DOI: 10.1002/adsc.200505491

A New Metal-Free Access to Vitamin K3

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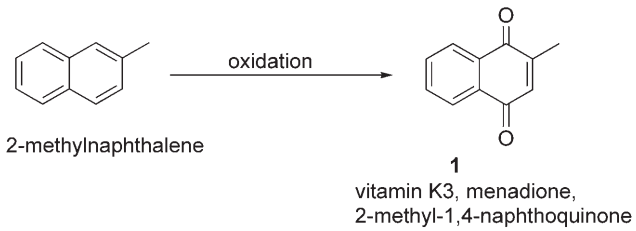
Received: December 22, 2005; Accepted: April 15, 2006

Abstract: 2-Methylnaphthalene is oxidized in about 80% yield with 7–9/1 regioselectivity to 2-methyl-1,4-naphthoquinone by hydrogen peroxide with a strong mineral acid as the catalyst. No (transition) metal catalyst is required for this transformation.

Keywords: acid catalysis; hydrogen peroxide; menadione; oxidation; vitamin K3



Scheme 1.

The controlled oxidation of organic molecules is still a challenging task. Often, partially oxidized species (e.g., alcohols) are much easier to oxidize than the corresponding precursor molecules (e.g., alkanes). This requires a well directed selection of the oxidizing agents as well as a strict control of reaction conditions. However, the economic benefit of a selective and high yield oxidation reaction will for sure justify such efforts.

The oxidation of arenes can be considered as a typical example for the statements made above. Different intermediates possessing different stabilities against overoxidation can be obtained more or less selectively by application of the appropriate oxidizing agents. One important technical product coming from arene oxidation is 2-methyl-1,4-naphthoquinone (**1**, menadione, vitamin K3), which is used as a supplement for the vitamins K1 and K2 in veterinary medicine. This application has implicated intense investigations on the evaluation of new synthetic methods for this compound. Most routes start from versatile 2-methylnaphthalene and thus include at least one oxidation step (Scheme 1).

They can be divided into three groups:

Reactions wherein a metal derivative is used as a stoichiometric oxidizing agent. This is mainly performed with chromium(VI),[1] the classical oxidizing agent in menadione chemistry, or with cerium(IV).[2] Both oxidizing agents can either be used directly or generated in situ, for example by anodic oxidation of low valent Cr^{III} or Ce^{III} precursors. From an economic as well as an ecologic point of view such procedures have become impracticable.

Reactions wherein a metal derivative is used as a catalyst in combination with hydrogen peroxide as the oxygen source. In some cases percarboxylic acids or dioxygen can be employed instead of H_2O_2. A whole series of (transition) metal complexes have shown catalytic activity for the oxidation of 2-methylnaphthalene to menadione: vanadium,[3] chromium,[4] molybdenum and tungsten,[5] rhenium,[6] palladium,[7] cerium,[8] phthalocyanine[9] or porphyrin complexes[10] and zeolites.[11] Depending on the catalyst used, these routes are obviously more environmentally benign than those discussed above.

Oxidation of 2-methylnaphthalene without any metal catalyst. Such reactions have only rarely been reported. Menadione can, for example, be obtained as a side product by the oxidation of 2-methylnaphthalene with ozone.[12] Adam et al. reported the oxidation of 2-methylnaphthalene by H_2O_2 with hexafluoroacetone hydrate as the catalyst.[13] The oxidation of condensed aromatic compounds in the presence of acetic acid was first described in 1940,[14] other combinations of carboxylic/percarboxylic acids have also been reported.[15]

We present here an improvement of the latter systems which opens up an efficient access to menadione (**1**) by Brønsted acid activation of hydrogen peroxide resulting in a product which is not contaminated by traces of (transition) metal catalysts.[16]

One of the most active catalysts for the oxidation of 2-methylnaphthalene to 2-methyl-1,4-naphthoquinone (**1**) is $MeReO_3$ (MTO). In contrast to MTO-cat-

alyzed olefin epoxidations, which are carried out in protic solvents under neutral or basic conditions, the oxidation of 2-methylnaphthalene requires a strongly acidic reaction system: the reaction is carried out with glacial acetic acid as the solvent and 85% H_2O_2 as the oxidizing agent, with a certain amount of acetic anhydride to remove the residual water (15% from aqueous H_2O_2).[6c,d] It was expected that the peroxo complex $MeReO(O_2)_2$ would be the active component,[17] as in olefin epoxidation. However, isostructural molybdenum peroxo complexes (L-L)$MoO(O_2)_2$ [L-L=2-(3-pyrazolyl)pyridine ligand] have turned out to be inactive in this reaction, although they show comparable reactivity in olefin epoxidation.[18]

However, considering a decomposition of the transition metal peroxo complexes to perrhenic acid or molybdic acid under the aggressive reaction conditions, could explain the differences in the catalytic activity by the differences in the strengths of these acids: while $HReO_4$ is a quite strong Brønsted acid ($pK_a=-1.60$[19] in aqueous solution), the pK_a of "H_2MoO_4" (hydrated molybdenum oxide, which rapidly will undergo condensation to MoO_3) is 5.40 orders of magnitude higher ($pK_a=3.80$[20] in aqueous solution).[21] This will have a severe impact on the composition of the reaction mixture, since the formation of peracetic acid from acetic acid and H_2O_2 is an acid-catalyzed reaction and is not catalyzed by acetic acid itself due to its high pK_a value ($pK_a=4.75$).

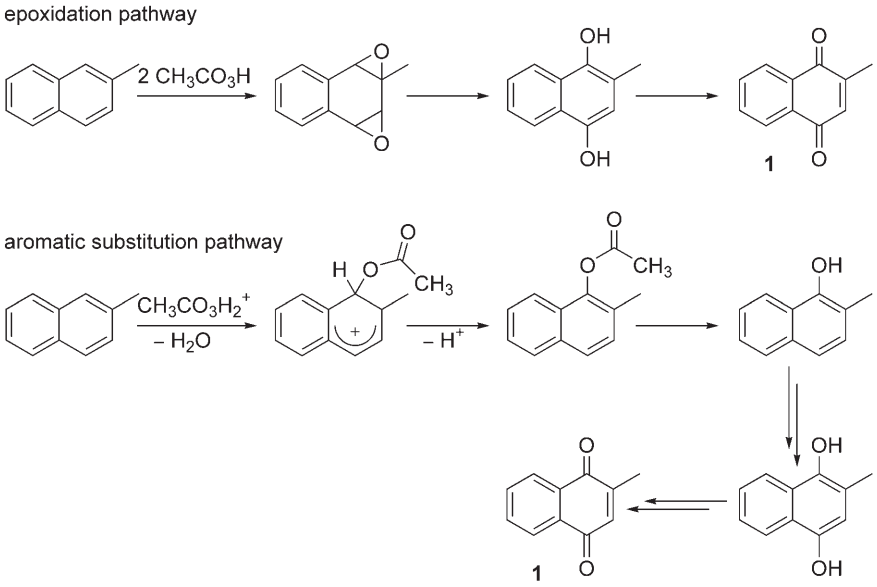
We thus replaced $MeReO_3$ by the strong Brønsted acids $HClO_4$, H_2SO_4 and H_3PO_4 and observed the formation of **1**. However, the use of 85% H_2O_2 gave lower yields than those reported for $MeReO_3$. This is probably due to overoxidation, for example, by cleavage of the C=C double bond in the quinone ring system and subsequent formation of carboxylic acids. Reduction of the concentration of the oxidizing agent to commercially available 50% H_2O_2 gave a pronounced enhancement of the isolated yield of **1**. Additionally, we found that the reaction temperature strongly influences the performance of the reaction: the optimum temperature is at about 60 °C. At lower temperatures, the reaction is too slow, at temperatures of 80 °C and higher, a series of side reactions starts to dominate and the reaction mixture turns dark brown instead of orange, which is the colour of **1**.

For safety reasons, the formation of explosive diacyl peroxide ($CH_3CO{-}O{-}O{-}COCH_3$), which is formed in the presence of highly concentrated H_2O_2 and acetic anhydride, has to be suppressed. This is best done by dropping the oxidizing agent (50% H_2O_2) and the acetic anhydride simultaneously into the solution of 2-methylnaphthalene, glacial acetic acid and the mineral acid by two dropping funnels. Additionally, the molar sum of H_2O_2 and H_2O (from 50% H_2O_2) ***must*** be higher than the molar amount of acetic anhydride added. We keep this ratio at about 2:1.

Following these ancillary conditions, isolated yields of about 80% for naphthoquinones can be obtained with regioselectivities for the desired 2-methyl-1,4-naphthoquinone (**1**) versus the isomer 6-methyl-1,4-naphthoquinone of about 7–9/1. Recrystallization from ethyl acetate/hexane yields pure **1** (for details, see Experimental Section). Leaving out the mineral acid drastically slows down the reaction rate, giving yields lower than 20%, while leaving out the anhydride has a less pronounced effect. The oxidation of 2-methylnaphthalene can also be carried out in glacial acetic acid with commercially available *meta*-chloroperbenzoic acid (*m*CPBA, 75% with H_2O) giving slightly lower yields (73% of **1**). In this protocol, no anhydride and no hydrogen peroxide were added. Leaving out the sulphuric acid in the oxidation with *m*CPBA again lowers the yields of **1**.

There are two possible mechanistic routes for the oxidative conversion of 2-methylnaphthalene to **1**. In the literature it was discussed that the oxidation of 2-methylnaphthalene by the system MTO/glacial acetic acid/85% H_2O_2 should proceed *via* a two-fold epoxidation with subsequent reorganization to 2-methyl-1,4-naphthodihydroquinone, which then should rapidly be further oxidized to **1** (Scheme 2, epoxidation pathway).[6c,g] On the other hand, the strong mineral acid will, in equilibrium, give protonated peracetic acid ($CH_3CO_3H_2^+$), an organic congener to $H_3O_2^+$ which was investigated by Olah et al. in (super)acidic media.[22] They showed that this cation is able to oxidize even benzene to a mixture of oxidized products and assumed an electrophilic substitution of the aromatic compound to occur. Corresponding to this, an electrophilic aromatic substitution of 2-methylnaphthalene by $CH_3CO_3H_2^+$ (Scheme 2, aromatic substitution pathway) could take place.[23] Here, the electron-donating methyl substituent in the 2-position of the starting material will consequently lead to a preferred attack at the more sterically hindered but more electron-rich substituted naphthalene ring, which corroborates with the observed regioselectivities.

At the moment, we cannot definitively decide which of the two mechanisms is the right one. Kotani et al. published in 1984 a protocol for the oxidation of various aliphatic and aromatic compounds, where H_2O_2 was used as the oxidizing agent in the presence of acetic anhydride and $[Fe(CH_3CN)_6]^{2+}$ in acetonitrile solution.[24] From aromatic substrates, they obtained mixtures of acylated mono-, di-, and trihydroxylated compounds as well as quinones (e.g., from naphthalene or 1,4-dimethylbenzene) in overall yields up to 50–60%. In contrast to the findings of Kotani et al., benzene and toluene are not oxidized under our conditions. However, in the beginning of the oxidation of 2-methylnaphthalene we can detect a monohydroxylated 2-methylnaphthalene by GC/MS, which is consumed during the course of the reaction. For a



Scheme 2.

final evaluation of the mechanism, a complete computational study on our oxidation system, including the regioselectiviy of the oxygen transfer and solvent effects, is going to be carried out.

In the present paper, we have shown, that activation of peracetic acid by Brønsted acids allows a high-yield oxidation of 2-methylnaphthalene to menadione in the absence of any metal catalyst. The selectivity of the two regioisomers is about 8/1 with menadione as the major compound. From the reaction conditions it may be assumed that the aromatic system undergoes an electrophilic aromatic substitution with protonated peracetic acid as the electrophile.

Experimental Section

General Remarks

Warning: Working with mixtures of acetic anhydride and hydrogen peroxide may lead to the formation of diacyl peroxide, a highly explosive compound. To keep the concentration of this compound as low as possible, it is required to add H_2O_2 and $(CH_3CO)_2O$ slowly and simultaneously by means of two dropping funnels and to calculate exactly the molar ratios in the reaction mixture.

2-Methyl-1,4-naphthoquinone (1)

2-Methylnaphthalene (7.10 g, 50.00 mmol) and 96% sulphuric acid (0.25 g, 2.45 mmol) were dissolved in 50 mL of glacial acetic acid in a 250 mL three-necked flask equipped with a magnetic stirring bar, a reflux condenser and two 50 mL dropping funnels. The mixture was heated to 60 °C. At this temperature, 20 g of 50% hydrogen peroxide (this contains 0.29 mol of H_2O_2 and 0.55 mol of H_2O; molar sum 0.84 mol) and 42.84 g (0.42 mol) of acetic anhydride were added simultaneously *via* the two dropping funnels over a period of 20 min. The reaction mixture turned black for some minutes and then orange. It was stirred for 6 h at 60 °C, then it was poured onto a mixture of 200 mL of $CHCl_3$ and 200 mL of cold water and the crude product was extracted into the organic phase. The $CHCl_3$ solution was first washed with 50 mL of a 0.1 M aqueous $NaHSO_3$ solution to remove residual H_2O_2 and then washed with 50 mL of $NaHCO_3$ solution (10% in water) to remove traces of acetic acid. It was dried over $MgSO_4$ and the solvent was removed leaving an oily residue from which a mixture of the isomeric methylnaphthoquinones crystallized; yield: 6.97 g (81%). The isomer ratio between **1** and 6-methyl-1,4-naphthoquinone was determined to be about 8/1 by integration of the resonances of the methyl groups in the ^1H NMR and by GC/MS. The regioisomers can be separated by repeated crystallization from ethyl acetate/hexane.

Acknowledgements

We would like to thank the Deutsche Forschungsgemeinchaft for support of this work.

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