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Potassium peroxydisulfate as an Efficient Oxidizing Agent for Conversion of Ethyl 3,4-Dihydropyrimidin-2(*1H*)-one-5-carboxylates to their Corresponding Ethyl Pyrimidin-2(*1H*)-one-5-carboxylates

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Various ethyl 3,4-dihydropyrimidin-2(*1H*)-one-5-carboxylates were oxidized to their corresponding ethyl pyrimidin-2(*1H*)-one-5-carboxylates by potassium peroxydisulfate in refluxing aqueous acetonitrile. The products were obtained in good to excellent yields. The effect of the nature of 4-substituent and also the nature of solvent play an important role on the rate of oxidation.

Keywords: Dihydropyrimidinone, Oxidation, Pyrimidinone, Potassium peroxydisulfate, Substituent effect

INTRODUCTION

Six-membered heterocyclic compounds are important constituents which often exist in biologically active natural products and also in synthetic compounds of medicinal interest [1,2]. Among them, pyrimidine cores are important classes of drugs [3-5]. The pyrimidine derivative, MKC-442, is one of the most important classes of drugs to inhibit the HIV virus [6]. In addition, Itami *et al*. have reported that pyrimidine cores with extended π-systems exhibited interesting fluorescent properties [7]. However, surprisingly little is known about the behavior of such partly reduced pyrimidine derivatives towards oxidizing agents. Dehydrogenation of 3,4-dihydropyrimidin-2(*1H*)-ones (DHPMs) is an important method for the preparation of pyrimidine derivatives. Although various methods for the dehydrogenation of specific 1,4-dihydropyridines exist [8-12], 3,4-dihydropyrimidin-2(*1H*)-ones are highly stable toward mild and powerful oxidants such as MnO_2 [13], $FeCl_3$ [14], $RuCl_3/O_2$ in AcOH [15], PCC [13], chloranil [13], $KMnO_4$/clay [13], DDQ [13], $NaNO_2$/AcOH [13], CAN/AcOH [16] and $Co(NO_3)_2.6H_2O/K_2S_2O_8$ [17] and also dehydrogenating agents such as Pd/C [13], Br_2 [18], Sulfur [19]. However, the application of these methods suffer from disadvantages such as the use of hazardous, expensive, less easily available oxidants, vigorous reaction conditions, prolonged reaction times, and especially low yields and formation of side products [17]. Furthermore, some of these methods require strictly anhydrous conditions. Consequently, there is a need for the development of protocols using readily available and safe reagents which lead to high yields of pyrimidin-2(*1H*)-one derivatives.

The peroxydisulfate ion is one of the strongest oxidizing agents known in aqueous solution. The standard oxidation-reduction potential for the reaction is estimated to be -2.01 V [20,21]. The oxidative application of peroxydisulfate ion in organic synthesis has been widely investigated [22-27].

$$2\ SO_4^{2-} \longrightarrow S_2O_8^{2-}(aq) + 2e^-$$

Potassium peroxydisulfate has been used for the

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oxidation of alkyl aryl sulfides to their corresponding sulfoxides [28], for the oxidation of 1,4-dihydropyridines to the pyridine derivatives [29], for free radical degradation of chitosan [30] and for the preparation of polymer/silicate nonocomposites [31]. Here we wish to introduce potassium peroxydisulfate as an effective oxidizing agent for the conversion of various ethyl 3,4-dihydropyrimidin-2(*1H*)-one-5-carboxylates to their corresponding ethyl pyrimidin-2(*1H*)-one-5-carboxylates.

The aim of the present work was:

i. To investigate the use of a reagent system which would overcome the above mentioned limitations, a system which would offer a clean and easy work-up, especially increased yield of product in comparison with the reported procedures.

ii. To elucidate the effect of the nature of 4-substituent on the rate of reaction.

EXPERIMENTAL

Melting points were determined on a Stuart Scientific SMP2 apparatus and were uncorrected. IR spectra were recorded from KBr discs on a Shimadzu apparatus IR 435. ^{1}H NMR spectra were recorded using a Brucker 300 MHz machine. They are reported as follows: chemical shifts, multiplicity, coupling constants *J* (Hz), number of protons, and assignment. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. UV spectra (in CH_3CN) were taken with Shimadzu UV-160 spectrometer. ^{13}C NMR spectra were recorded with a Bruker 75.48 MHz machine. 3,4-Dihydropyrimidin-2(*1H*)-ones (**1a-j**) were prepared according to a known procedure [32]. Preparative layer chromatography (PLC) was carried out on 20 × 20 cm^2 plates, coated with 1mm layer of Merck silica gel PF_{254}, prepared by applying the silica as slurry and drying in air.

General Procedure for Oxidation of 3,4-Dihydropyrimidin-2(*1H*)-ones

Potassium peroxydisulfate (123 mg, 0.46 mmol) was added to a solution of dihydropyrimidinones (0.46 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 was observed. Solvent was evaporated and the crude reaction mixture was purified by plate chromatography (PLC; *n*-hexane/ethyl acetate; 2:1), then recrystallized from *n*-hexane/ethyl acetate.

Ethyl 6-methyl-4-phenylpyrimidin-2(*1H*)-one-5-carboxylate (2a). Yellow solid. m.p.: 130-132 °C. (Lit. [13] 130-131 °C). IR: ν 3300-2600, 1730, 1650, 1600, 1460, 1280 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 314.8 (3.70), 289.6 (3.67), 244 nm (4.15). ^{1}H NMR ($CDCl_3$): δ 0.68 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 2.45 (s, 3H, 6-CH_3), 3.80 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 7.31 (d, *J* = 7.5 Hz, 1H, *m*-H), 7.36 (t, *J* = 6.9 Hz, 1H, *m*-H), 7.45 (d, *J* = 6.9 Hz, 2H, *o*-H), 7.47 (t, *J* = 6.3 Hz, 1H, *p*-H), 11.71 (s, 1H, NH). EI-MS: m/z (%): 258 (M^+, 5), 257 ((M^+-H, 3), 230 (M^+-CH_2=CH_2, 3), 229 (M^+-C_2H_5, 18), 213 (M^+-C_2H_5O, 11), 185 (M^+-$CO_2C_2H_5$, 15), 77 ($C_6H_5^+$, 100).

Ethyl 6-methyl-4-(4′-methylphenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2b). Yellow solid. m.p.: 138-140 °C. IR: ν 3200, 1720, 1700, 1645, 1520, 1440, 1220 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 328 (3.90), 276.0 (sh, 4.32), 249.6 nm (sh, 4.40). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 2.36 (s, 3H, 6-CH_3), 2.54 (s, 3H, 4'-CH_3), 4.05 (q, *J* = 6.6 Hz, 2H, CH_2CH_3), 7.18-7.20 (d, *J* = 6.9 Hz, 2H, *m*-H), 7.45-7.47 (d, *J* = 6.5 Hz, 2H, *o*-H), 12.25 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.77, 19.25, 21.33, 61.28, 109.58, 128.03, 129.19, 135.43, 140.45, 156.90, 162.56, 166.77, 170.15. EI-MS: m/z (%): 272 (M^+, 86), 271 (M^+-H, 50), 257 (M^+-CH_3, 6), 244 (M^+-CH_2=CH_2, 57), 243 (M^+-C_2H_5, 100), 227 (M^+-C_2H_5O, 94), 199 (M^+-$CO_2C_2H_5$, 76), 91 ($C_6H_4CH_3^+$, 45).

Ethyl 6-methyl-4-(4′-methoxyphenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2c). Yellow solid. m.p.: 150-152 °C. (Lit. [16] 172-173 °C). IR: ν 1715, 1665, 1595, 1435, 1270, 1260 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 302.2 (3.88), 238.8 nm (3.84). ^{1}H NMR ($CDCl_3$): δ 0.9 (t, *J* = 6.5 Hz, 3H, CH_2CH_3), 2.30 (s, 3H, 6-CH_3), 3.81 (s, 3H, 4'-OCH_3), 3.93 (q, *J* = 6.8 Hz, 2H, CH_2CH_3), 6.8 (m, 2H, *m*- H), 7.2 (t, *J* = 8.4 Hz, 2H, *o*-H), 9.7 (s, 1H, NH). EI-MS: m/z (%): 288 (M^+, 100), 287 (M^+-H, 68), 260 (M^+-CH_2=CH_2, 34), 259 (M^+-C_2H_5, 99.7), 243 (M^+-C_2H_5O, 86), 215 (M^+-$CO_2C_2H_5$, 73), 200 (M^+-$CO_2C_2H_5$, -CH_3, 16), 134 (4-$CH_3OC_6H_4$-C=NH^+, 84).

Ethyl 6-methyl-4-(3′-methoxyphenyl)pyrimidin-2

(*1H*)-one-5-carboxylate (2d). Yellow solid. m.p.: 102-105 °C. IR: ν 1720, 1650, 1590, 1480, 1250, 1220 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 293 (3.83), 241 nm (3.81). ^1H NMR ($CDCl_3$): δ 0.98 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.61 (s, 3H, 6-CH_3), 3.85 (s, 3H, 3'-OCH_3), 4.08 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 7.03 (dd, *J* = 8.11, 2.53 Hz, 1H, 4'-H), 7.13 (d, *J* = 7.53 Hz, 1H, 6'-H), 7.19 (brd s, 1H, 2'-H), 7.32 (dd, *J* = 7.87 Hz, 6.48 Hz, 1H, 5'-H), 13.63 (brd s, 1H, 8NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.72, 55.69, 61.33, 109.60, 113.11, 116.39, 120.20, 129.90, 155.86, 159.46, 166.34. EI-MS: m/z (%): 288 (M^+, 32), 287 (M^+-H, 19), 260 (M^+-CH_2=CH_2, 86), 259 (M^+-C_2H_5, 47), 243 (M^+-C_2H_5O, 37), 215 (M^+-$CO_2C_2H_5$, 51), 200 (M^+-$CO_2C_2H_5$, -CH_3, 18), 169 (M^+-$CO_2C_2H_5$, -CH_3, -OCH_3, 39), 134 (3-$CH_3OC_6H_4$-C=NH^+, 80), 69 (100).

Ethyl 6-methyl-4-(2′-methoxyphenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2e). Yellow solid. m.p.: 122-124 °C. IR: ν 1720, 1650, 1590, 1480, 1280, 1260 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 305.4, (3.88), 239.4 nm (3.98). ^1H NMR ($CDCl_3$): δ 0.92 (t, *J* = 7.05 Hz, 3H, CH_2CH_3), 2.62 (s, 3H, 6-CH_3), 3.74 (s, 3H, 2'-OCH_3), 4.00 (q, *J* = 6.9 Hz, 2H, CH_2CH_3), 6.86 (d, *J* = 8.23 Hz, 1H, 3'-H), 7.02 (brd t, 1H, 5'-H), 7.39 (brd t, 1H, 4'-H), 7.50 (d, *J* = 6.61 Hz, 1H, 6'-H), 12.50 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.68, 55.58, 60.63, 110.45, 110.94, 120.74, 130.04, 131.57, 155.92, 156.40, 165.39. EI-MS: m/z (%): 288 (M^+, 12), 287, 287 (M^+-H, 2), 259 (M^+-C_2H_5, 8), 243 (M^+-C_2H_5O, 17), 215 (M^+-$CO_2C_2H_5$, 100), 200 (M^+-$CO_2C_2H_5$, -CH_3, 8), 168 (M^+-$CO_2C_2H_5$, -CH_4, -OCH_3, 19), 134 (2-$CH_3OC_6H_4$-C=NH^+, 16).

Ethyl 6-methyl-4-(3′-chlorophenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2f). Yellow solid. Mp: 86-90 °C. IR: ν 3300, 1710, 1690, 1640, 1440, 1220 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 304.5 (3.58), 239.5 nm (3.99). ^1H NMR ($CDCl_3$): δ 1.00 (t, *J* = 6.82 Hz, 3H, CH_2CH_3), 2.61 (s, 3H, 6-CH_3), 4.09 (q, *J* = 6.87 Hz, 2H, CH_2CH_3), 7.36 (m, 1H, 6'-H), 7.44 (brd d, 2H, 4'-H and 5'-H), 7.6 (brd s, 1H, 2'-H), 13.05 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.51, 60.84, 109.42, 127.41, 129.34, 129.68, 130.59, 130.73, 164.66. EI-MS: m/z (%): 294 (M^{+37}Cl, 12), 293 (M^{+37}Cl -H, 11), 292 (M^{+35}Cl, 35), 291 (M^{+35}Cl -H, 14), 266 (M^{+37}Cl-CH_2=CH_2, 7), 265 (M^{+37}Cl-C_2H_5, 35), 264 (M^{+35}Cl-CH_2=CH_2, 15), 263 (M^{+35}Cl -C_2H_5, 100), 249 (M^+ ^{37}Cl-C_2H_5O, 23), 247 (M^+-C_2H_5O, 64), 221 (M^{+37}Cl -$CO_2C_2H_5$, 16), 219 (M^{+35}Cl-$CO_2C_2H_5$, 34), 140 (3-$^{37}ClC_6H_4$-C=NH^+, 38), 138 (3-$^{35}ClC_6H_4$-C=NH^+, 73), 113 ($C_6H_4{}^{37}Cl^+$, 15), 111 ($C_6H_4{}^{35}Cl^+$, 39).

Ethyl 6-methyl-4-(2′-chlorophenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2g). Yellow solid. m.p.: 181-184 °C. (Lit. (16) 164-166 °C). IR: ν 1705, 1655, 1590, 1420, 1280 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 305.4 (3.79), 240 nm (3.94). ^1H NMR ($CDCl_3$): δ 0.88 (t, *J* = 7.11 Hz, 3H, CH_2CH_3), 2.73 (s, 3H, 6-CH_3), 4.00 (q, *J* = 7.11 Hz, 2H, CH_2CH_3), 7.35 (m_c, 4H, aromatic H), 13.76 (brd s, 1H, NH). EI-MS: m/z (%): 257 (M^+ -^{37}Cl, 73), 247 (M^{+35}Cl -C_2H_5O, 10), 229 (M^+-^{37}Cl, -CH_2=CH_2, 100), 212 (M^+-^{37}Cl, -CH_3CH_2O, 50), 140 (M^+-$^{37}ClC_6H_4$-C=NH, 14), 138 (2-$^{35}ClC_6H_4$-C=NH^+, 27), 113 ($C_6H_4{}^{37}Cl^+$, 5), 111 ($C_6H_4{}^{35}Cl^+$, 7).

Ethyl 6-methyl-4-(2′-bromophenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2h). Yellow solid. m.p.: 179-180 °C. IR: ν 3400, 1710, 1660, 1595, 1420, 1280 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 303.5 (3.73), 237.5 nm (3.85). ^1H NMR ($CDCl_3$): δ 0.87 (t, *J* = 6.82 Hz, 3H, CH_2CH_3), 2.74 (s, 3H, 6-CH_3), 4.02 (q, *J* = 6.36 Hz, 2H, CH_2CH_3), 7.35 (m_c, 2H, 4'-H and 5'-H), 7.59 (brd d, *J* = 7.53 Hz, 2H, 3',6'-H), 11.97 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.49, 60.82, 109.23, 120.08, 127.81, 129.52, 130.70, 132.42, 155.42, 164.52. EI-MS: *m/z* (%): 308 (M^{+81}Br -C_2H_6, 4), 306(M^{+79}Br -C_2H_6, 4), 293 (M^{+81}Br -C_2H_5O, 29), 291 (M^{+79}Br -C_2H_5O, 31), 263 (M^{+79}Br -$CO_2C_2H_5$, 5), 257 (M^+-Br, 95), 229 (M^+ -Br, -C_2H_4, 100), 184 ($^{81}BrC_6H_4C$=NH^+, 76), 182 ($^{79}BrC_6H_4C$=NH^+, 28), 157 ($^{81}BrC_6H_4^+$, 29), 155 ($^{79}BrC_6H_4^+$, 33), 76 ($C_6H_4^+$, 71).

Ethyl 6-methyl-4-(4′-nitrophenyl)pyrimidin-2(*1H*)-one-5-carboxylate (2i). Yellow solid. m.p.: 154-156 °C. IR: ν 1710, 1650, 1590, 1420, 1200 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 336.0 (sh, 3.99), 300.0 (sh, 4.30), 252.0 nm (4.53). ^1H NMR ($CDCl_3$): δ 1.03 (t, *J* = 7.11 Hz, 3H, CH_2CH_3), 2.62 (s, 3H, 6-CH_3), 4.10 (q, *J* = 7.13 Hz, 2H, CH_2CH_3), 7.49 (d, *J* = 8.13 Hz, 2H, 2'-H and 6'-H), 7.59 (d, *J* = 8.13 Hz, 2H, 3'-H and 5'-H), 13.60 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.62, 18.97, 61.37, 108.93, 123.84, 129.33, 145.24, 148.49, 155.46, 165.47; EI-MS: *m/z* (%): 303(M^+, 27), 302 (M^+-H, 10), 288 (M^+-CH_3, 2), 286 (M^+-OH, 5), 274 (M^+-NO, 100), 257 (M^+-NO_2, 8), 256 (M^+-HNO_2, 8), 149 (4-$NO_2C_6H_4C$=NH^+, 34), 122 ($NO_2C_6H_4^+$, 14), 76 ($C_6H_4^+$, 47).

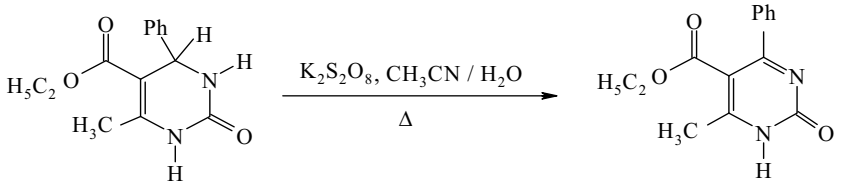
Ethyl 6-methyl-4-(2′-phenylethyl)pyrimidin-2(*1H*)-one-5-carboxylate (2j). Yellow solid. m.p.: 142-143 °C. IR: ν 3300, 1710, 1650, 1595, 1540, 1250, 1100 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) 296.5 (3.32), 241.5 nm (3.63). ^1H NMR ($CDCl_3$): δ 1.37 (t, *J* = 7.05 Hz, 3H, CH_2CH_3), 2.55 (s, 3H, 6-CH_3), 3.08 (brd s, 2H, 1'-CH_2), 3.12 (brd s, 2H, 2'-CH_2), 4.35 (q, *J* = 7.09 Hz, 2H, CH_2CH_3), 7.25 (m_c, 5H, Ph), 13.53 (brd s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d6): δ = 13.62, 18.97, 61.37, 108.93, 123.84, 129.33, 145.24, 148.49, 155.46, 165.47. EI-MS: m/z (%): 286 (M^+, 10), 285 (M^+-H, 4), 258 (M^+-CH_2=CH_2, 4), 257 (M^+-C_2H_5, 22), 241 (M^+-C_2H_5O, 5), 213 (M^+-$CO_2C_2H_5$, 20), 91 ($PhCH_2^+$, 100), 77 ($C_6H_5^+$, 22).

RESULTS AND DISSCUTION

Since the nature of solvent influences the rate of reaction, oxidation of 4-phenyl substituted dihydro-pyrimidinone **1a** as a model substrate was performed in absolute ethanol, dry acetonitrile and in aqueous ethanol or aqueous actonitrile (different ratios) under reflux condition (Scheme 1). According to the data presented in Table 1, a mixture of CH_3CN/H_2O (10:2) was chosen as the best solvent mixture for this purpose. According to the data presented in Table 1 we found out that:

1. The presence of water was necessary for the reaction since the reaction of **1a** in dry acetonitrile did not result in the occurrence of any reaction.

2. The optimized ratio of $K_2S_2O_8$/DHPM (1:1) indicated that the removal of two hydrogens was dependent on the presence of equimolar amounts of the oxidant and DHPM since the reaction was not completed by the ratio of 0.5:1 of oxidant/DHPM. It is noteworthy that with an increase of



1a **2a**

Scheme 1

Table 1. Oxidation of Ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(*1H*)-one-5-carboxylate (**1a**) to Ethyl 6-methyl-4-phenylpyrimidin-2(*1H*)-one-5-carboxylate (**2a**) by $K_2S_2O_8$ under Reflux Condition in Various Solvent Mixtures

Ratio $K_2S_2O_8$/(**1a**)	Solvent	Time (min)[a]	(**2a**) Yield (%)
0.5:1	CH_3CN/H_2O (10:1)	120	60[b]
1:1	CH_3CN/H_2O (10:1)	90	85[b]
2:1	CH_3CN/H_2O (10:1)	80	85[b]
1:1	CH_3CN/H_2O (10:2)	80	100[c]
1:1	CH_3CN/H_2O (10:3)	80	100[c]
1:1	CH_3CN/H_2O (9:2)	80	100[c]
1:1	Dry acetonitrile	90	No reaction
1:1	Absolute ethanol	90	<5[c]
1:1	C_2H_5OH/H_2O (10:1)	90	<10[c]
1:1	CH_3CN/H_2O (10:1)	150[d]	No reaction

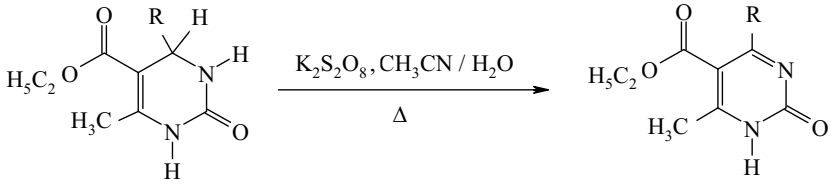
[a]The times are given after maximum progression of reaction. [b]Isolated yield. [c]Estimated according to TLC observation. [d]The reaction is carried out at room temperature.

oxidant/DHPM to 2:1 the time of oxidation was shortened, but only **2a** was formed and further oxidation or dealkylation of 6-CH_3 was not observed [16,17].

3. The performance of heating was necessary for the reaction due to failure of reaction when carried out at room temperature.

In an optimized reaction condition various dihydropyrimidinones (**1a-j**) were subjected to the oxidation reaction in the presence of potassium peroxydisulfate (PPS) in CH_3CN/H_2O (10:2) under reflux condition as shown in Scheme 2. The results are summarized in Table 2.

The results presented in Table 2 indicate that various DHPMs were converted to their corresponding pyrimidin-2(*1H*)-ones by using $K_2S_2O_8$ as oxidant in good to excellent yields. The advantage of this method is that it is mild, tolerates several substituted groups on 4-position and the use of lower molar ratio of DHPMs:oxidant (1:1) in our reactions compared with DHPMs/CAN (1:5) in AcOH (55-68% of yield of dealkylation-oxidation products under formation dihydropyrimidin-2,6-(*1H*)-diones after 1-2.5 h) [16] or with DHPMs/CAN/$NaHCO_3$ (1:3:5) in acetone (69-85% of yield of oxidation products under formation



1a-j **2a-j**

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: 3-ClC_6H_4, **g**: 2-ClC_6H_4, **h**: 2-BrC_6H_4, **i**: 3-$NO_2C_6H_4$, **j**: $PhCH_2CH_2$

Scheme 2

Table 2. Oxidation of DHPMs by PPS in Aqueous Acetonitrile

Compound	R	CH_3CN/H_2O (10:2)		CH_3CN/H_2O (10:1)	
		Time (min)[a]	Yield (%)[b]	Time (min)[c]	Yield (%)[d]
1a	C_6H_5-	80	93	90	85 (4)
1b	4-$CH_3C_6H_4$-	60	90	90	70 (15)
1c	4-$CH_3OC_6H_4$-	15	92	15	83 (5)
1d	3-$CH_3OC_6H_4$-	40	94	50	80 (10)
1e	2-$CH_3OC_6H_4$-	25	96	25	85 (7)
1f	3-ClC_6H_4-	15	94	25	80 (10)
1g	2-ClC_6H_4-	90	88	90	60 (23)
1h	2-BrC_6H_4-	90	94	110	80 (10)
1i	4-$NO_2C_6H_4$-	40	65[e]	90	60 (25)
1j	$PhCH_2CH_2$-	35	94	40	75 (15)

[a]The times are given after total disappearance of DHPMs (100% conversion according to TLC observation). [b]Isolated yields. [c]The times are given after maximum progression of reaction. [d]The values are given in parentheses refer to unconsumed starting material. [e]The reaction was not completed (20% of **1j** has been recovered).

dihydropyrimidin-2(*1H*)-ones after 0.5-3 h) [16], and with DHPMs/$Co(NO_3)_2.6H_2O$/$K_2S_2O_8$ (1:5:2.5) (69-81% of yield of demethylated pyrimidin-2(*1H*)-ones after 3-8 h) [17].

IR, UV, ^{1}H NMR and MS data gave useful information on the structural assignment of the products **2a-j**. A comparison of the IR spectra of the product **2a-j** with those of **1a-j** (Table 3) showed a decrease of the intensity of the NH vibration and a little shift to lower frequency, the small shift of the CO of the ester group (5-$CO_2C_2H_5$) to higher frequency, and the shift of 2-CO and C_5=C_6 double bond to lower frequency. These observations could be explained as follows:

I. The CO function of the 5-$CO_2C_2H_5$ group has extended conjugation with the lone pair of 1-NH. Due to oxidation of 3-NH-4-CH bond and conversion to the imino moiety, 1-NH is possibly more conjugated with the new formed planar imino-diene system than with freely rotating CO function of the ester group. Therefore, a shift of the CO group to higher frequency should be observed.

II. The 2-CO group in **1a-j** has cross-conjugation with both nitrogen lone pairs of 1-NH and 3-NH. Due to oxidation of 3-NH-4-CH bond and conversion to the imino moiety, the 2-CO group is now conjugated only with 1-NH. This leads to a shift of the 2-CO group to lower frequency.

III. The C_5=C_6 double bond of dihydropyrimidinone ring as a part of enamine moiety is conjugated with 1-NH. On the other hand, this double bond can also conjugate with the CO group of the 5-$CO_2C_2H_5$ moiety (α,ß-unsaturated carbonyl group) in the case of planarity with the CO group in both starting materials and products. Due to oxidation of 3-NH-4-CH bond and conversion to the imino moiety, the C_5=C_6 double bond as a part of the imino-diene system is more involved in this rigid system than conjugation with 5-CO group. Therefore, a shift of the C_5=C_6 double bond to lower frequency should be expected.

Due to the formation of the imino-diene system which is also cross-conjugated with 4-aryl substituent, the bathochromic shift of the UV spectra of **2a-j** was observed. These data are presented and compared in Table 4.

A comparison of the ^{1}H NMR spectra showed the shift of 1-NH absorption of **1a-j** to lower field, the lack of 3-NH and 4-H resonance in the ^{1}H NMR spectra of **2a-j,** and the shift of 6-CH_3 resonance to lower field due to attachment of this group to the imino-diene system.

According to the results summarized in Tables 1 and 2, especially the failure of the reaction when carried out at room temperature, we propose the following mechanism for the dehydrogenation of dihydropyrimidinones by potassium peroxydisulfate (Scheme 3).

Thermal decomposition of the weakest O-O bond in potassium peroxydisulfate yields the sulfate radicals (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 dihydropyrimidonyl radical intermediate and water (path 3). This step is followed by the loss of another hydrogen atom to generate pyrimidinone product (path 4).

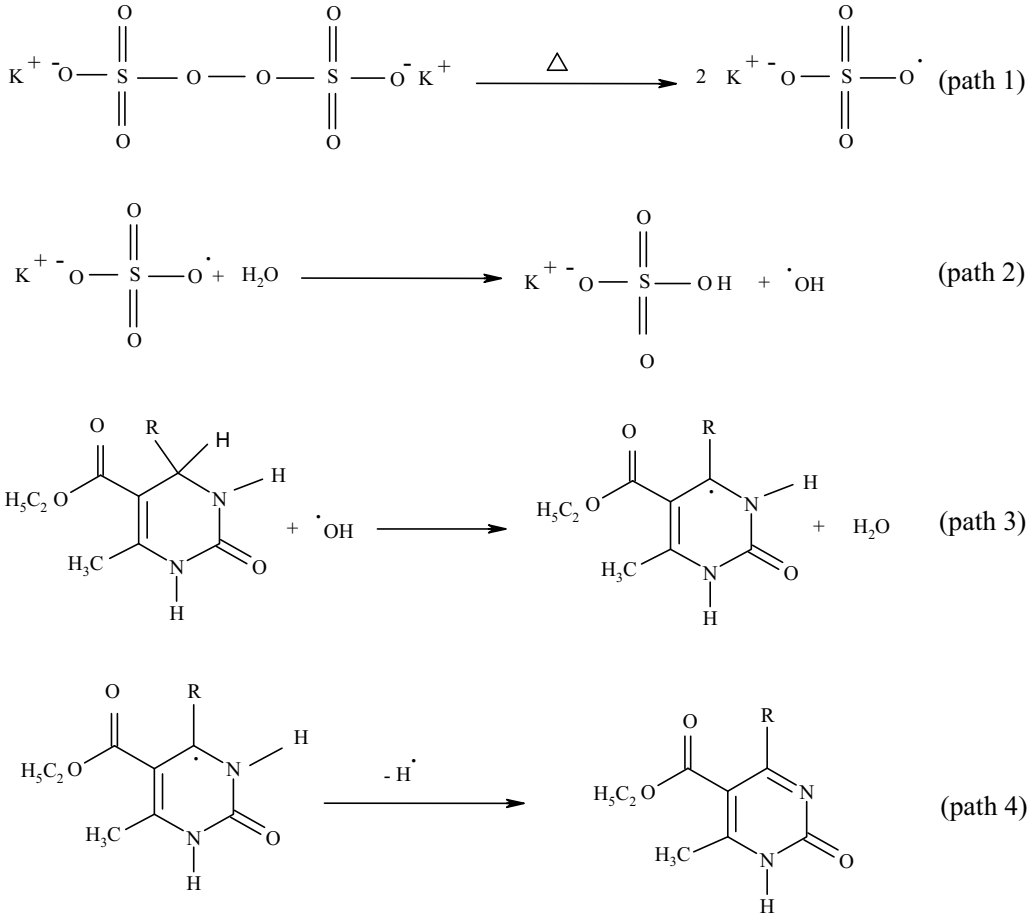
The following assertions support our argument regarding

Table 3. Comparison of the IR Spectra (ν, cm^{-1}) of **1a-j** with those of **2a-j**

1	$CO_2C_2H_5$	2-CO	C=C	**2**	$CO_2C_2H_5$	2-CO	C=C
a	1720	1700	1645	**a**	1730	1650	1600
b	1705	1700	1635	**b**	1720	1700	1645
c	1725	1700	1650	**c**	1715	1665	1559
d	1700	1645	1595	**d**	1720	1650	1590
e	1720	1695	1630	**e**	1720	1650	1595
f	1710	1690	1650	**f**	1710	1690	1640
g	1705	1690	1635	**g**	1705	1655	1590
h	1705	1690	1635	**h**	1710	1660	1595
i	1725	1700	1640	**i**	1710	1650	1590
j	1720	1700	1650	**j**	1710	1650	1595

Table 4. Comparison of the UV-Absorption (λ_{max}, nm) of the Starting Materials **1a-j** with those of the Products **2a-j** in Acetonitrile Solution

1	λ_{max} (log ε)	**2**	λ_{max} (log ε)
a	278.4 (4.01), 228.6 (3.91)	**a**	314.8 (3.70), 289.6 (3.67), 244 (4.15)
b	278.4 (4.12), 226.4 (4.07)	**b**	328 (3.90), 276.0 (sh, 4.32), 249.6 (sh, 4.40)
c	274 (3.47), 230 (3.75)	**c**	302.2 (3.88), 238.8 (3.84)
d	276.5 (3.52), 227 (3.36)	**d**	293 (3.83), 241 (3.81)
e	276 (3.58), 225 (3.47)	**e**	305.4 (3.88), 239.4 (3.98)
f	278.5 (3.23), 229 (3.07)	**f**	304.5 (3.58), 239.5 (3.99)
g	272.0 (3.92), 232.8 (3.85)	**g**	305.4 (3.79), 240 (3.94)
h	275.5 (3.87), 232 (3.81)	**h**	303.5 (3.73), 237.5 (3.85)
i	264 (3.31), 225 (3.17)	**i**	336.0 (sh, 3.99), 300 (sh, 4.30), 252.0 (4.53)
j	277 (3.24), 223 (2.77)	**j**	296.5 (3.32), 241.5 (3.63)



Scheme 3. Proposed mechanism for dehydrogenation of DHPMs by $K_2S_2O_8$

path 3 which is the rate determining step and the involvement of hydroxyl radical in this step.

A. The presence of enough water is necessary for the reaction, since the reaction would not take place in dry acetonitrile (due to insolubility of PPS in dry acetonitrile even under reflux condition), and when the reactions were carried out in CH_3CN/H_2O (10:1), they were not complete and unconsumed **1a-j** were isolated (Table 2).

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), there are enough hydrogen sources (C_2H_5OH and H_2O) to donate hydrogen to sulfate radical anion to form of hydroxyl and ethoxy radicals. The reason for inefficient reaction in C_2H_5OH/H_2O (10:2) may be due either to the competition between hydroxyl radical and 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 rather than the less covalent N-H bond is more likely; therefore, path 3 is the rate determining step.

D. The stability of dihydropyrimidinoyl radical intermediate which is also simultaneously a benzylic radical 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**) as electron-donating groups should stabilize the formation of the benzylic radical intermediate rather than the 4-nitro group (**1i**) as electron-withdrawing group. These data show also that the electron-donating groups such as methyl **1b** or methoxy groups **1c**, **1d** and **1e** decrease 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.

CONCLUSIONS

In brief, potassium peroxydisulfate was employed and shown to be an efficient oxidant for the synthesis of pyrimidin-2(*1H*)-ones. In addition, easy handling, non-toxicity of the oxidant, short reaction times, high product yields and easy work-up are main advantages of the new method Employed in this study.

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REFERENCES

[1] N. Nakamichi, Y. Kawashita, M. Hayashi, Org. Lett. 4 (2002) 3955.

[2] N. Nakamichi, Y. Kawashita M. Hayashi, Synthesis (2004) 1015.

[3] D.J. Brown, The pyrimidine, Interscience New York, N. Y., 1994.

[4] K.C. Majumdar, U. Das, N.K. Jana, J. Org. Chem. 63 (1998) 3550.

[5] R.C. Rizzo, J. Tirado-Rives, W.L. Jorgensen, J. Med. Chem. 44 (2001) 145.

[6] W. Zhou, G. Gumina, Y. Chong, J. Wang, R.F. Schinazi, C.K. Chu, J. Med. Chem. 47 (2004) 3399.

[7] K. Itami, D. Yamazaki, J. Yoshida, J. Am. Chem. Soc. 126 (2004) 15396.

[8] C.O. Kappe, Acc. Chem. Res. 33 (2000) 360 and references cited therein.

[9] C.P. Sar, O.H. Hankovszky, G. Jerkovich, I. Pallagi, K. Hideg, ACH-Models in Chemistry 131 (1994) 363.

[10] V.A. Salvinskaya, G. Duburs, D. Sile, D. Kreile, E.L. Khanina, USSR Patent (1978) 632695; Chem. Abstr. 90 (1979) 121631y.

[11] E.L. Khanina, G.Y. Dubur, Khim. Geterotsik. Soedin. (1982) 535.

[12] H.R. Memarian, M. Abdoli-Senejani, Döpp, D.J. Chin. Chem. Soc. 54 (2007) 131 and references cited therein.

[13] J.J. Vanden Eynde, N. Audiart V. Canonne, S. Michel, Y. Van Haverbeke, C.O. Kappe, Heterocycles

45 (1997) 1967.
[14] J. Lu, Y. Bai, Z. Wany, B. Yabg, W. Li, Synth. Commun. 31 (2001) 2625.
[15] S.H. Mashraqui, M. Kamik, Synthesis (1998) 713.
[16] P. Shanmugam, P.T. Perumal, Tetrahedron 62 (2006) 9726.
[17] P. Shanmugam, P.T. Perumal, Tetrahedron 63 (2007) 666.
[18] C.A. Synder, M.A. Thorn, J.E. Klijanowicz, P.L. Southwick, J. Heterocycl. Chem. 19 (1982) 603.
[19] R.S. Varma, D. Kumar, J. Chem. Soc. Perkin Trans. 1 (1999) 1755.
[20] D.A. Skoog, J.J. Leary, In Principles of Instrumental Analysis, Horcourt Brace College Publishers, 1992, p. A-60.
[21] D.A. House, Chem. Rev. 62 (1962) 185.
[22] R.C. Moschel, E.J. Behrman, J. Org. Chem. 39 (1974) 1983.
[23] A. Clerici, O. Porta, J. Chem. Soc. Perkin Trans. 2 (1980) 1234.
[24] W.E. Fristad, J.R. Peterson, Tetrahedron Lett. 24 (1983) 4547.
[25] G.I. Nikishin, E.I. Troyansky, M.I. Lazareva, Tetrahedron Lett. 25 (1984) 4987.
[26] T. Itahara, Y. Fujii, M. Tada, J. Org. Chem. 53 (1988) 3421 and references cited therein.
[27] S. Yamasaki, Chem. Lett. (1992) 323 and references cited therein.
[28] C. Srinivasan, P. Kuthalingam, N. Arumugam, Can. J. Chem. 56 (1978) 3043.
[29] H.R. Memarian, I. Mohammadpoor-Baltork, M.M. Sadeghi, Z.S. Samani, Indian J. Chem. 40B (2001) 727.
[30] S.-C. Hsu, T.-M. Don, W.-Y. Chiu, Polymer Degradation and Stability 75 (2002) 73.
[31] Y.S. Choi, H.T. Ham, I. Chung, J. Polymer. 44 (2003) 8147.
[32] M.M. Khodaei, A.R. Khosropour, M. Beygzadeh, Synth. Commun. 34 (2004) 1551.