

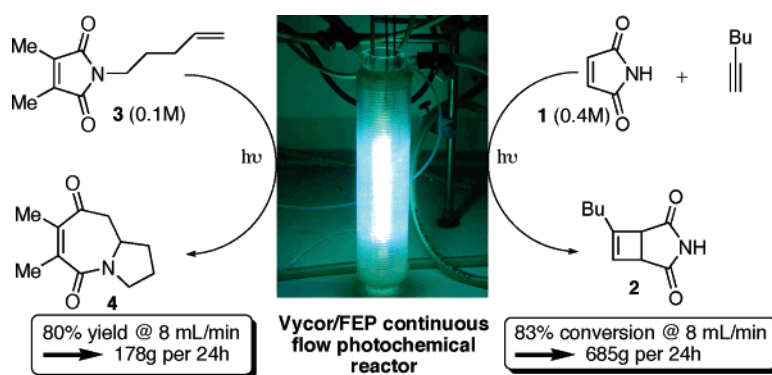
A Practical Flow Reactor for Continuous Organic Photochemistry

Benjamin D. A. Hook,[†] Wolfgang Dohle,[†] Paul R. Hirst,[†] Mark Pickworth,[†]
Malcolm B. Berry,^{*,‡} and Kevin I. Booker-Milburn^{*,†}

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K., and GlaxoSmithKline, Continuous Chemistry, Strategic Technologies, Gunnels Wood Road, Stevenage, Herts. SG1 2NY, U.K.

k.booker-milburn@bristol.ac.uk

Received April 8, 2005



Compact flow reactors have been constructed and optimized to perform continuous organic photochemistry on a large scale. The reactors were constructed from commercially available or customized immersion well equipment combined with UV-transparent, solvent-resistant fluoropolymer (FEP) tubing. The reactors were assessed using the [2 + 2] photocycloaddition of maleimide **1** and 1-hexyne forming the cyclobutene product **2** and the intramolecular [5 + 2] photocycloaddition of 3,4-dimethyl-1-pent-4-enylpyrrole-2,5-dione **3** to form the bicyclic azepine **4**. The reactors were shown to be capable of producing >500 g of **2** and 175 g of **4** in a continuous 24 h processing period. Due to the facile control of irradiation time, the continuous flow reactor was also shown to be superior to a batch reactor for performing a problematic photochemical reaction on a larger scale.

Introduction

Historically, synthetic organic photochemistry has provided an extremely powerful method for the conversion of simple substrates into often complex products.¹ In a modern context, as synthetic photochemistry generally uses no reagents or catalysts, it is one of the key technologies for clean synthesis. Within academe, synthetic organic photochemistry has made an enormous contribution to the construction of diverse molecular architectures. For example, many notable complex natural products have been synthesized using key photocycloaddition reactions.² However, despite several impressive large-scale industrial applications (e.g., caprolactam

synthesis for nylon production, vitamin D synthesis), the pharmaceutical industry has not generally embraced synthetic organic photochemistry in the routine synthesis of new drug substances. Specifically, the problems associated with performing preparative synthetic photochemistry on a large scale have been perceived as being preventative to its routine application in pharma.

Synthetic organic photochemistry is usually performed in solution using immersion well reactors. These are fixed volume batch reactors irradiated from within using a single mercury vapor discharge lamp (Figure 1). Other common systems include external irradiation using multiple lamps (Rayonet-type apparatus) and falling film reactors.³

[†] University of Bristol.

[‡] GlaxoSmithKline.

(1) For general reviews of preparative synthetic organic chemistry, see: (a) *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Royal Society of Chemistry: London, 1986; Special Publication No. 57. (b) *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, 2004.

(2) (a) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1454–1473. (b) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297–588. (c) Wender, P. A.; Siggel, L.; Nuss, J. M. *Org. Photochem.* (Padwa, A., Ed.) **1989**, *10*, 357–473.

(3) *Best Synthetic Methods: Photochemical Synthesis*; Ninomiya, I., Naito, T., Ed.; Academic Press: London, 1989.

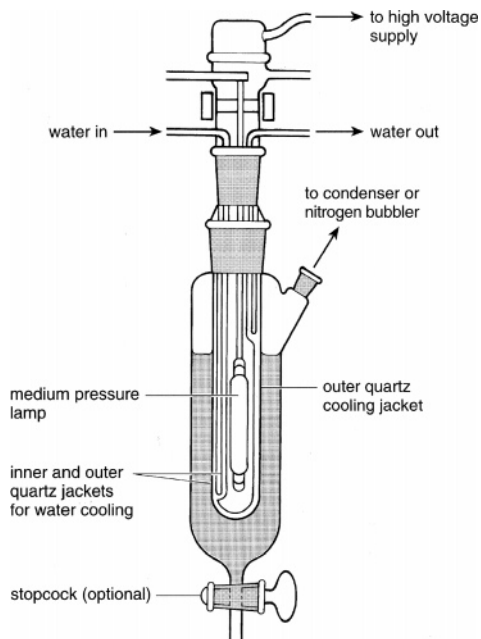


FIGURE 1. Immersion well batch photochemical reactor.⁴

These types of batch apparatus have a limited application for large-scale photochemical synthesis as the majority of the photochemistry occurs within a short radius of the lamp, and therefore, the amount of solution that can be effectively irradiated by the UV source is scale dependent. Although falling film reactors can partly alleviate these problems, the short gravity-controlled residence time with such systems means that the scaled up photosylate has to be continuously recycled to achieve high conversions. One option is to use highly concentrated reaction solutions in conjunction with higher power UV sources and Griesbeck et al recently described a very promising novel falling film reactor using a high-power selective UV excimer source.⁵

In this paper, we describe the design and construction of a practical *single pass continuous flow* photochemical reactor that demonstrates that large scale (~500 g) organic photochemical synthesis can be performed easily and efficiently within a standard laboratory fumehood. Unlike batch reactors the efficiency of this device is scale independent. The continuous flow reactor can produce any desired throughput of feedstock by flowing for longer periods of time and without redesigning the reactor for larger quantities of product.

Results and Discussion

It was conceived that a possible solution to the scale-up problem central to organic photochemistry was to construct a novel flow reactor consisting of coils of UV transparent tubing wound round a traditional water-

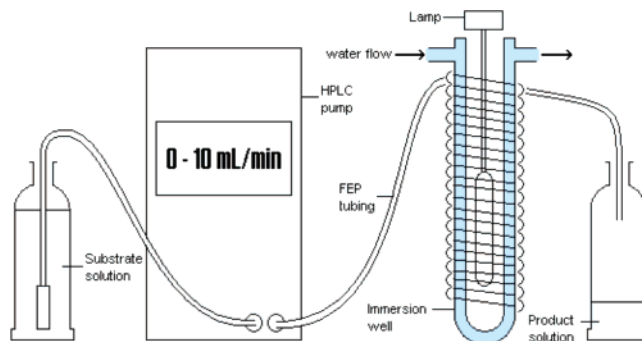


FIGURE 2. Schematic of FEP continuous flow reactor.

cooled immersion well. The reaction solution would be driven around the reactor via a common HPLC pump and irradiation time (residence time) defined by the flow rate. In this sense, it was envisioned that a large volume of photosylate could be processed continuously, and in a *single pass*, under conditions that closely resemble the first few millimeters around a UV lamp in any conventional immersion well batch reactor setup. The multiple coils of tubing would ensure a very large reactor surface area-to-volume ratio, yet the physical dimensions of the reactor required would be no larger than a standard batch immersion well.

Conventional materials such as quartz and Pyrex were considered unsuitable for the tubing since they are not easily manipulated into reactor coils. Consequently, UV-transparent fluoropolymer tubing was proposed as a viable alternative. Fluorinated ethylenepropylene (FEP) is a very versatile, solvent resistant, polymeric material, and tubing constructed from this has excellent UV-transmission properties. Such properties were first exploited by Feehs in 1971 in the construction of a gas-phase flow reactor for the photochemical synthesis of methyl chloride from methane and chlorine gas.⁶ Similarly, fluoropolymer tubing has been used extensively in postcolumn photochemical reaction detectors for HPLC since Scholten first compared the use of PTFE coils against quartz and Pyrex capillaries for this purpose in 1980.⁷

Initially, prototype reactors were constructed by winding FEP tubing around a cylindrical framework within which was placed the immersion well. The efficiency of these were tested using robust photochemical reactions previously developed by us.⁸ At low flow rates (0.5–1.0 mL/min) good conversions were achieved but results at higher flow rates were disappointing. An immediately better design was realized by simply wrapping the FEP tubing directly onto the outside of the immersion well, thus bringing the reaction solution much closer to the UV source (Figure 2). Except where stated, all reactions

(6) Feehs, R. H. US Pat. 3,554,887, 1971.

(7) For the use of PTFE and FEP tubing to construct postcolumn photochemical detectors for HPLC analysis, see: (a) Scholten, A. H. M. T.; Welling, P. L. M.; Brinkman, U. A. Th.; Frei, R. W. *J. Chromatogr. A* **1980**, *199*, 239–248. (b) Cicciooli, P.; Tappa, R.; Guiducci, A. *Anal. Chem.* **1981**, *53*, 1309–1311. (c) Shih, Y. T.; Carr, P. W. *Anal. Chim. Acta* **1984**, *159*, 211–228. (d) Selavka, C. M.; Jiao, K.-S.; Krull, I. S. *Anal. Chem.* **1987**, *59*, 2221–2224.

(8) For example, the intermolecular [2 + 2] photocycloaddition of tetrahydrophthalic anhydride with alkynols: Booker-Milburn, K. I.; Cowell, J. K.; Delgado Jimenez, F.; Sharpe, A.; White, A. *J. Tetrahedron* **1999**, *55*, 5875–5888.

(4) *Experimental Organic Chemistry, Standard and Microscale*, 2nd ed.; Harwood, L. M., Moody, C. J., Percy, J. M., Eds.; Blackwell Science Ltd.: Cambridge, MA, 1999; p 61.

(5) Recently, Griesbeck et al. have developed a novel falling film reactor based on the use of a high-power XeCl excimer lamp which is a monochromatic UV source at 308 nm. These authors have shown that this technology can deliver 50–200 g of photoproduct from various established photochemical reactions: Griesbeck, A. G.; Bondock, S.; Maptue, N.; Oelgemöller, M. *Photochem. Photobiol. Sci.* **2003**, *2*, 450–451.

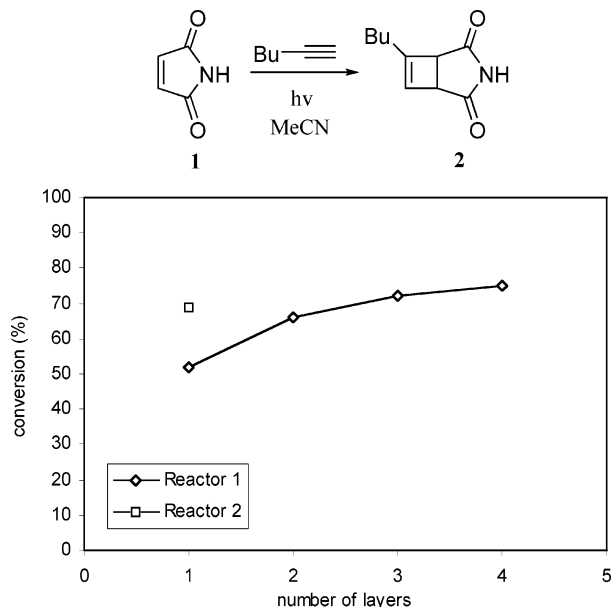


FIGURE 3. Effect of the number of layers of FEP on reactor 1 in the conversion of **1** to **2** (0.1 M at 4 mL/min).

were performed using a 400 W medium-pressure mercury vapor discharge lamp powered by a 400 W supply.

Reactor 1: Commercial Immersion Well/Narrow Bore FEP. The first reactor was constructed (see Figure 6) by winding FEP tubing of dimensions 0.7 mm inner diameter (i.d.) \times 1.1 mm outer diameter (o.d.) around a commercially available quartz immersion well (57 mm (d) \times 390 mm (l)) fitted with a Pyrex filter. The efficiency of this reactor was assessed using the [2 + 2] photocycloaddition reaction between maleimide **1** and 1-hexyne in conjunction with a 400 W medium-pressure Hg lamp. At full conversion, in a standard immersion well batch reactor this reaction gives >90% yield of cyclobutene **2** (0.1 M) and a small quantity of the maleimide [2 + 2] photodimer.⁸ Conversion was calculated by ¹H NMR analysis of samples of the photosylate expelled from the reactor.

The effect of the number of layers of tubing was investigated by repeating the [2 + 2] reaction at set concentration and flow rate (0.1 M at 4 mL/min) with one to four layers (Figure 3). Increasing the number of layers of tubing increases the internal volume of the reactor and subsequently the residence time. It was interesting to note that the majority of the conversion was achieved in the first layer and that four layers was essentially optimum for this system.

The direction of flow was investigated on the four-layer system. Previously, the direction of flow was such that the reaction solution entered the innermost layer of tubing first (when there were multiple layers). It was intriguing to find that when the flow was reversed and the reaction solution entered the outermost layer of tubing first, a higher conversion to **2** was achieved (85% at 0.1 M concentration and 4 mL/min flow rate vs 77% when the solution entered the innermost layer first).

Experiments were performed with varying concentration and flow rate to discover the optimum conditions for the [2 + 2] reaction in the four-layer reactor 1 (Figure 4). As expected, conversion decreased with increasing

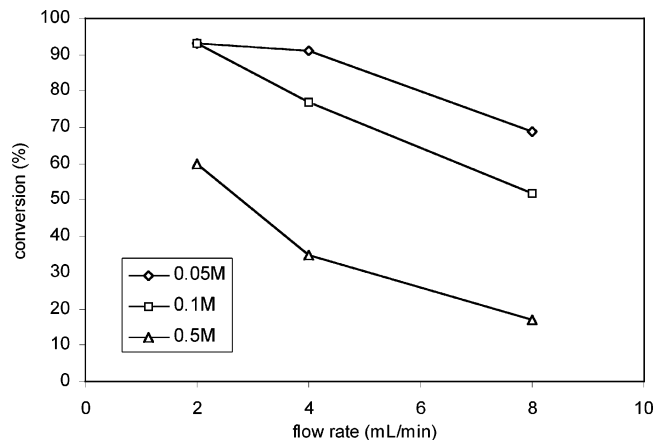


FIGURE 4. Effect of conversion of **1** to **2** with increasing flow rate using optimized four-layer reactor 1.

concentration and flow rate, consistent with the fact that more concentrated reaction solutions will involve more efficient absorption of photons. It was pleasing to note that at a concentration and flow rate of 0.1 M and 2 mL/min, respectively, complete conversion was achieved, representing a projected 24 h yield of **2** of almost 50 g. Greater projected 24 h yields could readily be achieved using faster flow rates and more concentrated solutions, but at lower conversion (e.g., 0.5 M at 8 mL/min, 17% conversion = 175 g of **2** per 24h).

Reactor 2: Custom Immersion Well/Narrow Bore FEP. The proximity of the reaction solution to the radiation source was considered a key factor governing the efficiency of the flow reactor. A custom immersion well of smaller dimensions (46 mm (d) \times 300 mm (l)) was constructed from Pyrex (Figure 6a), allowing the tubing to be held significantly closer to the lamp. Initially, one layer of FEP was used and the [2 + 2] reaction performed at 0.1 M at 4 mL/min to give a conversion of 69% (cf. 52% for the same experiment performed on reactor 1 (Figure 3)). As the internal volume, and therefore residence time, of both reactors 1 and 2 were essentially the same (ca. 13–14 mL), the conversion enhancement can be attributed to the increased proximity of the substrate to the radiation source and hence a more effective capture of the UV light. An optimized system for reactor 2 employed five layers of FEP tubing with the reaction solution entering the outermost layer of tubing first. At a flow rate of 0.1 M at 4 mL/min full conversion was achieved, representing a projected 24 h yield of 92 g of **2**, i.e., double that of reactor 1.

Reactor 3: Custom Immersion Well/Wide Bore Tubing. A key limitation of reactors 1 and 2 was the narrow bore FEP tubing initially employed (0.7 mm i.d.). Use of the five-layer reactor 2 at flow rates greater than 4 mL/min led to considerable back pressure and subsequent rupturing of the tubing. Furthermore, this narrow bore tubing was also susceptible to blockage in reactions where precipitation of products/byproducts was an issue. An ultimately more practical design was achieved by combining the custom immersion well from reactor 2 with wider bore tubing of dimensions 2.7 mm i.d. \times 3.1 mm o.d. As well as resolving the blockage issues, the new tubing proved to be considerably more resistant to damage acquired in the construction procedure and was

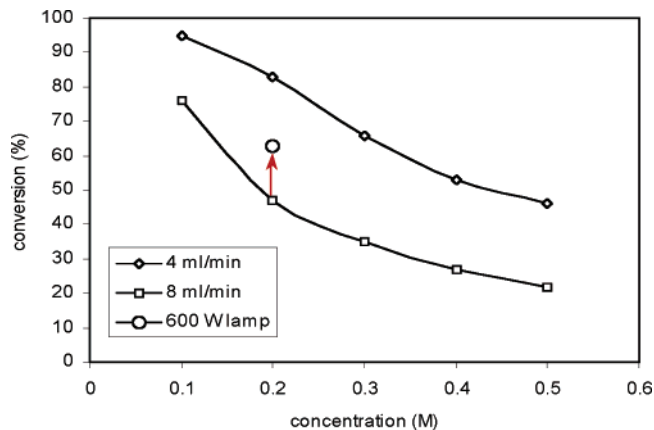


FIGURE 5. Conversion to **2** vs increasing concentration and power.

able to hold a much greater volume of liquid around the lamp without generating back-pressure, even at flow rates up to 10 mL/min.

Using an optimized system with three layers of FEP tubing (internal volume 210 mL), reactor 3 was investigated using the same experiments performed previously. The direction of flow such that the solution entered the outermost layer first was found to be superior (76% at 0.1 M at 8 mL/min versus 68% for innermost layer first), reaffirming the result from reactor 1.

A conversion vs concentration study was performed on reactor 3 at two flow rates (Figure 5). As well as being enormously superior in a practical sense, reactor 3 gave higher conversions than previous designs (76% at 0.1 M at 8 mL/min vs 69% reactor 2; 52% reactor 1). A reaction performed at 0.2 M at 4 mL/min gave 83% conversion, representing a 24 h yield of **2** of over 170 g.

To assess the impact of power vs conversion, reactor 3 was used in conjunction with a 600 W lamp. It was extremely gratifying to find that at 600 W the conversion increased to 62% (0.2 M at 8 mL/min) from 46% at 400 W. This represents a 35% relative increase in conversion for a 50% increase in power.

Vycor Reactor. Reactors 1–3 were either constructed from Pyrex or, when constructed from quartz, employed a Pyrex filter. The use of Pyrex effectively limits the transmission of radiation to wavelengths above approximately 280 nm. Considering that the λ_{\max} of the key maleimide chromophore for [2 + 2] photocycloaddition occurs in the approximate region 280–300 nm, it was evident that some of the available radiation of requisite energy was being absorbed by the Pyrex. It was proposed that Vycor, which filters below approximately 220 nm, was potentially a more useful material for this particular reaction.

A custom immersion well of dimensions 50 mm (d) × 300 mm (l) was constructed from Vycor. Using an optimized system with three layers of FEP the [2 + 2] reaction was performed with outstanding results compared to previous reactors. With the standard 400 W lamp an 88% conversion at 0.3 M at 6 mL/min was observed. Using a 600 W lamp, a conversion of 83% was achieved at 0.4 M at 8 mL/min representing a projected yield of **2** of over 685 g per 24 h (Table 1).

Twenty-Four Hour Reaction. To test the durability of the flow reactors and the validity of the projected 24 h

TABLE 1. Results from the Optimized Vycor Reactor Showing Conversion of **1** to **2** and Projected 24 h Yields

conc (M)	lamp (W)	layers of FEP	flow rate (mL/min)	conversion (%)	projected 24 h yield of 2 (g)
0.2	400	1	8	88	363
0.3	400	3	6	88	408
0.4	600	3	8	83	685

yields quoted thus far, the [2 + 2] reaction was performed continuously over a period of 24 h. The reaction was carried out on the three-layer reactor 3 at 0.1 M at 4 mL/min using a 400 W lamp and is projected to give full conversion (Figure 5) and approximately 105 g of cyclobutene product **2**. Purification of the resultant 6 L of photosylate afforded 85 g of pure **2**. Although this was slightly less than anticipated (82% actual isolated yield), the losses were attributed to the purification procedure (batch chromatography) rather than any losses during the reaction itself, since NMR analysis of the continuous photosylate at various times throughout the 24 h run showed full and clean conversion to product. It was gratifying to observe that the reactor performed continuously for this length of time with no blockages or overheating problems and with no apparent degradation or colorization of the FEP tubing.

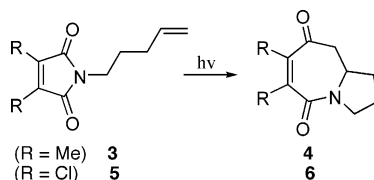
[5 + 2] Intramolecular Photocycloaddition of Maleimides. Previously, we have reported the intramolecular photocycloaddition of N-alkylated maleimides.⁹ In a batch reactor, photocycloaddition of 3,4-dimethyl-1-pent-4-enylpyrrole-2,5-dione **3** proceeds cleanly to 100% conversion, giving high isolated yields of bicyclic azepine **4**. It was proposed that this robust reaction was well suited to scale-up using an optimized flow reactor. Initially, reactor 3 was used (Pyrex immersion well, three layers of FEP) in conjunction with a 400 W lamp. A 0.1 M solution of **3** irradiated at 2 mL/min gave 79% isolated yield of **4**, representing a significant 24 h yield of 44 g.

Using the optimized Vycor reactor (three layers of FEP) and a 400 W lamp, a 0.1 M solution of **3** was irradiated at 8 mL/min flow rate, giving an isolated yield of **4** of 80%. This highly significant result represents a 24 h yield of **4** of 178 g, which is *over four times* the yield from the Pyrex reactor and at the same high conversion and clearly demonstrates the superiority of a Vycor based set up for maleimide photochemistry.

The reactors described so far have been optimized on the basis of two photochemical reactions that are clean and high yielding. The residence time, UV transmission, and lamp power were maximized to give the greatest possible conversion for these two cases. However, many photochemical reactions are not clean, particularly when the products of the initial reaction are able to undergo further photochemical transformations. In a batch reactor, the reaction must be stopped before significant product degradation occurs and the reaction repeated as required in order to acquire the desired quantity of product. Using a flow reactor, the residence time can be finely

(9) (a) Booker-Milburn, K. I.; Anson, E. A.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, 1473–1482. (b) Booker-Milburn, K. I.; Hirst, P.; Charmant, J. P. H.; Taylor, L. H. *J. Angew. Chem., Int. Ed.* **2003**, *42*, 1642–1644. (c) Booker-Milburn, K. I.; Baker, J. R.; Bruce, I. *Org. Lett.* **2004**, *6*, 1481–1484.

TABLE 2. Continuous [5 + 2] Photocycloaddition Showing Projected 24 h Yields



R	conc (M)	reactor	layers of FEP	flow rate (mL/min)	product	isolated yield (%)	projected 24 h yield (g)
Me	0.1	reactor 3	3	2	4	79 ^a	44
Me	0.1	Vycor	3	8	4	80 ^a	178
Cl	0.01	reactor 3	1	10	6	68 ^a	23
Cl	0.02	reactor 3	1	10	6	67 ^b	45

^a Based on purification of 50 mL of photosylate. ^b Based on purification of 1.5 L of photosylate.

tuned by adjusting the volume of reactor and flow rate. In this way, problematic photochemical reactions can be performed continuously, achieving the highest possible yield of product and limiting byproduct formation.

To demonstrate this principle, the [5 + 2] intramolecular photocycloaddition reaction of 3,4-dichloro-1-pent-4-enyl-pyrrole-2,5-dione **5** to form the bicyclic azepine **6** was selected.⁹ This reaction is currently used by us as the key step in the total synthesis of *Stemona* alkaloids, and the azepine **6** is required in multigram quantities. In a batch reactor, a maximum 66% yield of **6** can be achieved after 30 min irradiation with a 125 W lamp (0.02 M concentration). Further irradiation leads to degradation of product, possibly due to dimerization and a significant drop in yield is observed. Because of the volume constraints presented by the batch photochemical reactors in our possession (100–400 mL) this useful product could only ever be produced in a maximum of 0.5–1 g batches. In a continuous-flow system, product degradation was limited by employing a dilute reaction solution and reducing the irradiation time by using a Pyrex reactor (reactor 3) with only one layer of FEP tubing (volume 60 mL) and using the highest possible flow rate of 10 mL/min. Initially, irradiation of a 0.01 M solution of **5** in dichloromethane under these conditions afforded a 68% isolated yield of **6** representing a 24 h yield of 23 g. Gratifyingly, irradiation of a 0.02 M solution of **5** at the same flow rate afforded essentially the same isolated yield (67%) of **6**, representing a very significant 24 h yield of 45 g (Table 2). Use of the Vycor reactor in this case resulted in extensive degradation of product, a consequence of too long a residence time in this superior reactor. The limiting factor here was the HPLC pump available (maximum flow rate 10 mL/min). With pumps of greater flow rates, use of the much more efficient Vycor reactor should be viable allowing for significantly greater yields of **6** per unit time.

Conclusion

In conclusion, new and practical continuous flow photochemical reactors have been designed by using UV-transparent FEP tubing in conjunction with established UV lamp technology. These reactors have demonstrated, for the first time, that preparative synthetic organic photochemistry can be carried out continuously, on

various scales, using readily available components in a standard laboratory fumehood. Using the equipment described it would be possible to prepare over 500 g of cyclobutene **2** and over 175 g of bicyclic azepine **4** in a 24 h processing period. It is reasonable to speculate that using several reactors in parallel that it should be possible to synthesize kilograms of product per day.

The simplicity of the reactor design should ensure that customized versions can be easily constructed to best suit the UV source and photochemistry studied. This principle was demonstrated by the application of a flow reactor to the problematic photocyclization of dichloromaleimide **5**, which required a limited irradiation time. We hope that our developments in this area will stimulate chemists in industry and academe to consider continuous photochemistry as a viable method for the synthesis of complex organic molecules on scale.

Construction of Flow Reactors. 1. PTFE tape was wound around the top and bottom of the immersion well to allow the first layer of FEP tubing to grip to the surface (Figure 6b).

2. Leaving a surplus length of approximately 1 m, the tubing was wound on, starting at the top of the immersion well working downward. It was convenient to wind the tubing directly off its storage roll and on to the immersion well, employing two people. When the first few turns had been wound, the beginning of the layer was secured using sticky tape (Figure 6c).

3. When the first layer was complete, the second layer was wound on top of the first, working from the bottom of the immersion well upward. When the first few turns had been wound, the “junction” between layer 1 and layer 2 was secured using sticky tape.

4. When the required number of layers had been wound and secured in this way, the tubing was cut from its storage roll, leaving a further 1 m length surplus. The complete reactor (Figure 6d) was tightly covered in two layers of aluminum foil to prevent the escape of UV irradiation.

5. The appropriate end of tubing (depending on required direction of flow) was attached to the HPLC pump using standard HPLC connectors and the opposite end arranged so that expelled photosylate could be collected in a suitable vessel.

Individual Reactor Details. Reactor 1 was constructed by winding four layers of FEP tubing of dimensions 0.7 mm i.d. × 1.1 mm o.d. around a commercial

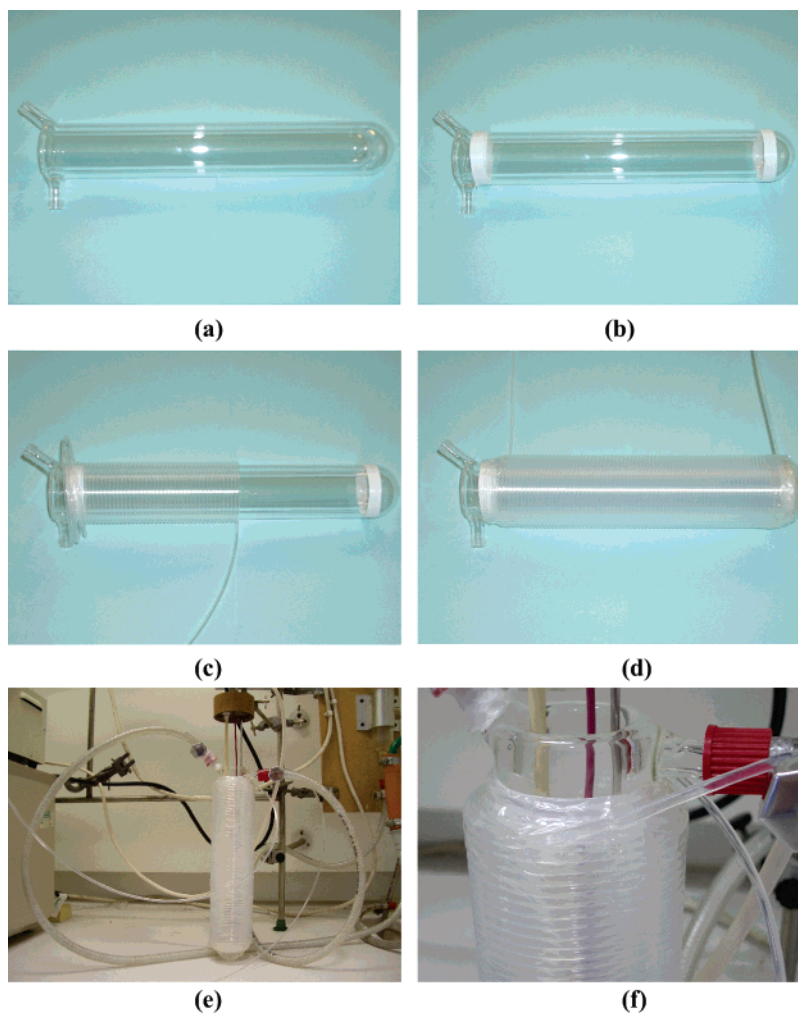


FIGURE 6. Construction pictures: (a) custom Pyrex/quartz/Vycor cooling jacket; (b) with Teflon tape; (c) halfway through the first layer; (d) complete with three layers; (e) attached to water supply and HPLC; (f) close-up of FEP tubing (2.7 mm i.d. \times 3.1 mm o.d.).

quartz immersion well, 57 mm (d) \times 39 cm (l), fitted with a Pyrex filter. The tubing covered 22 cm of the length of the immersion well, giving approximately 200 turns of tubing per layer, a total length of tubing of 150 m, and a total internal volume of the tubing of 60 mL.

Reactor 2 was constructed by winding five layers of FEP tubing of dimensions 0.7 mm i.d. \times 1.1 mm o.d. around a custom built Pyrex immersion well of dimensions 46 mm (d) \times 30 cm (l). The tubing covered 25 cm of the length of the cooling jacket, giving approximately 227 turns of tubing per layer, a total length of tubing of 176 m, and a total internal volume of the tubing of 67 mL.

Reactor 3 was constructed by winding three layers of FEP tubing of dimensions 2.7 mm i.d. \times 3.1 mm o.d. around the custom Pyrex immersion well. The tubing covered 25 cm of the length of the cooling jacket, giving approximately 80 turns of tubing per layer, a total length of tubing of 37 m, and a total internal volume of the tubing of 210 mL.

The Vycor reactor was constructed by winding three layers of FEP tubing of dimensions 2.7 mm i.d. \times 3.1 mm o.d. around a custom built Vycor immersion well of dimensions 50 mm (d) \times 30 cm (l). The tubing covered approximately 25 cm of the length of the immersion well,

giving approximately 80 turns of tubing per layer, a total length of tubing of 49 m, and a total internal volume of the tubing of 280 mL.

Experimental Section

General Methods. Reaction solutions were prepared by addition of the required reactants to degassed solvent, followed by thorough mixing. The flow reactors were washed before and after each experiment by pumping through clean solvent. More thorough cleaning was occasionally necessary and achieved by pumping through clean dimethyl sulfoxide. Lamps were allowed to warm for at least 5 min prior to the start of each experiment. For flow reactions, laboratory grade acetonitrile and dichloromethane were degassed via sonication at ambient temperature. Maleimide **1** and 1-hexyne were commercially available and used without purification. 3,4-Dimethyl-1-pent-4-enylpyrrole-2,5-dione **3** and 3,4-dichloro-1-pent-4-enylpyrrole-2,5-dione **5** were prepared by methods previously reported.⁹ Lamps were commercially available 400 W medium-pressure mercury discharge lamps, used with either a 400 or 600 W power supply as stated. Except where indicated, glassware used was commercially available standard quartz immersion well apparatus suitable for a 400 W lamp, fitted with a Pyrex filter. FEP tubing refers to commercially acquired fluorinated ethylenepropylene tubing. The lengths and dimen-

sions used were as indicated in the text.¹⁰ The HPLC pump used to deliver reaction solutions to the flow reactors was an LDC Analytical ConstaMetric 3500. Column chromatography was carried out using flash silica gel 60 (40–63 μm), eluting with the solvents stated. NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C) as solutions in the deuterated solvent stated, using tetramethylsilane as an internal standard.

General Procedure for the [2 + 2] Photocycloaddition of Maleimide 1 and 1-Hexyne. A solution of maleimide **1** (1 equiv) and 1-hexyne (1.5 equiv) in acetonitrile at the desired concentration was irradiated at the required flow rate. The reaction was considered to be in a state of continuous flow when a volume of reaction solution equal to twice the reactor volume had entered the reactor. A sample of the photosylate was then taken from the outlet tube, concentrated in vacuo and submitted directly for ^1H NMR analysis ($\text{DMSO}-d_6$). Conversion to product (%) was calculated on the basis of the ratio of integrals of maleimide **1** [$\delta^1\text{H}$ 6.86 (2H, s, CH)] and 6-butyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **2**: $\delta^1\text{H}$ 0.86 (t, $J = 7.3$ Hz, 3H), 1.29 (qt, $J = 7.8$ and 7.3 Hz, 2H), 1.42 (tt, $J = 7.8$ and 7.3 Hz, 2H), 2.10 (t, $J = 7.3$ Hz, 2H), 3.53 (s, 1H), 3.65 (d, $J = 2$ Hz, 1H), 6.13 (s, 1H); $\delta^{13}\text{C}$ (CDCl_3) 13.8, 22.3, 28.1, 29.7, 45.4, 50.1, 129.1, 154.1, 175.3, 176.4; ν_{max} (film)/ cm^{-1} 3214 (w), 3079 (w), 2958 (w), 2930 (w), 2873 (w), 1765 (m), 1697 (s), 1630 (w); m/z (CI) 180.1021 (MH^+ , 100, $\text{C}_{10}\text{H}_{14}\text{NO}_2$ requires 180.1025).

Twenty-Four Hour Reaction. A solution of maleimide (58.24 g, 0.6 mol) and 1-hexyne (104 mL, 0.9 mol) in acetonitrile (6 L) was irradiated (400 W lamp) in reactor 3 (Pyrex) with three layers of FEP at 4 mL/min flow rate. After 24 h, the resultant solution (ca. 5.8 L) was concentrated in vacuo and the resultant residue purified in batches by column chromatography (10% ethyl acetate/40–60 $^\circ\text{C}$ petroleum ether) to yield **2** (85 g, 82%) as a pale yellow oil.

7,8-Dimethyl-1,2,3,9a-tetrahydropyrrolo[1,2-*a*]azepine-6,9-dione 4. (a) A solution of 3,4-dimethyl-1-pent-4-enylpyrrole-2,5-dione **3** (11.6 g, 60 mmol) in acetonitrile (600 mL) was irradiated in reactor 3 (Pyrex) with three layers of tubing at a flow rate of 2 mL/min. When 500 mL of reaction solution had entered the reactor, a 50 mL sample of expelled photosylate was collected and concentrated in vacuo, and the resultant

residue was purified by column chromatography (2% MeOH/ CH_2Cl_2) to give 7,8-dimethyl-1,2,3,9a-tetrahydropyrrolo[1,2-*a*]azepine-6,9-dione **4** (0.762 g, 79%) as a colorless waxy solid identical to a sample prepared previously: mp (toluene) 79–81 $^\circ\text{C}$ (lit.⁹ mp 81 $^\circ\text{C}$); $\delta^1\text{H}$ (CDCl_3) 1.73–1.80 (br m, 1H), 1.90–2.01 (m, 2H) overlays 1.95 (s, 3H), 2.07 (s, 3H), 2.19–2.28 (m, 1H), 2.65–2.74 (dd, $J = 19.1$ and 3.6 Hz, 1H), 2.74–2.85 (dd, $J = 19.0$ and 12.2 Hz, 1H), 3.55 (dt, $J = 11.7$ and 7.8 Hz, 1H), 3.66 (m, 1H), 4.32 (m, 1H).

(b) A solution of **3** (11.6 g, 60 mmol) in acetonitrile (600 mL) was irradiated in the Vycor reactor with three layers of tubing at a flow rate of 8 mL/min. When 500 mL of reaction solution had entered the reactor, a sample (50 mL) of expelled photosylate was collected and concentrated in vacuo and the resultant residue purified by column chromatography (2% MeOH/ CH_2Cl_2) to give **4** (0.774 g, 80%) as a colorless waxy solid with characteristics identical to that prepared previously.

7,8-Dichloro-1,2,3,9a-tetrahydropyrrolo[1,2-*a*]azepine-6,9-dione 6. (a) A solution of 3,4-dichloro-1-pent-4-enylpyrrole-2,5-dione **5** (0.47 g, 2 mmol) in dichloromethane (200 mL) was irradiated in reactor 3 (Pyrex) with one layer of tubing (volume 60 mL) at a flow rate of 10 mL/min with a 400 W lamp. When 120 mL of reaction solution had entered the reactor, a sample (50 mL) of expelled photosylate was collected and concentrated in vacuo and the resultant residue purified by column chromatography (2% MeOH/ CH_2Cl_2) to give 7,8-dichloro-1,2,3,9a-tetrahydropyrrolo[1,2-*a*]azepine-6,9-dione **6** (80 mg, 68%) as a colorless solid identical to a sample prepared previously: mp (ethanol) 149–150 $^\circ\text{C}$ (lit.⁹ mp 149–150 $^\circ\text{C}$); $\delta^1\text{H}$ (CDCl_3) 1.83 (m, 1H), 2.02 (m, 2H), 2.35 (m, 1H), 2.93–2.97 (m, 2H), 3.67 (m, 2H), 4.42 (m, 1H).

(b) A solution of **5** (7.02 g, 30 mmol) in dichloromethane (1.5 L) was irradiated in reactor 3 (Pyrex) with one layer of tubing (volume 60 mL) at a flow rate of 10 mL/min with a 400 W lamp. The resultant solution was concentrated in vacuo and the residue purified by column chromatography (2% MeOH/ CH_2Cl_2). Recrystallization of the resultant crude product (ethanol) afforded **6** (4.72 g, 67%) as a colorless solid with characteristics identical to that prepared previously.

Acknowledgment. We thank EPSRC for generous funding (GR/R02382) and GlaxoSmithKline for provision of a CASE award (B.D.A.H.). We are grateful to Mr. Duncan Tarling (University of Bristol) and Mr. Robin Sealey and Mr. Robert Simmons (Applied Technology, GlaxoSmithKline) for glassblowing and apparatus construction.

JO050705P

(10) All commercially acquired immersion well apparatus, lamps, and power supplies were purchased from Photochemical Reactors Ltd. (U.K.), www.photochemicalreactors.com. Custom Pyrex and Vycor immersion well apparatus was constructed by Mr. Duncan Tarling (University of Bristol); FEP tubing was purchased from Adtech Polymer Engineering Ltd. (U.K.), www.adtech.co.uk. Vycor was purchased from Corning, www.corning.com.