Microreactors

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Monolithic and Flexible Polyimide Film Microreactors for Organic Microchemical Applications Fabricated by Laser Ablation**

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There is a growing interest in innovative chemical synthesis in microreactors owing to the potential for high efficiency, selectivity, and yield.[1] In microfluidic systems, the low-volume spatial and temporal control of reactants and products offers a novel method for chemical manipulation and product generation.[2] Glass, silicon, poly(dimethylsiloxane) (PDMS), and poly(methylmethacrylate) (PMMA) have been used for the fabrication of miniaturized devices. Fabrication with glass or silicon substrates requires relatively complex processes, and the fabrication costs are high. Relatively cheap polymers such as PDMS or PMMA are not suitable for application in organic chemical processes owing to their low chemical stability and easy swelling.[3] Therefore, there is a strong demand for economical organic-solvent-resistant materials that can be used for easy fabrication of microfluidic systems with reliable durability. Our group has recently reported novel polymer microreactors for organic syntheses, which involve two kinds of inorganic polymers that are manipulated in relatively simple microfabrication processes.[4] The improved solvent resistance allowed good performance in organic reactions, except in chlorinated solvents such as dichloromethane. Nevertheless, the bonding step was somewhat tricky and had a low rate of success. Alternatively, a monolithic thin-film microreactor can be used for applications in organic synthesis, which allows integration of electrodes, heaters, light-emitting diodes, and various electronics.[5]

There are many fabrication techniques available for microfluidic devices. Of these, laser ablation is convenient to use for polymer chips.[6] The whole microfabrication process could be completed in a few minutes instead of the days that are needed for wet photolithography processes. It is well known that polyimide (PI) offers advantages over other polymers, such as excellent chemical and thermal stability and low water uptake.[7] Recently Barrett et al. reported fabrication of PI-based microfluidic devices by laser ablation.[8] The devices were used for X-ray scattering experiments to yield a better spatial resolution for structural measurements. However, there has been no attempt to demonstrate the potential advantages of PI-based microreactors for chemical syntheses.

Herein, we introduce a monolithic and flexible PI film microreactor for organic synthesis. Mixing units, such as a staggered herringbone pattern on the channel surface, can easily be built into the reactor during the fabrication. The film microreactors were readily fabricated within several tens of minutes by ablation with either a 193 nm excimer laser (ArF) or a 355 nm UV laser. The excellent stability of the fabricated microreactors was successfully demonstrated by performing five chemical reactions under various harsh conditions. The simple and economical laser fabrication process and the facile adhesive sealing step facilitate mass production of the flexible PI film microfluidic devices for various microchemical applications. Furthermore, these devices could provide a platform for integrating microfluidic and electronic components that are necessary for a micro total analysis system (μ-TAS).

As described in the literature,[8] photoablation could be performed either dynamically by continuous moving and shooting of laser pulses to generate the channel or statically by shooting on specific spots assigned by the controlling program.[6] As shown in Figure 1 b, two types of microchannel designs, ArF and UV, were fabricated using the ArF excimer laser with a metal mask and a UV laser with a 25 μm diameter beam spot. Finally, 4 cm long ArF-type microchannels were ablated on the smooth PI film (ArF-1 type) or on a grooved surface with a staggered herringbone (SH) pattern (ArF-SH type). UV-type microchannels 53 cm long were directly ablated along the channel (UV-1 type) or across the channel (UV-2 type) in a repeated scanning mode, finally generating the line-grooved microchannels. The SH pattern was also grooved statically along the beginning part of the channel (UV-SH type).[9]

In general, it is reported that laser irradiation ablates by photochemical decomposition of chemical bonds in the polymer as well as by photothermal evaporation or melt expulsion.[6] It is also known that the laser is strong enough to

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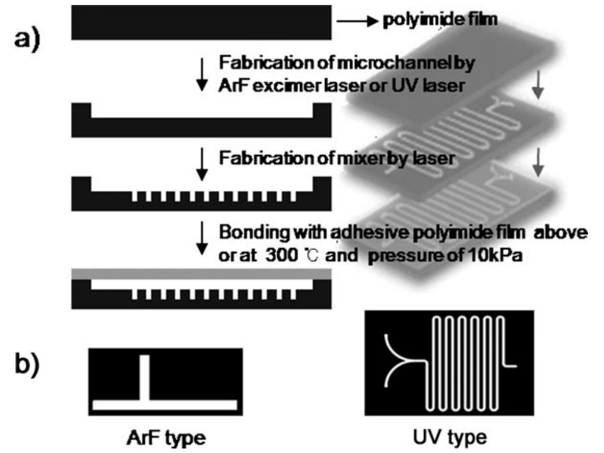


Figure 1. a) Fabrication of PI film microreactors. b) Microchannel designs fabricated by ArF, UV laser.

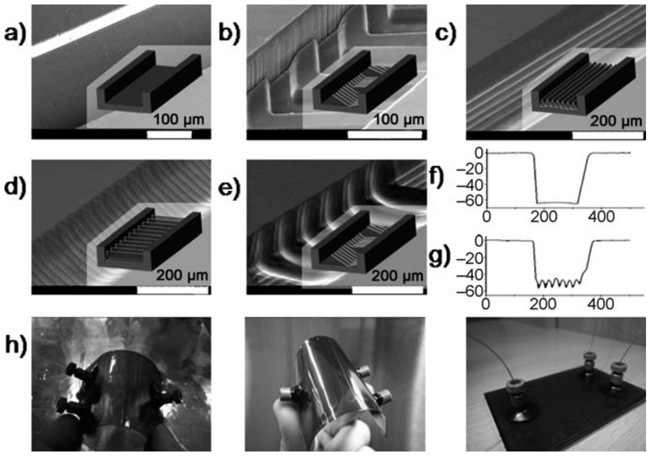


Figure 2. a–e) SEM images and diagrams of various PI film microchannels: a) ArF-1 type with no surface pattern, b) ArF-SH type with staggered herringbone pattern, fabricated by ArF laser, c) UV-1 type with line pattern along the channel, d) UV-2 type with line pattern across the channel, e) UV-SH type with staggered herringbone pattern, fabricated by UV laser. f,g) Cross-sectional surface profile graphs of ArF-1 type (f) and UV-1 type (g). h) Optical images for UV-type flexible PI microreactors.

break chemical bonds with little thermal damage, resulting in smooth patterned surfaces. In particular, the 193 nm ArF excimer laser with high energy first ablated throughout the square metal mask in a single-shot manner to fabricate the T-shaped microchannel on the PI film (ArF-1 channel, Figure 2a). The surface profile image in Figure 2f shows the concave channel with approximately 200 μm width and 60 μm depth and the smooth bottom surface with nearly vertical walls. Furthermore, the additional ablation with different masks rendered the grooved SH pattern with 17 μm depth and a total of 15 mixing cycles along the channel (ArF-SH channel, Figure 2b). Each mixing cycle in the ArF-SH channel is composed of two sequential regions of ridges; the direction of asymmetry of the herringbones switches with respect to the centerline of the channel from one region to the next, as presented by Stroock et al.[9]

Alternatively, UV-type microchannels with different surface patterns (Figure 2c–e) were fabricated by direct ablation of PI film using a UV laser in multiple scans. The repeated scanning ablation with a 25 μm diameter spot generated grooved lines on the surface; the ablation direction could be controlled to align along the channel (UV-1, Figure 2c) or across the channel (UV-2, Figure 2d). And the surface profile image of Figure 2g for the UV-1 channel displayed a channel with approximately 200 μm width and 55 μm depth and a grooved pattern with approximately 5 μm depth in a 25 μm period on the bottom surface. Moreover, we found that the economical, low-energy 355 nm UV laser enabled functionalization of the channel surface with an SH pattern. Moreover, the fast fabrication within several tens of minutes is a great advantage over the long processing time needed with the femtosecond laser.[8] It should also be emphasized that the extended and complex microchannels up to 53 cm long were readily sealed using a self-adhering PI composite film (PI core and PI adhesive layer) at 300 °C under a pressure of 10 kPa. More importantly, the sealed 53 cm long microchannels could endure high flow rates over 200 μL min^{-1} with no delamination. Eventually, the simple fabrication process and the facile adhesive sealing step with high fidelity should facilitate the mass production of flexible PI film microfluidic devices for practical applications in a manner as highly reproducible as PDMS microfluidics.

Chemical resistance is an essential characteristic in the development of materials for organic microreactors. Solvent resistance of the structural PI film material after thermal bonding at 300 °C was examined by soaking the film for 24 h in a range of solvents at different temperatures (Table 1). The PI sample exhibited reliable resistance to all solvents, showing insignificant weight change within 1–2 %. And there was no change in color or appearance even at long soaking times of 24 h. Particularly noteworthy are the excellent stability in dichloromethane (DCM) and strongly acidic H_2SO_4 solution at 100 °C, which are characteristics obviously superior to those of solvent-resistant poly(carbosilane),[4a] poly(vinylsilazane),[4a,b] and fluoropolymers[4c] reported recently. On the basis of these results, PI must be an excellent structural polymer for microchemical devices applicable to organic solvents as well as aqueous media in harsh conditions.

Table 1: Solvent resistance of PI film, evaluated by soaking the 1 × 1 cm film in a Soxhlet extractor at various temperatures for 24 h.

Solvent	T [°C]	W/W_0[a]	Solvent	T [°C]	W/W_0[a]
Water	100	1.00	*n*-Hexane	75	1.00
Acetone	RT	1.01	DMSO	100	1.01
Ethanol	75	1.01	DCM	RT	1.02
Toluene	100	1.02	DMF	100	1.02
THF	75	1.02	2 N H_2SO_4	100	1.00

[a] Experimentally measured swelling ratio W/W_0, where W and W_0 are the weight of the PI film after and before soaking in each solvent. THF = tetrahydrofuran, DMSO = dimethylsulfoxide, DCM = dichloromethane, DMF = dimethylformamide, RT = room temperature.

The mixing efficiencies of the sealed microchannels were determined by comparing the fluorescence images and the intensity profiles when the system was subjected to laminar flow of water or DMF. The ArF-SH microchannel presented excellent mixing efficiency and showed an aqueous homogeneous fluorescent phase after only 0.28 cm flow along the SH mixer portion. This result clearly contrasts that of the ArF-1 microchannel, for which significant mixing was observed after inflowing 3 cm from the inlet merging point (Figure 1S in the Supporting Information). This behavior is consistent with previous reports that natural diffusion and linear convection are not sufficient to mix the species in a short microchannel, even under low flow rates in the range of microliters per minute.[9] The result indicates that the mixer-supported microchannel remarkably enhances the mixing efficiency of inlet solutions compared to the mixer-free microchannel, and it promises fast chemical reactions. Figure 3 shows the fluorescence images and intensity profiles of DMF solution in UV-type microchannels with three different surface patterns at 4 cm from the two inlet merging positions along the microchannel. The image and the profile of the UV-SH microchannel exhibit less laminar flow and low gradient, respectively, when compared to those of the UV-1 and UV-2 microchannels, which maintained the laminar flow. The UV-SH pattern demonstrated superior mixing to other UV-type channels in the microfluidic devices, although the pattern shape was not as well-defined as for the Ar-SH channel, presumably owing to the thermal effect of the lasers. Therefore, it is favorable to use an economical 355 nm UV laser as an alternative ablation tool to an expensive 193 nm ArF excimer laser for polymer film microchannels with functional surface patterns.

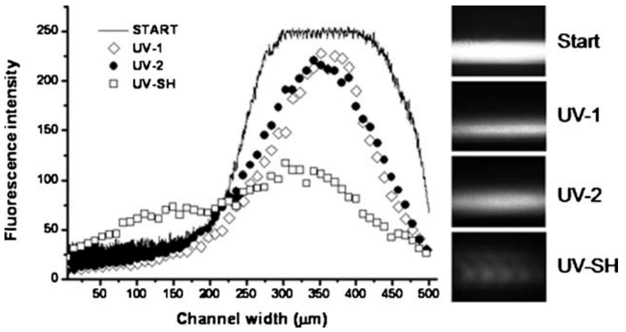
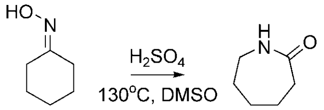


Figure 3. Comparative fluorescence distribution images and intensity profiles of various UV-type microchannels at 4 cm from the two inlet merging positions.

To test the chemical durability of the PI film microreactors, we selected a Beckmann rearrangement reaction under strongly acidic conditions up to 130 °C, exothermic bromination of benzyl alcohol at room temperature (RT), and two step-wise exothermic Vilsmeier formylations at RT and 100 °C. Furthermore, the Knoevenagel reaction and a tin hydride mediated radical reaction were also selected to compare the mixing effect of UV microchannels and the performance with conventional capillary microreactors.

Firstly, synthesis of ε-caprolactam demonstrates the stability of this PI microreactor (Scheme 1), as the reaction requires strongly acidic H_2SO_4 solvent at elevated temperature.[10] It is surprising that the PI microreactor (ArF-SH type) was successfully operated in the extremely acidic solvent (H_2SO_4/cyclohexanone oxime 1:1.5) without any leaking and swelling problems. And under the annealing temperature at 130 °C the synthetic yield of 46 % for 0.9 s retention time in the film microreactor was 1.6-fold higher than the 28 % achieved in a batch system for 1 h reaction time. Furthermore, the PI microreactor was sustained under the above condition over 10 days with no delamination and no defects, thus demonstrating the superior stability to the inorganic polymer microreactors, which showed leakage or deformity when exposed to a few organic solvents (THF, DCM) and acidic conditions.[4a,b] This excellent stability was not reported with any other polymer microreactors, except glass microreactors.



Scheme 1. Synthesis of ε-caprolactam in the ArF-SH microreactor.

The Knoevenagel condensation reaction was carried out in three microreactors, UV-1, UV-2, and UV-SH (each 53 cm length, 200 µm width, 50 µm depth), in ethyl alcohol (Scheme 1S in the Supporting Information).[11] As shown in Figure 4, the synthetic yields of product increased when retention time increased, as previously reported.[4a] As expected, the mixer-supported UV-SH microreactor showed the highest yields, which is more obvious at shorter retention times. And the UV-2 reactor exhibited higher yields than the UV-1 reactor, owing to slight breaking of the laminar flow (Figure 3). Moreover, extending the retention time to 300 s led to complete reaction with over 90 % yield by diffusion-dominated chemistry. In contrast, a noticeably longer reaction time of 20 min within a batch reaction vial (ID = 1 cm, working volume 1.57 mL) resulted in a yield of only 51 %.

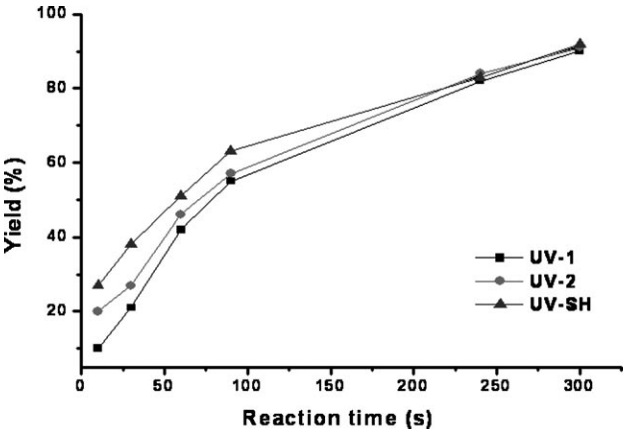
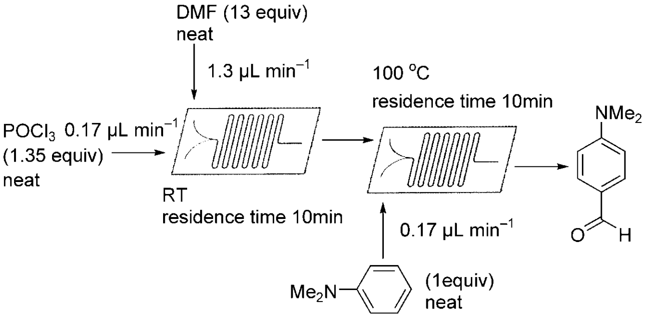


Figure 4. Knoevenagel condensation reaction in UV-type PI film microreactors as a function of surface pattern and reaction time.

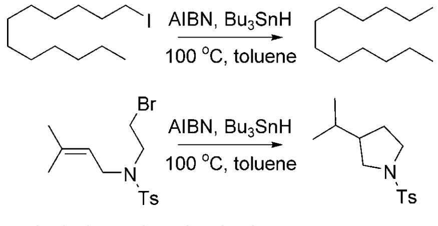
Using a single sheet of UV-2 film microreactor with a 53 cm long microchannel, we examined exothermic bromination of benzyl alcohol with highly toxic PBr_3 (Scheme 2S in the Supporting Information). When the reaction was carried out with 5 min residence time at room temperature, benzyl bromide was obtained in 75 % yield with 23 % starting benzyl alcohol.

The Vilsmeier–Haack formylation reaction (Scheme 2) was performed in a step-wise manner at significantly different temperatures using two serially connected sheets of UV-2 film microreactors (Figure 2S in the Supporting Information). In batch reaction systems, the Vilsmeier reagent is usually prepared by careful addition of phosphoryl chloride to DMF at 0 °C because this step is highly exothermic; the reaction mixture is then heated with electrophiles.[12] In our system, DMF and phosphoryl chloride were directly mixed in the first microchannel sheet at room temperature for 10 min residence time. Then *N*,*N*-dimethylaniline was introduced into the second microchannel sheet and allowed to react at 100 °C for 10 min residence time. The reaction was successful and gave the formylated product in 75 % yield (*ortho*/*para* 15:85).



Scheme 2. Vilsmeier–Haack formylation reaction in the UV-2 microreactor.

Tin hydride mediated radical reaction was carried out using a UV-2 microreactor with one inlet to compare the results with those obtained by the use of a stainless steel tube reactor (Scheme 3).[13] The reduction of 1-iodododecane with tributyltin hydride and AIBN with 5 min residence time at 100 °C in a continuous-flow system gave dodecane in 85 % yield. Radical cyclization was also tested with *N*-(2-bromoethyl)-*N*-(3-methylbut-2-enyl)-*p*-toluenesulfonamide, and the expected cyclization product was obtained in 59 % yield. Thus, we were gratified to know that similar efficiency was observed with the present polymer-based microreactors.



Scheme 3. Tin hydride mediated radical reaction in UV-2 microreactors. AIBN = azobisisobutyronitrile. Ts = *p*-toluenesulfonyl.

In conclusion, a monolithic and flexible film microreactor has been introduced for organic reactions and syntheses. The microreactor can easily be fabricated by photoablating a PI film and then simply placing an adhesive PI film on the patterned PI film for bonding. Mixing units that can assure complete mixing can also be built into the reactor surface during fabrication. Although it does not require the complicated processing needed for glass microreactors, the film microreactor is as inert, sturdy, and versatile as glass microreactors. The utility of the microreactor as an all-purpose reactor has been demonstrated with five different types of organic chemical reactions. These include Beckman rearrangement under strongly acidic conditions at up to 130 °C, Knoevenagel reaction in reactors with three different surface patterns, two highly exothermic reactions for bromination of benzyl alcohol and Vilsmeier–Haack formylation, and tin hydride mediated radical reaction at 100 °C. The easy fabrication should facilitate mass production of flexible PI microfluidic devices, which in turn could provide a platform for integrating thin-film electronics for a total micro analysis system.

Experimental Section

To evaluate the mixing efficiency of the UV-1, UV-2, and UV-SH channels, dimethylformamide (DMF) was infused at a flow rate of 2 μL min^{-1} through one inlet of the Y-shaped microchannel, and a 250 μM fluorescent rhodamine solution in DMF was provided from the other inlet of the microchannel at a flow rate of 2 μL min^{-1}. Fluorescent distribution images were taken at 4 cm from the inlet merging position, and the intensity profiles were extracted with aid of the Image J program.[14]

The Beckmann rearrangement for the synthesis of ε-caprolactam was performed within the ArF-SH microreactor, into which 20 mM cyclohexanone oxime in dimethylsulfoxide (DMSO) was introduced from one inlet at 10 μL min^{-1} and the strongly acid H_2SO_4 solution (30 mM, DMSO) from the other inlet with the same flow rate. The temperature of the microreactor was kept constant at 130 °C using a hotplate. The result was compared with that of the batch reaction.

During the Knoevenagel condensation reaction in UV-1, UV-2, and UV-SH microreactors, 50 mM ethyl cyanoacetate mixed with piperazine (v/v, 1:0.1) and 50 mM 4-bromobenzaldehyde in ethyl alcohol (EtOH) were separately introduced into each inlet at an equal flow at 60 °C. For comparison, this reaction was conducted within different surface pattern microreactors. This reaction was also carried out in a batch format using a glass vial.

Bromination of benzyl alcohol was performed in a UV-2 microreactor; benzyl alcohol (1.25 M) and PBr_3 (1.88 M) in THF were introduced into each inlet of the microreactor with 1.5 μL min^{-1} injection rate each at room temperature.

For the Vilsmeier–Haack formylation, two sheets of UV-2 film microreactors each 53 cm long were connected using a capillary tube to give a 106 cm long microchannel. DMF (1.3 μL min^{-1}) and $POCl_3$ (0.17 μL min^{-1}) were allowed to react in the first part of the microreactor. The resulting product was directly introduced into the second microreactor to perform a final-step reaction with *N*,*N*-dimethylaniline (0.17 μL min^{-1}).

Tin hydride mediated radical reaction was performed in a UV-2 microreactor with one inlet. Premixed toluene solution of 1-iodododecane (0.05 M), Bu_3SnH (0.06 M), and AIBN (0.01 M) was introduced with 3.2 μL min^{-1} injection rate at 100 °C. In a second reaction, *N*-(2-bromoethyl)-*N*-(3-methylbut-2-enyl)-*p*-toluenesulfonamide (0.05 M) was used instead of 1-iodododecane to give the cyclized 3-isopropyl-1-tosylpyrrolidine.

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