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Research Article

"Synthesis Of 3, 4-Dihydropyrimidin-2(1H)-Ones Catalyse By Trimethylsilyl Trifluoromethanesulfonate On Silica Gel"

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ABSTRACT
A successful one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using Trimethylsilyl Trifluoromethanesulfonate on Silica gel 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; $(CH_3)_3SiO_3SCF_3.SiO_2$ (Trimethylsilyl trifluoromethanesulfonate on silica gel); One-pot synthesis.

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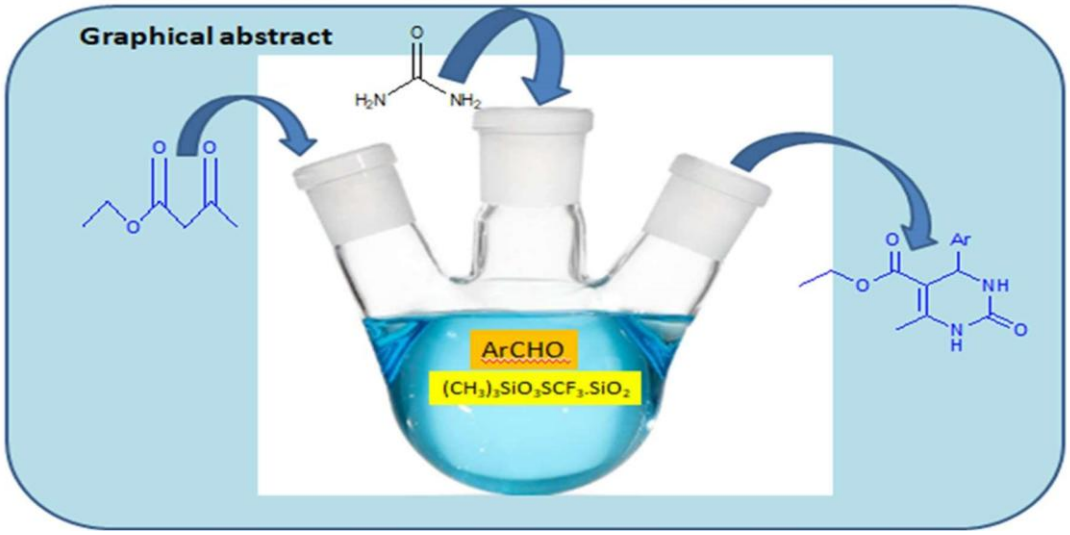


1. INTRODUCTION

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[1] such as antimicrobial antibacterial, antiviral, anticancer, antihypertensive, antitumor, antimalarial, activities [2-4], 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 [5-9] along with acids like H_3BO_3, Formic acid, p-Toluene sulfonic acid monohydrate, copper triflate, strontium triflate, Vanadium(III) chloride, $TaBr_5$, 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_2, 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_2-Cl, InX_3 (X=Cl, Br), $ZrCl_4$, $BiCl_3$, TMSOTF, Magnesium triflate, $Mn(OAc)_3$, $LiClO_4$, clays, etc have been reported.[10-53] Most of the repotared 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 Trimethylsilyl Trifluoromethanesulfonate on Silica gel is not explored yet. So considering all these facts, in the present work we wish to use Trimethylsilyl Trifluoromethanesulfonate on Silica gel catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one under microwave irradiation.

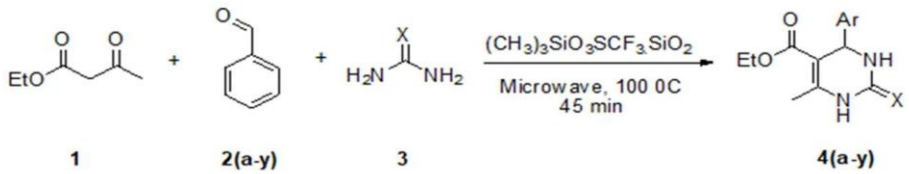
2. RESULTS AND DISCUSSION

As an effort to develop innovative methodology, we report herein a simple and efficient Trimethylsilyl Trifluoromethanesulfonate on Silica gel 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.

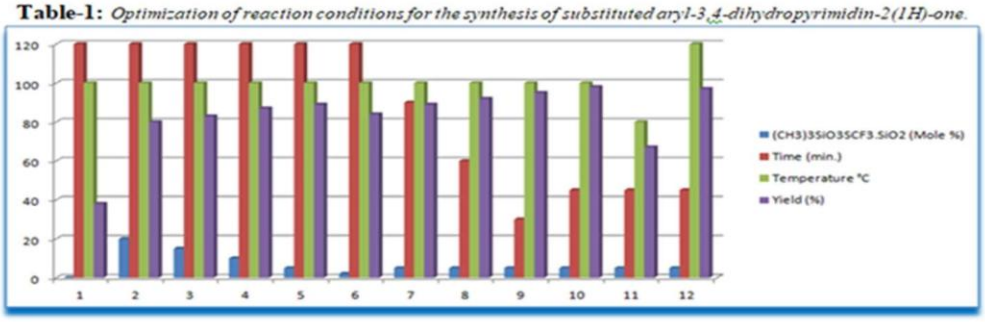
At the time of optimization, absence of catalyst resulted into lower yield (Entry-1, Table-1). Catalyst stoichiometry optimization screened such as such as 2, 5, 10, 15 and 20 (Entry-2-6, Table-1) and the outcome is 5 mole % Trimethylsilyl Trifluoromethanesulfonate on Silica gel is the minimum requirement 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 : *$(CH_3)_3SiO_3SCF_3.SiO_2$ catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-one*



1 2(a-y) 3 4(a-y)

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

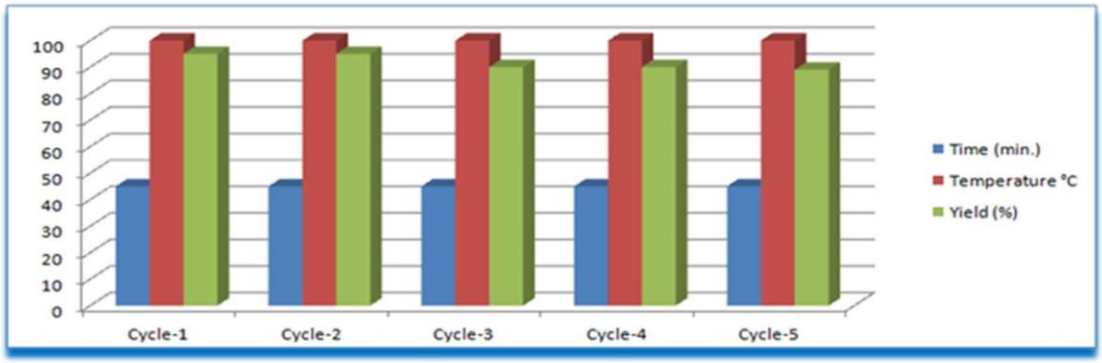


*** Reaction conditions:** 1 (1.0eq), 2 (1.0eq), 3 (1.5eq), catalyst (0.5eq) was maintained at 100°C for 45.0 min under microwave irradiation.

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

No	Ar	X	Product	Yield (%)	Melting Point (°C)
1.	-C_6H_5	O	4a	88	203
2.	-2,3(Cl)C_6H_3	O	4b	91	215
3.	-4OMe-C_6H_3	O	4c	92	204
4.	-5Cl-C_6H_3N	O	4d	86	221
5.	-4NO_2-C_6H_4	O	4e	96	213
6.	-2Br,4Cl-C_6H_3	O	4f	92	288
7.	-4Me-C_6H_4	O	4g	89	166
8.	-2,3,4(OMe)C_6H_2	O	4h	91	203
9.	-3CF_3-C_6H_4	O	4i	83	177
10.	-4(OH)C_6H_4	O	4j	88	227
11.	-4(Cl)C_6H_4	O	4k	70	221
12.	-4(NMe_2)C_6H_4	O	4l	83	263
13.	-C_6H_5	S	4m	79	219
14.	-2,3(Cl)C_6H_3	S	4n	90	211
15.	-4OMe-C_6H_3	S	4o	88	224
16.	-5Cl-C_6H_3N	S	4p	89	227
17.	-4NO_2-C_6H_4	S	4q	90	231
18.	-2Br,4Cl-C_6H_3	S	4r	95	304
19.	-4Me-C_6H_4	S	4s	83	181
20.	-2,3,4(OMe)C_6H_2	S	4t	88	213
21.	-3CF_3-C_6H_4	S	4u	87	187
22.	-4(OH)C_6H_4	S	4v	91	230
23.	-4(Cl)C_6H_4	S	4w	73	211
24.	-4(NMe_2)C_6H_4	S	4x	85	254

Table-3 *Recycle of $(CH_3)_3SiO_3SCF_3.SiO_2$ catalyst recovered from spent*



To further extend the scope of Trimethylsilyl Trifluoromethanesulfonate on Silica gel 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 Lab India MR. Vis+ apparatus. The 1H-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 1H-NMR values with reported values.

3.1 Preparation of Trimethylsilyl Trifluoromethanesulfonate on Silica gel.

The Trimethylsilyl Trifluoromethanesulfonate on Silica gel 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 $(CH_3)_3SiO_3SCF_3.SiO_2$ (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-d6, 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_2CH_3), 2.29 (s, 3H, CH_3), 1.08-1.12 (t, 3H, OCH_2CH_3).

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-d6, 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_2CH_3), 3.72 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 1.08-1.13 (t, 3H, OCH_2CH_3).

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-d6, 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_2CH_3), 2.29 (s, 3H, CH_3), 0.98-1.03 (t, 3H, OCH_2CH_3).

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-d6, 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_2CH_3), 2.30 (s, 3H, CH_3), 0.99-1.04 (t, 3H, OCH_2CH_3).

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-d6, 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_2CH_3), 3.81 (s, 3H, OCH_3), 3.74-3.76 (s, 6H, OCH_3), 2.26 (s, 3H, CH_3), 1.03-1.08 (t, 3H, OCH_2CH_3).

4. ANTIBACTERIAL ACTIVITY

There some of compounds and its derivatives are tested for antibacterial activities in presence of various test organism, like S. aureus (Staphylococcus aureus) and candida sp. (candida albicans) that are gram-positive microorganism and E. coli (Escherichia coli) and P. aeruginosa (Pseudomonas aeruginosa) gram-negative microorganism.

The tested results are shows high activity in S. aureus and E. coli, while some of show poor activity E. coli. Against P. aeruginosa and Candida sp.

Table 4: ***Antimicrobial studies of compounds***

Compound	Antimicrobial Activity (zone of inhibition in mm)			
	E. coli ATCC25922	***Pseudomonas aeruginosa ATCC27853***	***Staphylococcus aureus ATCC25922***	***Candida sp.***
Comp.no.1	No zone	No zone	10mm	16mm
Comp.no.2	No zone	10mm	No zone	09mm
Comp.no.3	No zone	No zone	No zone	No zone
Comp.no.4	No zone	No zone	12mm	16mm
Comp.no.5	No zone	No zone	No zone	No zone
Comp.no.6	No zone	No zone	15mm	22mm
Comp.no.7	No zone	No zone	No zone	No zone
Comp.no.8	No zone	No zone	No zone	No zone
Comp.no.9	23mm	40mm	21mm	No zone
Comp.no.10	42mm	42mm	42mm	24mm
Comp.no.11	43mm	No zone	42mm	No zone

Comp.no.12	29mm	11mm	28mm	No zone
Comp.no.13	14mm	No zone	11mm	No zone
Comp.no.14	No zone	No zone	No zone	No zone
Comp.no.15	13mm	No zone	No zone	No zone
Comp.no.16	No zone	No zone	No zone	No zone
Comp.no.17	28mm	No zone	12mm	No zone
Comp.no.18	13mm	No zone	17mm	35mm
Comp.no.19	20mm	No zone	27mm	32mm
Comp.no.20	No zone	No zone	No zone	No zone
Comp.no.21	14mm	No zone	No zone	27mm
Comp.no.22	No zone	20mm	No zone	12mm
Comp.no.23	11mm	No zone	No zone	17mm
Comp.no.24	16mm	No zone	17mm	No zone
Gentamicin	26mm	32mm	30mm	0
Nystatin	0	0	0	26mm

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 Trimethylsilyl Trifluoromethanesulfonate on Silica gel 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 and they have shown great antimicrobial activity. We believe that, the applicability of Trimethylsilyl Trifluoromethanesulfonate on Silica gel with the mentioned advantages makes our method superior among other reported methods.

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