NUCLEOPHILIC ADDITION OF HYDROXYMETHYL-1,2,3-TRIAZOLES TO MULTIPLE BONDS

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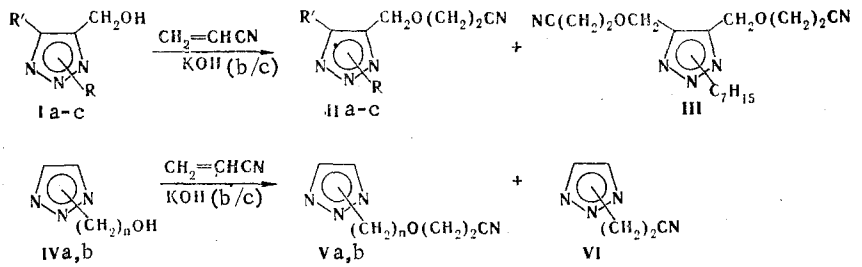
The addition of C- and N-hydroxymethyl-1,2,3-triazoles to the activated multiple bonds of acrylonitrile and benzoylacetylene was studied. The structures of the compounds obtained were proved by means of the PMR and IR spectra.

In order to further study the reactivities of triazoles and their derivatives [1, 2], in the present communication we examined the nucleophilic addition of C- and N-hydroxymethyl-1,2,3-triazoles to the activated multiple bonds of acrylonitrile and phenyl ethynyl ketone.

The addition of hydroxymethyltriazoles to the double bond of acrylonitrile takes place in an excess amount of the latter in the presence of catalytic amounts of anhydrous potassium hydroxide. The use of aqueous solutions promotes the occurrence of sideprocesses, particularly the addition of water to give β,β'-dicyanodiethyl ether [3]. A mixture of 1-heptyl-4(5)-(4'-cyano-2'-oxa-1'-butyl)-1,2,3-triazole regioisomers was obtained in the reaction of 1-heptyl-4(5)-hydroxymethyl-1,2,3,-triazole (Ia) with acrylonitrile, as evidenced by the presence in the PMR spectra of signals of two protons of the triazole ring at δ 7.54 and 7.88 ppm in a ratio equal to the ratio of the isomers in the starting 1-heptyl-4(5)-hydroxymethyl-1,2,3-triazole (65:35). The cyanoethylation of 1-heptyl-4,5-dihydroxymethyl-1,2,3-triazole (Ib) takes place primarily at one hydroxy group (42.8%); however, in addition to this, diaddition product III (9.8%) was isolated. The IR spectrum of monoadduct IIb contains an absorption band of a nitrile fragment at 2235 cm^{-1} and retains the band of the hydroxy group (3200-3500 cm^{-1}), which vanishes in the spectrum of diadduct III. The addition of N-unsubstituted 4-hydroxymethyl-1,2,3-triazole (Ic) to the double bond of acrylonitrile takes place with the participation of both the hydroxy group and the protonated nitrogen atom. The PMR spectrum of the dicyanotriazole IIc obtained in this case contains the signal of a proton of the triazole ring (7.68 ppm) and a series of protons of methylene groups of propionitrile fragments.

Scheme 1



Ia-c IIa-c III IVa,b Va,b VI

I, II a R=C_7H_{15}; b R=C_7H_{15}; I c R=H; II c R=$(CH_2)_2CN$; I, II a,c R'=H; b R^1=CH_2OH;
IV, V a n=1; b n=2

The cyanoethylation of 2-hydroxymethyl-1,2,3-triazole (IVa) gives two products, viz., 2-(4'-cyano-2'-oxa-1'-butyl)-1,2,3-triazole (Va) and 2-(β-cyano-1-ethyl)-1,2,3-triazole (VI). The successive splitting out of a hydroxymethyl fragment and the addition of the intermediately formed triazole to the double bond of acrylonitrile probably occur during the reaction. The PMR spectra of nitriles Va and VI each contain one signal of equivalent protons of the azole ring (7.63 and 7.65 ppm), and this confirms the presence of the substituent in the 2 position of the heteroring. 1-(β-Hydroxyethyl)-1,2,3-triazole (IVb) adds to acrylonitrile in the presence of anhydrous potassium hydroxide to give 1-(5'-cyano-3'-oxa-1'-pentyl)-1,2,3-

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TABLE 1. Characteristics of the Products of the Addition of Hydroxymethyl-1,2,3-triazoles to Multiple Bonds

Compound	mp, °C; bp, °C (mm)	IR spectrum,[a] cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	112—114 (1)	2260 (C≡N), 3040, 3080 (=CH)	62,2	8,9	22,7	$C_{13}H_{22}N_4O$	62,4	8,8	22,4	68
IIb	218—220 (1)	2249 (C≡N), 1090 (C—O—C)	60,0	8,6	20,7	$C_{14}H_{24}N_4O_2$	60,0	9,2	20,0	43
IIc	105—106 (2)	2260 (C≡N), 3090 (=CH), 1190 (C—O—C)	52,9	5,9	34,0	$C_9H_{11}N_5O$	52,7	5,4	34,1	59
III	116—118 (1)	2255 (C≡N), 1120 (C—O—C)	61,5	7,7	21,2	$C_{17}H_{27}N_5O_2$	61,2	8,2	21,0	10
Va	120—122 (2)	2240 (C≡N), 3013, 3020 (=CH), 1250 (C—O—C)	47,7	5,0	36,5	$C_6H_8N_4O$	47,4	5,3	36,8	25
Vb	169—190 (1)	2260 (C≡N), 3080 (=C—H), 1198 (C—O—C)	51,2	6,1	33,8	$C_7H_{10}N_4O$	50,6	6,0	33,7	78
VI	138—140 (2)	2250 (C≡N), 3020 (=CH)	48,8	5,1	46,1	$C_5H_6N_4$	49,2	4,9	45,9	41
VII	68—69	1689 (CO), 1600 (C=CPh), 1240—1070 (C—O—C)	67,2	7,6	11,7	$C_{20}H_{27}N_3O_3$	67,1	7,6	11,8	61
VIIIa[b]	131—132	1690 (CO), 1620 (C=C), 3160 (=CH)	66,5	5,0	21,0	$C_{11}H_9N_3O$	66,3	4,5	21,1	40 [3]

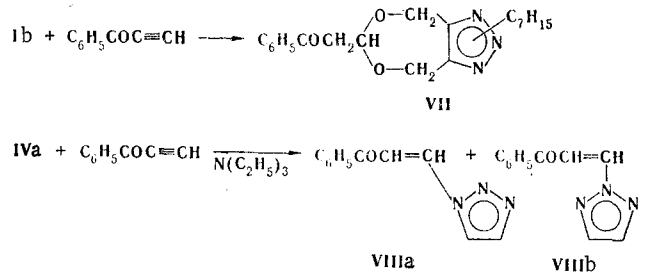
[a]Absorption bands of C=C and C=N bonds of the azole ring are characteristic for the IR spectra of triazoles IIa,b, III, Va,b, and VI: 890-910, 1030-1170, 1430-1470, and 1550-1580 cm^{-1}. [b]Two regioisomers were obtained; VIIIb, with mp 92-93°C, was obtained in 20% yield.

triazole (Vb) in high yield. The IR spectra of all of the triazolylpropionitriles II, III, V, and VI contain characteristic absorption bands of a triazole ring and a nitrile group (2240-2260 cm^{-1}), as well as, for most of them, bands of an ether oxygen atom at 1070-1240 cm^{-1} (Table 1).

The nucleophilic addition of 4,5-dihydroxymethyl-1,2,3-triazoles (Ic) to the activated triple bond of benzoylacetylene in the presence of catalytic amounts of sodium alkoxide leads, regardless of the experimental conditions, to cyclic acetal VII. Even in the case of excess acetylenic ketone we were unable to obtain the open-chain diether. It is known that in the nucleophilic addition of alcohols to α-acetylenic ketones the reaction generally stops at the step involving the production of alkoxy vinyl ketones [4]. In the case under consideration the favorable steric orientation of the hydroxy groups of the glycol (Ib), which facilitates the formation of cyclic acetal VII, is probably of decisive significance. The structure of this compound is confirmed unambiguously by IR spectroscopy by the band at 1690 cm^{-1}, which is peculiar to the carbonyl group attached to an aromatic ring, and by the group of four absorption bands of ether bonds at 1040-1200 cm^{-1}.

The reaction of N-hydroxymethyl-1,2,3-triazole (IVa) with benzoylacetylene proceeds through a step involving the elimination of a methyl group even in the presence of catalytic amounts of triethylamine. The resulting protonated 1,2,3-triazole is added to the triple bond by means of both the N_1 and N_2 atoms to give regioisomers of triazolyl vinyl ketones (VIIIa-b). Their IR and PMR spectra, as well as the melting point of VIIIa, are identical to the data described in [1]. However, the stereospecificity of the addition is not retained under the given conditions (i.e., in dioxane at 100°C), although the primary formation of the N_1 regioisomer is observed.

Scheme 2



Thus for hydroxymethylthiazoles, nucleophilic addition to the activated multiple bond is just as characteristic as for aliphatic alcohols, although certain deviations from the general principles of nucleophilic addition are possible because of the specific character of the properties of the triazole ring.

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian H-100 spectrometer with hexamethyldisiloxane as the internal standard on the δ scale. The course of the reactions was monitored by thin-layer chromatography on activity II aluminum oxide. The compounds were purified with chromatographic columns filled with aluminum oxide by elution with diethyl ether–petroleum ether (1:1 or 3:1) containing a very small amount of ethanol. The starting 1-alkyl-4(5)-hydroxymethyl- and dihydroxymethyl-1,2,3-triazoles (Ia,b) were obtained by reaction of the alkyl halides, sodium azide, and propargyl alcohol or butynediol by heating in dimethylformamide (DMF) [5]. Compound Ia was obtained in the form of an unseparable mixture of two regioisomers. In the PMR spectra the signals of two protons of the triazole ring appear at 7.96 and 7.62 ppm. The ratio of the isomers (1.4:1.5) according to the PMR spectra was 60:40. 2-Hydroxymethyl-1,2,3-triazole (IVa) was obtained by formylation of unsubstituted 1,2,3-triazole [6].

1-(β-Hydroxyethyl)-1,2,3-triazole (IVb). This compound was synthesized by the reaction of acetylene and ethanol azide in an autoclave at 110-120°C and an initial acetylene pressure of 12-14 atm by the method in [7]. Workup gave a product with bp 148-150°C (5 mm) in 95% yield. Found: C 42.7; H 7.2; N 37.0%. $C_4H_7N_3O$. Calculated: C 42.1; H 7.0; N 36.8%.

4-Hydroxymethyl-1,2,3-triazole (IIc). A 189-g (1 mole) sample of 1-benzyl-4(5)-hydroxymethyl-1,2,3-triazole was heated in 500 ml of dioxane for 20 h in an autoclave with stirring in the presence of 100 g of 2% palladium on activated charcoal at 110°C and a hydrogen pressure of 100-110 atm. The autoclave was cooled, the precipitate was removed by filtration, the solvent was removed, and the residue was distilled *in vacuo* to give a product with bp 128-130°C (2 mm) in 66% yield. Found: C 36.8; H 5.2; N 42.1%. $C_3H_5N_3O$. Calculated: C 36.4; H 5.0; N 42.4%.

Addition of Hydroxymethyltriazoles to Acrylonitrile. A) A solution of 0.01 mole of hydroxymethyl-1,2,3-triazole (Ia-c, IVa,b) in 5 ml of acrylonitrile was stirred in the presence of 0.1 g of potassium hydroxide at 25-40°C for 5-7 h. The precipitate was removed by filtration, the excess acrylonitrile was removed by distillation, and the residue was eluted with a column filled with aluminum oxide. Subsequent distillation *in vacuo* gave 1,2,3-triazole cyanoethyl ethers Ia-c, III, and Va,b and cyanoethyl-1,2,3-triazole VI.

B) A solution of 0.01 mole of hydroxyethyltriazole IVb in 5 ml of acrylonitrile was stirred in the presence of 0.1 g of potassium hyroxide in 0.3 ml of water at 25-35°C for 5-7 h, after which the solution was neutralized with hydrochloric acid and extracted with ethyl acetate. The solvent was removed by distillation, and the residue was distilled *in vacuo* to give β,β'-dicyanodiethyl ether [3].

Addition of Hydroxymethyl-1,2,3-triazoles to Benzoylacetylene. A) A catalytic amount of sodium was added to a solution of 2.2 g (0.01 mole) of 1-heptyl-4,5-dihydroxymethyl-1,2,3-triazole (Ia) in 10 ml of tetrahydrofuran (THF), and, after the glycolate had formed, a solution of 1.3 g (0.01 mole) of benzoylacetylene in 3 ml of THF was added dropwise. The mixture was heated for 2 h, cooled, treated with 3% hydrochloric acid, and extracted with ether. The extract was dried over magnesium sulfate, the solution was evaporated, and the residue was recrystallized from ethanol to give 2.17 g (61%) of VII.

B) A solution of 5 mmole of 1-heptyl-4,5-dihydroxymethyl-1,2,3-triazole in 5 ml of dioxane containing 0.01 g of sodium was added to a solution of 1.3 g (0.01 mole) of benzoylacetylene in 5 ml of dioxane, and the mixture was heated with stirring for 1 h. It was then worked up as in method A to give 1.22 g (68%) of acetal VIII with mp 68-69°C.

C) A solution of 1.3 g (0.01 mole) of benzoylacetylene, 0.9 g (0.01 mole) of 2-hydroxymethyl-1,2,3-triazole (IVa), and one to two drops of triethylamine in 5 ml of dioxane was heated for 3 h, after which the solution was concentrated, and the precipitated crystals of triazolyl vinyl ketone VIIIa were removed by filtration to give 0.6 g (30%) of a product with mp 130-131°C [1]. The evaporated mother liquor was chromatographed with a column filled with aluminum oxide, and the eluent was removed to give 0.2 g (10%) of VIIIa and 0.4 g (20%) of VIIIb with mp 92-93°C. The PMR spectra of triazolyl vinyl ketones VIIIa,b contain signals of protons of the triazole ring (8.81 and 8.04 for VIIIa and 8.07 ppm for VIIb) and of protons of a double bond (7.80, 8.45, 7.90, and 8.40 ppm). The IR spectra contain a band at 1680 cm^{-1}, which is characteristic for a carbonyl group, and a band at 1620 cm^{-1}, which is characteristic for a conjugated double bond. The principal constants of the compounds obtained are presented in Table 1.

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TETRAZOLES.

13.* PROTONATION OF TETRAZOLYLACETIC ACIDS

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The protonation of isomeric 1H-, 2H-, and 5H-tetrazolylacetic acids, as well as a series of 5-aryl-1H- and 5-aryl-2H-tetrazolylacetic acids, in aqueous sulfuric acid solutions was studied by IR, UV, and PMR spectroscopy. It is shown that all of the investigated tetrazolylacetic acids are protonated in the tetrazole ring at sulfuric acid concentrations up to 96%; the proton adds to the nitrogen atom in the 4 position.

The acid–base properties of tetrazolylacetic acids have not been adequately studied [2]. It is known that these compounds are stronger acids than acetic acid [3]. No information regarding the basicities of tetrazolylacetic acids is available. At the same time, such data are necessary in the investigation of the kinetics and mechanism of acid-catalyzed reactions of these compounds. In this connection we studied the protonation of isomeric 1H-,

*See [1] for communication 12.

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