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Highly Enantioselective Photocyclization of 1-Alkyl-2-pyridones to β-Lactams in Inclusion Crystals with Optically Active Host Compounds

Koichi Tanaka,*,† Takashi Fujiwara,† and Zofia Urbanczyk-Lipkowska‡

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Ehime 790-8577, Japan, and Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

tanaka@en3.ehime-u.ac.jp.

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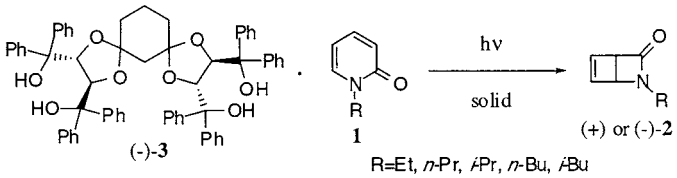
ABSTRACT



Upon photoirradiation of a 1:1 inclusion complex of (−)-3 and 2-alkyl-1-pyridone (1) (R = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu) in the solid state, optically active β-lactams (2) of 91–99.5% ee were obtained in good yield.

Intramolecular [2+2]photocyclization of 2-pyridones (**1**) is known to give chiral bicyclic β-lactams (**2**).[1] The disrotatory photocyclization of **1** in the *a* and *b* directions should give (*R*,*R*)- and (*S*,*S*)-**2**, respectively. However, control of the direction in the photochemical disrotatory ring closure is not easy in solution. For example, Bach et al. reported that photocylization of 2-pyridones proceeds with lower enantioselectivity (20−23% ee) in the presence of a chiral host compound in solution even at low temperature.[2] Relatively high enantioselectivity has been achieved in the absolute asymmetric photoreaction of chiral crystals of some 2-pyridones.[3] We have also reported the enantioselective photocyclization of 2-pyridones in the inclusion crystals with optically active (−)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol, in which the photocyclization products with high ee were obtained in low chemical yields.[4]

We have now found that highly enantioselective photocyclization of 2-pyridones (**1**) proceeds efficiently in the inclusion crystals with optically active host compounds (**3** and **4**)[5] derived from tartaric acid.

When a solution of (−)-**3** (3.0 g, 3.2 mmol) and 1-*n*-butyl-2-pyridone (**1e**) (0.49 g, 3.2 mmol) in toluene (30 mL) was kept at room temperature for 12 h, a 1:1 inclusion complex of (−)-**3** and **1e** was obtained as colorless prisms (3.04 g, 88% yield, mp 181−183 °C). Similarly, host (−)-**3** formed 1:1 inclusion complexes with **1b**−**f**, while the host compound (−)-**4** formed 1:1 inclusion complexes with **1a**, **1b**, and **1g**, and 2:1 inclusion complexes with **1c**, **1d**, **1e**, and **1f**, respectively (Table 1). On the other hand, a new host compound (−)-**5**[6] formed 1:2 inclusion complexes with **1a**, **1b**, and **1c**, respectively.

Photoirradiation of a suspension of powdered 1:1 inclusion complex of (−)-**3** and **1e** (2.73 g) in water (200 mL) containing hexadecyltrimethylammonium bromide (0.2 g) as a surfactant was carried out with a 100-W high-pressure Hg lamp (Pyrex filter) for 53 h under stirring. The reaction product was filtered, air-dried, and chromatographed on silica

† Ehime University.
‡ Polish Academy of Sciences.

(1) (a) Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950−951. (b) De Selms, R. C.; Schleigh, W. R. *Tetrahedron Lett.* **1972**, 3563.
(2) Bach, T.; Bergmann, H.; Harms, K. *Org. Lett.* **2001**, *3*, 601−603.
(3) Wu, L.-C.; Cheer, C. J.; Olovsson, G.; Scheffer, J. R.; Trotter, J.; Wang, S.-L.; Liao, F.-L. *Tetrahedron Lett.* **1997**, *38*, 3135−3138.

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Table 1. Host−Guest Ratios of Inclusion Complex[a]

guest	host **3**	host **4**	host **5**
1a	1:1	1:1	1:2
1b	1:1	1:1	1:2
1c	1:1	2:1	1:2
1d	1:1	2:1	–
1e	1:1	2:1	–
1f	1:1	2:1	–
1g	–[b]	1:1	–

[a] Host−guest ratios were determined by ^{1}H NMR. [b] No complexation occurred.

gel with hexanes−ethyl acetate (1:1) as an eluent to give (−)-2-butyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (**2e**) (0.11 g, 69% yield, $[\alpha]_D$ −169° (*c* 0.4, MeOH), >99.5% ee). Similar irradiation of a 1:1 inclusion complex of (+)-**3** and **1e** gave the other enantiomer (+)-**2e** of >99.5% ee in 62% yield. The optical purity was determined by HPLC on chiral stationary phase Chiralcel OD with hexane/2-propanol (9:1) as solvent.

When inclusion crystals of (−)-**3** with **1b**, **1c**, **1d**, and **1f** were irradiated as described above, optically active β-lactams **2b**, **2c**, **2d**, and **2f** were also obtained in 91, >99.5, >99.5, and >99.5% ee, respectively (Table 2). The host compound

Table 2. Enantioselective Photocyclization of 2-Pyridones (**1**) in the Inclusion Crystals with Optically Active Hosts (**3**−**5**)

guest	host	irradiation time (h)	conv (%)	product	yield (%)	$[\alpha]_D$ (deg) (MeOH)	ee (%)[a]
1b	(−)-**3**	168	66	(−)-**2b**	18	−134	91
1b	(+)-**5**	86	69	**6b**	90		
1c	(−)-**3**	109	63	(−)-**2c**	80	−210	>99.5
1c	(+)-**5**	55	92	**6c**	79		
1d	(−)-**3**	53	83	(+)-**2d**	58	+177	>99.5
1e	(−)-**3**	53	65	(−)-**2e**	69	−169	>99.5
1e	(+)-**3**	53	62	(+)-**2e**	62	+171	>99.5
1f	(−)-**3**	168	67	(+)-**2f**	32	+127	>99.5
1f	(−)-**4**	168	71	(−)-**2f**	26	−121	95
1g	(−)-**4**	47	42	(+)-**2g**	74	+22	>99.5

[a] Optical purity was determined by HPLC (Chiralcel OD, Daicel).

4 is effective for the enantioselective photocyclization of **1g** to optically active β-lactam **2g**, although host compound **3** did not form inclusion crystals with **1g**. For example, when a suspension of a powdered 1:1 inclusion complex of (−)-**4** and **1g** in water was irradiated at room temperature for 47 h, (+)-2-benzyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one (**2g**) of >99.5% ee was obtained in 74% yield.

Interestingly, however, host compound (−)-**5** formed 1:2 inclusion complexes with 2-pyridones (**1b** and **1c**) which, upon photoirradiation in the solid state, gave only [4+4] dimer (**6b** and **6c**) in 89 and 78% yield, respectively. The selectivity of the photodimerization in the 1:2 inclusion conlex of (−)-**5** with 2-pyridone (**1b** and **1c**) suggests that pairs of molecules of 2-pyridones are arranged at the best position to produce [4+4] dimer (**6b** and **6c**) upon photoirradiation. On the other hand, no photoreaction occurred for the inclusion crystals of **3** with **1a**, **4** with **1a**−**e**, and **5** with **1a**.

To elucidate the mechanism of the enantioselective photocyclization of 1-alkyl-2-pyridones to β-lactams in the inclusion crystals with optically active host compounds, X-ray crystal structure analysis of the inclusion complex was studied.[7−10] As can be seen from Figure 1, the molecular

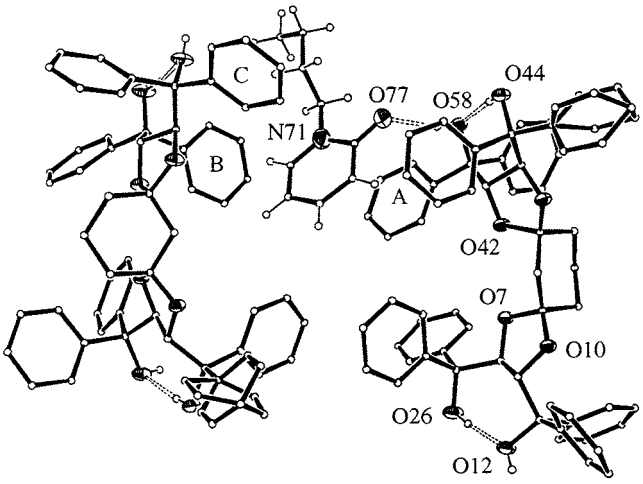


Figure 1. Solid-state structure of the (1:1) complex of **3** and **1e** showing heteroatoms as 30% probability thermal ellipsoids and carbon atoms as spheres**.** Hydrogen atoms in the host molecules are omitted for clarity. Dashed lines denote two intramolecular O−H···OH and one intermolecular O58−H···O77═C hydrogen bonds. Parallel arrangement of pyridone and A-ring of the host restricts molecular movement of the guest 2e**.**

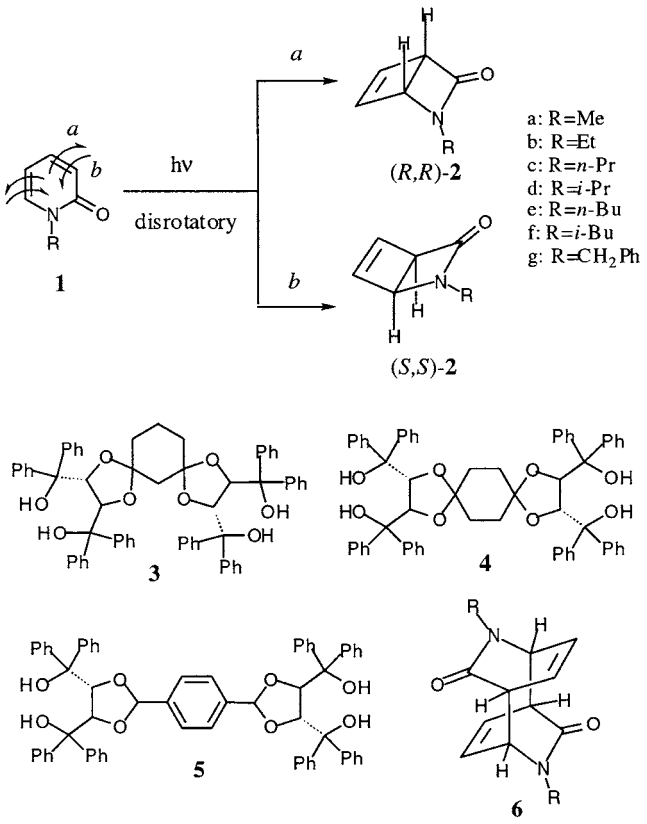
complex between host **3** and substrate **1e** is formed via formation of a strong hydrogen bond between two complementary partners [O58···O77 = 2.671(8) Å, H···O77 = 1.87(7) Å, angle 161(7)°]. Host **3** is particularly well

(4) (a) Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 4299−4302. (b) Fujiwara, T.; Tanaka, N.; Tanaka, K.; Toda, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 663.

(5) (a) Tanaka, K.; Honke, S.; Urbanczyk-Lipkowska, Z.; Toda, F. *Eur. J. Org. Chem.* **2000**, 3171−3176. (b) Tanaka, K.; Nagahiro, R.; Urbanczyk-Lipkowska, Z. *Org. Lett.* **2001**, *3*, 1567−1569.

(6) When a solution of (+)-diethyl tartarate (171 g, 0.8 mol) and terephthaldehyde (54 g, 0.4 mol) in toluene (500 mL) containing a catalytic amount of TsOH was heated under reflux for 120 h, tetraester was obtained in 58% yield after recrystallization from toluene (118 g, colorless needles, mp 69−71 °C, $[\alpha]_D$ −34° (*c* 1.0, MeOH)). A solution of the tetraester (20 g, 0.039 mol) in dry THF (50 mL) was added under stirring to a solution of PhMgBr in THF (500 mL) prepared from Mg (12 g, 0.5 mol) and bromobenzene (78.5 g, 0.5 mol) and the mixture was stirred for 6 h. The usual workup gave crude crystals of host **5**. Recrystallization of crude crystals from acetone gave a 1:1 inclusion complex of **5** with acetone as colorless prisms which upon heating gave pure **5** as a white powder (28 g, 31% yield, mp 291−293 °C, $[\alpha]_D$ +50 ° (*c* 1.0, $CHCl_3$)). **5**: IR (Nujol) (cm^{-1}) 3370 (OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 2 H, OH), 3.18 (s, 2 H, OH), 5.09 (d, J = 5.0 Hz, 2 H, CH), 5.11 (s, 2 H, CH), 5.28 (d, J = 5.0 Hz, 2 H, CH), 7.09−7.15 (m, 44 H, Ar). Anal. Calcd for $C_{64}H_{54}O_8$: C, 80.82; H, 5.72. Found: C, 80.03; H, 6.25.

Scheme 1



designed for accommodation of planar ring systems. As a result, a planar molecule of **2e** is inserted between aromatic rings of the hosts with an efficient overlap of the pyridone ring with the host's phenyl ring marked A [N71···C67 = 3.604(6) Å, O77···C65 = 3.385(6) Å]. The C···C distances between the two aromatic systems are as short as 3.81−4.2 Å. Two other rings labeled B and C do not have contacts below 4.3 Å with the pyridone ring. Additionally, the *n*-butyl chain works as an anchor, fixing the position of atoms in the vicinity of the amide system. The starting spacial situation is changed during the reaction pathway when two pyridone carbon atoms change their configuration from sp^2 to sp^3. Hydrogen atoms attached to them create large repulsion with ring A. Therefore, the only possible movement of the pyridone C-atoms during photoreaction is outward from ring A. This steric arrangement in the crystal would favor pathway b, shown in Scheme 1.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) **X-ray Studies of the 1:1 Complex of (−)-3 and 1e**. $C_{70}H_{98}NO_9$: A 0.35 × 0.15 × 0.15 mm^3 crystal covered by epoxy glue was used for data collection on a four-circle MACH3 diffractometer. Unit cell parameters: a = 14.347(1) Å, b = 14.4732(7) Å, c = 28.276(4) Å, orthorhombic system, space group $P2_12_12_1$, Z = 4, V = 5871(1) $Å^3$, D_{calc} = 1.242 mg m^{-3}. 6715 reflections have been collected in θ range 3.13−74.22°. 3537 independent reflections (R_{int} = 0.047), corrected for Lorentz, polarization, and φ-scan based absorption (max. and min. transmission 99.98 and 87.38, respectively), have been used for structure solution and refinement. SHELXS97[8] and SHELXL97[9] included in the WINGX suite of programs[10] have been used for structure solution and refinement. H-atoms from OH groups have been found from $\Delta\rho$ maps and refined, otherwise, they have been included at their calculated positions. Final atomic coordinates, bond lengths, bond angles, torsion angles, and geometry of H-bonds have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC188283. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44 1223 336033 or e-mail deposit@ccdc.cam.ac.uk).

(8) Sheldrick G. M. *Program for Crystal Structures Solution*; University of Göttingen: Göttingen, Germany, 1977.

(9) Sheldrick G. M. *Program for Refinemnt of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1977.

(10) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837−845.