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Electrochemical Conversion of Benzylamine to Dibenzylamine Using a Microreactor: Analogous System of Photocatalytic Redox Combined Synthesis

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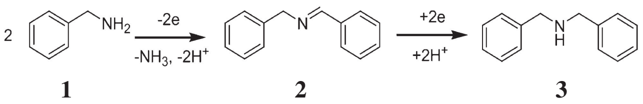
An electrochemical conversion of benzylamine to dibenzylamine using a microreactor has been investigated as an alternative of photocatalytic redox combined reaction. The use of the microreactor was clearly superior to the use of a more conventional batch type reactor.

Redox combined synthesis is a very efficient method for the preparation of desired compounds. In heterogeneous photocatalysis, a reduction by electron (e^-) and an oxidation by hole (h^+) proceed separately at each site on the particle (Figure 1b). Photocatalytic redox-combined synthesis purposely utilizes both simultaneous reduction and oxidation for the synthesis of desired compound(s).[1–3] On the other hand, electrochemical redox combined synthesis, which is a type of paired electrosynthesis, has also been proposed.[4–6] In this case, a single starting substrate is oxidized or reduced at the electrode to give an intermediate, which is further reduced or oxidized at the counter electrode to give the corresponding single final product (Figure 1c). Electrochemical methods generally afford a higher productivity than photocatalytic methods. Redox-combined synthesis can serve as a powerful tool for synthetic organic chemistry, and therefore, further extensive studies would be valuable.

In photocatalytic redox-combined synthesis, the reduction site and the oxidation site on the photocatalyst particle are located nearby (nano- or micrometer order), enabling the desired sequential reactions to proceed very smoothly. In contrast, in electrochemical redox-combined synthesis, the distance between the anode and cathode is on the order of centimeters when the reaction is carried out in a conventional batch type reactor. Consequently, electrochemically generated intermediates need specific time to diffuse from the electrode surface to the counter electrode surface, so that complete conversion of the intermediates would be difficult to achieve by passing only the theoretical amount of electricity. This damages the efficiency of the electrolysis reaction and hence the utility of the synthetic process.

In order to solve this problem, an electrochemical microreactor[7–9] was employed in this work. The short distance between the electrodes in the microreactor would enable fast molecular diffusion to the counter electrode, offering similar circumstances of the surface of photocatalyst particles (Figures 1b and 1c). Hence, efficient sequential electrochemical reactions would be achieved. In addition, an increase in throughput in microreactors can be achieved by a numbering-up approach.[10] With this consideration in mind, the aim of this work is to demonstrate a clear advantage of electrochemical microreactors over conventional batch-type reactors in an electrochemical redox-combined reaction. This demonstration will not only enhance the practical value of electrochemical microreactors but also show a possibility of the electrochemical microreactor system as an analog of photocatalytic redox-combined reaction systems.

(a) Model reaction



(b) Heterogeneous photocatalyst (c) Electrochemical microreactor

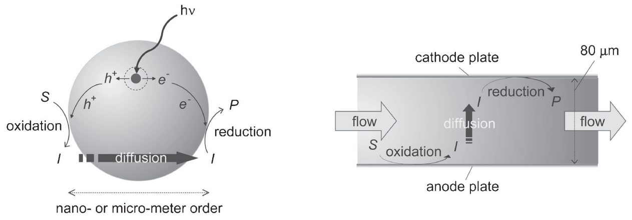


Figure 1. Schematic representations of the conversion of benzylamine to dibenzylamine. (a) Model reaction scheme. (b) The reaction by using a heterogeneous photocatalyst. (c) The reaction by using an electrochemical microreactor.

As a model reaction, an electrochemical conversion of benzylamine (**1**) to dibenzylamine (**3**) via *N*-benzylidenebenzylamine (**2**) as an intermediate was employed (Figure 1a). Oxidative condensation of benzylamines to *N*-benzylidenebenzylamines has been widely studied[11,12] because benzylideneamines are useful synthetic intermediates.[13,14] Furthermore, *N*-alkylation of primary amines has also been studied extensively.[15,16]

At first, the electrochemical behaviors of the substrate and intermediate were examined. As shown in Figure 2a, the linear sweep voltammograms for benzylamine (**1**), which were recorded at a Pt disk electrode, show specific wave changes. Wave I (ca. 1.6 V vs. SCE) was decreased with increasing the concentration of **1**, while wave II (ca. 2.2 V vs. SCE) was increased with increasing the concentration. The increase of wave II with almost a linear relationship between the peak current and the concentration of **1** indicates that this wave was derived from the oxidation of **1**. On the other hand, wave I may be derived from the oxidation of ethoxide ion contained in the electrolytic solution. The current of wave I decreased with increasing the concentration of **1** and it was much lower than that of wave II at a higher concentration of **1**. Therefore, it can be stated that the ethoxide oxidation is suppressed to some

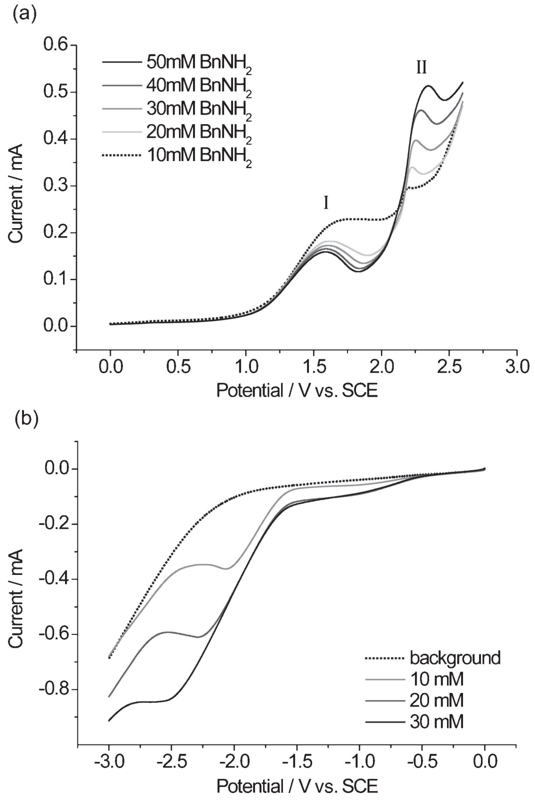


Figure 2. Linear sweep voltammograms of (a) benzylamine (**1**) and (b) *N*-benzylidenebenzylamine (**2**) in 250 mM n-Bu_4NClO_4 + 30 mM EtONa/EtOH. (a) Recorded at a Pt disk electrode (3 mm diameter). (b) Recorded at a graphite disk electrode (3 mm diameter). The scan rate was 50 mV s^{-1}.

extent while the desired amine oxidation occurs dominantly at a higher concentration of **1**.

Figure 2b shows the linear sweep voltammograms of **2** recorded at a graphite disk electrode. The reduction peak current of **2** was clearly observed in ca. −2.1 V vs. SCE in the case of 10 mM of **2**.

Next, preparative electrolysis for the conversion of **1** to dibenzylamine (**3**) was carried out using a microreactor with Pt anode and graphite cathode combination. For the operation of our electrochemical microreactor, there are too many parameters, and hence these parameters should be investigated systematically for system optimization. It was expected that the narrower electrode distance enhanced the desired redox reaction efficiency. However, as shown in Entries 1–3 of Table 1, the narrower electrode distance (50 µm) decreased the total product yield, while the broader electrode distance (130 µm) also resulted in a decrease in the product yield compared to the case with the 80 µm electrode distance. Therefore, an extremely narrow or broad electrode distance should be avoided to suppress unfavorable effects. As shown in Entry 4, when the faster flow rate was used, the yield of desired amine **3** was significantly decreased while the yield of intermediate imine **2** was slightly decreased. This was thought to result from the cathodic reduction of **2** being not enough to follow the anodic production of **2** under these conditions. On the other hand, the slower flow rate also gave unfavorable results, as shown in Entry 5. In this case, it can be presumed that the overoxidation of **3** at the anode would occurs to give by-products. Moreover, intermediate **2** would be reproduced by the overoxidation of **3**. As shown in Entry 6, the selectivity of the anodic oxidation of **1** to **2** decreased by applying higher current density. Overoxidation of **3** would be also enhanced. On the other hand, the lower current density also resulted in a decrease in the total product yield due to an insufficient bulk conversion of **1**, as shown in Entry 7.

Table 1. Preparative electrolysis results using microreactor[a]

Entry	Electrode distance /µm	Flow rate /mL min^{-1}	Current density /mA cm^{-2}	Total yield /%[b] **2 + 3**	Product ratio[b] **2:3**
1	80	0.1	5.0	97	58:42
2	50	0.1	5.0	61	67:33
3	130	0.1	5.0	88	56:44
4	80	0.16	5.0	76	66:34
5	80	0.05	5.0	28	71:29
6	80	0.1	10	18	67:33
7	80	0.1	3.2	74	66:34

[a] The structure of the electrochemical microreactor was described in the Supporting Information.[17] The reaction solution containing 30 mM of benzylamine, 250 mM of n-Bu_4NClO_4 as supporting electrolyte, 30 mM of sodium ethoxide, and ethanol as solvent was flowed through the electrochemical microreactor at 25 °C by using a syringe pump. Reactions were conducted galvanostatically. [b] Determined by HPLC.

Table 2. Preparative electrolysis results under several conditions

Entry	Reactor	Starting material	Total yield/%[c] **2 + 3**	Product ratio[c] **2:3**
1[a]	microreactor	**1**	97	58:42
2[b]	batch-type reactor	**1**	96	97:3
3[a]	microreactor	**3**	91	29:71
4[a]	microreactor	**2**	100	26:74

[a] The electrode distance was set to 80 µm. The flow rate was fixed at 0.1 mL min^{-1}. The current density was set at 5.0 mA cm^{-2}. 3.1 F mol^{-1} of charge was passed. [b] A beaker cell (50 mL) equipped with a 6 cm^2 Pt plate anode and a 6 cm^2 graphite plate cathode was used. The electrode distance was ca. 1.5 cm. The electrolyte volume was 40 mL and the reaction was carried out under vigorous stirring. The current density was set to 5.0 mA cm^{-2}. 3.1 F mol^{-1} of charge was passed. [c] Determined by HPLC.

Subsequently, a comparison with a conventional batch-type reactor was carried out. The electrode distance was set to approximately 1.5 cm while that of the microreactor was fixed at 80 µm. As shown in Entry 2 of Table 2, using the batch reactor product **3** was obtained in low yield. Instead, the reaction proceeded to give predominately intermediate imine **2**. This comparative experiment clearly shows that the more narrow spacing of the electrodes in the microreactor enables a highly efficient sequential redox reaction that dramatically increases the yield of the desired product **3**.

Finally, in order to improve the reaction yield of **3**, a possible side-reaction was confirmed. As shown in Entry 3 of

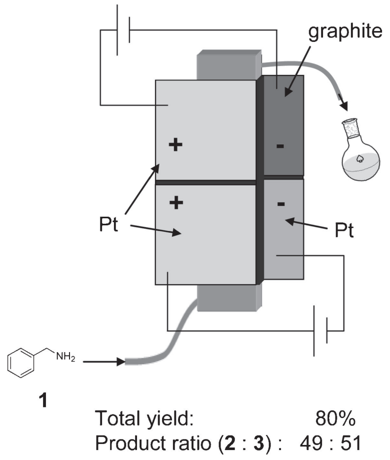


Figure 3. Schematic illustration of the newly designed microreactor. The first segment of the microreactor was a Pt plate anode and Pt plate cathode combination. The second segment of the microreactor was a Pt plate anode and graphite plate cathode combination. The first segment and second segment, which were separated by spacer tape, were connected to different galvanostats, respectively, and the electrolyses were conducted independently.

Table 2, when the electrolyte solution with **3** was introduced into the reactor instead of the solution with starting material **1**, 26% of intermediate imine **2** was obtained and 65% of **3** was recovered. This indicates that oxidation of the product can regenerate intermediate **2** as a side reaction. In addition, when the electrolyte solution with **2** was introduced into the reactor, 74% of **2** was converted into **3** (Entry 4). This suggests that it is possible to improve the yield of **3** by further optimization such as reactor structure modification.

Thus, a new microreactor was designed. As shown in Figure 3, in this new reactor, two separate reaction segments were utilized. In the first, a Pt plate anode and Pt plate cathode were employed, and in the second a Pt plate anode and graphite plate cathode were used. In this special microreactor, it was expected that intermediate imine **2** was generated and accumulated at the first segment, and promptly transported to the second segment without being reduced to **3** (Hydrogen evolution occurred dominantly at the Pt cathode of the first segment.). Consequently, a reaction condition similar to Entry 4 in Table 2 would be realized at the second segment. The transported **2** would be efficiently reduced at the second segment, and the yield of **3** would be improved. Actually, the use of this new reactor did lead to some improvement. An 80% yield of total product was obtained, 51% of which was the desired product **3**. This suggests that we are moving in the correct direction.

In summary, the electrochemical redox combined reaction of benzylamine to dibenzylamine was successfully accomplished using a microreactor. The key feature of the method is the extremely narrow separation between the electrodes in the microreactor. This sequential redox reaction hardly proceeded in the conventional batch type reactor. These results clearly show a significant advantage of the electrochemical microreactor for redox combined synthesis. It can be also concluded that the microreactor structure, which has the two electrode plates facing each other is effective. The use of this microreactor offers an alternative to photocatalytic redox combined reaction systems.

Our system would be applicable to the redox combined conversion of other substrates. To demonstrate this, further application of this new methodology is now under investigation.

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