

Communications

Photosensitized Oxygenations of Hexamethylbenzene in Phase Contact Enhanced Microreactor

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Photosensitized oxygenation conducted only with light and oxygen is playing an important role in organic synthesis as a green chemical process.¹ Activated singlet oxygen (¹O₂) has successfully been utilized in production of various compounds including fragrances, pharmaceuticals, and fine chemicals.² However, the traditional reaction required a prolonged reaction time due to the difficulty of introducing adequate light and oxygen into the solution. Low contact probability between four species of oxygen, photosensitizer, light, and reagent is an inherent drawback of the traditional photoreaction.

Molecular diffusion distance is the most important factor in the heterogeneous reactions including gas-liquid, gas-solid, liquid-solid, and immiscible liquid-liquid. Therefore, rates of reaction are closely depended on the distance. Microreactor has provided a distinct advantage in the short molecular diffusion distance due to the high surface-to-volume ratio driven by narrow fluidic channels.³ With the advantage, successful photoreactions in the microreactor were reported.⁴ Herein, we describe the appropriateness of droplet-based microreactor for the photosensitized oxygenation (Figure 1).⁵ The reaction conducted with segmented

mode of gas bubbles and liquid slugs has advantages of a simple set up and easy controlling of reaction parameters including solvent, temperature, concentration of photosensitizer, and reagent. More importantly, reaction conditions can be easily screened in a shorter amount of time without wasteful consumption of reagents.

To explore the reaction study for photosensitized oxygenation in a droplet-based microreactor, we performed the reaction of hexamethylbenzene **1**, which can result in the mixture of endoperoxide **2** and hydroperoxy-endoperoxide **3** (Scheme 1).⁶ We screened the solvents including methyl alcohol, acetonitrile, ethyl alcohol, and acetone, the solvents except acetone showed the poor solubility of hexamethylbenzene, and the microreactor was clogged with the insoluble particles. The reaction was carried out over the temperature range of 0–60 °C (Figure 2). The reaction has slowed down with an increase in reaction temperature, was almost stopped above 40 °C. The best yield in the microreactor was 96.4% after 30 min at 0 °C, while the yield in the

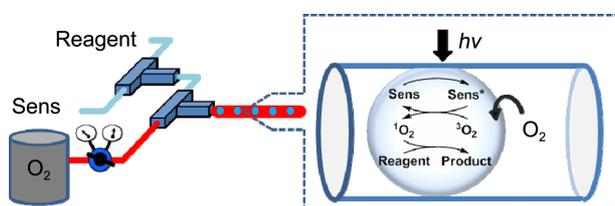
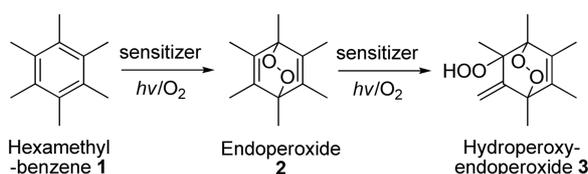


Figure 1. Photosensitized oxygenation in a droplet-based microreactor.



Scheme 1

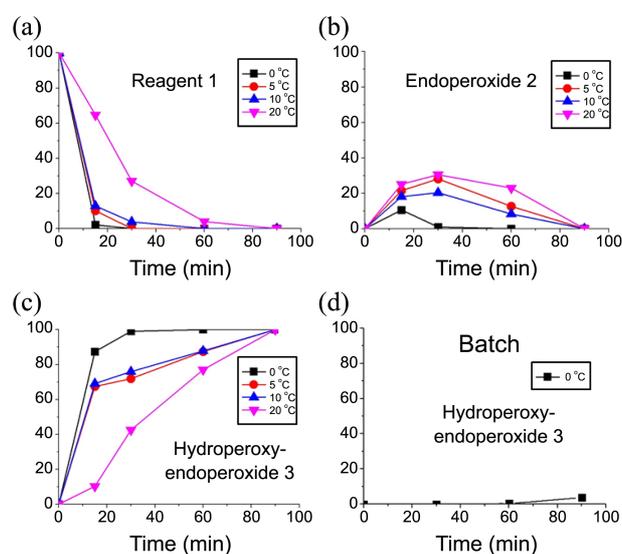


Figure 2. (a), (b), (c), Microchemical photosensitized oxygenation.⁷ (d) Batch reaction.

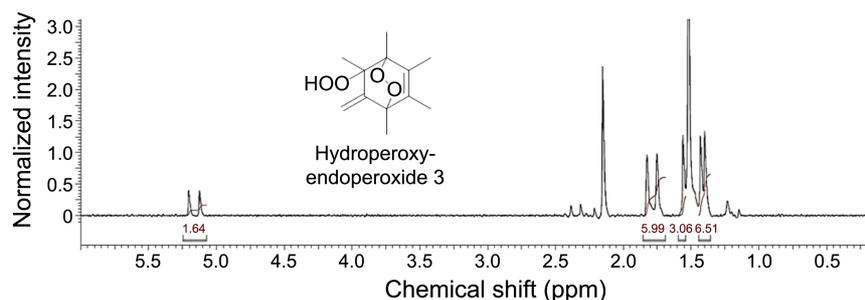


Figure 3. Crude NMR spectrum of the microchemical photosensitized oxygenation (30 min, 0 °C, 0.005 mmol photosensitizer/1.0 mL solution).

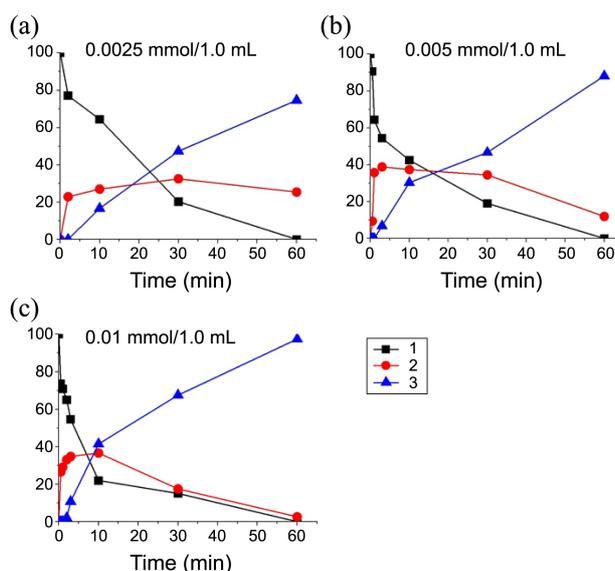


Figure 4. Variation of photosensitizer concentration.

batch system was only 1.4% endoperoxide **2** and 3.7% hydroperoxy-endoperoxide **3** after 90 min at 0 °C. In the batch reactor, slow diffusion of gaseous oxygen into solution delayed the generation rate of singlet oxygen ($^1\text{O}_2$) by activated photosensitizer; these results clearly demonstrate the superior efficiency of the microchemical reaction. The endoperoxide **2** generated in the first reaction has a very limited lifetime, and quickly transformed into hydroperoxy-endoperoxide **3** by the second reaction.⁸ The maximum concentration of endoperoxide **2** was only 11.7% after 30 sec at 0 °C, which was rapidly decreased in accordance with the reaction time. The NMR spectrum shown in Figure 3 clearly revealed the result, the singlet peak of hexamethylbenzene **1** (δ 2.21) was disappeared while appearing of the peaks of hydroperoxy-endoperoxide **3** (δ 5.21, 5.13, 1.83, 1.75, 1.56, 1.43, 1.40).

We investigated the reaction rate under different concentration of photosensitizer (methylene blue); results were arranged in Figure 4. We confirmed that the reaction rate could be lowered in proportion with the concentration of photosensitizer; the endoperoxide **2** can be detected after 60 min. In conclusion the photosensitized oxygenation in the microreactor has been demonstrated, the wasteful consumption of reagents and labor can be minimized while investigating optimum reaction conditions. The results can be con-

trolled with temperature and concentration of photosensitizer, the microchemical reactions are completed in 30 min rather than several hours that it takes to complete in the traditional batch reaction.

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- General reaction procedure:** Aceton- d_6 solution (10 mL) of hexamethylbenzene **1** (1 mmol) was loaded into a gas-tight Hamilton syringe, and delivered into the first inlet. In the same manner, aceton- d_6 solution (10 mL) of methylene blue (0.01 mmol) as photosensitizer was loaded into a gas-tight Hamilton syringe, and delivered into the second inlet. Oxygen was connected into the third inlet. The microreactor immersed into a Dewar flask was taken under LED lamp. The flow rates were regulated; the total residence time (reaction time) was controlled by injected amount of oxygen and tubing length. Because the efficient irradiation in photosensitized oxygenation determines the reaction efficiency, we choose the LED lamp as irradiation source (White 16 W, FAWOO, LH16-AFE39S, Korea).
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