REACTION OF NITRILES OF ENYNE ACIDS WITH HYDRAZINES. SYNTHESIS OF CYANO DERIVATIVES OF 2-PYRAZOLINES

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The reaction of nitriles of enyne acids with hydrazine, alkylhydrazines, and phenylhydrazine gives 5-cyanomethyl-2-pyrazolines. The possible mechanism of the cyclization is examined.

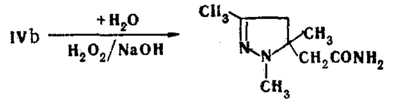
Enyne nitriles [1,2] are compounds that have an activated C ≡ C bond in which the activating cyano group is separated from the C ≡ C bond by an additional multiple bond. Very little study has been devoted to the reactions of compounds of this sort with nucleophilic reagents [3].

In the present research we have investigated the reaction of nitriles I-III with hydrazine, alkylahydrazines, and phenylhydrazine. The reaction products were pyrazolines IVa-i (Table 1).

I–III IVa

I $R=CH_3$; II $R=n\text{-}C_4H_9$; III $R=C_6H_5$
IV: a $R=CH_3$, $R'=H$; b $R=R'=CH_3$; c $R=CH_3$, $R'=n\text{-}C_3H_7$; d $R=CH_3$, $R'=C_6H_5$; e $R=n\text{-}C_4H_9$, $R'=H$; f $R=n\text{-}C_4H_9$, $R'=CH_3$; g $R=n\text{-}C_4H_9$, $R'=n\text{-}C_3H_7$; h $R=C_6H_5$, $R'=H$; i $R=C_6H_5$, $R'=CH_3$.

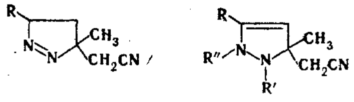
The IR spectra of IV are characterized by an absorption band of medium intensity at 2255-2260 cm^{-1}, which is related to the vibrations of an unconjugated C ≡ N or C ≡ C bond, and an absorption band at 1630 cm^{-1}, which is due to the vibrations of C = N, C = C, or N = N bonds. The presence of a nitrile group was shown by chemical means in the case of the product of the reaction of nitrile I with methylhydrazine (on the basis of proof presented further on, it has the 1,3,5-trimethyl-5-cyanomethyl-2-pyrazoline structure). The nitrile group was converted to an amide group via the Radziszewski reaction by hydrolysis in the presence of alkali and hydrogen peroxide [4].



V

The absorption at 2260 cm^{-1} is absent in the IR spectrum of V, but it does contain absorption bands at 1625, 1660, 3100, 3310, and 3400 cm^{-1}, which are characteristic for primary amides (amide I and II bands, and stretching vibrations of the NH_2 group of an amide) [5]. Absorption of the C = N bond of the pyrazoline ring is superimposed on the amide II absorption band (1625 cm^{-1}).

Thus addition of hydrazines to enyne nitriles proceeds at the C ≡ C bond with subsequent cyclization at the C = C bond to give pyrazolines that have an unconjugated C ≡ N group in the side chain.



VI VII

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TABLE 1. 5-Cyanomethyl-2-pyrazolines (IV)

Compound	R	R′	bp (mm), mp, deg °C	d_4^{20}	n_D^{20}	Empirical formula	Found, %			Calc., %			Chemical shifts, δ, ppm*				
							C	H	N	C	H	N	R	R′	5-CH_3	4-H	CH_2CN
IVa	CH_3	H	45—46	—	—	$C_7H_{11}N_3$	61,2	8,1	30,5	61,3	8,1	30,7	1,83	5,26	1,31	2,46; 2,49	2,46
IVb	CH_3	CH_3	79—80 (4)	1,0005	1,4800	$C_8H_{13}N_3$	63,4	8,9	27,9	63,5	8,7	27,8	1,89	2,65	1,27	2,48; 2,56	2,48
IVc	CH_3	n-C_3H_7	102—104 (4)	0,9700	1,4775	$C_{10}H_{17}N_3$	66,9	9,7	23,4	67,0	9,6	23,4	1,91	2,60	1,29	2,53; 2,61	2,40
IVd	CH_3	C_6H_5	60—60,5	—	—	$C_{13}H_{15}N_3$	73,2	7,2	19,9	73,3	7,0	19,7	1,99	7,11	1,50	2,77; 2,83	2,39
IVe	n-C_4H_9	H	132—133 (3)	0,9928	1,4750	$C_{10}H_{17}N_3$	66,8	9,7	23,6	67,0	9,6	23,4	2,26	4,88	1,36	2,52; 2,57	2,54
IVf	n-C_4H_9	CH_3	116—117 (3)	0,9620	1,4775	$C_{11}H_{19}N_3$	68,4	9,9	21,5	68,4	9,8	21,4	2,22	2,64	1,28	2,52; 2,60	2,45
IVg	n-C_4H_9	n-C_3H_7	123—124 (3)	0,9420	1,4731	$C_{13}H_{23}N_3$	70,4	10,4	19,1	70,6	10,4	19,0	2,23	2,59	1,28	2,51; 2,59	2,39
IVh	C_6H_5	H	69,5—70,5	—	—	$C_{12}H_{13}N_3$	72,4	6,7	21,2	72,4	6,5	21,1	7,24; 7,51	5,63	1,35	2,82; 2,85	2,49
IVi†	C_6H_5	CH_3	—	—	1,5840	$C_{13}H_{15}N_3$	73,2	7,2	19,9	73,3	7,0	19,7	7,21—7,49	2,81	1,37	2,91; 2,99	2,47

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*In the alkyl groups, the δ values for the CH_2 group closest to the pyrazoline ring are presented.

† Isolated chromatographically as a viscous liquid.

The reaction of hydrazine with enyne nitriles may lead to substituted 1- (VI), 2- (IV, R' = H), and 3-pyrazolines (VII, R' = R" = H).

The reaction of monosubstituted hydrazines with nitriles I-III may commence with attack at the C≡C bond by the substituted nitrogen atom. In this case, the formation of only 3-pyrazolines VII (R' = H, R" = Alk, C_6H_5) is possible. If the reaction commences at the C≡C bond by the unsubstituted nitrogen atom, the products may have 2- (IV, R' = Alk, C_6H_5) and 3-pyrazoline (VII, R" = H, R' = Alk, C_6H_5) structures. The IR spectra of the products of the reaction of nitriles with hydrazines (IVa,e,h) contain an absorption band in the region of the stretching vibrations of the NH bond at 3280-3330 cm^{-1}; this excludes the possibility that they exist as 1-pyrazolines (VI). Except for IVd,h,i, absorption at 3000-3100 cm^{-1}, which should have been expected if these compounds had the structure of 3-pyrazolines (VII) (stretching vibrations of the =C−H bond), is absent in the spectra of all of the compounds except for IVd,h,i. In addition, absorption in the region of the stretching vibrations of the NH bond is absent in the IR spectra of all of the compounds except IVa,e,h; this is also evidence in favor of the 2-pyrazoline structure (IV).

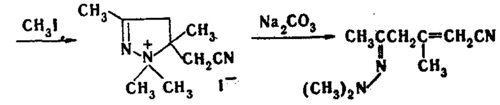
The absorption band of low intensity at 1625-1630 cm^{-1} in the IR spectra of IVa-c, e-g should be assigned to the vibrations of the C=N bond. The band of medium intensity at 1610 cm^{-1} in the spectrum of IVd is due to the superimposition of absorption bands of the C=N bond and the phenyl ring. The absorption bands at 1595 and 1570 cm^{-1} in the spectra of IVh,i are due to the vibrations of the phenyl ring and the C=N bond. It should be noted that the IR spectra of IVa-i in the region of the stretching vibrations of the double bonds have the form characteristic for the spectra of 3-substituted 2-pyrazolines [6].

The definitive structure of the products of the reaction of the enyne nitriles with hydrazines was proved by the PMR spectra and by comparison with the data in the literature regarding the PMR spectra of 2-pyrazolines [7, 8]. First of all, one should note the absence of the signal of a proton attached to the C=C bond in the PMR spectra. Consequently, the investigated compounds cannot have the 3-pyrazoline structure (VII). The signal that might have been assigned to the proton of the methylidyne group of the ring in the 1-pyrazoline structure (VI) is absent in the spectra of IVa,e,h.

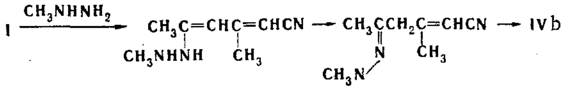
The PMR spectra of all of the investigated compounds (Table 1) contain singlets of the protons of a methyl group (δ 1.30-1.50 ppm) and a methylene group (δ 2.40-2.55 ppm) attached to a saturated carbon atom. In addition, the spectra of all of the compounds are characterized by two broad singlets at δ 2.40-2.90 ppm (each with an intensity of one proton), which should be assigned to the protons of the ring CH_2 group. Such a low position of the signal of a ring CH_2 group is not in agreement with the possible 1-pyrazoline structure (VI) for the products of the reaction of nitriles I-III with hydrazine. The signal at lower field is probably affiliated with the proton of the ring methylene group in the cis position relative to the CH_2CN group.

The structure of the carbon skeleton of the 2-pyrazolines was obtained for IVb by exhaustive methylation and subsequent Hofmann cleavage of the pyrazoline ring via the method in [9].

The isolated hydrazone (IX) was also obtained by reaction of nitrile I with dimethylhydrazine. The IR and PMR spectra of the hydrazones obtained by both methods were completely identical. We presented the proof of the structure of hydrazone IX in [10].


VIII IX

The investigated enyne nitriles were obtained as mixtures of the cis and trans isomers [2]. Both isomers of nitrile I were isolated and subjected to reaction with methylhydrazine. In both cases, pyrazoline IVb was obtained. The formation of pyrazolines IV in all of the investigated reactions of enyne nitriles I-III with hydrazines means that the reaction commences with interaction of the nucleophilic reagent with the triple bond, apparently with the formation of a conjugated enehydrazine. The subsequent formation of the pyrazolines may occur directly by cyclization of the enehydrazine or through tautomeric transition to the hydrazone form and conversion of it to the pyrazoline. In order to ascertain this, we made a detailed investigation of the reaction of nitrile I with methylhydrazine. The reaction occurs with heat liberation and the addition of methylhydrazine to nitrile I is practically complete after 2 h, according to thin-layer chromatography (TLC). Two absorption bands – an intense band at 1600 cm^{-1} and a band of medium intensity in the region of stretching vibrations of double bonds at 1635 cm^{-1} – are observed in the IR spectrum of the reaction mixture of equimolecular amounts of the reagents recorded 2 h after mixing. The form of the absorption in the region of vibrations of the $C \equiv N$ bond is complex. There is a very intense absorption band at 2210 cm^{-1} and bands at 2235 and 2260 cm^{-1}, which project as shoulders of the first band. The intensity of the band at 2235 cm^{-1} is higher than that of the band at 2260 cm^{-1}. The intensity of the band at 1600 cm^{-1} gradually decreases with time, while the intensity of the band at 1635 cm^{-1} initially remains approximately constant and then begins to increase; in the region of vibrations of the $C \equiv N$ bond, the intensity of the absorption at 2210 cm^{-1} decreases, and the intensity of the absorption at 2260 cm^{-1} increases. The absorption at 2235 cm^{-1} initially increases and then decreases. In the spectrum of the reaction mixture recorded after 11 h, the absorption at 1600, 2210, and 2235 cm^{-1} practically vanishes, while the low-intensity bands at 1635 and 2260 cm^{-1} remain. According to TLC, the reaction is complete after 11 h, and only pyrazoline IVb is present. The results can be interpreted as follows. In the reaction of nitrile I with methylhydrazine, the addition product – enehydrazine X – which has an extended system of multiple bonds, is formed quite rapidly. In its IR spectrum, it is apparently characterized by absorption bands at 1600 and 2210 cm^{-1}. Tautomeric transition to the hydrazone form of addition product XI, which is characterized by absorption bands at 1635 and 2235 cm^{-1}, gradually occurs. The final product of the reaction of nitrile I with methylhydrazine – pyrazoline IVb – to which the low-intensity bands at 2260 and 1635 cm^{-1} in the IR spectrum are related (the latter is overlapped by the absorption of the $C=N$ bond of the hydrazone form), forms simultaneously. The rate of conversion of enehydrazine form X of the addition product to hydrazone XI is higher than the rate of formation of pyrazoline IVb. This explains the initial increase in the intensity of the absorption at 1635 and 2235 cm^{-1}. It is most likely that precisely the hydrazone form is converted to the final pyrazoline, since an increase in the electron density in the reaction zone due to the inclusion of the unshared pair of the primary nitrogen atom in the conjugation system will hinder attack of the secondary nitrogen atom at the $C=C$ bond in the enehydrazine form. However, the results do not make it possible to completely exclude the possibility of cyclization of enehydrazine form X to a pyrazoline.



$$I \xrightarrow{CH_3NHNH_2} \underset{CH_3NHNH}{CH_3\overset{|}{C}}=CH\underset{CH_3}{C}=CHCN \longrightarrow CH_3\underset{\underset{CH_3N}{N}}{\overset{\|}{C}}CH_2\underset{CH_3}{C}=CHCN \longrightarrow IVb$$

X XI

The intermediate appearance of the hydrazone form was also fixed by means of PMR spectroscopy. Signals related to the hydrazone (XI) and enehydrazine (X) forms of the initial addition product can be noted in addition to the signals of pyrazoline IVb in the spectrum of an equimolecular mixture of nitrile I and methylhydrazine recorded 4 h after mixing. Thus, for example, the group of signals at δ 2.80, 2.86, 2.98, and 3.05 ppm can, on the basis of a comparison with the spectrum of the product of the reaction of nitrile I with dimethylhydrazine [10], be assigned to the signals of the protons of the CH_2 group of hydrazone XI; the signal at 5.16 ppm apparently belongs to the proton of the NH group of this form [11]. The signals at 4.48 and 5.38 ppm should be assigned to the protons attached to the double bonds of the enehydrazine and hydrazone forms.

The effect of a solvent on the course of the reaction was examined in the case of the reaction of methylhydrazine with nitrile I by means of TLC. The addition and subsequent cyclization to a pyrazoline occur rapidly in dimethyl sulfoxide (DMSO), more rapidly, in fact, than when nitrile I is mixed directly with excess methylhydrazine. Cyclization is slowed down in CCl_4 and proceeds most slowly in alcohol. The increase in the reaction rate in DMSO is explained by the fact that both addition of methylhydrazine to the enyne nitrile and cyclization at the double bond proceed through zwitter ion transition states, which are stabilized by a dipolar aprotic solvent. The nucleophilicity of hydrazine is apparently reduced in alcohol due to the formation of a hydrogen bond with the solvent, which reduces the rate of addition at the $C \equiv C$ bond. The cyclization process in this solvent can be slowed down due to an increase in the stability of the enehydrazine form also as a consequence of the formation of intermolecular hydrogen bonds, which decreases the concentration of the hydrazone form through which the formation of the pyrazolines most likely proceeds.

EXPERIMENTAL

The IR spectra of the pure compounds, mineral oil suspensions (thin layer), and carbon tetrachloride solutions (1-1.5%, thin layer, 603 μm) were recorded with a UR-20 spectrophotometer. The PMR spectra of 10% solutions of the compounds in carbon tetrachloride were recorded with a Varian HA-100 D/15 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard.

2-Methyl-1-penten-3-ynecarbonitrile (I). This compound was obtained in 70% yield by the method in [1] and had bp 46-48° (3 mm), d_4^{20} 0.9032, and n_D^{20} 1.5025.

2-Methyl-1-octen-3-ynecarbonitrile (II). This compound was similarly obtained in 75% yield and had bp 83-84° (4 mm), d_4^{20} 0.8726 and n_D^{20} 1.4912.

2-Methyl-4-phenyl-1-buten-3-ynecarbonitrile (III) [2]. This compound was obtained in 65% yield by vacuum distillation of 2-hydroxy-2-methyl-4-phenyl-3-butynecarbonitrile over P_2O_5 and had bp 124-125° (3 mm), d_4^{20} 1.0054 and n_D^{20} 1.6110. The cis and trans isomers of nitrile I were isolated by means of preparative TLC on activity II aluminum oxide [2]. Ether–petroleum ether (1 : 5) was used as the eluent, and the chromatograms were developed with a UV lamp. The separation of the cis and trans isomers was achieved by three to four repetitions of the separation operations.

cis-2-Methyl-1-penten-3-ynecarbonitrile. This isomer had bp 50.5-51° (3 mm), d_4^{20} 0.9043, n_D^{20} 1.4987.

trans-2-Methyl-1-denten-3-ynecarbonitrile. This isomer had bp 39.5-40° (3 mm), d_4^{20} 0.9018, n_D^{20} 1.5102.

3,5-Dimethyl-5-cyanomethyl-2-pyrazoline (IVa). A 10.5 g (0.1 mole) sample of nitrile I was mixed at room temperature with 3.8 g (0.12 mole) of anhydrous hydrazine. The temperature of the mixture rose spontaneously to 50-60°, after which it was held at room temperature for 5 h. The course of the reaction was monitored by TLC on activity II Al_2O_3 in ether–petroleum ether (2 : 1). Vacuum distillation yielded 12.3 g (90%) of pyrzoline IVa with bp 125.5-126° (4 mm); the liquid crystallized on standing to give a solid with mp 45-46°. The product was unstable and decomposed in air; this is characteristic for 1-unsubstituted pyrazolines [12]. IR spectrum (1% solution in CCl_4, cm^{-1}): 865 w, 890 m, 910 m, 960 m, 1045 m, 1095 w, 1110 w, 1135 w, 1160 w, 1175 w, 1200 m, 1225 m, 1245 w, 1270 w, 1280 w, 1330 s, 1380 s, 1420 s, 1440 s, 1460 s, 1630 m, 2255 m, 2850 m, 2920 s, 2950 s, 2970 s, 3270 s, 3330 s. The physical constants and results of analysis of the pyrazolines obtained are presented in Table 1.

1,3,5-Trimethyl-5-cyanomethyl-2-pyrazoline (IVb). Mixing of 10.5 g (0.1 mole) of nitrile I and 5.3 g (0.12 mole) of methylhydrazine for 13 h gave, after vacuum distillation, 14.3 g (95%) of pyrazoline IVb. IR spectrum (1% solution in CCl_4, cm^{-1}): 850 w, 890 w, 910 w, 928 m, 960 m, 1015 w, 1090 m, 1120 s, 1145 m, 1180 s, 1190 s, 1230 s, 1245 s, 1280 m, 1295 m, 1330 s, 1375 s, 1390 s, 1420 s, 1432 s, 1440 s, 1475 s, 1625 m, 2255 m, 2800 s, 2850 s, 2870 s.

3,5-Dimethyl-1-phenyl-5-cyanomethyl-2-pyrazoline (IVd). A mixture of 2.1 g (0.02 mole) of nitrile I and 2.5 g (0.022 mole) of phenylhydrazine was heated in a test tube with a stopper at 100° for 120 h. The reaction product was isolated by preparative TLC on activity II aluminum oxide in ether–petroleum ether (1 : 1) to give 0.9 g (41%) of pyrazoline IVd with mp 60-60.5°. IR spectrum (1% solution in CCl_4, cm^{-1}): 1020 m, 1045 m, 1090 w, 1115 w, 1140 w, 1165 w, 1185 w, 1210 m, 1230 m, 1280 s, 1290 s, 1305 s, 1355 s, 1400 s, 1445 s, 1465 m, 1505 s, 1610 s, 2260 m, 2850 w, 2860 w, 2920 m, 2950 m, 2985 m, 2995 m, 3035 w, 3050 w, 3075 w.

5-Methyl-3-phenyl-5-cyanomethyl-2-pyrazoline (IVh). A 5 g (0.03 mole) sample of nitrile III was mixed with 1.2 g (0.032 mole) of anhydrous hydrazine. Pronounced heating of the mixture was observed. After 15 h [monitoring by TLC on aluminum oxide in ether petroleum ether (9 : 1)], 5 g (80%) of pyrazoline

IVh, with mp 69.5-70.5° (from ether), was isolated. IR spectrum (thin layer in mineral coil, cm^{-1}): 835 s, 855 s, 900 s, 915 s, 960 w, 980 w, 1020 m, 1065 m, 1085 w, 1110 w, 1160 m, 1185 w, 1225 m, 1275 s, 1315 m, 1360 s, 1385 s, 1420 s, 1460 s, 1505 m, 1575 m, 1595 m, 2260 m, 2880 m, 2935 s, 2975 s, 3030 m, 3070 m, 3260 s, 3320 s.

1,3,5-Trimethyl-5-cyanomethyl-2-pyrazoline (VIII). A mixture of 5 g (0.033 mole) of pyrazoline IVb, 7 g (0.05 mole) of methyl iodide, and 60 ml of benzene was heated at 65° for 4 h. The precipitated VIII was crystallized from ethyl acetate–methanol (2 : 1) to give 8.6 g (90%) of a product with mp 157°. Found, %: C 36.9; H 5.6; N 14.0. $C_9H_{16}IN_3$. Calculated, %: C 36.8; H 5.4; N 14.2.

4-Dimethylhydrazono-2-methyl-1-pentenecarbonitrile (IX). A. A mixture of 8 g (0.026 mole) of methiodide VII, 5 g (0.04 mole) of Na_2CO_3, and 10 ml of water was heated at 50° for 4 h. The reaction mixture was extracted with chloroform, the chloroform extracts were dried with $MgSO_4$, and the solvent was removed. The residue was separated by preparative TLC on activity II aluminum oxide in ether–petroleum ether (1 : 1) to give 1.8 g (40%) of nitrile IX with d_4^{20} 0.9354 and n_D^{20} 1.4885. IR spectrum (thin layer, cm^{-1}): 800 m, 820 m, 860 w, 970 m, 1025 m, 1050 m, 1075 w, 1095, w, 1160 m, 1200 m, 1250 w, 1300 w, 1370 s, 1390 s, 1445 s, 1470 s, 1570 w, 1630 s, 2190 w, 2225 s, 2780 s, 2820 s, 2860 s, 2900 m, 2920 m, 2970 s, 2990 s, 3060 w. Found, %: C 65.5; H 9.2; N 25.5. $C_9H_{15}N_3$. Calculated, %: C 65.4; H 9.1; N 25.4.

B. A mixture of 2.1 g (0.02 mole) of nitrile I and 2 g (0.033 mole) of dimethylhydrazine was heated in a test tube with a ground-glass stopper at 40° for 70 h. The excess dimethylhydrazine was removed in vacuo to give 3.1 g (100%) of nitrile IX with d_4^{20} 0.9341 and n_D^{20} 1.4885. The IR spectrum was identical to the spectrum of the hydrazone obtained by degradation of methiodide VIII.

1,3,5-Trimethyl-5-amidomethyl-2-pyrazoline (V). A 10-g sample of NaOH was added gradually with stirring to 100 ml of 30% hydrogen peroxide, after which 1 g of pyrazoline IVb was added dropwise. The solution was neutralized and extracted repeatedly with ether. The ether extracts were dried with $MgSO_4$, and the ether was removed to give 0.5 g (45%) of amide V with mp 238-240° (dec.). IR spectrum (KBr pellet, cm^{-1}): 740 m, 760 w, 840 w, 950 s, 1020 m, 1040 m, 1090 m, 1235 m, 1320 m, 1390 s, 1430 s, 1505 m, 1530 s, 1625 s, 1660 s, 2760 m, 2870 m, 2940 m, 3100 s, 3310 m, 3400 m. Found, %: C 56.9; H 8.7; N 24.1. $C_8H_{15}N_3O$. Calculated, %: C 56.8; H 8.9; N 24.2.

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