

“(CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub>: A HETEROGENEOUS CATALYST FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES UNDER MICROWAVE IRRADIATION”Shrikrishna G More<sup>1</sup>, Mahesh P More<sup>2</sup>, Parimeeta Chanchani<sup>3\*</sup><sup>1,3\*</sup> Department of chemistry, Mansarovar Global University, Sehore,  
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## ABSTRACT

A successful one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> as an inexpensive and readily available reagent through Biginelli condensation reaction of variable aldehydes, β-keto ester and urea/thiourea is described. Outstanding yields, short reaction times, recovery and reuse of catalyst and simple work-up are some attractive features of this protocol.

Keywords: 3,4-dihydropyrimidin-2(1*H*)-ones; (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub>; One-pot synthesis.



## 1. INTRODUCTION

In 1893 Pitro Biginelli first time synthesized 3,4-dihydropyrimidin-2(1*H*)-ones from aldehyde, urea and β-keto ester, under harsh classical reaction condition. 3,4-dihydropyrimidin-2(1*H*)ones containing scaffolds are important class of organic chemistry with respect to biological as well as pharmaceuticals<sup>[1]</sup> such as antimicrobial antibacterial, antiviral, anticancer, antihypertensive, antitumor, antimalarial, activities<sup>[2-4]</sup>, etc. Due to this biological and pharmaceutical consequences, 3,4-dihydropyrimidin-2(1*H*)-ones have been intensively attracted in last few decades. In this periods 3,4-dihydropyrimidin-2(1*H*)-ones synthesized by using range of methods like using microwave, ultrasound, solvent free

reactions, under ultra violet light, and variety of catalysts <sup>[5-9]</sup> along with acids like H<sub>3</sub>BO<sub>3</sub>, Formic acid, p-Toluene sulfonic acid monohydrate, copper triflate, strontium triflate, Vanadium(III) chloride, TaBr<sub>5</sub>, cerium nitrate. hexahydrate, Zirconium oxide/sulfate, Samarium(III) perchlorate, Yttrium Nitrate Hexahydrate, Cerium(III) chloride heptahydrate, Ceric ammonium nitrate, ferric nitrate. Hexahydrate, Calcium bisulphate, zinc bisulphate, Tin(II) chloride/nano SiO<sub>2</sub>, copper(II) acetate, copper zirconium phosphate, Scandium trifluoromethanesulfonate, Ytterbium(III) triflate, and Zinc triflate, Lithium perchlorate, aluminum (III) chloride, Indium chloride, Boron trichloride, Bismuth(III) trifluoromethanesulfonate, Manganese(III) acetate, Copper (II) chloride, Iron(III) chloride, Zirconium(IV) chloride, Boron trifluoride etherate, Lanthanum chloride, Lanthanide triflates, SiO<sub>2</sub>-Cl, InX<sub>3</sub> (X=Cl, Br), ZrCl<sub>4</sub>, BiCl<sub>3</sub>, TMSOTF, Magnesium triflate, Mn(OAc)<sub>3</sub>, LiClO<sub>4</sub>, clays, etc have been reported.<sup>[10-53]</sup>

Most of the reported catalysts are suffering drawbacks like harsh reaction condition, longer reaction time, high catalyst loading, expensive reagents, corrosive reagents, low yields of products, required large amounts of solid supports while (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> is not explored yet. So considering all these facts, in the present work we wish to use (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one under microwave irradiation.

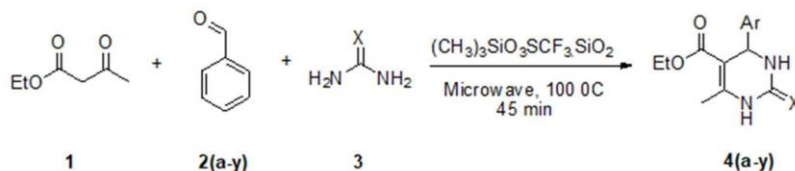
## 2. RESULTS AND DISCUSSION

As an effort to develop innovative methodology, we report herein a simple and efficient (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> catalysed microwave assisted solvent free one pot synthesis of substituted aryl-3,4-dihydropyrimidin-2(1*H*)-one from substituted benzaldehyde, ethyl-3-oxobutanoate and urea/thiourea.

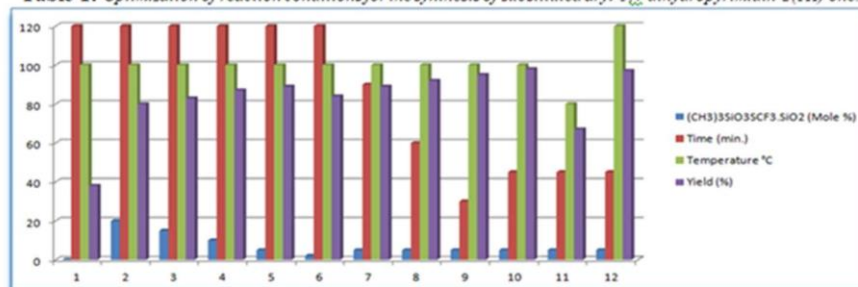
Initially, benzaldehyde, ethyl-3-oxobutanoate and urea were selected as reference substrates, for optimization of reaction condition. Different time, temperature and mole % of catalyst were screened as summarized in Table-1.

At the time of optimization, absence of catalyst resulted into lower yield (Entry-1, Table-1). Catalyst stoichiometry optimization screened such as such as 2, 5, 10, 15 and 20 (Entry-2-6, Table-1) and the outcome is 5 mole % (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> is the minimum requirement to get outstanding results. Time investigation of reaction (Entry-7-10, Table-1); reveals that 45 min., is enough time for reaction. During temperature screening (Entry-11-12, Table-1); it is observed that at lower and higher temperature yields are obtained less. The catalyst was recovered and recycled with standard optimized reaction condition using benzaldehyde, ethyl-3-oxobutanoate and urea as a reference substrate summarized in Table-3. Comparative yields were obtained by using recycled catalyst up to three cycles (Entries-1-3, Table-3).

**Scheme-1** :  $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3\cdot\text{SiO}_2$  catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-one



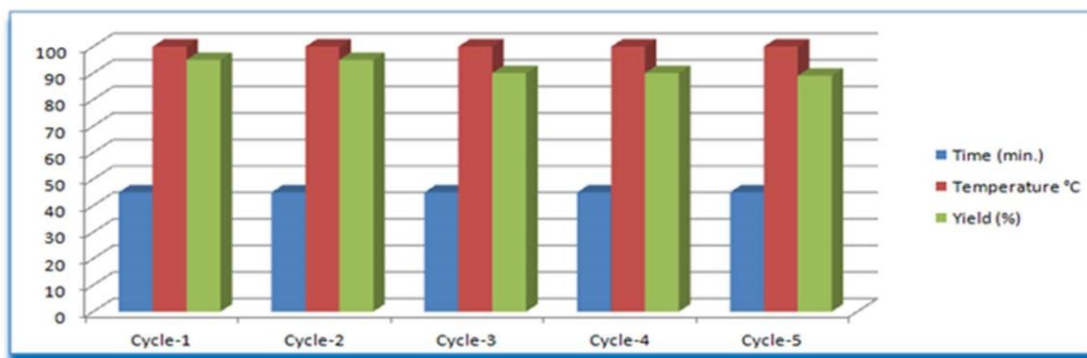
**Table-1**: Optimization of reaction conditions for the synthesis of substituted aryl-3,4-dihydropyrimidin-2(1H)-one.



\* Reaction conditions: 1 (1.0eq), 2 (1.0eq), 3 (1.5eq), catalyst (0.5eq) was maintained at 100°C for 45.0 min under microwave irradiation.

**Table-2**: Exploration of optimized reaction condition to obtain 4(a-y).

No	Ar	X	Product	Yield (%)	Melting Point (°C)
1.	-C <sub>6</sub> H <sub>5</sub>	O	4a	88	203
2.	-2,3(Cl)C <sub>6</sub> H <sub>3</sub>	O	4b	91	215
3.	-4OMe-C <sub>6</sub> H <sub>3</sub>	O	4c	92	204
4.	-5Cl-C <sub>6</sub> H <sub>3</sub> N	O	4d	86	221
5.	-4NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	O	4e	96	213
6.	-2Br,4Cl-C <sub>6</sub> H <sub>3</sub>	O	4f	92	288
7.	-4Me-C <sub>6</sub> H <sub>4</sub>	O	4g	89	166
8.	-2,3,4(OMe)C <sub>6</sub> H <sub>2</sub>	O	4h	91	203
9.	-3CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	O	4i	83	177
10.	-4(OH)C <sub>6</sub> H <sub>4</sub>	O	4j	88	227
11.	-4(Cl)C <sub>6</sub> H <sub>4</sub>	O	4k	70	221
12.	-4(NMe <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	O	4l	83	263
13.	-C <sub>6</sub> H <sub>5</sub>	S	4m	79	219
14.	-2,3(Cl)C <sub>6</sub> H <sub>3</sub>	S	4n	90	211
15.	-4OMe-C <sub>6</sub> H <sub>3</sub>	S	4o	88	224
16.	-5Cl-C <sub>6</sub> H <sub>3</sub> N	S	4p	89	227
17.	-4NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	S	4q	90	231
18.	-2Br,4Cl-C <sub>6</sub> H <sub>3</sub>	S	4r	95	304
19.	-4Me-C <sub>6</sub> H <sub>4</sub>	S	4s	83	181
20.	-2,3,4(OMe)C <sub>6</sub> H <sub>2</sub>	S	4t	88	213
21.	-3CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	S	4u	87	187
22.	-4(OH)C <sub>6</sub> H <sub>4</sub>	S	4v	91	230
23.	-4(Cl)C <sub>6</sub> H <sub>4</sub>	S	4w	73	211
24.	-4(NMe <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	S	4x	85	254

**Table-3** Recycle of  $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3\cdot\text{SiO}_2$  catalyst recovered from spent

To further extend the scope of  $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3\cdot\text{SiO}_2$  catalysed synthesis of 4-phenyl substituted aryl-3,4-dihydropyrimidin-2(1*H*)-one, a range of 3,4-dihydropyrimidin-2(1*H*)-ones were prepared under the optimized reaction conditions by changing the substrate from simple aryl group to substituted benzaldehyde. The detailed results were summarized in Table -2.

### 3. EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial resources like Avra, Spectrochem and Finar and utilized directly without purification. Reaction progress was monitored on TLC plate of silica-gel and visualized under UV light. Melting points were obtained by using LabIndia MR. Vis+ apparatus. The  $^1\text{H-NMR}$  spectra were determined using Bruker 300 MHz instrument using TMS as the internal standard. Isolated compounds were purified using recrystallization technique. All the synthesized products are reported in literature and were identified by comparison of their observed melting points and  $^1\text{H-NMR}$  values with reported values.

#### 3.1 Preparation of $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3\cdot\text{SiO}_2$ .

The  $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3\cdot\text{SiO}_2$  was prepared by mixing Silica gel (45.0 g, Merck grade 60, 100–200 mesh) with a solution of TMSOTF (5.0 g) in distilled water (30mL). The resulting mixture was stirred for 60 min to for absorption of TMSOTF on the surface of silica gel. After complete absorption, water removed by vacuum distillation on rotary evaporator. The isolated solid powder was dried at 120°C for 5 h under reduced vacuum.

#### 3.2 General procedure for the preparation of aryl-3,4-dihydropyrimidin-2(1*H*)-one 4(a-y).

A mixture of substituted benzaldehyde (9.43 mmol), ethyl 3-oxobutanoate (9.43 mmol), urea (14.14 mmol) and  $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3\cdot\text{SiO}_2$  (0.47 mmol, 5-mole %) (Scheme-1) was irradiated under microwave at 100°C for 45 min. The progression of reaction was monitored by TLC. After completion of reaction, the resulting mass was cooled to ambient temperature, and diluted with ethyl acetate. The heterogeneous solid catalyst was removed by filtration, washed with plenty of ethyl acetate. Then the filtrate was concentrated under vacuum to obtain crude product. The isolated crude product was re-crystallized from ethanol to afford a pure solid of 4- phenyl substituted 3,4-dihydropyrimidin-2(1*H*)-ones in excellent to good yields.

### 3.3 Recovery of Catalyst

The separated catalyst after reaction completion was washed with plenty of ethyl acetate, dried under vacuum tray dryer at 120°C for 5 h and reused for next reaction cycle under optimized reaction conditions (Table-1, Entry-10).

Some selected spectral data of aryl-3,4-dihydropyrimidin-2(1*H*)-ones (Table-2):

4a: 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Mp: 204–207 °C; MS: 261 (M+H); 1H-NMR (DMSO-d<sub>6</sub>, 300 MHz):d (ppm): 10.33 (s, 1H, NH), 9.65-9.66 (s, 1H, NH), 7.22-7.35 (m, 5H, ArH), 5.16-5.18 (s, 1H, CH), 3.97-4.04 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 1.08-1.12 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>).

4c: Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:-Mp: 201–204 °C; MS: 291 (M+H); 1H-NMR (DMSO-d<sub>6</sub>, 300 MHz):d (ppm): 10.29 (s, 1H, NH), 9.60 (s, 1H, NH), 7.11-7.14 (d, 2H, ArH), 6.98-6.91 (d, 2H, ArH), 5.105.12 (s, 1H, CH), 3.97-4.04 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 2.28 (s, 3H, CH<sub>3</sub>), 1.08-1.13 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>).

4e: Ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:-Mp: 245–248 °C; MS: 329.0,331.0,333.0 (M+H); 1H-NMR (DMSO-d<sub>6</sub>, 300 MHz):d (ppm): 9.33 (s, 1H, NH), 7.77 (s, 1H, NH), 7.57-7.58 (s, 1H, ArH), 7.41-7.44 (d, 1H, ArH), 7.31-7.33 (d, 1H, ArH), 5.59-5.60 (s, 1H, CH), 3.87-3.91 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 0.98-1.03 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>).

4g: Ethyl 4-(2-bromo-4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:-Mp: 288–291 °C; MS: 374.0,376.0,378.0 (M+H); 1H-NMR (DMSO-d<sub>6</sub>, 300 MHz):d (ppm): 9.33 (s, 1H, NH), 7.71-7.72 (s, 1H, NH), 7.76-7.77 (s, 1H, ArH), 7.45-7.49 (d, 1H, ArH), 7.30-7.33 (d, 1H, ArH), 5.58 (s, 1H, CH), 3.87-3.94 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.30 (s, 3H, CH<sub>3</sub>), 0.99-1.04 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>).

4j:Ethyl 6-methyl-2-oxo-4-(2,3,4-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate:-Mp: 201–203 °C; MS: 351.1 (M+H); 1H-NMR (DMSO-d<sub>6</sub>, 300 MHz):d (ppm): 9.11 (s, 1H, NH), 7.33 (s, 1H, NH), 6.71-6.81 (dd, 2H, ArH), 5.36-5.37 (s, 1H, CH), 3.92-3.94 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 3.74-3.76 (s, 6H, OCH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>), 1.03-1.08 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>).

## 4. CONCLUSION

A proficient and mild methodology has been developed for the synthesis of dihydropyrimidin-2(1*H*)-ones using ethyl acetoacetate, variable aldehydes, and urea in presence of heterogeneous recyclable (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> catalyst. The catalyst could be reused several times without noticeable reduction in the catalytic activity. Excellent yields, short reaction times, and easy isolation are some advantages of this methodology. This reaction condition allows a wide variety of synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones. We believe that, the applicability of (CH<sub>3</sub>)<sub>3</sub>SiO<sub>3</sub>SCF<sub>3</sub>.SiO<sub>2</sub> with the mentioned advantages makes our method superior among other reported methods.

## 5. ACKNOWLEDGMENT

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