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Parallel Microflow Photochemistry: Process Optimization, Scale-up, and Library Synthesis

Alexander Yavorskyy,[†] Oksana Shvydkiv,[†] Norbert Hoffmann,[‡] Kieran Nolan,[†] and Michael Oelgemöller*[,§]

Dublin City University, School of Chemical Sciences, Dublin 9, Ireland, UMR 7312 CNRS et Université de Reims Champagne-Ardenne, Institut de Chimie Moléculaire de Reims, UFR Sciences, B.P. 1039, 51687, Reims, Cedex 02, France, and James Cook University, School of Pharmacy and Molecular Sciences, CBMDT, Townsville, Queensland 4811, Australia

michael.oelgemoeller@jcu.edu.au

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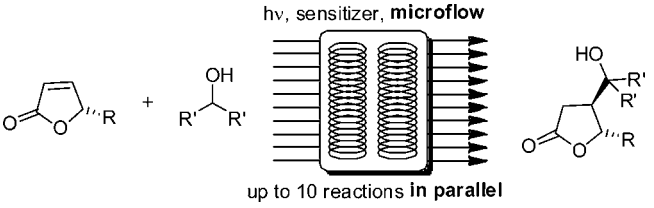
ABSTRACT



A novel, multimicrocapillary flow reactor (MμCFR) was constructed and applied to a series of sensitized photoadditions involving 2(5*H*)-furanones. The reactor allowed for rapid and energy-, time-, and space-efficient sensitizer screening, process optimization, validation, scale-up, and library synthesis.

Microflow reactors have recently emerged as a new technology in chemical synthesis and have seen a growing number of applications.[1] The small inner dimensions of these devices, in combination with their continuous flow operation, make them especially attractive for photochemical studies.[2] In particular, the narrow reaction channels enable extensive penetration by light, even at high chromophore concentrations (as dictated by the Beer–Lambert law). Also, the small dimensions allow for precise temperature control and thus superior regio- and stereoselectivity.[3] One of the major drawbacks of current microflow photoreactors is the need to perform individual reactions separately *in-series*. Automated reactor systems have been constructed but do not allow for parallel operation.[4] Likewise, small libraries were generated using segment flow, but this *in-series* synthesis does not reduce operation times significantly.[5] Clustering ('numbering-up') of reactors, as done successfully by Heraeus for the synthesis of

[†] Dublin City University.
[‡] CNRS et Université de Reims Champagne-Ardenne.
[§] James Cook University.

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anticancer drug precursors, causes significant installation costs.[6] Flexible polymer-based microcapillaries have been increasingly used for the construction of continuous flow reactors.[7] Their reaction capillaries are chemically inert, UV-transparent, inexpensive and can be almost any length. Using this general reactor concept, we have previously described a dual-microcapillary system for photochemical transformations in duplicates.[8] To further improve the utility for typical R&D processes,[9] we have constructed a novel multimicrocapillary flow reactor (MμCFR, Figure 1).[10]

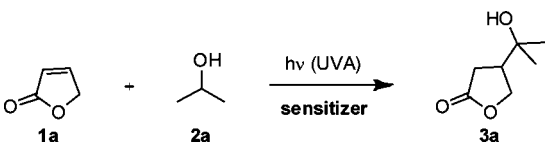
Figure 1. Multimicrocapillary flow reactor (MμCFR): (a) collection flasks; (b) FEP microcapillaries; (c) 10-syringe pump.

To realize a practical number of experiments in parallel, a 10-syringe pump was selected as the delivery system. Two bundles of five fluorinated ethylene propylene copolymer (FEP; outer/inner diameter: 1.6/0.8 mm) capillaries were wrapped tightly around two Pyrex glass columns ($\lambda \geq$ 300 nm; height: 60 cm; outer diameter: 6 cm; thickness: 2.2 mm). Each microtube had a total length of 11.5 m. Of these, 10 m covered the glass body therefore creating an irradiated volume of 5 mL inside each capillary. Assuming that only half of each capillary is irradiated, the effective surface-to-volume ratio per capillary was calculated to be 2514 m^2/m^3. The nonexposed ends (ca. 75 cm each) were connected to the syringe pump (influent) and an array of round-bottom flasks (effluent), which were protected from light during irradiations. UVA fluorescent tubes (λ_{max} = 365 nm; 2 × 18 W; height: 60 cm) were placed in the center of the glass columns, and small cooling fans were mounted in their bases. The entire reactor system was kept behind a light-tight curtain during operation. To avoid cross-irradiation, a black cardboard screen was placed in between the two parallel microcapillary towers. The MμCFR system was subsequently utilized to investigate sensitized additions of alcohols to furanones.[11] This transformation is well understood and has been used previously as a model reaction for microreactor evaluations.[12] Three typical R&D scenarios were investigated:

- Process optimization using 10 different reaction conditions;
- Process validation and scale-up using 10 identical conditions and
- Library synthesis using 10 different reagent mixtures.

Using the addition of isopropanol **2a** to the parent 2(5*H*)-furanone **1a** as a representative example, the microcapillary reactor was first applied to sensitizer screening (Scheme 1). The original reaction protocol utilized acetone as the sensitizer,[11a] which could not be used due to the poor overlap of its absorption spectrum with the emission maximum of the UVA fluorescent tube.[13] Hence, a range of aromatic ketones that are typically employed as sensitizers were screened (Table 1). Previously degassed solutions of **1a** and the sensitizer (except for the blank experiment) in isopropanol were pumped through the microcapillaries at a constant flow rate of 1 mL/min, thus giving an irradiation time of 5 min. The conversion rates were subsequently determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The highest conversion of 72% was observed when 4,4′-dimethoxybenzophenone (DMBP) was used as the sensitizer. In contrast, xanthone, 4-benzoylbenzoic acid, and benzophenone gave moderate conversion rates of 30−47%. Consumption of **1a** remained low with 4% for acetophenone, while all other sensitizers failed to induce any photoreactivity under the chosen conditions. Partial photoreduction was observed for benzophenone, DMBP, and xanthone.[14] No reaction was observed in the absence of sensitizer, and **1a** was recovered quantitatively.[15,16]

Scheme 1. Sensitized Addition of Isopropanol to Furanone **1a**



With DMBP as the best sensitizer, its concentration was optimized next. The furanone/isopropanol (**1a**/**2a**) pair was again chosen as a model system (Scheme 2). The conversion to **3a** increased steadily with increasing

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Table 1. Sensitizer Screening[a]

sensitizer	conv of **1a** (%)[b]	sensitizer	conv of **1a** (%)[b]
(none)	0[c]	xanthone	47
benzophenone	30	acetophenone	4
4,4′-dimethoxy-benzophenone	72	4-*tert*-butyl-acetophenone	0[c]
4-benzoylbenzoic acid	37	4-methoxy-acetophenone	0[c]
4,4′-bis(dimethyl-amino)benzophenone	0[c]	4-(dimethylamino)-benzaldehyde	0[c]

[a] Conditions: [**1a**] = 33.3 mM; [sens] = 6.7 mM; Vol = 15 mL; flow rate: 1 mL/min; residence time = 5 min. [b] Conversion determined by ^{1}H NMR spectroscopy (±3%). [c] No reaction (recovery of **1a**: >85%).

amounts of sensitizer until a maximum of 90% was achieved at a DMBP concentration of 10 mM (Table 2). Above this critical value, DMBP started to precipitate within the reactor. As a result, the conversion dropped to 73% due to scattering from the solid particles and the decrease of sensitizer dissolved in solution.[17]

Scheme 2. DMBP-Sensitized Addition to Furanone **1a**

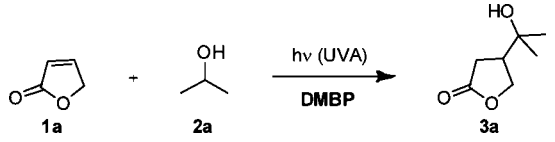

Table 2. DMBP Concentration Study[a]

[DMBP] (mM)	conv of **1a** (%)[b]	[DMBP] (mM)	conv of **1a** (%)[b]
0.0	0[c]	7.0	76
1.0	26	8.0	81
2.0	40	9.0	86
4.0	55	10.0	90
6.0	70	11.0[d]	73

[a] Conditions: [**1a**] = 33.3 mM; Vol = 15 mL; flow rate: 1 mL/min; residence time = 5 min. [b] Conversion determined by ^{1}H NMR spectroscopy (±3%). [c] No reaction (recovery of **1a**: >85%). [d] Precipitation of DMBP within microreactor creating light scattering.

The light penetration profiles at 365 nm were subsequently calculated from the adsorption spectra and the experimental conditions and were compared to the inner diameter of the FEP microcapillary of 0.8 mm (Figure 2).[18] For all concentrations studied, complete transmission through the microcapillary was achieved. In contrast, batch systems typically have much larger path lengths (≥1 cm) and thus show significantly lower transmission efficiencies.[8]

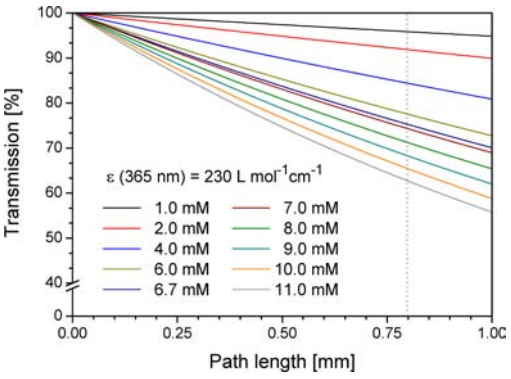

Figure 2. Light-penetration profiles of DMBP solutions at 365 nm. The vertical broken line represents the inner diameter of the microcapillary (0.8 mm).

The influence of the furanone (**1a**) concentration on the conversion rate was likewise investigated. Applying a fixed standard concentration of DMBP (10 mM) in isopropanol, [**1a**] was varied stepwise from 33.3 to 200 mM. A standard irradiation time of 5 min was set for this experimental run. As would be expected, the consumption of **1a** dropped significantly from 80% to 2% with increasing concentrations (Table 3). An acceptable

Table 3. Furanone (**1a**) Concentration Study[a]

[**1a**] (mM)	conv of **1a** (%)[b]	[**1a**] (mM)	conv of **1a** (%)[b]
33.3	80	116.7	9
50.0	51	133.3	7
66.7	34	150.0	5
83.3	23	166.7	3
100.0	14	200.0	2

[a] Conditions: [DMBP] = 10 mM; Vol = 15 mL; flow rate: 1 mL/min; residence time = 5 min. [b] Conversion determined by ^{1}H NMR spectroscopy (±3%).

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(17) A DMBP concentration of 6.7 mM was considered 'safe', and sensitizer precipitation was never observed.

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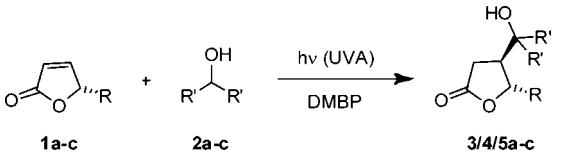
conversion of >20% was nevertheless maintained up to [**1a**] = 83.3 mM.

The photoaddition of isopropanol to **1a** was again selected for a validation and scale-up study. A solution of **1a** (33.3 mM) and DMBP (6.7 mM) in isopropanol was distributed over the 10 syringes and irradiated using a residence time of 5 min. The crude products were analyzed by ^{1}H NMR spectroscopy, and conversions of 66−75% were achieved. The reaction showed good reproducibility with an average conversion and a relative standard deviation (RSD) of 70.8 ± 4.2%. In a separate run, the residence time was increased to 10 min to achieve complete conversion. The product mixtures from all runs were combined, and **3a** was isolated in a reasonable quantity (ca. 0.5 g) and an excellent yield of 94%.

The multicapillary reactor was likewise applied to the synthesis of a small 3 × 3 product library (Scheme 3; Table 4). Furanone (**1a**) and its two 5-substituted derivatives **1b** (*rac*-OEt) and **1c** ((−)-OMent) were selected as model compounds. Isopropanol (**2a**), 3-pentanol (**2b**), and cyclopentanol (**2c**) were chosen as representative alcohols. The residence times were increased to 10 min (**2a**) and 20 min (**2b** and **2c**) to achieve high conversions and thus isolated yields. The photoaddition products **3/4/5a**−**c** were obtained in good to excellent yields of 57−94% after column chromatography. Due to the complete consumption of **1a**−**c** in most runs, small amounts of photoreduction and photopinacolization products of the sensitizer DMBP were detected in the crude products by ^{1}H NMR analysis.[14] In contrast, the corresponding batch reactions performed in a Pyrex test tube (inner diameter: 0.9 cm) and using a Rayonet chamber reactor (16 × 8 W) required prolonged irradiation times of up to 1 h to reach complete conversions.[8a]

Scheme 3. Library Synthesis



Compared to the original protocol involving acetone as the sensitizer,[11a] DMBP generally gave higher conversions and yields. Likewise, the addition of DMBP was never observed, probably due to the stability of its ketyl radical. When acetone is employed, its undesired addition to furanones (to yield **3a**−**c**) is commonly found.[11a]

Table 4. Experimental Details of Library Synthesis[a]

R	R′	time [min]	yield (%)[b]
H	CH_3	10	94 (**3a**)
OEt[c]	CH_3	10	60 (**3b**)
OMent[d]	CH_3	10	90 (**3c**)
H	C_2H_5	20	80 (**4a**)
OEt[c]	C_2H_5	20	57 (**4b**)
OMent[d]	C_2H_5	20	61 (**4c**)
H	-$(CH_2)_4$-	20	71 (**5a**)
OEt[c]	-$(CH_2)_4$-	20	73 (**5b**)
OMent[d]	-$(CH_2)_4$-	20	89 (**5c**)

[a] Conditions: [**1**] = 33.3 mM; [DMBP] = 6.7 mM; Vol = 15 mL; flow rate: 0.5 and 0.25 mL/min; residence time = 10 and 20 min. [b] Isolated yields after column chromatography. [c] As racemate. [d] (−)-OMent.

In conclusion, we have constructed a simple multimicrocapillary flow reactor that allowed for space-, time-, and resource-efficient process optimization and library-synthesis. As would be expected, the reactor offered significant operation time savings compared to *in-series* operations with a single-capillary reactor.[8,12a] The energy consumption for the synthesis of 1 kg of **3a** in the MμCFR setup was furthermore compared to a conventional chamber reactor (equipped with 16 × 8 W fluorescent tubes).[19] The microreactor consumed ∼30% less energy than the batch reactor and did not require any cooling water. These features, together with the small reaction scales and the possibility of using higher concentrations, make microflow photochemistry a resource-efficient and green technology.[20] A current disadvantage is the usage of a single multisyringe pump with identical flow rates for all capillaries. Automated pump systems with individual flow rate settings would easily overcome this drawback. It is thus hoped that this advanced microflow technology presented will be rapidly implemented into chemical R&D processes as a parallel photochemical synthesis tool.[1a,9]

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Supporting Information Available. Experimental procedures and NMR spectra of all photoproducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.