Synthesis of Biginelli Compounds Using Cobalt Hydrogen Sulfate

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Efficient synthesis of various 2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidines containing acetyl, carboethoxy, carbomethoxy and carboxamide groups on 5-position of the *N*1-substituted and *N*1-unsubstituted heterocyclic ring was achieved using cobalt hydrogen sulfate $Co(HSO_4)_2$ under thermal conditions. Good to high yield, shorter reaction times, easy work up and simple preparation of $Co(HSO_4)_2$ are the advantages using this synthetic method.

Keywords: Biginelli reaction; Cobalt hydrogen sulfate; Condensation; Lewis acid; 2-Oxo-1,2,3,4-tetrahydropyrimidines.

INTRODUCTION

The Biginelli reaction, a three components condensation reaction between an aldehyde, urea and an easily enolizable dicarbonyl compound in the presence of Brønsted acid under formation of 2-oxo-1,2,3,4-tetrahydropyrimidines (THPMs) was originally described by Italian chemist Pietro Biginelli in 1893.[1] The THPMs and their derivatives have shown a wide scope of important pharmacological and biological properties including antibacterial, antifungal, antiviral, antitubercular, anticancer and anti-malarial properties.[2-5] Due to the biological importance of THPMs, several new and improved procedures by applying microwave,[6] ultrasound[6] or UV irradiations[7] in the presence of various catalysts have been reported. Although many of these methods gave pure tetrahydropyrimidinones in good to excellent yields, but in most cases urea and ethyl acetoacetate were only used as reactants for the synthesis of 5-carboethoxy-2-oxo-1,2,3,4-tetrahydropyrimidines.[8-10] Therefore, introducing a suitable and efficient catalyst to facilitate the synthesis of various 1,2,3,4-tetrahydropyrimidines is highly interesting.

Much effort has been done to the use of inorganic reagents in organic transformation, because these reagents often provide milder reaction conditions and easier work up than reactions using organic reagents. Metal hydrogen sulfates (MHSs) have been used as an efficient reagent and heterogeneous catalyst in many organic reactions such as deprotection, oxidation, bond formation and bond cleavage.[11] Due to stability, cheapness and mild reaction conditions many works are devoted to the usage of MHSs.

Here, we wish to introduce cobalt hydrogen sulfate $Co(HSO_4)_2$ as an efficient catalyst for the synthesis of various *N*1-methyl substituted and unsubstituted 5-acetyl-, 5-carboethoxy-5-carbomethoxy- and 5-carboxamido-2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidines.

RESULTS AND DISCUSSION

For the optimization of the reaction condition, the synthesis of compound **1** as model substrate has been carried out in 0.2 mL of acetonitrile, ethanol and water in the presence of 0.3 mmol of $Co(HSO_4)_2$ (Table 1). These results and also the data of the optimization of the amount of the catalyst indicated that the best solvent for this synthesis is ethanol in the presence of 0.3 mmol of the catalyst (Table 2). It is noteworthy that by carrying the reaction with 1 mmol of 1,3-dicarbonyl compound or by using 0.1 and 0.2 mmol of catalyst, the formation of trace amount of two side products was observed and also by using of more than 0.2 mL ethanol, the yield of reaction was drastically decreased. The latter observation is possibly due to deactivation of the catalyst by the coordination of the ethanol oxygen lone pair to the empty orbital of the catalyst instead of coordination to the oxygen of the carbonyl compound to activate this group for the nucleophilic attack of urea.

In an optimized reaction condition various 2-oxo-(thioxo)-1,2,3,4-tetrahydropyrimidines were synthesized in the presence of 0.3 mmol of the catalyst in ethanol under thermal conditions (Scheme I and Table 3).

A comparison of the results obtained in the present study with those reported in other works indicates that the

Table 1. Solvent effect on the synthesis of **1** at reflux conditions

Solvent[a]	Time (h)	Yield (%)[b]
Acetonitrile	2.5	70
Ethanol	2.5	95
Water	4.5	51

[a] The mole ratio of aldehyde : dicarbonyl compound : urea is 1: 1.2 : 2.
[b] Isolated yield.

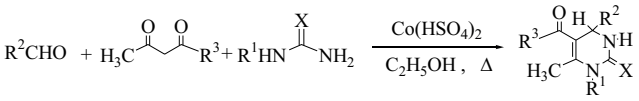
Table 2. Optimization of the amount of $Co(HSO_4)_2$ for the synthesis of **1** in ethanol

Catalyst (mmol)[a]	Conversion (%)[b]
0.1	~ 60
0.2	~ 80
0.3	100
0.4	100

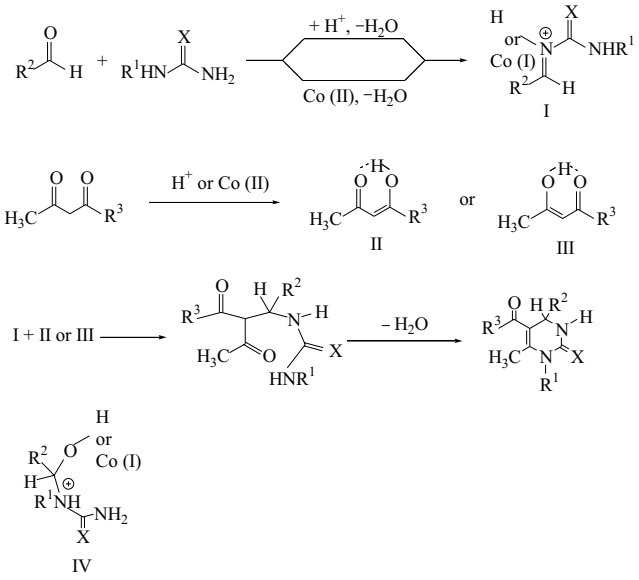
[a] The mole ratio of aldehyde: dicarbonyl compound: urea is 1: 1.2 : 2.
[b] Conversion after 2.5 h under thermal conditions.

use of $Co(HSO_4)_2$ which is simultaneously a Lewis acid and also a Brønsted acid facilitates smooth condensation of urea, thiourea or their methyl-substituted derivatives with aldehyde under formation of the imino-intermediate I (Scheme II). This is indicated by the effect of the nature of the aryl or alkyl group in the aldehyde molecule on the yield and time of reaction. On the other hand, the results indicated that the reaction with thiourea is slower than with urea. It seems that the nitrogen lone pair in the thiourea molecule is possibly delocalized to the sulfur d-orbitals, which causes a decrease of nucleophilic character of its nitrogen towards the aldehyde carbonyl group. It should be noted that by increasing the amount of the catalyst, the yield of the reaction with thiourea did not change too much. This explains the above suggestion and not the complex formation between the catalyst and soft sulfur atom in thiourea molecule. The reactions with *N*-methylurea or *N*-methylthiourea are also in many cases slower than those with urea or thiourea. It is clear that the presence of the methyl group increases the electron density on the nitrogen atom, which is expected to be a better nucleophilic species, but due to increasing the steric hindrance and also the failure of the possible elimination of water from the *N*-methylammonium intermediate IV, a slower reaction with *N*-methylurea or *N*-methylthiourea has been observed. This suggestion is supported by the formation of *N*1-methyl substituted 2-oxo(thioxo)-1,2,3,4-tetrahydropyrimidines and

Scheme I



Scheme II



also by the failure of the reaction with *N,N'*-dimethylurea.

This catalyst is especially suitable for the synthesis of THPM-5-carboxamides. Whereas the THPM-amides (entries 35-39) were synthesized using $ZrCl_4$ in 43-66% after 10-12 hours heating,[12] the same compounds were obtained in higher yield (72-92%) and shorter reaction time (1-4.5 hours) using $Co(HSO_4)_2$. This catalyst is also used for the synthesis of 4-alkyl-THPMs and 2-thioxo-1,2,3,4-tetrahydropyrimidines. This is the advantage of $Co(HSO_4)_2$ compared to $Bi(NO_3)_3$ and other catalysts which are not suitable for the synthesis of these derivatives.[8] The catalyst $Co(HSO_4)_2$ is easily prepared by the reaction of $CoCl_2$ with concentrated sulfuric acid. After completion of THPM synthesis, the catalyst and the excess of β-dicarbonyl compounds were easily removed by addition of water and small amount of ethanol. Recently $CoCl_2$ alone[13] or in combination with HCl[14] have been used for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidines. The advantages of $Co(HSO_4)_2$ over these catalysts are that $CoCl_2$ is also soluble in ethanol, which hinders purification of the product and also the presence of HCl may cause hydrolysis of the β-ketoesters or β-ketoamides in the presence of formed water under reflux conditions. All these decrease the yield of reaction.

Table 3. Synthesis of various Biginelli compounds in ethanol under thermal conditions

Entry	R^1	R^2	R^3	X	Time (h)[a]	Yield (%)[b]
1	H	C_6H_5	OC_2H_5	O	2.5	95
2	H	4-BrC_6H_4	OC_2H_5	O	2.75	79
3	H	4-FC_6H_4	OC_2H_5	O	3	84
4	H	4-$MeOC_6H_4$	OC_2H_5	O	2.5	95
5	H	3-$MeOC_6H_4$	OC_2H_5	O	3.5	78
6	H	2-$MeOC_6H_4$	OC_2H_5	O	2	78
7	H	4-$NO_2C_6H_4$	OC_2H_5	O	3	75
8	H	2-Pyridyl	OC_2H_5	O	0.75	43
9	H	2-Thienyl	OC_2H_5	O	6	71
10	H	C_6H_5	OCH_3	O	2	74
11	H	4-BrC_6H_4	OCH_3	O	3.75	84
12	H	4-FC_6H_4	OCH_3	O	5.5	87
13	H	4-$MeOC_6H_4$	OCH_3	O	2.5	90
14	H	4-$NO_2C_6H_4$	OCH_3	O	4.5	82
15	H	C_6H_5	OC_2H_5	S	6.5	70
16	H	4-BrC_6H_4	OC_2H_5	S	8	40
17	H	C_6H_5	OCH_3	S	6.5	77
18	H	4-BrC_6H_4	OCH_3	S	8	47
19	CH_3	C_6H_5	OC_2H_5	O	3.5	87
20	CH_3	4-BrC_6H_4	OC_2H_5	O	3	86
21	CH_3	4-FC_6H_4	OC_2H_5	O	2.5	81
22	CH_3	4-$MeOC_6H_4$	OC_2H_5	O	4	47
23	CH_3	4-$NO_2C_6H_4$	OC_2H_5	O	7.5	61
24	CH_3	4-BrC_6H_4	OCH_3	O	3	92
25	CH_3	4-FC_6H_4	OCH_3	O	6	77
26	CH_3	C_6H_5	OC_2H_5	S	8	73
27	CH_3	C_6H_5	OCH_3	S	8.5	74
28	H	C_6H_5	CH_3	O	1	83
29	H	2-BrC_6H_4	CH_3	O	1.5	82
30	H	4-BrC_6H_4	CH_3	O	1.5	88
31	H	4-FC_6H_4	CH_3	O	1	71
32	H	4-$MeOC_6H_4$	CH_3	O	3	78
33	H	4-$NO_2C_6H_4$	CH_3	O	2.5	74
34	H	C_6H_5	C_6H_5	O	4.5	75
35	H	C_6H_5	2-ClC_6H_4NH	O	4	91
36	H	C_6H_5	4-$MeOC_6H_4NH$	O	2	77
37	H	C_6H_5	$PhCH_2NH$	O	2.25	72
38	H	C_6H_5	4-ClC_6H_4NH	O	1	86
39	H	4-$MeOC_6H_4$	2-ClC_6H_4NH	O	4.5	92
40	CH_3	C_6H_5	2-ClC_6H_4NH	O	2.75	80
41	H	*n*-Pr	OC_2H_5	O	3	54

[a] The times are given after maximum progression of the reaction.
[b] Isolated yield.

EXPERIMENTAL

General procedure for the synthesis of THPMs under reflux conditions

A mixture of aldehyde (1 mmol), 1,3-dicarbonyl compound (1.2 mmol), urea or thiourea (2 mmol) and $Co(HSO_4)_2$ (0.3 mmol) in EtOH (0.2 mL) was heated at 85 ºC for appropriate time. After completion of the reaction indicated by TLC (*n*-hexane : ethyl acetate, 3:1), the mixture was cooled to room temperature and water was added. Stirring was continued for several minutes for dissolving the catalyst and the excess of urea or thiourea. The solid products were filtered and washed with water. The pure products were obtained by recrystallization from ethanol. The products have been characterized by comparison of their physical and spectroscopic data with those of the authentic samples. The physical and spectroscopic data of the new com-

pounds are reported below.

Ethyl 6-methyl-2-oxo-4-(2′-pyridyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (8)

Mp 204-205 °C; IR (KBr): ν = 3228, 3109, 2981, 2931, 1709, 1670, 1593 cm^{-1}; ^1H NMR (300 MHz, [D6]-DMSO): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.24 (s, 3H, 6-CH_3), 3.96 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 5.23 (d, ^3J = 2.9 Hz, 1H, 4-H), 7.24 (m_c, 2H, 3′-H, 5′-H), 7.70 (m_c, 2H, 4′-H, 6′-H), 8.50 (m_c, 1H, N_1-H), 9.20 (s, 1H, N_3-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 14.50 (OCH_2CH_3), 18.30 (6-CH_3), 56.13 (C-4), 59.54 (OCH_2CH_3), 98.47, 121.37, 123.05, 137.01, 149.40, 149.76, 152.93, 162.74 (5-C=O), 165.80 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 261 (47) $[M]^+$, 216 (18) $[M - C_2H_5O]^+$, 188 (19) $[M - C_2H_5OCO]^+$, 183 (100) $[M - C_5H_4N]^+$, 173 (17) $[M - C_2H_5OCO, -CH_3]^+$, 155 (64) $[M - C_5H_4N, -C_2H_4]^+$, 110 (12) $[M - C_2H_5OCO, -C_5H_4N]^+$, 78 (71) $[C_5H_4N]^+$, 67 (36), 52 (37).

Methyl 4-(4′-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (11)

Mp 222-225 °C; IR (KBr): ν = 3365, 3222, 3109, 2947, 1725, 1689, 1635, 1489 cm^{-1}; ^1H NMR (300 MHz, [D6]-DMSO): δ = 2.29 (s, 3H, 6-CH_3), 3.53 (s, 3H, OCH_3), 5.18 (s, 1H, 4-H), 7.22 (d, ^3J = 7.1 Hz, 2H, 2′-H, 6′-H), 7.51 (d, ^3J = 7.1 Hz, 2H, 3′-H, 5′-H), 7.87 (s, 1H, N_1-H), 9.36 (s, 1H, N_3-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 18.36 (6-CH_3), 51.26 (C-4), 53.89 (OCH_3), 99.06, 120.90, 128.96, 131.81, 144.44, 149.43, 152.63 (5-C=O), 166.55 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 326 (7) $[M\ ^{81}Br]^+$, 324 (7) $[M\ ^{79}Br]^+$, 311 (10) $[M\ ^{81}Br - CH_3]^+$, 309 (10) $[M\ ^{79}Br - CH_3]^+$, 294 (2) $[M\ ^{81}Br - CH_3OH]^+$, 292 (2) $[M\ ^{79}Br - CH_3OH]^+$, 267 (10) $[M\ ^{81}Br - CH_3OCO]^+$, 265 (13) $[M\ ^{79}Br - CH_3OCO]^+$, 184 (8), 169 (100) $[M - p\text{-}BrC_6H_4]^+$, 137 (45) $[M - p\text{-}BrC_6H_4, -CH_3OH]^+$, 110 (12) $[M - p\text{-}BrC_6H_4, -CH_3OCO]^+$, 94 (7) $[M - p\text{-}BrC_6H_5, -CH_3OCOCH_3]^+$, 59 (15) $[CH_3OCO]^+$.

Methyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (17)

Mp 223-226 °C; IR (KBr): ν = 3319, 3186, 2997, 1665, 1579 cm^{-1}; ^1H NMR (300 MHz, [D6]-DMSO): δ = 2.32 (s, 3H, 6-CH_3), 3.51 (s, 3H, OCH_3), 5.24 (s, 1H, 4-H), 7.27 (brd s, 5H, Ar-H), 9.70 (s, 1H, N_1-H), 10.39 (s, 1H, N_3-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 17.73 (6-CH_3), 51.47 (C-4), 54.49 (OCH_3), 100.95, 126.83, 128.15, 129.03, 145.77, 143.78, 166.08 (5-C=O), 174.75 (C=S) ppm; MS (EI, 70 eV): *m/z* (%) = 262 (96) $[M]^+$, 247 (48) $[M - CH_3]^+$, 231 (7) $[M - CH_3O]^+$, 230 (11) $[M - CH_3OH]^+$, 203 (24) $[M - CH_3OCO]^+$, 185 (100) $[M - Ph]^+$, 153 (87) $[M - Ph, -S]^+$, 126 (63) $[M - Ph, -CH_3OCO]^+$, 115 (53), 103 (41), 86 (34), 84 (36), 77 (47) $[Ph]^+$, 59 (22).

Methyl 4-(4′-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (18)

Mp 177-179 °C; IR (KBr): ν = 3174, 2997, 1714, 1651, 1585 cm^{-1}; ^1H NMR (300 MHz, [D6]-DMSO): δ = 2.30 (s, 3H, 6-CH_3), 3.55 (s, 3H, OCH_3), 5.16 (d, ^3J = 3.2 Hz, 1H, 4-H), 7.17 (d, ^3J = 8.3 Hz, 2H, 2′-H, 6′-H), 7.56 (d, ^3J = 8.3 Hz, 2H, 3′-H, 5′-H), 9.71 (s, 1H, N_1-H), 10.44 (s, 1H, N_3-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 17.71 (6-CH_3), 51.64 (C-4), 53.83 (OCH_3), 100.40, 121.35, 129.06, 132.04, 143.03, 146.14, 165.96 (5-C=O), 174.71 (C=S) ppm; MS (EI, 70 eV): *m/z* (%) = 342 (20) $[M\ ^{81}Br]^+$, 340 (19) $[M\ ^{79}Br]^+$, 283 (24) $[M\ ^{81}Br - CH_3OCO]^+$, 281 (25) $[M^{79}Br - CH_3OCO]^+$, 185 (100) $[M - p\text{-}BrC_6H_4]^+$, 153 (27) $[M - p\text{-}BrC_6H_4, -CH_3OH]^+$, 126 (12) $[M - p\text{-}BrC_6H_4, -CH_3OCO]^+$, 102 (18), 86 (17), 75 (43), 59 (20).

Ethyl 4-(4′-bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (20)

Mp 150-152 °C; IR (KBr): ν = 3215, 3087, 2933, 1711, 1680, 1628 cm^{-1}; ^1H NMR (300 MHz, [D6]-DMSO): δ = 1.11 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, 6-CH_3), 3.10 (s, 3H, N-CH_3), 4.03 (q, ^3J = 7 Hz, 2H, OCH_2CH_3), 5.15 (d, ^3J = 3.4 Hz, 1H, 4-H), 7.18 (d, ^3J = 8.3 Hz, 2H, 2′-H, 6′-H), 7.52 (d, ^3J = 8.3 Hz, 2H, 3′-H, 5′-H), 8.03 (d, ^3J = 3.6 Hz, 1H, N-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 14.50 (OCH_2CH_3), 16.50 (6-CH_3), 30.20 (N-CH_3), 52.37 (C-4), 60.06 (OCH_2CH_3), 102.33, 120.87, 128.83, 131.82, 143.87, 151.49, 153.34 (5-C=O), 165.89 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 354 (5) $[M\ ^{81}Br]^+$, 352 (5) $[M\ ^{79}Br]^+$, 339 (4) $[M\ ^{81}Br - CH_3]^+$, 337 (4) $[M\ ^{79}Br - CH_3]^+$, 325 (12) $[M\ ^{81}Br - C_2H_5]^+$, 323 (11) $[M\ ^{79}Br - C_2H_5]^+$, 281 (4) $[M\ ^{81}Br - C_2H_5OCO]^+$, 279 (4) $[M\ ^{79}Br - C_2H_5OCO]^+$, 197 (100) $[M - p\text{-}BrC_6H_4]^+$, 169 (37) $[M - p\text{-}BrC_6H_4, -C_2H_4]^+$, 152 (3) $[M - p\text{-}BrC_6H_4, -C_2H_5O]^+$, 151 (23) $[M - p\text{-}BrC_6H_4, -C_2H_5OH]^+$, 124 (3) $[M - p\text{-}BrC_6H_4, -C_2H_5OCO]^+$, 56 (78).

Ethyl 4-(4′-fluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (21)

Mp 124-125 °C; IR (KBr): ν = 3226, 3109, 2979, 1725, 1687, 1616 cm^{-1}; ^1H NMR (300 MHz, [D6]-DMSO): δ = 1.10 (brd s, 3H, OCH_2CH_3), 2.50 (s, 3H, 6-CH_3), 3.11 (s, 3H, N-CH_3), 4.02 (brd s, 2H, OCH_2CH_3), 5.2 (s, 1H, 4-H), 7.19 (m, 4H, Ar-H), 8.03 (s, 1H, N-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 14.40 (OCH_2CH_3), 16.42 (6-CH_3), 30.10 (N-CH_3), 52.33 (C-4), 59.97 (OCH_2CH_3),

102.73, 115.58 (d, ^2J = 21.28 Hz, C-3′, C-5′), 128.56 (d, ^3J = 8.15 Hz, C-2′, C-6′), 140.78 (C-1′), 151.22 (C-6), 153.41 (5-C=O), 161.84 (d, ^1J = 243.28 Hz, C′-4), 165.93 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 292 (12) $[M]^+$, 291 (4) $[M-H]^+$, 277 (13) $[M-CH_3]^+$, 263 (50) $[M-C_2H_5]^+$, 219 (16) $[M-C_2H_5OCO]^+$, 197 (29) $[M-p\text{-}FC_6H_4]^+$, 169 (44) $[M-p\text{-}FC_6H_4, -C_2H_4]^+$, 151 (52) $[M-p\text{-}FC_6H_5, -C_2H_5O]^+$, 124 (12) $[M-p\text{-}FC_6H_5, -C_2H_5OCO]^+$, 95 (17) $[p\text{-}FC_6H_4]^+$, 84 (9), 56 (100).

Ethyl 4-(4′-methoxyphenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (22)

Mp 136-139 °C; IR (KBr): ν = 3221, 3091, 2983, 1725, 1682, 1635 cm^{-1}; ^{1}H NMR (300 MHz, [D6]-DMSO): δ = 1.12 (brd s, 3H, OCH_2CH_3), 2.48 (s, 3H, 6-CH_3), 3.10 (s, 3H, N-CH_3), 3.71 (s, 3H, OCH_3), 4.01 (brd s, 2H, OCH_2CH_3), 5.11 (s, 1H, 4-H), 6.88 (brd s, 2H, 3′-H, 5′-H), 7.12 (brd s, 2H, 2′-H, 6′-H), 7.93 (s, 1H, N-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 14.52 (OCH_2CH_3), 16.45 (6-CH_3), 30.12 (N-CH_3), 52.25 (C-4), 55.46 (OCH_3), 59.94 (OCH_2CH_3), 103.19 (C-5), 114.18, 127.68, 136.63, 153.57, 150.71, 158.92 (5-C=O), 166.07 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 304 (39) $[M]^+$, 303 (15) $[M-H]^+$, 289 (27) $[M-CH_3]^+$, 275 (100) $[M-C_2H_5]^+$, 231 (64) $[M-C_2H_5OCO]^+$, 197 (36) $[M-p\text{-}CH_3OC_6H_4]^+$, 169 (47) $[M-p\text{-}CH_3OC_6H_4, -C_2H_4]^+$, 151 (66) $[M-p\text{-}CH_3OC_6H_5, -C_2H_5O]^+$, 124 (36) $[M-p\text{-}CH_3OC_6H_4, -C_2H_5OCO]^+$, 84 (37), 77 (17) $[Ph]^+$, 56 (78).

Methyl 4-(4′-bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (24)

Mp 157-159 °C; IR (KBr): ν = 3195, 3087, 2947, 1725, 1685 cm^{-1}; ^{1}H NMR (300 MHz, [D6]-DMSO): δ = 2.51 (s, 3H, 6-CH_3), 3.11 (s, 3H, N-CH_3), 3.57 (s, 3H, O-CH_3), 5.17 (s, 1H, 4-H), 7.20 (d, ^3J = 7.5 Hz, 2H, 2′-H, 6′-H), 7.52 (d, ^3J = 7.3 Hz, 2H, 3′-H, 5′-H), 8.07 (s, 1-H, N-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 16.54 (6-CH_3), 30.23 (N-CH_3), 51.56 (C-4), 52.23 (OCH_3), 102.08, 120.94, 128.79, 131.85, 143.69, 151.79, 153.40 (5-C=O), 166.39 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 340 (17) $[M\ ^{81}Br]^+$, 338 (19) $[M\ ^{79}Br]^+$, 325 (38) $[M\ ^{81}Br-CH_3]^+$, 323 (39) $[M\ ^{79}Br-CH_3]^+$, 309 (5) $[M\ ^{81}Br-CH_3O]^+$, 307 (9) $[M\ ^{79}Br-CH_3O]^+$, 281 (36) $[M\ ^{81}Br-CH_3OCO]^+$, 279 (41) $[M^{79}Br-CH_3OCO]^+$, 183 (93) $[M-p\text{-}BrC_6H_4]^+$, 151 (58) $[M-p\text{-}BrC_6H_4, -CH_3OH]^+$, 124 (13) $[M-p\text{-}BrC_6H_4, -CH_3OCO]^+$, 56 (100).

Methyl 4-(4′-fluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (25)

Mp 132-134 °C; IR (KBr): ν = 3221, 3103, 2927, 1682, 1622 cm^{-1}; ^{1}H NMR (300 MHz, [D6]-DMSO): δ = 2.51 (s, 3H, 6-CH_3), 3.11 (s, 3H, N-CH_3), 3.56 (s, 3H, OCH_3), 5.21 (s, 1H, 4-H), 7.12 (brd s, 2H, 3′-H, 5′-H), 7.29 (brd s, 2H, 2′-H, 6′-H), 8.05 (s, 1H, N-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 16.45 (6-CH_3), 30.12 (N-CH_3), 51.44 (C-4), 52.15 (OCH_3), 102.46, 115.62 (d, ^2J = 21.20 Hz, C-3′, C-5′), 128.51 (d, ^3j = 8.07 Hz, C-2′, C-6′), 140.60, 151.55, 153.54 (5-C=O), 161.87 (d, ^1J = 243.36 Hz, C-4′), 166.45 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 278 (8) $[M]^+$, 263 (23) $[M-CH_3]^+$, 247 (3) $[M-CH_3O]^+$, 219 (35) $[M-CH_3OCO]^+$, 183 (100) $[M-p\text{-}FC_6H_4]^+$, 152 (9) $[M-p\text{-}FC_6H_4, -CH_3O]^+$, 151 (73) $[M-p\text{-}FC_6H_4, -CH_3OH]^+$, 96 (4) $[p\text{-}FC_6H_5]^+$, 95 (13) $[p\text{-}FC_6H_4]^+$, 56 (92).

Methyl 1,6-dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (27)

Mp 160-162 °C; IR (KBr): ν = 3215, 2972, 2947, 1684, 1639 cm^{-1}; ^{1}H NMR (300 MHz, [D6]-DMSO): δ = 2.53 (s, 3H, 6-CH_3), 3.49 (s, 3H, N-CH_3), 3.62 (s, 3H, OCH_3), 5.25 (d, ^3J = 3.9 Hz, 1H, 4-H), 7.29 (m_c, 5H, Ph), 9.93 (d, ^3J = 3.9 Hz, 1H, N-H) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 16.74 (6-CH_3), 36.67 (N-CH_3), 51.4 (C-4), 52.6 (OCH_3), 105.53, 126.48, 128.17, 129.12, 142.47, 148.78, 166.21 (5-C=O), 178.54 (C=S) ppm; MS (EI, 70 eV): *m/z* (%) = 276 (61) $[M]^+$, 261 (39) $[M-CH_3]^+$, 245 (5) $[M-CH_3O]^+$, 243 (8) $[M-CH_3OH, -H]^+$, 217 (56) $[M-CH_3OCO]^+$, 199 (85) $[M-Ph]^+$, 167 (42) $[M-Ph, -CH_3OH]^+$, 140 (6) $[M-Ph, -CH_3OCO]^+$, 91 (20) $[C_7H_7]^+$, 77 (61) $[Ph]^+$, 56 (100).

5-Benzoyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine (34)

Mp 208-210 °C, (lit. [43] mp 203-204 °C); IR (KBr): ν = 3300, 3109, 2924, 1705, 1647, 1595 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 292 (48) $[M]^+$, 277 (21) $[M-CH_3]^+$, 215 (72) $[M-Ph]^+$, 187 (76) $[M-PhCO]^+$, 105 (65) $[PhCO]^+$, 77 (100) $[Ph]^+$.

1,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-(2-chlorophenylcarboxamide) (40)

Mp 205-207 °C; IR (KBr): ν = 3234, 3099, 2924, 1695, 1630 cm^{-1}; ^{1}H NMR (300 MHz, [D6]-DMSO): δ = 2.29 (s, 3H, 6-CH_3), 3.09 (s, 3H, N-CH_3), 5.31 (s, 1H, 4-H), 7.29 (m_c, 9H, Ar-H), 7.81 (s, 1H, N-H), 9.43 (5-NH-amide) ppm; ^{13}C NMR (75.47 MHz, [D6]-DMSO): δ = 17.16 (6-CH_3), 29.87 (N-CH_3), 54.37 (C-4), 108.68, 126.72, 127.22, 127.74, 127.79, 127.90, 128.67, 128.98, 129.90, 135.49, 141.13, 143.94, 153.93 (5-C=O), 166.44 (2-C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 355 (4) $[M]^+$, 340 (6) $[M-CH_3]^+$, 229 (76) $[M-C_6H_4ClNH]^+$, 228 (8) [M

$-C_6H_4ClNH_2]^+$, 201 (31) $[M-C_6H_4ClNHCO]^+$, 186 (20) $[M-C_6H_4ClNHCOCH_3]^+$, 151 (7), 132 (12), 77 (35) $[Ph]^+$, 56 (100).

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