SYNTHESIS OF 1,2,4-TRIAZOLO[3,2-b]-1,3-THIAZINES

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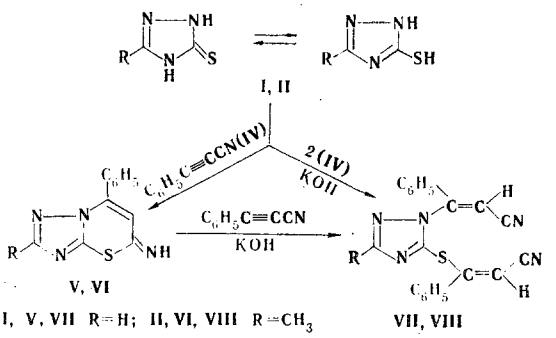
1,2,4-Triazolo[3,2-b]-1,3-thiazines were obtained by the reaction of 1,2,4,-triazole-3-thiones with an equimolar amount of 1-phenyl-2-cyanoacetylene in the presence of triethylamine or potassium hydroxide. It is shown that triazolethiones form N,S diadducts upon reaction with a twofold excess of cyanoacetylene. The nature of the heteroatom in the exo position of the heteroring affects the direction of addition to phenylcyanoacetylene. 2,4-Bis(1-phenyl-2-cyanovinylene)-1,2,4-triazol-3-one was synthesized.

In connection with the search for biologically active substances and continuing our earlier studies [1, 2], in the present research we attempted to realize heterocyclization on the basis of 1,2,4-triazole derivatives. Wtih this in mind, we studied the behavior of 1,2,4-triazole-3-thione (I), 5-methyl-1,2,4-triazole-3-thione (II), and 1,2,4-triazole-3-one (III) in reactions with 1-phenyl-2-cyanoacetylene (IV).

The experience of other researchers has shown that the addition of 1,2,4-triazole-3-thione to acetylenic ketones leads to 2-N-addition products [3]. The presence of several reaction centers in starting triazolethiones I and II ensures the possibility of the synthesis of various isomeric products.

We have established that the addition of thiones I and II to acetylene IV proceeds in the presence of basic catalysts such as triethylamine and potassium hydroxide and is accompanied by intramolecular cyclization; 5-imino-7-phenyl-1,2,4-triazolo[3,2-b]-1,3-thiazine (V) and 5-imino-2-methyl-7-phenyl-1,2,4-triazolo[3,2-b]-1,3-thiazine (VI) [4] were obtained for the first time in high yields. The PMR spectrum of thiazine V contains signals of protons of thiazine (7.01 ppm, s) and triazole (8.15 ppm, s) rings, an imino group (9.23 ppm, broad signal), and aromatic protons (7.49 ppm, m). An intense band of stretching vibrations of an imino group at 3290 cm^{-1} is observed in the IR spectrum of V, but an absorption band of a nitrile group is absent.



Products of addition at the two heteroatms, viz., the nitrogen and sulfur atoms, are formed when triazolethiones I and II are treated with a twofold excess of cyanoacetylene IV in the presence of potassium hydroxide. We found that 1,2,4-triazole-3-thione (I) reacts with excess acetylene IV to give only 2-(1-phenyl-2-cyanovinylene)-2-[(1-phenyl-2-cyanovinylene)thio]-1,2,4-triazole (VII). In contrast to it, methyl-substituted thione II forms a mixture of isomeric diadducts VIII. On the basis of an analysis of the PMR spectra of

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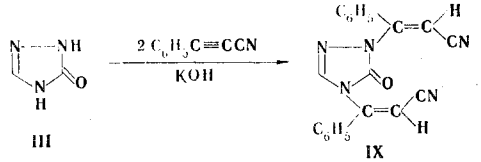
this mixture, it was estabished that the isomers exist in a ratio of 2:1 and differ with respect to the positions of the acrylonitrile groups. The formation of isomeric compounds is evidently due to the presence of an electron-donor methyl group, which activates the azole ring in its reaction with the electrophile.

With triethylamine as the catalyst, the reaction of thiones I and II with a twofold excess of acetylene IV stops with the formation of thiazines V and VI.

In contrast to imidazolo-1,3-thiazines [2], triazolo-1,3-thiazines V and VI are not cleaved by the action of a 20-30% solution of KOH, which constitutes evidence that the nature of the azole condensed with the 1,3-thiazine ring has a substantial effect on the resistance of the latter to the action of alkalis. At the same time, the interesting fact of a decrease in the stability of the thiazine rings of V and VI when cyanoacetylene IV is present in the reaction medium was observed. Thus opening of the thiazine ring to give diadducts VII and VIII occurred in an attempt to add acetylene IV to the available imino group in the presence of a 5-10% solution of KOH. This makes it possible to assume that the synthesis of disubstituted triazolethiones VII and VIII proceeds through a step involving heterocyclization with subsequent opening of the thiazine ring.

The nature of the heteroatom in the exo position of the heteroring affects the direction of the addition to acetylene IV. Thus, when the sulfur atom in triazolethione I is replaced by an oxygen atom, heterocyclization is not observed, regardless of the ratio of the starting reagents. Ketone III forms only an N,N diadduct, viz., 2,4-bis(1-phenyl-2-cyanovinylene)-1,2,4-triazol-3-one (IX), with acetylene IV. The IR spectrum of new ketone IX contains intense absorption bands of carbonyl (1732 cm^{-1}) and nitrile (2230 cm^{-1}) groups. The PMR spectrum of IX contains signals of olefin protons (6.19 ppm, s; 6.48 ppm, s), and a heteroring proton (8.33 ppm, s) and a multiplet of aromatic protons (7.51 ppm).



EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla BS 487B spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

1-Phenyl-2-cyanoacetylene (IV). This compound was obtained by the method in [5].

5-Imino-7-phenyl-1,2,4-triazolo[3,2-b]-1,3-thiazine (V). A solution of 1.27 g (10 mmole) of acetylene IV in dioxane was added dropwise at room temperature to a solution of 1.01 g (10 mmole) of thione I and 0.5 ml of triethylamine in dioxane. After 6 h, the dioxane was removed by vacuum distillation, and the solid residue was recrystallized from hot ethanol to give 2.18 g (95%) of imine V with mp 169°C. Found: C 58.0; H 3.6; S 13.8%. $C_{11}H_8N_4S$. Calculated: C 57.9; H 3.5; S 14.0%.

5-Imino-2-methyl-7-phenyl-1,2,4-triazolo[3,2-b]-1,3-thiazine (VI). This compound, with mp 151-152°C, was similarly obtained in 95% yield from thione II. IR spectrum: 3260 (=NH) and 1624 cm^{-1} (N—C=C). PMR spectrum: 2.41 (3H, s, CH_3), 6.97 (1H, s, =CH—), 8.99 (1H, broad signal, =NH), and 7.49 ppm (5H, s, C_6H_5). Found: C 59.1; H 4.0; S 13.1%. $C_{12}H_{10}N_4S$. Calculated: C 59.1; H 4.1; S 13.2%.

2-(1-Phenyl-2-cyanovinylene)-3-[(1-phenyl-2-cyanovinylene)thio]-1,2,4-triazole (VII). A solution of 2.54 g (20 mmole) of acetylene IV was added to a solution of 1.01 g (10 mmole) of thione I and 0.36 g of KOH in dioxane. After 6 h, workup gave 2.8 g (80%) of triazole VII with mp 119°C. IR spectrum: 2228 (C≡N), 1626 (N—C=CH), and 1584 cm^{-1} (S—C=CH). PMR spectrum: 5.54 (1H, s, S—C=CHCN), 5.79 (1H, s, N—C=CHCN), 8.21 (1H, s, N=CH—N), and 7.05-7.67 ppm (10H, m, C_6H_5). Found: C 67.6; H 3.6; S 8.8%. $C_{20}H_{13}N_5S$. Calculated: C 67.6; H 3.7; S 9.0%.

Reaction of 5-Methyl-1,2,4-triazole-3-thione (II) with 1-Phenyl-2-cyanoacetylene (IV). A solution of 2.54 g (20 mmole) of acetylene IV was added to a solution of 1.15 g (10 mmole) of thione II and 0.37 g of KOH in dioxane. After 6 h, workup gave a mixture of isomeric

VIII with mp 131-134,C in 93% yield. IR spectrum: 2230, 2220 (C≡N); 1620 (N—C=CH); 1590 cm^{-1} (S—C=CH). The PMR spectrum of mixture VIII contained signals of protons of methyl groups (2.20 and 2.27 ppm) and olefin protons (5.59, 5.73, 5.95, and 6.31 ppm) and multiplets of aromatic protons (6.99 and 7.35 ppm). Found: C 68.1; H 4.2; S 8.6%. $C_{21}H_{15}N_5S$. Calculated: C 68.3; H 4.1; S 8.7%.

Reaction of 5-Imino-7-phenyl-1,2,4-triazolo[3,2-b]-1,3-thiazine (V) with 1-Phenyl-2-cyanoacetylene (IV). A mixture of 1.14 g (5 mmole) of V and 0.1 g of KOH in dioxane was treated with a solution of 0.63 g (5 mmole) of acetylene IV in dioxane. After 6 h, workup gave 1.53 g (86%) of diadduct VII with mp 119°C.

2,4-Bis(1-phenyl-2-cyanovinylene)-1,2,4-triazol-3-one (IX). This compound, with mp 213°C, was obtained similarly from ketone III in 88% yield. Found: C 70.5; H 3.9; N 20.4%. $C_{20}H_{13}N_5O$. Calculated: C 70.8; H 3.9; N 20.6%.

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HETEROGENEOUS-CATALYTIC FISCHER REACTION.

13.* CATALYTIC SYNTHESIS OF 4-, 5-, 6-, AND 7-METHOXYINDOLES

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Methoxy-substituted acetaldehyde phenylhydrazones were cyclized in the vapor phase on a GIPKh-115 catalyst to give 4-, 5-, 6-, and 7-methoxyindoles. 5-Methoxyindole was obtained in 50% yield, 4- and 6-methoxyindoles were obtained in 85% yield, and 7-methoxyindole was obtained in 45% yield.

Methoxy-substituted indoles are finding wide application as starting substances for the synthesis of various sorts of medicinal preparations [2]. The presently known methods for the preparation of methoxyindoles involve many steps and are laborious [3, 4], and the problem of finding a simple and cheap method for the preparation of indoles with a methoxy group in the benzene ring therefore remains an urgent one.

We have previously reported the heterogeneous-catalytic synthesis of 4-, 5-, 6-, and 7-methoxyindoles on aluminum oxide [5], but we were unable to recommend this method as a preparative procedure because of the low yields of the desired products. These results can be explained by the low activity of the catalyst in this reaction at its operating temperature (∿300°C) and also by the low thermal stabilities of acetaldehyde p- and o-methoxyphenylhydrazones. One might have assumed that a catalyst based on GIPKh-115 aluminum oxide [6], which has higher activity at lower temperatures than aluminum oxide itself, would prove to be effective in this case.

*See [1] for Communication 12.

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