Oxalylation of the 3-oxo-*N*-phenyl-3-R-propanethioamides

V. N. Britsun, A. N. Borisevich, L. S. Samoylenko, A. N. Chernega, and M. O. Lozynskii*

Institute of Organic Chemistry, National Academy of Sciences of Ukraine,
5 ul. Murmanskaya, 02094 Kiev-94, Ukraine.
E-mail: esipenko@iflab.kiev.ua

Oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides in aprotic solvents in the temperature range from –40°C to +20°C results in 4-acyl-5-phenylamino-2,3-dihydrothiophene-2,3-diones and 2-(2-oxo-2-R-ethylidene)-3-phenyl-1,3-thiazolidine-4,5-diones, while in the presence of potassium carbonate, potassium 4-acyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolates are formed.

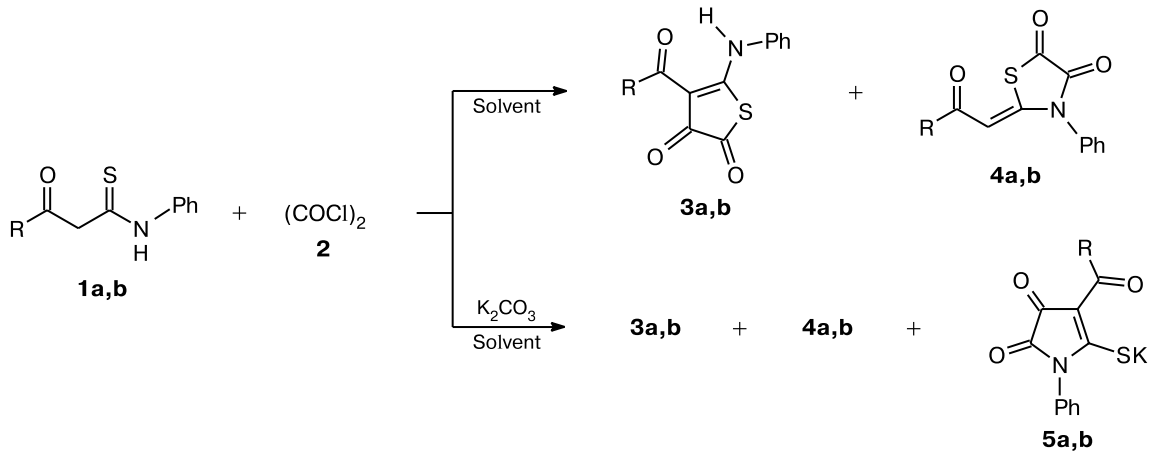
Key words: oxalylation, 3-oxo-*N*-phenyl-3-R-propanethioamides, cyclization, ring transformation, 5-phenylamino-4-acyl-2,3-dihydrothiophene-2,3-diones, 2-(2-oxo-2-R-ethylidene)-3-phenyl-1,3-thiazolidine-4,5-diones, potassium 4-acyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolates, 4-acyl-1-phenyl-5-thioxopyrrolidine-2,3-diones.

3-Oxo-*N*-phenyl-3-R-propanethioamides react with electrophilic reagents as ambident nucleophiles,[1,2] which makes them promising starting compounds for the synthesis of diverse heterocycles such as pyrazoles,[3] thiazoles,[4] and 1,2,4-dithiazolidines.[5] However, the presence of several reaction centers in 3-oxo-*N*-phenyl-3-R-propanethioamides does not always allow one to predict unambiguously the reaction route or reaction selectivity.

The reaction of 3-oxo-*N*,3-diphenylpropanethioamide with oxalyl chloride has been reported[6,7] to proceed as [3+2]-cyclocondensation giving rise to 2-(2-oxo-2-phenylethylidene)-3-phenyl-1,3-thiazolidine-4,5-dione and 4-benzoyl-1-phenyl-5-thioxopyrrolidine-2,3-dione, the yield of each product being 30%. Since 3-oxo-*N*-phenyl-3-R-propanethioamides can be acylated by oxalyl chloride at the S atom and the active methylene group, the formation of 2,3-dihydrothiophene-2,3-diones is also possible. This study deals with the influence of solvents, compounds of a basic nature, and the temperature conditions on the oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides and the synthesis of 2,3-dihydrothiophene-2,3-diones.

Since S-acylation is thermodynamically less favorable than N-acylation,[8—10] it appeared reasonable to carry out oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides in various aprotic solvents under kinetic control conditions, *i.e.*, at ambient or lower temperatures. The results of oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides are summarized in Scheme 1 and in Table 1.

Scheme 1



1, **3**, **4**, **5** : R = Me (**a**), Ph (**b**)

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Table 1. Effect of the nature of the solvent and the base on the product ratio in oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides **1a** and **1b**

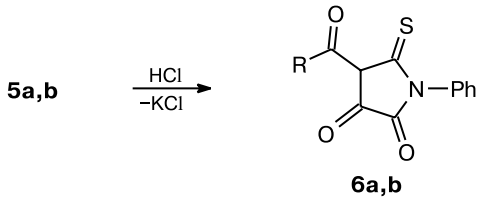
Run*	Solvent	**3a**	**4a**	**5a**	**3b**	**4b**	**5b**
1	Tetrachloromethane	1.0	1.1	—	1.0	1.2	—
2	Chloroform	1.0	1.0	—	1.0	1.6	—
*3***	Chloroform	1.0	0.3	—	1.0	0.4	
4	Chloroform + *N*,*N*-dimethylaniline	1.0	2.0	—	1.0	1.9	—
5	Diethyl ether	1.0	1.4	—	1.0	0.9	—
6	Diethyl ether + *N*,*N*-dimethylaniline	1.0	1.7	—	1.0	1.5	—
7	Diethyl ether + K_2CO_3	1.0	0.4	3.3	1.0	1.3	4.1
8	Dioxane	1.0	0.7	—	1.0	0.4	—
9	Acetone	1.0	1.0	—	1.0	0.6	—
10	Acetone + K_2CO_3	1.0	0.3	3.0	1.0	1.2	3.4

* The reaction time is 1 h, $T \approx 20$ °C.
** The reaction time is 10 h, $T = -40$ °C.

We found that, unlike oxalylation in boiling dioxane for 3 h,[6,7] the reaction of 3-oxo-*N*-phenyl-3-R-propanethioamides **1a**,**b** with oxalyl chloride carried out for 1 h at 20 °C in aprotic solvents of different polarity affords the products of acylation at the S atom and the active methylene group, namely, 4-acyl-5-phenylamino-2,3-dihydrothiophene-2,3-diones (**3a,b**), and the oxalylation products at the S and N atoms, namely, 2-(2-oxo-2-R-ethylidene)-3-phenyl-1,3-thiazolidine-4,5-diones **4a,b**. The nature of the solvent has little influence on the ratio of the reaction products, which are formed in approximately equal amounts (see Table 1, runs *1*, *2*, *5*, *8*, *9*). The oxalylation of **1a**,**b** at −40 °C results in a mixture of **3a,b** and **4a,b** in which thiophene-2,3-diones **3a,b** predominate (run *3*). The acylation of propanethioamides **1a,b** in chloroform and diethyl ether in the presence of *N*,*N*-dimethylaniline yields a mixture of compounds **3a,b** and **4a,b** in which thiazolidine-4,5-diones **4a,b** are the major components (runs *4* and *6*), whereas oxalylation of **1a,b** in diethyl ether or acetone in the presence of K_2CO_3 affords mainly potassium 4-acyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolates **5a,b**, together with thiophene-2,3-diones **3a,b** and thiazolidine-4,5-diones **4a,b** (runs *7* and *10*). Compounds **5a,b** were converted into 4-acyl-1-phenyl-5-thioxopyrrolidine-2,3-diones **6a,b** on treatment with hydrochloric acid (Scheme 2).

It has been reported previously[6] that 1,3-thiazolidine-4,5-dione **4b** is a thermodynamically unstable compound and, on refluxing in a dioxane—hydrochloric acid mixture for 2 h, it is converted into pyrrolidine-2,3-dione **6b** in 10% yield. Therefore, we studied the thermal and chemical stability of thiophene-2,3-dione **3a** and 1,3-thiazolidine-4,5-dione **4a**. It was found that, unlike the described **4b**, these compounds do not change on refluxing in hydrogen chloride-containing dioxane (2 h) or 1,3-dichlorobenzene (1 h). However, stirring of a solution of thiophene-2,3-dione **3a** in acetone in the presence of K_2CO_3 at 20 °C results in ring transformation of **3a** to give potassium 2,3-dioxopyrrole-5-thiolate **5a** in 57% yield (after 1 h) or in 85% yield (after 3 h). Similarly, on treatment with K_2CO_3 in acetone, 1,3-thiazolidine-4,5-dione **4a** is converted into potassium thiolate **5a**. In all probability, the ring transformations in thiophene-2,3-diones **3a,b** and thiazolidine-4,5-diones **4b** to give pyrrole-2,3-diones **5a,b** are due to the low stability of the S—C=O bond.[9,10]

Scheme 2



6a,b

Since the ^{1}H NMR signals of the NH protons of thiophene-2,3-diones **3a,b** and the OH protons of 5-thioxopyrrolidine-2,3-diones **6a,b** are close (13.65—13.67 and 14.62—15.25, respectively), for unambiguous identification of compounds **3a,b** and **6a,b**, we studied thiophene-2,3-dione **3a** by X-ray diffraction.

The general view and selected geometric parameters of molecule **3a** are shown in Fig. 1. The thiophene ring is planar (the deviations of atoms from the root-mean-square plane do not exceed 0.008 Å), the amine fragment, C(1)N(1)H(1)C(7), lying virtually in this plane (the corresponding dihedral angle is only 2.0°). The benzene ring forms a dihedral angle of 65.0° with the thiophene ring. The N(1) atom has a planar trigonal configuration, the sum of the bond angles at this atom being 359.9°. The effective conjugation of the lone pair of N(1) with the thiophene ring results in a substantial shortening of the N(1)—C(1) bond (1.313(2) Å) with respect to the 1.43—1.45 Å value typical of a single N(sp^2)—C(sp^2) bond. A characteristic feature of the molecular structure of compound **3a** is the formation of rather strong[11] intramolecular hydrogen bond, N(1)—H(1)...O(3), which becomes even stronger "due to the resonance."[12] The geometric parameters of this H-bond are as follows: N...O, 2.649(2); N—H, 0.87(2); O...H, 1.96(2) Å; N—H—N, 136(1)°.

Thus, it was shown that oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides in aprotic solvents in the temperature range from −40 °C to +20 °C results in kinetically controlled products, 5-phenylamino-4-acyl-2,3-dihydrothiophene-2,3-diones and 2-(2-oxo-2-R-ethylidene)-3-phenyl-1,3-thiazolidine-4,5-diones, while oxalylation in the presence of potassium carbonate yields

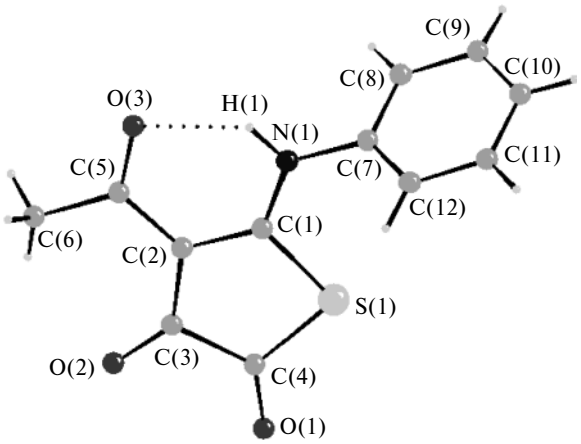


Fig. 1. General view of molecule **3a**. Selected bond lengths (Å): S(1)—C(1), 1.765(2); S(1)—C(4), 1.801(2); C(1)—C(2), 1.407(2); C(2)—C(3), 1.423(2); C(3)—C(4), 1.553(3); and bond angles (deg): N(1)—C(1), 1.313(2); N(1)—C(7), 1.434(2); C(1)—S(1)—C(4), 121.6(1); C(1)—N(1)—C(6), 89.68(8).

predominantly thermodynamically controlled potassium 4-acyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolate.

Experimental

NMR spectra were recorded on a Varian-300 instrument operating at 300 MHz (^{1}H) or 75 MHz (^{13}C) in DMSO-d_6 or $CDCl_3$ with Me_4Si as the internal standard. IR spectra were measured on a UR-20 instrument in KBr pellets.

X-Ray diffraction of compound 3a. The single crystals of compound **3a** were prepared by slow crystallization from CH_3COOH. The X-ray diffraction experiment was carried out for a crystal with the linear dimensions 0.37×0.40×0.47 mm at room temperature on a CAD-4 Enraf—Nonius automated four-circle diffractometer (Cu-Kα radiation, λ = 1.54178 Å, scanning rate ratio 2θ/ω 1.2, θ_{max} = 69°). Altogether 4181 reflections were collected, 1874 of which were symmetrically independent (R_{int} = 0.026). The crystals of compound **3a** are monoclinic, a = 23.195(3), b = 5.678(1), c = 19.527(2) Å, β = 120.47(1)°, V = 2214.6(9) Å^3, $C_{12}H_9NO_3S$, M = 247.3, Z = 8, d_{calc} = 1.48 g cm^{-3}, μ = 25.78 cm^{-1}, F(000) = 1024.0, space group $C2/c$ (No. 15). The structure was solved by the direct method and refined by least squares in the full-matrix anisotropic approximation using the CRYSTALS software.[13] The refinement included 1731 reflections with $I > 3\sigma(I)$ (190 refined parameters, the number of reflections per parameter 9.1). All hydrogen atoms were revealed from the difference electron density synthesis and refined isotropically. The refinement was performed using the Chebyshev weighing scheme[14] with five parameters: 2.77, −2.38, 1.08, −1.42, and −0.75. The final R factors were R = 0.047 and R_W = 0.047, GOOF = 0.934. The residual electron density from the difference Fourier series was 0.22 and −0.26 e·Å^{-3}. The absorption corrections were applied by azimuthal scanning.[15] The full set of X-ray diffraction data for compound **3a** is deposited with the Cambridge Structural Database (CCDC 244043).

Oxalylation of 3-oxo-*N*-phenyl-3-R-propanethioamides (general procedure). Oxalyl chloride **2** (10.5 mmol) in 3 mL of a solvent was added dropwise with stirring to a solution of 3-oxo-*N*-phenyl-3-R-propanethioamide **1a,b** (10 mmol) in 10 mL of the solvent. The reaction mixture was kept for 0.5 h at 20 °C and the solvent was evaporated. The product ratio was determined by ^{1}H NMR, the integration accuracy being ±5%.

4-Acetyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (3a) and 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (3b). A solution of oxalyl chloride **2** (1.33 g, 10.5 mmol) in 3 mL of chloroform was added dropwise with stirring over a period of 0.5 h to a solution of 3-oxo-*N*-phenyl-3-R-propanethioamide **1a,b** (10 mmol) in 10 mL of chloroform at −40 °C. The reaction mixture was kept for 9.5 h at −40 °C, chloroform was evaporated, and the crystals that formed were recrystallized from acetic acid (**3a**) or twice recrystallized from toluene (**3b**). Yield **3a** 1.48 g (60%), m.p. 180—182 °C. Found (%): C, 58.42; H, 3.56; N, 5.64; S, 12.83. $C_{12}H_9NO_3S$. Calculated (%): C, 58.29; H, 3.67; N, 5.66; S, 12.97. ^{1}H NMR ($CDCl_3$), δ: 2.62 (s, MeCO); 7.33—7.48 (m, Ph); 13.65 (br.s, NH). ^{13}C NMR (DMSO-d_6), δ: 23.9 (Me); 110.6 (N—C=S); 127.6, 128.3, 128.9, 133.3, 160.8, 176.5, 187.1, 198.0 (Me<u>C</u>O). IR, ν/cm^{-1}: 3050 (Ph); 1760 (C=O); 1710 (C=O); 1620 (C=O); 1430, 1360, 1330. Yield **3b** 1.33 g (43%), m.p. 191—193 °C. Found (%): C, 65.81; H, 3.44; N, 4.67; S, 10.08. $C_{17}H_{11}NO_3S$. Calculated (%): C, 66.01; H, 3.58; N, 4.53; S, 10.36. ^{1}H NMR ($CDCl_3$), δ: 7.41—7.77 (m, 2 Ph); 13.67 (br.s, NH). IR, ν/cm^{-1}: 3100 (Ph); 1750 (C=O); 1700 (C=O); 1630 (C=O); 1590, 1420.

2-Acetonylidene-3-phenyl-1,3-thiazolidine-4,5-dione (4a) and 2-(2-oxo-2-phenylethylidene)-3-phenyl-1,3-thiazolidine-4,5-dione (4b). A solution of oxalyl chloride (1.33 g, 10.5 mmol) in 3 mL of chloroform was added dropwise with stirring at 20 °C over a period of 0.5 h to a solution of 3-oxo-*N*-phenyl-3-R-propanethioamide **1a,b** (10 mmol) and *N*,*N*-dimethylaniline (3.03 g, 25 mmol) in 10 mL of chloroform. The reaction mixture was kept for 0.5 h and washed with 20 mL of 10% HCl and the chloroform layer was separated, dried with $MgSO_4$, and concentrated. The crystals that formed were recrystallized from 1,3-dichlorobenzene. Yield **4a** 1.28 g (52%), m.p. 179—181 °C. Found (%): C, 58.12; H, 3.80; N, 5.53; S, 13.19. $C_{12}H_9NO_3S$. Calculated (%): C, 58.29; H, 3.67; N, 5.66; S, 12.97. ^{1}H NMR (DMSO-d_6), δ: 2.15 (s, MeCO); 5.81 (s, CO—CH=); 7.44—7.62 (m, Ph). ^{13}C NMR (DMSO-d_6), δ: 30.9 (Me); 104.2 (N—C=S); 127.9, 130.0, 134.4, 145.8, 156.0, 185.0, 196.9 (Me<u>C</u>O). IR, ν/cm^{-1}: 3100 (Ph); 1745 (C=O); 1690 (C=O); 1600 (C=C—C=O); 1580, 1520, 1470, 1430, 1380, 1330. Yield **4b** 1.67 g (54%), m.p. 195—197 °C (*cf.* Ref. 6: 198—199 °C). Found (%): C, 65.82; H, 3.51; N, 4.79; S, 10.53. $C_{17}H_{11}NO_3S$. Calculated (%): C, 66.01; H, 3.58; N, 4.53; S, 10.36. The ^{1}H NMR and IR spectra **4b** corresponded to those reported previously.[6]

Preparation of potassium 4-acetyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolate (5a) and 4-benzoyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolate (5b). A solution of oxalyl chloride (1.33 g, 10.5 mmol) in 3 mL of acetone was added dropwise with stirring at 20 °C over a period of 0.5 h to a suspension of 3-oxo-*N*-phenyl-3-R-propanethioamide **1a,b** (10 mmol) and freshly calcined K_2CO_3 (4.28 g, 31 mmol) in 10 mL of acetone. The reaction mixture was kept for 0.5 h, the precipitate was filtered off and treated with hot water (2×7 mL), the aqueous solution was filtered and cooled, and the crystals of

5a,b precipitated. The yield of **5a** was 1.71 g (60%), m.p. 294—296 °C. Found (%): C, 50.32; H, 2.57; N, 5.05; S, 11.03. $C_{12}H_8KNO_3S$. Calculated (%): C, 50.51; H, 2.83; N, 4.91; S, 11.24. ^{1}H NMR (DMSO-d_6), δ: 2.34 (s, Me); 7.16—7.41 (m, Ph). ^{13}C NMR (DMSO-d_6), δ: 30.8 (Me); 113.8 (N—C=S); 127.7, 128.2, 129.5, 134.7, 163.1, 175.2, 190.3, 197.7 (Me<u>C</u>O). IR, ν/cm^{-1}: 3000 (Ph); 1730 (C=O); 1680 (C=O); 1620 (C=O); 1570, 1520, 1460, 1410, 1370. Yield **5b** 1.84 g (53%), m.p. 290—293 °C. Found (%): C, 59.02; H, 3.11; N, 3.92; S, 9.01. $C_{17}H_{10}KNO_3S$. Calculated (%): C, 58.77; H, 2.90; N, 4.03; S, 9.23. ^{1}H NMR (DMSO-d_6), δ: 7.24—7.63 (m, 2 Ph). ^{13}C NMR (DMSO-d_6), δ: 113.1 (N—C=S); 127.3, 129.0, 129.2, 129.5, 130.6, 135.0, 140.7, 163.4, 173.1, 189.3, 197.3 (Ph—<u>C</u>O). IR, ν/cm^{-1}: 3100 (Ph); 1740 (C=O); 1670 (C=O); 1610 (C=O); 1510, 1460, 1440.

4-Acetyl-5-thioxo-1-phenylpyrrolidine-2,3-dione (6a) and 4-benzoyl-5-thioxo-1-phenylpyrrolidine-2,3-dione (6b). 10% HCl (2 mL) was added dropwise to a solution of potassium thiolate **5a** or **5b** (5 mmol) in 8 mL of hot water. The precipitate that formed was filtered off and dried. The yield of **6a** was 1.12 g (91%), m.p. 180—182 °C. Found (%): C, 58.02; H, 3.46; N, 5.77; S, 13.04. $C_{12}H_9NO_3S$. Calculated (%): C, 58.29; H, 3.67; N, 5.66; S, 12.97. ^{1}H NMR ($CDCl_3$), δ: 2.72 (s, Me); 7.26—7.52 (m, Ph); 14.62 (s, OH). IR, ν/cm^{-1}: 3100 (Ph); 2600 (SH); 1790 (C=O); 1740 (C=O); 1600 (C=O); 1510, 1460, 1400, 1370. The yield of **6b** was 1.44 g (93%), m.p. 213—215 °C (*cf.* Ref. 6: 215 °C). Found (%): C, 65.90; H, 3.44; N, 4.78; S, 10.54. $C_{17}H_{11}NO_3S$. Calculated (%): C, 66.01; H, 3.58; N, 4.53; S, 10.36. The ^{1}H NMR and IR spectra of **6b** corresponded to those reported previously.[6] ^{13}C NMR (DMSO-d_6), δ: 114.0 (N—C=S); 127.9, 128.5, 129.3, 132.4, 134.0, 138.2, 164.2, 165.1, 188.4, 198.1 (Ph—<u>C</u>O).

Recyclisation of 4-acetyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (3a) and 2-acetonylidene-3-phenyl-1,3-thiazolidine-4,5-dione (4a) to potassium 4-acetyl-2,3-dioxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-5-thiolate (5a). A suspension of thiophene-2,3-dione **3a** (or 1,3-thiazolidine-4,5-dione (**4a**)) (5 mmol) and freshly calcined K_2CO_3 (1.38 g, 10 mmol) in 6 mL of acetone was stirred for 3 h at 20 °C. The precipitate was filtered off and dissolved in 8 mL of hot water, and the solution was filtered and cooled, resulting in crystallization of **5a**, yield 1.21 g, 85% (1.05 g, 74%).

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