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Tetrachlorosilane catalyzed multicomponent one-step fusion of biopertinent pyrimidine heterocycles

Chennan Ramalingan, Young-Woo Kwak *

Department of Chemistry, Kyungpook National University, Taegu 702-701, Republic of Korea

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ABSTRACT

Multicomponent one-step fusion of a variety of pharmacologically pertinent pyrimidine heterocycles has efficiently been achieved from their respective aldehydes, β-dicarbonyl compounds, and urea/thiourea in the presence of a catalytic amount of tetrachlorosilane in DMF/AN mixture at normal ambient temperature.

1. Introduction

Multicomponent one-pot synthesis to furnish new chemical entities possessing partial structures of each reactant undoubtedly receives much attention in organic and medicinal chemistries.[1] Biginelli's dihydropyrimidone (DHPM) synthesis,[2] a venerable acid catalyzed multicomponent one-pot assembly of aldehyde, β-ketoester, and urea, discovered in 1893, which was largely ignored for many years apart from a series of publications by Folkers[3] in the early 1930s, has recently attracted a great deal of attention since DHPMs are important heterocyclic motif in the realm of natural and synthetic organic chemistries due mainly to their wide spectra of biological activities.[4–6] Synthetic DHPM analogous apart, several marine natural products with interesting biological activities containing the DHPM scaffold have recently been isolated[7] and many of them were synthesized employing a 'tethered Biginelli condensation' as one of the key steps.[8]

Although Biginelli's one-pot methodology is appealing due to its simplicity, the demerits, however, associated with this synthetic protocol are represented by the modest yield (20–50%) and/or the cumbersome method of product isolation.[3,9] To preserve its simplicity with better yield, extensive efforts including catalytic methods with robust reaction conditions have been devoted in the recent past.[10–16] Despite the other significant developments, catalytic versions of the Biginelli reaction are particularly arousing interest for practical applications because they normally simplify processing conditions while minimizing reactant use as well as waste production. The catalytic protocols reported to-date, however, require high/low reaction temperature and/some additives: e.g., L-pro–OMe·HCl, $Yb(NTf_2)_2$, $Cu(OTf)_2$, and $In(OTf)_3$ catalyzed reactions require high/low reaction temperature while $LaCl_3 \cdot 7H_2O$, $FeCl_3$, and CuCl catalyzed reactions require concd HCl, tetraethylorthosilicate, and $AcOH/BF_3 \cdot OEt_2$, respectively, in addition to high reaction temperature to effect the DHPMs. Further, the catalysts used in most of the methods are either expensive or need to be synthesized. Considering the above demerits, disclosed herein is an efficient, simple, and high yielding protocol for the synthesis of DHPMs/DHPM thiones involving the three-component, one-pot assembly of aldehydes, β-dicarbonyl compounds, and urea/thiourea into DHPMs/DHPM thiones using readily available tetrachlorosilane ($SiCl_4$) as a catalyst at normal ambient temperature.

2. Results and discussion

First, the optimization of the reaction was groped, for which the reaction of benzaldehyde, ethylacetoacetate, and urea was selected as a model. It was hypothesized that a critical choice of metal halide might efficiently catalyze the one-step fusion of DHPMs/DHPM thiones by forming a better activated intermediate (see the Scheme 2). A preliminary examination showed that $SiCl_4$ in *N*,*N*-dimethylformamide (DMF)/acetonitrile (AN) in the ratio of 1:2, respectively, among several solvents effectively catalyzed the model reaction at ambient temperature. Of the reactions using different quantities of reactants, the best results were obtained using 1.0:1.0:1.3 ratios of benzaldehyde, ethylacetoacetate, and urea, respectively.

When a mixture of benzaldehyde, ethylacetoacetate, and urea in DMF/AN (1:2) was stirred in the presence of $SiCl_4$ (10 mol %) at ambient temperature for 4 h under nitrogen atmosphere, the fused heterocyclic product, 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, was produced in excellent yield (95%, Scheme 1). At the same time, decreasing the amount of catalyst from 10 mol % to 5 mol % lowered the DHPM yield (59%) while increasing the amount of catalyst from 10 mol % to 25 mol % did not show any significant impact on the DHPM yield indicating that the above reaction condition was appropriate for the one-pot assembly.

* Corresponding author. Tel.: +82 53 950 5339; fax: +82 53 950 6330.
E-mail address: ywkwak@knu.ac.kr (Y.-W. Kwak).

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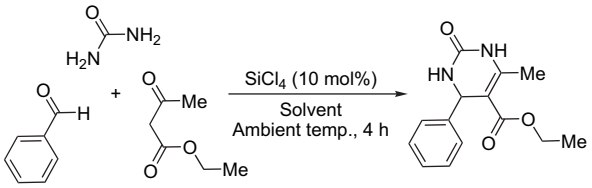
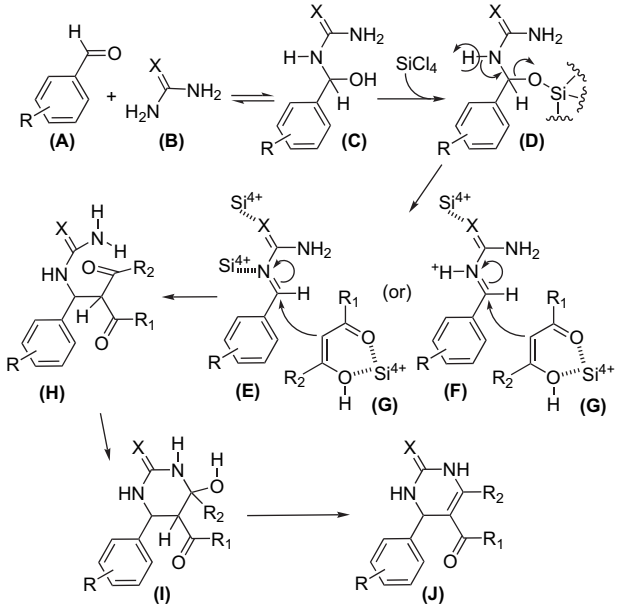


Scheme 1. Synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one.



Scheme 2. Mechanism for the tetrachlorosilane catalyzed one-step fusion of pyrimidine heterocycles.

The attention was then focused toward the effect of solvents on the yields of the one-pot assembly of the model and the results are depicted in Table 1. Replacing DMF/AN (1:2) by dimethyl sulfoxide (DMSO)/AN (1:2) produced the model in an appreciable yield (entry 2) albeit lower than that of the one produced by the former (entry 1). Other solvents such as AN, DMF, DMSO, tetrahydrofuran (THF), benzene, and 1,4-dioxane accomplished the model in moderate yields (60–69%; entries 3–5 and 7–9) while diethyl ether, dimethoxy ethane (DME), toluene, *n*-hexane, acetone, and dichloromethane (DCM) produced still lower yields (30–50%; entries 6 and 10–14).

Optimized condition was established in DMF/AN mixture (1:2) as a solvent system using a reaction temperature and time of ambient and 4 h, respectively. This remarkable activation in reaction rate prompted us to explore the potential of this protocol for the synthesis of a variety of DHPMs/DHPM thiones and the results are summarized in Table 2. All the aforementioned reactions proceeded expeditiously and delivered better to excellent product yields accommodating a wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents. The overall yields ranged from 98% of 5-ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 6) to 75% of 5-methoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (entry 28).

Of the one-pot assembly of various substituted aldehydes, ethylacetoacetate, and urea, the use of aldehydes possessing electron-withdrawing substituents produced the corresponding DHPMs with higher yields compared to the use of aldehydes possessing electron releasing substituents (compare the entries 2 and 3 or entries 4/5 and 6). Thiourea was also used with similar success along with substituted aldehydes and ethylacetoacetate (entries 7–11) although the yields of DHPM thiones were slightly lower than those of their corresponding DHPMs.

Replacing the β-ketoester, ethylacetoacetate, by a diketone, 2,4-pentadione, in the model one-pot assembly also produced an excellent yield of its corresponding DHPM (entry 12). Consequently, one-pot assembly of various substituted aldehydes, 2,4-pentadione, and urea delivered their corresponding DHPMs in better to excellent yields (entries 12–16). Of those, the use of *ortho* methoxybenzaldehyde produced its corresponding DHPM in the lowest yield (entry 14) while *para* chlorobenzaldehyde produced its corresponding DHPM in the highest yield (entry 16). One-pot assembly of various substituted aldehydes, 2,4-pentadione, and thiourea as well afforded their corresponding DHPM thiones in better to excellent yields (entries 17–20). As DHPM analogues, the DHPM thione analogue containing *ortho* methoxy substituent on the aryl moiety was also formed in the lowest yield (entry 18) while its *para* chloro analogue was afforded in the highest yield (entry 20).

Switching over to the use of methylacetoacetate in place of ethylacetoacetate in the model one-pot assembly delivered its corresponding DHPM with similar success (entry 21). The use of various substituted aldehydes, methylacetoacetate, and urea afforded their corresponding DHPMs in better to excellent yields (entries 21–26). Akin to the DHPMs, DHPM thiones were also formed in better to excellent yields when urea was replaced by thiourea (entries 27–30).

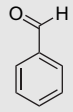
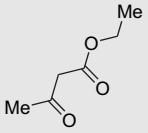
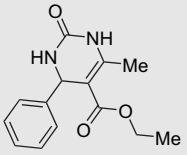
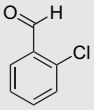
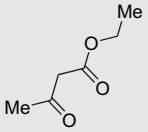
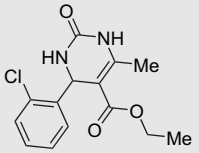
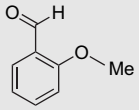
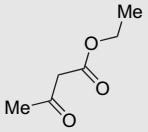
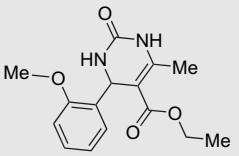
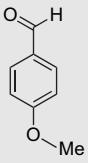
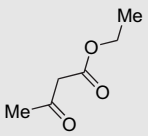
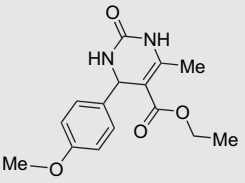
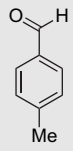
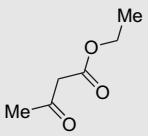
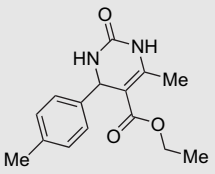
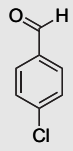
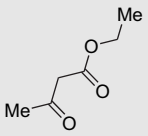
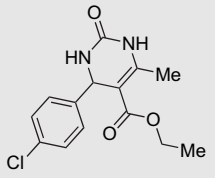
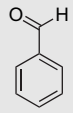
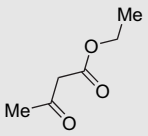
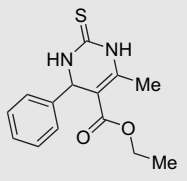
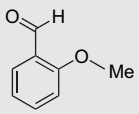
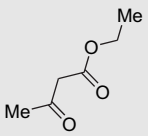
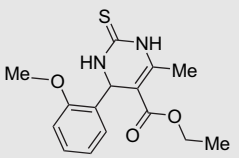
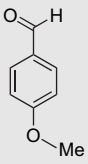
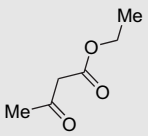
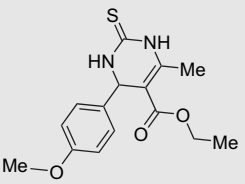
The one-pot assembly of *ortho* substituted aldehydes, ethylacetoacetate/2,4-pentadione/methylacetoacetate, and urea produced their DHPMs in lower yields compared to the one-pot assembly of their corresponding *para* substituted/unsubstituted aldehydes, ethylacetoacetate/2,4-pentadione/methylacetoacetate, and urea. A similar trend has been noticed in the case of DHPM thiones as well. Probably, the bulky *ortho* substituent partially hinders either the initial nucleophilic addition reaction of aldehyde and urea/thiourea or the formation of the open chain intermediate **H** (see the Scheme 2) due to steric effect.

Considering the mechanism for the formation of DHPMs via acylimine intermediate, described by Folkers et al.,[3] the following mechanism has been proposed (Scheme 2). The mechanism consists of an initial step of a reaction between the respective aldehydes (**A**) and urea/thiourea (**B**) to form their corresponding hemiaminals, *N*-(1-hydroxybenzyl/substituted benzyl)ureas/thioureas (**C**) via standard nucleophilic addition reaction. Although the above nucleophilic addition reaction is likely to be an equilibrium reaction, the hemiaminals **C** are expected to undergo rapid condensation with $SiCl_4$ to provide the intermediate **D**, which may be formulated as a highly reactive intermediate either **E** or **F**.[17] Simultaneously, the respective β-ketoesters/β-diketone possibly

Table 1
Effect of solvents on the yield of the one-step fusion of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one

Entry	Solvent	Yield (%)
1	DMF/AN (1:2)	95
2	DMSO/AN (1:2)	79
3	AN	60
4	DMF	65
5	DMSO	61
6	Diethyl ether	48
7	THF	69
8	Benzene	66
9	1,4-Dioxane	62
10	DME	33
11	Toluene	31
12	*n*-Hexane	50
13	Acetone	37
14	DCM	30

Table 2
Tetrachlorosilane catalyzed one-step fusion of pyrimidine heterocycles

Entry	Aldehyde	Dicarbonyl compound	Urea/thiourea	Pyrimidone/pyrimidinethione (%)	Yield (%)
1					95
2					90
3					79
4					85
5					86
6					98
7					91
8					77
9					82

(*continued on next page*)

Table 2 (*continued*)

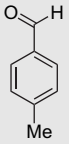
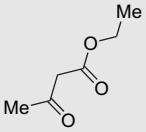
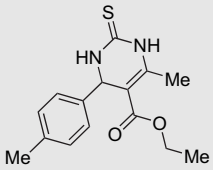
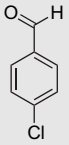
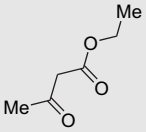
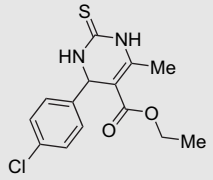
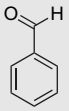
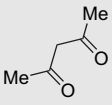
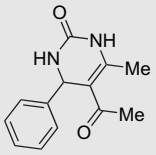
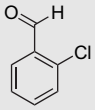
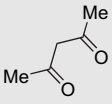
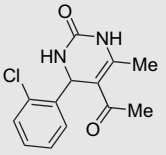
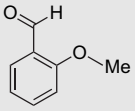
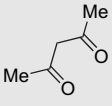
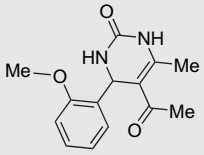
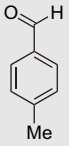
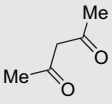
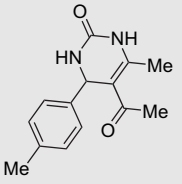
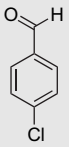
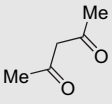
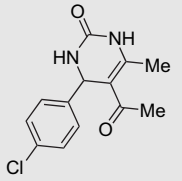
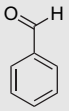
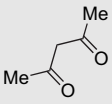
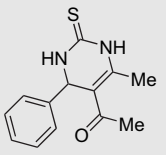
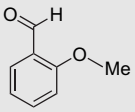
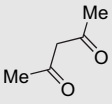
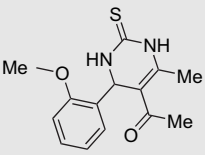
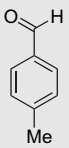
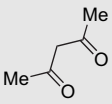
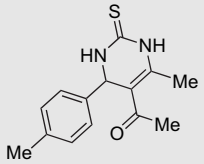
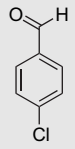
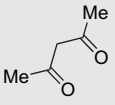
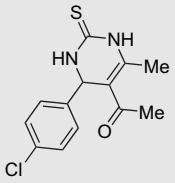
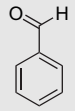
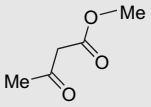
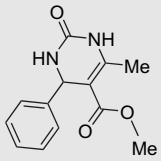
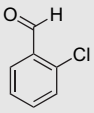
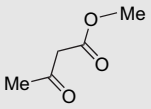
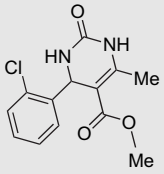
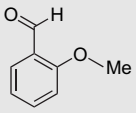
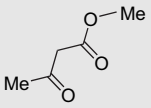
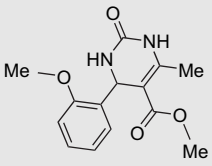
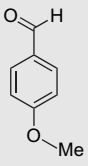
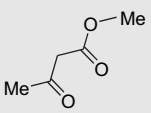
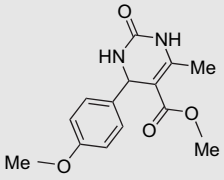
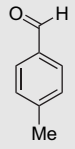
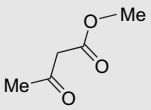
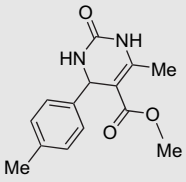
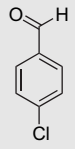
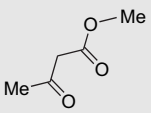
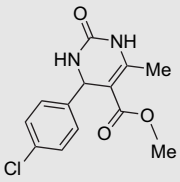
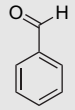
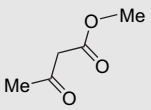
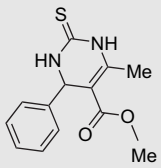
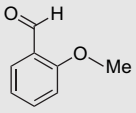
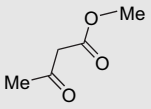
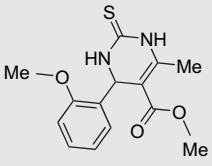
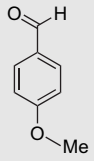
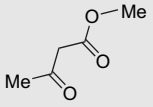
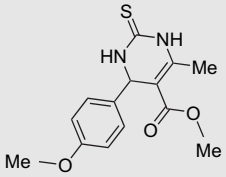
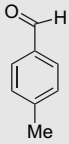
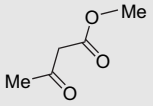
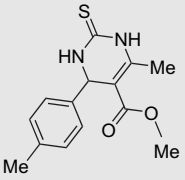
Entry	Aldehyde	Dicarbonyl compound	Urea/thiourea	Pyrimidone/pyrimidinethione (%)	Yield (%)
10					85
11					92
12					94
13					93
14					78
15					82
16					95
17					90
18					76
19					83

Table 2 (*continued*)

Entry	Aldehyde	Dicarbonyl compound	Urea/thiourea	Pyrimidone/pyrimidinethione (%)	Yield (%)
20					94
21					95
22					92
23					80
24					85
25					86
26					96
27					89
28					75

(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Dicarbonyl compound	Urea/thiourea	Pyrimidone/pyrimidinethione (%)	Yield (%)
29					81
30					84

their enol form activated by Si^{4+} (**G**) attacks the iminium carbon of the active intermediate either **E** or **F** to afford the open chain intermediates **H**. The cyclized intermediate possessing hydroxyl group **I** is produced from **H** by further nucleophilic addition, which in turn eventually undergoes dehydration to furnish the DHPMs/DHPM thiones (**J**).

Furthermore, in order to clarify whether a silicon species or only an in situ generation of HCl, as it is possible in the Biginelli reaction, is involved in the acceleration of the reaction, a couple of experiments were carried out using only HCl (40 mol %) as a catalyst. Replacing $SiCl_4$ by HCl in the multicomponent reaction of *p*-chlorobenzaldehyde, ethylacetoacetate, and urea under similar experimental conditions provided the corresponding DHPM in 54% yield while similar replacement in the reaction of *o*-methoxybenzaldehyde, 2,4-pentadione, and thiourea afforded its corresponding DHPM thione in 28% yield unlike better to excellent yields in their original reactions (Table 2, entries 6 and 18). These results suggest that silicon species might have played a major role in the activation/promotion of the reaction by possibly forming the intermediates either **E** or **F** and **G** as shown in the mechanism.

3. Conclusion

In conclusion, a catalytic amount of tetrachlorosilane efficiently catalyses the multicomponent one-step fusion of DHPMs/DHPM thiones in a DMF/AN solvent system at normal ambient temperature. This procedure does not require any additives or activators or high/low reaction temperatures. This protocol not only preserves the simplicity of the Biginelli reaction, but also produces excellent yields of the DHPMs/DHPM thiones. β-Diketones and thiourea have also been used with similar success to produce their corresponding DHPM analogues, which are also of much interest with respect to their biological activities.

4. Experimental

4.1. General

All melting points were measured in open capillaries and are uncorrected. Reagent grade reagents were purchased and were used without further purification. All solvents used herein were distilled prior to use. ^{1}H NMR spectra were acquired at 400 MHz by using DMSO-d_6 as a solvent and TMS as an internal standard. The NMR multiplicities br s, s, d, dd, q, t, and m stand for broad singlet, singlet, doublet, doublet of doublet, quartet, triplet, and multiplet, respectively.

4.1.1. Tetrachlorosilane catalyzed multicomponent one-step fusion of pyrimidine heterocycles: synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 1)

To a stirring mixture of benzaldehyde (0.20 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), and urea (0.16 g, 2.6 mmol) in DMF/AN (2.5 mL/5.0 mL) under a nitrogen atmosphere was added tetrachlorosilane (0.024 mL, 0.2 mmol). After being stirred at ambient temperature for 4 h, water (10 mL) was added to the reaction mixture and was stirred for a couple of minutes. The obtained precipitate was filtered and washed with water followed by ethanol/water mixture (1:1) and dried. Crystallization from aqueous ethanol afforded pure 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one as a white solid (0.49 g, 95%), mp 208–209 °C.[16d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.22 (1H, br s), 7.76 (1H, br s), 7.34–7.30 (2H, m), 7.25–7.23 (3H, m), 5.15 (1H, d, *J*=3.52 Hz), 3.98 (2H, q, *J*=7.03 Hz), 2.25 (3H, s), 1.09 (3H, t, *J*=7.02 Hz).

Similar procedure was adopted for the synthesis of the following compounds.

4.1.2. 5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 2)

2-Chlorobenzaldehyde (0.23 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.53 g, 90%). Mp 214–215 °C.[10d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.29 (1H, br s), 7.73 (1H, br s), 7.41 (1H, d, *J*=7.52 Hz), 7.32–7.25 (3H, m), 5.63 (1H, d, *J*=3.00 Hz), 3.89 (2H, q, *J*=7.03 Hz), 2.30 (3H, s), 0.99 (3H, t, *J*=7.02 Hz).

4.1.3. 5-Ethoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 3)

2-Methoxybenzaldehyde (0.24 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) produced 5-ethoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.46 g, 79%). Mp 256–257 °C.[14b] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.14 (1H, br s), 7.30 (1H, br s), 7.25–7.21 (1H, m), 7.05 (1H, dd, *J*=7.54, 1.50 Hz), 6.98 (1H, d, *J*=8.00 Hz), 6.87 (1H, t, *J*=7.28 Hz), 5.49 (1H, d, *J*=3.00 Hz), 3.91 (q, *J*=3.00 Hz), 3.79 (3H, s), 2.28 (3H, s), 1.02 (3H, t, *J*=7.04 Hz).

4.1.4. 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 4)

4-Methoxybenzaldehyde (0.24 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane

(0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.49 g, 85%). Mp 202–203 °C.[16d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.17 (1H, br s), 7.69 (1H, br s), 7.15 (2H, d, *J*=8.52 Hz), 6.88 (2H, d, *J*=8.56 Hz), 5.09 (1H, d, *J*=3.52 Hz), 3.98 (2H, q, *J*=7.19 Hz), 3.72 (3H, s), 2.24 (3H, s), 1.10 (3H, t, *J*=7.02 Hz).

4.1.5. 5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 5)

4-Methylbenzaldehyde (0.24 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.47 g, 86%). Mp 210–211 °C.[10d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.18 (1H, br s), 7.71 (1H, br s), 7.12 (4H, s), 5.11 (1H, d, *J*=3.52 Hz), 3.98 (2H, q, *J*=7.01 Hz), 2.26 (3H, s), 2.24 (3H, s), 1.10 (3H, t, *J*=7.04 Hz).

4.1.6. 5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 6)

4-Chlorobenzaldehyde (0.28 g, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.58 g, 98%). Mp 212–213 °C.[16d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.27 (1H, br s), 7.80 (1H, br s), 7.40 (2H, d, *J*=8.52 Hz), 7.26 (2H, d, *J*=8.52 Hz), 5.15 (1H, d, *J*=3.04 Hz), 3.98 (2H, q, *J*=7.19 Hz), 2.26 (3H, s), 1.10 (3H, t, *J*=7.04 Hz).

4.1.7. 5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 7)

Benzaldehyde (0.20 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) produced 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.50 g, 91%). Mp 203–205 °C.[14b] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.36 (1H, br s), 9.68 (1H, br s), 7.37–7.33 (2H, m), 7.30–7.22 (3H, m), 5.18 (1H, d, *J*=3.52 Hz), 4.01 (2H, q, *J*=7.03 Hz), 2.30 (3H, s), 1.10 (3H, t, *J*=7.02 Hz).

4.1.8. 5-Ethoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 8)

2-Methoxybenzaldehyde (0.24 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-ethoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.47 g, 77%). Mp 200–202 °C.[4] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.24 (1H, br s), 9.26 (1H, br s), 7.28–7.24 (1H, m), 7.05 (1H, dd, *J*=7.54, 1.50 Hz), 7.00 (1H, d, *J*=8.52 Hz), 6.90 (1H, t, *J*=7.26 Hz), 5.50 (1H, d, *J*=3.52 Hz), 3.97–3.91 (2H, m), 3.79 (3H, s), 2.29 (3H, s), 1.04 (3H, t, *J*=7.02 Hz).

4.1.9. 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 9)

4-Methoxybenzaldehyde (0.24 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) yielded 5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.50 g, 82%). Mp 152–153 °C.[18] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.31 (1H, br s), 9.62 (1H, br s), 7.13 (2H, d, *J*=8.52 Hz), 6.90 (2H, d, *J*=8.52 Hz), 5.12 (1H, d, *J*=3.52 Hz), 4.00 (2H, q, *J*=7.01 Hz), 3.72 (3H, s), 2.29 (3H, s), 1.11 (3H, t, *J*=7.02 Hz).

4.1.10. 5-Ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 10)

4-Methylbenzaldehyde (0.24 mL, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-ethoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.49 g, 85%). Mp 190–192 °C.[15a] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.32 (1H, br s), 9.63 (1H, br s), 7.15 (2H, d, *J*=8.00 Hz), 7.10 (2H, d, *J*=8.52 Hz), 5.13 (1H, d, *J*=3.52 Hz), 4.00 (2H, q, *J*=7.01 Hz), 2.29 (3H, s), 2.26 (3H, s), 1.11 (3H, t, *J*=7.02 Hz).

4.1.11. 5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 11)

4-Chlorobenzaldehyde (0.28 g, 2 mmol), ethylacetoacetate (0.25 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.57 g, 92%). Mp 193–194 °C.[18] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.40 (1H, br s), 9.68 (1H, br s), 7.43 (2H, d, *J*=7.04 Hz), 7.22 (2H, d, *J*=7.04 Hz), 5.16 (1H, br s), 4.00 (2H, q, *J*=7.01 Hz), 2.29 (3H, s), 2.26 (3H, s), 1.10 (3H, t, *J*=7.04 Hz).

4.1.12. 5-Acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 12)

Benzaldehyde (0.20 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) provided 5-acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.43 g, 94%). Mp 233–235 °C.[16d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.19 (1H, br s), 7.84 (1H, br s), 7.34–7.31 (2H, m), 7.26–7.23 (3H, m), 5.26 (1H, d, *J*=3.52 Hz), 2.29 (3H, s), 2.10 (3H, s).

4.1.13. 5-Acetyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 13)

2-Chlorobenzaldehyde (0.23 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) yielded pure 5-acetyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.49 g, 93%). Mp 228–229 °C.[19] ^{1}H NMR δ_H(400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.28 (1H, br s), 7.74 (1H, br s), 7.44 (1H, dd, *J*=7.28, 1.76 Hz), 7.34–7.25 (3H, m), 5.67 (1H, d, *J*=3.52 Hz), 2.34 (3H, s), 2.06 (3H, s).

4.1.14. 5-Acetyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 14)

2-Methoxybenzaldehyde (0.24 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-acetyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.41 g, 78%). Mp 249–250 °C.[20] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.14 (1H, br s), 7.36 (1H, br s), 7.28–7.23 (1H, m), 7.05–7.00 (2H, m), 6.89 (1H, t, *J*=7.54 Hz), 5.57 (1H, d, *J*=3.04 Hz), 3.82 (3H, s), 2.29 (3H, s), 2.02 (3H, s).

4.1.15. 5-Acetyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 15)

4-Methylbenzaldehyde (0.24 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-acetyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.40 g, 82%). Mp 203–205 °C.[15a] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.15 (1H, br s), 7.78 (1H, br s), 7.13 (4H, br s), 5.21 (1H, d, *J*=3.52 Hz), 2.28 (3H, s), 2.26 (3H, s), 2.08 (3H, s).

4.1.16. 5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 16)

4-Chlorobenzaldehyde (0.28 g, 2 mmol), acetylacetone (0.21 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) provided 5-acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.50 g,

95%). Mp 204–206 °C.[16d] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.24 (1H, br s), 7.87 (1H, br s), 7.39 (2H, d, J=8.04 Hz), 7.26 (2H, d, J=8.56 Hz), 5.26 (1H, d, J=3.52 Hz), 2.29 (3H, s), 2.13 (3H, s).

4.1.17. 5-Acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 17)

Benzaldehyde (0.20 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.44 g, 90%). Mp 222–224 °C.[18] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.29 (1H, br s), 9.77 (1H, br s), 7.37–7.33 (2H, m), 7.29–7.23 (3H, m), 5.30 (1H, d, J=3.48 Hz), 2.34 (3H, s), 2.16 (3H, s).

4.1.18. 5-Acetyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 18)

2-Methoxybenzaldehyde (0.24 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) yielded 5-acetyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.42 g, 76%). Mp 179–180 °C. ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.21 (1H, br s), 9.33 (1H, br s), 7.30–7.26 (1H, m), 7.05–7.02 (2H, m), 6.91 (1H, t, J=7.52 Hz), 5.60 (1H, d, J=3.52 Hz), 3.81 (3H, s), 2.29 (3H, s), 2.09 (3H, s).

4.1.19. 5-Acetyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 19)

4-Methylbenzaldehyde (0.24 mL, 2 mmol), acetylacetone (0.21 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) provided 5-acetyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.43 g, 83%). Mp 215–217 °C. ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.25 (1H, br s), 9.72 (1H, br s), 7.16–7.10 (4H, m), 5.26 (1H, d, J=3.52 Hz), 2.33 (3H, s), 2.27 (3H, s), 2.13 (3H, s).

4.1.20. 5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 20)

4-Chlorobenzaldehyde (0.28 g, 2 mmol), acetylacetone (0.21 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.53 g, 94%). Mp 207–208 °C.[19] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.34 (1H, br s), 9.78 (1H, br s), 7.42 (2H, d, J=8.52 Hz), 7.24 (2H, d, J=8.04 Hz), 5.30 (1H, d, J=3.52 Hz), 2.34 (3H, s), 2.18 (3H, s).

4.1.21. 5-Methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 21)

Benzaldehyde (0.20 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.47 g, 95%). Mp 208–210 °C.[10b] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.17 (1H, br s), 7.71 (1H, br s), 7.34–7.30 (2H, m), 7.25–7.22 (3H, m), 5.16 (1H, d, J=3.52 Hz), 3.53 (3H, s), 2.26 (3H, s).

4.1.22. 5-Methoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 22)

2-Chlorobenzaldehyde (0.23 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) yielded 5-methoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.52 g, 92%). Mp 223–225 °C.[21] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.25 (1H, br s), 7.65 (1H, br s), 7.40 (1H, d, J=7.52 Hz), 7.31–7.24 (3H, m), 5.62 (1H, d, J=3.00 Hz), 3.45 (3H, s), 2.30 (3H, s).

4.1.23. 5-Methoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 23)

2-Methoxybenzaldehyde (0.24 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-methoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.44 g, 80%). Mp 282–283 °C.[16a] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.09 (1H, br s), 7.23 (1H, br s), 7.19 (1H, br s), 7.01–6.98 (2H, m), 6.87 (1H, br s), 5.48 (1H, br s), 3.80 (3H, s), 3.47 (3H, s), 2.28 (3H, s).

4.1.24. 5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 24)

4-Methoxybenzaldehyde (0.24 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) provided 5-methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.47 g, 85%). Mp 195–196 °C.[10b] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.14 (1H, br s), 7.65 (1H, br s), 7.16 (2H, d, J=8.56 Hz), 6.88 (2H, d, J=8.52 Hz), 5.11 (1H, d, J=3.04 Hz), 3.73 (3H, s), 3.54 (3H, s), 2.26 (3H, s).

4.1.25. 5-Methoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 25)

4-Methylbenzaldehyde (0.24 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-methoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.45 g, 86%). Mp 208–210 °C.[13a] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.14 (1H, br s), 7.66 (1H, br s), 7.13 (4H, br s), 5.13 (1H, d, J=3.52 Hz), 3.54 (3H, s), 2.27 (3H, s), 2.26 (3H, s).

4.1.26. 5-Methoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 26)

4-Chlorobenzaldehyde (0.28 g, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), urea (0.16 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-methoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (0.54 g, 96%). Mp 204–206 °C.[10b] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 9.23 (1H, br s), 7.75 (1H, br s), 7.38 (2H, d, J=7.04 Hz), 7.24 (2H, d, J=7.00 Hz), 5.15 (1H, br s), 3.53 (3H, s), 2.25 (3H, s).

4.1.27. 5-Methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 27)

Benzaldehyde (0.20 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-methoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.46 g, 89%). Mp 237–239 °C.[10b] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.30 (1H, br s), 9.62 (1H, br s), 7.36–7.33 (2H, m), 7.28–7.21 (3H, m), 5.19 (1H, d, J=3.52 Hz), 3.56 (3H, s), 2.30 (3H, s).

4.1.28. 5-Methoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 28)

2-Methoxybenzaldehyde (0.24 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) yielded 5-methoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.44 g, 75%). Mp 253–255 °C. ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.22 (1H, br s), 9.18 (1H, br s), 7.25 (1H, br s), 6.95 (3H, br d), 5.48 (1H, br s), 3.81 (3H, s), 3.51 (3H, s), 2.31 (3H, s).

4.1.29. 5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 29)

4-Methoxybenzaldehyde (0.24 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) afforded 5-methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.47 g, 81%). Mp 182–183 °C.[22] ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.28 (1H, br s), 9.59 (1H, br s), 7.13 (2H, br s), 6.90 (2H, br s), 5.13 (1H, br s), 3.73 (3H, s), 3.56 (3H, s), 2.30 (3H, s).

4.1.30. 5-Methoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 30)

4-Methylbenzaldehyde (0.24 mL, 2 mmol), methylacetoacetate (0.22 mL, 2 mmol), thiourea (0.20 g, 2.6 mmol), and tetrachlorosilane (0.024 mL, 0.2 mmol) in DMF/AN (2.5 mL/5.0 mL) gave 5-methoxycarbonyl-4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (0.46 g, 84%). Mp 155–156 °C. ^{1}H NMR δ_H (400 MHz, DMSO-d_6, Me_4Si, 25 °C) 10.29 (1H, br s), 9.60 (1H, br s), 7.11 (4H, br d), 5.14 (1H, br s), 3.56 (3H, s), 2.30 (3H, s), 2.27 (3H, s).

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