GENERATION AND CYCLIZATION OF α-DIAZOCARBOTHIOIMIDATES. SYNTHESIS AND STRUCTURE OF DERIVATIVES OF 5-MERCAPTO-1,2,3-TRIAZOLE

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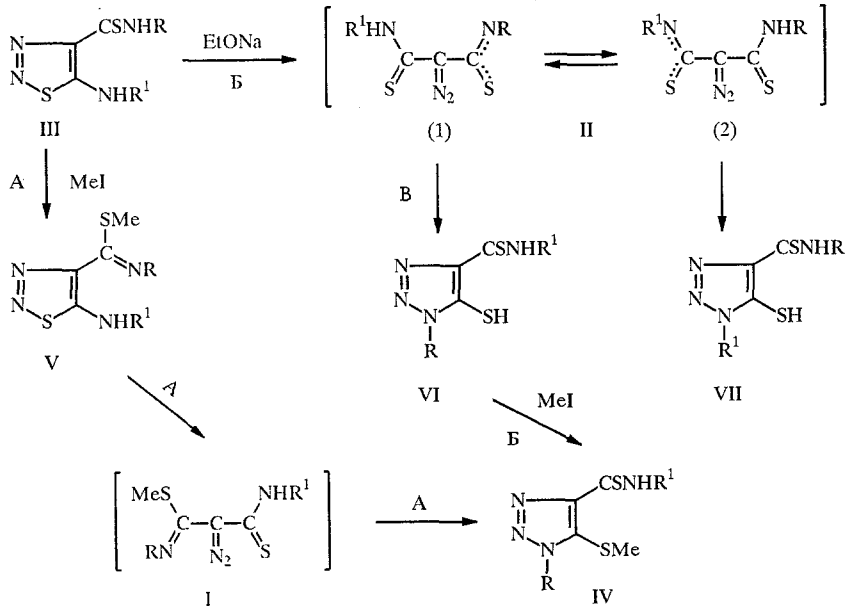
The reaction of 5-amino-1,2,3-thiadiazol-4-carbothioamides with methyl iodide basically generates α-diazo-S-methylthioimidates and -carbothioimidolates. It is shown that the reactivity of the latter increases when either alkyl or aryl substituents are introduced at the nitrogen atom of the carbothioamide group.

Diazoalkanes having a carboimidate or thioamide group in the α-position are highly reactive and are converted under the conditions of their preparation into various derivatives of 1,2,3-thiadiazole [1] and 1,2,3-triazole. They are intermediate compounds in the rearrangements in a number of these heterocycles [2] as well as in reactions of α-diazocarbonyl and -carbonitrile compounds with nucleophilic and electrophilic reagents [3]. A search for methods of generation and an investigation of the direction of cyclization and reactivity of these compounds have considerable value in the development of the directed synthesis of heterocycles with the given structure, among which are some with biological activity.



I—VII a R=R¹=H; b R¹=H, R=Me; c R=Ph; d R=C₆H₄Me-*p*; e R=C₆H₄OMe-*p*; f R=H, R¹=Ph; g R¹=C₆H₄Me-*p*; h R¹=C₆H₄OMe-*p*; i R¹=CONHPh

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TABLE 1. Bond Angles and Atomic Coordinates 5-Methylmercapto-1-(4-methoxyphenyl)-1,2,3-triazol-4-carbothioamide (IVc)

Bond angles		Atomic coordinates × 10^4			
angle	ω(σ)°	atom	x/A	y/B	z/C
$C_{(2)}$—$S_{(1)}$—$C_{(11)}$	102,93(2)	$S_{(1)}$	8269(1)	2653(1)	2970(1)
$C_{(7)}$—$O_{(1)}$—$C_{(10)}$	119,67(3)	$S_{(2)}$	5956(1)	3617(1)	4069(1)
$C_{(2)}$—$N_{(1)}$—$C_{(4)}$	132,06(3)	$O_{(1)}$	12670(2)	5187(4)	1234(2)
$N_{(2)}$—$N_{(1)}$—$C_{(4)}$	118,94(3)	$N_{(1)}$	9339(3)	5645(4)	3480(2)
$N_{(2)}$—$N_{(1)}$—$C_{(2)}$	108,96(3)	$N_{(2)}$	9334(3)	7071(4)	4019(3)
$N_{(1)}$—$N_{(2)}$—$N_{(3)}$	108,56(3)	$N_{(3)}$	8454(3)	6985(4)	4432(3)
$N_{(2)}$—$N_{(3)}$—$C_{(1)}$	109,32(4)	$N_{(4)}$	6504(3)	6482(5)	5015(3)
$N_{(3)}$—$C_{(1)}$—$C_{(3)}$	117,16(4)	$C_{(1)}$	7882(3)	5524(5)	4156(3)
$N_{(3)}$—$C_{(1)}$—$C_{(2)}$	107,39(4)	$C_{(2)}$	8451(3)	4626(4)	3551(3)
$C_{(2)}$—$C_{(1)}$—$C_{(3)}$	135,16(4)	$C_{(3)}$	6781(3)	5276(5)	4451(3)
$N_{(1)}$—$C_{(2)}$—$C_{(1)}$	105,76(3)	$C_{(4)}$	10205(3)	5463(5)	2916(3)
$S_{(1)}$—$C_{(2)}$—$C_{(1)}$	134,60(3)	$C_{(5)}$	9969(3)	4846(5)	1941(3)
$S_{(1)}$—$C_{(2)}$—$N_{(1)}$	119,61(3)	$C_{(6)}$	10816(3)	4721(5)	1420(3)
$N_{(4)}$—$C_{(3)}$—$C_{(1)}$	116,95(4)	$C_{(7)}$	11912(3)	5284(5)	1838(3)
$S_{(2)}$—$C_{(3)}$—$C_{(1)}$	121,26(3)	$C_{(8)}$	12149(4)	5915(5)	2820(3)
$S_{(2)}$—$C_{(3)}$—$N_{(4)}$	121,77(3)	$C_{(9)}$	11301(3)	5976(5)	3347(3)
$N_{(1)}$—$C_{(4)}$—$C_{(9)}$	120,18(4)	$C_{(10)}$	13835(4)	5625(8)	1662(4)
$N_{(1)}$—$C_{(4)}$—$C_{(5)}$	124,63(4)	$C_{(11)}$	8363(5)	1259(6)	4024(4)
$C_{(5)}$—$C_{(4)}$—$C_{(9)}$	115,14(4)				
$C_{(4)}$—$C_{(5)}$—$C_{(6)}$	122,98(4)				
$C_{(5)}$—$C_{(6)}$—$C_{(7)}$	122,10(4)				
$O_{(1)}$—$C_{(7)}$—$C_{(6)}$	117,66(4)				
$C_{(6)}$—$C_{(7)}$—$C_{(8)}$	114,88(4)				
$O_{(1)}$—$C_{(7)}$—$C_{(8)}$	127,45(4)				
$C_{(7)}$—$C_{(8)}$—$C_{(9)}$	122,32(4)				

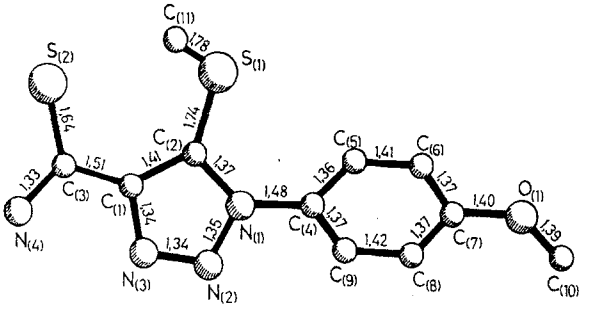


Fig. 1. Molecular structure and bond lengths of triazole IVc.

The present report deals with the development of methods of synthesis and an investigation of the properties of α-diazocarbothioimidates, as well as a study of the structure of the products of their cyclization — derivatives of 5-mercapto-1,2,3-triazole.

It was noted earlier in brief reports [4, 5] that α-diazothioimidates I and II can be generated by treatment of 5-amino-1,2,3-thiadiazol-4-carbothioamides III with alkylating reagents or bases.

In order to determine the range and confirm the mechanism of the new rearrangement of 1,2,3-thiadiazol-4-S-methylcarbothioimidates to 5-methylmercapto-1,2,3-triazoles, and to investigate the effect of substituents on the reactivity of α-diazocarbothioimidates, we studied these reactions in a more convenient series of 5-amino-1,2,3-thiadiazol-4-carbothioamides III, containing substituents with different electron-accepting properties. It was observed that compounds IIIa, b, e, h, i react with methyl iodide in the presence of bases, and IIIa, b do so even in their absence. It should be noted that the reaction of aryl-substituted thiadiazoles IIIe, h with methyl iodide was studied in a mixture of 25% isomer IIIe and 75% isomer IIIh which could not be separated because of their identical chromatographic mobilities and similar physicochemical properties [6]. As a result of the reaction, as in the case, too, of the methylation of thiadiazoles IIIa, b [4], 5-methylmercapto-1-(4-

TABLE 2. Deviations of the Atoms from the Root-Mean-Square Plane in a 5-Methylmercapto-1-(4-methoxyphenyl)-1,2,3-triazol-4-carbothioamide (IVc) Molecule

Plane A		Plane B		Plane C	
Atom	deviation, δ, Å	atom	deviation, δ, Å	atom	deviation, δ, Å
$N_{(1)}$	0,0036	$C_{(4)}$	0,0034	$S_{(2)}$	0,0023
$N_{(2)}$	0,0010	$C_{(5)}$	0,0116	$N_{(4)}$	0,0027
$N_{(3)}$	-0,0053	$C_{(6)}$	-0,0173	$C_{(1)}$	0,0024
$C_{(1)}$	0,0073	$C_{(7)}$	0,0082	$C_{(3)}$	-0,0074
$C_{(2)}$	-0,0065	$C_{(8)}$	0,0066		
		$C_{(9)}$	-0,0124		

methoxyphenyl)-1,2,3-triazol-4-carbothioamide (IVe) was uniquely evolved. Its structure was confirmed by x-ray structural analysis.

Crystals of triazole IVd are monoclinic: a = 12.049(5), b = 7.922(2), c = 13.586(4) Å, β = 107.6(1)°, V = 1236.3(7) Å^3, M = 280.4, d_{calc} = 1.5 g/cm^3, Z = 4, space group $P2_{1/n}$. The atomic coordinates and bond angles are given in Table 1, and the bond lengths are shown in Fig. 1. Atoms of the triazole ring lie in plane A, the benzene ring is plane B, and the atoms of the carbothioamide group and $C_{(1)}$ form plane C. The angle between planes A and B is 40.61°, that between B and C, 37.32°. The deviation of the atoms from the mean-square plane is presented in Table 2.

The fact that the methylation of a mixture of aryl-substituted thiadiazoles, IIIh, e results in the single product, triazole IVe, supports the supposition that these isomers enter into reaction with methyl iodide by different mechanisms.

Probably the first step in this reaction for all the thiadiazoles, IIIa, b, e, h, i, is the splitting off of a proton from the carbothioamide function. At the second step, two processes are possible. One is the formation of carbothioimidate V by the methylation of the thioamide group by methyl iodide, which is stable in the case of ureide-substituted thiadiazole IIIi [4], or which rapidly recyclizes through intermediate diazo compound I to triazole IV (path A). An alternative mechanism proposes that the second step of the reaction is a rapid opening of the ring to diazothioimidates II and closing to triazole VI, which then reacts with methyl iodide through the mercapto group (path B).

It is known that 5-amino-1,2,3-thiadiazoles are converted to 5-mercapto-1,2,3-triazoles only by the action of bases [1]. It can be concluded, therefore, that the alkylation of compounds IIIa, b by methyl iodide in the absence of base takes place by mechanism A. Study of a methanolic solution of thiadiazole IIIb in a PMR spectrometer cell over a period of 51 h at 60°C showed the absence of triazole IVb in the solution, thus further confirming our conclusion regarding the mechanism of alkylation of thioamides IIIa, b.

In the case of the methylation of triazole IIIe, which contains an aryl substituent on the carbothioamide group, it is difficult to give preference to any of the mechanisms under consideration. At the same time, the reaction of its isomer, 5-aryl substituted triazole IIIh, with methyl iodide takes place unambiguously by mechanism B, evidence for which is the structure of the end product, triazole IVe.

Since diazothioimidolates II, forming when the thiadiazole ring of compounds III opens under the action of bases, can exist in two tautomeric forms, 1 and 2, the reaction can be expected to form the two isomeric triazoles, VI and VII. And as a result of the irreversibility of the cyclization of diazo compounds $II_{(1)}$ and $II_{(2)}$, one can draw conclusion about the effect of substituents on the rate of cyclization of thioimidolates II from the ratio of heterocycles VI and VII that are formed.

However, in a study of this recyclization in a wide range of 5-amino-1,2,3-thiadiazol-4-carbothioamides with substituents of different donor–acceptor properties in the amino as well as in the carbothioamido groups, IIIa-h, we established the formation of individual triazoles VIa-e. Evidence for this were the single proton and carbon atom signals in the ^{1}H and ^{13}C-NMR spectra. Proof of the structure of triazoles VIa, b is given in [5]. The location of the aryl substituents in triazoles VIc-e was determined from the splitting of the signals of the phenyl ring carbon atoms in the ^{13}C NMR spectrum of VIe, taken without uncoupling from the protons (see Experimental) and a comparison of the PMR spectra of triazoles VIc-e with the corresponding spectrum of mercapto derivative IVe, the structure of which was confirmed by x-ray structural analysis (see above). A mass-spectroscopic study also gave evidence in favor of the assigned structure.

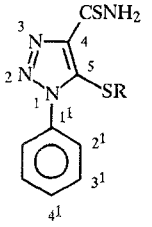
From what has been presented, it can be concluded that the introduction of either an electron donating methyl group or an electron accepting aryl substituent at the nitrogen atom of a α-diazoacetothioimidolates leads to an increase in its reactivity to cyclize to 5-mercapto-1,2,3-triazoles.

TABLE 3. Characteristics of the Compounds Synthesized

Compound	T_{mp}, °C	IR spectrum, ν, cm^{-1}	Mass spectrum, m/z, (%)*	Yield, %
IV	145	3330, 3260, 3160 (NH), 2890, 2820 (CH)	M^+280 (10), 246 (28), 218 (52), 203 (100), 171 (20)	67 (method A); 75 (method B)
VI	180...182 (with decomp.)	3320,3300, 3195 (NH)	M^+266 (45), 221 (31), 134 (36), 107 (100), 81 (55)	80
VI	179...181 (with decomp.)	3320, 3300, 3200 (NH)	M^+250 (50), 205 (33), 118 (35), 91 (100), 65 (65)	85
VI	173 (with decomp.)	3320, 3300, 3190 (NH)	M^+236 (8), 208 (36), 142 (32), 77 (100), 51 (50)	75

*Values of the five strongest peaks in the mass spectrum are shown.

TABLE 4. ^1H- and ^{13}C-NMR Spectra of the Compounds Synthesized



Compound	PMR spectrum (in DMSO-D_6),	13C-NMR spectrum (in DMDO-D_6) δ, ppm
IVe	2,2 (3H, s, SMe); 3,9 (3H, s, OMe); 7,1...7,7 (4H, m, C_6H_4); 9,6; 9,9 (2H, s, s, NH_2)*	17,69 (3H, q, *J*=143 Hz, SMe); 55,54 (3H, q, *J*=145 Hz OMe); 114,44 (3'-C); 127,47 (2'-C); 128,50 (1'-C); 135,10 (5-C); 146,29 (4-C); 160,24 (4'-C); 187,70 (C=S)
VIe	3,9 (3H, s, OMe); 7,0...7,7 (4H, m, C_6H_4); 9,9; 10,6 (2H, 2 br.s, NH_2)*	55,62 (3H, q, *J*=144 Hz, OMe); 114,75 (3'-C); 125,41 (5-C); 126,80 (1'-C); 138,63 (4-C); 160,79 (4'-C); 185,87 (C=S)
VId	2,4 (3H, s, Me); 7,2...7,7 (4H, m, C_6H_4); 9,6; 11,0 (2H, 2 br.s, NH_2)*	
VIc	7,6 (5H, s, Ph); 9,6; 10,8 (2H, 2 br.s, NH_2)*	

*Signals of nonequivalent protons of the carbothioamide group.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer in KBr disks. The PMR spectra were obtained on Bruker WR-80 (80.13 MHz) and Varian VXR-400 (400 MHz) instruments in DMSO-D6; TMS internal standard. The ^{13}C NMR spectra were taken on Bruker WR-80 (20.13 MHz) and Varian VXR-400 (101 MHz) spectrometers. The mass spectra were recorded on a Varian MAT-311A instrument (70 eV potential). The x-ray structural investigation was conducted on a Syntex-P21 4-circle, automatic diffractometer ($\lambda CuC\alpha$, graphite monochromator, $\theta/2\theta$ scanning, $2\theta_{max} \leq 124°$), no correction for absorption was introduced. In the calculation, 1,750 independent reflections with $I > 2\sigma(F)$ were used. The structure was deciphered by the direct method and initially refined to $R = 0.14$ in the full matrix, isotropic approximation, the refined in the full matrix, anisotropic approximation. All hydrogen atoms were located by a difference synthesis. The final value was $R = 0.071$ ($R_W = 0.065$).

The course of the reactions and the purity of the resultant products were monitored by means of TLC on Silufol UV-254 plates.

Elementary analyses corresponded to the calculated values.

Yields, physico chemical, and spectral characteristics of the substances prepared are shown in Tables 3 and 4.

The syntheses of substances IVa, b, IIIi, and Vi are given in [4]. Compounds IIIa-h are described in [6].

5-Methylmercapto-1-(4-methoxyphenyl)-1,2,3-triazol-4-carbothioamide (IVe). A. A solution of sodium ethylate is prepared from 0.8 g (3.5 mmole) of sodium and 9 ml of absolute ethanol, and to it is added 0.92 g (3.5 mmole) of a 1:3 mixture of thiadiazoles IIIe and IIIh [6]. Then, with mixing and cooling, 0.36 ml (3.5 mmole) of methyl iodide is added dropwise. The

heavy precipitate that forms over 10 min is filtered off, dissolved in the minimum amount of 1:1 alcohol/chloroform and applied to a chromatographic column. On elution with chloroform, the first fraction is taken. The chloroform is evaporated off. 5-Methylmercapto-1-(4-methoxyphenyl)-1,2,3-triazol-4-carbothioamide (IVe) crystallizes as yellow needles with a regular hexagonal cross section.

B. A solution of sodium ethylate is prepared from 0.8 g (3.5 mmole) of sodium and 9 ml of absolute ethanol, and to it is added 0.92 g (3.5 mmol) of triazole VIe. Then, with mixing and cooling, 0.36 ml (3.5 mmole) of methyl iodide is added dropwise. The precipitate that forms over 30 min is filtered off and crystallized from ethanol. The physico chemical characteristics of samples prepared by both methods are in complete agreement.

5-Mercapto-1-R'-1,2,3-triazol-4-carbothioamide VIc-e. A suspension of 1 mole of the appropriate mixture of 5-amino-1,2,3-thiadiazol-4-carbothioamides IIIe, h, IIId, g, or IIIc, i in 1.5 liters of 25% aqueous ammonia is refluxed until the solids are completely dissolved. The reaction mixture is evaporated to one-third of its initial volume. The precipitate formed after acidification to pH 1 is filtered off and crystallized from ethanol.

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