ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 1, pp. 149–152. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © Yu.D. Markovich, T.N. Kudryavtseva, M.I. Brylev, V.Yu. Markovich, I.A. Koroleva, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 1, pp. 152–155.

Kinetic Parameters of the Intramolecular Condensation of Diphenylamine-2-carboxylic Acid under Microwave Radiation

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Received October 28, 2010

Abstract—The cyclization of diphenylamine-2-carboxylic acid under microwave radiation was investigated. The kinetic parameters of the processes were measured. The use of microwave radiation was found to reduce the reaction duration and to increase the target product yield. The optimal conditions for processes were determined.

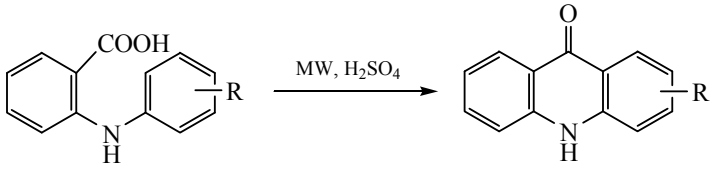
DOI: 10.1134/S1070363212010240

The investigation of the possibility of using microwave radiation in the synthesis of various heterocyclic compounds is an urgent task, as this method has several advantages over the other types of activation of the chemical reaction: reducing the reaction duration, high energetic efficiency of the process, etc. [1, 2].

The target products of condensation of substituted diphenylamine-2-carboxylic acid (**Ia–Ig**) are the acridones that are used as starting materials in the synthesis of various drugs [3].

Among the affordable ways of getting the majority of acridones is the cyclization of appropriate acid **I** in concentrated sulfuric acid at 90–100°C for 4 h, the recommended mole ratio of diphenylamine-2-carboxylic acid : sulfuric acid is from 1:7.5 to 1:9 [4, 5]. It was interesting to compare the reaction rate and yield for the reactions under the microwave and the traditional conditions of heating.

Under both microwave and traditional heating, the cyclization reaction proceeds according to the scheme:

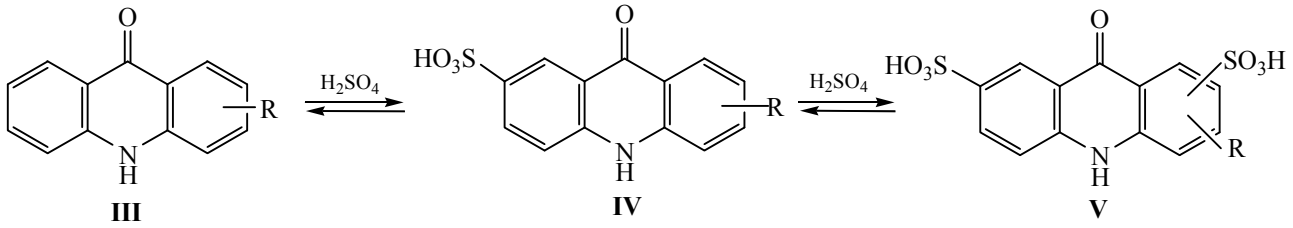


I **II**

R = H (**a**), 2'-CH_3 (**b**), 3'-CH_3 (**c**), 4'-CH_3 (**d**), 2'-COOH (**e**), 4'-COOH (**f**), 2'-NO_2 (**g**).

The use of sulfuric acid as a cyclizing agent favors side reactions of sulfonation. As shown by earlier research [6], the use of microwave radiation increases the yield of the mono- and disulfo-derivatives (compounds **IV** and **V**, respectively):

To determine the effect of microwave heating on the intramolecular condensation of substituted diphenylamine-2-carboxylic acids we measured the kinetic characteristics of the reaction. After processing the chromatograms, we calculated the degree of consumption of the initial acid **I** and the degree of accumulation of the corresponding acridone ($\alpha = c_{\mathbf{I}}/c_{\mathbf{I}}^0$). The kinetic curves of consumption of unsubstituted acid **Ia** and accumulation of acridone and acridonesulfonic acid in sulfuric acid at 90°C at the



R = H (**a**), 4-CH_3 (**b**), 1– and -3-CH_3 (**c**), 2-CH_3 (**d**), 4-COOH (**e**), 2-COOH (**f**), 4-NO_2 (**g**).

traditional method of heating (a) and under the microwave conditions (b) are presented in the figure.

As shown in the figure, in the microwave the acid **Ia** is consumed at a higher rate, and over a shorter period of time. At the traditional heating the half-period of the DFACA – acridone transformation is 60 min, while at the application of microwave heating only 20 min. The same regularities are found for other studied compounds.

We were able from the data obtained to determine the reaction rate constants and to calculate therefrom the activation energy of the process under the microwave conditions and to compare the results with those obtained with the traditional method of heating (Table 1).

As seen from Table 1, the use of microwave radiation significantly increases the rate of the cyclization reaction and reduces the activation energy.

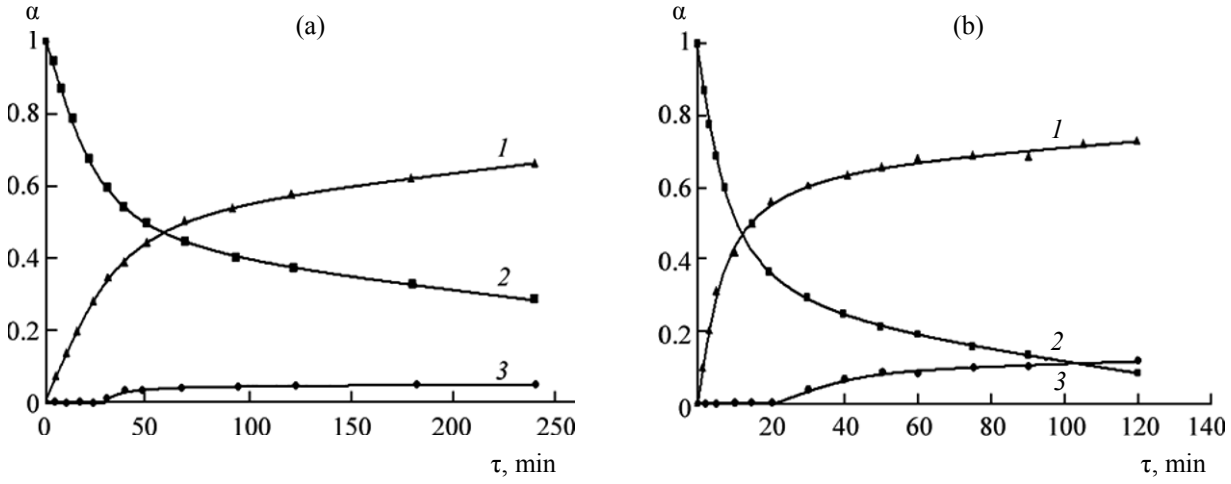
The acridones obtained were isolated, their structure was confirmed by the data of IR spectroscopy and gas chromatography–mass spectrometry using a database of mass spectra "NIST2005." The spectra of the acridones synthesized under the microwave radiation and by the traditional method of heating are identical [9]. The reaction conditions and yields of target compounds at the traditional heating and microwave radiation are listed in Table 2.

As seen from Table 2, the effect of microwave radiation on the acridone yield becomes most noticeable at the cyclization of a diphenylamine-2-carboxylic acid at lower temperatures.

Thus, the use of microwave radiation as an activator of the process of synthesis of substituted acridones reduces reaction time and leads to a higher yield of the target product,

EXPERIMENTAL

The studies were carried out using a laboratory microwave installation MARS of CEM Corporation with a temperature control system, at a microwave power 400 W, the molar ratio diphenylamine-2-carboxylic acid : sulfuric acid = 1:8.



Kinetic curves of the accumulation of (*1*) acridone **IIa** and (*3*) acridonesulfonic acid **IIIa**, and (*2*) the consumption of diphenylamine-2-carboxylic acid **Ia**, in a medium of concentrated sulfuric acid at 90 ± 2°C at the traditional method of (a) heating and (b) under microwave radiation.

Table 1. Kinetic parameters of the diphenylamine-2-carboxylic acids cyclization in concentrated sulfuric acid

Acid	Traditional heating [5, 8]						Microwave radiation					
	$k\times10^5$, s^{-1} at T (°C)					E_a, kJ mol^{-1}	$k\times10^5$, s^{-1} at T (°C)					E_a, kJ mol^{-1}
	60	70	80	90	100		60	70	80	90	100	
Ia	–	2.12± 0.08	6.88± 0.25	21.00± 0.81	56.30± 2.17	116.5	–	–	12.17± 0.48	32.15± 1.28	66.41± 2.64	93.2
Id	–	1.37± 0.05	6.11± 0.24	14.92± 0.59	45.28± 1.81	121.3	–	3.46± 0.13	10.28± 0.40	16.72± 0.66	31.56± 1.25	76.1
Ie	–	7.87± 0.31	27.79± 1.11	89.22± 3.56	294.00± 11.76	127.9	7.76± 0.31	43.12± 1.71	254.90± 10.1	–	–	115.0
If	7.51± 0.30	22.31± 0.89	61.28± 2.45	142.81± 2.45	–	99.0	19.33± 0.77	32.27± 1.28	52.02± 2.07	–	–	49.1

Table 2. Effect of the cyclization conditions on the yield of substituted acridones

Acridone	Temperature, °C	Traditional heating		Microwave radiation	
		reaction duration, min	yield, %	reaction duration, min	yield, %
IIa	90	240	76.2±0.5	120	86.6±0.6
	120	10	73.4±0.6	10	85.6±0.7
IIb	90	120	53.0±0.5	120	65.5±0.7
IId	100	120	71.3±0.7	120	77.7±0.5
IIe	80	90	78.2±0.7	30	78.4±0.5
IIg	90	12	78.5±0.5	10	84.4±0.4

The kinetic studies were carried out using thin layer chromatography with densimetry. Chromatograms obtained were processed on a Sorbfil videodensimeter at the 254 nm wavelength with the Sorbfil 1.8 program [7].

The IR spectra were taken on a FT-IR spectrometer Nicolet IR-200. The mass-spectrometric investigations were carried out using a Thermo Scientific HPLC-MS system.

General procedure. To 0.047 mol of compound **I** was added 20 ml (0.37 mol) of 93.4% sulfuric acid. The mixture was stirred without heating until complete dissolution of acid **I**. The reactor was placed in a microwave system and the temperature in the reactor was raised to the desired value. At regular intervals samples were taken from the reaction mixture for analysis of content of the parent acid and the reaction products. Upon completion, the mixture was poured into 300 ml of water heated to 80–90°C. The product was filtered off, treated with sodium carbonate solution to remove traces of diphenylamino-2-carboxylic acid, the precipitate was filtered off and dried at 90°C in an oven with forced air circulation.

The composition of the reaction mixtures was determined by TLC by comparison with reference samples. (Plates "Sorbfil" PTSH-P-B-UV, eluent toluene–acetone–ethanol–1% HCl in a ratio of 7:6:5:0.5.

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