Antimony(III) chloride impregnated on alumina — An efficient and economical Lewis acid catalyst for one-pot synthesis of dihydropyrimidinones under solvent-free conditions

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Abstract: The antimony(III) chloride impregnated on alumina efficiently catalyses a one-pot, three-component condensation reaction among an aldehyde, a β-ketoester, and urea or thiourea to afford the corresponding dihydropyrimidinones in good to excellent yields. The reactions are probed in microwave (MW), ultrasonic, and thermal conditions and the best results are found using MW under solvent-free conditions.

Key words: Biginelli dihydropyrimidinones synthesis, $SbCl_3$–Al_2O_3, MW, sonication, solid supported.

Résumé : Le chlorure d'antimoine(III) imprégné sur de l'alumine catalyse efficacement la réaction de condensation monotope de trois composants, un aldéhyde, un β-cétoester et une urée ou une thiourée, pour conduire à la formation des dihydropyrimidinones correspondants avec des rendements allant de bons à excellents. Les réactions ont été réalisées sous l'influence de micro-ondes (MO), d'ultrasons ou de la chaleur et on a trouvé que les conditions de micro-ondes, sans solvant, donnent les meilleurs résultats.

Mots clés : synthèse de Biginelli de dihydropyrimidinones, $SbCl_3$–Al_2O_3, micro-ondes, soniquation, supporté sur un solide.

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Introduction

The dihydropyrimidinones (DHPMs) and their derivatives have attracted considerable interest in organic and medicinal chemistry because of their fascinating array of pharmacological and therapeutic properties such as antiviral, antitumor, antibacterial, and antiinflammatory calcium channel blockers, antihypertensives, α_{1a}-adrenergic antagonists, and neuropeptide Y (NPY) antagonists (1, 2). Moreover, the potent HIVgp–120–CD_4 inhibitor batzelladine alkaloids (3) basically contain a dihydropyrimidine core unit. A simple synthesis of this biologically important pharmacophore was reported (4) by Biginelli in 1893 by one-pot reflux of a β-ketoester, an aromatic aldehyde, and urea in ethanol containing a catalytic amount of HCl. The major drawbacks of this protocol are low yields of products (20%–50%) and less functional group tolerance on the reactants. Consequently, this has led to the discovery of multistep strategies producing somewhat higher yields, but lacking the simplicity of original Biginelli reaction (5). Therefore, this reaction continues to be the focus of the researchers striving to find milder and more efficient procedures for the synthesis of DHPMs. This has led to the development of several synthetic methodologies using various catalysts (6) such as $BF_3{\cdot}OEt_2$, $InCl_3$, $BiCl_3$, $LiCl_4$, $ZrCl_4$, $La(OTf)_3$, $NiCl_2$, $FeCl_3$, KSF, $Yb(OTf)_3$, PPE, $Bi(OTf)_3$, CAN, $CuCl_2$, $CeCl_3$, $Cu(OTf)_2$, Me_3SiI, $LiBr_2$, $MgBr_2$, $InBr_3$, NH_4Cl, $SrCl_2$, silica-sulphuric acid, boric acid, and ionic liquids. However, in spite of their potential utility, many of these methods involve expensive reagents, a stoichiometric amount of catalysts, strongly acidic conditions, longer reaction times, high temperature, unsatisfactory yields, and tedious work-up.

The use of reagents impregnated on inorganic supports (7) offer advantages such as (*a*) simple work-up and product purification, (*b*) enhanced or reduced reactivity of the functional groups, (*c*) selectivity that may be different from that in solution, and (*d*) manipulative simplicity. Among the large number of Lewis acids used in organic synthesis, antimony(III) chloride has not been explored much for its catalytic activity. Recently, synthesis of some novel heterocycles catalyzed by antimony(III) chloride under solvent-free conditions has been reported from our laboratory (8). We wished to explore the use of antimony(III) chloride impregnated on alumina for the synthesis of DHPMs.

The condensation reaction between benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), and urea (10 mmol) was carried out in a microwave (MW) under solvent-free conditions for 1 min with 0.5 mmol (5 mol%, 0.05 equiv.) of antimony(III) chloride, (*i*) alone and (*ii*) impregnated on different amounts of alumina (1–8 g), which gave yields of 42%, 70%, 96%, 93%, 90%, 74%, 60%, and 45%, respectively, as shown in Fig. 1. In the absence of alumina, the reaction gave a low yield of the product (**4a**). However, increasing the amounts of antimony(III) chloride to 0.1, 0.2, 0.5, and 1.0 equiv. resulted in the formation of an unidentifiable tarry

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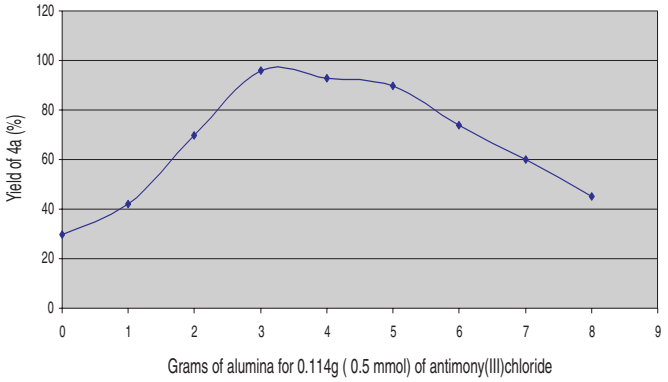
Fig. 1. The influence of the amount of alumina on the yields of reaction.



material. It is evident that the amount of alumina used for impregnation is decisive in the completion of the three-component reaction. The results reveal that the most appropriate ratio of antimony(III) chloride and alumina is approximately 1:26 (*w*/*w*), which gives 96% isolated yield of **4a**. The decrease or increase of the amount of alumina led to the decrease in the yield of the desired product. It is presumed that the alumina acts as a carrier increasing the surface area of the heterogeneous reaction, and it is very probable that the antimony salt interacts with the oxide groups at the surface of the support forming new active sites on the alumina local structure.

In another set of experiments, when the reaction mixture comprised of benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (10 mmol), and 5 mol% of antimony(III) chloride (0.5 mmol) impregnated on 3 g of alumina was (*i*) heated at 100 °C on an oil bath without any solvent, a clean conversion to **4a** (95% yield) was noticed in less than 1 h and (*ii*) sonicated in an ultrasonicator in a variety of solvents such as water, tetrahydrofuran, acetonitrile, chloroform, toluene, and THF–H_2O, produced the results summarized in Table 1. From Table 1, acetonitrile appears to be the best solvent (yield 94% in 1 h) of all the solvents tested under similar reaction conditions. The present findings in the ultrasonicator are superior in terms of yield and time to the earlier reported method (6*q*).

Encouraged by these results and to establish the versatility of antimony(III) chloride impregnated on alumina, various substrates were subjected to the optimized condensation reaction and the results are depicted in Table 2.

The efficiency of $SbCl_3$–Al_2O_3 as a Lewis acid catalyst is comparable to those reported in the literature (6), such as BF_3·OEt, $FeCl_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $InCl_3$, $Sc(OTf)_3$, $YbCl_3$, $MgBr_3$, and $SrCl_2$, as is evident from Table 3. The present catalyst, $SbCl_3$–Al_2O_3, enjoys benefits in terms of easy handling, economy, and simple workup (Scheme 1).

The reaction is believed to proceed through the acylimine intermediate formed in situ by reaction of the aldehyde with urea. The subsequent addition of the β-diketon enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding DHPMs (Scheme 2).

Conclusion

In conclusion, we have unraveled a newer application of $SbCl_3$ as a Lewis acid supported on alumina for the synthesis of DHPMs.The present catalyst is cheap, easily available, easy to handle, and works efficiently in MW, thermal, and ultrasonic conditions.

Table 1. Various solvents used for the synthesis of **4a** in an ultrasonicator.

Entry	Solvent	Time (h)	Yield (%)
1	H_2O	3	15
2	THF	4	40
3	THF–H_2O (3:2)	3	20
4	$CHCl_3$	5	45
5	CH_3CN	1	94
6	Toluene	5	50

Experimental

General

Melting points were measured in open capillaries on a Perfit melting point apparatus and are uncorrected. IR on KBr were recorded on a Bruker-4800 IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer. The mass spectra were obtained on a JEOL D-300 mass spectrometer. TLC was performed on 0.5 mm thick plates using BDH silica gel G as adsorbent and eluted in a 1:1 mixture of EtOAc and petroleum ether. The plates were developed with iodine vapors, 2,4-dinitrophenylhydrazone in acidic methanol solution, and anisaldehyde solution in acidic alcohol. All solvents were distilled before use. Microwave irradiation was carried out in an IFB microwave oven at the 5 power level and the sonication was carried out in a Bransonic-2510 ultrasonic cleaner.

General procedures

Preparation of the catalyst $SbCl_3$–Al_2O_3

To an antimony(III) chloride (2.28 g, 10 mmol) solution in 100 mL of distilled ethanol was added 60 g of neutral alumina. The mixture was stirred at room temperature for 1 h, followed by removal of solvent under reduced pressure on a rotovap. The resultant free-flowing powder was then activated at 110 °C in an oven for 2 h and was used throughout the experimentation.

Typical procedures for the three-component condensation reaction

(i) Under microwave irradiation

A mixture of ethyl acetoacetate (10 mmol), aryl aldehyde (10 mmol), urea (10 mmol), and the 3.1 g of the catalyst was placed in a 100 mL beaker. It was then irradiated in an IFB microwave oven at the 5 power level until the completion of reaction as monitored by TLC. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added, stirred well, and filtered through Celite under suction. The organic layer was washed twice with water (30 mL) and brine (30 mL). After drying over anhydr. Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol to afford the pure product.

Table 2. $SbCl_3$–Al_2O_3 catalyzed synthesis of DHPMs.

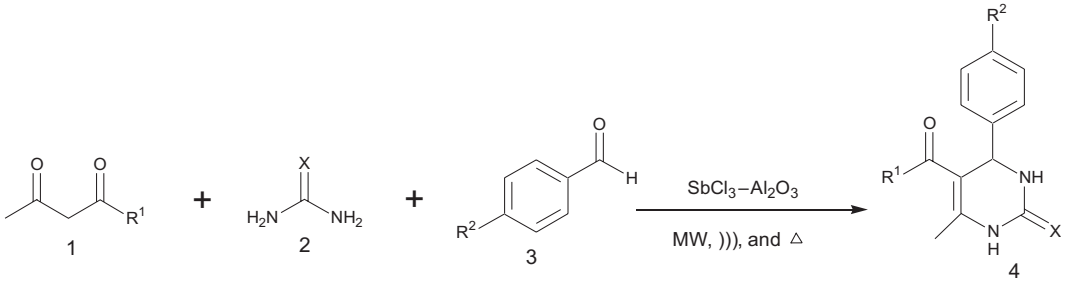
	Subsititution			Time (min), (yield in %)[b]			Melting point[c] (°C)	
Product[a]	R^1	R^2	X	Thermal	MW	Sonication	Obs.	Lit. (ref. 6)
4a	OEt	H	O	55 (95)	1.0 (96)	60 (94)	203 to 204	202–204
4b	OEt	OMe	O	70 (92)	1.5 (94)	75 (92)	201 to 204	201–203
4c	OEt	Cl	O	50 (89)	1.0 (90)	80 (90)	211–214	213–215
4d	OEt	F	O	75 (91)	1.5 (92)	90 (87)	177 to 178	175–177
4e	OEt	NO_2	O	60 (88)	2.0 (90)	60 (86)	210–212	208–211
4f	OEt	OH	O	65 (90)	2.5 (92)	90 (90)	233–235	232 to 233
4g	Me	H	O	45 (90)	1.0 (96)	75 (87)	240–242	242–244
4h	OMe	H	O	50 (83)	2.0 (96)	90 (84)	209–212	208–210
4i	OMe	OMe	O	75 (84)	2.0 (95)	90 (91)	193–195	192–194
4j	OMe	Cl	O	60 (91)	1.5 (94)	70 (89)	203–205	204–207
4k	OMe	NO_2	O	65 (80)	1.5 (82)	60 (93)	234 to 235	235–237
4l	OMe	F	O	70 (92)	2.0 (94)	65 (87)	190 to 191	192–194
4m	OEt	H	S	80 (89)	2.0 (95)	65 (89)	205–207	207 to 208
4n	OMe	H	S	80 (90)	1.5 (94)	85 (90)	235–237	236–238
4o	OEt	OMe	S	65 (81)	2.0 (91)	90 (84)	152 to 153	152 to 153

[a]All products were characterized by ^{1}H NMR, IR, and mass spectra.
[b]Isolated yields.
[c]Melting points are uncorrected.

Table 3. Comparison of various catalysts with $SbCl_3$–Al_2O_3 for the synthesis of **4a**.

Entry	Catalyst used	Reaction conditions	Amount of catalyst (mol%)	Yield (%)	Reference
1	$SbCl_3$–Al_2O_3	CH_3CN, sonication, 1 h	5	94	—
2	BF_3·OEt–CuCl	THF, reflux, 18 h	130	94	6*o*
3	$FeCl_3$–HCl	EtOH, reflux, 4 h	60	93	6*n*
4	$Bi(OTf)_3$	CH_3CN, rt, 1 h	2	90	6*b*
5	$Yb(OTf)_3$	CH_3CN, reflux, 6 h	5	83	6*r*
6	$InCl_3$	THF, Δ, 7 h	10	95	6*v*
7	$SbCl_3$–Al_2O_3	No solvent, 100 °C	5	95	—
8	$Sc(OTf)_3$	No solvent, 100 °C	5	96	6*r*
9	$YbCl_3$	No solvent, 100 °C	5	66	6*r*
10	MgBr	No solvent, 100 °C	10	92	6*u*
11	$La(OTf)_3$	No solvent, 100 °C	5	89	6*r*
12	$SbCl_3$	No solvent, MW	5	30	—
13	$SbCl_3$–Al_2O_3	No solvent, MW	5	96	—

Scheme 1.



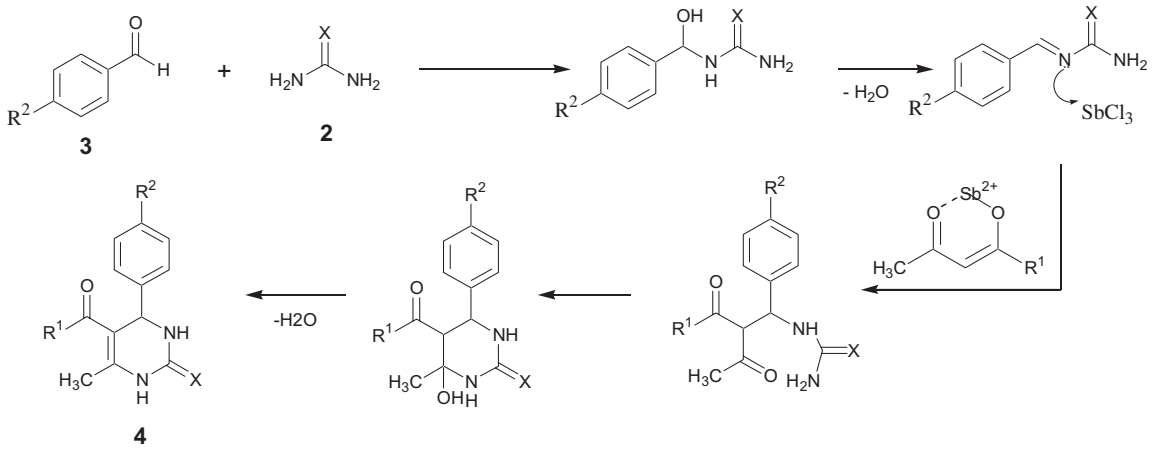
(ii) Under thermal conditions

A mixture of ethyl acetoacetate (10 mmol), aryl aldehyde (10 mmol), urea (10 mmol), and 3.1 g of the catalyst was placed in a 100 mL round bottom flask was heated on an oil bath at 100 °C until the completion of the reaction as monitored by TLC. The reaction mixture was cooled to room temperature and worked up in the same manner as mentioned in (*i*).

(iii) Under sonication

A mixture of ethyl acetoacetate (10 mmol), aryl aldehyde (10 mmol), urea (10 mmol), and the 3.1 g of catalyst was

Scheme 2.



placed in a 100 mL round bottom flask containing 15 mL of acetonitrile. After the completion of the reaction (TLC), the solvent was removed and ethyl acetate was added to the residue and worked up in the same manner as mentioned in (*i*).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4a)

Melting point 203 to 204 °C. IR (KBr, cm^{-1}): 3233, 3110, 2975, 2938, 1725, 1708, 1650, 1595. ^{1}H NMR (DMSO-d_6) δ: 1.12 (t, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.19 (d, *J* = 2.7 Hz), 7.27–7.42 (m, 5H), 7.75 (d, *J* = 2.7 Hz, 1H), 9.21 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 14.1, 17.9, 54.2, 59.3, 99.5, 126.4, 127.4, 128.5, 145.0, 148.5, 152.3, 165.5. MS *m*/*z*: 261 (M^+ + 1).

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

Melting point 202 to 203 °C. IR (KBr, cm^{-1}): 3222, 3095, 2932, 2831, 1713, 1650, 1615, 1584, 1516. ^{1}H NMR (DMSO-d_6) δ: 1.09 (t, *J* = 7 Hz, 3H), 2.23 (s, 3H), 3.70 (s, 3H), 3.97 (q, *J* = 7 Hz, 2H), 5.09 (d, *J* = 3.1 Hz), 6.87–7.15 (m, 4H), 7.66 (s, 1H), 9.12 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 15.0, 18.6, 54.3, 55.9, 60.1, 100.5, 114.6, 128.3, 138.0, 148.9, 153.1, 159.4, 166.3. MS *m*/*z*: 291 (M^+ + 1).

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4c)

Melting point 213 to 214 °C. IR (KBr, cm^{-1}): 3230, 3091, 2974, 2935, 1700, 1642. ^{1}H NMR (DMSO-d_6) δ: 1.10 (t, *J* = 6.7 Hz, 3H), 2.24 (s, 3H), 3.97 (q, *J* = 6.7 Hz, 2H), 5.14 (d, *J* = 3.1 Hz), 7.23–7.38 (m, 4H), 7.76 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 14.9, 18.7, 54.3, 60.1, 99.7, 129.0, 129.2, 132.7, 144.6, 149.6, 152.8, 166.2. MS *m*/*z*: 295 (M^+ + 1).

4-(4-Fluorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4d)

Melting point 177 to 178 °C. IR (KBr, cm^{-1}): 3235, 3090, 2975, 2930, 1705, 1645. ^{1}H NMR (DMSO-d_6) δ: 2.0 (t, *J* = 6.9 Hz, 3H), 2.26 (s, 3H), 3.99 (q, *J* = 6.9 Hz, 2H), 5.15 (d, *J* = 3.1 Hz), 7.21–7.40 (m, 4H), 7.76 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 14.5, 17.5, 53.3, 60.1, 99.1, 116.0, 129.2, 142.7, 148.6, 153.6, 165.2.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4e)

Melting point 208–211 °C. IR (KBr, cm^{-1}): 3232, 3108, 2977, 1701, 1641, 1591, 1522. ^{1}H NMR (DMSO-d_6) δ: 9.37 (s, 1H), 8.20–7.50 (m, 4H), 7.91 (d, *J* = 2.46 Hz, 1H), 5.27 (d, *J* = 1.6 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ: 164.9, 151.9, 151.7, 149.3, 146.6, 127.5, 123.7, 59.3, 53.6, 17.8, 13.9. MS *m*/*z*: 306 (M^+ + 1).

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

Melting point 233–235 °C. IR (KBr, cm^{-1}): 3510, 3276, 3125, 2970, 1682, 1642. ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, *J* = 6.90 Hz), 2.21 (s, 3H), 3.94 (q, 2H, *J* = 6.90 Hz), 5.02 (d, 1H, *J* = 2.76 Hz), 6.67–7.0 (m, 4H), 7.64 (s, 1H), 9.11 (s, 1H), 9.30 (s, 1H).

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4g)

Melting point 240–242 °C. IR (KBr, cm^{-1}): 3270, 3008, 2975, 2835, 1702, 1645, 1588. ^{1}H NMR (DMSO-d_6) δ: 2.12 (s, 3H), 2.30 (s, 3H), 5.28 (s, 1H), 7.24–7.32 (m, 5H), 7.82 (s, 1H), 9.20 (s, 1H).

5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4h)

Melting point 209–212 °C. IR (KBr, cm^{-1}): 3368, 3240, 3092, 3032, 2948, 1750, 1708, 1655. ^{1}H NMR (DMSO-d_6) δ: 8.06 (s, 1H), 7.32 (m, 5H), 5.74 (s, 1H), 5.40 (d, *J* = 2.7 Hz, 1H), 3.64 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 165.5, 152.2, 148.8 144.5, 128.3, 127.2, 126.0, 98.9, 53.9, 50.7, 17.8. MS *m*/*z*: 247 (M^+ + 1).

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

Melting point 192–194 °C. IR (KBr, cm^{-1}): 3238, 3102, 3000, 2952, 2838, 1692, 1640, 1609, 1516. ^{1}H NMR (DMSO-d_6) δ: 8.58 (s, 1H), 7.25–6.80 (m, 4H), 5.95 (s, 1H), 5.30 (d, *J* = 2.0 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 163.5, 151.2, 143.6, 133.5, 125.4, 111.2, 52.7, 52.5, 48.5, 16.2. MS *m*/*z*: 277 (M^+ + 1).

4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4j)

Melting point 204–207 °C. IR (KBr, cm^{-1}): 3240, 3114, 2950, 2875, 1702, 1645. ^1H NMR (DMSO-d_6) δ: 9.28 (s, 1H), 7.76 (s, 1H), 7.35–7.25 (m, 4H), 5.14 (d, J = 3.3 Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 165.5, 152.0, 148.8, 143.5, 131.8, 128.3, 128.0, 98.5, 53.2, 50.7, 17.6. MS m/z: 281 (M^+ + 1).

5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4k)

Melting point 235–237 °C. IR (KBr, cm^{-1}): 3265, 3234, 3111, 2952, 1700, 1648, 1599, 1522. ^1H NMR (DMSO-d_6) δ: 9.36 (s, 1H), 8.22–7.52 (m, 4H), 7.95 (s, 1H), 5.26 (s, 1H), 3.54 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 165.5, 151.7, 149.5, 146.6, 127.5, 123.7, 97.9, 53.4, 50.8, 17.8. MS m/z: 292 (M^+ + 1).

4-(4-Fluorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4l)

Melting point 190 to 191 °C. IR (KBr, cm^{-1}): 3260, 3135, 2992, 2898, 1725, 1658. ^1H NMR (DMSO-d_6) δ: 9.30 (s, 1H), 7.7 (s, 1H), 7.45–7.27 (m, 4H), 5.15 (d, J = 3.3 Hz, 1H), 3.55 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 164.6, 150.8, 147.9, 143.6, 130.9, 128.3, 128.2, 99, 53, 50.6, 17.6.

Ethyl 6-methyl-4-phenyl-2-thiooxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)

Melting point 206–208 °C. IR (KBr, cm^{-1}): 3330, 3172, 3105, 2980, 1670, 1575, 1467. ^1H NMR (DMSO-d_6) δ: 1.08 (t, 3H, J = 7.02 Hz), 2.26 (s, 3H), 3.98 (q, 2H, J = 7.02 Hz), 5.15 (d, 1H, J = 3.57 Hz), 7.20–7.35 (m, 5H), 9.65 (s, 1H), 10.35 (s, 1H).

6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (4n)

Melting point 235–237 °C. IR (KBr, cm^{-1}): 3296, 3203, 2994, 1610, 1577, 1462. ^1H NMR (DMSO-d_6) δ: 2.14 (s, 3H), 2.32 (s, 3H), 5.26 (d, 1H, J = 3.57 Hz), 7.20–7.38 (m, 5H), 9.75 (s, 1H), 10.28 (s, 1H). MS m/z: 247 (M^+ + 1).

Ethyl 6-methyl-4-methoxyphenyl-2-thiooxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o)

Melting point 152 to 153 °C. IR (KBr, cm^{-1}): 3446, 3315, 3178, 2965, 1669, 1619, 1578, 1512. ^1H NMR (DMSO-d_6) δ: 1.09 (t, 3H, J = 6.93 Hz), 2.26 (s, 3H), 3.74 (s, 3H), 3.98 (q, 2H, J = 6.93 Hz), 5.12 (d, 1H, J = 3.6 Hz), 6.88–7.10 (m, 4H), 9.62 (s, 1H), 10.30 (s, 1H).

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