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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Nitration of Phenol in 1,4-Dioxane

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Abstract—The nitration of phenol with excess nitric acid in aqueous dioxane, in contrast to the nitration in aqueous ethanol, yields exclusively 2,4-dintrophenol, whereas at equimolar ratio of phenol and nitric acid the major reaction products are mononitrophenols (99%), among which the *p*-isomer prevails.

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2,4-Dinitrophenol (DNP) is an important product of organic synthesis, a synthetic precursor of various organic compounds, including sulfurous dyes [1], herbicides, pesticides, and fungicides [2]. DNP inhibits the metal corrosion [3] and styrene polymerization [4]; antiseptic properties of DNP are used in preparing formulations for wood impregnation [5]; DNP stimulates the plant growth, influences the oxidative phosphorylation in cells [6], and exhibits catalytic properties [7].

Numerous nitration procedures have been developed for the DNP synthesis: nitration with the classical nitrating mixture, with liquid N_2O_4, oxidative nitration of benzene with nitric acid or with air in the presence of mercury(II) hydroxide and a small amount of nitrite. Nitrosophenol and 2,4-dinitrochlorobenzene can also be used as starting compounds for preparing DNP. A procedure using sodium nitrite, oxalic acid, and wet silicon dioxide has been developed for preparing mono- and dinitrophenol; the reaction is performed in methylene chloride [8]. From nitropropanedial hydrate and 1-nitro-2-propanol, DNP is synthesized in alkaline medium at room temperature within 18 h [9].

1,4-Dioxane is a specific and versatile solvent widely used in chemistry and biochemistry [10–18]. It was interesting to study the nitration of phenol with nitric acid in 1,4-dioxane.

EXPERIMENTAL

The following chemicals were used in the study: freshly distilled phenol (boiling point 182°C), 63% nitric acid (chemically pure grade), 1,4-dioxane (chemically pure grade), and ethanol (rectified, 96%).

To perform the phenol nitration, a 50-mL glass flask equipped with a reflux condenser was charged with 1 g of phenol and with the required volume of the reagent, which was prepared by mixing the required volume of concentrated nitric acid with 20 mL of 1,4-dioxane or ethanol. The volumes of nitric acid were 0.8, 1.2, and 5 mL, which corresponds to the phenol : nitric acid molar ratio of 1 : 1, 1 : 1.5, and 1 : 6.2, respectively.

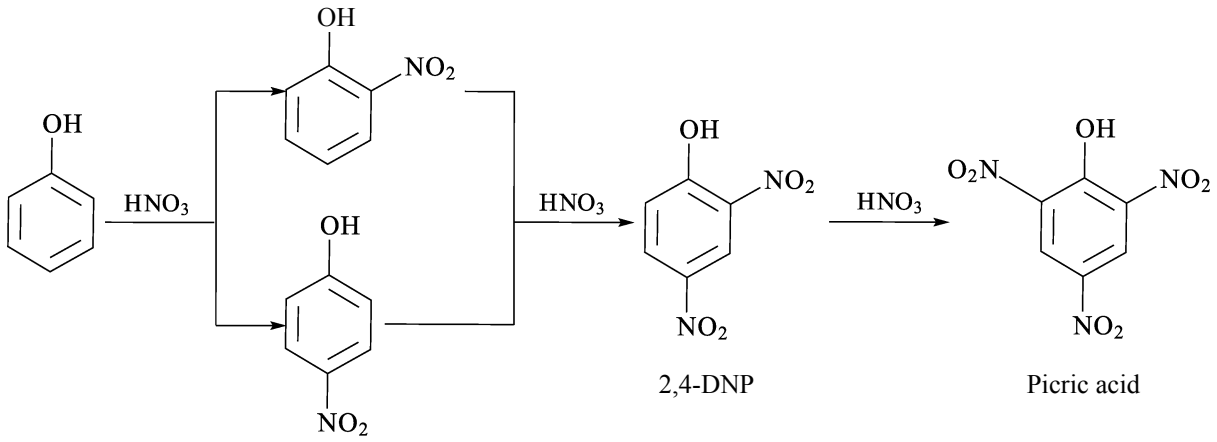
To determine the reaction mixture composition, 2-mL samples of the liquid were taken 10, 20, 30, and 60 min after the start of the reaction. The samples were quickly cooled in an ice bath, after which 10 mL of water and 2 mL of chloroform were added. The resulting mixture was thoroughly shaken, and the lower layer was taken after the phase separation. The extract was filtered through a membrane filter with the pore diameter of 0.2 μm and was injected into a chromatographic column without further pretreatment.

Analysis by chromatography–mass spectrometry was performed with an LCMS-8030 HPLC/MS–MS system (Shimadzu, Japan) equipped with two LC-30

pump, a DGU-5A degasser, an SIL-30 autosampler, an STO-20A column thermostat, an SPD-M20A diode-array spectrophotometric detector, and a tandem mass-spectrometric detector. Chromatographic separation was performed by reversed-phase HPLC on a TitanC18 column, 100 × 2.1 mm, 1.9 μm (Supelco, the United States). A 40% solution of acetonitrile in 0.5% aqueous formic acid was used as mobile phase. The flow rate was 0.4 mL min^{-1}. The injected sample volume was 1 μL. The electronic absorption spectra were recorded continuously in the range 200–500 nm. The mass spectra were recorded in the electrospray ionization mode with the capillary voltage of 4.5 kV. The following compounds were used as references for identification of the reaction mixture components: phenol, *p*-nitrophenol, *o*-nitrophenol, 2,4-dinitrophenol, and picric acid.

RESULTS AND DISCUSSION

Synthesis of 2,4-dinitrophenol from phenol is a stepwise process. In accordance with the orienting effect of substituents, it can be presented by the following scheme:



The mononitrophenols formed in the first step undergo further nitration with excess nitric acid to form 2,4-dinitrophenol. In the second nitration step, *o*-nitrophenol might transform not only into 2,4-, but also into 2,6-dinitrophenol. At a large excess of nitric acid, the formation of picric acid might be possible. However, in all the experiments performed, neither 2,6-dinitrophenol nor picric acid were detected.

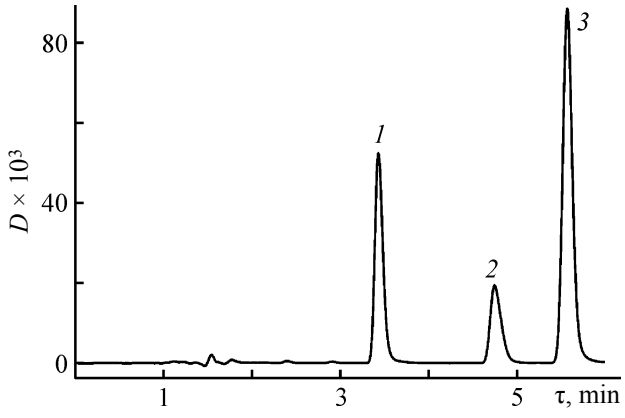


Fig. 1. Chromatogram of the products of phenol nitration with nitric acid in aqueous alcohol. Reaction time 30 min, molar ratio of nitric acid and phenol 6.2; the same for Fig. 2. (*D*) Optical density and (τ) time; the same for Fig. 2. (*1*) *p*-NP, (*2*) DNP, and (*3*) *o*-NP.

The phenol nitration was performed at three temperatures: 60, 70, and 80°C. Chromatographic analysis showed that the nitration product consisted of 2,4-DNP and *o*- and *p*-nitrophenols (*o*-NP, *p*-NP), with 2,4-DNP prevailing; the retention times of these compounds are 4.73, 5.54, and 3.42 min, respectively. In the mass spectrum, *m*/*z* for the most intense ions $[M - H]^-$ is 183.138 Da. In addition, the results are confirmed by data of electronic spectroscopy (the absorption in the UV and visible ranges corresponds to the spectra of the pure samples and to the spectra from the NIST electronic database, http://webbook.nist.gov/chemistry/). The absorption maxima were observed at the following wavelengths (nm); for phenol, 271; for *o*-nitrophenol, 276 and 351; for *p*-nitrophenol, 316; for 2,4-dinitrophenol, 258; and for *p*-nitrosophenol, 245.

The examples of the chromatograms are shown in Figs. 1 and 2. Peak *1* (Fig. 2) was identified on the basis of the mass spectrum as the peak of *p*-nitrosophenol. In the MS^1 spectrum, there is an ion with *m*/*z* 122 Da, corresponding to the $[M - H]^-$ ion. In the MS^2 spectrum of the deprotonated molecule, obtained at the collision

energy of 25 eV, there is the only fragment ion with *m*/*z* 92 Da, formed by elimination of the nitroso group from the parent ion ($\Delta m/z$ = 30 Da). The presence of small amounts of *p*-nitrosophenol suggests that the phenol nitration can involve not only electrophilic nitration, but also nitrosation with the initial formation of *p*-nitrosophenol, which is subsequently oxidized to *p*-nitrophenol.

Nitration of phenol with nitric acid in aqueous ethanol. To obtain comparable results, the nitration of phenol with nitric acid in the presence of ethanol was performed at 80°C. The results of determining the reaction mixture composition from the ratios of the areas of the chromatographic peaks at a wavelength of 280 nm for phenol nitration with nitric acid (Table 1) shows that phenol is completely consumed in the first 10 min of the reaction, and the main reaction products are *o*- and *p*-nitrophenols, and also 2,4-dinitrophenol. The total content of these derivatives in the reaction products was more than 99.5%. The ratio of the *o*- and *p*-isomers after the 10-min reaction was close to 2 : 1, which corresponds to the ratio of the amounts of the sites accessible to nitration in the *o*- and *p*-positions of the phenol molecule. Then, the ratio of the mononitrophenol isomers changes with time. *o*-Nitrophenol is consumed faster, and its content in the reaction products decreases from 57.4 to 22%, whereas the content of *p*-nitrophenol decreases from 29.1 to 24.4%.

Nitration of phenol with nitric acid in aqueous dioxane. The phenol nitration in aqueous dioxane appeared to be very efficient and considerably faster than in aqueous ethanol. Up to five different reaction products were detected by HPLC. With dioxane as solvent, similarly to the reaction in ethanol, phenol is completely consumed within 10 min, but the content of 2,4-dinitrophenol in the reaction products is as high as 87.5%, whereas the content of mononitrophenols does not exceed 10%. In the subsequent process, p-nitrophenol fully disappears, and the content of the *o*-nitrophenol impurity decreases from 8.3 to 0.8%.

The influence of the ratio of nitric acid and phenol in nitration in aqueous dioxane is shown in Table 2. With equimolar amounts of nitric acid and phenol, the major products are mononitrophenols, with less than 1% content of 2,4-dinitrophenol. As expected, *o*- and *p*-nitrophenols are the major products, but their ratio in the reaction mixture, in contrast to the results

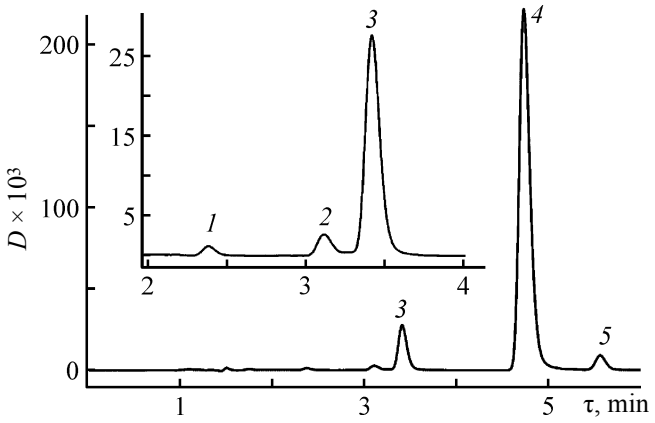


Fig. 2. Chromatogram of the products of phenol nitration with nitric acid in aqueous dioxane. (*1*) *p*-Nitrosophenol, (*2*) phenol, (*3*) *p*-NP, (*4*) DNP, and (*5*) *o*-NP.

obtained with ethanol, is close to 1 : 2 instead of the expected 2 : 1. This may be due to strong solvating action of dioxane molecules. Solvation occurs with the participation of phenol hydroxy groups. The solvates shield the *o*-positions in the phenol molecule. As the nitric acid amount was increased to 1.5 mol per mole of phenol, the content of 2,4-DNP regularly increased (to 19%). The content of p-nitrophenol did not noticeably change with time, whereas *o*-nitrophenol was consumed. In both cases, phenol was consumed in the first 10 min of the reaction.

Thus, in phenol nitration in aqueous dioxane at equimolar ratio of nitric acid and phenol, the major reaction products are mononitrophenols, among which p-nitrophenol prevailed. With excess nitric acid, 2,4-dinitrophenol is formed exclusively. Nitration of phenol in aqueous dioxane occurs considerably faster than in aqueous ethanol.

Table 1. Variation of the reaction mixture composition with time in the course of phenol nitration with nitric acid in aqueous ethanol

τ, min	Component content in reaction products, %		
	p-NP	DNP	*o*-NP
10	28.1	14.1	57.4
20	29.1	25.2	45.6
30	25.5	32.5	41.9
60	24.4	53.4	22.0

Table 2. Composition of the products of phenol nitration with nitric acid in aqueous dioxane in relation to the reactant ratio

Reaction conditions			Content in reaction products, %		
T, °C	HNO_3/phenol molar ratio	τ, min	*p*-NP	DNP	*o*-NP
80	1	10	59.0	0.6	34.7
80	1	20	58.2	0.4	36.7
80	1	30	46.6	0.3	50.1
80	1	60	49.7	0.4	47.3
80	1.5	10	52.3	7.7	39.2
80	1.5	20	62.4	8.7	28.2
80	1.5	30	55.2	12.4	31.8
80	1.5	60	50.7	19.6	29.2
60	6.2	10	44.3	18.0	36.7
60	6.2	20	39.7	31.3	27.7
60	6.2	30	34.4	42.6	21.7
60	6.2	60	29.0	58.2	11.3
70	6.2	10	33.6	47.0	18.1
70	6.2	20	24.8	64.7	9.0
70	6.2	30	17.6	76.1	4.4
70	6.2	60	8.9	87.5	1.4
80	6.2	10	8.3	87.5	3.2
80	6.2	20	5.4	92.4	0.5
80	6.2	30	2.6	95.5	–
80	6.2	60	0.8	96.1	–

CONCLUSIONS

The use of dioxane as solvent in phenol nitration allows directional synthesis of 2,4-dinitrophenol and can favor the development of a highly efficient process for 2,4-dinitrophenol production.

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