Oxidation of Hydroquinones and Hydroquinone Monomethyl Ethers to Quinones with *tert*-Butyl Hydroperoxide and Catalytic Amounts of Ceric Ammonium Nitrate (CAN)

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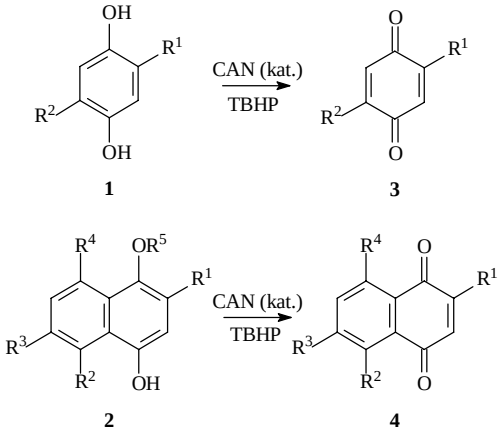
Abstract. Mono- and bicyclic hydroquinones and hydroquinone monomethyl ethers 1, 2 are oxidized in 82–91% yield to the corresponding quinones using only 2 mol% of ceric ammonium nitrate (CAN) and 2.5 equivalents of *tert*-butyl hydroperoxide.

In connection with the synthesis of anthrapyran antibiotics in our group, the efficient oxidation of hydroquinones and hydroquinone monomethyl ethers to quinones was required. A large number of reagents for the oxidation of hydroquinones to quinones, in particular silver oxide [1] or chromium (VI) reagents [2–4] (review [5]), are used in such dehydrogenations. Recently, ceric ammonium nitrate (CAN) has emerged as the reagent of choice in such transformations because also hydroquinone mono and dimethyl ethers are converted to the corresponding quinones [6, 7]. The mechanism is believed to occur *via* two successive electron transfer processes from the electron-rich hydroquinone to the cerium(IV) species [8]. The generation of radical intermediates (compare [9]) can lead to the dimerization of the intermediates [10, 11], to hydroxylation of electron-rich aromatics [12] or in special cases even to hydroxylation of benzylic positions [13, 14] (for reviews on cerium(IV) oxidations see [5, 15, 16]). However, usually at least two equivalents of CAN are required, which is very costly on larger scale oxidations (ca. DM 50 for 100 g of CAN) and a deplorable waste of the precious cerium metal. We therefore initiated a systematic investigation on a catalytic variation of mono- and bicyclic hydroquinone and hydroquinone mono ether oxidations. With exception of an ultrasonic irradiation assisted solid state procedure [17] using $KBrO_3$ as the cooxidant, catalytic procedures are not described in the literature. In this solid state procedure of Morey and Saá, only the oxidation of hydroquinones on a small millimolar scale was described.

Initial experiments, using hydrogen peroxide as the oxidant in homogeneous as well as heterogeneous procedures under phase transfer catalysis, failed to give clean and high yield conversions. We then turned our attention to *tert*-butyl hydroperoxide (TBHP) as the oxidation reagent. Using TBHP as the cooxidant has the advantage that this oxygen source is virtually inert to most functional groups. However, from extensive studies in our group it was known that phenols and also hydroquinone monomethyl ethers were oxidized to the *ortho*-quinones in transition metal alkoxide-catalyzed oxidations with TBHP [18, 19]. Thus, for the present purpose of exclusive reoxidation of Ce (III) to Ce (IV), it was essential that the alkoxide formation and ligand exchange observed in the transition metal alkoxide-catalyzed oxidations would not occur in the cerium-catalyzed oxidations.

Ideal substrates to test the reaction were benzohydroquinone **1a** and methyl benzohydroquinone **1b** (see Scheme 1, Table 1, entries 1 and 2). The oxidation to **3a** and **3b** proceeded rapidly (30 min) with the usual two equivalents of CAN but, gratifyingly, also with a catalytic amount of CAN (10 mol%) and 5 equivalents of TBHP. The decrease in reaction rate corresponded approximately to the reduced amount of CAN used, indicating that the dehydrogenation of the hydroquinone and not the reoxidation of Ce (III) to Ce (IV) was the rate determining step. In subsequent experiments, the amount of CAN could be reduced to 2 mol% without any decrease in yield. To avoid ineffective decomposition of the hydroperoxide by the radical process, TBHP was added slowly to the reaction mixture by way of a syringe pump. Employing this way of TBHP addition, the amount of TBHP could be reduced to 2.5 equivalents (see Table 1) as monitored by GC of the reaction. The conversions in entries 1–3 were >98%



Scheme 1 Catalytic CAN oxidation of hydroquinones **1** and **2** to the quinones **3** and **4**

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Table 1 Yields and conditions in the catalytic CAN oxidation of hydroquinones

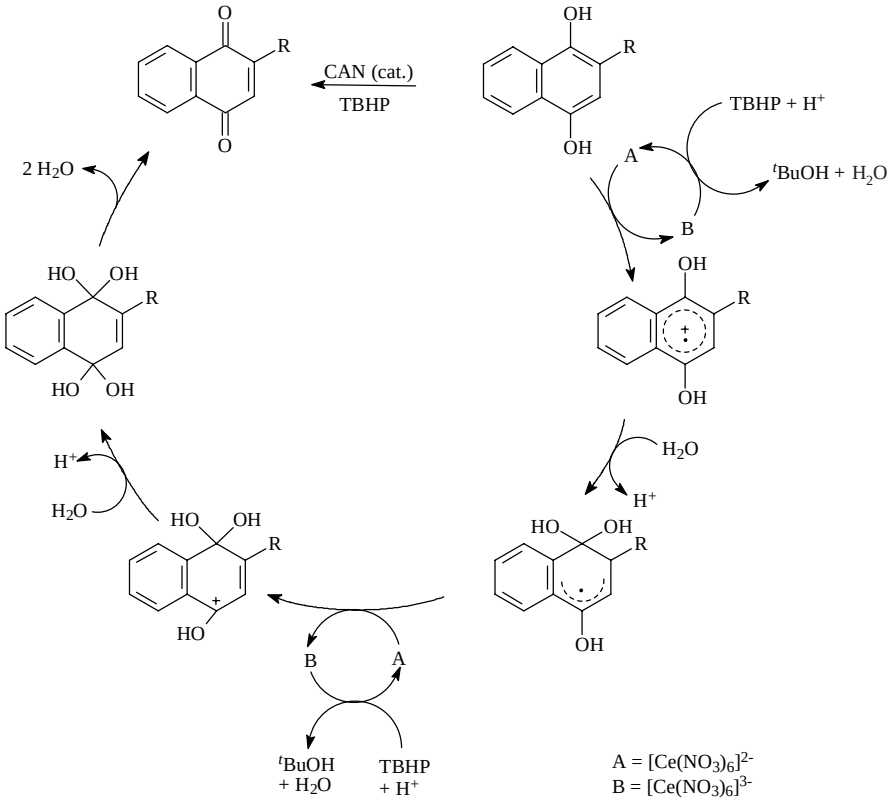
entry	ed.	R^1	R^2	R^3	R^4	R^5	CAN (mol%)	TBHP (equ).	temp (°C)	time (h)	prod.	yield (%)
1	**1a**	H	H	–	–	–	2	5	22	10	**3a**	84 [a], [b]
2	**1b**	CH_3	H	–	–	–	2	5	22	10	**3b**	83 [a], [b]
3	**1c**	^{t}Bu	^{t}Bu	–	–	–	2	2.5	22	18	**3c**	91 [b]
4	**1d**	Br	H	–	–	–	2	2.5	22	14	**3d**	83 [a], [c]
5	**1e**	Br	Br	–	–	–	2	2.5	22	18	**3e**	90 [c]
6	**1f**	CO_2CH_3	H	–	–	–	2	5	22	24	**3f**	0 [d]
7	**1g**	$COCH_3$	H	–	–	–	10	5	22	24	**3g**	0 [d]
8	**2a**	H	H	OCH_3	OCH_3	H	2	2.5	22	18	**4a**	92 [c]
9	**2b**	Cl	H	OCH_3	OCH_3	H	2	2.5	22	14	**4b**	85 [c]
10	**2c**	Br	OAc	H	H	H	2	2.5	22	18	**4c**	91 [c]
11	**2d**	$COCH_3$	H	H	H	H	2	2.5	20	22	**4d**	82 [c]
12	**2e**	H	H	H	H	CH_3	2	2.5	50	11	**4e**	91 [c], [e]

[a]) product sublimates *in vacuo*; [b]) conversion as determined by GC; [c]) no other product than quinone detectable by TLC; [d]) starting material recovered; [e]) addition of 2,6-pyridine-*N*-oxide dicarboxylic acid

by GC; the isolated yields of quinones **3a**–**c** were somewhat lower due to the volatility of these benzoquinones.

Steric hindrance, as in the 2,6-di-*tert*-butylhydroquinone **1c** (entry 3), increased the reaction time but the conversion (>98% by GC) and the isolated yield of quinone **3c** (91%) was not reduced. Halogen atoms on the aromatic nucleus such as in the bromide **1d** or the dibromide **1e** were not affected. On the other hand, strong electron acceptors on monocyclic substrates as in the ester **1f** or the acetyl compound **1g** (entries 6 and 7) inhibited the catalytic as well as the stoichiometric CAN oxidation. Yields and conditions in the catalytic CAN oxidation of hydroquinones are shown in Table 1.

The substituted bicyclic naphthohydroquinones **2a**–**c** were converted in overnight reactions in excellent 85–91% isolated yields to the naphthoquinones **4a**–**c**. Again, the halogen atoms in **4b** or **4c** remained untouched. Surprisingly, the acetylated naphthohydroquinone **2d** was converted smoothly to the naphthoquinone **4d** in 82% isolated yield. The naphthoquinone **4d** has a very high oxidation potential and is easily hydrogenated in methanolic solution back to the hydro-



Scheme 2 Catalytic cycle of CAN oxidation of a naphthohydroquinone with TBHP

quinone **2d**. Thus, electron acceptors are tolerated in bicyclic hydroquinones.

Finally, the monomethyl ether **2e** was tested in the catalytic CAN oxidation. The reaction was very slow at room temperature but heating to 50 °C and addition of 2,6-pyridine-*N*-oxide dicarboxylic acid [6] increased the reaction rate and a 91% yield of naphthoquinone **4a** was isolated after 11 h of reaction time. However, hydroquinone dimethyl ethers are not oxidized to the quinones in acceptable time employing the catalytic procedure. The entire catalytic cycle is shown in Scheme 2, showing the established stepwise electron transfer and water addition to the intermediate carbocations [8].

In summary, an operationally simple catalytic variation of the CAN oxidation of hydroquinones and hydroquinone monomethyl ethers to quinones is presented, requiring only 1% of the usual amount of CAN and 1.25 equiv. of TBHP as the cooxidant. The procedure is amenable to scale-up without decrease in yield compared to stoichiometric CAN oxidations.

Experimental

Catalytic CAN Oxidation of Hydroquinones and Hydroquinone Monomethyl Ethers (General Procedure)

A solution of the hydroquinone or hydroquinone monomethyl ether (1 mmol) (Hydroquinone **1d** was oxidized on a 0.23 molar scale and **1e** and **2d** on 10 mmolar scale in comparable yield) in acetonitrile (15 mL) and water (5 mL) was added to a solution of CAN (0.2 mL, 0.1 mol/L, 2 mol%) and pyridine-*N*-oxide-2,6-dicarboxylic acid (4 mg, 2 mol%; for monomethyl ethers such as **2e**) in water (5 mL). To this mixture was added an aqueous solution of TBHP (70%) diluted with acetonitrile using a syringe pump (for reaction times and other conditions see Table 1). The progress of the reaction was monitored by TLC. After complete conversion of the starting material, CH_2Cl_2 (50 mL) was added, the phases were separated, and the organic phase was washed with water (10 mL) and brine (10 mL). The solution was dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue crystallized from ether/petroleum ether (yields see Table 1).

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