Chemistry of Heterocyclic Compounds, Vol. 46, No. 4, 2010

SYNTHESIS OF NITROPHENYL-SUBSTITUTED 1,3-THIAZOLINE-2-THIONES BY OXIRANE RING OPENING WITH SEVERAL DITHIOCARBAMATES

I. V. Kulakov[1]*, A. M. Gazaliev[1], O. A. Nurkenov[1], and D. M. Turdybekov[2]

Thiazolo-2(3H)-thiones have been prepared by the reaction of triethylamine dithiocarbamates and 4-nitrophenyloxirane via formation of intermediate 2-hydroxy-2-(4-nitrophenyl)ethyldithiocarbamates with simultaneous dehydrogenation of the thiazolidine ring to a thiazoline. It was found that both the basicity of the starting amines and the temperature influenced the course of the reaction.

Keywords: 2-(4-nitrophenyl)oxirane, carbon disulfide, thiazole-2(3H)-thione, intramolecular heterocyclization, X-ray structural analysis.

We have previously [1] reported the opening of a 4-nitrophenyloxirane ring by triethylammonium benzyldithiocarbamate which is accompanied not only by intermediate cyclization to a thiazolidinethione but also to its subsequent oxidative aromatization giving 3-benzyl-5-(4-nitrophenyl)thiazole-2(3H)-thione. It was also found that the process of oxidative dehydrogenation of the thiazolidine ring to a thiazoline is due to the presence of a nitro group in the starting compound. This was proved by the addition of nitrobenzene which led to an increase in the yield of the target compound as well as to the discovery of aniline (the reduction product of nitrobenzene) in the reaction mixture.

For further synthesis of novel thiazolidinethiones from the corresponding dithiocarbamates and oxirane and also the possibility of establishing the reaction mechanism we carried it out for a series of examples involving triethylammonium dithiocarbamates which had been obtained from amines of different basicity (N-aminomorpholine, 4-chlorobenzylamine, and 3-(2-methylpiperidin-1-yl)propan-1-amine). The reaction was also performed in alcohol with an equimolar ratio of reagents at different temperatures with the participation of nitrobenzene as oxidant.

It was found that, for example, triethylamine 3-(2-methylpiperidin-1-yl)propyldithiocarbamate reacts with oxirane **1** according to the previously reported scheme [1] via route II to form the corresponding 1,3-thiazoline-2-thione **2** whose structure was unambiguously proved by X-ray structural analysis.

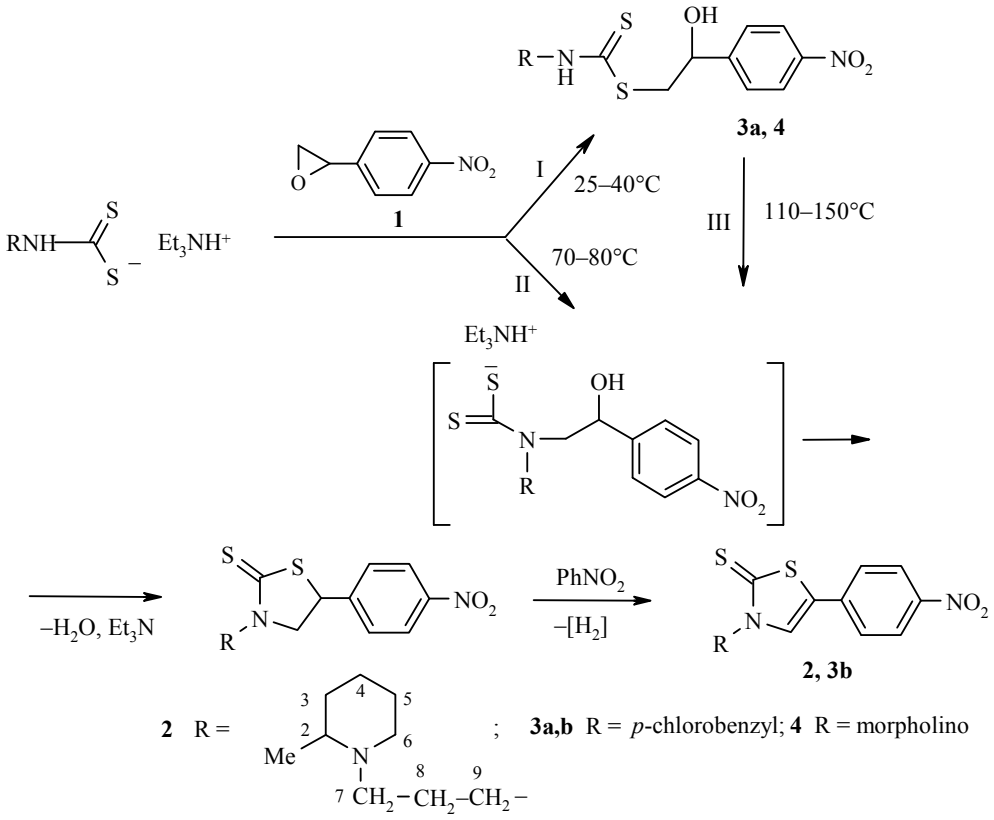
Both under mild conditions (room temperature) and also when heating the reaction mixture to 80ºC, triethylamine N-aminomorpholinodithiocarbamate reacts with oxirane **1** *via* route I to form just the product of

* To whom correspondence should be addressed, e-mail: kulakov_iv@mail.ru.

[1]Institute of Organic Synthesis and Coal Chemistry of Kazahstan Republic, Karaganda 100008, Kazakhstan Republic.
[2]International Scientific and Production Holding, "Phytochemistry", Karaganda 100009, Kazakhstan Republic.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 618-623, April 2010. Original article submitted October 30, 2009.

S-nucleophilic opening of the oxirane ring by the dithiocarbamate fragment, i.e. 2-hydroxy-N-morpholino-2-(4-nitrophenyl)ethyldithiocarbamate (**4**). Its structure was proved by X-ray analysis. The cyclization process did not occur in this case.



4-Chlorobenzylamine, differing from benzylamine in slightly lower basicity, forms triethylamine 4-chlorobenzyldithiocarbamate. Under mild conditions (room temperature) it also forms the product of nucleophilic opening of the oxirane ring by the dithiocarbamate fragment, i.e. N-(4-chlorobenzyl)-2-hydroxy-2-(4-nitrophenyl)ethyldithiocarbamate (**3a**) *via* route I. However, analysis of the ^{1}H NMR spectrum of the twice recrystallized compound **3a** showed the presence of a small aromatic proton singlet from a thiazoline ring which indicated the formation of ~ 4% of an admixture of the cyclization product 3-(4-chlorobenzyl)-5-(4-nitrophenyl)thiazole-2(3H)-thione (**3b**). This gave us the grounds to propose that the cyclization process to

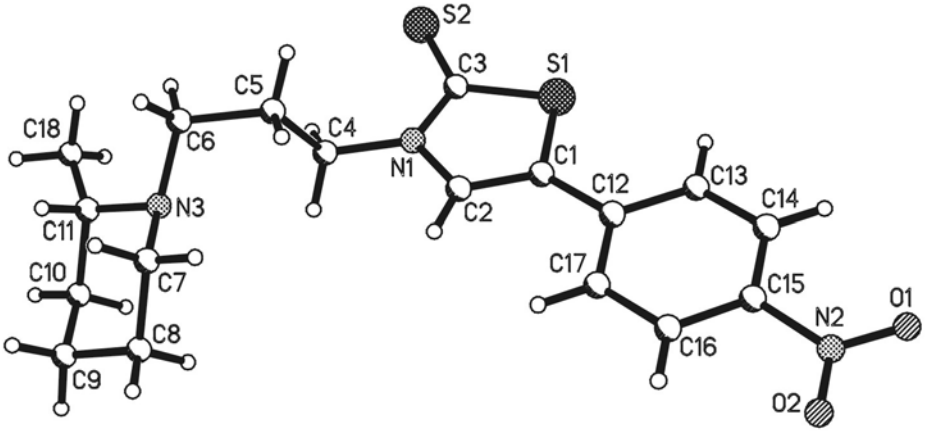


Fig. 1. Structure of the 3-[3-(2-methylpiperidino)propyl]-5-(4-nitrophenyl)thiazole-2(3H)-thione molecule (**2**).

compound **3b** can occur either by S → N rearrangement of compound **3a** *via* route III in the reaction scheme or through an initial process of opening the oxirane ring by the N-nucleophile of the amine fragment of the triethylamine 4-chlorobenzyldithiocarbamate and cyclization to compound **3b** by route II. Attempts to carry out a possible cyclization starting with reaction of compound **3a** or with 2-hydroxy-N-morpholino-2-(4-nitrophenyl)ethyldithiocarbamate (**4**) by heating in different high boiling solvents (toluene, xylene, nitrobenzene) did not give the expected cyclization product. In this connection we have considered the probable process to be opening of the oxirane ring by the N-nucleophile fragment of the starting triethylamine 4-chloro-benzyldithiocarbamate. Hence the basic reaction product when it is carried out in refluxing 2-propanol solution is the cyclic 1,3-thiazoline-2-thione **3b**.

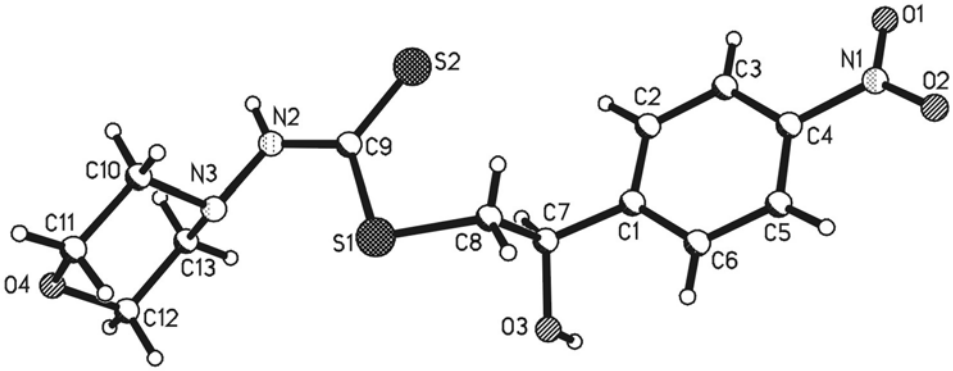


Fig. 2. Structure of the 2-hydroxy-N-morpholino-2-(4-nitrophenyl)ethyldithiocarbamate (**4**) molecule.

Hence the reaction described of triethylamine dithiocarbamates with oxirane **1** is affected by the basicity of the starting primary amine (more basic amines form dithiocarbamates most reactive for N-nucleo-philic attack and those less basic giving only the product of S-nucleophilic attack). It is also under thermo-dynamic control: under mild conditions the main product is that of S-nucleophilic opening of the oxirane ring and at high temperatures there occurs an N-nucleophilic opening of the oxirane by the amine fragment with subsequent cyclization and aromatization to the corresponding 1,3-thiazoline-2-thione.

It should be noted that the reversed order of carrying out this reaction, i.e. opening of the oxirane ring by the corresponding amine and then reaction of the aminoalcohol obtained with carbon disulfide does not occur with the cyclization reported above.

EXPERIMENTAL

IR spectra were obtained on an AVATAR-320 spectrometer for KBr tablets. ^{1}H NMR Spectra were recorded on a Bruker DRX 500 (500 MHz) spectrometer using DMSO-d_6 with TMS as internal standard. Mass spectra (EI) were registered on a Finnigan MAT Incos 50 instrument with direct introduction of the sample into the ion source and an ionization energy of 70 eV.

X-ray structural experiment 1. The unit cell parameters and intensities of 4367 independent reflections for compound **2** were measured at 24ºC on a Bruker APEX-II CCD four circle automatic diffractometer with graphite monochromator and using MoKα radiation (θ/2θ scanning, 2θ < 50º). The yellow-colored crystals (0.03×0.11×0.55 mm) are triclinic, a = 7.284(2), b = 7.539(2), c = 18.523(6) Å, α = 89.441(13)º, β = 79.414(12)º, γ = 73.770(12)º, V = 959.0(5) Å^3, d_{calc} = 1.307 g/cm^3, Z = 2 ($C_{18}H_{23}N_3O_2S_2$). Space group $P\bar{1}$.

1943 reflections with intensity $I > 2\sigma(I)$ were used in the calculations. The structure was solved by a direct method using the SHELXS-93 program package [2] and refined in full matrix least squares analysis in the anisotropic approximation for non hydrogen atoms. H atoms were fixed geometrically and located using the "riding" method, the final difference factors being $R = 0.0723$ and $wR_2 = 0.1711$. Refinement of the geometry was carried out using the SHELXL-97 program [2]. The data for the structure was placed in the Cambridge structural database (CCDC 751926).

X-ray structural experiment 2. The unit cell parameters and intensities of 3914 independent reflections for compound **4** were measured at 20ºC on a Bruker P4 four circle automatic diffractometer with graphite monochromator and using MoKα radiation (θ/2θ scanning, 2θ < 56º). Crystals are rhombic, $a = 9.033$, $b = 13.824$, $c = 26.020$ Å, $V = 3249.2$ Å^3, $d_{calc} = 1.322$ g/cm^3, Z = 8 ($C_{13}H_{17}N_3O_4S_2$). Space group *Pbca*.

2935 reflections with intensities I > 2σ(*I*) were used in the calculation. The structure was solved by a direct method using the "Sir-2002" program [3] and refined in full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms. H atoms were revealed from electron density difference synthesis. The final difference factors were $R = 0.0386$ and $wR_2 = 0.0980$. Refinement of the geometry was carried out using the SHELXL-97 program [2]. Data for the structure was placed in the Cambridge Structural database (CCDC 751927).

3-(3-(2-Methylpiperidino)propyl)-5-(4-nitrophenyl)thiazole-2(3H)-thione (2). A solution of carbon disulfide (0.55 g, 7.2 mmol) in 2-propanol (10 ml) was added dropwise to a stirring solution of 1-(3-amino-propyl)-2-pipecoline (1.1 g, 7.0 mmol) and triethylamine (0.73 g, 7.2 mmol) in 2-propanol (10 ml) cooled to 0-5ºC and stirred for ~ 2 h. (4-Nitrophenyl)oxirane (1.15 g, 7.0 mmol) and nitrobenzene (1.23 g, 10 mmol) were added at room temperature, stirring was continued for ~ 6 h at this temperature, and the product was cooled. The precipitate was filtered off and washed several times with cold 2-propanol. Yield of compound **2** 1.08 g (41%) as bright-gold flaked crystals with mp 170-171ºC (2-propanol). Yellow needles for X-ray analysis were obtained by slow evaporation of the mother liquor of compound **2** after it was recrystallized from 2-propanol. IR spectrum, ν, cm^{-1}: 1595 (–C=S), 1518, 1339 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 (3H, d, $J = 6.3$, CH_3); 1.15-1.56 (6H, m, H-3,4,5 R substituent); 1.95 (2H, m, H-8 R substituent); 2.04 (1H, m, H-2 R substituent); 2.26 (2H, m, H-6 R substituent); 2.73 (2H, m, H-7 R substituent); 4.18 (2H, m, H-9 R substituent); 7.75 (2H, d, $J = 8.9$, 2H *m*-Ar); 8.28 (2H, d, $J = 8.9$, 2H *o*-Ar); 8.45 (1H, s, NCH). Mass spectrum, *m/z* (I_{rel}, %): 377 $[M]^+$ (5.41), 344 (17.9), 279 (36.9), 278 (33.5), 233 (20.2), 138 (67) 124 (52), 112 (82.9), 98 (44.7), 97 (41.7), 56 (49.6), 55 (88.2), 44 (40.9), 42 (63.8), 41 (100). Found, %: C 57.71; H 6.46; N 11.44. $C_{18}H_{23}N_3O_2S_2$. Calculated, %: C 57.27; H 6.14; N 11.13.

N-**4-Chlorobenzyl-2-hydroxy-2-(4-nitrophenyl)ethyldithiocarbamate (3a)**. A solution of carbon disulfide (1.60 g, 0.021 mol) in 2-propanol (10 ml) was added dropwise with stirring to a solution of 4-chloro-benzylamine (2.83 g, 0.02 mol) and triethylamine (2.12 g, 0.021 mol) in 2-propanol (15 ml) cooled to 0-5ºC. The product was stirred for ~ 2 h and (4-nitrophenyl)oxirane (3.30 g, 0.02 mol) and nitrobenzene (2.46 g, 0.02 mol) were added at room temperature gradually increasing the heating to 35-40ºC. After 5-7 h the solution with a yellow precipitate was cooled. Yield of compound **3a** 5.51 g (72%) as fine, yellow crystals with mp 143-145ºC (from 2-propanol). IR spectrum, ν, cm^{-1}: 3329 (OH), 1597 (C=S), 1526, 1343 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.41 (1H, dd, $J = 7.9$ and 13.6, SCH_a); 3.67 (1H, dd, $J = 4.3$ and 13.6, SCH_b); 4.81 (2H, br. d, $J = 5.0$, NCH_2); 4.95 (1H, m, C<u>H</u>(OH)); 6.06 (1H, d, $J = 4.7$, OH); 7.28 (2H, d, $J = 8.4$, Ar); 7.39 (2H, d, $J = 8.4$, Ar[Cl]); 7.69 (2H, d, $J = 8.7$, Ar); 8.22 (2H, d, $J = 8.7$, $ArNO_2$); 10.49 (1H, br. t, $J = 5.47$, NH). Found, %: C 50.53; H 4.31; N 7.74. $C_{16}H_{15}ClN_2O_3S_2$. Calculated, %: C 50.19; H 3.95. N 7.32.

3-(4-Chlorobenzyl)-5-(4-nitrophenyl)thiazole-2(3H)-thione (3b) was prepared similarly to compound **2** from 4-chlorobenzylamine (1.42 g, 0.01 mol), triethylamine (1.11 g, 0.011 mol), carbon disulfide (0.83 g, 0.011 mol), (4-nitrophenyl)oxirane (1.65 g, 0.01 mol), and nitrobenzene (1.23 g, 0.01 mol) but with the addition of the oxirane at a temperature of 75-80ºC in the final reaction stage. Yield of compound **3b** 1.70 g (47%) as bright-yellow, needle like crystals with mp 189-190ºC (ethanol). IR spectrum, ν, cm^{-1}: 1592 (C=S), 1515, 1343

(NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.42 (2H, s, CH_2); 7.46 (4H, s, Ar[Cl]); 7.76 (2H, d, *J* = 8.9, Ar); 8.27 (2H, d, *J* = 8.9, $ArNO_2$); 8.56 (1H, s, NCH). Mass spectrum, *m/z* (I_{rel}, %): 362 $[M]^+$ (1.7), 127 (34.3), 125 (100), 89 (38.6), 63 (16.2). Found, %: C 53.37; H 3.39; N 8.09. $C_{16}H_{11}ClN_2O_2S_2$. Calculated, %: C 52.96; H 3.06; N 7.72.

N-Morpholino-2-hydroxy-2-(4-nitrophenyl)ethyldithiocarbamate (4) was prepared by analogy with compound **3a** from 4-aminomorpholine (1.02 g, 0.01 mol), triethylamine (1.11 g, 0.011 mol), carbon disulfide (0.83 g, 0.011 mol), (4-nitrophenyl)oxirane (1.65 g, 0.01 mol), and nitrobenzene (1.23 g, 0.01 mol). Yield of compound **4** 2.30 g (67%) as light beige, needle like crystals with mp 177-178ºC (ethanol). Crystals for X-ray analysis were grown by slow evaporation of a solution of compound **4** in ethanol. IR Spectrum, ν, cm^{-1}: 3349 (OH), 1601 (-C=S), 1521, 1347 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.79 (4H, br s, $N(CH_2)_2$); 3.17 (1H, dd, *J* = 8.7 and 13.6, SCH_a); 3.58 (1H, dd, *J* = 3.8 and 13.6, SCH_b); 3.70 (4H, br. s, $O(CH_2)_2$); 4.94 (1H, m, C<u>H</u>(OH); 5.93 (1H, d, *J* = 5.1, OH); 7.70 (2H, d, *J* = 8.7, Ar); 8.22 (2H, d, *J* = 8.8, $ArNO_2$); 11.02 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 242 (8), 178 (26), 153(59), 151 (90), 106 (55), 86 (92), 59 (88), 42 (100). Found, %: C 45.81; H 5.27; N 12.53. $C_{13}H_{17}N_3O_4S_2$. Calculated, %: C 45.47; H 4.99; N 12.24.

This work was carried out with the financial support of the General Fund from the First President of the Kazakhstan Republic (grant No. 112-09).

REFERENCES

1. I. V. Kulakov, G. M. Isabaeva, O. A. Nurkenov, and S. D. Fazylov, *Khim. Geterotsikl. Soedin.*, 631 (2009). [*Chem. Heterocycl. Comp.*, **45**, 498 (2009)].
2. G. M. Sheldrick, SHELXL-97. Crystal Structure Refinement dos/win95/nt version +1993-97, Release 97-2.
3. M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, and R. Spagna, SIR2002*:* the program, *J. Appl. Crystallogr.*, **36**, 1103 (2003).