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ORIGINAL PAPER

Light-induced dehydrogenation of 3,4-dihydropyrimidin-2(*1H*)-ones

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Abstract UV light irradiation of Biginelli 3,4-dihydropyrimidin-2(*1H*)-ones in chloroform in an argon atmosphere leads to dehydrogenation of these compounds to their corresponding pyrimidin-2(*1H*)-ones in excellent yields. Irradiation in the same solvent under an oxygen atmosphere generates, in addition, various hitherto unidentified products. A light-induced electron transfer from the substrate to the solvent is proposed as the initial event, supported by the detection of dichloromethane and hydrogen chloride in the photolysate.

Keywords Dihydropyrimidinones · Electron-transfer · Heterocycles · Pyrimidinones · Photochemistry

Introduction

Dihydropyrimidinone derivatives are of considerable interest in industry as well as in pharmaceutical research because of their biological activities as antihypertensive [1] and anti-cancer agents [2], as calcium channel blockers [3], as antibacterial agents, and also as anti-staphylococcal antibiotics [4]. In particular, batzelladine alkaloids 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 development of various thermal or photochemical oxidation methods for conversion of different organic compounds, especially with pharmaceutical properties, to their oxidized form is an important way to study the stability of these compounds towards oxidizing agents and also to investigate their photochemical behavior, since they may readily lose their activity due to partial oxidation during preparation and storage, which is a point of concern for drug designers.

Ethyl 1,2,3,4-tetrahydro-2-oxopyrimidine-5-carboxylates can be dehydrogenated by various mild and powerful oxidizing agents, such as MnO_2 [7], PCC [7], chloranil [7], $KMnO_4$/Clay [7], DDQ [7], $NaNO_2$/AcOH [7], Pd/C [6], $RuCl_3/O_2$ in AcOH [8], Br_2 [9], sulfur [10], $FeCl_3$ [11], HNO_3 [12], $CuCl_2/K_2CO_3$/*tert*-butylhydroperoxide [13], CAN/AcOH [14], and $Co(NO_3)_2 \cdot 6H_2O/K_2S_2O_8$ [15]. However, many of these methods suffer from disadvantages, such as the use of strong oxidants, extended reaction times, the need of excess oxidant, and especially low yields. To the best of our knowledge, there is no report on the photo-oxidation of dihydropyrimidinones.

Oxidation and photo-oxidation of a range of symmetrical and unsymmetrical 1,4-dihydropyridines, as widely used calcium channel blockers, to the pyridine derivatives has been reported and is still under investigation by many research groups. Among them, especially photo-oxidation of these compounds as a cost-effective procedure is of interest, since it avoids the use of harmful or expensive oxidizing agents [16–21]. The interesting aspect is that the light sensitivity of 1,4-dihydropyridines should motivate medicinal chemists to protect these compounds from light during their preparations. Recently, we have reported on sono-thermal oxidation of various ethyl 1,2,3,4-tetrahydro-2-oxopyrimidine-5-carboxylates by $K_2S_2O_8$ to their corresponding pyrimidin-2(*1H*)-one derivatives to explain the effect of the 4 substituent on the rate of the reaction [22]. In continuation of our work and also the studies on the light sensitivity of 1,4-dihydropyridines, we were interested in investigating the photochemical behavior of the

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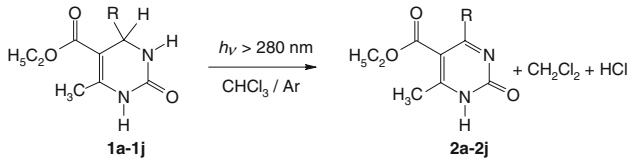
title compounds to elucidate the effect of the substituent in position 4 of the dihydropyrimidinone ring and also the presence of oxygen and argon atmospheres on the rate of possible photo-oxidation.

Results and discussion

Since the rate of photo-oxidation of organic compounds is dependent on the spin multiplicity of the excited state of the light absorbing compounds, singlet or triplet states, which can be affected by the presence of oxygen atmosphere during UV irradiation, we first carried out irradiation of 4-phenyl substituted compound **1a** as a model substrate in $CHCl_3$ as solvent under oxygen and argon atmospheres. Irradiation of **1a** under oxygen atmosphere resulted in the formation of the oxidation product **2a** besides various hitherto unidentified by-products, while irradiation under argon atmosphere led to the formation of the sole product **2a**. In continuation, a 0.003 M solution of each of the 3,4-dihydropyrimidinones **1a–1j** in chloroform was irradiated under argon atmosphere until total disappearance of **1a–1j** as monitored by TLC (Scheme 1). The solvent was evaporated, and the pure products were obtained by recrystallization from *n*-hexane/ethyl acetate. The results are summarized in Table 1.

IR, UV, ^{1}H NMR, ^{13}C NMR, and MS data gave useful information on the structural assignment of the photoproducts **2a–2j**. Owing to tautomerization of N(1) to N(3) and N(1) or N(3) to 2-CO in solution, three different structures for the photoproducts types **2**, **2′**, and **2″** should be considered (Scheme 2). Yamamoto et al. have reported the formation of various enol forms type **2″** by oxidation of various 1,2,3,4-tetrahydro-2-oxopyrimidine-5-carboxylates using $CuCl_2/K_2CO_3$/*tert*-butylhydroperoxide [13]. A comparison of the UV data of the photoproducts **2a–2j** with those of the starting materials **1a–1j** showed a bathochromic shift in the spectra and an increased molar extinction coefficient ($\lambda > 300$ nm, log $\varepsilon \sim 3$–4) owing to the formation of the 4-amino-1-aza-1,3-diene system [due to elimination of 3- (or 1-) and 4-hydrogens], which is also cross-conjugated or conjugated with the 4-aryl substituent upon photo-oxidation. In case of aromatization of the ring



Scheme 1

Table 1 Photo-oxidation of **1a–1j** in $CHCl_3$ under argon atmosphere

1	R	2	Irrad. time/h[a]	Yield/%[b]
a	$C_6H_5^-$	**a**	26	93
b	$4\text{-}CH_3C_6H_4^-$	**b**	7.5	95
c	$4\text{-}CH_3OC_6H_4^-$	**c**	9.15	94
d	$3\text{-}CH_3OC_6H_4^-$	**d**	12.5	92
e	$2\text{-}CH_3OC_6H_4^-$	**e**	11.5	96
f	$3\text{-}ClC_6H_4^-$	**f**	20	92
g	$2\text{-}ClC_6H_4^-$	**g**	13.5	92
h	$2\text{-}BrC_6H_4^-$	**h**	16	96
i	$4\text{-}NO_2C_6H_4^-$	**i**	28.45	95
j	$PhCH_2CH_2^-$	**j**	20.5	92

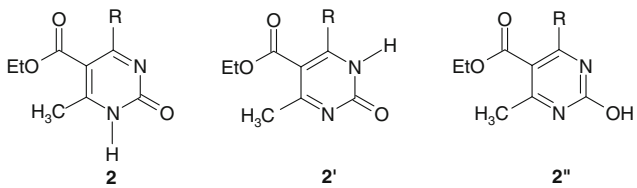
[a] The times are given after total disappearance of **1a–1j** (100% conversion according to TLC observation)

[b] Isolated yields after recrystallization

and formation of product type **2″**, namely the pyrimidine ring, a bathochromic shift of the UV spectra should be expected ($\lambda > 300$ nm, log $\varepsilon \sim 1$–2) [23], which was not observed in this study. It should also be noted that the X-ray structure of **2 g** has confirmed that the CO NH(1) group existed in amide form in solid state [14], which supports the formation of product type **2**. The UV data are presented in Table 2.

A comparison of the IR spectra of the products **2a–2j** with those of **1a–1j** showed a decrease in the intensity of the NH vibration and a little shift to lower frequency, a small shift of the CO group ($5\text{-}CO_2C_2H_5$) to higher frequency, and the shift of 2-CO and $C^5{=}C^6$ double bond to lower frequency. These data are presented in Table 3.

The data shown in Table 1 indicate that the nature of the 4-substituent plays an important role in the rate of photo-oxidation of the 3,4-dihydropyrimidinone ring. As is expected the electron-donating groups such as methyl (**1b**) or methoxy groups (**1c**, **1d**, and **1e**) decrease the time of photo-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 the 4-, 3-, and 2-positions, respectively. Another interesting point is the effect of oxygen atmosphere on the number of products derived on the irradiation of **1a** as a model substrate under this atmosphere, which leads to the formation of **2a** and some



Scheme 2

Table 2 Comparison of the UV absorption [λ_{max}/nm] of the starting materials **1a–1j** with those of the photoproducts **2a–2j** in acetonitrile solution

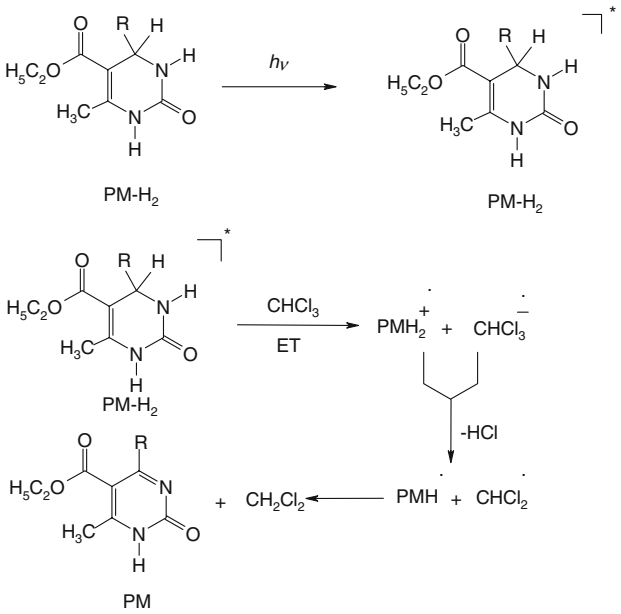
1	λ_{max}/nm (log ε)	**2**	λ_{max}/nm (log ε)
a	278.4 (4.01), 228.6 (3.91)	**a**	314.8 (3.70), 289.6 (3.67), 244 (4.15)
b	278.4 (4.12), 226.4 (4.07)	**b**	328 (3.90), 276.0 (sh, 4.32), 249.6 (sh, 4.40)
c	274 (3.47), 230 (3.75)	**c**	302.2 (3.88), 238.8 (3.84)
d	276.5 (3.52), 227 (3.36)	**d**	293 (3.83), 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)

Table 3 Comparison of the IR spectra ($\bar{\nu}$/cm^{-1}) of **1a–1j** with those of **2a–2j**

1	$CO_2C_2H_5$	2-CO	C=C	**2**	$CO_2C_2H_5$	2-CO	C=C
a	1,720	1,700	1,645	**a**	1,730	1,650	1,600
b	1,705	1,700	1,635	**b**	1,720	1,700	1,645
c	1,725	1,700	1,650	**c**	1,715	1,665	1,559
d	1,700	1,645	1,595	**d**	1,720	1,650	1,590
e	1,720	1,695	1,630	**e**	1,720	1,650	1,595
f	1,710	1,690	1,650	**f**	1,710	1,690	1,640
g	1,705	1,690	1,635	**g**	1,705	1,655	1,590
h	1,705	1,690	1,635	**h**	1,710	1,660	1,595
i	1,725	1,700	1,640	**i**	1,710	1,650	1,590
j	1,720	1,700	1,650	**j**	1,710	1,650	1,595

hitherto unidentified products. As a control experiment, we have carried out the irradiation of the photoproduct **2a** under oxygen and argon atmospheres. The results of the reactions of **2a** after 8 h irradiation showed that only one product is formed under oxygen atmosphere in ~10% yield, which has also been obtained by irradiation of **1a** under this atmosphere according to TLC observation, whereas the irradiation of **2a** under argon atmosphere did not result in the occurrence of these products. This is an indication that the other products observed by irradiation of **1a** under oxygen atmosphere may be formed by the reaction of oxygen with the other active sites of the molecule **2a** on further irradiation under oxygen atmosphere.

Owing to the formation of dichloromethane during the reaction, which has been confirmed by GC analysis of the reaction mixture and by testing for acidity of the solution after irradiation (due to formation of HCl), we propose an electron-transfer mechanism for this conversion in which chloroform is involved in the reaction (Scheme 3). According to the proposed mechanism, excited 3,4-dihydropyrimidinone (PM-H_2^*) donates an electron to chloroform with formation of PM-$H_2^{\cdot+}$ and $CHCl_3^{\cdot-}$ radicals. Elimination of HCl from both intermediates leads to the formation of a



Scheme 3

radical pair, namely hydropyrimidinoyl (PM-H·) and dichloromethyl (·$CHCl_2$) radicals. Hydrogen abstraction by $CHCl_2$ radical completes the reaction by formation of the pyrimidinone compound PM and dichloromethane. Other studies have also proposed this mechanism for the photo-oxidation of symmetrical 1,4-dihydropyridines in CCl_4 [24] and $CBrCl_3$ solutions [25, 26] and unsymmetrical 1,4-dihydropyridines in $CHCl_3$ solution [21].

Conclusion

In conclusion, this work describes electron-transfer-induced photo-oxidation of various 3,4-dihydropyrimidinones to their corresponding pyrimidinones in chloroform solution. The presence of an oxygen or argon atmosphere plays an important role in the rate of reaction and also the formed products. The nature of the 4-substituent influences the rate of reaction.

Experimental

Melting points were determined on a Stuart Scientific SMP2 apparatus. IR spectra were recorded from KBr discs on a Shimadzu apparatus IR 435. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker instrument at 300 and 75.48 MHz. Mass spectra were obtained on a Platform II spectrometer from Micromass; EI mode at 70 eV. UV spectra (in CH_3CN) were taken with a Shimadzu UV-160 spectrometer.

A solution of 3,4-dihydropyrimidinones (0.03 mmol) in 10 cm^3 of distilled chloroform ($c = 0.003$ M) was irradiated with a 400-W high-pressure mercury lamp in a Pyrex tube while bubbling argon through the solution at ambient temperature. The reaction was followed by thin layer chromatography (TLC) until total disappearance of dihydropyrimidinones. The solvent was evaporated at room temperature under reduced pressure, and the products were recrystallized from *n*-hexane/ethyl acetate. The photoproducts **2a–2j** were identified by comparing melting points, IR, ^{1}H NMR, MS, and UV spectra with those reported earlier [22].

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**2a**, $C_{14}H_{14}N_2O_3$)
Yellow solid. Mp: 130–132 °C (Ref. [7]: 130–131 °C, Ref. [14]: 216–218 °C, Ref. [27]: 191–192 °C).

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(4-methylphenyl) pyrimidine-5-carboxylate (**2b**, $C_{15}H_{16}N_2O_3$)
Yellow solid. Mp: 138–140 °C.

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(4-methoxyphenyl) pyrimidine-5-carboxylate (**2c**, $C_{15}H_{16}N_2O_4$)
Yellow solid. Mp: 150–152 °C (Ref. [14]: 172–173 °C).

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(3-methoxyphenyl) pyrimidine-5-carboxylate (**2d**, $C_{15}H_{16}N_2O_4$)
Yellow solid. Mp: 102–105 °C.

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(2-methoxyphenyl) pyrimidine-5-carboxylate (**2e**, $C_{15}H_{16}N_2O_4$)
Yellow solid. Mp: 122–124 °C.

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(3-chlorophenyl) pyrimidine-5-carboxylate (**2f**, $C_{14}H_{13}ClN_2O_3$)
Yellow solid. Mp: 86–90 °C.

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(2-chlorophenyl) pyrimidine-5-carboxylate (**2g**, $C_{14}H_{13}ClN_2O_3$)
Yellow solid. Mp: 181–184 °C (Ref. [14]: 164–166 °C).

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(2-bromophenyl) pyrimidine-5-carboxylate (**2h,** $C_{14}H_{13}BrN_2O_3$)
Yellow solid. Mp: 179–180 °C.

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(4-nitrophenyl) pyrimidine-5-carboxylate (**2i,** $C_{14}H_{13}N_3O_5$)
Yellow solid. Mp: 154–156 °C

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-(2-phenylethyl) pyrimidine-5-carboxylate (**2j**, $C_{16}H_{18}N_2O_3$)
Yellow solid. Mp: 142–143 °C.

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References

1. Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, Hedberg A, ÓReilly BC (1991) J Med Chem 34:806
2. Blacquiere JM, Sicora O, Vogels CM, Čuperlović-Culf M, Decken A, Ouellelte RJ, Westcott SA (2005) Can J Chem 83:2052
3. Atwal KS, Rovnyak GC, Kimball SD, Floyd DM, Moreland S, Swanson BN, Gougoutas JZ, Schwartz J, Smillie KM, Malley MF (1990) J Med Chem 33:2629
4. Brands M, Endermann R, Gahlmann R, Krüger J, Raddatz S (2003) Bioorg Med Chem Lett 13:241
5. Snider B, Chen J, Patil AD, Freyer A (1996) Tetrahedron Lett 37:6977
6. Rizzo RC, Tirado-Rives J, Jorgensen WL (2001) J Med Chem 44:145
7. Vanden Eynde JJ, Audiart N, Canonne V, Michel S, Van Haverbeke Y, Kappe CO (1997) Heterocycles 45:1967
8. Mashraqui SH, Kamik M (1998) Synthesis 713
9. Synder CA, Thorn MA, Klijanowicz JE, Southwick PL (1982) J Heterocycl Chem 19:603
10. Varma RS, Kumar D (1991) J Chem Soc Perkin Trans 1:1755
11. Lu J, Bai Y, Wany Z, Yabg B, Li W (2001) Synth Commun 31:2625
12. Kappe CO (2000) J Heterocycl Chem 38:1345
13. Yamamoto K, Chen YG, Buono FG (2005) Org Lett 7:4673
14. Shanmugam P, Perumal PT (2006) Tetrahedron 62:9726
15. Shanmugam P, Perumal PT (2007) Tetrahedron 63:666
16. Memarian HR, Sadeghi MM, Aliyan H (1998) Indian J Chem 37B:219
17. Memarian HR, Sadeghi MM, Momeni AR (1999) Indian J Chem 38B:800
18. Memarian HR, Sadeghi MM, Momeni AR, Döpp D (2002) Chem Mon 133:661
19. Memarian HR, Bagheri MM, Döpp D (2004) Chem Mon 135:833
20. Memarian HR, Mirjafari A (2005) Bioorg Med Chem Lett 15:3423
21. Memarian HR, Abdoli-Senejani M, Döpp D (2007) J Chin Chem Soc 54:131
22. Memarian HR, Farhadi A (2008) Ultrasonic Sonochem 15:1015
23. Pretsch E, Clerc T, Seibl J, Simon W (1981) Tabellen zur Strukturaufklärung organischer Verbindungen. Springer, Berlin, Heidelberg, New York, p U315
24. Jin M-Z, Yang L, Wu L-M, Liu Y-C, Liu Z-L (1998) Chem Commun 2451
25. Kurz JL, Hutton R, Westheimer FH (1961) J Am Chem Soc 83:584
26. Julliard M, Chanon M (1983) Chem Rev 83:425
27. Puchala A, Belay F, Bergman J, Kappe CO (2001) J. Heterocycl Chem 38:1345