Chemistry of Heterocyclic Compounds, Vol. 40, No. 1, 2004

THIAZOLECARBOXYLIC ACID DERIVATIVES. 1. N-SUBSTITUTED 2-AMINO-4-METHYLTHIAZOLE-5-CARBOXYLIC ACID DERIVATIVES

V. V. Dovlatyan, K. A. Eliazyan, V. A. Pivazyan, E. A. Kazaryan, and A. P. Engoyan

Acylation of the ethyl ester and anilide of 2-amino-4-methylthiazole-5-carboxylic acid gave 2-acetyl(arylsulfonyl)amino derivatives. Methylation of acetylaminothiazole and subsequent deacetylation gave 2-methylamino-4-methylthiazole-5-carboxylic acid, which was then converted into esters. The ethyl ester and anilide of thiazole-2-carboxylic acid were used as starting compounds for the synthesis of 2-dimethylaminoformimino- and 2-chlorobenzenesulfonylureido derivatives.

Keywords: aminoformiminothiazole, acylaminoformiminothiazole, dimethylaminoformiminothiazole, thiazole-5-carboxylic acid, thiazole-5-carboxylate esters.

In a continuation of a study of the synthesis and derivatives of thiazoline-5-carboxylic acid [1], we sought new pesticides and pharmaceuticals among products obtained from the available ethyl ester (**1**) and anilide **2** of 2-amino-4-methylthiazole-5-carboxylic acid [2].

In the present work, we describe several transformations of **1** and **2** at the amino group. Acylation of aromatic and heterocyclic amines may lead to the appearance or enhancement of the biological activity of these derivatives [3]. This led us to study the acylation of **1** and **2**, which can undergo amino–imino tautomerization, and, thus, may react in either the amine or imine form, as in the case of their closest analog, 2-aminothiazole [4].

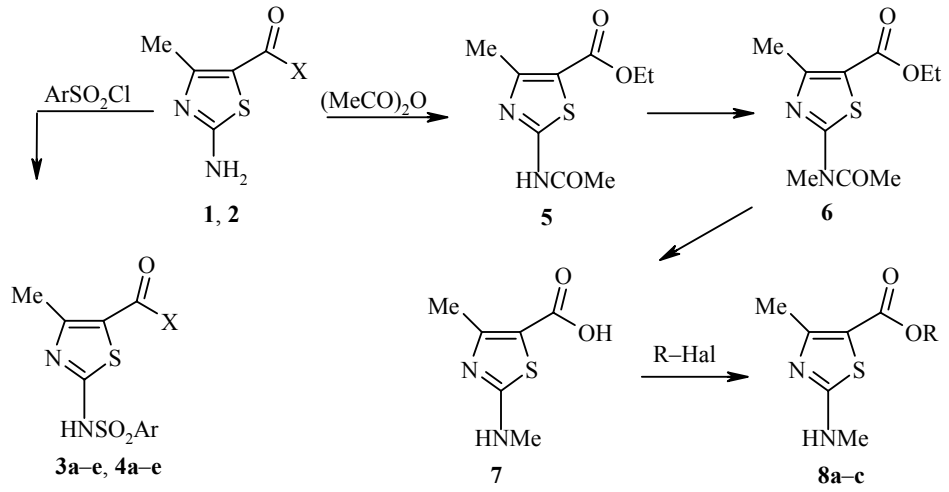
Methylthiazoles **1** and **2** react regioselectively in acetic anhydride or by the action of arylsulfonyl chlorides in pyridine to give exclusively acylaminothiazoles **3a-e, 4a-e,** and **5**. Ester **5** is an NH-acid readily methylated to give **6**, which may be deacylated to give 2-methylamino-4-methylthiazole-5-carboxylic acid (**7**) and, then, some of its esters **8a-c**.

The action of thionyl chloride on **1** and **2** was studied in an attempt to obtain N,N'-thionyldi(aminothiazole), which is a possible fungicide. However, 2-N-dimethylaminoformimino derivatives **9a** and **9b**, which are the products of the condensation of **1** and **2** with the DMF solvent, are formed instead of the expected thionyldi(aminothiazoles).

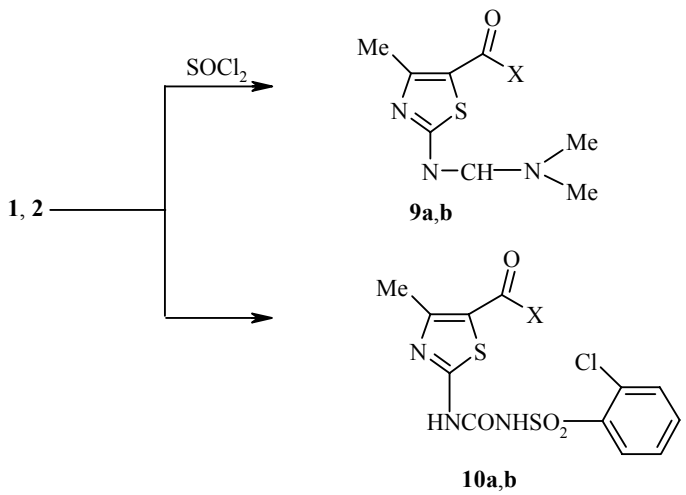
We also found that aminothiazoles **1** and **2** react with 2-chlorobenzenesulfonyl isocyanate to give **10a** and **10b**, which are related to the highly active herbicide, thiamethuronmethyl (harmony) [6] and, thus, may hold some interest.

Armenian Agricultural Academy, Yerevan 375009, Armenia; e-mail: artak@dolphin.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 90-95, January, 2004. Original article submitted July 6, 2001.

 0009-3122/04/4001-0084



1, **3a–e** X = OEt, **2**, **4a–e** X = NHPh; **3**, **4 a** Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 2-ClC_6H_4, **d** Ar = 2,5-$Me_2C_6H_3$, **e** Ar = 4-$AcNHC_6H_4$; **8 a** R = CH_2Ph, **b** R = CH_2COOMe, **c** R = $(CH_2)_2OPh$



9, **10 a** X = OEt, **b** X = NHPh

EXPERIMENTAL

The ^1H NMR spectra were taken in DMSO-d_6 on a Mercury-300 spectrometer at 300 MHz. Thin-layer chromatography was carried out on Silufol UV-254 plates using 1:1 or 1:2 acetone–heptane as the eluent and 2% $AgNO_3$ + 0.4% bromophenol blue + 4% citric acid as the developer.

Ethyl Esters (3a-e) and Anilides (4a-e) of 2-Arylsulfamido-4-methylthiazole-5-carboxylic Acids. A sample of arylsulfonyl chloride (10 mmol) was added in portions to a solution of ethyl ester of 2-amino-4-methylthiazole-5-carboxylic acid (**1**) (1.86 g, 10 mmol) or corresponding anilide **2** (2.33 g, 10 mmol) in pyridine (5 ml). The mixture was maintained for 48 h at 20°C and, then, ice water (20 ml) was added. The precipitate formed of **3a-e** or **4a-e** was filtered off, washed with water, and dried in the air. The products were purified by dissolution in alkali and reacidification by adding acetic acid.

TABLE. 1. Physicochemical and Spectral Characteristics of Compounds **3a-e** and **4a-e**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	^{1}H NMR spectrum, δ, ppm	Yield, %
		N	S			
3a	$C_{13}H_{14}N_2O_4S_2$	8.80 / 8.59	19.27 / 19.63	157-158	1.38 (3H, t, *J* = 6.5, CH_3CH_2); 2.43 (3H, s, CH_3); 4.27 (2H, q, *J* = 6.5, CH_2); 7.43-7.83 (5H, m, Ph); ~12.50 (1H, v. br. s, NH)	77
3b	$C_{14}H_{16}N_2O_4S_2$	8.41 / 8.24	19.12 / 18.82	198-200	1.36 (3H, t, *J* = 6.5, CH_3CH_2); 2.00 (3H, s, CH_3–Ar); 2.42 (3H, s, CH_3); 4.17 (2H, q, *J* = 6.5, CH_2); 7.22-7.75 (4H, m, Ar); 12.20 (1H, br. s, NH)	76
3c	$C_{13}H_{13}ClN_2O_4S_2$	7.93 / 7.77	17.31 / 17.75	192-194	1.30 (3H, t, *J* = 6.5, CH_3CH_2); 2.50 (3H, s, CH_3); 4.25 (2H, q, *J* = 6.5, CH_2CH_3); 7.60-8.20 (4H, m, Ar); 12.30 (1H, br. s, NH)	80
3d	$C_{15}H_{18}N_2O_4S_2$	7.76 / 7.91	18.40 / 18.08	174-175	1.35 (3H, t, *J* = 6.5, CH_3CH_2); 2.08 (3H, s, CH_3); 2.20 (3H, s, CH_3); 2.45 (3H, s, CH_3); 4.22 (2H, q, *J* = 6.5, CH_2); 7.70-8.10 (3H, m, Ar); 12.20 (1H, br. s, NH)	86
3e	$C_{15}H_{17}N_3O_5S_2$	11.22 / 10.97	17.09 / 16.71	136-137	1.38 (3H, t, *J* = 6.5, CH_3CH_2); 2.08 (3H, s, C(=O)CH_3); 2.40 (3H, s, CH_3); 4.25 (2H, q, *J* = 6.5, CH_2); 7.70 (4H, s, Ar); 10.02 (1H, s, NHC=O); 12.90 (1H, v. br. s, $NHSO_2$)	79
4a	$C_{17}H_{15}N_3O_3S_2$	11.45 / 11.26	17.59 / 17.16	222-224	2.45 (3H, s, CH_3); 7.10-7.80 (10H, m, 2Ph); 10.10 (1H, s, NH); 12.40 (1H, br. s, $NHSO_2$)	80
4b	$C_{18}H_{17}N_3O_3S_2$	10.61 / 10.85	16.07 / 16.54	230-231	2.05 (3H, s, CH_3–Ar); 2.45 (3H, s, CH_3); 6.90-7.80 (9H, m, Ar); 10.20 (1H, s, NH); 12.30 (1H, br. s, $NHSO_2$)	94
4c	$C_{17}H_{14}ClN_3O_3S_2$	10.57 / 10.31	16.09 / 15.71	140-141	2.50 (3H, s, CH_3); 7.05-8.20 (9H, m, Ar); 10.15 (1H, s, NH); 12.30 (1H, br. s, $NHSO_2$)	95
4d	$C_{19}H_{19}N_3O_3S_2$	10.70 / 10.47	16.32 / 15.96	142-143	2.10 (3H, s, CH_3); 2.25 (3H, s, CH_3); 2.45 (3H, s, CH_3); 6.90-8.00 (8H, m, Ar); 10.10 (1H, s, NH); 12.25 (1H, br. s, $NHSO_2$)	96
4e	$C_{19}H_{18}N_4O_4S_2$	12.83 / 13.02	15.21 / 14.88	213-214	2.07 (3H, s, C(=O)CH_3); 2.43 (3H, s, CH_3); 6.95-7.80 (9H, m, Ar); 9.70 (1H, s, NHPh); 10.05 (1H, s, NHPh); 12.80 (1H, br. s, $NHSO_2$)	55

TABLE 2. Characteristics of Compounds **8a-c**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	^{1}H NMR spectrum, δ, ppm	Yield, %
		N	H			
8a	$C_{13}H_{14}N_2O_2S$	11.00 / 10.69	12.52 / 12.21	125-127	2.43 (3H, s, CH_3); 2.90 (3H, d, J = 5.5, N–CH_3); 5.20 (2H, s, CH_2); 7.23-7.38 (H, m, Ph); 7.96 (1H, br. s, NH)	61
8b	$C_9H_{12}N_2O_4S$	11.71 / 11.48	13.43 / 13.11	160-162	2.45 (3H, s, CH_3); 2.90 (3H, d, J = 5.5, N–CH_3); 3.75 (3H, s, OCH_3); 4.65 (2H, s, CH_2); 8.20 (1H, br. s, NH)	62
8c	$C_{14}H_{16}N_2O_3S$	9.47 / 9.59	11.21 / 10.96	118-120	2.45 (3H, s, CH_3); 2.90 (3H, d, J = 5.5, N–CH_3); 4.25 (2H, t, J = 6.2, OCH_2); 4.56 (2H, t, J = 6.2, CH_2OPh); 6.90-7.30 (5H, m, Ph); 8.00 (1H, br. s, NH)	55

* 1:1 Heptane–benzene for **8a** and **8b,** heptane for **8c**.

The physicochemical and spectral data are given in Table 1.

Ethyl Ester of 2-Acetylamino-4-methylthiazole-5-carboxylic Acid (5). A suspension of **1** (1.86 g) in acetic anhydride (5 ml) was heated for 5 h at 105-110°C. Excess acetic anhydride was distilled off and the residue was treated with water (10-15 ml). The precipitate of **5** was filtered off, washed with water, and dried to give 2.1 g (92%) of compound **5**; mp 215-217°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, t, *J* = 6.5, $\underline{CH_3}CH_2$); 2.40 (3H, s, CH_3); 3.55 (3H, s, C(=O)CH_3); 4.25 (2H, q, *J* = 6.5, CH_2); 8.10 (1H, br. s, NH). Found, %: N 12.45; S 13.69. $C_9H_{12}N_2O_3S$. Calculated, %: N 12.28; S 14.04.

Ethyl Ester of 2-N-Acetylamino-N-methyl-4-methylthiazole-5-carboxylic Acid (6). A sample of **5** (2.3 g, 10 mmol) was added with stirring to a solution of 84% KOH (0.7 g, 10 mmol) in DMF (10 ml). After 30 min, freshly distilled dimethyl sulfate (ρ 1.26 g/cm^3) (1 ml, 10 mmol) was added dropwise at 0°C. The mixture was maintained for 24 h at 20°C and DMF was evaporated off. The precipitate was treated with water and filtered off to give 1.86 g (83%) of compound **6**; mp 102-104°C (octane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (3H, t, *J* = 6.5, $\underline{CH_3}CH_2$); 2.40 (3H, s, CH_3); 2.57 (3H, s, C(=O)CH_3); 3.67 (3H, s, N–CH_3); 4.25 (2H, q, *J* = 6.5, CH_2). Found, %: N 11.39; S 13.56. $C_{10}N_{14}N_2O_3S$. Calculated, %: N 11.57; S 13.22.

2-Methylamino-4-methylthiazole-5-carboxylic Acid (7). A sample of **6** (2.42 g, 10 mmol) was added to a solution of 84% KOH (1.4 g, 20 mmol) in ethanol (20 ml) and the mixture was heated at reflux for 2 h. Ethanol was distilled off. The residue was dissolved in water (10 ml) and acidified by adding acetic acid. The precipitate was filtered off to give 1.1 g (64%) of compound **7**; mp 159-160°C, R_f 0.41. ^{1}H NMR spectrum, δ, ppm: 2.40 (3H, s, CH_3); 2.85 (3H, s, N–CH_3); 7.83 (1H, br. s, NH); ~11.0 (1H, v. br. s, OH). Found, %: N 16.47; S 18.97. $C_6H_8N_2O_2S$. Calculated, %: N 16.28; S 18.60.

Esters of 2-Methylamino-4-methylthiazole-5-carboxylic Acid (8a-c). Benzyl chloride (1.52 g, 12 mmol) (for **8a**), methyl chloroacetate (for **8b**) (1.30 g, 12 mmol), or phenoxyethyl bromide (for **8c**) (2.00 g, 12 mmol) was added to a solution of potassium salt (2.1 g, 10 mmol) of acid **7** and the mixture was heated for 3 h at 50-60°C. The suspension was poured into a Petri dish and DMF was evaporated off. The residue was treated with 15 ml water and the precipitates of **8a-c** were filtered off (Table 2).

Ethyl Ester (9a) and Anilide (9b) of 2-Dimethylaminoformimino-4-methylthiazole-5-carboxylic Acid. A sample of DMF (4 ml) and, then, thionyl chloride (0.8 ml, 11 mmol) were added slowly in portions with stirring to **1** (1.86 g, 10 mmol) or **2** (2.33 g, 10 mmol) cooled to 0°C. The mixture was maintained for 24 h at 20°C and ice water (20 ml) was added. The solution was filtered to remove turbidity and the filtrate was neutralized by adding $NaHCO_3$. The precipitated product was filtered off.

Ethyl Ester 9a was obtained in 87% yield (2.1 g); mp 60-62°C (heptane), R_f 0.51. ^{1}H NMR spectrum, δ, ppm: 2.50 (3H, s, CH_3); 3.07 (3H, s, $N(CH_3)_2$); 3.20 (3H, s, $N(CH_3)_2$); 6.95-7.70 (5H, m, Ph); 8.40 (1H, s, CH=N); 9.35 (1H, s, NH). Found, %: N 17.63; S 13.58. $C_{10}H_{15}N_3O_2S$. Calculated, %: N 17.43; S 13.28.

Anilide 9b was obtained in 86% yield (2.48 g); mp 93-95°C (1:1 heptane–benzene), R_f 0.45. ^{1}H NMR spectrum, δ, ppm: 2.50 (3H, s, CH_3); 3.10 (3H, s, $N(CH_3)_2$); 3.20 (3H, s, $N(CH_3)_2$); 6.95-7.70 (5H, m, Ph); 8.42 (1H, s, N=CH); 9.35 (1H, s, NH). Found, %: N 19.62; S 11.48. $C_{14}H_{16}N_4OS$. Calculated, %: N 19.44; S 11.11.

N-Thiazolyl-N'-(2-chlorobenzenesulfonyl)ureas (10a,b). A sample of 2-chlorobenzenesulfonyl isocyanate (2.2 g, 10 mmol) and five drops of pyridine were added to a solution of **1** (1.86 g, 10 mmoles) or **2** (2.33 g, 10 mmol) in absolute toluene (10 ml). The mixture was heated at reflux for 2 h and urea **10a** or **10b** was filtered off.

Urea 10a was obtained in 93% yield (3.75 g); mp 246-247°C (dec.) (heating at reflux in 50% ethanol), R_f 0.35. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 6.5, $\underline{CH_3}CH_2$); 2.50 (3H, s, CH_3); 4.0 (2H, q, *J* = 6.5, $\underline{CH_2}CH_3$); 7.55-8.15 (4H, m, Ar). Found, %: Cl 8.80; N 10.12; S 16.17. $C_{14}H_{14}ClN_3O_5S_2$. Calculated, %: Cl 8.80; N 10.41; S 15.86.

Urea 10b was obtained in 95% yield (4.3 g); mp 292-293°C (dec.), R_f 0.44. ^{1}H NMR spectrum, δ, ppm: 2.45 (3H, s, CH_3); 6.09-8.20 (9H, m, Ar); 9.70 (1H, s, NH); 10.20 (1H, s, NH); 12.80 (1H, br. s, NH–SO_2Ar). Found, %: Cl 8.17; N 12.64; S 14.65. $C_{18}H_{15}ClN_4O_4S_2$. Calculated, %: Cl 7.88; N12.43; S 14.21.

REFERENCES

1. V. V. Dovlatyan, K. A. Eliazyan, V. A. Pivazyan, E. A. Kazaryan, A. P. Engoyan, R. T. Grigoryan, and R. G. Mirzoyan, *Khim. Geterotsikl. Soedin.*, No. 677 (2000).
2. Y. Sawa and R. Maeda, *J. Pharm. Soc. Jpn.,* **76**, 301 (1956); *Chem. Abstr.*, 13875 (1956).
3. W. Schäfer, K. Sasse, L. Eue, and H. Hack, West Ger. Pat. 1277241 (1969); *Ref. Zh. Khim.*, 5N095P (1970).
4. H. Martin, O. Rohr, S. Janiak, and L. Edrer, Swiss Pat. 479247 (1969), *Ref. Zh. Khim.*, 11 N976 (1970).
5. G. A. Melent'eva, *Pharmaceutical Chemistry* [in Russian], Meditsina, Moscow 91968), p. 300.
6. Yu. A. Baskakov, *Zh. Vses. Khim. Obshch. im. D. I. Mendeleeva*, **33**, 634 (1988).