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SYNTHESES BASED ON 3,4-DIMETHYL-2-THIOXOTHIAZOLINE-5-CARBOXYLIC ACID HYDRAZIDE AND AZIDE

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Treatment of 3,4-dimethyl-2-thioxothiazoline-5-carboxylic acid hydrazide with NH_4SCN and PhCONCS gave the corresponding thiosemicarbazides, arylsulfochlorides yielded the arylsulfonylhydrazides, and diazotization conditions gave the corresponding azide. The interactions of the latter with different nucleophiles have been studied and a series of novel carbamic acid, urea, and semicarbazide derivatives containing a thiazoline fragment have been prepared.

Keywords: arylsulfohydrazide, hydrazide, carbamic acid, semicarbazide, thiazolineisocyanate, thiosemicarbazide.

In continuation of our search for a novel series of biologically active substances based on the previously reported 3,4-dimethyl-2-thioxothiazoline-5-carboxylic acid hydrazide (**1**) [1] we now report the preparation of its arylsulfonyl and thiocarbamoyl derivatives **2a-e** and **3, 4** respectively as well as the azide product of its diazotization **5**. Compounds **2a-e** are related in structure to known sulfonylamides [2] or thiourea derivatives [3] and hence attract particular interest as potential medicinal agents and pesticides. The azide **5**, being a thiazolineisocyanate donor under Curtius reaction conditions can serve as a valuable starting compound for the development of novel routes to functionalize a thiazoline system and this has been demonstrated in a series of examples.

When treated with arylsulfochlorides in pyridine medium at 20°C the hydrazide **1** gave high yields (80-90%) of the arylsulfonylhydrazides **2a-e** and when refluxed with ammonium thiocyanate in ethanol or with benzoylisothiocyanate in dioxane the thiosemicarbazide **3** (yield 61%) or benzoylthiosemicarbazide **4** (yield 78%) respectively (Scheme 1).

A single unsuccessful attempt to carry out the reaction of thiazolecarboxylic acid hydrazides to the corresponding azide has been reported in the literature. In [3] it was shown that 2-substituted 5-phenylthiazolecarboxylic acid hydrazides in excess acetic acid and the presence of $NaNO_2$ underwent a more extensive reaction and, in place of the expected azides, gave the N,N'-bis(2-substituted-5-phenyl)thiazolylureas.

Despite this data we have found in our work that hydrazide **1** readily forms the azide **5** when treated with an equimolar amount of HNO_2 in aqueous medium in 91% yield. The reactions of the azide with various nucleophiles have been studied. It was found that, at 100-120°C in absolute toluene, the azide indicated underwent a Curtius rearrangement reaction to the corresponding isocyanate which reacts with alcohols, amines, and hydrazides to form novel derivatives of carbamic acid **6a-g**, urea **7a-k**, and semicarbazide **8a-d** containing a thiazoline fragment.

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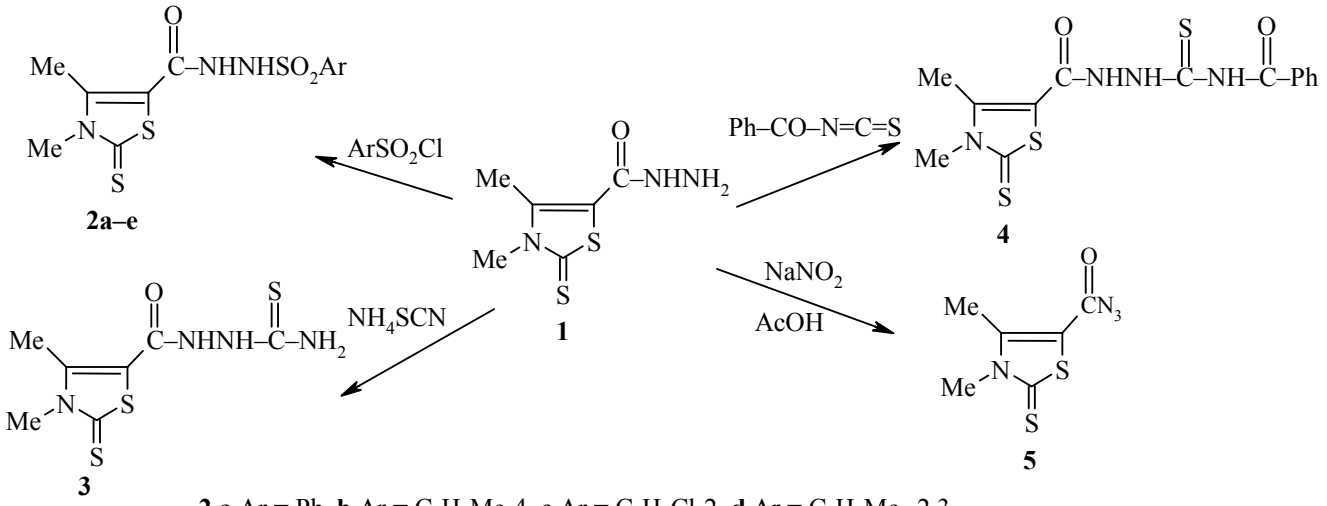
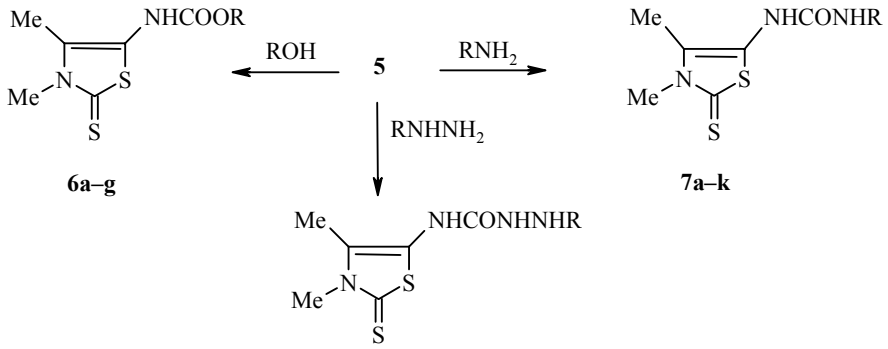
Scheme 1

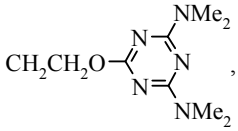


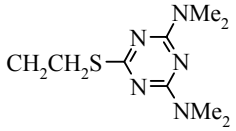
2 a Ar = Ph, **b** Ar = C_6H_4Me-4, **c** Ar = C_6H_4Cl-2, **d** Ar = $C_6H_3Me_2$-2,3, **e** Ar = $C_6H_4NHCOMe$-4

The composition and structure of the synthesized compounds were confirmed by elemental analytical data and by ^{1}H NMR spectroscopy (Tables 1 and 2). The structure of azide **5** agrees also with the IR data (Table 1).



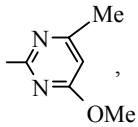
6 a R = Et; **b** R = Pr-*i*; **c** R = Ph; **d** R = $(CH_2)_2Cl$; **e** R = $(CH_2)_2NMe_2$;

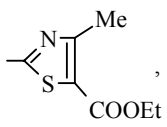
f R = 

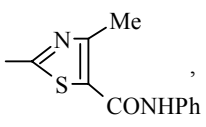
, **g** R = 

7 a R = Bu-*t*; **b** R = Ph; **c** R = C_6H_4Cl-2; **d** R = C_6H_4Cl-4; **e** R = $C_6H_3Cl_2$-2,4;

f R = $(CH_2)_2OPh$; **g** R = $(CH_2)_2OC_6H_4Me$-4; **h** R = $(CH_2)_2OC_6H_3Cl_2$-2,4;

i R = 

, **j** R = 

, **k** R = 

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8 a R = SO_2Ph; **b** R = $SO_2C_6H_4Me$-4; **c** R = $SO_2C_6H_4NHAc$-4; **d** R = Ac

TABLE 1. Characteristics of Compounds **2-5**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	^{1}H NMR spectrum, δ, ppm	Yield, %
		N	S			
2a	$C_{12}H_{13}N_3O_3S_3$	12.49 / 12.25	28.25 / 27.99	208-210	2.67 (3H, s, 4-CH_3); 3.62 (3H, s, 3-CH_3); 7.25-7.85 (5H, m, C_6H_5); 9.60 (1H, br. s, NH); 10.42 (1H, br. s, NH)	90
2b	$C_{13}H_{15}N_3O_3S_3$	11.54 / 11.76	26.62 / 26.89	212-214	2.38 (3H, s, CH_3-C_6H_4); 2.65 (3H, s, 4-CH_3); 3.62 (3H, s, 3-CH_3); 7.20-7.72 (4H, m, C_6H_4); 9.45 (1H, br. s, NH); 10.28 (1H, br. s, NH)	82
2c	$C_{12}H_{12}ClN_3O_3S_3$	11.47 / 11.13	25.71 / 25.43	190-191	2.65 (3H, s, 4-CH_3); 3.63 (3H, s, 3-CH_3); 7.27-7.70 (4H, m, C_6H_4); 9.55 (1H, br. s, NH); 10.35 (1H, br. s, NH)	80
2d	$C_{14}H_{17}N_3O_3S_3$	11.00 / 11.32	26.22 / 25.88	200-202	2.36 (3H, s, $CH_3C_6H_3$); 2.40 (3H, s, $CH_3C_6H_3$); 2.65 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 7.15-7.67 (3H, m, C_6H_3); 9.55 (1H, br. s, NH); 10.30 (1H, br. s, NH)	82
2e	$C_{14}H_{16}N_4O_4S_3$	14.29 / 14.00	23.75 / 24.00	235-237	2.12 (3H, s, $COCH_3$); 2.66 (3H, s, 4-CH_3); 3.62 (3H, s, 3-CH_3); 7.25-7.80 (4H, m, C_6H_4); 9.60 (1H, br. s, NH); 10.70 (1H, br. s, NH); 11.45 (1H, br. s, NH)	87
3	$C_7H_{10}N_4OS_3$	21.61 / 21.37	37.00 / 36.64	218-219	2.62 (3H, s, 4-CH_3); 3.65 (3H, s, 3-CH_3); 7.40 (2H, br. s, NH_2); 9.23 (1H, br. s, NH); 9.85 (1H, br. s, NH)	61
4	$C_{14}H_{14}N_4O_2S_3$	15.51 / 15.30	25.82 / 26.23	232-233	2.70 (3H, s, 4-CH_3); 3.70 (3H, s, 3-CH_3); 7.45-8.10 (5H, m, C_6H_5); 10.50 (1H, v. br. s, NH); 11.50 (1H, v. br. s, NH); 12.60 (1H, v. br. s, NH)	78
5*	$C_6H_6N_4OS_2$	26.42 / 26.17	29.57 / 29.91	109-110		91

* IR spectrum, ν, cm^{-1}: 2140 (N_3), 1660 (C=C), 1550 (C=S).

TABLE 2. Characteristics of Compound **6-8**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	^{1}H NMR spectrum, δ, ppm (spin-spin coupling constant, *J*, Hz)	Yield, %
		N	S			
1	2	3	4	5	6	7
6a	$C_8H_{12}N_2O_2S_2$	12.34 / 12.07	27.09 / 27.59	115-117	1.30 (3H, t, *J* = 6.0, CH_3); 2.20 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 4.15 (2H, q, *J* = 6.0, CH_2); 9.62 (1H, br. s, NH)	73
6b	$C_9H_{14}N_2O_2S_2$	11.71 / 11.38	26.41 / 26.02	133-135	1.30 (6H, q, *J* = 6.2, 2-CH_3); 2.20 (3H, s, 4-CH_3); 3.58 (3H, s, 4-CH_3); 3.58 (3H, s, 3-CH_3); 4.90 (1H, m, *J* = 6.2, CH); 9.50 (1H, br. s, NH)	65
6c	$C_{12}H_{12}N_2O_2S_2$	9.81 / 10.00	22.54 / 22.86	136-138	2.27 (3H, s, 4-CH_3); 3.62 (3H, s, 3-CH_3); 7.10-7.42 (5H, m, C_6H_5); 10.18 (1H, br. s, NH)	71
6d	$C_8H_{11}ClN_2O_2S_2$	10.77 / 10.51	23.76 / 24.02	156-158	2.21 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 3.77 (2H, t, *J* = 5.5, CH_2Cl); 4.36 (2H, t, *J* = 5.5, OCH_2); 9.82 (1H, br. s, NH)	85
6e	$C_{10}H_{17}N_3O_2S_2$	15.54 / 15.27	22.90 / 23.27	110-111	2.20 (3H, s, 4-CH_3); 2.23 (6H, s, $N(CH_3)_2$); 2.55 (2H, t, *J* = 5.5, NCH_2); 3.58 (3H, s, 4-CH_3); 4.18 (2H, t, *J* = 5.5, OCH_2); 9.62 (1H, br. s, NH)	92
6f	$C_{15}H_{23}N_7O_3S_2$	24.09 / 23.73	15.83 / 15.50	180-182	2.20 (3H, s, 4-CH_3); 3.10 (12H, s, $N(CH_3)_2$); 3.62 (3H, s, 3-CH_3); 4.38-4.50 (4H, m, OCH_2CH_2O); 9.90 (1H, br. s, NH)	83
6g	$C_{15}H_{23}N_7O_2S_3$	22.63 / 22.84	22.71 / 22.38	139-140	2.20 (3H, s, 4-CH_3); 3.12 (12H, s, $N(CH_3)_2$); 3.28 (2H, t, *J* = 5.8, SCH_2) 3.60 (3H, s, 3-CH_3); 4.35 (2H, t, *J* = 5.8, OCH_2); 9.68 (1H, br. s, NH)	90
7a	$C_{10}H_{17}N_3OS_2$	16.41 / 16.22	25.02 / 24.71	215-218	1.30 (9H, s, 3-CH_3); 2.20 (3H, s, 4-CH_3); 3.58 (3H, s, 3-CH_3); 6.0 (1H, br. s, NH); 8.40 (1H, br. s, NH)	86
7b	$C_{12}H_{13}N_3OS_2$	15.30 / 15.05	22.58 / 22.94	226-228 (hexane–PhH, 1:1)	2.25 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 6.90-7.45 (5H, m, C_6H_5); 8.80 (1H, br. s, NH); 9.06 (1H, br. s, NH)	94
7c	$C_{12}H_{12}ClN_3OS_2$	13.59 / 13.40	20.75 / 20.42	275-276 (EtOH)	2.22 (3H, s, 4-CH_3); 3.58 (3H, s, 3-CH_3); 7.03-7.50 (4H, m, H_{Ar}); 8.75 (1H, br. s, NH); 9.25 (1H, br. s, NH)	95

TABLE 2 (continued)

1	2	3	4	5	6	7
7d	$C_{12}H_{12}ClN_3OS_2$	13.47 / 13.40	20.06 / 20.42	234-236 (EtOH)	2.20 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 7.00-7.48 (4H, m, H_{Ar}); 8.72 (1H, br. s, NH); 9.15 (1H, br. s, NH)	92
7e	$C_{12}H_{11}ClI_2N_3OS_2$	11.84 / 12.07	18.82 / 18.39	249-250 (PhMe)	2.20 (3H, s, 4-CH_3); 3.62 (3H, s, 3-CH_3); 7.15-7.55 (4H, m, H_{Ar}); 8.90 (1H, br. s, NH); 9.18 (1H, br. s, NH)	91
7f	$C_{14}H_{17}N_3O_2S_2$	12.75 / 13.00	20.22 / 19.81	137-138 (PhH)	2.20 (3H, s, 4-CH_3); 3.52 (2H, m, NCH_2); 3.60 (3H, s, 3-CH_3); 4.12 (2H, t, J = 5.6, OCH_2); 6.50 (1H, t, J = 5.4, NH); 6.90-7.25 (5H, m, C_6H_5); 8.80 (1H, br. s, NH)	93
7g	$C_{15}H_{19}N_3O_2S_2$	12.69 / 12.46	18.59 / 18.99	189-190 (70% EtOH)	2.12 (3H s, CH_3–Ar); 3.55 (2H, m, NCH_2); 3.60 (3H, s, 3-CH_3); 4.10 (2H, t, J = 5.6, OCH_2); 6.60 (1H, t, J = 5.4, NH); 6.85-7.22 (4H, m, H_{Ar}); 8.92 (1H, br. s, NH)	85
7h	$C_{14}H_{15}ClI_2N_3O_2S_2$	11.05 / 10.71	16.71 / 16.33	195-197 (PhH)	2.20 (3H, s, 4-CH_3); 3.55 (2H, m, NCH_2); 3.58 (3H, s, 3-CH_3); 4.10 (2H, t, J = 5.5, OCH_2); 6.42 (1H, t, J = 5.4, NH); 7.10-7.35 (3H, m, H_{Ar}); 8.75 (1H, br. s, NH)	66
7i	$C_{12}H_{15}N_5O_2S_2$	21.76 / 21.54	19.28 / 19.69	246-247	2.21 (3H, s, 4-CH_3); 2.48 (3H, s, CH_3–Ar); 3.60 (3H, s, 3-CH_3); 3.72 (3H, s, OCH_3); 6.95 (1H, s, H_{Het}); 9.15 (1H, br. s, NH); 10.25 (1H, br. s, NH)	96
7j	$C_{13}H_{16}N_4O_3S_3$	14.83 / 15.05	26.26 / 25.81	266-267 (Me_2CO)	1.35 (3H, t, J = 6.2, CH_3); 2.23 (3H, s, 4-CH_3); 2.53 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 4.23 (2H, q, J = 6.2, CH_2); 9.28 (1H, br. s, NH); 10.50 (1H, br. s, NH)	90
7k	$C_{17}H_{17}N_5O_2S_3$	16.39 / 16.71	23.48 / 22.91	265-266 boiling (EtOH)	2.25 (3H, s, 4-CH_3); 2.55 (3H, s, 4-CH_3); 6.95-7.72 (5H, m, C_6H_5); 9.22 1H, br. s, NH); 9.58 (1H, s, NH); 10.72 (1H, br. s, NH)	85
8a	$C_{12}H_{14}N_4O_3S_3$	15.29 / 15.64	27.17 / 26.82	210-211	2.42 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 7.45-7.90 (5H, m, C_6H_5); 9.70 (1H, br. s, NH); 10.42 (1H, br. s, NH)	97
8b	$C_{13}H_{16}N_4O_3S_3$	14.76 / 15.05	26.11 / 25.81	184-185	2.10 (3H, s, CH_3-Ar); 2.45 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 7.25-7.77 (4H, m, Ar); 8.50 (1H, s, NH); 8.62 (1H, br. s, NH); 9.40 (1H, s, NH)	96
8c	$C_{14}H_{17}N_5O_4S_3$	17.12 / 16.87	22.85 / 23.13	178-180	2.05 (3H, s, $COCH_3$); 2.45 (3H, s, 4-CH_3); 3.58 (3H, s, 3-CH_3); 7.60-8.00 (4H, m, Ar); 8.20 (1H, br. s, NH); 8.55 (1H, s, NH) 8.70 (1H, br. s, NH); 9.35 (1H, br. s, NH)	90
8d	$C_8H_{12}N_4O_2S_2$	21.86 / 21.54	25.00 / 24.62	218-220	2.02 (3H, s, $COCH_3$); 2.45 (3H, s, 4-CH_3); 3.60 (3H, s, 3-CH_3); 8.30 (1H, br. s, NH); 8.62 (1H, br. s, NH); 8.75 (1H, br. s, NH)	96

EXPERIMENTAL

^{1}H NMR spectra were taken on a Mercury-300 (300 MHz) instrument using DMSO-d_6 and with TMS as internal standard. IR spectra were recorded on a UR-20 instrument (vaseline oil paste). Monitoring of the course of the reaction and the purity of the compounds obtained was carried out by TLC using Silufol UV-254 plates and eluent acetone–hexane (2:1).

3,4-Dimethyl-2-thioxothiazoline-5-carboxylic Acid Arylsulfonylhydrazides 2a-e. Hydrazide **1** (2.03 g, 10 mmol) was added in small portions with stirring to a solution of the arylsulfochloride (10 mmol) in pyridine (5 ml) at 0°C. The mixture was held for 2 days at 20-25°C, diluted with iced water (20 ml), and the separated crystals of compounds **2a-e** were filtered off and recrystallized from 25% EtOH.

3,4-Dimethyl-2-thioxothiazoline-5-carboxylic Acid Thiosemicarbazide (3). A mixture of the hydrazide **1** (2.03 g, 10 mmol), NH_4SCN (1.25 g, 15 mmol), and 36% HCl (1.2 ml, 15 mmol) was refluxed in EtOH (10 ml) for 1 h. The EtOH was distilled off and the residue was treated with H_2O (10 ml). The precipitated crystals were filtered off to give compound **3** (1.6 g).

3,4-Dimethyl-2-thioxothiazoline-5-carboxylic Acid Benzoylthiosemicarbazide (4). PhCOCl (1.4 g, 10 mmol) was added portionwise to a solution of NH_4SCN (0.84 g, 11 mmol) in dry dioxane (10 ml). The mixture obtained was refluxed for 15 min and the hydrazide **1** (2.03 g, 10 mmol) was added to it at such a rate that gentle refluxing continued. After cooling, the reaction product was treated with water (20 ml) and the precipitate was filtered off to give compound **4** (2.88 g).

3,4-Dimethyl-2-thioxothiazoline-5-carboxylic Acid Azide (5). $NaNO_2$ (1.75 g, 25 mmol) was added to a suspension of the hydrazide **1** (2.03 g, 10 mmol) in water (30 ml) and AcOH (1.50 g, 25 mmol) was added portionwise slowly at 0°C. The mixture was stirred for 3 h at 20-25°C. The precipitate was filtered off, washed on the filter with water (30 ml), and dried in air to give the azide **5** (1.95 g).

Esters of 3,4-Dimethyl-2-thioxothiazoline-5-carbamic Acid (6a-g), N-Alkyl(aryl, heteryl)-N'-(3,4-dimethyl-2-thioxothiazolin-5-yl)ureas (7a-k), and 4-Acetyl-(arylsulfonyl)-1-(3,4-dimethyl-2-thioxothiazolin-5-yl)semicarbazides (8a-d). A suspension of azide **5** (2.14 g, 10 mmol) and the nucleophile (alcohol, amine, or substituted hydrazine) (10 mmol) in absolute toluene (10 ml) (in the case of aliphatic alcohols the latter are the solvent) was held in the presence of a catalytic amount of pyridine at 100-120°C for 2 h. After cooling the reaction mixture the precipitated product was filtered off and washed with petroleum ether. Most of the products **7** were additionally purified by recrystallization (solvent given in Table 2).

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