

# Enhancement of Reaction Rates by Segmented Fluid Flow in Capillary Scale Reactors

Batoul Ahmed,<sup>a, b</sup> David Barrow,<sup>b,\*</sup> and Thomas Wirth<sup>a,\*</sup>

<sup>a</sup> Cardiff School of Chemistry, Cardiff University, Cardiff, CF10 3AT, U.K.

Fax: (+44)-29-2087-6968; e-mail: wirth@cf.ac.uk

<sup>b</sup> Laboratory for Applied Microsystems, Cardiff School of Engineering, Cardiff University, Cardiff, CF24 3AA, U.K.

Fax: (+44)-29-2087-4716; e-mail: barrow@cf.ac.uk

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**Abstract:** For a simple biphasic hydrolysis, we show that the application of various reaction conditions in microreactors using segmented flow can dramatically increase the reaction rate. A tandem diazotation/Heck reaction served as an example that even homo-

geneous reactions can be accelerated by segmentation in microreactors.

**Keywords:** biphasic reactions; Heck reaction; hydrolysis; microreactors; segmented flow

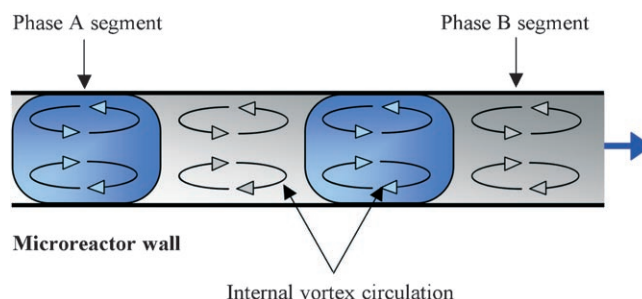
## Introduction

The miniaturisation of chemical processes using chip-based microreactors can exhibit significant advantages over existing conventional techniques. The properties and reaction conditions in such microreactors are different to large-scale systems. A high surface-to-volume ratio, short diffusion distances, fast and efficient heat dissipation and mass transfer enable novel and diverse applications.<sup>[1]</sup> These properties have been advantageously used in organic synthesis.<sup>[2]</sup>

## Results and Discussion

A microchip system applied in synthetic chemistry usually consists of an arrangement of microstructures such as capillary scale ducts, sensors and actuators. A combination of such microcomponents and a chip-to-world interface of fluidic, electrical, optical and other interconnects may form a microreactor which can be fabricated in different geometries and from a variety of materials. The majority of chemical reactions in solution carried out in microreactors involve homogeneous reactions at room temperature. Recently, an interest in applying microreactors utilising multiphase flow (gas/liquid or liquid/liquid biphasic systems) has emerged.<sup>[3]</sup> In a microchannel, the contact interface between immiscible liquids can follow various flow patterns, due to the forces at the interface generated from the different physical properties of both phases such as viscosity and surface tension. The most

common mode of multiphase interface is known as parallel flow in which the respective fluid phases align side-by-side and mixing between them occurs principally *via* diffusion. Another multiphase mode, segmented flow, can be created in a microchannel when two (or more) fluid phases form serial trains of fluid packets, each phase being separated by the other. Once these fluid packets or segments are formed, an internal fluid vortex is generated which causes rapid mixing within a given segment by continuously refreshing the diffusion interface as shown in Figure 1. The area of this interface is approximately proportional to the cross-sectional area of the microchannel. The cross-section must be smaller than the length of the segments, otherwise emulsions are formed.<sup>[4]</sup> Furthermore, the constructional material of the micro-

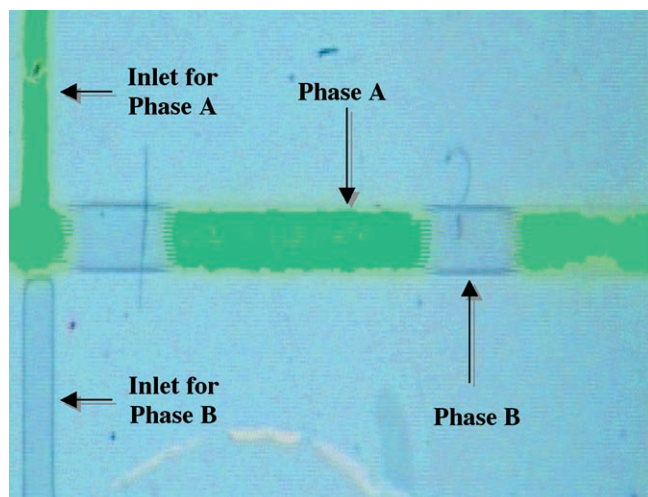


**Figure 1.** Schematic representation of segmented flow in a microchannel: Rapid mixing within a given fluid segment is caused by the internal vortex fluid flow; mass transfer between contiguous fluid segments is enhanced by the continuously refreshing interface.

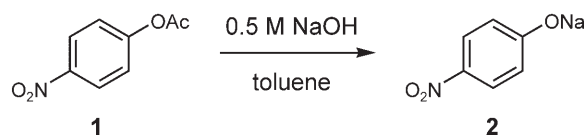
channel plays a significant role in the formation of segments and influences their shape due to the effects of interfacial tension and surface energies.<sup>[5]</sup> The comparison of microreactors with conventional processing has become of interest recently as exploitation of their industrial usage is increasing.<sup>[6]</sup>

Herein we report the effect of internal vortex circulation in segmented flow systems and compare these data with results obtained using conventional flasks. Firstly, we performed biphasic reactions in which a mass-transfer between two phases is necessary in order for a reaction to proceed. Secondly, we describe the acceleration of homogeneous reactions taking place only in one phase, which is rapidly mixed by an immiscible, second inert phase.

For the generation of segmented flow, a microreactor or PTFE (polytetrafluoroethylene) tube with a T-junction geometry was used. One fluid phase moves into the channel whilst the other phase is forced into the junction, thus cutting the flow of the first phase due to the high interfacial forces between the phases. Pressure build up then reverses the configuration, and as these events are repeated a regular segmented flow stream is formed (Figure 2). The lengths of segments are dependent on flow velocities and surface properties. Additionally, a material with a high surface energy with respect to one phase (i.e., larger contact angle) will lead to more rounded fluid segments. For example, in the case of an organic/aqueous system in a channel made of perfluoro polymeric material, the aqueous phase will have a larger contact angle and hence a higher surface energy compared to the organic phase, leading to the formation of “rounder” aqueous segments and expanded organic ones.



**Figure 2.** Photo image of segmented flow during biphasic hydrolysis reaction in PMMA microreactor with T-junction; Phase A is the aqueous layer and Phase B is the organic layer.

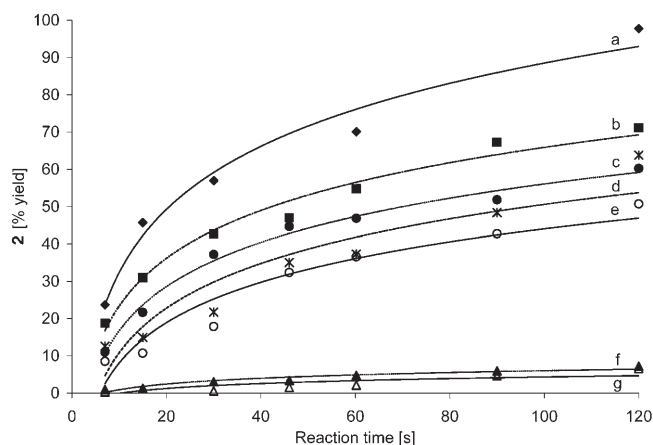


**Scheme 1.** Hydrolysis of *p*-nitrophenyl acetate (**1**).

We investigated the hydrolysis of *p*-nitrophenyl acetate (**1**), dissolved in toluene, with aqueous sodium hydroxide as a biphasic reaction (Scheme 1). The reaction progress was monitored by the UV absorption of phenolate **2** at  $\lambda_{\text{max}} = 400$  nm. The reaction was performed in a microreactor as described in the Experimental Section ( $300 \mu\text{m} \times 300 \mu\text{m}$  microchannel, 400 mm length) or in a PTFE tube ( $300 \mu\text{m}$  internal diameter, 400 mm length). The yield of the reaction is dependent upon reaction time which is inversely proportional to the flow rate. Additionally, the size of the segments will also have an effect on the reaction rate as the ratio of volume:interfacial area increases with increasing size of the segments (Figure 3).

A solution of substrate **1** in toluene (0.05 M) and an aqueous solution of sodium hydroxide (0.5 M) were passed through the two inlets of the microreactor or into a T-junction of PTFE tubes using a dual syringe pump.

The hydrolysis of *p*-nitrophenyl acetate (**1**) was carried out under different reaction conditions in different reactors. It is possible to deduce a number of trends from the results shown in Figure 3. A comparison



**Figure 3.** Hydrolysis of **1** using different flow types and reaction times: (a) Short segmented flow (approx. 2 mm) under microwave irradiation at 50 °C. (b) Long segmented flow (approx. 10 mm) under microwave irradiation at 50 °C. (c) Segmented flow in PTFE tubing heated in an oil bath at 50 °C. (d) Segmented flow at room temperature in a PMMA reactor. (e) Segmented flow at room temperature in PTFE tubing. (f) Hydrolysis reaction at 50 °C in a flask with stirring. (g) Hydrolysis reaction at room temperature in flask with stirring.

son of the results of reactions labelled (f) and (g) in Figure 3 with the other results is obvious. The reaction rate of the hydrolysis using a conventional flask is much lower than using microreactors and the difference between hydrolysis at room temperature (g) and at 50 °C (f) is not significant at that timescale.

Reactions labelled (d) and (e) were both carried out under similar reaction conditions, but in different reactors. These results show that the reaction in the PMMA (polymethyl methacrylate) microreactor (d) performs slightly better than in the PTFE tubing (e). The better performance in the PMMA microreactor is probably due to the visually slightly shorter segments and their higher regularity. The different T-junctions for creating the segmented flow might also play a role. As the PMMA microreactor with its metal housing cannot be inserted in the microwave, the experiments at elevated temperature (a, b, c) have been performed using PTFE tubing.

An increase of the reaction rate by heating can be seen by comparison of (e) and (c). A further increase is observed by microwave irradiation of the microreactor in a water bath (b) instead of heating with a conventional oil bath (c). By microwave irradiation of the microreactor without a surrounding fluid, insufficient energy is absorbed to cause significant heating. This is due to the low loss microwave materials (PMMA, PTFE) used in construction and the low absorption characteristics of the fluidic duct geometry. Those are known properties and microwave heating of microreactors with outside deposition of gold metal to increase microwave absorbance is known.<sup>[7]</sup> Macroscale flow reactors suitable for microwave irradiation have also recently been reported.<sup>[8]</sup>

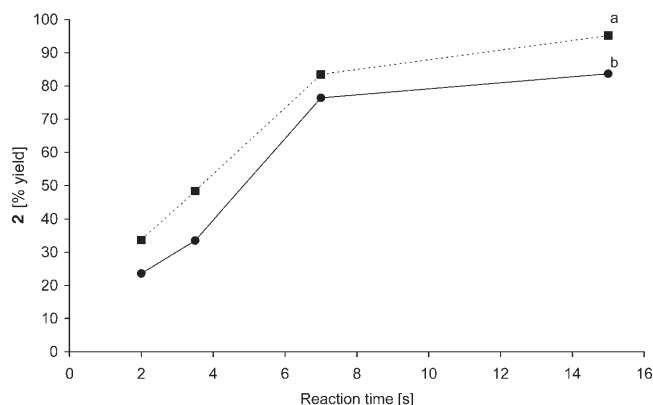
The reactions labelled (a) and (b) in Figure 3 have both been carried out under microwave irradiation, but the segment size in (a) is smaller than in (b). The reaction rate is further increased by the generation of shorter segments, which was achieved by applying a higher flow rate (1.5 times higher) of the aqueous phase compared to the organic phase using two different sized syringes in the syringe pump.

The effect of the channel size on the segmented flow system was also studied. In microchannels of smaller diameter (either PMMA microreactor or PTFE tubing), higher reaction rates were observed as detailed in the Supporting Information, which suggests the influence of a relatively larger interfacial area to volume ratio in the smaller microchannels.<sup>[9]</sup> As flow rate increases, mass transfer increases and leads to a larger conversion rate, but for a given length of the microchannel, the reaction time (residence time) will be smaller and the overall reaction may be less efficient. However, the length of individual fluid segments will also have an effect on the conversion rate. Ramshaw has expressed the relationship between the mass transfer time, the flow rate and the

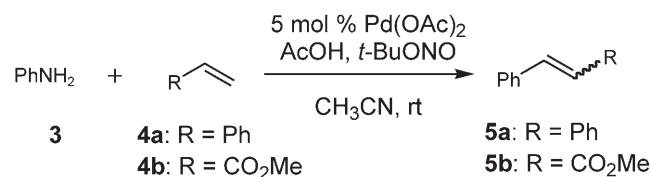
segment length for a given system with defined geometry and used this approximation for the estimation of mass transfer coefficients.<sup>[4a,10]</sup> This numerical model suggests that with increasing segment length and decreasing flow rate, the mass transfer time increases.

As homogeneous reactions are as important as biphasic reactions, we successfully attempted their acceleration by using the segmented flow technique. The hydrolysis of the acetate **1** was now performed using acetonitrile as a solvent together with aqueous sodium hydroxide to create a homogeneous system of laminar flow in the microchannel (Figure 4). This acetonitrile/water phase was then combined with an inert immiscible solvent (hexane) to divide the reaction solution into segments and to achieve intense mixing in the microchannel as described above. In this homogeneous reaction with a second immiscible organic solvent there will be almost no mass transfer occurring at the interface; only rapid internal vortex fluid flow is achieved. The rate constant calculated for the homogeneous segmented flow ( $k=0.2031\text{ s}^{-1}$ ) is larger than the rate for homogeneous laminar flow ( $k=0.129\text{ s}^{-1}$ ) (for details see Supporting Information). The rate constants have been calculated under the assumption of pseudo-first order kinetics.

Finally, we enabled the enhancement of other homogeneous reactions by introducing an immiscible solvent such as hexane to generate segmented flow. As an example, we performed tandem diazotation/Heck reaction sequences (Scheme 2).<sup>[11]</sup> Heck reac-



**Figure 4.** Homogeneous hydrolysis of **1** (at room temperature): (a) homogeneous segmented flow and (b) homogeneous laminar flow.



**Scheme 2.** Heck reactions using homogeneous segmented flow conditions.

tions have already been investigated in microreactors using a different set-up and reaction conditions.<sup>[12]</sup>

This palladium(II)-catalysed arylation reaction of aniline (**3**) with styrene (**4a**) was performed *via* the diazonium intermediate. When the reaction was carried out in a conventional manner using a flask, stilbene (**5a**) was isolated in 83 % yield after 20 h reaction time. Initially we compared homogeneous laminar flow with homogeneous segmented flow using the substrates **4a** and **4b**.<sup>[13]</sup> GC analysis using an internal standard (decane) showed that the yields were improved when switching from laminar flow to segmented flow conditions. With homogeneous laminar flow **5a** was obtained in 52 % yield (**5b**: 68 %). Introduction of hexane using an additional feeding line into the microreactor resulted in segmentation and under these homogeneous segmented flow conditions **5a** was obtained in 66 % yield (**5b**: 77 %). The product dissolves also in the hexane segments which could have an effect on the reaction rate as the product concentration in the acetonitrile segments decreases. The internal standard can dissolve in the hexane segments, but after the reaction all solvents were removed without separation, and the residue analysed. Further optimisation of the segmented reaction conditions led to even higher conversions in the microreactor (300  $\mu\text{m}$   $\times$  300  $\mu\text{m}$  microchannel, 900 mm length). This was observed after 20 min reaction time and stilbene (**5a**) was isolated in 79 % yield. The reaction with methyl acrylate (**4b**) led to methyl cinnamate (**5b**) in 54 % isolated yield using the homogeneous segmented flow conditions.<sup>[14]</sup>

## Conclusions

In conclusion, by utilizing the large specific interfacial area provided by a microreactor, the hydrolysis reaction of *p*-nitrophenyl acetate (**1**) was found to be much more efficient than applying conventional methods. This is particularly the case when the technologies of segmented flow microreactor and microwave irradiation were used. Even homogeneous reactions could be enhanced by using the segmented flow technique. In the hydrolysis of **1** mentioned above but also in transition metal-catalysed processes like the Heck reaction higher reaction rates were found than using conventional reaction flasks. Application of this microreactor system towards other synthetically useful methods are in progress.

## Experimental Section

### Device Microfabrication

PMMA (polymethylmethacrylate) and PTFE (polytetrafluoroethylene) were the chosen material for the microchannel used for the study. LPKF milling machine was used to microfabricate the PMMA microdevices. Microchannels were fabricated using a 250  $\mu\text{m}$  2FM double edge cutter milling tool to produce 300  $\mu\text{m}$  channels size of uniform depth and width. The microchannels were enclosed with a PMMA cover plate consisting of z-axis inlet and outlet ports that will enable access from the chemical reservoirs into the microreactor channels. Inlet and outlet ports, with an internal diameter of 1.6 mm, were fabricated using a 1 mm 4FM double edge cutter milling tool, to form a tight fit for the connection tubings. The two plates were fused by thermal bonding at 127 °C. Successful fusion of the two polymer substrates required each surface to be scrupulously cleaned by washing several times with methanol and 2-propanol to remove contaminants, followed by drying with nitrogen gas and heating for 48 h at 95 °C prior to fusion (see Figure S2 in the Supporting Information).

### Experimental Set-Up

A stainless steel housing was designed to hold the fabricated microdevice which was then connected to the chemical reservoirs using PEEK tubings (1/16"  $\times$  5 cm, i.d. 0.030") fitted with tight seal connections using flangeless nut and ferrule (M6, Sigma-Aldrich Supelco) to the chemical reservoirs which are air-tight glass syringes (10 mL, Sigma-Aldrich Supelco). Stock solutions of the chemical reagents were loaded into the syringe and delivered to the microreactor using a syringe pump (KD Scientific Inc).

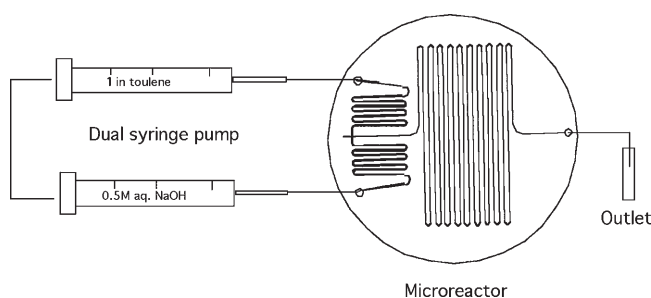
### General Remarks

Reactions at room temperature were performed in a PMMA microreactor (300  $\mu\text{m}$   $\times$  400 mm), with a T-junction to create segmented flow, using the stainless steel housing. PTFE microchannel tube (300  $\mu\text{m}$   $\times$  400 mm) was used for raised temperature reactions with a KEL-F Tee connector (Sigma-Aldrich Supelco). The hydrolysis reaction transformation was monitored and analysed quantitatively using UV (Jasco, V-570, UV/Vis/NIR). For the Heck reaction quantitative analysis using GC was carried out on Varian 3900 gas chromatography equipped with a flame ionisation detector (FID) using a Varian Factorfour capillary column (VF-1 ms, 15 m  $\times$  0.25 mm). All reaction products were analysed by <sup>1</sup>H and <sup>13</sup>C NMR in CDCl<sub>3</sub>.



**Method for the Biphasic/Homogeneous Laminar flow Hydrolysis of *p*-Nitrophenyl Acetate (**1**) in a PMMA Microreactor at Room Temperature:**

A solution of *p*-nitrophenyl acetate (**1**) in toluene/acetonitrile (10 mL, 0.05 M) was loaded into syringe A and an aqueous solution of sodium hydroxide (10 mL, 0.5 M) was loaded in syringe B. Syringes A and B were attached to a syringe pump (KD Scientific) and connected to the microreactor housing through PEEK tubings. The reagents were delivered in controlled flow rates. The reacted mixture was collected in a small vial immersed in an ice container. The reaction product was analysed quantitatively using UV and NMR.

**Method for the Biphasic Hydrolysis of *p*-Nitrophenyl Acetate (**1**) in a PTFE Microreactor at 50 °C using an Oil Bath**

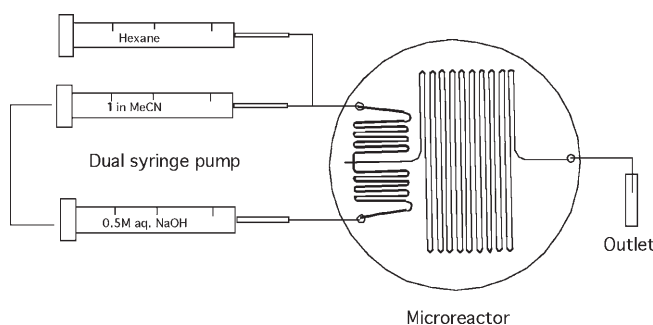
A solution of *p*-nitrophenyl acetate (**1**) in toluene (10 mL, 0.05 M) was loaded in syringe A and an aqueous solution of sodium hydroxide (10 mL, 0.5 M) was loaded in syringe B. Syringes A and B were fitted on a syringe pump (KD Scientific) and connected to the PTFE microchannel through PEEK tubings using a KEL-F Tee connector. The microchannel was submerged in oil bath maintained at 50 °C. The reagents were delivered in controlled flow rates. The reacted mixture was collected in a small vial immersed in an ice container. The reaction product was analysed quantitatively using UV.

**Method for the Biphasic Hydrolysis of *p*-Nitrophenyl Acetate (**1**) in a PTFE Microreactor at 50 °C using Microwave Irradiation**

Same as the hydrolysis reaction at 50 °C except that the microchannel was irradiated with CEM focused microwave at 50 °C (50 watts). The reagents were delivered in controlled flow rates. The reacted mixture was collected in a small vial immersed in an ice container. The reaction product was analysed quantitatively using UV.

**Method for the Homogeneous Segmented Flow Hydrolysis of *p*-Nitrophenyl Acetate (**1**) in a PMMA Microreactor at Room Temperature**

A solution of *p*-nitrophenyl acetate (**1**) in acetonitrile (10 mL, 0.05 M) was loaded in syringe A and an aqueous solution of sodium hydroxide (10 mL, 0.5 M) was loaded in syringe B. An extra syringe, loaded with hexane, was introduced (C). Syringes A, B and C were fitted on a syringe pump (KD Scientific) and connected to the microreactor housing through PEEK tubings. Syringes A and C were joined first using a three-way connector then connected to one of the inlet ports of the microdevice. The reagents were delivered in controlled flow rates. The reacted mixture was collected in a small vial immersed in an ice container. The reaction product was analysed quantitatively using UV.

**Method for the Homogeneous Laminar Flow Diazonium-Heck reaction in a PMMA Microreactor**

A solution of aniline (30 mg, 0.322 mmol) and the alkene **4** (0.322 mmol) in acetonitrile (5 mL) was loaded in syringe A. In syringe B, a prepared solution mixture of palladium acetate catalyst (5 mol %) in acetonitrile (5 mL) was loaded. A neat mixture (total of 2.2 mL) of *tert*-butyl nitrite (2.80 mmol) and acetic acid (0.1 mL/0.129 mmol of aniline) was loaded in syringe C. Syringes A, B and C were fitted on syringe pumps (KD Scientific) and connected to the microreactor housing through PEEK tubings. Syringes A and C were joined first using a three-way connector then connected to one of the inlet ports of the microdevice, while syringe B was connected to the other port. The reagents were delivered in controlled flow rates using the pump. The reacted mixture was collected in a small vial immersed in an ice container. The reaction product was analysed quantitatively using GC and NMR.

**Method for the Homogeneous Segmented Flow Heck Reaction in a PMMA Microreactor**

A solution mixture of aniline (30 mg, 0.322 mmol) and the alkene **4** (0.322 mmol) in acetonitrile (5 mL) was loaded in syringe A. In syringe B, a prepared solution mixture of palladium acetate catalyst (5 mol %) in acetonitrile (5 mL) was loaded. A neat mixture (total of 2.2 mL) of *tert*-butyl nitrite

(2.80 mmol) and acetic acid (0.1 mL/0.129 mmol of aniline) was loaded in syringe C. An extra syringe (D), loaded with hexane (5 mL) was introduced. Syringes A, B C and D were fitted on KD Scientific syringe pumps and connected to the microreactor housing through PEEK tubings. Syringes A and C were joined first using a three-way connector and then connected to one of the inlet ports of the microdevice. Syringes B and D were joined first using also a three-way connector then connected to the other inlet port of the microdevice. The reagents were delivered in controlled flow rates using the pump. The reacted mixture was collected in a small vial immersed in an ice container. The reaction product was analysed quantitatively using GC and NMR.

## Acknowledgements

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## References

- [1] a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors, New Technology for Modern Chemistry*, Wiley, New York, **2000**; b) M. Matlosz, W. Ehrfeld, J. P. Baselt, (Eds.), *Microreaction Technology - IMRET 5: Proceedings of the Fifth International Conference on Microreaction Technology*, Springer, Berlin, **2001**; c) S. J. Haswell, R. J. Middleton, B. O'Sullivan, V. Skelton, P. Watts, P. Styring, *Chem. Commun.* **2001**, 391–398; d) P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong, X. Zhang, *Tetrahedron* **2002**, 58, 4735–4757; e) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, 116, 410–451; *Angew. Chem. Int. Ed.* **2004**, 43, 406–446.
- [2] a) P. Watts, S. J. Haswell, *Chem. Eng. Technol.* **2005**, 28, 290–301; b) P. He, P. Watts, F. Marken, S. J. Haswell, *Electrochem. Commun.* **2005**, 7, 918–924; c) T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J. Yoshida, *Angew. Chem.* **2005**, 117, 2465–2468; *Angew. Chem. Int. Ed.* **2005**, 44, 2413–2416; d) T. Honda, M. Miyazaki, H. Nakamura, H. Maeda, *Lab Chip* **2005**, 5, 812–818.
- [3] a) V. Hessel, W. Ehrfeld, T. Herweck, V. Haverkamp, H. Lowe, J. Sechiewe, C. Wille, *Gas/liquid Microreactors; Hydrodynamics and mass transfer*, Proceedings of the Fourth International Conference on Microreaction Technology, **2000**; b) B. Zheng, L. S. Roach, R. F. Ismagilov, *J. Am. Chem. Soc.* **2003**, 125, 11170–11171; c) J. M. Kohler, T. Henkel, A. Grodrian, T. Kirner, M. Roth, K. Martin, J. Metze, *Chem. Eng. J.* **2004**, 101, 201–216; d) A. Günther, S. A. Khan, M. Thalmann, F. Trachsel, K. F. Jensen, *Lab Chip* **2004**, 4, 278–286; e) D. Belder, *Angew. Chem.* **2005**, 117, 3587–3588; *Angew. Chem. Int. Ed.* **2005**, 44, 3521–3522; f) B. Zheng, R. F. Ismagilov, *Angew. Chem.* **2005**, 117, 2576–2579; *Angew. Chem. Int. Ed.* **2005**, 44, 2520–2523; g) B. K. H. Yen, A. Günther, M. A. Schmidt, K. F. Jensen, M. G. Bawendi, *Angew. Chem.* **2005**, 117, 5583–5587; *Angew. Chem. Int. Ed.* **2005**, 44, 5447–5451.
- [4] a) J. R. Burns, C. Ramshaw, *Lab Chip* **2001**, 1, 10–15; b) T. Thorsen, R. W. Roberts, F. H. Arnold, S. R. Quake, *Phys. Rev. Lett.* **2001**, 86, 4163–4166; c) T. Nisisako, T. Torii, T. Higuchi, *Lab Chip* **2002**, 2, 24–26; d) S. Sugiura, M. Nakajima, M. Seki, *Langmuir* **2002**, 18, 5708–5712; e) J. D. Tice, H. Song, A. D. Lyon, R. F. Ismagilov, *Langmuir* **2003**, 19, 9127–9133; f) S. Okushima, T. Nisisako, T. Torii, T. Higuchi, *Langmuir* **2004**, 20, 9905–9908.
- [5] a) A. Serizawa, Z. Feng, Z. Kawara, *Experimental Thermal and Fluid Science* **2002**, 26, 703–714; b) G. M. Greenway, S. J. Haswell, D. O. Morgan, V. Skelton, P. Styring, *Sensors and Actuators B* **2000**, 63, 153–158; c) N. Harries, J. R. Burns, D. A. Barrow, C. Ramshaw, *Int. J. Heat Mass Transfer* **2003**, 46, 3313–3322; d) G. Dummann, U. Quittmann, L. Gtoschel, D. W. Agar, O. Worz, K. Morgenschweis, *Cat. Today* **2003**, 79–80, 433–439; e) T. J. Jonson, D. Ross, L. E. Locascio, *Anal. Chem.* **2002**, 74, 45–51.
- [6] H. Pennemenn, P. Watts, S. J. Haswell, V. Hessel, H. Löwe, *Org. Proc. Res. Develop.* **2004**, 8, 422–439.
- [7] P. He, S. J. Haswell, P. D. I. Fletcher, *Sensors Act. B* **2005**, 105, 516–520.
- [8] M. C. Bagley, R. L. Jenkins, M. C. Lubinu, C. Mason, R. Wood, *J. Org. Chem.* **2005**, 70, 7003–7006.
- [9] M. Ueno, H. Hisamoto, S. Kabayashi, T. Kitamori, *Chem. Commun.* **2003**, 936–937.
- [10] a) J. R. Burns, C. Ramshaw, *Chem. Eng. Res. Des.* **1999**, 77, 206–211; b) J. R. Burns, C. Ramshaw, *Chem. Eng. Commun.* **2002**, 189, 1611–1628.
- [11] M. Beller, H. Fischer, K. Kühlein, *Tetrahedron Lett.* **1994**, 35, 8773–8776.
- [12] a) S. Liu, T. Fukuyama, M. Sato, I. Ryu, *Org. Process Res. Dev.* **2004**, 8, 477–481; b) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, 4, 1691–1694.
- [13] Reagents in DMF: 2.5  $\mu\text{L min}^{-1}$ ; substrates in DMF: 2.5  $\mu\text{L min}^{-1}$ ; hexane: 16.5  $\mu\text{L min}^{-1}$ .
- [14] **5a**: 85% conversion; **5b**: 68% conversion (determined by GC).