The Addition of Alcohol to 1,2-Naphthoquinone Promoted by Metal Ions. A Facile Synthesis of 4-Alkoxy-1,2-naphthoquinones

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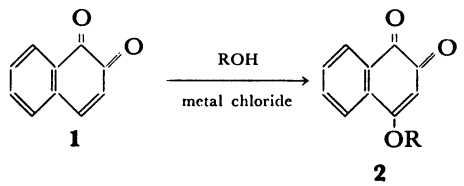
Synopsis. In the presence of some metal ions and sodium iodate, 1,2-naphthoquinone (**1**) readily reacted with methanol to give 4-methoxy-1,2-naphthoquinone (**2a**). The activity of the metal ions increased in the following order: Co(II)<Ni(II) ≪ Cu(II)<La(III) ≪ Ce(III). The reaction was remarkably affected by the reaction temperature, reaction time, and molar ratio of the chelating agent. By the use of 1 equivalent of cerium salt to **1**, the yield of **2a** increased to 81% at 20 °C for 30 min. In higher alcohols, the addition reaction proceeded under similar conditions to give 4-alkoxy-1,2-naphthoquinones (**2b—f**) in 46—75% yields.

The quinone moiety plays an extremely important role in biological systems. A large number of methods have been applied for preparations of *o*- and *p*-quinones.[1] In these methods, two main approaches have been frequently used to synthesize 1,2-naphthoquinones, either by the oxidation of 1-amino-2-naphthols or a suitably substituted naphthol, or by the Michael addition of a nucleophile to the parent quinone.[1] In the addition reaction of a nucleophile, alcohols do not normally add to the quinones and, therefore, methyl or ethyl alcohol has been used as a recrystallizing solvent for some 1,2-naphthoquinone derivatives.[2]

Recently, M. Matsuoka et al.[3] and M. Hida et al.[4] independently reported an excellent direct amination of aminoanthraquinone or anthraquinone in the presence of metal salts or a metal complex. Moreover, hypervalent iodine oxides have been found to oxidize various dihydroxy aromatics to the corresponding quinones in high yields under very mild conditions.[5]

In this paper, we wish to report a novel and simple method for the preparation of 4-alkoxy-1,2-naphthoquinones (**2**) from the addition reaction of 1,2-naphthoquinone (**1**) with aliphatic alcohols in the presence of metal halides and sodium iodate as the oxidizing agent. The quinones, except for 4-methoxy-1,2-naphthoquinone, are unknown.



1 **2**

a: R=CH_3, **b**: R=C_2H_5, **c**: R=*n*-C_3H_7,
d: R=*i*-C_3H_7, **e**: R=*n*-C_4H_9,
f: R=$CH_2CH{=}CH_2$

Results and Discussion

No reaction of **1** with methanol occurred in the absence of metal chlorides; however, in the presence of metal chlorides, methanol was added to **1** at room temperature to afford **2a**. The activities of metal chlorides in this methoxylation are shown in Table 1. Metal chlorides were arranged in the order of reactivities as follows: Ce(III) ≫ La(III)>Cu(II) ≫ Ni(II)> Co(II). The activity of the cerium(III) ion was particularly superior to those of other metal ions examined in this work. The water of crystallization was slightly effective regarding the activities of cobalt(II) and copper(II) salts (Runs 3 and 6).[6]

The effect of the reaction time and temperature on the reaction of **1** with methanol in the presence of cerium(III) chloride heptahydrate is shown in Table 2. The yield of **2a** increased up to 30 min at 20 °C and gradually decreased with a prolonged reaction time. Suprisingly, an unexpected product, i.e., 2-methoxy-1,4-naphthoquinone (**3**), began to be produced after 1 h; it became the exclusive product after 10 h (Runs 11—13). The reaction was also considerably affected by the reaction temperature. Within 30 min, only **2a** was obtained at temperatures below 20 °C; at higher temperatures, the yield of **3** increased and it was the sole product under reflux for 30 min (Run 18). These results indicate that **2a** is converted into **3** under these conditions.[7]

Next, we examined the effect of the molar ratio of

Table 1. Effect of Metal Chloride on the Reaction of **1** with Methanol[a]

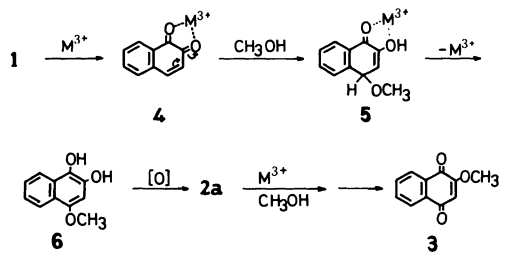
Run	Metal chloride	Yield[b),c)]/% **2a**
1	None	0
2	$CoCl_2$	3
3	$CoCl_2 \cdot 6H_2O$	10
4	$NiCl_2 \cdot 6H_2O$	15
5	$CuCl_2$	40
6	$CuCl_2 \cdot 2H_2O$	51
7	$LaCl_3 \cdot 7H_2O$	66
8	$CeCl_3 \cdot 7H_2O$	79

a) A methanol solution of **1**(0.4 mmol) was stirred for 30 min in the presence of a metal salt(0.4 mmol) and sodium iodate(0.4 mmol) at room temperature. b) Yields were based on the quinone used. c) Determined by ^1H NMR spectra.

Table 2. Effect of the Reaction Temperature and Time on the Methoxylation of **1** in the Presence of $CeCl_3 \cdot 7H_2O$[a]

Run	Time / min	Temperature / °C	Yield[b,c]/% **2a**	Yield[b,c]/% **3**
9	15	20	60	0
10	30	20	81	0
11	60	20	51	8
12	120	20	39	17
13	600	20	0	63
14	30	4	36	0
15	30	20	81	0
16	30	30	72	trace
17	30	50	25	35
18	30	Reflux	0	60

a) Reactions of **1** in methanol were carried out in the presence of cerium salt(1 equiv) and sodium iodate(1 equiv). b), c) See footnote in Table 1.



Scheme 1.

Table 3. Effect of the Molar Ratio of $CeCl_3 \cdot 7H_2O$ in the Reaction of **1** with Methanol at 20 °C for 30 min[a]

Run	Metal/**1**	Yield[b,c]/% **2a**
19	0.1	15
20	0.5	68
21	1.0	81
22	2.0	70
23	3.0	70
24	5.0	70

a) Reactions were carried out in the presence of 1 equivalent of sodium iodate. b), c) See footnote in Table 1.

Table 4. Reactions of **1** with Various Alcohols[a]

Run	Alcohol	Time / h	Yield[b]/% **2**
25	Methanol	0.5	**2a** (72)
26	Ethanol	0.5	**2b** (70)
27	Propanol[c]	0.6	**2c** (75)
28	2-Propanol[c,d]	4.0	**2d** (46)
29	Butanol[c,d]	1.2	**2e** (75)
30	Allyl alcohol[c,d]	2.0	**2f** (52)

a) The reactant, **1**(0.8 mmol) was stirred in alcohol with $CeCl_3 \cdot 7H_2O$(0.8 mmol) and sodium iodate(0.8 mmol). b) Isolated yield. c) Cerium salt was dissolved in 0.4 ml of water. d) The quinone was dissolved in acetonitrile(3 ml).

cerium salt to **1** on the yield of **2a**; the results are shown in Table 3. The yield of **2a** increased with an increase in the molar ratio of cerium salt up to 1.0. The additional amounts of the cerium ion slightly depressed the yield to 70% (Runs 22—24). Therefore, the optimum reaction conditions for the preparation of **2a** were as follows: 20 °C for the temperature, 30 min for the reaction time, and one equivalent mol of cerium(III) chloride heptahydrate to **1**.

On the bases of our experimental results, a tentative reaction mechanism is proposed as shown in Scheme 1. The formation of a chelate complex (**4**), in which 1- and 2-carbonyl oxygens of **1** are coordinated to the metal ion,[8] enhances the electrophilic character of the C_4-carbon in **1**, and facilitates a nucleophilic attack of methanol on that carbon. A similar role of the cerium ion has been observed during the addition of aromatic amines to 5,8-quinolinedione.[9] The 2,5-cyclohexadienone intermediate (**5**) may be enolized to afford 4-methoxy-1,2-naphthalenediol (**6**), and **6** is oxidized into **2a**. For a prolonged reaction time, the metal ion presumably recoodinates to **2a** and the methanol adds to the chelated quinone to give a hemiacetal. It finally results in the formation of **3**.[7] The details of the reaction mechanism for each step are still not clear, however, and are under investigation.

Other aliphatic alcohols also reacted with **1** in the presence of $CeCl_3 \cdot 7H_2O$ under similar conditions to afford **2b—f** in good yields (Table 4). Since cerium salt and **1** were slightly soluble in higher alcohols, a minimum amount of water and acetonitrile were necessarily added to dissolve both components (Runs 27—30). In addition, a prolonged reaction time was required for some alcohols in order to improve the yields of **2d—f**. Thus, the direct alkoxylation of 1,2-naphthoquinone in the presence of $CeCl_3 \cdot 7H_2O$ is synthetically useful method for the preparation of 4-alkoxy-1,2-naphthoquinones.

Experimental

1,2-Naphthoquinone was prepared according to a method described in the literature.[10] All metal chlorides and sodium iodate were reagent-grade and were used without further purification. Alcohols were purified by distillation. Column chromatography was performed on silica gel (Merck Kisel gel 60, Art. 7734), using chloroform as an eluent. Authentic samples of **2a**[11] and **3**[12] were prepared by the methods described in the literatures. All the yields were based on **1** that was used.

General Procedure. (a) A mixture of **1**, metal salt, sodium iodate, and methanol was stirred in a flask (see Tables 1, 2, and 3). The mixture was then poured into a 10%

aqueous solution of ammonium chloride, and extracted with chloroform. The organic layer was thoroughly washed with water, dried (Na_2SO_4), and concentrated in vacuo. The yields of **2a** and **3** were determined by ^1H NMR integrations of methoxyl and quinonoid protons. The products were isolated by TLC (ether:hexane=4:1) (R_f 0.28 for **2a**; 0.43 for **3**). The physical properties of **2a** and **3** were identical with those of authentic samples. The reaction with ethanol was carried out by the same procedure, and **2b** was separated by column chromatography. (Table 4).

(b) As cerium salt and **1** were slightly soluble in higher alcohols, the reactions were modified as follows: An alcohol (11 ml) was added to acetonitrile (3 ml) solution of **1** (0.8 mmol), and then cerium salt dissolved in 0.4 ml of water and sodium iodate (0.8 mmol) were added to the solution. The mixture was stirred for the time indicated in Table 4 at 20 °C. After a workup as described above, the product was separated by column chromatography. The yields of the products are summarized in Table 4.

Identification of the Products. 4-Ethoxy-1,2-naphthoquinone (2b): Orange needles (benzene-hexane); mp 121—123 °C; IR (KBr) 1705 (m) and 1657 (s) cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.55 (t, 3H, J=7.0 Hz), 4.23 (q, 2H, J=7.0 Hz), 5.90 (s, 1H), and 7.52—8.11 (m, 4H). Found: C, 71.01; H, 4.82%. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98%.

4-Propoxy-1,2-naphthoquinone (2c): Yellow needles (benzene-hexane); mp 115.5—116.5 °C; IR (KBr) 1700 (m) and 1650 (s) cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.11, (t, 3H, J=7.0 Hz), 1.95 (sex, 2H, J=7.0 Hz), 4.12 (t, 2H, J=7.0 Hz), 5.95 (s, 1H), and 7.52—8.18 (m, 4H). Found: 72.49; H, 5.49%. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%.

4-Isopropoxy-1,2-naphthoquinone (2d): Orange yellow needles (benzene-hexane); mp 124—125 °C; IR (KBr) 1700 (m) and 1645 (s) cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.48 (d, 6H, J=7.0 Hz), 4.72 (sev, 1H, J=7.0 Hz), 5.90 (s, 1H), and 7.50—8.10 (m, 4H). Found: C, 71.19; H, 5.67%. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%.

4-Butoxy-1,2-naphthoquinone (2e): Yellow needles (benzene-hexane); mp 95.5—96.5 °C; IR (KBr) 1690 (m) and 1640 (s) cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.02 (t, 3H, J=7.0 Hz), 1.36—1.72 (m, 2H), 1.90 (quint, 2H, J=7.0 Hz), 4.13 (t, 2H, J=7.0 Hz), 5.91 (s, 1H), and 7.48—8.12 (m, 4H). Found: C, 78.55; H, 6.77%. Calcd for $C_{14}H_{14}O_3$: C, 78.48; H, 6.59%.

4-Allyloxy-1,2-naphthoquinone (2f): Yellowish brown needles (benzene-hexane); mp 121.5—123.5 °C; IR (KBr) 1700 (m) and 1650 (s) cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=4.65 (m, 2H, OCH_2), 5.35—5.57 (m, 2H, C=CH_2), 5.91 (s, 1H), 5.96—6.44 (m, 1H, CH=C), and 7.49—8.11 (m, 4H). Found: C, 72.61; H, 4.55%. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71%.

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