Vitamin K_3 Obtaining by the Diene Synthesis Reaction in Solutions of Mo–V Phosphoric Heteropoly Acids

M. V. SIMONOVA[1,2] and E. G. ZHIZHINA[1]

[1]*Boreskov Institute of Catalysis, Boreskov Institute of Catalysis, Siberian Branch of the Russian Academy of Sciences,*
Pr. Akademika Lavrentyeva 5, Novosibirsk 630090 (Russia)

E-mail: smv@catalysis.nsk.su

[2]*Novosibirsk State University,*
Ul. Pirogova 2, Novosibirsk 630090 (Russia)

(Received October 10, 2004; in revised form February 8, 2005)

Abstract

The possibility in principle for obtaining vitamin K_3 (2-methyl-1,4-naphthoquinone) by the diene synthesis reaction from such available substrates as 2-methylphenol (*o*-cresol) and 2-methyl aniline (*o*-toluidine) has been shown. Solutions of Mo–V phosphoric heteropoly acids represent bifunctional catalysts for these processes that make it possible to conduct oxidizing and diene synthesis reactions as a one-stage process.

INTRODUCTION

Vitamin K_3 (2-methyl-1,4-naphthoquinone, menadione) is in general use in medical practice for treatment and preventive procedures against many diseases and also in animal industries to increase the efficiency of agricultural animals [1]. The basic process for industrial production of menadione is non-catalytic oxidation of 2-methylnaphthalenes by sulphochromic acid [2]. Toxicity of chrome compounds, a great amount of waste products, and a low yield of product (less than 50 %) make searching the new technologies for menadione production to be an urgent problem.

Solutions of Mo–V phosphoric heteropoly acids of composition $H_{3+x}PMo_{12-x}V_xO_{40}$ (HPA-x, where x is the number of vanadium atoms in a molecule that is equal to 3–4) are applied as selective catalysts of partial oxidation of various organic compounds by oxygen [3–6]. Reactions in the presence of HPA-x generally are performed as a two-stage process:

$$\tfrac{m}{4}H_2Su + \tfrac{m}{4}H_2O + HPA\text{-}x \rightarrow \tfrac{m}{4}SuO + H_mHPA\text{-}x \quad (1)$$

$$H_mHPA\text{-}x + \tfrac{m}{4}O_2 \rightarrow HPA\text{-}x + \tfrac{m}{2}H_2O \quad (2)$$

Overall reaction:

$$H_2Su + O_2 \xrightarrow{HPA\text{-}x} SuO + H_2O \quad (3)$$

In these processes, HPA-x plays the part of a reversible oxidizer.

In the works [7–10], HPA-x solutions (x = 4–6) are suggested as catalysts for 2-methylnaphtol-1 oxidation into vitamin K_3. Selectivity of such a reaction amounts to as much as 90 %. Application of this technology in Russia is limited by shortage in raw material*. Thus, we have made a search for alternative methods of menadione obtaining in HPA-x solutions from more feasible substrates.

In the work [11], it has been demonstrated that HPA-x solutions are capable to show multifunctional properties, as they catalyse simultaneously the diene synthesis and oxidizing reactions. Accordingly, 9,10-anthraquinone can be obtained in HPA-x solutions in the 1,3-

*Naphthol-1 to produce 2-methylnaphtol-1 is not manufactured in Russia.

ppm

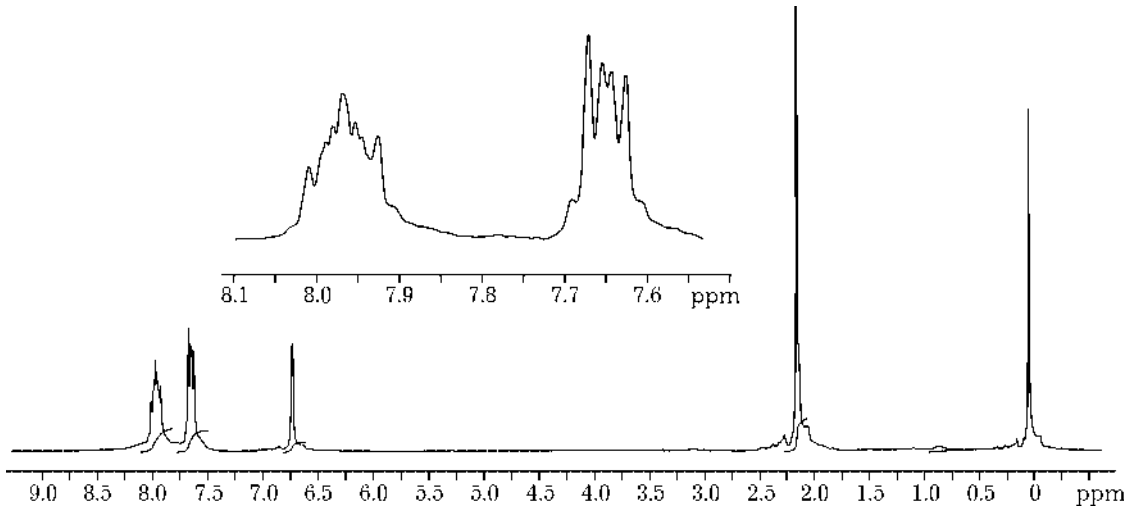


Fig. 1. H^1 NMR spectrum of isolated menadione in CCl_4.

butadiene atmosphere starting from 1,4-naphthoquinone or from hydroquinone. In this case, the oxidation processes and the Diels–Alder reaction run as a one-stage process [11].

This work demonstrates that through combining the diene synthesis reaction and oxidation in the presence of HPA-*x* solutions, menadione can be obtained by one-stage process from 2-methylphenol (*o*-cresol) or 2-methylaniline (*o*-toluidine) in the presence of 1,3-butadiene.

EXPERIMENTAL

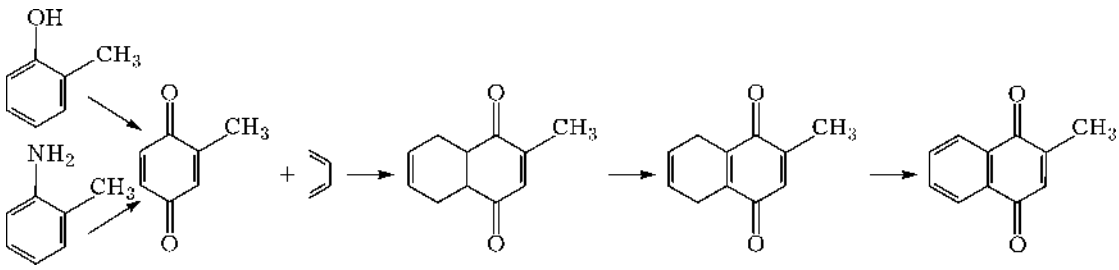
Process of menadione obtaining by the reaction (1) was conducted in a temperature-controlled glass double-necked flask (capacity of 100 ml) under stirring of a reaction mixture with magnetic stirrer in the 1,3-butadiene atmosphere. Precisely weighted sample of *o*-cresol or the calculated volume of *o*-toluidine was put in a flask with the definite quantity of 0.2 M HPA-4 solution. The flask was connected to the chamber filled with 1,3-butadiene, then it was blown through the long tube lowered to the solution surface; the second neck was closed and a reaction was conducted at a preset temperature (20–60 °C). The reaction was monitored with the GLC method (a capillary column of the SE-30 type, thermoprogramming in an interval 100–250 °C). In addition, decreasing redox potential of HPA-*x* solution was controlled at regular intervals by the procedure [12].

Reaction products were extracted with benzene or ethyl oxide, were dried from water over calcium chloride; then the solvent was distilled off and the residue was weighed. Selection of an appropriate solvent has allowed virtually quantitative extraction of reaction products from the reaction mixture (this was

TABLE 1

Vitamin K_3 obtaining from *o*-cresol and *o*-toluidine by the diene synthesis reaction in the presence of 0.2 M HPA-4 solution (1,3-butadiene atmosphere, 2 h, conversion of substrate is 100 %)

Substrate	Substrate quantity		HPA-4, ml	HPA-4/substrate	*T*, °C	Yield, %
	g	mmol		molar ratio		
o-Cresol	0.27	2.5	18.8	1.5	60	20.9
	0.27	2.5	18.8	1.5	40	16.7
	0.27	2.5	25.1	2.0	40	18.0
o-Toluidine	0.13	1.25	12.5	2.0	60	28.5
	0.13	1.25	12.5	2.0	40	24.3
	0.13	1.25	23.5	3.75	40	21.1



Scheme 1.

shown by GLC of HPA-*x* solution). Isolation of menadione was conducted by chromatography through silica gel (chloroform was the eluent); the solvent was distilled off, quantity of menadione (in grams) was determined, and a yield was calculated. Further, its H^1 NMR spectrum in CCl_4 was recorded (Fig. 1). Purification degree of the isolated product comprised no less than 98 %. The Silufol plates were also applied for menadione express-determination. The results are presented in Table 1.

It is necessary to note that with the use of *o*-toluidine as a substrate, filtering a reaction mixture from a deposit was conducted before extraction and the deposit represented the product of *o*-toluidine oxidative polymerisation.

To identify by-products of transformation of 1,3-butadiene in HPA-*x* solution, chromatomass spectrometry method was applied.

Solutions of HPA-4 were obtained by the procedure [13]; recovery of solutions was performed at 160–190 °C under oxygen pressure following the procedure [14]. Recovered solutions of HPA-4 completely recovered their initial activity, so they were recycled.

RESULTS AND DISCUSSION

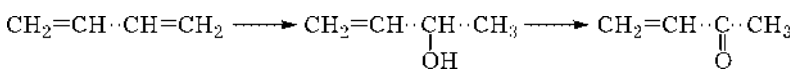
In the present work, we have made an attempt to obtain menadione from such easily available substrates as *o*-cresol and *o*-toluidine using $H_7PMo_8V_4O_{40}$ (HPA-4) solution as a multifunctional catalyst (Scheme 1).

According to this Scheme, upon adding the mentioned substrates to HPA-4 solution in the 1,3-butadiene atmosphere, their oxidation first occurs with formation of 2-methyl-1,4-benzoquinone (toluquinone), which condenses in the subsequent process with 1,3-butadiene by the Diels-Alder reaction. At the final stage, HPA-4 oxidizes the diene synthesis adducts into appropriate *para*-quinone.

Process of menadione obtaining in 0.2 M HPA-4 solution according to the schematic diagram 1 was a one-stage process. The data acquired are presented in Table 1.

It is evident that the yield of menadione when obtaining it from *o*-cresol and *o*-toluidine does not exceed 30 %. In the case of *o*-cresol that is a very reactive molecule, formation of a great quantity of the condensed by-products (resins) was observed. In the case of *o*-toluidine, a low yield is determined by the fact that formation of polytoluidine owing to oxidative polymerisation of *o*-toluidine [15] occurred at the first stage of the process coincidentally with menadione formation according to the Scheme 1. The black polymer deposit was then partially dissolved through its oxidation into 2-methyl-1,4-benzoquinone.

In addition, the possibility of side reactions of 1,3-butadiene in HPA-*x* solutions has been studied. With this end in view, a blank run has been performed, whereby 1,3-butadiene was fed into the HPA-4 solution for 5 h under conditions of no alternative substrates. Analysis of the reaction products has demonstrated that hydration of 1,3-butadiene to form 2-butene-2-ol and its further transformation into



Scheme 2.

3-butene-2-one (Scheme 2) runs with insignificant rates.

In addition, minor amounts of the linear branched oxygen-containing polymerisation products of 1,3-butadiene (molecular mass 123, 165, and 166) are produced. It has been found that the total amount of by-products from 1,3-butadiene during the diene synthesis does not exceed 2–3 %.

The process of phenol oxidative polymerization makes the basic contribution to the formation of by-products in the case of *o*-cresol. Analogous reactions of oxidative polymerisation for 2-methylnaphtol-1 have been studied in [9] where it has been demonstrated that the selectivity of catalyst on the basis of HPA-*x* with respect to menadione depends on the ratio between the rate of oxidative polymerisation of intermediate compounds and the rate of the reaction to form a target product. These ratios depend on the composition of HPA-*x* molecule, on the procedure, and conditions of carrying out the process. In work [9], it has been possible to achieve significant (from 40–50 up to 90 %) gain in yield of menadione. We believe that the process of vitamin K_3 synthesis from *o*-cresol under the Scheme 1 can also be optimised.

With the use of *o*-toluidine as a substrate, a secondary process of oxidative polymerisation gives rise to polytoluidine. It is our belief that the variation of the process conditions will allow changing the ratio of rates of target and side reactions in the direction of an increased rate of vitamin K_3 formation. Note also that polytoluidine being formed in toluidine oxidation can be separated from the reaction mixture; further it can be oxidized into 2-methyl-1,4-benzoquinone and recycled into the reaction under Scheme 1. Also important is the circumstance that polytoluidine, as well as polyaniline, represents a valuable product [16].

The way of vitamin K_3 obtaining from *o*-toluidine (as compared to *o*-cresol), in our opinion, is more promising one, since with optimising the process, it is probable that we will manage to reduce the quantity of formed polymer (polytoluidine) and to increase the yield of toluquinone and hence menadione. At present, we also investigate the alternative possible ways of increasing the yield of menadione by modification of initial substrates.

CONCLUSIONS

The possibility in principle was shown for catalytic obtaining of vitamin K_3 from such substrates as *o*-cresol and *o*-toluidine in the presence of HPA-*x* solutions, this being the one-stage process. In so doing, HPA-*x* acts as the bifunctional (acidic and oxidizing) catalyst. Despite the low (less than 30 %) yield, the new way is attractive in that the menadione synthesis occurs through application of readily available raw material, and many-stage process runs as a one-stage process. The property for recovery of HPA-*x* solutions by oxygen opens prospects for working out the effective methods to produce vitamin K_3 in the presence of HPA-*x*.

Acknowledgement

M. V. Simonova expresses her thanks to the International K. I. Zamaraev Charitable Scientific Fund for financial support of the work.

REFERENCES

1 Vitaminy, in M. I. Smirnova (Ed.), Meditsina, Moscow, 1974.
2 L. O. Shneidman, Proizvodstvo vitaminov, Pishchepromizdat, Moscow, 1973.
3 I. V. Kozhevnikov, *Chem. Rev.*, 98 (1998) 171.
4 I. V. Kozhevnikov, Catalysis by Polyoxometalates, John Wiley & Sons Ltd., Chichester, 2002.
5 I. V. Kozhevnikov, K. I. Matveev, *Appl. Catal.*, 5 (1983) 135.
6 T. Okuhara, N. Mizuno, M. Misono, *Appl. Catal. A: General,* 222 (2001) 63.
7 K. I. Matveev, V. F. Odyakov, E. G. Zhizhina, *J. Molec. Catal. A: Chemical,* 114 (1996) 151.
8 K. I. Matveev, E. G. Zhizhina, V. F. Odyakov *et al.*, *Kinetika i Kataliz,* 38 (1997) 76.
9 K. I. Matveev, E. G. Zhizhina, V. F. Odyakov, V. N. Parmon, *Izv. RAN. Ser. Khim.*, 7 (1994) 1208.
10 Pat. 2162837 RF, 2001.
11 E. G. Zhizhina, K. I. Matveev, V. V. Russkikh, *Chem. Sust. Dev.*, 1 (2004) 47.
12 V. F. Odyakov, E. G. Zhizhina, K. I. Matveev, *Zh. Neorg. Khim.*, 45 (2000) 1379.
13 V. F. Odyakov, E. G. Zhizhina, R. I. Maksimivskaya, K. I. Matveev, *Kinetika i Kataliz,* 36 (1995) 795.
14 E. G. Zhizhina, M. V. Simonova, V. F. Odyakov, K. I. Matveev, *Chem. Sust. Dev.*, 6 (2004) 683.
15 E. G. Zhizhina, M. V. Simonova, V. V. Russkikh, K. I. Matveev, *Zh. Prikl. Khim.*, 78 (2005) 772.
16 E. M. Geniиs, M. Lapkowski, C. Tsintavis, *New J. Chem.*, 12 (1988) 181.