

Microflow Photochemistry – Acetone sensitized Addition of Isopropanol to (5R)-5-Menthylxy-2-(5H)-furanone

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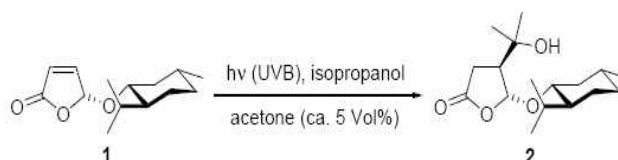
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ABSTRACT : Acetone sensitized photoadditions of isopropanol to (5R)-5-menthylxy-2-(5H)-furanone were investigated in two different microflow reactor systems. Setup A employed a commercially available glass reactor under a UVB-panel. Setup B utilized a FEP microcapillary wrapped tightly around a Pyrex cylinder with a single UVB fluorescent tube at its center. The reactions under flow conditions were subsequently compared to analogue reactions conducted in a batch chamber reactor. Overall, the microflow systems gave faster conversions and higher isolated yields. The flexible microcapillary setup, however, showed the best performance and promise in terms of future scale-up and reactor optimization.

Flow photochemistry has recently extended the technology portfolio of synthetic organic photochemistry. Microreactors in particular offer some clear advantages over conventional batch systems.^{1–5} The thin reaction channels or capillaries of these devices enable effective transmission of light through the reaction mixture. This feature results in improved energy and photonic efficiencies.^{6,7} The flow operation furthermore minimizes the risk of product photodegradation through undesired follow-up reactions.⁸ We have recently described UVA-induced photoaddition reactions of alcohols to furanones. This model transformation was used successfully in the development of various, novel microreactor systems.⁹

The reactor types ranged from a UVA-LED-driven microchip for microscale synthesis to a dual- and eventually a multicapillary reactor for parallel photochemistry.^{10–12} UVA-irradiation required the application of solid 4,4'-dimethoxybenzophenone (DMBP) as a photosensitizer. While effective in mediating the desired transformation, photoreductions of DMBP are frequently observed upon exhaustive irradiation.¹³ In addition, DMBP (and its photoreduction products) must be removed by time- and resource-consuming column chromatography. The original batch protocol utilized acetone as a photosensitizer instead.¹⁴ While acetone requires the application of UVB light, it can be easily removed by evaporation and is much less prone to photoreductions. In addition, the ketyl (i.e. hydroxyisopropyl) radicals resulting from the sensitizer and isopropanol are identical, which minimizes the formation of side products. We have thus reinvestigated this protocol under batch and microflow conditions using (5R)-5-menthylxy-2-(5H)-furanone (**1**) as a model compound (Scheme 1).

Scheme 1. Acetone sensitized stereoselective photoaddition of isopropanol to (5R)-5-menthylxy-2-(5H)-furanone (**1**).



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For batch irradiations, a standard Rayonet chamber reactor (RMR600) equipped with 8×4 W UVB lamps and a cooling fan was employed (Figure 1). A Pyrex tube ($\lambda \geq 300$ nm; outer/inner diameter: 1.7/1.5 cm) filled with the reaction mixture was placed in the center of the irradiation chamber. After a set irradiation time, the reaction mixture was carefully evaporated and conversions of **1** were determined by integration of baseline separated signals in the $^1\text{H-NMR}$ spectrum of the crude product mixture. The addition of isopropanol was highly stereoselective and solely the corresponding *trans*-diastereoisomer **2** was obtained.¹⁴ In selected cases, product **2** was furthermore isolated by column chromatography to account for any losses due to photodecomposition.

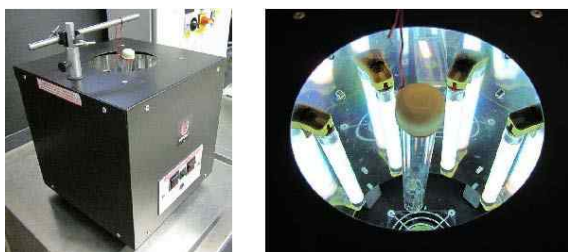


Figure 1. Rayonet chamber reactor with Pyrex test tube (Batch setup).

Conversion rates of **1** gradually increased with irradiation times (Table 1) and an almost complete conversion of 96% was obtained after 15 min (entry 3). From this experiment, product **2** was isolated in an excellent yield of 91%. Upon prolonged irradiations for 30, 60 and 120 min (entries 4-6), no degradation of **2** could be observed. Continuous excitation of acetone thus did not initiate any photochemical decomposition. Likewise, dimerization reactions of **1** could not compete with the desired photoaddition¹⁵

Table 1. Experimental results for the batch reactor.^a

Entry	Irradiation time (min)	Conversion of 1 (%) ^b
1	5	15
2	10	83
3	15	96 (91 ^c)
4	30	100
5	60	100
6	120	100

^aConditions: degassed solution of 0.33 mmol of **1** and 0.5 mL of acetone and 10 mL of isopropanol.

^bDetermined by $^1\text{H-NMR}$ spectroscopic analysis ($\pm 3\%$).

^cYield of **2** after isolation.

The reaction protocol from the batch process was subsequently transferred to microflow conditions. Microreactor setup A is shown in Figure 2 and utilized a commercially available dwell device (mikroglas chemtech GmbH).^{16,17} The reactor block is

made from FoturanTM glass ($\lambda \geq 300$ nm) with a top cooling and a bottom reaction channel. The reaction channel was 0.5 mm deep, 2 mm wide and 1.15 m long (over 20 turns) with an internal volume of 1.68 mL. The whole device was positioned under a UV panel (Luzchem) equipped with 5 UVB-lamps (5×8 W). A small electrical fan was placed in the back of the unit. A previously degassed reaction mixture was pushed through the device with a syringe pump and was collected in a flask outside the irradiated area. Conversions of **1** were again determined by $^1\text{H-NMR}$ analysis of the crude product mixture

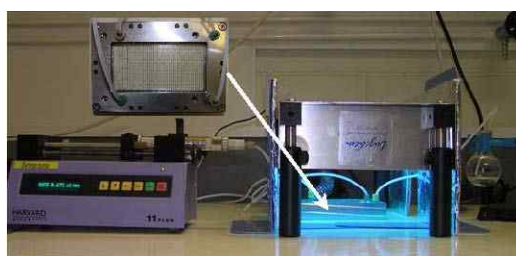


Figure 2. Dwell device (insert) under a UV-panel (Microreactor setup A).

With increasing residence time conversions improved (Table 2) and complete consumption of **1** was reached after 10 min (entry 4). Isolation by column chromatography furnished **2** in a high yield of 93%. Solely the *trans*-diastereoisomer **2** was again obtained. Experiments conducted in the dark or in the absence of acetone with residence times of 15 min showed no conversions and furanone **1** was recovered in >95%.

Table 2. Experimental results for the dwell device.^a

Entry	Irradiation time (min)	Conversion of 1 (%) ^b
1	2.5	15
2	5	38
3	7.5	77
4	10	100 (93 ^c)
5	15	100

^aConditions: degassed solution of 0.33 mmol of **1** and 0.5 mL of acetone and 10 mL of isopropanol.

^bDetermined by $^1\text{H-NMR}$ spectroscopic analysis ($\pm 3\%$).

^cYield of **2** after isolation.

Microreactor setup B employed a UV-transparent capillary made from fluorinated ethylene propylene copolymer (FEP; outer/inner diameter: 1.6/0.8 mm), which was firmly wrapped around a Pyrex glass cylinder ($\lambda \geq 300$ nm; outer diameter: 6.5 cm).^{11,12,18}

The capillary had a total length of 11.4 m, of which 10 m covered the cylinder body (internal volume: 5 mL). In its center, the cylinder incorporated a single

UVB (1 × 8 W) lamp, which was cooled from the bottom by a small fan. The reactor was kept in a light-tight box with an additional cooling fan on its side (Figure 3). The degassed reaction mixture was delivered from a syringe pump. The product mixture was collected in a flask outside the irradiation box and conversion rates of **1** were established after evaporation by ¹H-NMR analysis.

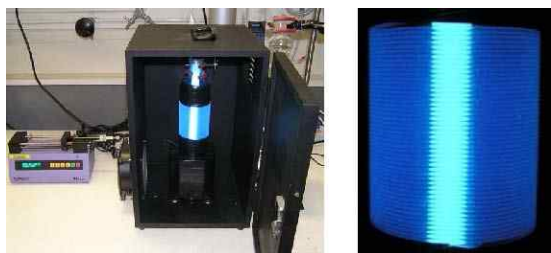


Figure 3. FEP-microcapillary wrapped around a Pyrex mantle with inserted UVB-fluorescent tube (Microreactor setup B).

In contrast to the batch or dwell device, the microcapillary reactor gave notable conversion even after very short residence times (Table 3). Consequently, a near complete conversion of **1** of 96% was achieved after just 5 min (entry 3). The addition product **2** was exemplarily isolated in a yield of 94% from the experiment using a residence time of 10 min (entry 5). When conducted in the dark or in the absence of acetone with residence times of 5 min, no conversions were noted and furanone **1** was recovered in >95%.

Table 3. Experimental results for the microcapillary reactor.^a

Entry	Irradiation time (min)	Conversion of 1 (%) ^b
1	1	17
2	2.5	63
3	5	96
4	7.5	99
5	10	100 (94 ^c)

^aConditions: degassed solution of 0.33 mmol of **1** and 0.5 mL of acetone and 10 mL of isopropanol.

^bDetermined by ¹H-NMR spectroscopic analysis (±3%).

^cYield of **2** after isolation.

Despite having the lowest light power emitted from a single fluorescent tube of just 8 W, the simple microcapillary reactor (setup B) showed the best performance and achieved almost complete consumption of **1** after 5 minutes. It was thus three-times more efficient than the batch reactor, which needed 15 minutes to reach near complete conversion, and twice as effective as the dwell device

(setup A), which required 10 minutes. This superior performance likely results from its favorable design features. The central fluorescent tube allows for efficient irradiation in all directions (inside-out) and about 40% of its length is covered by the capillary coil. In contrast, the UV-panel delivered the light solely from one direction (top-down) and the much smaller dwell device utilized less than 10% of its emissive area. Since the reaction channel only occupies half of the aperture of the entire reactor block, the emissive to irradiated area ratio is further reduced. The chamber reactor used for batch irradiations delivered light from an outer ring of eight fluorescent tubes (outside-out), but the small test tube covered less than 2% of its emissive area. The reflective chamber may have compensated for this low emissive to irradiated area ratio. In conclusion, acetone-sensitized additions of isopropanol to (5R)-5menthylxy-2-(5H)-furanone have been successfully conducted in two microreactor systems. Compared to batch reactions, these devices gave higher conversions and isolated yields after shorter irradiation times.¹⁹ Due to its design features, the simple microcapillary reactor showed the best overall performance. The matching of the light source and the reaction vessel (batch vessel or microstructure) is thus important for achieving a high reactor performance.

KEYWORDS: flow photochemistry, photoaddition, furanones, microreactor

Received October 27, 2013; Accepted November 22, 2013

ACKNOWLEDGEMENT

This work was financially supported by the Australian Research Council (ARC, Discovery Project, DP130100794), the Global Initiatives Program and partially a Grant-in-Aid for Scientific Research (Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government) and the Student Exchange Support Program from the Japan Student Service Organization (JASSO). The authors wish to thank Assoc.-Prof. Bruce Bowden and Dr. Oksana Shvydkiv for technical support.

SUPPORTING INFORMATION Experimental procedures and NMR data for product **2**. This material is available free of charge via the Internet at <http://photos.or.kr>

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