Intramolecular [4 + 4]-Photocycloadditions of 2-Pyrones: An Efficient Approach to Cyclooctanoid Construction[1]

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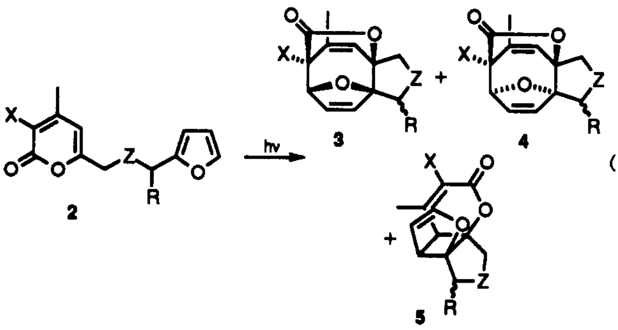
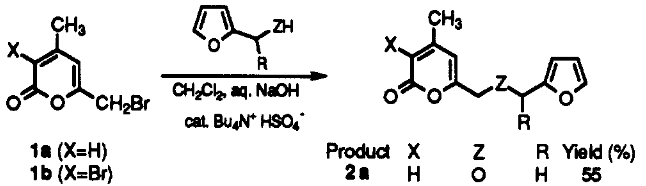
Summary: 2-Pyrones **2** bearing pendant furans underwent efficient intramolecular crossed [4 + 4]-cycloaddition to give fused bicyclic cyclooctadienes **3** and **4** bridged by lactones and ethers, along with varying amounts of [2 + 2]-adducts **5**.

The wealth of biologically important and synthetically challenging cyclooctanoid natural products has prompted numerous approaches to the construction of eight-membered rings.[2] A [4 + 4]-type construction is a convergent and conceptually simple route to the cyclooctane ring. Although thermally forbidden, [4 + 4]-cycloadditions of butadienes can be effected either photochemically or with metal catalysis.[3] Wender and co-workers have elegantly applied nickel(0)-catalyzed [4 + 4]-cycloadditions to the total synthesis of natural products such as asteriscanolide.[4] In these reactions, the entropic challenge of bringing both sets of reactive termini within bonding distance is met using the templating effect of the metal. An alternative strategy employs cyclic dienes, producing bridged cycloadducts, as illustrated in the photodimerization of tethered bis(2-pyridones) reported by Sieburth.[5] The early work of de Mayo and others[6] suggested that 2-pyrones could serve as four carbon units in cycloaddition reactions with 1,3-dienes. We report here the application of 2-pyrone photochemistry to a concise approach to fused bicyclic cyclooctanoids with lactone bridges (eq 1), utilizing the first reported examples of intramolecular crossed [4 + 4]-photocycloadditions of 2-pyrones.



Preparation of substrates followed a general route in which the two heterocycles were joined using bromide displacement (Scheme I). Thus, radical bromination at the C-6 methyl followed by displacement with furan-containing nucleophiles gave products in which the 2-pyrone and the furan were separated by a three-atom tether. Hydroxyl-, malonate- and thiol-substituted furans all underwent alkylation by 6-(bromomethyl)-4-methyl-2-pyrone (**1a**) to give substrates **2a–c**, and ring-brominated (bromomethyl)-2-pyrone **1b** also underwent clean displacement to give **2d**. Reaction of **1a** with 1-furylethanol gave **2e**, bearing a stereogenic center next to the furan.

Scheme I



1a (X=H)
1b (X=Br)

Product	X	Z	R	Yield (%)
2a	H	O	H	55
2b	H	$C(CO_2Me)_2$	H	91
2c	H	S	H	92
2d	Br	S	H	99
2e	H	O	Me	28

In initial studies using **2a**, the outcome of the reaction was quite sensitive to solvent (Table I).[7] Photolysis (Pyrex) in hydrocarbon solvents gave poor yields of diastereomeric [4 + 4]-cycloadducts **3a** and **4a**, along with comparable amounts of [2 + 2]-cycloadduct **5a**.[8] However, irradiation as a dilute *aqueous* solution (entry 3) led to much higher conversion. Carrying out the reaction in aqueous LiCl further enhanced the yield (entry 4) and also led to a preference for endo cycloadduct **3a**. These results suggest a "hydrophobic effect",[9] in which the structured solvent compels the nonpolar substrate to assume a compact conformation which maximizes overlap of the two heterocyclic π systems. Small amounts of polar byproduct were determined to be an acyclic, unsaturated carboxylic acid, which may arise from either a ring-opened vinyl ketene[10] or a bicyclic β-lactone.[11]

On the other hand, irradiation in 5 M ethereal $LiClO_4$ also gave good conversion (entry 5), but with a preference

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† All inquiries regarding crystallographic data should be directed to this author.

[1] Presented in preliminary form: West, F. G.; Chase, C. E. *Abstracts of Papers*, 203rd National Meeting of the American Chemical Society, San Fransisco, CA, April 1992; American Chemical Society: Washington, DC, 1992; ORGN 4.

[2] For recent reviews of cyclooctanoid synthesis, see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Oishi, T.; Ohtsuka, Y. Synthetic Studies on Natural Products Possessing Eight- or Nine-Membered Rings. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed., Elsevier: Amsterdam, 1989; Vol. 3.

[3] (a) Review: Rigby, J. H. In *Comprehensive Organic Synthesis, Vol. 5: Combining C–C π-Bonds*; Trost, B. M., Fleming, I., Eds., Pergamon: Oxford, 1991; Chapter 5.2. (b) Kaupp, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 422.

[4] (a) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Wiley: New York, 1975. (b) Brun, P.; Tenaglia, A.; Waegell, B. *Tetrahedron Lett.* **1983**, *24*, 385. (c) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *Ibid.* **1988**, *110*, 5904.

[5] Sieburth, S. McN.; Chen, J. *J. Am. Chem. Soc.* **1991**, *113*, 8163.

[6] (a) deMayo, P.; Yip, R. W. *Proc. Chem. Soc. London* **1964**, 84. (b) Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1964**, *86*, 4212. (c) Rieke, R.; Copenhafer, R. A. *Tetrahedron Lett.* **1971**, 879.

[7] Solvent effects have also been observed in intramolecular 2-pyridone dimerizations: Sieburth, S. McN.; Joshi, P. V. *J. Org. Chem.* **1993**, *58*, 1661.

[8] For recent examples of intramolecular [2 + 2]-photocycloadditions of 2-pyrones, see: (a) Shimo, T.; Yasuda, M.; Tajima, J.; Somekawa, K. *J. Heterocycl. Chem.* **1991**, *28*, 745. (b) Shimo, T.; Tajima, J.; Suishu, T.; Somekawa, K. *J. Org. Chem.* **1991**, *56*, 7150.

[9] Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

[10] The intermediacy of ketenes in 2-pyrone ring-opening products is controversial: (a) McIntosh, C. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1973**, *95*, 247. (b) Pong, R. G. S.; Shirk, J. S. *J. Am. Chem. Soc.* **1973**, *95*, 248. (c) Guthrie, J. P.; McIntosh, C. L.; de Mayo, P. *Can. J. Chem.* **1969**, *48*, 237. (d) Arnold, B. R.; Brown, C. E.; Lusztyk, J. *J. Am. Chem. Soc.* **1993**, *115*, 1576.

[11] (a) Pirkle, W. H.; McKendry, L. H. *J. Am. Chem. Soc.* **1969**, *91*, 1179. (b) Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950.

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Table I. Effect of Solvent on Photolysis of 2a[a]

entry	solvent	ratio **3a:4a:5a**	combined yield[b] (%)
1	$PhCH_3$	1:1:1	15
2	acetone/0.3 M $LiClO_4$	1:1:15	60
3	H_2O	2.1:2.3:1.0	59
4	H_2O/4.7 M LiCl	3.9:2.1:1.0	86
5	Et_2O/5 M $LiClO_4$	1.0:5.7:trace	56
6	H_2O/4.7 M LiCl[c]	1.5:1.0:0	66

[a] See eq 1: X = H, Z = O, R = H. Standard photolysis conditions: **2a** was dissolved in the appropriate solvent in a Pyrex vessel at a concentration of 5–10 mM. After degassing, the reaction was photolyzed (450-W Hannovia medium-pressure Hg lamp) until starting material was consumed (0.5–3 h). [b] Isolated yields after chromatography. Satisfactory IR, ^1H and ^{13}C NMR, and combustion analysis or HRMS data were obtained for **2a–5a**. [c] Reaction was irradiated until all **5a** was consumed (3 h).

for exo [4 + 4]-cycloadduct **4a**. We are currently seeking an explanation for this fortuitous reversal of selectivity.[12] Photolysis in acetone (entry 2) gave mainly [2 + 2]-adduct **5a**.[13] Finally, the ratio of the three cycloadducts was found to be time dependent, with eventual disappearance of **5a** upon extended photolysis (entry 6). This suggested a photolytic cycloreversion of **5a** to **2a**, which was confirmed by the clean photochemical conversion (aqueous LiCl) of a sample of **5a** to a mixture of **3a** and **4a** (1.4:1 ratio). Cycloadducts **3a** and **4a** were photochemically inert.

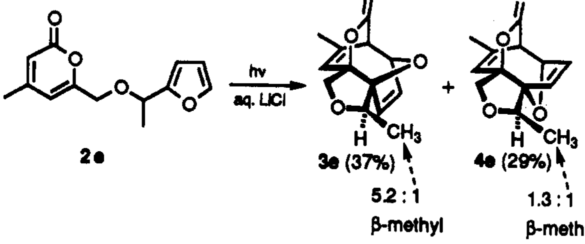
Structural assignments of **3a** and **4a** were accomplished as follows. Warming of [2 + 2]-adduct **5a** in refluxing toluene led to a 1:2 equilibrium mixture of **5a** and endo cycloadduct **3a** via [3,3]-sigmatropic rearrangement.[14] The ability to interconvert **5a** and **3a** further increases the effective endo/exo ratio of the [4 + 4]-cycloadducts. X-ray diffraction analysis of **4a** confirmed its exo stereochemistry.[15] Consistent trends in the ^1H and ^{13}C NMR spectra permitted the assignment by analogy of the isomeric cycloadducts from the other substrates discussed below.

Table II. Effect of Tether and Ring Substitution[a]

substrate	X	Z	R	ratio 3:4	combined yield[b] (%)
2a	H	O	H	1.5:1	66
2b	H	CE_2	H	1:2.4[c]	49
2c	H	S	H	2.4:1	61
2d	Br	S	H	1:1.2	56
2e	H	O	Me	1.3:1[d]	67

[a] See eq 1. All substrates were photolyzed in aqueous LiCl as per Table I, entry 6, except **2b** ($MeOH/H_2O$ (15:85)) and **2d** ($MeOH/H_2O$ (55:45)). [b] Isolated yields. Satisfactory IR, ^1H and ^{13}C NMR, and combustion analysis or HRMS data were obtained for all products. [c] Recovered starting material (7%) also isolated. [d] Isolated as 5.2:1 (**3e**) and 1.3:1 (**4e**) mixtures of diastereomers.

Given optimum conditions for generation of the [4 + 4]-adducts, we tested the effect of tether and pyrone ring substituents using **2a–e** (Table II).[16] The nature of the tether had little effect on the reaction. Thus, malonate (**2b**) and sulfide[17] (**2c,d**) linkages also underwent efficient conversion to cycloadducts. Bromine substitution on the pyrone ring was also tolerated (**2d**). Interestingly, endo [4 + 4]-adduct **3d** underwent a slow, room-temperature thermal conversion to cyclobutane **5d**. Substrate **2e** merits further discussion, since it contains a stereogenic center in the tether (eq 2). Along with the usual endo selectivity, we were pleased to observe significant stereochemical induction by the preexisting center in the endo series. Relative stereochemistry was determined via difference NOE NMR spectroscopy.



(2)

In summary, we have shown that intramolecular [4 + 4]-photocycloaddition of 2-pyrones to pendant furans is an efficient process. Substrates can be easily prepared in one step from simple, readily available heterocyclic precursors. Variation of conditions permits control of endo/exo diastereoselectivity, and the [2 + 2]-cycloadduct can be equilibrated thermally with the endo [4 + 4]-cycloadduct or converted photochemically to a mixture of both [4 + 4]-cycloadducts. Inclusion of a stereogenic center in the tether leads to significant diastereoselectivity in the endo product. Attempts to understand and enhance cycloaddition stereoselectivity are currently underway, and further applications of the photochemistry of 2-pyrones will be reported elsewhere.

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Supplementary Material Available: Experimental procedures for the preparation and photolysis of **2a–e**, with physical data for **2a–e**, **3a–e**, **4a–e** and **5a**, and an ORTEP drawing of **4a** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] For recent discussions of the use of $LiClO_4$–Et_2O in organic synthesis, see: (a) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (b) Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1306. (c) Föhlisch, B.; Krimmer, D.; Gerlach, E.; Käshammer, D. *Chem. Ber.* **1988**, *121*, 1585.

[13] Product **5a** may arise from a triplet pathway. Triplet-sensitized photolysis of 2-pyrones does not lead to [4 + 4]-dimerization, giving instead [2 + 2]- or [4 + 2]-cycloadducts: (a) Pirkle, W. H.; McKendry, L. H. *Tetrahedron Lett.* **1968**, 5279. (b) Van Meerbeck, M.; Toppet, S.; DeSchryver, F. C. *Ibid.* **1972**, 2247.

[14] Heating **3a** in toluene led to an identical ratio of **3a** and **5a**. This suggests a possible approach to equilibrating the initial reaction mixture entirely to the exo [4 + 4]-cycloadduct through combined thermal interconversion of the endo [4 + 4]-cycloadduct with the [2 + 2]-cycloadduct and photochemical isomerization of the [2 + 2]-cycloadduct to [4 + 4]-cycloadducts as per Table I, entry 6. Preliminary studies will be described elsewhere.

[15] The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

[16] To date, cyclic dienes such as furan appear to be required. Preliminary attempts at [4 + 4]-photocycloadditions of 2-pyrones with pendant *acyclic* dienes led to only ring-opened products.

[17] Sulfur-linked adducts **3c,d** and **4c,d** can be considered equivalent to *inter*molecular adducts, since the sulfide linkage should undergo reductive cleavage. All attempts at direct intermolecular crossed [4 + 4]-photocycloadditions between 2-pyrones and excess furan have been unsuccessful.