SbCl_5.SiO_2$ (0.02)	S-F	100 °C	-	5	95	-
3	60% $SbCl_5.SiO_2$ (0.02)	S-F	100 °C	-	4:30	95	-
4	50% $SbCl_5.SiO_2$ (0.01)	S-F	100 °C	-	7:30	30	-
5	50% $SbCl_5.SiO_2$ (0.02)	S-F	100 °C	-	5	95	-
6	50% $SbCl_5.SiO_2$ (0.03)	S-F	100 °C	-	4:30	96	-
7	50% $SbCl_5.SiO_2$ (0.02)	n-Hexane	r.t	-	4	25	-
8	50% $SbCl_5.SiO_2$ (0.02)	$CHCl_3$	r.t	-	4	27	-
9	50% $SbCl_5.SiO_2$ (0.02)	Ethanol	r.t	-	4	25	-
10	50% $SbCl_5.SiO_2$ (0.02)	Water	Reflux	-	2	45	-
11	50% $SbCl_5.SiO_2$ (0.02)	S-F	60°C	-	6	70	-
12	50% $SbCl_5.SiO_2$ (0.02)	S-F	90°C	-	5:30	80	-
13	50% $SbCl_5.SiO_2$ (0.02)	S-F	120°C	-	4:40	96	-
14	50% $SbCl_5.SiO_2$ (0.02)	Water	M.W	-	5min	20	-
15	50% $SbCl_5.SiO_2$ (0.02), 2nd run	S-F	100 °C	-	5	95	-
16	50% $SbCl_5.SiO_2$ (0.02), 3rd run	S-F	100 °C	-	5	92	-
17	50% $SbCl_5.SiO_2$ (0.02), 4th run	S-F	100 °C	-	5	90	-
18	Nano 50% $SbCl_5.SiO_2$ (0.02)	S-F	100 °C	-	5	96	-
19	Nano 50% $SbCl_5.SiO_2$ (0.007)	S-F	100 °C	-	5	95	-
20	Nano 50% $SbCl_5.SiO_2$ (0.003)	S-F	100 °C	-	5	75	-
21	12-Molybdophosphoric acid	AcOH	Reflux	-	5	80	3
22	12-Tungstophosphoric acid	AcOH	Reflux	-	6-7	75	4
23	$KAl(SO_4)_2.12H_2O.SiO_2$	S-F	80°C	-	4	92	5
24	chloroacetic acid	S-F	90°C	-	3	92	6
25	$LaCl_3.7H_2O$	Ethanol	Reflux	-	5	95	7
26	KSF	S-F	130°C	-	48	82	8
27	$TaBr_5$	S-F	75°C	-	40min	97	9
28	T_3P	Ethyl acetate	Reflux	-	6	77	10
29	HBF_4	S-F	45°C	-	35min	95	11
30	PPh_3	S-F	100°C	-	10	70	12

[a] Benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.2 mmol) were applied.

Next, the synthesis of various Biginelli type products was studied and summarized in Table 2. In all the cases, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones in moderate to good yields. In summary, we have described nano-silica supported antimony pentachloride (nano-$SbCl_5.SiO_2$) as an efficient, eco-friendly catalyst for the synthesis of Biginelli-type compounds under solvent-free conditions. Most of the products were known and characterized by FT-IR and ^{1}H-NMR and through a comparison of their physical properties with those reported in the literature.

Table 2. Synthesis of dihydropyrimidinones/thiones in the presence of 50% nano-$SbCl_5.SiO_2$.

Entry	R	R^1	R^2	X	Time (h)/ Yield (%)	m.p. (°C)	
						Found	Reported^{lit}
1	C_6H_5	OEt	Me	O	5/95	203-204	205-206[3]
2	4-MeO-C_6H_4	OEt	Me	O	3/80	197-198	198-200[3]
3	4-$(Me)_2N$-C_6H_4	OEt	Me	O	2/95	255-257	256-258[11]
4	2-NO_2-C_6H_4	OEt	Me	O	7/90	218-220	220[18]
5	4-Me-C_6H_4	OEt	Me	O	4/91	211-213	214-216[4]
6	C_6H_5-CH=CH	OEt	Me	O	5/88	222-224	225-227[11]
7	4-NO_2-C_6H_4	OEt	Me	O	2/90	205-207	206-208[4]
8	3-MeO-C_6H_4	OEt	Me	O	5/80	201-203	207-208[18]
9	4-Cl-C_6H_4	OEt	Me	O	5/84	214-216	209-211[5]
10	C_6H_5	OEt	Ph	S	6/84	188-190	192[19]
11	C_6H_5	Me	Me	S	6/81	183-185	185[11]
12	4-MeO-C_6H_4	Me	Me	S	7/80	178-180	183-184[20]
13	4-Cl-C_6H_4	Me	Me	S	6/89	205-207	189-191[21]
14	4-Me-C_6H_4	OEt	Me	S	7/87	191-193	192-194[22]
15	4-$(Me)_2N$-C_6H_4	OEt	Me	S	2/95	207-208	209-210[23]

[a] A mixture of aldehyde (1 mmol):urea/thiourea (1 mmol):ethylacetoacetate (acetylacetone) (1 mmol) and 0.02 g of 50% $SbCl_5.SiO_2$ was stirred at 100 °C in solvent free condition.

Nano-$SbCl_5.SiO_2$ has been applied for the preparation of 3,4-dihydropyrimidinones/thiones of aldehydes, ethyl acetoacetate or acetylacetone and urea or thiourea in a simple and straightforward protocol. Short reaction time, high yields, simplicity of operation, and easy work-up are some advantages of this method.

The biginelli products (scheme 2, X=O, R^3= CH_3CH_2O) have an α,β-unsaturated carbonyl group and two s-cis and s-trans isomeric forms. The stability of s-trans is higher than that of s-cis form. In FT-IR spectra of these products, two carbonyl signals are appeared and in their ^{1}H-NMR spectra, two overlapped signals for ethoxy and benzylic protons are observed.

4. CONCLUSION

In conclusion, we report efficient procedures for the synthesis of 4-dihydropyrimidin-2(1H)-ones (thiones) using $SbCl_5.SiO_2$ or nano-$SbCl_5.SiO_2$ as re-usable, eco-friendly and efficient heterogeneous catalysts. Some advantages of these protocols are easy work-up, improved yields, clean reaction, and low loading of catalysts.

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