SYNTHESIS OF SUBSTITUTED 1,3-THIAZINOAZOLES

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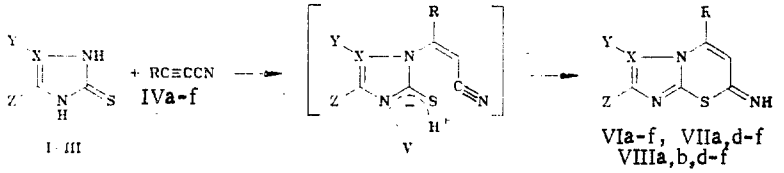
Substituted 1,3-thiazinoazoles were obtained by treating benzimidazole-2-thione, 4,5-diphenylimidazole-2-thione, and 1,2,4-triazole-3-thione with tertiary cyanoacetylenic alcohols and their acetals in the presence of lithium hydroxide. Treatment of the 1,3-thiazinobenzimidazoles with base destroyed the thiazino ring forming benzimidazol-2-one.

The reaction of azolethiones with phenylcyanoacetylene to form condensed 1,3-thiazines has been reported previously [1, 2]. We now report the addition of benzimidazole-2-thione (I), 4,5-diphenylimidazole-2-thione (II), and 1,2,4-triazole-3-thione (III) to tertiary cyanoacetylenic alcohols and their acetals (IVa-f).

We have shown [3] that thione I undergoes heterocyclization with alcohols IVa, b in the presence of KOH to give 1,3-thiazinobenzimidazoles VIa, b. The comparatively low yield (38-55%) of VIa, b is apparently due to the ready tendency of the tertiary cyanoacetylenic alcohols to decompose to the corresponding ketones and cyanoacetylene [4] in the presence of the strong base. Conducting the reaction in the presence of organic base (e.g., triethylamine) avoided this decomposition for IVa, b but the yields of VIa, b were not raised above 57%.

The yield of the 1,3-thiazinoazoles VI-VIII has now been raised to 98% with the aid of the specific reaction catalyst lithium hydroxide [5].



I, VI X=C, Y and Z forming a benzo ring; II, VII X=C, Y=Z=C_6H_5; III, VIII X=N, Y and Z absent IV, VI—VIII a R=$(CH_3)_2C(OH)$, b R=$(C_2H_5)(CH_3)C(OH)$; c R=$(C_4H_9)(CH_3)C(OH)$; d  , e  f R=$(CH_3)_2COCH(CH_3)OC_4H_9$

The reactions of thiones I-III with cyanoacetylenyl alcohols IVa-f should be carried out with equimolar amounts of starting materials in organic solvent at 20°C and in the presence of 10% (by weight) LiOH. The heterocyclic products VI-VIII were evolved in high yields (Table 1). Dioxan was the preferred medium because other solvents (e.g., ethanol, acetonitrile, or DMSO) led to yields of the target products lowered by 20-30%. The reaction takes place regiospecifically. PMR spectral analysis of the course of the reaction has shown that an unstable N-adduct (V) was formed in the first stage [6].

The intermediate product V has been identified with the help of IR spectroscopy for the reaction between thione I and alcohol IVa in absolute chloroform. The IR spectra of the reaction mixture were periodically recorded as dilute solutions (Fig. 1). After 3 h, in addition to absorption bands for the starting materials (OH at 3586 and broad CN attached to C≡C at 2280-2300 cm^{-1} for alcohol IVa and NH at 3442 cm^{-1} for thione I) there were found bands at 2215 cm^{-1} (CN attached to C=C in V) and 3310 cm^{-1} (imino group in product VIa). The intensity of the absorption bands for the starting material were markedly decreased after 8 h

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TABLE 1. 1,3-Thiazinoazoles VI-VIII

Compound	mp, °C*	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
VIc**	168—169	63.3	6.3	13.6	10.7	$C_{15}H_{19}N_3OS$	63.7	6.4	13.9	10.6	97
VId	201—203	63.9	5.8	13.9	10.6	$C_{16}H_{17}N_3OS$	64.2	5.7	14.0	10.7	77
VIe	194—196	62.8	5.3	14.9	11.0	$C_{15}H_{15}N_3OS$	63.1	5.3	14.7	11.2	86
VIf	73—75	64.0	7.0	11.9	9.0	$C_{19}H_{25}N_3O_2S$	63.5	7.0	11.7	8.9	84
VIIa	176—178	69.4	5.3	11.3	9.1	$C_{21}H_{19}N_3OS$	69.6	5.3	11.6	8.9	97
VIId	177—179	71.9	6.1	10.0	7.5	$C_{24}H_{23}N_3OS$	71.8	5.8	10.5	8.0	56
VIIe	190—193	71.8	5.7	10.7	8.0	$C_{23}H_{21}N_3OS$	71.3	5.5	10.8	8.3	60
VIIf	101—104	70.5	6.7	8.6	6.8	$C_{27}H_{31}N_3O_2S$	70.3	6.8	9.1	7.0	91
VIIIa	148—150	45.1	4.9	26.3	14.9	$C_8H_{10}N_4OS$	45.7	4.8	26.6	15.2	98
VIIIb	99—100	48.1	5.6	25.0	14.1	$C_9H_{12}N_4OS$	48.2	5.4	25.0	14.3	95
VIIId	124—126	52.8	5.5	22.6	12.8	$C_{11}H_{14}N_4OS$	52.8	5.6	22.4	12.8	66
VIIIe	142—144	50.9	5.3	24.0	13.2	$C_{10}H_{12}N_4OS$	50.8	5.1	23.7	13.6	81
VIIIf	87—88	54.1	7.0	18.2	10.4	$C_{14}H_{22}N_4O_2S$	54.2	7.1	18.1	10.3	93

*Compounds VIa-e, VIIa, and VIIIe were recrystallized from benzene, VIId from hexane:acetone (3:1), VIIe from acetone, VIf, VIIIf from hexane, and VIIIa, b, d were reprecipitated from chloroform with hexane.
**According to [3]: compound VIa, mp 140-143°C, yield 98%; VIb, mp 129-131°C, yield 83%.

TABLE 2. PMR Spectra of VIa, b, f; VIIa, f; and VIIIa

Compound	Chemical shift, δ, ppm			
	3-H (s)	CH_3 (s)	other signals	Ar*
VIa	6.41	1.53		7.23
VIb	6.43	1.48	0.86 t (CH_3), 1.76 t (CH_2)	7.25
VIf	6.38	1.50	0.81 t (CH_3), 3.36 t (OCH_2), 4.76 q (OCH_2)	7.27
VIIa	6.52	1.43		7.12
VIIf	6.50	1.64	0.96 t (CH_3), 3.47 t (OCH_2), 4.89 q (OCH)	7.40
VIIIa	6.52	1.43		7.12

*Center of aromatic proton multiplet.

and the intensity of the imino band at 3310 cm^{-1} was increased. The frequency of the CN (C=C) band at 2215 cm^{-1} remained unchanged. The starting material (I and IVa) bands had completely disappeared after 10 h with increased intensity for the band for VIa at 3310 cm^{-1} and a band remaining at 2215 cm^{-1} for the acrylonitrile derivative V. The absence of a secondary amino band in the spectrum infers that the reaction occurs at the nitrogen atom. The reactive nitrile in intermediate V leads to further intramolecular cyclization at the exocyclic sulfur atom.

In contrast to [7], the products of heterocyclization with dichydrofuran substituents were not observed.

The course of the reaction was not significantly affected by the nature of the R substituent in the cyanoacetylenes IV.

Increasing the amount of alcohol IV in the reaction led to the formation of a mixture which was hard to separate, e.g., a twofold excess of IVa (relative to I) gave rise to 15-37% of benzimidazole IX. The low melting, yellow powdered residue appeared by IR and PMR (CD_3OD) to be a mixture of the intermediate acrylonitrile V (2215 cm^{-1} nitrile, olefin proton singlet at 6.98 ppm) and the cyclic thiazine VIa (1630 cm^{-1} (N–C=C), thiazine proton singlet at 6.70 ppm). The mixture could not be separated by TLC or GLC.

The IR spectra of VI-VIII show intense absorption bands (dilute absolute chloroform solution) at 3596 (OH), 3313 (=NH), and 1630 cm^{-1} (N–C=C) and the absence of the bands for the C≡C and C≡N groups in the starting cyanoacetylene IV at 2300-2280 cm^{-1}. The C–O–C absorption bands for the acetals VIf, VIIf, and VIIIf were found at 1200-1080 cm^{-1}.

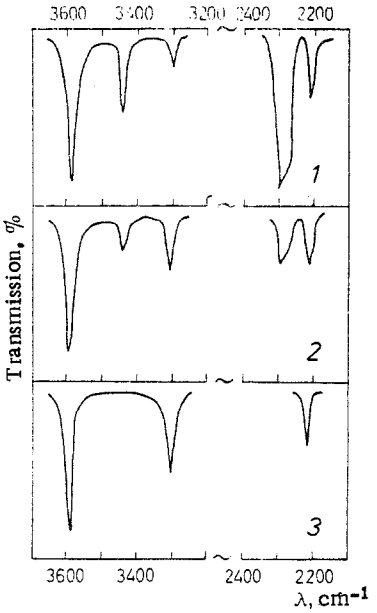
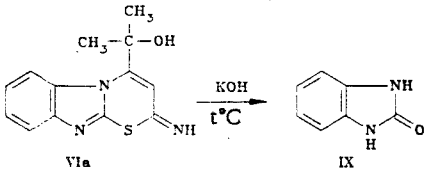


Fig. 1. IR spectrum of reaction mixture of thione I and alcohol IVa in absolute chloroform. 1) after 3 h; 2) 8 h; 3) 10 h.

The PMR spectra of 1, 3 thiazinoazoles VI-VIII show the presence of thiazine and thiazole rings and alkyl and aryl protons (Table 2).

By contrast to 4-phenyl substituted 1,3-thiazines [1], 2-imino-4-(1-hydroxy-1-methylethyl)-1,3-thiazino[2,3-b]benzimidazole (VIa) did not break down in base to the acrylonitrile derivative of thione I. In the presence of 20% KOH at 20°C for 3 days VIa remained unchanged. Raising the temperature to 90-100°C led to destruction of the 1,3-thiazine ring and formation of benzimidazol-2-one IX.



VIa IX

Thus, the reported condensation of azolethiones with tertiary cyanoacetylenic alcohols and their acetals is a simple and convenient method for preparing condensed 1,3-thiazinoazoles.

EXPERIMENTAL

IR Spectra were recorded on Specord 75-IR and UR-20 instruments as KBr disks and in $CHCl_3$ solution (20-5 mmolar, 0.4-2 cm absorption layer thickness). PMR Spectra were obtained on a BS 487B Tesla spectrometer (80 MHz) using $CDCl_3$ solvent and HMDS internal standard. Mass spectra were recorded by direct probe insertion into an MAT-212 instrument with an electron ionization energy of 70 eV.

Cyanoacetylenic alcohols IVa-e were obtained by [8] and acetal IVf by [4]. Physical parameters for the synthesized compounds are given in Table 1 and PMR spectral data in Table 2.

2-Imino-4-(1-hydroxy-1-methylethyl)-1,3-thiazino[2,3-b]benzimidazole (VIa). 4-Methyl-4-hydroxy-2-pentynnitrile (IVa, 0.22 g, 2 mmoles) in dioxan (3 ml) was added dropwise to a stirred mixture of thione I (0.3 g, 2 mmoles) and LiOH (0.03 g, 10% of the weight of thione) in dioxane (10 ml) and stirring was continued at 20°C for 13 h. The reaction mixture was passed through an alumina column (to remove base), dioxane distilled off and the residue recrystallized from benzene. Yield 0.51 g, M^+ 259.

The 1,3-thiazinoazoles VIb-e, VIIa, d, e, and VIIIa, b, d, e were obtained similarly.

2-Imino-4-(2,4-dimethyl-3,5-dioxanonane)-1,3-thiazino[2,3-b]benzimidazole (VIf). A mixture of thione I (0.3 g, 2 mmoles), 4,4,6-trimethyl-5,7-dioxa-2-undecynnitrile (IVf) (0.41 g, 2 mmoles) LiOH (0.07 g, 10% of total mass of I and IVf) in dioxane (15 ml) were stirred at 20°C for 13

h. The reaction mixture was passed through Al_2O_3, the dioxane distilled off and the oily product triturated with cold hexane. VIf (0.6 g) was obtained as a white powder.

1,3-Thiazinoazoles VIIf and VIIIf were obtained similarly.

Benzimidazol-2-ones (IX). A mixture of VIa (0.3 g, 0.0012 mmoles) and KOH solution (20%, 0.06 g) in dioxane (10 ml) was stirred at 20°C. After 3 days only VIa was found (by TLC in chloroform). Heating the mixture at 90-100°C for 5 h, cooling, passage through an Al_2O_3 column, removal of dioxane, washing of the crystalline residue with ether (2 × 3 ml) and drying gave benzimidazolone IX (0.1 g, 65%) with mp 317°C (alcohol); literature data [9], mp 308°C. The IR spectrum was identical to that of a known sample.

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SYNTHESIS AND MASS-SPECTROMETRIC STUDY OF 2-AMINO- and 2-CHLORO-5-ARYL-1,3,4-THIADIAZOLES

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The cyclization of aldehyde thiosemicarbazones with ferric chloride yielded 2-amino-5-aryl-1,3,4-thiadiazoles, forming 2-chloro-5-aryl-1,3,4-thiadiazoles in the Sandmeyer reaction. The mass-spectrometric behavior of the 2-amino- and 2-chloro-5-aryl-1,3,4-thiadiazoles was studied; the typical routes of fragmentation characteristic of each group of compounds were found.

Substances with a varying spectrum of biological action have been found among the derivatives of 1,3,4-thiadiazoles, the chemistry of which is developing intensively at the present time [1]. The broad practical application of derivatives of 1,3,4-thiadiazoles in agriculture and medicine requires their reliable and rapid identification. Mass spectrometry is one of the methods permitting the solution of the given undertaking.

We obtained the thiosemicarbazones from the corresponding aromatic aldehydes and thiosemicarbazide [2]; the cyclization of the thiosemicarbazones with ferric chloride led to the 2-amino-5-aryl-1,3,4-thiadiazoles (I)-(IX) [3]. Under the conditions of the Sandmeyer

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