HETEROCYCLIZATION OF COMPOUNDS CONTAINING DIAZO AND CYANO GROUPS.

5.* 2-DIAZO-2-CYANOACETAZIDE IN THE SYNTHESIS OF 5-HALO-1H-1,2,3-TRIAZONE-4-CARBOXYLIC ACID AZIDES

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A method for the synthesis of 2-diazo-2-cyanoacetazide was developed, and its reaction with various nucleophilic reagents was investigated. 5-Halo-1H-1,2,3-triazole-4-carboxazides and their 4-carbamoyl and 4-ethoxycarbonylamino derivatives were obtained.

We have previously shown that the reactions of derivatives of diazoacetonitrile (DAN) with hydrogen halides, aliphatic amines, and sulfur-containing reagents constitute a simple and efficient method for the synthesis of 5-halo-, 5-hydroxy-, and 5-amino-1H-1,2,3-triazoles and 5-amino-1,2,3-thiadiazoles [1-4]. The present research is devoted to an investigation of the peculiarities of the reactivity of 2-diazo-2-cyanoacetazide (I) that are associated with the presence in it of a labile carboxazido group together with cyano and diazo groups. The investigation was carried out in order to develop a method for the synthesis of 5-substituted-1,2,3-triazole- and -thiadiazole-4-carboxazides as starting compounds in the synthesis of substances that have a broad spectrum of biological activity [5-10].

To obtain 2-diazo-2-cyanoacetazide (I) we synthesized 2-amino-2-cyanoacethydrazide (II) by the reaction of ethyl 2-amino-2-cyanoacetate (III) with anhydrous hydrazine in methanol. Reaction with both the amino and hydrazido groups occurs in its diazotization in aqueous hydrochloric acid, and diazo azide I is formed in 2-3% yield. Varying the reaction conditions did not lead to an increase in the yield. Decomposition of diazo azide I evidently occurs in an aqueous medium. The diazotization of amine II with alkyl nitrites in dioxane or tetrahydrofuran in the presence of 0.1 mole of hydrogen chloride leads to an increase in the yield of diazo azide I to 30-40%. To confirm the structure diazo azide I was synthesized by a diazo transfer reaction from cyanoacetazide (IV) and 3-ethyl-2-azidobenzothiazolium tetrafluoroborate. To simplify the method and because of its low stability the 2-ethyl-2-azidobenzothiazolium tetrafluoroborate was used at the instant of its production [11].

Double absorption bands at 1685 and 1705 cm^{-1} (C=O) and at 2218 and 2235 cm^{-1} (C≡N) and the superimposition of the absorption bands at 2115 (sh), 2122 (sh), 2132, and 2150 cm^{-1} (N=N, N=N=N) are observed in the IR spectrum of diazo azide I; this constitutes evidence for retarded rotation about the $C_{(3)}-C_{(6)}$ bond and its existence in the form of a mixture of cis and trans isomers [12].

We have previously observed the dual reactivity of carbonyl derivatives of DAN in reactions with nucleophilic reagents and have shown that, depending on its hardness, the nucleophile reacts either at the cyano group or at the diazo group of carbonyl derivatives of DAN [3].

One might have expected that the introduction of a carboxazido group into the DAN molecule would lead to additional pathways of the reaction of diazo compounds with nucleophiles.

To predict the reactivity of diazo azide I we made quantum-chemical calculations of the charges, energies, and coefficients of the boundary orbitals by the CNDO/2 method with

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*See [1] for Communication 4.

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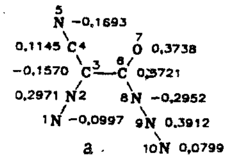
TABLE 1. Properties of the Synthesized Compounds (I, II, V-XII)

Compound	T_{mp}*, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Hal, P, S	N		C	H	Hal, P, S	N	
I	41					C_3N_6O	26,5	—	—	61,8	39 (A) 85 (B)
II	95—96	30,7	5,1	—	48,8	$C_3H_6N_4O$	31,6	5,3	—	49,1	78
V	139—140	62,5	4,5	7,7	21,6	$C_{21}H_{18}N_6OP$	62,8	4,5	7,7	20,9	90
VI	128—130	74,5	4,8	9,7	8,7	$C_{39}H_{30}N_4OP_2$	74,1	4,8	9,8	8,9	88
VII	170—171**	32,1	3,6	—	50,1	$C_3H_4N_4O$	32,4	3,9	—	50,0	56
VIII	98—145	29,0	1,7	—	60,8	$C_3H_2N_6O$	26,1	1,5	—	60,9	22
IX	153—154	21,4	1,3	18,5	49,2	$C_3H_2N_6OS$	21,2	1,2	18,8	49,2	5
Xa	65	21,2	0,5	20,5	49,1	C_3HClN_6O	20,9	0,6	20,5	48,7	91
Xb	98	16,9	0,7	37,0	38,5	C_3HBrN_6O	16,6	0,5	36,8	38,7	95
XIa	163—164	36,5	4,1	15,4	24,1	$C_7H_9ClN_4O_3$	36,1	3,9	15,2	24,1	63
XIb	165—168	30,1	3,4	29,0	20,5	$C_7H_9BrN_4O_3$	30,4	3,3	28,8	20,2	69
XIc	193—195	48,8	3,7	15,9	25,1	$C_9H_7ClN_4O$	48,6	3,7	15,9	25,2	87
XId	186—188	40,7	2,7	30,0	20,7	$C_9H_7BrN_4O$	40,5	2,6	30,0	21,0	69
XIIa	133—135	31,4	3,5	18,5	29,9	$C_5H_7ClN_4O$	31,5	3,7	18,6	29,4	75
XIIb	125—127	25,9	3,3	33,8	3,8	$C_5H_7BrN_4O$	25,5	3,0	34,0	23,8	72

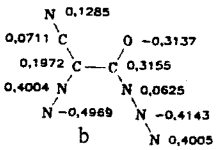
*Compounds I and VIII melted explosively, while II, V, VI, IX, and Xa,b melted with decomposition.

†According to the data in [2], this compound had mp 170-171°C.

complete optimization of the geometry of the molecule and obtained the following results:*

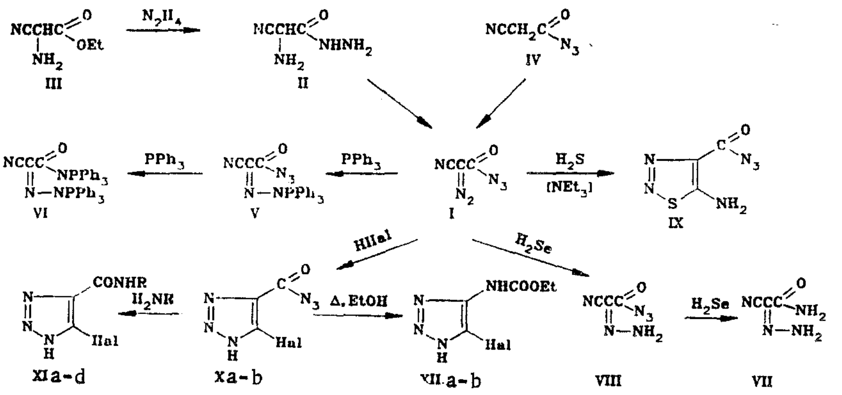


a



b

It is apparent that the charges and coefficients of the atomic orbitals (AO) of the lowest vacant molecular orbitals (LVMO) for the atoms of the three active groups are arranged in the following orders: $q_4 \gg q_{10} > q_1$, and $C_1 > C_{10} > C_4$. It should be noted that the carbon atom of the cyano group differs substantially from the nitrogen atoms of the diazo and azido groups with respect to the reactivity indices. One therefore might have expected that with sufficiently hard nucleophilic reagents the reaction would proceed selectively at the cyano group, whereas with soft nucleophiles it would proceed at the diazo and azido groupings. The calculated energy of the LVMO of diazo azide I (1.4558 eV) is substantially lower than the corresponding value for 2-diazo-2-cyanoacetamide (2.2813 eV [1]); this indicates the high tendency of I to undergo reduction.



X a, XI a, c, XII a Hal=Cl; X b, XI b, d, XII b Hal=Br; XI a, b R=OH₂COOEt; c, d R=Ph

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*Here, diagram a shows the charges on the atoms, and diagram b shows the coefficients of the lowest vacant molecular orbitals (LVMO).

TABLE 2. Spectral Properties of the Synthesized Compounds

Compound	IR spectrum (KBr), cm^{-1}		UV spectrum (in water), λmax, nm (log ε)	PMR spectrum	Mass spectrum,* m/z (%)
	stretching	deformation			
I	2235, 2218 (CN), 2150, 2132, 2122, 2115 (sh.) ($N_{(2)}$, $N_{(3)}$), 1705, 1685 (CO)	1288, 1355 ($N_{(3)}$)	212 (3,98), 263 (4,01)		
II	3315—3188 (NH), 2895 (CH), 2741 (CN), 1700 (CO)				
V	3070 (CH), 2230 (CN), 2173, 2143 ($N_{(3)}$), 1322 ($N_{(3)}$), 1670 (CO)			8,8—7,4 (15H, m, $3C_6H_5$)	
VI	3070 (CH), 2218 (CN), 1615 (CO)		285 (4,3)	8,85—7,45 (30H, m, $6C_6H_5$)	
VII	3440—3150 (NH), 2228 (CN), 1695 (CO)		230 (3,64), 286 (4,09)		
VIII	2230 (CN), 2218, 2150 ($N_{(3)}$), 1690 (CO)	1340 ($N_{(3)}$)			138 (65,9), M^+ 96 (100), 68 (87,9), 67 (50,5), 53 (41,8)
IX	3370—3190 (NH), 2195, 2138 ($N_{(3)}$), 1670 (CO)	1328 ($N_{(3)}$)	215 (3,92), 290 (3,95)		M^+ 170 (53), 142 (50), 72 (71), 60 (100)
Xa	3210 (NH), 2190, 2172 ($N_{(3)}$), 1690 (CO)	1300 ($N_{(3)}$)	245 (4,03)		
Xb	3040, 2980 (NH), 2210, 2175 ($N_{(3)}$), 1720 (CO)	1300 ($N_{(3)}$)	249 (3,91)		188 (14), 137 (56), 136 (100), 109 (28)
XIa	3345, 3190 (NH), 3010, 2900 (CH), 1730, 1683 (CO)	1570 (NH)	212 (3,79), 237 (3,81)	8,77 (1H, t, J=6 Hz, H); 4,12 (2H, q, J=7,2 Hz, CH_2); 3,95 (2H, t, J=3 Hz, CH_2); 1,18 (3H, t, J=7,2 Hz, CH_3)	232 (4,2), M^+ 161 (33,3), 159 (100), 132 (24,2), 130 (72,7)
XIb	3350, 3190 (NH), 3010, 2880 (CH), 1680, 1725 (CO)	1565 (NH)	207 (3,79), 233 (3,94)	8,79 (1H, t, J=6 Hz, NH); 4,15 (2H, q, J=7,2 Hz, CH_2); 3,99 (2H, t, J=3 Hz., CH_2); 1,21 (3H, t, J=7,2 Hz, CH_3)	
XIc	3395, 3120 (NH), 2975, 2885 (CH), 1680 (CO)	1565 (NH)	201 (4,12), 261 (4,03)	10,42 (1H, s, NH); 7,9—7,12 (5H, m, C_6H_5)	224 (29,2), 222 (83,3), M^+ 132 (16,7), 130 (50,0), 93 (100)
XIc	3400, 3105 (NH), 2972, 2887 (CH), 1680 (CO)	1560 (NH)	262 (4,18)	10,4 (1H, s, NH); 7,88—7,12 (5H, m, C_6H_5)	268 (57,8), 266 (57,8), M^+ 176 (24,4), 94 (33,3), 93 (100)
XIIa	3300—3140 (NH), 3010, 2955 (CH), 1720 (CO)	1562 (NH)		9,46 (1H, s, NH); 4,1 (2H, q, J=7,2 Hz, CH_2), 1,2 (3H, t, J=7,2 Hz, CH_3)	190 (27,2), M^+ 133 (19,6), 131 (59,8), 120 (32,6), 118 (100)
XIIb	3280—3120 (NH), 2990, 2940 (CH), 1720 (CO)	1560 (NH)		9,38 (1H, s, NH); 4,1 (2H, q, J=7,2); 1,2 (3H, t, J=7,2 Hz, CH_3)	236 (42,3), 234 (42,3), M^+ 177 (69,0), 175 (70,4), 164 (98,0), 162 (100)

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*The maximum peaks in the spectra are presented.

Our experiments confirmed the results of the calculations completely. When diazo amide I is treated with triphenylphosphine, the diazo group reacts, and phosphazine V is formed. The use of 2 moles of triphenylphosphine leads to the formation of phosphazene VI. Hydrogen selenide reduces diazo azide I to 2-cyano-2-hydrazonoacetamide (VII). Since 2-cyano-2-hydrazonoacetazide (VIII) was isolated as an intermediate, one might conclude that in reactions with soft nucleophilic reagents the diazo group has a higher reactivity than the carboxazido grouping.

According to TLC data, the formation of a mixture of five compounds, from which only 5-amino-1,2,3-thiadiazole-4-carboxazide (IX) was isolated in 5% yield, occurs in the reaction in diazo azide I with hydrogen sulfide in the presence of triethylamine. In the reaction of I with hydrogen sulfide all three electrophilic centers of the molecule are evidently involved.

In contrast to hydrogen sulfide, a harder nucleophile, viz., the chloride ion, which is formed in the reaction of diazo azide I with hydrogen chloride, reacts exclusively with the cyano group to give 5-chloro-1H-1,2,3-triazole-4-carboxazide (Xa). The same compound is formed as a side product in the diazotization of amine II in tetrahydrofuran in the presence of excess hydrogen chloride. Similarly, 5-bromo-1H-1,2,3-triazole-4-carboxazide (Xb) is formed in the reaction of diazo azide I with hydrogen bromide.

Thus diazo azide I reacts ambiguously with nucleophilic reagents: the cyano group reacts with hard nucleophiles, whereas, depending on the amount of reagent, either the diazo group or the diazo and azido groups simultaneously react with soft nucleophiles.

Compounds Xa,b undergo the reactions that are characteristic for carboxazides. Thus replacement of the azido group occurs in the reaction with aniline and glycine ethyl ester, and amides XIa-d are formed. When halotriazoles X are heated in alcohol, they undergo smooth conversion to urethanes XIIa,b.

The structures of the products were confirmed by data from IR, PMR, and UV spectroscopy and mass spectrometry.

EXPERIMENTAL

The UV spectra of solutions of the compounds in water and ethanol were recorded with a Beckmann M-26 spectrophotometer. The IR spectra of KBr pellets and solutions in CCl_4 were recorded with UR-20 and Specord 75 spectrometers. The PMR spectra were obtained with a Perkin-Elmer R 12 B spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with an MAT-212 mass spectrometer (70 eV) under standard conditions.

The properties of the synthesized compounds are presented in Tables 1 and 2.

2-Amino-2-cyanoacethydrazide (II). A 2.5-g (78 mmole) sample of anhydrous hydrazine was added at 20°C to a solution of 10 g (77.5 mmole) of ethyl 2-amino-2-cyanoacetate (III) in 40 ml of methanol. The precipitate that formed after the mixture was cooled was removed by filtration, washed with ether, and crystallized from methanol.

2-Diazo-2-cyanoacetazide (I). A) A 40-ml (0.48 mole) sample of ethyl nitrite and 10 ml of tetrahydrofuran saturated with dry hydrogen chloride were added simultaneously in the course of 1-2 min with vigorous stirring at 5-10°C to a suspension of 23 g (0.2 mole) of amino hydrazide II in 800 ml of absolute tetrahydrofuran or dioxane. After 20 min, the reaction mass was filtered, and the filtrate was concentrated to a volume of 40 ml at reduced pressure. The residue was treated with 50 ml of chloroform, and the undissolved material was removed by filtration. The filtrate was applied to a column packed with silica gel (L 40/100) and eluted with chloroform. The fraction containing diazo azide I (tested with m-phenylenediamine) was concentrated at reduced pressure to give a yellow oil, which crystallized when it was cooled.

B) A 5.5-g (50 mmole) sample of 3-ethyl-2-chlorobenzothiazolium tetrafluoroborate and 3.3 g (50 mmole) of sodium azide were added with stirring at −5°C to a solution of 14.3 g (50 mmole) of cyanoacetazide IV in 100 ml of ethanol and 60 ml of water. After 25 min, the mixture was extracted with hexane (six 800-ml portions), and the extract was dried with anhydrous sodium sulfate and evaporated in vacuo to give a yellow oil, which crystallized when it was cooled.

2-Cyano-2-triphenylphosphazinoacetazide (V). A solution of 2.63 g (10 mmole) of triphenvlphosphine in 10 ml of chloroform was added with stirring at 0°C to a solution of 1.36 g (10 mmole) of diazo azide I in 10 ml of chloroform. Phosphazine V was precipitated by means of hexane and was crystallized from methanol to give yellow lamellar crystals.

2-Cyano-2-triphenylphosphazino-N-triphenylphosphinoacetamide (VI). This compound was similarly obtained from diazo azide I and 2 moles of triphenylphosphine. The product was obtained in the form of colorless crystals.

2-Cyano-2-hydrazonoacetamide (VII). A solution of 1.36 g (10 mmole) of diazo compound I in 50 ml of chloroform was saturated at 0°C with hydrogen selenide. After 2 h, the resulting precipitate was removed by filtration, and VII was separated from the selenium by crystallization from ethanol to give colorless acicular crystals. The chloroform filtrate was evaporated, and the residue was separated with a column (elution with chloroform) to give an additional amount of VII and 2-cyano-2-hydrazonoacetazide (VIII) in the form of colorless lamellar crystals.

5-Amino-1,2,3-thiadiazole-4-carboxazide (IX). Two drops of triethylamine were added to a solution of 1.7 g (12.5 mmole) of diazo azide I in 50 ml of chloroform, after which hydrogen sulfide was passed through the mixture for 2 h. The resulting precipitate was removed by filtration and crystallized from methanol to give colorless or slightly yellow acicular crystals.

5-Chloro-1H-1,2,3-triazole-4-carboxazide (Xa). A solution of 1.7 g (12.5 mmole) of diazo azide I in 100 ml of chloroform was saturated with hydrogen chloride at 0°C. After 3 days, the chloroform was removed by distillation, and the residue was reprecipitated from solution in chloroform by means of hexane to give colorless acicular crystals.

5-Bromo-1H-1,2,3-triazole-4-carboxazide (Xb). This compound was obtained by a procedure similar to that used to prepare chlorotriazole Xa. The reaction of diazo azide I and hydrogen bromide gave colorless acicular crystals.

5-Chloro-1H-1,2,3-triazole-4-N-ethoxycarbonylmethylcarboxamide (XIa). A 2.1-ml sample of triethylamine was added to 2.1 g (15 mmole) of glycine ethyl ester hydrochloride suspended in 50 ml of chloroform. After 5 min, 2.6 g (1.5 mmole) of chlorotriazole Xa was added.

5-Bromo-1H-1,2,3-triazole-4-N-ethoxycarbonylmethylcarboxamide (XIb). This compound was similarly obtained from bromotriazole Xb in the form of colorless acicular crystals.

5-Chloro-1H-1,2,3-triazole-4-carbanilide (XIc). A 1.7-g (10 mmole) sample of chlorotriazole Xa was added to a solution of 1 ml of aniline in 50 ml of chloroform. After 2 days, the chloroform was removed by distillation, and the residue was crystallized from water to give colorless lamellar crystals.

5-Bromo-1H-1,2,3-triazole-4-carbanilide (XId). This compound was similarly obtained from bromotriazole Xb in the form of colorless lamellar crystals.

4-Ethoxycarbonylamino-5-chloro-1H-1,2,3-triazole (XIIa). A solution of 1.7 g (10 mmole) of chlorotriazole Xa in 50 ml of absolute ethanol was refluxed for 3 h, after which the ethanol was removed by distillation, and the residue was crystallized from water to give a finely crystalline colorless powder.

4-Ethoxycarbonylamino-5-bromo-1H-1,2,3-triazole (XIIb). This compound was obtained by a procedure similar to that used to prepare urethane XIIa. Bromotriazole Xb gave a finely crystalline colorless powder.

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