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1,2,4-TRIAZOLE AND ITS DERIVATIVES IN THE REACTION OF ADDITION TO α-ACETYLENE KETONES

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It is well-known that 1,2,4-triazole is capable of being added to acetylacetylene with the formation of (1-(1-buten-3-one)-1,2,4-triazole [1]. The present article is devoted to an investigation of the reaction of the nucleophilic addition of 1,2,4-triazole (Ia, b) to α-acetylene ketones. In distinction from primary and secondary amines [2], symmetrical triazoles react with ethynyl ketones (II) only in the presence of triethylamine; the reaction stops at the stage of the formation of monoadducts, i.e., triazolylvinyl ketones (III). Addition to an unsubstituted ketone with a triple bond (IIb) is possible with the course of a reaction under rigid conditions in an excess of triethylamine. In the PMR spectra of triazolylvinyl ketone (IIIa) there are recorded nonequivalent signals of the protons of the triazole ring (8.42 and 7.98 ppm), which points to the addition of triazole to a vicinal atom of nitrogen. There are observed also the signals of the protons of the ketovinyl grouping (8.17 and 7.72 ppm), characteristic for the trans isomer [1]. In the IR spectra of these adducts there are noted absorption bands in the regions 1640-1675 and 1620-1610 cm^{-1}. The first band must be ascribed to vibrations of the α,β-unsaturated carbonyl group, and the second to a polarized double bond. The structure of triazolylvinyl ketones (III) is confirmed by their hydrolysis in 1-phenylpropanedione (IV), which was obtained by the hydration of benzoylacetylene (IIa) [3]. (See Scheme 1.)

With an attempt to add a molecule of piperidine to the multiple bond of 1-(3-phenyl-1-propen-3-one)-1,2,4-triazole (IIIa), there was a substitution of the triazole radical by an amine residue with the formation of the compound V.

The interaction of functionally substituted derivatives of triazole, i.e., 1,2,4-triazole-3-thiones (VIa, b) and 3-amino-1,2,4-triazole (VII) is somewhat more complex. The presence of several reaction centers offers the possibility of obtaining different isomeric adducts, whose structure is determined by the direction of the addition of an electrophile

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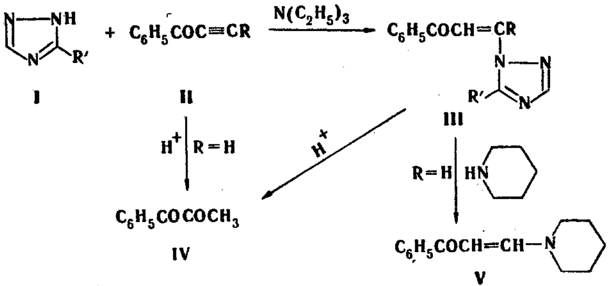
Scheme 1

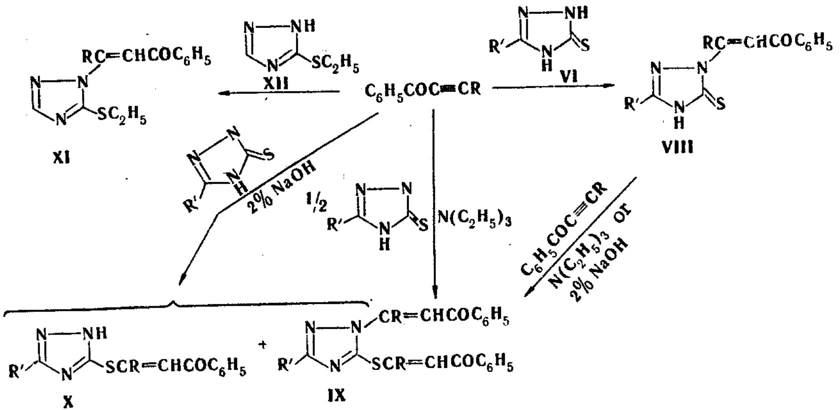


a R=R'=H; b R=H, R'=CH_3; c R=C_6H_5, R'=H

to one of the heteroatoms of the heterocycle. It is known from literature data that the cyanoethylation of 1,2,4-triazole-3-thione in the presence of triethylamine [4-6] or sodium ethylate [7, 8] leads to the formation of 2-N-derivatives. In only one piece of work [9] is it indicated that this reaction in a 2% aqueous alkaline solution can take place with the participation of a thione group.

Experience shows that the addition of 1,2,4-triazole-3-thione (VIa) to acetylene ketones, both without a catalyst and in the presence of triethylamine, with an equimolecular ratio of the reagents leads to products of 2-N-addition (VIIIa-d). In the IR spectra of these substances there is an intense band in the region 1660-1640 cm^{-1}, corresponding to the vibrations of the carbonyl group, and a band at 1570-1540 cm^{-1}, characteristic of the double bond of such systems. In the PMR spectrum of the adduct VIIIa there are observed the signals of vinyl protons (7.38 and 8.54 ppm), characteristic for the trans isomer, and the signal of a cyclic proton (8.56 ppm).

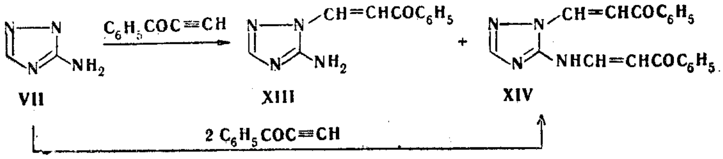
With a reaction between 1,2,4-triazole-3-thione and benzoylacetylene in a 2% aqueous alkaline solution, there is formed a diadduct with respect to the S- and 2-N-heteroatoms of (IX). Along with this, the main product from the reaction mixture was a monoadduct, which, according to the IR spectroscopy data of its elementary structure, and on the basis of the absence of the C=S [10] group, is thiotriazolylvinyl ketone (X). The diadduct IX was also obtained with the treatment of 1,2,4-triazole-3-thione with a twofold excess of terminal ketone in the presence of triethylamine. As a confirmation of the formation of diadduct IX, the latter was obtained by the successive addition of 2 moles of benzoylacetylene to 1,2,4-triazole-3-thione. The first stage takes place with the formation of 2-(3-phenyl-1-propen-3-one)-3-thio-1,2,4-triazole (VIII). The second stage is possible in the presence of both potassium hydroxide and triethylamine as catalysts. In the IR spectrum of the diadduct IX there are two bands of conjugated carbonyl groups (1670-1645 cm^{-1}) and of double bonds (1618, 1605, 1580, and 1540 cm^{-1}) of the ketovinyl system and the heteroaromatic ring. The absence of a qualitative test for the C=S grouping points to the presence of a ketovinyl radical with a sulfur atom. The PMR spectrum of adduct IXa contains a group of protons, which it is not possible to identify, as well as signals of the proton at the carbon atom of the heterocycle (9.16 and 9.12 ppm). In the IR spectrum of vinyl ketone Xa, there are absorption bands in the regions 1668 and 1560 cm^{-1}, which we attribute to vibrations of the carbonyl group and the double bond, respectively. For the attribution of the absorption bands in the diadduct IX, 2-(3-phenyl-1-propen-3-one)-3-ethylthio-1,2,4-triazole (XIa) was synthesized from benzoyl-



a R=R'=H; b R=H, R'=CH_3; c R=C_6H_5, R'=H; d R=C_6H_5, R'=CH_3

acetylene and 3-ethylthio-1,2,4-triazole (XII) with a fixed position of the vinyl ketone grouping at the nitrogen of the triazole cycle. In the spectrum of the adduct XIa there are two intense absorption bands in the regions 1670 and 1610 cm^{-1}, characteristic for triazolylvinyl ketones. Analogous frequencies appear in the spectra of the adducts III, which points to an identical action of the thiotriazole cycle, regardless of the character of the substituent with sulfur atom, on the spectral characteristics of the ketovinyl groupings. A reaction with the participation of the thio group takes place only in an excess of acetylene ketone and in the presence of catalyst of the basic type.

A reaction between 3-amino-1,2,4-triazole (VII) and acetylene ketone is possible both at an atom of nitrogen of the triazole cycle, and at an amine radical.



The presence of an electron donor should somewhat activate the azole cycle in its reaction with an electrophile. In actuality, the addition of aminotriazole to benzoylacetylene proceeds without a catalyst and gives a mixture of the monoadduct (XIII) and diadducts (XIV) in the ratio 1:1.5. The use of a twofold excess of benzoylacetylene in the presence of triethylamine shift the reaction toward the side of the formation of the diadduct (XIV). In the IR spectrum of the monoadduct XIII there are intense absorption bands of the carbonyl group and the double bond in the regions 1674 and 1610 cm^{-1}. The IR spectrum of the diadducts XIV contains a series of bands with the frequencies 1670, 1640, 1612, and 1570 cm^{-1}. The first two relate to carbonyl groups, existing in conjugation with a nitrogen atom in the ring and an amino group. The second correspond to vibrations of a conjugated double bond.

EXPERIMENTAL

The IR spectra were recorded in a UR-10 spectrometer in the form of suspensions of the substances in Vaseline oil or in a solution of chloroform. The PMR spectra were obtained in a Varian HA-100 instrument. The internal standard was hexamethyldisiloxane.

Addition of 1,2,4-Triazoles to Benzoylacetylene. A solution of 0.05 mole benzoylacetylene, 0.05 mole 1,2,4-triazole or its derivative (Ia, b), and 2-3 drops of triethylamine in 50 ml of ethanol are heated to the boiling point for 2-3 h. The end of the reaction is followed from the disappearance of a spot of the starting benzoylacetylene on a thin layer of aluminum oxide. The eluent is acetone—alcohol—water (8:2:1). At the end of the reaction, the content of the flask is poured into 50 ml of cold water and extracted with ether or ethyl acetate; the extract is dried with magnesium sulfate. After removal of the solvent, the residue is recrystallized from benzene.

Analogously, by heating 0.05 mole of 1,2,4-triazole, 0.05 mole of 1,3-diphenylpropyn-1-one, and 0.5 ml of triethylamine in 50 ml of ethanol for 20 h, 1-(1,3-diphenyl-1-propen-3-one)-1,2,4-trizole (IIIc) is obtained. The yields and principal constants of the triazolylpropenes IIIa-c are given in Table 1.

1-Phenylpropane-1,2-dione (IV). A) A solution of 2.0 g (0.01 mole) 1-(3-phenyl-1-propen-3-one)-1,2,4-triazole (IIIa) in 40 ml of water and 10 ml of ethanol is boiled in the presence of 1 ml of sulfuric acid for the course of 10-12 h. After cooling, they are extractec with ether, and dried with magnesium sulfate. After the solvent has been removed, the remaining oil is distilled. The yield is 0.6 g (44.5%), the boiling point is 99°C (18 mm), n_D^{20} 1.5340 [3]. The IR spectrum (thin layer): 1692 cm^{-1} (C=O). 2,4-Dinitrophenylhydrazone, mp 248-249°C (from ethyl acetate). Found: C 55.1; H 3.9. $C_{15}H_{12}N_4O_5$. Calculated: C 54.9; H 3.6%.

B) A solution of 0.8 g (0.0035 mole) 5-methyl-2-(3-phenyl-1-propen-3-one)-3-thio-1,2,4-triazole (VIIIb), 20 ml ethanol, 5 ml water, and 1 ml concentrated H_2SO_4 is boiled for 6 h. After cooling, the reaction mixture is diluted with water, extracted with ether, and dried with magnesium sulfate. The extract is concentrated, a few drops of water are added, and the usual procedure is used to obtain 2,4-dinitrophenylhydrazone, mp 246-248°C (from ethyl acetate); there is no depression of the melting point with the dinitrophenylhydrazone of diketone IV, obtained by the hydrolysis of 1-(3-phenyl-1-propen-3-one)-1,2,4-triazole (IIIa).

TABLE 1. Products of the Addition of 1,2,4-Triazole and Its Derivatives to α-Acetylene Ketones

Compound	mp, °C	IR spectrum, cm^{-1}			Found, %			Empirical formula	Calculated, %			Yield, %
		C–O	C–C	N–H	C	H	N		C	H	N	
IIIa	170–172	1673	1612		66,41	4,70	21,03	$C_{11}H_9N_3O$	66,33	4,52	21,10	81,6
IIIb	150–153	1675	1610	—	67,65	5,34	19,78	$C_{12}H_{11}N_3O$	67,60	5,16	19,72	56,4
IIIc	137–138	1664	1615	—	73,86	4,97	15,07	$C_{17}H_{13}N_3O$	74,18	4,72	15,27	69,2
VIIIa	118–123	1640	1560 1540	3130–3200	56,93	3,85	18,04	$C_{11}H_9N_3OS$	57,14	3,89	17,77	86,9
VIIIb	168–169	1645	1547	3180	58,80	4,43	17,30	$C_{12}H_{11}N_3OS$*	58,77	4,49	17,14	55,0
VIIIc	132–135	1650	1570	3190	66,44	4,05	13,82	$C_{17}H_{13}N_3OS$	66,44	4,23	13,68	88,2
VIIId	170–173	1649	1555	3250	67,26	4,84	12,82	$C_{18}H_{16}N_3OS$	67,08	4,96	13,04	75,0

*Found: S 13.01%. Calculated: S 13.06%.

1-Piperidino-3-phenyl-1-propen-3-one (V). To a solution of 0.005 mole of 1-(3-phenyl-1-propen-3-one)-1,2,4-triazole (IIIa) in 20 ml of ethanol are added 0.01 mole piperidine in 5 ml of ethanol. The mixture is held at room temperature for 20 min, and is duluted with a threefold excess of water. The crystals falling out are filtered. The yield is 0.7 g (64.8%), mp 90-91.5°C (from alcohol). The IR spectrum (thin layer): 1640 (C=O), 1560, 1540 cm^{-1} (C=C). Found: C 77.9; H 7.7; N 6.4%. $C_{14}H_{17}NO$. Calculated: C 78.1; H 7.9; N 6.5%.

Addition of 1,2,4-Triazolyl-3-thione to Benzoylacetylene. A) A solution of 0.01 mole of triazolylthione VI and 0.01 mole of acetylene ketone in 25-30 ml of ethanol is held with boiling of the solvent for 2-3 h, or the reaction mixture is heated for 30 min in the presence of 2-3 drops of triethylamine. It is diluted with water, extracted with ether, and dried with magnesium sulfate. The yields and the principal constants of 2-(3-phenyl-1-propen-3-one)-3-thio-5-R'-1,2,4-triazoles (VIIIa-d) are given in Table 1.

B) To 2.52 g (0.025 mole) of 1,2,4-triazole-3-thione in 20 ml of a 2% aqueous solution of caustic soda and 10 ml ethanol there is added 3.25 g (0.025 mole) of benzoylacetylene in 15 ml of ethanol. The reaction mixture is boiled for 4 h; the crystals falling out are filtered and washed with water. There are obtained 3.0 g (33.0%) of the diadduct IXa, mp 215-217°C (from dimethylformamide). IR spectrum (in Vaseline oil): 1670, 1645 (C=O), 1618, 1605, 1580, 1540 cm^{-1} (C=C). Found: C 66.7; H 4.4; N 11.5%. $C_{20}H_{15}N_3O_2S$. Calculated: C 66.5; H 4.2; N 11.6%. The filtrate is diluted with a threefold volume of water and carefully extracted with ether. After drying and solvent removal, there are obtained 0.7 g (12%) of the monoadduct X. The crystals are bright yellow, mp 244-246°C (from ethanol). IR spectrum (in Vaseline oil): 1668 (C=O), 1560 cm^{-1} (C=C). PMR spectrum (in DMSO): 8.70 (CH ring); 8.43 (–S–CH=); 7.55 (=CH–CO); 13.15 ppm (N–H). Found: C 57.5; H 3.8; N 17.8%. $C_{11}H_9N_3OS$. Calculated: C 57.1; H 3.9; N 18.2%.

C) A mixture of 1.3 g (0.01 mole) of benzoylacetylene, 0.5 g (0.0049 mole) of 1,2,4-triazole-3-thione, 2-3 drops of triethylamine, and 45 ml ethanol is boiled for 3 h. The reaction mixture is cooled and diluted with water; the crystals of the diadduct falling out are filtered. There are obtained 0.9 g (50.1%) of the compound IXa, mp 182-186°C (from acetone). IR spectrum (in Vaseline oil): 1680, 1650 (C=O), 1621, 1580 cm^{-1} (C=C). Found: C 66.8; H 4.2; N 11.2; S 8.8%. $C_{20}H_{15}N_3O_2S$. Calculated: C 66.5; N 4.2; N 11.6; S 8.8%. The substance has an identical value of R_f with the diadduct IX, obtained in an aqueous alkaline medium.

2-(3-Phenyl-1-propen-3-one)-3-(1-thio-4-phenyl-2-propen-4-one)-1,2,4-triazole (IXa). A) A solution of 0.33 g (0.0025 mole) of 2-(3-phenyl-1-propen-3-one)-3-thio-1,2,4-triazole (VIIIa), 0.32 g (0.0025 mole) of benzoylacetylene, and two drops of triethylamine in 15 ml of ethanol is boiled for 2 h; the crystals falling out are filtered. There are obtained 0.55 g (84.6%) of the diadduct IXa, mp 213-217°C (from dimethylformamide). IR spectrum (in Vaseline oil): 1675, 1642 (C=O), 1615, 1580 cm^{-1} (C=C). Found C 66.5; H 4.2; N 11.9%. $C_{20}H_{15}N_3O_2S$. Calculated: C 66.5; H 4.1; N 11.6%.

B) Analogously, from 0.5 g (0.0021 mole) of 2-(3-phenyl-1-propen-3-one)-3-thio-1,2,4-triazole and 0.15 g (0.0021 mole) of benzoylacetylene in 5 ml ethanol in the presence of 2 ml of 2% caustic soda there are obtained 0.5 g (76.7%) of the adduct IXa, mp 215-217°C. The compound has no depression of the melting point with a diadduct obtained with a reaction with 1,2,4-triazole-3-thione with a twofold excess of benzoylacetylene in an aqueous alkaline medium, and with a diadduct, obtained by method A.

3-Ethylthio-1,2,4-triazole (XII). Into a solution of sodium ethylate (from 0.1 g-at of sodium) in 100 ml of absolute ethanol there are introduced by small portions, 0.1 mole of 1,2,4-triazolethione. The mixture is mixed at room temperature for 1 h, and 0.1 mole of ethyl bromide in 20-30 ml of ethanol is added. The reaction mixture is boiled for 16 h, the solvent is distilled off up to a syrupy state, and the mixture is carefully extracted with boiling benzene. The yield is 83.5%, mp 55-57° (from benzene). Found: C 37.3; H 5.3; N 32.6%. $C_4H_7N_3S$. Calculated: C 37.2; H 5.4; N 32.5%.

2-(3-Phenyl-1-propen-3-one)-3-ethylthio-1,2,4-triazole (XI). To a solution of 1.3 g (0.01 mole) of 3-ethylthio-1,2,4-triazole (XII) in 25 ml of ethanol there are added 3-4 drops of triethylamine and 1.3 g (0.01 mole) of benzoylacetylene in 15 ml of alcohol. The reaction mixture is boiled for 20 h, cooled, diluted with a threefold volume of water, and extracted with ether. The residue is crystallized from n-butanol. Yield 1.7 g (65.5%), mp 105-107°C. IR spectrum (in Vaseline oil): 1670 (C=O), 1610 cm^{-1} (C=C). Found: C 60.4; H 5.2; S 12.3%. $C_{13}H_{13}N_3OS$. Calculated: C 60.2; H 5.2; S 12.4%.

Addition of 3-Amino-1,2,4-triazole to Benzoylacetylene. A boiling solution of 0.84 g (0.01 mole) of 3-amino-1,2,4-triazole in 30 ml of ethanol is added to a solution of 1.3 g (0.01 mole) of benzoylacetylene in 15 ml of ethanol. The reaction mixture is mixed at room temperature for 2 h 30 min and diluted with water; the residue falling out is filtered. There is obtained 0.6 g (28.0%) of 2-(3-phenyl-1-propen-3-one)-3-amino-1,2,4-triazole (XIII), mp 194-197°C (alcohol—dimethylformamide 2:1). IR spectrum (in Vaseline oil): 1674 (C=O), 1610 cm^{-1} (C=C). PMR spectrum (in DMSO): 8.52 (CH ring); 9.33, 7.92 (CH=CH, J = 7.0 Hz, cis isomer). Found: C 62.0; H 5.0%. $C_{11}H_{10}N_4O$. Calculated: C 61.7; H 4.7%. With long standing, dark orange crystals of the diadduct XIV fell out from the filtrate. Yield 0.7 g (20.3%), mp 198-205°C (dimethylformamide—alcohol 1:2). IR spectrum (in Vaseline oil): 1675, 1648 (C=O), 1615, 1570 cm^{-1} (C=C). Found: N 16.0%. $C_{20}H_{16}N_4O_2$. Calculated: N 16.3%.

2-(3-Phenyl-1-propen-3-one)-3-(4-phenyl-1-aza-2-buten-4-one)-1,2,4-triazole (XIV). A mixture of 2.6 g (0.02 mole) benzoylacetylene, 0.81 g (0.01 mole) of 3-amino-1,2,4-triazole, 3 drops of triethylamine in 50 ml of ethanol is heated for 8-10 h at 50°C and cooled; the residue falling out is filtered. Yield 2.4 g (82.3%), mp 198-201°C (dimethylformamide—alcohol 1:2). IR spectrum: 1670, 1640 (C=O), 1612, 1590, 1570 cm^{-1} (C=C). Found: C 69.6; H 5.1%. $C_{20}H_{16}N_4O_2$. Calculated: C 69.8; H 5.6%.

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