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Sulphated silica tungstic acid as a highly efficient and recyclable solid acid catalyst for the synthesis of tetrahydropyrimidines and dihydropyrimidines

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ABSTRACT

For the first time sulphated silica tungstic acid (SSTA) has been synthesized and used as an acidic catalyst in organic synthesis. The catalyst was prepared by a simple method based on the reaction of silica with $SOCl_2$ followed by addition of sodium tungstate and then functionalization with chlorosulfonic acid. The three-component Biginelli-like condensation of different heteroaldehydes, urea and ethyl cyanoacetate or phenyl acetic acid catalyzed by SSTA under solvent-free conditions afforded novel tetrahydropyrimidines in high yields. The catalyst tolerated different heteroaldehydes and also catalyzed the synthesis of Biginelli compounds efficiently giving excellent yield of products. The catalyst was characterized by FT-IR, XRD and SEM-EDX analyses. The stability of the catalyst was evaluated by DSC and TG analyses. The major advantages of the present method are high yields, short reaction times, and solvent-free reaction conditions. The activity and simple recyclability without losing catalytic activity make this catalyst a good replacement to literature methods.

1. Introduction

The catalysts which make the organic reactions environmentally benign and economically feasible are extremely demanded by the chemical industries. In recent years, preparation of new heterogeneous catalysts with improved efficiency has been the subject of immense interest [1]. The ideal method for combining the advantages of homogeneous catalysts (high activity and selectivity, etc.) with the advantages of heterogeneous catalysts (available active sites, easy catalyst separation, long catalytic life, thermal stability, low hygroscopic properties, easy handling and reusability) is by immobilization of catalysts on solid support, which leads to clean chemical synthesis from both environmental and commercial point of view [2–5]. In modern material science, silica is the ubiquitous inorganic platform used in systems designed for catalysis, separation, filtration, sensing, optoelectronics and environmental technology. Due to the favourable chemical and physical properties of silica surfaces, it is possible to impart nearly any reactive functional group that one requires on a silica surface (e.g., sulfonic, amine, carboxyl, thiol, epoxy, and so forth) through well-known silane chemistry [6–8]. As a result, numerous variations can be made for specific applications with the use of a combination of inorganic materials and functional groups which often result in synergetic effects that lead to increased physical stability and enhanced chemical functionality [9,10].

The Biginelli multicomponent reaction is a very elegant methodology to obtain 3,4-dihydropyrimidin-2(1H)-one (DHPMs) derivatives in a one-step procedure [11]. DHPMs usually display various biological activities such as calcium channel modulators, adrenergic receptor antagonists, mitotic kinesin inhibitors, antivirals, antibacterials [12] and compounds such as enastron, monastrol, piperastrol and other derivatives [13] are well known biologically active compounds which have already been developed into drugs.

Moreover tetrahydropyrimidine ring is found in both natural as well as synthetic organic compounds. Many tetrahydropyrimidines containing an amino acid show interesting and diverse pharmacological activities like HIV protease inhibiting activity [14], antineoplastic activity [15], antiproliferative [16], herbicidal activity [17], muscarinic agonist activity [18], anti-inflammatory [19] and antiviral properties [20]. The presently known MCR protocols for the synthesis of THPMs are via Biginelli-like transformation [21] or alternatively, using the two-step operation of Knoevenagel condensation and urea annulation [22]. To the best of our knowledge, not a single multicomponent protocol for the synthesis of THPMs tolerating heteroaldehydes under heterogeneous

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conditions is presently available. It is therefore highly desirable to develop new methods for the efficient synthesis of THPMs. In the present work, taking advantage of the above mentioned properties of silica, we have designed and synthesized novel, sustainable sulphated silica immobilized tungstic acid (SSTA) and as our continuous efforts in developing novel protocols for the synthesis of useful heterocyclic scaffolds [23], we wish to report herein, SSTA catalyzed novel three-component synthesis of THPMs by using different heteroaldehydes, cyanoethyl acetate/phenylacetic acid and urea under solvent-free conditions.

2. Experimental

2.1. General

Melting points of all synthesized compounds were taken in a Riechert Thermover instrument and are uncorrected. The IR spectra (KBr) were recorded on Perkin Elmer RXI spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d$_6$/CDCl$_3$ as solvent. Mass spectra were recorded on Micromass Quattro II (ESI) spectrometer. Elemental analyses (C, H and N) were conducted using the Elemental vario EL III elemental analyzer and their results were found to be in agreement with the calculated values. DSC, TGA and DTA data were obtained with DSC-60 Shimadzu instrument. X-ray diffractograms (XRD) of the catalyst were recorded in the range of 0–80 with scan rate of 4°/min on a Rigaku Minifax X-ray diffractometer with Ni-filtered Cu Kα radiation at a wavelength of 1.54060 Å. The SEM-EDX characterization of the catalyst was performed on a JEOL JSM-6510 scanning electron microscope equipped with energy dispersive X-ray spectrometer operating at 20 kV. DSC analysis was performed in the temperature range of 20–500 °C, DTA and TGA analyses were performed in the temperature range of 0–1000 °C at a constant heating rate of 20 °C/min in the nitrogen atmosphere. All solvents and chemicals used were AR grade. The purity of compounds was checked by thin layer chromatography (TLC) on glass plates coated with silica gel G254 (E. Merck) using chloroform-methanol (3:1) mixture as mobile phase and visualized by iodine vapours and alcoholic ferric chloride. All acid catalysts such as $SiO_2–OSO_3H$ [24], $ZrO_2–OSO_3H$ [25], $NH_2SO_3H–SiO_2$ [8], cellulose–OSO_3H [26], xanthan–OSO_3H [27], PEG–OSO_3H [28] used in optimization study were synthesized by reported procedures.

2.2. Preparation of silica chloride

$SOCl_2$ (20 g) was added drop wise to the silica gel (20 g) in dry CH_2Cl_2 (50 mL) at room temperature under stirring. Evolution of copious amounts of HCl and SO_2 occurred instantaneously. After stirring for another 1 h, the solvent was removed under reduced pressure. The silica chloride thus obtained was used in the following experiments [29].

2.3. Preparation of silica tungstic acid

A mixture of silica chloride (6.00 g) and sodium tungstate (7.03 g) in dry n-hexane (10 mL) was stirred under refluxing conditions for 6 h. After completion of the reaction, the reaction mixture was filtered, washed with distilled water, dried and then stirred in the presence of 0.1 N HCl (40 mL) for an hour. Finally, the mixture was filtered, washed thoroughly with distilled water, and dried to afford STA [30].

2.4. Preparation of sulphated silica tungstic acid (S-STA)

A 0.5 L suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. STA (2.5 g) was added into the flask and stirred for 10 min in dry CH_2Cl_2 (0.075 L). Chlorosulfonic acid (1.75 g) was added drop wise over a period of 30 min at room temperature. After completion of the addition, the mixture was stirred for 90 min, while the residual HCl was eliminated by suction. Then the sulphated-STA was separated from the reaction mixture and washed several times with dried CH_2Cl_2. Finally sulphated-STA was dried at 120 °C for 3 h.

2.5. General procedure for synthesis of tetrahydropyrimidines

Aldehyde (3 mmol), ethyl cyanoacetate or phenyl acetic acid (3 mmol), urea (4.5 mmol) and SSTA (200 mg) were mixed by stirring in a 25 mL round bottom flask for specified time (Table 4) at a temperature of 70 °C. The reaction mixture was cooled and ethanol was added to solubilize the product. The remaining solid catalyst was filtered, washed with ethanol (3 × 15 mL) and ethyl acetate (2 × 10 mL) and reused for further catalytic cycles. The filtrate was evaporated under reduced pressure to obtain the product. The crude product was further purified by recrystallization from suitable solvent (ethanol or DMSO).

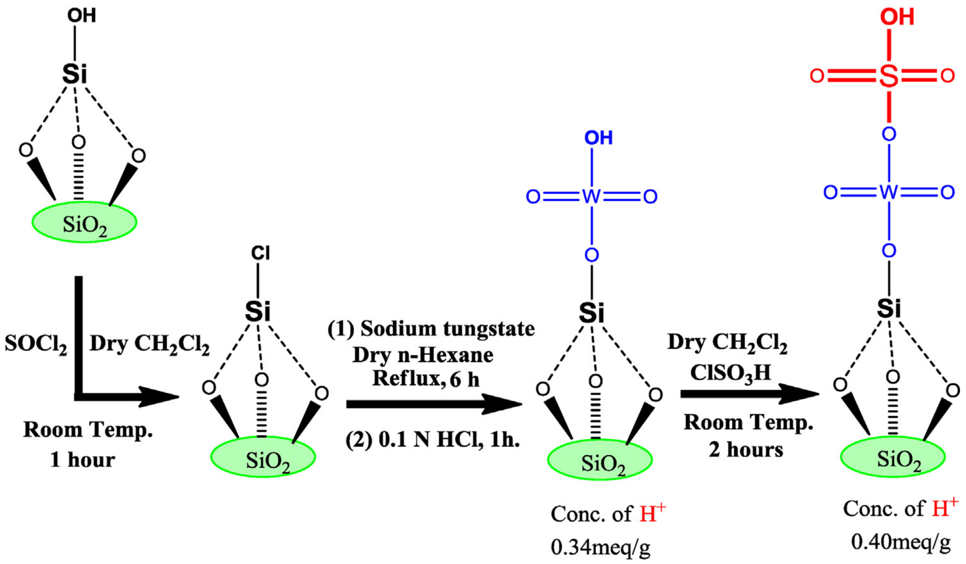
2.6. General procedure for synthesis of dihydropyrimidines

Aldehyde (3 mmol), ethyl acetoacetate or acetyl acetone (3.5 mmol), urea (4.5 mmol) and SSTA (200 mg) were mixed in a 25 mL round bottom flask for specified time (Table 4) at a temperature of 70 °C. The reaction mixture was cooled and added ethanol to solubilize the product. Catalyst was recovered by above-mentioned procedure. The filtrate was evaporated under reduced pressure to obtain the product. The compounds were recrystallized from ethanol.

3. Result and discussion

The SSTA catalyst was prepared by the concise route outlined in Scheme 1. Sodium tungstate reacted with silica chloride to produce silica tungstic acid (STA) which on further sulfonation with chlorosulfonic acid gave sulphated silica tungstic acid (SSTA). The optimum concentration of H^+ was determined by titration of the aqueous suspension of the weighed amount of thoroughly washed catalyst with standard NaOH solution. The strength of NaOH solution was kept very low (0.01 N) in order to minimize errors caused by reaction of NaOH with Lewis acid groups and to avoid the consumption of the base in the hydrolysis of the silica frameworks. The optimum concentration of H^+ was 0.40 mequiv/g of the support.

After successive experiments the concentrations of the residual H^+ on the recovered catalyst were measured (provided in recycling study) which showed very small or marginal loss of H^+. It signified that SO_3H moiety was tightly anchored with STA, probably through a covalent linkage. The reaction between 6-methyl-3-formyl chromone, urea and ethylcyano acetate in the presence of SSTA (preheated at 120 °C for 3 h) occurred with high efficiency giving 94% product yield and the reaction between 6-methyl-3-formyl chromone, urea and ethylcyano acetate in the presence of SSTA after keeping it at an ambient atmosphere for 5 days produced similar observation. This showed that there was no deteriorating effect of atmospheric oxygen or moisture towards the activity of the catalyst. The catalyst thus, showed considerable stability towards heat and moisture which provided further evidence for covalent linkage and the potential of efficient recycling.



Scheme 1. Schematic representation of the synthesis of the catalyst.

3.1. FT-IR spectral analysis of the catalyst

In order to evaluate incorporation of sulfonic groups and tungsten moieties on silica surface, FT-IR spectra of the respective sodium tungstate, STA and SSTA have been analyzed (Fig. 1). The FT-IR spectrum of sodium tungstate shows the WO_4^{2-} stretching frequency at 1683 cm^{-1}, STA showed this frequency at 1650 and also showed peaks corresponding to SiO_2 stretching. The intensity of WO_4^{2-} stretching in STA decreased due to bonding with silica. The introduction of SO_3^{2-} groups in STA led to further decrease in the intensity of the WO_4^{2-} stretching. The SSTA also showed OH stretching frequency at 3448 cm^{-1}. The asymmetric and symmetric stretching vibrations of SO_3 group obtained around 1300 and 1200 cm^{-1} merged with the broad absorption peak between 1000 and 1500 cm^{-1}, which showed some increase in intensity and little increase in broadening compared to broad peak of STA. The SSTA also showed the peaks corresponding to SiO_2–Cl and SiO_2 stretching. Thus the IR spectrum confirms the successful sulfonation of STA.

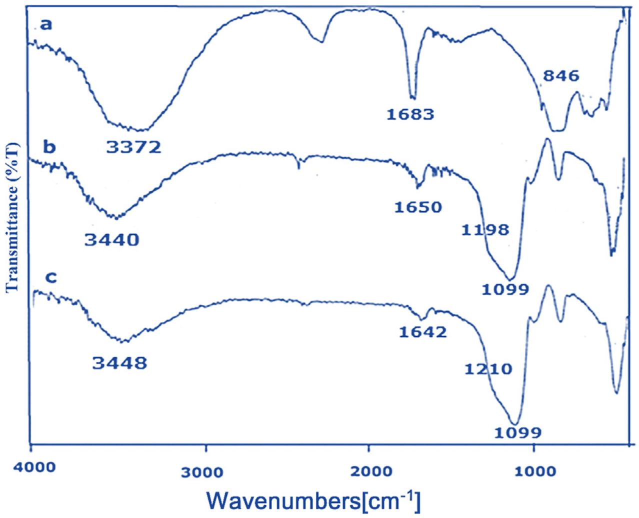


Fig. 1. FT-IR spectra of (a) sodium tungstate (b) silica tungstic acid and (c) SSTA.

3.2. XRD spectral analysis

The XRD analysis showed that the XRD patterns of the catalyst (Fig. 2b) were similar to that of the support (Fig. 2a). The WO_3 group exhibits a broad peak around $2\theta = 22^\circ$ which merges with the

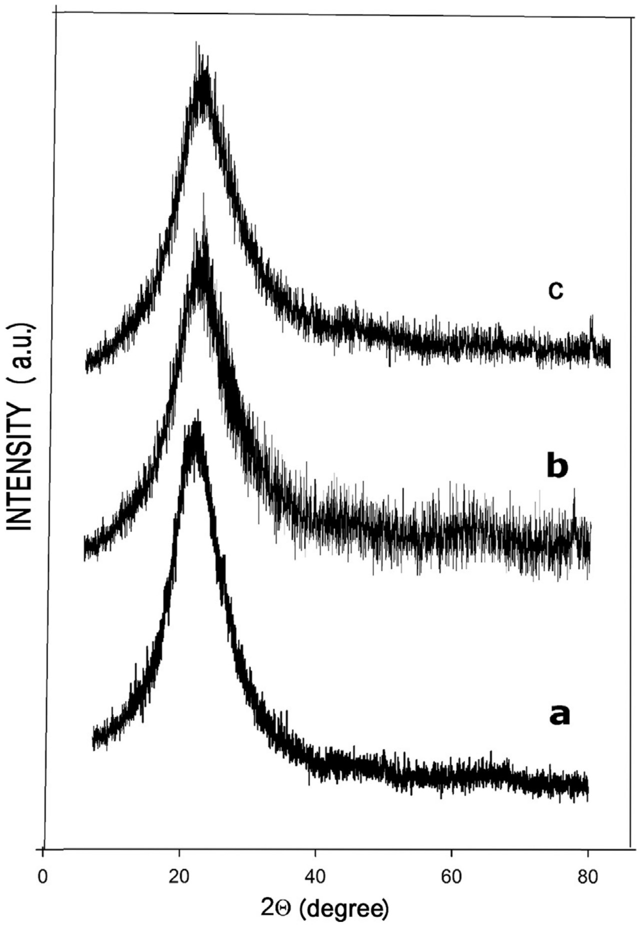


Fig. 2. (a) Powder XRD pattern of SiO_2 (b) XRD pattern of fresh SSTA (c) XRD pattern of the catalyst after six catalytic cycles.

broad peak shown by SiO_2 at around $2\theta = 20–25°$ [30,31]. This also indicates that the acids are highly dispersed on the support surface.

3.3. *SEM/EDX analysis of the catalyst*

The SEM image (Fig. 3b) of the catalyst showed the surface morphology of functionalized silica. The image shows the change in the surface morphology of silica gel (Fig. 3a) upon functionalization. Furthermore, the formation of expected sulphated catalytic system was also confirmed by EDX analysis (Fig. 4) which showed the presence of sulphur in addition to silicon and tungsten.

3.4. *DSC/TG analysis of the catalyst*

The thermal stability of the catalyst was evaluated by DSC and TG analyses. The DSC graph (Fig. 5a) shows a small endothermic transition around 100 °C which is due to the loss of surface-physisorbed water molecules on silica matrix. The graph further does not show any transition up to 450 °C after which a peak begins to appear which may be due to the loss of bonded sulphate groups. Thus it can be inferred that the catalyst is stable up to 450 °C.

TG curve (Fig. 5b) provided further information about the thermal stability of the catalyst. The TG curve showed a weight loss of 19% around 100 °C which can be attributed to the loss of water molecules present in silica gel framework. The catalyst then did not show any further weight loss up to 550 °C. This confirms that the catalyst is stable up to this temperature, shown also by DSC analysis. Further weight loss of ~7% at 550 °C can be attributed to the decomposition of sulphate groups from the surface of silica. Thus, DSC and TG analyses showed that the catalyst can tolerate wide range of temperature.

3.5. *Optimization of reaction conditions*

3.5.1. *Effect of different reaction media*

In order to determine the optimum conditions, the solvent effect, the proportions of catalyst to substrate and the reaction time were examined. At the beginning of this study, the reaction of 6-methyl-3-formyl chromone, urea and ethylcyano acetate was carried out in the presence of sulphuric acid in ethanol at reflux temperature (Table 1). Use of sulphuric acid gave product **4b** with 52% yield and the conversion was still low after 8 h (entry 1). Furthermore, a nearly equal amount of the product **4b** was observed, using sulphuric acid under solvent-free condition at 70 °C, thereby urging us to identify conditions that provide the product in good yield in less time. As the solvent-free approach produced same yield in less time, this approach was further explored for optimization of reaction conditions. In the first optimization, the effect of the differently supported sulphuric acids under solvent-free condition at 70 °C was examined. Organic polymers like cellulose, xanthan, PEG and camphor supported sulphuric acid gave unsatisfactory yields. Among silica and zirconia supported sulphuric acids the use of silica–SO_3H led to the preferential formation of **4b** with good conversion (entry 4). In order to further improve our protocol we then turned our attention towards recently synthesized catalyst silica tungstic acid (STA). The use of STA under solvent-free condition showed results better than different organic polymers supported acid but still unsatisfactory than silica–SO_3H. As a facile means to improve it, we then introduced SO_3H groups in STA. This strategy was found to be effective in decreasing not only the time period but also increasing the product yield. The sulphated STA (SSTA) gave 94% product yield in 15 min. The efficiency of this catalytic system was further tested by comparing it with different Lewis acids under solvent-free condition. $FeCl_3$ and $ZnCl_2$ gave less product yield and took 5–6 h to complete whereas ZnO and MgO could not show satisfactory results. In order to further optimize the reaction conditions we explored the behaviour of SSTA in different solvents. The use of polar solvents like ethanol, methanol and isopropanol gave yields better than non-polar solvents like hexane and toluene but still were unsatisfactory than solvent-free approach.

Table 1
Effect of various reaction media for the model reaction.[a]

Entry	Catalyst	Condition	Time[b]	Yield%[c]
1	H_2SO_4 (10 mol%)	Ethanol/reflux	8 h	56
2	H_2SO_4 (10 mol%)	Iso-propanol/reflux	8.5 h	53
3	H_2SO_4 (10 mol%)	Solvent-free/70 °C	4.2 h	67
4	H_2SO_4-SiO_2 (200 mg)	Solvent-free/70 °C	40 min	82
5	H_2SO_4–ZrO_2 (200 mg)	Solvent-free/70 °C	2 h	62
6	H_2SO_4–cellulose (200 mg)	Solvent-free/70 °C	65 min	65
7	H_2SO_4–xanthan (200 mg)	Solvent-free/70 °C	60 min	68
8	H_2SO_4–PEG (200 mg)	Solvent-free/70 °C	90 min	58
9	CSA (200 mg)	Solvent-free/70 °C	2.5 h	45
10	NH_2SO_3H–SiO_2 (200 mg)	Solvent-free/70 °C	55 min	71
11	Na_2WO_3 (10 mol%)	Solvent-free/70 °C	3.2 h	67
12	STA (200 mg)	Solvent-free/70 °C	90 min	78
13	STA–OSO_3H (200 mg)	Solvent-free/70 °C	15 min	94
14	STA–OSO_3H (200 mg)	Ethanol/reflux	2 h	73
15	STA–OSO_3H (200 mg)	Iso-propanol/reflux	2.5 h	65
16	STA–OSO_3H (200 mg)	Methanol/reflux	3.1 h	59
17	STA–OSO_3H (200 mg)	CH_2Cl_2/reflux	3.5 h	46
18	STA–OSO_3H (200 mg)	Hexane/reflux	4.2 h	23
19	STA–OSO_3H (200 mg)	Toluene/reflux	4.5 h	25
20	$FeCl_3$ (10 mol%)	Solvent-free/70 °C	6 h	36
21	$ZnCl_2$ (10 mol%)	Solvent-free/70 °C	5.4 h	41
22	ZnO (10 mol%)	Solvent-free/70 °C	–	–
23	MgO (10 mol%)	Solvent-free/70 °C	–	–

[a] Reaction of 6-methyl-3-formylchromone (1 mmol), urea (1.5 mmol) and ethyl cyanoacetate (1 mmol) in presence of different reaction media.

[b] Reaction progress monitored by TLC.

[c] Isolated yield.

3.5.2. *Effect of catalyst loading*

Taking SSTA under solvent-free condition as the right catalyst for the experiment, we next investigated right amount of catalyst for further optimization of reaction conditions. Performing the reaction with a higher than 200 mg of catalyst had no significant effect on yield. However, if the amount of the catalyst was reduced to 150 and 100 mg, the product yield was reduced to 68% and 43% respectively (Table 2). Therefore, 200 mg of SSTA at 70 °C under solvent-free condition gave best results for the model reaction giving conversion of 94% in 15 min.

3.5.3. *Effect of temperature*

The effect of temperature plays an important role in the catalytic synthesis of tetrahydropyrimidines. It was examined in the temperature range from room temperature to 100 °C in the absence of solvent, using SSTA as catalyst. At room temperature the reaction was not successful and with further increase in temperature the yield of product increased with decrease in time taken for completion of the reaction. At 70 °C and 80 °C the reaction was completed in 15 min with almost same yield. With further increase in the temperature the yield of product decreased which may be due to the

Table 2
Effect of catalyst loading on the model reaction.[a]

Entry	Amount of catalyst (mg)	Time (min)[b]	Yield[c] (%)
1	300	15	91
2	200	15	94
3	150	30	68
4	100	45	43

[a] Reaction of 6-methyl-3-formyl chromone (1 mmol), urea (1.5 mmol) and ethyl cyanoacetate (1 mmol) in presence of different amounts of SSTA under solvent-free condition at 70 °C.

[b] Reaction progress monitored by TLC.

[c] Isolated yield.

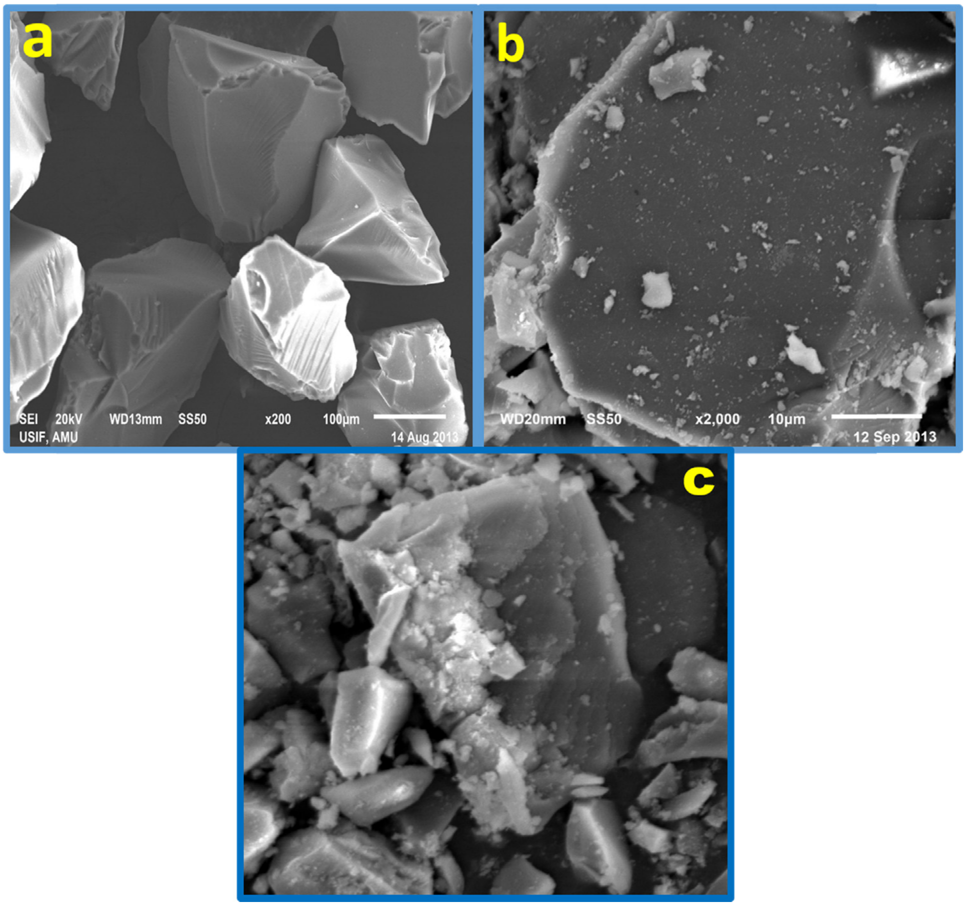


Fig. 3. SEM images (a) of SiO_2 support (b) of freshly synthesized SSTA and (c) of recycled SSTA.

formation of some side product (Table 3). So 70 °C was chosen as the optimum temperature for performing the reaction.

3.6. *Catalytic reaction*

3.6.1. *Synthesis of tetrahydropyrimidines*

With these encouraging results in hand, we turned to explore the scope of the reaction using different heterocyclic aldehydes, ethylcyano acetate or phenyl acetic acid and urea as substrates under the optimized reaction conditions (Scheme 2). The reaction proceeded smoothly offering excellent yield of products successfully. Further, on replacement of ethylcyano acetate with phenyl acetic acid the reaction proceeded with little longer reaction time, however, desired compounds were obtained in good yields (Table 4). Thus, it was observed that the reaction tolerated aldehydes with different heterocyclic substituents successfully to furnish the final products in good yields.

The structures of the final products were well characterized by using spectral (IR, ^{1}H, ^{13}C NMR and ESI-MS) and elemental analysis data. IR spectrum of **4b** showed peaks at 3281 and 3446 cm^{-1} which were assigned to two secondary NH groups. The absorption band at 2924 cm^{-1} was assigned to CN stretching. The two

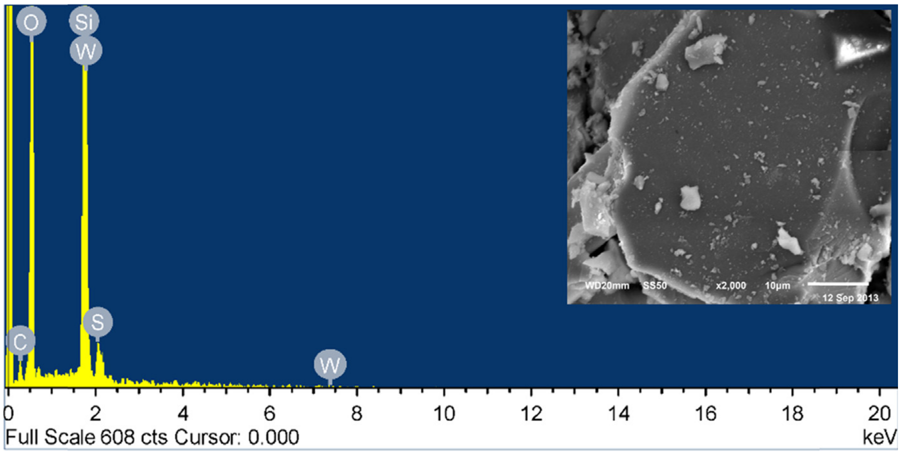


Fig. 4. EDX analysis of SSTA showing presence of S in addition to W and Si.

Table 4
Synthesis of tetrahydropyrimidines and dihydropyrimidinones using SSTA catalyst under solvent free conditions at 70 °C.

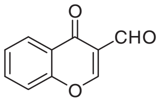
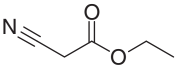
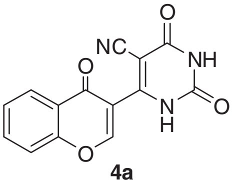
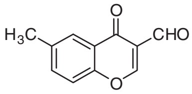
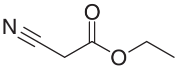
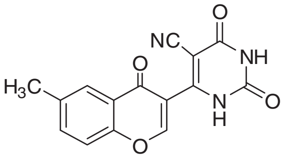
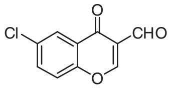
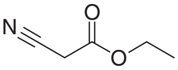
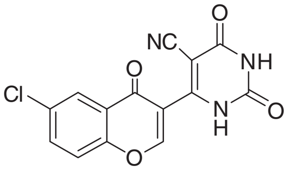
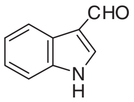
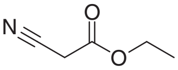
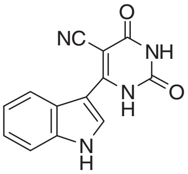
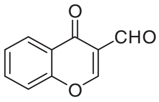
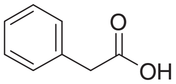
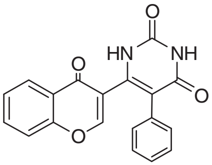
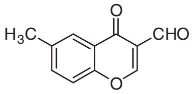
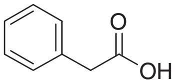
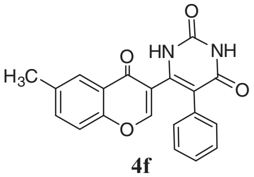
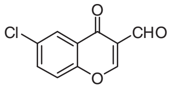
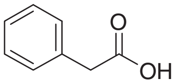
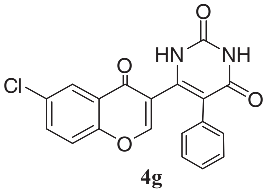
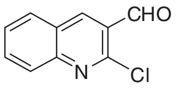
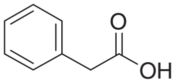
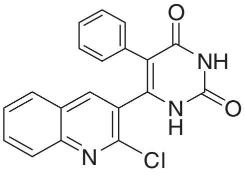
Entry	**1a–m**	**3a–d**	Product (**4a–w**)	Time (min)[a]	Yield (%)[b]
1	 1a		 **4a**	16	91
2	 **1b**		 **4b**	15	94
3	 **1c**		 **4c**	15	90
4	 **1d**		 **4d**	20	88
5	 1a		 **4e**	21	87
6	 **1b**		 **4f**	20	90
7	 **1c**		 **4g**	20	86
8	 **1e**		 **4h**	25	85

Table 4 (*Continued*)

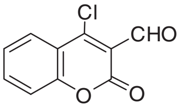
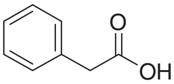
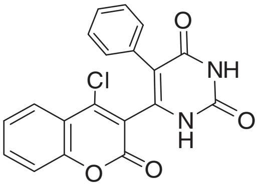
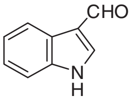
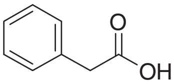
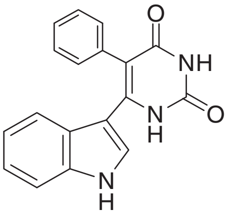
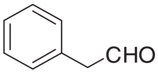
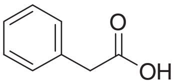
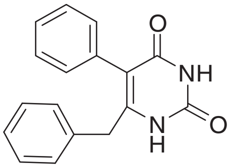
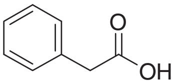
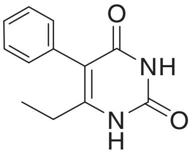
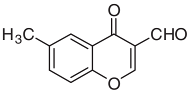
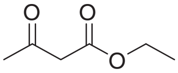
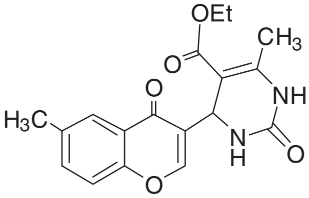
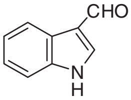
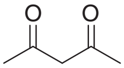
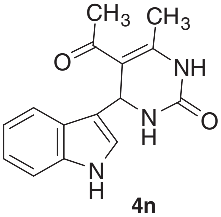
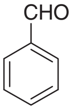
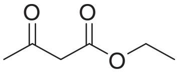
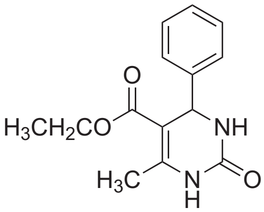
Entry	**1a–m**	**3a–d**	Product (**4a–w**)	Time (min)[a]	Yield (%)[b]
9	 **1f**		 **4i**	31	82
10	 **1d**		 **4j**	22	84
11	 **1g**		 **4k**	23	83
12	CH_3CH_2CHO **1h**		 **4l**	27	82
13	 **1b**		 **4m**	10	94
14	 **1d**		 **4n**	12	92
15[c]	 **1i**		 **4o**	10	96

Table 4 (*Continued*)

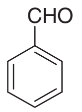
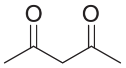
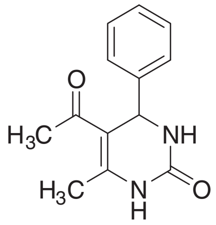
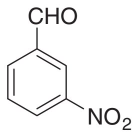
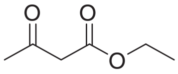
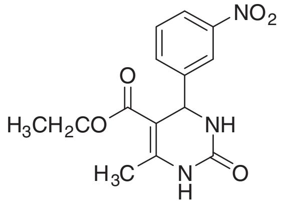
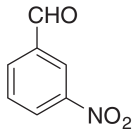
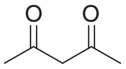
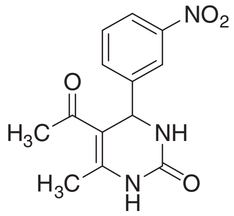
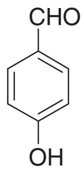
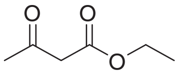
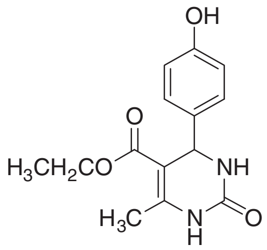
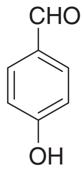
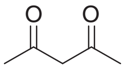
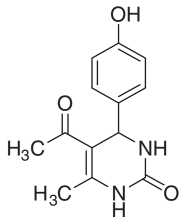
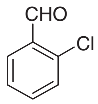
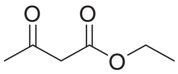
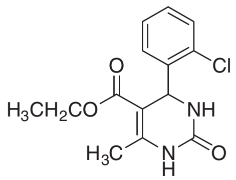
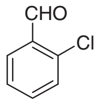
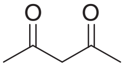
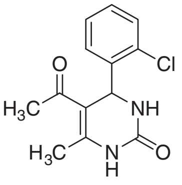
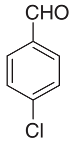
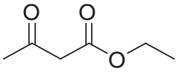
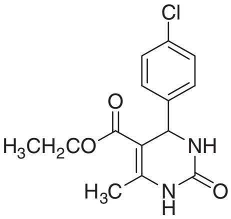
Entry	**1a–m**	**3a–d**	Product (**4a–w**)	Time (min)[a]	Yield (%)[b]
16[c]	 **1i**		 **4p**	12	95
17[c]	 **1j**		 **4q**	08	95
18[c]	 **1j**		 **4r**	10	94
19[c]	 **1k**		 **4s**	09	94
20[c]	 **1k**		 **4t**	12	95
21[c]	 **1l**		 **4u**	08	93

Table 4 (*Continued*)

Entry	**1a–m**	**3a–d**	Product (**4a–w**)	Time (min)[a]	Yield (%)[b]
22[c]	 **1l**		 **4v**	10	93
23[c]	 **1m**		 **4w**	10	94

[a] Reaction of different aldehydes (3 mmol), urea (4.5 mmol) and active methylene compounds (3/3.5 mmol) in presence of SSTA (200 mg) under solvent-free condition at 70 °C. Reaction progress was monitored by TLC. Compounds were purified by recrystallization from ethanol or DMSO.

[b] Isolated yield.

[c] Compounds characterized by their melting points, NMR spectra and comparing them with authentic samples.

C=O groups of tetrahydropyrimidine moiety merged into a broad peak at 1730 cm^{-1}. The C=O group of chromone moiety showed absorption band at 1654 cm^{-1}. The ^{1}H NMR Spectrum showed two distinctive singlets at δ 11.21 and δ 8.74 which were assigned to the protons of two secondary amines. The proton of chromone moiety showed a singlet at δ 7.37. The three protons of aromatic region showed a multiplet in the range of δ 7.2–7.8 and the three protons of methyl group showed a singlet at δ 3.36. ^{13}C NMR also showed

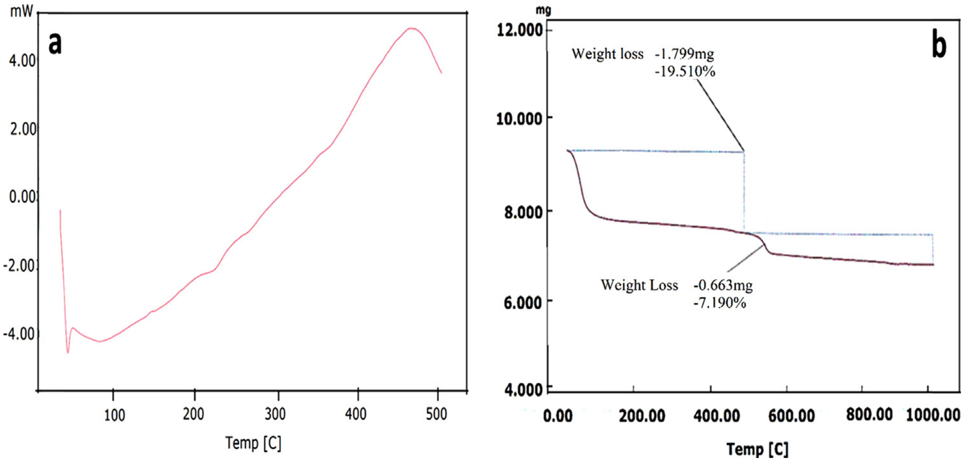
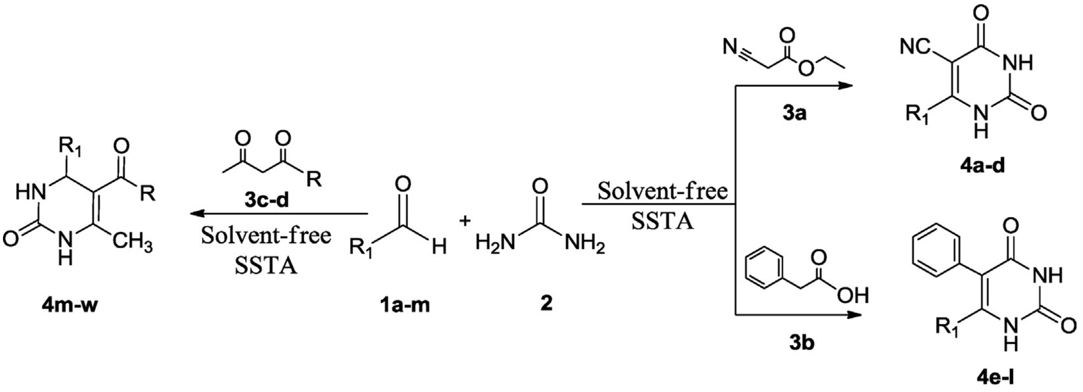


Fig. 5. (a) DSC analysis and (b) TG analysis of SSTA.



Scheme 2. Synthesis of different tetrahydropyrimidines (4a–l and dihydropyrimidinone derivatives 4m–w).

Table 3
Effect of different temperatures on the model reaction[a].

Entry	Temp (°C).	Time[b]	Yield[c] (%)
1	Room temp	–	–
2	40	7 h	45
3	70	15 min	94
4	80	15 min	92
5	100	15 min	87

[a] Reaction of 6-methyl-3-formylchromone (1 mmol), urea (1.5 mmol) and ethyl cyanoacetate (1 mmol) in presence of SSTA (200 mg) under solvent-free condition at different temperatures.

[b] Reaction progress monitored by TLC.

[c] Isolated yield.

distinctive peaks for C=O group of chromone moiety at 180.22 and C=O groups of tetrahydropyrimidine at 168.21 and 162.44 respectively.

3.6.2. *Catalytic activity of SSTA for Biginelli reaction*

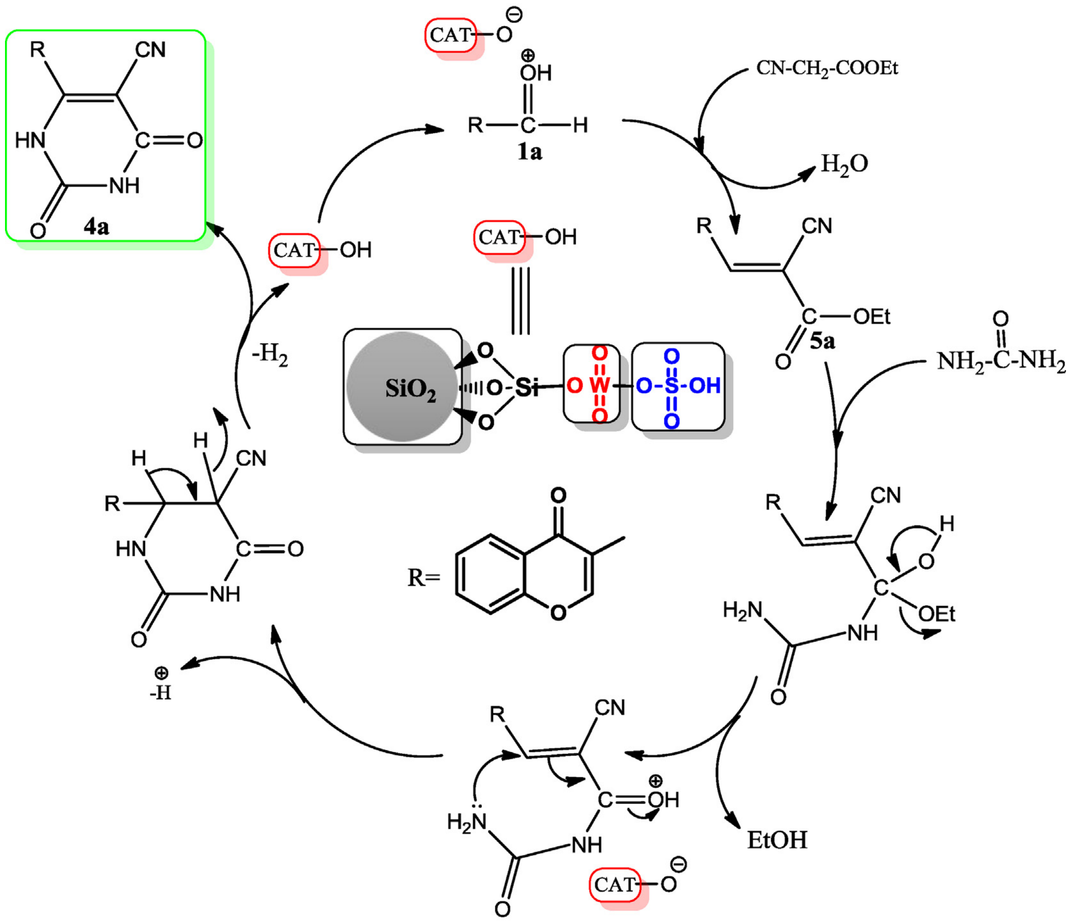
In order to further evaluate the catalytic activity of SSTA, we explored this catalyst for the synthesis of dihydropyrimidinones via Biginelli condensation of several aromatic and heterocyclic aldehydes with 1,3-dicarbonyl compounds and urea under similar reaction conditions. The reaction comprising benzaldehyde, urea and ethylaceto acetate gave 96% product yield in only 10 min. All substrates reacted efficiently and afforded high to excellent yields of the corresponding dihydropyrimidinones within short reaction times. Both β-ketoesters and β-diketones were found to be equally active and provided excellent yields of the products (Table 4, entries 13–23). Moreover, aldehydes contained both electron-with drawing and electron donating substituents reacted very efficiently therefore, the effect of substituents was not so marked. In order to show the efficiency of our catalyst it was further compared with other reported catalysts in the literature like sulphated tungstate [32], PS–PEG–SO_3H [33], silica sulphuric acid [34], β-cyclodextrin [35], $[Al(H_2O)_6](BF_4)_3$ [36], Fe_3O_4/PAA–SO_3H [37], cellulose sulphuric acid [26], $Cu(OTf)_2$ [38], tetra-butyl ammonium bromide [39], and showed the superiority of our catalyst in terms of reaction conditions, time and product yield (Table 5).

3.7. *Reaction mechanism*

A plausible mechanism for the formation of tetrahydropyrimidine **4a** is depicted in Scheme 3. Probably, this transformation is triggered by an initial activation of 3-formylchromone (**1a**) by protonation which then undergoes Knoevenagel condensation with ethyl cyanoacetate (**3a**) forming alkene derivative (**5a**). This step is followed by the addition of urea and elimination of ethoxy group. Then intramolecular Michael addition followed by dehydrogenation affords the product (**4a**). The catalyst is regenerated in the last step and can be reused for six catalytic cycles [40].

4. Recyclability of the catalyst

Recyclability of the catalyst was evaluated by the reaction of 6-methyl-3-formylchromone (**1b**), ethylcyano acetate (**3a**) and urea in the presence of SSTA under solvent-free conditions. After



Scheme 3. Plausible mechanism for the formation of tetrahydropyrimidine derivative by the reaction of 3-formylchromone, ethyl cyanoacetate and urea in presence of SSTA under solvent-free conditions.

Table 5
Effect of different reported catalysts for formation of dihydropyrimidines.

Entry	Catalyst	Condition	Yield (%)	Time	No. of recycles
1	SSTA	70 °C/solvent-free	96	10 min	06
2	Sulphated tungstate	80 °C/solvent free	92	60 min	04
3	PS–PEG–SO$_3$H	80 °C/dioxane:2-propanol (4:3)	80	10 h	06
4	Silica sulphuric acid	Reflux/ethanol	91	6 h	05
5	β-Cyclodextrin	100 °C/solvent-free	85	3 h	05
6	[Al(H$_2$O)$_6$](BF$_4$)$_3$	Reflux/CH$_3$CN	85	20 h	04
7	Fe$_3$O$_4$/PAA-SO$_3$H	Room temp./solvent-free	90	2 h	06
8	Cellulose sulphuric acid	100 °C/water	85	4.5 h	04
9	Cu(OTf)$_2$	100 °C/ethanol	65	60 min	–
10	Tetra-butyl ammonium bromide	100 °C/KOH	96	40 min	–

Table 6
Recycling data of SSTA for the model reaction[a] showing Concentrations of residual H$^+$ on the used support after successive experiments.

Catalyst recycles	Time[b] (min)	Yield (%)[c]	Conc. of residual H$^+$ (mequiv/g)
1	15	94	0.40
2	15	94	0.40
3	15	94	0.35
4	15	92	0.35
5	15	91	0.30
6	15	89	0.25

[a] Reaction of 6-methyl-3-formylchromone (1 mmol), urea (1.5 mmol) and ethyl cyanoacetate (1 mmol) in presence of SSTA (200 mg) under solvent-free condition at 70 °C.

[b] Reaction progress monitored by TLC.

[c] Isolated yield.

completion of the reaction catalyst was recovered by extracting the mixture with ethanol. The catalyst was then recovered by filtration, washed with ethanol (3 × 15 mL), ethyl acetate (2 × 10 mL), dried at 100 °C for 1 h and reused for subsequent cycles. The catalyst exhibited good catalytic activity up to six cycles after which the yield started to decrease (Table 6). The catalyst morphology was preserved during the catalytic recycling studies as can be seen from XRD (Fig. 2c) and SEM images (Fig. 3c) of the catalyst after six catalytic cycles.

5. Conclusion

In conclusion, an efficient, eco-compatible method for the synthesis of various tetra- and dihydropyrimidines by one pot reaction of aldehydes, urea and active methylene compounds, in presence of sulphated silica tungstic acid (SSTA) has been successfully developed for the first time. SSTA catalyst is easy to prepare, highly efficient, and easily recoverable by simple filtration. The recovered catalyst can be reused for six cycles without any significant loss of activity.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2014.02.019.

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