HETEROCYCLIZATION OF COMPOUNDS CONTAINING DIAZO AND CYANO GROUPS. 3.* TWO PATHWAYS IN THE CYCLIZATION OF 2-DIAZO-2-CYANOACETIC ACID DERIVATIVES UNDER THE INFLUENCE OF BASES

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1,2,3-Triazol-5-olates are formed in the reaction of diazomalonodiamide and 2-diazo-2-cyanoacetic acid amide and N-methylamide with sodium ethoxide, triethylamine, and ammonia. The products of the reaction of 2-diazo-2-cyanoacetamide with primary amines are mixtures of 4-cyano-1,2,3-triazol-5-olates and 5-amino-1-alkyl-1,2,3-triazole-4-carboxamides.

In a previous communication [1] we showed that diazoacetonitrile derivatives, including 2-diazo-2-cyanoacetamide (Ia), 2-diazo-2-cyanoacetic acid N-methylamide (Ib), and ethyl 2-diazo-2-cyanoacetate (Ia), react with hydrogen sulfide, hydrogen selenide, and ethanethiol at either the cyano or diazo group, depending on the "hardness" of the nucleophile. One should expect that, when "harder" nucleophiles are introduced into the reaction, it would proceed via two pathways: at the cyano group and at the even "harder" center of diazo amides Ia,b, viz., the hydrogen atom of the amide function.

Capable of reacting via the first pathway are sodium alkoxides, ammonia, and primary amines, the addition of which to the cyano group of Ia-c may lead to the formation of α-diazo imine system A, which undergoes rapid cyclization to 1,2,3-triazoles [2]. In the case of primary amines the initially formed α-diazo-N-alkylamidines can undergo cyclization at either of the two nitrogen atoms of the amidine group.

Attack by nucleophilic reagents at the amide function (the second pathway) may lead to α-diazoimidolates B, which undergo cyclization to 4-cyano-1,2,3-triazol-5-olates.

The subject of the present research was a study of the relative reactivities of the nitrogen, carbon, and hydrogen atoms, respectively, of the diazo, cyano, and amido groups of 2-diazo-2-cyanoacetic acid derivatives with respect to alkoxides, ammonia, and aliphatic amines.

We selected 2-diazomalonodiamide (II) as a compound that models 2-diazo-2-cyanoacetic acid amides Ia,b but does not contain a cyano group. Ammonium 4-carbamoyl-1H-1,2,3-triazol-5-olate (IIIa) and methylammonium 4-carbamoyl-1H-1,2,3-triazol-5-olate (IIIb) were obtained in the reaction of II with ammonia and methylamine. A band of stretching vibrations of a diazo group is absent in the IR spectra of triazolates IIIa,b, and a band of stretching vibrations of an amide carbonyl group is observed (Table 3). In the PMR spectrum of IIIb, just as in the PMR spectrum of methylammonium trifluoroacetate in d_6-DMSO, the signal of the protons of the methyl group appears in the form of a singlet at 2.4 ppm, which is in agreement with the salt nature of amides IIIa,b. A molecular-ion peak (M^+) is absent in the mass spectrum of triazolate IIIb (Table 2), and an intense signal of $[M - 31]^+$ pseudomolecular ions is observed. These ions correspond to 5-hydroxy-1H-1,2,3-triazole-4-carboxamide (IV), which is formed as a result of the elimination of methylamine from the M^+ ions in the ion source. At the same time, triazolates IIIa,b do not undergo thermal decomposition, as evidenced by the substantial difference in the melting points of triazoles IIIa,b and IV.

*See [1] for communication 2.

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TABLE 1. Conditions and Products of the Reactions of Diazo Compounds Ia-c and II with Bases

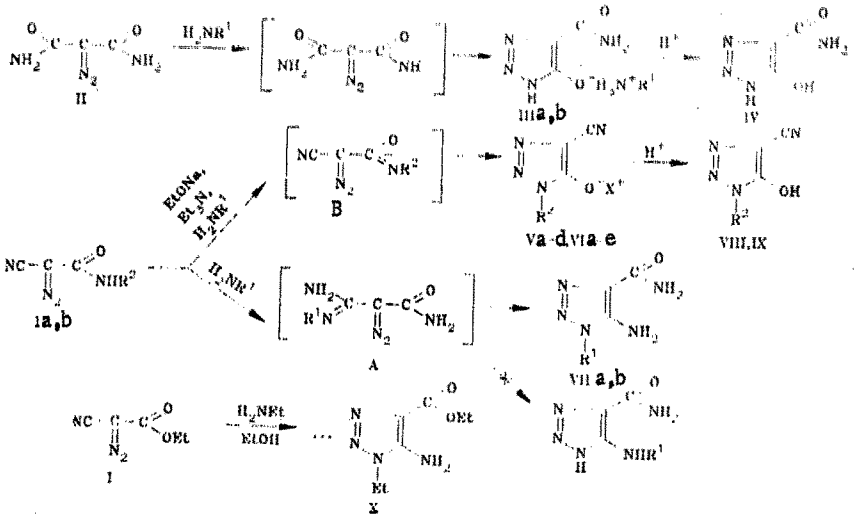
No.	Diazo compound	Base	Solvent	Reaction time, min	Yield, %	
					Triazolates	Aminotriazoles
1	II	NH_3	H_2O	210	IIIa (94)	(0)
2		H_2NMe	H_2O	50	IIIb (89)	(0)
3		H_2NMe	EtOH	4320	IIIb (75)	(0)
4	Ia	EtONa	EtOH	5	Va (84)	(0)
5		NH_3	H_2O	20	Vb (83)	(0)
6		NH_3	EtOH	150	Vb (82)	(0)
7		H_2NMe	H_2O	5	Vc (0)	VIIa (70)
8		H_2NMe	EtOH	5	Vc (61)	VIIa (36)
9		H_2NEt	H_2O	5	Vd (59)	VIIb (4)
10		H_2NEt	EtOH	5	Vd (83)	VIIb (16)
11	Ib	EtONa	EtOH	15	VIa (89)	(0)
12		NEt_3	EtOH	85	VIb (92)	(0)
13		NH_3	H_2O	990	VIc (79)	(0)
14		NH_3	EtOH	10	VIc (83)	(0)
15		H_2NMe	H_2O	5	VId (89)	(0)
16		H_2NMe	EtOH	5	VId (92)	(0)
17		H_2NEt	H_2O	5	VIe (86)	(0)
18		H_2NEt	EtOH	5	VIe (93)	(0)
19	Ic	H_2NEt	EtOH	5	—	X (5)

TABLE 2. Properties of the Synthesized Compounds

Compound	mp,* °C (dec.)	Mass spectrum, m/z (relative intensity)†	Found, %			Empirical formula	Calc., %		
			C	H	N (Na)		C	H	N (Na)
IIIa	199—200		24,7	4,7	48,3	$C_3H_7N_5O_2$	24,8	4,8	48,2
IIIb	167 (without dec.)	128 (100), 71 (40), 54 (17), 44 (62)	30,1	5,8	44,4	$C_4H_9N_5O_2$	30,2	5,7	44,0
IV	190—191,5 (191—192 [3])	128 (100), 71 (33), 54 (14), 44 (60)	27,9	3,3	43,7	$C_3H_4N_4O_2$	28,1	3,2	43,7
Va	298		24,0	2,2	37,6	$C_3HN_4NaO \cdot H_2O$	24,0	2,0	37,3
Vb	220	110 (100), 58 (9), 53 (34), 38 (6)	25,3	5,0	48,9	$C_3H_5N_5O \cdot H_2O$	24,8	4,8	48,3
Vc	156—157	110 (100), 58 (13), 53 (39), 38 (7)	35,3	5,3	50,9	$C_4H_7N_5O$	34,0	5,0	49,6
Vd	147—150		37,7	6,0	43,7	$C_5H_9N_5O \cdot 0{,}5\ H_2O$	36,7	6,1	42,6
VIa	370		32,6	2,0	(15,9)	$C_4H_3N_4NaO$	32,9	2,1	(15,7)
VIc	206—206,5	124 (100), 67 (70), 58 (19), 53 (94)	35,2	5,3	50,1	$C_4H_7N_5O$	34,0	5,0	49,6
VId	117—123 (without dec.)	124 (100), 67 (61), 58 (21), 53 (85)	38,5	5,9	44,8	$C_5H_9N_5O$	38,7	5,8	45,1
VIe	113—117 (without dec.)		42,9	6,7	41,4	$C_6H_{11}N_5O$	42,6	6,6	41,4
VIIa	241—243 (243 [4])	141 (100), 86 (22), 70 (19), 45 (15)	33,8	5,1	50,0	$C_4H_7N_5O$	34,0	5,0	49,6
VIIb	206—206,5 (209—210 [4])	155 (28), 55 (31), 45 (80), 44 (100)	39,1	6,0	44,7	$C_5H_9N_5O$	38,7	5,8	45,1
VIII	156	110 (100), 58 (9), 53 (34), 38 (6)	29,8	2,0	47,1	$C_3HN_4O \cdot 0{,}5\ H_2O$	30,3	2,3	47,1
IX	148	124 (100), 67 (63), 58 (17), 53 (84)	38,6	3,5	45,2	$C_4H_4N_4O$	38,7	3,2	45,1
X	132	184 (56), 169 (52), 137 (36), 123 (100)	45,3	6,5	30,4	$C_7H_{12}N_4O_2$	45,6	6,6	30,4

*The melting points were not corrected.
†The four most intense signals are presented.

Hydroxytriazole IV was obtained preparatively by acidification of an aqueous solution of triazolate IIIa. With respect to its melting point, triazole IV synthesized in this way was identical to an authentic sample [3]. The chromatographic mobilities of hydroxytriazole IV and triazolates IIIa,b coincide in systems of solvents that contain a base or an acid as a consequence of hydrolysis of salts IIIa,b.



Va VIa $X^+=Na^+$; VIb $X^+=HNEt_3^+$; Vb—d, VIc—e $X^+=H_3NR^{1+}$; IIIa, Vb, VIc $R^1=H$; IIIb, Vc, VId, VIIa $R^1=Me$; Vd VIe, VIIb $R^1=Et$; Va—d, VIII $R^2=H$; VIa—e, IX $R^2=Me$

Thus in a model experiment it was shown that ammonia and aliphatic amines do not react at the diazo group but rather attack the hydrogen atom in 2-diazoacetic acid amides, which leads to their cyclization to 1,2,3-triazol-5-olates.

In a study of the reaction of diazo amides Ia,b with ethanol solutions of sodium ethoxide, triethylamine, and ammonia, as well as with ammonium hydroxide, and of diazo methylamide Ib with methylamine and ethylamine in water and ethanol it was observed that these reactions proceed in the same way as the model reaction and that their only products are 4-cyano-1H- (Va,b) and -1-methyl-1,2,3-triazol-5-olates (VIa-e) of the corresponding cations. However, another mechanism, which consists in the addition of the amines to the cyano group, is also realized in the reaction of diazo amide Ia with methylamine and ethylamine, and 5-amino-1-alkyl-1,2,3-triazole-4-carboxamides VIIa,b are formed along with triazolates Vc,d in this case.

With respect to the character of the IR, mass, and PMR spectra, as well as the chromatographic mobilities in a thin layer, triazolates Va-d and VIa-e are similar to salts IIIa,b. 5-Hydroxy-1H- (VIII) and -1-methyl-1,2,3-triazole-4-carbonitrile (IX), respectively, were obtained in the acidification of Vb and VIb. The singlet from the protons of the 1-methyl group in the PMR spectrum of hydroxytriazole IX is shifted ~ 0.4 ppm to weaker field as compared with the corresponding signal in the spectra of salts VIa-e (Table 3). The same shift of the singlet of the methyl group is also observed in the recording of the PMR spectra of VIa-e in d_6-DMSO after the addition of trifluoroacetic acid to the spectrometer cell. The weak-field shift of the signal from the protons of the methyl group is due to weakening of their shielding as a result of a decrease in the negative charge on both the oxygen atom and in the 1,2,3-triazole ring as a whole on passing from triazolates VIa-e to hydroxytriazole IX.

The structure of aminotriazoles VIIa,b was confirmed by data from IR, PMR, and mass spectroscopy, as well as by coincidence of the melting points of VIIa,b with the melting points of genuine samples [4].

Amidation of one ester group with subsequent ring closure of the α-diazo amides to the corresponding 1,2,3-triazol-5-olates occurs in the reaction of dimethyl diazomalonate with primary amines [5]. However, mixtures of compounds that could not be separated into components because of the closeness of their R_f values were obtained in the case of treatment of ethyl 2-diazo-2-cyanoacetate (Ic) with aqueous solutions of methylamine and ethylamine, as well as with an ethanol solution of methylamine. The individual compounds could be isolated only from the mixture obtained in the reaction of diazo ester Ic with an ethanol solution of ethylamine. The ethyl 5-amino-1-ethyl-1,2,3-triazole-4-carboxylate (X) structure was assigned to it on the basis of spectral data. The retention of an ethoxycarbonyl group in triazole X in the presence of excess ethylamine is in agreement with the previously noted

TABLE 3. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum (KBr), cm^{-1}			UV spectrum (in water), λ_{max}, nm (log ε)	PMR spectrum (in d_6-DMSO), δ, ppm
	C=O	C≡N	N—H		
IIIa	1650		3395	222 (3,78), 265 (3,98)	7,60 (2H, s, NH_2); 6,55 (1H, s, NH; 2,40 (3H, s, Me)
IIIb	1665		3425	222 (3,80), 265 (4,00)	
IV	1670		3460	223 (3,76), 268 (3,95)	
Va		2240	3340	219 (3,86), 259 (3,89)	
Vb		2225		219 (3,96), 258 (3,91)	
Vc		2215		219 (4,00), 258 (3,93)	2,38 (3H, s, Me)
Vd		2240	2840 (ν_{CH})	218 (4,08), 258 (4,06)	2,82 (2H, q, J=7,2 Hz, CH_2); 1,12 (3H, t, J=7,2 Hz Me)
VIa		2245		218 (3,70), 262 (3,68)*	3,35 (3H, s, Me)
VIb		2240†	3310†	220 (3,87), 262 (3,87)*	3,40 (3H, s, N—Me); 3,09 (6H, g, J=7,2 Hz CH_2); 1,20 (9H, t, J=7,2 Hz, C—Me)
VIc		2230		218 (3,64), 262 (3,67)*	7,18 (1H, s, N—H); 3,36 (3H, s, Me)
VId		2230		219 (3,86), 262 (3,90)*	3,36 (3H, s, $N_{(1)}$—Me); 2,40 (3H, s, N—Me)
VIe		2230		219 (3,69), 261 (3,74)*	3,31 (3H, s, $N_{(1)}$—Me); 2,82 (2H, кв, J=7,2 Hz, CH_2); 1,10 (3H, t, J=7,2 Hz, C—Me)
VIIa	1640		3300, 3430	223 (3,89), 257 (3,87)	7,43 (2H, s, CO—NH_2); 3,80 (3H, s, Me)
VIIb	1655		3410, 3440	228 (3,79), 258 (3,83)*	7,2 (2H, s, CO—NH_2); 6,24 (2H, s, $C_{(5)}$—NH_2); 4,15 (2H, q, J=7,2 Hz, CH_2); 1,30 (3H, t, J=7,2 Hz, Me)
VIII		2270		223 (3,76), 268 (3,95)	
IX		2260		219 (3,68), 261 (3,71)*	3,72 (3H, s, Me)
X	1720		3485	230 (3,93), 261 (4,01)	6,63 (2H, s, NH_2); 4,37 (2H, q, J=7,2 Hz, CH_2); 4,28 (2H, q, J=7,5 Hz CH_2); 1,34 (3H, t, J=7,5 Hz, Me); 1,31 (3H, t, J=7,2 Hz, Me)

*In ethanol.
†Thin layers.

[6] fact of the lower activity of ethylamine as compared with methylamine in reactions involving the amidation of esters of heterocyclic carboxylic acids.

The following principles were observed in an analysis of the compositions of the products of the reaction of diazo amides Ia,b and II with bases (Table 1). On passing from ammonia to primary amines the reaction rate increases; this is associated with an increase in the nucleophilicity of the reagent. Aminotriazoles were obtained only in the reaction of diazo amide Ia with primary amines. The methyl group in diazo methylamide Ib increases the electron-donor character of the amide function, which increases the rate of the competing process, viz., reaction of the amide and electron-acceptor diazo fragments. The same factor directs the cyclization of α-diazo-N-alkylamidines A exclusively to the alkylated nitrogen atom, which leads to the formation of 5-amino-1-alkyltriazoles VIIa,b and X.

Thus all of the bases investigated in this research react with the amide group of diazo amides Ia,b and II. Primary amines also attack the cyano group of diazo nitriles Ia-c; the products of these reactions are 1,2,3-triazol-5-olates and 5-aminol-1-alkyl-1,2,3-triazoles. The bases used in the present research do not involve the diazo group of Ia-c and II.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with UR-20 and Specord IR-75 spectrometers. The UV spectra of solutions in water (pH 6.5-6.8) and ethanol were recorded with a Beckmann Model 26 spectrophotometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Perkin-Elmer R12B spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with an MAT-311A mass spectrometer with

direct introduction of the samples into the ion source at a sample temperature of 20°C (IIIb, IV, Vb,c, VIc,d, VIII, and IX) and also with an MKh-1303 spectrometer with a system for direct introduction of the samples at a sample temperature of 100°C (VIIa,b and X). The course of the reactions, the compositions of the reaction mixtures, and the purity of the synthesized compounds were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in the following systems: chloroform–ethanol (9:1) (A), propanol–3 N ammonium hydroxide (3:1) (B), and butanol–water–acetic acid–ethyl acetate (4:1:1:1) (C). The chromatograms were developed in UV light; the diazo compounds were determined from the color reaction of the chromatographic spots after spraying the chromatograms with an ethanol solution of m-phenylenediamine, and the hydroxytriazole derivatives were determined from the red-brown coloration with an aqueous solution of iron(III) chloride.

The properties of the synthesized compounds are presented in Tables 2 and 3.

Cyclization of Ia-c and II. A 2.72-mmole sample of the diazo compound was added with stirring at 0°C to 0.9 ml of an 8 N solution of the base. At the end of the reaction, the solvent was removed by vacuum evaporation to dryness. Chromatographically homogeneous products were obtained in experiments Nos. 1-7 and 11-18 (Table 1). Amides IIIa,b were crystallized from water–ethanol–ether to give fine colorless crystals. Triazolates Va,b were reprecipitated from solutions in ethanol by means of ether, and aminotriazole VIIa was crystallized from water. After purification, salts Va,b were obtained in the form of colorless hygroscopic powders, and triazole VIIa was obtained in the form of colorless lamellar crystals. 1-Methyltriazolates VIa-e were purified by reprecipitation from absolute ethanol–ether. Compound VIb was obtained in the form of a light-brown oil, while the remaining triazolates VIa, c-e were fine, colorless, hygroscopic crystals. Mixtures of substances were obtained in experiments Nos. 8-10 and 19. Separation of the mixtures obtained in experiments Nos. 8-10 was carried out by means of column chromatography on 40/100 μ silica gel. The composition of the eluent was changed from chloroform–ethanol (9:1) to pure ethanol.

5-Amino-1-alkyl-1,2,3-triazole-4-carboxamides VIIa,b. These compounds were detected in the eluate with the composition chloroform–ethanol (3:1). After crystallization from ethanol–chloroform–hexane, VIIa,b were obtained in the form of colorless lamellar crystals. The TLC data for VIIa were as follows: R_f 0.13 (A), 0.35 (B), and 0.38 (C). The TLC data for VIIb were as follows: R_f 0.20 (A), 0.65 (B), and 0.61 (C).

4-Cyano-1H-1,2,3-triazol-5-olates Vc,d. These compounds were isolated from the eluate with the composition chloroform–ethanol (1:2). Fine colorless crystals were obtained after reprecipiation from ethanol–ether.

5-Hydroxy-1,2,3-triazoles IV, VIII, and IX. Sulfuric acid diluted with water in a ratio of 1:1 by volume was added up to pH 5-4 to a solution of 3.63 mmole of triazolates IIa, Vb, and VIb in 7 ml of water, after which the reaction mixture was cooled to 0°C. The method used to isolate hydroxytriazoles IV, VIII, and IX was due to their solubility in water. The precipitated carboxamide IV was removed by filtration, washed with cold water, and crystallized from water to give fine colorless crystals. With respect to the TLC data, hydroxytriazole IV coincided with triazolates IIIa,b: R_f 0.24 (B) and 0.59 (C). Water-soluble carbonitriles VIII and IX were extracted with ether (five 20-ml portions). The ether was removed by distillation, and the residue was reprecipitated from water–ethanol–ether to give colorless fluffy crystals. With respect to its chromatographic mobility, hydroxytriazole VIII coincided with salts Va-d: R_f 0.52 (B) and 0.66 (C). With respect to its chromatographic mobility, hydroxytriazole IX coincided with triazolates VIa-e: R_f 0.58 (B) and 0.34 (C).

Ethyl 5-Amino-1-ethyl-1,2,3-triazole-4-carboxylate (X). This compound was obtained by the general cyclization method (experiment No. 19 in Table 1). The residue after evaporation of the solvent was treated with ether (four 30-ml protions). The ether was removed by distillation, and the residue was reprecipitated from absolute ethanol–heptane to give light-red crystals. The TLC data were as follows: R_f 0.56 (A),0.74 (B), and 0.76 (C).

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REACTIONS OF 4-NITRO-1,2,3-TRIAZOLE WITH ALKYLATING AGENTS AND COMPOUNDS WITH ACTIVATED MULTIPLE BONDS

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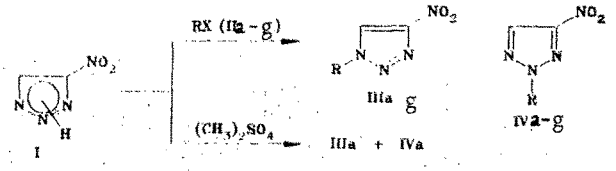
When 4-nitro-1,2,3-triazole is alkylated, a mixture of N_1- and N_2-isomers is formed, with the latter usually predominating. The same behavior is also observed in addition reactions of 4-nitrotriazole to activated multiple bonds.

Electrophilic substitution reactions in a number of vicinal triazoles have been studied very insufficiently. Thus, on alkylation of mono-and di-substituted 1,2,3-triazoles, a mixture of all three isomers [1], the 1,4- and 2,4-isomers with one of them predominating [2-5], as well as only the N_1 or N_2 alkylation products [2, 3, 5] were obtained. Not only the nature of the substitutent in the ring but also the reaction conditions have a given orienting effect on the direction of attack of the electrophile. It is shown, for example [5], that reaction of unsubstituted 1,2,3-triazole with picryl fluoride under conditions of basis catalysis leads to the formation of 2-picryltriazole, while without catalyst 1-picryltriazole is formed. As far as 4-nitrotriazole is concerned, it is known [5] that when it is alkylated with picryl fluoride in DMF only 1-picryl-4-nitrotriazole is obtained.

In order to elucidate the orienting role of the nitro group, the alkylation of 4-nitro-1,2,3-triazole (I) with various alkylating agents has been examined. Owing to the fact that triazole I has three potential reaction centers, the formation of all three alkyltriazoles is possible. The interaction of the Na salt of I with alkyl halides (II) and dimethyl sulfate was studied in acetone at 25°C. It transpired that in all cases a mixture of two isomeric products — 1-R- and 2-R-4-nitrotriazoles (III and IV) with the N_2-isomer often predominating — was formed. The absence of the 1,5-isomer may be explained by steric factors and also the negative inductive effect of the nitro group, lowering the nucleophilicty of the neighboring nitrogen atom.



II—IV a R=CH_3; b R=C_2H_5; c R=*n*-C_3H_7; d R=*iso*-C_3H_7; e R=$C_2H_5O_2CCH_2$, f R=$C_6H_5CH_2$; g R=$C_6H_5COCH_2$; IIa X=I; b—e, g X=Br; e, f X=Cl

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