A One-pot Multi-component Synthesis of Dihydropyrimidinone/Thione and Dihydropyridine Derivatives *via* Biginelli and Hantzsch Condensations using *t*-BuOK as a Catalyst Under Solvent-free Conditions

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Abstract: The synthesis of various substituted Biginelli 3,4-dihydropyrimidinone/thione and Hantzsch 1,4-dihydropyridine derivatives has been achieved using a modified procedure in the presence of potassium *ter*-butoxide (*t*-BuOK) as a catalyst under solvent-free conditions, in good to excellent yields.

Keywords: *t*-BuOK, Biginelli 3,4-dihydropyrimidinones/thiones, Hantzsch 1,4-dihydropyridines, one-pot condensation, solvent-free conditions.

1. INTRODUCTION

Dihydropyridines (DHPs) have attracted increasing interest due to their diverse therapeutic and pharmacological properties such as insecticidal, bactericidal and herbicidal effects [1]. DHP drugs, namely nifedipine, nicardipine and amlodipine, are cardiovascular agents for the treatment of hypertension [2]. A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure [3]. In addition, dihydropyridines find applications in stereo specific hydrogen transfer reduction of phenylglyoxylic and pyruvic acid to biomimetic models of lactase dehydrogenase [4]. Recently, DHPs are used as organocatalysts for asymmetric reactions such as hydrogenation of quinolines in the synthesis of alkaloids [5], asymmetric reductive amination of aldehydes [6] and hydrogenation of α,β-unsaturated aldehydes and ketones [7]. Classical Hantzsch synthesis of these compounds is carried out in acetic acid or by refluxing in alcohol for a long time [8]. Several other methods are reported including use of microwaves [9], molecular iodine [10], cyanuric chloride [11], ionic liquids [12], silica gel/$NaHSO_4$ [13], TMSCl-NaI [14], metal triflates [15] and ultrasound irradiations [16].

Additionally, dihydropyrimidinones (DHPMs) have exhibited important therapeutic and pharmacological properties as the integral backbone of several calcium channel blockers [17], antihypertensive agents [18], and α_{1a}-antagonists [19a]. A broad range of biological effects including antiviral, antitumor, antibacterial and anti-inflammatory activities has been described for these compounds [20, 19b,c]. Some of the representative compounds of this class possess antiviral, antibacterial, antihypertensive and antitumor activities [21, 19d]. Several alkaloids isolated from marine sources also exhibit interesting biological activities, molecular structures of which contain the dihydropyrimidinone moiety [20]. Therefore, their synthesis has been the focus of great interest for organic and medicinal chemists [21]. The original Biginelli protocol for the preparation of DHPMs consisted of heating a mixture of three components which included β-ketoester, aldehyde and urea in ethanol containing a catalytic amount of HCl [22]. The major drawbacks associated with this protocol are the use of strong acid as well as the low yields in the case of substituted aromatic and aliphatic aldehydes. To enhance the efficiency of the Biginelli reaction, various catalysts and reaction conditions have been studied including classical conditions with ultrasound [23] or microwave-assisted irradiations [24], solid-support [25], ionic liquids [26], Lewis acid catalysts such as LiBr [27], NH_4Cl [28], $MgBr_2$ [29], CaF_2 [30], $FeCl_3.6H_2O$ [31], $Mn(OAc)_3$ [32], $InBr_3$ [33], ZnI_2 [34], $CdCl_2$ [35], H_3BO_3 [36], $PhB(OH)_2$ [37] and CuI [38]. The catalytic effect of metal cations is even more pronounced with methods based on metal salts with non-nucleophilic anions such as $LiClO_4$ [39], $CuSO_4.5H_2O$ [40], $Cu(OTf)_2$ [41], $Al(HSO_4)_3$ [42], trimethylsilyl triflate [43], which allow the preparation of DHPMs in good to high yields. The use of $BF_3.OEt_2$ [44], polyphosphate ester [45], $(NH_4)_2CO_3$ [46], NaCl [47] and $\{Fe_2CuO\}$ clusters [48] has also been described. The Biginelli reaction can strongly be accelerated by various procedures including heteropoly acids [49], silica sulfuric acid [50] and ferric chloride/tetraethyl orthosilicate [51].

On the other hand, a number of the reported protocols to synthesize DHPs and DHPMs requiring solvents and catalysts are not acceptable in the context of green synthesis;

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utilize reagents and catalysts which are either toxic or expensive and stoichiometric use of reagents with respect to reactant. Also, the clean handling of some anhydrous metal halides is not easy enough in the laboratory apart from their hygroscopic nature due to strong tendency for hydrolysis. However, the developments in this area demand further searches for better catalysts that could be superior to the existing ones with regard to toxicity, handling, and recyclability. In this respect, we are interested to introduce potential catalysts to overcome these limitations.

2. RESULTS AND DISCUSSION

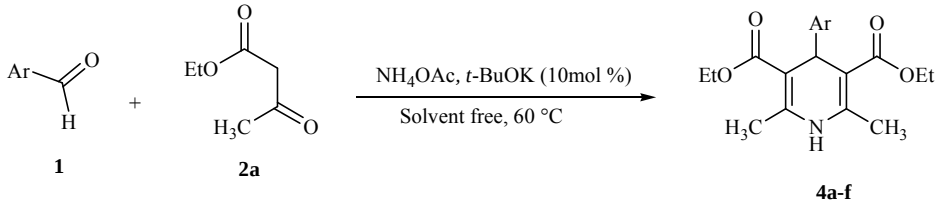
Recently, we have reported that Biginelli and Hantzsch condensation reactions are facilitated in the presence of a catalytic amount of triethylamine and triphenylphosphine as Brønsted and Lewis bases respectively [52]. Very recently, Z-L. Shen and co-workers [53] reported that *t*-BuOK catalyzes one-pot synthesis of DHPMs *via* a Biginelli-type condensation from aldehydes and 2-phenylacetophenone.

A literature survey clearly shows that there is no report on the application of *t*-BuOK as Brønsted base catalyst for classic Biginelli and Hantzsch condensation reactions. Here, we wish to report the capacity of potassium *tet*-Butoxide as potential Brønsted base catalyst for the one-pot synthesis of 3,4-dihydropyrimidinones and 1,4-dihydropyridines and their analogues *via* solvent-free Hantzsch and Biginelli condensation protocols, respectively.

In the efforts to develop an efficient and environmentally benign method for the synthesis of DHPs and DHPMs we initiated our study with the base-catalyzed Hantzsch condensation by subjecting catalytic amount of *t*-BuOK to the mixture of 2-furaldehyde (1 equiv.), which usually gives good yields of the corresponding product, ethyl acetoacetate (2 equiv.) and ammonium acetate (2 equiv.) in ethanol at room temperature. Unfortunately, the resulted yield was very poor even after 24 h of stirring. To see the effect of reaction, various solvent systems were tested at different temperatures. We found that the synthesis of DHP **4f** was efficiently catalyzed by *t*-BuOK in solvent free condition at elevated temperature leading to a good yield of product (Table **1**, entry 6). The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. The different experiments show that the best result was obtained by the application of 10 mol% of *t*-BuOK in solvent free condition at 60°C (Scheme **1**). Other amounts of the catalyst substantially reduced the yield as side products were formed.

In order to study the scope and generality of this methodology, a variety of substituted aromatic aldehydes were subjected to the previous reaction with 2-furaldehyde. Unfortunately, it was observed that even under optimized conditions, that the corresponding 1,4-DHPs were isolated in very moderate yields due to the formation of many other side products, also, the starting material **2a** was still present in the crude products (according to ^{1}H NMR spectra). In comparison, good yield was obtained when 2-thiophenecarboxaldehyde was employed (Table **1**, entry 5). However, the reaction of other aromatic aldehydes led to lower yields.

After many trials, we decided to employ other more reactive β-ketoesters such as dimedone **2d** (5,5-dimethylcyclohexan-1,3-dione) as a second equivalent with ethyl acetoacetate. Thus, the reaction of benzaldehyde (1 equiv.), dimedone (1 equiv.), ethyl acetoacetate (1 equiv.) and ammonium acetate (2 equiv.) in the presence of 10 mol% of *t*-BuOK in solvent free condition at 60°C affords after only 2h, the corresponding polyhydroquinoline in excellent yield (Scheme **2**). So, the reaction was amenable to a wide range of aromatic and heteroaromatic aldehydes and



Scheme (1).

Table 1. *t*-BuOK-Catalyzed Hantzsch Synthesis of 1,4-dihydropyridines Under Optimized Reaction Conditions[a]

Entry	DHP	Ar	Time (h)	Yield[b] (%)	M.p. (°C)	
					Measured	Reported
1	4a	C_6H_5	5	48	158-160	158-160 [54a]
2	4b	2-(OCH_3)-C_6H_4	10	23	141-143	140-142 [54b]
3	4c	4-(NO_2)-C_6H_4	6	36	130-132	129-131[54a]
4	4d	3-(NO_2)-C_6H_4	8	31	162-164	162-164 [54a]
5	4e	2-thienyl	2	80	171-173	171-173 [54a]
6	4f	2-furyl	3	84	160-162	160-161 [54a]

[a]: The reactions were carried out at 60°C using aldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimedone (2 mmol) ammonium acetate (4 mmol) and *t*-BuOK (0.2 mmol) under solvent-free conditions. [b]: Yields were measured by ^{1}H NMR spectra.

gave in all cases the desired products in very good yields and the results are summarized in Table **2**. It is noteworthy that the reactions proceeded at a faster rate with electron donating aldehydes (entries 1-4) and were slightly slow with electron withdrawing ones (entry 6) with the exception of polyhydroquinoline **4k** (entry 5) which gave the desired product in excellent yield. Good yields were also achieved for heterocyclic aldehydes such as 2-furaldehyde (entry 7). However, aliphatic aldehydes such as acetaldehyde and isobutyraldehyde afforded very poor results.

In addition, we also investigated the reactions using 2-methoxybenzaldehyde or 4-methoxybenzaldehyde with two equivalents of dimedone as a β-dicarbonyl compound under the above optimized reaction conditions. As described in experimental part, the corresponding products (**4o** and **4p**) were obtained in good yields [55].

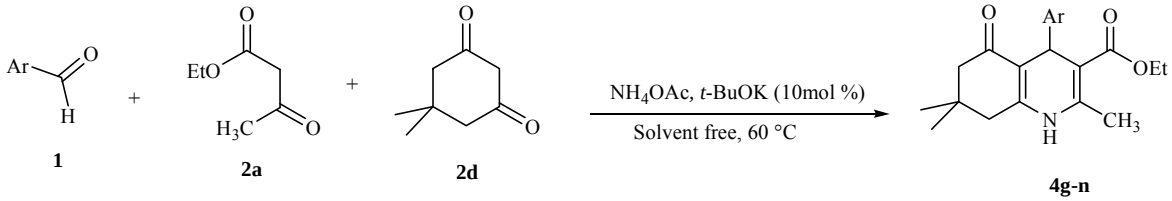
In a typical procedure, 2 mmol of aldehyde, 2 mmol of dimedone, 2 mmol of ethyl acetoacetate and 4 mmol of ammonium acetate were mixed in solvent free condition in the presence of 0.2 mmol of *t*-BuOK and the reaction mixture was stirred for 1-7 h at 60°C, after work-up, it produced the corresponding polyhydroquinolines in good yields.

A plausible mechanism of the *t*-BuOK catalyzed Hantzsch condensation is shown in Scheme (**3**) based on the previous reports, our observations and obtained results.

Encouraged by these results, we next focused our efforts to study the effect of *t*-BuOK on the Biginelli condensation reaction (Scheme **4**). In order to achieve the optimum conditions, the reaction of benzaldehyde **1a** with ethyl acetoacetate **2a** and urea **3a** was selected as a model. We began our trials by comparing the catalytic efficiency of *t*-BuOK with traditional Lewis acid. The reactions proceeded in moderate to good yields. The effect of the catalyst amount on the synthesis of DHPM **5a** was also investigated and the results show that the reactants hardly react when no catalyst is added, and the yield of Biginelli product is up to 70% with modifying the amount of *t*-BuOK from 20 to 10% mol. It was observed that similar results were obtained by decreasing the amount of the catalyst to 50% mol. The effect of different solvents was then studied. In water, the reactants do not react well, probably owing to the lower solubility of reactants in water. In ethanol, CH_3CN or THF, Biginelli product is obtained in moderate to good yields. However, the reaction at 80°C, under solvent-free condition gave very good yield of the desired product (Table **3**, entry 1).

With these results in hand, we set out to examine the scope of this reaction. As shown in Table **3**, different reactants are employed under the same conditions as entry 1 under smooth reactions, and the corresponding DHPMs were isolated in good to excellent yields. The results show that the generality of the present protocol is effective for both ethyl acetoacetate **2a** and 1,4-pentanedione **2b** of different aldehydes. For aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents, the products are obtained in high yields (entries 1-8). By replacing urea with thiourea **3b** in the reaction system under the proportion of 1:1:1.5 (benzaldehyde: ethyl acetoacetate : thiourea), the corresponding Biginelli products are also obtained in high yields (entries 9 and 10).

Next, we investigated the effect of others β-ketoesters such as 1,3-cyclohexanedione **2c** or 5,5-dimethyl-1,3-cyclohexanedione **2d** (Scheme **5**). Aromatic aldehydes such as benzaldehyde and different substituted benzaldehydes

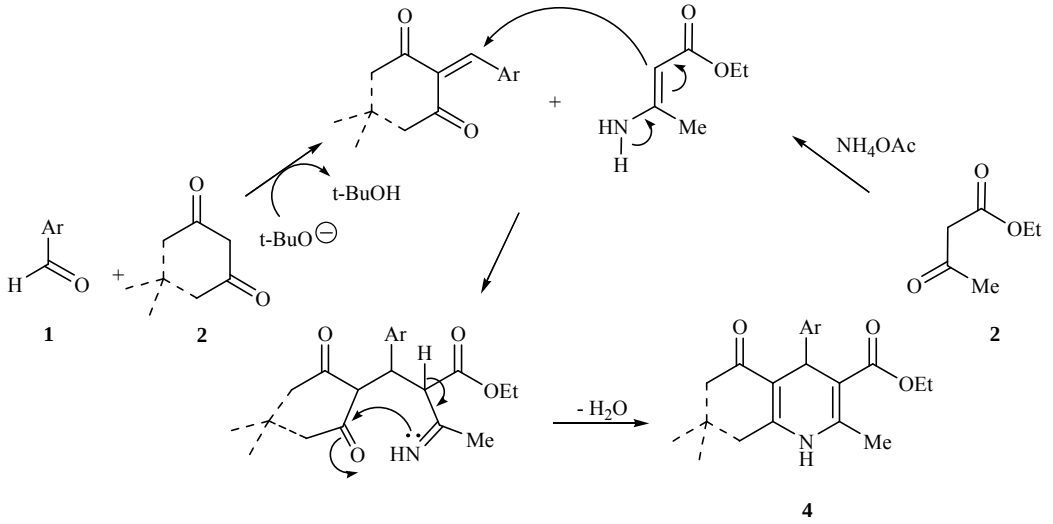


Scheme (2).

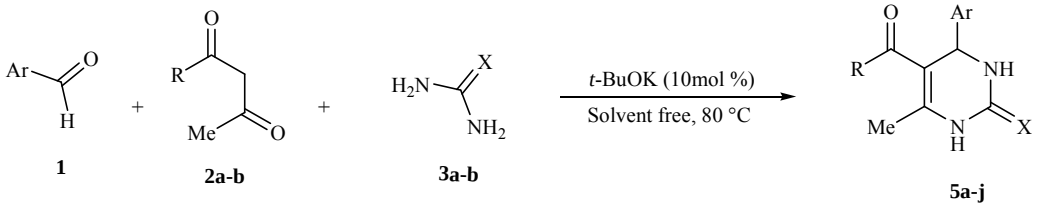
Table 2. *t*-BuOK-Catalyzed Hantzsch Synthesis of Polyhydroquinolines Under Optimized Reaction Conditions[a]

Entry	DHP	Ar	Time (h)	Yield[b] (%)	M.p. (°C)	
					Measured	Reported
1	4g	C_6H_5	2	73	205-207	202-204 [56a]
2	4h	4-(CH_3)-C_6H_4	2	92	260-262	260-262 [56a]
3	4i	4-(CH_3O)-C_6H_4	1	85	256-258	255-257 [56a]
4	4j	4-(OH)-C_6H_4	1	94	232-234	232-234 [56a]
5	4k	4-(Br)-C_6H_4	2	94	251-253	253-254 [56a]
6	4l	4-(NO_2)-C_6H_4	7	90	240-242	242-244 [56b]
7	4m	2-furyl	3	72	246-248	248-249 [56c]
8	4n	Styryl	3	65	206-208	206-207 [56c]

[a]: The reactions were carried out at 60°C using aldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimedone (2 mmol), ammonium acetate (4 mmol) and *t*-BuOK (0.2 mmol) under solvent-free conditions. [b]: Isolated yields.



Scheme (3).



Scheme (4).

Table 3. *t*-BuOK-Catalyzed Biginelli Synthesis of 3,4-dihydropyrimidinones Under Optimized Reaction Conditions[a]

Entry	DHPM	Ar	R	X	Time (h)	Yield[b] (%)	M.p. (°C)	
							Measured	Reported
1	5a	C_6H_5	OEt	O	3	81	203-205	206-207 [57a]
2	5b	4-(CH_3)-C_6H_4	OEt	O	3	81	212-214	215-216 [57a]
3	5c	3-(CH_3)-C_6H_4	OEt	O	8	65	210-212	208-209 [52c]
4	5d	2-(CH_3O)-C_6H_4	OEt	O	3	74	250-252	257-259 [57a]
5	5e	2-(OH)-C_6H_4	OEt	O	6	59	203-205	202-203 [36]
6	5f	Styryl	OEt	O	5	54	223-225	223-225 [52c]
7	5g	C_6H_5	Me	O	8	68	236-238	233-235 [57b]
8	5h	4-(CH_3)-C_6H_4	Me	O	8	76	202-204	203-205 [57b]
9	5i	C_6H_5	Me	S	6	62	224-226	222-224 [57b]
10	5j	C_6H_5	OEt	S	3	80	200-202	203-205 [57b]

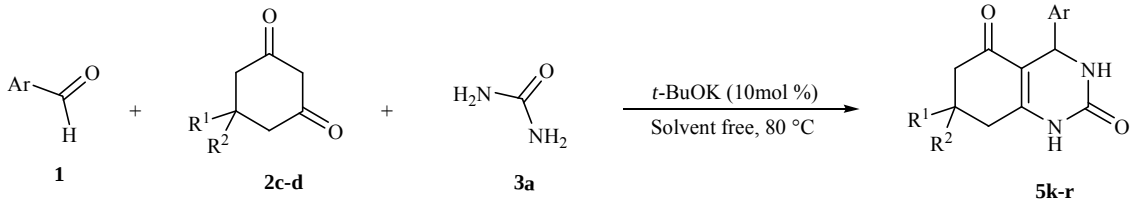
[a]: The reactions were carried out at 80°C using aldehyde (2 mmol), β-ketoester (2 mmol), urea or thiourea (3 mmol) and *t*-BuOK (0.2 mmol) under solvent-free conditions. [b]: Isolated yields.

react with dimedone and urea in the presence of *t*-BuOK to afford the corresponding octahydroquinazolines in excellent yields in reduced reaction time compared with ethyl acetoacetate (Table **4**).

The mechanism of this multicomponent reaction is similar to the one previously reported in papers for the Biginelli reaction; the formation of product **5** may involve an acylimine intermediate, the addition of β-ketoester to the iminium ion, and subsequent cyclization and dehydration (Scheme **6**).

3. CONCLUSION

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 4-substituted-1,4-dihydropyridine and 3,4-dihydropyrimidinone derivatives from the reaction of different aromatic or heteroaromatic aldehydes, β-ketoesters and ammonium acetate or urea in the presence of catalytic amount of *t*-BuOK under solvent-

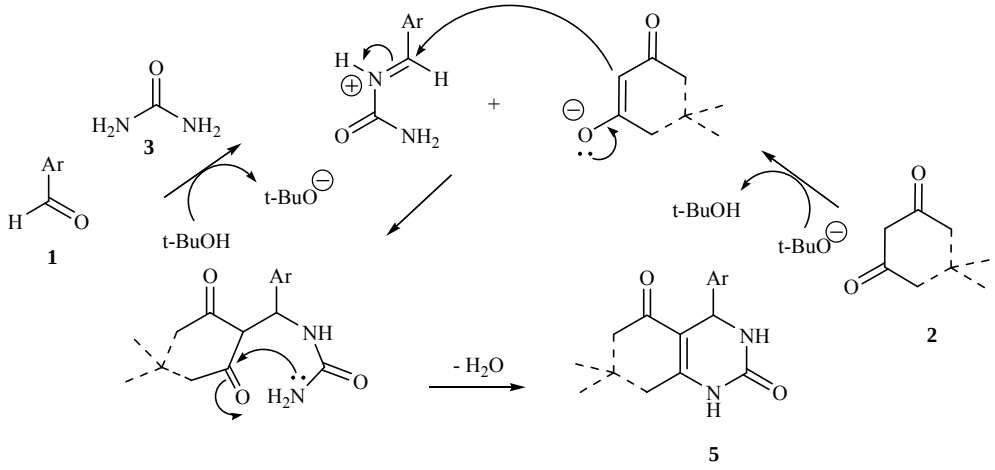


Scheme (5).

Table 4. *t*-BuOK-Catalyzed Biginelli Synthesis of Octahydroquinazolines Under Optimized Reaction Conditions[a]

Entry	DHPM	Ar	R^1	R^2	Time (h)	Yield[b] (%)	M.p. (°C)	
							Measured	Reported
1	5k	C_6H_5	Me	Me	5	76	288-290	287-290 [58a]
2	5l	4-(CH_3)-C_6H_4	Me	Me	6	66	> 300	> 300 [58a]
3	5m	4-($CH_{33}O$)-C_6H_4	Me	Me	4	67	241-243	-
7	5n	4-(Br)-C_6H_4	Me	Me	8	79	> 300	> 300 [58a]
4	5o	C_6H_5	H	H	8	68	> 300	308 [58b]
5	5p	4-(CH_3)-C_6H_4	H	H	3	62	296-298	298 [58b]
6	5q	4-(CH_3O)-C_6H_4	H	H	5	80	282-284	284 [58b]
8	5r	4-(Br)-C_6H_4	H	H	8	69	295-297	298 [58b]

[a]: The reactions were carried out at 80°C using aldehyde (2 mmol), β-ketoester (2 mmol), urea (3 mmol) and *t*-BuOK (0.2 mmol) under solvent-free conditions. [b]: Isolated yields.



Scheme (6).

free conditions. The catalytic activity of *t*-BuOK is notable and the use of low cost, commercially available materials for the synthesis of Hnatzsch and Biginelli products in good to excellent yields is also significant under the aspect of environmentally benign processes. These advantages make *t*-BuOK as a powerful catalyst for the synthesis of 1,4-DHPs and 3,-DHPMs and their analogs.

4. EXPERIMENTAL

4.1. General Procedure for the Synthesis of 1,4-dihydropyrines and Polyhydroquinolines 4

Aldehyde (2 mmol), β-ketoester (4 mmol), NH_4OAc (4 mmol) and *t*-BuOK (0.2 mmol) were stirred at 60 °C. After completion of the reaction as indicated by TLC, the crude product was purified by recrystallization from ethanol to yield the highly pure Hantzsch 1,4-dihydropyridine derivatives. The physical data (M.p., IR, NMR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

Ethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

M.p. 158-160°C, IR (KBr): 3335, 1692, 1651, 1490, 1239, 1122, 720 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.32-7.14 (m, 5H, CH_{Ar}), 5.71 (s, 1H, NH), 5.01 (s, 1H, CH), 4.11 (q, *J*=7.1, 4H, $2CH_2$), 2.36 (s, 6H, $2CH_3$), 1.24 (t, *J*=7.1, 6H,

$2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 167.6, 145.4, 143.8, 135.6, 128.4, 127.9, 104.2, 59.7, 39.6, 19.5, 14.2.

Ethyl 4-(2-thienyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e)

M.p. 171-173°C, IR (KBr): 3421, 1647, 1512, 1485, 1213, 1115, 752 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.06-6.79 (m, 3H, CH_{Ar}), 6.55 (s, 1H, NH), 5.35 (s, 1H, CH), 4.16 (q, *J*=7.0 Hz, 4H, $2CH_2$), 2.32 (s, 6H, $2CH_3$), 1.28 (t, *J*=7.0 Hz, 6H, $2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 167.5, 152.1, 145.0, 143.7, 126.3, 123.1, 103.3, 59.9, 34.3, 19.2, 14.3.

Ethyl 4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f)

M.p. 160-162°C, IR (KBr): 3344, 1701, 1649, 1485, 1371, 1207, 1120, 727 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.22 (s, 1H, NH); 6.22-5.94 (m, 3H, CH_{Ar}), 5.20 (s, 1H, CH), 4.11 (q, *J*=7.1 Hz, 4H, $2CH_2$), 2.32 (s, 6H, $2CH_3$), 1.27 (t, 6H, *J*=7.1 Hz, $2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 167.5, 158.7, 145.2, 140.8; 110.0, 104.4, 100.5, 59.8, 33.3, 19.4, 14.3.

Ethyl 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,4a,5,6,7,8,8a-octahydroquinoline-3-carboxylate (4g)

M.p. 205-207 °C, IR (KBr): 3293, 3058, 2958, 1676, 1610 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.75 (s, 1H, NH), 7.34-7.08 (m, 5H, CH_{Ar}), 5.07 (s, 1H, CH), 4.10 (q, *J*=7.1 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.22-2.10 (m, 4H, $2CH_2$), 1.23 (t, *J*=7.1 Hz, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). ^{13}C ($CDCl_3$, 63 MHz) δ: 196.1, 167.7, 153.5, 150.2, 147.3, 144.4, 128.0, 126.7, 126.0, 115.5, 111.4, 105.7, 59.8, 50.8, 40.4, 36.6, 32.6, 29.5, 27.0, 19.0, 14.2.

Ethyl 2,7,7-trimethyl-5-oxo-4-p-tolyl-1,4,4a,5,6,7,8,8a-octahydroquinoline-3-carboxylate (4h)

M.p. 260-262°C, IR (KBr): 3294, 3058, 2955, 1645, 1610, 1485, 1218 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.21 (d, *J*=8.1 Hz, 2H, CH_{Ar}), 7.01 (d, *J*=8.1 Hz, 2H, CH_{Ar}), 6.87 (s, 1H, NH), 5.02 (s, 1H, CH), 4.04 (q, *J*=7.1 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.32-2.18 (m, 4H, $2CH_2$), 1.24 (t, 3H, *J*=7.1 Hz, CH_3), 1.09 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C ($CDCl_3$, 63 MHz) δ: 195.8, 167.6, 149.0, 144.3, 143.7, 135.4, 128.6, 127.8, 127.3, 111.9, 106.1, 77.5, 76.5, 59.8, 50.7, 40.8, 36.1, 32.7, 29.4, 27.1, 19.2, 14.2.

Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8-aoctahydroquinoline-3-carboxylate (4i)

M.p. 256-258°C, IR (KBr): 3449, 3348, 3101, 2978, 1647, 1489, 1207 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.23 (d, *J*=6.7 Hz, 2H, CH_{Ar}), 6.8 (s, 1H, NH); 6.75 (d, 2H, *J*= 6.7, CH_{Ar}); 5.00 (s, 1H, CH), 4.08 (q, 2H, *J*=7.1 Hz, CH_2), 3.74 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3), 2.28-2.17 (m, 4H, $2CH_2$), 1.23 (t, *J*=7.1 Hz, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{13}C ($CDCl_3$, 63 MHz,) δ: 195.9, 167.6, 157.7, 148.8, 143.5, 139.7, 133.0, 128.9, 113.2; 106.1, 59.8; 50.7, 40.8, 35.7, 32.6, 29.5, 27.1, 19.2, 14.2.

3,3,6,6-tetramethyl-9-(2-metoxyphenyl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (4o)

M.p. 183-185°C, IR (KBr): 3396, 1643, 1095, 1026 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 8.48 (s, 1H, NH); 7.10-6.78 (m, 4H, CH_{Ar}), 5.24 (s, 1H), 3.72 (s, 3H, OCH_3), 2.35-2.10 (m, 8H, $4CH_2$), 1.25-0.95 (m, 12H, $4CH_3$). ^{13}C ($CDCl_3$, 63 MHz,) δ: 196.0, 157.5, 129.8, 128.9, 115.8, 113.2, 55.2, 47.0, 46.4, 32.7, 32.5, 31.4, 29.7.

3,3,6,6-tetramethyl-9-(4-metoxyphenyl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (4p)

M.p. 249-251°C, IR (KBr): 3423, 1643, 1045, 1014 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 12.00 (s, 1H, NH); 7.02 (d, 2H, *J*=8.6 Hz, CH_{Ar}); 6.83 (d, *J*=8.6 Hz, 2H, CH_{Ar}); 5.51 (s, 1H); 3.78 (s, 3H, OCH_3); 2.44-2.18 (m, 8H, $4CH_2$); 1.24 (s, 6H, $2CH_3$); 1.12 (s, 6H, $2CH_3$). ^{13}C ($CDCl_3$, 63 MHz,) δ: 194.5; 172.6; 151.2, 146.3, 129.3, 127.6, 111.8, 55.3, 47.0, 46.4, 32.9, 32.7, 31.2, 29.4.

4.2. General Procedure for the Synthesis of 3,4-dihydropyrimidinones and Octahydroquinazolines 5

A mixture of aldehydes (2 mmol), β-ketoester (2 mmol), urea or thiourea (3 mmol) and *t*-BuOK (0.2 mmol) was heated at 80°C for an appropriate time (monitored by TLC). After completion of the reaction, the mixture was cooled to room temperature and the solid was filtered and recrystallized from EtOH to afford the pure products. The products were characterized by their M.p, IR, ^1H and ^{13}C NMR spectral data and their melting points were compared with reported values. Data for selected compounds as shown below:

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

M.p. 212-214°C, IR (KBr): 3244, 1705, 1649, 1223 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 9.17 (s, 1H, NH), 7.71 (s, 1H, NH), 7.12 (m, 4H, CH_{Ar}), 5.11 (s, 1H, CH), 3.95 (q, *J*=7.1, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.10 (t, *J*=7.1, 3H, CH_3). ^{13}C (DMSO-d_6, 63 MHz) δ: 165.8, 152.6, 148.7, 142.3, 136.8, 129.3, 126.6, 99.9, 59.6, 54.0, 21.1, 18.8, 14.5.

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

M.p.. 203-205°C, IR (KBr): 3290, 1701, 1620, 1238 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 7.80 (s, 1H, NH), 9.76 (s, 1H, NH), 7.28-7.14 (m, 4H, CH_{Ar}), 5.43 (s, 1H, CH), 2.36 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.13(s, 3H, CH_3). ^{13}C (DMSO-d_6, 63 MHz,) δ: 195.3, 153.1, 145.8, 139.8, 138.1, 129.7, 126.5, 110.5, 55.7, 30.3, 21.1, 19.7.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-thione (5i)

M.p. 224-226°C, IR (KBr): 3229, 1670, 1176, 725 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 10.34 (s, 1H, NH), 9.76 (s, 1H, NH), 7.50-7.21 (m, 5H, CH_{Ar}), 5.19 (d, 1H, *J*=7.0, CH), 4.01 (q, *J*=7.0, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.09 (t, *J*=7.0, 3H, CH_3). ^{13}C (DMSO-d_6, 63 MHz) δ: 174.7, 165.6, 145.4, 143.9; 129.0; 128.1, 127.8, 126.8, 101.2, 60.0, 54.5, 17.6, 14.4.

7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (5k)

M.p: 288-290°C, IR (KBr): 3240, 1701, 1634, 1221 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz,) δ: 7.97-7.24 (m, 5H, CH_{Ar}), 6.79 (s, 1H, NH), 5.96 (s, 1H, NH), 4.31 (s, 1H, CH), 2.22-2.34 (m, 4H, $2CH_2$), 1.02-1.13 (s, 6H, $2CH_3$). ^{13}C (DMSO-

d_6, 63 MHz) δ: 195.6, 167.1, 145.2, 141.3, 127.7, 126.8, 125.4, 114.8, 101.1, 46.9, 33.1, 32.8, 31.6, 28.2, 26.9.

7,7-dimethyl-4-(p-tolyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (5l)

M.p. > 300°C, IR (KBr): 3244, 1705, 1649, 1223 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 9.49 (s, 1H, NH), 7.76 (s, 1H, NH), 7.20-6.89 (m, 4H, CH_{Ar}), 5.13 (s, 1H), 2.54-1.89 (m, 7H, CH_3, $2CH_2$), 1.02 (s, 3H, CH_3). ^{13}C (DMSO-d_6, 63 MHz) δ: 193.3, 163.2, 152.5; 149.5, 142.2, 136.6, 128.7, 126.8, 108.0, 52.1, 50.4, 32.6, 29.2, 27.2, 21.1.

CONFLICT OF INTEREST

None Declared.

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