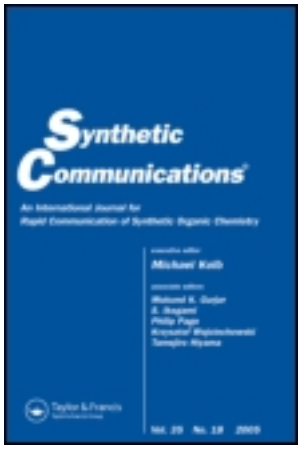

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Jian Wang [a], Peng Li [b], Chengliang Ni [a], Hong Yan [a] & Rugang Zhong [a]

[a] College of Life Science and Bio-engineering, Beijing University of Technology, Beijing, China

[b] Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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EFFICIENT SYNTHESIS OF CAMPHORQUINONE FROM CAMPHOR

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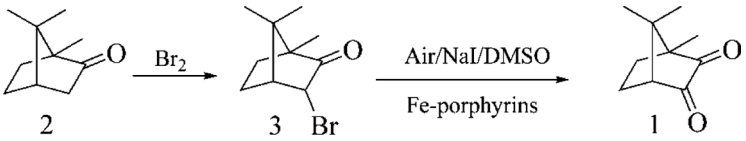
[1]*College of Life Science and Bio-engineering, Beijing University of Technology, Beijing, China*
[2]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

GRAPHICAL ABSTRACT



Abstract *In this study, we discussed an efficient approach for the synthesis of camphorquinone from camphor by the continuous reaction of bromination and oxidation. The oxidation of 3-bromocamphor was catalyzed by Fe-porphyrins with air. The catalytic activity of iron-metallated functional porphyrins was investigated under optimization conditions. The results showed that this method was a milder alternative to the reported methods, with a simple, greener procedure in which the advantages were the utilization of air as the oxidant and the use of metalloporphyrins as catalysts.*

Keywords 3-Bromocamphor; camphor; camphorquinone; Fe-porphyrin; oxidation

INTRODUCTION

Camphorquinone (**1**), or 1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione, is known as an initiator for visible-light-sensitive polymerization in a dental area[1] and is widely used as a chiral intermediate for the synthesis of natural products.[2,3] Methods for the preparation of **1** have been previously documented. Several of these methods started with the oxidation of camphor (**2**) with selenium dioxide[4,5] or phenylselenous acid anhydride,[6] but a few began with the oxidation of 3-bromocamphor (**3**) by air in the presence of NaI.[7] Although there have been reports that the oxidation by selenium dioxide was simple with good yields, this method could not be widely applied because of the toxic residue from selenium dioxide. The

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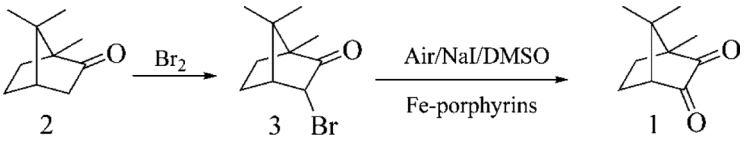
Address correspondence to Hong Yan, College of Life Science and Bio-engineering, Beijing University of Technology, Pingleyuan Street No. 100, Chaoyang District, Beijing 100124, China. E-mail: hongyan@bjut.edu.cn



Scheme 1. Synthesis of camphorquinone (**1**).

oxidation of **3** by air proved to be a good method with a yield of 97%, but required a large quantity of NaI (as much as four times that of **3**), and the procedure could not be scaled to amounts of **2** larger than 5 mmol. Although cobalt acetate was used to decrease the quantity of NaI, the toxicity of the cobalt salt was still a concern.[8]

As part of our interest in simplifying this process and continuing our studies on the application of metalloporphyrins,[9] we describe a two-step process starting from **2** (Scheme 1), in which **2** is brominated to **3**, and without isolation, **3** is directly oxidized by air with Fe-porphyrins, which can not only eliminate the toxicity that the catalysts cause but also increase industrial scale production. The effects of the method are studied in detail with respect to the optimization of reaction conditions and the role of the catalysts.

EXPERIMENTAL

All solvents and reagents were purchased from commercial sources unless otherwise stated. Fe-porphyrins were prepared as previously described,[10,11] and dimethylsulfoxide (DMSO) was purified by stirring over KOH overnight at room temperature and was distilled under a vacuum, Melting points (uncorrected) were determined on an X-5 instrument. ^{1}H NMR was measured on a Bruker Advance 400-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard.

A total of 15.2 g (0.10 mol) **2** was dissolved in 125 mL DMSO, followed by the addition of 12.0 g (0.08 mol) liquid Br_2. The mixture was stirred at 80 °C for 1 h and the color of Br_2 faded. Air was bubbled into the mixture at the speed of 20 L/h; 10 minutes later, 0.01 mmol tetraarylporphyrinatoiron(III) acetate [TPPFe(III)OAc] and 30.0 g (0.20 mol) NaI were added to the mixture. The air continued to be bubbled at 120 °C for 1.5 h. A lengthened condenser was used to reduce the loss of Br_2. After cooling, ice water and a small amount of sodium hyposulfite were added to the mixture. Then, the mixture was extracted with ethyl acetate (3×60 ml). The organic layer was washed with water twice and dried over anhydrous sodium sulfate, 15.4 g of **1** was obtained after the removal of ethyl acetate, and the yield was 92.9%.

Camphorquinone: Mp 198.1–199.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.95 (3H, s, CH_3), 1.05(3H, s, CH_3), 1.09 (3H, s, CH_3), 1.60–1.66 (2H, m, CH_2), 1.87–1.98(1H, m, CH_2), 2.07–2.18 (1H, m CH_2), 2.61 (1H, d, $J = 5.2$ Hz, CH).

RESULTS AND DISCUSSION

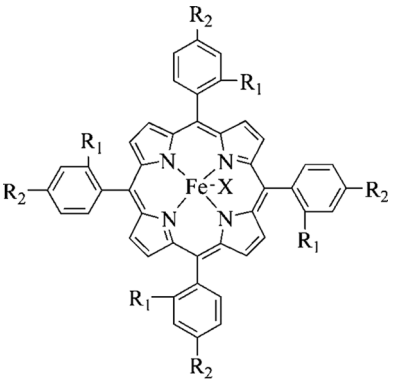
With respect to the optimization of reaction conditions and the role of the catalysts, the effects of the Fe-porphyrin structures, ratio of materials, reaction temperature, and time were studied in detail. All the experiments were conducted

under the conditions that **2** was first treated with an equivalent quantity of liquid Br_2 in DMSO at 80 °C and the air was bubbled into the mixture at the speed of 20 L/h at 120 °C. NaI (2 equivalents.) and Fe-porphyrins (0.01% equivalents) were then added to the reaction solution.

Catalysts

To study the catalytic activity of the various Fe-porphyrins (Fig. 1), we examined the effects of variations in the aryl substituents (R_1 and R_2) of tetraaryl-porphyrinatoiron(III) chloride [TAPFe(III)Cl] and tetraarylporphyrinatoiron(III) acetate [TAPFe(III)OAc]. The results were presented in Table 1. Compared with the blank experiment (Table 1, entry 1), the catalysts could decrease the time and increase the percentage yield.

It was interesting to note that different Fe-porphyrin catalysts exhibited slightly different catalytic activities (entries 2–9), which related to the inductive effects of the aryl substituents. The oxidation catalyzed by TPPFe(III)OAc (entry 3) gave a 93.2% yield; however, the less potent catalysts, $(NO_2)_8$TPPFe(III)OAc and Cl_8TPPFe(III)OAc (entries 5 and 11), which bore electron-withdrawing groups on the phenyl rings, gave 89.8% and 86.2% yields of **1**, respectively. The lower yields (83.3% and 83.8%) of **1** were found in the case of $(OCH_3)_8$TPPFe(III)OAc and Me_8TPPFe(III)OAc (entries 7 and 9), which were the catalysts with electron-donating substituents. It was seen that the even-numbered entries that had chloride as the counterion gave lower yields than the odd-numbered entries that had acetate as the counterion. The catalytic activities of the substituents of TAPFe(III)Cl and TAPFe(III)OAc were as follows: -H > -NO_2 > -Cl > -CH_3 > -OCH_3. The differences were attributed to increased generation of the electrophilic, reactive, high-valence, oxo-iron-cation radical intermediate (FeIV = O+•).[12–14] As the electrophilic activity of the substituents of aromatic ring increased, the redox potential of the intermediates increased and the duration of the intermediates declined. The variations of the two



R_1, R_2 = H, NO_2, OCH_3, CH_3, Cl;
X = OAc, Cl.

Figure 1. Structures of Fe-porphyrins.

Table 1. Yields of camphorquinone (**1**) with different structures of Fe-porphyrins

Entry	R_1	R_2	X	Time (h)	Yield (%)
1[a]				7.5	72.6
2	H	H	Cl	2.5	90.6
3	H	H	OAc	2.5	93.2
4	NO_2	NO_2	Cl	3.5	87.1
5	NO_2	NO_2	OAc	3.5	89.8
6	OCH_3	OCH_3	Cl	2.5	81.6
7	OCH_3	OCH_3	OAc	2.5	83.3
8	CH_3	CH_3	Cl	3.0	82.5
9	CH_3	CH_3	OAc	3.0	83.8
10	Cl	Cl	Cl	3.0	85.9
11	Cl	Cl	OAc	3.0	86.2

[a]Fe-porphyrin catalyst is not used in entry 1.

effects induced by the substituents caused the variation of the catalysts' catalytic activities. When there were no substituents on the aromatic ring, the two effects reached the best balance that made the catalyst in the greatest catalytic activities.

Other Conditions

To optimize the synthesis of **1**, the tests were conducted under different conditions in terms of the ratio of Br_2 to **2** and variations in temperature. The results are summarized in Table 2.

When **2** was not brominated but just treated with air in the presence of the Fe-porphyrin catalyst, no **1** was obtained. This showed that the oxidation reaction started from **3** rather than **2**. When the ratio of Br_2 to **2** was at an equal stoichiometric value, **1** was attained in a 93.2% yield. The bromination mainly occurred at the 3-position, although the methyl of **2** could be brominated at the 1- and 7-positions. By controlling the reaction temperature and the amount of Br_2, we were able to reinforce the single bromination. The amount of Br_2 should not exceed one molar fold of **2** because excess Br_2 led to other bromo-products.[15] Surprisingly, when the quantity of Br_2 was reduced, there was no obvious decrease in the product yield, and a 92.9% yield was obtained with 0.8 equivalents of Br_2. The Br_2 in the process may be reused partly, the mechanism may be related to the oxidation of 3-bromocamphor catalyzed by Fe-porphyrins, which needs further study to prove.

Table 2. Yields of camphorquinone (**1**) catalyzed by Fe^{III}(TPP)OAc

	Br_2/camphor (molar ratio)				
Temperature (°C)	0.7	0.8	0.9	1.0	1.1
100	66.8	77.3	81.8	88.9	91.0
120	86.5	92.9	93.1	93.2	84.7
140	83.7	88.1	88.4	89.7	80.4

Overall Reaction Scheme

The influence of temperature was also shown in Table 2. Within the range of 100 to 140 °C, the reaction temperature had an effect on the yield of **1**. At the temperature of 120 °C, the yield of **1** was the greatest. An unsatisfactory yield was obtained when the temperature was less than 100 °C. The yield markedly decreased when the temperature was more than 140 °C, and the formation of by-products increased. In view of the costs, a suitable oxidation condition consisted of a temperature of 120 °C, 2, equivalents of NaI, 0.8 equivalents of Br_2 to **2**, and TPPFe(III)OAc as the catalyst.

The overall reaction process was speculated as follows: camphor (**2**) was first converted to 3-bromocamphor (**3**) by and Br_2, and **3** was decomposed to camphor free radical and Br free radical by the initiation of NaI. The camphor radical was combined with the high-valent iron-oxo species of Fe-porphyrins, known as porphyrin radical cation iron(IV)-oxo species, which were the key intermediates and produced by binding molecular oxygen to Fe-porphyrin. The radicals were reacted with additional molecules of substrate to form the observed products, propagating a radical chain reaction.[16,17] The Br radical may bromate the camphor, and it is speculated that the Br_2 may be reused in the whole reaction; the fact that the amount of Br_2 less than the stoichiometric ratio is proved by it.

CONCLUSION

We have developed an efficient procedure to prepare camphorquinone (**1**); the process consists of the bromination of camphor (**2**) and oxidation of 3-bromocamphor (**3**) with air catalyzed by Fe-porphyrins. By investigating variations in the reaction, the suitable conditions are found to be a temperature of 120 °C, 2 equivalents of NaI, 0.8 equivalents of Br_2 to **2**, and a catalyst of TPPFe(III)OAc. The advantages of this method are as follows: It is not necessary to separate **3**; the reduction in the amount of Br_2 lowers the level of pollution and improves the atom economy of the reaction; and the application of Fe-porphyrins as the catalyst and air as the oxidant eliminates the toxicity of the product and makes the reaction more environmentally friendly.

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