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ORIGINAL PAPER

Free-radical oxidation of 1,2,3,4-tetrahydro-2-oxopyrimidines

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Abstract Free-radical oxidation of 4-substituted 5-acetyl- and 5-carboethoxy-1,2,3,4-tetrahydro-2-oxopyrimidines using benzoyl peroxide under thermal conditions has been investigated to elucidate the effects of the nature of the substituents in the 4- and 5-positions on the rate of reaction. Whereas the presence of the acetyl group instead of the carboethoxy group in position 5 decreases the rate of oxidation, the nature of the additional substituent (electron-releasing or electron-withdrawing group) and also its location on the phenyl ring attached to C-4 of the tetrahydropyrimidinone ring effectively influence the rate of reaction. The latter observation supports the proposal that the removal of the 4-hydrogen on the heterocyclic ring occurs in the rate-determining step.

Keywords Benzoyl peroxide · Tetrahydropyrimidinones · Free radical · Oxidation · Substituent effects

Introduction

The synthesis of 1,2,3,4-tetrahydro-2-oxopyrimidines (THPMs), also known as 3,4-dihydropyrimidin-2(1*H*)-ones or Biginelli compounds, has gained importance because these compounds and their substituted derivatives have well-known biological and medicinal applications, such as antifungal, antiviral, anticancer, antibacterial, anti-inflammatory, antitubercular, and antihypertensive effects [1–6].

The development of efficient methods for the oxidation of various organic compounds is of interest [7]. The course of the dehydrogenation of THPMs as a route to the synthesis of 1,2-dihydropyrimidinones (DHPMs) depends on the effects of the nature of the substituents located on the 4- and 5-positions of the heterocyclic ring. Various methods have been utilized for the synthesis of DHPMs by oxidation of the corresponding THPMs, but many methods faced major drawbacks due to harsh reaction conditions, longer reaction time, low yield, and formation of undesirable side products [8–10]. Recently, we reported the efficient oxidation of these compounds by potassium peroxydisulfate in aqueous acetonitrile under thermal [11], sono-thermal [12, 13], and microwave [14] activation. According to the proposed mechanism removal of the 4-hydrogen is the rate-determining step. The hydroxyl radical formed by the reaction of potassium sulfate radical and water acts as the active hydrogen-abstracting species. This argument is supported by the influence of the steric and electronic effects of the substituents attached to C-4 and C-5 of the heterocyclic ring on the rate of the hydrogen removal.

Benzoyl peroxide (BPO) is used as a catalyst, initiator, oxidizing, and curing agent [15, 16]. The half-life of BPO is one of the lowest for the cross-linking peroxides (10 h at 73 °C and 1 h at 92 °C) [17]. BPO decomposes thermally to produce high energy benzoyloxy radicals (~500 kJ/mol [18]) and is a widely used initiator for radical reactions. Major examples are intermolecular additions and cyclization reactions [19]. Also the oxidation of different types of 1,4-dihydropyridines to pyridine derivatives with BPO as free-radical oxidizing agent is reported [20, 21].

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In continuation to these works, we were interested to investigate the oxidation of the title compound by another radical species to elucidate the steric and electronic effects of substituents on the rate of reaction and also to confirm the earlier proposed mechanism, namely oxidation by way of radicals. Herein, we wish to report the results concerning thermal oxidation of THPMs by BPO on free-radical oxidation and analyze the following aspects:

1. To determine the effect of the substituent in the 4- and 5- positions of the THPM ring on the rate of oxidation
2. To determine the occurrence of any possible side reactions due to the presence of allylic hydrogen in the methyl group in position 6.

Results and discussion

Optimization of reaction conditions

To optimize the reaction conditions and evaluate the factors that influence the rate of reaction, the following points were taken into account:

1. The nature and effects of solvent and its boiling point on the solubility of the starting material and especially on the lifetime of BPO
2. The presence of an oxygen or argon atmosphere
3. The molar ratios of the reactants.

We first investigated the oxidation of ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**1a**) as a model compound in the presence of various amounts of BPO by refluxing in ethanol/acetonitrile under an argon atmosphere. The results presented in Table 1 indicate that acetonitrile is a suitable solvent for this purpose. These results also indicate that in this oxidative reaction a 3.5:1 ratio of BPO/**1a** is necessary for the effective removal of two hydrogens from **1a** in a shorter reaction time. It is noteworthy that with an increase of the BPO/**1a** ratio, the time of oxidation was shortened, but only

Table 1 Oxidation of **1a** by BPO in refluxing acetonitrile and ethanol under an argon atmosphere

1a/BPO	Solvent	Time/h[a]	Yield/%
1:1	Acetonitrile	8	50
1:2	Acetonitrile	8	70
1:3	Acetonitrile	6	95
1:3.5	Acetonitrile	3	95
1:4	Acetonitrile	3	95
1:3.5	Ethanol	10	95

[a] Maximum progression of the reaction

Table 2 Oxidation of **1a** by BPO in dry acetonitrile under different atmospheres

Atmosphere	Time/h[a]	Yield/%
Air saturated	6	95
Oxygen	6	70
Argon	3	95

1a/BPO = 1:3.5

[a] Maximum progression of the reaction

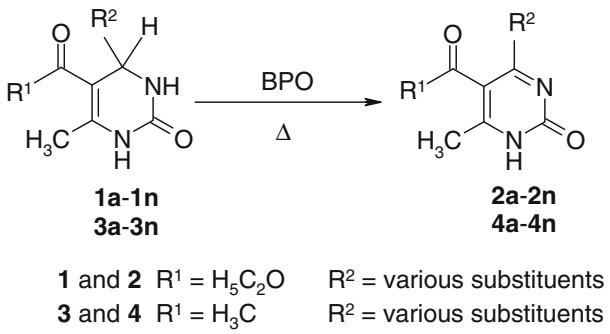
2a was formed and possible further oxidation or dealkylation of 6-CH_3 was not observed, as are reported by using other oxidants [9, 10].

Since oxygen inhibits the radical reactions, the oxidation of **1a** was performed in air-saturated acetonitrile and also by bubbling oxygen or argon during the reaction under reflux conditions. The data presented in Table 2 indicate that the presence of oxygen decreases the rate and yield of reaction.

Under optimized reaction conditions, various 5-carboethoxy-1,2,3,4-tetrahydro-2-oxopyrimidines **1a**–**1n** and 5-acetyl-1,2,3,4-tetrahydro-2-oxopyrimidines **3a**–**3n** were subjected to the oxidation reaction by BPO in acetonitrile under an argon atmosphere at 100 °C (Scheme 1). The results are summarized in Tables 3 and 4.

The results presented in Tables 3 and 4 indicate that 5-carboethoxy-THPMs **1a**–**1n** were oxidized faster than the corresponding 5-acetyl-THPMs **3a**–**3n**. The same trends were also observed in the oxidation reactions of these compounds by potassium peroxydisulfate under thermal conditions [11], sono-thermal reaction [12, 13], or under microwave irradiation [14]. These observations led us to propose the following mechanism for the oxidation of THPMs by BPO (Scheme 2).

According to the proposed mechanism, thermolysis of the weakest O–O bond in BPO in the first step leads to the formation of a benzoyloxy radical (BO·). In the next step, BO· abstracts a hydrogen atom from the more covalent C–H bond rather than from the less covalent N–H bond leading to formation of a trihydropyrimidinyl radical



Scheme 1

Table 3 Oxidation of 5-carboethoxy-1,2,3,4-tetrahydro-2-oxopyrimidines **1a–1n** to **2a–2n** by BPO under thermal conditions

1,**2**	R^2	Time/h[a]	Yield/%
a	C_6H_5–	3	85
b	2-$CH_3OC_6H_4$–	2.5	80
c	3-$CH_3OC_6H_4$–	6	70
d	4-$CH_3OC_6H_4$–	2	83
e	2-ClC_6H_4–	3.5	78
f	3-ClC_6H_4–	8	71
g	4-ClC_6H_4–	2.5	85
h	4-BrC_6H_4–	4	80
i	4-$NO_2C_6H_4$–	6	60
j	4-$CH_3C_6H_4$–	2.5	80
k	3,4-$(CH_3O)_2C_6H_3$–	3	82
l	$PhCH_2CH_2$–	2.5	87
m	4-$(CH_3)_2NC_6H_4$–	1	89
n	2-Thienyl	8	86

[a] Maximum progression of the reaction

Table 4 Oxidation of 5-acetyl-1,2,3,4-tetrahydro-2-oxopyrimidines **3a–3n** to **4a–4n** by BPO under thermal conditions

3,**4**	R^2	Time/h[a]	Yield/%
a	C_6H_5–	6	86
b	2-$CH_3OC_6H_4$–	7	82
c	3-$CH_3OC_6H_4$–	8	70
d	4-$CH_3OC_6H_4$–	4	86
e	2-ClC_6H_4–	7	80
f	3-ClC_6H_4–	9	78
g	4-ClC_6H_4–	5	88
h	4-BrC_6H_4–	7	85
i	2-$NO_2C_6H_4$–	6	60
j	3-$NO_2C_6H_4$–	8	70
k	4-$NO_2C_6H_4$–	6	50
l	4-$CH_3C_6H_4$–	5	83
m	4-$(CH_3)_2NC_6H_4$–	3	86
n	2-Thienyl	10	80

[a] Maximum progression of the reaction

(TrHPM·) and benzoic acid. The abstraction of a second hydrogen atom in the final step by another BO· completes the reaction with formation of dihydropyrimidinone product (DHPM).

The observed effects of substituents on the rate of reaction, especially the substituents in the 4-position of the heterocyclic ring, indicate that the removal of the first hydrogen atom, namely 4-H, occurs in the rate-determining step (step 2). This suggestion is supported by the fact that the stability of a trihydropyrimidinyl radical intermediate (TrHPM·), which is formally a benzylic and an allylic radical, should decrease the activation energy of its formation (Scheme 3).

A comparison of BPO oxidation of these two classes of compounds under thermal conditions can be explained by the ab initio calculation at the B3LYP/6-311++G** level of theory for the optimized structures of THPMs considered in this study [22]. According to these results, the heterocyclic ring appears as quasi-planar structure (boat conformation), in which the aryl groups occupy a pseudo-axial position. In this structure, the C-4 and N-1 atoms are not in the same plane as the other remaining four atoms (C-2, N-3, C-5, and C-6). The interesting points in this study were to find the factors which influence the following items:

1. The degree of deviations of the C-4 and N-1 centers from planarity
2. The dihedral angles of the 5-CO groups of the ester or the acetyl moiety with respect to the C_5=C_6 bond
3. The dihedral angles formed by $C_2' - C_1'$ and C_4–N_3
4. The electron density of the heterocyclic ring atoms.

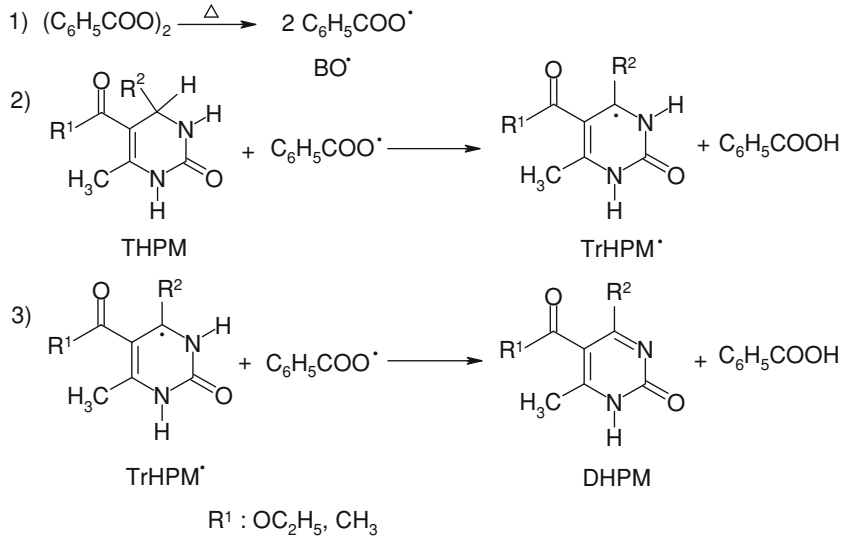
The results showed that items 1–4 were influenced by the orientation of the aryl group attached to C-4 of the heterocyclic ring, especially the position of the additional substituent on the phenyl ring, and also by the stereoelectronic effect of the carboethoxy and the acetyl groups located on C-5.

The results shown in Tables 3 and 4 indicate that the rate of oxidation of 5-acetyl-THPMs is less than that of 5-carboethoxy-THPMs. The substituents on the phenyl ring located in the 4-position of the THPM ring also affect the rate of oxidation. Electron-donating substituents at the *ortho*- or *para*-positions of the phenyl ring increase the rate of the reaction by stabilizing the trihydropyrimidinyl radical intermediate and by facilitating the homolytic cleavage of the C-4–H bond. Whereas the presence of the methoxy group in the correct position (2- or 4-, **1b**, **1d** and **3b**, **3d**) decreases the reaction time, the presence of the same substituent but in the 3-position (**1c**, **3c**) increases the reaction time. This indicated that as expected the electron-donating group (located in the correct position) increases the rate of reaction because these groups stabilize the formation of the trihydropyrimidinyl radical intermediate. This suggestion is also supported by the influence of the electron-withdrawing group 4-nitro (**1i** and **3 k**) vs. the electron-releasing group 4-$(H_3C)_2N$ (**1m** and **3m**) on decreasing the rate of oxidation.

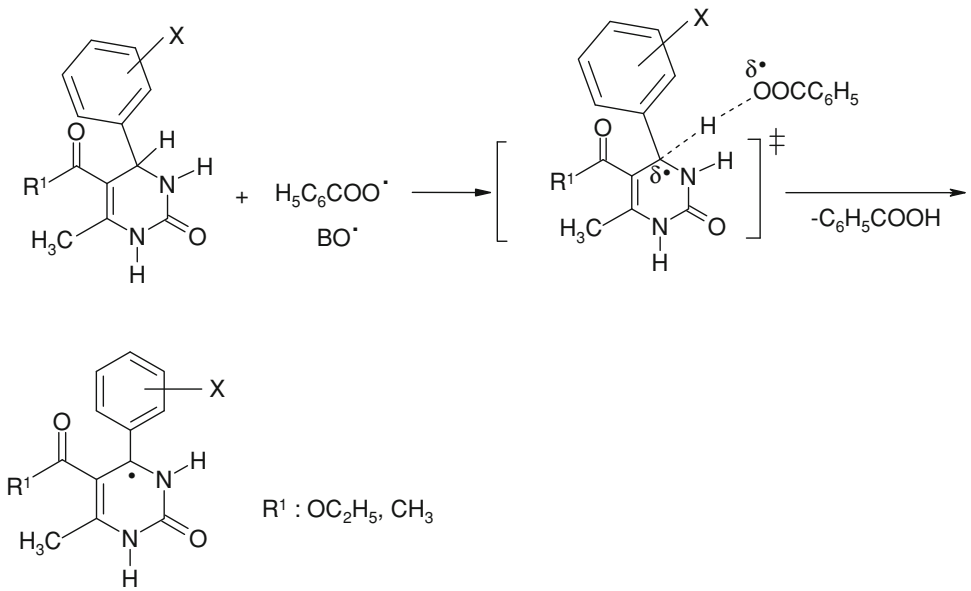
Experimental

THPMs were prepared by adoption of the known procedure [23]. Melting points were determined on a Stuart Scientific SMP2 apparatus. IR spectra were recorded using KBr discs

Scheme 2



Scheme 3



on a Shimadzu IR spectrometer IR-435. The ^{1}H and ^{13}C NMR spectra (DMSO-d_6) were recorded on Bruker DRX-300 Avance and Bruker Avance III 400 spectrometers at 300 and 100.62 MHz. Mass spectra were obtained on a Micromass Platform II spectrometer in EI mode at 70 eV. UV spectra were recorded with a Shimadzu UV-160 spectrometer. Elemental analyses were done with a Leco 932 CHNS-analyzer, and results agreed favorably with calculated values.

General procedure for oxidation of 1,2,3,4-tetrahydro-2-oxopyrimidines

BPO (3.5 mmol) was added to a solution of THPM (1 mmol) in 10 cm^3 dry acetonitrile, and then the reaction mixture was refluxed at 100 °C (bath temperature) under an argon atmosphere. The results are given in Tables 3 and 4. The reaction was monitored by TLC (*n*-hexane/ethyl acetate, 2:1) until maximum progression of the reaction. Solvent was evaporated and the product was isolated by column chromatography (*n*-hexane/ethyl acetate, 2:1). The known products were characterized by comparison of their physical and spectral data with those of authentic samples [11, 14], and the data of the new products are given below.

Ethyl 4-(4-bromophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidin-5-carboxylate (**2h**, $C_{14}H_{13}BrN_2O_3$)

M.p.: 186–188 °C; IR (KBr): $\bar{\nu} = 3{,}350$ (NH), 1,705 ($CO_2C_2H_5$), 1,665 (2-CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.87$ (t, $J = 7.09$ Hz, 3H, CH_2CH_3), 2.39 (s, 3H, 6-CH_3), 3.97 (q, $J = 7.10$ Hz, 2H, CH_2CH_3), 7.38

(d, $J = 8.33$ Hz, 2H, 3′-H, 5′-H), 7.67 (d, $J = 8.30$ Hz, 2H, 2′-H, 6′-H) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): $\delta = 13.26$ (CH_3CH_2O), 17.94 (6-CH_3), 60.91 (CH_3CH_2O), 108.50, 123.63, 129.56, 131.22, 137.64, 155.07, 160.82, 165.54, 171.33 (CH_3CH_2OC=O) ppm; MS (70 eV): *m/z* (%) = 338 (M^{+81}Br, 2), 337 (M^{+81}Br–H, 3), 336 (M^{+79}Br, 2), 309 (M^{+81}Br–C_2H_5, 11), 307 (M^{+79}Br–C_2H_5, 8), 293 (M^{+81}Br–C_2H_5O, 2), 291 (M^{+79}Br–C_2H_5O, 3), 229 (M^+–Br–C_2H_4, 4), 181 (M^+–C_6H_4Br, 3), 155 ($C_6H_4^{79}Br^+$, 3), 76 ($C_6H_4^+$, 14), 57 (100); UV–Vis (CH_3CN, $c = 6.23 \times 10^{-5}$ mol dm^{-3}): λ_{max} (ε) = 326 (sh, 5,457), 250.2 (14,559) nm (mol^{-1} dm^3 cm^{-1}).

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(2-thienyl)pyrimidin-5-carboxylate (**2n**, $C_{12}H_{12}N_2O_3S$)
M.p.: 220 °C (dec.); IR (KBr): $\bar{\nu}$ = 3,400 (NH), 1,705 ($CO_2C_2H_5$), 1,660 (2-CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.18$ (t, $J = 7.05$ Hz, 3H, CH_2CH_3), 2.30 (s, 3H, 6-CH_3), 4.26 (q, $J = 7.08$ Hz, 2H, CH_2CH_3), 7.18 (t, $J = 3.94$ Hz, 1H, 4′-H), 7.35 (d, $J = 3.56$ Hz, 1H, 3′-H), 7.87 (d, $J = 4.93$ Hz, 1H, 5′-H), 12.28 (s, 1H, NH) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): $\delta = 13.57$ (CH_3CH_2O), 17.50 (6-CH_3), 61.69 (CH_3CH_2O), 108.10, 128.60, 130.0, 132.57, 140.66, 155.13, 158.86, 162.28, 166.39 (CH_3CH_2OC=O) ppm; MS (70 eV): *m/z* (%) = 264 (M^+, 83), 235 (M^+–C_2H_5, 14), 219 (M^+–C_2H_5O, 49), 191 (M^+–$CO_2C_2H_5$, 17), 136 (M^+–C_4H_3S–C_2H_5O, 23), 110 (M^+–C_4H_3S–$CO_2C_2H_5$, 100), 94 (M^+–C_4H_3S–$CO_2C_2H_5$–CH_3, 12), 83 ($C_4H_3S^+$, 21); UV–Vis (CH_3CN, $c = 1 \times 10^{-4}$ mol dm^{-3}): λ_{max} (ε) = 318.4 (15,720), 271.2 (sh, 5,850), 246 (9,250) nm (mol^{-1} dm^3 cm^{-1}).

5-Acetyl-3,4-dihydro-6-methyl-4-(2′-thienyl) pyrimidin-2(1H)-one (**3n**, $C_{11}H_{12}N_2O_2S$)
M.p.: 226–228 °C; IR (KBr): $\bar{\nu}$ = 3,300 (NH), 1,720 (CH_3CO), 1,680 (2-CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.19$ (s, 3H, 6-CH_3), 2.27 (s, 3H, CH_3CO), 5.52–5.53 (d, $J = 2.99$ Hz, 1H, 4-H), 6.95 (m, 2H, 3′-H and 4′-H), 7.35–7.37 (dd, $J_{4'5'} = 4.7$ Hz, $J_{3'5'} = 1.5$ Hz, 1H, 5′-H), 7.99 (s, 1H, 1-NH), 9.34 (s, 1H, 3-NH) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): $\delta = 18.83$ (6-CH_3), 30.14 (CH_3CO), 49.23 (C4), 110.46, 123.90, 124.85, 126.70, 148.20, 148.59, 152.24 (2-CO), 193.80 (CH_3C=O) ppm; MS (70 eV): *m/z* (%) = 236 (M^+, 100), 221 (M^+–CH_3, 47), 193 (M^+–$COCH_3$, 31), 153 (M^+–C_4H_3S, 21), 138 (M^+–C_4H_3S–CH_3, 10), 110 (M^+–C_4H_3S–$COCH_3$, 36), 83 ($C_4H_3S^+$, 26); UV–Vis (CH_3CN, $c = 1 \times 10^{-4}$ mol dm^{-3}): λ_{max} (ε) = 290.5 (11,490), 238.0 (9,410) nm (mol^{-1} dm^3 cm^{-1}).

5-Acetyl-6-methyl-4-(2′-thienyl)pyrimidin-2(1H)-one (**4n**, $C_{11}H_{10}N_2O_2S$)
M.p.: 240 °C (dec.); IR (KBr): $\bar{\nu}$ = 3,000 (NH), 1,695 (CH_3CO), 1,640 (2-CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.24$ (s, 3H, 6-CH_3), 2.27 (t, 3H, CH_3CO), 7.20 (dd, $J_{3'4'} = 3.91$ Hz, $J_{4'5'} = 4.89$ Hz, 1H, 4′-H), 7.27 (m, 1H, 3′-H), 7.92 (dd, $J_{5'3'} = 0.8$ Hz, $J_{5'4'} = 4.41$ Hz, 1H, 5′-H), 12.15 (br s, 1H, NH) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): $\delta = 17.31$ (6-CH_3), 32.25 (CH_3CO), 116.32, 128.77, 130.78, 132.82, 140.76, 155.32, 157.64, 162.07, 201.97 (CH_3C=O) ppm; MS (70 eV): *m/z* (%) = 234 (M^+, 41), 219 (M^+–CH_3, 48), 191 (M^+–CH_3CO, 2), 136 (M^+–C_4H_3S–CH_3, 9), 110 (100), 108 (M^+–C_4H_3S–CH_3CO, 4); UV–Vis (CH_3CN, $c = 1 \times 10^{-4}$ mol dm^{-3}): λ_{max} (ε) = 313.6 (12,770), 258 (10,720) nm (mol^{-1} dm^3 cm^{-1}).

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