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SOME CONVERSIONS OF THIAZOLINE CARBOXYLIC ACID ESTERS

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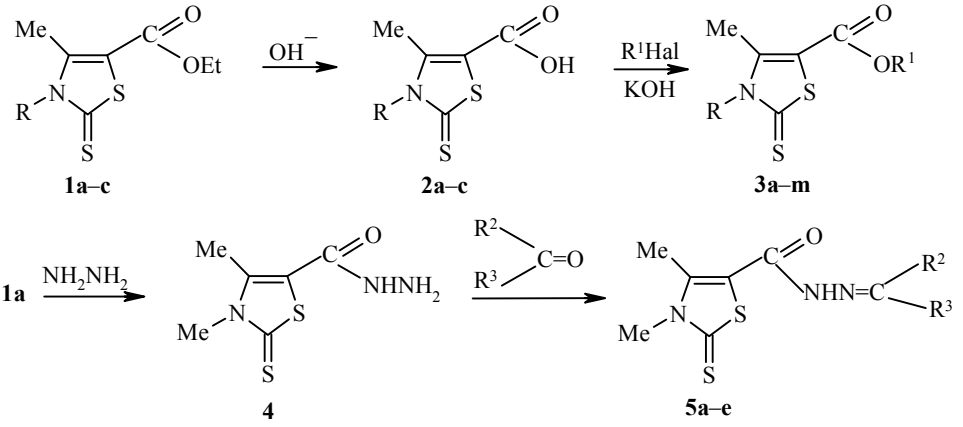
We have carried out solvolysis of the previously described ethyl esters of 3-methyl(aryl)-4-methyl-2-thioxothiazoline-5-carboxylic acids, leading to the corresponding acids without breaking down the heterocycle. We synthesized a series of novel esters from the latter by treatment with dimethyl sulfate or reactive halides. Of these, only in the case of the ethyl ester of 3,4-dimethyl-2-thioxothiazoline-5-carboxylic acid did we obtain the hydrazinolysis product (the hydrazide), from which we synthesized novel hydrazones by treatment with aldehydes and ketones.

Keywords: 3,4-dimethyl-2-thioxothiazoline-5-carboxylic acid hydrazide, N-(3,4-dimethyl-2-thioxothiazolinylcarbonyl)hydrazones of aromatic and heteroaromatic aldehydes, acetophenone and *p*-benzoquinone, 3-aryl-4-methyl-2-thioxo-1,3-thiazoline-5-carboxylic acid esters, solvolysis.

In continuing our search for new physiologically active substances in a series of thiazole derivatives and related compounds [1, 2], we carried out solvolysis of the ethyl esters of 3-methyl(aryl)-4-methyl-2-thioxothiazoline-5-carboxylic acids **1a-c** that we obtained earlier [3]. We showed that under solvolysis conditions, the dithiocarbamate group of these esters is not involved: when treated with an aqueous or alcoholic base, they react exclusively at the ester functional group, with retention of the heterocycle and formation of acids **2a-c**.



1a, **2a**, **3a-g** R =Me; **1b**, **2b**, **3h-j** R = Ph; **1c**, **2c**, **3k-m** R = C_6H_4Cl-4; **3a**,**h**,**k** R^1 = Me; **b**,**i**,**l** R^1 = CH_2COOMe; **c**,**j**,**m** R^1 = CH_2Ph; **d** R^1 = CH_2CH_2OPh; **e** R^1 = $CH_2CH_2OC_6H_4Me$-4; **f** R^1 = $CH_2CH_2OC_6H_3Cl_2$-2,4; **g** R^1 = CH(Ac)COOEt; **5a–c** R^2 = H; **d** R^2 = Me, **a** R^3 = Ph, **b** R^3 = 2-furyl, **c** R^3 = 5-nitro-2-furyl; **d** R^3 = Ph; **e** R^2, R^3 =

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TABLE 1. Characteristics of Synthesized Compounds ^{1}H NMR spectrum, δ, ppm, spin–spin coupling constants (*J*, Hz)

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	^{1}H NMR spectrum, δ, ppm, SSCC (*J*, Hz)	Yield, %
		N (Cl)	S			
1	2	3	4	5	6	7
2b	$C_{11}H_9NO_2S_2$	—	25.11 / 25.50	230-232	2.25 (3H, s, 4-CH_3); 6.85-7.58 (5H, m, Ph); 11.80 (1H, v. br. s, OH)	85
2c	$C_{11}H_8ClNO_2S_2$	(12.68) / (12.43)	22.09 / 22.42	226-228	2.28 (3H, s, 4-CH_3); 7.32-7.60 (4H, m, C_6H_4); 11.50 (1H, v. br. s, OH)	87
3a	$C_7H_9NO_2S_2$	7.11 / 6.90	31.14 / 31.53	102-104	2.68 (3H, s, 4-CH_3); 3.65 (3H, s, 3-CH_3); 3.81 (3H, s, OCH_3)	83
3b	$C_9H_{11}NO_4S_2$	5.29 / 5.36	24.70 / 24.52	138-140	2.70 (3H, s, 4-CH_3); 3.67 (3H, s, 3-CH_3); 3.75 (3H, s, OCH_3); 4.77 (2H, s, CH_2)	60
3c	$C_{13}H_{13}NO_2S_2$	5.37 / 5.10	23.51 / 23.27	105-107	2.70 (3H, s, 4-CH_3); 3.64 (3H, s, 3-CH_3); 5.25 (2H, s, CH_2); 7.30-7.40 (5H, m, Ph)	65
3d	$C_{14}H_{15}NO_3S_2$	4.70 / 4.53	20.98 / 20.71	70-72	2.67 (3H, s, 4-CH_3); 3.63 (3H, s, 3-CH_3); 4.22 (2H, t, *J* = 5.8, $COOCH_2$); 4.55 (2H, t, *J* = 5.8, Ph$O\underline{CH_2}$); 6.90-7.25 (5H, m, Ph)	65
3e	$C_{15}H_{17}NO_3S_2$	4.58 / 4.33	20.13 / 19.81	136-138	2.27 (3H, s, CH_3 in Ar); 2.67 (3H, s, 4-CH_3); 3.65 (3H, s, 3-CH_3); 4.22 (2H, t, *J* = 5.9, $COOCH_2$); 4.55 (2H, t, *J* = 5.8, Ar$O\underline{CH_2}$); 6.75-7.07 (4H, m, Ar)	74
3f	$C_{14}H_{13}ClNO_3S_2$	(19.05) / (18.78)	17.31 / 16.93	150-152	2.68 (3H, s, 4-CH_3); 3.65 (3H, s, 3-CH_3); 4.32 (2H, t, *J* = 5.9, $COOCH_2$); 4.57 (2H, t, *J* = 5.9, Ar$O\underline{CH_2}$); 7.10-7.38 (3H, m, Ar)	73
3g	$C_{12}H_{15}NO_5S_2$	4.61 / 4.42	20.58 / 20.19	64-65	1.33 (3H, t, *J* = 6.2, CH_3 in Et); 2.35 (3H, s, $COCH_3$); 2.73 (3H, s, 4-CH_3); 3.68 (3H, s, 3-CH_3); 4.28 (2H, q, *J* = 6.2, CH_2 in Et); 5.72 (1H, s, COCH)	88
3h	$C_{12}H_{11}NO_2S_2$	5.47 / 5.28	24.49 / 24.15	165-167	2.30 (3H, s, 4-CH_3); 3.85 (3H, s, OCH_3); 7.25-7.62 (5H, m, Ph)	83

TABLE 1 (continued)

1	2	3	4	5	6	7
3i	$C_{14}H_{13}NO_4S_2$	4.54 / 4.33	20.22 / 19.81	95-97	2.32 (3H, s, 4-CH_3); 3.78 (3H, s, OCH_3); 4.81 (2H, s, CH_2); 7.30-7.62 (5H, m, Ph)	93
3j	$C_{18}H_{15}NO_2S_2$	4.41 / 4.11	19.00 / 18.77	107-109	2.30 (3H, s, 4-CH_3); 5.28 (2H, s, OCH_2); 7.25-7.60 (10H, m , 2Ph)	73
3k	$C_{12}H_{10}ClNO_2S_2$	(11.62) / (11.85)	21.63 / 21.37	133-135	2.30 (3H, s, 4-CH_3); 3.83 (3H, s, OCH_3); 7.30-7.60 (4H, m, Ar)	70
3l	$C_{14}H_{12}ClNO_4S_2$	(9.67) / (9.93)	18.23 / 17.90	89-91	2.32 (3H, s, 4-CH_3); 3.77 (3H, s, OCH_3); 4.82 (2H, s, CH_2); 7.30-7.60 (4H, m, Ar)	83
3m	$C_{18}H_{14}ClNO_2S_2$	(9.80) / (9.45)	17.38 / 17.04	82-84	2.30 (3H, s, 4-CH_3); 5.28 (2H, s, CH_2); 7.30-7.60 (9H, m, Ph and Ar)	72
4	$C_6H_9N_3OS_2$	20.45 / 20.69	31.82 / 31.53	202-204	2.58 (3H, s, 4-CH_3); 3.63 (3H, s, 3-CH_3); 4.50 (2H, v. br. s, NH_2); 9.10 (1H, v. br. s, NH)	84
5a	$C_{13}H_{13}N_3OS_2$	14.25 / 14.43	21.58 / 21.99	237-239	2.70 (3H, s, 4-CH_3); 3.70 (3H, s, 3-CH_3); 7.36-7.83 (5H, m, Ph); 8.00 (1H, s, N=CH); 11.60 (1H, br s, NH)	91
5b	$C_{11}H_{11}N_3O_2S_2$	14.38 / 14.95	23.01 / 22.78	216-218	2.76 (3H, s, 4-CH_3); 3.70 (3H, s, 3-CH_3); 6.50, 6.80 and 7.70 (1H, d. d, J = 5.4 and 5.0; 1H, d, J = 5.4 and 1H, d, J = 5.0, 4-, 3- 5-H, respectively, in furyl); 7.90 (1H, s, N=CH); 11.63 (1H, br. s, NH)	89
5c	$C_{11}H_{10}N_4O_4S_2$	17.41 / 17.18	20.04 / 19.63	252-253	2.76 (3H, s, 4-CH_3); 3.70 (3H, s, 3-CH_3); 7.13 and 7.60 (1H, d, J = 5.2 and 1H, d, J = 5.2, 3- and 4-H, respectively, in nitrofuryl); 8.00 (1H, s, N=CH); 12.16 (1H, br. s, NH)	87
5d	$C_{14}H_{15}N_3OS_2$	14.04 / 13.77	21.27 / 20.98	240-242	2.33 (3H, s, =CCH_3); 2.76 (3H, s, 4-CH_3); 3.70 (3H, s, 3-CH_3); 7.30-7.85 (5H, m, Ph); 10.60 (1H, br. s, NH)	92
5e	$C_{12}H_{11}N_3O_2S_2$	13.99 / 14.33	21.57 / 21.84	189-190	2.73 (3H, s, 4-CH_3); 3.70 (3H, s, 3-CH_3); 6.80 and 7.63 [2H, d, J = 9.2 and 2H, d, J = 9.2, $(CH_2)_2C$=O and $(CH_2)_2C$=N respectively]; 9.60 (1H, br. s, NH)	85

The latter, as their potassium salts, were esterified in water or DMF by dimethyl sulfate or various reactive halides, and in this case a series of novel esters **3a-m** was formed.

In studying hydrazinolysis of compounds **1a-c**, we observed that only compound **1a** is readily converted to the expected hydrazide **4** when treated with excess hydrazine hydrate at room temperature. When this reaction is carried out at elevated temperature, as described for the methyl ester of 2-methyl-5-phenylthiazolecarboxylic acid [4], breakdown of the thiazoline ring occurs.

We synthesized new potentially biologically active hydrazones **5a-e** from respectively hydrazide **4** and benzaldehyde, furfural, 5-nitrofurfural, acetophenone, or *p*-benzoquinone.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Mercury-300 spectrometer (300 MHz) in DMSO-d_6.

The composition and structure of the synthesized compounds were confirmed by the results of elemental analysis and ^{1}H NMR spectra (see Table 1).

3,4-Dimethyl-2-thioxo-1,3-thiazolinyl-5-carboxylic Acid (2a) was obtained according to the known procedure in [3].

3-Aryl-4-methyl-2-thioxo-1,3-thiazolinyl-5-carboxylic acid 2b,c. Ester **1b,c** (10 mmol) was added to a solution of 84% KOH (10 mmol) in ethanol (10 ml) and the reaction mixture was refluxed for 3 h. Then the ethanol was distilled off and the residue was dissolved in H_2O (10 ml) and the solution was filtered; the filtrate was acidified with HCl to pH 4 and the precipitate formed of product **2b,c** was filtered out.

Esters of Acids 2a-c (3a-m). Acid **2a-c** (10 mmol) was added to a suspension of 84% KOH powder (10 mmol) in DMF (10 ml); the mixture was stirred for 1 h, and then the halide (10 mmol) was added in portions. The reaction mass was held for 3 h at 50-60°C and then cooled, and the potassium halide was filtered out. The filtrate was evaporated down, the residue was treated with H_2O (10 ml), the precipitate of product **3a-m** was filtered out and dried in air.

3,4-Dimethyl-2-thioxothiazolinyl-5-carboxylic Acid Hydrazide (4). Ester **1a** (2.2 g, 10 mmol) was added with stirring to 55% hydrazine hydrate (10 ml), and the reaction mixture was held for 24 h at 20°C. Then the product **4** was filtered out and washed with water (10 ml).

N-(3,4-Dimethyl-2-thioxothiazolinylcarbonyl)hydrazones of Benzaldehyde (5a), Furfural (5b), 5-Nitrofurfural (5c), Acetophenone (5d), and *p*-Benzoquinone (5e). 36% HCl (0.86 ml) was added to compound **4** (2.03 g, 10 mmol) in H_2O (30 ml) and then the carbonyl compound (10 mmol) were added to the solution obtained at 0°C. The mixture was held for 4 h at 20°C, and the precipitate of product **5a-e** was filtered out, washed on the filter with H_2O (10 ml) and dried in air. Compounds **5** were purified by grinding with acetone and then filtered out.

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