Some heterocyclic derivatives of sterically hindered phenols

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Five- and six-membered heterocyclic compounds containing sterically hindered phenols as structural fragments were obtained by dipolar 1,3-cycloaddition of substituted nitrile oxides to olefins, azomethines, and acetylenes.

Key words: sterically hindered phenols, nitrile oxide, oxazole, oxazoline, oxadiazoline, 1,4-dioxa-3,6-diazine, 1,3-cycloaddition.

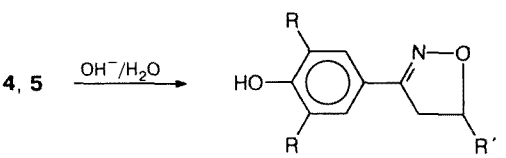
Derivatives of sterically hindered phenols (SHP) are well known as substances with anti-oxidative properties. We have obtained heterocyclic derivatives of SHP by dipolar cycloaddition of nitrile oxides to olefins, azomethines, and acetylenes.[1]

In most cases, nitrile oxides are reactive intermediates that readily react *in situ* with a substrate (sterically hindered nitrile oxides, *e.g.*, of the mesitylene series, are more stable[2]). The most widely used method for their preparation is dehydrohalogenation of haloaldoximes by bases.[3] The halogenation of aromatic aldoximes by the classical method is carried out by a halogen in ether, chloroform, or concentrated HCl.[4] However, this method cannot be used with SHP derivatives, since quinohalides or products of their transformation are formed in the course of the reaction.[5] Therefore, we carried out the chlorination of 4-hydroxy-3,5-di-*tert*-butylbenzaldehyde oxime (**1**) with *N*-chlorosuccinimide in DMF. This variant allows one to obtain the required hydroximoyl chloride (**2**) in a yield of up to 60 %.

Compound **2** is sufficiently stable in the solid state, but in solution in the presence of moisture it is converted (similarly to nitrile oxide) into the corresponding hydroxamic acid. Therefore, dry DMF was used in the reactions, and 1,3-cycloaddition was carried out without isolation of compound **2**, by direct addition of a dipolarophile and a base at 4—5 °C. The reaction proceeds comparatively fast (from 10 min to 1 h). The target products were isolated chromatographically after separation of the hydrochloride of the base and removal of DMF *in vacuo*.

Depending on the dipolarophile used, we obtained heterocyclic derivatives of sterically hindered phenols containing isoxazoline (**3—6**), isoxazole (**7**), and oxadiazoline (**8**) fragments, in agreement with the literature data[1,6,7] (Scheme 1).

As follows from IR and ^{1}H NMR spectral data (Tables 1 and 2), the compounds isolated contain both phenol and heterocyclic fragments. The structure of compounds **4** and **5** is confirmed by their hydrolytic decomposition. Mild alkaline hydrolysis of compounds **4** and **5** affords the corresponding 5-hydroxy- and 5-carboxyisoxazolines (**9**, **10**) in a quantitative yield:



9, 10

9: R′ = OH
10: R′ = COOH

Compound **9** is quickly converted into ketoaldehyde **11** under conditions of acid hydrolysis, whereas compound **10** remains unchanged under comparatively drastic conditions (refluxing in aqueous dioxane in the presence of concentrated HCl). Since compound **9** is a specific semiacetal, one should expect that isoxazoline ring of **9** would be readily opened under conditions of acid hydrolysis (Scheme 2).

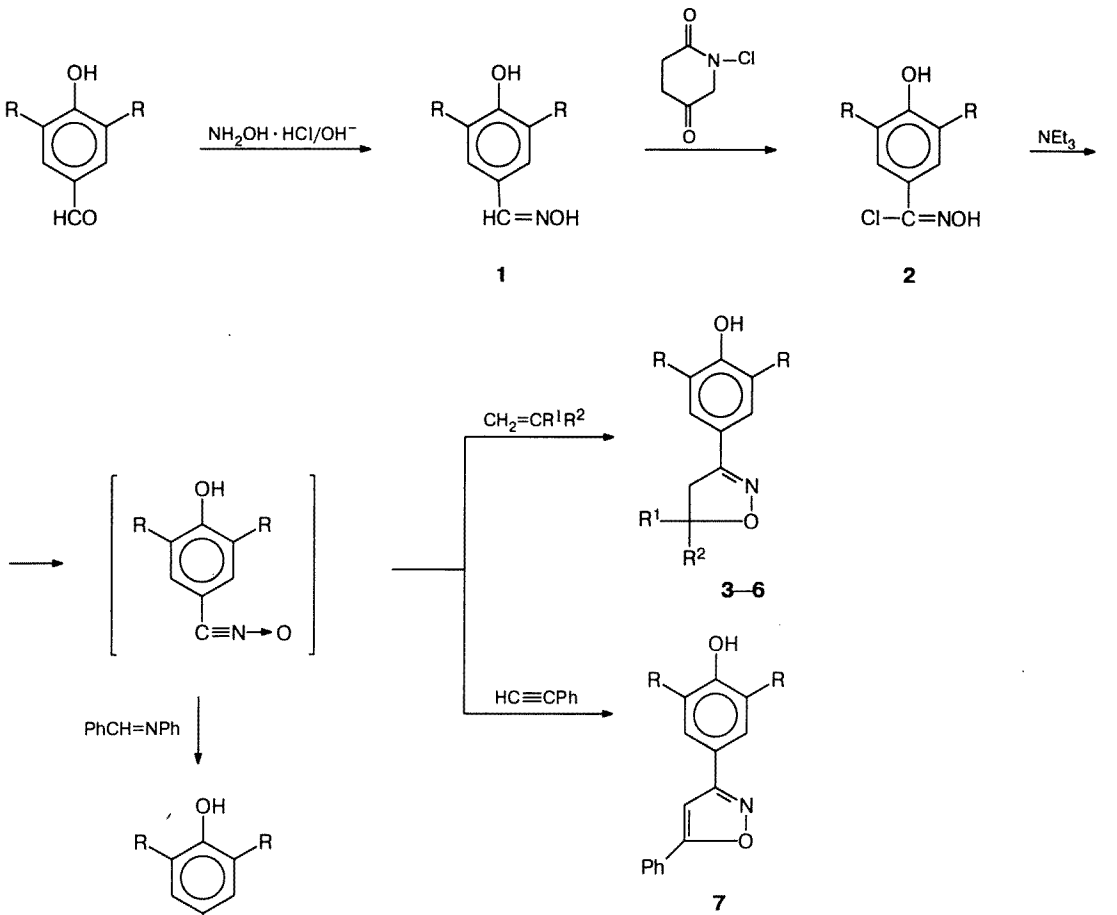
The structure of ketoaldehyde **11** was confirmed by ^{1}H NMR spectral data (Table 3).

This compound is practically totally enolized both in $CDCl_3$ and acetone-d_6, which is proved by the existence of doublets from =CH and CHO and singlets from H_m and ArO<u>H</u> (the signals from =CH and OH disappear when deuteromethanol is added).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 2, pp. 426—429, February, 1996.

1066-5285/96/4502-0410 $15.00

Scheme 1



R = Bu^t (hereinafter)

3: R^1 = H, R^2 = Ph
4: R^1 = H, R^2 = OAc
5: R^1 = H, R^2 = COOMe
6: R^1 = Me, R^2 = COOMe

Scheme 2

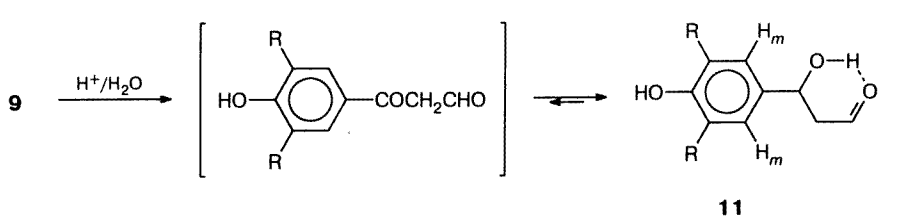
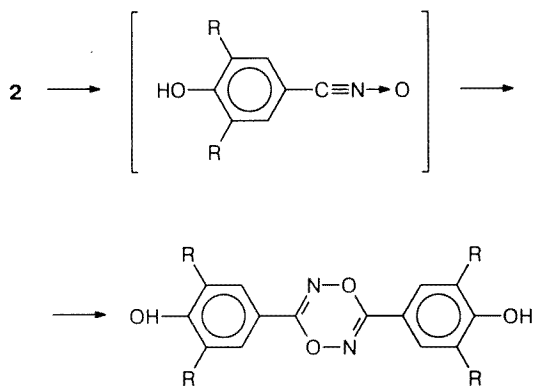


Table 1. ^{1}H NMR spectra of compounds **3—10**

Compound	Solvent	^{1}H NMR, δ (*J*/Hz)													
		Bu^t	ArOH	H(arom.)	C(4)H$_A$(het.)	C(4)H$_B$(het.)	C(5)H$_C$(het.)	J_{AC}^{gem}	J_{AC}	J_{BC}	Ph	Me	OCOMe	COOMe	OH
3	C_6D_6	1.32	5.14	7.69	2.87	3.18	5.38	16.0	8.5	10.0	7.16	—	—	—	—
4	C_6D_6	1.30	5.17	7.60	2.63	2.77	6.72	17.4	0.5	6.7	—	—	1.51	—	—
	$CDCl_3$	1.46	5.53	7.53	3.30	3.64	6.80	17.6	1.9	6.2	—	—	2.07	—	—
5	C_6D_6	1.34	5.17	7.66	2.86	3.14	4.79	16.2	5.9	11.8	—	—	—	3.29	—
6	C_6D_6	1.31	5.15	7.66	2.78	3.79	—	16.7	—	—	—	1.51	—	3.29	—
7	$CDCl_3$	1.52	5.46	7.69	6.78	—	—	—	—	—	7.49 7.87	—	—	—	—
8	CD_3CN	1.31	5.78	7.35	—	—	6.59	—	—	—	7.04 7.52	—	—	—	—
9	$CDCl_3$	1.45	5.52	7.51	3.26	3.41	6.02	17.1	1.5	6.4	—	—	—	—	3.72
10	C_6D_6	1.28	5.15	7.54	2.74	3.24	4.58	16.8	5.8	11.6	—	—	—	—	—
	$CHCl_3$	1.45	5.57	7.49	3.73		5.19	—	6.7	10.1	—	—	—	—	—

When compounds **3—8** are obtained as by-products (up to 10—15 %), according to the ^{1}H NMR spectral data (a double set of similar-type signals in 1 : 1 ratio), a compound containing two phenol fragments is formed. Elemental analysis, ^{1}H NMR, and mass-spectral data prove that the structure of this compound corresponds to the dimer of intermediate nitrile oxide, 2,5-diaryl-1,4-dioxa-3,6-diazine (**13**):



13

Compound **13** is also formed in 20—25 % yield on treatment of compound **2** with triethylamine in the absence of a dipolarophile.

Experimental

^{1}H NMR spectra were recorded on Bruker WP-80 and Bruker WM-400 spectrometers, IR spectra were obtained on a Specord M-80 spectrometer, and the mass spectrum was obtained on a Finnigan MAT INCOS-50 quadrupole chromatomass-spectrometer (EI, 70 eV, 0.24 mm × 30 m capillary column, 0.25 μ grafted phase, polydimethylsiloxane).

4-Hydroxy-3,5-di-*tert*-butylbenzaldehyde oxime (1) was obtained by the known procedure[8] in 85.6 % yield, m.p. 136—137 °C.

Table 2. Yields, m.p., and IR spectra of compounds **3—8**

Compound	Yield (%)	M.p. /°C	IR, ν/cm^{-1}				
			OH	CH	C=O	C=N	C=C
3	42.9	117—118	3584	2968	—	1576	1596
4	52.1	157—158	3592	2960	1760	1564	1600
5	58.0	138—139	3584	2960	1744	1568	1600
6	60.3	112—113	3632	2960	1744	1576	1600
7	48.6	137—138	3616	2960	—	1576	1568 1612
8	42.7	157—158	3528	2960	—	1552	1592

Table 3. ^{1}H NMR spectra of compound **11**

Solvent	^{1}H NMR, δ						*J*/Hz
	Bu^t	ArOH	OH$_{en}$	=CH	H$_m$	CHO	
$CDCl_3$	1.49	5.47	7.64	6.61	7.64	8.41	1.8
Acetone-d_6	1.49	6.49	3.83	6.95	7.71	8.73	1.8

4-Hydroxy-3,5-di-*tert*-butylbenzhydroxymoyl chloride (2). *N*-Chlorosuccinimide (4.02 g, 0.03 mol) was added to a solution of oxime **1** (7.5 g, 0.03 mol) in DMF (75 mL) in portions with stirring at 40 °C, so that the temperature did not exceed 50 °C. The mixture was kept for 0.5 h, cooled, and poured into water. The resin that precipitated was extracted with ether, washed three times with water, and dried with $MgSO_4$. The ether was removed, and the residue was crystallized from hexane to give 4.6 g (53.9 %) of compound **2**, m.p. 163—165 °C. Found (%): C, 63.20; H, 7.99; N, 4.71. $C_{15}H_{22}ClNO_2$. Calculated (%): C, 63.47; H, 7.81; N, 4.93. ^{1}H NMR, C_6D_6, δ: 1.33 (Bu^t); 5.16 (OH); 6.97 (OH); 7.96 (H$_m$).

Typical procedure of dipolar 1,3-cycloaddition. *N*-Chlorosuccinimide (1.34 g, 0.01 mol) was added to a solution of oxime **1** (2.5 g, 0.01 mol) in DMF (15 mL), the mixture was heated and kept at 40 °C for 1 h with permanent stirring, then cooled to 5 °C. Triethylamine (1.42 g, 0.01 mol) was added dropwise, and the mixture was stirred at ~20 °C for 1 h. The

precipitate of triethylamine hydrochloride that formed was separated, and the residue was concentrated and chromatographed on a column (silica gel *L* 40/100 μ, *n*-C_6H_{14}—$CHCl_3$ as the eluent). The yields, m.p., and spectral data for compounds **3—8** obtained are given in Tables 1 and 2. Deviations of the results of elemental analysis are within the acceptable range.

Alkaline hydrolysis of acetoxyisoxazoline (4). Aqueous 2 % KOH (1 mL) was added to a solution of compound **4** (0.5 g) in methanol (10 mL); the mixture was refluxed for 1 h, cooled, and diluted with 100 mL of water. The solution obtained was acidified with HCl to pH 5.0 and extracted with chloroform. Removal of chloroform gave 0.4 g (93 %) of 3-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)-5-hydroxyisoxazoline-2 (**9**), m.p. 94—95 °C (from C_6H_6—*n*-C_6H_{14}, 1 : 1). Found (%): C, 68.60; H, 8.89; N, 5.31. $C_{16}H_{25}O_3N$. Calculated (%): C, 68.78; H, 9.02; N, 5.01. ^{1}H NMR spectral data are given in Table 1.

Alkaline hydrolysis of methoxycarbonylisoxazoline (5). Similarly to compound **9**, the hydrolysis of **5** afforded 0.45 g (94 %) of 3-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)-5-carboxyisoxazoline-2 (**10**), m.p. 183—184 °C (from $CHCl_3$). Found (%): C, 66.60; H, 8.32; N, 4.32. $C_{17}H_{25}O_4N$. Calculated (%): C, 66.42; H, 8.20; N, 4.56. ^{1}H NMR spectral data are given in Table 1.

Acid hydrolysis of hydroxyisoxazoline (9). Water (0.5 mL) and concentrated HCl (0.01 mL) were added to a solution of compound **9** (0.5 g) in dioxane (5 mL). The mixture was refluxed for 30 min, cooled, and diluted with 30 mL of water. The crystals that precipitated were separated, washed with water, and dried to give 0.45 g (92 %) of ketoaldehyde **11**, m.p. 134.5—135.5 °C (from *n*-C_6H_{14}). Found (%): C, 73.96; H, 8.81. $C_{17}H_{24}O_3$. Calculated (%): C, 73.88; H, 8.73.

2,5-Di-(4′-hydroxy-3′,5′-di-*tert*-butylphenyl)-1,4-dioxa-3,6-diazine (13). *N*-Chlorosuccinimide (1.34 g, 0.01 mol) was added to a solution of compound **1** (2.5 g, 0.01 mol) in DMF (15 mL). The mixture was kept at 40 °C for 2 h with permanent stirring, then triethylamine (1.42 g, 0.01 mol) was added, and the mixture was heated for an additional 1 h. The precipitate of triethylamine hydrochloride was separated; the residue was concentrated and chromatographed on a column (silica gel *L* 40/100 μ, *n*-C_6H_{14}—$CHCl_3$ as the eluent) to give 1.21 g (24.6 %) of dioxadiazine **13**, m.p. 228—230 °C. Found (%): C, 72.94; H, 8.70; N, 5.70. $C_{30}H_{42}O_4N_2$. Calculated (%): C, 72.87; H, 8.50; N, 5.66. IR, ν/cm^{-1}: 3592 (OH), 2960 (CH), 1596 (C=C), 1480 (C=N). ^{1}H NMR ($CDCl_3$), δ: 1.35 and 1.36 (Bu^t); 5.49 and 5.51 (OH); 7.29 and 7.32 (H_m). MS, *m/z*: 494 $[M]^+$.

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Received April 26, 1995;
in revised form September 18, 1995