An Improved Synthesis of Benzo- and Naphthoquinones from Hydroquinone Dimethyl Ethers

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The demethylation of arylxy methyl ethers to quinones has been a problem in organic synthesis. The oxidation of 1,4-dimethoxybenzene (1, Scheme A) and 1,4-dimethoxy-naphthalene (3, Scheme B) derivatives to the corresponding benzo- or naphthoquinones (2 or 4, respectively) has been accomplished using a variety of oxidizing agents, particularly nitric acid or silver(II) oxide in acidic media. Nitric acid is suitable for highly substituted 1,4-dimethoxybenzene derivatives, but in some cases nitration of the aromatic ring occurs as the main process or in addition to demethylation. A more convenient method is oxidation with silver(II) oxide. However, this method requires strongly acidic medium with the result that some substituents participate in side reactions. Recently, a new method of oxidative demethylation of hydroquinone dimethyl ethers with ceric ammonium nitrate has been reported. This way seems to be quite good, but only a few compounds have been checked. Furthermore, it has been known that, for some substituted 1,4-dimethoxybenzenes, condensation reactions also take place, thus reducing the yield.

In continuation of our investigations on the oxidation of organic compounds with metal cations having high redox potentials, we have found that ceric ammonium nitrate (CAN) or silver(II) oxide (AgO) are more effective oxidizing agents when pyridinecarboxylic acids, pyrazinecarboxylic acids or their derivatives are applied as catalysts. In these cases the reaction is carried out in the presence of a weak organic acid. It is generally a fast reaction, requiring a short time and low temperature (0°-20°). Selectivity of this process is illustrated by the fact that a variety of substituents are not affected by the reaction conditions. No side condensation reactions were observed. The yields of benzo- and naphthoquinones are higher compared to the methods described previously.

![Scheme A](image1)

![Scheme B](image2)

The mode of action of the azinecarboxylic acids and their derivatives is probably due to their ability to complex Ag(II) or Ce(IV). In effect, an electron transfer between the organic molecule and the metal cation becomes easier, similar to the oxidation of inorganic salts.

The best yields of various quinones are obtained with AgO or CAN when pyridine-2,6-dicarboxylic acid N-oxide is used as a ligand. This compound is easily prepared by the oxidation of pyridine-2,6-dicarboxylic acid with hydrogen peroxide in the presence of Na2WO4.

The results of the oxidative demethylation of the various hydroquinone ethers 1 and 3 are listed in Tables 1 and 2. Application of CAN as oxidizing agent is more convenient because the yields of quinones are better than in the case of AgO. The product isolation is facile because there are no unsoluble inorganic salts present in the reaction mixture.

**Oxidation of Hydroquinone Ethers 1 and 3 with Silver(II) Oxide: General Procedure:**

To the hydroquinone ether (4.0 mmol) dissolved in a mixture of acetonitrile (28 ml) and water (12 ml) containing suspended pyridine-2,6-dicarboxylic acid N-oxide (3.86 g, 20 mmol), silver(II) oxide (2.46 g, 20 mmol) is added slowly with vigorous stirring within 30 min. During this addition the reaction mixture is cooled in an ice water bath. Then the reaction mixture is diluted with water (40 ml) and insoluble compounds filtered. The solid is washed several times with dichloromethane. The same solvent is used for extraction of the filtrate. The combined extracts are washed with water, dried with anhydrous magnesium sulfate, and the solvent evaporated under a water pump vacuum. The crude quinone is purified by the column chromatography through silica gel using dichloromethane as eluent. The solid crude quinones can be further purified by recrystallization from methanol.
### Table 1. Oxidative Demethylation of 1,4-Dimethoxybenzene Derivatives 1a–f (see Scheme A)

<table>
<thead>
<tr>
<th>Product</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Yield [%] with AgO or CAN</th>
<th>m.p.</th>
<th>Molecular formula</th>
<th>I.R. (KBr) ν&lt;sub&gt;υ-O&lt;/sub&gt; [cm&lt;sup&gt;-1&lt;/sup&gt;]</th>
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<tr>
<td>2a</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>91</td>
<td>125-126&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1638, 1658</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>86</td>
<td>63±69&lt;sup&gt;18&lt;/sup&gt;</td>
<td>68,70±98&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>92</td>
<td>110-114&lt;sup&gt;17&lt;/sup&gt;</td>
<td>1635</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>82</td>
<td>74±70&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1600</td>
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<tr>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>92</td>
<td>82±85&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1640</td>
<td></td>
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<tr>
<td>2f</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>84</td>
<td>104-105&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1663</td>
<td></td>
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<sup>a</sup> The 1H-N.M.R. spectra were in agreement with the proposed structures.

<sup>b</sup> The microanalyses for the new compounds 2e, 2f, and 2f were in satisfactory agreement with the calculated values (C ± 0.25, H ± 0.23).

### Table 2. Oxidative Demethylation of 1,4-Dimethoxynaphthalene Derivatives 3a–d (see Scheme B)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Yield [%] with AgO or CAN</th>
<th>m.p.</th>
<th>Lit. m.p.</th>
<th>I.R. (KBr) ν&lt;sub&gt;υ-O&lt;/sub&gt; [cm&lt;sup&gt;-1&lt;/sup&gt;]</th>
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<tr>
<td>3a</td>
<td>H</td>
<td>99</td>
<td>104-105&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1663</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C≡CH-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>84</td>
<td>74-75&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1660</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>(H&lt;sub&gt;2&lt;/sub&gt;C≡CH-CH&lt;sub&gt;2&lt;/sub&gt;-)</td>
<td>84</td>
<td>80-85&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1658</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>(H&lt;sub&gt;2&lt;/sub&gt;C≡CH-CH&lt;sub&gt;2&lt;/sub&gt;-)</td>
<td>84</td>
<td>104-105&lt;sup&gt;10&lt;/sup&gt;</td>
<td>1659</td>
<td></td>
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</table>

<sup>a</sup> The 1H-N.M.R. spectra were in agreement with the proposed structures.

<sup>b</sup> C<sub>14</sub>H<sub>12</sub>O<sub>2</sub> calc.: C 79.22, H 5.69 (212.3) found: C 79.25, H 5.90

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**Oxidation of Hydroquinone Ethers 1 and 3 with Ceric Ammonium Nitrate: General Procedure:**

To the hydroquinone ether (8.0 mmol) dissolved in a mixture of acetonitrile (20 mL) and water (12 mL) containing suspended pyridine-2,6-dicarboxylic acid N-oxide (3.36 g, 20 mmol), a cooled solution of ceric ammonium nitrate (10.96 g, 20 mmol) in a mixture of acetonitrile (20 mL) and water (20 mL) is slowly added with vigorous stirring within 20 min. During this addition, the reaction vessel is cooled in an ice/water bath. Then the mixture is stirred for an additional 20 min. The bath is removed and, after 10 min, the mixture is poured into a separatory funnel, water (40 mL) is added, and the mixture is extracted several times with dichloromethane. The combined extracts are washed with water, dried with anhydrous magnesium sulfate, and the solvent removed under a water pump vacuum. The crude quinone is purified by column chromatography through silica gel using dichloromethane as an eluent. The solid crude quinones can be further purified by recrystallization from methanol.

**Pyridine-2,6-Dicarboxylic Acid N-Oxide:**

Pyridine-2,6-dicarboxylic acid (16.7 g, 100 mmol) and a solution of Na<sub>2</sub>WO<sub>4</sub>, 2H<sub>2</sub>O (1.0 g, 3.3 mmol) in 30% hydrogen peroxide (50 mL) are heated at 90-100° with vigorous stirring for 30 min. Then an additional amount of 30% hydrogen peroxide (120 mL) is added portionwise over a period of 2 h until all insoluble substance has vanished. After an additional 3 h of heating, the reaction mixture is allowed to stand for several hours. The crystalline solid is filtered, washed with several portions of the cold water, and dried in the air. The filtrate is extracted with chloroform. Evaporation of the solvent gives a residue which is combined with the main portion of crude N-oxide. The pure pyridine-2,6-dicarboxylic acid N-oxide is obtained by recrystallization of the crude product from water; yield: 13.8 g (75%); m.p. 158-160°; Lit. m.p. 155-157°.

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