Novel *N*-Hydroxymethylation of Phthalimide by Titanium Dioxide Photocatalyst in Methanol

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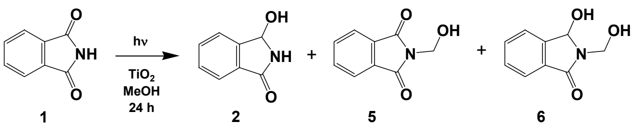
Photochemical reactions of some nitrogen-containing compounds catalyzed by semiconductors such as titanium dioxide (TiO_2) in solution phase have been extensively investigated.[1-7] It was reported that various type of compounds are produced depending on the structures of reactants. For example, secondary amines were generated from primary amines by an aqueous suspension of TiO_2/Pt.[3] Photocatalytic oxidation of primary amines on irradiated TiO_2 powders suspended in anhydrous acetonitrile led to the corresponding symmetrical *N*-alkylidene amines in good yields.[4] UV irradiation of methylamine in the presence of TiO_2 and oxygen gave ammonia, carbon dioxide, etc.[5] Trimethylamine can be bound to TiO_2 surface. With photoirradiation in the presence of oxygen, the adsorbed trimethylamine decomposed and formed CO_2, NCO, etc.[6] Imides were also generated from the reaction of *N*-acetylamine in the presence of oxygenated aqueous suspensions of TiO_2.[7] We have been interested in heterogeneous photocatalysis with dispersed titanium dioxide in the viewpoint of synthetic photochemistry. Chemical transformations of organic compounds by TiO_2 photocatalyst are of great interest, because of the diversity in its role. Several attempts have been made to get some useful organic molecules in organic solvent, instead of aqueous phase. It was found that anhydrides were cleaved to give the monoesters of dicarboxylic acids in good yields, when they were irradiated on TiO_2 in methanol with UV light.[8]

Herein we report that 350 nm UV irradiation of phthalimide **1** in methanol in the presence of TiO_2 photocatalyst afforded *N*-hydroxymethylphthalimide **5** and *N*-hydroxymethyl-3-hydroxyphthalimidine **6** as the major product. A literature survey of existing photochemical reactions of phthalimides without TiO_2 indicates that irradiation of phthalimide **1** with UV light gave several kinds of photoreduction products such as 3-hydroxyphthalimidine **2**, its dimer **3**, and *C*-hydroxymethyl-3-hydroxyphthalimidine **4** depending on the reaction conditions.[9-13] Similarly, upon irradiation of **1** in methanol gave **2** in low yield. Meanwhile, irradiation of phthalimide **1** in methanol (40 mL) in the presence of NaOH (1.5 M) reported the production of **3** and **4** in moderate yields, 35% and 40% yields, respectively.

As shown in Table 1, when phthalimide **1** was just irradiated in methanol without TiO_2 photocatalyst with 350 nm UV light for 24 h, only 3-hydroxyphthalimidine **2** was produced as a simple reduction product (< 5% yield), in which *ca.* 95% of **1** was recovered. In contrast, irradiation of **1** in methanol in the presence of 1 equivalent of TiO_2 afforded *N*-hydroxymethylphthalimide **5** in 74% yield, as well as **2** (14% yield) with a quantitative conversion of the starting material. When **1** was irradiated in methanol in the presence of TiO_2 containing 3×10^{-1} vol% of water, only **5** was produced in 21% yield, as determined by TLC and NMR of the reaction mixture. It is well understood that formaldehyde is produced from the oxidation of methanol by TiO_2 photocatalyst.[14-16] Thus, the hydroxymethylation of phthalimide **1** could be rationalized by the formation of formaldehyde molecules from methanol by TiO_2 photocatalyst. Interestingly, when this reaction was carried in methanol containing 3×10^{-2} vol% of water, *N*-hydroxymethyl-3-hydroxyphthalimidine **6** was observed in 85% yield as the major product along with **2** (15% yield). ^{1}H-NMR spectrum of **6** taken in chloroform-d shows a singlet peak of methyne proton (CH) at δ 6.04. Methylene protons (CH_2) of *N*-hydroxymethyl group appeared at δ 5.22 (J = 11.2 Hz) and δ 5.00 (J = 11.2 Hz) as doublet peaks. GC/MS spectrum of **6** shows a parent ion peak at m/e 179 ($C_9H_9O_3N$: Calculated. 179.175).

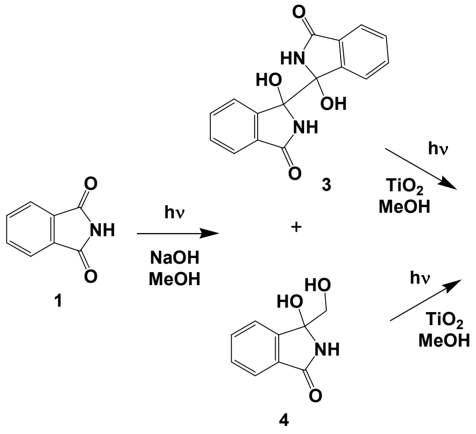
Because 3-hydroxyphthalimidine **2** is one of heterocyclic compounds of biological relevance that have attracted considerable interest in recent years,[17] it is also interesting to note that while *N*-hydroxymethylation was not observed in the photoreactions of *N*-substituted phthalimides such as *N*-methylphthalimide and *N*-phenylphthalimide, only 3-hydroxyphthalimidines were produced in 79% and 75% yield, respectively. Especially, *N*-bromophthalimide was completely inert, when irradiated in methanol in the presence of TiO_2.

Table 1. TiO_2-mediated photoreactions of phthalimide **1** in methanol.

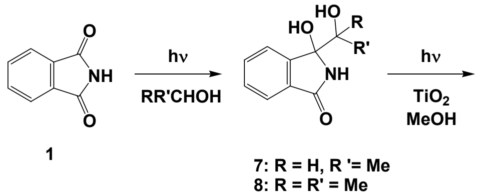


TiO_2 (mmol)	H_2O added	Conversion of **1** (%)	Photoproducts and Yields[a]		
			%**2**	%**5**	%**6**
0	-	5	< 5	-	-
1	-	100	14	74	-
1	$3 \times 10^{-1\,b}$	21	-	21	-
1	$3 \times 10^{-2\,b}$	100	15	-	85

[a] Isolated chemical yields from 1 mmol of **1** in methanol (40 mL). [b] volume% based on methanol solvent.



Scheme 1



Scheme 2

In worth to note, some other semiconductors such as SnO, SnO_2, ZrO_2, WO_3, and ZnO had no effect on the photoreactions of phthalimides in methanol. Scheme 1 shows that when the reductive dimerization product **3** and *C*-hydroxymethylation product **4**, which were yielded as reduction products by the irradiation of phthalimide **1** in methanol containing sodium hydroxide, were irradiated in the methanol in the presence of TiO_2, the two types of 1,2-diols were converted into *N*-hydroxymethylation product **6** in quantitative yields as the final product.

In the same manner, Scheme 2 shows that the primary photoreduction products (**7** and **8**) were produced with > 90% conversion of **1** by the direct irradiation of **1** in ethanol and *i*-propyl alcohol, respectively, and that **7** and **8** were also converted into **6** in quantitative yields, when they were irradiated in methanol in the presence of TiO_2.

In summary, we observed for the first time that irradiation of phthalimide **1** in methanol in the presence of TiO_2 affords *N*-hydroxymethyl-3-hydroxyphthalimidine **6** as the final product in good yield. The chemical yield of **6** depends on the amount of water in methanol solvent. Maximum yield was achieved when **1** was irradiated in methanol containing 3×10^{-2} vol% of water. The primary photoreduction products, *i.e.*, reductive dimer **3** and *C*-hydroxymethyl-3-hydroxyphthalimidine **4**, were converted into the *N*-hydroxymethyl derivative **6** in quantitative yields by the TiO_2-mediated photoreactions. In addition, *C*-hydroxyethyl-3-hydroxyphthalimidine **7** and *C*-hydroxyisopropyl-3-hydroxyphthalimidine **8**, produced in ethanol and *i*-propyl alcohol, respectively, were also converted into **6** by the TiO_2-mediated photoreactions. Mechanistic study and synthetic application of this photoreaction are under progress.

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References

1. Kasturirangan, H.; Ramakrishman, V.; Kuriacose, J. C. *J. Catal.* **1981**, *69*, 216.
2. Fox, M. A.; Chen, M.-J. *J. Am. Chem. Soc.* **1983**, *105*, 4497.
3. Nishimoto, S.; Ohtani, B.; Yoshikawa, T.; Kagiya, T. *J. Am. Chem. Soc.* **1983**, *105*, 7180.
4. Fox, M. A.; Younathan, J. N. *Tetrahedron* **1986**, *42*, 6285.
5. Liao, L.-F.; Wu, W.-C.; Chuang, C.-C.; Lin, J.-L. *J. Phys. Chem. B* **2001**, *105(25)*, 5928.
6. Lien, C.-F.; Lin, Y.-F.; Lin, Y.-S.; Chen, M.-T.; Lin, J.-L. *J. Phys. Chem. B* **2005**, *109*, 10962.
7. Pavlik, J. W.; Tantayanon, S. *J. Am. Chem. Soc.* **1981**, *103*, 6755.
8. Kim, S. S.; Mah, Y. J.; Lee, H. J.; Park, S. K. *J. Photosci.* **2003**, *10*(3), 241.
9. Kanaoka, Y. *Acc. Chem. Res.* **1978**, *11*, 407.
10. Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2001**, *34*(*7*), 523.
11. Griesbeck, A. G.; Kramer, W.; Schmickler, H. *Org. Lett.* **2001**, *3*(4), 537.
12. Yoon, U. C.; Kwon, H. C.; Hyung, T. G.; Choi, K. H.; Oh, S. W.; Yang, S.; Zhao, Z.; Mariano, P. S. *J. Am. Chem. Soc.* **2004**, *126*(4), 1110.
13. Najera, F.; Garcia-Segura, R.; Perez-lnestrosa, E.; Sanchez-Sanchez, C.; Suau, R. *Photochem. Photobiol.* **2006**, *82*, 248.
14. Effects of water addition on the methanol oxidation on Pt/TiO_2 photocatalyst was studied by time-resolved infrared absorption spectroscopy: Yamakata, A.; Ishibashi, T.-A.; Onishi, H. *J. Phys. Chem. B* **2003**, *107,* 9820.
15. Bronkema, J. L.; Leo, D. C.; Bell, A. T. *J. Phys. Chem. C* **2007**, *111*, 14530.
16. Gondal, M. A.; Hameed, A.; Yamani, Z. H.; Arfaj, A. *Chem. Phys. Lett.* **2004**, *392*, 372.
17. Alajarin, M.; Sanchez-Andrada, P.; Lopez-Leonardo, C.; Alvarez, A. *J. Org. Chem.* **2005**, *70*, 7617.