Microflow photo-radical reaction using a compact light source: application to the Barton reaction leading to a key intermediate for myriceric acid A

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A B S T R A C T

The Barton reaction (nitrite photolysis) of a steroidal substrate **1**, to give **2**, a key intermediate for the synthesis of myriceric acid A, an endothelin receptor antagonist, was successfully carried out in a continuous microflow system using a Pyrex glass-covered stainless-steel microreactor having a one lane microchannel (Type A: 1000 μm width, 107 μm depth, 2.2 m length). We found that using a low-power black light (peak wavelength: 352 nm) and UV-LED light (peak wavelength: 365 nm) as the light source will suffice for the Barton reaction, creating a compact energy-saving photo-microreaction system. A multi-gram-scale production was attained using a multi-lane microreactor (Type B: 1000 μm width, 500 μm depth, 0.5 m length, 16 lanes) in conjunction with a black light.

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1. Introduction

The Barton reaction (nitrite photolysis), which represents the remote functionalization of saturated alcohols, uses photo-irradiation conditions for nitrite esters prepared from the corresponding alcohols and nitrosyl chloride.[1] Having the unique potential of site-selective C–H bond cleavage at the δ-position via a 1,5-radical translocation from O to C,[2] the Barton reaction has found widespread application in synthesis processes, which includes steroid functionalization. Steroidal substrate **2** is a key intermediate in the synthesis of myriceric acid A, an endothelin receptor antagonist, and can be prepared from alcohol **5** via nitrite **1** by the Barton reaction (Scheme 1).[3]

The recent rapid progress of microreaction technology allows for organic chemists to use microreactors for a variety of organic syntheses.[4,5] One of our focuses in this area has been the development of a practical gram- to multi-gram-scale synthesis using microreactors.[6–10] We have reported on a number of organic reactions using microreactors, such as Pd-catalyzed coupling reactions[7a,b] and carbonylation,[7c] where ionic liquids were used for catalyst support. We also reported that a tin hydride-mediated radical reaction of organic bromides and iodides can be conducted with the effective use of microreactors.[8,11]

Among a variety of organic reactions, photo-chemical transformation using a microreactor has promise regarding the efficient use of light energy.[9,10,12,13] Photo-microreactors have advantages over conventional batch reactors from several viewpoints: (1) the efficiency of light penetration is improved because of the thinness of the reaction mixture in the microspace; (2) the short residence time allows the avoidance of undesirable side reactions; (3) a continuous-flow system can be created and allows for the use of the same microdevices for large quantity production; and (4) an energy-saving compact light irradiation system can be accommodated by the reaction system. We believed that the Barton reaction leading to **2** would be efficiently carried out by using a glass-covered stainless-steel microreactor, coupled with the use of an energy-saving compact light source.[10] In this article, we report the full details of our work on the Barton reaction in a continuous-microflow system.

2. Results and discussion

2.1. Microdevices for photo-irradiation

The Barton reaction in a batch system typically uses a high-pressure mercury vapor lamp as the light source. Thus, we began with a 300 W, high-pressure mercury lamp in combination with a glass-covered, stainless-steel microreactor Type A (channel dimensions: 1000 μm width, 107 μm depth, 2.2 m length; 0.2 mL hold-up volume) (Fig. 1). The type A reactor was employed to optimize the reaction conditions, whereas a gram-scale continuous operation will be carried out under optimized conditions in a multi-lane reactor Type B (1000 μm width, 500 μm depth, 0.5 m length, 16 lanes, 4 mL hold-up volume) that has 20 times the hold-up volume of a Type A (Fig. 2).

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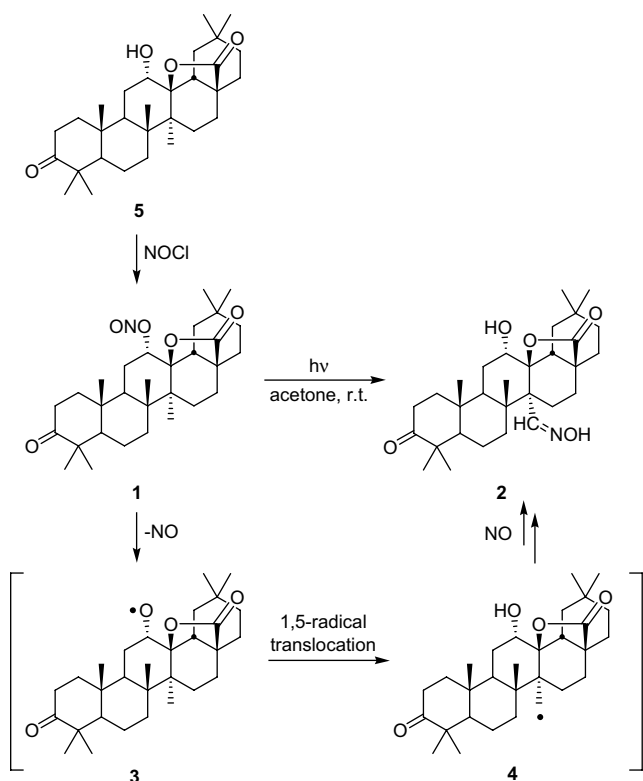
Scheme 1. Barton nitrite photolysis of a steroidal compound **1** leading to an oxime **2**.

Figure 2. Microreactor type B.

2.2. The effect of light sources and filters

As a microreactor top, quartz glass (thickness: 10 mm), Pyrex glass (thickness: 10 mm), and soda lime glass (thickness: 12 mm) were tested in combination with high-pressure mercury lamp irradiation (Table 1). The mercury lamp and the microreactor were set at a distance of 15 cm, and the reaction performance was compared for the different glass materials at a residence time of 6 min. As anticipated, the quartz cover glass resulted in a complex mixture of products involving a trace amount of the desired **2** due to no filtration effect against the short wavelength inherent of the mercury light source. The use of the Pyrex cover glass produced a complex mixture, including **2** in 21% yield with hydroxy lactone **5**. In the case of the soda lime glass, the conversion was not as good as with the Pyrex glass, which had a cleaner reaction.

To understand the variable results of different glass tops, the characteristics of the light that transmits through each type of glass were measured (Fig. 3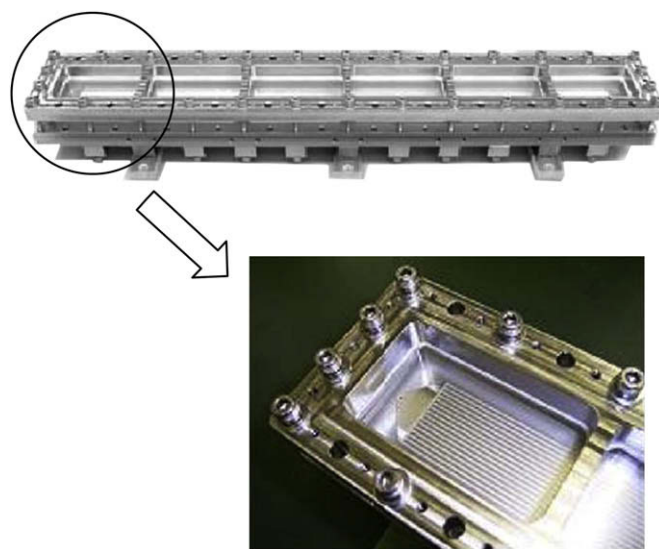). Only the soda lime glass could cut off a wavelength shorter than 320 nm, which is the level that is considered to be responsible for decomposition of the substrate and/or the product.

Then, we measured the intensity of the light at 365 nm, which is required for the present Barton reaction. It was found that with either quartz or Pyrex, at 365 nm the light did not decline, whereas soda lime glass caused a significant decline (Fig. 4). It was also confirmed that when the distance between the light and the reactor is doubled (15 cm), the light reaching the reactor declines considerably.

Using a microreactor Type A with a soda lime glass top cover, we examined the optimal distance between the microreactor and a high-pressure mercury lamp. In this experiment, the residence time was fixed at 6 min (Fig. 5). When the reactor was placed 7.5 cm from the light source, **2** was obtained in 59% yield. By moving the light source farther away from the reactor, understandably, the yield for **2** dropped due to the decrease in light intensity reaching the reactor. On the other hand, a closer distance, such as 5 cm, gave an inferior yield for **2** (33%). This prompted us to examine the influence of heat generated by photo-irradiation. Figure 5 clearly shows that at a distance of 5 cm the temperature rose to 50 °C.

To evaluate the influence of temperature on the reaction, the distance between the light source and the microreactor surface was kept at 15 cm, and the microreactor was placed in a constant temperature bath to maintain a fixed reaction temperature. There was no large difference in the yield of **2** in a range of 0–40 °C.
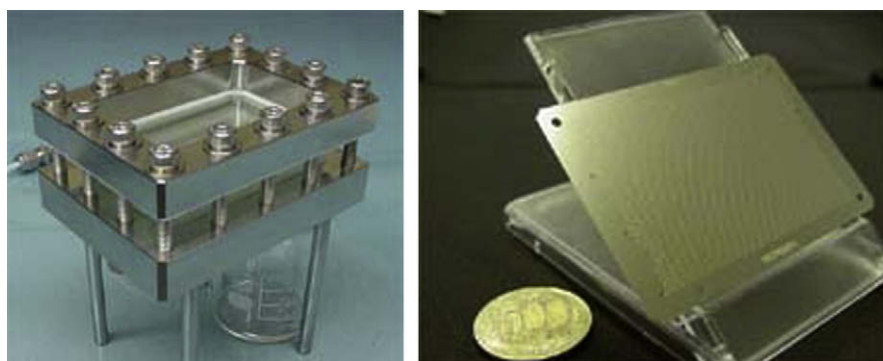

Figure 1. Microreactor type A, left: overview; right: microchannel etched on a stainless-steel plate.

Table 1
The microflow Barton reaction of **1** with a varied glass top[a]

$$1 \xrightarrow[\substack{\text{acetone, r.t., pyridine (0.2 equiv)} \\ \text{flow rate: 2.0 mL/h, residence time: 6 min}}]{\substack{h\nu \\ \text{microreactor: Type A}}} 2$$

Entry	Reactor top	**1** (%)[b]	**2** (%)[b]
1	Quartz	Trace	Trace
2	Pyrex glass	7	21
3	Soda lime glass	46	19

[a] Microreactor type A, [**1**]: 9 mM in acetone, pyridine 0.2 equiv, distance between light and the microreactor surface: 15 cm.
[b] HPLC yield.
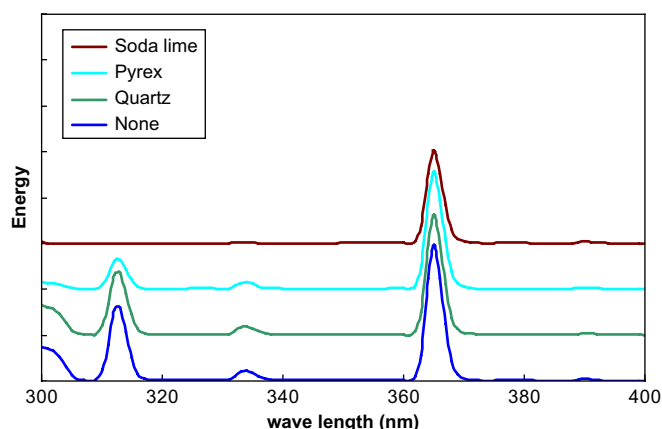
Figure 3. Spectrum comparison of a high-pressure mercury lamp with varied glass tops.
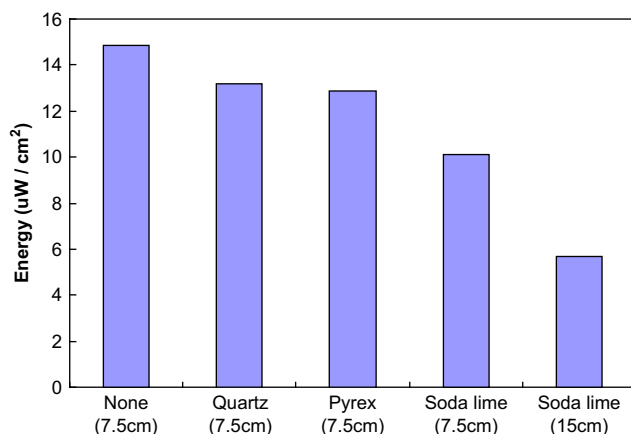
Figure 4. Light intensity comparison for different glass materials at 365 nm. Numbers in parenthesis represent the distances between the light and the reactor.

However, at 50 °C the decomposition of the substrate was pronounced. In a separate experiment under dark conditions, nitrite **1** remained intact without decomposition at 50 °C. Accordingly, the decomposition of nitrite at 50 °C could occur accompanied by the photo-induced homolysis of **1**. Taking these results into consideration, we concluded that the initial system based on the combination of a high-pressure mercury lamp and soda lime glass is not ideal for this reaction because of declining photo-efficiency and heat evolution. Thus, we decided to pursue a compact energy-saving light source with a narrow range of wavelength, which would allow us to use the more efficient Pyrex glass.
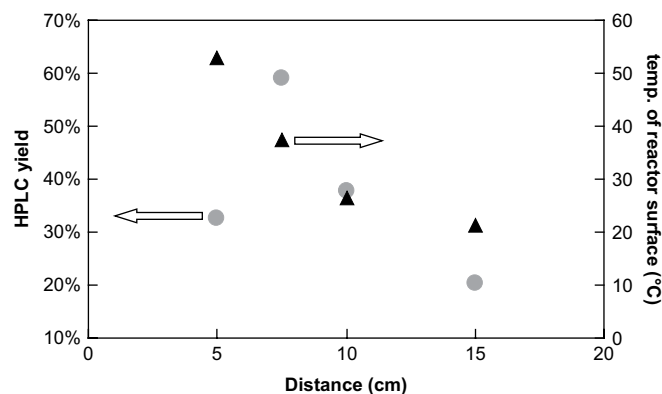
Figure 5. Optimization of the distance between the light source and the microreactor surface.
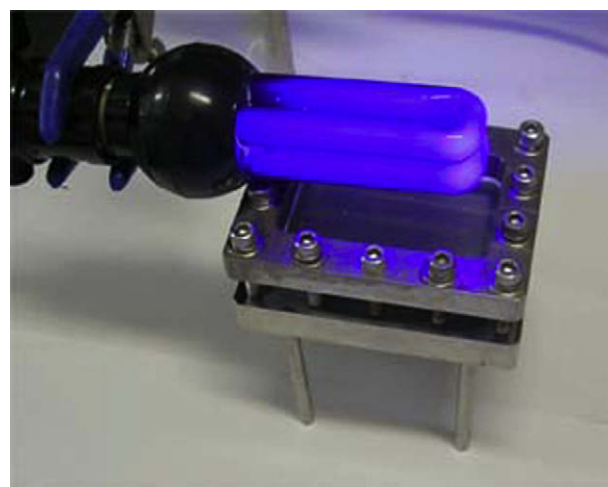
Figure 6. 15 W black light and type A microreactor.

As we discussed above, a high-pressure mercury vapor lamp (300 W) radiates short wavelength light that can cause power loss of the light and an undesirable evolution of heat. It occurred to us that a black light (15 W, Fig. 6), which has a maximum peak wavelength at 352 nm, might be suitable for the Barton reaction. The results of the microflow reaction using a black light are summarized in Table 2. When using a black light, the Pyrex top glass gave better results than the soda lime glass (entries 3 and 4). This is because Pyrex glass has the advantage of better transparency for the wavelength used compared with soda lime glass, and the shorter wavelengths (<340 nm) produced by a black light are very weak. Since the power of a black light (15 W) is considerably weaker than that of a mercury lamp (300 W), we adjusted the residence time to compensate for this deficiency. Gratifyingly, we found that a slight extension of the residence time to 12 min resulted in a 71% HPLC yield for the desired oxime (entry 5). It is worth noting that the energy efficiency of the black light was 10 times greater than that of the mercury lamp, based on the calculated values of yields per Wh (entries 2, 4, and 5).

We also examined another light source, UV-LED (Fig. 7, a wavelength of 365 nm, and 35 mW×48 pieces), which emits light at only the wavelength required for this reaction—similar to black light, albeit lower in energy (1.7 W). From the viewpoint of energy consumption, the UV-LED light source is by far the most efficient (entry 6), and another consideration is that its design permits it to be placed in much closer proximity to the reactor. Since both the black light

Table 2
Energy efficiency of the microflow Barton reaction[a]

$$1 \xrightarrow[\substack{\text{acetone, rt.} \\ \text{pyridine (0.2 equiv)}}]{\substack{h\nu \\ \text{microreactor: Type A}}} 2$$

Entry	Light source/ reactor top	Flow rate (mL/h)	Residence time (min)	Yield of 2 (%)[b]	Wh	Yield/Wh
1	300 W Hg lamp/ Pyrex glass	2.0	6	21	30	0.70
2	300 W Hg lamp/ soda lime glass	2.0	6	56[c]	30	1.89
3	15 W black light/ soda lime glass	2.0	6	15	1.5	10.0
4	15 W black light/ Pyrex glass	2.0	6	29	1.5	19.3
5	15 W black light/ Pyrex glass	1.0	12	71[c]	3	23.7
6	1.7 W UV-LED/ Pyrex glass	1.0	12	70[c]	0.34	206

[a] Microreactor type A, [1]: 9 mM in acetone, pyridine 0.2 equiv, distance between light and the microreactor surface: 7.5 cm (Hg), 3.0 cm (black light), 1.5 cm (UV-LED).
[b] HPLC yield.
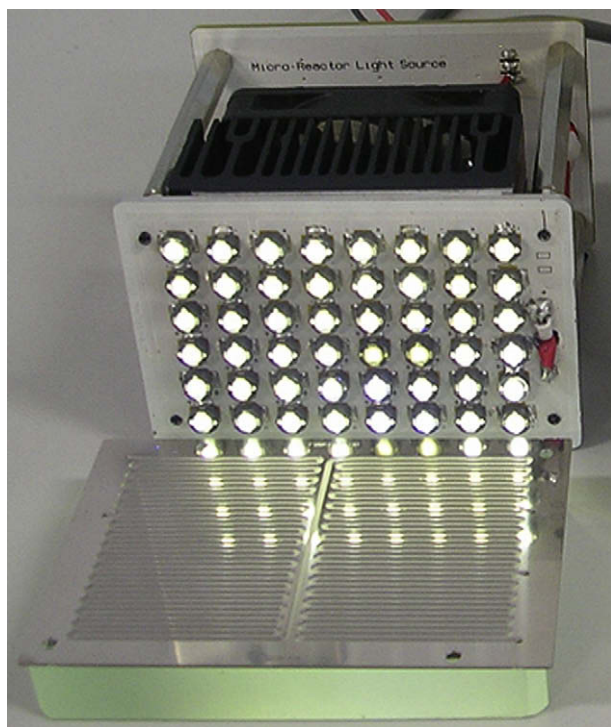[c] Small amount of byproduct 7 formed.

Figure 7. UV-LED.

and the UV-LED emit only the required wavelength, using an optical filter is not necessary. It is obvious that the intensity of these light sources is much weaker than that of a high-pressure mercury lamp. Nevertheless, they have sufficient strength to activate the substrate that exists in solution at a depth in the order of a micrometer.

2.3. Side reaction course leading to a nitrate ester 7

The desired reaction was often plagued by the formation of a nitrate ester 7 as a byproduct, and we suspected that adventitious air in the solution might play a key role in this (Scheme 2). Indeed, the batch reaction in the presence of oxygen led nitrate 7 to be

a principal byproduct (Table 3, entry 1).[14] Maintaining the reaction under a nitrogen atmosphere was effective (entry 2). In the turn of a microreactor, the solution is confined inside the microchannel, and air penetration is restricted by its design (entry 3). Thus, the initial degassing of the substrate solution is sufficient.
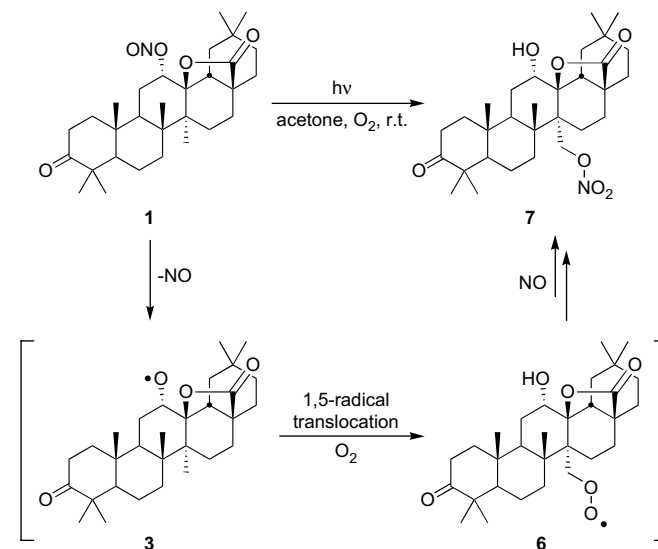
Scheme 2. Barton nitrite photolysis of steroidal compound 1 leading to a byproduct 7.

Table 3
Effect of oxygen

$$1 \xrightarrow[\text{acetone, r.t.}]{h\nu \text{ (black light, 15 W)}} 2 + 7$$

| Entry	Reactor[a]	2 (%)[b]	7 (%)[b]
1	Batch, air	12	30
2	Batch, N$_2$	58	8
3	Microreactor, type A	56	9

[a] Conditions. Batch reaction: the reactions were carried out using a 20 mL Pyrex round-bottom flask. [1]: 9 mM in acetone; pyridine 0.2 equiv; reaction time: 3 h. Microreactor type A: [1]: 9 mM in acetone; pyridine 0.2 equiv; flow rate: 2.0 mL/h; residence time: 6 min; distance between light and the microreactor surface: 7.5 cm.
[b] HPLC yield.

2.4. Gram-order synthesis in the microflow system

Although acetone is a good solvent for the Barton reaction, the solubility of steroidal substrate 1 is limited in this solvent, and it does not permit high throughput production. To address this problem, we screened several solvents and found that the solubility of 1 in DMF is approximately four times higher than that in acetone. Thus, using a 36 mM DMF solution of 1, we carried out a continuous microflow reaction using two serially connected microreactors (Type B: 1000 μm width, 500 μm, 0.5 m length, 16 lanes; total hold-up volume: 8 mL) and eight 20 W black light lamps. As a result, after continuous operation for 20 h, we obtained 3.1 g of the desired product 2 (60% isolated yield after silica gel column chromatography) (Scheme 3).

Encouraged by the successful gram-scale synthesis, we then carried out a continuous microflow reaction using an automated photo-microreactor system, DS-AMS-1, manufactured by Dainippon Screen Mfg. Co., Ltd, which is a PC-controlled station. This system consists of two HPLC pumps, valves, a Type B microreactor, a black light, and thermo control. All operation is commanded by in-house software via PC control. In automated operation, this
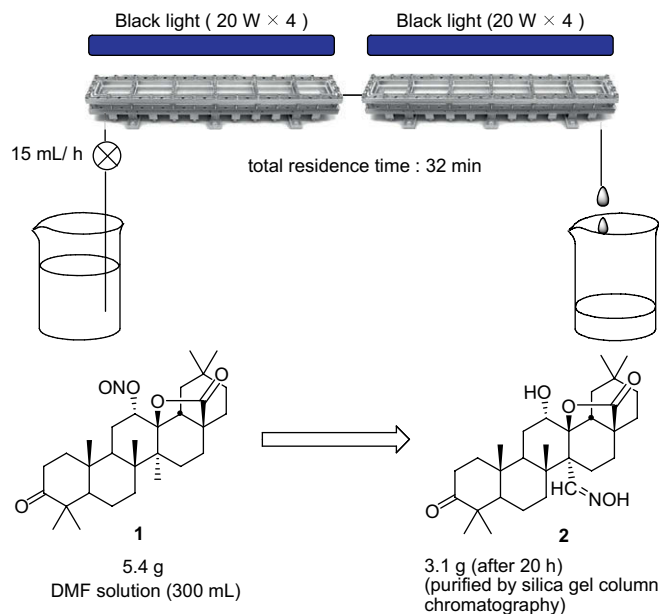
Scheme 3. Gram-scale synthesis of **2**.

system has safety functions such as a solvent leak perception sensor, an exhaust fan, and a sensor for abnormalities in pump pressure. This automated system employed one set of a Type B microreactor and six small (15 W) black light lamps. For this reaction system, a 20 min residence time (with 12 mL/h flow rate) was found to be optimal. The temperature of the reactor was kept at 20 °C by a circulating coolant. Monitoring of the operation can be supervised with the software. After continuous operation for 40 h, we obtained 5.3 g of the desired product **2** (61% isolated yield) by

purification using silica gel chromatography (Scheme 4). This system serves the dual purpose of process optimization and gram- to multi-gram-scale synthesis.

3. Conclusion

In summary, we have demonstrated that the Barton reaction (nitrite photolysis) of a steroidal substrate **1** can be successfully carried out using a stainless-steel microreactor covered by Pyrex glass with DMF as the solvent, giving oxime product **2**, which is a key intermediate for the synthesis of myriceric acid A. We have proven that the combination of energy-saving compact light sources, such as a low-power black light or a UV-LED, will suffice as the light source for such a microflow system. Using the photo-microreactor system, a gram-scale synthesis of **2** was successfully attained either in a manual or an automated continuous microflow system. We believe that the results shown here would be convincing that our developed system is useful for other photo-reactions.

4. Experimental section

4.1. General information

¹H NMR spectra were recorded with a VARIAN OXFORD (300 MHz) spectrometer using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (δ) downfield from internal TMS at 0.00. ¹³C NMR spectra were recorded with a VARIAN OXFORD (75 MHz) spectrometer and referenced to the solvent peak at 77.00 ppm. The products were purified by flash chromatography on silica gel (Merck, Silica Gel 60, 70–230 mesh) with hexane/ethyl acetate (4/1). HPLC analysis was performed under the following conditions: column, WATERS Symmetry RP8 (4.6×150 mm); solvent, $MeCN/H_2O/H_3PO_4$ (80/20/0.1); flow rate, 1 mL/min; detection,
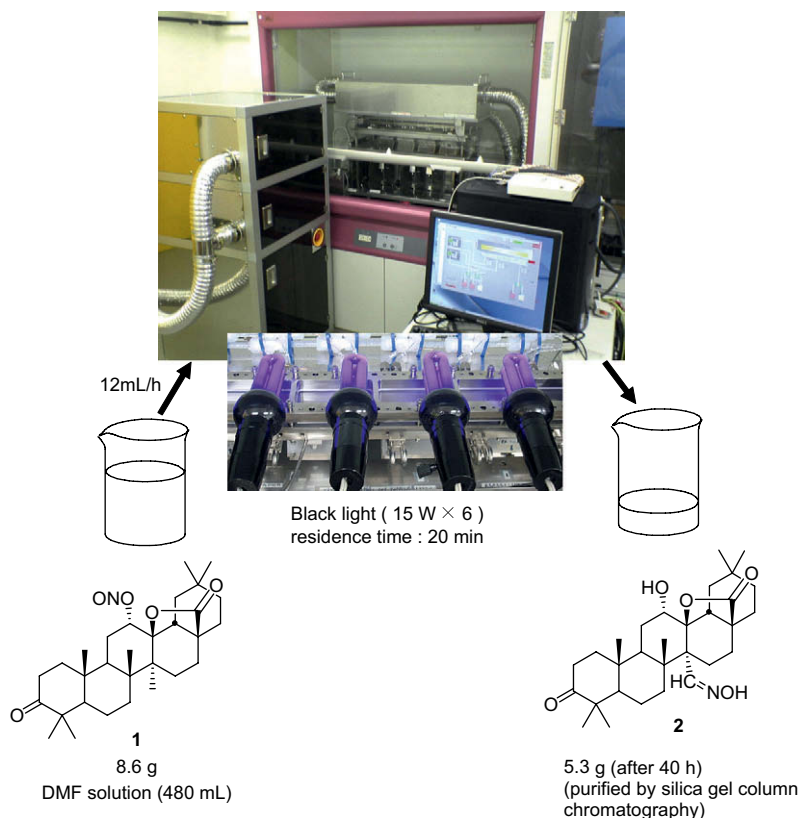
Scheme 4. Gram-scale synthesis of **2** using an automated photo-microreactor system DS-AMS-1.

197 nm. HPLC yields were determined by comparing the peak area with that of the standard solution containing an authentic sample. Compounds **1**, **2**, **5**, and **7** are known.[3]

Microflow reactions were carried out using microreactors Types A and B (Dainippon Screen Mfg. Co., Ltd), a 300 W high-pressure Hg lamp, 15 W or 20 W black lights, and a UV-LED (SEOUL OPTO DEVICE Co., Ltd). The substrate solution was fed to the photo-microreactor by syringe pump or HPLC pump. An automated photo-microreactor system, DS-AMS-1, was developed by Dainippon Screen Mfg. Co., Ltd.

4.2. General procedure for a microflow Barton reaction using a microreactor type A

A continuous microflow reaction was performed by irradiating a solution of nitrite **1** (45 mg, 0.09 mmol) in acetone (10 mL) containing pyridine (0.2 equiv) using either a high-pressure Hg lamp (300 W) or a black light (15 W) through a glass cover (flow rate: 1.0–2.0 mL/h; residence time: 6–12 min). Yield of **2** was determined by HPLC analysis.

4.3. General procedure for batch reaction (Table 3)

The Batch reaction was performed by irradiating a solution of nitrite **1** (45 mg, 0.09 mmol) in acetone (10 mL) containing pyridine (0.2 equiv of **1**) with a black light (15 W) in a 20 mL Pyrex round-bottom flask under either air or nitrogen. Yields of **2** and **7** were determined by HPLC analysis.

4.4. Procedure for a continuous microflow reaction using microreactor type B

A continuous microflow reaction was performed by irradiating a solution of nitrite **1** (5.4 g, 10.8 mmol) in DMF (300 mL) containing pyridine (0.2 equiv) with two microreactors (Type B, 1000 μm width, 500 μm depth and 0.5 m length, 16 lanes and total hold-up volume: 8 mL) and eight 20 W black lights through a Pyrex glass cover (flow rate: 15 mL/h, residence time: 32 min, reaction time: 20 h). Water (600 mL) was added to the photo-reaction mixture and the resultant slurry was collected by filtration and washed with water (100 mL) to give white crystals. The crystals were handled by silica gel column chromatography to give oxime **2** (3.1 g, 60% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.90 (s, 3H), 0.95 (s, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 1.07 (s, 3H), 1.26 (s, 3H), 1.2–1.8 (m, 13H), 1.8–2.2 (m, 8H), 2.2–2.4 (m, 2H), 3.88 (d, 1H), 7.62 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 16.7, 18.1, 18.9, 21.0, 24.2, 24.6, 26.9, 27.1, 28.4, 31.4, 33.1, 33.8, 34.0, 35.4, 36.4, 39.0, 39.5, 42.9, 43.5, 44.2, 45.0, 47.3, 48.8, 50.2, 54.6, 75.1, 88.6, 156.8, 179.2, 218.1. Mp 285–289 °C.

4.5. Procedure for a continuous microflow reaction using an automated microreactor system (DS-AMS-1)

A continuous microflow reaction using an automated micro-reactor system was performed by irradiating a solution of nitrite **1** (8.64 g, 17.3 mmol) in DMF (480 mL) containing pyridine (0.2 equiv) (flow rate: 12 mL/h; residence time: 20 min; reaction time: 40 h). Water (600 mL) was added to the photo-reaction mixture and the resultant slurry was collected by filtration and washed with water (100 mL) to give white crystals. The crystals were handled by silica gel column chromatography to give oxime **2** (5.3 g, 61% yield).

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