Optimization of Phenol ortho-Alkylation with Styrene

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Abstract—The results of statistical treatment of experimental data on phenol alkylation with styrene in the presence of aluminum phenoxide as a catalyst are presented. The optimization of the process provides the maximum yield of 2,6-di- α -methylbenzylphenol. The structures of the synthesized compounds were determined on the basis of mass spectrometric, IR, and ¹H NMR data.

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10.1134/S0965544107010070Sterically hindered phenols, being effective inhibitors of free-radical processes, are widely used as antioxidants for the stabilization of fuels, oils, polymeric materials, food stuff, etc. [1]. It is noteworthy that these phenols combine their high efficiency with a much lower toxicity as compared to their unsubstituted analogs. It is this circumstance that has stirred the interest of researchers in compounds of this class in recent years.

The inhibiting activity of these antioxidants is mainly due to steric hindrance of the hydroxyl group and depends on the size of ortho-substituents. The introduction of bulky substituents (e.g., tert-butyl) that optimally shield the hydrogen atom of the hydroxy group enhances the stability of the phenoxyl radicals formed and, correspondingly, their inhibiting activity. Therefore, phenol derivatives with tert-butyl substituents in the ortho-position (for example, ionol) are the most popular as high-performance antioxidants. Specific difficulties in the preparation of sterically hindered phenols, in particular, with the unsubstituted para-position, are caused by the selectivity of introduction of alkyl groups into the ortho-position of phenol, because some amounts of 2-, 2,4-, and 2,4,6-substituted phenols are formed along with 2,6-dialkylphenol, which is the most interesting for syntheses of antioxidants [1].

The hydroxyl group in substituted phenols can efficiently be screened, along with the widely used *tert*-butyl radical, by the introduction of α -methylbenzyl substituents into the [*ortho*]-position of a phenol molecule.

There are some data in the literature on the use of α -methylbenzyl-substituted phenols obtained from available feedstock (phenol, styrene) as rubber stabilizers [2]. These phenols are mainly applied as a technical mixture consisting of 2- and 4- α -methylbenzyl-, 2,4- and 2,6-di- α -methylbenzyl-, and 2,4,6-tri- α -methylbenzylphenols. Disubstituted α -methylbenzylphenols were shown to be the most effective [3].

We have previously described the results of syntheses of α -methylbenzyl-substituted phenols with efficient antibacterial properties revealed later [4]. The optimization of the synthesis of these alkylphenols and investigation of their structure and functional properties are of theoretical and practical interest.

In this paper, we present the results of statistical treatment of experimental data on the optimization of the synthesis of 2-, 2,6-, and 2,4,6-substituted α - methylbenzylphenols via the alkylation of phenol with styrene in the presence of aluminum phenoxide. Taking into account that the introduction of bulky radicals that screen the hydroxyl group into the phenol molecule enhances the functional properties of compounds of this class, we attempted to obtain 2,6-di- α -methylbenzylphenol at the highest yield.

EXPERIMENTAL

Synthesis and Physicochemical Properties of 2-, 2,6-, and 2,4,6-Substituted α*-Methylbenzylphenols*

Freshly distilled phenol (47 g, 0.5 mol) was placed into a four-necked reaction flask equipped with a mechanical stirrer, a reflux condenser with a calcium chloride tube, a thermometer, and a tubing for the withdrawal of nitrogen gas. Aluminum chips (0.65 g) were added in portions for 1 h at 140°C in a nitrogen atmosphere. Then the temperature was increased to 180–190°C, and styrene (57.2 g, 0.55 mol) was added from a dropping funnel for 1 h. The reaction mixture was stirred for 4 h under nitrogen. The product was treated with a 1% hydrochloric acid solution, washed with water to the neutral reaction, and dried over anhydrous sodium sulfate. After solvent removal by vacuum distillation, mono-, di-, and trisubstituted α -methylbenzylphenols were separated by column chromatography (adsorption column 36 cm long, diameter 3 cm, Al_2O_3 as adsorbent, hexane-ethyl ether (3:1) as an eluent).

Table 1. Physicochemical properties of synthesized α -methylphenols R = -CHCH₃

		$T_{\rm bp}$, °C, p, Pa	Yield, %	$n_{\rm D}^{20}$	d_4^{20}	MR _D			Elemental analysis			
com- pound no.	Formula of compound					found	calc	Empirical formula	found, %		calculated, %	
									С	Н	С	Н
1	HO	172–174 266.7	23	1.5932	1.0842	61.00	61.18	C ₁₄ H ₁₄ O	84.78	7.31	84.84	7.08
2	HO R	173–175 266.7	5	1.5936	1.0920	61.20	61.18	C ₁₄ H ₁₄ O	84.62	7.42	84.84	7.08
3	R R	192–194 266.7	46	1.5945	1.0913	94.52	94.10	C ₂₂ H ₂₂ O	87.12	7.02	87.42	7.28
4	R R R R	210–215 266.7	8	1.6020	1.0931	94.47	94.10	C ₂₂ H ₂₂ O	87.15	7.05	87.42	7.28
5	R R R R	210–215 266.7	10	1.6032	1.0862	128.20	127.86	C ₃₀ H ₃₀ O	88.55	7.22	88.68	7.37

The column separation was monitored by TLC and GLC.

The physicochemical constants of mono-, di-, and trisubstituted α -methylbenzylphenols are given in Table 1.

The composition and structure of the prepared *ortho*-substituted phenols were determined by elemental analysis, mass spectrometry, IR spectroscopy, and ¹H NMR. The purity of the compounds was determined by GLC.

The IR spectra of the alkylation products contain characteristic absorption bands corresponding to the formation of the above alkylphenols. The spectrum of 2,6-di- α -methylbenzylphenol exhibits a narrow intense band characteristic of hindered phenols. This band is shifted to 3540 cm⁻¹, a result that is due to the interac-

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tion of the electron cloud of the OH-group with the α -methylbenzyl radicals.

The 1 H NMR spectrum displays the following signals: δ 1.60–1.51 ppm from protons of the CH₃ groups of the side chains; signals at 4.58 and 4.61 ppm, which are characteristic of protons of two asymmetric CH groups; the protons of the benzene rings appeared as a multiplet at δ = 7.21–7.23 ppm; a signal from the proton of the hydroxyl group at δ = 7.6 ppm. Proton NMR spectra were recorded on a Varian T-60 spectrometer.

The adequacy of the obtained and calculated molecular-ion and fragment masses of 2,6-di- α -methylbenzylphenol and their intensities (I) were determined by mass spectrometry. The mass spectra were measured on an MX-1309 GC–MS spectrometer with an ionizing energy of 1.28 × 10⁻¹⁷J and an emission current of 100 mA.

Mass spectrum, m/z (I_{rel}, %): 302(55) [M]⁺, 287(70), 272(9), 225(30), 209(90), 197(48), 105(90).

GLC analysis was carried out on a Tsvet-102 chromatograph with a column (0.3×200 cm) using 10% Apiezon- α on Spherochrome as the adsorbent (column temperature, 190°C; evaporator temperature, 250°C).

RESULTS AND DISCUSSION

The molar ratio of the components, temperature regime, and reaction time considerably affect the yields of α -methylbenzylphenols. We studied the influence of these factors on the yields of the desired products during phenol alkylation with styrene in the presence of aluminum phenoxide in order to determine the optimum reaction conditions that ensure the maximum yield of 2,6-di- α -methylbenzylphenol.

Phenol to styrene ratios of 1.5:1, 1:1, 1:1.5, and 1:2 were tested in the investigation of the influence of the reactants ratio on the yields of the desired products of phenol alkylation with styrene in the presence of aluminum phenoxide.

The optimum phenol to styrene ratio resulting in the maximum amount (46%) of desired 2,6-di- α -methylbenzylphenol was found to be 1 : 1.5. This reaction also affords monoalkylphenols, insignificant amounts of 2,4-di- and 2,4,6-tri- α -methylbenzylphenols, and an undistillable tarlike mixture in the residue. The maximum yield of 2,6-di- α -methylbenzylphenol should be expected at a reactant ratio of 1 : 2. However, a larger amount of trisubstituted α -methylbenzylphenols is obtained in this case and the amount of the tarred non-distillable residue increases. When the phenol to styrene ratio was 1 : 1.5, a large amount of unreacted phenols remained in the reaction product.

The further experiments were carried out at a ratio of phenol : styrene = 1 : 1.5, which provided the maximum yield of 2,6-di- α -methylbenzylphenols.

It is known that temperature conditions exert a substantial effect on the alkylation process, since they determine both the alkylation reaction rate and second-



Fig. 1. Graphical matrix of the Box–Benkin plan: experimental values in the coded form.

ary isomerization and dealkylation processes of substituted phenols and, therefore, their influence on the structure of the forming alkylation products is significant.

We studied the temperature dependence of the yields of α -methylbenzylphenols at a molar ratio of 1:1.5 in the temperature interval 170–200°C.

Monosubstituted phenols prevail in the reaction products at 170° C. The maximum yield of the desired product is observed in the temperature range from 180 to 190° C. The amounts of di- and trialkylphenols decrease simultaneously with an increase in the reaction temperature to $200-205^{\circ}$ C.

The method of active planning of experiments followed by the mathematical statistical treatment of experimental data was used to establish quantitative ratios that reflect the influence of the main factors of the regime, which are the temperature X_1 (°C), phenol : styrene (M : M) reactant ratio X_2 , and reaction rime X_3 (h), on the parameters of the process, such as the yields (%) of mono- (Y₁), di- (Y₂), and trisubstituted (Y₃) phenols and phenol (Y₄).

For this purpose, we used the function D = bbdesign(nfactors) of the Matlab-6.5 program [5], which makes it possible to obtain the D matrix of the Box–Benkin plan for the *nfactors* factors. The number of entries in the matrix is equal to the number of factors. The elements of the D matrix are 1 and –1 coding the maximum and minimum values of the factors, respectively. Blocks make it possible to group entries in such a manner that the influence of changing the external conditions on the values of the estimated parameters would be minimized.

The matrix of the Box–Benkin plan for 3 factors can graphically be presented as follows (Fig. 1). The factor experiments were carried out for the following limits of changing the input parameters: $170 \le X_1 \le 200$; $0.67 \le X_2 \le 1.5$; $2 \le X_3 \le 6$.

Quantitative relationships between the parameters of the process and its conditions were determined.

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Y _i			Approxi-	Student							
	<i>a</i> ₀	<i>a</i> ₁	<i>a</i> ₂	<i>a</i> ₃	<i>a</i> ₁₂	<i>a</i> ₁₃	<i>a</i> ₂₃	a_{22}^2	a_{33}^2	mation error	criterion
Monosubstituted alkylphenol											
Y_1	1.653	0.3047	6.52	1.96	-0.012	-0.06	6.82	-6.87	-0.126	0.67	0.58
Disubstituted alkylphenol											
Y_2	4.78	-7.695	2.5	113.9	4.764	0.53	-150.	-111.5	-2.98	0.78	0.79
Trisubstituted alkylphenol											
Y_3	27.35	0.54	-14.0	3.89	0.324	0.07	-10.7	6.11	0.205	0.14	0.86
Phenol											
Y ₄	-3.01	0.08	-41.0	63.8	1.25	-0.5	-8.5	-71.9	4.06	0.39	0.91

Table 2. Numerical values of the coefficients in the regression equation for phenol ortho-alkylation with styrene

Table 3. Limits of variation of the factors and fitting of experimental to calculated values

X ₁	X ₂	X ₃	Y _{1exp}	Y _{1calc}	Y _{2exp}	Y _{2calc}	Y _{3exp}	Y _{3calc}	Y _{4exp}	Y _{4calc}
180	0.67	4	25	24.21306	10	9.639237	0.0001	0.075389	6	6.960568
180	1	3	17	18.6595	33	34.2668	10	9.13707	30	31.089
187	1.2	4	23	23.8702	42	41.98696	10	9.13707	10	10.7551
170	1.5	3.9	20	21.9655	25	25.3063	15	14.43175	5	4.8126
170	1	4	30	27.9152	25	25.16452	0.001	0.089442	25	25.22
185	1.3	4	23	23.8702	46	45.97109	10	9.13707	10	9.5609
200	1.2	3.9	25	25.0222	35	35.74472	7	7.42163	5	5.259
180	1.2	2	26	26.6942	13	12.78696	0.001	0.07232	56	55.2752
190	1.1	4	23	23.8702	42	41.98696	10	9.13707	10	9.2829
180	1.2	6	20	20.0382	38	38.11336	18	17.26232	8	7.1472

Polynomial dependences were obtained, which can be represented in general form as follows:

$$Y_{j} = a_{0} + \sum_{i=1}^{n} a_{i}x_{i} + \sum_{i=1}^{n} a_{ij}x_{i}x_{j} \qquad j = 1, m, \quad (1)$$

where Y_j is the response, X_j is the factor, *n* is the number of factors, and a_i are the coefficients in the regression equation.

To determine the coefficients for the equations, we used the S-plus 2000 professional program developed by Mathworks Co. for automated mathematical processing of experimental data, i.e., for the statistical analysis of data and calculation of regression coefficients and pair correlation coefficients for the indicated samplings.

The estimation of the significance of the regression coefficients was confirmed by the significant multiple

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Fig. 2. Response surface of the solution for the optimization problem on the reaction regime for phenol *ortho*-alkylation with styrene.

correlation coefficient, the Student criterion, and the error of experiment approximation. The calculated data for the coefficients of the regression equation are given in Table 2.

The experimental and calculated values of the output parameters are compared in Table 3. The adequacy of the mathematical model was verified by the Fisher criterion for the degrees of freedom $f_1 = 3$ and $f_2 = 9$, which is $F_{\text{theor}}(f_1, f_2) = 8.84$, whereas its calculated value is $F_{\text{calc}} = 3.047$. Since $F_{\text{calc}} < F_{\text{theor}}$, the statistical model adequately describes the process under study and can be used to determine the optimum condition parameters of processes.

The interpretation of the results by the statistical model revealed the influence of particular factors on the yield of the reaction products. The main significant factor in the equation is temperature. As the factor X_1 goes from the lower level ($X_{1^-} = 170^{\circ}$ C) to the upper level ($X_{2^+} = 1.5$, $X_{3^+} = 4$ h) of the X_2 and X_3 factors, the response alteration effect is $\Delta \overline{Y}_2 = |\overline{Y}_2 - \overline{Y}'_2| = |53.69-20.49| = 33.20$ wt %. In other words, the mass yield of disubstituted alkylphenol increases by 33.20 wt %.

The second significant factor is X₂, which is the reactant ratio. As the factor X₂ climbs from the lower level $(X_{2^-} = 0.67)$ to the upper level $(X_2^+ = 1.5)$ at the unchanged lower level $(X_{1^-} = 170^{\circ}\text{C})$ of the factor X₁ and the upper level $(X_{3^+} = 4 \text{ h})$ of the factor X₃, the response alteration effect is $\Delta \overline{Y}_2 = |\overline{Y}_2 - \overline{Y}_2'| = |33.35 - 9.47| = 23.88 \text{ wt }\%$. In other words, the mass yield of disubstituted alkylphenol increases by 23.88%.

The factor X_3 (reaction time) ranks third in significance. On going of the factor X_3 from the lower level $(X_{3^-} = 2 \text{ h})$ to the upper level $(X_3^+ = 4 \text{ h})$ at the unchanged lower level $(X_{1^-} = 170^{\circ}\text{C})$ of the factor X_1 and the upper level $(X_{2^+} = 1.5)$ of the factor X_2 , the response alteration effect is $\Delta \overline{Y}_2 = |\overline{Y}_2 - \overline{Y}_2'| =$ |25.91-21.91| = 4.00 wt %. In other words, the mass yield of disubstituted alkylphenol increases by 4.00 wt %.

Regression equations (1) make it possible to predict the value of the response function for specified experimental conditions and can also provide information on the shape of the response surface. The examination of these surfaces is necessary to choose the optimum conditions of processes.

The program [5, 6] containing the modern algorithms for the solution of the linear programming problem was applied to solve the optimization problem.

The maximum of the yield of disubstituted alky-lphenol Y_{2max}

$$F_{\text{max}} = f(x_1, x_2, x_3)$$

and the minimum of the functional characterizing the yield of monohydric phenol (Y₁) and unsubstituted phenol (Y₄) were taken as optimization criteria at the following constraints on the parameters of the process: $170^{\circ}C \le X_1 \le 200^{\circ}C$; 0.67 mol/mol $\le X_2 \le 1.5$ mol/mol; $2 h \le X_3 \le 6 h$.

The solution of the optimization problem showed that a maximum in the yield of disubstituted alky-lphenol $Y_{2max} = 46\%$ is achieved at $X_1 = 190^{\circ}$ C, $X_2 = 1 : 1.5$ mol/mol, and $X_3 = 4$ h. We also obtained $Y_{1min} = 10.437$ wt % at $X_1 = 190^{\circ}$ C, $X_2 = 1 : 1$ mol/mol,

and $X_3 = 6$ h; $Y_{4min} = 2.7105$ wt % at $X_1 = 200^{\circ}$ C, $X_2 = 1 : 1.5$ mol/mol, and $X_3 = 6$ h.

To study the configuration of the response surface, let us transform Eq. (1) into the canonical form.

The coordinates of the point *S* (center of the surface) are determined by the solution of the system of equations:

$$\frac{\partial y_2}{\partial x_1} = -7.695 + 4.764X_2 + 0.533X_3 = 0,$$

$$\frac{\partial y_2}{\partial x_2} = 2.5 + 4.764X_1 - 149.796X_3 - 233.0X_2 = 0,$$

$$\frac{\partial y_2}{\partial x_3} = 113.99 + 0.533X_1 - 149.7X_2 - 5.8X_3 = 0,$$

which make it possible to find the canonical form of Eq. (2)

$$Y_s = 0.375X_1 - 45.6X_2 - 38.74X_3.$$
(3)

The values of the coefficients have different signs; i.e., the response surface is the hyperbolic paraboloid "saddle" with the "minimax" at the center of the surface (Fig. 2).

Thus, the statistical processing of experimental data and the solution of the problem of optimization of the conditions for phenol *ortho*-alkylation with styrene in the presence of aluminum phenoxide allow us to determine the optimum conditions of the process, namely, a reaction temperature of 190°C, a reactant ratio of 1:1.5, and a reaction time of 4 h. At these parameters, the maximum yield of 2,6-di- α -methylbenzylphenol is 46%.

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