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A Novel Process for Selective Ruthenium-Catalyzed Oxidation of Naphthalenes and Phenols

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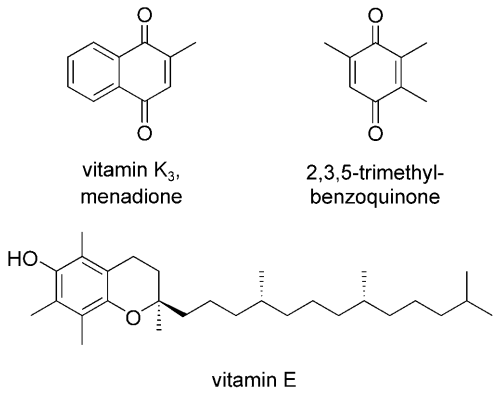
Abstract: Arenes are selectively oxidized to the corresponding quinones employing ruthenium-(2,2′,6′:2″-terpyridine)(2,6-pyridinedicarboxylate) [Ru(tpy)(pydic] as catalyst and hydrogen peroxide as the terminal oxidant. Applying alkylated naphthalenes and phenols, benzo- and naphthoquinones are obtained in up to 93% yield. The industrially interesting oxidation of 2-methylnaphthalene gave 74% of the corresponding quinones and 60% of menadione (vitamin K_3). 2,3,5-Trimethylbenzoquinone which constitutes the key intermediate for vitamin E is obtained in 83% yield.

Keywords: arenes; hydrogen peroxide; menadione; oxidation; ruthenium; vitamin E

Quinones take part in many biological processes due to their versatile redox chemistry.[1] Beside their involvement in photosynthesis and the respiratory chain, quinone-based vitamins are important food additives, e.g., menadione (vitamin K_3) and 2,3,5-trimethylbenzoquinone, a crucial intermediate for vitamin E (Scheme 1). More specifically, menadione shows antihaemorrhagic effects and is applied as an animal feed additive.[2] In addition, it is used as a vitamins K_1 and K_2 precursor. Vitamin E is a well known antioxidant, which is applied as a food additive and in cosmetics.[3] Both vitamins are produced on a multi-thousand ton scale per year.

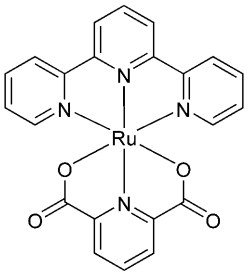


Scheme 1. Vitamins K_3 and E, and vitamin E precursor.

The industrial production of menadione is based on the selective oxidation of 2-methylnaphthalene. Up to now, this arene oxidation is performed by using stoichiometric amounts of chromium trioxide in sulphuric acid. Depending on the reaction conditions product yields in the range 38–60% have been reported. Due to the large amount of chromium-containing waste, e.g., 18 kg per kg of product,[4] significant efforts have been made to replace this process by more environmentally benign routes. For example, several catalytic routes were developed using molecular oxygen, percarboxylic acids or hydrogen peroxide as more benign oxidants to replace stoichiometric amounts of chromium,[5] cerium,[6] or manganese[7] heavy metal salts. With respect to the catalyst a range of metal complexes based on palladium,[8] rhenium,[9] vanadium,[10] chromium,[11] and cerium[12] have been applied. Moreover, phthalocyanine,[13] and porphyrin[14] complexes as well as zeolites[15] were used in the catalytic oxidation of 2-methylnaphthalene to menadione.

The current state-of-art oxidation system has elegantly been developed by W. Thiel and co-workers leading to 71% of menadione using sulphuric acid as catalyst in a mixture of glacial acetic acid/acetic anhydride as solvent and hydrogen peroxide as oxidant.[16] However, the strong acidic conditions cause potential corrosion problems for production on a larger scale. In addition, the use of hydrogen peroxide in high concentrations (50–80%) is an inherent safety risk. Therefore, improved catalytic oxidation methods, which work under milder reaction conditions, are still desirable.

Recently, we developed a biphasic reaction system for the oxidation of 2-methylnaphthalene (**1**) using the ruthenium(2,2′,6′:2″-terpyridine)(2,6-pyridinedicarboxylate) complex **A** shown in Scheme 2.[17] The



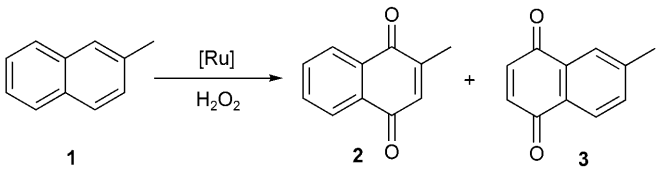
A

Scheme 2. Ruthenium(2,2′,6′:2"-terpyridine)(2,6-pyridinedicarboxylate) catalyst.

resulting quinones **2** and **3** were obtained in 64% yield. Unfortunately, the selectivity for the desired regioisomer menadione **2** was only 3:1.

Herein, we describe an improved Ru-catalyzed oxidation of 2-methylnaphthalene with increased yields and (regio)selectivity and the extension of this procedure towards other arenes and phenols.

For our initial investigations, the oxidation of **1** using 0.5 mol% of catalyst **A** and 3.5 equivalents of hydrogen peroxide (<30 wt%) was explored in more detail (Scheme 3). First, the reaction was performed



Scheme 3. Ru-catalyzed oxidation of 2-methylnaphthalene to the corresponding quinones.

in different polar solvents, especially alcohols, to optimize the solubility of complex **A** (Table 1).[18] As shown in Table 1 only protic solvents allow for significant conversion of **1**. Applying dimethylformamide, dimethyl sulfoxide or dioxane led to no activity at all (Table 1, entries 6–8).

This finding is in agreement with previous calculations for a similar complex in the epoxidation of olefins.[19] Hence, we propose the formation of a solvent-coordinated active catalyst species. Among the different protic solvents the selectivity towards **2** is increasing with growing polarity. In methanol and ethanol up to 35% selectivity is obtained (Table 1, entries 1 and 2). The ratio of quinones **2** and **3** increased up to 15:1 (Table 1, entry 2) and is significantly higher compared to our previous work![17]

For the further experiments methanol was selected as the solvent. Next, we investigated the influence of the concentration of hydrogen peroxide and catalyst as well as the temperature on the reaction system. Surprisingly, the amount of applied oxidant showed no influence on the selectivity (Table 2, entries 1–4). In general, three equivalents of hydrogen peroxide are required for full conversion. However, a total of 4.4 equivalents is necessary due to some decomposition of the oxidant which is catalyzed by the ruthenium complex (Table 2, entry 2), too. In order to minimize this decomposition, hydrogen peroxide is added by a syringe pump to keep its concentration low. By raising the temperature from 0 °C to 40 °C, a slight increase of the chemoselectivity is observed with no influence on the regioselectivity (Table 2, entries 5 and 6). Notably, variation of the catalyst concentration exhibited the strongest effect on the reactivity of the system. Increasing its concentration to 1 mol% gave full conversion and selectivity up to 44%, however, a further raise did not improve the outcome of the reaction (Table 2, entries 8 and 9). Changing the time for addition of the hydrogen peroxide did not affect the reaction (Table 2, entries 10 and 11).

To our delight continuous addition of the substrate by a separate syringe pump parallel to the hydrogen peroxide resulted in a significant increase in the selectivity (Table 2, entry 13). Hence, oxidation of 2-methylnaphthalene in the presence of 1 mol% catalyst and 4.4 equivalents hydrogen peroxide at room temperature proceeded smoothly to yield 58% of **2** (Table 2, entry 14). To increase the selectivity further on and to

Table 1. Influence of different polar solvents on yield and selectivity.[a]

Entry	Solvent	Conversion [%][b]	Yield of **2**+**3** [%][b]	Selectivity **2** [%][b]	Ratio **2:3**[b]
1	methanol	92	35	35	10:1
2	ethanol	99	36	34	15:1
3	*n*-propanol	100	27	25	11:1
4	*n*-butanol	100	27	23	05:1
5	*tert*-amyl alcohol	81	14	15	08:1
6	DMF	–	–	–	–
7	DMSO	–	–	–	–
8	dioxane	–	–	–	–

[a] *Reaction conditions:* 0.5 mmol **1**, 0.5 mol% **A**, 3.5 equiv. H_2O_2 (30 wt%), addition time 1 h, 20 °C.
[b] Determined by GC using dodecane as internal standard.

Table 2. Testing of different parameters and optimizing the reaction conditions.[a]

Entry	Cat. [mol%]	T [°C]	H_2O_2/**1**	t [h]	Conversion[b] [%]	Yield **2**+**3**[b] [%]	Selectivity for **2**[b] [%]	Ratio of **2**:**3**[b]
1	0.5	20	3.5	1	92	36	35	10:1
2	0.5	20	4.4	1	100	40	36	9:1
3	0.5	20	7.7	1	100	42	38	8:1
4	0.5	20	11	1	100	39	34	8:1
5	0.5	0	3.5	1	90	31	31	10:1
6	0.5	40	3.5	1	83	35	39	10:1
7	0.1	20	3.5	1	15	2	13	–
8	1	20	3.5	1	100	49	44	9:1
9	2	20	3.5	1	100	49	44	9:1
10	0.5	20	3.5	0	97	39	36	10:1
11	0.5	20	3.5	24	100	34	32	14:1
12[c]	0.5	20	3.5	1	93	34	33	11:1
13[c]	0.5	20	3.5	24	99	47	42	9:1
14[c]	1	20	4.4	24	100	67	58	6:1
15[c]	**1**	**40**	**4.4**	**7**	**100**	**74 (70)**[d]	**60 (58)**[d]	**5:1**[e]
16[c]	1	40	4.4	3	100	71	57	4:1

[a] *Reaction conditions:* 0.5 mmol **1**, MeOH (9 mL).
[b] Determined by GC using dodecane as internal standard.
[c] The substrate was solved in MeOH (1 mL) and added to the solution by a syringe pump.
[d] Isolated yield.
[e] Determined by ^{1}H NMR.

shorten the reaction time the temperature was raised to 40 °C, producing a maximum yield of 74% of the corresponding quinones, respectively (Table 2, entry 15)! An additional cutback of the reaction time appears to be possible without a significant loss of selectivity (Table 2, entry 16).

To explore a possible reuse of the catalyst, the reaction mixture was separated by column chromatography and a second run was performed with the catalyst, but showed no reactivity at all.

After having optimized the oxidation of 2-methylnaphthalene, we were interested in the general scope and limitations of this process (Table 3). Using non-substituted naphthalene, the corresponding quinone is obtained in 63% yield (Table 3, entry 1). On the other hand, the dialkylated 2,6-dimethylnaphthalene gave

Table 3. Oxidation of naphthalene derivates and monohydroxylated arenes.[a]

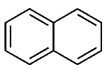
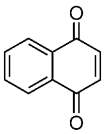
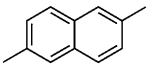
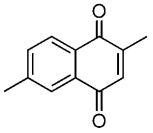
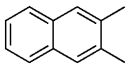
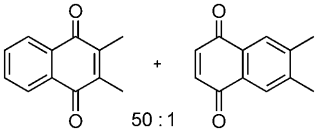
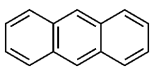
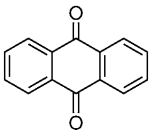
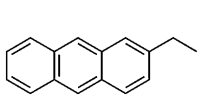
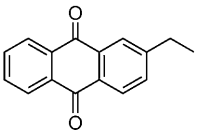
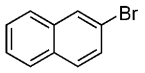
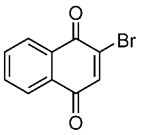
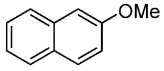
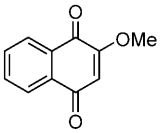
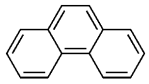
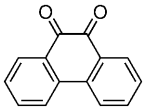
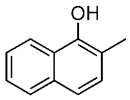
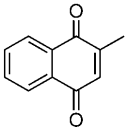
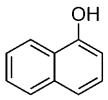
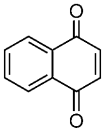
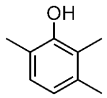
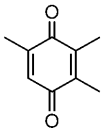
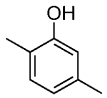
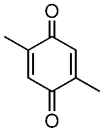
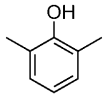
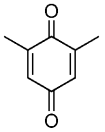
Entry	Substrate	Product	Conversion[b] [%]	Yield[b] [%]
1			100	63
2[c]			100	90
3[c]		 50 : 1	100	93
4[d]			100	39

Table 3. (Continued)

Entry	Substrate	Product	Conversion[b] [%]	Yield[b] [%]
5			100	77
6			100	-
7[c]			100	45
8[c]			100	34
9			100	78
10			100	78
11			100	83
12			100	75
13			100	78

[a] *Reaction conditions:* 1 mol% **A** in MeOH (8 mL), addition of 4.4 equiv. H_2O_2 (30 wt%) and 0.5 mmol substrate by syringe pump over 7 h at 40 °C.
[b] Determined by GC using dodecane as internal standard.
[c] Substrate was solved in dichloromethane and added by a syringe pump.
[d] Substrate was insoluble and added directly into the MeOH solution.

an excellent yield of 90% of the corresponding quinone (Table 3, entry 2).

This result clearly demonstrates the beneficial influence of electron-donating methyl groups on the selective oxidations of arenes. Furthermore, 2,3-dimethylnaphthalene is converted into the corresponding quinones in high yield (93%, Table 3, entry 3). Noteworthy, the ratio between the two isomers of 50:1 is also significantly increased compared to the oxidation of **1**. Similar results are observed using anthracene and 2-ethylanthracene. While anthraquinone gave a yield of 39%, the alkylated species 2-ethyl-9,10-anthraquinone is obtained in 77% yield, demonstrating again the influence of the alkyl group (Table 3, entries 4 and 5). Electron-rich 2-methoxynaphthalene gave the quinone in a yield of 45%, while the oxidation of the

electron-poor 2-bromonaphthalene yielded no quinone at all (Table 3, entries 6 and 7).

Finally, the oxidation of monohydroxylated arenes was studied. This reaction is also of significant industrial interest, especially for the preparation of vitamin E intermediates.[20] To our delight yields up to 83% were achieved for the tested substrates.

More specifically, 2-methyl-1-naphthol, a possible intermediate in the oxidation of **1** towards **2**,[16] and 1-naphthol are both oxidized in a yield of 78% (Table 3, entries 9 and 10). In addition, different methylated benzoquinones are obtained in 75–83% yield (Table 3, entries 11–13).

In summary, we demonstrated the successful optimization of the ruthenium-catalyzed oxidation of 2-methylnaphthalene with environmentally benign hydrogen peroxide as oxidant. In our novel system no strong acids are required and practical hydrogen peroxide (30% solution in water) can be used, so making the process safer. Various naphthalene derivatives are oxidized with good to excellent yields and high regioselectivity for the alkylated substrates. Applying monohydroxylated arenes yields of the corresponding quinones of about 80% are achieved. Notably, industrial important vitamin K_3 and 2,3,5-trimethylbenzoquinone are obtained in 78% and 83% yields, respectively.

Experimental Section

Reagents and Methods

The ruthenium complex was synthesized according to previously reported protocols.[18] H_2O_2 (29–31 wt%) was purchased from Merck and used as received. The naphthalene derivatives and other aromatic compounds were of analytical purity and used without further purification. Dimethylnaphthoquinones and 2,3,5-trimethylbenzoquinone were prepared according to literature methods.[21]

General Procedure for the Ruthenium-Catalyzed Oxidation of Arenes

A solution of ruthenium(2,2′,6′:2″-terpyridine)(2,6-pyridinedicarboxylate) (2.5 mg, 0.005 mmol) in methanol (8 mL) was treated with ultrasound for 5 min. Then a solution of 2-methylnaphthalene (71.11 mg, 0.5 mmol) in methanol (1 mL) and a solution of hydrogen peroxide (30 wt%) (227.5 μL, 2.2 mmol) in methanol (772.5 μL) were added parallel over the reaction time by syringe pumps. After 7 h of stirring at 40 °C, dodecane (100 μL) was added as an internal standard and a sample of the mixture was directly subjected to GC analysis. Conversion and yield were determined by GC-FID (HP6890 with FID detector, column HP5 30 m × 250 μm × 0.25 μm) and compared with authentic samples.

Acknowledgements

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