Enhanced Efficiency and Regioselectivity of Intramolecular $(2\pi + 2\pi)$ Photocycloaddition of 1-Cyanonaphthalene Derivative Using Microreactors

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The intramolecular photocycloaddition of a 1-cyanonaphthalene derivative in microreactors made of poly(dimethylsiloxane) (PDMS) was examined. By using the microreactors and flow system, both the efficiency and regioselectivity increased compared with those under batch conditions.

Recently, microreactors having microchannels have attracted much attention as a new reaction vessel in organic synthesis.[1] There are many reports about thermal and catalytic reactions using the characteristics of microreactors.[2] Although the flow system and high surface area per volume of microreactors are expected to be effective for synthetic organic photochemistry and for combinatorial chemistry, photoreactions conducted in microreactors have been much less reported. To the best of our knowledge, the photocyanation of pyrene,[3] photochemical formation of benzopinacol from benzophenone and alcohols,[4] the addition of photochemically generated singlet oxygen to α-terpinene,[5] the photochlorination of alkylarenes,[6] the photoacid generation,[7] and the photodecomposition of organic molecules by a TiO_2 photocatalyst[8] have been investigated in microreactors.[9] We now report herein the dramatic effects of microreactors on the intramolecular $(2\pi + 2\pi)$ photocycloaddition of 1-cyano-2-[(3-methyl-2-butenyloxy)methyl]naphthalene (**1**).

The microreactors used in this study were made of poly(dimethylsiloxane) (PDMS) by photolithography (Figure 1).[10] Pyrex glass spin-coated by a positive type photoresist was irradiated by a tungsten lamp through a contacted photomask. The development and wet-etching by an HF–NH_4F aqueous solution gave a template having a protruded curve line. The PDMS was molded by the template, and was attached to another flat PDMS plate. Finally, capillary tubes (diameter = 100 µm) were inserted. The channel width of the microreactor was 300 µm, the depth was 50 µm, and the lengths were 45 and 202 mm. The sample solution was injected by a syringe pump (flow rate = 0.03–0.05 mL/h).

The intramolecular photocycloaddition of **1** has already been reported to give an intramolecular photocycloadduct **2** at the 1, 2-position on the naphthalene ring and a photocycloadduct **3** at the 3, 4-position (Scheme 1).[11] Indeed, the photoirradiation of an acetonitrile solution of **1** by a Xenon lamp through a UV-29 filter ($\lambda > 290$ nm) for 180 min under batch conditions gave the intramolecular photocycloadducts **2** and **3** in 56 and 17% yields, respectively (Table 1, Entry 1). However, we found that, when the photoreaction was carried out in a microreactor with a flow system, both the regioselectivity of the products and efficiency were higher than those under batch conditions. For example, only a 0.7 min irradiation of the flowed solution of **1** in a microreactor gave **2** and **3** in 11 and 1% yields, respectively (Entry 2). An extended flow length (Entry 3) and/or lowered flow rate (Entry 5) increased the product yields due to the longer residence time. The acceleration of the efficiency using microreactors was obvious because a 3.4 min irradiation under batch conditions gave poor product yields (Entry 4). Moreover, the addition of $Eu(hfc)_3$ was effective for the regioselective photocycloaddition due to the coordination of $Eu(hfc)_3$ to the cyano and ether groups of **1**–**3** (Entry 6).[11e–g]

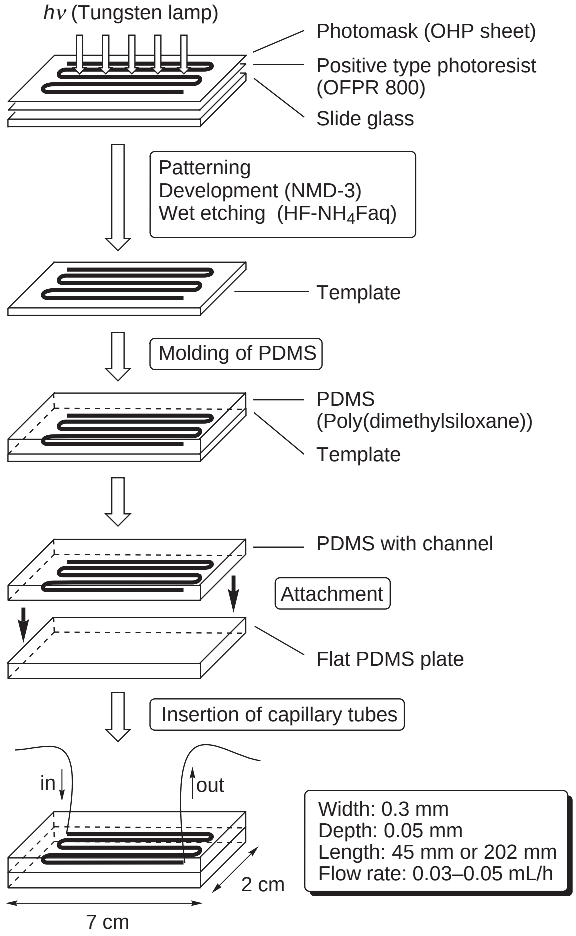
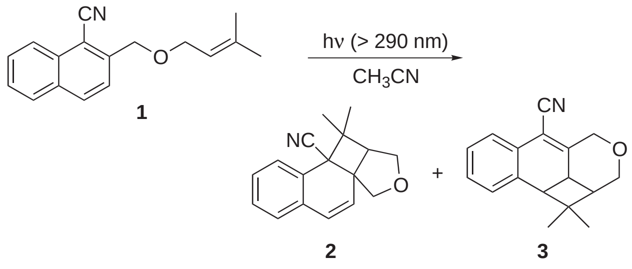


Figure 1. Preparation of microreactors made of PDMS.

Resolution of the enantiomers of **2** can be achieved by chiral HPLC (CHIRALCEL OD–H, eluent: hexane/ethanol = 99/1). HPLC charts of the injection of the racemic **2** detected by UV and CD (both at 270 nm) are shown in Figure 2. From the integral ratio of these signals, the enantiomeric excess when the reaction was carried out in the presence of $Eu(hfc)_3$ was determined. When equimolar amount of $Eu(hfc)_3$ was flowed together, 2.0 ± 0.3% ee of **2** was given (Entry 7), while very low chem-



Scheme 1.

Table 1. Effects of microreactor and Eu(hfc)$_3$ on the intramolecular photocycloaddition of **1**[a]

entry	condition	length /mm	flow rate /mL h^{-1}	irradn time /min	product ratio[b]/% **2**	**3**	recovery of **1**	ee of **2**/%
1	batch[c]	—	—	180	56	17	27	—
2	flow[d]	45	0.05	0.7	11	1	88	—
3	flow[d]	202	0.05	3.4	55	7	38	—
4	batch[c]	—	—	3.4	5	trace	94	—
5	flow[d]	202	0.03	5.6	59	9	32	—
6[e]	flow[d]	202	0.05	3.4	46	3	51	0.5
7[f]	flow[d]	202	0.05	3.4	12	1	87	2.0
8[g]	batch[c]	—	—	180	2	trace	98	—[h]

[a] [**1**] = 3×10^{-2} M, in CH$_3$CN, rt. [b] Determined by ^{1}H NMR. [c] Xenon lamp, Pyrex tube (diameter = 10 mm). [d] Xenon lamp, UV–29 filter, microreactor made of PDMS, width: 0.3 mm, depth: 0.05 mm. [e] Eu(hfc)$_3$ (Tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III)) was flowed together. [Eu(hfc)$_3$] = 3×10^{-3} M. [f] Eu(hfc)$_3$ was flowed together. [Eu(hfc)$_3$] = 3×10^{-2} M. [g] [Eu(hfc)$_3$] = 3×10^{-2} M. [h] Not determined.

ical yields were obtained under batch conditions even for 180 min irradiation due to the higher absorption coefficient of Eu(hfc)$_3$ (Entry 8).

These successful results can be explained on the basis of the inherent characteristics of microreactors. Light was thoroughly absorbed by the moving solution in the thin ditch. An increase in the regioselectivity can be attributed to the flow system. It is known that under batch conditions, the photocycloadduct **2** was predominantly obtained during the initial stage of the reaction, but prolonged irradiation afforded the photocycloadduct **3** as a major product, because photocycloreversion from **2** to **1** efficiently takes place under the reaction conditions, but that from **3** to **1** does not occur.[11e–g] Thus, an improved regioselectivity was reasonably explained by the quick movement of the initial product **2** out of the reaction system.

In conclusion, the efficiency and regioselectivity for the intramolecular ($2\pi + 2\pi$) photocycloaddition both increased using the microreactor flow system. The enantiomeric excess (2.0 ± 0.3% ee) in the presence of Eu(hfc)$_3$ was low, but it was significant.

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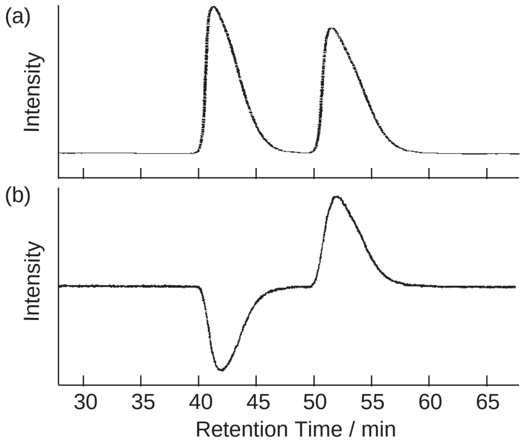

Figure 2. HPLC charts of enantiomer resolution of **2** detected by (a) UV and (b) CD detectors, both at 270 nm.

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