Quick Execution of [2+2] Type Photochemical Cycloaddition Reaction by Continuous Flow System Using a Glass-made Microreactor

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A photochemical [2+2] cycloaddition reaction was executed in a microflow system using glass-made microchannels having 1000-µm width and 500-µm depth. The reaction of cyclohexenones with vinyl acetates in a microflow system under irradiation (300 W, Hg lamp) gave [2+2] cycloaddition products in good yield with a residence time of 2 h, which is a remarkably shortened reaction time compared with a batch system using the same light source.

Photochemical reactions are recognized as useful and practical methods for synthetic chemistry.[1] However, many photochemical processes require long irradiation times, which can lead to decreased yields due to decomposition of the product caused by unfavorable photochemical reactions. Since light strength attenuates exponentially with increasing optical path length according to the Lambert–Beer law [$\log(I_0/I) = \varepsilon cl$], reactions run in microflow systems would be expected to terminate in considerably shortened irradiation time. Effectively, the shorter optical path length would ensure more efficient irradiation. The recent development of microstructured devices such as microreactors provide a good opportunity to use microdevices,[2] even for photochemical reactions. However, to the best of our knowledge, applications of microreactors to practical photochemical reaction, available for organic synthesis, have yet to be fully investigated.[3] The photochemical [2+2] cycloaddition reaction is one of the most powerful and versatile methods for the formation of four-membered rings, and has been extensively applied in organic synthesis.[4] In this communication, we report that photoinduced [2+2] cycloadditions can be highly efficiently carried out using a microflow system, which can reduce irradiation time significantly, compared with the traditional batch reaction system.

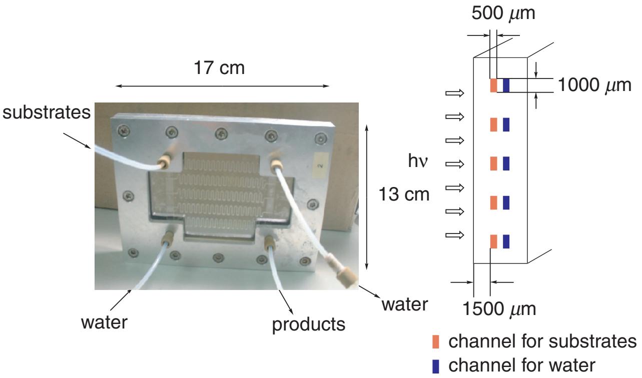
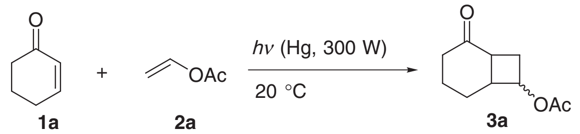


Figure 1. FOTURAN® glass microdevice used for photoirradiation reaction.[5]

The photochemical [2+2] cycloaddition of cyclohex-2-enone (**1a**) with vinyl acetate (**2a**)[4c] was examined as a model reaction. The photo-microreactor employed is made of FOTURAN glass and has a channel 500 µm in depth, 1000 µm in width, and 1.4 m in length (Figure 1).[5] The device is equipped with two separate channels. One channel through which water flows is a heat exchanger, allowing us to examine the photoirradiation reaction at a controlled temperature (20 °C).[6] A mixture of **1a** and **2a** is then introduced through an inlet of the other channel by means of a syringe pump. The reactor was irradiated using a 300-W high pressure mercury lamp, 1 cm from the reactor.

When the reaction of **1a** with **2a** was carried out in a flow system with a flow rate of 0.5 mL/h (residence time: 2 h), the cycloaddition product **3a** was obtained in 88% GC yield (Table 1, Run 1). In principle, a longer channel length would allow substrate to be introduced in faster flow rate. Indeed, the reaction of **1a** with **2a**, using a flow rate of 1.0 mL/h via two serially connected microreactors gave a similar result (Run 2).[7] When the identical reaction was run in batch mode using a 10-mL Pyrex flask with the same light source, the cycloaddition product was obtained in 8 and 22% yields after irradiation of 2 and 4 h, respectively (Runs 3 and 4). Thus, the present microflow system dramatically shortened the reaction time, and increased the yield.

Table 1. Photochemical [2+2] cycloaddition of **1a** with **2a**[a]

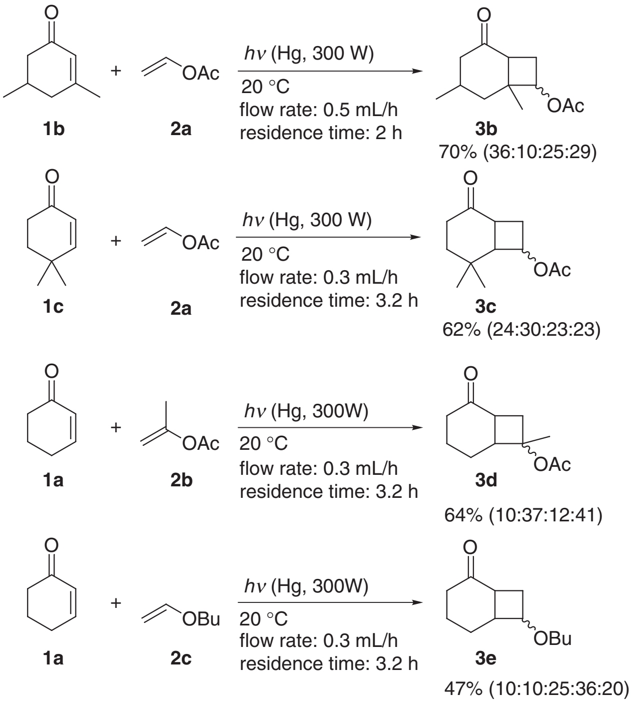


Run	Device	Channel Length/m	Flow Rate mL/h	Reaction time/h	Yield/%
1	microdevice	1.4	0.5	2[b]	88[c,d]
2	microdevice × 2	2.8	1	2[b]	85[e,f]
3	10-mL Pyrex flask[g]	—	—	2	8[h,i]
4	10-mL Pyrex flask[g]	—	—	4	22[h,i]

[a] **1a** (1 equiv.), **2a** (27 equiv.), irradiation from 300-W high pressure mercury lamp. [b] Residence time was given, which was calculated according to the equation, t (h) × flow rate (mL/h) = volume of microchannel (mL). [c] Yield was determined by GC analysis of a sample taken after 2 h operation with tetradecane as an internal standard. [d] Diastereomer ratio, 34:23:43, was determined by GC. [e] Isolated yield for samples collected for 45 h by silica gel chromatography. For details see a footnote. [f] Diastereomer ratio: 32:22:46. [g] Reaction was carried out using 0.38 mmol of **1a** and 1 mL (27 equiv.) of **2a**. [h] Yield was determined by GC analysis using tetradecane as an internal standard. [i] Diastereomer ratio: 32:22:46.

In order to test the generality of the photochmical [2+2] cycloaddition in a microflow system, two more cyclohexenones, **1b** and **1c**, and two more alkenes, **2b** and **2c**, were examined

(Scheme 1). The reaction of 3,5-dimethylcyclohex-2-enone (**1b**) with **2a** proceeded smoothly to give the desired product **3b** in 70% yield. The reaction of 4,4-dimethylcyclohex-2-enone (**1c**) with **2a** gave **3c** in 62% yield. The reaction of **1a** with isopropenyl acetate (**2b**) and butyl vinyl ether (**2c**) gave the corresponding cycloaddition products **3d** and **3e** in 64 and 47% yields, respectively.



Scheme 1.

In conclusion, photochemical [2+2] cycloaddition reactions have been successfully conducted in a microflow system using a glass-made microreactor having 500-μm channel in depth, which resulted in significant reduction of the reaction time compared to that in a batch reaction system. We believe that photoirradiation in a microflow system has good potential for many other photochemical reactions, and applications to other systems are presently in progress in this laboratory.

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References and Notes

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5 The photo-microreactor, Mikroglas Dwell Device, was purchased from Mikroglas Chemtech GmbH. FOTURAN® glass allowed light with $\lambda > 250$ nm to be transmitted.

6 Without water coolant, the reactor was heated to about 60 °C.

7 Procedure for Photochemical [2+2] Cycloaddition in a Microflow System. A mixture of cyclohex-2-enone (**1a**) (1.9 g, 20 mmol), vinyl acetate (**2a**) (50 mL, 540 mmol) was loaded in a syringe. The syringe was connected to an inlet of two serially connected microreactors by a Teflon tube. The microreactors were placed at 1 cm apart from a 300-W high pressure mercury lamp. The substrates were introduced to the microreactor by a syringe pump at the rate of 1 mL/h (residence time: 2 h). The mixture of the product was collected from the outlet. The reaction mixture (ca. 2 mL) from the first 2 h operation was discarded and the subsequent portion was collected for 45 h. Diastereomer ratio of the products was determined by GC analysis of the crude reaction mixture (32:22:46). Excess vinyl acetate was removed under reduced pressure. The residue was choromatographed on silica gel to give 2.9 g of **3a** as a diastereomers mixture. Spectral data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63–1.60 (m, 1H), 1.77–1.88 (m, 2H), 1.92–2.00 (m, 4H), 2.10–2.22 (m, 2H), 2.34–2.42 (m, 1H), 2.54–2.60 (m, 1H), 2.70 (t, $J = 10.1$ Hz, 1H), 2.92–3.00 (m, 1H), 4.79 (q, $J = 7.8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.95, 22.63, 24.67, 31.44, 38.11, 41.21, 45.27, 69.19, 170.46, 213.49; MS (EI), m/z (relative intensity) 182 (M^+, 0.1), 140 (11), 122 (76), 111 (35), 97 (100).

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