Chemistry of Heterocyclic Compounds, Vol. 36, No. 5, 2000

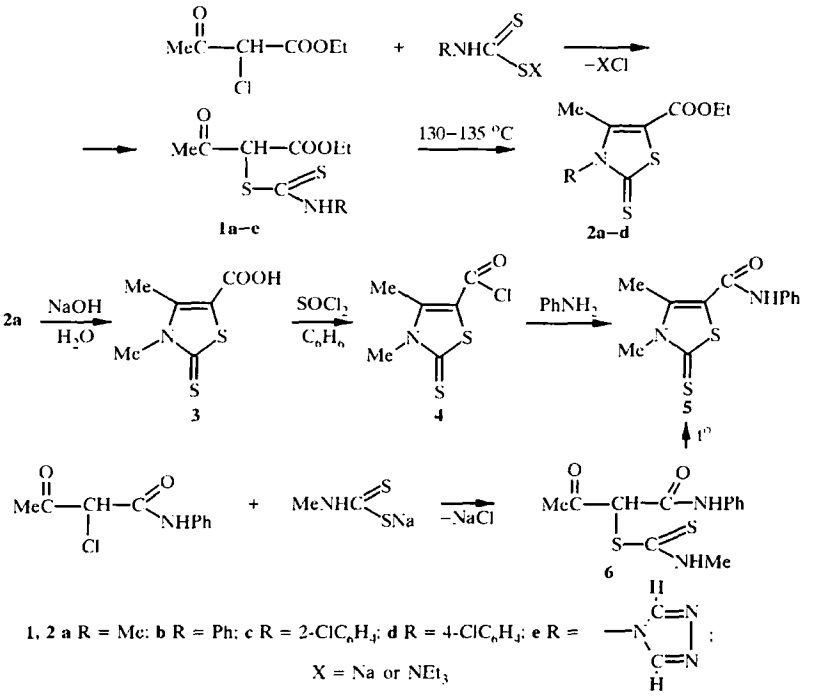
SYNTHESIS AND HETEROCYCLIZATION OF DITHIOCARBAMOYLACETOACETIC ESTERS AND ANILIDES

V. V. Dovlatyan[1], K. A. Eliazyan[1], V. A. Pivazyan[1], E. A. Ghazaryan[1], A. P. Engoyan[1], R. T. Grigoryan[2], and R. G. Mirzoyan[2]

The action of salts of N-monosubstituted dithiocarbamic acids on α-chloroacetoacetic ester and the corresponding anilide led to the isolation of the α-dithiocarbamoyl derivatives. These derivatives are converted, on standing or heating, to the ethyl ester and anilide of 4-methyl-3-methyl(aryl)-2-thiooxy-1,3-thiazolyl-5-carboxylic acids, which can be converted to the corresponding acid, acid chloride, and anilide.

Keywords: dithiocarbamates, thiourea, thiazolines, α-chloroacetic acid, heterocyclization.

Salts of N-alkyldithiocarbamic acids with chloroacetonitrile, chlorocyanoacetic ester, and the corresponding amide instead of S-substituted derivatives of dithiocarbamates with an open chain form products of their intramolecular heterocyclization – thiazoline derivatives [1-4].



[1] Armenian Agricultural Academy, Yerevan 375009. [2] Institute of Fine Organic Chemistry of the Republic of Armenia, Yerevan 375014; e-mail: agacad@arminco.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 677-681, May, 2000. Original article submitted January 22, 1999; revision submitted August 25, 1999.

0009-3122/00/3605-0593$25.00©2000 KluwerAcademic/Plenum Publishers

With the object of involving new functionally substituted halogen derivatives within the scope of this reaction, we studied the reaction of the indicated salts with α-chloroacetoacetic ester and the corresponding anilide. Interest in the study of the given reaction and the assumption of the possible consequent formation of sulfur-containing heterocycles are also supported by the fact that the action of thiourea, thioacetamide, mercaptoethanol, and other related to dithiocarbamate compounds usually leads to the synthesis of pesticides of the thiazole and oxathiine series [5-7].

The action of aqueous solutions of salt of N-monosubstituted dithiocarbamates on α-chloroacetoacetic ester leads to the formation of dithiocarbamoyl derivatives of acetoacetic ester **1a-e**, which are cyclized on standing, and the more so by heating, to give ethyl 4-methyl-3-methyl(aryl)-2-thiooxy-1,3-thiazolinyl-5-carboxylates (**2a-d**).

Taking into account the high fungicidal activity of some anilides of substituted derivatives of furan-, thiazole-, and oxathiinecarboxylic acids [8], we converted some of the esters synthesized by us into anilides. For this purpose, the hydrolysis of ester **2a** afforded the corresponding acid **3**, which was readily converted by thionyl chloride to acid chloride **4**. The last reacts with aniline in the presence of pyridine to form the expected anilide **5**, which is also formed by direct synthesis – the dithiocarbamoylation of α-chloroacetoacetic acid anilide and the subsequent heterocyclization of anilide **6**.

Shown below are routes of the formation of characteristic fragments in the mass spectra of the compounds synthesized, confirming the proposed structure:

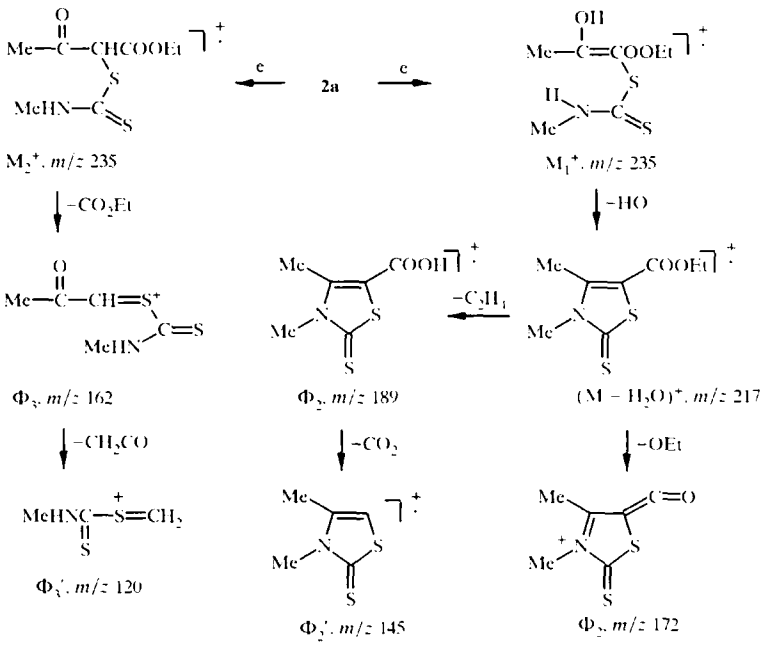


TABLE 1. Mass Spectra of the Compounds **1a** and **2a-d**

Compound	*m/z* (I_{rel}, %)
1a	235 (75), 217 (74), 192 (6), 162 (16), 145 (14), 131 (28), 120 (70), 116 (44), 105 (11), 103 (18), 92 (22), 88 (13), 85 (19), 74 (60), 56 (27), 45 (34), 43 (100)
2a	217 (100), 189 (37), 172 (18), 145 (16), 116 (7), 98 (8), 88 (6), 74 (15), 72 (15), 71 (12), 70 (10), 56 (30), 45 (17), 43 (10)
2b	279 (100), 251 (19), 250 (51), 234 (14), 207 (9), 206 (12), 134 (14), 118 (14), 77 (47), 43 (21)
2d	315 (47), 313 (100), 287 (4), 285 (11), 284 (30), 270 (45), 268 (14), 241 (10), 240 (7), 162 (16), 161 (11), 160 (15), 152 (16), 116 (20), 111 (34)

TABLE 2. Physicochemical Characteristics of the Compounds **1b-e**

Compound	Empirical formula	Found, % Calculated, %				M+	mp, °C		Yield, %
		C	H	N	S				
1b	$C_{13}H_{13}NO_3S_2$	52.80 52.53	5.36 5.05	5.03 4.71	21.10 21.55	297	89-91	1.3 (3H, t, $\underline{CH_3}CH_2$); 1.55 (3H, s, CH_3CO); 4.25 (2H, q, CH_2); 4.45 (1H, s, CH); 7.0-7.4 (5H, m, Ph)	67
1c	$C_{13}H_{12}ClNO_3S_2$	47.40 47.06	4.53 4.22	4.41 4.22	19.58 19.31	331/333	100-102	1.3 (3H, t, $\underline{CH_3}CH_2$); 1.55 (3H, s, CH_3CO); 4.25 (2H, q, CH_2); 4.45 (1H, s, CH); 7.2-7.6 (4H, m, Ar)	89
1d	$C_{13}H_{12}ClNO_3S_2$	46.82 47.06	4.49 4.22	4.53 4.22	19.04 19.31	331/333	116-118	1.28 (3H, t, $\underline{CH_3}CH_2$); 1.55 (3H, s, CH_3CO); 4.25 (2H, q, CH_2); 4.45 (1H, s, CH); 7.05-7.45 (4H, m, Ar)	88
1e*	$C_9H_{12}N_2O_3S_2$	37.73 37.50	4.41 4.17	19.73 19.44	22.59 22.22	288	118-120	1.27 (3H, t, CH_3); 1.77 (3H, s, CH_3CO); 4.28 (2H, q, CH_2); 4.95 (1H, s, CH); 8.5 (2H, s, CH=N)	63

* ^{1}H NMR spectrum in $CDCl_3 + (CD_3)_2CO$.

TABLE 3. Physicochemical Characteristics of the Compounds **2b-d**

Compound	Empirical formula	Found, % Calculated, %		M+	mp, °C	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)	Yield, %
		N	S				
2b	$C_{13}H_{13}NO_2S_2$	6.27 5.02	23.40 22.94	279	156-157	1.3 (3H, t, $\underline{CH_3}CH_2$); 2.25 (3H, s, CH_3); 4.30 (2H, q, CH_2); 7.35-7.65 (4H, m, Ar)	87
2c	$C_{13}H_{12}ClNO_2S_2$	4.69 4.47	20.72 20.41	313 315	128-130	1.3 (3H, t, $\underline{CH_3}CH_2$); 2.3 (3H, s, CH_3); 4.25 (2H, q, CH_2); 7.0-7.4 (4H, m, Ar)	79
2d*	$C_{13}H_{12}ClNO_2S_2$	4.73 4.47	20.83 20.41	313/315	130-131	1.3 (3H, t, $\underline{CH_3}CH_2$); 2.2 (3H, s, CH_3); 4.2 (2H, q, CH_2); 7.0-7.4 (4H, m, Ar)	90

* ^{1}H NMR spectrum in $CDCl_3$.

The fragmentation of the compounds **2a-d** proceeds mainly by analogy with the decomposition of the $(M - H_2O)^+$ ion (cf. Scheme 1). The mass spectra of the compounds **2b,d** contain characteristic peaks of the Φ_1-Φ_3' ions with corresponding displacements (Table 1).

EXPERIMENTAL

IR spectra of the compounds were recorded on UR-20 instrument in vaseline oil. ^{1}H NMR spectra were recorded on Mercury-300 spectrometer in $CDCl_3$ and DMSO-d_6. Mass spectra were obtained on MX-1321A instrument with direct input of the sample at the ion source, and the 70 eV energy of the ionizing electrons.

Ethyl α-(N-Methyl)dithiocarbamoylacetoacetate (1a). Ethyl α-chloroacetoacetate (1.65 g, 0.01 mol) are added in portions with stirring to solution of sodium methyldithiocarbamate (2.0 g, 0.012 mol) in of water (10 ml) at 0°C, and the mixture is stirred for 3 h at 15-20°C. The residue is then filtered off prior to the isolation of compound **1a**. Yield 2.2 g (94%); mp 124-125°C. ^{1}H NMR spectrum ($CDCl_3$): 1.32 (3H, t, $\underline{CH_3}CH_2$); 1.60 (3H, s, $\underline{CH_3}CO$); 2.9 (3H, d, N–CH_3); 4.30 (2H, q, CH_2); 4.48 (1H, s, CH); 7.5 ppm (1H, br. s, NH). M^+ 235. Found, %: N 6.12; S 27.41. $C_8H_{13}NO_3S_2$. Calculated, %: N 5.96; S 27.23.

The compounds **1b-e** are obtained by the analogous method (Table 2).

Ethyl 3,4-Dimethyl-2-thiooxy-1,3-thiazolinyl-5-carboxylate (2a). A solution of compound **1a** (2.35 g, 0.01 mol) in abs. toluene (10 ml) is boiled for 6 h at 125-130°C in the presence of catalytic amounts of *p*-toluenesulfonic acid. The suspension is evaporated, and the residue is treated with petroleum ether, and filtered off. Yield of compound **2a** 1.8 g (83%); mp 76-78°C. IR spectrum: 1600 ($C{=}C_{conj}$), 1730 cm^{-1} (C=O). ^{1}H NMR spectrum (DMSO-d_6): 1.35 (3H, t, $\underline{CH_3}CH_2$); 2.7 (3H, s, CH_3); 3.8 (3H, s, N–CH_3); 4.28 ppm (2H, q, CH_2). M^+ 217. Found, %: N 6.67; S 29.13. $C_8H_{11}NO_2S_2$. Calculated, %: N 6.45; S 29.49.

The constants and yields of the compounds **2b-d** are presented in Table 3.

3,4-Dimethyl-2-thiooxy-1,3-thiazolinyl-5-carboxylic Acid (3). Compound **2a** (2.2 g, 0.01 mol) are added in portions with stirring to a solution of NaOH (0.44 g, 0.011 mol) in water (15 ml). The resulting solution of sodium salt of compound **3** is acidified with CH_3COOH after 24 h, and is filtered off. Yield of compound **3** 1.5 g (80%); mp 214-216°C. ^{1}H NMR spectrum (DMSO-d_6): 2.73 (3H, s, CH_3); 3.72 (3H, s, N–CH_3); 13.6 ppm (1H, br. s, OH). M^+ 189. Found, %: N 7.27; S 34.05. $C_6H_7NO_2S_2$. Calculated, %: N 7.41; S 33.86.

3,4-Dimethyl-2-thiooxy-1,3-thiazolinyl-5-carboxylic Acid Chloride (4). Thionyl chloride (1 ml, 0.013 mol) is added in portions with stirring to compound **3** (1.9 g, 0.01 mol) in abs. benzene (10 ml) at 0°C. The mixture is boiled for 3 h until the release of SO_2 and HCl ceased. The excess of thionyl chloride and benzene is then distilled off. The residue is triturated with petroleum ether (2 × 10 ml) and filtered off. The filter with the residue is stored in a desiccator. Yield of compound **4** 1.7 g (81%); mp 92-94°C. Found, %: Cl 17.32; N 6.98; S 31.07. $C_6H_6ClNOS_2$. Calculated, %: Cl 17.11; N 6.75; S 30.84.

3,4-Dimethyl-2-thiooxy-1,3-thiazolinyl-5-carboxylic Acid Anilide (5). A mixture of compound **4** (2.1 g, 0.01 mol) and aniline (1.9 g, 0.02 mol) in abs. benzene (10 ml) is boiled for 7 h. Benzene is distilled off, and the residue is treated with water (10 ml) and filtered off. Yield of compound **5** 2.0 g (75%); mp 182-184°C. ^{1}H NMR spectrum ($CDCl_3$): 2.7 (3H, s, CH_3); 3.7 (3H, s, N–CH_3); 7.0-7.4 (5H, m, Ph); 8.0 ppm (1H, br. s, NH). IR spectrum: 1510, 1600 (C=C); 1660 (C=O amide); 3300 cm^{-1} (NH). Found, %: N 10.47; S 23.04. $C_{12}H_{22}N_2OS_2$. Calculated, %: N 10.22; S 23.36.

α-(N-Methyl)dithiocarbamoylacetoacetanilide (6). Anilide of α-chloroacetoacetic acid (2.12 g, 0.01 mol) are added in portions to a solution of sodium methyldithiocarbamate (1.55 g, 0.012 mol) in water (10 ml) at 0-5°C. The mixture is held for 24 h at 20°C and filtered off. Yield of compound **6** 2.3 g (86%); mp 146-148°C. ^{1}H NMR spectrum ($CDCl_3$): 1.6 (3H, s, CH_3CO); 2.9 (3H, d, N–CH_3); 4.48 (1H, s, CH); 7.0-7.4 (5H, m, Ph); 8.0 ppm (1H, br. s, NH). Found, %: N 9.70; S 23.00. $C_{12}H_{14}N_2O_2S_2$. Calculated, %: N 9.93; S 22.70.

Cyclization of Compound 6 to 5 is accomplished by analogy with the synthesis of compound **2a**. Yield 84%; mp 182-184°C. The mixed test with the sample obtained from compound **4** does not give a melting point depression.

REFERENCES

1. F. V. Avetisyan, *Theses Cand. Sc. (Chem.)*, Yerevan (1972).
2. V. V. Dovlatyan and F. V. Avetisyan, *Arm. Khim. Zh.*, **36**, 494 (1973).
3. V. V. Dovlatyan and F. V. Avetisyan, USSR Author's Certificate 335947. *Biull. Izobret.*, No. 13, (1972).
4. V. V. Dovlatyan and F. V. Avetisyan, USSR Author's Certificate 392690. *Biull. Izobret.*, No. 32, (1973).
5. N. N. Mel'nikov, *Chemistry and Technology of Pesticides* [in Russian], Khimiya, Moscow (1974), 629.
6. B. von Shmeling and M. Kulka, *Science*, **152**, 659 (1966).
7. L. V. Edgington, G. S. Walton, and P. M. Miller, *Science*, **153**, 307 (1966).
8. N. N. Mel'nikov, K. A. Novozhilov, S. R. Belan, and T. N. Pylova, *Reference Book on Pesticides* [in Russian], Khimiya, Moscow (1985), pp. 238, 290.