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Photosensitized addition of isopropanol to furanones in a continuous-flow dual capillary microreactor

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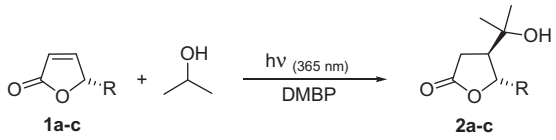
ABSTRACT

A novel continuous-flow photoreactor with parallel capillaries was constructed and successfully tested for the DMBP-sensitized addition of isopropanol to furanones. Complete conversions were achieved after a maximum of 10 min of irradiation with a single 350 nm lamp. The results were compared to analogous batch experiments using a conventional Rayonet chamber reactor equipped with 16 UVA lamps. The capillary tower generally showed higher space-time yields.

Organic synthesis in microreactors has recently emerged as a promising new methodology.[1] The small dimensions of microreactors make them especially advantageous for photochemical applications and numerous photochemical transformations have been reported so far.[2] In particular, the narrow reaction channels of microreactors allow efficient penetration of light even at high chromophore concentrations. Their continuous flow operation also minimizes follow-up reactions of target products as often encountered in batch processes. Microphotochemistry has also been successfully adopted by the chemical industry.[3]

Major disadvantages of conventional (commercially available) microreactors are, however, the fixed length of the reaction channel and the single-channel design. Although numbering-up can be achieved using an array of microreactors,[4] this strategy causes significant investment costs. Flexible capillaries represent a cost-efficient alternative and isolated examples have been reported in macro- as well as micro-formats.[5,6]

For the present study the diastereoselective addition of isopropanol to furanones was selected as a model transformation in a novel microcapillary photoreactor (Scheme 1).[7] The original protocol used acetone as a sensitizer, however, the limited chemical stability of some connections and fittings made a replacement necessary. Related photoadditions of amines used 4,4′-dimethoxybenzophenone (DMBP) as an efficient sensitizer.[8] A disadvantage of DMBP is the necessity for its removal, but it has been applied successfully to the isopropanol addition in a 365 nm UV-LED microchip.[9]



Scheme 1. DMBP-sensitized isopropanol addition to furanones.

The experimental set-up is shown in Figure 1. To allow for the synthesis of larger amounts of product material in a single run, a dual syringe pump was implemented. The pump was connected to two parallel UV-transparent polytetrafluoroethylene (PTFE) capillaries of 460 cm length and 558 μm inner diameter (each, internal volume per capillary: 1.12 mL). The capillary pair was tightly wrapped around a Pyrex glass cylinder (transmission: $\lambda \geqslant 300$ nm) of 6.5 cm diameter and 20 cm height (22 windings covering 14 cm). A single UVA (RPR-3500 Å, 8 W, $\lambda = 350 \pm 25$ nm) lamp was placed in the centre of this dual-microcapillary tower. A small cooling fan was mounted on the bottom of the tower encapsulated in the base.

A series of reactions were examined in continuous-flow mode using this dual microcapillary reactor. The irradiation time was controlled simply by changing the flow rate. The results obtained

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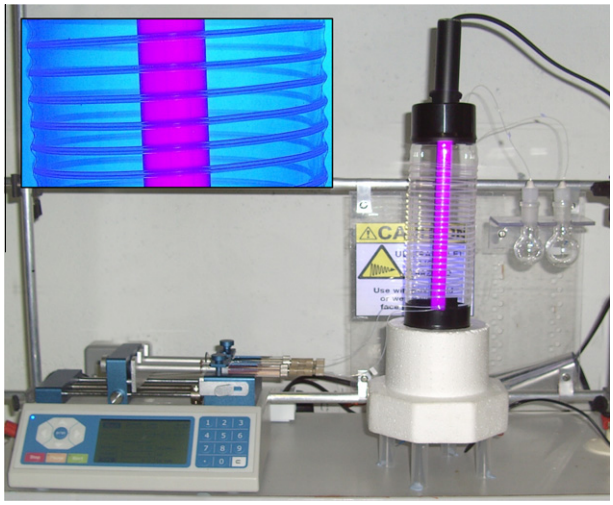

Figure 1. Experimental set-up. Inset shows a close-up of the double capillary.

were compared to reactions in a conventional chamber (Rayonet) reactor under batch conditions.[7b]

Initially, the performance of the capillary microreactor in terms of conversion rates was evaluated. A previously degassed solution of furanone **1a–c** and catalytic amounts of DMBP in isopropanol were irradiated while passing through the microcapillaries at various flow rates. The reaction mixture was collected in separate flasks (protected from light) outside the irradiated area. The conversion rates were subsequently determined by ^{1}H-NMR spectroscopy (Table 1).[10] Three furanone derivatives were investigated and complete conversions were achieved after just 7.5 (**1c**) and 10 (**1a** and **1b**) minutes of irradiation, respectively.

Next, a comparison study (continuous-flow versus batch) was conducted using a fixed reaction time of 5 min. The microcapillary reactor gave conversion rates of 75% (**1a**), 96% (**1b**) and 99% (**1c**), respectively. The same experiments were repeated under batch conditions in a much larger Rayonet chamber reactor. After irradiation with a set of 16 UVA lamps, incomplete conversion rates of 90% (**1a**), 90% (**1b**) and 87% (**1c**) were achieved.[11]

With the exception of the parent furanone **1a**, the microcapillary reactor gave higher conversion rates compared to the batch process. To explain this trend we have recorded the UV-spectrum of DMBP and matched it to the emission spectrum of the UVA lamp (Fig. 2). The crucial $n\pi^*$ absorption band of DMBP showed a good overlap with the emission band of the light source. At its emission maximum at 350 nm in acetonitrile, DMBP showed an extinction coefficient (ε_{350nm}) of 496 L mol^{-1} cm^{-1}.

Based on these data, the light penetration was calculated at 350 nm and matched with the inner diameters of the capillary

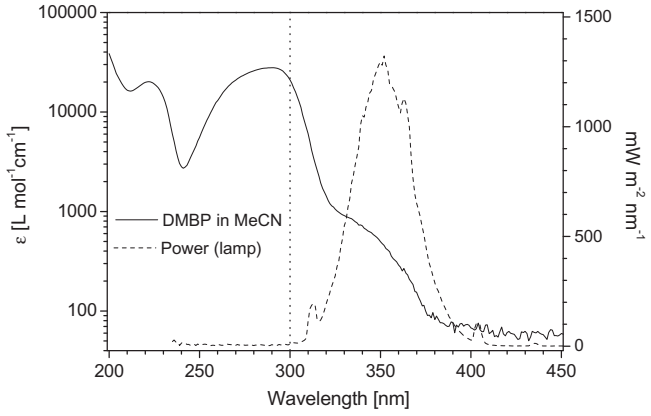

Figure 2. UV-spectrum of DMBP (in MeCN) vs the emission spectrum of the UVA lamp. The vertical dotted line represents the cut-off wavelength of Pyrex at 300 nm.

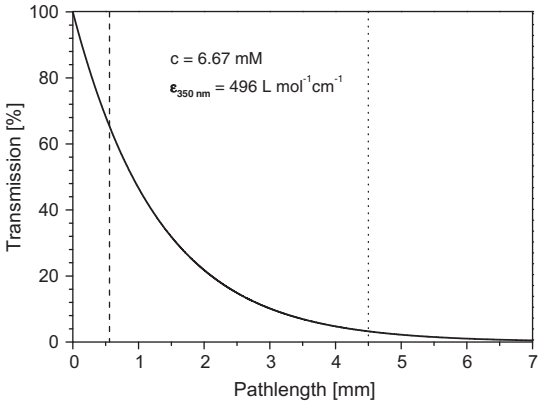

Figure 3. Light-penetration profile for a 6.67 mM solution of DMBP at 350 nm. The vertical lines represent the inner diameter of the microcapillary (dashed) vs the effective pathlength of the Pyrex test tube (dotted).

(558 μm) and the Rayonet Pyrex test tube (9 mm), respectively.[12] Due to the circular arrangement of the lamps around the reaction vessel in the Rayonet (batch) reaction, its effective pathlength was reduced to 4.5 mm. At the chosen concentration of DMBP, both set-ups allowed for complete penetration of light (Fig. 3). Whereas the batch reactor had reached its optimum in terms of the concentration of DMBP, the microcapillary reactor set-up allows for much higher sensitizer concentrations to be used. This may ultimately give higher conversions (and yields).

Due to its much larger surface-to-volume ratio,[1] in combination with a superior light penetration within the microcapillaries, the continuous-flow system resulted in significantly higher space-time yields (STY).[13] For the 5 min irradiations the reactor performance data are summarized in Table 2. For compound **1a**, the larger number of lamps fitted in the Rayonet reactor resulted in a somewhat higher conversion rate.

In conclusion, isopropanol additions to furanones have been realized in a novel dual-capillary microreactor. The easy design

Table 1
Experimental details

Residence time (min)	Flow rate (μl/min)	Conversion (%)[a]		
		R = H (**2a**)	R = OEt (**2b**)[b]	R = OMent (**2c**)
2.5	460	35	50	64
5	230	75 (90[c])	96 (90[c])	99 (87[c])
7.5	153.3	95	99	100
10	115	100	100	100
15	76.7	100	n.d.[d]	n.d.[d]
20	57.5	100	100	100

[a] Determined by ^{1}H NMR spectroscopy.
[b] Used as racemate.
[c] Conversion under batch conditions in a chamber reactor.
[d] Not determined.

Table 2
Reactor performance data for 5 min reactions

Reactor	Surface-to-volume ratio (m^2/m^3)[a]	STY (mmol L^{-1} min^{-1})		
		1a	**1b**	**1c**
Microcapillary	7,169	22.4	28.6	29.5
Batch (test tube)	466	6.0	6.0	5.8

[a] Assuming a cylindrical geometry for both, capillary and test tube.

of the reactor makes it an interesting synthetic tool for chemical research and development (rather than production).[14] The generally small volumes additionally help to reduce the amounts of chemicals and solvents, thus contributing to Green Chemistry.[15,16] The set-up also allows for parallel synthesis using multiple capillaries and this modification is currently being investigated using an improved reactor with up to 10 microcapillaries.[17] This modified design will also increase the overall aperture of the microcapillary with a tighter wrapping around the central glass column.

Acknowledgements

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10. *General procedure for irradiation in the capillary microreactor*: A solution of the furanone (0.334 mmol) and DMBP (0.066 mmol) in isopropanol (10 mL) was purged with nitrogen and loaded into a dual syringe pump. The reaction mixture was pumped through the microcapillaries while being irradiated by a single UVA lamp (RPR-3500 Å, $\lambda = 365 \pm 25$ nm, 8 W). After evaporation of the solvent, the conversion was determined by ^{1}H NMR spectroscopy of the crude product. The signal integration for the proton at the β-position of **1a**–**c** was compared to the signal integration for the acetal proton of **2a**–**c**. Pure products were isolated by column chromatography.[9]
11. General procedure for irradiation under batch conditions: A solution of the furanone (0.5 mmol) and DMBP (0.1 mmol) in isopropanol (15 mL) was added to a Pyrex glass tube (inner diameter: 9 mm) and purged with argon. The tube was stoppered and the reaction mixture was irradiated for 5 min at 350 ± 25 nm (Rayonet RPR-100, equipped with $16 \times$ RPR-3500 Å lamps, 16×8 W). After evaporation of the solvent, the conversion was determined by ^{1}H NMR spectroscopy of the crude product. Pure products were isolated by column chromatography.[9]
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