# Selective Oxidative Coupling of *p*-Cresol Producing an *ortho-ortho* Direct-linked Dimer

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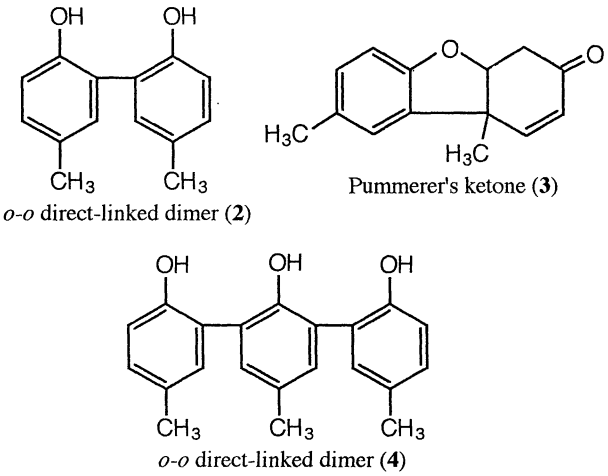
The oxidative coupling reactions of *p*-cresol were carried out in its aqueous solution using $FeCl_3$ as the oxidizing agent. In a highly concentrated *p*-cresol solution, the oxidative dimeric compound readily precipitated as oil droplets and was prevented from further oxidation to the trimeric compound. The formation of an *ortho-ortho* linkage has become superior to that of the *ortho-para* linkage in a more concentrated solution.

The oxidative coupling reactions of *p*-cresol (**1**) are known to produce the corresponding direct-linked oligomers.[1] When $FeCl_3$ was used as the oxidizing agent, two kinds of dimeric products, the *ortho-ortho* (*o-o*) direct-linked dimer (**2**) and *ortho-para* (*o-p*) direct-linked dimer (Pummerer's ketone) (**3**), and the *o-o* direct-linked trimer (**4**) shown in Figure 1 were produced along with the other oligomeric products.

In our previous study, the *p*-cresol oligomer obtained by enzymatic oxidation was shown to exhibit better antioxidant effects[2] and antimicrobial activities.[3] During the polymerization, the formation of the *o-p* linkage leads to the loss of a hydroxyl group as shown by the structure of **3** in Figure 1. Since the hydroxyl group is essential for the antioxidant effects and antimicrobial activities, the reaction system to produce the oligomer possessing the *o-o* linkage with higher selectivity is required. In addition, the *o-o* linked dimer **2** is a useful raw material for macrocyclic ionophores.[4]

The yield of **2** obtained by simple oxidations, however, has never exceeded 28 %.[1] To obtain compound **2** in higher yield, more expensive and complicated processes have been required. The application of a rhodium complex[5] and preparation of the dichloroaluminum salt of **1** prior to the oxidation[6] have been attempted.

In the present study, the oxidative coupling of **1** using $FeCl_3$ was carried out in its aqueous solution by varying the concentrations of **1** and $FeCl_3$. The desired compound **2** was successfully obtained in a yield greater than 50 % in a highly concentrated aqueous solution.




*o-o* direct-linked dimer (**2**)

Pummerer's ketone (**3**)

*o-o* direct-linked dimer (**4**)

**Figure 1.** Oxidative dimeric and trimeric compouds of *p*-cresol.

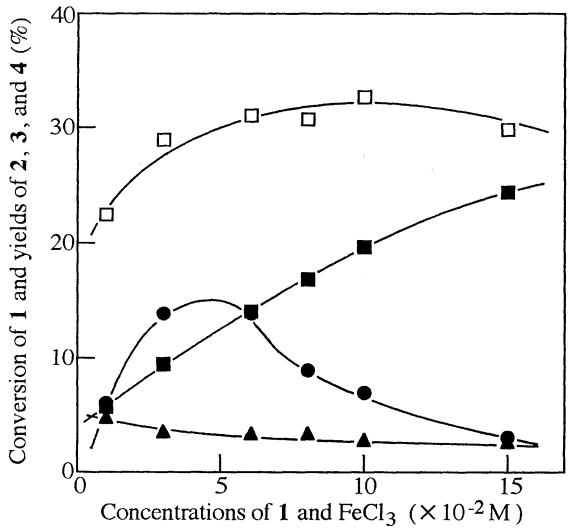



**Figure 2.** Effect of concentrations of **1** and $FeCl_3$ on product distributions of oxidative coupling reaction. (-□-: **1**; -■-: **2**; -▲-: **3**; -●-: **4**).

The prescribed amount of **1** was dissolved in water, and then equimolar $FeCl_3$ with **1** was added to the solution. The solution was stirred for 24 h at 25 °C. The mixture of oxidative coupling products mixture thus obtained was dissolved in a mixed solvent of water and methanol (1:3 v/v %) and analyzed by HPLC.[7]

As shown in Figure 2, the product distributions were influenced by the concentrations of **1** and $FeCl_3$. The compound **2** is more readily obtained in the more concentrated solutions. On the other hand, the production of the trimeric compound **4** was prevented in the highly concentrated solutions.[8]

Each oxidative compound produced in the initial 10 h was determined in order to explain the influences of the concentrations on the product distributions. Figure 3 shows the

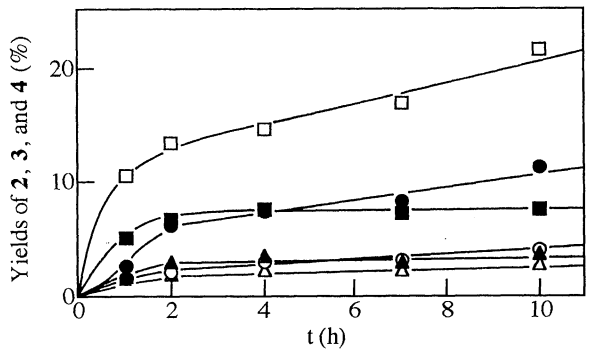



**Figure 3.** Change of the yields of oxidative products obtained under different concentration. ($3.0 \times 10^{-1}$ M: -■-: **2**, -▲-: **3**, -●-: **4**; $1.5 \times 10^{-1}$ M: -□-: **2**, -△-: **3**, -○-: **4**).

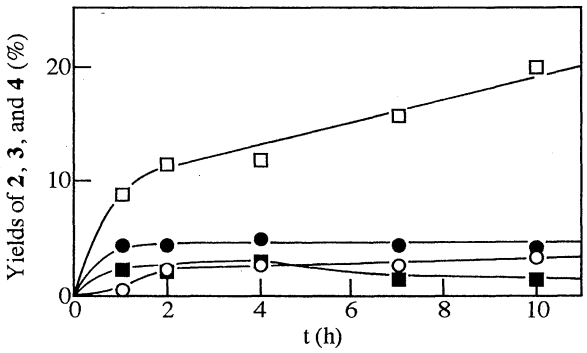



**Figure 4.** *O-o* dimer (**2**) existing in the aqueous solution and in the oil droplets under different concentration. (3.0 $\times 10^{-2}$ M: -●-: aqueous solution, -■-: oil droplets; 1.5 $\times 10^{-1}$ M: -○-: aqueous solution, -□-: oil droplets).

results in the case when the concentrations were $3.0 \times 10^{-2}$ M and $1.5 \times 10^{-1}$ M. The yield of **2** kept increasing with reaction time when the concentrations were $1.5 \times 10^{-1}$ M, while it has nearly reached a maximum after 4 h when the concentrations were $3.0 \times 10^{-2}$ M.

As the reaction proceeded, oil droplets separated from the reaction system, since the oxidized oligomeric products are almost insoluble in water. Only if they were coordinated to $Fe^{3+}$ or $Fe^{2+}$ ions they could then be dissolved in the aqueous phase. Figure 4 shows the change in the yield of **2** existing in the aqueous solution and in the oil droplets.

It is obvious that most of compound **2** produced in the reaction system is immediately precipitated as oil droplets and excluded from the oxidative system when the concentrations were $1.5 \times 10^{-1}$ M. In the case of dilute concentrations, such as $3.0 \times 10^{-2}$ M, a large portion of **2** existed in the aqueous phase and was further oxidized into the trimeric compound.

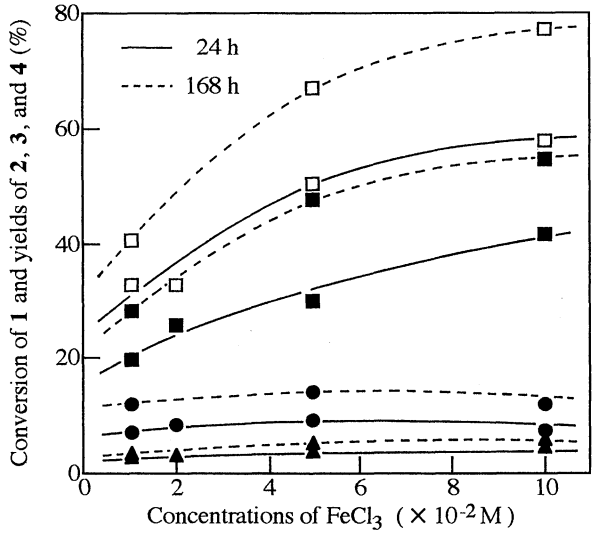



**Figure 5.** Conversion of **1** and yields of oxidative products in the case of the concentration of **1** was $1.0 \times 10^{-1}$ M. (-□-: **1**; -■-: **2**; -▲-: **3**; -●-: **4**).

The production of **3** tended to decrease in the concentrated solution as shown in Figure 1. Although the mechanisms have yet to be determined, the formation of the *o-o* linkage has become superior to that of the *o-p* linkage in more concentrated solutions.

Under the constant concentration of **1** at $1.0 \times 10^{-1}$ M, a large amount of $FeCl_3$ was used for the oxidations to increase the yield of **2**. The oxidations were carried out at 25 °C for 24 h and 168 h, and the results are shown in Figure 5.

In this case, the product distributions were scarcely influenced by the $FeCl_3$ concentration. The yield of **2** was thus increased as the amount of oxidizing agent increased. We successfully obtained **2** in a yield of 55 %, which is far beyond the highest value of 28 %,[1] which has already been reported.

The procedure introduced in this report could produce the *o-o* direct-linked dimer of *p*-cresol in a significantly simple process at a considerably lower cost. It could thus significantly affect industrial processing.

## References and Notes

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7 HPLC analyses have been carried out using silica gel column, GL Science Inc. Inertsil ODS-2 (5mm, 4.6 × 250 mm), and methanol-water (3:1 v/v%) as an eluent. Rate of elution was 0.5 $cm^3 \cdot min^{-1}$. Retention time of **1**, **2**, **3**, and **4** was 8.2, 15.0, 10.0, and, 25.0 min, respectively.

8 To guarantee the accuracy of the HPLC analyses, each oxidized product was isolated by silica gel column chromatography using a mixed solvent of ethyl acetate and hexane (1:4 v/v%). (**2**: Rf = 0.20; **3**: Rf = 0.22; **4**: Rf = 0.13) The yield of each product was as follows at each condition.

$3.0 \times 10^{-2}$ M: HPLC: **2**: 9.3%; **3**: 3.4%; **4**: 13.7%.
isolated: **2**: 9.4%; **3**: 2.4%; **4**: 14.8%.
$1.5 \times 10^{-1}$ M: HPLC: **2**: 24.4%; **3**: 2.6%; **4**: 2.7%.
isolated: **2**: 21.9%; **3**: 1.5%; **4**: 3.2%.