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Full Paper

Synthesis of 4-Aryl Substituted 3,4-Dihydropyrimidinones Using Silica-chloride Under Solvent Free Conditions

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Abstract: This paper describes an improved procedure for the efficient and facile synthesis of 4-aryl substituted 3, 4-dihydropyrimidinones under mild reaction conditions with excellent yields using inexpensive silica chloride under solvent free conditions.

Keywords: Biginelli reaction; Dihydropyrimidinones; silica chloride; solvent free.

Introduction

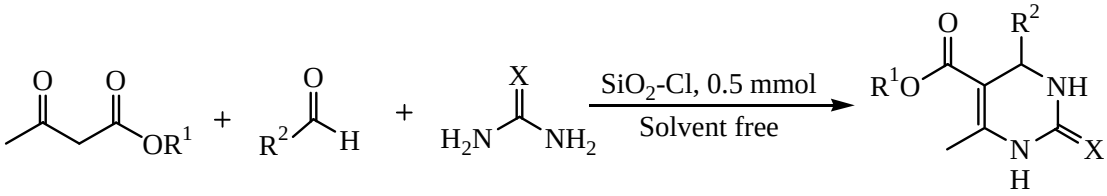
The Biginelli reaction is one of the most important multi-component reactions for the synthesis of dihydropyrimidinones. Dihydropyrimidinone are known to exhibit a wide range of biological activities such as antiviral, antitumour, antibacterial, and anti-inflammatory properties [1]. In addition, these compounds have emerged [2] as potential calcium channel blockers, antihypertensive, α_{1a}–adrenergic antagonists and neuropeptide antagonists. Furthermore the 2-oxodihydropyrimidine-5-carboxylate core unit is also found in many marine natural products [3], including the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD_4 inhibitors. The classical Biginelli reaction requires long reaction times (20 hrs) and often suffers from low yields of products in case of substituted aromatic and aliphatic aldehydes [4]. Multi-step synthesis [5] produces somewhat higher yields but lacks the simplicity of original one-pot Biginelli protocol, hence the Biginelli reaction continues to attract the attention of organic chemists interested in finding milder and more efficient procedures for the

synthesis of dihydropyrimidinones. A plethora of reagents/methods have been reported for this purpose such as Amberlyst-15, Nafion-H, KSF clay with dry acetic acid under microwave irradiation [6], ionic liquids [7], cerric ammonium nitrate under ultrasonication [8], Lewis acids (such as $BF_3 \cdot OEt_2$) in combination with transition metals and a suitable proton source [9], lanthanide triflates [10], lanthanide chloride [11], and indium chloride [12]. Although these methods each have their own merits, they also suffer from the drawbacks with respect to reaction time, cost of reagent and reaction work-ups. Consequently the Biginelli reaction still requires an efficient protocol for the synthesis of pyrimidinone compounds. In recent years, the use of reagents and catalysts supported on solid supports has received much attention. Such reagents not only simplify purification processes but also help in preventing the release of reaction residues into the environment. Silica gel is one of the more extensively used surface material supports for different chemical transformations in organic synthesis [13]. One such modified silica is silica-chloride (SiO_2-Cl), which has been reported to be an efficient catalyst for a variety of chemical transformations [14]. As a part of our research program directed towards the development of new and rapid synthetic methods for the construction of biologically active structural motifs, we intend to develop rapid, efficient and an inexpensive procedure for the synthesis of 4-aryl substituted 3,4-dihydropyrimidinones using silica-chloride as heterogeneous catalyst. As compared to expensive Lewis acid catalysts, such as lanthanide chlorides and lanthanide triflates; silica chloride is very inexpensive and can be prepared very easily (details given in Experimental section). This method allows us to obtain excellent yields of required product in shorter reaction times as compared to those of classical methods.

Results and Discussion

Silica chloride is one of the most versatile and utilized catalyst for the selective construction of heterocyclic ring systems, in particular for the synthesis of 3, 4- dihydropyrimidinones (Scheme 1).

Scheme 1.



This new synthetic strategy resulted in a remarkable improvement in synthetic efficiency, and more importantly, it enhanced the utilization efficiency of the modified silica chloride, decreases the production of chemical waste without using highly toxic reagent for the synthesis of 3,4-dihydro-pyrimidinones. The Si-Cl bond is labile and can give rise to Lewis acid centers on silica (Scheme 2). The Cl is easily displaced selectively by acetyl oxygen of ketone by a nucleophilic substitution reaction generating a cationic centre on the carbonyl carbon which is easily attacked by the nucleophile i.e. urea to form acyl imine **2** intermediate formed by the reaction of aldehyde and urea which is the key rate-limiting step. Interception of this imine intermediate by ethyl acetoacetate produces an open chain **3** ureide [15], which subsequently cyclizes to the corresponding 4a-4t (Table 1) dihydropyrimidinone. The completion of reaction was monitored by TLC (Hexane/AcOEt 8:2).

Scheme 2.

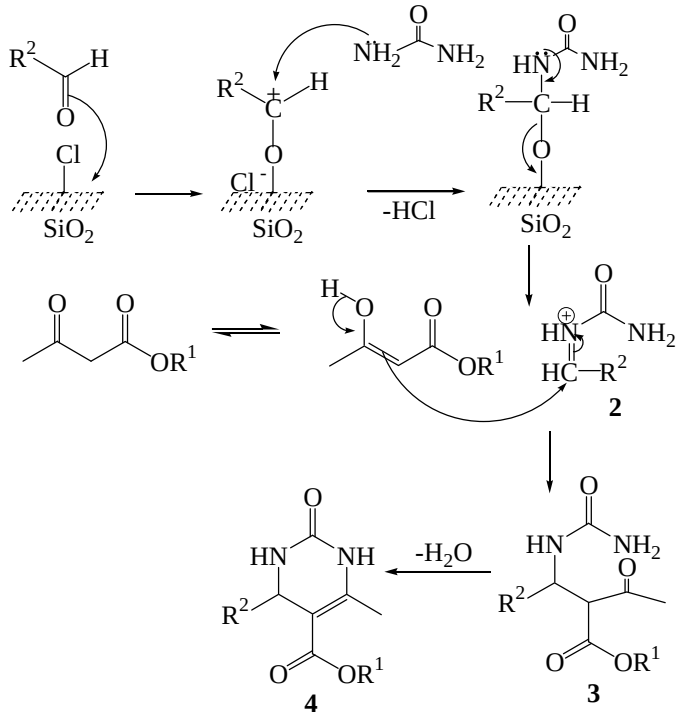


Table 1. Synthesis of 3, 4-dihydropyrimidinone using silica chloride under solvent free conditions

Entry	R^1	R^2	X	Product	Yield [a] (%)	Mp (°C)
1.	Et	C_6H_5	O	**4a**	88	206-208
2.	Et	4-(CH_3O)-C_6H_4	O	**4b**	90	201-202
3.	Et	4-(NMe_2)-C_6H_4	O	**4c**	80	255-257
4.	Et	4-NO_2-C_6H_4	O	**4d**	94	211-213
5.	Et	4-(Cl)-C_6H_4	O	**4e**	90	215-216
6.	Et	3-(Cl)-C_6H_4	O	**4f**	88	192-193
7.	Et	3-(Br)-C_6H_4	O	**4g**	81	185-186
8.	Et	2,4-$(Cl)_2$-C_6H_3	O	**4h**	92	249-250
9.	Me	4-Cl-C_6H_4	O	**4i**	89	204-205
10.	Me	4-(NO_2)C_6H_4	O	**4j**	95	236-238
11.	Me	4-(CH_3O)-C_6H_4	O	**4k**	85	192-194
12.	Me	C_6H_5	O	**4l**	86	209-211
13.	Et	4-F-C_6H_4	O	**4m**	92	182-184
14.	Et	3-O_2N-C_6H_4	O	**4n**	91	227-229
15.	Et	2-NO_2-C_6H_4	O	**4o**	96	208-210
16.	Et	C_6H_5-CH=CH	O	**4p**	90	230-232
17.	Me	2-4-$(Cl)_2$-C_6H_3	O	**4q**	93	252-253
18.	Et	C_6H_5	S	**4r**	89	208-210
19.	Et	3-O_2N-C_6H_4	S	**4s**	92	205-207
20.	Et	4-(CH_3O)-C_6H_4	S	**4t**	89	153-155

[a] Yield of isolated product

Several aromatic aldehydes (Table 1) carrying either electron releasing or electron withdrawing sustituents in the ortho, meta and para positions afforded high yields of the products. An important feature of this procedure is the survival of variety of functional groups such as ether, nitro groups, and halides under the reaction conditions. Thiourea also reacts under similar conditions to give the corresponding 3, 4-dihydropyrimido-2(1H)-thiones **4r**-**4t**. Studies on the application of silica chloride [16, 17] have shown that it is an excellent source for the generation of HCl..

The extent of chlorination of the silica surfaces was determined by suspending 1 gram of silica chloride in 25 mL of boiled distilled water and titrating with 0.1N NaOH (9.3 mL). The amount of immobilized Cl has thus been found to be 0.93 miliquivalents per gram of SiO_2. Our studies have shown that thionyl chloride is a satisfactory chlorinating agent for silica, if used undiluted. When diluted with dry benzene, a lesser numbers of silanol groups were replaced by chlorine. The extent of reaction with thionyl chloride gives values for active silanols per unit area of silica surface, comparable to other method, for determining available activities. In our studies we consistently have been able to replace a higher percentage of silanol groups with chlorine. The structures of the products were established from their spectral data and found to have excellent match with the reported data [18].

Conclusions

In summary, we have described an improved procedure for the Biginelli reaction. The use of silica-chloride as heterogeneous catalyst has made this method very cost effective. Another advantage of this method is excellent yields in shorter reaction time with high purity of the products.

Experimental

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 solutions on a Bruker AVANCE 400 NMR spectrometer operating at 400 (^{1}H) and 100 (^{13}C) MHz. LCMS analysis (EI, 70V) were performed on a Hewlett-Packard HP 5971 instrument.

Preparation of silica chloride

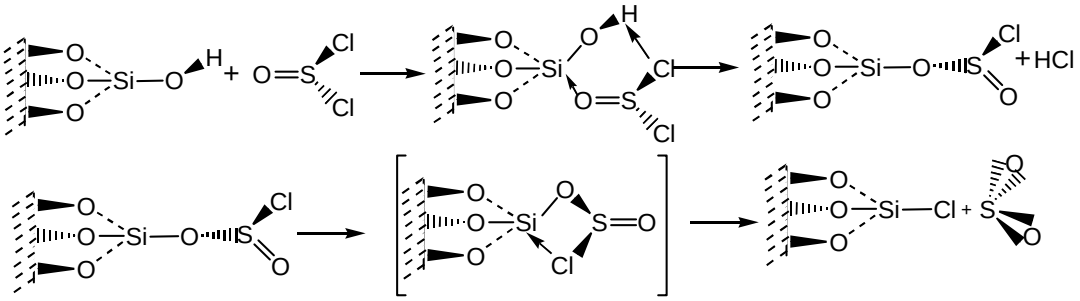
To a well–stirred silica gel (20 g) in CH_2Cl_2 (50 mL) was added drop wise $SOCl_2$ (20 g) at room temperature. Evolution of copious amounts of HCl and SO_2 occurred instantaneously. After stirring for another 1h, the solvent was removed to dryness under reduced pressure (1 torr). The silica chloride thus prepared was used in the following experiments and could be stored in sealed vessels for 6 months without any critical decline of activity.

Structure of silica chloride

The interaction of silica silanol groups with thionyl chloride is very often used as a simple and efficient method for surface modification. However, the mechanisms of these surface reactions have

not yet been studied in detail. It was stated by Strelko and co-workers that the process of $SOCl_2$ chemisorptions on the silica surface proceeds by the following mechanisms [19] (Figure 1).

Figure 1. Chemisorption of thionyl chloride on silica surface.



General procedure for the synthesis 4-aryl substituted 3, 4 dihydropyrimidinones

Ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and urea or thiourea (1.5 mmol) were mixed with silica chloride (2.5 mol%) and heated at 80°C under solvent free conditions for three hours. After completion of the reaction as indicated by TLC (hexane/ethyl acetate 8:2), the reaction mixture was brought to room temperature. Reaction mixture was washed by cold water to remove excess urea or thiourea and then filtered. The remaining solid material was washed with hot ethyl acetate. The filtrate was concentrated and the solid product was recrystallized from ethanol to give the pure product.

5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–one (**4a**): Mp 206–208 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.97 (q, 2H, *J* = 7.1 Hz, OCH_2), 5.05 (d, 1H, *J* = 2.15 -CH), 7.28 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.11, 17.94, 54.91, 60.05, 100.95, 112.85, 113.05, 125.15, 125.81, 129.05, 131.20, 150.16, 155.47, 163.81; IR ($\nu_{max.}$; KBr, cm^{-1}): 3240, 1722, 1638; ESI-MS 261 (M+H); HRMS calcd. for $C_{14}H_{16}N_2O_3$ 260.1161 found 260.1163.

5–(Ethoxycarbonyl)–4–(4–methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4b**): Mp 201–202 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.12 Hz, OCH_2CH_3), 2.33 (s, 3H, CH_3), 3.78 (s, 3H, -OCH_3), 4.06 (q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.34 (d, 1H, *J* = 2.28 -CH), 6.82 (d, 2H, *J* = 8.60, Ar-H), 7.22 (d, 2H, *J* = 8.60, Ar-H), 7.76 (s, 1H, NH), 9.26 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.32, 18.80, 55.23, 55.40, 60.17, 101.68, 114.06, 127.97, 136.22, 146.16, 153.59, 159.30, 165.87; IR ($\nu_{max.}$; KBr, cm^{-1}): 3232, 1720, 1638; ESI-MS 291 (M+H); HRMS calcd. for $C_{15}H_{18}N_2O_4$ 290.1267 found 290.1265.

5–(Ethoxycarbonyl)–4–(4-dimethylamino-phenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4c**): Mp 255–257 °C; ^{1}H-NMR (DMSO-d_6) δ: 0.99 (t, 3H, *J* = 7.12 Hz, OCH_2CH_3), 2.11 (s, 3H, CH_3), 2.84 (s, 6H, $N(CH_3)_2$), 4.09(q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.05 (d, 1H, *J* = 2.21, -CH), 6.42 (d, 2H, *J* = 8.55, Ar-H), 7.12 (d, 2H, *J* = 8.56, Ar-H), 7.15 (s, 1H, NH), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ:

14.28, 18.78, 44.47, 55.23, 60.15, 101.60, 112.05, 125.65, 134.25, 141.16, 153.46, 159.02, 165.24; IR ($\nu_{max.}$; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 304 (M+H); HRMS calcd. for $C_{16}H_{21}N_3O_3$ 303.1583 found 303.1585.

5–(Ethoxycarbonyl)–4–(4-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4d**): Mp 211–213 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H, *J* = 7.04 Hz, OCH_2CH_3), 2.32 (s, 3H, CH_3), 4.03 (q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.78 (d, 1H, *J* = 2.28, -CH), 7.51 (d, 2H, *J* = 9.18, Ar-H), 7.69 (s, 1H, NH), 8.16 (d, 2H, *J* = 9.16, Ar-H), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.22, 18.71, 55.81, 60.15, 101.60, 118.15, 130.37, 138.34, 152.26, 153.41, 159.15, 165.85; IR ($\nu_{max.}$; KBr, cm^{-1}): 3235, 1740, 1631; ESI-MS 306 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1010.

5–(Ethoxycarbonyl)–4–(4-chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4e**): Mp 215–216 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.12 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.91 (q, 2H, *J* = 7.16 Hz, OCH_2CH_3), 5.70 (d, 1H, *J* = 2.28, -CH), 7.21 (d, 2H, *J* = 9.18, Ar-H), 7.69 (s, 1H, NH), 7.94 (d, 2H, *J* = 9.18, Ar-H), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.18, 18.62, 55.72, 60.21, 101.55, 118.17, 130.32, 142.29, 152.31, 153.39, 159.17, 165.83; IR ($\nu_{max.}$; KBr, cm^{-1}): 3225, 1720, 1615; ESI-MS 295 (M+H); HRMS calcd. for $C_{14}H_{15}ClN_2O_3$ 294.0771 found 294.0773.

5–(Ethoxycarbonyl)–4–(3-chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4f**): Mp 192–193 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.28 (s, 3H, CH_3), 3.88 (q, 2H, *J* = 7.16 Hz, OCH_2CH_3), 5.65 (d, 1H, *J* = 2.28, -CH), 7.25-7.41 (m, 4H, Ar-H), 7.61 (s, 1H, NH), 9.11 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.17, 18.60, 55.70, 60.20, 101.52, 126.312, 127.92, 128.42, 130.29, 135.51, 142.21, 153.23, 159.32, 165.75; IR ($\nu_{max.}$; KBr, cm^{-1}): 3234, 1724, 1631; ESI-MS 295 (M+H); HRMS calcd. for $C_{14}H_{15}ClN_2O_3$ 294.0771 found 294.0772.

5–(Ethoxycarbonyl)–4–(3-bromophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4g**): Mp 185–186 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.02 (t, 3H, *J* = 7.05 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.75 (q, 2H, *J* = 7.05 Hz, OCH_2CH_3), 5.41 (d, 1H, J = 2.25, -CH), 7.05-7.34 (m, 4H, Ar-H), 7.51 (s, 1H, NH), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.16, 18.59, 55.74, 60.18, 101.57, 126.35, 127.82, 128.48, 130.32, 135.59, 143.94, 153.21, 159.30, 165.74; IR ($\nu_{max.}$; KBr, cm^{-1}): 3212, 1731, 1620; ESI-MS 339 (M+H); HRMS calcd. for $C_{14}H_{15}BrN_2O_3$ 338.0266 found 338.0268.

5–(Ethoxycarbonyl)–4–(2,4-dichlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4h**): Mp 249–250 °C; ^{1}HNMR (DMSO-d_6) δ: 1.18 (t, 3H, *J* = 7.23 Hz, OCH_2CH_3), 2.64 (s, 3H, CH_3), 4.07 (q, 2H, *J* = 7.24 Hz, OCH_2CH_3), 5.92 (d, 1H, *J* = 2.30, -CH), 7.21-7.51 (m, 3H, Ar-H), 7.69 (s, 1H, NH), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.20, 18.60, 55.75, 60.24, 101.56, 127.82, 128.91, 129.52, 131.29, 142.52, 143.25, 153.23, 159.32, 165.75; IR ($\nu_{max.}$; KBr, cm^{-1}): 3255, 1731, 1651; ESI-MS 329 (M+H); HRMS calcd. for $C_{14}H_{14}Cl_2N_2O_3$ 328.0381 found 328.0379.

5–(Methoxycarbonyl)–4–(4-chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4i**): Mp 204–205 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3), 3.92 (s, 3H, $COOCH_3$), 5.44 (d, 1H, *J* = 2.15, -CH), 7.14 (d, 2H, *J* = 9.05, Ar-H), 7.51 (s, 1H, NH), 7.87 (d, 2H, *J* = 9.06, Ar-H), 9.02 (s, 1H, NH);

^{13}C-NMR (DMSO-d_6) δ: 18.65, 52.05, 54.36, 109.59, 113.19, 128.23, 136.25, 148.25, 153.39, 159.17, 167.75; IR ($\nu_{max.}$; KBr, cm^{-1}): 3240, 1711, 1647; ESI-MS 281 (M+H); HRMS calcd. for $C_{13}H_{13}ClN_2O_3$ 280.0615 found 280.0617.

5–(Methoxycarbonyl)–4–(4-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4j**): Mp 236–238 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.90 (s, 3H, -$COOCH_3$), 5.51 (d, 1H, *J* = 2.15, -CH), 7.42 (d, 2H, *J* = 9.11, Ar-H), 7.44 (s, 1H, NH), 8.05 (d, 2H, *J* = 9.10, Ar-H), 9.05 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.64, 52.40, 55.40, 109.60, 113.23, 128.31, 137.20, 149.65, 155.45, 160.36, 166.20; IR ($\nu_{max.}$; KBr, cm^{-1}): 3232, 1724, 1631; ESI-MS 292 (M+H); HRMS calcd. for $C_{13}H_{13}N_3O_5$ 291.0855 found 291.0853.

5–(Methoxycarbonyl)–4–(4-methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4k**): Mp 192–194 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 3.92 (s, 3H, -$COOCH_3$), 3.75 (s, 3H, -OCH_3), 5.22 (d, 1H, *J* = 2.21 -CH), 6.76 (d, 2H, *J* = 8.58, Ar-H), 7.18 (d, 2H, *J* = 8.58, Ar-H), 7.62 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.61, 53.36, 55.05, 55.87, 108.54, 113.21, 128.47, 137.64, 148.54, 154.16, 160.81, 165.94; IR ($\nu_{max.}$; KBr, cm–1): 3242, 1721, 1637; ESI-MS 277 (M+H); HRMS calcd. for $C_{14}H_{16}N_2O_4$ 276.1110 found 276.1108.

5–(Methoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–one (**4l**): Mp 209–211 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 3.87 (s, 3H, -$COOCH_3$), 5.02 (d, 1H, *J* = 2.07 -CH), 7.25 (m, 5H, Ar-H), 7.64 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.65, 52.32, 54.70, 108.47, 113.36, 122.41, 131.17, 130.51, 154.11, 160.20, 164.42; IR ($\nu_{max.}$; KBr, cm^{-1}): 3246, 1732, 1664; ESI-MS 247 (M+H); HRMS calcd. for $C_{13}H_{14}N_2O_3$ 246.1004 found 246.1004.

5–(Ethoxycarbonyl)–4–(4-flurophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4m**): Mp 182–184 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.16 Hz, OCH_2CH_3), 2.41 (s, 3H, CH_3), 4.12 (q, 2H, *J* = 7.17 Hz, OCH_2CH_3), 5.88 (d, 1H, *J* = 2.25, -CH), 7.69 (s, 1H, NH), 7.81 (d, 2H, *J* = 8.5, Ar-H), 7.94 (d, 2H, *J* = 9.18, Ar-H), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.18, 18.62, 55.72, 60.21, 101.55, 121.19, 132.42, 144.20, 153.39, 157.25, 159.17, 165.83; IR ($\nu_{max.}$; KBr, cm^{-1}): 3250, 1741, 1654; ESI-MS 279 (M+H); HRMS calcd. for $C_{14}H_{15}FN_2O_3$ 278.1067 found 278.1069.

5–(Ethoxycarbonyl)–4–(3-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4n**): Mp 227–229 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.12 (t, 3H, *J* = 7.10 Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.65 (q, 2H, *J* = 7.14 Hz, OCH_2CH_3), 5.71 (d, 1H, *J* = 2.20, -CH), 7.21-7.54 (m, 4H, Ar-H), 7.74 (s, 1H, NH), 9.26 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.16, 18.59, 55.74, 60.18, 101.57, 126.25, 127.45, 128.74, 130.56, 135.46, 144.81, 153.64, 159.45, 165.30; IR ($\nu_{max.}$; KBr, cm^{-1}): 3229, 1724, 1630; ESI-MS 306 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1013.

5–(Ethoxycarbonyl)–4–(2-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4o**): Mp 208–210 °C;^{1}H-NMR (DMSO-d_6) δ: 1.14 (t, 3H, *J* = 7.15 Hz, OCH_2CH_3), 2.27 (s, 3H, CH_3), 3.72 (q, 2H, *J* = 7.17 Hz, OCH_2CH_3), 5.81 (d, 1H, *J* = 2.05, -CH), 7.31-7.64 (m, 4H, Ar-H), 7.81 (s, 1H, NH), 9.24 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.16, 18.59, 55.74, 60.18, 101.57, 127.32, 128.46, 129.64,

131.43, 134.31, 145.01, 153.62, 159.32, 165.16; IR ($\nu_{max.}$; KBr, cm^{-1}): 3242, 1722, 1627; ESI-MS 306 (M+H); HRMS calcd. For $C_{14}H_{15}N_3O_5$ 305.1012 found 305.1011.

5–(Ethoxycarbonyl)–6–methyl-4-styryl–3,4–dihydropyrimidin–2(1H)–one (**4p**): Mp 230–232 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.20 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 2.21 (s, 3H, CH_3), 4.09 (q, 2H, *J* = 7.05 Hz, OCH_2CH_3), 4.74 (d, 1H, *J* = 4.80, -CH), 6.20 (dd, *J* = 15.8, 6.0 Hz, 1H, CH=C–H), 6.37 (d, *J* = 15.9 Hz, 1H, H–C=CH) 7.21-7.46 (m, 5H, Ar-H), 7.53 (s, 1H, NH), 9.14 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.21, 17.31, 51.84, 59.45, 98.54, 127.34, 128.54, 129.54, 130.59, 131.24, 135.24, 145.34, 153.62, 165.23; IR ($\nu_{max.}$; KBr, cm^{-1}): 3242, 1704, 1652; ESI-MS 287 (M+H); HRMS calcd. for $C_{16}H_{18}N_2O_3$ 286.1317 found 286.1316.

5–(Methoxycarbonyl)–4–(2,4-dichlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**4q**): Mp 252–253 °C; ^{1}H-NMR (DMSO-d_6) δ: 2.61 (s, 3H, CH_3), 3.84 (s, 3H, -$COOCH_3$), 5.79 (d, 1H, *J* = 2.05, -CH), 7.05-7.31 (m, 3H, Ar-H), 7.69 (s, 1H, NH), 9.16 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 18.60, 52.45, 55.25, 102.32, 113.21, 128.47, 137.64, 139.24, 142.65, 148.54, 154.16, 160.81, 164.94; IR ($\nu_{max.}$; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 315 (M+H); HRMS calcd. for $C_{13}H_{12}Cl_2N_2O_3$ 314.0225 found 314.0227.

5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydropyrimidin–2(1H)–thione (**4r**): Mp 208–210 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H, *J* = 7.21 Hz, OCH_2CH_3), 2.29 (s, 3H, CH_3), 4.12 (q, 2H, *J* = 7.24 Hz, OCH_2), 5.16 (d, 1H, *J* = 2.05 -CH), 7.51 (m, 5H, Ar-H), 7.81 (s, 1H, NH), 9.41 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.23, 17.91, 54.85, 60.15, 100.90, 112.84, 115.12, 125.15, 126.85, 129.64, 131.45, 150.27, 162.63, 180.25; IR ($\nu_{max.}$; KBr, cm^{-1}): 3240, 1720, 1640, 1595, 1530; ESI-MS 277 (M+H); HRMS calcd. for $C_{14}H_{16}N_2O_2S$ 276.0932 found 276.0932.

5–(Ethoxycarbonyl)–4–(3-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**4s**): Mp 205–207 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.27 (s, 3H, CH_3), 4.02 (q, 2H, *J* = 7.11 Hz, OCH_2CH_3), 5.81 (d, 1H, *J* = 2.06, -CH), 7.23-7.37 (m, 4H, Ar-H), 7.78 (s, 1H, NH), 9.34 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.14, 18.60, 55.64, 60.21, 101.34, 126.25, 128.02, 129.32, 130.75, 135.65, 144.34, 160.40, 165.64, 182.65; IR ($\nu_{max.}$; KBr, cm^{-1}): 3245, 1725, 1632, 1575, 1545; ESI-MS 322 (M+H); HRMS calcd. for $C_{14}H_{15}N_3O_4S$ 321.0783 found 321.0781.

5–(Ethoxycarbonyl)–4–(4–methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**4t**): Mp 153–155 °C; ^{1}H-NMR (DMSO-d_6) δ: 1.17 (t, 3H, *J* = 7.11 Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 4.12 (s, 3H, -OCH_3), 4.15 (q, 2H, *J* = 7.10 Hz, OCH_2CH_3), 5.44 (d, 1H, *J* = 2.15 -CH), 7.11 (d, 2H, *J* = 8.15, Ar-H), 7.37 (d, 2H, *J* = 8.11, Ar-H), 7.84 (s, 1H, NH), 9.43 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ: 14.32, 18.05, 55.24, 55.49, 60.45, 101.84, 114.32, 127.74, 137.25, 147.15, 159.45, 165.62, 182.48; IR ($\nu_{max.}$; KBr, cm^{-1}): 3240, 1725, 1635, 1574, 1540; ESI-MS 307 (M+H); HRMS calcd. for $C_{15}H_{18}N_2O_3S$ 306.1038 found 306.1040.

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