PREPARATION OF SYDNONEIMINES BY BASIC CYCLIZATION OF N-NITROSOAMINOACETONITRILES

V. G. Yashunskii, V. V. Ogorodnikova,
and L. E. Kholodov

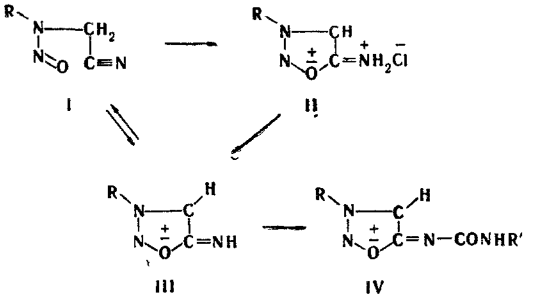
UDC 547.793.1

The results of a kinetic study of the cyclization of N-nitrosoaminoacetonitriles in the presence of tertiary amines are presented. The dependence of the reaction rate on the character of the substituents attached to the nitrogen atom in the starting N-nitrosoaminoacetonitrile, concentration and temperature dependences, and the effect of solvents were established.

The only method for the formation of N-exocyclic five-membered mesoionic heterocycles that was known up until recently was protocyclization [1]. It is used most widely for the synthesis of derivatives of sydnoneimines. Some of them are used as medicinal preparations [2]. The cyclization of substituted N-nitroso-N-aminoacetonitriles (I) to sydnoneimine hydrochlorides (II) under the influence of hydrogen chloride is a thoroughly studied process [3] that is realized smoothly under laboratory and factory conditions.

We have recently demonstrated [4] that the formation of a sydnoneimine ring from nitriles I may also take place in the presence of bases. This fact is of interest not only from a theoretical point of view but also from a practical point of view [5].

In the present communication we present the results of a study of the principles and mechanism of a new reaction by means of a kinetic method.



During a study of alkaline ring opening in sydnoneimine salts II it was shown [6] that this process takes place under certain conditions to give N-nitrosoaminoacetonitriles (I) reversibly and that interconversion of two tautomeric forms, viz., linear I and cyclic III, occurs under these conditions, i.e., ring closing of I to give a sydnoneimine ring may occur. However, because of the instability of base III, it is impossible to isolate it in alkaline media, and it is therefore necessary to exclude water and tie up the resulting base III by converting it to the stable exocyclic derivative, thereby shifting the tautomeric equilibrium, for cyclization of nitrosoaminoacetonitriles I in the presence of bases. We selected phenyl isocyanate, which reacts with sydnoneimine salts to give N_6-phenylcarbamoyl derivatives (IV, R' = C_6H_5) [7], as the binding (or fixing) agent.

In preliminary experiments we demonstrated that a single reaction product, viz., N_6-phenylcarbamoyl-3-phenylisopropylsydnoneimine (IVa), is formed rapidly when N-nitroso-N-phenylisopropylaminoacetonitrile (Ia) is heated with phenyl isocyanate in benzene solution in the presence of triethylamine.

A spectrophotometric method proves to be convenient for the study of the kinetics of the process, since the intense absorption band of IVa [λ = 345 nm (ε = 20000)] is not over-

---

Institute of Biophysics of the Ministry of Public Health of the USSR, Moscow 123182.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1244-1247, September, 1980.

0009-3122/80/1609-0941$07.50

TABLE 1. Effect of Solvents on the Rate of Reaction of N-Nitrosoaminoacetonitrile (Ia) (c $1 \cdot 10^{-2}$ mole/liter) with Phenyl Isocyanate (c $1 \cdot 10^{-1}$ mole/liter) and Triethylamine (c $3 \cdot 10^{-2}$ mole/liter) at 50°C

Solvent	ε	I [8]*	$k_1 \cdot 10^3$, min^{-1}
Toluene	2,4	−5,66	1,03
Benzene	2,3	−5,56	1,70
Chlorobenzene	5,6	−5,06	1,77
Dichlorobenzene	9,9	−4,69	1,90
Dichloroethane	10,4	−4,30	4,55

*This is the ionizing capacity of the solvent.

TABLE 2. Effect of Aryl Isocyanates on the Rate of Reaction with N-Phenylisopropylnitrosoaminoacetonitrile (Ia) (c $1 \cdot 10^{-2}$ mole/liter) and Triethylamine (c $3 \cdot 10^{-2}$ mole/liter) at 50°C in Benzene

Isocyanates	$k_1 \cdot 10^3$ min^{-1}
Phenyl	1,70
p-Tolyl	1,61
m-Trifluoromethylphenyl	1,75

lapped with the absorption bands of nitrosoaminoacetonitrile Ia [λ = 245 nm (ε = 10000)] and phenyl isocyanate (λ = 280 nm).

The reaction rate constants were determined from the accumulation of the final reaction product according to the formula

$$k_1 = \frac{\ln(D_\infty^{IV} - D_n^{IV}) - \ln(D_\infty^{IV} - D_{n+1}^{IV})}{t_{n+1} - t_n},$$

where D_n^{IV} and D_{n+1}^{IV} are the instantaneous optical densities of sydnoneimine IV at times t_n and t_{n+1}, and D_∞^{IV} is the final optical density of IV.

No changes in the UV spectra of the reaction medium (nitrosoaminoacetonitrile Ia, phenyl isocyanate, and triethylamine in benzene) were observed at room temperature after several hours. However, when the temperature is raised to 33°C, the reaction rate becomes appreciable ($k_1 = 3 \cdot 10^{-4}$ min^{-1}) and increase by a factor greater than three ($k_1 = 1 \cdot 10^{-3}$ min^{-1}) when the temperature is increased up to 65°C.

The effect of solvents on the reaction conditions was studied. The reaction cannot be carried out in proton solvents (water and alcohol) because of interaction of the latter with isocyanates; the reaction proceeds rapidly in polar aprotic solvents [dimethyl sulfoxide (DMSO) and dimethylformamide (DMF)] but is complicated by the significant formation of side products. The reaction does not occur in chloroform or carbon tetrachloride over the investigated temperature range; the reaction rate increases symbatically in benzene, toluene, chlorobenzene, dichlorobenzene, and dichloroethane as the polarity of the solvent increases (Table 1). Thus on passing from nonpolar benzene to polar dichloroethane, the dielectric permeability of which is greater by a factor of five, the rate of the process increases by a factor greater than two.

In a study of the effect of the reagent ratio on the rate of the process we found that the latter does not depend on the phenyl isocyanate concentration. Replacement of phenyl isocyanate by the p-tolyl- orm-trifluoromethylphenyl derivatives also did not lead to a reliable change in the rate of the investigated process.

TABLE 3. Effect of the Triethylamine Concentration on the Rate of Reaction of N-Nitrosoaminoacetonitrile (c $1 \cdot 10^{-2}$ mole/liter) with Phenyl Isocyanate (c $1 \cdot 10^{-1}$ mole/liter) at 50°C in Benzene

Triethylamine conc., mole/liter	$k_1 \cdot 10^3$ min^{-1}
0,02	1,30
0,03	1,70
0,04	2,50
0,06	3,60
0,08	6,00

TABLE 4. Effect of Substituents in N-Nitrosoaminoacetonitriles (c $1 \cdot 10^{-2}$ mole/liter) on the Rate of Reaction with Phenyl Isocyanate (c $1 \cdot 10^{-1}$ mole/liter) and Triethylamine (c $3 \cdot 10^{-2}$ mole/liter) in Benzene at 50°C

R	$k_1 \cdot 10^3$ min^{-1}	$-\lg k_1$	σ^*	E_s^c	$0{,}3\sigma^*$	$0{,}46E_s^c$	Calc. $-\log k_1$
CH_3	0,49	3,30	0,00	0,00	0,00	0,00	3,30
C_2H_5	0,87	3,06	−0,10	−0,38	−0,028	−0,174	3,09
iso-C_3H_7	1,70	2,77	−0,19	−0,08	−0,053	−0,500	2,75
n-C_4H_9	0,98	3,01	−0,13	−0,70	−0,036	−0,320	2,95
iso-C_4H_9	1,41	2,85	−0,125	−1,24	−0,035	−0,520	2,75
cyclo-C_6H_{11}	1,29	2,89	−0,15	−1,40	−0,042	−0,645	2,70
$C_6H_5—CH_2—$	1,15	2,94	0,215	−0,69	−0,060	−0,320	3,02
$C_6H_5—CH_2—CH_2—$	1,38	2,82	0,08	−0,71	0,002	−0,325	2,98
$C_6H_5—CH_2—CH(CH_3)—$	1,77	2,75	0,02	−1,20	0,006	−0,550	2,74
1'-Adamantyl	4,10	2,39	−0,30	−1,7	0,084	−0,785	2,60
1'-Adamantylmethyl	8,40	3,07					

We observed that the rate of formation of the phenylcarbamoyl derivative increases in proportion to the increase in the triethylamine concentration (Table 3), i.e., $k_1 = k_2 \cdot c_{TEA}$, and $k_2 = 1.07$.

To ascertain the effect of substituents attached to the nitrogen atom in N-nitrosoaminoacetonitriles (I) on the reaction rate we determined the rate constants (k_1) at the same reagent ratio for a number of alkyl-, arylalkyl-, and cycloalkylnitrosoaminoacetonitriles (I). Under the selected conditions N-nitroso-N-phenylaminoacetonitrile reacts very slowly. It follows from Table 4 that the reaction rate depends both on the inductive effect and the steric effect of the substituents. The correlation equation makes it possible to make a quantitative estimate of the contributions of these effects of the substituents:

$$\lg k_1 = -3.30 + 0.30\sigma^* - 0.46E_s^c \quad (r = 0.97).$$

In contrast to the cyclization of N-nitrosoaminoacetonitriles in acidic media [3], in which the reaction rate increases as the volumes of the substituents, as well as their electron-donor properties, are increased, in the investigated process the rate increases as the size of the substituent increases but decreases as the electron-donor properties become more pronounced (Table 4).

In addition to triethylamine, other tertiary amines, viz., N-methylmorpholine and dimethylbenzylamine, can also be used in this reaction. It follows from Table 5 that the reaction rate increases substantially as the basicity of the amine increases.

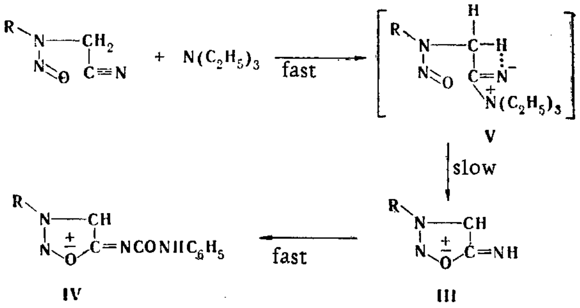
Thus it was established as a result of a kinetic study of the reaction to give N_6-phenylcarbamoylsydnoneimines (IV) under the influence of bases that the reaction rate depends on the temperature, the character of the substituents in the starting nitrosoaminoacetonitrile, the nature of the solvent, the concentration of the tertiary amine, and the basicity of the latter but does not depend on the amount of isocyanate and its reactivity.

TABLE 5. Dependence of the Rate Constants for the Reaction of N-Nitroso-N-phenylisopropylaminoacetonitrile (Ia) (c $1 \cdot 10^{-2}$ mole/liter) and Phenyl Isocyanate (c $1 \cdot 10^{-1}$ mole/liter) in Benzene at 50°C on the Basicity of the Tertiary Amine

Tertiary amines	pK_a (in water)	$k_1 \cdot 10^3$ min^{-1}
Pyridine	5,2	—
N-Methylmorpholine	7,5	0,20
Dimethylbenzylamine	9,0	0,53
Triethylamine	11,4	1,75

Several ideas regarding the mechanism of the investigated reaction can be expressed on the basis of these data.

It is unlikely that the initial step in the process is deprotonation of the α-carbon atom in the I molecule, since it is difficult to imagine the formation of a carbanion in solvents that have weak ionizing capacities. Taking into account the literature data on the nucleophilic character of the carbon atom of the nitrile group [9, 10] and our results, viz., the fact that the reaction is first-order in the amine, the dependence of the reaction rate on the basicity of the amine, and the absence of an effect of the phenyl isocyanate concentration, it may be assumed that the first step in the process is the addition of triethylamine to the carbon atom of the nitrile group in nitrosoaminoacetonitrile I to give intermediate V. The next step involves intramolecular prototropic rearrangement of V, which is probably realized through a number of intermediate complexes, and cyclization, which leads to sydnoneimine base III. The last step in the process consists in the reaction of base III with phenyl isocyanate.



The slowest step in the investigated process is, in all likelihood, cyclization to a sydnoneimine ring. The absence of a concentration effect on the part of phenyl isocyanate constitutes evidence in favor of this assumption.

In contrast to arylcarbamoyl derivatives, N_6-acylsydnoneimines are formed under milder conditions. It was demonstrated in the case of the reaction of N-nitrosoaminoacetonitriles with anhydrides or chlorides of carboxylic acids that the reaction is realized at room temperature in benzene in the presence of triethylamine.

The starting N-nitrosoaminoacetonitriles were obtained by the method in [11].

LITERATURE CITED

1. W. D. Ollis and C. A. Ramsden, Adv. Heterocycl. Chem., 19, 1 (1976).
2. M. D. Mashkovskii, Medicinals [in Russian], Meditsina, Moscow (1972).
3. V. V. Ogorodnikova, L. E. Kholodov, and V. G. Yashunskii, Khim. Geterotsikl. Soedin., No. 1, 39 (1977).
4. V. G. Yashunskii, Z. A. Olovyanishnikova, V. V. Ogorodnikova, and L. E. Kholodov, Khim. Geterotsikl. Soedin., No. 1, 117 (1980).
5. L. E. Kholodov, V. V. Ogorodnikova, A. S. Vitvitskaya, and V. G. Yashunskii, USSR Inventor's Certificate No. 690008; Byull. Izobr., No. 37, 88 (1979).

6. L. E. Kholodov, E. M. Peresleni, and V. G. Yashunskii, Zh. Obshch. Khim., 33, 3699 (1963).
7. L. E. Kholodov, V. G. Yashunskii, R. A. Al'tshuler, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 1, 50 (1973).
8. A. Gordon and R. Ford, The Chemist's Guide [Russian translation], Mir, Moscow (1976), p. 31.
9. E. N. Zil'berman, The Reactions of Nitriles [in Russian], Khimiya, Moscow (1972).
10. H. A. Lillevik and R. A. Gortner, J. Org. Chem., 7, 164 (1972).
11. H. V. Daineker and J. Druey, Helv. Chim. Acta, 45, 2426 (1962).

CYCLODIMERIZATION OF VINYLPYRIDINES

P. B. Terent'ev, V. G. Kartsev,
A. V. Gorelov, I. P. Gloriozov,
Yu. A. Gulevich, and A. N. Kost*

UDC 547.82'828'831'833

When isomeric 2- and 4-vinylpyridines, as well as 2-methyl-5-vinylpyridine, are heated in polyphosphoric or acetic acid, they undergo dimerization, which proceeds via a 1,4-cycloaddition scheme to give pyridyl-substituted 5,6,7,8-tetrahydroquinolines or isoquinolines. Quantum-chemical calculations with the use of the concepts of molecular orbital perturbation theory make it possible to predict the regiospecificity of the reaction. The regiospecific cross cycloaddition of 4-vinylpyridine to 2-methyl-5-vinylpyridine was proposed theoretically and proven experimentally.

In 1967 Winterfeld and Nann [1], in the course of dehydration of 2-(2-hydroxyethyl)-pyridine in polyphosphoric acid (PPA) unexpectedly obtained 5-(2-pyridyl)-5,6,7,8-tetrahydroquinoline, the formation of which they explained by dimerization of the initially formed 2-vinylpyridine via the scheme of the diene synthesis. However, no proof for this assumption was presented in [1]. In addition, the boundaries of applicability of this reaction and the problems of its regioselectivity remained unclear.

We studied the processes involved in the cyclodimerization of substituted 2-vinylpyridines (Ia-f), as well as 2-methyl-5-vinyl- and 4-vinylpyridines (II and III, respectively). We found that the reaction is quite selective with respect to the selection of the solvent and proceeds successfully only in acids of medium strength such as acetic, polyphosphoric, etc. Dimerization is not observed in strong acids (sulfuric and hydrochloric) or in neutral and basic solvents [nitrobenzene, hexametapol, and dimethylformamide (DMF)]. This makes it possible to assume that the protonated vinylpyridine molecule acts as the dienophile in the dimerization reaction, while the unprotonated vinylpyridine molecule acts as the diene. An increase in the "dienophile" activity of 2- and 4-vinylpyridines when they are protonated has already been noted [2]. This also explains the success of the reaction on passing from DMF to polyphosphoric acid (PPA). Strong electrostatic repulsion of each pair of such molecules occurs in strongly acidic media, in which all of the vinylpyridine molecules are protonated, and this constitutes a hindrance to dimerization.

Considering the fact that the molecules of vinylpyridines I contain two pseudodiene systems, viz., N=C—C=O and C=C—C=C, one must assume that the formation of four regiospecific compounds is fundamentally possible during their dimerization (Table 2).

In recent years the regioselectivity of electrocyclic reactions and, in particular, the reactions of the diene synthesis has been predicted successfully by means of the computational methods of molecular orbital (MO) perturbation theory [3]. We recently demonstrated

---

*Deceased.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1248-1254, September, 1980. Original article submitted March 4, 1980.

0009-3122/80/1609-0945$07.50