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2,3,5-TRIMETHYL-4-NITROSOPHENOL SYNTHESIS

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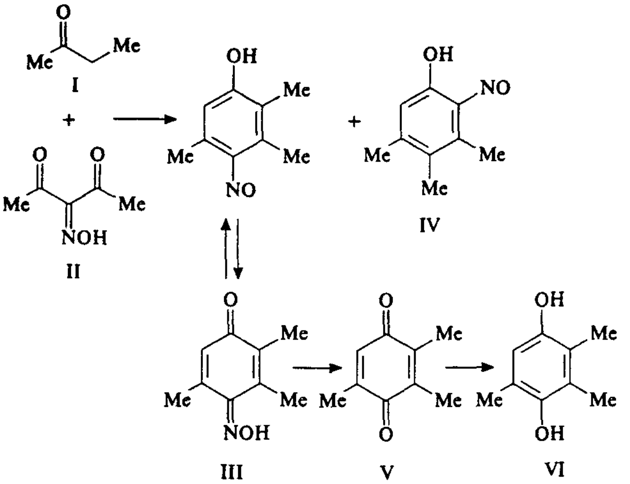
In view of the great significance of vitamin E in medicine and agriculture, several reviews [1 – 3] have been published in the past decade on the methods of synthesizing vitamin E and its key intermediate – trimethylhydroquinone (VI). However, there is one more method for the synthesis of compound VI, which was not considered in the papers cited. This method consists in the cyclocondensation of methyl ethyl ketone (I) from isonitrosoacetyl acetone (II) with the formation of 2,3,5-trimethyl-4-nitrosophenol (III), followed by hydrolysis (to trimethylbenzoquinone) and reduction [4 – 6]:



A key stage in the synthesis of compound VI is the cyclocondensation of compounds II and I. The subsequent stages of hydrolysis and reduction proceed readily with good yields (95 % [7] and 100 % [8]). Recently, a single-stage process was suggested for directly converting spatially constrained nitrosophenols into the corresponding hydroquinones [9].

Belyaev and Gidaspov [10] revealed several laws governing the cyclocondensation of isonitroso-β-dicarbonyl compounds. Previously, a condensating agent for this reaction was selected from alcoholates and hydroxides of alkali metals [4, 11 – 14]. It was demonstrated that the process may lead to the formation of both compound III and 2,3,5-trimethyl-2-nitrosophenol (IV), the isomer ratio depending on the solvent character and metal cation type [14]. In particular, using aprotic solvents of medium polarity (such as DMSO) and lithium hydroxides favors an increase in the proportion of compound III. At the same time, compound III is not at all formed in water (a strongly polar protonated solvent). The solvent effect is apparently related to differences in the course of selective solvation activating the reagent [14].

Because compound III is an intermediate product in the synthesis under consideration, we have attempted to improve and optimize the conditions for cyclocondensation of compounds I and II. The yield of III depends on the degree of comminution of the initial base [4]. However, the grinding of solid bases in a dry atmosphere protected from CO_2 is a task that is difficult to solve under commercial process conditions. We have suggested that the solid NaOH–DMSO system can be replaced by a 50% aqueous NaOH–DMSO system. Concentrated aqueous alkali solutions possess high drying capacity and water is virtually absent in the organic phase, while the solubility of organic compounds in concentrated alkali solutions is low. Moreover, the proton affinity of free hydroxyl ions in these solutions is almost the same as that in solid alkalis [15].

Indeed, it was established that the use of a 50% aqueous NaOH with DMSO as the condensation agent leads to the formation of compound III, the yield depending on the reaction time and temperature, the II–I–NaOH molar ratio, the amount of DMSO, and the rate of reaction mass stirring. A significant factor affecting the product yield is the molar ratio II / NaOH. Note that, for the reaction conducted in the presence of solid NaOH, the yield of III increases with the amount of alkali; the process in a 50% aqueous sodium hydroxide shows a reverse trend. As the reaction temperature increased to 28°C, the yield of compound III increased; however, the further increase in the temperature was accompanied by a sharp drop in the yield (to virtually zero). For this reason, the process conditions were optimized at a temperature definitely below that at which the yield of III began to decrease. It was found that reaction in a 50% aqueous NaOH at 24°C (molar ratio II / I / NaOH = 1 : 1.61 : 2) ceased after 5 h.

Adding an interphase transfer catalyst (tetrabutyl ammonium bromide, 10 wt.%) leads to a 10% decrease in the yield (for both solid NaOH and its 50% aqueous solution), which is

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TABLE 1. Optimization of the Synthesis of Compound III

No.	x_1	x_2	x_3	Yield, %		y_{iav}	$\frac{\sum(y_{ij}-y_{av})^2}{2}$	x_1y_{iav}	x_2y_{iav}	x_3y_{iav}
				y_{i1}	y_{i2}					
1	–	–	–	50.59	52.64	51.62	1.0507	–51.62	–51.62	–51.62
2	+	–	–	49.12	49.32	49.22	0.01	49.22	–49.22	–49.22
3	–	+	–	54.31	56.16	55.24	0.8557	–55.24	55.24	–55.24
4	+	+	–	48.83	50.69	49.76	0.8449	49.76	49.76	–49.76
5	–	–	+	54.40	53.23	53.82	0.3423	–53.82	–53.82	53.82
6	+	–	+	50.20	50.10	50.15	0.0025	50.15	–50.15	50.15
7	–	+	+	54.89	56.26	55.58	0.4693	–55.58	55.58	55.58
8	+	+	+	52.06	51.37	51.71	0.1191	51.71	51.71	51.71

TABLE 2. Steepest Ascent Procedure

No.	50% NaOH, ml	*I*, ml	DMSO, ml	Yield, %
1	0.264	0.410	1.430	50.88
2	0.253	0.415	1.441	52.70
3	0.243	0.420	1.453	54.40
4	0.232	0.425	1.464	55.77
5	0.222	0.430	1.475	53.23

TABLE 3. Levels of Factor Variation

Factor	Base level	Variation step
50% Aqueous NaOH, mmole	5	0.625
Compound I, mmole	4.58	0.31
DMSO, ml	1.43	0.2

Note. Compound II (0.16 g; 1.24 mmole); reaction time, 5 h; reaction temperature, 24°C.

probably explained by a change in the mechanism of aldole condensation [15].

The search for optimum conditions by variation of the different factors affecting the yield (y) is a rather difficult task. For this reason, we have used the steepest ascent procedure (the Box – Wilson method) [16] taking into account three factors affecting the y value, namely, the amounts of a 50% NaOH solution (x_1), compound I (x_2), and DMSO (x_3). The rate of the reaction mass stirring was selected so as to ensure that the further increase in the rate of reagent mixing led to no growth in the product yield. Using the data of Table 1, we have derived a linear regression equation for the reaction of compounds I and II:

$$y = 52.14 - 1.93x_1 + 0.94x_2 + 0.68x_3. \qquad (1)$$

It was found that all coefficients entering into this equation are significant. Upon checking the adequacy of equation (1), we have calculated new steps for all factors and performed the ascent procedure in the direction of the gradient. As is seen from Table 2, a nearly optimum region was achieved on the fourth step of regression. The yield of the target product increased by 5%. A more than two-fold excess of NaOH is related to the fact that the alkali is consumed not only for the ionization of compound II, but for the formation of the target products salt as well.

Thus, we have established that the cyclocondensation of compounds I and II can be conducted using a 50% aqueous solution of NaOH in DMSO, and found optimum conditions for the reaction studied.

EXPERIMENTAL CHEMICAL PART

The UV spectra of the synthesized compounds were recorded on a KFK-3 spectrophotometer using 1-cm sample cells.

Compounds I (0.16 g, 1.24 mmole), II, NaOH (solid or a 50% aqueous solution), and a catalyst (if necessary) were charged into a flat-bottom cone-shaped flask and intensively stirred with a magnetic stirrer. Upon termination of the process, the reaction mass was quantitatively transferred into a 100-ml measuring flask. The flask was filled with distilled water to mark, after which an 0.125 ml aliquot was taken and placed into a 25-ml measuring flask. The flask was filled with 0.1 N NaOH to mark, and the yield of compound III was determined by spectrophotometry (0.1 N NaOH; $\lambda = 390$ nm; $\varepsilon = 116\,490$).

Complete factor experiment. Compound II (1.24 mole), a 50% aqueous NaOH solution, compound I, and DMSO were mixed in a cone-shaped flask according to the scheme presented in Tables 2 and 3. The reaction mixture was stirred for 5 h with a magnetic stirrer. The yield of compound III was determined spectrophotometrically as described above.

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