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ORIGINAL ARTICLE

Solvent free synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones catalyzed by *N*,*O*-bis(trimethylsilyl)acetamide and dicyclohexyl carbodimide

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KEYWORDS

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Solvent free;
3,4-Dihydropyrimidinones;
3,4-Dihydropyrimidithiones

Abstract We report herein, the usage of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and dicyclohexyl carbodimide (DCC) as two new catalysts for three component condensation of an aldehyde, ethyl acetoacetate and urea/thiourea under solvent free conditions at 100 °C to afford the corresponding 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones (DHPMs) in good to excellent yields. A comparative study of these two catalysts was made and presented.

1. Introduction

In the recent decades, the developments of multi component condensations (Ugi et al., 1994; Domling, 2006) (MCCs) are of increasing importance in organic and medicinal chemistry for modern drug discovery. It was soon established that DHPMs exhibit similar therapeutic and pharmacological profile to 1,4 dihydropyridines (DHPs) calcium channel modulator of the nefidine (Domling, 1998; Plunlett and Ellman, 1997; Schreiber, 2000). From the past two decades synthesis of DHPMs and their derivatives being a hot area of research due to their wide spectrum of biological activities (Bryzgalov et al., 2006; Holla et al., 2004; Zorkun et al., 2006; Kappe, 1993, 1998, 2000a,b; Chitra et al., 2010; Atwal et al., 1991; Rovnyak et al., 1992), including antibacterial, antiviral, antitumor, anti-inflammatory, antiarrhythmic activity, antifungal activities, and antihypertensive as well as the most potent Ca^{2+} channel blockers (Rovnyak et al., 1995; Aswal et al., 1990). Recently, inhibitors of the fatty acid transporter FATP4 (Christopher et al., 2006), one of the DHPMs derivative monastrol has emerged as a new chemical tool for investigating human mitotic kinesin Eg5 (Emmanuel et al., 2007) motor protein inhibitor for the development of anticancer drugs. Furthermore, the marine alkaloids attributed to the dihydro pyrimidinones moiety in the structure isolated from natural

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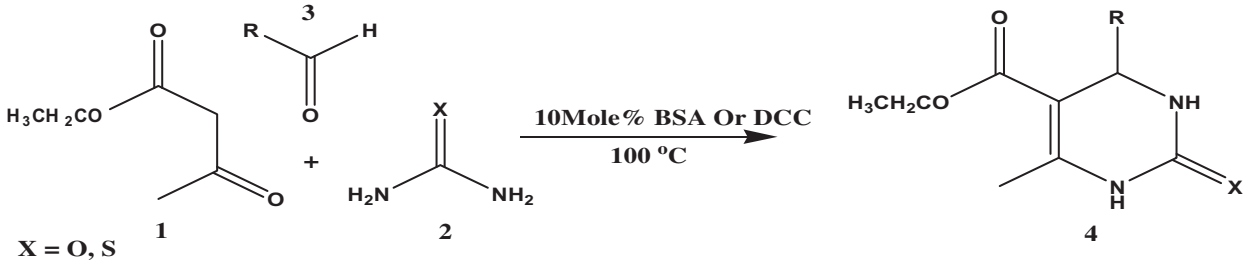


Scheme 1 Synthesis of 3,4-dihydropyrimidinones/thiones catalyzed by BSA or DCC under solvent free conditions.

marine sources such as crambine, batzelladine B (potent HIV-gp-120CD4 inhibitors) (Rama Rao et al., 1995).

The classical Biginelli reaction (Biginelli et al., 1888); Kolosov et al., 2009) is the MCCs of aldehyde, ethyl acetoacetate and urea/thiourea refluxed at100 °C in ethanol, in the presence of acetic acid for 8 h. Several synthetic methodologies such as solvent free (Weike, 2005; Bahrami et al., 2009; Besoluk et al., 2008; Jing et al., 2009), ultrasounds (Yadav et al., 2001), ionic liquids (Sushilkumar et al., 2004; Jiajian, 2001), microwave synthesis (Kalyan Kumar, 2011; Kidwai et al., 2002; Khabazzadeh et al., 2008), Green approach synthesis (Ranu et al., 2002; Subhas et al., 2003; Rafiee and Jafari, 2006; Zheng-Jun et al., 2009; Mridula et al., 2010), phase-transfer catalysis (Bahar, 2009), baker's yeast (Atu and Ram, 2007), Brønsted acids (Yang et al., 2007; Shutalev and Sivova, 1998; Renwei, 2006), Brønsted bases (Zhi-Liang et al., 2010), Lewis acids (Ramalingan et al., 2008; Paraskar et al., 2003; Kumar et al., 2001; Anil et al., 2007; Ma et al., 2000; Brindaban et al., 2000; Zhua, 2004; Surya et al., 2005; Hamid Reza et al., 2009), were developed to synthesize the 3,4 dihydro pyrimidinones/thiones. Out of all these methodologies to the best of our knowledge, there are two reports employing (PPh_3) as a Lewis base (Debache et al., 2008). Herein, we report two new catalysts *viz*. (a) BSA (*N*,*O*-bis-(trimethylsilyl)acetamide) (b) DCC (dicyclohexyl carbodimide) for the synthesis of DHPMs under solvent free conditions at 100 °C, in an efficient way, good to excellent yields are obtained (Scheme 1).

2. Results and discussions

BSA and DCC are the two good moisture absorbents. These two reagents were employed individually as a catalyst in the Biginelli reaction to produce DHPMs from aromatic aldehyde, ethyl acetoacetate and urea (**4a-1** to **4j-1** and **4a-3** to **4j-3**) or thiourea (**4a-2** to **4j-2** and **4a-4** to **4j-4**). In an initial endower the reaction was performed with 10 mole % of catalyst at RT in different solvents *viz*. ethanol, methanol, tetrahydrofuran, *t*-butanol, dioxan, acetonitrile and under solvent free conditions. Even after 24 h the reaction was not moved at RT, when the reaction temperature was raised to 100 °C after 24 h only 20–30% of the product was obtained under solvent free and catalyst free conditions. In the presence of BSA or DCC catalyst yielded better results with low reaction times under solvent free conditions. To optimize the amount of the catalyst we have carried out the reaction with various mole % of the catalysts. However there is no recognizable change in either % of yield or the reaction time by the increased amounts in catalysts over 10 mol % of both BSA and DCC (Table 1). To elaborate the catalysts efficiency we have examined the same reaction with other Brønsted bases, Lewis bases and Lewis acids under solvent free conditions the results are recorded in (Table 2). To define the scope and limitations, the efficiency of the catalysts (BSA and DCC) was examined with several aldehydes, ethyl acetoacetate and urea/thiourea. Between these two catalysts, the best results are produced with BSA. The final product (DHPMs) yields affected by the substitutions in the benzene ring, electron withdrawing groups like nitro groups leads relatively higher yields than electron donating groups like alkyl, alkoxy and hydroxy groups (Table 3).

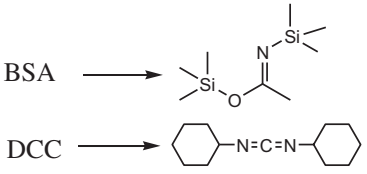


Table 1 Optimization of catalysts (BSA or DCC) under solvent free conditions.

Entry	Solvent	Mole % of BSA/DCC	Time (h)	Yield (%)			
				X = O		X = S	
1	EtOH	10	20	50[a]	47[b]	46[a]	42[b]
2	MeOH	10	20	47[a]	45[b]	35[a]	39[b]
3	THF	10	18	20[a]	27[b]	13[a]	17[b]
4	Dioxan	10	24	20[a]	15[b]	16[a]	13[b]
5	CH_3CN	10	24	30[a]	33[b]	32[a]	32[b]
6	Solvent free	05	3–4	30[a]	15[b]	43[a]	12[b]
7	Solvent free	10	3–4	80[a]	71[b]	57[a]	54[b]
8	Solvent free	15	3–4	82[a]	68[b]	55[a]	51[b]
9	Solvent free	20	3–4	81[a]	70[b]	56[a]	55[b]

[a] Isolated yields of DHPMs with BSA.
[b] Isolated yields of DHPMs with DCC.

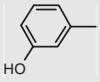
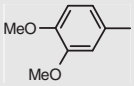
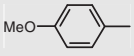
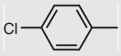
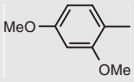
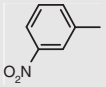
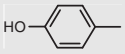
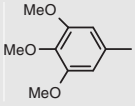
Table 2 Comparison of BSA/DCC catalyzed synthesis of DHPMs with other basic and acidic catalysts.

Entry	Catalyst	Time (h)	Yield (%)	
1	*t*-BuOK	10–12	57[a]	55[b]
2	BSA	1.2–4	80[a]	57[b]
3	DCC	1.3–4	71[a]	54[b]
4	PPh_3	10–12	30[a]	29[b]
5	BF_3et_2O	6–8	43[a]	40[b]
6	$AlCl_3$	8–10	40[a]	40[b]
7	Catalyst free	15–20	30[a]	20[b]

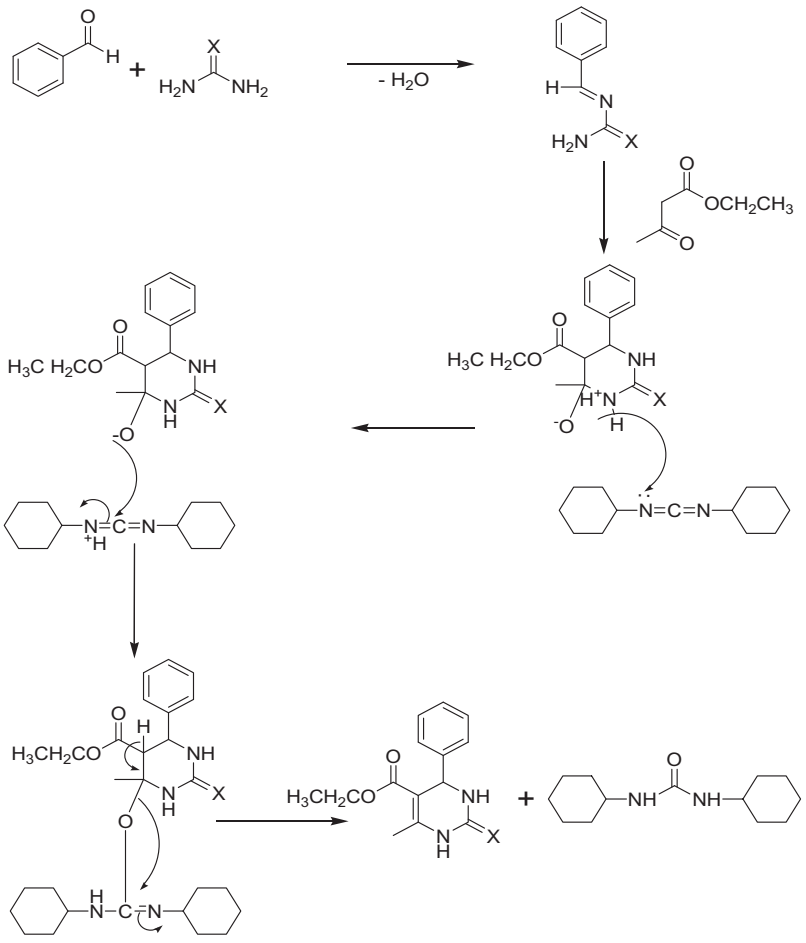
[a] Isolated yields of dihydro pyrimidinones.
[b] Isolated yields of dihydro pyrimidithiones.

The reaction may proceed via acylimine intermediate, formed by the reaction of the aldehyde and urea/thiourea. Subsequent addition of β-ketoester enolate to the acylimine, followed by cyclization and dehydration by the catalysts BSA or DCC, afforded the corresponding 3, 4-dihydropyrimidinones/thiones. Schemes 2 and 3 were the deniable mechanisms in the synthesis Biginelli 3,4-dihydropyrimidinones/thiones. More recently similar kind of mechanism was explained by Debache et al. (2008), Slimi et al. (2016), Folkers et al. (1932), Mamaev and Dubovenko (1970) and Valverde et al. (2001).

Table 3 BSA or DCC catalyzed synthesis of 3, 4-dihydropyrimidinones/thiones under solvent free conditions.

Entry	R-CHO	Catalyst	x	Product	Time (min)	Yield[a] (%)	Mp found	Mp reference
1		BSA	O	**4a-1**	200	80	182–183[b]	
			S	**4a-2**	260	54	180–181[c]	184–186 (Besoluk et al., 2008)
			O	**4a-3**	230	71		183–184(Besoluk et al., 2008)
			S	**4a-4**	260	57		
2		BSA	O	**4b-1**	140	85		
			S	**4b-2**	180	72	172–173[b]	175–177 (Bahrami et al., 2009)
		DCC	O	**4b-3**	170	83	210–212[c]	212–214 Bahar, 2009
			S	**4b-4**	130	75		
3		BSA	O	**4c-1**	140	78		
			S	**4c-2**	170	66	201–202[b]	202–203[18a]
		DCC	O	**4c-3**	150	72	150–152[c]	152–153 (Khabazzadeh et al., 2008)
			S	**4c-4**	180	61		
4		BSA	O	**4d-1**	170	90		
			S	**4d-2**	200	81	208–210[b]	210–212 (Debache et al., 2008)
		DCC	O	**4d-3**	170	81	182–183[c]	184–185 (Debache et al., 2008)
			S	**4d-4**	200	80		
5		BSA	O	**4e-1**	100	87		
			S	**4e-2**	80	85	210–212[b]	214–215 (Besoluk et al., 2008)
		DCC	O	**4e-3**	130	86	218–220[c]	219–221 (Besoluk et al., 2008)
			S	**4e-4**	120	74		
6		BSA	O	**4f-1**	180	88		
			S	**4f-2**	220	79	200–202[b]	204–205 (Besoluk et al., 2008)
		DCC	O	**4f-3**	190	89	161–162[c]	163–164 (Besoluk et al., 2008)
			S	**4f-4**	240	75		
7		BSA	O	**4g-1**	140	90		
			S	**4g-2**	110	75	229–230[b]	230–232 (Besoluk et al., 2008)
		DCC	O	**4g-3**	90	85	204–205[c]	206–207 (Besoluk et al., 2008)
			S	**4g-4**	110	73		
8		BSA	O	**4h-1**	260	85		
			S	**4h-2**	220	87	234–235[b]	237–238 (Slimi et al., 2016)
		DCC	O	**4h-3**	200	84	192–194[c]	193–195 (Mridula et al., 2010)
			S	**4h-4**	150	76		
9		BSA	O	**4i-1**	240	85		
			S	**4i-2**	260	75	180–181[b]	180–182[18b]
		DCC	O	**4i-3**	290	78	200–201[c]	202–204 (Subhas et al., 2003)
			S	**4i-4**	300	72		
10		BSA	O	**4j-1**	230	90		
			S	**4j-2**	260	78	200–202[b]	202–204 (Mridula et al., 2010)
		DCC	O	**4j-3**	230	82	200–201[c]	200–205 (Mridula et al., 2010)
			S	**4j-4**	240	75		

[a] Isolated yields,
[b] Melting points of 3,4-dihydropyrimidinone,
[c] Melting points of 3,4-dihydropyrimidithione.



Scheme 2 Plausible mechanism for the synthesis of 3,4-dihydropyrimidinones/thiones with DCC.

3. Conclusion

To sum up, we have developed novel methodologies for the synthesis of DHPMs carried out by BSA/DCC under solvent free conditions, excellent catalysts for one pot synthesis of dihydropyrimidinones/thiones under solvent free conditions, short reaction time, high yields of products, simple work up procedures and easy isolation making it an important supplement to the existing methods. Further, we are studying the scope of these catalysts to the other organic multicomponent reactions.

4. Experimental

4.1. General procedure for synthesis of 3,4-dihydropyrimidinones/thiones under solvent free conditions

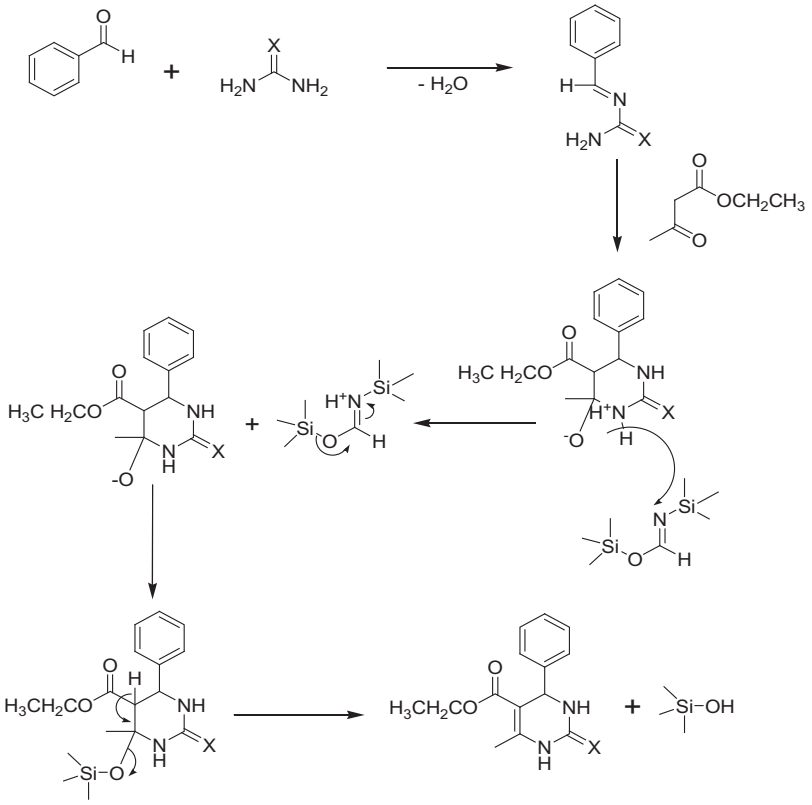
Aromatic aldehyde (0.01 moles), ethyl acetoacetate (0.012 moles) and urea/thiourea (0.01 moles) were stirred at 100 °C in the presence of BSA/DCC (10 mol %) for 110–300 min, the reaction was monitored by thin layer chromatography (TLC) [6:4 hexane–ethyl acetate]. After the completion of the reaction the reaction mixture was cooled and washed with ice cooled water, the separated solid was filtered and dried in vacuum, the solid product passed over a column of silica gel (60–100 mesh), finally recrystallized from alcohol to afford the desired product in pure form. Melting points were measured on Polmon melting point apparatus Mp 96. IR spectra were recorded on a Shimadzu IR Affinity-1. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 200 spectrometer and 50 MHz, respectively. NMR spectra were obtained on solutions in $CDCl_3$ and DMSO-d_6. Mass spectra were recorded on water XEVO QTof mass spectrometer.

*4.2. 4-(3-Hydroxy-phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4a-2**)*

Mp 182–183 °C; IR (KBr): 3423, 3095, 2920, 2823, 1719, 1658, 1517 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.16 (t, J = 7.2 Hz, 3H OCH_2CH_3), 2.21 (s, 3H, CH_3), 4.02 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.17 (d, J = 3.0 Hz, 1H, CH-Ar), 6.81 (s, 1H, Ar-H), 6.90 (d, J = 8.2 Hz, 1H, Ar-H), 7.11 (d, J = 7.2 Hz, 1H, Ar-H), 7.25–7.35 (m, 1H, Ar-H) 7.28 (d, J = 8.2 Hz), 7.24 (br s, N–H), 8.90 (br s, N–H), 9.15 (s, 1H, OH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 174.5, 165.2, 157.2, 144.8, 144, 129, 117.3, 114.9, 113.6, 102.3, 59.5, 54.7, 17.5, 13.9; EIMS: m/z $[M+1]^+$: 292.

*4.3. 4-(3Hydroxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4a-1**)*

Mp 180–181 °C; IR (KBr): 3512, 3352, 3244, 3119, 2980, 1718, 1678, 1600, 1460, 1229, 1094, 872, 779 cm^{-1}; ^{1}H NMR



Scheme 3 Plausible mechanism for the synthesis of 3,4-dihydropyrimidinones/thiones with BSA.

(200 MHz, DMSO-d_6): δ 1.12 (t, 3H, J = 7.2 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.99 (q, 2H, J = 7.2 Hz, OCH_2–CH_3), 5.07 (d, 1H, J = 3.0 Hz, CH-Ar), 6.61–6.68 (m, 3H, Ar-H), 7.09 (t, 1H, J = 8.0 Hz, Ar-H), 7.68 (s, 1H, NH), 9.15 (s, 1H, OH), 9.35 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.8, 157.8, 152.7, 148.5, 146.7, 129.7, 117.3, 114.6, 113.5, 99.9, 59.7, 54.3, 18.2,14.6; EIMS m/z $[M+1]^+$: 277.11.

*4.4. 4-(3,4-Dimethoxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4b-1**)*

Mp 171–173 °C; IR (KBr): 3350, 3220, 3190, 2984, 1668, 1650, 1620 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15(t, J = 8.2 Hz, 3H OCH_2CH_3), 2.14(s, 3H, CH_3), 3.86 (s, 6H, 2×OCH_3), 4.01(q, J = 8.2 Hz, 2H, OCH_2CH_3), 5.20(d, J = 3.0 Hz, 1H, CH-Ar), 6.78–6.82 (m,3H, Ar-H), 7.15(br s, N–H), 8.90(br s, N–H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 164.6, 152.7, 152.1, 147.6, 147.1, 136.3, 117.5, 110.2, 109.2, 98.5, 58.5, 54.9, 53.2, 24.7, 14.0; EIMS: m/z $[M+1]^+$: 321.

*4.5. 4-(4-Methoxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4c-1**)*

Mp 201–202 °C; IR (KBr): 3223, 3095, 2929, 2833, 1710, 1655, 1512 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15(t, J = 7.2 Hz, 3H CH_3), 2.24 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.01 (q, J = 8.2 Hz, 2H, OCH_2CH_3), 5.18 (d, J = 3.0 Hz, 1H, CH-Ar), 6.88 (d, J = 8.2 Hz, 2H, Ar-H), 7.28 (d, J = 8.2 Hz), 7.24 (br s, N–H), 8.90(br s, N–H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165, 158.8, 152, 147.7, 137, 127.1, 113.7, 97.8, 58.6, 54.6, 53.4, 17.6, 13.9; EIMS: m/z $[M+1]^+$: 291.

*4.6. 4-(4Chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4d-1**)*

Mp 217–218 °C; IR (KBr): 3237, 3117, 2978, 1701, 1647, 1460, 1288, 1221, 1088, 781 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.09 (t, 3H, J = 7.2 Hz, OCH_2–CH_3), 2.25 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.2 Hz, OCH_2–CH_3), 5.14 (d, 1H, J = 3.0 Hz, CH-Ar), 7.25 (d, 2H, J = 8.4 Hz, Ar-H), 7.39 (d, 2H, J = 8.4 Hz, Ar-H), 7.77 (s, 1H, NH), 9.24 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.7 152.4, 149, 144.3, 132.2, 128.9, 128.6, 99.3, 59.7, 53.9, 18.3, 14.5; EIMS: m/z $[M+1]^+$ 295.08.

*4.7. 4-(2Chloro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4e-1**)*

Mp 223–224 °C; IR (KBr): 3354, 3223, 3107, 2978, 1694, 1639, 1450, 1368, 1230, 1098, cm^{-1};^{1}H NMR (200 MHz, DMSO-d_6): δ 0.97 (t, 3H, J = 7.2 Hz, CH_3). 2.28 (s, 3H, CH_3), 3.87 (q, 2H, J = 7.2 Hz, OCH_2–CH_3), 5.61 (d, 1H, J = 2.8 Hz, CH-Ar), 7.24–7.40 (m, 4H, Ar-H), 7.68 (s, 1H, NH), 9.25 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.4, 151.8, 149.8, 142.2, 132.1, 129.8, 129.5, 129.2, 128.2, 98.3, 59.5, 51.9, 18.1, 14.4, EIMS: m/z $[M+1]^+$: 295.08.

*4.8. 4-(2,4-Dimethoxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylicacid ethyl ester (**4f-1**)*

Mp 200–202 °C; IR (KBr): 3223, 3095, 2929, 2833, 1710, 1655, 1512 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15 (t, J = 7.2 Hz, 3H CH_3), 2.24 (s, 3H, CH_3), 3.81 (s, 3H,

OCH_3), 3.85 (s, 3H, OCH_3), 4.01 (q, J = 8.2 Hz, 2H, OCH_2CH_3), 5.18 (d, J = 3.2 Hz, 1H, CH-Ar), 6.38 (d, J = 7.8 Hz, 2H, Ar-H), 7.28 (s, 1H, Ar-H), 6.80 (br s, N–H), 6.90 (d, J = 7.8 Hz, 2H, Ar-H), 9.00 (br s, N–H); ^{13}C NMR (50 MHz, DMSO-d_6); δ 164.6, 153.7, 152.1, 148.6, 147.1, 136.3, 116.5, 112.2, 105.2, 98.5, 59.5, 54.9, 53.2, 23.7, 13.0. EIMS: m/z $[M+1]^+$: 320.

*4.9. 4-(3-Nitro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**4g-1**)*

Mp 229–230 °C; IR (KBr): 3238, 3123, 2986, 1730, 1705, 1645, 1522, 1348, 1219, 1096, 854, 783 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.2 Hz, CH_3), 2.27 (s, 3H, CH_3), 3.99 (q, 2H, J = 7.2 Hz, OCH_2–CH_3), 5.27 (d, 1H, J = 3.0 Hz, CH-Ar), 7.50 (d, 2H, J = 8.6 Hz, Ar-H), 7.89 (s, 1H, NH), 8.22 (d, 2H, J = 8.6 Hz, Ar-H), 9.35 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.5, 152.5, 152.2149.9147.2 128.1, 124.3, 98.6, 59.9, 54.1, 18.3,14.5; EIMS m/z $[M+1]^+$: 306.10.

*4.10. 4-(4-Hydroxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**4h-1**)*

Mp 234–235 °C; IR (KBr): 3235, 3113, 2955, 1703, 1647, 1514, 1456, 1279, 1221, 1088, 837, 791 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.10 (t, 3H, J = 7.2 Hz, CH_3); 2.25 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.2 Hz, OCH_2–CH_3), 5.09 (d, 1H, J = 3.0 Hz, CH-Ar), 6.87 (d, 2H, J = 8.6 Hz, Ar-H), 7.15 (d, 2H, J = 8.6 Hz, Ar-H), 7.67 (s, 1H, NH), 9.13 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 166.8, 157.9, 150.6, 147.5, 136.5, 125.9, 112.2, 100.0, 56.5, 53.8, 18.2, 15.6; EIMS m/z $[M+1]^+$: 277.12.

*4.11. 4-(3,4,5-Trimethoxy-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**4i-1**)*

Mp 171–173 °C; IR (KBr): 3350, 3220, 3190, 2984, 1668, 1650, 1620 cm^{-1};^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15 (t, J = 7.2 Hz, 3H OCH_2CH_3), 2.14 (s, 3H, CH_3), 3.86 s, 9H, 3xOCH_3), 4.01 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.20 (d, 1H, J = 3.0 Hz, CH-Ar), 6.78–6.82 (m, 3H, Ar-H), 7.15 (br s, N–H), 8.90 (br s, N–H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 164.6152.3, 152.7, 152.1, 147.6, 147.1, 136.3, 117.5, 110.2, 109.2, 98.5, 58.5, 54.9, 53.2, 24.7, 14.0; EIMS: $m/z$$[M+1]^+$: 320.

*4.12. 4Phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (**4j-1**)*

Mp 202–204 °C; IR (KBr): 3256, 3121, 2945, 1730, 1703, 1647, 1464, 1290, 1226, 1090, 756 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.09 (t, 3H, J = 7.0 Hz, CH_3); 2.25 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.0 Hz, OCH_2–CH_3), 5.15 (d, 1H, J = 3.2 Hz, CH-Ar), 7.21–7.35 (m, 5H, Ar-H), 7.73 (s, 1H, NH), 9.19 (s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.8, 152.6, 148.8, 145.3, 128.8, 127.7, 126.7, 99.7, 59.6, 54.4, 18.2 14.5; EIMS m/z $[M+1]^+$: 261.12.

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