

Communications to the Editor

[Chem. Pharm. Bull.]
[31(1) 341-343 (1983)]

THE CERIC AMMONIUM NITRATE MEDIATED SYNTHESIS OF QUINOLINE AND
ISOQUINOLINE QUINONES

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The use of ceric ammonium nitrate(CAN) for the oxidative demethylation of various quinoline and isoquinoline hydroquinone 5,8-dimethylethers and 5,6,8- or 5,7,8-trimethylethers, and its application to the preparation of isoquinoline quinone antibiotics, mimocin (5f) and renierone (5g) are described.

KEYWORDS — ceric ammonium nitrate; CAN; oxidative demethylation; heterocyclic quinone; quinoline quinone; isoquinoline quinone; mimocin; renierone

There has been a continuing interest in the chemistry and biological activities of heterocyclic quinones.¹⁾ In connection with our studies on the synthesis of isoquinoline quinone antibiotics, mimocin (5f)^{2a)} and renierone (5g)^{3b)}, we required a mild and efficient method for the preparation of heterocyclic quinones.

Although many synthetic routes to heterocyclic quinones have been described,⁴⁾ most of them require drastic reaction conditions and thus they are not applicable to complex or highly sensitive substances.

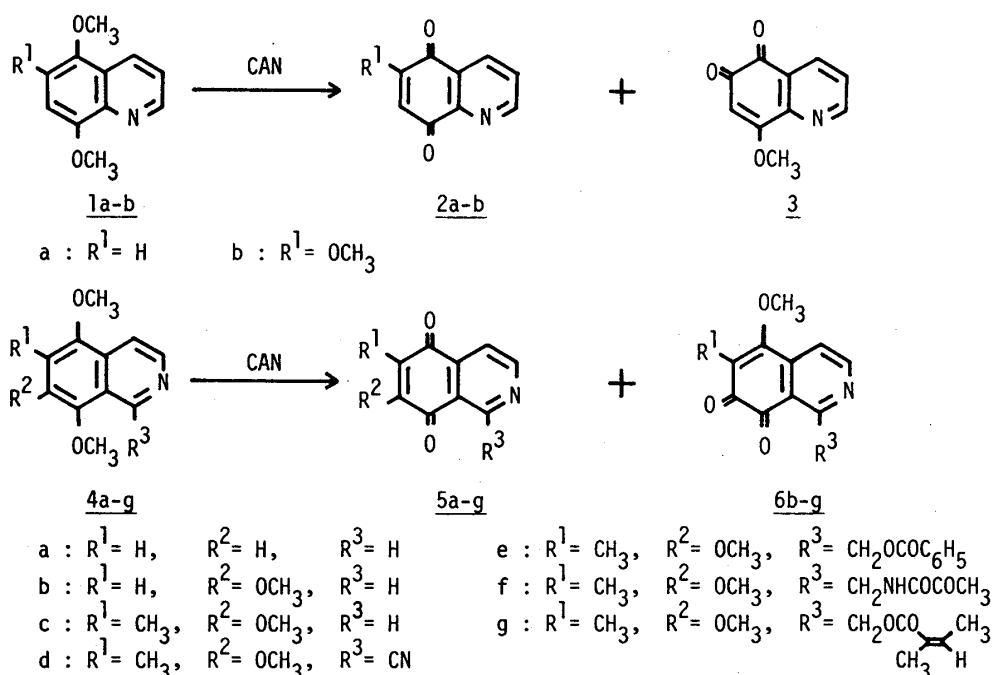
Recently oxidative demethylation of hydroquinone dimethylethers has proved to be a key synthetic reaction to the corresponding benzo- and naphthoquinones using a variety of the oxidizing agents, particularly nitric acid,⁵⁾ argentic oxide (AgO)⁶⁾ or ceric ammonium nitrate(CAN).⁷⁾ Both nitric acid and AgO, however, have the disadvantage that they require strongly acidic media, and therefore acid-sensitive functional groups may not be tolerated.

On the other hand, the reaction using CAN can be carried out in aqueous acetonitrile and it requires a short reaction time and low temperature(0-2°C).⁷⁾

We now report the results of the oxidative demethylation of various quinoline and isoquinoline hydroquinone 5,8-dimethylethers and 5,6,8- or 5,7,8-trimethylethers with CAN.

The oxidative demethylation of the quinoline hydroquinone ethers (1a-b) and the isoquinoline hydroquinone ethers (4a-g) with CAN in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid N-oxide,⁷⁾ afforded the corresponding para- and/or ortho-quinones⁸⁾ in 46-92% total yield. These results are summarized in Table 1.

It is interesting to note that in the case of trimethylethers both methoxy para-quinones and rare heterocyclic methoxy ortho-quinones⁴⁾ were obtained under

Table 1. Oxidative Demethylation of Heterocyclic Hydroquinone Ethers (1a-b and 4a-g) with CAN

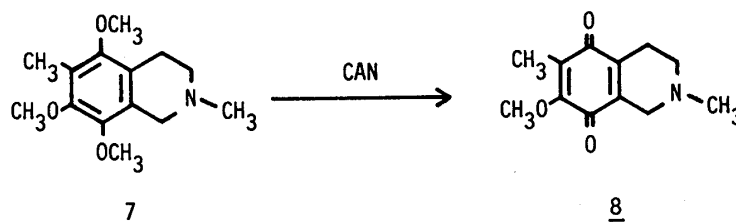
Starting hydroquinone ethers (<u>1a-b</u> and <u>4a-g</u>)			Heterocyclic quinones			
R^1	R^2	R^3	Yield [%]	para:ortho quinone ratio ^a	mp [°C] or Lit. mp[°C]	IR(KBr) $\nu_{\text{C=O}}$ [cm ⁻¹]
<u>1a</u>	H		72		<u>2a</u> :113-116 113-115(dec.) ¹⁰⁾	1670
<u>1b</u>	OCH ₃		92	32:60	<u>2b</u> :245-248(dec.) <u>3</u> :218-220(dec.)	C ₁₀ H ₇ NO ₃ 1670,1685 C ₁₀ H ₇ NO ₃ 1642,1700
<u>4a</u>	H	H	88		<u>5a</u> :136-137(dec.)	135-138 ¹¹⁾ 1665
<u>4b</u>	H	OCH ₃	46	20:26	<u>5b</u> :219-220 <u>6b</u> :184-186(dec.)	215-216 ¹²⁾ C ₁₀ H ₇ NO ₃ 1650,1680 1650,1700
<u>4c</u>	CH ₃	OCH ₃	52	8:44	<u>5c</u> :124-126 <u>6c</u> :142-144	C ₁₁ H ₉ NO ₃ C ₁₁ H ₉ NO ₃ 1658,1670 1665,1700
<u>4d</u>	CH ₃	OCH ₃	76	35:41	<u>5d</u> :175-177 <u>6d</u> :183-186(dec.)	C ₁₂ H ₈ N ₂ O ₃ C ₁₂ H ₈ N ₂ O ₃ 1648,1680 1665,1700
<u>4e</u>	CH ₃	OCH ₃	47	18:29	<u>5e</u> :138-139 <u>6e</u> :148-149	C ₁₉ H ₁₅ NO ₅ C ₁₉ H ₁₅ NO ₅ 1670,1720 1688,1727
<u>4f</u>	CH ₃	OCH ₃	83	31:52	<u>5f</u> :189-191(dec.) <u>6f</u> :167-170(dec.)	189-191(dec.) ^{2a)} C ₁₅ H ₁₄ N ₂ O ₅ 1665,1680, 1720 1665,1690, 1713
<u>4g</u>	CH ₃	OCH ₃	66	26:40	<u>5g</u> : 92-92.5 <u>6g</u> :140-141	91.5-92.5 ¹³⁾ C ₁₇ H ₁₇ NO ₅ 1643,1670, 1718 1642,1694, 1710

^a Ratio determined by the isolated yields.

these mild conditions. The unstable methoxy ortho-quinones are known to give the corresponding para isomers in nearly quantitatively yield in two steps.^{3a)}

Compared with AgO ,^{2b,3a)} oxidative demethylation with CAN provides an efficient and alternative way to synthesize the isoquinoline quinone antibiotics, mimocin (**5f**) and renierone (**5g**), amenable to their large-scale preparation.

Finally, treatment of 5,7,8-trimethoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinoline (**7**) with CAN under similar conditions gave a very unstable methoxy para-quinone (**8**) [$\text{C}_{12}\text{H}_{15}\text{NO}_3$] in 42% yield, but no methoxy ortho-quinone.



In summary, the present method involving milder conditions should be of general applicability for the synthesis of heterocyclic quinones possessing a labile functional group.⁹⁾ We are currently investigating the oxidative demethylation of the other heterocyclic hydroquinone ethers with CAN and the biological activities of the ortho-quinone isomers (**6f** and **6g**) of mimocin (**5f**) and renierone (**5g**).

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(Received November 2, 1982)