Synthesis of New 1,2,4-Triazolines and 1,3,4-Thiadiazolines from Bithioureas

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2,4-Disubstituted thiosemicarbazides **1** react with acyl isothiocyanates to give bithioureas **2**, which by the action of sodium ethanolate cyclize to 1,2,4-triazoline-3-thiones **3** and **5**, respectively. Treatment of **2** with methyl iodide yields 1,3,4-thiadiazoline-2-imines **8** isomeric with **3**. Compound **8d** undergoes a thermal induced DIMROTH rearrangement to give **3d** in good yield.

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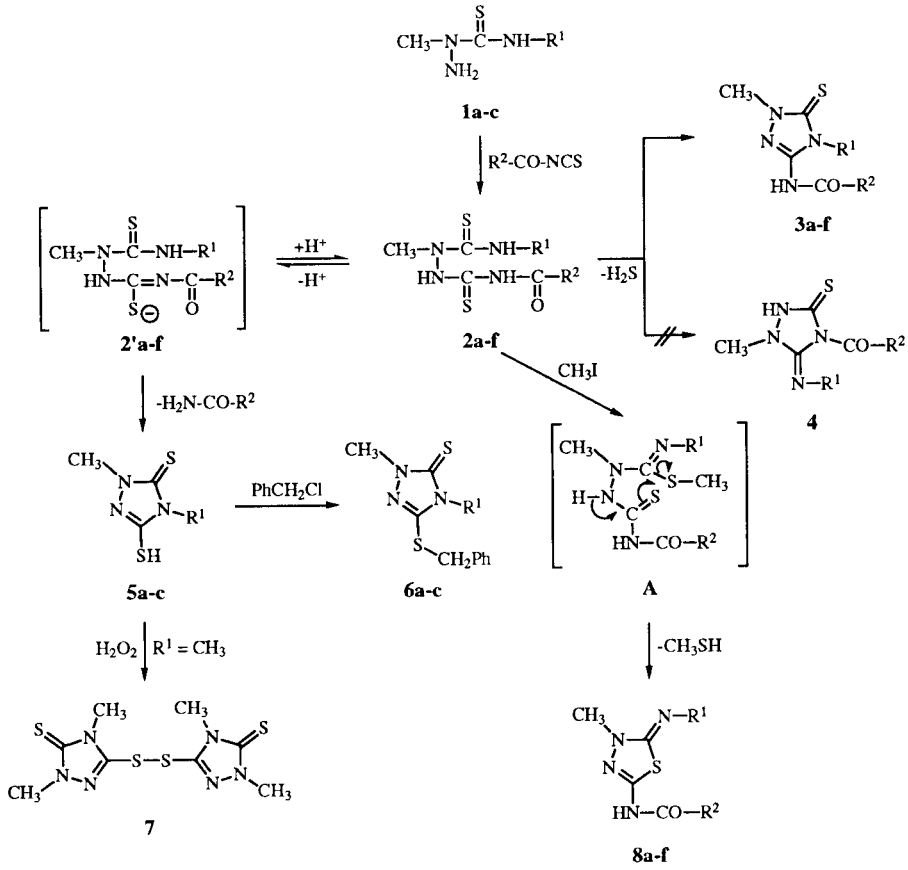
Thiosemicarbazides and their derivatives are important as bio-active compounds and precursors for many heterocycles. Thus, convenient methods synthesizing 1,2,4-triazolines and 1,3,4-thiadiazolines include cyclization of acyl thiosemicarbazides, reaction of thiosemicarbazides with derivatives of carboxylic acids and oxidation of aldehyde thiosemicarbazones [1]. Another well investigated route to derivatives of triazole and thiadiazole involves the cycliza-

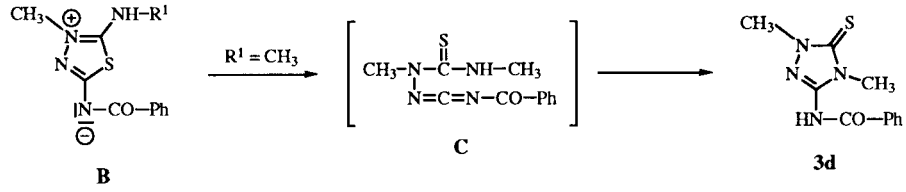
Scheme 1



1,5,6	R^1
a	Methallyl
b	Methyl
c	Phenyl

2,3,8	R^1	R^2
a	Methallyl	Ethoxy
b	Methallyl	Phenyl
c	Methyl	Ethoxy
d	Methyl	Phenyl
e	Phenyl	Ethoxy
f	Phenyl	Phenyl

Scheme 2



B C 3d

tion of bithioureas. The latter are readily available from the reaction of hydrazine with double molar amounts of alkyl or aryl isothiocyanates or by sequential treatment of the hydrazine with two differently substituted isothiocyanates *via* 4-substituted thiosemicarbazides [1].

Although numerous addition-cyclization reactions of ethoxycarbonyl isothiocyanate with hydrazino compounds are known [2-5], until now only a few were reported concerning the addition-cyclizations of acyl isothiocyanates with 2,4-disubstituted thiosemicarbazides [6,7].

In connection with our study on the reaction of ketones with 2,4-disubstituted thiosemicarbazides [8] derived from monosubstituted hydrazines and isothiocyanates [9], a number of bithioureas **2** were prepared (Scheme 1). These compounds were obtained by interaction of equimolar quantities of the thiosemicarbazides **1** and ethoxycarbonyl as well as benzoyl isothiocyanate with a yield ranging from 76-95%. The structure of the bithioureas **2** was determined by means of ^1H nmr and mass spectroscopy as well as elemental analysis. The mass spectra of **2a**, **c** and **d** include peaks of their molecular ion, but displayed more prominent signals corresponding to the loss of SH and H_2S. In the case of compounds **2b**, **e** and **f** the molecular ion peaks are entirely absent.

Bithioureas are known to cyclize by an intramolecular nucleophilic attack of one of the nitrogen or sulfur atoms on one of the thiocarbonyl groups. In basic media *N*-ring closure to derivatives of triazole will be expected [10].

We found that the evolution of hydrogen sulfide occured by heating the bithioureas **2** in ethanolic sodium ethanolate (0.5 mole equivalents) to give alkali-soluble products formulated as 1,2,4-triazoline-3-thiones **3** in 63-90% yield. The mass spectra of these compounds show the molecular ion peaks due to the elimination of hydrogen sulfide. Support for the assigned structure **3** was provided by nmr spectroscopy. In addition, the isomeric triazolidine structure **4** could be excluded. The proton chemical-shift values of the methallyl group in **3a** and **b** are consistent with those previously observed for 4-methallyl substituted triazolinethiones (allylic methylene protons appearing as singlet at 4.6-4.7 ppm, clearly separated singlets of vinylic protons between 4.7 and 5.0 ppm) [11,12]. Similarly, the ^{13}C chemical shifts of the substituents R^1, *i.e.* methyl carbons in **3c** and **d** as well as *N*-phenyl carbon atoms in **3e** and **f**, are characteristic for a substitution on the endocyclic nitrogen atom [13]. Moreover, the chemical-shift values of NH-protons clearly show the presence of acylamino-grouping because of their dependence on the substituent R^2.

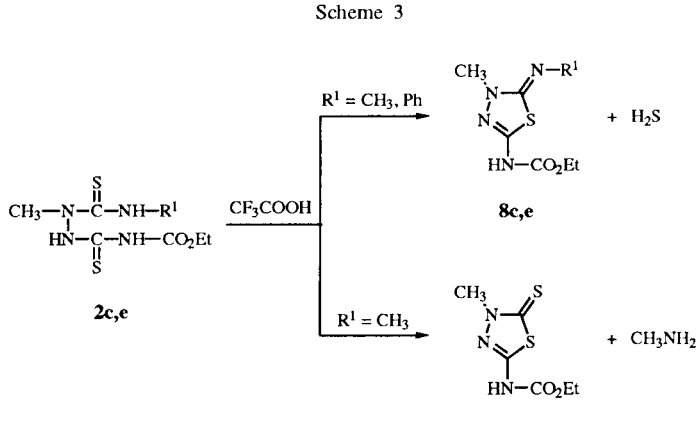
Our results indicate that the initial attack of the nitrogen atom with the higher nucleophilicity (R^1-NH) is involved in the cyclization pathway [14,15].

By treating the bithioureas **2** with 1.2 molar amounts of sodium ethanolate the formation of 5-mercapto-1,2,4-triazoline-3-thiones **5** was observed. These compounds were converted to their more stable *S*-benzyl derivatives **6**. Compound **5b** is identical with the product synthesized from 2,4-dimethylthiosemicarbazide (**1b**) and carbon disulfide in pyridine [16] and was oxidized by hydrogen peroxide to disulfide **7** (Scheme 1).

In the formation of **5** the excess base gave rise to complete deprotonation of **2** to the mercaptide **2'**. After *N*-ring closure further stabilization proceeded with loss of the corresponding amide rather than hydrogen sulfide. Catalytic amounts of sodium ethanolate (0.1 to 0.5 mole equivalents), however, promoted the elimination of hydrogen sulfide from the bithioureas **2** to form compounds **3**. This is explicable by the existence of un-ionized **2** in equilibrium with **2'**. Finally, depending on the amounts of sodium ethanolate employed, the cyclization of **2** occurs cleanly to form either **3** or **5**.

When the cyclization of **2d** was carried out with catalytic amounts of sodium ethanolate the 1,3,4-thiadiazolineimine **8d** was unexpectedly isolated as a side prod-

Scheme 3



2c,e 8c,e 9

Table 1

Physical Data of Compounds **2**, **3**, **6** and **8**

Compound No.	Yield [a] (%)	Mp (°C) (recrystallization solvent)	Molecular Formula (Molecular Weight)	Analysis (%) Calcd./Found C	H	N	S
2a	90	113	$C_{10}H_{18}N_4O_2S_2$ (290.41)	41.36 41.64	6.25 6.18	19.29 19.63	
2b	95	119	$C_{14}H_{18}N_4OS_2$ (322.46)	52.15 52.15	5.63 5.47	17.38 17.32	
2c	90	143	$C_7H_{14}N_4O_2S_2$ (250.35)	33.58 33.60	5.64 5.45	22.38 22.65	
2d	79	141	$C_{11}H_{14}N_4OS_2$ (282.39)	46.79 46.94	5.00 5.06	19.84 20.02	
2e	76	123	$C_{12}H_{16}N_4O_2S_2$ (312.42)	46.13 46.36	5.16 5.08	17.93 18.17	
2f	85	133	$C_{16}H_{16}N_4OS_2$ (344.46)	55.79 55.70	4.68 4.35	16.27 16.24	
3a	89	99 (toluene/cyclohexane)	$C_{10}H_{16}N_4O_2S$ (256.33)	46.86 46.86	6.29 6.45	21.86 21.48	12.51 12.68
3b	90	131 (chlorobenzene)	$C_{14}H_{16}N_4OS$ (288.37)	58.31 58.29	5.59 5.67	19.43 19.46	11.12 11.45
3c	83	142-143 (toluene)	$C_7H_{12}N_4O_2S$ (216.26)	38.88 39.20	5.59 5.76	25.91 25.69	14.83 14.86
3d	63	169-170 (toluene)	$C_{11}H_{12}N_4OS$ (248.31)	53.21 53.14	4.87 5.24	22.56 22.37	12.91 13.27
3e	88	128 (toluene)	$C_{12}H_{14}N_4O_2S$ (278.33)	51.78 51.72	5.07 5.24	20.13 19.89	11.52 11.64
3f [b]	74	171-173 (acetic acid)	$C_{18}H_{18}N_4O_3S$ (370.43)	58.36 58.42	4.90 5.06	15.13 15.19	8.66 8.91
6a	66	81-82 (ethanol/water)	$C_{14}H_{17}N_3S_2$ (291.44)	57.70 57.77	5.88 5.86	14.42 14.44	22.01 22.10
6b	72	87-89 (ethanol)	$C_{11}H_{13}N_3S_2$ (251.38)	52.56 52.22	5.21 5.32	16.72 16.86	25.51 25.35
6c	64	84-86 (ethanol)	$C_{16}H_{15}N_3S_2$ (313.45)	61.31 61.34	4.82 4.81	13.41 13.39	20.46 20.82
8a	79	112.5-113.5 (cyclohexane)	$C_{10}H_{16}N_4O_2S$ (256.33)	46.86 47.00	6.29 6.07	21.86 21.69	12.51 12.35
8b	80	185-188 (ethanol/water)	$C_{14}H_{16}N_4OS$ (288.37)	58.31 58.09	5.59 5.37		11.12 11.30
8c	39	180-182 [c]	$C_7H_{12}N_4O_2S$ (216.26)	38.88 39.27	5.59 5.67	25.91 25.51	14.83 14.81
8d [d]	85	200-214 [e] (ethanol/water)	$C_{11}H_{14}N_4O_2S$ (266.32)	49.61 49.36	5.30 5.07	21.04 20.93	12.04 12.03
8e	86	136-137 (ethanol/water)	$C_{12}H_{14}N_4O_2S$ (278.33)	51.78 51.56	5.07 4.71		11.52 11.17
8f	29	177-178 (acetonitrile)	$C_{16}H_{14}N_4OS$ (310.38)	61.92 61.83	4.55 4.60	18.05 18.06	10.33 10.00

[a] Yield of crude products. [b] Crystallizing with 1 mole acetic acid. [c] Sublimed *in vacuo* (p = 1.5 torr, bath temperature = 160°). [d] Crystallizing with 1 mole water. [e] Unsharp melting point due to DIMROTH rearrangement.

uct. The preparation of 1,3,4-thiadiazolineimines **8** as main products was achieved by refluxing the bithioureas **2** with methyl iodide in methanol [17]. We assume the intermediate formation of *S*-methyl compound **A** followed by *S*-ring closure and elimination of methyl mercaptan giving the 1,3,4-thiadiazolineimines **8**. The latter are obtained as hydriodides and they can be released upon treatment with sodium hydroxide [18].

The structure of the 1,3,4-thiadiazolineimines as **8a**, **c**, **e** and **f** was elucidated on the basis of the resonance position of the C-2 atom at 156-157 ppm [19]. In comparison, compounds **3** exhibit the resonance of the thiocarbonyl-carbon (C-3) at 166-167 ppm. The presence of an exocyclic C=N bond in **8** is also apparent from the carbon-chemical shifts of the substituents R^1 [13] and the observed basicity of compounds **8** (formation of hydriodides). In **8b** and **d** the high acidity of NH-group gives rise to protonation of the imino-nitrogen atom. These compounds therefore should be formulated as mesomerically stabilized zwitterionic structure **B** (Scheme 2) in accordance with their nmr-spectral data. Thus, the ring carbons C-2 and C-5 appear at 161-163 ppm and 154-157

Table 2

^{1}H-NMR and Mass Spectral Data of Compounds **2**, **3**, **6** and **8**

Compound No.	^{1}H-NMR, δ (ppm) [a] CH_3N	NH	R^1	R^2/other signals	MS, m/z
2a	3.63 (s, 3H)	6.36 (t, 5.8 Hz, 1H) 8.76 (s, 1H) 10.98 (s, 1H)	1.74 (s, 3H, CCH_3) 4.21 (d, 5.5 Hz, 2H, $NHCH_2$) 4.82 (s, 1H, CCH_2) 4.87 (s, 1H, CCH_2)	1.33 (t, 7.1 Hz, 3H, CH_2CH_3) 4.27 (q, 7.1 Hz, 2H, CH_2CH_3)	290 (5, M^+), 257 (48, M^+-SH), 256 (44, M^+-H_2S), 143 (73), 55 (100, $C_4H_7^+$)
2b	3.69 (s, 3H)	6.41 (t, 5.3 Hz, 1H) 9.31 (s, 1H) 11.93 (s, 1H)	1.76 (s, 3H, CCH_3) 4.25 (d, 5.6 Hz, 2H, $NHCH_2$) 4.84 (s, 1H, CCH_2) 4.90 (s, 1H, CCH_2)	7.55 (t, 2H, C_6H_5) 7.69 (t, 1H, C_6H_5) 7.88 (d, 2H, C_6H_5)	289 (8, M^+-SH), 288 (8, M^+-H_2S), 105 (100, $C_6H_5CO^+$)
2c	3.44 (s, 3H)	8.02 (q, 4.2 Hz, 1H) 11.24 (s, 1H) 11.34 (s, 1H)	2.87 (d, 4.2 Hz, 3H, $NHCH_3$)	1.26 (t, 7.1 Hz, 3H, CH_2CH_3) 4.19 (q, 7.1 Hz, 2H, CH_2CH_3)	250 (23, M^+), 217 (76, M^+-SH), 216 (23, M^+-H_2S), 74 (90), 71 (100)
2d	3.51 (s, 3H)	8.13 (q, 4.1 Hz, 1H) 11.71 (s, 1H) 12.09 (s, 1H)	2.91 (d, 4.3 Hz, 3H, $NHCH_3$)	7.56 (t, 2H, C_6H_5) 7.68 (t, 1H, C_6H_5) 7.99 (d, 2H, C_6H_5)	282 (4, M^+), 249 (57, M^+-SH), 248 (28, M^+-H_2S), 149 (66), 105 (100, $C_6H_5CO^+$)
2e	3.69 (s, 3H)	9.67 (s, 1H) 11.40 (s, 1H) 11.46 (s, 1H)	7.33 (s, 5H, C_6H_5)	1.26 (t, 7.1 Hz, 3H, CH_2CH_3) 4.20 (q, 7.1 Hz, 2H, CH_2CH_3)	278 (12, M^+-H_2S), 177 (81), 135 (91, $C_6H_5NCS^+$), 77 (100, $C_6H_5^+$)
2f	3.61 (s, 3H)	9.82 (s, 1H) 11.77 (s, 1H) 12.32 (s, 1H)		7.20-8.02 (m, 10H, C_6H_5)	310 (9, M^+-H_2S), 135 (27, $C_6H_5NCS^+$), 105 (54, $C_6H_5CO^+$), 78 (100)
3a	3.79 (s, 3H)	6.96 (s, 1H)	1.73 (s, 3H, CCH_3) 4.64 (s, 2H, NCH_2) 4.73 (s, 1H, CCH_2) 4.96 (s, 1H, CCH_2)	1.29 (t, 7.2 Hz, 3H, CH_2CH_3) 4.23 (q, 7.1 Hz, 2H, CH_2CH_3)	256 (100, M^+), 241 (15, M^+-CH_3), 223 (14, M^+-SH), 210 (7, M^+-C_2H_5OH)
3b	3.74 (s, 3H)	8.39 (s, 1H)	1.69 (s, 3H, CCH_3) 4.70 (s, 2H, NCH_2) 4.74 (s, 1H, CCH_2) 4.92 (s, 1H, CCH_2)	7.48 (t, 2H, C_6H_5) 7.60 (t, 1H, C_6H_5) 7.81 (d, 2H, C_6H_5)	288 (100, M^+), 273 (19, M^+-CH_3), 255 (22, M^+-SH), 105 (65, $C_6H_5CO^+$)
3c	3.77 (s, 3H)	7.22 (s, 1H)	3.51 (s, 3H, NCH_3)	1.31 (t, 7.2 Hz, 3H, CH_2CH_3) 4.27 (q, 7.4 Hz, 2H, CH_2CH_3)	216 (100, M^+), 170 (43, M^+ -C_2H_5OH), 143 (44, M^+ -$C_2H_5OCO^+$)
3d	3.70 (s, 3H)	8.85 (s, 1H)	3.44 (s, 3H, NCH_3)	7.49 (t, 2H, C_6H_5) 7.62 (t, 1H, C_6H_5) 7.92 (d, 2H, C_6H_5)	248 (93, M^+), 105 (100, $C_6H_5CO^+$)
3e	3.84 (s, 3H)	6.55 (s, 1H)	7.29-7.66 (m, 5H, C_6H_5)	1.19 (t, 7.0 Hz, 3H, CH_2CH_3) 4.13 (q, 7.2 Hz, 2H, CH_2CH_3)	278 (100, M^+), 232 (17, M^+-C_2H_5OH), 205 (25, M^+ -$C_2H_5OCO^+$), 136 (38)
3f	3.80 (s, 3H)	8.46 (s, 1H)	7.37-7.62 (m, 10H, C_6H_5)		310 (22, M^+), 205 (4, M^+-$C_6H_5CO^+$), 136 (78), 105 (100, $C_6H_5CO^+$)
6a	3.81 (s, 3H)	—	1.72 (s, 3H, CCH_3) 4.47 (s, 2H, NCH_2) 4.60 (s, 1H, CCH_2) 4.91 (s, 1H, CCH_2)	4.30 (s, 2H, SCH_2) 7.31 (s, 5H, C_6H_5)	291 (22, M^+), 200 (39, M^+-$C_7H_7^+$), 91 (100, $C_7H_7^+$)
6b	3.77 (s, 3H)	—	3.33 (s, 3H, NCH_3)	4.27 (s, 2H, SCH_2) 7.30 (s, 5H, C_6H_5)	251 (25, M^+), 160 (47, M^+-$C_7H_7^+$), 91 (100, $C_7H_7^+$)
6c	3.87 (s, 3H)	—	7.29-7.50 (m, 10H, C_6H_5)	4.28 (s, 2H, SCH_2)	313 (29, M^+), 222 (9, M^+-$C_7H_7^+$), 91 (100, $C_7H_7^+$)

Table 2 (continued)

Compound No.	^{1}H-NMR, δ (ppm) [a] CH_3N	NH	R^1	R^2/other signals	MS, m/z
8a	3.35 (s, 3H)	[b]	1.75 (s, 3H, CCH_3) 3.62 (s, 2H, NCH_2) 4.73 (s, 1H, CCH_2) 4.94 (s, 1H, CCH_2)	1.25 (t, 7.2 Hz, 3H, CH_2CH_3) 4.16 (q, 7.1 Hz, 2H, CH_2CH_3)	256 (37, M^+), 213 (63), 201 (41, M^+-$C_4H_7^+$), 169 (30), 142 (28), 55 (100, $C_4H_7^+$)
8b	3.74 (s, 3H)	[b]	1.82 (s, 3H, CCH_3) 3.97 (s, 2H, NCH_2) 4.96 (s, 1H, CCH_2) 5.07 (s, 1H, CCH_2)	7.47-8.25 (m, 5H, C_6H_5)	288 (16, M^+), 247 (49, M^+-$C_3H_5^+$), 233 (16, M^+ -$C_4H_7^+$), 105 (100, $C_6H_5CO^+$), 77 (40, $C_6H_5^+$)
8c	3.27 (s, 3H)	[b]	2.95 (s, 3H, NCH_3)	1.25 (t, 7.1 Hz, 3H, CH_2CH_3) 4.15 (q, 7.0 Hz, 2H, CH_2CH_3)	216 (64, M^+), 170 (5, M^+-C_2H_5OH), 143 (8, M^+ -$C_2H_5OCO^+$), 74 (98), 42 (100)
8d	3.71 (s, 3H)	[b]	3.12 (s, 3H, NCH_3)	7.46-8.26 (m, 5H, C_6H_5)	248 (99, M^+), 105 (100, $C_6H_5CO^+$)
8e	3.56 (s, 3H)	9.1 (bs, 1H)	7.02 (t, 1H, C_6H_5) 7.04 (d, 2H, C_6H_5) 7.28 (t, 2H, C_6H_5)	1.23 (t, 7.0 Hz, 3H, CH_2CH_3) 4.18 (q, 7.1 Hz, 2H, CH_2CH_3)	278 (83, M^+), 136 (82), 77 (68, $C_6H_5^+$), 43 (100)
8f	3.51 (s, 3H)	9.2 (bs, 1H)	7.05 (t, 1H, C_6H_5) 7.06 (d, 2H, C_6H_5) 7.32 (t, 2H, C_6H_5)	7.46 (t, 2H, C_6H_5) 7.57 (t, 1H, C_6H_5) 7.82 (d, 2H, C_6H_5)	310 (29, M^+), 105 (100, $C_6H_5CO^+$), 77 (78, $C_6H_5^+$)

[a] The spectra were taken in deuteriochloroform (**2a,b**, **3a-f**, **6a-c**, **8e,f**); dimethyl sulfoxide-d_6 (**2c-f**); tetrahydrofuran-d_8 (**8a,c**) and dimethylformamide-d_7 (**8b,d**). [b] Exchanged with deuterium.

Table 3

^{13}C-NMR Data of Compounds **3**, **6** and **8**

Compound No.	^{13}C-NMR, δ (ppm) CH_3N	ring carbons	R^1	R^2/other signals
3a	36.4	166.5 (C-3) 142.5 (C-5)	19.7 (CH_3), 49.9 (CH_2) 113.2 (=CH_2), 138.4 (>C=)	14.1 (CH_3), 62.9 (CH_2) 152.6 (CO)
3b	36.6	166.8 (C-3) 142.9 (C-5)	19.7 (CH_3), 50.5 (CH_2) 113.7 (=CH_2), 138.9 (>C=)	131.5, 128.9, 127.5, 133.2 (Ph-C) [a] 165.9 (CO)
3c	36.5	167.0 (C-3) 142.7 (C-5)	31.9 (CH_3)	14.3 (CH_3), 63.3 (CH_2) 153.3 (CO)
3d	36.6 ($^1J_{C,H}$ = 142 Hz)	167.0 (C-3) 143.2 (C-5)	32.2 (CH_3) ($^1J_{C,H}$ = 143 Hz)	131.2, 129.1, 127.9, 133.6 (Ph-C) 166.7 (CO)
3e	36.3	166.8 (C-3) 141.8 (C-5)	132.7, 127.6 129.5, 129.9 (Ph-C)	13.9 (CH_3), 62.7 (CH_2) 152.1 (CO)
3f	36.6	167.3 (C-3) 142.4 (C-5)	127.6, 128.8, 129.8, 130.1, 131.5, 133.0, 133.1 (Ph-C) [b]	165.9 (CO)
6a	37.6	168.1 (C-3) 148.3 (C-5)	20.6 (CH_3), 50.8 (CH_2) 113.7 (=CH_2), 138.4 (>C=)	37.2 (SCH_2) 135.9, 129.3, 129.5, 128.6 (Ph-C)
6b	37.8	167.9 (C-3) 147.5 (C-5)	32.2 (CH_3)	37.2 (SCH_2) 136.0, 129.3, 129.4, 128.6 (Ph-C)
6c	36.9	168.7 (C-3) 148.5 (C-5)	128.3, 128.6, 129.2, 129.6, 130.1, 130.5, 134.2, 135.8 (Ph-C) [b]	37.3 (SCH_2)
8a	34.8	156.1 (C-2) 144.4 (C-5)	20.7 (CH_3), 62.3 (CH_2) 110.1 (=CH_2), 141.4 (>C=)	14.5 (CH_3), 62.4 (CH_2) 154.2 (CO)
8b	36.6	161.1 (C-2) 154.7 (C-5)	20.0 (CH_3), 55.4 (CH_2) 112.1 (=CH_2), 141.6 (>C=)	137.6, 128.4, 128.8, 131.3 (Ph-C) 171.2 (CO)
8c	34.6	157.2 (C-2) 141.1 (C-5)	42.4 (CH_3)	14.6 (CH_3), 62.3 (CH_2) 154.3 (CO)
8d	36.6 ($^1J_{C,H}$ = 142 Hz)	162.6 (C-2) 156.9 (C-5)	34.7 (CH_3) ($^1J_{C,H}$ = 140 Hz)	138.5, 128.3, 128.8, 131.0 (Ph-C) 172.2 (CO)
8e	35.1 ($^1J_{C,H}$ = 141 Hz)	155.7 (C-2) 141.8 (C-5)	151.5, 129.4 121.1, 123.2 (Ph-C)	14.1 (CH_3), 62.6 (CH_2) 152.9 (CO)
8f	35.3	156.1 (C-2) 140.3 (C-5)	151.5, 129.6 121.2, 123.5 (Ph-C)	131.5, 129.0, 127.4, 133.2 (Ph-C) 164.6 (CO)

[a] Aromatic C-signals arranged in order of *ipso*, *ortho/meta*, *para*. [b] Impossible to assign correctly.

ppm, respectively. In deviation to the characteristic carbon-chemical shifts of the =N-CH_2 group in **8a** as well as =N-CH_3 group in **8c**, the appropriate carbons in **8b** and **d** appear in a higher field. The coupling constant of the exocyclic methyl group determined in **8d** ($^1J_{C,H}$ = 140 Hz) also deviates from that of a typical methylimino-group ($^1J_{C,H}$ = 136-137 Hz, [13]). Furthermore, the signals of the carbonyl-carbon and *ipso*-carbon atom of the phenyl group are shifted downfield due to delocalization of electronegative charge at the amidate moiety. The expected coupling between NH and the substituent R^1 which would contribute to the final confirmation of the proposed zwitterionic structure was not observed as a result of H/D-exchange.

The 5-benzoylamino-3-methyl-2-methylimino-1,3,4-thiadiazoline (**8d**) was shown to isomerize into 1,2,4-triazoline-3-thione **3d** upon melting. This conversion is a typical DIMROTH rearrangement which probably occurs starting from zwitterionic structure **B** *via* the open-chain carbodiimide **C** as shown in Scheme 2.

Bithioureas may be cyclized by acetanhydride to acetyl derivatives of 2,5-diimino-1,3,4-thiadiazoles [20]. However, the corresponding experiment on compounds **2** failed. In this connection we also investigated the effect of trifluoroacetic acid in boiling chloroform on the bithioureas **2c** and **e**. Under these conditions compound **2c** (R^1 = CH_3) formed the 1,3,4-thiadiazolineimine **8c** (55%) and 1,3,4-thiadiazoline-2-thione **9** (45%) with loss of hydrogen sulfide and methyl amine, respectively [21]. On the other hand, bithiourea **2e** (R^1 = Ph) underwent ring-closure with the elimination of hydrogen sulfide and gave as the only product the 1,3,4-thiadiazolineimine **8e** in 83% yield (Scheme 3). The different cyclization behavior of **2c** and **e** under acidic conditions appears to be caused in the different basicity of the R^1-NH moiety. This is also confirmed with the studies of other authors [3].

EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus. The nmr spectra were recorded on the Varian Gemini-200 (^{1}H nmr: 200 MHz, ^{13}C nmr: 50 MHz) and Unity-400 (^{1}H nmr: 400 MHz, ^{13}C nmr: 100 MHz) spectrometer. The chemical shifts given in ppm are referenced to the deuterated solvent. Mass spectra were measured with the CH 6 Varian-MAT and MAT 212 mass spectrometer. The elemental analyses were performed using the CHN-Rapid Heraeus Elemental Analyzer.

General Procedure for the Preparation of Bithioureas **2a-f**.

To a stirred suspension of the 2,4-disubstituted thiosemicarbazide **1** (0.04 mole) in 40 ml of toluene (for **1a**) or acetonitrile (for **1b,c**), ethoxycarbonyl as well as benzoyl isothiocyanate (0.04 mole) was added. During this procedure a temperature of 40° should not be exceeded. The bithiourea was allowed to crystallize from the resulting solution. After filtration, the colorless precipitate was washed with the solvent used during the reaction and finally with ether. The bithioureas thus obtained can be used without further purification.

To isolate compound **2e**, the reaction mixture was reduced *in vacuo* to one-third of its volume. After addition of toluene (80 ml) crystallization took place.

General Procedure for the Preparation of 5-Acylamino Substituted 1,2,4-Triazoline-3-thiones **3a-f**.

A solution of the appropriate bithiourea **2** (0.01 mole) in ethanol (50 ml), treated with 1*M* sodium ethanolate in ethanol (5 ml, 5 mmoles), was refluxed until evolution of hydrogen sulfide ceased (after approximately 1 hour). After further addition of 1*M* sodium ethanolate solution (5 ml), ethanol was evaporated *in vacuo*. The residue was dissolved in the required amount of water and acidified with diluted hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, dried and crystallized from the solvents given in Table 1.

5-Benzoylamino-3-methyl-2-methylimino-1,3,4-thiadiazoline (**8d**).

This compound was obtained after separation of **3d** and neutralization of the hydrochloric acid solution with diluted sodium hydroxide in 2% yield. Physical and spectral data are given in Tables 1, 2 and 3.

General Procedure for the Preparation of 5-Mercapto-1,2,4-triazoline-3-thiones **5a-c**.

A solution of the bithiourea **2a,c** as well as **e** (0.01 mole) in ethanol (50 ml), treated with 1*M* sodium ethanolate in ethanol (12 ml, 0.012 mole), was refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in water. After addition of an equal volume of chloroform, concentrated hydrochloric acid was added with strong stirring so that the precipitated 5-mercapto-1,2,4-triazoline-3-thione transfered from the water to the chloroform phase. The yellow colored organic phase was dried with sodium sulfate and the solvent was removed *in vacuo*.

According to this procedure, the bithioureas **2b,d** and **f** could be cyclized by refluxing the reaction mixture for 1 hour. In the case of **2f**, after removal of ethanol and dissolving the residue in water, colorless crystals with mp 124-127° were isolated. It was identified as benzamide by comparison with authentic material.

5-Mercapto-2,4-dimethyl-1,2,4-triazoline-3-thione (**5b**).

This compound was obtained from **2c** in 62% yield as colorless crystals which gradually change to yellow color in air as a result of oxidation, mp 130° (dioxane), lit [16] 124.5-127°; ^{1}H nmr (deuteriochloroform): δ 3.60 (s, 3H, CH_3), 3.80 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 32.8 (CH_3), 36.9 (CH_3), 142.7 (C-5), 168.0 (C-3); ms: (70 eV) m/z 161 (100, M^+), 88 (23, M^+-CH_3NCS).

General Procedure for the Preparation of 5-Benzylmercapto-1,2,4-triazoline-3-thiones **6a-c**.

The crude 5-mercapto-1,2,4-triazoline-3-thione **5** which was obtained after removal of chloroform (see above) was dissolved in ethanol (30 ml). After addition of benzyl chloride (0.9 g, 7.5 mmoles) and 2*M* sodium hydroxide (4 ml, 8 mmoles), the reaction mixture was stirred for 1 hour at room temperature. Finally

it was reduced to half of its volume and stirred into water. The precipitate was filtered off and crystallized from the solvents given in Table 1.

Bis(2,4-dimethyl-3-thiono-1,2,4-triazolin-5-yl) Disulfide (**7**).

Crude 5-mercapto-2,4-dimethyl-1,2,4-triazoline-3-thione (**5b**), prepared from 0.01 mole of **2c**, was dissolved in 50% ethanol (30 ml). After addition of 30% hydrogen peroxide (1.2 g, 0.01 mole) yellow crystals precipitated which were filtered off and crystallized from acetonitrile to yield 0.8 g (50%) of **7** as yellow needles, mp 186-189°; ^{1}H nmr (deuteriochloroform): δ 3.56 (s, 3H, CH_3), 3.72 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 33.2 (CH_3), 37.5 (CH_3), 143.5 (C-5), 169.5 (C-3); ms: (70 eV) m/z 320 (59, M^+), 160 (100, $M^+/2$), 87 (28).

Anal. Calcd. for $C_8H_{12}N_6S_4$ (320.49): C, 29.98; H, 3.77; N, 26.22; S, 40.02. Found: C, 30.14; H, 3.98; N, 26.18; S, 40.29.

General Procedure for the Preparation of 1,3,4-Thiadiazoline-2-imines **8a-f**.

A solution of the appropriate bithiourea **2** (0.01 mole) in methanol (40 ml), treated with methyl iodide (1.7 g, 0.012 mole), was refluxed for 4 hours (evolution of methyl mercaptane). The hydriodides crystallized by cooling or obtained by distilling off methanol were crystallized from methanol or methanol/ether, respectively. For releasing the 1,3,4-thiadiazolineimines, the corresponding hydriodides were dissolved in water (**8a**.HI, **8c**.HI) as well as in ethanol/water (for all remaining hydriodides) and neutralized with diluted sodium hydroxide. The precipitate which is soluble in excess sodium hydroxide was filtered off, dried and crystallized from the solvents given in Table 1.

5-Benzoylamino-2,4-dimethyl-1,2,4-triazoline-3-thione (**3d**).

5-Benzoylamino-3-methyl-2-methylimino-1,3,4-thiadiazoline (**8d**) (1.3 g, 5 mmoles) was heated for 10 minutes at 245°. After cooling, the yellow colored solid residue was crystallized twice from toluene to yield 0.9 g (73%) of **3d**, mp 167-169°. Spectral data are given in Tables 2 and 3.

5-Ethoxycarbonylamino-3-methyl-1,3,4-thiadiazoline-2-thione (**9**).

Bithiourea **2c** (0.01 mole) was refluxed for 1 hour in chloroform (20 ml) and trifluoroacetic acid (1.2 g, 0.01 mole); evolution of hydrogen sulfide occured. The reaction mixture was evaporated to dryness, and after treatment with diluted hydrochloric acid, the solid was filtered off, washed with water and dried to give **9** as colorless crystals in 59% yield, mp 181-182° (ethanol), lit [22] 178-180°; ^{1}H nmr (deuteriochloroform): δ 1.34 (t, 7.0 Hz, 3H, CH_2CH_3), 3.79 (s, 3H, NCH_3), 4.29 (q, 7.1 Hz, 2H, CH_2CH_3), 11.10 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.2 (CH_3), 38.3 (NCH_3), 62.8 (CH_2), 151.8 (C-5), 153.7 (CO), 181.7 (C-2); ms: (70 eV) m/z 219 (100, M^+), 147 (38), 105 (31), 72 (40).

Anal. Calcd. for $C_6H_9N_3S_2O_2$ (219.29): C, 32.86; H, 4.14; N, 19.16; S, 29.25. Found: C, 32.88; H, 3.96; N, 19.09; S, 29.13.

5-Ethoxycarbonylamino-3-methyl-2-phenylimino-1,3,4-thiadiazoline (**8e**).

A solution of bithiourea **2e** (0.01 mole) in chloroform (20 ml) and trifluoroacetic acid (1.2 g, 0.01 mole) was refluxed for 1 hour (evolution of hydrogen sulfide). After removal of chloroform, the residue (trifluoroacetate of **8e**) was dissolved in 50% ethanol and neutralized with diluted sodium hydroxide. The resulting precipitate was filtered off, washed with water and dried to give **8e** in 83% yield. Physical and spectral data are given in Tables 1, 2 and 3.

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