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Research Note

Nano $SbCl_5.SiO_2$: An efficient and heterogeneous catalyst for synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (thione) derivatives under solvent-free conditions

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KEYWORDS
Nano $SbCl_5.SiO_2$; Heterogeneous acid catalyst; 3,4-dihydropyrimidin-2(1*H*)-ones(thiones); Solvent-free conditions.

Abstract. In this study, a green approach is reported for efficient and rapid synthesis of biologically active substituted 3,4-dihydropyrimidin-2(1*H*)-one(thione) derivatives using nano $SbCl_5.SiO_2$ as a heterogeneous catalyst under solvent-free conditions. The catalyst is characterized by FT-IR, XRD, SEM, TEM and TG-DTG analysis. Compared to the classical reactions, this method consistently has the advantages of excellent yields, simple operation, short reaction time, eco-friendly and avoidance of the use of organic solvents.

1. Introduction

Heterogeneous solid catalysts have gained much attention in recent years, as they possess a number of advantages such as cleaner reaction, easier work-up, reduced reaction time, and eco-friendliness [1,2]. These considerations are currently driving our effort to develop heterogeneous organic transformations. The solid-supported reagents have improved activity and selectivity more than the individual reagents, because the surface area of the reagent increases into a manifold area [3]. Antimony pentachloride ($SbCl_5$) – a thin, colored, and fuming liquid – is used in industry and organic synthesis. Since antimony pentachloride is a liquid with a high specific gravity, it fumes in air and reacts with moisture to form HCl, so its handling and usability in the liquid form is laborious. Thus, the supported form is indeed preferable. It has been claimed that the supported $SbCl_5$ is a solid super acid. $SbCl_5$ is used extensively in organic synthesis as a Lewis acid for enhancing a variety of organic reactions such as Friedel-Crafts alkylation [4], electrophilic additions to alkenes and 1,3-dienes [5], and aromatization of enamines [6].

During the last decade, multi-component reactions have increasingly become important in organic and medicinal chemistry as efficient and low-cost tools for combinatorial synthesis [7,8]. Biginelli has reported a multi-component reaction of ethyl acetoacetate, benzaldehyde, and urea to obtain dihydropyrimidinone. Dihydropyrimidinone and its derivatives are important classes of compounds in the field of pharmaceuticals and exhibit significant biological properties such as antiviral, antihypertensive, and antibacterial as well as anti-HIV and antitumor activities [9]. Some of them are also successfully used as calcium channel blockers and a-1α-antagonists [10-12]. In the rest of this study, different types of catalysts are reported for promotion of the Biginelli reaction which of them are Silica-Bonded S-Sulfonic Acid (SBSSA) [13], Sulfonated Car-

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bon Materials (SCM) [14], bentonite/PS-SO_3H [15], MCM-41-R-SO_3H [16], zeolites [17], $HClO_4/SiO_2$ [18], $Yb(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_3$, and $Bi(OTf)_3$ [19], different types of ionic liquids [20-22], and melamine trisulfonic acid (MTSA) [23]. Many of the existing methods involve expensive reagents, stoichiometric amount of catalyst, strongly acidic conditions, long reaction times, high temperatures, unsatisfactory yields, incompatibility with other functional groups, and environmental pollution. Therefore, it is a need for versatile, simple, and environmentally friendly processes for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones). Development of alternative methods would extend the scope of this useful Biginelli reaction. Currently, nano-size solid acid catalysts are applied in many fields of organic synthesis to shorten the reaction time, improve reaction yields, and make work-up matching easier with 'green chemistry' protocols.

In the rest of our investigation on application of solid acids in organic synthesis [24-29], we have used nano $SbCl_5.SiO_2$ for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones(thiones) by the three-component coupling of substituted arylaldehydes (1), β-ketoester (2), and urea or thiourea (3) under solvent-free conditions (Scheme 1). Using nano $SbCl_5.SiO_2$ with high surface area and uniform pore size as the heterogeneous acid catalyst may be appropriate for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones(thiones) with high yields. The effects of solvent, characterization of catalyst, amount of catalyst, catalyst type, recycling of catalyst, reaction temperature, and reaction time were investigated.

2. Results and discussion

2.1. Catalyst characterization

2.1.1. FT-IR spectrum of nano $SbCl_5.SiO_2$

To identify the structure of nano $SbCl_5.SiO_2$, we have studied IR spectra of $SbCl_5$, nano $SbCl_5.SiO_2$, and nano SiO_2. In all spectra, OH stretching bands were not observed clearly and were very broad. In comparison to Si-OH and Si-O-Si, the moisture in $SbCl_5$ caused presence of OH stretching band in its infrared spectra. Infrared spectra of nano $SbCl_5.SiO_2$ and nano SiO_2 were similar. In both of them, the absorption bands of Si-OH and Si-O-Si appeared in $\sim$ 800 cm^{-1} and $\sim$ 1065 cm^{-1}, respectively. In $SbCl_5$ spectrum, the absorption of Sb-Cl is observed in 1567 cm^{-1}. In the IR spectrum of nano $SbCl_5.SiO_2$, Si-OH,Si-O-Si, Sb-Cl, and Sb-O were observed in 3340, 1065, 1567, and 560 cm^{-1}, respectively (Figure 1) [30]. Based on these results, we have suggested the following structure for nano $SbCl_5.SiO_2$ (Scheme 2). Nano $SbCl_5.SiO_2$ can act as either a Bronsted or a Lewis acid (empty π orbital of Sb in nano $SbCl_5.SiO_2$) catalyst, as illustrated in Scheme 2.

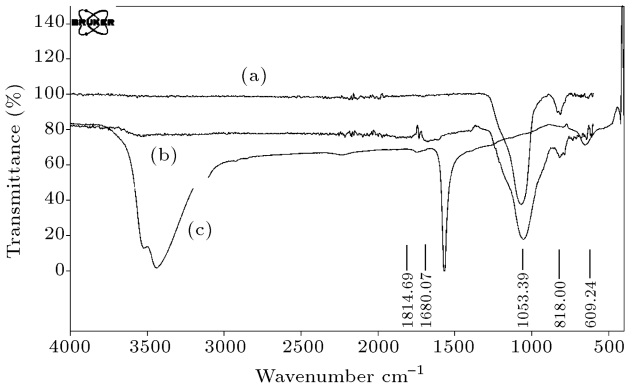
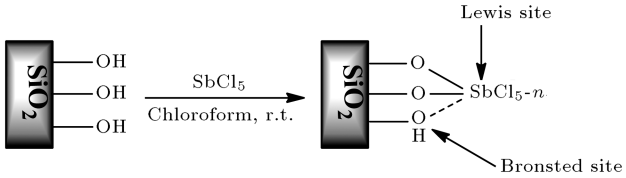


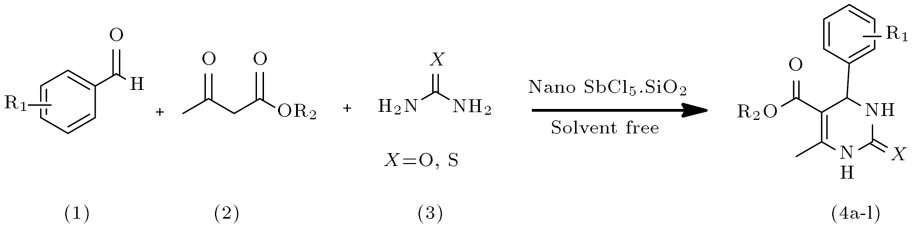
Figure 1. FT-IR spectrum of (a) $SbCl_5$, (b) nano $SbCl_5.SiO_2$, and (c) nano SiO_2.



Scheme 2. Proposed structure for nano $SbCl_5.SiO_2$.

2.1.2. Powder X-Ray Diffraction (XRD) analysis of nano $SbCl_5.SiO_2$

Nano silica gel XRD pattern displayed a broad strong peak in 2θ value of 21.8024 with Full Width at Half Maximum (FWHM) equal to 0.1771. $SbCl_5.SiO_2$ nanoparticles XRD pattern showed four main sharp peaks in 14.8408 with FWHM of 0.8266, in 19.9438 with FWHM of 1.8893, in 30.0256 with FWHM of 0.8266, and in 50.1424 with FWHM of 1.4170. In addition, there was a short broad peak in 35.4929 with FWHM of 0.1771 related to amorphous nano silica gel. The broadness of peak in Figure 2(a) verified



Scheme 1. Three-component coupling of substituted arylaldehyde (1), β-ketoester (2), and urea or thiourea (3) under solvent-free conditions using nano $SbCl_5.SiO_2$ as catalyst.

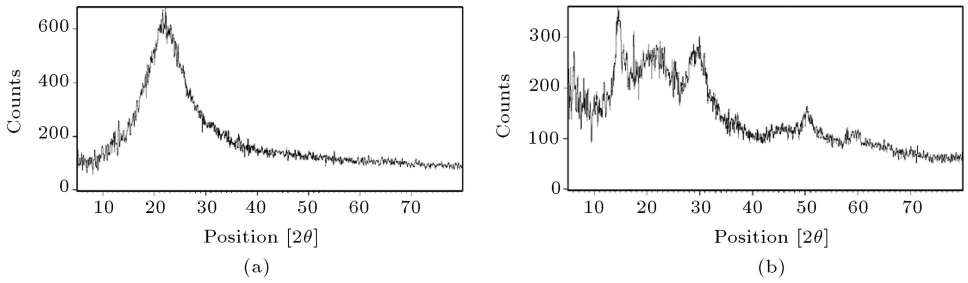


Figure 2. The XRD pattern of (a) nano SiO_2, and (b) nano $SbCl_5.SiO_2$.

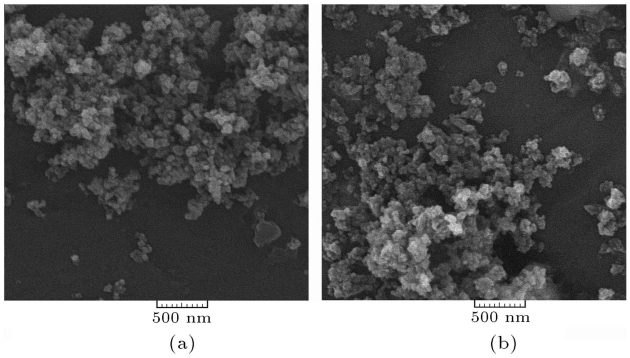


Figure 3. a) SEM image of nano SiO_2. b) SEM image of nano $SbCl_5.SiO_2$.

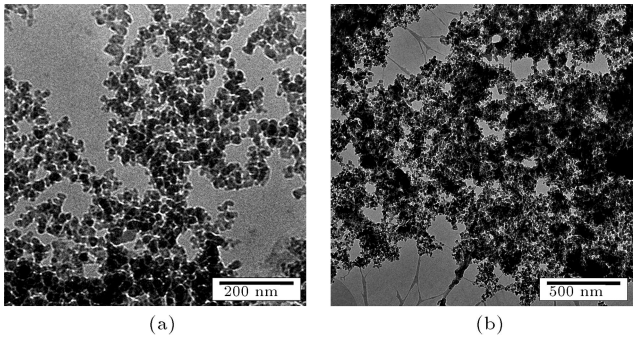


Figure 4. a) TEM image of nano SiO_2. b) TEM image of nano $SbCl_5.SiO_2$.

the amorphous nature of nano silica gel and peaks sharpness in Figure 2(b) represented the crystal-like structure of $SbCl_5.SiO_2$ nanoparticles.

2.1.3. SEM and TEM analysis of the catalyst

To obtain a visual image of the $SbCl_5.SiO_2$ nanoparticles, Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) were carried out. From SEM image, some information about the morphology of the nano catalyst was obtained as presented in Figure 3(a) and (b). From this image, it is clear that $SbCl_5.SiO_2$ nanoparticles have nano sphere like the morphology with particles of 25-50 nm dimensions and these are distributed uniformly throughout the material.

By TEM image, some information about the morphology of the nano catalyst was obtained as presented in Figure 4(a) and (b). As can be seen from the figures, the sample shows a nano crystalline structure.

2.1.4. TGA of the catalyst

Thermal Gravimetric Analyses (TGA) of the nano SiO_2 (Figure 5(a)) and nano $SbCl_5.SiO_2$ (Figure 5(b)) were performed in a temperature range between 21.68 and 511.68°C at a constant heating rate of 10°C/min under nitrogen atmosphere. By heating nano SiO_2 (Figure 4(a)) between 21.68 to 511.68°C, its weight reduction was 0.99%. The TG curve of nano $SbCl_5.SiO_2$ shows 6.8% weight loss at 131.5°C, which is due to the loss of water molecules trapped in the support matrix. The weight loss of 14.9% at a temperature of 511°C may be due to decomposition of nano $SbCl_5.SiO_2$.

2.1.5. EDX (EDS) of the catalyst

Quantitative elemental information (EDX) of nano $SbCl_5.SiO_2$ was measured by SEM/EDX instrument (Figure 6). According to this data, the weight percentage of Sb, Cl and Si are 9.6, 2.1, and 23.4, respectively.

2.2. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones in presence of nano $SbCl_5.SiO_2$ under solvent-free conditions

It is clear from Table 1 that β-ketoester, substituted arylaldehyde, and urea or thiourea are coupled together by this procedure to produce the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones. It is also clear that aromatic aldehydes, carrying either electron-withdrawing or electron-donating substituents afford high yields of products with high purity, and another important feature of this procedure is that of the survival of a variety of functional groups such as halides, nitro, hydroxyl, and ether. Acid sensitive aldehydes like 2-furaldehyde also worked well without formation of side products (Table 1, entries 11 and 12), and α, β-unsaturated aldehydes produced, a good yield of the product and there was no decomposition or polymerization under the reaction conditions. Thiourea has been used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones (Table 1, entries 8-10); these products are also of much interest with

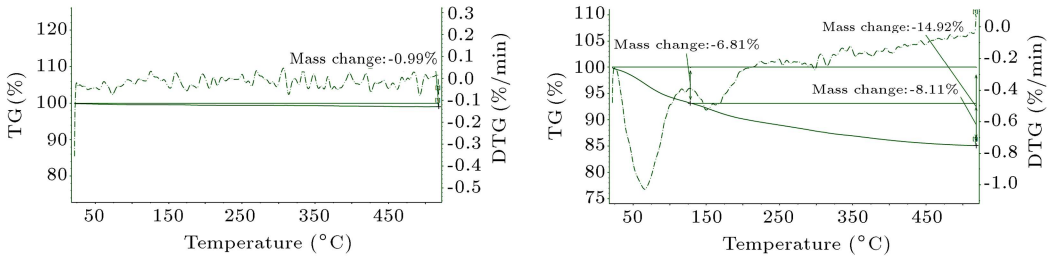


Figure 5. TGA of (a) nano SiO_2, and (b) nano $SbCl_5.SiO_2$.

Table 1. Nano $SbCl_5.SiO_2$ catalyzed synthesis of 3,4-dihydropyrimidine-2-(1H)-ones/thiones[a].

Entry	R^1	R^2	X	Product	Time (min)	Yield[b] (%)
1	H	Et	O	4a	12	95
2	4-NO_2	Et	O	4b	10	92
3	4-CH_3	Et	O	4c	20	90
4	4-Cl	Et	O	4d	20	93
5	4-OCH_3	Et	O	4e	10	94
6	4-OH	Et	O	4f	10	90
7	4-F	Et	O	4g	10	93
8	4-F	Et	S	4h	12	95
9	4-OCH_3	Et	S	4i	12	94
10	4-Cl	Et	S	4j	12	92
11	2-furyl	Et	O	4k	12	91
12	C_6H_4-CH=CH	Et	O	4l	12	90

[a]: Reaction conditions: aldehyde derivatives (5 mmol), β-ketoester (5 mmol), urea (thiourea) (7.5 mmol), and nano $SbCl_5.SiO_2$ (0.1 g) in solvent free condition at room temperature.

[b]: Isolated yields.

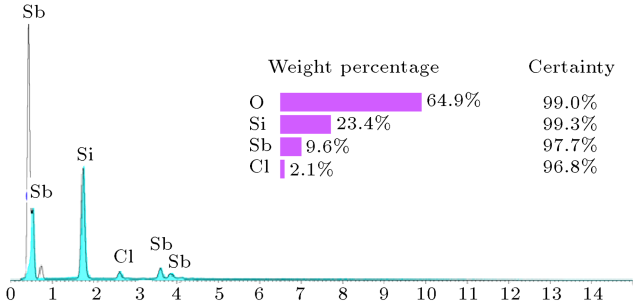


Figure 6. EDX (EDS) analysis diagram of nano $SbCl_5.SiO_2$.

respect to their biological activities. This method utilizes readily available reagents and affords high yields of different substituted 3,4-dihydropyrimidin-2(1*H*)-ones (thione) in short reaction times. The proposed mechanism for synthesis of 4a may be visualized to occur *via* reactions as depicted in Scheme 3.

2.3. Effect of different catalysts

In order to emphasize the efficiency of nano $SbCl_5.SiO_2$ in comparison with other catalysts, the model reaction was carried out with various catalysts such as $H_3PMo_{12}O_{40}$ [31], 12-Tungstophosphoric acid [32], Chloroacetic acid [33], CuI [34], $Fe(CF_3CO_2)_3$ [35], $NaHSO_4.SiO_2$ [36], Trichloroisocyanuric acid [37], $ZrCl_4$ [38], NH_2SO_3H [39], $Y(NO_3)_3.6H_2O$ [40], $SbCl_5$, and $SbCl_5.SiO_2$ (Table 2). When the reaction was performed with some catalyst, it was completed after a long time period or lower yield in comparison with nano $SbCl_5.SiO_2$. When nano $SbCl_5.SiO_2$ was used as a catalyst, the reaction completed in a shorter reaction time with an excellent yield of the product in room temperature condition (Table 2, entry 13).

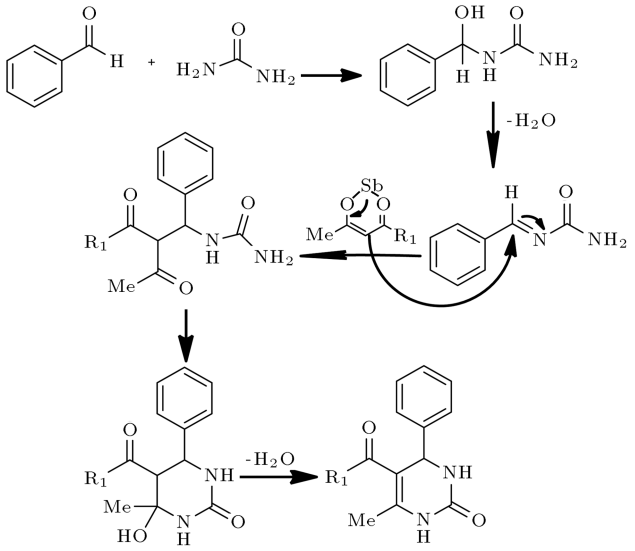
2.4. Effect of solvents

To choose the most appropriate medium in this heterocyclization reaction, condensation of β-ketoester, substituted arylaldehyde, and urea or *thiourea* for the synthesis 3,4-dihydropyrimidin-2(1*H*)-ones(thione) was examined at room temperature in presence of a catalytic amount of nano $SbCl_5.SiO_2$ in various solvents. It seems that EtOH, CH_3CN and THF gave excellent conversions. EtOH was the best among the solvents tested, but we find that the reaction preceded the best under solvent-free conditions rather than using solvents (Table 3).

Table 2. Representation of different catalysts in the synthesis of product 4a.

Entry	Catalyst	Solvent	Condition	Time (min)	Yield[a] (%)
1	$H_3PMo_{12}O_{40}$	HOAc	Reflux	240	75
2	12-tungstophosphoric acid	HOAc	Reflux	360	70
3	Chloroacetic acid	-	90°C	180	86
4	CuI	-	90°C	25	87
5	$Fe(CF_3CO_2)_3$	-	70°C	20	95
6	$NaHSO_4.SiO_2$	CH_3CN	Reflux	120	88
7	Trichloroisocyanuric acid	EtOH	Reflux	720	92
8	$ZrCl_4$	EtOH	Reflux	240	88
9	NH_2SO_3H	EtOH	Ultrasound	40	87
10	$Y(NO_3)_3.6H_2O$	-	70°C	45	80
11	$SbCl_5$	-	r.t	120	71
12	$SbCl_5.SiO_2$	-	r.t	25	92
13	Nano $SbCl_5.SiO_2$	-	r.t	12	95

[a]: Reaction conditions: aldehyde (5 mmol), β-ketoester (5 mmol), urea (thiourea) (7.5 mmol), and catalyst in various condition.



Scheme 3. Proposed mechanism for synthesis of 4a.

2.5. Loading of the catalyst

In the absence of nano $SbCl_5.SiO_2$, the reaction did not yield any product at room temperature even after a long reaction time (24 h). Next, nano $SbCl_5.SiO_2$ with different $SbCl_5$ loadings was used and it was observed that as $SbCl_5$ loading increased from 0 to 0.25 g, the yield of 3,4-dihydropyrimidin-2(1*H*)-one also increased. However, on further increasing the $SbCl_5$ loading to 0.15 and 0.25g, the yield decreased with the formation of side products. Thus, 0.10g of nano $SbCl_5.SiO_2$ was used as the preferred catalyst for further studies (Table 4).

2.6. Recycling of catalyst

The possibility of recycling the catalyst was examined using the model reaction for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one under the optimized conditions. Upon completion of the reaction, the mixture was poured into crushed ice with stirring. The crude product was filtered, washed with cold water, and recrystallized from hot ethanol. The catalyst was recovered as described in the experimental section and the recycling ability of the catalyst was tested for

Table 3. Effects of the solvents in the synthesis of product 4a[a].

Entry	Solvent	Time (min)	Yield[b] (%)
1	EtOH	25	90
2	CH_3CN	25	85
3	THF	25	77
4	H_2O	240	25
5	Solvent-free	12	95

[a]: Reaction conditions: aldehyde (5 mmol), β-ketoester (5 mmol), urea (thiourea) (7.5 mmol), and nano $SbCl_5.SiO_2$ (0.1 g) in solvent free condition at room temperature.

[b]: Isolated yields.

Table 4. Effects of the amounts of nano $SbCl_5.SiO_2$ on the synthesis of product 4a[a].

Entry	Catalyst (g)	Time (min)	Yield (%)
1	0	24 h	0
2	0.05	45	68
3	0.1	12	95
4	0.15	12	91
5	0.25	12	90

[a]: Reaction conditions: aldehyde (5 mmol), β-ketoester (5 mmol), urea (thiourea) (7.5 mmol), in presence of nano $SbCl_5.SiO_2$ in solvent free condition at room temperature.

Table 5. Effects of recycling nano $SbCl_5.SiO_2$ catalyst on the synthesis of product 4a.

Entry	Cycle	Yield (%)[a]
1	0	95
2	1	92
3	2	89
4	3	86
5	4	83

[a]: Isolated yields of product 4a.

further runs. As shown in Table 5, when the recycled catalyst was used for further runs, the yields ranged from 95% to 83%.

3. Conclusion

In conclusion, an efficient method for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones(thiones) by one pot multicomponent reaction from arylaldehydes, β-ketoester, and urea or thiourea in absence of a solvent using nano $SbCl_5.SiO_2$ heterogeneous catalyst has been successfully developed. This method has the ability to tolerate a wide variety of substitutions in all the three components which is lacking in existing reported procedures. Thus, this procedure will offer an easy access to substituted 3,4-dihydropyrimidin-2(1*H*)-ones(thione) with a different substitution pattern in high yields. Furthermore, the catalyst is easily recovered by simple filtration avoiding tedious work up process. The recovered catalyst is further utilized to carry the multicomponent reaction without loss of any significant activity.

4. Experimental

4.1. Materials

Chemicals were purchased from Merck Chemical Company in high purity. FT-IR (ATR) spectra were run on a Bruker, Eqinox 55 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker Avance 400 MHz DRX spectrometer. Melting points were determined without correction using a Buchi melting point B-540 BUCHI apparatus. SEM and TEM analyses were carried out on a VEGA/TESCAN scanning electron microscopy and a Leo 912AB OMEGA transmission electron microscopy, respectively. The X-Ray Diffraction (XRD) patterns of materials were prepared by employing a Philips Xpert MPD diffract meter equipped with a Cu Kα anode ($\lambda = 1.54$ Å) in the 2θ range from 5 to 80°. The Thermal Gravimetric Analysis (TGA) was done with "NETZSCH TG 209 F1 Iris" instrument.

4.2. Preparation of catalyst

The catalyst was prepared by stirring a mixture of $SbCl_5$ (0.7 mL) and nano silica gel (20 nm, 1 g) in 5 mL chloroform for 1 h at room temperature. The slurry was filtered and washed with chloroform (2 × 5 mL). The obtained solid nano $SbCl_5.SiO_2$ was dried at ambient temperature for 2 h and then stored in a dry container.

4.3. General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (thiones) under solvent-free condition

Combinations of aromatic aldehyde (5 mmol), β-ketoester (5 mmol), urea (thiourea) (7.5 mmol), and nano $SbCl_5.SiO_2$ (0.1 g) were mixed together and stirred at room temperature. After completion of the reaction (indicated by TLC), the mixture was dissolved in ethanol and poured into ice cold water. The resulting precipitate was filtered and recrystallized from ethanol.

4.4. Spectroscopic data

4.4.1. Table 1, entry 1

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-oxopyrimidine-5-carboxylate

M.P.: 200°C (201-203°C [41]); IR (KBr): $\bar{\nu}$ = 3520, 3230, 3150, 1705, 1690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (br. s, 1H), 7.71 (br. s, 1H), 7.20-7.32 (m, 5H), 5.11(d, J = 2.7 Hz, 1H), 3.96 (q, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz DMSO-d_6: δ 163.3, 150.2, 143.1, 126.4, 125.3, 124.4, 97.4,57.3, 52.1, 16.0, 12.2 ppm.

4.4.2. Table 1, entry 2

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxylate

M.P: 212°C (209-210°C [41]); IR (KBr): $\bar{\nu}$ = 3243, 3011, 1710, 1687, 1626 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.32 (br. s, 1H), 8.21 (d, J = 8.3 Hz, 2H), 7.84 (br. s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 5.22 (d, J = 2.7 Hz, 1H), 3.94 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.10 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 164.7, 151.3,149.3, 146.4, 126.8, 123.7, 59.3, 52.8,17.8, 13.7 ppm.

4.4.3. Table 1, entry 3

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-p-tolylpyrimidine-5-carboxylate

M.P: 213°C (214-215°C [41]); IR(KBr): $\bar{\nu}$ = 3262, 3169, 1701, 1689, 1637 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (br. s, 1H), 7.65 (br. s, 1H), 7.10 (m, 4H), 5.12 (d, J = 2.8 Hz, 1H), 3.95 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 2.27 (s, 3H), 1.13 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 165.2, 152.0, 148.0, 140.2, 135.0, 127.9, 126.9, 99.0, 58.9,52.9, 20.0, 17.2, 13.9 ppm.

4.4.4. Table 1, entry 4

Ethyl 4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate

M.P: 210°C (211-212°C [41]); IR(KBr): $\bar{\nu}$ = 3239, 3087, 1704, 1672, 1621 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (br. s, 1H), 7.61 (br. s, 1H), 7.23-7.38

(m, 4H), 5.22 (d, $J = 2.7$ Hz, 1H), 3.95 (q, $J = 7.2$ Hz, 2H), 2.19 (s, 3H), 1.02 (t, $J = 7.2$, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 165.0, 151.4, 148.9, 141.2, 131.7, 129.2, 128.7, 98.2, 58.9, 51.9, 17.9 ppm.

4.4.5. Table 1, entry 5
Ethyl 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl -2-oxopyrimidine-5-carboxylate
M.P: 203°C (200-201°C [41]); IR(KBr): $\bar{\nu}$ = 3228, 3109, 2949, 1719, 1648, 1501 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 7.59 (s, 1H), 7.15-6.81 (m, 4H), 5.00 (s, 1H), 3.89 (q, $J = 6.7$ Hz, 2H), 3.70 (s, 3H), 2.19 (s, 3H), 1.07 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 165.1, 157.9, 151.8, 148.3, 137.5, 126.8, 112.7, 99.2, 58.9, 54.9, 17.9 ppm.

4.4.6. Table 1, entry 6
Ethyl 1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate
M.P: 225°C (227-228°C [42]); IR(KBr): $\bar{\nu}$ = 3417, 3241, 3120, 2984, 1687, 1649, 1512 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 1H), 9.10(s, 1H), 7.64 (s, 1H), 7.03-6.65 (m, 4H), 5.02 (s, 1H), 3.96 (q, $J = 7.0$ Hz, 2H), 2.21 (s, 3H), 1.08 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 165.4, 156.6, 152.2, 147.8, 135.5, 127.4, 115.0, 99.8, 59.1,53.5, 17.8, 14.3 ppm.

4.4.7. Table 1, entry 7
Ethyl 4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate M.P: 177°C (174-176°C [42]); IR(KBr): $\bar{\nu}$ = 3243, 1698, 1638 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.25 (s, 1H), 7.77 (s, 1H), 7.21 (m, 4H), 5.15 (s, 1H), 3.99 (q, $J = 7.1$ Hz, 2H), 2.26 (s, 3H), 1.09 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz DMSO-d$_6$): δ 165.9, 159.8, 152.0, 148.6, 141.1, 128.3, 115.1, 99.2, 59.5, 53.9, 17.7, 14.6 ppm.

4.4.8. Table 1, entry 8
Ethyl 4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate
M.P: 207°C (209-210°C [43]); IR (KBr): $\bar{\nu}$ = 3258, 1657, 1569 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (s, 1H), 9.71 (s, 1H), 7.38-7.21 (m, 5H), 5.21 (d, $J = 3.5$ Hz, 1H) 4.05 (q, $J = 7.0$ Hz, 2H), 2.31 (s, 3H), 1.09 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 162.8, 151.0, 142.0, 125.9, 124.9, 125.0, 95.9, 57.0, 51.8, 16.3, 12.0 ppm.

4.4.9. Table 1, entry 9
Ethyl.1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate
M.P: 154°C (151-152°C [43]); IR-(KBr): $\bar{\nu}$ = 3256, 1659, 1595, 1569 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (br. s, 1H), 9.33 (br. s, 1H), 7.19 (d, $J = 8.1$ Hz, 2H), 6.69 (d, $J = 8.1$ Hz, 2H), 5.16 (s, 1H), 4.06 (q, $J = 7.1$ Hz, 2H), 2.28 (s, 3H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz DMSO-d_6): δ 173.9, 174.3, 165.9, 126.8, 158.5, 145.2, 135.9,128.0, 114.0, 101.5, 59.8, 55.3, 53.6, 17.4, 14.3 ppm.

4.4.10. Table 1, entry 10
Ethyl 4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate
M.P: 190°C (192-194°C [43]); IR-(KBr): $\bar{\nu}$ = 3258, 1661, 1566 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.0 (br. s, 1H), 9.33 (br.s, 1H), 7.17 (m, 4H), 5.28 (s, 1H) 4.12 (q, $J = 7.1$ Hz, 2H), 2.46 (s, 3H), 1.15 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (100 MHz DMSO-d_6): δ 174.8, 165.3, 145.5, 142.7, 132.0, 127.9, 128.9, 100.4, 59.3, 53.4, 17.2, 14.2 ppm.

4.4.11. Table 1, entry 11
Ethyl 4-(furan-2-yl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate
M.P: 206°C (204-205°C [43]); IR-(KBr): $\bar{\nu}$ = 3334, 3238, 3129, 2987, 1698, 1657, 1460, 1082, 876 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 7.7 (s, 1H), 7.56 (s, 1H), 6.36 (d, $J = 3.5$ Hz, 1H) 4.27 (q, $J = 6.5$ Hz, 2H), 2.40 (s, 3H), 1.29 (t, $J = 6.5$ Hz, 3H) ppm; ^{13}C NMR (100 MHz DMSO-d_6): δ 165.5, 157.0, 152.8, 149.5, 142.6, 110.2, 105.3, 96.0, 60.3,47.5, 18.1, 14.2 ppm.

4.4.12. Table 1, entry 12
Ethyl 1,2,3,4-tetrahydro-6-methyl-4-styryl-2-thioxopyrimidine-5-carboxylate
M.P: 230°C (232-233°C [41]); IR-(KBr): $\bar{\nu}$ = 3245, 1711, 1658 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 (br. s, 1H), 7.87 (br. s, 1H), 7.29 (m, 5H), 6.49 (d, $J = 14.3$ Hz, 1H) 6.18 (dd, $J = 14.5$, 4.1 Hz, 1H), 5.30 (d, $J = 4.1$ Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.26 (s, 3H), 1.16 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (100 MHz DMSO-d_6): δ 165.7, 152.9, 148.3, 137.0,130.1, 127.2, 126.2, 97.5, 59.1, 52.0, 17.9, 14.2 ppm.

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