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N-Alkylation of amines by photocatalytic reaction in a microreaction system

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Abstract

A photocatalytic microreaction system was developed and photocatalytic *N*-alkylation process of benzylamine, aniline, and piperidine was examined. The reaction proceeded quite rapidly in the microreactors with immobilized Pt-free TiO_2 as well as Pt-loaded TiO_2, while it has been reported that the *N*-alkylation did not occur by the irradiation of Pt-free TiO_2 in conventional batch reactors. It was revealed that by using the unique features of the continuous-flow microreactor, for instance spatial illumination homogeneity and precise control of flow and irradiation conditions, one can control the selectivity of *N*-alkylation and *N*,*N*-dialkylation processes. These results suggest the possibilities of a photocatalytic microreaction system on organic synthetic reactions.

Keywords: *N*-Alkylation; Photocatalytic reaction; Microreaction system

1. Introduction

Study of light-induced electron-transfer reactions on semiconductor catalyst has become one of the most attractive research areas in photochemistry. In addition to the well-examined photodegradation process of organic compounds, wide varieties of organic synthetic reactions were successfully investigated by using semiconductor photocatalyst [1,2]. A photocatalytic reaction can take place on an irradiated surface. Therefore most research on the reaction is carried out using dispersed powders with conventional batch reactors to increase the illuminated surface area per unit volume. A separation step of the powders is required after the reaction. Furthermore, light absorption and scattering by the dispersed powders tend to spoil spatial illumination homogeneity and better light penetration through the entire reactor depth. Though systems with immobilized catalyst can avoid the step, they tend to have low interfacial surface areas. To solve these problems, we developed a photocatalytic microreaction system.

Recently, microreaction systems have attracted much attention and developed using the features unique to micro-space such as short molecular diffusion distance and fast mixing, extremely effective heat exchange, laminar flow, and large surface-to-volume ratio [3–7]. Although microreaction systems are successfully applied to a wide range of applications of organic chemistry, there are only small number of reports on the application of microreactors to photochemical [8–12] and photocatalytic reactions [13–15]. One can expect microreactors to exhibit some distinct properties for photoreactions, such as higher spatial illumination homogeneity and better light penetration through the entire reactor depth in comparison to large-scale reactors. In addition to this, if we apply micro-reactors for photocatalytic reactions, its high interfacial surface area may be an advantage over the conventional large-scale reactors. Therefore, we are examining photocatalytic reaction processes in microreactors [16–20].

In a previous communication [17], we reported the result on the photocatalytic *N*-alkylation of benzylamine in microreactors. We have further developed our photocatalytic microreaction system to have much higher specific illuminated surface area per unit volume and optical power output of the UV light source. In this report we will describe the photocatalytic

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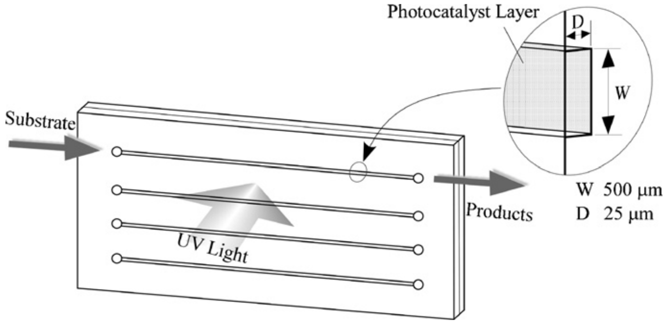


Fig. 1. Schematic view of a photocatalytic microreactor.

N-alkylation process of amines in the newly developed microreaction system. The enhancement of the reaction selectivity by using unique features of microreactors will be also discussed.

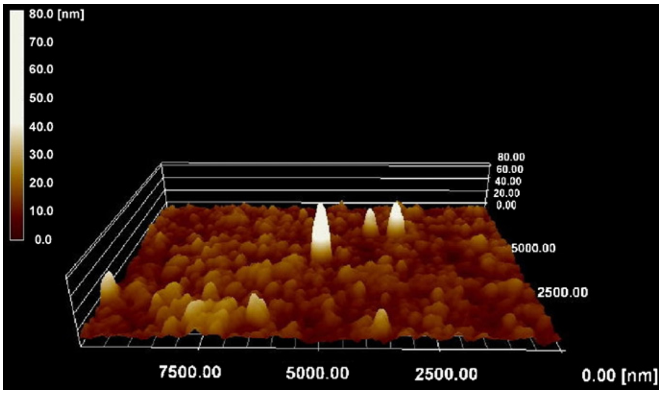
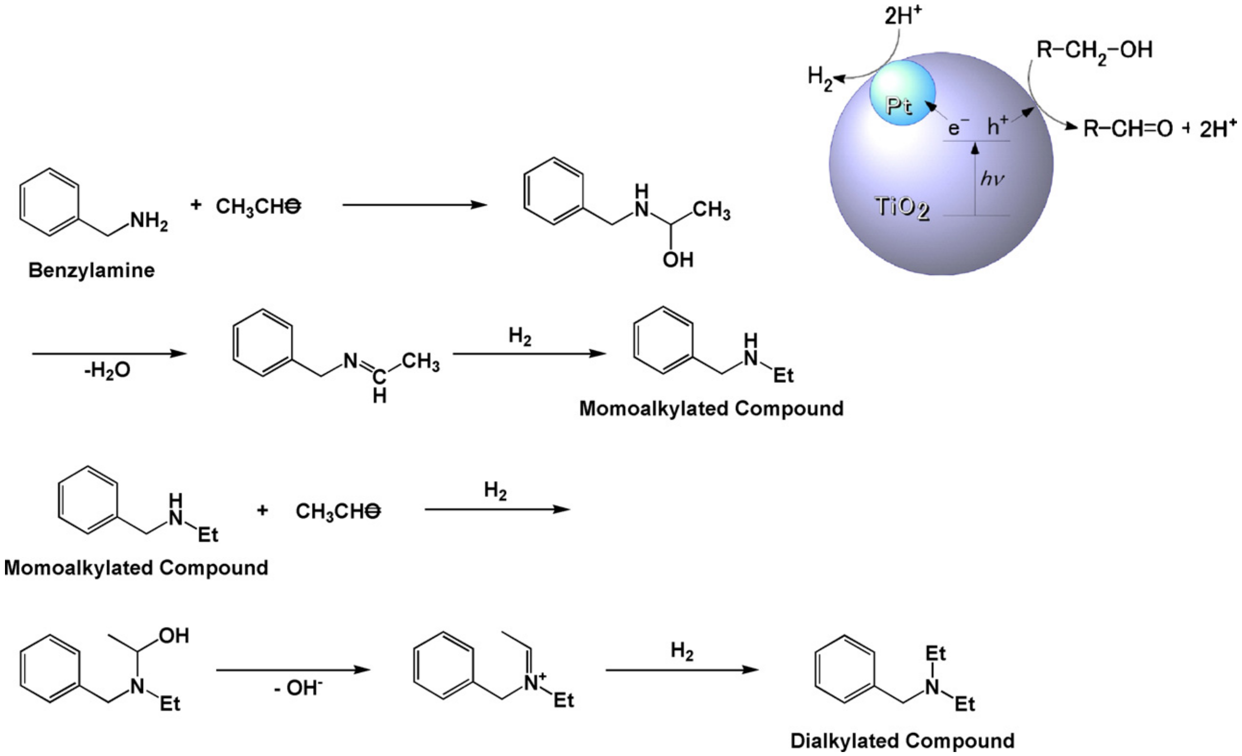


Fig. 2. AFM image of an inner wall of the photocatalytic microreactor.

2. Experimental

Photocatalytic reaction was carried out in microreactors made of Tempax (Schott AG) plates and a thin film of self-welding fluorinated polymer which has straight microchannels of 500 μm in width, 25 μm in depth, and 50 mm in length. Four parallel channels were cut out from a polymer film of 25 μm in thickness by laser ablation for optimization of reaction conditions, such as the amount of immobilized Pt co-catalyst. The thin film was placed between two Tempax plates (7.0 cm in length, 3.0 cm in width, and 1.5 mm in thickness) and heated up to 450 K to make a sandwich type leak-free structure. Typical experimental setup is schematically shown in Fig. 1. The bottom wall (one of the Tempax plates) of the microchannel was coated with a photocatalytic TiO_2 layer by using sol–gel process [21]. A solution of titanium tetraisopropoxide (Ti-(-O-iso-C_3H_7)$_4$-acetylacetone, NDH-510C; Nippon Soda Co. Ltd., TiO_2 concentration: 0.5 mol/l) was spin-coated on the microchannel surface and then calcinated at 770 K for 2 h in air. An AFM image of an inner wall of the photocatalytic microreactor is shown in Fig. 2. The crystalline phase of the thin layer was evaluated to be nearly identical anatase form by means of X-ray diffraction analysis. Particles of Pt were loaded on the TiO_2 layer of the microreactor by using a photodeposition method [22]. An aqueous solution of 0.1 mM chloroplatinic acid (H_2PtCl_6) and 1 M methanol (electron donor) was loaded into a microchannel with immobilized TiO_2 and irradiated with a mercury lamp. The amount of immobilized Pt co-catalyst was controlled by the irradiation time.



Scheme 1. Ethylation of benzylamine on photocatalyst surface.

It has been widely accepted that the illuminated specific surface area of photocatalyst within a reactor is the most important design parameter of photocatalytic reactors. The illuminated specific surface areas per unit of liquid of the microreactor with a microchannel of 25 μm in depth was calculated to be 5.4×10^4 m^2/m^3 without taking into account of roughness of the photocatalyst surface, whereas that of microreactor employed in the previous communication was 7.3×10^3 m^2/m^3 (300 μm in depth). Thus the microreactors with immobilized photocatalyst have much larger values of illuminated specific surface area of photocatalyst than typical conventional batch reactors [23].

To show the advantages of the miniaturized reaction vessel, a light source of minimal space and lower photon cost is suitable for the microreaction system. Thus we employed UV light emitting diodes (UV-LEDs) for the excitation light source of photocatalyst. The degradation of organic compounds in a photocatalytic microreactor excited with 385 nm UV-LED has been already reported by Gorges et al. [13] Considering from the band gap energy and the absorption spectrum of TiO_2, one can expect higher reaction efficiencies with a light source of shorter wavelength [19]. Therefore, in the previous investigation, we employed an array of 365-nm UV-LEDs (Nichia NSHU590B, Total Optical Power Output: 9.8 mW/LED). In this report, we will describe the results obtained by the 365-nm UV-LED array of much higher optical power output (Nichia NCSU033A, 7 LEDs/array, 50 mm in length and 6.8 mm in width, Total Optical Power Output: 490 mW) for the excitation light source of the photocatalytic microreactor.

Ethanol solution of 1.0 mM benzylamine, aniline, or piperidine saturated with nitrogen was fed into the microreactor with a syringe pump with a flow rate between 2 and 40 μl/min and irradiated with the UV-LEDs. The irradiation time was controlled precisely by changing the flow rate. Reaction products were analyzed by gas chromatograph (GC, SHIMAZU GC-14B or GC-2014) with a 25 m-capillary column (SHIMAZU; CBP20-M25-025 PEG or CBP1-M25-025 silicon). All experiments were carried out at room temperature.

3. Results and discussion

3.1. Reaction yield of amine N-alkylation in the microreactors with immobilized Pt-loaded and Pt-free TiO_2

It has been known that *N*-alkylation of aromatic amines proceeds by UV irradiation of Pt-loaded TiO_2 (TiO_2/Pt) suspended in alcoholic solvents (Scheme 1). Ohtani et al. studied photocatalytic preparation of asymmetrical secondary and tertiary amines by Pt-loaded TiO_2 (TiO_2/Pt) particles suspended in a variety of alcohols as solvents by using conventional batch reactors [24]. They reported that *N*-alkylation of benzylamine occurred with the yield up to 84.4% by 4 h irradiation of 400-W high-pressure Hg lamp in ethanol solvent. They also reported that *N*-alkylation of amines could not be observed by the irradiation of Pt-free TiO_2.

In our previous report [17], the alkylation process of benzaldehyde was examined in three alcohol media, methanol, ethanol, and 2-propanol. Photoirradiation (2.2 mW/cm^2) of benzylamine in the solvents introduced into the microreactor of 500 μm in depth with immobilized Pt-loaded TiO_2 (TiO_2/Pt) led to *N*-alkylation. The reaction in ethanol proceeded within only 90 s UV irradiation to yield 43% of *N*-ethylbenzylamine. The reaction proceeded much faster in our newly developed photocatalytic microreaction system. Photoirradiation by using an array of UV-LEDs (365 nm, 70 mW × 7, ~85 mW/cm^2) of benzylamine in ethanol introduced into the microreactor of 25 μm in depth with the immobilized TiO_2/Pt led to *N*-ethylation very rapidly as indicated in Fig. 3(a). The reaction proceeded within only 6 s UV irradiation to yield 62% of *N*-ethylbenzylamine and 3.8% of *N*,*N*-diethylbenzylamine. The reaction proceeded very quickly also in the case of aniline

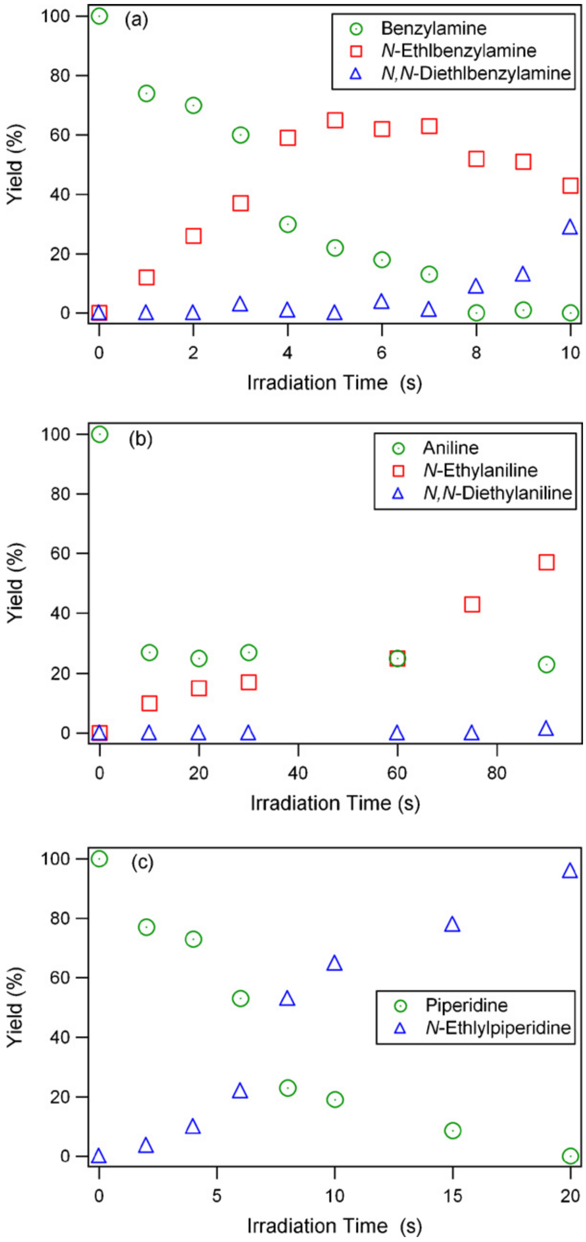


Fig. 3. Photocatalytic *N*-alkylation of benzylamine (a), aniline (b), and piperidine (c) in the photocatalytic microreactor of 25 μm in depth with immobilized TiO_2/Pt excited with 365-nm UV-LEDs (490 mW).

Table 1
Photocatalytic *N*-ethylation of amines (1.0×10^{-3} M in ethanol) in a microreactor of 25 μm in depth with immobilized photocatalyst excited with 365-nm UV-LEDs (490 mW)

Substrate	Photocatalyst	Irradiation time	Yield (%)	
			N-Ethyl-benzylamine	*N*,*N*-Diethyl-benzylamine
Benzylamine	TiO_2/Pt	6 s	68	3.8
	TiO_2/Pt[a]	5 h	84.4	2.4
	TiO_2	90 s	57	2.8
Aniline	TiO_2/Pt	90 s	57	1.5
	TiO_2/Pt[a]	20 h	8.1	0
	TiO_2	90 s	1.9	0
Piperidine	TiO_2/Pt	20 s	–	96
	TiO_2/Pt[a]	20 h	–	75.8
	TiO_2	150 s	–	6

[a] In suspended solution excited with a mercury lamp (Ref. [24]).

(Fig. 3(b)) and piperidine (Fig. 3(c)) in the photocatalytic microreactor with immobilized TiO_2/Pt. The reaction of aniline proceeded within 90 s to yield 57% of *N*-ethylaniline and 1.5% of *N*,*N*-diethylaniline. The reaction of piperidine proceeded within 20 s UV irradiation to yield 96% of *N*-ethylpiperidine.

The reaction mechanism can be interpreted as illustrated in Scheme 1. Dehydrogenation of alcohol occurs on the surface of photocatalyst to form H_2 and a corresponding carbonyl compound via alkoxy radical intermediate. Substrate amine is converted to an imine by condensation of the photoproduct carbonyl with the amine. The reduction of the imine by H_2 occurs to yield an *N*-alkylated product. If the product is a secondary amine, it is highly active for further *N*-alkylation and the consecutive reaction takes place quickly to form an *N*,*N*-dialkylated product.

In contrast to the result in a batch reactor, we successfully observed *N*-alkylation of benzylamine by using the microreactor with immobilized Pt-free TiO_2 as well as TiO_2/Pt. The *N*-ethylation yields of benzylamine, aniline and piperidine excited with the UV-LEDs in the photocatalytic microreactors are summarized in Table 1. The results marked with underline indicate that these reactions were observed only in the microspace, namely the yields of these reactions were reported to be zero in conventional batch reactors [24]. This must be due to the fact that the photocatalytic microreaction system with remarkably large surface-to-volume ratio enables us to observe some reactions which cannot be observed in a batch reactor due to its low reaction efficiency.

The reaction efficiencies are influenced by a series of processes including the electron transfer from the conduction band of TiO_2 to the substrate and the oxidation of the solvent by electron–hole. It has been known that depositing Pt on TiO_2 enhances the photocatalytic activity by serving as an electron sink and slowing charge recombination in consequence. Since the electron–hole recombination within the photocatalyst is in competition with the reaction process, the reaction efficiencies must be strongly affected by the surface-to-volume ratio of a photocatalytic reactor. The apparent reaction rate of the microreaction system which has a remarkably large surface-to-volume ratio is very fast and thus it may be able to overcome the rate of charge recombination process. As reported in our previous communication [17], the reaction efficiency increased as decreasing the depth of the microchannel, namely as increasing the surface-to-volume ratio. For the above reason, the *N*-alkylation of amines can be observed even in the microreactor without Pt co-catalyst.

3.2. Enhancement of reaction selectivity by using the features of a microreaction system

Ohtani et al. reported that UV irradiation of TiO_2/Pt suspended in ethanol led to *N*-alkylation and *N*,*N*-dialkylation

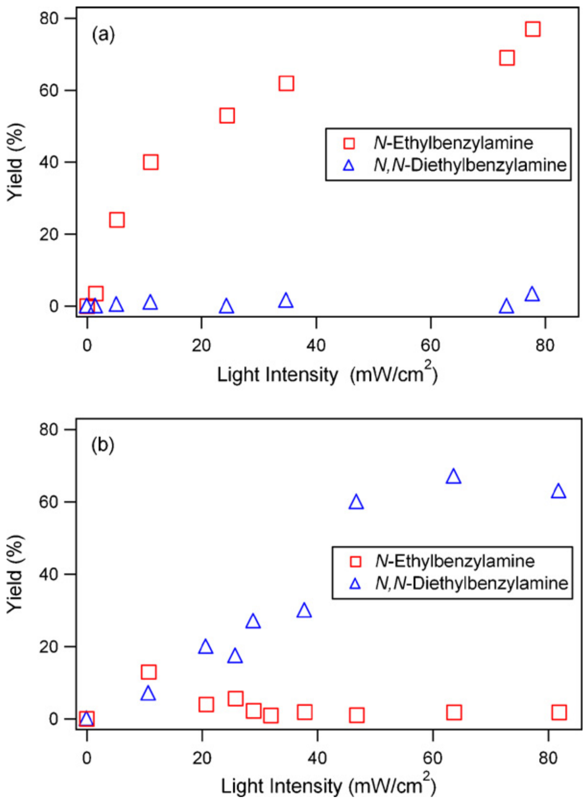


Fig. 4. Light intensity dependence of the yields of *N*-ethylbenzylamine (□) and *N*,*N*-diethylbenzylamine (△) obtained by the irradiation of 365-nm UV-LEDs for 5 s (a) and 60 s (b) in the photocatalytic microreactor of 25 μm in depth with immobilized TiO_2/Pt.

Table 2
Reaction yields of *N*-ethyl-benzylamine and *N*,*N*-diethyl-benzylamine obtained by photocatalytic *N*-ethylation of benzylamine (1.0×10^{-3} M in ethanol) in microreactors excited with 365-nm UV-LEDs

Photocatalyst	Microchannel depth (μm)	Light intensity (mW/cm^2)	Irradiation time (s)	Yield (%)	
				N-Ethyl-benzylamine	*N*,*N*-Diethyl-benzylamine
TiO_2/Pt	25	36	5	64	2.0
TiO_2/Pt	25	36	60	1.8	63
TiO_2[a]	300	2.6	90	98	0

[a] Ref. [17].

[24]. In contrast, irradiation of benzylamine by the 9.8 mW UV-LED array in the photocatalytic microreactor with Pt-free TiO_2 as well as TiO_2/Pt did not yield any detectable *N*,*N*-dialkylated products [17]. To further investigate the reaction process, the dependence of the yields of *N*-alkylated and *N*,*N*-dialkylated products on the flow and irradiation conditions was examined.

Fig. 4 indicates the yield of *N*-ethylation of benzylamine obtained by varying the excitation light intensity of UV-LEDs. Fig. 4(a) is the result of 5 s irradiation, while Fig. 4(b) displays the result of 60 s irradiation. In the case of 5 s irradiation, the main product was secondary amine (*N*-ethylbenzylamine) and the amount of the secondary amine formed by UV irradiation increased as the excitation light intensity. In contrast, the tertiary ethylated product (*N*,*N*-diethylbenzylamine) was not observed or its yield was very low regardless of the excitation light intensity. In the case of 60 s irradiation (Fig. 4(b)), both the secondary and tertiary amines were produced by UV excitation. At low excitation energy (ca. ~10 mW/cm^2), the yield of the secondary amine was higher than that of the tertiary amine. The higher light intensity (>20 mW/cm^2) excitation gave rise to the tertiary amine as the main product. Especially, with the light intensity of 50 mW/cm^2 or higher, the consecutive *N*-alkylation process of *N*-ethylbenzylamine proceeded efficiently. Since some derivatives of aromatic secondary amines can be used as pharmaceutical production intermediates, the development of their efficient and selective synthetic method has been attracted much attention. Table 2 summarizes the reaction yields in some distinctive experimental conditions. The experimental results clearly demonstrate that the two types of reaction products (secondary and tertiary amines) can be obtained selectively by precise control of the irradiation and flow conditions. Our results on the *N*-alkylation process suggest the possibilities of photocatalytic microreaction system for synthetic organic reactions.

4. Conclusion

In conclusion, we have developed a photocatalytic microreaction system and examined amine *N*-alkylation process in microspace. The reaction of benzylamine, aniline, and piperidine proceeded quite quickly due to the extremely large specific illuminated area per unit volume of photocatalyst. In contrast to the result in a batch reactor, we successfully observed *N*-alkylation process of these amines by using the microreactor with immobilized Pt-free TiO_2 as well as TiO_2/Pt. The experimental results clearly demonstrate that the two types of reaction products, secondary and tertiary amines can be obtained selectively by precise control of the irradiation and flow conditions. At shorter irradiation time, the formation of *N*,*N*-dialkylated products was inhibited. The absence of *N*,*N*-dialkylated products can be attributed to the nature of continuous-flow microreaction system. In the micro-flow system, the irradiation time is very short and the initial reaction product quickly flows out from the reaction vessel. The fact may prevent the consecutive *N*-alkylation process. These results suggest the possibilities of a catalytic microreaction system on organic synthetic reactions.

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