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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Optimization of Conditions for Preparing Vitamin K_3 by Oxidation of 2-Methylnaphthalene with Chromium Trioxide in Acid Solutions

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Abstract—Optimal conditions were found for oxidation of 2-methylnaphthalene to 2-methyl-1,4-naphthoquinone with chromium trioxide in sulfuric and acetic acids. The following factors were varied: degree of acid dilution with water, substrate to oxidant weight ratio, and reaction temperature and time. The influence of the rate of reactant mixing and of the reaction temperature on the reaction course was evaluated.

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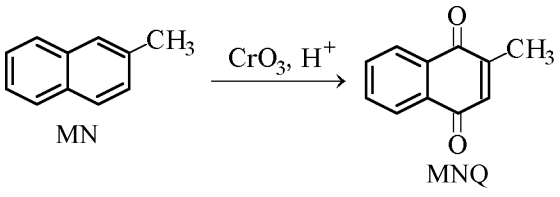
Vitamin K_3 (2-methyl-1,4-naphthoquinone, menadione, MNQ) belongs to the fat-soluble vitamins of group K. It is widely used in medicine and animal and especially poultry husbandry as an agent for improving blood coagulation [1]. Its relatively high activity against various tumor cells was revealed [2]. The water-soluble form of vitamin K_3 is Vicasol (sodium 2,3-dihydro-2-methyl-1,4-naphthoquinone-2-sulfonate).

The most widely used procedure for commercial production of MNQ is oxidation of by-product coke 2-methylnaphthalene (MN) in sulfuric or acetic acid with chromium(VI) compounds [3–5]:



An advantage of this procedure that Cr(III) compounds formed in the process are starting compounds for preparing commercial products, leather and fur hardeners. However, under the conditions ensuring high quality of the vitamin and hardener, the reaction yield with respect to the vitamin does not exceed 50–60% because of the concomitant oxidation processes.

This process is not described in detail in the available literature. The effect of temperature, degree of acid dilution with water, substrate to oxidant weight ratio, and other process parameters on the reaction kinetics have not been reported. Only oxidation of 2-methylnaphthalene with hydrogen peroxide in acetic acid was studied in detail [6]. By varying various process parameters, conditions ensuring the maximal yield of vitamin K_3 were found. In view of the fact that vitamin K_3 is demanded but is not produced in Russia, studies aimed to improve its production procedures suitable for commercial implementation are quite topical.

We optimized the conditions for 2-methylnaphthalene oxidation to MNQ with chromium trioxide in acetic and sulfuric acids. As optimization parameters we chose the yield of vitamin K_3 and the conversion of 2-methylnaphthalene. As factors affecting the optimization parameters we chose the degree of acid dilution with water, the oxidant to substrate weight ratio, and the reaction temperature.

The reaction progress was monitored by the kinetic curves. By so doing, we automatically determined the fourth factor, reaction time. The experimental design showed that the full factorial experiment in which all the possible combinations of factor values are tested is impossible because of enormous number of experiments. In this model, the number of experiments $N = k^p$ (k is the

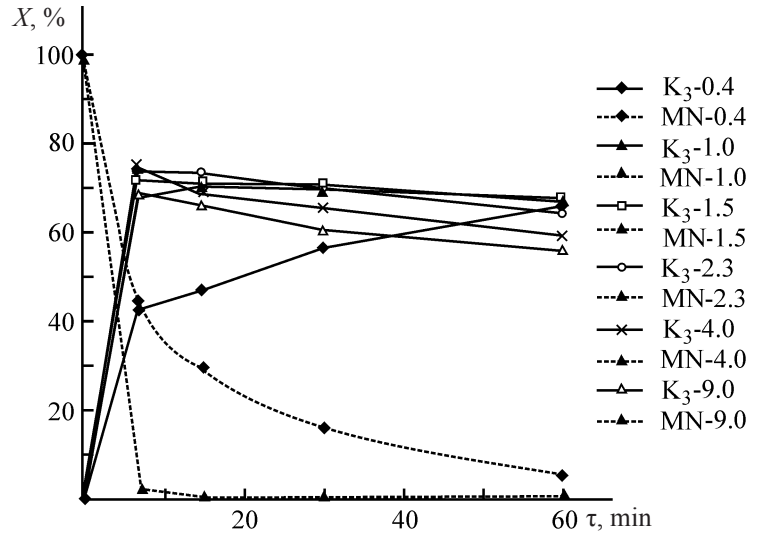


Fig. 1. Influence of the volume ratio of CH_3COOH to H_2O on oxidation of 2-methylnaphthalene in acetic acid. 80°C; CrO_3 to MN weight ratio 3.6. (*X*) Yield of K_3 or unchanged MN; (τ) time; the same for Figs. 2–6. The acid to water volume ratios are separated by hyphen from substance designations; the same for Fig. 2.

number of values of a given factor, and p, the number of factors) would be 64 (4^3) for one acid. Furthermore, each experiment would involve taking a reaction isotherm [7]. Therefore, we chose a model in which one factor is varied and the other two factors are fixed. After that, the varied factor is fixed at is optimal value, and the other factor is varied, and so on. Thus, the number of experiments is reduced to 10–12.

EXPERIMENTAL

2-Methylnaphthalene, 2-methyl-1,4-naphthoquinone, chromium trioxide, and biphenyl were of analytically pure grade. Acetic acid, sulfuric acid, and chloroform were of chemically pure grade. The amounts of MNQ and unchanged MN were determined with a Kristall-5000.2 gas chromatograph equipped with a flame ionization detector. The stationary phase was SE-30 (5%), and the column temperature, 180°C. The carrier gas was helium. Biphenyl was used as internal reference.

A weighed portion of 2-methylnaphthalene was placed in a reactor equipped with a power-driven stirrer, a reflux condenser, and a temperature-control device. 2-Methylnaphthalene was heated to the required temperature, after which the oxidizing mixture (chromium trioxide, water, and acid) was added, and the mixture was vigorously stirred for a definite time. Then a threefold excess of water was added, and the reaction products were extracted with chloroform. The solvent was evaporated to dryness at room temperature, a weighed portion of the internal reference (biphenyl) was added, and the mixture was dissolved in acetone and analyzed on a gas chromatograph.

The kinetic curves were constructed by stopping the process. Monitoring the reaction by kinetic curves was chosen because of convenience of comparing them with each other and of the dependence of the product yield and MN conversion on time.

The degree of acid dilution with water strongly affects the reaction progress. Acid deficiency leads to decreased reaction rate and low 2-methylnaphthalene conversion. Acid excess decreases the solubility of chromium trioxide, enhances further oxidation of MNQ, and leads to excessive acid consumption.

The reactor was charged with 0.413 g of MN and heated to 80°C. Then the oxidizing mixture consisting of 1.5 g of CrO_3 and various volumes of acetic acid and water was added with vigorous stirring, and the mixture was kept at the same temperature for a definite time. The total volume of acetic acid and water was 10 ml, and their ratio was 0.4, 1.0, 1.5, 2.3, 4.0, and 9.0 (Fig. 1).

Our results show that the optimal volume ratio of acetic acid and water is in the range 1–2.3. As seen from the kinetic curves, the reaction is complete in 10 min, with the degree of 2-methylnaphthalene conversion being 100%.

To evaluate the influence of the volume ratio of water and sulfuric acid on the oxidation, the reactor was

Conditions of reactant mixing at various rates of addition of the oxidizing mixture to molten 2-methylnaphthalene

Run no.	Composition of oxiding mixture per gram of MN	Temperature at which the oxidant was added, °C	Time of oxidant addition, min	Temperature of keeping the reaction mixture, °C	Time of keeping the reaction mixture, min	Residual MN, %	Yield of K_3, %
1	17 ml of CH_3COOH 7 ml of H_2O 3.65 g of CrO_3	40	5	70	5	–	62.5
2	"	70	10	–	–	–	60.8
3	"	70	30	–	–	0.3	54.3
4	5 ml of H_2SO_4 19 ml of H_2O 3,65 g of CrO_3	40	6	80	30	–	45.9
5	"	40	12	80	30	0.8	55.3
6	"	80	30	–	–	0.3	56.6
7	"	80	60	–	–	0.2	43.6

charged with 0.413 g of MN and heated to 80°C. Then the oxidizing mixture consisting of 1.2 g of CrO_3 and various volumes of sulfuric acid and water was added with vigorous stirring, and the mixture was kept at the same temperature for a definite time. The total volume of sulfuric acid and water was 10 ml, and their ratio was 0.11, 0.25, 0.43, and 0.67 (Fig. 2).

The optimal volume ratio of sulfuric acid and water is 0.25. As seen from the kinetic curves, the reaction is complete in 30 min, with the conversion of 2-methylnaphthalene reaching 95–98%. At higher volume ratios of sulfuric acid and water, noticeable amounts of tars (up to 20%) appear in the reaction product. Therefore, even at a good yield of vitamin K_3, the need for the product purification makes high sulfuric acid concentrations undesirable.

After determining the optimal degree of dilution of acids with water, we determined the oxidant to 2-methylnaphthalene weight ratio at which the substrate conversion would approach 100% and the yield of vitamin K_3 would be maximal. It should be noted that this is a very

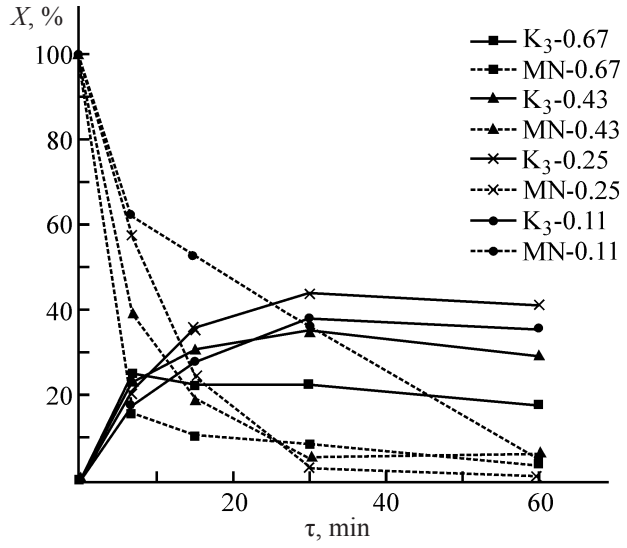


Fig. 2. Influence of the volume ratio of H_2SO_4 to H_2O on oxidation of 2-methylnaphthalene in sulfuric acid. 80°C; CrO_3 to MN weight ratio 2.9.

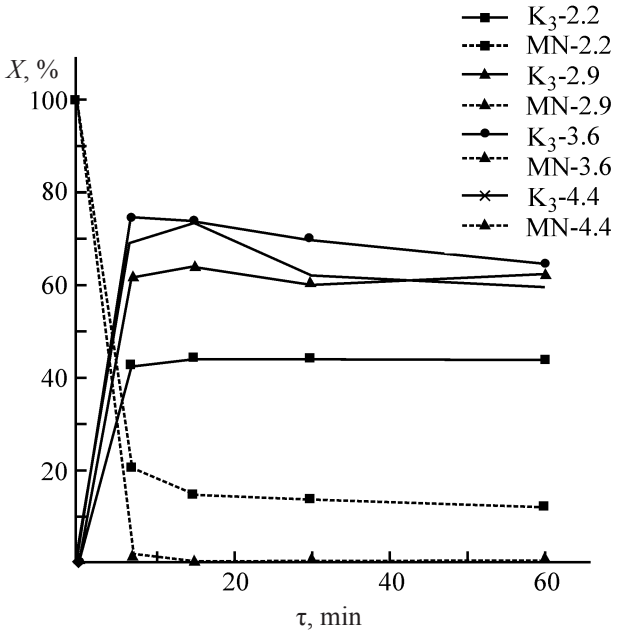


Fig. 3. Influence of the weight ratio of CrO_3 to MN on oxidation of 2-methylnaphthalene in acetic acid. 80°C; CH_3COOH to H_2O volume ratio 2.3. The CrO_3 to MN weight ratios are separated by hyphen from substance designations; the same for Fig. 4.

significant parameter, because the oxidant deficiency leads to incomplete conversion of the substrate, and its excess, to further oxidation of MNQ, excessive consumption of the oxidant, and presence of residual Cr(VI) which should be reduced to avoid its discharge to wastes.

The reactor was charged with 0.413 g of MN and heated to 80°C. Then the oxidizing mixture consisting of 7 ml of acetic acid, 3 ml of water, and a definite amount of CrO_3 (0.9, 1.2, 1.5, or 1.8 g) was added with vigorous stirring. After that the mixture was kept at the same temperature for the required time (Fig. 3).

Our results show that the optimal weight ratio of CrO_3 to MN is 3.6.

To evaluate the influence of the CrO_3 to 2-methylnaphthalene weight ratio on oxidation of MN in sulfuric acid, the reactor was charged with 0.413 g of MN and heated to 80°C. Then the oxidizing mixture consisting of 2 ml of sulfuric acid, 8 ml of water, and a definite amount of CrO_3 (0.9, 1.2, 1.5, or 1.8 g) was added with vigorous stirring. After that the mixture was kept at the same temperature for the required time (Fig. 4).

The kinetic curves show that the optimal weight ratio of CrO_3 to MN is the same as in the reaction in acetic acid: 3.6.

After having determined the optimal values of the acid to water volume ratio and oxidant to substrate weight ratio, we examined the influence of temperature on the reaction. It is common knowledge that increasing temperature considerably accelerates chemical reactions, but heating large volumes of liquids to high temperatures involves large power consumption. Therefore, the temperature is an important parameter in feasibility studies of commercial processes.

The reactor was charged with 0.413 g of MN and heated to the required temperature (50, 60, 70, or 80°C). Then the oxidizing mixture consisting of 7 ml of acetic acid, 3 ml of water, and 1.5 g of CrO_3 was added with vigorous stirring. The reaction mixture was kept at the same temperature for a definite time (Fig. 5).

Our results show that the reaction is fairly fast at all the tested temperature, with the substrate conversion reaching almost 100% in all the cases. However, at 80°C the product yield is the highest.

When examining the influence of temperature on the MN oxidation in sulfuric acid, the reactor was charged with 0.413 g of MN and heated to the required temperature (50, 60, 70, or 80°C). Then the oxidizing mixture consisting of 2 ml of acetic acid, 8 ml of water, and 1.5 g of CrO_3 was added with vigorous stirring. The reaction mixture was kept at the same temperature for a definite time (Fig. 6).

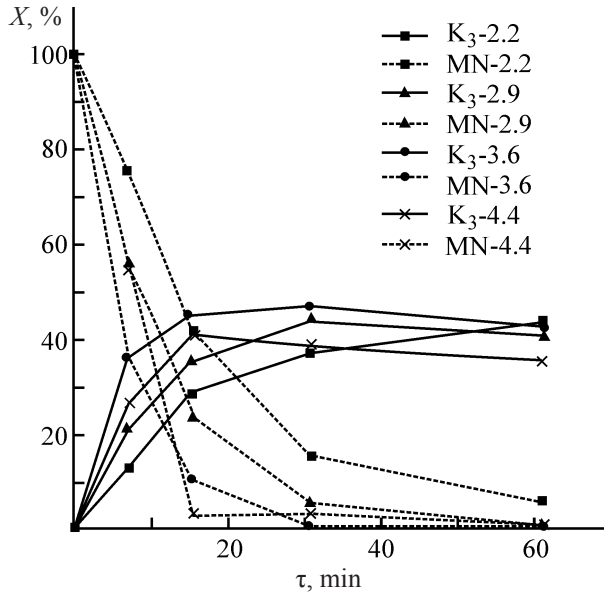


Fig. 4. Influence of the weight ratio of CrO_3 to MN on oxidation of 2-methylnaphthalene in sulfuric acid. 80°C; H_2SO_4 to H_2O volume ratio 0.25.

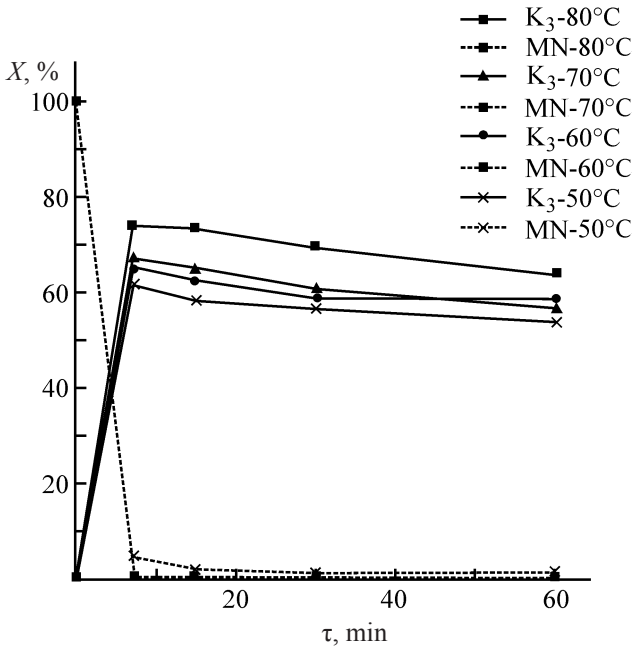


Fig. 5. Influence of temperature on oxidation of 2-methylnaphthalene in acetic acid. CH_3COOH to H_2O volume ratio 2.3, CrO_3 to MN weight ratio 3.6. The temperatures are separated by hyphen from substance designations; the same for Fig. 6.

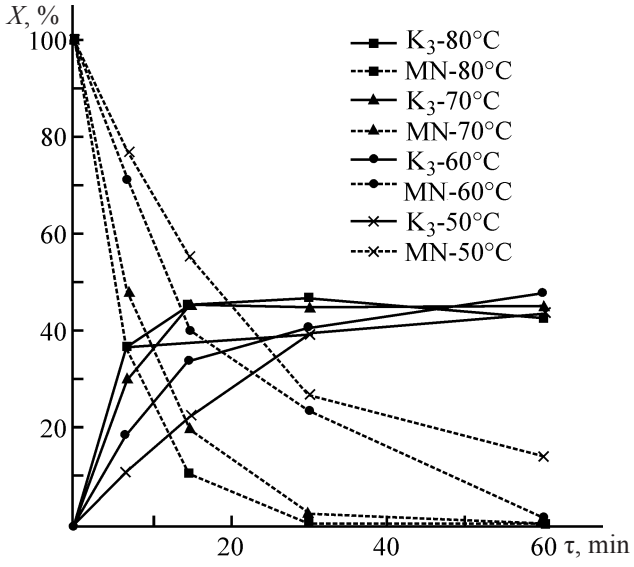


Fig. 6. Influence of temperature on oxidation of 2-methylnaphthalene in sulfuric acid. H_2SO_4 to H_2O volume ratio 0.25, CrO_3 to MN weight ratio 3.6.

Our results show that the reaction rate strongly depends on the temperature. The preferable temperatures are 70 and 80°C, at which the product yield is the highest and virtually equal. The MN is fully oxidized in 30 min.

Along with finding optimal reaction conditions to increase the yield of vitamin K_3, we tested various modes of reactant mixing. The first procedure consisted in slow addition of the oxidizing mixture to MN preheated to 40°C. In the course of adding the oxidant, the temperature in the reactor remained on the same level. Then the mixture was heated to 70–80°C and kept at this temperature for a definite time. The second procedure consisted in slow addition of the oxidizing mixture to MN heated to 70–80°C. Immediately after the oxidant, the mixture was diluted with water and extracted with chloroform. The results are given in the table.

This order of mixing the reactants is appropriate because vitamin K_3 formed in the reaction continues to be oxidized with the formation of tars. Therefore, excess oxidant decreases the yield of the desired reaction product. If the reaction is performed under the conditions when the oxidant is always in deficiency, the side process of vitamin K_3 oxidation can be reduced to a minimum and the yield of the desired product can be increased. In run nos. 5 and 6 (see table), the yield of vitamin K_3 was 55–56%, i.e., 6–8% higher than in addition of the whole amount of the oxidant to MN in one portion.

CONCLUSIONS

(1) The optimal conditions for oxidation of 2-methylnaphthalene with chromium trioxide in acid solutions are as follows: acid to water volume ratio (1–2.3) : 1 for acetic acid and 0.25 : 1 for sulfuric acid; CrO_3 to 2-methylnaphthalene weight ratio 3.6 : 1 for both acids; 70–80°C.

(2) Slow addition of the oxidant to the substrate in sulfuric acid allows the product yield to be increased by 6–8%.

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