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Ultrasound-assisted dehydrogenation of 5-acetyl-3,4-dihydropyrimidin-2(*1H*)-ones

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ABSTRACT

In this study, various 5-acetyl-3,4-dihydropyrimidin-2(*1H*)-ones were synthesized and the dehydrogenation of these compounds by potassium peroxydisulfate in aqueous acetonitrile under thermal and sono-thermal conditions were investigated. Whereas the effect of the nature of 4-substituent influences the rate of reaction, the application of sonic waves decreases drastically the time of thermal reaction.

1. Introduction

Azaheterocyclic systems such as six-membered nitrogen-containing compounds, 3,4-dihydropyrimidin-2(*1H*)-ones are very interesting in medicinal chemistry because of their application as antihypertensive agents [1], anti-cancer [2], calcium channel modulators [3], and also as anti-staphylococcal antibiotics [4]. In particular, batzelladine alkaloids as pyrimidine derivatives have been found to be potent HIV gp-120 CD4 inhibitors [5] and MKC-442 is also one of the most important classes of drugs to inhibit the HIV virus [6].

The dehydrogenation of *Hantzsch*-type 1,4-dihydropyridines (DHPs) and 3,4-dihydropyrimidin-2(*1H*)-ones (DHPMs) have attracted interest in organic chemistry [7–11], but in contrast to DHPs, where aromatization of them to their corresponding pyridines is typically facile, the oxidation of DHPMs is known to be nontrivial [12]. However, many oxidizing agents were used for the oxidation of DHPMs, but the application of these reagents suffer from some disadvantages such as the use of hazardous or expensive, less easily available oxidants, vigorous reaction conditions, prolonged reaction times, especially low yields and formation of side products [12–20].

The effect of ultrasound on different reactions is widely studied during the last two decades both in cavitation and pre-cavitation regime [21–25]. The success and advantages of ultrasound-assisted chemical reactions include shorter reaction times, higher yields and milder reaction conditions when compared with classical methods. The effect of ultrasound has mostly been shown by increasing the yields of reactions and in some cases the ratio of formed products. The mostly important effect of ultrasound by passing its waves through a liquid medium is the generation of many cavities. This leads to development of high temperatures and high pressures within the cavities during their collapse. Recently we have reported on the effect of the combination of ultrasound and UV-light in the ring opening reaction of α-epoxyketones [26] and in the oxidation reaction of 1,4-dihydropyridines [27], the combination of ultrasound and heat in the oxidation of some ethyl 3,4-dihydropyrimidin-2(*1H*)-one-5-carboxylates [28] and also the effect of sonic waves on thiocyanation of aromatic and heteroaromatic compounds [29]. In all of these reactions, it was found that ultrasound accelerates the reactions by comparison the time of reactions without applying the sonic waves.

Peroxydisulfate ion is known as one of the strongest oxidizing agents with $E^0(S_2O_8^{2-}/SO_4^{2-}) = -2.01$ V [30,31] for oxidation of alkyl aryl sulfides to their corresponding sulfoxides [32], oxidation of 1,4-dihydropyridines to the pyridine derivatives [9], free radical degradation of chitosan [33] and for the preparation of polymer/silicate nanocomposites [34]. In our recent studies, we have used potassium peroxydisulfate (PPS) as an efficient oxidant for the dehydrogenation of various ethyl 3,4-dihydropyrimidin-2(*1H*)-one-5-carboxylates under thermal [35] and sono-thermal conditions [28]. The aim of the work was to elucidate the effect of the nature and the steric hindrance of the substituent on position 4 of the dihydropyrimidinone ring on the rate of reaction. Our computational studies concerning the optimized structures of various 5-acetyl and 5-carboethoxy substituted 4-aryl-3,4-dihydropyrimidinones revealed that the polar effects and the steric hindrances of the substituents located at 4- and 5-positions of the dihydropyrimidinone ring influence the dihedral angles of both

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CO moieties in carboethoxy and the acetyl groups at 5-position and the dihedral angle of the aromatic rings with respect to dihydropyrimidinone ring [36]. All these points, especially the presence of the acetyl group instead of the carboethoxy group in position 5 affect the amount of the electron density on the atoms involved in the oxidation process of these compounds. These observations prompted us to synthesis various 5-acetyl-4-aryl-3,4-dihydropyrimidin-2(*1H*)-ones and investigated their oxidation by PPS under thermal and sono-thermal conditions to investigate the following points on the rate of reaction:

II The effect of the acetyl group instead of the carboethoxy group in position 5.
III The effect of the nature of the additional substituent and its location on the phenyl ring located on C-4.
IIII The effect of ultrasound irradiation on the rate of reaction and comparison of the obtained results with those obtained under thermal conditions.

2. Results and discussion

2.1. Solvent effect and optimization of the reactants

Since the nature of solvent has a great effect on the solubility of the oxidant which influences the rate of reaction, we first studied the oxidation of 4-phenyl derivative **1a** by PPS in different solvents such as absolute ethanol, dry acetonitrile, aqueous ethanol or aqueous acetonitrile (different ratios) under reflux condition (Scheme 1).

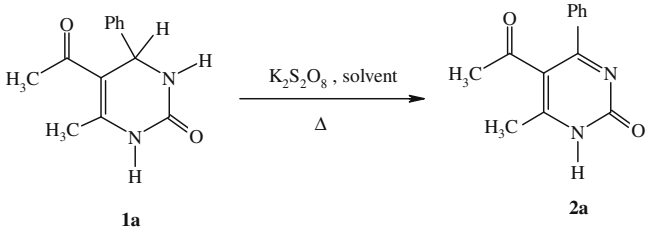
According to the data presented in Table 1, a mixture of CH_3CN/H_2O (10:2) has been chosen as the best solvent mixture for this purpose. According to the data presented in Table 1 we found out that:

1. Owing to better solubility of the oxidant, the presence of H_2O is necessary for the reaction, since the reaction does not occur in dry acetonitrile.
2. The optimized mole ratio of PPS/DHPM (1:1) indicates that the removal of two hydrogens from **1a** depends on the presence of the equimolar amounts of the oxidant, since the reaction is not completed by the 0.5:1 ratio of oxidant/DHPM.

In an optimized reaction conditions various 5-acetyl-3,4-dihydropyrimidin-2(*1H*)-ones (**1a–l**) (0.23 mmol) were subjected to the oxidation reaction in the presence of PPS (0.23 mmol) in 12 ml acetonitrile and water (10:2) under reflux condition and under ultrasound irradiation with simultaneous heating the reaction mixture at 70 °C (sono-thermal) and stirring the reaction mixture (Scheme 2). The reaction was followed by TLC until total disappearance of DHPMs. These results are summarized in Table 2.

A comparison of the results presented in Table 2 indicates that:

1. The combination of ultrasound and heat (sono-thermal) decreases drastically the time of reaction compared with the reaction under thermal condition, but the same products were obtained under both reaction conditions. It should be noted that stirring the reaction mixture by simultaneous sonication and heat affects also the shortening the reaction time.
2. The performance of heating is necessary for the reaction either under ultrasound irradiation or under thermal reaction, since the cleavage of O–O bond in the $S_2O_8^{2-}$ has relatively high activation energy of around 130 kJ/mol [37,38].



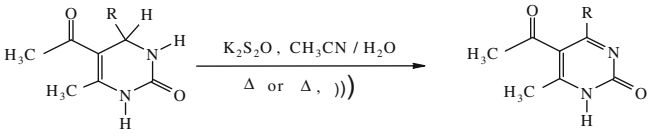
1a **2a**

Scheme 1.

Table 1
Oxidation of 5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(*1H*)-one (**1a**) to 5-acetyl-6-methyl-4-phenylpyrimidin-2(*1H*)-one (**2a**) by $K_2S_2O_8$ under reflux condition in various mixture of solvents.

$K_2S_2O_8$/**1a**	Solvent	Time (min)[a]	(**2a**) Yield (%)
0.5:1	CH_3CN/H_2O (10:2)	180	~60[b]
1:1	CH_3CN/H_2O (10:1)	190	100
2:1	CH_3CN/H_2O (10:1)	180	100
1:1	CH_3CN/H_2O (10:2)	180	95[c]
1:1	Dry acetonitrile	180	No reaction
1:1	Absolute ethanol	180	No reaction
1:1	CH_3CN/H_2O (10:2)	180[d]	~5[b]

[a] The times are given after maximum progression of reaction.
[b] Estimated according to TLC observation.
[c] Isolated yield.
[d] The reaction is carried out at room temperature.



1a-l **2a-l**

R = **a**: C_6H_5, **b**: 4-$CH_3C_6H_4$, **c**: 4-$CH_3OC_6H_4$, **d**: 3-$CH_3OC_6H_4$, **e**: 2-$CH_3OC_6H_4$ **f**: 4-ClC_6H_4, **g**: 3-ClC_6H_4 , **h**: 2-ClC_6H_4, **i**: 4-BrC_6H_4, **j**: 2-BrC_6H_4, **k**: 4-$NO_2C_6H_4$, **l**: 3-$NO_2C_6H_4$

Scheme 2.

Table 2
Oxidation of **1a–l** by PPS in aqueous acetonitrile under reflux condition and simultaneous sonication and heating by stirring the reaction mixture.

Compound	R	Thermal		Sono-thermal	
		Time (min)[a]	Yield (%)[b]	Time (min)[a]	Yield (%)[b]
1a	C_6H_5–	180	95	17	97
1b	4-$CH_3C_6H_4$–	110	95	12	90
1c	4-$CH_3OC_6H_4$–	75	90	12	90
1d	3-$CH_3OC_6H_4$–	110	95	14	95
1e	2-$CH_3OC_6H_4$–	60	90	10	90
1f	4-ClC_6H_4–	105	90	14	95
1g	3-ClC_6H_4–	120	90	16	90
1h	2-ClC_6H_4–	90	85	12	85
1i	4-BrC_6H_4–	160	90	15	90
1j	2-BrC_6H_4–	85	90	12	93
1k	4-$NO_2C_6H_4$–	360	90	27	90
1l	3-$NO_2C_6H_4$–	420	90	40	90

[a] The times are given after total disappearance of DHPMs (100% conversion by TLC monitoring).
[b] Isolated yields.

Density functional theory (DFT) B3LYP with 6-31++G (d,p) basis set, as implemented in the G98W software, is used to obtain the optimized structures of compounds **1a** and **2a**, including position of the acetyl group conformation with respect to the C=C bond

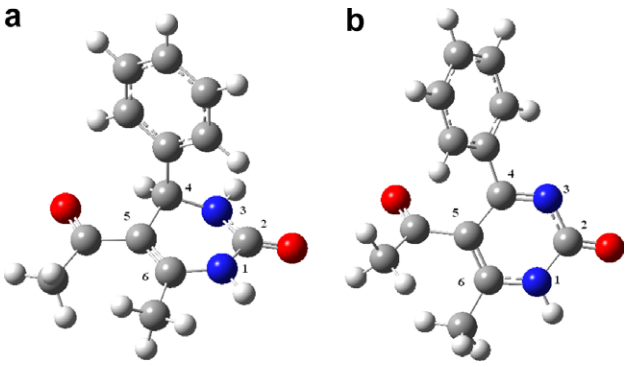


Fig. 1. The B3LYP/6-31++G** optimized structures of **1a** (a) and **2a** (b).

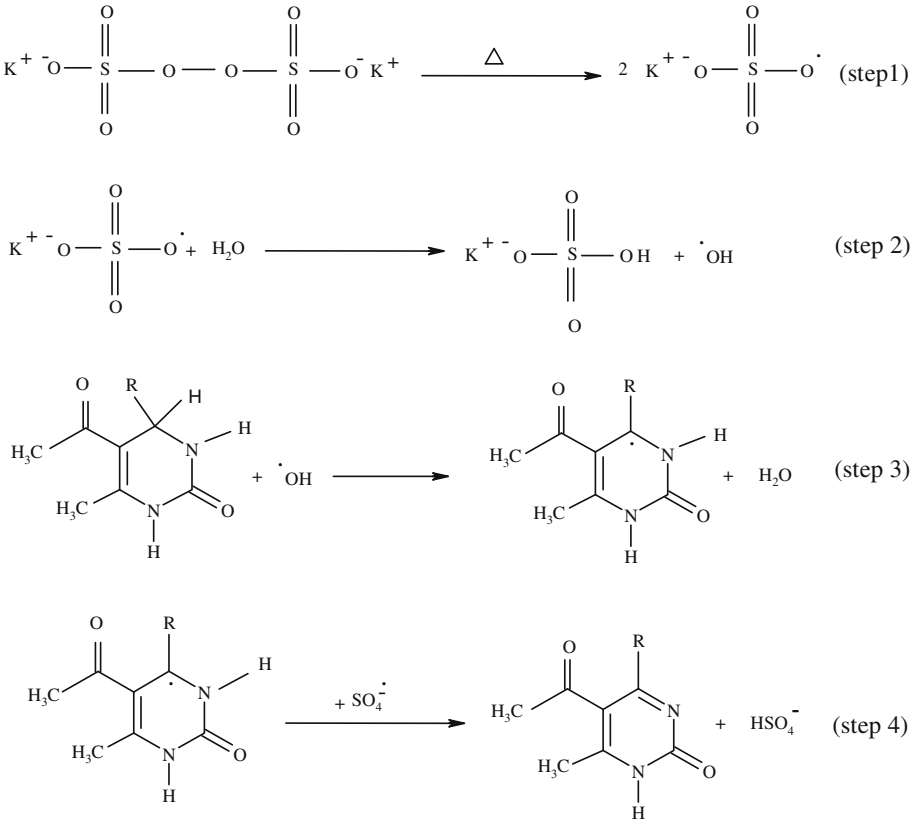
of the heterocyclic ring. Fig. 1a and b shows the optimized structures of **1a** and **2a**, respectively. Interesting results is the shift of 6-CH_3 resonances in **2a–l** to higher field in the ^{1}H NMR spectra. This can be explained as follows: a comparison of the dihedral angles of C=C–C=O moiety in **1a** (175.0°) and in **2a** (122.9°) indicate that: (i) the electron-withdrawing character of oxygen in **2a** is more efficient than in **1a**, therefore the 6-C in **2a** is more positive than in **1a** (**+**0.291 vs. **+**0.259, as found from NBO charge analysis), (ii) the anisotropy effect of carbonyl group on the 6-CH_3 in **2a** due to smaller dihedral angle. The 1-NH and 3-NH resonances in **1a–l** appear between 7 and 8 and around 9 ppm, respectively, which indicate that 3-NH is more acidic than 1-NH. This can be supported by the observation of acylation of 3-N in the presence of *n*-BuLi as the base [39] or preparation of *N*3-acetoxymethyl-3,4-dihydropyrimidinones [40] and also by our computational studies. As we showed in Fig. 1a, the greater bond-length 3N–H (1.0099 Å) compared with 1N–H (1.0091 Å), and the shorter bond-length C2–C3 (1.3567 Å) compared with 1N–C2 (1.4045) indicate that 3N nitrogen lone pair is conjugated with 2-CO more strongly than the 1N nitrogen lone pair. These observations support the assignment of the chemical shifts for 1-NH and 3-NH in the ^{1}H NMR spectra.

According to the results summarized in Tables 1 and 2, especially the failure of the reaction by carrying out at room temperature, we will confirm the proposed mechanism for the dehydrogenation of 5-carboethoxy-3,4-dihydropyrimidinones by potassium peroxydisulfate [35] in the present study (Scheme 3).

Thermal decomposition of the weakest O–O bond in potassium peroxydisulfate yields the sulfate radical anions (path 1), which should preferably abstract a hydrogen atom from the present water to give hydroxyl radicals (path 2). The oxidation of DHPMs is presumed to be initiated by a hydrogen abstraction from 4-position by hydroxyl radical to produce hydropyrimidinoyl radical intermediate and water (path 3). This step is followed by the loss of another hydrogen atom to generate pyrimidinone product (path 4).

Following points will support our argument that path 3 is the rate determining step either in the case of carboethoxy or acetyl derivatives and the hydroxyl radical is involved as active species in this step:

A. Due to insolubility of PPS in dry acetonitrile even under reflux condition, the presence of enough water is necessary for the reaction, since the reaction did not work in dry acetonitrile.
B. Although the oxidant is not completely soluble in C_2H_5OH/H_2O (10:2) under reflux condition in comparison to CH_3CN/H_2O (10:2), but there are enough hydrogen sources (C_2H_5OH and H_2O) for donation hydrogen to sulfate radical



Scheme 3.

anion and formation of hydroxyl and ethoxy radicals. The reason of inefficient reaction in C_2H_5OH/H_2O (10:2) should be either the competition between hydroxyl radical with ethoxy radical for removal of 4-H or the solvation of sulfate radical anion by the polar protic solvent such as ethanol. It seems that solvation of the sulfate radical anion prevents the formation of hydroxyl radical, as a more reactive hydrogen abstracting species.

C. The observed substituent effect in 4-position on the rate of reaction indicates that the removal of a hydrogen atom from the more covalent C–H bond compared with the less covalent N–H bond is more possible; therefore, path 3 is the rate determining step.

D. The stability of hydropyrimidinoyl radical intermediate formed in the rate determining step which is simultaneously a benzylic radical (stabilized by interaction with the aromatic ring) or allylic radical (by conjugation with C5=C6 bond) should lower the activation energy of its formation. This influences the rate of path 3, as the rate determining step. The presence of the 4-methyl (**1b**) or 4-methoxy (**1c**) substituents as electron-donating species on the phenyl group attached to dihydropyrimidinone ring should stabilize the formation of the benzylic radical intermediate rather than the 4-nitro substituent (**1k**) as electron-withdrawing species. These data show also that the electron-donating substituents such as methyl **1b** or methoxy substituents **1c**, **1d** and **1e** decreases the time of oxidation. It is interesting to compare the time of reactions of **1c**, **1d** and **1e**, which is dependent on the balance of the inductive and the resonance effects of the methoxy group located on 4-, 3- and 2-positions, respectively.

E. A comparison of the results obtained in this study (Table 1) with those obtained by oxidation of 5-carboethoxy derivatives either under thermal [35] or sono-thermal conditions [28] indicates that the reaction is slower in the case of 5-acetyl derivatives under both reaction conditions and the same products were also obtained.

The results obtained from *ab initio* calculation at the B3LYP/6-31++G** level of theory for the optimized structures of both classes of compounds can partially explain the observed comparative behavior of the acetyl-DHPMs vs. the DHPM-esters based on the following arguments:

1. Due to the presence of formal three sp^3-centers in these molecules (N1, N3 and C4), the dihydropyrimidinone ring adopts a boat conformation, flatted at N1 toward an envelope conformation, with a pseudoaxial orientation of the C4-substituent. The extent of deviation of C4 atom from planarity depends on the orientation of the aryl group attached to this atom, especially on the position of an additional substituent at the phenyl ring and also on the nature and the size of this substituent.
2. The dihedral angle of the carbonyl function in the ester and the acetyl groups with respect to the C5–C6 double bond depends on the type of the substituent on the C4 atom and the extent of conjugation with C5=C6 bond.
3. The dihedral angle formed by the C2′–C1′–C4–N3 bonds depends on the stereoelectronic effect of the carboethoxy or acetyl groups located on C5 and also on the location of the additional substituent on the phenyl ring located on C4. Fig. 2 shows the optimized structures of **1e** and the corresponding ester derivative obtained at the B3LYP/6-31++G (d,p) level of theory. This figure shows clearly that the orientation of the 2-methoxy group with respect to dihydropyrimidinone ring is dependent on the substituent on C5; acetyl or carboethoxy groups.

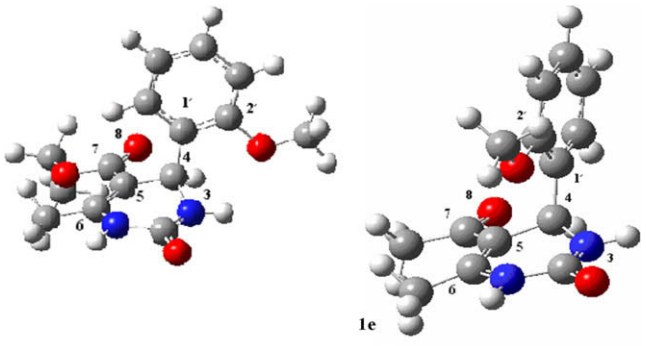
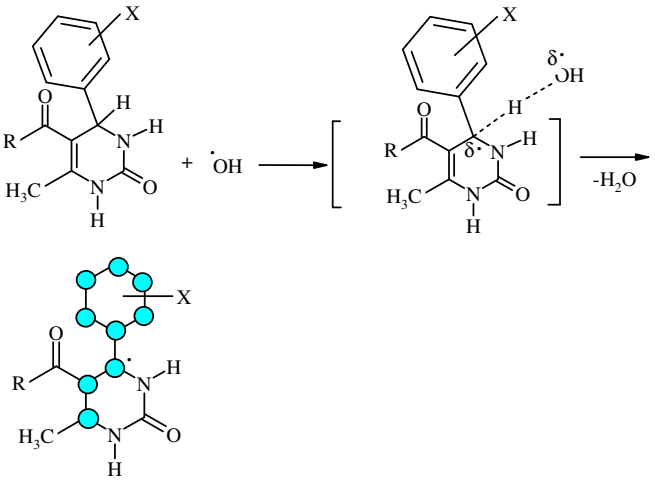


Fig. 2. The optimized structures of **1e** and corresponding ester derivative obtained at the B3LYP/6-31++G (d,p) level of theory.



Scheme 4.

All experimental facts obtained by thermal and sono-thermal reactions of both classes of compounds support our argument that removal of 4-H by a hydroxyl radical is occurred in the rate determining step. As is shown in Scheme 4, the interaction of a hydroxyl radical with 4-H in the transition state leading to a hydropyrimidinoyl radical intermediate. In this case, when the aromatic ring is perpendicular to the radical center formed on C-4 (the ring π-orbital are parallel to the radical p-orbital), the stabilization of the radical center through conjugation with the aromatic ring is more possible and simultaneously the steric hindrance for the linear approach of the hydroxyl radical to 4-H is diminished. This leads to an increase of the rate of reaction. In this case and as a comparative example, accomplished oxidations of **1e** and the corresponding ester derivative are observed after 60 and 25 min under thermal and 10 and 6 min under sono-thermal conditions, respectively. As a result, the balances of steric and electronic effects of the additional substituent on the phenyl ring located on C-4 and also those of the acetyl and the carboethoxy groups influence the rate of oxidation.

2.2. Effect of intensity of sonication and stirring

The important result in the present study was the acceleration of thermal reaction by applying the sonic waves (sono-thermal) and stirring the reaction mixture, which is clearly presented in Ta-

Table 3
The effect of maximum power intensity of ultrasound on the rate of oxidation of **1a** by PPS in aqueous CH_3CN at 70 °C.

Max. power density (min)	20% (92 W cm^{-2})	40% (276 W cm^{-2})	60% (276 W cm^{-2})	80% (368 W cm^{-2})	100% (460 W cm^{-2})
Time[a]	34	29	27	22	17

[a] The times are given after total disappearance of DHPMs.

ble 2. This led us also to study the effect of intensity on sono-thermal oxidation. This was studied for the reaction of **1a** in CH_3CN/H_2O (10:2) solution in the presence of PPS at 20%, 40%, 60%, 80% and 100% of the rated power of the ultrasonic horn (92, 184, 276, 368 and 460 W cm^{-2}, respectively). The presented data in Table 3 show that by increasing the ultrasound intensity, a decrease in the time of reaction is observed. This observation can be explained as follows:

(i) The homogeneous distribution of the reactants throughout the solution, namely, the effective mass transfer by applying the sonic waves and stirring the solution.
(ii) The increasing of temperature by applying the sonic waves, since the temperature of solution of **1a** with PPS after 3 and 5 min sonication at 100% intensity without using the water-bath is raised to 47 and 53 °C, respectively, whereas by using the water-bath at 70 °C, sonication of this solution for 5 min at 100% intensity causes an increase of temperature to 75–80 °C.
(iii) The maximum cavitation is normally created around the probe. It seems, using simultaneous sonic wave and magnetic stirrer causes homogenization the reaction solution, therefore an enhancement of the rate constant of decomposition of PPS compared with the rate constant in the absence of stirring and sonic waves (thermal).

3. Conclusion

From the results of the present work, combination of ultrasound, heat and stirring accelerate the oxidation of 5-acetyl-3,4-dihydropyrimidin-2(*1H*)-ones, compared with reaction without applying the sonic waves, but in comparison to the oxidation of 5-carbothoxy-3,4-dihydropyrimidin-2(*1H*)-ones the time of reaction is longer. Easy work-up of the reaction due to complete consumption of DHPMs and short reaction times are the advantages of this oxidative method.

4. Experimental

4.1. Materials

5-Acetyl-3,4-dihydropyrimidin-2(*1H*)-ones (**1a–l**) have been prepared by adoption of the known procedure [41]. Acetonitrile was purchased from Merck and distilled before used.

4.2. Equipments

The ultrasonic device used was an UP 400 S instrument from Dr. Hielscher GmbH. A S3 immersion horn emitting 24 kHz ultrasound at intensity levels tunable up to maximum sonic power density of 460 W cm^{-2} was used. Sonication was carried out at 100% (maximum amplitude 210 μm). A 3 mm long sonotrode (maximum immerse depth of 90 mm) was immersed directly into the reaction mixture. Melting points were determined on a Stuart Scientific SMP2 apparatus and are uncorrected. IR spectra were recorded from KBr discs on a Shimadzu apparatus IR 435. ^{1}H NMR spectra were recorded with a Bruker 300 MHz machine. They are reported as follows; chemical shifts [multiplicity, coupling constants *J* (Hz), number of protons, and assignment]. ^{13}C NMR spectra were recorded with a Bruker 75.48 MHz machine. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. UV spectra were taken with Shimadzu UV-160 spectrometer.

4.3. General procedure for the oxidation of 5-acetyl-6-methyl-3,4-dihydropyrimidin-2(1H)–ones (1a–*l*)

(i) *Thermal:* Potassium peroxydisulfate (61.5 mg, 0.23 mmol) was added to a solution of dihydropyrimidinones (0.23 mmol) in acetonitrile and water (10:2 mL). The reaction mixture was refluxed for the times given in Table 2. TLC monitoring of the reaction using *n*-hexane/ethyl acetate (2:1) as eluent was followed until total disappearance of the DHPMs. Solvent was evaporated and the crude reaction mixture was purified by column chromatography (2/1 *n*-hexane/ethyl acetate), then recrystallized from *n*-hexane/ethyl acetate.
(ii) *Sono-thermal:* The same reaction mixture was immersed in at 70 °C preheated water-bath by simultaneous ultrasound irradiation and stirring the solution for the times given in Table 2 until total disappearance of DHPMs was observed (TLC). Solvent was evaporated and the crude reaction mixture was extracted with 2 × 10 ml diethyl ether/water mixture, the organic layer was evaporated and the residue was recrystallized form *n*-hexane/ethyl acetate. It should be noted that the reactions were carried out in 5 min sonication and 2 min relaxation to prevent the splashing of solvent until total disappearance of DHPMs. The water-bath has been removed during the relaxation times to prevent the thermal oxidation and better comparison of the times under ultrasound irradiation. The physical and spectral data of the starting material and the products are as following.

4.3.1. 5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (***1a***)

White solid. Mp: 228–230 °C. Ref. Mp [41]: 233–236 °C.

4.3.2. 5-Acetyl-6-methyl-4-(4′-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (***1b***)

White solid. Mp: 234–236 °C. IR: ν 1640, 1590, 1505 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 288.8 (3.80), 241.4 nm (3.41). ^{1}H NMR (DMSO-d_6): δ 2.07 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 2.27 (s, 3H, 4′-CH_3), 5.20 (s, 1H, 4-H), 7.12 (br, s, 4H, H-aromatic), 7.76 (s, 1H, 1-NH), 9.13 (s, 1H, 3-NH). EI-MS: *m*/*z* (%): 244 (M^+, 14), 243 (M^+-H, 25), 229 (M^+-CH_3, 49), 201 (M^+-CH_3CO, 32), 153 ($M^+-C_7H_7$, 100), 91 (Ph–CH_2^+, 30).

4.3.3. 5-Acetyl-4-(4′-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (***1c***)

White solid. Mp: 182–184 °C. Ref. Mp [41]: 168–170 °C.

4.3.4. 5-Acetyl-4-(3′-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (***1d***)

White solid. Mp: 226–228 °C. Ref. Mp [42]: 228–230 °C.

*4.3.5. 5-Acetyl-4-(2′-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1e**)*

White solid. Mp: 250–252 °C. IR: ν 1670, 1580, 1430 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 283.6 (4.42), 240.2 nm (3.90). ^1H NMR (DMSO-d_6): δ 2.00 (s, 3H, CH_3), 2.28 (s, 3H, CH_3CO), 3.81 (s, 3H, CH_3O), 5.56 (s,1H, 4-H), 7.06 (m_c, 4H, H-aromatic), 7.33 (s, 1H, 1-NH), 9.11 (s, 1H, 3-NH). EI-MS: *m*/*z* (%): 260 (M^+, 61), 259 (M^+-H, 80), 245 (M^+-CH_3,51), 229 (M^+-CH_3O, 92), 217 (M^+-CH_3CO, 85),153 (M^+–2-$CH_3COC_6H_4$, 100).

*4.3.6. 5-Acetyl-4-(4′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1f**)*

White solid. Mp: 249–251 °C. Ref. Mp [43]: 223–225 °C.

*4.3.7. 5-Acetyl-4-(3′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1g**)*

White solid. Mp: 285–287 °C. IR: ν 1700, 1615, 1525 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 291.4 (3.08), 239.8 nm (2.70). ^1H NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 5.27 (d, J = 3.25 Hz, 1H, 4-H), 7.27 (m_c, 4H, H-aromatic), 7.87 (s, 1H, 1-NH), 9.28 (s, 1H, 3-NH). EI-MS: *m*/*z* (%): 266 ($M^{+37}Cl$, 49), 265 ($M^{+37}Cl-H$, 64), 264 ($M^{+35}Cl$, 32), 263 ($M^{+35}Cl-H$, 79), 249 ($M^{+35}Cl-CH_3$, 80), 229 ($M^{+35}Cl-{}^{35}Cl$, 42), 223 ($M^{+37}Cl-CH_3CO$, 28), 221 ($M^{+35}Cl-CH_3CO$, 74), 170 (2-$^{37}ClC_6H_4$–CH=NH^+, 3), 169 (2-$^{37}ClC_6H_4$–C=NH^+, 8), 168 (2-$^{35}ClC_6H_4$–CH=NH^+, 9), 167 (2-$^{35}ClC_6H_4$–C=NH^+, 9), 153 (M^+–2-ClC_6H_4, 100).

*4.3.8. 5-Acetyl-4-(2′-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1h**)*

White solid. Mp: 262–264 °C. IR: ν 1690, 1615, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 291.0 (3.99), 240.2 nm (3.62). ^1H NMR (DMSO-d_6): δ 2.05 (s, 3H, CH_3), 2.33 (s, 3H, CH_3CO), 5.66 (s,1H, 4-H), 7.36 (m_c, 4H, H-aromatic), 7.72 (s, 1H, 1-NH), 9.27 (s, 1H, 3-NH). EI-MS: *m*/*z* (%): 266 ($M^{+37}Cl$, 4), 265 ($M^{+37}Cl-H$, 7), 264 ($M^{+35}Cl$, 10), 263 ($M^{+35}Cl-H$, 16), 249 ($M^{+35}Cl-CH_3$,10), 231 ($M^{+37}Cl-{}^{37}Cl$, 6), 229 ($M^{+35}Cl-{}^{35}Cl$, 94), 223 ($M^{+37}Cl-CH_3CO$, 6), 221 ($M^{+35}Cl-CH_3CO$, 72), 170 (2-$^{37}ClC_6H_4$–CH=NH^+, 14), 169 (2-$^{37}ClC_6H_4$–C=NH^+, 18), 168 (2-$^{35}ClC_6H_4$–CH=NH^+, 17), 167 (2-$^{35}ClC_6H_4$–C=NH^+, 8), 153 (M^+–2-ClC_6H_4, 100).

*4.3.9. 5-Acetyl-4-(4′-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1i**)*

White solid. Mp: 232–233 °C. IR: ν 1650, 1580, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 290.8 (4.04), 240.2 nm (3.85). ^1H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 2.28 (s, 3H, CH_3CO), 5.23 (s, 1H, 4-H), 7.18 (d, J = 6.90 Hz, 2′- and 6′-H), 7.51 (d, J = 6.77 Hz, 3′- and 5′-H), 7.88 (s, 1H, 1-NH), 9.23 (s, 1H, 3-NH).

*4.3.10. 5-Acetyl-4-(2′-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**1j**)*

White solid. Mp: 254–257 °C. IR: ν 1700, 1620, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 292.2 (3.98), 239.8 nm (3.70). ^1H NMR (DMSO-d_6): δ 2.04 (s, 3H, CH_3), 2.33 (s, 3H, CH_3CO), 5.62 (d, J = 2.85 Hz, 1H, 4-H), 7.39 (m_c, 4H, H-aromatic), 7.69 (brd s, 1H, 1-NH), 9.28 (s, 1H, 3-NH). EI-MS: *m*/*z* (%): 267 ($M^{+81}Br-CH_3CO$, 10), 265 ($M^{+79}Br-CH_3CO$, 11), 231 ($M^{+81}Br-{}^{81}Br$, 2), 229 ($M^{+79}Br-{}^{79}Br$, 97), 214 ($M^{+79}Br-{}^{79}Br$, $-CH_3$, 13) 168 (2-BrC_6H_4–CH=NH^+, 5), 153 (M^+–2-BrC_6H_4, 100).

*4.3.11. 5-Acetyl-6-methyl-4-(4′-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**1k**)*

Yellow solid. Mp: 229–230 °C (dec.). Ref. Mp [41]: 230 °C (dec.).

*4.3.12. 5-Acetyl-6-methyl-4-(3′-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**1l**)*

Yellow solid. Mp: 286–288 °C. IR: ν 1650, 1585, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 282.6 nm (3.98). ^1H NMR (DMSO-d_6): δ 2.19 (s, 3H, CH_3), 2.32 (s, 3H, CH_3CO), 5.45 (d, J = 3.24 Hz, 1H, 4-H), 7.99 (brd s, 1H, 1-NH), 8.11 (m_c, 4H, H-aromatic), 9.34 (s, 1H, 3-NH). EI-MS: *m*/*z* (%): 259 (M^+-OH, 5), 258 (M^+-H_2O, 32), 232 (M^+-CH_3CO, 7), 228 (M^+-HNO_2, 27), 153 (3-$O_2NC_6H_4$–CH=NH^+, 100).

*4.3.13. 5-Acetyl-6-methyl-4-phenylpyrimidin-2(1H)-one (**2a**)*

Pale yellow solid. Mp: 162–163 °C. IR: ν 1700, 1670, 1590 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 307.5 (2.32), 249.0 nm (2.52). ^1H NMR (DMSO-d_6): δ 1.84 (s, 3H, 6-CH_3), 2.30 (s, 3H, CH_3CO), 7.52 (m_c, 5H, H-aromatic), 12.33 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 18.82, 32.37, 118.33, 128.63, 129.25, 131.32, 155.89, 201.05. EI-MS: *m*/*z* (%): 228 (M^+, 42), 227(M^+-H, 49), 213 (M^+-CH_3, 100), 185 (M^+-CH_3CO, 11), 104 (C_6H_5–C=NH^+, 61), 103 (C_6H_5–CN^+, 7), 77 ($C_6H_5^+$, 44).

*4.3.14. 5-Acetyl-6-methyl-4-(4′-methylphenyl)pyrimidin-2(1H)-one (**2b**)*

Pale yellow solid. Mp: 219–221 °C. IR: ν 1695, 1590, 1510 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 320.0 (sh, 3.48), 259.5 nm (3.70). ^1H NMR (DMSO-d_6): δ 1.85 (s, 3H, CH_3), 2.29 (s, 3H, CH_3CO), 2.50 (s, 3H, 4′-CH_3), 7.31 (d, J = 7.83 Hz, 2H, 2-H′ and 6-H′), 7.37 (d, J 8.52 Hz, 2H, 3-H′ and 5-H′), 12.26 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 19.05, 21.41, 32.42, 118.18, 128.67, 129.80, 135.06, 141.33, 156.26, 161.12, 201.29. EI-MS: *m*/*z* (%): 242 (M^+, 46), 241 (M^+-H, 32), 227 (M^+-CH_3, 100), 199 (M^+-CH_3CO, 11), 117 (4-$CH_3C_6H_4$–C=NH^+, 4), 116 (4-$CH_3C_6H_4$–CN^+, 8), 91 (–C_6H_4–CH_3, 37).

*4.3.15. 5-Acetyl-4-(4′-methoxyphenyl)-6-methylpyrimidin-2(1H)-one (**2c**)*

Pale yellow solid. Mp: 189–191 °C. IR: ν 1670, 1680, 1425 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 296.5 (3.08), 255.0 nm (3.08). ^1H NMR (DMSO-d_6): δ 1.87 (s, 3H,6-CH_3), 2.28 (s, 3H, CH_3CO), 3.82 (s, 3H, CH_3O), 7.06 (d, J = 8.55 Hz, 2H, 2-H′ and 6-H′), 7.45 (d, J = 8.52, 2H, 3-H′ and 5-H′), 12.18 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 18.83, 32.34, 55.84, 114.67, 117.91, 130.53, 155.97, 161.99, 155.97, 161.99, 201.35. EI-MS: *m*/*z* (%): 258 (M^+, 84), 257 (M^+-H, 40), 243 (M^+-CH_3, 100), 227 (M^+-CH_3O, 10), 215 (M^+-CH_3CO, 11), 200 (M^+-CH_3CO, $-CH_3$, 18), 134 (4-$CH_3OC_6H_4$–CH=NH^+, 71), 133 (4-$CH_3OC_6H_4$–C=NH^+, 4), 132 (4-$CH_3OC_6H_4$–CN^+, 3).

*4.3.16. 5-Acetyl-4-(3′-methoxyphenyl)-6-methylpyrimidin-2(1H)-one (**2d**)*

Pale yellow solid. Mp: 163–164 °C. IR: ν 1675, 1595, 1425 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 303.5 (3.75), 250.0 nm (3.88). ^1H NMR (DMSO-d_6): δ 1.85 (s, 3H, 6-CH_3), 2.28 (s, 3H, CH_3CO), 3.80 (s, 3H, 4′-CH_3O), 6.98 (d, J 7.33 Hz, 2H, 4′-H), 7.12 (d, J = 8.20 Hz, 2H, 6′-H), 7.03 (s, 1H, 2′-H),7.41 (t, J = 6.67 Hz, J = 7.55 Hz, 1H). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 30.87, 55.60, 111.79, 119.23, 121.19, 130.54, 132.43, 155.94, 156.40, 198.86. EI-MS: *m*/*z* (%): 258 (M^+, 3), 257 (M^+-H, 2), 243 (M^+-CH_3, 2), 200 (M^+-CH_3CO, $-CH_3$, 2), 134 (4-$CH_3OC_6H_4$–CH=NH^+, 14), 133 (4-$CH_3OC_6H_4$–C=NH^+, 7), 132 (4-$CH_3OC_6H_4$–CN^+, 8), 77 (100).

*4.3.17. 5-Acetyl-4-(2′-methoxyphenyl)-6-methylpyrimidin-2(1H)-one (**2e**)*

Pale yellow solid. Mp: 166–167 °C. IR: ν 1960, 1590, 1550 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 303.0 (4.15), 258.0 nm (4.15). ^1H NMR (DMSO-d_6): δ 1.87 (s, 3H, CH_3), 2.32 (s, 3H, CH_3CO), 3.70 (s, 3H, CH_3O), 7.24 (m_c, 4H, H-aromatic), 12.12 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 30.85, 55.58, 111.78, 119.24, 121.18,

130.54, 132.44, 155.96, 198.82. EI-MS: *m*/*z* (%): 258 (M^+, 6), 257 (M^+-H, 4), 243 (M^+-CH_3, 13), 227 (M^+-CH_3O, 100), 215 (M^+-CH_3CO, 22), 134 (2-$CH_3OC_6H_4$–CH=NH^+, 38), 133 (2-$CH_3OC_6H_4$–C=NH^+, 10), 132 (2-$CH_3OC_6H_4$–CN^+, 6).

*4.3.18. 5-Acetyl-4-(4′-chlorophenyl)-6-methylpyrimidin-2(1H)-one (**2f**)*

Pale yellow solid. Mp: 235–237 °C. IR: *v* 1650, 1580, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 313.0 (3.34), 252.0 nm (3.56). ^1H NMR (DMSO-d_6): δ 1.90 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 7.49 (d, *J* 8.27 Hz, 2H, 3-H′ and 5-H′), 7.58 (d, *J* = 8.21 Hz, 2H, 2-H′ and 6-H′),12.21 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 18.97, 32.53, 118.30, 129.33, 130.51, 136.09, 137.02, 156.35, 161.11, 168.92, 200.99. EI-MS: *m*/*z* (%): 264 ($M^{+37}Cl$, 27), 263 ($M^{+37}Cl-H$, 32), 262 ($M^{+35}Cl$, 78), 261 ($M^{+35}Cl-H$, 59), 249 ($M^{+37}Cl-CH_3$, 69), 247 ($M^{+35}Cl-CH_3$, 99), 227 (M^+-Cl, 17), 221 ($M^{+37}Cl-CH_3CO$, 5), 219 ($M^{+35}Cl-CH_3CO$, 13), 140 (4-$^{37}ClC_6H_4C$=NH^+, 42), 139 (4-$^{37}ClC_6H_4CN^+$, 19), 138 (4-$^{35}ClC_6H_4C$=NH^+, 87), 137 (4-$^{35}ClC_6H_4CN^+$, 12).

*4.3.19. 5-Acetyl-4-(3′-chlorophenyl)-6-methylpyrimidin-2(1H)-one (**2g**)*

Pale yellow solid. Mp: 196–198 °C. IR: *v* 1650, 1580, 1430 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 320 (sh, 3.99), 304 (4.03), 259.0 nm (4.18). ^1H NMR (DMSO-d_6): δ 1.90 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 7.54 (m_c, 4H, H-aromatic), 9.27 (s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 19.13, 32.55, 118.37, 127.31, 128.32, 130.89, 131.09, 133.93, 140.37, 156.73, 161.39, 168.58, 200.95. EI-MS: *m*/*z* (%): 264 ($M^{+37}Cl$, 21), 263 ($M^{+37}Cl-H$, 23), 262 ($M^{+35}Cl$, 58), 261 ($M^{+35}Cl-H$, 38), 249 ($M^{+37}Cl-CH_3$, 45), 247 ($M^{+35}Cl-CH_3$, 100), 227 (M^+-Cl, 14), 221 ($M^{+37}Cl-CH_3CO$, 5), 219 ($M^{+35}Cl-CH_3$- CO, 9), 140 (3-$^{37}ClC_6H_4C$=NH^+, 36), 139 (3-$^{37}ClC_6$- H_4CN^+, 18), 138 (3-$^{35}ClC_6H_4C$=NH^+, 78), 137 (3-$^{35}ClC_6H_4CN^+$, 9).

*4.3.20. 5-Acetyl-4-(2′-chlorophenyl)-6-methylpyrimidin-2(1H)-one (**2h**)*

Pale yellow solid. Mp: 175–176 °C. IR: *v* 1700, 1620, 1430 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 305.0 (3.34), 259.0 nm (3.45). ^1H NMR (DMSO-d_6): δ 1.90 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 7.47 (m_c, 4H, H-aromatic),12.26 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 20.23, 31.50, 119.22, 127.88, 130.06, 130.54, 131.00, 131.61, 137.32, 156.67, 163.00, 198.89. EI-MS: *m*/*z* (%): 247 ($M^{+35}Cl-CH_3$, 5), 227 (M^+-Cl, 100), 219 ($M^{+35}Cl-CH_3CO$, 3), 140 (2-$^{37}ClC_6H_4C$=NH^+, 24), 139 (2-$^{37}ClC_6H_4CN^+$, 13) 138 (2-$^{35}ClC_6$-H_4C=NH^+, 47), 137 (2-$^{35}ClC_6H_4CN^+$, 8).

*4.3.21. 5-Acetyl-4-(4′-bromophenyl)-6-methylpyrimidin-2(1H)-one (**2i**)*

Pale yellow solid. Mp: 239–240 °C. IR: *v* 1670, 1620, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 332 (sh, 3.36), 304 (sh, 3.48), 252.0 nm (3.76). ^1H NMR (DMSO-d_6): δ 1.91 (s, 3H, CH_3), 2.30 (s, 3H, CH_3CO), 7.41 (d, *J* = 8.18 Hz, 2H, 3-H′ and 5-H′), 7.72 (d, *J* = 8.12, 2H, 2-H′ and 6-H′), 12.30 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 19.02, 32.56, 118.30, 124.88, 130.70, 132.24, 137.40, 156.52, 161.20, 168.92, 201.01. EI-MS: *m*/*z* (%): 308 ($M^{+81}Br$, 38), 307 ($M^{+81}Br-H$, 32), 306 ($M^{+79}Br$, 37), 305 ($M^{+79}Br-H$, 26), 293 ($M^{+81}Br-CH_3$, 81), 291 ($M^{+79}Br-CH_3$, 83), 265 ($M^{+81}Br-$ CH_3CO, 6), 263 ($M^{+79}Br-CH_3CO$, 7), 227 (M^+-Br, 24), 185 (4-$^{81}BrC_6H_4CH$=NH^+, 16), 183 (4-$^{79}BrC_6H_4CH$=NH^+, 61), 182 (4-$^{79}BrC_6H_4C$=NH^+, 16), 181 (4-$^{79}BrC_6H_4CN^+$, 45).

*4.3.22. 5-Acetyl-4-(2′-bromophenyl)-6-methylpyrimidin-2(1H)-one (**2j**)*

Pale yellow solid. Mp: 202–204 °C. IR: *v* 1700, 1615, 1420 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 301.5 (3.89), 264.0 nm (3.86). ^1H NMR (DMSO-d_6): δ 1.85 (s, 3H, CH_3), 2.37 (s, 3H, CH_3CO), 7.43 (m_c, 3H, H-aromatic), 7.73 (d, *J* = 7.82 Hz, 1H, 6-H′), 12.36 (brd s, 1H, NH). EI-MS: *m*/*z* (%): 227 (M^+-Br, 100), 185 (2-$^{81}BrC_6H_4CH$=NH^+, 10), 184 (2-$^{81}BrC_6H_4C$=NH^+, 26) 183 (4-$^{79}BrC_6H_4CH$=NH^+, 3), 182 (4-$^{79}BrC_6H_4C$=NH^+, 6).

*4.3.23. 5-Acetyl-6-methyl-4-(4′-nitrophenyl)-pyrimidin-2(1H)-one (**2k**)*

Pale yellow solid. Mp: 265–267 °C. IR: *v* 1665, 1600, 1505 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 330 (sh, 3.71), 302 (sh, 3.86), 262.0 nm (4.07). ^1H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3CO), 1.95 (s, 3H, CH_3), 7.73 (d, *J* = 8.52 Hz, 2H, 2-H′ and 6-H′), 8.33 (d, *J* = 8.49, 2H, 3-H′ and 5-H′), 9.27 (s, 1H, NH), 12.48 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 18.83, 124.33, 130.06, 144.44, 148.98. EI-MS: *m*/*z* (%): 273 (M^+, 20), 272 (M^+-H, 13), 258 (M^+-CH_3, 100), 256 (M^+-OH, 25), 226 (M^+-HNO_2, 12).

*4.3.24. 5-Acetyl-6-methyl-4-(3′-nitrophenyl)-pyrimidin-2(1H)-one (**2l**)*

Pale yellow solid. Mp: 256–258 °C. IR: *v* 1675, 159, 1520 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 305.0 (3.57), 259.0 nm (3.85). ^1H NMR (DMSO-d_6): δ 1.97 (s, 3H, CH_3), 2.35 (s, 3H, CH_3CO), 7.80 (t, *J* = 8.80 Hz, 1H, 5-H′), 7.88 (d, *J* = 7.49 Hz, 1H, 6-H′), 8.29 (s, 1H, 2-H′), 8.39 (d, *J* = 7.96 Hz, 1H, 4-H′), 12.48 (brd s, 1H, NH). EI-MS: *m*/*z* (%): 273 (M^+, 15), 272 (M^+-H, 8), 258 (M^+-CH_3, 100), 256 (M^+-OH, 30), 226 (M^+-HNO_2, 16).

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