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# *In situ* electrogeneration of *o*-benzoquinone and high yield reaction with benzenethiols in a microflow system†

**Tsuneo Kashiwagi,[a] Fumihiro Amemiya,[a] Toshio Fuchigami[a] and Mahito Atobe*[ab]**

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**We have successfully demonstrated that a microflow reactor is extremely useful in controlling reactions involving an unstable *o*-benzoquinone. The key features of the method are an effective *o*-benzoquinone generation and its rapid use for the following reaction without decomposition in a microflow system.**

*o*-Quinones are useful and important synthetic building blocks in organic and medicinal chemistry.[1–15] However, *o*-quinones are too reactive and unstable to store and not easy to handle because of their lability; that is, decomposition, isomerization, or polymerization often occur during storage. Therefore, these *o*-quinones are usually prepared by the *in situ* oxidation of the corresponding catechols in the presence of a reaction partner.[14,15] However, the oxidation potentials of the reaction partners, especially nucleophiles, are often the same or lower than those of the corresponding catechols, and therefore the presence of the partners would prevent the desired oxidation of the catechols.[14] To avoid the decomposition of *o*-quinones and competing oxidation, catechols must be oxidized in the absence of organic substrate and then used immediately for the following reaction.

Microflow reactors are ideal for conducting such transformations because they enable the precise control of short-lived species. In doing so, they facilitate highly selective reactions that are difficult to achieve in a conventional reactor. In addition, microflow reactors offer advantages such as large specific interfacial area, short molecular diffusion distance, and short residence time in the reactors.[16] Yoshida *et al.* have successfully demonstrated that the short-lived species such as *o*-bromophenyllithium can be generated in a microflow system and then immediately transferred to a vessel in which a following electrophilic reaction takes place to give final products in high yields.[17]

In this communication, we wish to demonstrate that a microflow reactor is extremely useful in controlling reactions involving an unstable *o*-quinone. We chose a Michael addition reaction between *o*-benzoquinone generated from electrochemical oxidation of catechol and benzenethiols as a model reaction (Fig. 1). The reaction products are diphenyl sulfide derivatives, which are valuable synthetic intermediates frequently found in bioactive compounds and polymeric materials.[18]

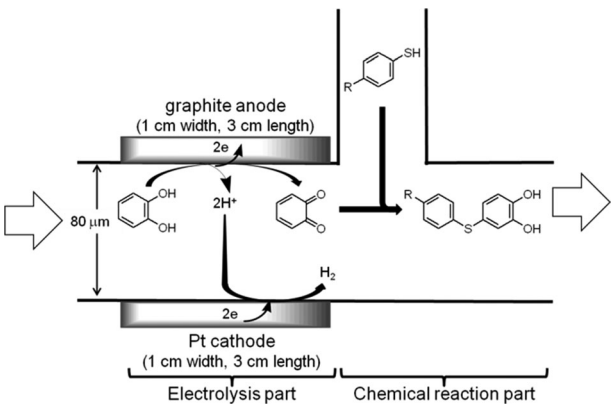


**Fig. 1** Schematic representation of the electrogeneration of *o*-benzoquinone and the following reaction with a benzenethiol in the microflow reactor.

The microflow reactor fabricated for the model reaction consists of two parts, an electrolysis part for the generation of *o*-benzoquinone and a chemical reaction part for its rapid use for Michael addition reaction. The electrochemical generation of *o*-benzoquinone capitalized on the oxidation of catechol.[15] This method enables rapid generation of *o*-benzoquinone and does not require the use of a chemical oxidant that can complicate downstream processes. In order to obtain a sufficient bulk conversion, we chose a graphite plate as an anode material for the microreactor because of its large superficial area in a specific size. On the other hand, a Pt plate was employed as a cathode material since a cathodic process in the electrosynthesis is hydrogen evolution.

Prior to using the microflow reactor, the model reaction was examined in a conventional batch type cell using 4-isopropylbenzenethiol as a nucleophile (Table 1, entry 1). At first, when catechol and 4-isopropylbenzenethiol were mixed in the same electrolytic cell (in-cell method), the desired product was obtained in 13% yield. According to *I–E* curves of catechol and 4-isopropylbenzenethiol, oxidation potentials of both catechol and 4-isopropylbenzenethiol were relatively close to each other (Fig. 2). Hence, the competing oxidation that most likely occurred is an issue for this reaction.

[a] *Department of Electronic Chemistry, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, 226-8502, Japan*
[b] *Department of Environment and System Sciences, Yokohama National University, 79-7 Tokiwadai, Hodogaya-ku, Yokohama, 240-8501, Japan. E-mail: atobe@ynu.ac.jp; Fax: +81-45-339-4214; Tel: +81-45-339-4214*

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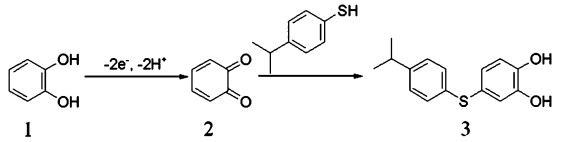
**Table 1** Chemical yields of **3** in the sequential reaction using a batch type cell and microreactor[a]




1 2 3

| Entry | Reactor type | Yield[c] (%) |
|---|---|---|
| 1 | Batch type cell (in-cell) | 13 |
| 2 | Batch type cell (ex-cell) | 32 |
| 3 | Microflow reactor[b] | 88 |

[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; current density, 1.5 mA $cm^{-2}$; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM $NaClO_4$; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine. [b] Electrode distance, 80 μm; flow rate, 0.1 mL $min^{-1}$. [c] Determined by HPLC.

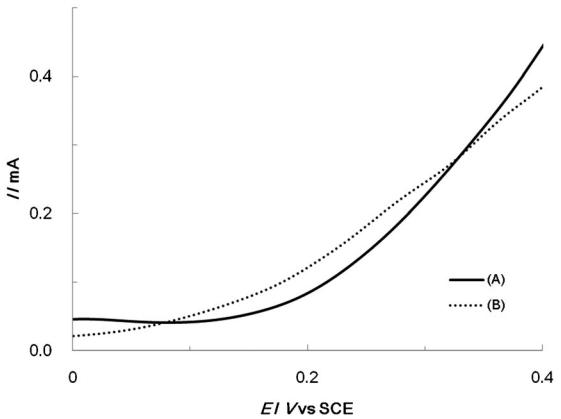



**Fig. 2** *I–E* curves of (A) 10 mM catechol and (B) 10 mM 4-isopropylbenzenethiol at a graphite disk anode (4 mm ∅) in 100 mM $NaClO_4$ + 10 mM 2,6-lutidine acetonitrile solution.

Subsequently, 4-isopropylbenzenethiol was added to the batch type electrolytic cell after the catechol electrochemical oxidation (ex-cell method) in order to prevent the competing oxidation (Table 1, entry 2). In this case, the product yield improved to 32%. However, black precipitates were confirmed before addition of 4-isopropylbenzenethiol. The formation of the precipitate indicated decomposition of the *o*-benzoquinone[19] during the extended electrolysis time needed to accumulate sufficient quantities of the intermediate. On the other hand, by using the microflow reactor, the desired product yield was significantly improved to 88% (the productivity was 13.8 mg $h^{-1}$). This result apparently suggests that *o*-benzoquinone could be generated effectively without interference of the thiol oxidation, and in addition the generated *o*-benzoquinone could be used rapidly for the reaction with 4-isopropylbenzenethiol without decomposition (Table 1, entry 3).

Then the influence of the flow rate and current density on the model sequential reaction using the microflow reactor was examined (Table 2). The yield of **3** increased with an increase in the flow rate, and the highest value was obtained at 0.1 mL $min^{-1}$ (Table 2, entries 1, 2, and 3). At lower flow rates, the decomposition and overoxidation of *o*-benzoquinone occurred due to a longer residence time in the reactor. In fact, black precipitates

**Table 2** Effect of the flow rate and current density on yield of **3**[a]

| Entry | Flow rate/mL $min^{-1}$ | Current density/mA $cm^{-2}$ | Yield[b] (%) |
|---|---|---|---|
| 1 | 0.01 | 1.5 | 8 |
| 2 | 0.05 | 1.5 | 48 |
| 3 | 0.10 | 1.5 | 88 |
| 4 | 0.14 | 1.5 | 66 |
| 5 | 0.10 | 1.1 | 48 |
| 6 | 0.10 | 3.0 | 48 |
| 7 | 0.10 | 6.0 | 32 |

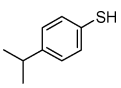
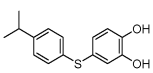
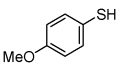
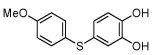
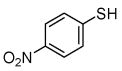
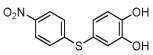
[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; electrode distance, 80 μm; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM $NaClO_4$; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine. [b] Determined by HPLC.

could be observed in these cases. On the other hand, at 0.14 mL $min^{-1}$ of the flow rate (Table 2, entry 4), the yield decreased again. This can be explained by an insufficient bulk conversion due to a higher flow rate. Actually, *ca.* 30% of the starting material was recovered in this case. At 1.1 mA $cm^{-2}$ of the current density (Table 2, entry 5), the yield was less than 50% due to an insufficient bulk conversion. On the other hand, at higher current densities (Table 2, entries 6 and 7), the yield was 50% or worse since overoxidation took place. Actually, black precipitates were confirmed in these cases.

Finally, to demonstrate the generality of this methodology, we also investigated Michael addition reactions between *o*-benzoquinone generated from electrochemical oxidation of catechol and other benzenethiols using the microflow reactor, and compared with those using the batch type electrolytic cell (in-cell method).

As shown in Table 3, the yields in all cases were higher for reactions run with the microflow reactor. The generation amount of *o*-benzoquinone in the first electrochemical oxidation step of the microreactor process should be the same for all the reactions since the electrolysis part of the reactor is the same. Therefore, overall yields for the two-step sequence are reflection of the Michael addition. Since the nucleophilicity of

**Table 3** Michael addition reactions between *o*-benzoquinone generated from electrooxidation of catechol and benzenethiols[a]

| Nucleophile | Product | Reactor type | Yield[b] (%) |
|---|---|---|---|
|  |  | Microflow reactor[b] | 88 |
| | | Batch type cell | 13 |
|  |  | Microflow reactor[b] | 79 |
| | | Batch type cell | n.d. |
|  |  | Microflow reactor[b] | 81 |
| | | Batch type cell | 7 |

[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; electrode distance, 80 μm; current density, 1.5 mA $cm^{-2}$; flow rate, 0.1 mL $min^{-1}$; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM $NaClO_4$; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine. [b] Determined by HPLC.

all three thiols studied is roughly equivalent, the three reactions led to similar yields. On the other hand, in batch processes (in-cell method), product yields would be dependent on the oxidation potential of benzenethiols used because catechol and benzenethiols are mixed in the same electrolytic cell in these cases. Hence, the yields for batch processes are all low because of competitive oxidation of the thiol nucleophile.

In summary, we have developed an effective method for the generation and reaction of *o*-benzoquinone using a microflow system. The key features of the method are an effective *o*-benzoquinone generation and its rapid use for the following reaction in the microflow system. It is hoped that this facile and novel reaction system will highlight the utility of flow reactors for optimizing reactions involving sensitive intermediates.

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