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Formation and Cyclization of *N*′-(Benzoyloxy)benzenecarboximidamides

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Abstract—The formation of *N*′-(benzoyloxy)benzenecarboximidamides and their subsequent cyclization to 3,5-disubstituted 1,2,4-oxadiazoles in different solvents were studied. A probable reaction mechanism was proposed on the basis of the obtained results.

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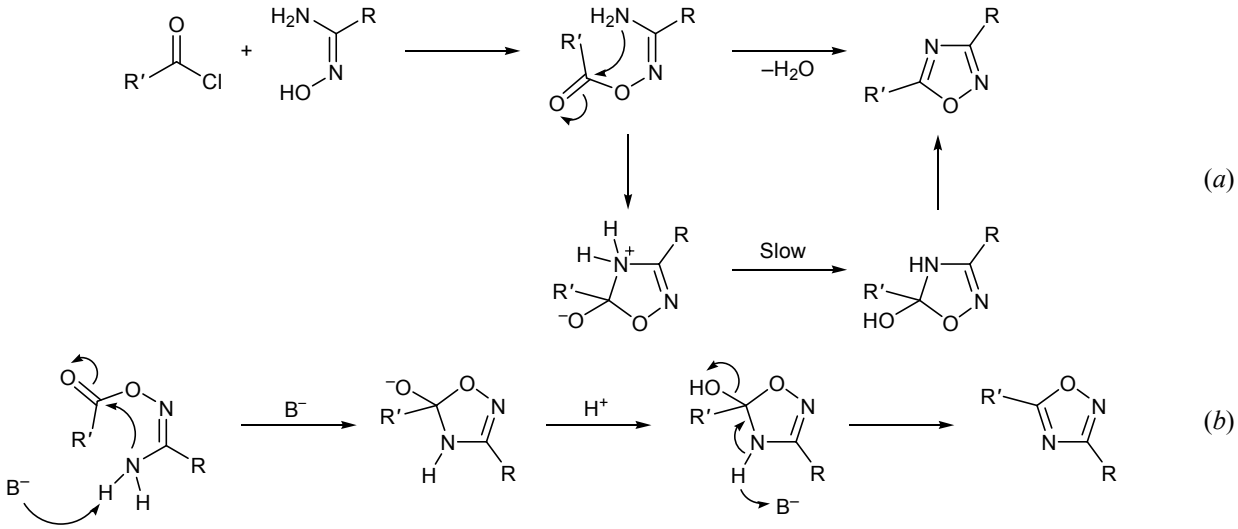
Compounds containing a 1,2,4-oxadiazole ring are active components of medical agents used for the treatment of asthma, ischemia, and Parkinson's disease. There are published data on antibacterial, anti-inflammatory, and anticancer properties of such compounds [1]. Therefore, studies on the formation of 1,2,4-oxadiazoles with a view to improve the existing methods of their synthesis and develop new more efficient procedures constitute an important problem.

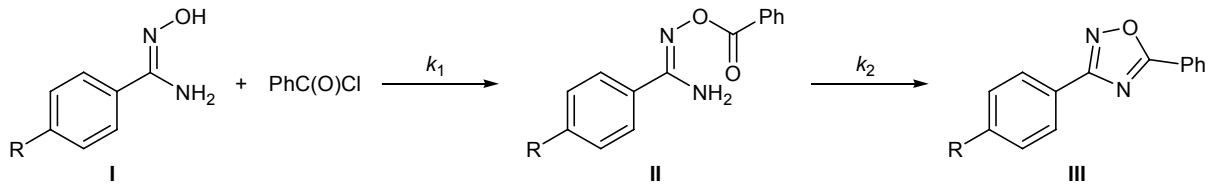
Several possible ways (*a*, *b*) for the formation of 1,2,4-oxadiazoles from *N*′-hydroxyamidines have been proposed. Ooi and Wilson [2] described a scheme for the reaction of carboxylic acid chlorides with *N*′-hydroxyamidines (Scheme 1, *a*). Here, the slow reaction step is the transformation of zwitterion into 3,5-disubstituted 4,5-dihydro-1,2,4-oxadiazol-5-ol via proton transfer from the nitrogen atom to oxygen. In the presence of strong bases [3, 4] 3,5-disubstituted 1,2,4-oxadiazoles are formed from *O*-acyl-*N*′-hydroxyamidines according to path *b* (Scheme 1).

We examined [5–8] the formation of a series of 3,5-disubstituted 1,2,4-oxadiazoles (Scheme 2) and determined the rate constants k ($k_1 + k_2$) for the reaction **I**→**III** and the rate constants for the cyclization of preliminarily synthesized compound **II** (k_2). The latter was obtained by reaction of *N*′-hydroxybenzimidamide

Scheme 1.



Scheme 2.



R = H, O_2N, Br, Me, MeO.

(**I**) with benzoyl chloride in toluene at 80°C. The rate constants were determined following accumulation of final product **III**.

The acylation with benzoyl chloride was carried out using equimolar amounts of the reactants, the initial concentration of amidine **I** being 0.49 M. According to the IR data, compound **II** is formed immediately after mixing solutions of *N*′-hydroxybenzimidamide and benzoyl chloride in pyridine at 100°C, and the initial reactants are consumed completely. The IR spectra of samples of the reaction mixture contained absorption bands at 1733, 1251, and 1090 cm^{-1}, which are typical of esters, while no band at 1774 cm^{-1} (νC=O in benzoyl chloride) was present.

The following values were obtained in pyridine at 100°C: $k = 2.44\times10^{-4}\pm1.1\times10^{-5}$ ($R^2 = 0.97$), $k_2 = 2.40\times10^{-4}\pm1.4\times10^{-5}$ s^{-1} ($R^2 = 0.99$). The linear relation between the logarithm of the current concentration of **III** and reaction time ($R^2 = 0.97$–0.99) indicates that the process conforms to first-order kinetics. We also determined the rate constants for the formation of compound **III** at different molar reactant ratios (100°C).

Ratio **I**–BzCl	2:1	1:1	1:2
$k\times10^4$, s^{-1} ($R^2 = 0.99$)	2.58±0.07	2.44±0.11	2.17±0.16

A conclusion can be drawn that intramolecular cyclization of **II** is the rate-determining stage and that it is described by first-order kinetic equation. The activation parameters were estimated from the temperature dependence of k ($\ln k$—$1/T$, $R^2 = 0.99$) in pyridine at 95–110°C (Table 1).

The preexponential factor suggests first order of the reaction. The entropy of activation indicates insignificant difference in the structures of the transition state and product **III**, which may be illustrated by comparing the structures of **II** and **III**. The cyclization rules out the possibility for rotation about the N–O and O–C bonds in molecule **II** [9].

We also estimated the effect of substituents in the *para* position of the benzene ring of *N*′-hydroxybenzimidamide (**I**) on the reaction rate and determined the corresponding rate constants (Table 2). It is seen that the cyclization is favored by electron-donating substituents (cationic transition state). Presumably, the small absolute value of ρ is related to a weak effect of the substituent on the carbonyl carbon atom in **II** and to the fact that elimination of water molecule from *O*-benzoyl derivative **II** occurs almost synchronously with its formation [10].

The reaction was also performed in other solvents: 1,4-dioxane, toluene, and acetic acid. The corresponding values of k and k_2 are given in Table 3. The reaction in acetic acid was slow (Table 3), and the yield of **III** was 6.3% (20 min, 100°C); in pyridine, the yield of **III** was 24.3%, other conditions being equal. Under analogous conditions the cyclization of *O*-benzoyl

Table 1. Activation parameters for the formation of compound **III** ($c_{\mathbf{I}} = 0.49$ M, **I**–BzCl ratio 1:1, pyridine)

Temperature, K	$\Delta H^{\neq}$, J/mol	$A\times10^{-13}$, s^{-1}	$\Delta S^{\neq}$, J mol^{-1} K^{-1}
368	115783.12	1.04	–5.71
373	115741.57	1.15	–5.01
378	115700.02	1.21	–4.71
383	115700.02	1.02	–6.20
$\Delta S^{\neq}_{av.} = -5.41$ J mol^{-1} K^{-1}; $E_a = 118.84\pm1.217$ kJ/mol ($R^2 = 0.985$), $\Delta H^{\neq}_{av} = 115.72$ kJ/mol			

Table 2. Logarithms of rate constants k and correlation parameters with substituent constants σ (100°C, pyridine)

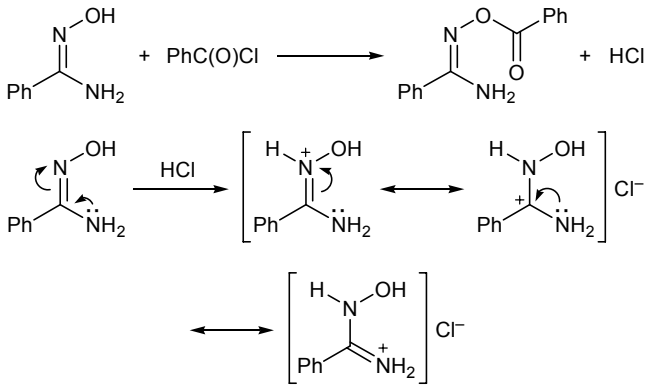
R	log$k$	σ^+	σ^-	σ
H	–3.59	0.00	0.00	0.00
O_2N	–3.77	0.79	1.27	0.79
Br	–3.65	0.15	0.23	0.23
Me	–3.50	–0.30	–0.17	–0.17
MeO	–3.38	–0.76	–0.27	–0.27
		ρ = –0.255 ($R^2 = 0.98$)	$R^2 = 0.75$	$R^2 = 0.88$

Table 3. Apparent rate constants k and k_2 in different solvents (100°C, $c_{\mathbf{I}}^0 = 0.49$ M)

Solvent	$k\times10^4$, s^{-1}	$k_2\times10^4$, s^{-1}
Pyridine	2.44±0.14	2.44±0.11
Toluene	–	0.30±0.02
Acetic acid	0.51±0.05	12.31±0.51
1,4-Dioxane	1.02±0.05	1.17±0.02

derivative **II** in acetic acid was faster than in pyridine (Table 3); this means that the rate-determining stage in acetic acid is the formation of compound **II** (Scheme 2). Compound **II** was formed in toluene, and *N*′-hydroxybenzimidamide salt precipitated (Scheme 3).

Scheme 3.



The cyclization of **II** in toluene was slower than in pyridine. Both reactions in 1,4-dioxane (Table 3) occurred at a higher rate than in toluene, but they were slower than in pyridine. Figure shows the plots of concentration of compound **III** versus time in the cyclization of amidine **II** in different solvents.

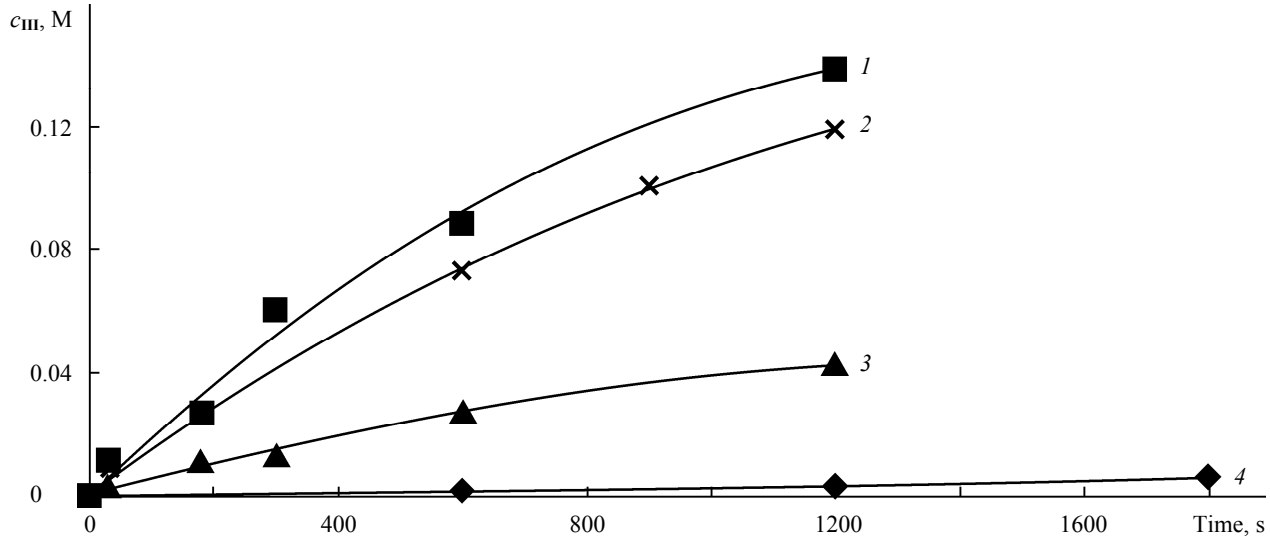
When the reaction is carried in pyridine, liberated hydrogen chloride is bound with the solvent, whereas in toluene and acetic acid initial *N*′-hydroxybenzimidamide molecule takes up liberated HCl (Scheme 3). Presumably, this is the factor responsible for the lower reaction rate. Moreover, pyridine is capable of reacting with benzoyl chloride with formation of active ionic compound which is a strong acylating agent [9]; therefore, addition of pyridine accelerates the process.

$c_{\mathbf{I}}:c_{\mathrm{Py}}$	$k\times10^4$, s^{-1}	R^2
1:0.25	1.244±0.099	0.969
1:0.5	2.066±0.171	0.967
1:1.2	2.089±0.229	0.943

Taking the above into account, we can conclude that the mechanism of reaction of carboxylic acid chlorides with *N*′-hydroxy amidines is determined by the reaction medium.

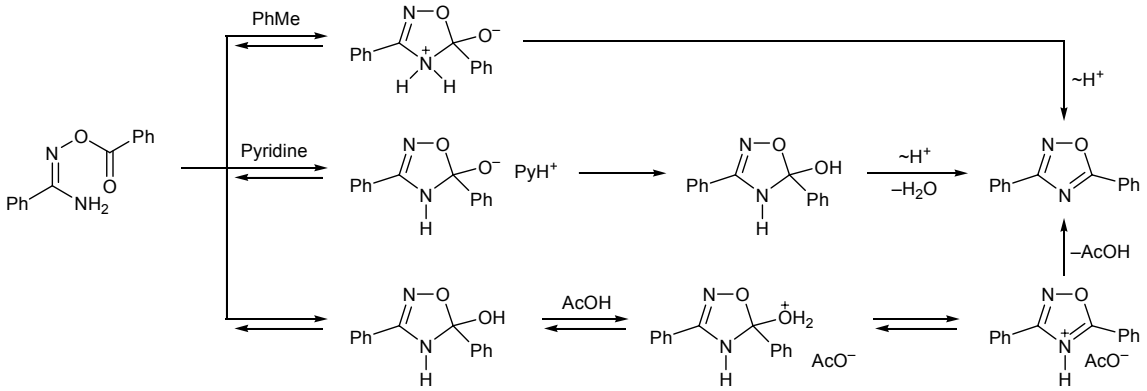
In basic medium (pyridine, dioxane) the rate-determining stage is intramolecular cyclization of *N*′-(benzoyloxy)benzimidamide (**II**), which is likely to follow Scheme 4. Base catalyzes proton transfer in the dehydration stage.

In acid (acetic acid) and neutral media (toluene) the rate-limiting step is the formation of compound **II**. The higher rate of cyclization in acetic acid is likely to be determined by protonation of 3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazol-5-ol, which facilitates its subsequent transformation into iminium cation (Scheme 4).



Cyclization of *N*′-(benzoyloxy)benzimidamide (**II**) in (*1*) glacial acetic acid, (*2*) pyridine, (*3*) 1,4-dioxane, and (*4*) toluene.

Scheme 4.



EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer Spectrum RX-1 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker MSL 300 spectrometer from solutions in DMSO-d_6 using tetramethylsilane as reference. Solvents and auxiliary reagents were prepared according to the procedures described in [11, 12].

The kinetic studies were performed at a constant temperature (±0.5°C) in a reactor equipped with a stirrer, reflux condenser, thermometer, and dropping funnel (the latter was also maintained at a constant temperature). A sample of initial compound was dissolved in ($10 - V_K$) ml of a solvent (V_K is the volume of a solution placed into the dropping funnel). The dropping funnel was charged with a solution of the second component. The reactor and the dropping funnel were kept for 10 min at a required temperature, and the solution in the dropping funnel was quickly added to the reactor. Samples of the reaction mixture were withdrawn during the process and diluted with 15–20 volumes of acetonitrile. The reaction rate was determined from the accumulation of final product **III**, which was quantitated by HPLC using a Perkin–Elmer Series LS-20 chromatograph [15-cm×4-mm column charged with Separon-C18; eluent acetonitrile–water (80:20); UV detector, λ 254 nm]. Each sample was analyzed at least thrice using biphenyl as standard.

***N*′-(Benzoyloxy)benzimidamide (II).** A mixture of 10 g (0.074 mol) of *N*′-hydroxybenzimidamide and 10.3 g (0.074 mol) of benzoyl chloride in 50 ml of toluene heated to 80°C was kept for 5 min, the mixture was filtered while hot, the filtrate was cooled to 20°C and kept for 2 h at room temperature, and the precipitate was filtered off and dried. Yield 4.6 g (26%), colorless powder, mp 124–125°C. IR spectrum, ν, cm^{-1}: 3309 (NH_2), 1732 (C=O), 1640 (C=N), 1250 (C–O), 1090 (C–O). ^{1}H NMR spectrum, δ, ppm: 6.99 s (2H, NH_2), 7.51 m (5H, H_{arom}), 7.65 t (1H, H_{arom}, J = 7.4 Hz), 7.79 d (2H, H_{arom}, J = 7.7 Hz), 8.20 d (2H, H_{arom}, J = 7.4 Hz).

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