Ultrasonics Sonochemistry 15 (2008) 1015–1018

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultsonch

Sono-thermal oxidation of dihydropyrimidinones

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ARTICLE INFO

Article history:
Received 6 January 2008
Received in revised form 23 February 2008
Accepted 28 February 2008
Available online 18 March 2008

PACS:
37.54.De

Keywords:
Dihydropyrimidinones
Potassium peroxydisulfate
Pyrimidinones
Sono-thermal
Ultrasound

ABSTRACT

Combination of ultrasound and heat has been used for the oxidation of some ethyl 3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylates to their corresponding ethyl pyrimidin-2(1*H*)-one-5-carboxylates by using potassium peroxydisulfate in aqueous acetonitrile. An ultrasonic probe of 24 kHz frequency has been used for this study. Whereas the use of ultrasound increases the rate of reactions compared with reactions at reflux conditions, the nature of 4-substituent on the dihydropyrimidinone ring affects also the rate of reaction.

1. Introduction

The development of efficient methods for the oxidation of various organic compounds is focuses of increasing interest [1–5]. 3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are an important classes of compounds, which possess widespread pharmacological properties [6,7] such as antiviral, antitumor, antibacterial activities. Oxidations of DHPMs are important because of formation of core pyrimidin-2(1*H*)-ones, which are important for the pharmacological activity such as pyrimidine MKC-442, one of the most important classes of drugs for the treatment of the HIV virus [8]. In contrast to facile aromatization of 1,4-dihydropyridines by various oxidative methods [9] and failure of aromatization of dihydropyrimidinone ring, oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones to their corresponding pyrimidin-2(1*H*)-ones requires hard reaction conditions and the yields are mostly low. For example, variety of mild or powerful oxidants such as MnO_2 [9], $FeCl_3$ [10], $RuCl_3/O_2$ in AcOH [11], PCC [9], chloranil [9], $KMnO_4$/clay [9], DDQ [9], $NaNO_2$/AcOH [9], CAN/AcOH [12], $Co(NO_3)_2 \cdot 6H_2O/K_2S_2O_8$ [13] and dehydrogenating agents such as Pd/C [9], Br_2 [14] and sulfur [15] have been used for this purpose. But these compounds are highly stable toward the above mentioned oxidizing reagents.

Ultrasound has increasingly been used in organic synthesis in the last three decades both in cavitations and per-cavitations regimes [16–21]. The success and advantages of sonochemical reactions include higher yields, shorter reaction times and milder reaction conditions when compared with classical methods [22–25]. 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 effects 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]. All theses results indicated of an increase of the rate of reaction compared with reaction by applying of only the UV irradiation (in the absence of ultrasound irradiation). Price and Clifton have reported on sonochemical acceleration of potassium peroxydisulfate decomposition [28]. Their results indicated that an increase of temperature up to 65 °C during sonication (sono-thermal) causes the enhancement of the rate constant of decomposition compared with the rate constant in the absence of sonic waves (thermal).

Peroxydisulfate ion is known as one of the strongest oxidizing agents in aqueous and protic organic solvents with redox potential about −2.01 V [29,30] and the mixtures of metal salts with potassium peroxydisulfate are commonly used as radical sources in aqueous solution [31]. The mechanism of the thermal decomposition of peroxydisulfate ion is believed to form the sulfate radical ion which can abstract hydrogen from water to produce hydroxyl radical [31], which causes dehydrogenation of compound to be oxidized. The oxidative application of peroxydisulfate ion in organic synthesis has been widely investigated [32–37].

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doi:10.1016/j.ultsonch.2008.02.014

Now we wish to report on the effect of sonic waves on thermal oxidation of various 3,4-dihydropyrimidin-2(1*H*)-ones by using $K_2S_2O_8$ as oxidant.

2. Experimental

2.1. Materials

3,4-Dihydropyrimidin-2(1*H*)-ones (**1a–j**) have been prepared according to the known procedure [38]. Acetonitrile was purchased from Merck and distilled before use.

2.2. 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 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 were taken with Shimadzu UV-160 spectrometer.

2.3. General procedure for sono-thermal oxidation of 3,4-dihydropyrimidin-2(1H)-ones

Potassium peroxydisulfate (61.5 mg, 0.23 mmol) was added to a solution of dihydropyrimidinones (0.23 mmol) in 12 ml acetonitrile and water (10:2). The reaction mixture was immersed in at 70 °C preheated water-bath by simultaneous ultrasound irradiation for the times given in Table 1 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 as following: in the beginning of reaction, 3 min irradiation followed by 2 min relaxation to prevent the splashing of solvent, the next steps 2 min irradiation and 2 min relaxation 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.

2.3.1. Ethyl 6-methyl-4-phenylpyrimidin-2(1H)-one-5-carboxylate (**2a**)

Yellow solid. Mp: 130–132 °C. Ref. Mp [9]: 130–131 °C IR: *ν* 3300–2600, 1730, 1650, 1600, 1460, 1280 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) 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).

Table 1
Oxidation of DHPMs by PPS in aqueous acetonitrile under sono-thermal condition

Compound	R	Time (min)[a]	Yield (%)[b]
1a	C_6H_5–	11	92
1b	4-CH_3–C_6H_4	7	90
1c	4-CH_3O–C_6H_4	7	92
1d	3-CH_3O–C_6H_4	5	90
1e	2-CH_3O–C_6H_4	6	95
1f	3-Cl–C_6H_4	10	90
1g	2-Cl–C_6H_4	5	90
1h	2-Br–C_6H_4	6	95
1i	4-NO_2–C_6H_4	27	93
1j	$PhCH_2CH_2$–	5	90

[a] The times refer to total disappearance of DHPMs.
[b] Isolated yield.

2.3.2. Ethyl 6-methyl-4-(4′-methylphenyl)pyrimidin-2(1H)-one-5-carboxylate (**2b**)

Yellow solid. Mp: 138–140 °C. IR: *ν* 3200, 1720, 1700, 1645, 1520, 1440, 1220 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) 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). 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).

2.3.3. Ethyl 6-methyl-4-(4′-methoxyphenyl)pyrimidin-2(1H)-one-5-carboxylate (**2c**)

Yellow solid. Mp: 150–152 °C. Ref. Mp [12]: 172–173 °C. IR: *ν* 1715, 1665, 1595, 1435, 1270, 1260 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) 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).

2.3.4. Ethyl 6-methyl-4-(3′-methoxyphenyl)pyrimidin-2(1H)-one-5-carboxylate (**2d**)

Yellow solid. Mp: 102–105 °C. IR: *ν* 1720, 1650, 1590, 1480, 1250, 1220 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) 293 (3.83), 241 nm (3.81). ^{1}H 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, NH). 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).

2.3.5. Ethyl 6-methyl-4-(2′-methoxyphenyl)pyrimidin-2(1H)-one-5-carboxylate (**2e**)

Yellow solid. Mp: 122–124 °C. IR: *ν* 1720, 1650, 1590, 1480, 1280, 1260 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) 305.4, (3.88), 239.4 nm (3.98). ^{1}H 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* = 6.90 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). 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).

2.3.6. 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} ($\log\varepsilon$) 304.5 (3.58), 239.5 nm (3.99). ^{1}H 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). EI-