

Photocatalytic oxidation of dihydropyrimidinones using titanium dioxide suspension

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Abstract

Photocatalytic oxidation 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 using a TiO₂/O₂ system under UV irradiation by a 400 W high pressure mercury lamp in acetonitrile. The results revealed that the order of photocatalytic activity for photooxidation was TiO₂ (anatase) > TiO₂ (rutile). The effects of some other physicochemical parameters such as amount of photocatalyst, pH, solvent and time of irradiation were studied. The pyrimidinones were attained from the related dihydropyrimidinones after 2-4.5 h. The results showed the photo stability of this type of compound.

Keywords: Titanium dioxide, photocatalytic, photooxidation, dihydropyrimidinone

Introduction

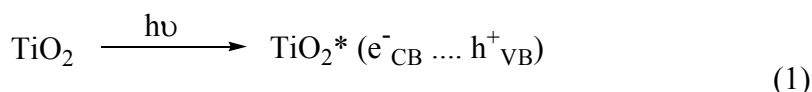
3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) belong to an important class of heterocyclic compounds that have attracted interest due to their pharmacological and biological properties, such as antihypertensive, calcium channel blocking, alpha-1a-antagonism, neuropeptide Y(NPY) antagonism, antitumor, antibacterial, and antiinflammatory activities.¹⁻⁶

Oxidation of DHPMs to pyrimidine-2(1*H*)-ones is relevant to MKC-442, a HEPT(1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine) analogue which is in clinical trials, and similar compounds are also expected to inhibit the HIV virus.⁷ Several nucleosides containing 5-substituted pyrimidine moiety have been shown to inhibit the growth of murine mammary carcinoma virus.⁸ Pyrimidine-cores with extended π -systems have interesting fluorescent properties and similar compounds are useful in the development of advanced electronic and photonic materials.⁹ Furthermore, it is of interest to synthesize structurally diverse pyrimidines by the oxidation of DHPMs.¹⁰

In contrast to the easy oxidation of typical Hantzsch dihydropyridines methods,¹¹⁻¹³ the dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones is nontrivial.^{14,15} Oxidants such as HNO₃,¹⁶ PCC,¹⁷ chloranil,¹⁷ KMnO₄/clay,¹⁷ DDQ,¹⁸ Co(NO₃)₂·6H₂O/K₂S₂O₈,¹⁹ electrochemical oxidation²⁰ and Pd/C²¹ as well as sono-thermal oxidation²² have been examined. None of these oxidations are efficient, some use excessively corrosive or harmful reagents, strong reaction conditions, or present difficulties in product isolation, and/or mostly low yields. Therefore, an alternative procedure is needed.

The potential of heterogeneous photocatalysis in chemistry is now a well-established procedure.²³ The strong oxidizing power of the photogenerated holes of semiconductors (large band gap material), the chemical inertness and resistance to both photocorrosion and decomposition reactions, which plague other band gap materials (e.g., Si, GaAs, GaP, InP, CdS, etc.), low cost and wide availability in addition to the nontoxicity of TiO₂ (anatase and rutile) and zinc oxide have made them superior photocatalysts.²⁴ Several articles and reviews have been written on the use of semiconductor oxides as photocatalysts.²³⁻³⁰

With illumination of a semiconductor photocatalyst such as TiO₂ by photons whose energy is equal to or higher than their band-gap energy (for anatase, E_g = 3.23 eV), absorption of these photons occurs and the bulk of electron-hole pairs generate. These electron-hole pairs dissociate into free photoelectrons in the conduction band e⁻_{CB} and photoholes in the valence band hP⁺_{VB} (equation 1).

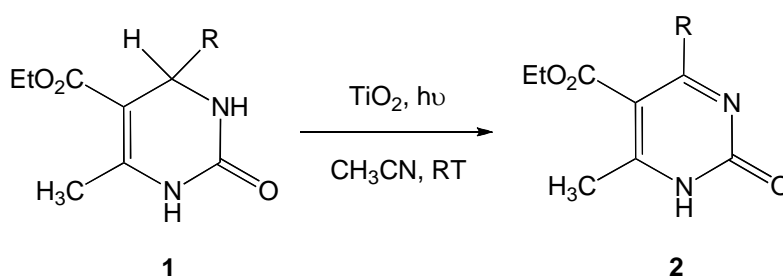


Some of the photoelectrons and photoholes can reach the surface of the photocatalyst and then an electron transfer proceeds towards adsorbed acceptor molecules and positive photoholes are transferred to adsorbed donor molecules. The photohole transfer corresponds to the cession of an electron by donor molecules to the photocatalyst. A chemical acceptor species can be photocatalytically reduced by e_{CB}⁻ only if the conduction band potential of the photocatalyst is more negative than the redox potential of the acceptor species. In the same way, a chemical donor species can be photocatalytically oxidized by hB_{VB}⁺ only if the valence band potential of the photocatalyst is more positive than the redox potential of the donor species. Both reactions should occur simultaneously because electroneutrality has to be maintained.^{31,32}

In continuation of our previous studies on photochemical reactions,³³⁻³⁷ we report here the photocatalytic oxidation of DHPMs. To the best of our knowledge this is the first report of the oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones using photocatalytic system.

Results and Discussion

Our investigation showed us that UV irradiation is necessary for the effective progress of the oxidation reactions and, without the selected oxidant and oxygen, oxidation did not occur. With this preliminary result, the optimization of important operational parameters was performed in the photooxidation reaction of 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 1).



Scheme 1

The type of photocatalyst

TiO₂ (anatase or rutile) (40 mg) was used for the photocatalytic conversion of 1 mmol of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one or 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one in acetonitrile with oxygen bubbling, under irradiation. The time required for completion of the oxidation was used to compare the photocatalytic activity of semiconductor oxides. As shown in Table 1, titanium dioxide (anatase) > titanium dioxide (rutile) in progressing the oxidation reaction. Perhaps, the higher oxygen uptake quantum yields and slower recombination of photogenerated electron/hole couples are responsible for the better photocatalytic activity of TiO₂ anatase with respect to TiO₂ rutile.

Table 1. The effect of photocatalyst type on the photocatalytic oxidation of DHPMs

Entry	R	Type of catalyst			
		Anatase		Rutile	
		Time (h)	Yields (%) ^a	Time (h)	Yields (%)
1	C ₆ H ₅	3	90	5	50
2	4-CH ₃ OC ₆ H ₄	3	80	6	60

^aIsolated yields

The amount of photocatalyst

Using the better photocatalyst, the optimum amount of it required for photocatalytic oxidation was investigated. Thus, oxidations were run using various amounts of TiO₂. As shown in Table 2, oxidation times were decreased by increasing the photocatalyst quantity, then reached the

lowest time of completion and finally remained constant at a value of 40 mg. It is interesting to note that this phenomenon has been observed previously in other photocatalytic reactions.³⁸⁻⁴¹ This can be rationalized in terms of availability of active sites on the TiO₂ surface and the poor penetration of photoactivating light into the suspension. The availability of active sites increases with the suspension of photocatalyst loading, but the light penetration and hence the photoactivated volume of the suspension shrinks. Moreover, the increase in the time of oxidation at higher photocatalyst loading may be due to deactivation of activated molecules by collision with ground state molecules. Shielding by TiO₂ may also take place (equation 2).



Where TiO₂^{*} is the TiO₂ with active species adsorbed on its surface and TiO₂ is the deactivated form.

Table 2. The effects of photocatalyst amounts of Titanium dioxide on the oxidation of typical 3,4-dihydropyrimidin-2(1H)-one^a

Entry	Amount of TiO ₂ (mg)	Time (h)	Yields (%) ^b
1	10	6	85
2	20	4.5	88
3	40	3	90
4	60	4	86
5	80	5.5	84

^aTiO₂ (anatase) as photocatalyst and 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one as typical DHPMs were used.

^bIsolated yields.

Effect of pH

The potentials of both valence and conduction bands of TiO₂ follow a pH dependence, according to equations 3 and 4, that show decreasing 59 mV per pH unit and consequently, the ability of electrons and holes to participate in redox processes is determined by the pH of the medium.⁴² These equations are associated with TiO₂ in anatase form at 25 °C.

$$E_{\text{CB}} = -0.05 - 0.059 \text{ pH} \quad (3)$$

$$E_{\text{VB}} = 3.15 - 0.059 \text{ pH} \quad (4)$$

The effects of varying of pH from 3-11 are summarized in Table 3. From the table we see that pH 7 was optimum in the presence of TiO₂ (anatase). It seems that, since TiO₂ usually has an isoelectric point of charge at a pH about ~7, its surface will gain a positive charge at pHs lower than ~7 via protonation (equation 5) and a negative charge when the material is suspended in a

solution with pHs higher than ~7 via deprotonation (equation 6), respectively. At pHs lower than ~7, both the titled compounds and TiO₂ surface are present mostly in positively charged and protonated form and therefore repel each other. At pH 7, both the DHPMs and photocatalyst surface are mostly in neutral and in an un-protonated form and therefore the substrate molecules are more readily adsorbed on to the photocatalyst surface and the DHPMs oxidation reaction is favored.⁴³

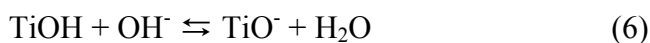


Table 3. Effect of pH on the photocatalytic oxidation of DHPMs^a

Entry	pH	Time (h)	Yields (%) ^c
1	3	6	85
2	5	4.5	87
3	7	3	90
4	9	4	86
5	11	7	88

^aTiO₂ (anatase) as photocatalyst and 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one as typical DHPMs were used.

^bThe typical DHPMs were converted to the corresponding ethyl pyrimidin-2(1*H*)-one-5-carboxylate.

^cIsolated yields.

Photocatalytic oxidation of dihydropyrimidinones

In the optimum conditions, the photocatalytic reactions (Scheme 1) proceed efficiently in high yields. The results are summarized in Table 4. DHPMs with electron withdrawing substituents take longer reaction times than those with electron donor substituents.

Table 4. Photocatalytic oxidation of 3,4-Dihydropyrimidin-2(1H)ones with TiO₂ / O₂ system

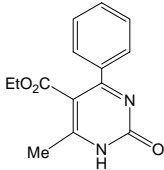
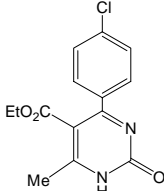
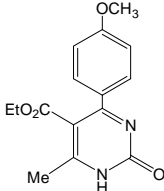
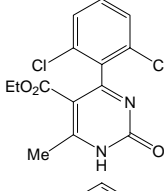
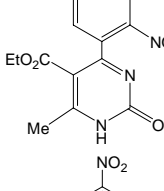
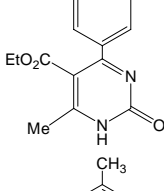
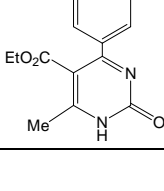
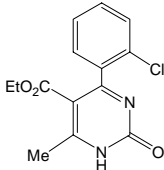
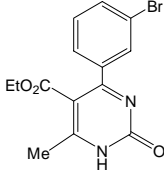
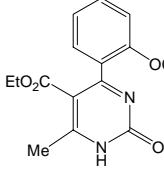
Entry	Products ^a	TiO ₂ (anatase)		TiO ₂ (rutile)		mp °C
		Time (h)	Yields (%) ^b	Time (h)	Yields (%)	
1		3	90	5	50	133-134 ²²
2		2.5	95	5	57	180-182
3		3	85	6	50	151-153 ²²
4		2	96	4.5	55	185-186
5		4.5	80	8	45	190-192 ⁴⁴
6		4	85	6	35	152-154 ²²
7		2	95	4	53	136-138 ²²

Table 4. Continued

8		2.5	85	5	40	165-167 ⁴⁴
9		2	95	4.2	49	167-168
10		2	80	4	43	121-123 ²²

^a Characterized by spectral analysis and comparison with authentic samples.^{22,44}

^b Yields refer to isolated and purified products.

Comparative results

To demonstrate the potential of our new approach, the presently obtained experimental results and the data acquired with the other methodologies are compared in Table 5. The yield/time ratios of the present method are better or comparable with others.

Table 5. Comparison of some our results with those reported in the literature^a

Entry ^b	A ^c	B	C
1	90/3	83/1	92/11
2	95/2.5	-	-
3	85/3	81/1	92/7
5	80/4.5	80/1	-
6	85/4	-	90/27
7	95/2	-	90/7
8	85/2.5	85/1	90/5

^a Values refer to yield(%) / time(h for A, B, C and min for D) ratios;

^b The entries refer to those in Table 4;

^c A: Our method; B: CAN (3 eq.), NaHCO₃ (5 eq.), aq. Acetone, argon atm., -5 °C;⁴⁴ C: K₂S₂O₈, aq. CH₃CN, 70 °C, Ultrasonic.²²

Conclusions

The reported work demonstrates that using the TiO₂/O₂ photocatalytic system for dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones enhances the reaction rate compared to thermal oxidation. The results also show that TiO₂ in anatase form is more effective than its rutile form in the oxidation. Easy reaction progress, moderate reaction times and good to excellent yields are some advantages of this oxidative method.

Experimental Section

General Procedures. Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. The commercially available TiO₂ powders were *anatase* in crystalline form with a surface area about 50 m²/g and primary particle size of 30 nm and *rutile* with approximate 0.2 micron in size and surface area of about 14.747 m²/g. 3,4-Dihydropyrimidin-2(1*H*)-ones were prepared according to the reported procedures.⁴⁵ Reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with authentic samples. IR spectra were recorded on FT-IR 680-Jasco-instrument model. ¹H NMR data were obtained on 300 MHz DPX-Brucker model.

General procedure for the photocatalytic oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones

Titanium dioxide (40 mg, TiO₂) was added to a solution containing a DHPM (1 mmol) in 20 mL acetonitrile through which oxygen was bubbling. The mixture was stirred at room temperature with irradiation by UV light (400 W high pressure mercury lamp) for the appropriate time (2-6 h). After completion of the reaction, as monitored by TLC (CCl₄: EtOAc), the titanium dioxide was separated by centrifugation. Evaporation of the solvent followed by chromatography on a silica-gel plate afforded the pure products.

Ethyl 6-methyl-4-(4-chlorophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2). Pale yellow solid; mp 180–182 °C. IR (KBr): 3255, 1705, 1642, 1410 and 1250 cm⁻¹. ¹H NMR (DMSO-d₆): δ= 1.15 (t, 3H, *J* = 7.2 Hz), 2.52 (s, 3H), 4.03 (q, 2H, *J* = 7.2 Hz), 7.24-7.41 (m, 4H), 10.73 (s, 1H) ppm. Anal. Calcd. for C₁₄H₁₃ClN₂O₃: C 57.44, H 4.48, N 9.57% found: C 57.3, H 4.4, N 9.4%

Ethyl 6-methyl-4-(2,6-dichlorophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (4). Pale yellow solid; mp 185–186 °C. IR (KBr): 3235, 2930, 1700, 1670, 1430 1200 cm⁻¹. ¹H NMR (DMSO-d₆): δ= 0.85 (t, 3H, *J* = 7.3 Hz), 2.50 (s, 3H), 3.94 (q, 2H, *J* = 7.3 Hz), 7.17-7.29 (m, 3H), 12.73 (s, 1H) ppm. Anal. Calcd. for C₁₄H₁₂Cl₂N₂O₃: C 51.40, H 3.70, N 8.56% found: C 51.5, H 3.8, N 8.7%

Ethyl 6-methyl-4-(3-bromophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (9). Pale yellow solid; mp 167–168 °C. IR (KBr): 3230, 2900, 1700, 1650, 1470 and 1226 cm⁻¹. ¹H NMR (DMSO-d₆): δ= 0.92 (t, 3H, *J* = 7.2 Hz), 2.41 (s, 3H), 3.88 (q, 2H, *J* = 7.2 Hz), 7.20-7.45 (m, 3H), 9.25 (s,

1H) ppm. Anal. Calcd. for C₁₄H₁₃BrN₂O₃: C 49.87, H 3.89, N 8.31% found: C 50.0, H 3.8, N 8.4%

Acknowledgements

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References

1. Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898.
2. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.
3. Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803.
4. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
5. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806.
6. Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289.
7. Rizzo, R. C.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2001**, *44*, 145.
8. Chen, C.; Wilcoxon, K. M.; Huang, C. Q.; Xie, Y. -F.; McCarthy, J. R.; Webb, T. R.; Zhu, Y. -F.; Saunders, J.; Liu, X. -J.; Chen, T. -K.; Bozigian, H.; Grigoriadis, D. E. *J. Med. Chem.* **2004**, *47*, 4787.
9. Itami, K.; Yamazaki, D.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 15396.
10. Kang, F. -A.; Kodah, J.; Guan, O.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957.
11. Moghadam, M.; Nasr-Esfahani, M.; Tangestaninejad, S.; Mirkhani, V.; Zolfigol, M. A. *Can. J. Chem.* **2006**, *84*, 1.
12. Montazerzohori, M.; Karami, B.; Nasr-Esfahani, M.; Musavi, S. A. *Heterocycl. Commun.* **2007**, *13*, 289.
13. Nasr-Esfahani, M.; Moghadam, M.; Valipour, G. *J. Iran. Chem. Soc.* **2008**, *5*, 244.
14. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
15. Vanden Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Van Haverbeke, Y.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.
16. Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345.
17. Vanden Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Van Haverbeke, Y.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.
18. Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437.

19. Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 666.
20. Kadysh, V.; Stradins, J.; Khanina, H.; Duburs, G. *Electrochim. Acta* **1989**, *34*, 899.
21. Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 55.
22. Memarian, H. R.; Farhadi, A. *Ultrason. Sonochem.* **2008**, *15*, 1015.
23. Fox, M. A.; Dulay, M. T. *Chem. Rev.* **1993**, *93*, 341.
24. Fox, M. A. in *Photocatalysis- Fundamentals and Applications*; Wiley-Interscience: New York, 1990, p. 421.
25. Bard, A. J. *J. Phys. Chem.* **1982**, *86*, 172.
26. Fox, M. A. in *Advances in photochemistry*, Volman, Hammond, Gollnick (Ed.), Vol 13, Wiley & Sons Inc., 1986.
27. Serpone, N. *J. Photochem. Photobiol. A; Chem.* **1997**, *104*, 1.
28. Fujishima, A. *XI International Conference on Photochemical Conversion and Strong of Solar Energy* (IPS-11), V, Krishnan, Ed., July 28-August 2, 1996, Bangalore, India, 1996, p 11.
29. Linsebigler, A. L.; Lu, G. Q.; Yates, J. T. *Chem. Rev.* **1995**, *95*, 735.
30. Hoffmann, M. R.; Martin, S. T.; Choi, W. Y.; Bahnemann, D. W. *Chem. Rev.* **1995**, *95*, 69.
31. Herrmann, J. -M. *Top. Catal.* **2005**, *34*, 49.
32. Litter, M. I. *Appl. Catal. B: Environ.* **1999**, *23*, 89.
33. Memarian, H. R.; Nasr-Esfahani, M.; Döpp, D. *New J. Chem.* **2001**, *25*, 476.
34. Memarian, H. R.; Nasr-Esfahani, M.; Döpp, D. *New J. Chem.* **2001**, *25*, 1605.
35. Memarian, H. R.; Nasr-Esfahani, M.; Böese, R., Döpp, D. *Liebigs Ann.* **1997**, 1023.
36. Habibi, M. H.; Isfahani, A. Z.; Mohammadkhani, A.; Montazerzohori, M. *Monatsh. Chem.* **2004**, *135*, 1121.
37. Habibi, M. H.; Tangestaninejad, S.; Mohammadpoor-Baltork, I.; Montazerzohori, M. *Phosphorus Sulfur Silicon Relat. Elem.* **2004**, *179*, 597.
38. Sakthivel, S.; Neppolian, B.; Shankar, M. V.; Arabindoo, B.; Palanichamy, M.; Murugesan, V. *Sol. Energ. Mat. Sol. C.* **2003**, *77*, 65.
39. Ohno, T.; Sarukawa, K.; Matsumura, M. *J. Phys. Chem. B* **2001**, *105*, 2417.
40. Davis, R. J.; Gainer, J. L.; O'Neal, G.; Wu, I. W. *Water Environ. Res.* **1994**, *66*, 50.
41. Saien, J.; Ardjmand, R. R.; Iloukhani, H. *Phys. Chem. Liq.* **2003**, *41*, 519.
42. Chen, D.; Ray, A. K. *Chem. Eng. Sci.* **2001**, *56*, 1561.
43. Konstantinou, I. K.; Albanis, T. A. *Appl. Catal. B: Environ.* **2004**, *49*, 1.
44. Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2006**, *62*, 9726.
45. Nasr-Esfahani, M.; Karami, B.; Montazerzohori, M.; Abdi, K. *J. Heterocycl. Chem.* **2008**, *45*, 1183.