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.

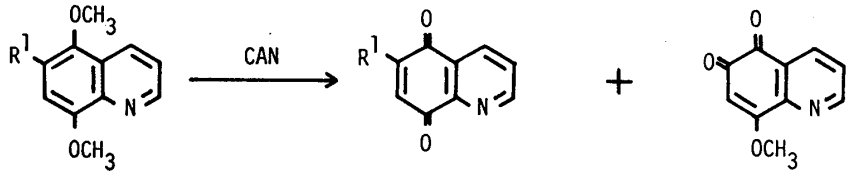
Recently oxidative demethylation of hydroquinone dimethylethers has proved to be a key synthetic reaction to the corresponding benzo- and naphthoquinones using a variety of the oxidizing agents, particularly nitric acid,[5] argentic oxide (AgO)[6] or ceric ammonium nitrate(CAN).[7] Both nitric acid and 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.

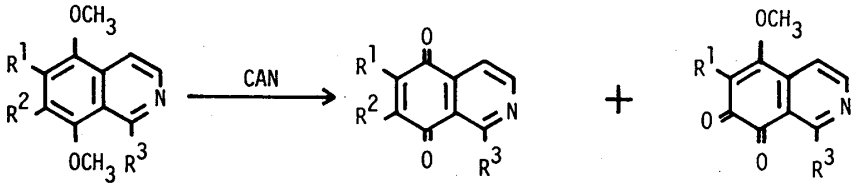
The oxidative demethylation of the quinoline hydroquinone ethers (1a-b) and the isoquinoline hydroquinone ethers (4a-g) with CAN in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid N-oxide,[7] afforded the corresponding para- and/or ortho-quinones[8] in 46-92% total yield. These results are summarized in Table 1.

It is interesting to note that in the case of trimethylethers both methoxy pará-quinones and rare heterocyclic methoxy ortho-quinones[4] were obtained under



1a-b 2a-b 3

a : R^1= H b : R^1= OCH_3



4a-g 5a-g 6b-g

a : R^1= H, R^2= H, R^3= H
b : R^1= H, R^2= OCH_3, R^3= H
c : R^1= CH_3, R^2= OCH_3, R^3= H
d : R^1= CH_3, R^2= OCH_3, R^3= CN
e : R^1= CH_3, R^2= OCH_3, R^3= $CH_2OCOC_6H_5$
f : R^1= CH_3, R^2= OCH_3, R^3= $CH_2NHCOCOCH_3$
g : R^1= CH_3, R^2= OCH_3, R^3= CH_2OCO(CH$_3$)=CH(H)CH$_3$

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

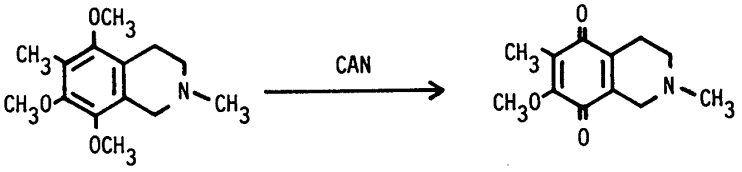
Starting hydroquinone ethers (1a-b and 4a-g)				Heterocyclic quinones				
	R^1	R^2	R^3	Yield [%]	para:ortho quinone ratio[a]	mp [°C]	Molecular formula or Lit. mp[°C]	IR(KBr) νC=O[cm^{-1}]
1a	H			72		2a:113-116	113-115(dec.)[10]	1670
1b	OCH_3			92	32:60	2b:245-248(dec.)	$C_{10}H_7NO_3$	1670,1685
						3:218-220(dec.)	$C_{10}H_7NO_3$	1642,1700
4a	H	H	H	88		5a:136-137(dec.)	135-138[11]	1665
4b	H	OCH_3	H	46	20:26	5b:219-220	215-216[12]	1650,1680
						6b:184-186(dec.)	$C_{10}H_7NO_3$	1650,1700
4c	CH_3	OCH_3	H	52	8:44	5c:124-126	$C_{11}H_9NO_3$	1658,1670
						6c:142-144	$C_{11}H_9NO_3$	1665,1700
4d	CH_3	OCH_3	CN	76	35:41	5d:175-177	$C_{12}H_8N_2O_3$	1648,1680
						6d:183-186(dec.)	$C_{12}H_8N_2O_3$	1665,1700
4e	CH_3	OCH_3	$CH_2OCOC_6H_5$	47	18:29	5e:138-139	$C_{19}H_{15}NO_5$	1670,1720
						6e:148-149	$C_{19}H_{15}NO_5$	1688,1727
4f	CH_3	OCH_3	$CH_2NHCOCOCH_3$	83	31:52	5f:189-191(dec.)	189-191(dec.)[2a]	1665,1680, 1720
						6f:167-170(dec.)	$C_{15}H_{14}N_2O_5$	1665,1690, 1713
4g	CH_3	OCH_3	CH_2OCO(CH$_3$)=CH(H)CH$_3$	66	26:40	5g: 92-92.5	91.5-92.5[13]	1643,1670, 1718
						6g:140-141	$C_{17}H_{17}NO_5$	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 paraquinone (8) [$C_{12}H_{15}NO_3$] in 42% yield, but no methoxy ortho-quinone.



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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)