Stereocontrol of 2-Pyridone [4 + 4] Photocycloaddition: A Thermal–Photochemical Cycle To Produce Exclusively Trans Cycloadducts

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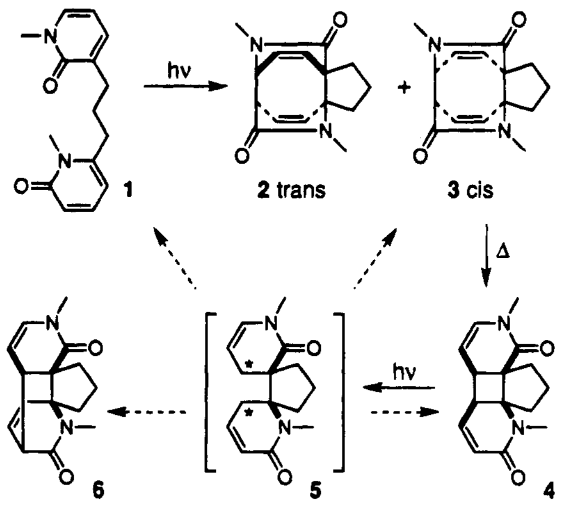
Intramolecular [4 + 4] photocycloaddition of 2-pyridones tethered by a three-carbon chain yield mixtures of trans and cis products. A general method is described for producing the trans isomer from the cis isomer by Cope rearrangement of the latter followed by photolysis. Photocleavage of the Cope product transiently reforms the tethered pyridones which then undergo a new [4 + 4] photocycloaddition. The trans isomer is inert to the reaction conditions and so the transformations can be performed without isolation steps. Two cycles of heating and irradiation transform an initial trans/cis ratio of 2:1 to nearly 20:1, with a corresponding increase in the yield of the trans isomer. Combination of this chemistry with control from a tether substituent allows for the facile synthesis of a single [4 + 4] product with five stereogenic centers.

The photodimerization of 2-pyridone efficiently assembles an eight-membered carbocyclic ring with an intriguing density and arrangement of functionality. This singlet-mediated [4 + 4] cycloaddition can be performed intramolecularly to give fused 5-8 and 6-8 ring systems in good to excellent yields.[1,2] Our investigations have found that a tether substituent can substantially influence relative stereochemistry, whereas the proportions of trans and cis [4 + 4] products have remained insensitive to tether substitution and to solvent effects.[3] The simplest case of an unsubstituted tether (**1**) is a good example, yielding a 2:1 ratio of isomers **2** and **3** (84%, Scheme 1).[2] Clearly, synthetic applications of this cycloaddition would profit if the reaction could be enticed to produce only one of these isomers. *We report herein a general method for the production of purely trans isomers, employing a combination of photochemistry and thermal chemistry.* This solution is predicated on a sequence of chemical tranformations that act on the cis isomer **3** but not on the trans isomer **2**.

Scheme 1



Both of the [4 + 4] products **2** and **3** contain a 1,5-diene that could, in principle, undergo a thermal [3,3]-sigmatropic (Cope) rearrangement (Scheme 1). The bridging lactams lock each structure into a rigid conformation in which the cis isomer is properly staged for rearrangement and the trans isomer cannot achieve the required orbital overlap. Cope rearrangement of **3** would give **4**, a product that contains a conjugated π-system, in contrast to **2** and **3** in which regions of unsaturation are isolated.

Subsequent photoexcitation of **4** could lead to cleavage of the cyclobutane ring, heterolytically or homolytically, to yield transient **5**. This species would partition among four possible paths: reversion to cyclobutane **4**, allylic closure to [4 + 2] isomer **6** (one of two possible isomers is shown), doubly allylic closure to cis [4 + 4] isomer **3**, or cleavage of a second bond of the cyclobutane to give bis-2-pyridone **1**. Should the latter pathway dominate, newly formed **1** would again participate in a [4 + 4] photocycloaddition. Optimistically, the overall result would be a transformation of a large part of the minor cis isomer into the major trans isomer. Successful application of this sequence, without intermediate isolation steps, would rest on the thermal and photochemical stability of trans **2** as well as high-yield thermal and photochemical transformations for **3** and its progeny. The thermal chemistry of **2** and **3** and the photochemistry of **4** were first tested individually.

Results and Discussion

Whereas 1,5-cyclooctadiene is formed in high yield *from* Cope rearrangement of *cis*-1,2-divinylcyclobutane,[4] the thermodynamics are transposed when the 1,5-diene is embedded in a polycyclic system where nonbonded interactions override the strain of the cyclobutane.[5] Thermal rearrangement of **3** proved to be both facile and efficient.

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(2) Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80–87.

(3) A similar solvent insensitivity has also been found for intermolecular photodimerization of 2-pyridones, see: Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187–1191.

(4) Vogel, E. *Liebigs Ann. Chem.* **1958**, *615*, 1–14.

(5) Yang, N. C.; Libman, J. *J. Am. Chem. Soc.* **1972**, *94*, 9228–9229. Eaton, P. E.; Chakraborty, U. R. *J. Am. Chem. Soc.* **1978**, *100*, 3634–3635. Paquette, L. A.; Doecke, C. W.; Klein, G. *J. Am. Chem. Soc.* **1979**, *101*, 7599–7604. Tobe, Y.; Hirata, F.; Nishida, K.; Fujita, H.; Kimura, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1981**, 786–787.

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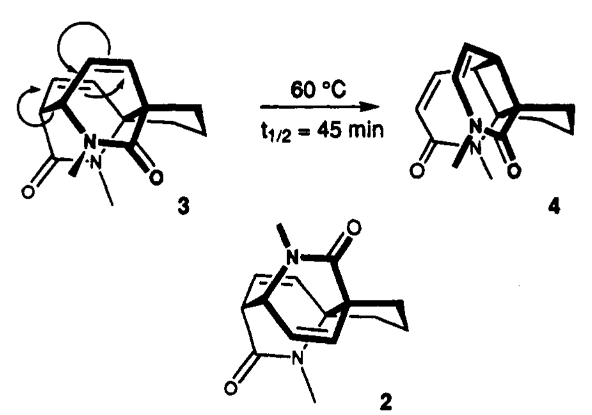


Figure 1. The cis [4 + 4] adduct **3** undergoes a facile Cope rearrangement while the trans isomer **2** is stable.

Warming a sample in $CDCl_3$ or methanol to 60 °C (Figure 1) gave a very smooth transformation to **4**, with a half-life of 45 min.[6] After 4 h no trace of **3** could be detected by TLC or ^1H NMR. In contrast, the trans isomer was completely stable under these conditions for 24 h.[7]

The anticipated photocleavage of cyclobutane **4** was then investigated. Photocleavage of cyclobutane bonds adjacent to a chromophore has been well documented.[8-10] In several cases, cyclobutane cleavage has been efficiently promoted by exogenous electron-transfer agents.[11] It may therefore be significant that enone and enamine groups flank the cyclobutane. In the event, irradiation in methanol at ambient temperature fully transformed **4** into a mixture of **2** and **3**. The ratio of products was identical (2:1, NMR) to that found in the photocycloaddition of **1** and therefore the phototransformation of **4** must proceed largely, or exclusively, through the intermediacy of bis-2-pyridone **1**. Traces of **1** could be detected at low conversions of **4**.[12]

Serial combination of these photochemical and thermal steps proved to be simple.[13] Beginning with **1**, irradiation in methanol gave a mixture of **2** and **3** (2:1). After warming for 6 h and irradiation again, the ratio was found to be 7:1 (NMR). After subjecting the solution to another cycle of warming and irradiation, NMR analysis indicated that the ratio of products was in the range of 20:1. Concentration and chromatography confirmed this analysis, giving a 72% yield of **2** and 4% of **3** (18:1).[14]

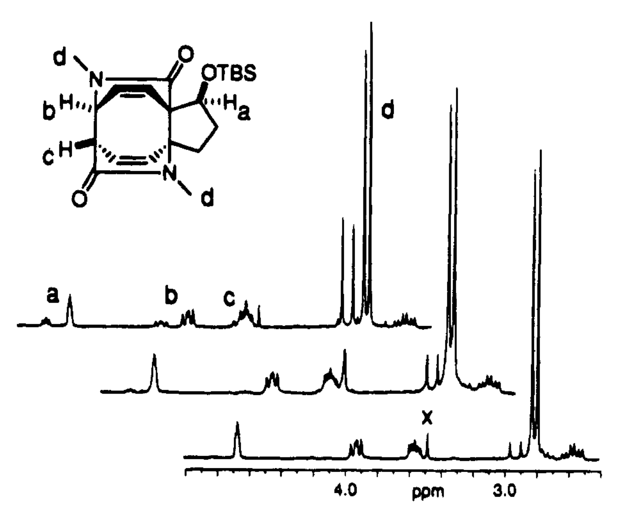
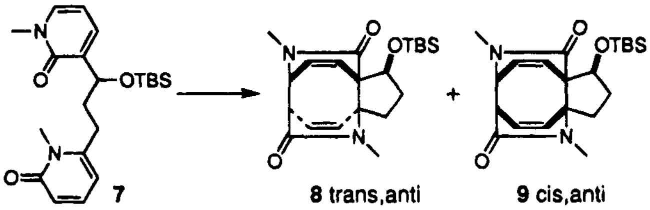


Figure 2. Partial proton NMR spectra (250 MHz) of crude reaction aliquots taken at the end of each irradiation. The upper plot is after irradiation of **7**, the middle plot is after a single thermal/photochemical cycle, and the lower plot is after two cycles. X indicates the residual methanol solvent.

Table 1

conditions	ratio (isolated yield)	
	2:3	**8:9**
hν	2:1 (84%)	2:1 (89%)
hν, Δ, *hν*	7:1	10:1
hν, Δ, *hν*, Δ, *hν*	18:1 (76%)	22:1 (86%)

As a further test of this sequence we turned to the (*tert*-butyldimethylsilyl)oxy-substituted **7**. The cycloaddition of this substituted precursor yields only anti isomers of the trans and cis [4 + 4] products. We have reported[2] that irradiation of **7** in methanol gave trans-anti **8** and cis-anti **9** (89%, 2:1) (Table 1). Repetition of this experiment gave a similar mixture of products (NMR ratio 2.5:1). Warming this solution followed by irradiation gave an **8**/**9** ratio of 10:1. A second cycle of warming, irradiation, and NMR analysis indicated the ratio to be greater than 20:1. Trans-anti isomer **8** and cis-anti isomer **9** were isolated in 86% overall yield and in a ratio of 22:1. No other isomers could be detected by NMR or TLC. Figure 2 shows the progress of the reaction as monitored at the end of each irradiation by NMR.



7 **8** trans,anti **9** cis,anti

By simply combining a short series of thermal and photochemical steps, cis isomers are virtually eliminated and trans isomers are isolated in much higher yield.[15] The cis-to-trans conversion sequence described here is

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[6] Of the two Cope rearrangements conceivable for **3**, one is prohibited by the constraints of the tether.

[7] Trans photo-[4 + 4]-dimers of 2-pyridone have been reported to thermally cleave, regenerating the parent 2-pyridone: Taylor, E. C.; Paudler, W. W. *Tetrahedron Lett.* **1960**, No. 25, 1–3.

[8] Photoisomerization of verbenone and related compounds may involve cyclobutane cleavage and recombination. Erman, W. F. *J. Am. Chem. Soc.* **1967**, *89*, 3828–3841. For a recent application of this photochemistry, see: Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878–5879.

[9] Thermal Cope rearrangement and subsequent photochemical cleavage of an intramolecular photo-[4 + 4]-dimer of naphthalene has been reported. The [4 + 4] photoproduct retains a good chromophore and is in photoequilibrium with the tethered dinaphthyl: Chandross, E. A.; Dempster, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 703–704.

[10] For a related photocleavage of 2-pyridone-derived cyclobutanes, see: Nakamura, Y.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 2841–2854.

[11] Cyclobutane photocleavages have been promoted by the presence of amines, tetracyanoethylene, trityl and pyryllium salts, and aromatic radical cations: Majima, T.; Pac, C.; Sakurai, H. *J. Am. Chem. Soc.* **1980**, *102*, 5265–5273. Mukai, T.; Sato, K.; Yamashita, Y. *J. Am. Chem. Soc.* **1981**, *103*, 670–672. Okada, K.; Hisamitsu, K.; Mukai, T. *Tetrahedron Lett.* **1981**, *22*, 1251–1254. Okada, K.; Hisamitsu, K.; Miyashi, T.; Mukai, T. *J. Chem. Soc., Chem. Commun.* **1982**, 974–976. Bischof, E. W.; Mattay, J. *Tetrahedron Lett.* **1990**, *31*, 7137–7140. Cossy, J.; Aclinou, P.; Bellosta, V.; Furet, N.; Baranne-Lafont, J.; Sparfel, D.; Souchaud, C. *Tetrahedron Lett.* **1991**, *32*, 1315–1316.

[12] The UV absorption of **1** (λ_{max} = 306 nm, ϵ = 12 100) relative to **4** (λ_{max} = 268 nm, ϵ = 2800) prevents buildup of significant levels of the former during this irradiation.

[13] Combining the photochemistry and thermal chemistry into a single operation by irradiating a solution of **1** at reflux led to a more complex mixture.

[14] A third, as yet unidentified, product is also isolated in ca. 4% yield. Its spectral characteristics make it unlikely to be any of the compounds illustrated in Scheme 1.

not inherently restricted to the intramolecular reaction and may account for the absence of cis [4 + 4] isomers in studies of 2-pyridone photodimerization prior to the work of Nakamura.[16] In the context of intramolecular reactions, this simple and general approach to trans selectivity, juxtaposed with the stereogenic control of tether substitution, allows for the synthesis of these polycyclic products as nearly a single isomer. The concepts and transformations may additionally apply to related photochemical methods.[17,18]

Experimental Section[19]

The general procedure is described for 3-[3-(1,6-dihydro-1-methyl-6-oxo-2-pyridinyl)-1-((dimethyl(1,1-dimethylethyl)silyl)oxy)propyl]-1-methyl-2(1*H*)-pyridone (**7**). A stream of dry nitrogen was passed through a solution of **7** (157 mg, 0.40 mmol) in methanol (8 mL, 0.05 M) for several minutes and the Pyrex test tube was then affixed with a septum and a nitrogen balloon. This solution was irradiated for 12 h using a 450-W medium pressure mercury lamp fitted with a Pyrex filter and housed in a water-cooled quartz cooling jacket. The test tube was then placed in a 55 °C oil bath for 12 h. After cooling to rt, the solution was again irradiated for 12 h, warmed to 55 °C for 12 h, cooled, and then irradiated for an additional 12 h. Concentration and flash chromatography (methanol:ethyl acetate 1/19) gave trans-anti **8** (129 mg, 82%) and cis-anti **9** (6.0 mg, 3.8%).

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Supplementary Material Available: A complete set of ^{1}H NMR spectra for each step of the photochemistry and thermal chemistry of **7** plus characterization data for **4** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered form the ACS; see any current masthead page for ordering information.

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(15) For an example of simultaneous photoisomerization and thermal rearrangement, see: Wender, P. A.; Eissenstat, M. A.; Filosa, M. P. *J. Am. Chem. Soc.* **1979**, *101*, 2196–2198.

(16) Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 620–621 and ref 3. For studies reporting only a single trans, head-to-tail product, see: Slomp, G.; MacKellar, F. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 4472–4473. Taylor, E. C.; Kan, R. O.; Paudler, W. W. *J. Am. Chem. Soc.* **1961**, *83*, 4484–4485. Ayer, W. A.; Hayatsu, R.; de Mayo, P.; Reid, S. T.; Stothers, J. B. *Tetrahedron Lett.* **1961**, 648–653. Paquette, L. A.; Slomp, G. *J. Am. Chem. Soc.* **1963**, *85*, 765–769. Taylor, E. C.; Kan, R. O. *J. Am. Chem. Soc.* **1963**, *85*, 776–784. Meyers, A. I.; Singh, P. *J. Org. Chem.* **1970**, *35*, 3022–3030. Dilling, W. L.; Tefertiller, N. B.; Mitchell, A. B. *Mol. Photochem.* **1973**, *5*, 371–409. Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans 2* **1985**, 1445–1448. Sharp and Hammond observed other photodimers but were unable to fully assign the structure: Sharp, L. J., IV; Hammond, G. S. *Mol. Photochem.* **1970**, *2*, 225–250.

(17) West has recently reported that an intramolecular 2-pyrone–furan [2+2] adduct undergoes photocleavage and [4 + 4] recombination similar to that of **4**: West, F. G.; Chase, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 3794–3795.

(18) The photocleavage of the cyclobutane in these studies may be mechanistically related to pyrimidine photodimer cleavage in DNA repair. For a recent study and lead references, see: McMordie, R. A. S.; Altmann, E.; Begley, T. P. *J. Am. Chem. Soc.* **1993**, *115*, 10370–10371.

(19) All compounds were fully characterized by NMR, IR, UV, MS, and analysis or HRMS. See supplementary material and ref 2.