SYNTHESIS OF 1,3,4-THIADIAZOLE DERIVATIVES BY THE REACTION OF THIOSEMICARBAZIDE OR ITS 1- OR 4-SUBSTITUTED DERIVATIVES WITH SOME 1-BROMO-2-ACYLACETYLENES

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The reaction of thiosemicarbazide, 4-methyl-, 4-phenyl-, or 1-phenylthiosemicarbazides with 1-bromo-2-benzoyl(thenoyl-2)acetylenes in acetonitrile or glacial acetic acid yielded 2-acylmethylene- and 2-acylmethyl-5-amino-1,3,4-thiadiazoles. Heating of the latter in alcohol or aqueous alcohol gave the free bases.

Terminal α-acetylenic ketones react with 1-phenylthiosemicarbazide to form 2-acylmethyl-5-imino-3-phenyl-4H-1,3,4-thiadiazoles [1], whereas 1-acyl-2-phenylacetylenes react with thiosemicarbazide to form 2-amino-7-hydroxy-6,7-dihydro-1,3,4-thiadiazepines [2]. Dimethyl acetylenedicarboxylate reacts with thiosemicarbazide and its 1-substituted derivatives to give 2-hydrazino-5-methoxycarbonylmethylene-1,3-thiazolin-4-one [3], but with a 4-substituted thiosemicarbazide it gives 3-amino-2-imino-6-methoxycarbonyl-1,3-thiazin-4-one [4].

In order to investigate the reactivity of the 1-bromo-2-acylacetylenes (I) and (II) we have studied the reaction of these compounds with thiosemicarbazide (III) and 4-methyl-, 4-phenyl-, and 1-phenylthiosemicarbazides (IV-VI).

At equimolar reagent ratio at 20°C in acetonitrile or glacial acetic acid the reaction forms the 2-substituted-5-amino-1,3,4-thiadiazole hydrobromides (XIV-XXI) in yields of 57-85%.

The reaction of 1-bromo-2-acylacetylenes (I, R = Ph; II, R = α-C_4H_3S) with thiosemicarbazide and its substituted derivatives (III-VI) probably proceeds by nucleophilic replacement of bromine at the ethinyl carbon [5] to form the intermediate ethinyl sulfides (VII).

Under the experimental conditions (VII) undergoes intramolecular cyclization to form the 2-acylmethylene-5-amino-3H-1,3,4-thiadiazole hydrobromides (VIII-XV). Those compounds in which R^1 = H (VIII-XIII) are easily converted to the more stable 2-acylmethyl-5-amino-1,3,4-thiadiazole hydrobromides (XVI-XXI).

Attempts to carry out the reaction in MeOH or EtOH at 20°C or with cooling (at +5 to –20°C) were unsuccessful.

The IR spectra of (XIV) and (XV) contain C–S bands at 680-690 cm^{-1}, C=C and C=N bands at 1530-1600 cm^{-1}, C=O bands at 1650-1680 cm^{-1}, and two primary amine bands at 3050-3140 and 3220-3340 cm^{-1}.

TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	Yield, %		Compound	Empirical formula	Yield, %
		A	B			
XIV	$C_{16}H_{14}BrN_3OS$	84	74	XXII	$C_{16}H_{13}N_3OS$	80
XV	$C_{14}H_{12}BrN_3OS_2$	—	57	XXIII	$C_{14}H_{11}N_3OS_2$	71
XVI	$C_{10}H_{10}BrN_3OS$	80	—	XXIV	$C_{10}H_9N_3OS$	82
XVII	$C_8H_8BrN_3OS_2$	71	72	XXV	$C_8H_7N_3OS_2$	75
XVIII	$C_{11}H_{12}BrN_3OS$	84	—	XXVI	$C_{11}H_{11}N_3OS$	74
XIX	$C_9H_{10}BrN_3OS_2$	74	77	XXVII	$C_9H_9N_3OS_2$	71
XX	$C_{16}H_{14}BrN_3OS$	85	—	XXVIII	$C_{16}H_{13}N_3OS$	85
XXI	$C_{14}H_{12}BrN_3OS_2$	82		XXIX	$C_{14}H_{11}N_3OS_2$	79

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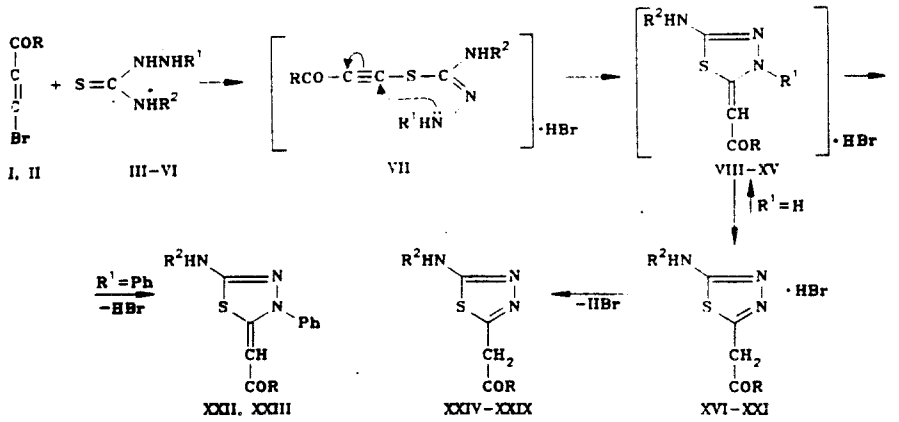
The IR spectra of the hydrobromides (XVI-XXI) show a broad ammonium band in the 2550-3350 cm^{-1} region, the C–S bond at 670-720 cm^{-1}, C=C and C=N bonds at 1540-1615 cm^{-1}, and C=0 at 1630-1660 cm^{-1}.

When hydrobromides (XIV-XXI) are heated in alcohol or aqueous alcohol, HBr is split off and the free bases (XXII-XXIX) are formed in 71-85% yield.

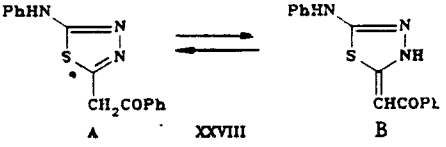
The IR spectra of 2-acylmethylene-5-amino-Δ^4-1,3,4-thiadiazolines (XXII, XXIII) and 2-acylmethyl-5-amino-1,3,4-thiadiazoles (XXIV-XXIX) contain bands of the C–S bond at 670-700 cm^{-1}, C=C and C=N bonds at 1490-1590 cm^{-1}, two primary amino bands at 3095-3280 and 3290-3430 cm^{-1} for (XXII-XXV), and a secondary amino band at 3230-3410 cm^{-1} for (XXVI-XXIX).



Compound	R	R^2	Compound	R	R^2	Compound	R	R^2
VIII	Ph	H	XVI	Ph	H	XXIII	α-C_4H_3S	H
IX	α-C_4H_3S	H	XVII	α-C_4H_3S	H	XXIV	Ph	H
X	Ph	Me	XVIII	Ph	Me	XXV	α-C_4H_3S	H
XI	α-C_4H_3S	Me	XIX	α-C_4H_3S	Me	XXVI	Ph	Me
XII	Ph	Ph	XX	Ph	Ph	XXVII	α-C_4H_3S	Me
XIII	α-C_4H_3S	Ph	XXI	α-C_4H_3S	Ph	XXVIII	Ph	Ph
XIV	Ph	H	XXII	Ph	H	XXIX	α-C_4H_3S	Ph
XV	α-C_4H_3S	H						

* VIII—XIII, XVI—XXI, XXIV—XXIX R^1=H, XIV, XV, XXII, XXIII R^1=Ph

Using (XXVIII) (R = R^2 = Ph, R^1 = H) as an example, the dependence of tautomeric equilibrium on temperature and solvent was studied by PMR spectroscopy.



A solution of (XXVIII) in DMSO-D_6 at 20°C shows singlets for the CH_2 protons at 4.92 ppm and for the CH= protons at 6.53 ppm. The exocyclic NH groups of both forms give two signals, at 10.28 and 10.16 ppm. The A:B ratio is 70:30.

In DMFA-D_7 at 20°C the equilibrium is completely shifted to tautomer A. When the temperature is lowered to –40°C the A:B ratio is 70:30.

The main differences between the PMR spectrum of hydrobromide (XX) and that of free base (XXVIII) in DMSO-D_6 (or DMFA-D_7) solution at 20°C are the broadening of the CH_2 proton signal at 4.94 ppm (or 5.15 ppm in DMFA-D_7) and the presence of a narrow NH signal at 10.8 ppm (or 12.06 ppm in DMFA-D_7). At –40°C in DMFA-D_7 solution the ratio of A and B hydrobromides is 30:70, and the NH group gives four signals, at 12.97, 11.92, 11.78, and 9.07 ppm. Thus, when a solution of hydrobromide (XX) in DMFA-D_7 is cooled the tautomeric equilibrium, in contrast to that of the free base (XXVIII), is shifted toward the Δ^4-1,3,4-thiadiazoline form B.

The structures of the substituted Δ^4-1,3,4-thiadiazolines (XXII) and (XXIII) and of the 1,3,4-thiadiazoles (XXIV-XXIX) were confirmed by ^1H and ^{13}C NMR data.

EXPERIMENTAL

IR spectra were obtained with a UR-20 spectrometer in KBr tablets; ^1H and ^{13}C NMR spectra were obtained with a Tesla BS-567A spectrometer (100 MHz) in DMSO-D_6, with HMDS internal standard.

The properties of the synthesized compounds are shown in Table 1. Elemental composition (C, H, BR, N, S) of (XIV-XXIX) agreed with the calculated values.

5-Amino-2-benzoylmethylene-3-phenyl-Δ^4-1,3,4-thiadiazoline Hydrobromide (XIV). A. To a solution of 1.05 g (5 mmoles) of 1-bromo-2-benzoylacetylene in 15 ml of MeCN was added 0.84 g (5 mmoles) of 1-phenylthiosemicarbazide with stirring. The mixture was stirred for 1.5 h at 20°C, and the resulting precipitate was filtered off and dried in vacuum. Yield 1.57 g (84%), orange crystals with mp 225-230°C (from glacial AcOH).

B. The reaction was carried out similarly, but in glacial AcOH. Yield 1.4 g (74%).

Compounds (XV-XXI) were obtained similarly.

5-Amino-2-benzoylmethylene-3-phenyl-Δ^4-1,3,4-thiadiazoline (XXII). Hydrobromide (XIV), 1 g (2.7 mmoles) was dissolved in 50 ml of EtOH with heating. The solution was cooled to 0°C and the precipitate was filtered off. Gold needles, mp 191-194°C (from EtOH). Yield 0.63 g (80%).

Free bases (XXIII-XXV) and (XXVIII, XXIX) were obtained analogously.

Compounds (XXVI, XXVII) (R^2 = Me) were obtained by heating hydrobromides (XVIII, XIX) in 3:1 water–alcohol in the presence of an equimolar amount of Et_3N.

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