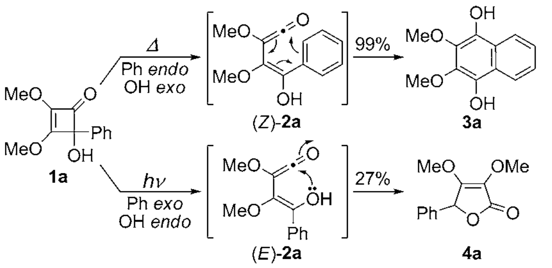
DOI: 10.1002/ange.201200281

An Efficient Flow-Photochemical Synthesis of 5*H*-Furanones Leads to an Understanding of Torquoselectivity in Cyclobutenone Rearrangements**

David C. Harrowven, Mubina Mohamed, Théo P. Gonçalves, Richard J. Whitby, David Bolien, and Helen F. Sneddon*

Dedicated to Professor Philip Parsons on the occasion of his 60th birthday

Thermal rearrangements of cyclobutenones give access to numerous ring systems and have proven especially valuable for the de novo synthesis of quinones, benzoquinones, and related heteroaromatics with dense substitution.[1–3] A classic example is the rearrangement of arylcyclobutenone **1a**→**3a**,[1a] where the emergence of a protocol to realize this transformation in near quantitative yield means it achieves many of the ideals for a green-chemical reaction.[2,4] In principle, such criteria could also be met by the related photochemical rearrangement of **1a** to 5*H*-furanone **4a**, yet this reaction has lain almost dormant since its introduction by Moore et al. in 1988 because of the low yields attained in each of the published examples (27–51 %, Scheme 2).[5]



Scheme 1. Thermal and photochemical rearrangements of 4-hydroxycyclobutenone **1**.

Herein we show how the photochemical rearrangement of 4-hydroxycyclobutenones can be realized in near quantitative yield under continuous flow using a simple, low-cost device with an interchangeable low-energy light source.[6,7] In addition, our results challenge the long-established view that the electrocyclic opening of cyclobutenones is a torquoselective process, with the thermochemical and photochemical rearrangements displaying complimentary torquoselectivity,[1e] as implicated by the aforementioned examples (Scheme 1).

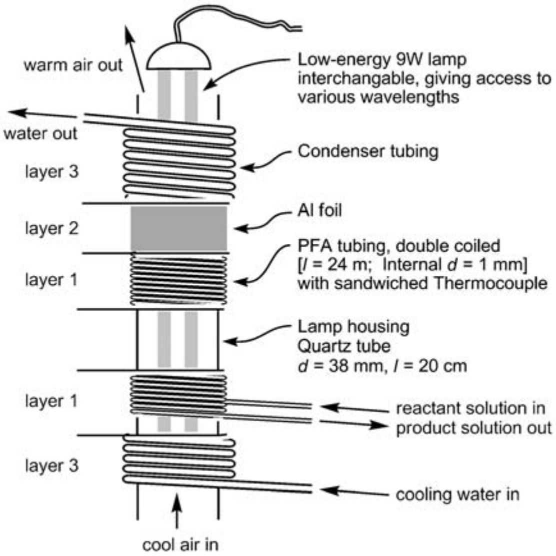


Figure 1. Flow photochemical reactor (cut-away between grey lines). PFA = perfluoroalkoxy.

Before our investigation could begin, we needed to construct a photochemical reactor for use under flow. Taking inspiration from the pioneering work of Booker-Milburn and co-workers,[6] we assembled the apparatus depicted in Figure 1.[8] A key difference between this and the published setup was our use of inexpensive, low-energy 9 W lamps in place of the more conventional 400–600 W medium-pressure mercury discharge lamps. While recognizing that this might limit the throughput of material, we hoped that it would allow optimization for the wavelength to become "as simple as changing a light bulb", since lamps spanning a wide spectrum of wavelengths have become available at low cost in recent years.[8]

Our study began with an investigation of the rearrangement of phenylcyclobutenone **1a** to 5*H*-furanone **4a** as the reported yield of 27 % was among the lowest disclosed in the original study.[5] When conducted under flow using tetrahydrofuran (THF) as solvent, a 9 W broad-spectrum UVB lamp

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[*] Prof. D. C. Harrowven, M. Mohamed, T. P. Gonçalves, Prof. R. J. Whitby, D. Bolien
Chemistry, University of Southampton
Highfield, Southampton, SO17 1BJ (UK)
E-mail: dch2@soton.ac.uk
Dr. H. F. Sneddon
GlaxoSmithKline, Stevenage, Hertfordshire, SG1 2NY (UK)

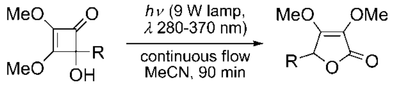
[**] Financial support from GlaxoSmithKline, the ERDF (IS:CE-Chem & InterReg IVa) and the EPSRC (including support for the Iridis cluster) are gratefully acknowledged. Rob Wheeler and Andy Craven are thanked for valuable advice.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201200281.

(280–370 nm)[8] and a residence time of 120 min, we were pleased to attain 5*H*-furanone **4a** in 54% isolated yield, double that given using a conventional photochemical setup. NMR analysis of crude product mixtures given at various residence times showed many side products, with the ratio of product to by-products worsening as the residence times were increased. In seeking to eliminate side reactions involving the product, a comparison was made between its UV–visible spectrum and that of the starting material. Each showed strong absorbance below 275 nm, with cyclobutenone **1a** exhibiting additional absorbance bands at 295 and 315 nm. A switch to a 9 W UVB narrow-spectrum lamp giving greatest intensity in the region 310–320 nm was therefore implicated and, in the event, this did lead to a modest improvement in yield to 65%.

The step-change in performance we sought was realized with a switch of solvent from THF to acetonitrile. Indeed, through this simple expedient the rearrangement of cyclobutenone **1a** to furanone **4a** was achieved in 97% isolated yield at 0.05 M concentration with a residence time of 1 h. Interestingly, under irradiation from a UVA lamp (350–395 nm) the rearrangement was clean but proceeded at a much slower rate (<10% conversion after 1 h). The broad-spectrum UVB lamp (280–370 nm) proved as effective as the narrow band lamp, while irradiation for 1 h using a UVC lamp (254 nm) gave complete conversion but the product **4a** was heavily contaminated with by-products which accounted for around 5% of the total mass balance.[8]

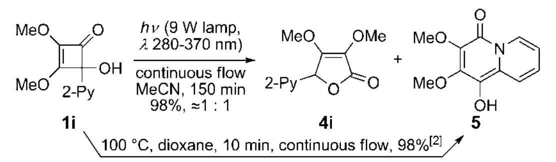
To explore the generality of the method, a range of 4-hydroxycyclobutenones **1b–h** were prepared by the addition of alkyl-, aryl-, alkyny-, and heteroaryl-lithium reagents to dimethyl squarate.[1–3] Pleasingly, under the aforementioned conditions, each underwent smooth rearrangement to the corresponding furanones **4b–h** in excellent yield (Scheme 2).



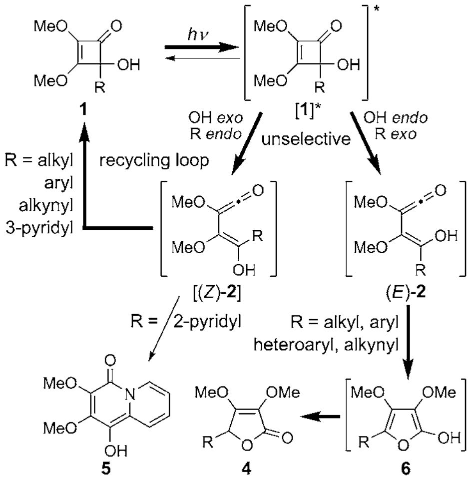
1	yield,	lit. yield	**4**
a, R = Ph	99%	[27%]	**a**, R = Ph
b, R = *n*Bu	95%		**b**, R = *n*Bu
c, R = *t*Bu	96%	[39%]	**c**, R = *t*Bu
d, R = Ph-CC	95%	[28%]	**d**, R = Ph-CC
e, R = *o*-MeOC$_6$H$_4$	97%	[51%]	**e**, R = *o*-MeOC$_6$H$_4$
f, R = *p*-Me$_3$SiC$_6$H$_4$	93%		**f**, R = *p*-Me$_3$SiC$_6$H$_4$
g, R = *p*-*t*BuC$_6$H$_4$	92%		**g**, R = *p*-*t*BuC$_6$H$_4$
h, R = 3-Pyridyl	94%		**h**, R = 3-Pyridyl

Scheme 2. Photochemically induced cyclobutenone rearrangements of **1a–h** [in a flask] and under continuous flow.

Our survey revealed a striking anomaly in respect of the (2-pyridyl)-cyclobutenone **1i**. In this case the photochemical rearrangement took longer to run to completion and gave a 1:1 mixture of furanone **4i** and quinolizinone **5** (Scheme 3). This anomalous result casts doubt on the view that rearrangements of 4-hydroxycyclobutenones **1** each proceed by torquoselective opening to a vinylketene, with thermolysis giving (*Z*)-**2** and photolysis giving its geometric isomer (*E*)-**2** (Scheme 1).[1e] Rather, it suggests that the photoinduced electrocyclic opening of **1** gives rise to a mixture of (*E*)- and (*Z*)-vinylketenes **2**, with (*E*)-**2** giving cyclization to furan **6** en route to furanone **4** while (*Z*)-**2** reverts back to cyclobutenone **1** unless it too can be captured by an internal nucleophile (Scheme 4).

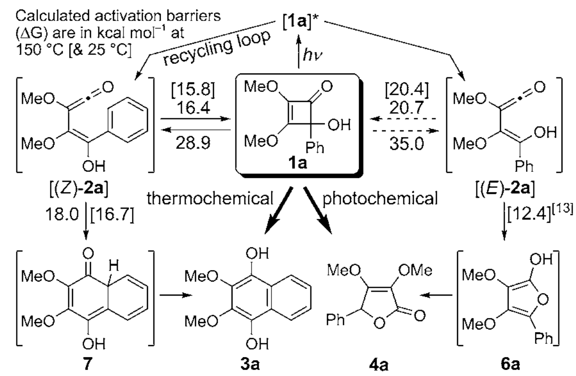


Scheme 3. Photochemical rearrangement of (2-pyridyl)-cyclobutenone **1i** under continuous flow.



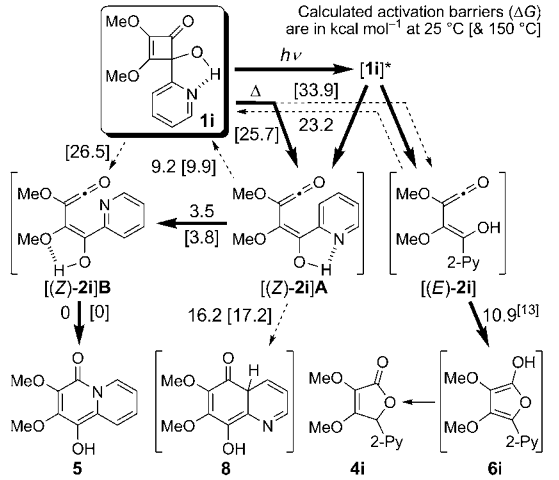
Scheme 4. Revised mechanism for the photochemical rearrangement of 4-hydroxycyclobutenones.

To explore this hypothesis we decided to model the available cyclization pathways for the intermediate (*E*)- and (*Z*)-vinylketenes, **2a** and **2i**, bearing phenyl- and (2-pyridyl)-residues, respectively. The method chosen used DFT calculations at the B3LYP/6-311G(d,p) level to establish the course of the reaction (Gaussian 09),[9–11] with energies refined for required points using the coupled cluster method CCSD(T)/6-31G(d) (GAMESS(US), Schemes 5 and 6).[2,12] Notably, the calculated barrier for 6π-electrocyclic closure of vinylketene (*Z*)-**2a** to **7** at 25 °C (16.7 kcal mol^{-1}) exceeded that for 4π-electrocyclic closure to the starting material **1a** (15.8 kcal mol^{-1}), consistent with the recycling of this intermediate. The situation was reversed for its geometric isomer (*E*)-**2a**, where the calculated barrier for returning cyclobutenone **1a** (20.4 kcal mol^{-1}) exceeded that for cyclization to furan **6a** (12.4 kcal mol^{-1}[13]) leading to the observed product **4a**. For the thermal rearrangement of cyclobutenone **1a** torquoselective opening was evidenced by the calculated activation energies for formation of vinylketenes (*E*)-**2a** (35.0 kcal mol^{-1}) and (*Z*)-**2a** (28.9 kcal mol^{-1}), respectively, at 150 °C.



Scheme 5. Calculated energy barriers in photo- and thermochemical rearrangements of cyclobutenone **1b**.

For 2-pyridylcyclobutenone **1i** (Scheme 6), calculations showed that cyclization of vinylketene (*Z*)-**2i** to quinolizinone **5** was spontaneous on adoption of an appropriate reactive conformer, thereby diverting it away from the usual recycling loop. In parallel, the geometric isomer (*E*)-**2i** favors cyclization to furan **6i** (10.9 kcal mol^{-1})[13] over 4π-electrocyclic closure to cyclobutenone **1i** (23.2 kcal mol^{-1}) and gives the expected furanone **4i**. Torquoselectivity in the thermal opening of cyclobutenone **1i** to vinylketene (*Z*)-**2i** was again evidenced, with calculations additionally indicating that a hydrogen bond between the pyridine and hydroxyl residues leads to a significant rate enhancement. This is manifest experimentally by the realization of a near quantitative yield for the thermolysis of **1i** to **5** at 100 °C for 10 min under continuous flow (Scheme 3), when related aryl- and heteroaryl-cyclobutenone rearrangements typically require prolonged heating at 150 °C to achieve a similar outcome.[2] Further observations relating to torquoselectivity in the thermochemical rearrangements of cyclobutenones are given in the Supporting Information.



Scheme 6. Calculated activation energies in the photo- and thermochemical rearrangement of cyclobutenone **1i**.

In conclusion, we have shown that many 4-hydroxycyclobutenones can be transformed into 5*H*-furanones in near quantitative yield using an inexpensive flow-photochemical setup. The results attained challenge a long-held view that the thermal and photochemical rearrangements of cyclobutenones display complementary torquoselectivity in their electrocyclic opening to a vinylketene.[1e] Indeed, they provide a detailed mechanistic understanding of both the thermal and photochemical rearrangements of 4-hydroxycyclobutenones giving valuable insights into their scope and limitations.

Received: January 11, 2012
Revised: March 6, 2012

Keywords: cyclobutenones · density functional calculations · photochemistry · rearrangements · small ring systems

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