N,N′-Dialkyl-4-Aryl-3,4-Dihydropyrimidinones and Thiones: Ceric Ammonium Nitrate Catalyzed Synthesis and Molecular Structure Determination by X-ray Crystallography

Chingrishon Kathing,[a] Sushil Kumar,[b] Shokip Tumtin,[c] Nongthombam Geetmani Singh,[a] Jims World Star Rani,[a] Ridaphun Nongrum,[a] and Rishanlang Nongkhlaw[a]*

[a]Centre for Advanced Studies in Chemistry, North-Eastern Hill University, Shillong, Meghalaya 793022, India
[b]Department of Chemistry, University of Delhi, Delhi 110007, India
[c]Department of Chemistry, Kirori Mal College, University of Delhi, Delhi 110007, India
E-mail: rlnongkhlaw@nehu.ac.in

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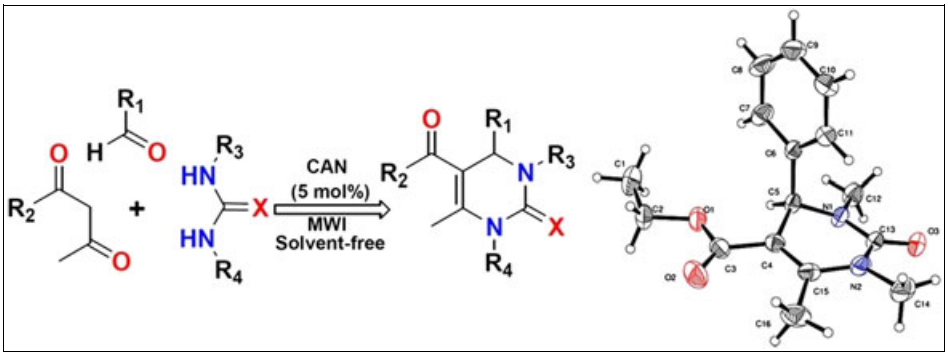

This work presents a microwave assisted solvent-free synthesis of *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones/thiones in the presence of Ceric Ammonium Nitrate (CAN) via direct condensation of aromatic aldehydes, β-keto ester, and *N,N′*-dialkylurea/thiourea. The highlights of the methodology adopted are (i) facile condensation of the reactants into product without any side-products, and (ii) short reaction time with high yield and good purity. All the compounds synthesized were characterized and established by spectroscopic techniques such as FTIR, ^{1}H NMR, ^{13}C NMR, and Mass. The structure of the compound is further corroborated by single crystal X-ray diffraction analysis.

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INTRODUCTION

"Multicomponent reaction" (MCR) plays a vital role in the field of medicinal chemistry [1] for the rapid synthesis of diverse classes of biologically potent organic molecules for modern drug discovery [2]. Operational simplicity in one pot is one of the key features of MCR, apart from being cost effective, atom-economy, and minimization of waste generation [3–5]. As far as the activation of any synthetic reaction is concerned, environmentally benign microwave induced reactions provide spectacular accelerations on the reactions with a clean reaction profile [6]. Therefore, combination of MCR and microwave irradiation (multicomponent microwave synthesis) [7] has emerged as a powerful technique, for the construction of complex heterocyclic scaffolds [8].

The so-called "Biginelli compound", i.e. 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) has prompted a widespread research because of its multifaceted pharmacological profiles [9]. The importance of DHPMs has also been intensified because of their apparent structure–activity similarities with the well-known Hantzsch-type dihydropyridines (DHP) (e.g. nifedipine) [10,11].

Despite extensive research on this area, direct synthesis of *N,N′*-dialkyl DHPM through "a classical Biginelli condensation" of aromatic aldehyde, β-keto ester, and *N,N′*-dialkylurea/thiourea has not been well documented. Exhaustive literature survey revealed that, Singh *et al.* [12] have reported the synthesis of *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones using Dowex-50 W ion exchange resin. Sangran and co-workers [13] have also carried out the work using low melting tartaric acid urea mixtures. In addition, Biginelli reaction for the preparation of *N*-substituted ureas and thioureas promoted by Chlorotrimethylsilane has also been achieved by Ryabukhin [14]. C. Mukhopadhya *et al.* [15] have also employed alkaline metal (II) sulfates as a catalyst to synthesize *N,N′*-dimethyl substituted and unsubstituted 4-aryl-3,4-dihydropyrimidones (thiones). Direct condensation for the preparation of *N*1 monoalkyl DHPM using monoalkylated ureas has also been studied by Kappe and Co-workers [16]. Furthermore, the use of high pressure technique for the synthesis of DHPM has also been reported by G. Jenner [17]. Even though there have been extensive work on the synthesis of DHPM, their methodologies have been rendered ineffective despite the

satisfactory results because of prolonged reaction time, low yield, and multitude of side-products [18].

With an aim to develop an efficient methodology, we have synthesized *N,N′*-dialkyl DHPM under solvent-free condition in the presence of Ceric Ammonium Nitrate (CAN) in catalytic amount of 5 mol% as an activator under microwave irradiation. The involvement of CAN in catalytic amount gives an edge to the synthetic method as it has emerged as a versatile reagent for various organic transformations in modern chemical synthesis because of its various characteristic features such as electron transfer capacity, Lewis acid property, higher solubility in organic solvents, low toxicity, and ease of handling [19,20]. Furthermore, the activation of MCR by environmentally benign microwave irradiation is expected to provide a clean synthetic route.

RESULTS AND DISCUSSION

As a preliminary investigation, different quantities of reactants were explored and the best results were obtained using 1:1:1.5 mol ratios of aromatic aldehydes, β-keto ester and *N,N′*-dimethylurea/thiourea respectively. As a model reaction (Scheme 1), benzaldehyde, ethyl acetoacetate, and *N,N′*-dimethylurea (1:1:1.5) with catalytic amount of CAN (5 mol%) under solvent-free conditions were subjected to microwave irradiation at 80°C for 90 s which resulted the product 4b with an excellent yield of 96% (Table 1).

Under normal room temperature stirring, product 4b was formed in 12 h with a mere 40% yield and no product formation was observed in the absence of catalyst. The catalytic efficiency of CAN for the synthesis of *N,N′*-dialkyl DHPM is compared with various catalysts such as PTSA, $NaHSO_4$, $AlCl_3$, and $SnCl_2{\cdot}2H_2O$ (Table 2). The comparative study shows that CAN exhibits superior catalytic efficiency over the other catalysts.

Furthermore, various operational parameters such as temperature and catalyst loading which affects the product formation was investigated and optimized. It was found that the highest yield could be achieved at 80°C with 5 mol% of catalyst loading and further increase in temperature from 80°C to120°C resulted in the formation of side products with low product yield. Similarly, no significant impacts on the yield of the reactions were observed upon increasing the amount of catalyst from 5 mol% up to 25 mol%.

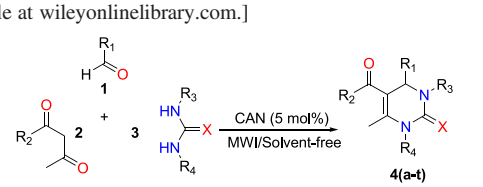
In order to generalize the scope of this methodology, a series of reactions were carried out to synthesize *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones (4a–4n) as shown in Table 1 and the products were isolated by recrystallization without column chromatography in good yield (>80%) along with enhanced purity as determined from the spectra. The reaction was also extended to thiourea and their derivatives (4o–4t, Table 1) using *N,N′*-dimethylthiourea, which are immensely important with regard to their biological activities such as monastrol, [21] which act as mitotic kinesin Eg5 inhibitors; notable results similar to *N,N′*-dimethylurea derivatives were observed. Upon further analysis, it was found that various aromatic aldehydes bearing electron donating and electron withdrawing groups undergo smooth transformation with no major effect on the yield of the products. Apart from simplicity in operation, the efficacy of our methodology is furthermore validated by the survivals of varieties of functional groups such as NO_2, OH, Cl, OMe, etc.

The mechanistic pathway for the formation of *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones is shown in Scheme 2. The reaction is proposed to proceed through the formation of carbonium ion (6) via an aldol condensation between aldehyde (1) and enolate of 1,3-dicarbonyl compound (2) activated by Ce^{4+}. The carbonium ion (6) in turn reacts with *N,N′*-dimethylurea/thiourea (3) to generate an open chain intermediate uriede (7) which then undergoes intramolecular cyclization to afford *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones/thiones (4).

In order to compare the efficacy of our methodology with the conventional method, the reaction was investigated under reflux condition, using ethanol as a best candidature as the reaction medium because ethanol has been considered as a green solvent [22]. The products 4 (b,c,f,o,t) with yields of 60–70% could be achieved at 80°C in 1–3 h (Table 3). The satisfactory result provides the scope of employing CAN as catalyst not only under microwave irradiation but under conventional heating as well. However, in spite of satisfactory results in conventional method, the microwave induced method under dry media is still preferable over conventional method as it is more economical and meet the fundamental challenges to conserve the environment.

All the compounds synthesized were characterized by spectroscopic techniques such as FTIR, ^{1}H NMR, ^{13}C NMR, and Mass. The various analytic results for all the compounds prepared were found to be in accordance with the expected structure. As a representative, the

Scheme 1. Synthesis of *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones/thiones. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



R_1 = C_6H_5, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 2-HO-C_6H_4, 4-HO-C_6H_4, 4-HO, 3-MeO-C_6H_3, 4-Me-C_6H_4, 4-Cl-C_6H_4, 2-Furyl
R_2 = OMe, OEt
R_3/R_4 = Me
X = O, S

Table 1

CAN catalyzed synthesis of *N,N′*-dimethyl-4-aryl-3,4-dihydropyrimidinones and thiones (**4a–4t**).

Entry	R_1	R_2	R_3	R_4	X	Time (s)	Yield[a] (%)	Mp°C
4a	C_6H_5	OMe	Me	Me	O	110	93	121–123
4b	C_6H_5	OEt	Me	Me	O	90	96	69–70
4c	4-MeO-C_6H_4	OMe	Me	Me	O	100	92	97–103
4d	4-Me-C_6H_4	OMe	Me	Me	O	90	94	93–95
4e	4-NO_2-C_6H_4	OMe	Me	Me	O	120	90	145–147
4f	4-NO_2-C_6H_4	OEt	Me	Me	O	120	89	102–104
4g	3-NO_2-C_6H_4	OMe	Me	Me	O	115	90	137–140
4h	4-OH,3-MeO-C_6H_3	OMe	Me	Me	O	100	92	155–157
4i	4-OH,3-MeO-C_6H_3	OEt	Me	Me	O	115	90	121–123
4j	4-OH-C_6H_4	OMe	Me	Me	O	120	85	186–188
4k	4-Cl-C_6H_4	OMe	Me	Me	O	110	91	80–82
4l	4-Cl-C_6H_4	OEt	Me	Me	O	110	93	50–52
4m	2-Cl-C_6H_4	OMe	Me	Me	O	100	84	135–137
4n	2-Furyl	OMe	Me	Me	O	145	81	59–61
4o	C_6H_5	OMe	Me	Me	S	155	85	133–135
4p	C_6H_5	OEt	Me	Me	S	146	83	70–72
4q	4-Cl-C_6H_4	OMe	Me	Me	S	140	87	125–127
4r	4-OH-C_6H_4	OMe	Me	Me	S	135	87	149–151
4s	4-Me-C_6H_4	OEt	Me	Me	S	120	90	88–90
4t	4-OH,3-MeO-C_6H_3	OMe	Me	Me	S	125	86	130–132

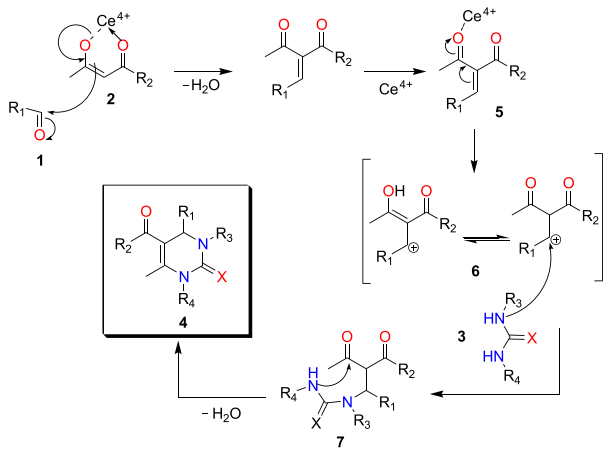
[a]Isolated yield.

Table 2

Effect of catalyst for the synthesis of **4b**.

Sl. no	Catalyst	Time (min)	Yield (%)
1	$NaHSO_4$	45	55
2	PTSA	30	75
3	$AlCl_3$	55	40
4	$SnCl_2.2H_2O$	60	30
5	CAN	1.5	96

Scheme 2. Plausible mechanism for the formation of *N,N′*-dialkyl-4-aryl-3,4-dihydropyrimidinones/thiones. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



compound 4b (Fig. 1) was selected whose spectral data is interpreted as follows. The occurrence of absorption bands at 1719 cm^{-1} and 1690 cm^{-1} in IR spectrum depicts the

Table 3

Comparative study under microwave and reflux condition.

Entry	Compound (**4**)	MWI Time (s)	MWI Yield (%)	RC Time (min)	RC Yield (%)
1	**4b**	90	96	60	70
2	**4c**	100	92	90	68
3	**4f**	120	89	130	64
4	**4o**	155	85	180	60
5	**4t**	125	86	150	62

MWI = microwave irradiation; RC = reflux condition.

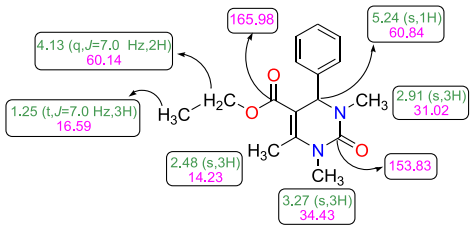


Figure 1. Selected ^1H and ^{13}C NMR data of **4b**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

stretching frequency of the two carbonyl (C=O) groups. In ^1H NMR spectrum, the methine (CH) proton appears as a singlet at δ 5.24 and the singlet observed at δ 2.48 corresponds to the methyl group of ethyl acetoacetate moiety on dihydropyrimidine ring. The two methyl groups of *N, N′*-dimethylurea resonate at different fields as two singlets

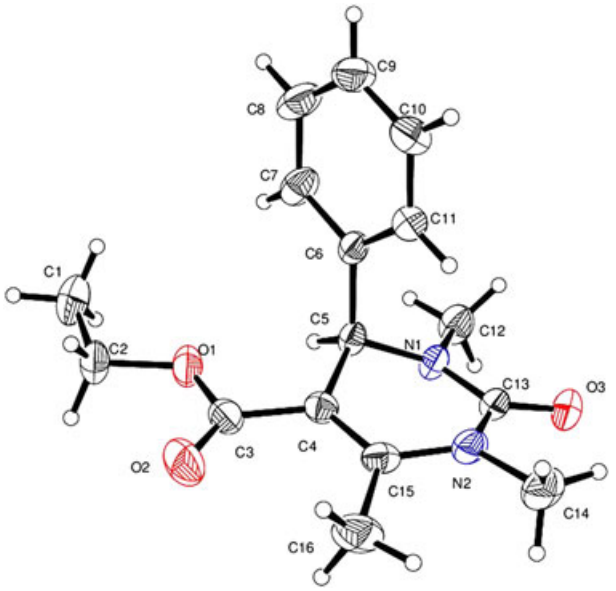


Figure 2. Molecular structure of **4b**; thermal ellipsoids are drawn at 30% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in the shielded region at δ 3.27 and δ 2.91 for *N*1-methyl and *N*3-methyl respectively. In addition to the IR information, the two carbonyl (C=O) groups are also confirmed from the ^{13}C NMR spectrum by the chemical shift values at δ 165.98 and δ 153.83.

The structure is further being elucidated from a single crystal X-ray analysis of 4b; the crystal was obtained by slow evaporation method from hexane. The molecular structure of 4b is shown in Figure 2 and its crystallographic data are listed in Table 4.

Table 4

Crystal data of the compound **4b**.

Empirical formula	$C_{16}H_{20}N_2O_3$
Formula weight	288.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P\ 2_1/c$
a	8.7884(7) Å
b	11.3956(11) Å
c	15.3417(14) Å
α	90°
β	92.255(7)°
γ	90°
Volume	1535.3(2) Å3
Z	4
Density (calculated)	1.247 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	616
Crystal size	0.24 × 0.22 × 0.21 mm^3
Theta range for data collection	3.20 to 25.00°
Index ranges	−10 ≤ h ≤ 10, −11 ≤ k ≤ 13, −18 ≤ l ≤ 18
Reflections collected	5450
Independent reflections	2696 [*R*(int) = 0.0230]
Completeness to theta = 25.00°	99.8%
Absorption correction	Multi-scan
Max. and min. transmission	0.9820 and 0.9795
Refinement method	Full-matrix least-squares on *F*2
Data/restraints/parameters	2696/0/195
Goodness-of-fit on *F*2	1.061
Final *R* indices [I > 2sigma (I)][a, b]	$R_1 = 0.0560$, $wR_2 = 0.1584$
R indices (all data)	$R_1 = 0.0757$, $wR_2 = 0.1704$
Largest diff. peak and hole	0.246 and −0.175 e.Å^{-3}

[a] $R = \Sigma(\|Fo\| - \|Fc\|)/\Sigma\|Fo\|$.
[b] $wR = \{\Sigma[w(Fo^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]\}^{1/2}$

CONCLUSIONS

In summary, a novel and efficient methodology with an excellent yield and short time of reaction has been devised for the direct synthesis of *N,N′*-dialkyl DHPM and its derivatives. The process involves the microwave assisted reactions under solvent-free condition which have ensued the rapid generation of a library of compounds as well as minimization of waste production thereby making the process more economical and environment friendly. The efficacy of the synthetic process is evident from the fact that the complete product formation could be accomplished within 90–155 s of reaction time with 81–96% of product yield. The preparation of the compounds, which were presumed to be complicated because of bulky nature of *N,N′*-dimethylurea/thiourea compared to unsubstituted urea/thiourea, was found to be rather facile and efficient which is substantiated by X-ray crystallography as well as spectroscopic techniques such as FTIR, ^{1}H NMR, ^{13}C NMR, and Mass. Convenient experimental work up and product isolation procedures without any tedious column chromatography for purification of the compounds further augment the efficacy of the methodology.

EXPERIMENTAL SECTION

Microwave reactions were carried out in a CEM Discover Benchmate microwave digester. Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument using KBr pellets and the frequencies are expressed in cm^{-1}. ^{1}H and ^{13}C NMR (400 MHz) spectra were recorded on a Bruker Avance II-400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm downfield from internal tetramethyl silane and are given on the δ scale. Mass spectral data were obtained with a JEOL D-300 (ESI) mass spectrometer. All reactions were

monitored by TLC using precoated aluminum sheets (silica gel 60 F 254 0.2-mm thickness) and developed in an iodine chamber or under UVGL-15 mineral light 254-nm lamp.

General procedure for microwave assisted synthesis. A mixture of aromatic aldehyde (1 mmol), β-keto ester (1 mmol), and *N,N′*-dimethylurea/thiourea (1.5 mmol) in the presence of a catalytic amount of CAN (5 mol%) was taken in a microwave reaction vial and irradiated in microwave digester at 80°C, 15–20 bar, 80–120 W for 90–155 s. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate and wash with brine (1 × 10 mL) followed by water (3 × 10 mL). The combine extract was evaporated in rotavapor and finally a solid was obtained. The solid obtained was almost a pure product; however, in some cases the products were further purified by recrystallization from hexane or ethanol.

General procedure for conventional method of synthesis. In a round bottom flask, the reactants aromatic aldehyde (1 mmol), β-keto ester (1 mmol), and *N,N′*-dimethylurea/thiourea (1.5 mmol) were taken with a catalytic amount of CAN (5 mol%) in the presence of ethanol and refluxed at 80°C for 1–3 h. After the completion of the reaction (monitored by TLC), the resultant reaction mixture was extracted and purified to afford the compounds following the same procedure as microwave method.

X-ray structure analysis. The intensity data was collected on an Oxford Xcalibur CCD diffractometer equipped with graphite monochromatic Mo-Kα radiation ($\lambda = 0.71073$ Å) at 293(2) K [23]. A multi-scan correction was applied. The structure was solved by the direct methods using SIR-92 and refined by full-matrix least-squares refinement techniques on F^2 using SHELXL97 [24]. The hydrogen atoms were placed into the calculated positions and included in the last cycles of the refinement. All calculations were done using Wingx software package [25].

Crystallographic data for the structure of the compound 4b have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1008429. Copies of the data can be obtained, free of charge, on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.Uk).

Characterization data of selected compounds are listed below

Ethyl 1,2,3,4-tetrahydro-1,3,6-trimethyl-2-oxo-4-phenylpyrimidine-5-carboxylate (4b). Colorless solid, yield 96%, mp 69–70°C; IR (KBr): 3029 (Ar—CH), 2977 (Alkyl–CH), 1701 (C=O), 1674 (C=O), 1208 (O—CO), 1032 (O—CH_2CH_3) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, $J = 7.0$ Hz, $CH_2\underline{CH_3}$), 2.48 (s, 3H, CH_3), 2.91 (s, 3H, N3—CH_3), 3.27 (s, 3H, N1—CH_3), 4.13 (q, $J = 7.0$ Hz, $\underline{CH_2}CH_3$), 5.24 (s, 1H, CH), 7.21–7.31 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.23, 16.59, 31.02, 34.43, 60.14, 60.84, 103.60, 126.62, 127.84, 128.59, 140.99, 149.24, 153.83, 165.98; MS (ESI): *m/z* 289 [M + 1]; *Anal.* cald. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; O, 16.65; Found: C, 66.90; H, 6.85; N, 9.55.

Methyl 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-1,3,6-trimethyl-2-oxopyrimidine-5-carboxylate (4c). Light yellow solid, yield 92%, mp 97–103°C; IR (KBr): 3049 (Ar—CH), 2945 (Alkyl–CH), 1702 (C=O), 1667 (C=O), 1214 (O—CO), 1031 (O—CH_3) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 2.90 (s, 3H, N3—CH_3), 3.26 (s, 3H, N1—CH_3), 3.67 (s, 3H, OCH_3), 3.78 (s, 3H, $COOCH_3$), 5.18 (s, 1H, CH), 6.81 (d, $J = 8.4$ Hz, 2H, Ar), 7.13 (d, $J = 8.4$ Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.63, 31.02, 34.33, 51.23, 55.21, 60.21, 103.63, 113.95, 127.75, 133.08, 149.20, 153.79, 159.19, 166.46; MS (ESI): m/z 305 [M + 1]; *Anal.* cald. for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20; O, 21.03; Found: C, 63.35; H, 6.52; N, 9.38.

Methyl 1,2,3,4-tetrahydro-1,3,6-trimethyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxylate (4e). Light yellow solid, yield 90%, mp 145–147°C; IR (KBr): 3078 (Ar—CH), 2959 (Alkyl–CH), 1681 (C=O), 1667 (C=O), 1219 (O—CO), 1029 (O—CH_3) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.87 (s, 3H, N3—CH_3), 3.21 (s, 3H, N1—CH_3), 3.64 (s, 3H, OCH_3), 5.30 (s, 1H, CH), 7.33 (d, $J = 8.0$ Hz, 2H, Ar), 8.10 (d, $J = 8.0$ Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.78, 30.22, 33.69, 50.48, 59.26, 101.32, 123.02, 126.38, 146.53, 147.13, 149.61, 152.47, 165.00; MS (ESI): *m/z* 320 [M + 1]; *Anal.* cald. for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16; O, 25.05; Found: C, 56.60; H, 5.52; N, 13.05.

Ethyl 1,2,3,4-tetrahydro-1,3,6-trimethyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxylate (4f). Yellow solid, yield 89%, mp 102–104°C; IR (KBr): 3038 (Ar—CH), 2991 (Alkyl–CH), 1678 (C=O), 1661 (C=O), 1214 (O—CO), 1028 (O—CH_2CH_3) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, $J = 6.9$ Hz, $CH_2\underline{CH_3}$), 2.50 (s, 3H, CH_3), 2.94 (s, 3H, N3—CH_3), 3.28 (s, 3H, N1—CH_3), 4.16 (q, $J = 6.9$ Hz, $\underline{CH_2}CH_3$), 5.37 (s, 1H, CH), 7.41 (d, $J = 8.4$ Hz, 2H, Ar), 8.17 (d, $J = 8.4$ Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.27, 16.74, 31.19, 34.64, 60.48, 60.37, 102.52, 123.97, 127.48, 147.53, 148.24, 150.31, 153.47, 165.56; MS (ESI): m/z 334 [M + 1]; *Anal.* cald. for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61; O, 24.00; Found: C, 57.80; H, 5.89; N, 12.45.

Methyl 1,2,3,4-tetrahydro-1,3,6-trimethyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxylate (4g). Yellow solid, yield 90%, mp 137–140°C; IR (KBr): 3094 (Ar—CH), 2947 (Alkyl–CH), 1703 (C=O), 1678 (C=O), 1205 (O—CO), 1032 (O—CH_3) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H, CH_3), 2.94 (s, 3H, N3—CH_3), 3.30 (s, 3H, N1—CH_3), 3.70 (s, 3H, OCH_3), 5.35 (s, 1H, CH), 7.48–8.15 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.71, 31.19, 34.59, 51.47, 60.42, 102.36, 121.81, 123.00,

129.78, 132.51, 143.14, 148.47, 150.64, 153.32, 165.93; MS (ESI): *m/z* 320 [M + 1]; *Anal*. cald. for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16; O, 25.05; Found: C, 56.59; H, 5.22; N, 13.25.

Methyl 1,2,3,4-tetrahydro-1,3,6-trimethyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (4o). Offwhite solid, yield 85%, mp 133–135°C; IR (KBr): 3018 (Ar—CH), 2948 (Alkyl–CH), 1702 (C=O), 1691 (C=S), 1211 (O—CO), 1068 (O—CH_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.48 (s, 3H, N3—CH_3), 3.57 (s, 3H, N1—CH_3), 3.78 (s, 3H, OCH_3), 5.59 (s, 1H, CH), 7.12–7.32 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.93, 38.11, 43.02, 51.70, 61.26, 105.72, 125.81, 128.01, 128.87, 139.47, 147.79, 166.10, 179.64; MS (ESI): *m/z* 291 [M + 1]; *Anal*. cald. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65; O, 11.02; S, 11.04; Found: C, 62.26; H, 6.15; N, 9.48.

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