Sequential Paired Electrosynthesis of a Diaryl Ether Derivative Using an Electrochemical Microreactor

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A paired electrosynthetic conversion of a phenol to a diaryl ether derivative by using an electrochemical microreactor has been demonstrated. Sequential anodic C–O coupling reaction of phenol 1 to dienone aryl ether 2 and following reduction of 2 took place to give diaryl ether derivative 3 selectively by simply passing an electrolytic solution through the electrochemical microreactor.

Diaryl ethers are important structural motifs that form the central building block in a large number of naturally occurring compounds and pharmaceutical agents. For instance, combrestatin,¹ aspercyclide,² and vancomycin³ contain a diaryl ether moiety and show interesting biological activities. The Williamson ether synthesis is the most classical and reliable method to construct ethers. However, diaryl ethers cannot be synthesized by just mixing a metal phenoxide and aryl halide. Therefore, transition-metal-catalyzed or -mediated reaction⁴ between phenol and aryl halide has been the most widely used method. On the other hand, synthetic methods without need for metal reagents, especially oxidative C–O coupling, have been reported recently.³

One of the authors (S. Nishiyama) has developed electrochemical construction of diaryl ethers and applied this protocol to total synthesis of natural products.⁵ In this reaction, anodic one electron oxidation of phenol takes place to give a dimeric product (dienone aryl ether) and then, reduction of dienone aryl ether with zinc yields desired diaryl ether derivatives. If natural products containing a diaryl ether structure become a lead compound in drug discovery, the use of oxidants difficult to handle on a large reaction scale or expensive transition-metal reagents should be avoided. In contrast, since electrochemical reaction is driven by electric potential, it has cost advantages over other methods and the reaction is easily controlled by switching the electrical power supply on and off. In this regard, electrochemical methods would be ideal for diaryl ether synthesis.

In electrochemical reactions, the working electrodes have received much attention because the desired reaction takes place on its surface. In contrast, the reaction taking place on the counter electrode has often been neglected. On the other hand, electrolytic systems that utilize both the reactions at the anode and cathode are known as "paired electrolysis."⁶ If the reduction of dienone aryl ether with zinc in the diaryl ether synthesis could be altered by cathodic reduction, and the entire reaction sequence could be performed in a manner of paired electrolysis, the process could become more sustainable. With this consideration in mind, herein we wish to demonstrate a paired electrosynthesis of diaryl ether.

To meet this challenge, an efficient sequential oxidation of phenol and the following reduction must be achieved in one electrolytic cell. However, in general, efficient sequential oxidation (or reduction) and the following reduction (or oxidation) of a single starting material has been difficult⁷ because the distance between the anode and cathode is centimeter order when the reaction is carried out in a conventional batch-type reactor. In other words, electrochemically generated intermediates need specific time to diffuse from the electrode surface to the counter electrode surface, so that complete conversion of the intermediates is difficult with the theoretically required amount of electricity. This reduces the efficiency of the electrolysis as well as utility of the synthetic process.

In order to solve this problem, an electrochemical microreactor⁸ was employed in this study. The short distance between the electrodes in the microreactor enable fast molecular diffusion from anode to cathode, offering ideal circumstances for the desired paired electrolysis (Figure 1).

At first, the effect of anode material on the desired reaction was examined because the total yield (yield of 2 + 3) depends on the anodic oxidation step. On the other hand, a Zn plate was commonly employed as a cathode material in the reduction of 2 avoiding hydrogen evolution. According to the linear sweep voltammograms, both graphite and glassy carbon electrodes show clear anodic peaks. In contrast, an anodic peak was not observed in this potential region when Pt electrode was used although the current was greater than that recorded by other electrode materials (Figure 2). Subsequently, preparative elec-



Figure 1. Schematic representation of electrochemical conversion of dichlorophenol to diaryl ether in methanol solution using an electrochemical microreactor.



Figure 2. Linear sweep voltammograms of 10 mM of 1 recorded at (A) graphite disc, (B) glassy carbon disc, and (C) platinum disc electrodes. Scan rate is 20 mV s^{-1} .



^aSubstrate, 10 mM of 1; supporting electrolyte, 100 mM of LiClO₄; electrode distance, 80 µm; solvent, methanol. ^bYields and product ratios were determined by HPLC analysis. Yields are based on the theoretical amount of dimeric product.

trolysis for the conversion of 1 to 3 was carried out using an electrochemical microreactor with various anode materials (Table 1).

The microreactor with carbon anodes such as graphite and glassy carbon electrodes exhibited better performance and especially, graphite anode gave best yield of 3. In contrast, Pt anode gave desired product 3 in low yield in spite of better anodic behavior expected by linear sweep voltammetry. The product selectivities for 3 was excellent regardless of anode materials, which indicates that the intermediate 2 was sufficiently consumed under the applied experimental conditions (current density, flow rate, and charge passed).

Next, reactions with various flow rate and current density were carried out in order to determine the behavior of the reaction (Table 2). At low flow rate, 3 was obtained in excellent selectivity as a result of the sufficient consumption of 2 (Table 2, Entries 1-3). On the other hand, selectivity for **3** gradually decreased with increase of flow rate indicating that high flow rate (short residence time in the reactor) is unfavorable for the effective consumption of 2 (Table 2, Entries 4-6). This is because anodically generated 2 passes through the reactor before sufficient reduction to 3. Additionally, it was expected that applying a lower current density was favorable for improving total yield because a lower current density is favorable for one electron oxidation. However, low current density did not give

Table 2. Effect of flow rate and current density on the reaction^a



37

2

0.2

0.01

| - | | | | | | | |
|---|--|-------|-----|----|----|-------|--|
| 3 | 0.2 | 0.012 | 3.1 | 75 | 41 | 0:100 | |
| 4 | 0.2 | 0.017 | 2.2 | 70 | 41 | 5:95 | |
| 5 | 0.5 | 0.025 | 3.7 | 87 | 31 | 10:90 | |
| 6 | 1 | 0.05 | 3.7 | 89 | 30 | 33:67 | |
| ^a Substrate, 10 mM of 1 ; supporting electrolyte, 100 mM of | | | | | | | |
| LiCl | LiClO ₄ ; electrode distance, $80 \mu\text{m}$; solvent, methanol. ^b Yields | | | | | | |
| and | $iClO_4$; electrode distance, 80 µm; solvent, methanol. ^b Yields | | | | | | |

80

36

0.100

and product ratios were determined by HPLC analysis. Yields are based on the theoretical amount of dimeric product.



Figure 3. Linear sweep voltammograms of (A) 10 mM substrate 1 and (B) 10 mM product 3 recorded at a graphite disc electrode. Scan rate is 20 mV s^{-1} .

the best total yield (Table 2, Entry 1). In this case, the over oxidation of 3 occurs because more charge was applied.

Linear sweep voltammograms of starting material 1 and 3 indicate that 3 is more easily oxidized than 1 (Figure 3), that is, complete consumption of 1 is difficult without the overoxidation of 3.

Finally, comparison with a conventional batch-type reactor was carried out. The electrode distance of the microreactor was fixed at 80 µm, while that of the conventional reactor was approximately 1.5 cm. As shown in Figure 4, the desired diaryl ether 3 was hardly obtained with the conventional reactor, and the reaction proceeded to give intermediate 2 selectively in low yield. This clearly shows that the significantly short electrode distance of the microreactor enables a highly efficient sequential redox reaction, remarkably increasing the ratio of desired product 3.

In conclusion, a paired electrosynthetic conversion of a phenol to diaryl ether derivative by using an electrochemical microreactor was demonstrated. Sequential anodic C-O coupling reaction of phenol 1 to dienone aryl ether 2 and the following reduction of 2 took place to give a diaryl ether derivative 3 selectively. In sharp contrast, only intermediate 2 was obtained when a conventional batch reactor was used.9



Figure 4. Comparison of the preparative electrolysis between a microreactor and a conventional batch reactor. Reactions were carried out in methanol solution containing 100 mM of LiClO₄ at 25 °C.

This work was financially supported by The Grant-in-Aid for Scientific Research on Innovative Areas "Organic Synthesis based on Reaction Integration. Development of New Methods and Creation of New Substances" (No. 2105).

References and Notes

 a) S. D. Rychnovsky, K. Hwang, J. Org. Chem. 1994, 59, 5414. b) G. R. Pettit, P. D. Quistorf, J. A. Fry, D. L. Herald, E. Hamel, J.-C. Chapuis, J. Nat. Prod. 2009, 72, 876.

- K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem., Int. Ed.* 1999, 38, 240.
- 3 T. Yoshino, I. Sato, M. Hirama, Org. Lett. 2012, 14, 4290.
- 4 a) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem., Int. Ed.* 2006, 45, 4321. b) M. Akkoç, N. Gürbüz, E. Çetinkaya, I. Özdemir, *Synlett* 2008, 1781. c) X. Liu, S. Zhang, *Synlett* 2011, 268.
- 5 a) M. Takahashi, H. Konishi, S. Iida, K. Nakamura, S. Yamamura, S. Nishiyama, *Tetrahedron* 1999, 55, 5295. b) T. Tanabe, F. Doi, T. Ogamino, S. Nishiyama, *Tetrahedron Lett.* 2004, 45, 3477. c) S. Nishiyama, M. H. Kim, S. Yamamura, *Tetrahedron Lett.* 1994, 35, 8397. d) Y. Naito, T. Tanabe, Y. Kawabata, Y. Ishikawa, S. Nishiyama, *Tetrahedron Lett.* 2010, *51*, 4776.
- 6 a) M. M. Baizer, R. C. Hallcher, J. Electrochem. Soc. 1976, 123, 809. b) M. M. Baizer, Tetrahedron 1984, 40, 935.
 c) Organic Electrochemistry, 4th ed., ed. by H. Lund, O. Hammerich, Marcel Dekker, New York, 2001.
- 7 M. M. Baizer, T. Nonaka, K. Park, Y. Saito, K. Nobe, J. Appl. Electrochem. 1984, 14, 197.
- 8 a) F. Amemiya, T. Kashiwagi, T. Fuchigami, M. Atobe, *Chem. Lett.* 2011, 40, 606. b) T. Kashiwagi, F. Amemiya, T. Fuchigami, M. Atobe, *Chem. Commun.* 2012, 48, 2806. c) T. Kashiwagi, F. Amemiya, T. Fuchigami, M. Atobe, *J. Flow. Chem.* 2013, *3*, 17. d) T. Kashiwagi, B. Elsler, S. R. Waldvogel, T. Fuchigami, M. Atobe, *J. Electrochem. Soc.* 2013, 160, G3058.
- 9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/ index.html.