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Reaction-Phase-Selective Inter- and Intramolecular Photochemical Reaction of 2-Pyridone Derivatives

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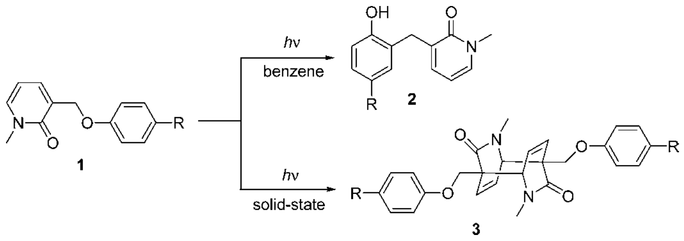
ABSTRACT



Phase-selective photochemical reaction of 2-pyridone derivatives was examined. Irradiation of 1 in benzene mainly gave rearrangement products 2. However, intermolecular [4 + 4] photocycloaddition proceeded quantitatively in the solid state, affording photodimers 3. An effective π–π stacking and dipole–dipole interaction between two pyridone moieties might play important roles in an effective arrangement of 1 for photodimerization in their crystal structures.

Irradiation of 2-pyridone derivatives is widely known to undergo [4 + 4] photocycloaddition to produce cyclooctanoids, which is one of the efficient and direct methods to prepare eight-membered carbocyclic rings.[1] An intramolecular version of this photocycloaddition is applicable to natural product synthesis. A typical example is the synthesis of the carbocyclic skeleton of Taxol.[2] Although many reports have described the photochemical reaction of 2-pyridones since 1960,[3] there is no example of an efficient and quantitative intermolecular [4 + 4] photocycloaddition of them because the intermolecular reaction is strongly concentration dependent in the solution phase.[4] In many cases, intramolecular 1,4-electrocyclization[5] was observed together with intermolecular [4 + 4] cycloaddition. To develop an efficient route to intermolecular [4 + 4] photocycloaddition of 2-pyridone derivatives, we considered their solid-state photochemical reaction. It is well-known that photochemical conversion proceeds under topochemical control in the solid state.[6] However, only a few examples of solid-state photoreaction of 2-pyridones have been reported. Moreover, even in those examples, intramolecular 1,4-electrocyclization leading to the corresponding β-lactam has been dominantly described instead of [4 + 4] photodimerization.[7] These facts challenged us to study the reaction-mode-selective photochemistry[8] of 2-pyridones, in which a selection of a reaction phase, either

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(1) (a) Ayer, W. A.; Hayatsu, R.; de Mayo, P.; Reid, S. T.; Stothers, J. B.; *Tetrahedron Lett.* **1961**, *18*, 648. (b) Slomp, G.; Mackellar, F. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 4472.

(2) (a) Sieburth, S. McN.; Chen, J.; Ravindran, K.; Chen, J. *J. Am. Chem. Soc.* **1996**, *118*, 10803. (b) Lee, Y.; McGee, K. F., Jr.; Chen, J.; Rucando, D.; Sieburth, S. McN. *J. Org. Chem.* **2000**, *65*, 6676.

(3) Taylor, E. C.; Paulder, W. W. *Tetrahedron Lett.* **1960**, *25*, 1.

(4) (a) Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187. (b) Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445.

(5) Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950.

(6) Ramamuthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433.

(7) (a) Kuzuya, M.; Noguchi, A.; Yokota, N.; Okuda, T.; Toda, F.; Tanaka, K. *Nippon Kagaku Kaishi* **1986**, 1746. (b) Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 4299. (c) Wu, L. C.; Cheer, C. J.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1997**, *38*, 3135. (d) Tanaka, K.; Fujiwara, T.; Urbanczyk-Lipkowska, Z. *Org. Lett.* **2002**, *4*, 3255.

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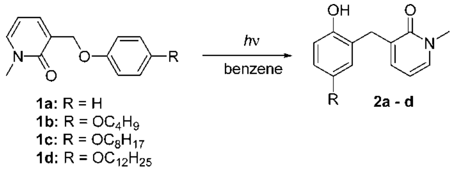
Scheme 1



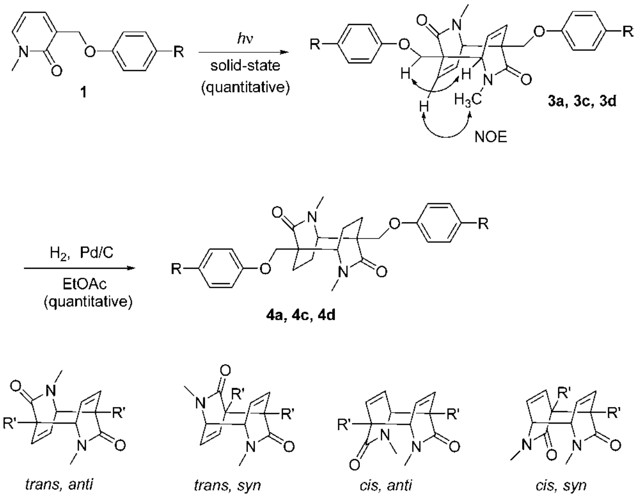
solution or solid state, can control a mode of reaction. Such a control, a choice of specific reaction out of some possible reactions from the same starting material, is attractive not only from synthetic viewpoints but also from a mechanistic understanding. However, successful examples of this kind of control are very limited. Photochemical reaction of 2,4-cyclohexadienones is an example in which the mode of reaction can be controlled by the irradiation wavelength or the solvent polarity of the reaction media.[9] Herein we report the novel reaction mode control in photochemical reaction of 2-pyridone derivatives.

To carry out [4 + 4] photodimerization effectively in the solid state, we designed phenyl ether derivatives **1a**−**d**. These derivatives were prepared by Williamson ether synthesis from 3-chloromethyl-2-pyridone[10] and 4-alkoxyphenols. The phenyl rings are expected to assist crystal packing through an intermolecular aromatic interaction such as face-to-face or edge-to-face stacking.[11] In addition to this, the 2-pyridone moiety also contributes to an efficient stacking for [4 + 4] dimerization via bimolecular dipole−dipole interaction.[4b] Prior to the solid-state reaction of **1**, their photoreaction in solution was examined.

Irradiation was conducted externally with a 450W high-pressure mercury lamp through a Pyrex filter. A benzene solution of **1a**−**d** at 0.3 or 0.03 M was irradiated at 0 °C for 8 h under an argon atmosphere. After evaporation of solvent, the reaction mixture was chromatographed on silica gel with ethyl acetate−hexane (2:1) as an eluent. A photo-[1,3] migration of pyridone methylene group, relatively well-known for benzyl phenyl ethers,[12] gave **2a**−**d** in an isolated yield of 30∼40% (Scheme 1). No concentration dependency was observed for product ratios in this photolysis.

In contrast to the photolysis in solution, an alteration of the mode of photochemical reaction occurred in solid-state photolysis. Irradiation of **1a**, **1c**, and **1d** in the solid state at 0 °C for 20 h resulted in a quantitative formation of the [4 + 4] cycloadducts **3a**, **3c**, and **3d**, respectively (Scheme 2). The syn-anti configuration of photodimers could be determined from a coupling pattern of bridgehead protons in their

Scheme 2



^{1}H NMR spectra. Syn isomers should show a ddd coupling pattern for their bridgehead protons, whereas dd should be the characteristic coupling pattern for those of anti isomers. The bridgehead protons of photodimers **3a**, **3c**, and **3d** showed a dd ($J = 7.0$ and 1.2∼1.5 Hz) coupling pattern that confirmed their stereochemistry to be anti. More specifically, the stereochemistry of four possible [4 + 4] photodimers (trans-anti, trans-syn, cis-anti, and cis-syn)[4a] derived from 2-pyridones can be defined from their Nuclear Overhauser Effects (NOEs).[13] Photodimers **3** were confirmed to have a trans-anti configuration on the basis of NOEs observed between *N*-methyl protons and the olefinic proton distant from the bridgehead proton and between the bridgehead proton and one of the geminal protons of phenoxymethyl group (Scheme 2). Since the photodimers were thermally unstable, their mass spectra (FAB) did not show the corresponding molecular peaks. Instead, the *m*/*z* corresponding to **1** was observed. The quantitative retro [4 + 4] cycloaddition presumably took place. Therefore, the structures of photodimers were confirmed by carrying out their reduction by hydrogenation in ethyl acetate. The reduced photodimers **4a**, **4c**, and **4d** showed the exact mass spectra for them. The formation of cycloadducts implies that there is a close overlapping between the two pyridone rings in their crystal structures. However, irradiation of **1b** in the solid state gave **2b** in 9% yield. In this case, no preference to photodimerization was observed even in the solid state.

To elucidate solid-state photochemical behavior, we examined the single-crystal X-ray structures of **1a**[14] and **1b**[15] (Figure 1). In the crystal structure of **1a**, an efficient face-

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[8] (a) Kohmoto, S.; Miyaji, Y.; Tsuruoka, M.; Kishikawa, K.; Yamamoto, M.; Yamada, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2082. (b) Ihmels, H.; Schneider, M.; Waidelich, M. *Org. Lett.* **2002**, *4*, 3247. (c) Zimmerman, H. E.; Sereda, G. A. *J. Org. Chem.* **2003**, *68*, 283.

[9] Uppili, S.; Ramamurthy, V. *Org. Lett.* **2002**, *4*, 87.

[10] Sieburth, S. McN.; McGee, K. F., Jr.; Zhang, F.; Chen, Y. *J. Org. Chem.* **2000**, *65*, 1972.

[11] (a) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Miyaji, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104. (b) Sinnokrot, M. O.; Valeev, E. F.; Sherrill, C. D. *J. Am. Chem. Soc.* **2002**, *124*, 10887.

[12] Kelly, D. P.; Pinhey, J. T.; Rigby, R. D. G. *Tetrahedron Lett.* **1966**, 5953.

[13] Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80.

[14] Crystal data for **1a**: $C_{13}H_{13}NO_2$, $M_w = 215.25$, colorless prism, orthorhombic *Pbca*, $a = 10.759(2)$, $b = 8.835(2)$, $c = 23.277(5)$ Å $V = 2212.6(8)$ Å^3, $Z = 8$, $D_{calc} = 1.292$ g/cm^3, λ(Mo Kα) = 0.71069 Å, $\mu = 0.088$ mm^{-1}, $R = 0.049$, $R_w = 0.075$, $T = 100$ K.

[15] Crystal data for **1b**: $C_{17}H_{21}NO_3$, $M_w = 287.36$, colorless prism, monoclinic $P2_1/n$, $a = 13.007(1)$, $b = 11.100(1)$, $c = 13.003(1)$ Å, $\beta = 56.808(5)°$, $V = 1571.0(3)$ Å^3, $Z = 4$, $D_{calc} = 1.215$ g/cm^3, λ(CuKα) = 1.54178 Å, $\mu = 0.670$ mm^{-1}, $R = 0.060$, $R_w = 0.072$, $T = 298$ K.

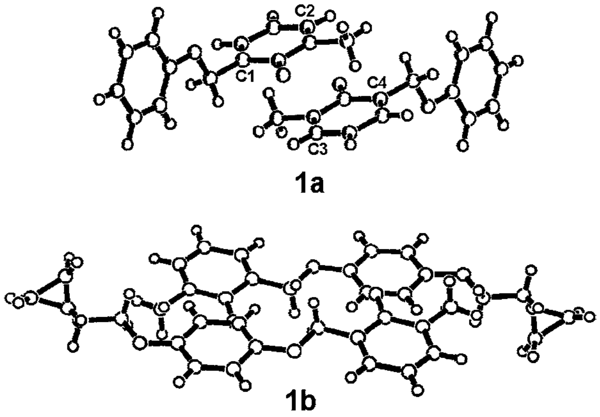

Figure 1. Bimolecular association in the crystal structures of **1a** and **1b**.

to-face $\pi-\pi$ stacking operates between two pyridone rings. The distances between the two sets of two carbon atoms to be reacted are 3.8 Å (C1−C3 and C2−C4). This value is within the range of Schmidt's rule (4.2 Å) for [2 + 2] photocycloaddition[16] and our previous observation for aromatic [4 + 4] photocycloaddition (4.5 Å).[17] The torsional angle between the two pyridone rings (C1−C2−C4−C3) is 0°. As a result, the two pyridone rings are overlapped well in a parallel manner. In addition, this bimolecular association preorganizes the two pyridone moieties to the trans-anti orientation due to the dipole−dipole interaction. Furthermore, the networks of edge-to-face aromatic interaction between the two phenyl rings and between the pyridone and phenyl rings are confirmed in the packing structure. The distances between the two (centroid-to-centroid) are 5.26 Å (phenyl−phenyl) and 4.94 Å (pyridone−phenyl), respectively, and the tilt angle is ca. 100°. These are typical values for the edge-to-face geometry.[18] Due to these intermolecular interactions, the pyridone and phenyl moieties in **1a** are located orthogonally to each other, which assists the molecular orientation in the crystal packing on the whole. As a result, the intermolecular interactions play a dominant role in solid-state [4 + 4] cycloaddition. In contrast, the molecular orientation of **1b** in its crystal structure is far from ideal for [4 + 4] cycloaddition because the pyridone ring forms a π-stacked structure intermolecularly with the phenyl ring. The centroid-to-centroid distance between the two rings is 3.59 Å. The molecular arrangement of **1b** in the crystal seems to be affected by the length of alkyl chain in addition to this $\pi-\pi$ stacking. The C_4 alkyl chain adopts a *pseudo-gauche* conformation at its terminal, and disorder is observed there.

In summary, we have demonstrated the novel reaction-phase-selective photochemical reaction of 2-pyridone derivatives in which [4 + 4] photocycloaddition proceeded exclusively in the solid state, while photorearrangement occurred in solution.

Supporting Information Available: Experimental procedures and spectral data of **1a**−**d**, **2a**−**d**, **3a**, **3c**, **3d**, **4a**, **4c**, and **4d**; X-ray structural information for **1a** and **1b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Schmidt, G. M.; *Pure Appl. Chem.* **1971**, *27*, 647.

[17] Kohmoto, S.; Ono, Y.; Masu, H.; Yamaguchi, K.; Kishikawa, K.; Yamamoto, M. *Org. Lett.* **2001**, *3*, 4153.

[18] Grossel, M. C.; Cheetham, A. K.; Hope, D. A. O.; Weston, S. C. *J. Org. Chem.* **1993**, *58*, 6654 and references therein.