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Exploiting silver trifluoromethanesulfonate as efficient and reusable catalyst for the synthesis of dihydropyrimidine derivatives under different reaction environments

Dipak Kumar Roy[1] | **Kashyap Jyoti Tamuli**[1,2] | **Manobjyoti Bordoloi**[1,2]

[1] Natural Products Chemistry Group, Chemical Sciences and Technology Division, CSIR-North East Institute of Science and Technology, Jorhat, Assam, India

[2] Academy of Scientific and Innovative Research, CSIR, New Delhi, India

Correspondence
Manobjyoti Bordoloi, Natural Products Chemistry Group, Chemical Sciences and Technology Division, CSIR-North East Institute of Science and Technology, Jorhat 785006, Assam, India.
Email: mjb_rrljt@yahoo.co.in; m.j.bordoloi.pub@gmail.com

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Abstract

Different results were generated under different reaction conditions for the multicomponent reactions. Herein, an efficiently improved and mild protocol for the synthesis of dihydropyrimidine derivatives using cheap silver trifluoromethanesulfonate (CF_3SO_3Ag) as reusable catalyst is explained. With conventional heating and microwave irradiation method, the synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione was achieved in different solvent environments like acetonitrile, water, and under solvent free neat condition. Moreover, the solvents (CH_3CN and H_2O) containing the CF_3SO_3Ag were reused for several times without loss of much catalytic activity after separation from the desired products. Thus, the method provides much improved and efficient alternative pathway to the original Biginelli reaction.

1 | INTRODUCTION

From the past few decades, we have witnessed that multicomponent reactions enjoy an outstanding status in organic and pharmaceutical chemistry. In the field of applications of diversity-oriented cascade synthesis to form active organic molecules from simple and easily available synthons in a single-reaction chamber has become a central point in chemical research.[1] 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione including 2-imino analogues (dihydropyrimidinones [DHPM]) are important biologically active compounds of immense human health importance,[2] such as, calcium channel modulator,[3] HIV gp120-CD4 inhibition,[4] anticancer activity,[5] inhibition of Walker carcinosarcoma,[6,7] blood platelet aggregation inhibition,[8] antitumor,[9] and antifungul.[10] Such compounds are also useful as α1-adrenoreceptorselective antagonists, inhibitor of benign prostatic hyperplasia, orally active antihypertensive and have antiviral activities.[2] Thus, from over the years, the core moiety of this heterocycles has gained a tremendous importance and several modified methodologies of the original Biginelli protocol.[11,12] The literature is enumerated with numerous synthetic efforts concerning Biginelli reaction, which were developed either by use of metal catalysts[13] like $CaCl_2$, $FeCl_3$ or $NiCl_2$, $RuCl_3$, $SnCl_2$, and $GaCl_3$, metal triflates[14] like Bi $(OTf)_3$, Yb $(OTf)_3$, La $(OTf)_3$, Ni $(OTf)_2$, In $(OTf)_3$, and Cu $(OTf)_2$, morpholinium acetate/polyphosphonate ester,[15] or by various expensive nano catalysts[16] and ionic liquids.[17]

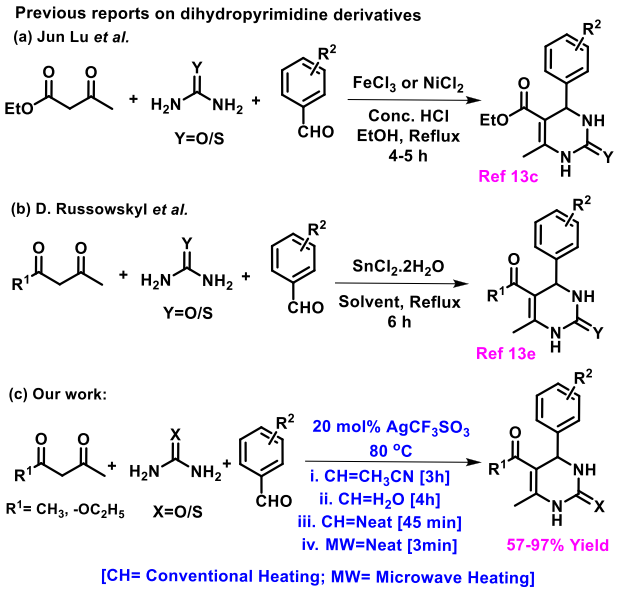
Despite several of these reported procedures have limitations such as use of expensive reagents, use of toxic solvents or catalyst, use of concentrated acids, drastic workup conditions, long reaction time give low to moderate yields. Although many catalysts have been used in Biginelli reaction, but little attention has been paid to recover the used catalyst and reused for several cycles. Moreover, from the point of green chemistry, in most of the cases, it is not desirable that catalysts cannot be reused.[18]

In the recent past, silver trifluoromethanesulfonate has been used with other substances as cocatalyst or copromoters for various organic transformations.[19] In addition to that, silver trifluoromethanesulfonate has also been used to synthesize various nitrogen containing heterocycles recently.[20] Whereas, reports on microwave-assisted simple metal catalyzed cascade processes are very rare. Therefore, we opted to explore the higher chances of silver trifluoromethanesulfonate as catalyst for the synthesis of dihydropyrimidine derivatives.

Herein, we report a mild, cheap, environment friendly, and feasible method for the synthesis of dihydropyrimidine using silver trifluoromethanesulfonate as catalyst alone in microwave irradiation (Scheme 1c). Additionally, a comparative study has been performed for the assessment of CF_3SO_3Ag using different solvents such as CH_3CN and H_2O including under solvent free conditions. After the completion of the reaction, the product was separated out from the reaction mixture, and solvent containing the catalyst can be reused for several times.

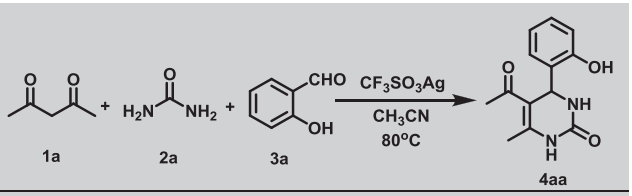
2 | RESULTS AND DISCUSSION

The catalytic potential of silver trifluoromethanesulfonate was first examined for one model reaction containing acetyl acetone **1a**, urea **2a**, and 2-hydroxybenzaldehyde **3a** under different catalytic conditions using acetonitrile as solvent (Table 1). Initially, without using the catalyst, the reaction does not yield any product (Table 1, entry 1). Then, the reaction was observed with 0.1 mmol of silver



SCHEME 1 Processes for the synthesis of dihydropyrimidine derivatives [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Effect of amount of the catalyst to optimize the synthesis of dihydropyrimidinones (DHPM) under different conditions



Entry	Urea, mmol	Catalyst, mmol	Yield,[a] %
1	1	-	0
2	1	0.1	65
3	1.1	0.1	73
4	1.2	0.1	75
5	1.7	0.1	82
6	2.0	0.1	79
7	1.5	0.05	50
8	1.2	0.15	85
9	1.2	0.20	94
10	1.2	0.25	93
11	1.2	0.20	97[b]

Note. Reaction conditions: acetyl acetone **1a** (1 mmol), urea **2a**, 2-hydroxybenzaldehyde **3a** (1 mmol); acetonitrile: 5 mL; time: 3 h for conventional heating (CH); and 3 min for microwave (MW).

[a]Isolated yield.

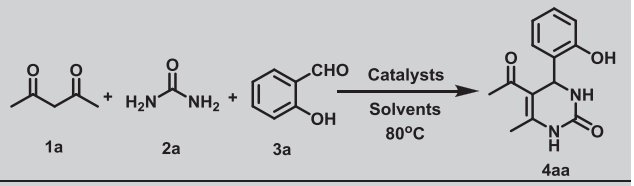
[b]Using microwave irradiation in CH_3CN.

trifluoromethanesulfonate using different amount of urea **2a**. In the model reaction, with acetonitrile (5 mL), it stirred at refluxed temperature for 3 hours at 80°C. By varying the amount of urea **2a**, the reaction was carried out till the formation of product in high yields. Excellent yield was observed (based upon 2-hydroxybenzaldehyde) when loading of urea was increased from 1 to 1.2 mmol. But the yield remained the same even after addition of urea up to 2 mmol. Hence, 1.2 equivalent of urea **2a** was found to be optimum for the best yield of dihydropyrimidines. Thereafter, keeping the reaction time (3 hours) constant, the reaction was appraised by changing the concentrations of catalyst (0.5-0.25 mmol) (Table 1, entries 7-10). In addition to that, use of 20 mmol of silver trifluoromethanesulfonate is sufficient for the reaction to accomplish with excellent yield up to 94% (Table 1, entry 9). Higher amount of the catalyst loading results almost the same in terms of yield percentage. Therefore, an optimum of 1.2 mmol of urea **2a** and 0.20 mmol of silver trifluoromethanesulfonate in the reaction mixture was quintessential for attaining the best results. However, no urea or thiourea is remaining in the solvents after the completion of the reactions, since we were using 1.2 mmol of them. The dilution effects of other starting materials were

explained and included in ESI (Table S1). With the all optimum best results, we studied the model reaction with microwave-assisted method (Table 1, entry 11). Since to our delight, the reaction was completed within 3 minutes with 97% of yield with CH_3CN.

Again, to study the effects of different metal triflates and solvents for the synthesis of DHPM derivatives, some initial experiments were carried out by taking the same model reaction (Table 2). At first, we took acetonitrile, water, and neat conditions with our catalyst to evaluate the solvent effects (Table 2, entries 1-3). From the results, it showed that acetonitrile works as better solvent (yield 94% in CH and 97% in MW) than water (yield 68% in CH and 72% in MW) or neat condition (yield 93% in CH and 95% in MW). These all model reactions were studied up to the production of maximum yield formation in their respective reaction time. The same reaction was performed in an oil bath (CH), the reaction proceed lethargically and required 3 to 4 hours to completion of the reaction, whereas in MW, heating method takes 3 minute to obtain the resulting products. In contrast, various metal triflates were also screened to study the in-depth optimization condition (Table 2, entries 4-9). Following the pioneering works on metal triflates for Biginelli type reactions,[14] we have chosen the same solvent systems as they have used. All the examined metal triflates showed good catalytic activity with our model reaction, but CF_3SO_3Ag was particularly effective for this transformation than other metal triflates. This method also comprises of simple and easy purification process for getting the products and enhances the scope of reusability of the metal catalyst up to seven runs.

TABLE 2 Effect of different metal triflates and solvents for the synthesis of dihydropyrimidinones (DHPM)



Entry	Catalyst, mmol	Solvents, mL	Yield,[ac] (%) CH[b]	Time, min	MW[c]	Time, min
1	AgOTf	CH_3CN	94	182	97	3
2	AgOTf	H_2O	68	240	72	10
3	AgOTf	Neat	93	45	95	5
4	Bi $(OTf)_3$	CH_3CN[14d]	82	60	90	10
5	Yb $(OTf)_3$	CH_3CN[14c]	83	20	88	5
6	La $(OTf)_3$	CH_3CN[14c]	74	20	81	5
7	Sc $(OTf)_3$	CH_3CN[14c]	77	20	83	5
8	Cu $(OTf)_2$	CH_3CN[12j]	90	60	94	10
9	In $(OTf)_3$	Ethanol[14e]	81	780	87	20

Note. Reaction conditions: acetyl acetone **1a** (1 mmol), urea **2a** (1.2 mmol), 2-hydroxybenzaldehyde **3a** (1 mmol); catalysts (20 mmol); solvent 5 mL.

Abbreviations: CH, conventional heating; MW, microwave.

[a]Isolated yield.

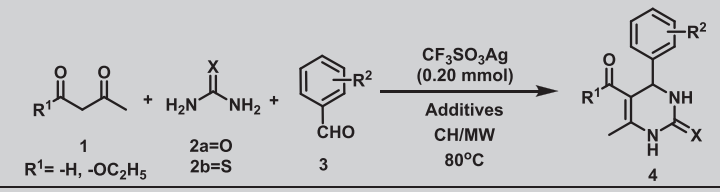
[b]In conventional heating.

[c]In microwave irradiation.

With the established optimized reaction conditions, we have extended all the possible methods to investigate the flexibility of the catalytic environments in different reaction conditions. The reactions were carried out by heating mixture of substituted aldehydes (1 mmol), acetyl acetone or ethylacetoacetate (1 mmol), and urea or thiourea (1.2 mmol) with silver trifluoromethanesulfonate (0.20 mmol) at 80°C (bath temperature) for appropriate time (3 hours) for conventional heating method and at 35 W in 80°C (set at the programmer of the reactor) for 3 minutes for microwave-irradiated methods. All results were summarized in Table 3. At first, to study the solvent effects, different solvents were also screened for this multicomponent reaction. To analyze the greener aspects in organic synthesis, we studied the adaptability of the reaction with solvent water and solvent free conditions, although the resulting yields were reasonably low and the rate of the reaction was slow while using water as solvent. Therefore, we evoked of improving the method by carrying out the reaction under solvent-free neat condition, which is a new move in organic synthesis in recent times.[21] But no significant variations in yield percentage were observed including the reaction time differed, as compared with acetonitrile solvent-mediated reactions. Equipped with these encouraging preliminary results, we explored the various prospects of improving the method further by execute the reaction under solvent-free neat condition under microwave irradiation in a microwave reactor. Here also, we observed that there is compelling improvement in yield percentage as well as DHPM were obtained within a short span of time (3 minutes) regardless of the nature of aldehydes. The reaction takes place more efficiently in solvent-free condition than those in solvents, since the catalysts or reagents are organized more firmly when solvents were not used.

Under all these optimized condition, the substrates consist of electron-withdrawing or electron-donating groups on aromatic ring of aldehydes were well tolerated in the reaction, affording the corresponding DHPM adducts (**4aa–4at**) to give good to excellent yields (83%-97%). Hence, a series of functional groups on aromatic aldehydes including methyl, methoxy, hydoxy, and benzyloxy moieties were also well tolerated in this reaction. Notably, aldehydes-containing halogens as functional groups on the aromatic ring are also compatible

TABLE 3 Synthesis of functionalized dihydropyrimidinones using silver trifluoromethanesulfonate as reusable catalyst



					Yield[a]							
					Acetonitrile		Water		Neat (Δ)		Microwave	
Entry	EAA or AA (R^1)	U or T (X)	RCHO (R^2)	Product Code (4)	Time, min	Yield, %	Time, min	Yield, %	Time, min	Yield, %	Time, min	Yield, %
1	AA	U	2-(OH)-C_6H_4	4aa	180	94	240	68	45	93	3	97
2	AA	T	3-(OH)-C_6H_4	4bb	180	93	240	69	45	91	3	96
3	AA	U	4-CH_3O-C_6H_4	4ac	180	94	240	70	45	93	3	97
4	AA	U	4-OH-3-CH_3O-C_6H_3	4ad	180	91	240	65	45	90	3	93
5	AA	U	4-(F)-C_6H_4	4ae	180	87	240	63	45	88	3	90
6	AA	U	2,4-(Cl)-C_6H_3	4af	180	88	240	65	45	90	3	91
7	AA	T	4-(Br)-C_6H_4	4be	180	82	240	60	45	81	3	86
8	AA	U	4-(benzyloxy)-C_6H_4	4ah	180	85	240	62	45	87	3	89
9	AA	U	4-(thiophenyl)-C_6H_4	4ai	180	86	240	65	45	89	3	90
10	AA	U	4-(pyridinyl)-C_6H_4	4aj	180	83	240	64	45	85	3	87
11	AA	U	1*H*-indolyl-C_6H_4	4ak	180	80	240	61	45	82	3	85
12	EAA	U	3-(OH)C_6H_4	4al	180	91	240	66	45	87	3	95
13	EAA	U	4-(OH)C_6H_4	4am	180	92	240	64	45	88	3	96
14	EAA	T	4-(OH)C_6H_4	4bn	180	90	240	61	45	86	3	91
15	EAA	U	4-CH_3O-C_6H_4	4ao	180	87	240	60	45	85	3	90
16	EAA	T	4-CH_3O-C_6H_4	4bp	180	85	240	59	45	82	3	87
17	EAA	T	4-OH-3-CH_3O-C_6H_3	4bq	180	81	240	61	45	83	3	86
18	EAA	U	2,4-(Cl)-C_6H_3	4ar	180	84	240	60	45	82	3	85
19	EAA	T	2,4-(Cl)-C_6H_3	4bs	180	80	240	57	45	81	3	83
20	EAA	U	4-(Br)-C_6H_4	4at	180	82	240	61	45	83	3	85

Note. Reaction conditions: acetyl acetone (AA) or ethylacetoacetate (EAA) $\mathbf{R^1}$ (1 mmol), urea (U) or thiourea (T) **X** (1.2 mmol) with aldehydes $\mathbf{R^2}$ (1 mmol) and Silver trifluoromethanesulfonate (0.20 mmol at 80°C Temperature; acetonitrile 5 mL; water 5 mL; time: 3 h in CH_3CN, 4 h in water, 45 min in neat (conventional heating [CH]), and 3 min in CH_3CN (microwave [MW]).

[a]Isolated yield.

under standard reaction conditions, producing the desired products (Table 3, entries 1-8). Moreover, it was fascinating to identify that excellent amount of conversion of dihydropyrimidine was observed when we used heterocyclic aldehydes in the optimized reaction condition (Table 3, entries 9-11). Additionally, by changing the 1,3-diketone source acetyl acetone by ethyl acetoacetate and allowing to react with urea or thiourea (Table 3, entries 12-20), the desired dihydropyrimidine products were found in good to excellent yields by up to 83% to 96%. After separation of the precipitate obtained on addition of ice cold water to the reaction mixture, the water phase with the catalyst was distilled to dryness and utilized again for the transformation. Yield of the obtained product was found to be similar to the reaction did in water or acetonitrile. Since the silver trifluoromethanesulfonate is soluble in water and some organic solvents, even though $CF_3SO_3^-$ is an extremely stable anion. Due to strong solvation ability of the densely occupied used solvents with the catalyst, here, silver triflate incorporated with the reactants to results excellent catalytic performance to afford desired products. Inclusion of that, in water medium, triflates act as more acidic by nature since triflate anion is an outstanding leaving group. Conversely, in gas phase or other organic solvent medium also, it serves as acidic in nature.[22]

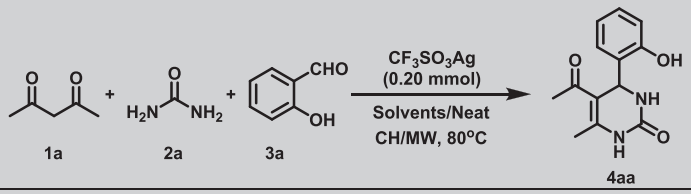
As reusability of the catalyst after the completion of the reaction are the main advantages of reactions. Since triflates are active in accord with many Lewis bases having oxygen, nitrogen, sulfur, etc. Thus, in common organic solvents along with water, the triflate catalysts can be recovered from the aqueous phase and reused without attenuated activity.[23] So, we opted to improve a simple synthetic pathway, which allows to reuse the catalyst for numerous time. Since the yield getting after separation of the product by filtration is relatively lower when water was used over acetonitrile as solvents, the recovered solvent containing silver trifluoromethanesulfonate was reused up to seven times without any significant loss of catalytic activity (Table 4). Under the neat condition, recyclability of the catalyst was not tested. But here in microwave mediated reaction, we are using acetonitrile as solvent to reuse of catalyst. These results clearly indicate the potent nature and stability of the catalyst by maintaining the activity.

In this view of sustainable research, we studied the change of size and morphology of the reused catalyst by transmission electron microscopy (TEM) (Figure 1). From Figure 1, we observed that the catalysts consist of spherical particles with well distribution. Comparing TEM images of fresh silver trifluoromethanesulfonate (Figure 1A-C) with TEM images of the catalyst after multiple reuses (Figure 1D-F), there was no apparent change in respect to size and morphology of the recovered catalyst. With this type of alluring, results revealed that the catalyst is stable and sustains for such catalytic conditions.

Since we have carried out many conventionally heating and microwave-assisted reactions under different environments, so the energy consumed by the reactions was calculated as we mentioned in our earlier report.[24] Herein, when the reaction reached its respective yield, we examined the energy consumptions as well as energy efficiency by the aforesaid reaction (Scheme 2). Apparently, it has been observed that for this reaction, the microwave-irradiated method is far more energy efficient and preferable than conventional heating method.

The most possible mechanism of the reaction is depicted in Scheme 3. As described in the pathway, we proposed that the reaction proceeds via the formation of the *N*-acylimine formed from aldehyde and urea (or thiourea). The coordination of the lone pair of the nitrogen atom in the *N*-acylimine with the salt (silver trifluoromethanesulfonate) could lead to the in situ formation of an *N*-carbamoyliminium ion **I**. This possibly formed a complex with silver trifluoromethanesulfonate ion along with NO_3^- anion similar to the reported one.[25] *N*-carbamoyliminium ion **I** is sufficiently electrophilic in the complex to react with the enol form of β-dicarbonyl **II** promoted by the NO_3^- ions. Thus, **I** and **II** afford an open chain intermediate **III**, which on further intra-molecular cyclization, with loss of H_2O, produces 3,4-dihydropyrimidine-2(1*H*)-one (or 3,4-dihydropyrimidine-2(1*H*)-thione) **IV**.

TABLE 4 Reusabilty study on silver trifluoromethanesulfonate as catalyst for the synthesis of dihydropyrimidinones



Number of cycles	Yield[a]					
	Acetonitrile		Water		Microwave	
	Time, min	Yield, %	Time, min	Yield, %	Time, min	Yield, %
1st run	180	94	240	68	3	97
2nd run	180	94	240	68	3	95
3rd run	180	93	240	67	3	94
4th run	180	92	240	65	3	94
5th run	180	91	240	65	3	91
6th run	180	90	240	63	3	90
7th run	180	85	240	63	3	87

Note. Reaction conditions: acetyl acetone **1a** (1 mmol), urea **2a** (1.2 mmol), 2-hydroxybenzaldehyde **3a** (1 mmol); acetonitrile 5 mL, water 5 mL; time: 3 h in CH_3CN, 4 h in water for conventional heating (CH), and 3 min for microwave (MW) using CH_3CN.

[a]Isolated yield.

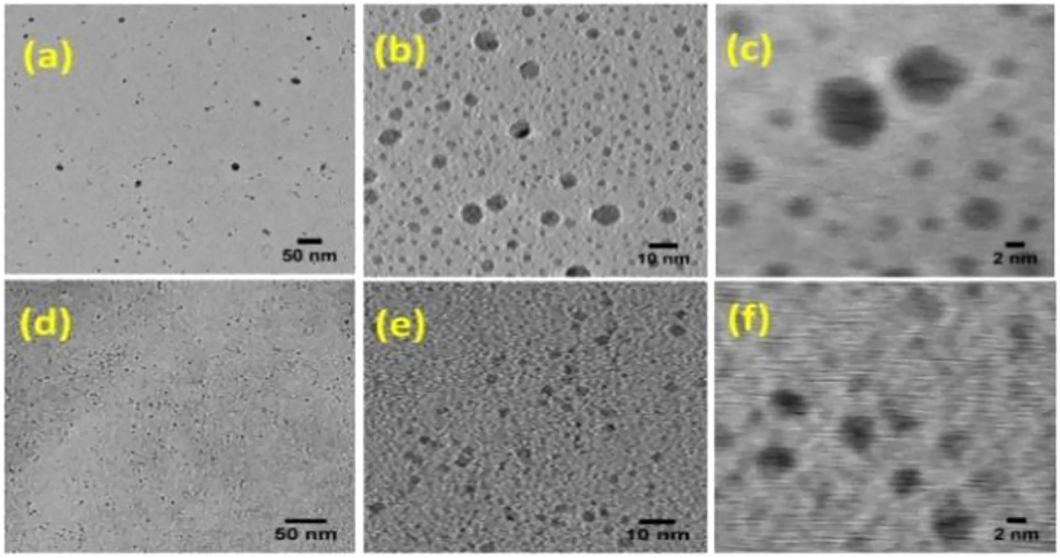
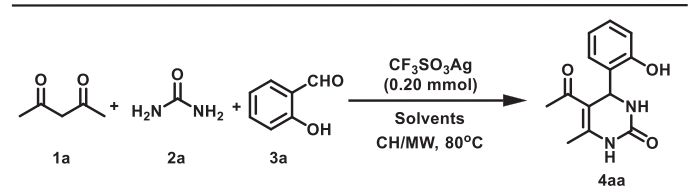
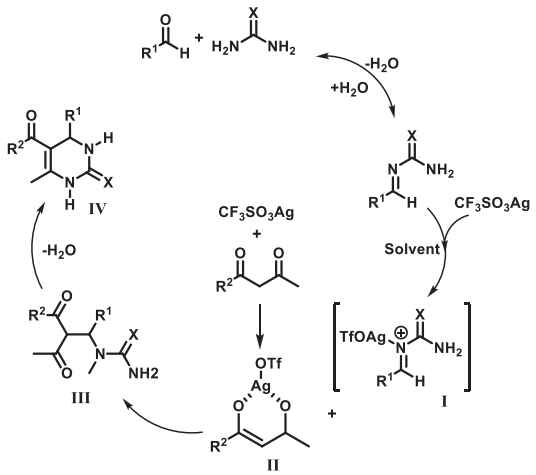


FIGURE 1 A to C, Transmission electron microscopy (TEM) images of fresh silver trifluoromethanesulfonate; D to F, TEM images of reused silver trifluoromethanesulfonate after 7th run [Color figure can be viewed at wileyonlinelibrary.com]



	Yields (%)	Energy Use (kWh)	Energy Efficiency (kWh/%)
$MW_{0.05h}$	95	0.0017	0.0018
CH_{3h}	95	0.9	0.0094

SCHEME 2 Energy efficiency of the reaction by microwave (MW) and conventional heating (CH) methods



SCHEME 3 Plausible mechanism for the synthesis of dihydropyrimidinones (DHPM) derivatives using CF_3SO_3Ag

3 | CONCLUSIONS

From our experiments, we have demonstrated a simple, mild, economic, and environmental friendly protocol for three-component condensation of substituted aldehydes, acetylacetone, or ethylacetoacetate with urea or thiourea to produce 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione using silver trifluoromethanesulfonate as reusable catalyst (seven times) with or without microwave irradiation. The high level of diversity is achievable in terms of employing different catalytic environments in one-pot multicomponent protocol without doing column chromatography. Thus, with various salient features, this method provides much improved and efficient alternative route to the existing Biginelli methods for the synthesis of dihydropyrimidine derivatives.

4 | EXPERIMENTAL SECTION

All chemicals were purchased from commercially available sources and were used without further purification. ^1H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were 125 MHz in $CDCl_3$ and/or DMSO-d_6

using tetramethylsilane (TMS, δ = 0.000 ppm) as an internal standard with Bruker Avance DPX. All chemical shifts (δ) are reported in ppm and coupling constant (*J*) in Hz. IR spectra were obtained from Elmer FT-IR-2000 spectrometer either on a thin film using chloroform or by potassium bromide pellets. Mass spectra data were recorded on Trace DSQ GC-MS instrument. All microwave-irradiated experiments were carried out on a Prolabo Synthwave Microwave reactor 402 in quartz reaction vessels. In conventional heating method, reactions were performed in Remi Magnetic Stirrers with Hotplate, 2MLH. Melting points were determined in open capillary tubes with a Buchi-540 micro melting point apparatus. TLC experiments were performed using pre-coated Silica gel 60 F_{254} sheets (Merck). Aqueous mother liquor was concentrated using HETO lyophilizer working at −54°C and 10 to 38 milibar pressure. High-resolution transmission electron microscopy (HRTEM) was recorded on an electron microscope JEM-2100, 200 kV, JEOL.

4.1 | Experimental details

4.1.1 | General experimental procedures

Syntheses of 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione (DHPM) were carried out in four different conditions. Initially, the reaction was carried out using acetonitrile as solvent. Then, the process was extended using water as well as under solvent-free neat conditions under heating and microwave irradiation using microwave reactor. While the reaction was carried out using solvent such as water, the solvent was reused after separating the product by filtration. In case of second and subsequent runs, no extra amount of catalyst were used.

4.1.2 | Procedure for synthesis of 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione in acetonitrile or water

Aldehydes (1 mmol), acetyl acetone or ethyl acetoacetate (1 mmol) and urea or thiourea (1.2 mmol) with silver trifluoromethanesulfonate (0.20 mmol) were mixed with acetonitrile or water (5 mL) in a 25-mL round bottom (RB) flask and refluxed for appropriate time. The reaction mixture was cooled in ice, and the precipitated solid was filtered through a sintered funnel. The crude product was further purified by recrystallization from ethanol to afford pure 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione. The filtrate obtained was reused for the next reaction after evaporated to the dryness.

4.1.3 | Procedure for solvent-free synthesis of 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione

A 10-mL RB flask along with a magnetic stirring bar was charged with aldehyde (1 mmol), acetyl acetone or ethyl acetoacetate (1 mmol) and urea or thiourea (1.2 mmol) with silver trifluoromethanesulfonate (0.20 mmol). The flask was dipped in preheated oil bath at 80°C (bath temperature). The contents were stirred till the solution mixture turned to solid mass. Ice cold water (10 mL) was added, and mixture was swirled with a glass rod. Thereafter, the solid product was separated by filtration, washed with ice-cold water (2 × 5 mL), and dried. The crude product was purified by recrystallization from ethanol.

4.1.4 | Procedure for synthesis of 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione under microwave irradiation

In a typical reaction, a mixture of 1 mmol of an aldehyde, 1.2 mmol of thiourea (or urea), and 1 mmol of acetylacetone (or ethyl acetoacetate) was mixed thoroughly with 0.20 mmol of silver trifluoromethanesulfonate and acetonitrile (5 mL) in a quartz reaction vessel of Prolabo Synthwave Microwave reactor 402 and allowed to react under microwave irradiation at a temperature of 80°C for 3 minutes in 35 W. During the reaction, the temperature was not allowed to rise above 80°C by setting the programmer. Then, ice cold water was added to the reaction mixture, and precipitated solid was separated by filtration, washed with ice-cold water (2 × 5 mL), and then recrystallized from ethanol to get 3,4-dihydropyrimidine-2(1*H*)-one and 3,4-dihydropyrimidine-2(1*H*)-thione. The solvent containing the catalyst was lyophilized to remove the solvents, and resulting substance was reused further for catalysis.

5-acetyl-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4aa)

Using the general experimental procedure to afford 4aa as white solid, (239 mg, 97% yield), M. P.: 208°C, ^{1}H NMR (DMSO, 500 MHz): δ 7.18 (s, 1H), 7.51 (s, 1H), 6.90-6.88 (m, 2H), 5.70 (d, 1H, J = 3.0 Hz), 2.28 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (DMSO, 125 MHz): 203.11, 154.69, 150.76, 129.66, 128.84, 125.98, 120.22, 116.47, 83.22, 49.74, 28.90, 23.51; FT-IR (KBR, cm^{-1}): 3247, 3003, 2939, 1706, 1695, 1441, 1239, 902; MS (*m/z*): 246.1 [M^+].

5-acetyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4bb)

Using the general experimental procedure to afford 4bb as white solid, (254 mg, 96% yield), M. P.: 211°C, ^{1}H NMR (DMSO, 500 MHz): δ 8.88 (s, 1H), 8.41 (s, 1H), 7.41 (t, 3H, J = 10 Hz, 10 Hz), 6.76 (t, 1H, J = 7 Hz, 5 Hz), 5.30 (d, 1H, J = 2.5 Hz), 2.35 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (DMSO, 125 MHz): 195.23, 157.52, 152.31, 146.97, 144.78, 129.62, 117.46, 115.00, 113.61, 109.38, 55.49, 30.00, 19.35; FT-IR (KBR, cm^{-1}): 3243, 3103, 2931, 1708, 1664, 1456, 1241, 768; MS (*m/z*): 262.1 [M$^+$].

5-acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4ac)

Using the general experimental procedure to afford 4ac as yellow solid, (253 mg, 97% yield), M. P.: 171°C, ^{1}H NMR (DMSO, 500 MHz): δ 9.90 (s, 1H), 7.83 (s, 1H),7.21(d, 2H, J = 6.0 Hz), 6.85 (d, 2H, J = 6.0 Hz), 5.39 (s, 1H), 3.78 (s, 3H), 2.34 (s, 3H), 2.11 (s, 3H),; ^{13}C NMR (DMSO, 125 MHz): 195.47, 159.52, 153.42, 145.57, 135.25, 127.90, 114.39, 110.69, 55.24, 55.29, 30.74, 19.59; FT-IR (KBR, cm^{-1}): 3306, 1698, 1614, 1466, 1364, 1235, 1178, 832; MS (*m/z*): 260.88 [M$^+$].

5-acetyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4ad)

Using the general experimental procedure to afford 4ad as yellow solid, (258 mg, 93% yield), M. P.: 215°C, ^{1}H NMR (DMSO, 500 MHz): δ 9.11 (s, 1H), 8.96 (s, 1H), 7.70 (q, 1H), 6.85 (d, 2H, J = 2 Hz), 6.58–6.71 (m, 1H), 5.16 (d, 1H), 3.73 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 195.29, 152.75, 148.46, 148.12, 146.55, 135.70, 119.08, 115.93, 111.82, 109.88, 56.69, 54.36, 30.71, 19.19; FT-IR (KBR, cm^{-1}): 3388, 1659, 1555, 1425, 1119, 1022, 729; MS (*m/z*): 276.0 [M$^+$].

5-acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4be)

Using the general experimental procedure to afford 4be as white solid, (224 mg, 90% yield), M. P.: 220°C, ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 8.86 (s, 1H), 7.42 (s, 1H), 7.32 (d, 1H, J = 3.0 Hz), 6.94 (d, 1H, J = 10 Hz), 5.40 (d, 1H, J = 3 Hz), 2.31 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 195.04, 163.72, 152.92, 147.26, 139.44, 128.40, 115.30, 110.22, 54.56, 30.27, 19.42; FT-IR (KBR, cm^{-1}): 3294, 1708, 1677, 1614, 1509, 1331, 1236, 1157, 839; MS (*m/z*): 248.0 [M$^+$].

5-acetyl-4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4af)

Using the general experimental procedure to afford 4af as white solid, (275 mg, 91% yield), M. P.: 225°C, ^{1}H NMR (DMSO, 500 MHz) δ 9.30 (s, 1H), 8.30 (s, 1H), 7.78 (q, 1H, J = 15 Hz), 7.25-7.41 (m, 3H), 5.62 (d, 1H, J = 3.5 Hz), 2.33 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (DMSO, 125 MHz): 194.54, 152.06, 149.72, 140.72, 133.49, 133.43, 130.58, 129.62, 128.65, 109.06, 51.82, 30.93, 19.18; FT-IR (KBR, cm^{-1}): 3429, 1712, 1668, 1620, 1466, 1384, 1230, 1102, 1046, 825; MS (*m/z*): 302.0 [M$^+$].

5-acetyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4ag)

Using the general experimental procedure to afford 4ag as white solid, (266 mg, 86% yield), M. P.: 216°C, ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 8.98 (s, 1H), 7.55 (s, 1H), 7.85 (d, 1H, J = 10 Hz), 7.04 (d, 1H, J = 10 Hz), 5.85 (d, 1H, J = 5 Hz), 2.44 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 196.54, 164.70, 154.77, 149.88, 138.99, 129.54, 116.42, 111.86, 55.32, 31.29, 18.62; FT-IR (KBR, cm^{-1}): 3289, 1718, 1622, 1599, 1512, 1349, 1207, 1124, 809; MS (*m/z*): 308.0 [M$^+$].

5-acetyl-4-(4-(benzyloxy)phenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4ah)

Using the general experimental procedure to afford 4ah as white solid, (294 mg, 89% yield), M. P.: 221°C, ^{1}H NMR (DMSO, 500 MHz): δ 9.08 (s, 1H), 7.76 (s, 1H), 6.91-7.40 (m, 4H), 5.19 (d, 1H, J = 5 Hz), 2.25 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (DMSO, 125 MHz): 196.04, 158.21, 152.93,148.82, 137.54, 136.89, 129.15,128.56, 128.26, 115.44, 110.46, 69.81, 53.83, 30.74, 19.44; FT-IR (KBR, cm^{-1}): 3295, 1699, 1608, 1509, 1453, 1383, 1236, 1173, 830; MS (*m/z*): 329.1 [M$^+$].

5-acetyl-6-methyl-4-(thiophen-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (4ai)

Using the general experimental procedure to afford 4ai as brown solid, (213 mg, 90% yield), M. P.: 212°C, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (s, 1H), 7.20 (s, 1H), 7.09 (s, 1H), 6.45 (s, 1H),, 6.44 (d, 1H, J = 5.0 Hz), 5.43 (d, 1H, J = 2.5 Hz), 2.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 194.90, 147.79, 145.57, 137.28, 123.96, 117.35, 111.96, 119.41, 105.59, 48.10, 30.49, 25.13; FT-IR (KBR, cm^{-1}): 3268, 1788, 1674, 1588, 1322, 1177, 899; MS (*m/z*): 236.1 [M$^+$].

5-acetyl-6-methyl-4-(pyridin-4-yl)-3,4-dihydropyrimidin-2(1*H*)-one (4aj)

Using the general experimental procedure to afford 4aj as yellow solid, (202 mg, 87% yield), M. P.: greater than 300°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 9.50 (s, 1H), 8.97 (s, 1H), 6.67-6.88 (m, 1H), 5.31 (s, 1H), 2.37 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 195.67, 147.32, 146.02, 133.69, 119.27, 115.06, 110.33, 55.66, 29.86, 18.59; FT-IR (KBR, cm^{-1}): 3293,

3183, 2990, 1630, 1583, 1449, 1367, 1274, 1191, 949; MS (*m/z*): 231.1 [M^+].

5-acetyl-4-(1*H*-indol-3-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4ak)

Using the general experimental procedure to afford 4ak as white solid, (228 mg, 85% yield), M. P.: 222°C, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.83 (s, 1H), 8.31 (s, 1H), 7.56 (d, 1H, J = 10 Hz), 7.35 (d, 1H, J = 10 Hz), 6.88-7.12 (m, 2H), 4.21 (s, 1H), 2.48 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 206.42, 157.57, 151.52, 136.33, 127.43, 122.41, 122.11, 121.76, 119.11, 119.03, 115.52, 110.94, 32.11, 22.20, 18.74; FT-IR (KBR, cm^{-1}): 3400, 1608, 1439, 1239, 1015, 745; MS (*m/z*): 269.1 [M^+].

ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4al)

Using the general experimental procedure to afford 4al as white solid, (263 mg, 95% yield), M. P.: 166°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 8.87 (s, 1H), 8.62 (s, 1H), 7.09 (d, 1H, J = 10 Hz), 6.88 (d, 1H, J = 10 Hz), 5.28 (d, 1H, J = 3 Hz), 4.07 (q, 2H, J = 4 Hz), 2.33 (s, 3H), 1.19 (t, 3H, J = 5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 165.71, 157.26, 152.68, 152.27, 146.73, 129.31, 117.52, 114.80, 113.56, 55.19, 18.43, 14.01; FT-IR (KBR, cm^{-1}): 3245, 1725, 1643, 1454, 1221, 1091, 777; MS (*m/z*): 276.0 [M^+].

ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4am)

Using the general experimental procedure to afford 4am as white solid, (266 mg, 96% yield), M. P.: 193°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 8.80 (s, 1H), 8.58 (s, 1H), 7.41 (s, 1H), 7.13 (d, 1H, J = 5 Hz), 6.75 (d, 1H, J = 5 Hz), 5.26 (d, 1H, J = 2.5 Hz), 4.05 (q, 2H, J = 5 Hz), 2.32 (s, 3H), 1.16 (t, 3H, J = 5 Hz, 5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 165.74, 156.43, 153.11, 146.62, 135.22, 127.55, 115.07, 100.76, 59.36, 54.38, 18.05, 13.92; FT-IR (KBR, cm^{-1}): 3199, 1709, 1589, 1470, 1310, 1196, 1047, 813; MS (*m/z*): 276.1 [M^+].

ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4bn)

Using the general experimental procedure to afford 4bn as white solid, (263 mg, 91% yield), M. P.: 195°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 8.80 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 7.13 (d, 1H, J = 10 Hz), 6.75 (d, 1H, J = 10.0 Hz), 5.26 (d, 1H, J = 2.5 Hz), 4.05 (q, 2H, J = 4.0 Hz), 2.32 (s, 3H), 1.16 (t, 3H, J = 5 Hz, 5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 174.33, 165.73, 157.00, 143.68, 134.37, 128.12, 115.45, 102.41, 59.94, 54.97, 17.87, 14.10; FT-IR (KBR, cm^{-1}): 3207, 1716, 1585, 1476, 1315, 1189, 1084, 834; MS (*m/z*): 291.9 [M^+].

ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4ao)

Using the general experimental procedure to afford 4ao as white solid, (262 mg, 90% yield), M. P.: 208°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 7.49 (s, 1H), 7.24 (s, 1H), 7.23 (d, 1H, J = 5 Hz), 6.83 (d, 1H, J = 10 Hz), 5.35 (d, 1H, J = 15 Hz), 4.07 (q, 2H, J = 7.5 Hz), 3.78 (s, 3H), 2.34 (s, 3H), 1.17 (t, 3H, J = 5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 165.55, 159.14, 152.67, 145.48, 135.90, 127.72, 113.87, 101.69, 59.96, 55.17, 18.73, 14.06; FT-IR (KBR, cm^{-1}): 3230, 3121, 1722, 1628, 1543, 1380, 1230, 1040, 799; MS (*m/z*): 290.1 [M+].

ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4bp)

Using the general experimental procedure to afford 4bp as white solid, (2767 mg, 87% yield), M. P.: 218°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 9.57 (s, 1H), 8.88 (s, 1H), 7.49 (d, 1H, J = 5 Hz), 6.81 (d, 1H, J = 10 Hz), 5.29 (d, 1H, J = 3 Hz), 4.07 (q, 2H, J = 7.5 Hz), 3.82 (s, 3H), 2.92 (s, 3H), 1.18 (t, 3H, J = 5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 179.11, 170.36, 163.71, 148.90, 140.57, 132.76, 118.41, 106.63, 64.55, 59.86, 59.26, 22.45, 18.78; FT-IR (KBR, cm^{-1}): 3246, 3115, 1706, 1652, 1514, 1384, 1225, 1089, 791; MS (*m/z*): 306.0 [M+].

ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4bq)

Using the general experimental procedure to afford 4bq as yellow solid, (278 mg, 86% yield), M. P.: 238°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 9.43 (s, 1H), 8.74 (s, 1H), 6.82 (d, 1H, J = 8 Hz), 6.74-6.79 (m, 2H), 5.27 (d, 1H, J = 3 Hz), 4.07 (q, 2H, J = 2.0 Hz), 3.84 (s, 3H), 2.35 (s, 3H), 1.18 (t, 3H, J = 1.5 Hz, 1.5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 184.63, 174.28, 165.58, 146.93, 145.73, 134.83, 119.29, 114.81, 110.00, 102.01, 59.80, 55.70, 54.99, 17.74, 13.96; FT-IR (KBR, cm^{-1}): 3246, 3118, 1698, 1645, 1516, 1453, 1222, 1092, 799; MS (*m/z*): 322.1 [M^+].

ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4ar)

Using the general experimental procedure to afford 4ar as white solid, (280 mg, 85% yield), M. P.: 229°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 8.98 (s, 1H), 7.10-7.45 (m, 2H), 6.10 (d, 1H, J = 10 Hz), 5.72 (d, 1H, J = 10 Hz), 4.10 (q, 2H, J = 5 Hz), 2.21 (s, 3H), 1.28 (t, 3H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 168.69, 153.54, 150.24, 139.51, 133.71, 130.78, 128.64, 98.92, 58.74, 52.23, 18.72, 11.95; FT-IR (KBR, cm^{-1}): 3359, 1750, 1454, 1390, 1219, 1110, 809; MS (*m/z*): 328.0 [M^+].

ethyl 4-(2,4-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4bs)

Using the general experimental procedure to afford 4bs as white solid, (283 mg, 83% yield), M. P.: 236°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 8.66 (s, 1H), 7.19-7.39 (m, 1H), 6.04 (d, 1H, J = 6.0 Hz), 5.79 (d, 1H, J = 6.0 Hz), 4.01 (q, 2H, J = 4.0 Hz), 2.17 (s, 3H), 1.10 (t, 3H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 165.19, 152.00, 149.19, 138.95, 132.98, 129.13, 127.51, 97.97, 59.65, 51.47, 18.12, 13.85; FT-IR (KBR, cm^{-1}): 3361, 1704, 1466, 1384, 1227, 1100, 817; MS (m/z): 344.8 [M^+].

ethyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4at)

Using the general experimental procedure to afford 4at as pale yellow solid, (288 mg, 85% yield), M. P.: 215°C, ^{1}H NMR ($CDCl_3$ and DMSO, 500 MHz): δ 8.75 (s, 1H); 7.85 (d, 1H, J = 10 Hz), 7.65 (d, 1H, J = 10 Hz), 7.12-7.40 (m, 1H), 5.81 (d, 1H, J = 3.0 Hz), 4.01 (q, 2H, J = 2.0 Hz), 2.44 (s, 3H), 1.06 (t, 3H, J = 3 Hz, 5 Hz); ^{13}C NMR ($CDCl_3$ and DMSO, 125 MHz): 165.26, 152.15, 148.88, 141.65, 132.88, 129.12, 122.55, 98.46, 59.47, 54.25, 17.94, 13.79; FT-IR (KBR, cm^{-1}): 3346, 2978, 1693, 1440, 1227, 1097, 744; MS (m/z): 338.0 [M^+].

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ORCID

Kashyap Jyoti Tamuli https://orcid.org/0000-0002-3110-5644

Manobjyoti Bordoloi https://orcid.org/0000-0003-0478-6824

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