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LOPHTOR: a convenient flow-based photochemical reactor

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ABSTRACT

A flow-through photochemical reactor which enables facile control of irradiation time, temperature, and wavelength with minimal manual intervention is described. A series of intramolecular [2+2] enone cycloadditions were performed in this reactor in excellent yield and significantly shorter reaction time than conventional batch processes.

There is considerable interest in the pharmaceutical industry in the generation of structurally diverse small molecules.[1,2] Photochemistry provides an extremely powerful methodology for the generation of complex products and provides a convenient method to transform reactive moieties (e.g., activated double bonds) to novel, pharmacologically interesting units. While photochemistry has been used extensively in academic settings, and in certain cases on an industrial/drug development scale,[3] utilization within the pharmaceutical industry during the drug discovery phase has been lagging. Potential reasons for the poor uptake include the lack of suitable devices for performing photochemical transformations on a milligram scale with precise control of parameters such as irradiation time, wavelength, and sample size.

Microreactors are devices where chemical reactions are performed in very narrow channels.[4] A full discussion of microreactors is beyond the scope of this Letter, but a few key advantages attracted us to the potential utility of this technique for photochemistry. Due to their very high surface area to volume ratio they have very efficient rates of energy transfer. As a direct consequence of the precise temperature control and the high level of energy transfer, reactions in microreactors can be more controlled compared to conventional systems, and as such reaction selectivity and yield can be improved, particularly where by-products form due to reaction hot-spots. Short residence times within microreactors can also limit the opportunity for products to degrade, a major concern with bulk photochemical reactions. Because microreactors allow for synthesis on a small scale, evaluation of multiple reaction conditions utilizing small amounts of precious starting materials can be performed. Last but not the least, safety is the most commonly discussed benefit of the use of microreactors.

To this end, we have developed a flow-based photochemical reactor (LOPHTOR) composed of channels fabricated from stainless steel that contains integral cooling lines. The flow of reactants is contained within the channels using a thin fluorinated ethylene propylene (FEP) membrane (CS Hyde Company) held in place with pressurized nitrogen (Fig. 1). This simple design allows reactions to be irradiated by a powerful light source while maintaining control of the temperature. An additional advantage of this design element is that the system may easily be cleaned in the event of clogging. While other work[5] has been done using stainless steel channels sealed directly against quartz plates, in our experience there is significant leakage between channels that makes them unacceptable, particularly when scouting for optimal reaction conditions. Serpentine flow cell channels were fabricated in 316 stainless steel using electrical discharge machining and electropolished (Abel Electropolishing) for a final volume of 0.98 ml (1000 μm width, 250 μm depth, and 3.93 m length). The channels were covered with a sheet of 250 μm thick fluorinated ethylene propylene reversibly sealed against the channels with nitrogen at a pressure of 15 psi during reactions (Fig. 2). Irradiation was produced using a medium pressure mercury arc lamp with an elliptical concentrator and integral

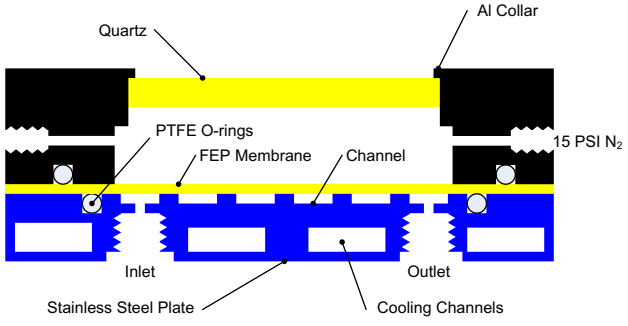

Figure 1. Cross-sectional view of microreactor. Pressurized nitrogen pushes produces a robust seal between the FEP and the channels formed in stainless steel.

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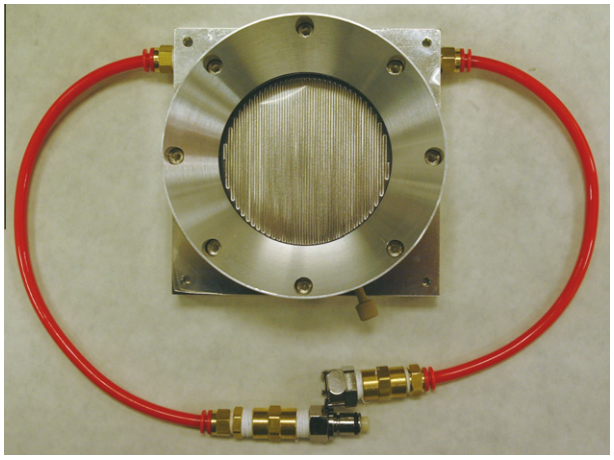


Figure 2. Fully assembled microreactor.

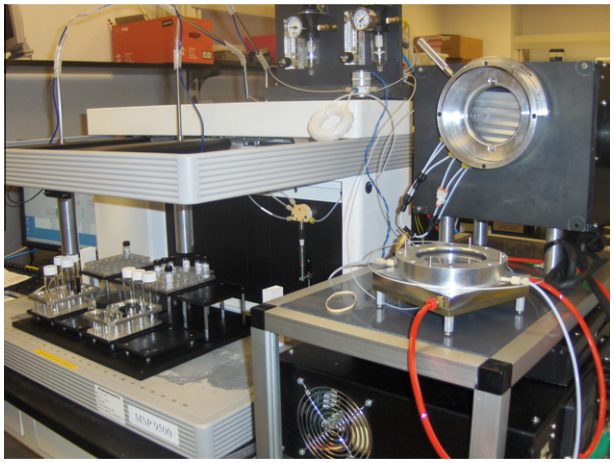
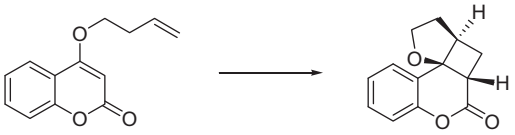


Figure 3. Fluidic system.

cold mirror (UVEXS). Additionally, selective filtering could be provided by a set of uranium-doped quartz plates (Andover Corporation), which can be inserted without disassembling the system. Water from a chiller (Julabo Inc.) was used to cool the reaction through the integral channels in the back of the flow cell while cooling of the optical filters was done using compressed air.

The ability to investigate various reaction parameters such as residence time, irradiation wavelength, and concentration on mil-

Table 1
Conversion of substrate **1** to **2** using batch and flow-conditions (LOPHTOR)



1 **2**

Wavelength (nm)	Solvent	Duration (h)	Yield (%)	Format
300	Benzene	24	30	Conventional Batch reactor
300	Benzene	0.5	43	LOPHTOR
300	Benzene	1	67	LOPHTOR
300	Benzene	2	98	LOPHTOR

All reactions performed at 0.085 M.

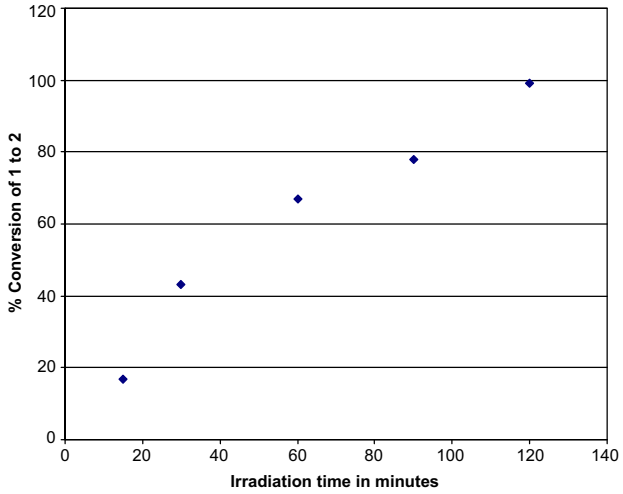


Figure 4. Identification of optimal irradiation time for conversion of **1** to **2**. All reactions performed at 0.085 M.

ligram quantities of starting material is of great importance in the early stages of drug discovery.[6] Once the conditions are established, it is important that these results be translated to larger quantities with little effort. The system described here accomplishes this by drawing in small segments of reactant separated from a carrier solvent by air gaps through the flow cell using a syringe pump (Fig. 3). These air gaps prevent the dilution of reactant concentration that would normally occur in the pressure driven flow of a homogenous fluid.[7]

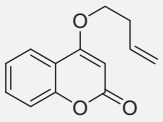
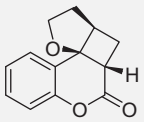
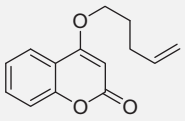
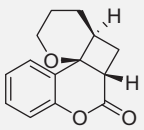
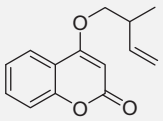
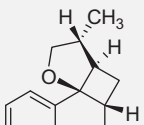
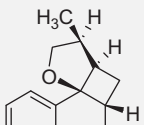
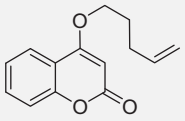
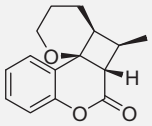
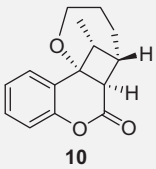
We initially set out to evaluate the utility of LOPHTOR in facilitating a known intramolecular [2+2] cycloaddition.[8] Alkylation of 4-hydroxycoumarin with 4-bromo-1-butene using K_2CO_3 in *N*,*N*-DMF afforded **1**. For comparison purposes, the same transformation was attempted using a medium pressure mercury lamp source in a batch mode,[9] and the results are shown in Table 1. Intramolecular cycloaddition of **1** to form the bicycloheptane product **2** was effectively completed in 48 h in 67% yield.[10]

By comparison, performing the same transformation under similar conditions (concentration, solvent) in LOPHTOR resulted in complete conversion to **2** in two hours. The ease of set-up and convenience of chip residence/irradiation time enabled investigation of several reaction conditions within a few hours, as demonstrated in Figure 4. Integration with an auto-sampler enabled a set of conditions to be programmed and executed without human intervention.

We then sought to broaden the substrate scope (Table 2). Alkylation of 4-hydroxycoumarin with various alkenyl-bromides afforded substrates shown in Table 2. Irradiation of **3** in the LOPHTOR afforded the anticipated bicyclo[4.2.0]octane product **4** in excellent yield, whereas incorporation of a methyl on the tether (**5**) afforded a mixture of diastereomers **6** and **7**, with the predominant isomer being the one where the methyl moiety and the oxygen atom are antarafacial. Intramolecular cycloaddition of **8**, wherein the alkene moiety is substituted, afforded the anticipated [4.2.0]bicyclooctane **9**, along with a minor amount of the [4.1.1]bicyclooctane **10**. In all cases, the yields of these transformations were significantly lower using conventional batch photochemical set-up, despite longer reaction times, and characterized by extensive formation of side-products.

Finally, we wished to evaluate the effect of reaction concentration and evaluated the conversion of **1** to **2** at five concentrations and same irradiation time. As demonstrated in Figure 5, there was no decrease in the yield of this reaction, thus providing a convenient manner to scale-up this process to generate 100's of

Table 2
Substrate scope of [2+2] cycloaddition using LOPHTOR

Substrate	Product	Irradiation time (h)	Yield (conversion, ratio)	Format
 **1**	 **2**	2	98% (100%)	LOPHTOR
1	**2**	24	30%	Batch
 **3**	 **4**	4	99% (100%)	LOPHTOR
3	**4**	48	67%	Batch
 **5**	 **6**  **7**	7	50% (100%, 1:1)	LOPHTOR
5	**6** **7**	24	30% (1:1)	Batch
 **8**	 **9**  **10**	5	40% (100%, 7:1)	LOPHTOR
8	**9** **10**	24	25% (8:1)	Batch

All reactions performed at 0.12 M.

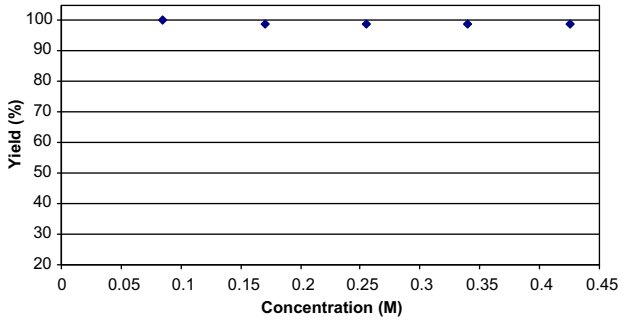


Figure 5. Conversion of **1** to **2** at various concentrations.

milligrams of material, ideally suited for early drug discovery applications. Alternately, maintaining the same reaction concentration (0.085 M), but increasing the scale 10-fold, allowed the generation of **2** in an unattended manner via continuous flow, with no change in the yield (data not shown).

In conclusion, we have designed a flexible flow-based reactor for photochemistry.[11] Utilization of this reactor to facilitate an intramolecular [2+2] cycloaddition results in excellent yields of the desired product. The ease of reaction set-up, control of temperature, irradiation time, and clean-up coupled with the efficiency of generating larger amounts of material in an unattended manner following identification of optimal reaction conditions make this a very attractive tool in the drug discovery chemist's tool-box.

Acknowledgments

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9. To a round bottom flask, fitted with a magnetic stirring bar and condenser, was added starting material, dissolved in benzene (0.085 M). The solution was irradiated with a 450 W UV lamp (Ace photochemical reaction assembly), while stirring for 24 h. Solvent was evaporated to give crude product, which was then purified and analyzed by 500 MHz NMR.
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