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The Barton reaction using a microreactor and black light. Continuous-flow synthesis of a key steroid intermediate for an endothelin receptor antagonist

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Abstract—The Barton reaction (nitrite photolysis) of a steroidal substrate **1**, to give **2**, a key intermediate for the synthesis of an endothelin receptor antagonist, was successfully carried out in a continuous microflow system using a pyrex glass-covered stainless-steel microreactor having a microchannel (Type A: 1000 μm width, 107 μm depth, 2.2 m length). We found that a 15 W black light (peak wavelength: 352 nm) as the light source, suffices for the Barton reaction, creating a compact photo-micro reaction system. Multi-gram scale production was attained using two serially connected, multi-lane microreactors (Type B).

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 with 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 applications in synthesis, including steroid functionalization.[3] The recent rapid progress in the area of microreaction technology[4] prompted us to examine such synthetic reactions using a compact continuous microflow system.[5] In this letter we report that the Barton reaction of a key steroidal substrate **1**, to give **2**, a key intermediate in the synthesis of an endothelin receptor antagonist (Scheme 1),[6] can be successfully carried out by using a glass-covered stainless-steel microreactor (Dainippon Screen Mfg.), coupled with the use of an energy saving compact light source.[7]

Photo-microreactors have advantages over conventional batch reactors from several viewpoints:[8] (1) the efficiency of the photoenergy is improved because of the thinness of the reaction mixture in the micro space, (2) the low residence time avoids undesirable side reactions, (3) a continuous-flow system can be created which 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. Thus, we hypothesized that the Barton reaction could be carried out using a downsized reactor and an inexpensive light source with good energy efficiency.

The Barton reaction typically uses a high-pressure mercury-vapor lamp as the light source. Thus, we began with the use of a 300 W high-pressure mercury lamp in combination with a stainless-steel microreactor (Type A) having a serpentine single lane microchannel (1000 μm width, 107 μm depth, 2.2 m length, hold-up volume 0.2 mL) the top of which was covered by a glass plate (Fig. 1).

Whereas the use of a quartz cover glass resulted in a complex mixture of products due to the low wavelength (high energy) of the mercury light source, the use of soda

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Keywords: Barton reaction; Microreactor; Continuous microflow synthesis; Black light; Endothelin receptor antagonist.

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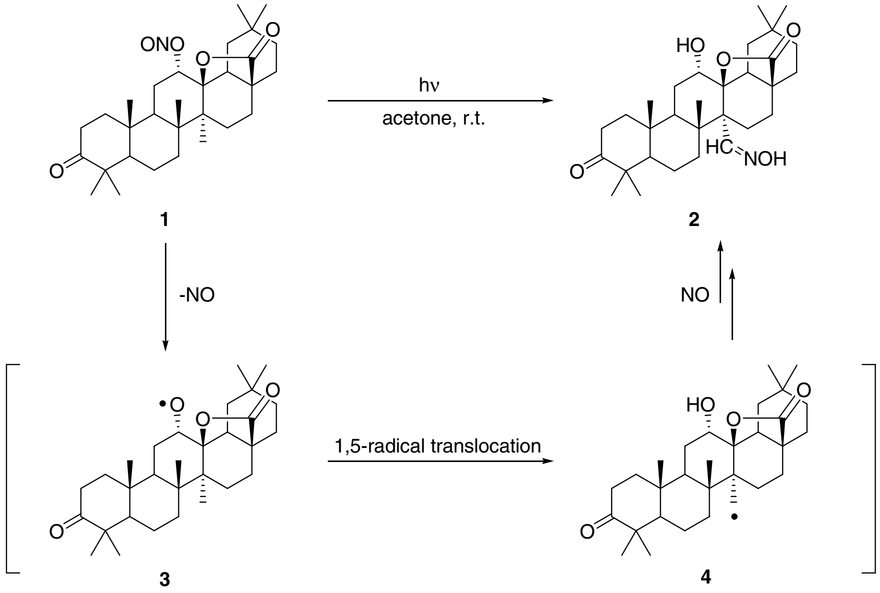


Scheme 1. Barton nitrite photolysis of a steroidal compound **1** leading to an oxime **2**.

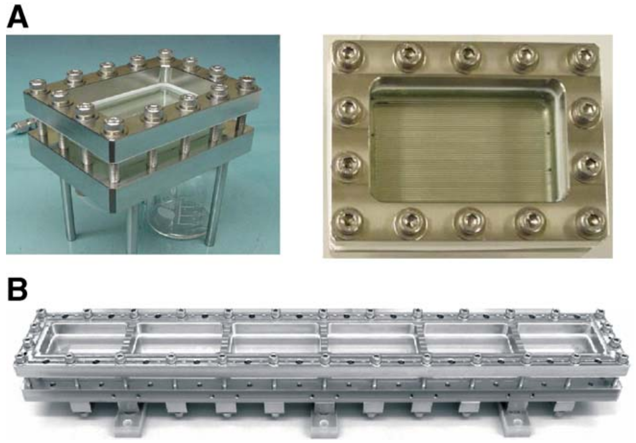


Figure 1. Photos of two microreactors (Type A and Type B) used for this study. Type A (channel size: 1000 μm width, 107 μm depth, 2.2 m length, hold-up volume 0.2 mL). Type B (channel size: 1000 μm width, 500 μm depth, 0.5 m length, 16 lanes, hold-up volume 4 mL).

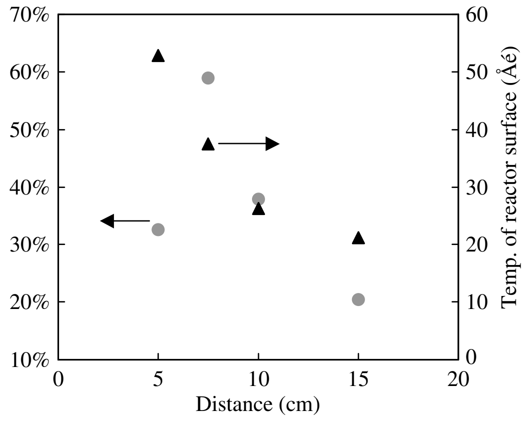


Figure 2. Optimization of the distance between the light source (300 W high-pressure Hg) and the Microreactor surface (soda lime glass).

lime glass as a top cover gave good yields of the rearranged product **2**. Using the microreactor with a soda lime glass top cover, we examined the optimal distance between the microreactor and the lamp, while the residence time was fixed at 6 min (Fig. 2). When the reaction was carried out using a distance of 7.5 cm from the reactor, the oxime **2** was obtained in 59% yield. The yield of oxime **2** became low at distances greater than 7.5 cm, but a closer distance, such as 5 cm, gave an inferior yield of **2** (33%) presumably due to the excess thermal energy evolving from the light source. In a separate experiment, we confirmed a tendency for temperatures greater than 50 °C to cause extensive degradation of the product, and indeed a closer distance, such as 5 cm, caused heat evolution.

A high-pressure mercury-vapor lamp (300 W) radiates short wavelength light that is not necessary for this reaction, and which can cause power loss of the light and the undesirable evolution of heat. It occurred to us that a black light, which has a maxim peak wavelength at 352 nm, might be suitable for the Barton reaction. The results are summarized in Table 1. In the case of a black light, the Pyrex top glass gave better results than soda lime glass (entries 3 and 4). Probably the use of Pyrex glass has the advantage of better transparency at the wavelength used over soda lime glass, since the shorter wavelengths produced by a black light are weak. Since the power of the black light (15 W) is considerably weaker than that of mercury lamp (300 W), we adjusted the residence time so as to compensate for this deficiency. Gratifyingly, we found that the extension of the residence time to 12 min resulted in a 71% HPLC yield of the desired oxime (entry 5). This is worthy of note, since the energy efficiency of the black light is 10 times superior to that of the mercury lamp based on the calculated values of yields per Watt hour (entries 2, 4, and 5).

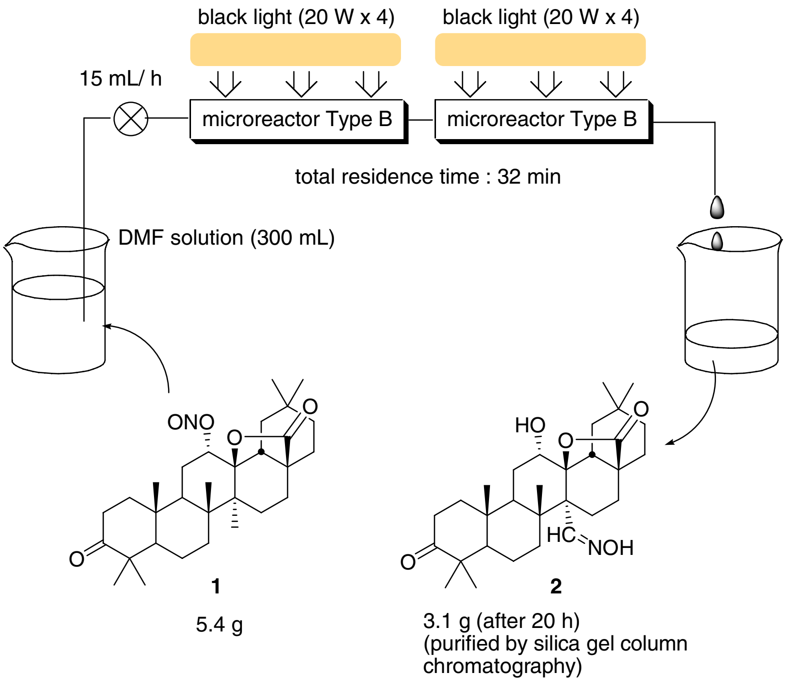
Table 1. Energy efficiency of the microflow Barton reaction[a]

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

Entry	Light source/reactor top	Flow rate (mL/h)	Residence time (min)	Yield of **2**[b] (%)	W h	Yield/W h
1	300 W Hg lamp/pyrex glass	2.0	6	21	30	0.70
2	300 W Hg lamp/lime soda glass	2.0	6	56	30	1.89
3	15 W black light/lime soda glass	2.0	6	15	1.5	10.3
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	3	23.7

[a] Microreactor Type A, [**1**]: 9 mM in acetone, pyridine 0.2 equiv. Distance between the lamp and the microreactor surface: 7.5 cm (Hg), 3.0 cm (black light).

[b] HPLC yield.



Scheme 2. Gram-scale production of **2**.

Although toluene and acetone are good solvents for the Barton reaction, steroidal substrate **1** has limited solubility in these solvents, which does not permit high throughput production. To investigate this further, we screened solvents and, as a result, found that the solubility of **1** in DMF is nearly 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 depth, 1 m total 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) (Scheme 2).[9]

In summary, we demonstrated herein 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, a low power black light as the light source, and DMF as the solvent. Thus, a gram scale synthesis of oxime product **2** was attained in a continuous-flow reaction.

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9. The continuous-flow reaction was performed by irradiating a solution of nitrite **1** (5.4 g, 10.8 mmol) in DMF (300 mL) containing a small amount of pyridine (0.2 mol equiv of **1**) with two microreactors (Type B) and eight 20 W black lights through a Pyrex glass cover (flow rate: 15 mL/h, resident time: 32 min, reaction time: 20 h). Water (600 mL) was added to the photoreaction mixture and the resulting slurry was collected by filtration and washed with water (100 mL) to give a white solid. The solid was purified by silica gel column chromatography to give oxime **2** in 60% isolated yield (3.1 g).