

## Synthesis of 2-(2-R<sup>1</sup>-Hydrazino)-5-(R<sup>2</sup>-benzyl)-2-thiazolines on the Basis of Meerweins Arylation Products of Allyl Isothiocyanate

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**Abstract:** 3-Aryl-2-chloropropylisothiocyanates (**1**) are formed by interaction of arene-diazonium chlorides with allyl isothiocyanate. Adducts **1** react with monoacylhydrazines to form 1-acyl-4-(3-aryl-2-chloropropyl)thiosemicarbazides (**2a–d**). Thiosemicarbazides **2a–d** in the presence of bases selectively transform into 2-(2-R<sup>1</sup>-hydrazino)-5-(R<sup>2</sup>-benzyl)-2-thiazolines (**3a–d**).

**Keywords:** Arylation, allyl isothiocyanate, thiosemicarbazides, 2-thiazolines, cyclizations.

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### Introduction

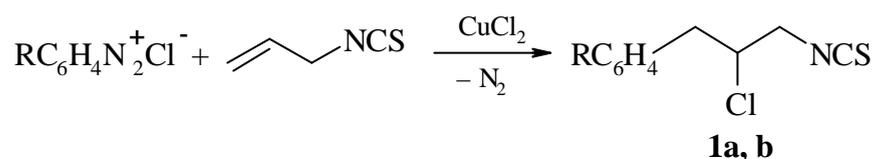
There are different approaches to the synthesis of 2-thiazoline derivatives [1, 2]. One of the most convenient methods is cyclization of compounds containing the CH(X)CH<sub>2</sub>NHC(S) fragment that take place when they are heated or when they are subjected to base-catalysis. Another well-known method involves an addition of an electrophilic reagent to the double bond of the allylic fragment of the thiourea or a related compound.

To obtain five- or six-membered heterocycles, allyl isothiocyanate or its dibromo-derivative [3] were used as starting materials. We now offer a new approach to the synthesis of such compounds by the use of chloro- or bromoarylation products of allyl isothiocyanate in reaction with arenediazonium halides. Taking into account that Ar and Hal add to the double bond as the result of catalytic dediazonation of arenediazonium halides in the presence of unsaturated compounds [4], we used this approach with allyl isothiocyanate to obtain suitable reagents for the synthesis of 2-thiazolines [5, 6].

## Results and Discussion

It had been shown before that allyl isothiocyanate takes part in a catalytic reaction with arenediazonium chlorides [4, 5]. The result is formation of the addition products of an aryl group and a chlorine atom to the C=C double bond (Meerwein reaction).

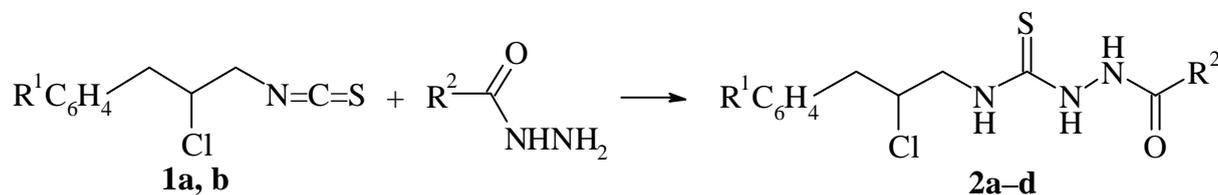
**Scheme 1.**



R = H (**1a**) and 3-Cl (**1b**).

Compounds **1a,b** are suitable reagents for obtaining five-membered heterocycles. Specifically, these compounds react with primary and secondary amines to form 1,3-disubstituted thioureas, which were converted to 2-thiazoline-derivatives in the presence of bases [5, 6]. In this work the interaction of chloroarylation products of allyl isothiocyanate **1a,b** with some monoacylhydrazines was investigated. It was shown that the result of this reaction was formation of 1,4-disubstituted thiosemicarbazides **2a-d**.

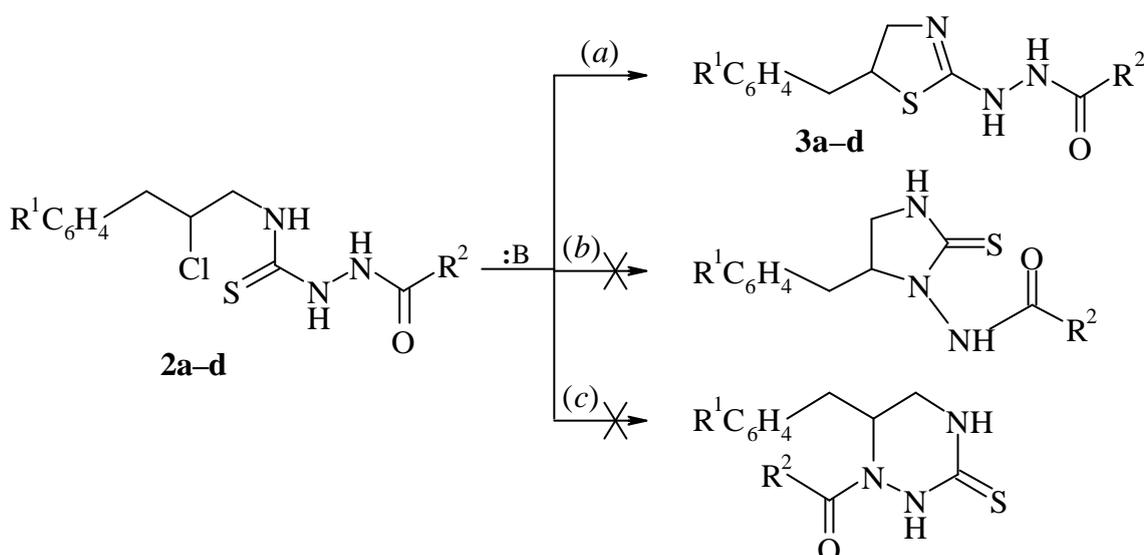
**Scheme 2.**



	<b>2a</b>	<b>2b</b>	<b>2c</b>	<b>2d</b>
R <sup>1</sup>	H	H	3-Cl	3-Cl
R <sup>2</sup>	C <sub>5</sub> H <sub>11</sub>	Ph	C <sub>5</sub> H <sub>11</sub>	Ph

Thiosemicarbazides **2a–d** contain in the side chain the chlorine atom and several other nucleophilic centers. For this reason they can be used for intramolecular cyclisations with subsequent formation of heterocycles. Actually, compounds **2a–d** cyclize in the presence of bases to form 2-thiazoline derivatives **3a–d**, which contain hydrazino groups in the 2 position of the ring (pathway *a*). It has been noted that other variants of this cyclization – formation of imidazolidine-2-thione derivatives (pathway *b*), or hexahydro-1,2,4-thiazine-3-thione derivatives (pathway *c*) do not take place. This may be caused by the high nucleophilicity of the sulfur atom relative to the nitrogen atoms:

Scheme 3.



The heterocyclization reactions of thiosemicarbazides **2a–d** were carried out in acetone, in the presence of organic bases (triethylamine or *N*-methylmorpholine). It is important to note that 2-thiazoline derivatives **3a–d**, which contain the hydrazino group in the 2 position of the ring, are difficult to obtain by other methods. The structure of the synthesized compounds has been confirmed by  $^1\text{H-NMR}$ -spectroscopy. The spectra of the compounds **2a–d** and **3a–d** (see Experimental) contain two ABX spin systems ( $\text{CH}_2\text{CHXCH}_2$ ). It is significant that the chemical shifts of the proton in the  $\text{CHCl}$  group (thiosemicarbazides **2a–d**) and those of the protons in the  $\text{CHS}$  group (thiazolines **3a–d**) differ by  $\sim 0.5$  ppm. The protons of the  $\text{NHC(S)NH}$  fragments in compounds **2a–d** and the  $\text{NHNH}$  in thiazolines **3a–d** do not give sharp signals in the  $^1\text{H-NMR}$  spectra.

## Conclusions

We have presented a facile route for the formation of 1-acyl-4-(3-aryl-2-chloropropyl)-thiosemicarbazides and 2-(2- $\text{R}^1$ -hydrazino)-5-( $\text{R}^2$ -benzyl)-2-thiazolines.

## Experimental

### General

All melting points are uncorrected.  $^1\text{H-NMR}$  spectra were obtained using a Bruker AC-200 spectrometer and were recorded at 200 MHz in DMSO- $d_6$ . Chemical shifts are reported in ppm relative to the residual signal of the solvent. When the signals of the  $\text{CH}_2\text{N}$  or  $\text{CH}_2\text{Ar}$  groups in compounds **2a–d** and **3a–d** were not sharp, coupling constants were not determined. For narrow multiplets the centres of the signals is indicated. The chloroarylation of allyl isothiocyanate was carried by the method described in [4]. The data of 3-phenyl-2-chloropropylisothiocyanate (**1a**) are presented there.

*3-(3-Chlorophenyl)-2-chloropropylisothiocyanate (1b)*; yield 27%, b.p. 108–110°C (0.5 mm),  $n_D^{20}$  1.6066; Found: C, 48.58; H, 3.77; S, 13.25.  $\text{C}_9\text{H}_9\text{Cl}_2\text{NS}$  requires C, 48.79; H, 3.69; S, 13.03%;  $^1\text{H-NMR}$ :  $\delta$  2.98 (dd, 1H,  $\text{CH}_2\text{Ar}$ ,  $J_{13}$  8.0 Hz,  $J_{12}$  14.2 Hz), 3.19 (dd, 1H,  $\text{CH}_2\text{Ar}$ ,  $J_{13}$  5.0 Hz), 3.89 (dd, 1H,  $\text{CH}_2\text{N}$ ,  $J_{13}$  5.8 Hz,  $J_{12}$  15.2 Hz), 4.04 (dd, 2H,  $\text{CH}_2\text{N}$ ,  $J_{13}$  4.0 Hz), 4.53 (m, 1H, CH), 7.20–7.60 (m, 4H,  $\text{C}_6\text{H}_4$ ).

*1-Acyl-4-(3-aryl-2-chloropropyl)thiosemicarbazides (2a–d)*. A mixture of 3-aryl-2-chloropropylisothiocyanate (**1**, 5 mmole) and the corresponding monoacylhydrazine (5 mmole) was boiled in benzene (5 mL) for 1 hour. The precipitates obtained were filtered and recrystallized from the solvent indicated.

*1-Caproyl-4-(3-phenyl-2-chloropropyl)thiosemicarbazide (2a)*; yield 61%, m.p. 170–171°C (from dioxane); Found: C, 56.14; H, 7.22; S, 9.21;  $\text{C}_{16}\text{H}_{24}\text{ClN}_3\text{OS}$  requires C, 56.21; H, 7.08; S, 9.38%;  $^1\text{H-NMR}$ :  $\delta$  0.90 (t, 3H,  $\text{CH}_3$ ), 1.24–1.36 (m, 4H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.50–1.64 (m, 2H,  $\text{CH}_2\text{CH}_2\text{C}=\text{O}$ ), 2.22 (t, 2H,  $\text{CH}_2\text{C}=\text{O}$ ), 3.01 (dd, 1H,  $\text{CH}_2\text{Ar}$ ), 3.17 (dd, 1H,  $\text{CH}_2\text{Ar}$ ), 3.78 (dd, 1H,  $\text{CH}_2\text{N}$ ), 4.03 (dd, 1H,  $\text{CH}_2\text{N}$ ), 4.49 (m, 1H, CH), 7.26 (m, 5H,  $\text{C}_6\text{H}_5$ ), 10.98 (s, 1H,  $\text{NHC}=\text{O}$ ).

*1-Benzoyl-4-(3-phenyl-2-chloropropyl)thiosemicarbazide (2b)*; yield 72%, m.p. 172–173°C (from toluene); Found: C, 58.81; H, 5.32; S, 9.43;  $\text{C}_{17}\text{H}_{18}\text{ClN}_3\text{OS}$  requires C, 58.69; H, 5.21; S, 9.22%;  $^1\text{H-NMR}$ :  $\delta$  3.05 (dd, 1H,  $\text{CH}_2\text{Ar}$ ), 3.19 (dd, 1H,  $\text{CH}_2\text{Ar}$ ), 3.77 (m, 1H,  $\text{CH}_2\text{N}$ ), 4.02 (m, 1H,  $\text{CH}_2\text{N}$ ), 4.50 (m, 1H, CH), 7.04–7.36 (m, 5H,  $\text{C}_6\text{H}_5$ ), 7.44–7.63 (m, 3H,  $\text{C}_6\text{H}_5$ ), 7.98–8.08 (m, 2H,  $\text{C}_6\text{H}_5 - o\text{-H}$ ), 11.69 (s, 1H,  $\text{NHC}=\text{O}$ ).

*1-Caproyl-4-[3-(3-chlorophenyl)-2-chloropropyl]thiosemicarbazide (2c)*; yield 53%, m.p. 161–162°C (from toluene); Found: C, 50.89; H, 6.04; S, 8.64;  $\text{C}_{16}\text{H}_{23}\text{Cl}_2\text{N}_3\text{OS}$  requires C, 51.06; H, 6.16; S, 8.52%;  $^1\text{H-NMR}$ :  $\delta$  0.88 (t, 3H,  $\text{CH}_3$ ), 1.20–1.40 (m, 4H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.48–1.67 (m, 2H,  $\text{CH}_2\text{CH}_2\text{C}=\text{O}$ ), 2.23 (t, 2H,  $\text{CH}_2\text{C}=\text{O}$ ), 3.01 (dd, 1H,  $\text{CH}_2\text{Ar}$ ,  $J_{13}$  8.6 Hz,  $J_{12}$  13.6 Hz), 3.19 (dd, 2H,  $\text{CH}_2\text{Ar}$ ,  $J_{13}$  7.0 Hz), 3.80

(dd, 1H, CH<sub>2</sub>N), 4.06 (dd, 1H, CH<sub>2</sub>N), 4.50 (m, 1H, CH), 7.20–7.45 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 11.00 (s, 1H, NHC=O).

*1-Benzoyl-4-[3-(3-chlorophenyl)-2-chloropropyl]thiosemicarbazide (2d)*; yield 46%, m.p. 188–189°C (from benzene); Found: C, 53.57; H, 4.31; S, 8.23; C<sub>17</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>OS requires C, 53.41; H, 4.48; S, 8.39%; <sup>1</sup>H-NMR: δ 3.09 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 8.0 Hz, J<sub>12</sub> 14.4 Hz), 3.21 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 6.4 Hz), 3.80 (dd, 1H, CH<sub>2</sub>N), 4.04 (dd, 1H, CH<sub>2</sub>N), 4.55 (m, 1H, CH), 7.20–7.40 (m, 4H, Ar), 7.56 (m, 3H, Ar), 8.04 (m, 2H, C<sub>6</sub>H<sub>5</sub> – *o*-H), 11.64 (s, 1H, NHC=O).

*2-(2-Acylhydrazino)-5-benzyl-2-thiazolines (3a–d)*. Triethylamine (or N-methylmorpholine) (5 mmoles) was added to a solution of the corresponding thiosemicarbazide **2a–d** (2 mmoles) in acetone (5 mL) and the mixture was boiled for 30 min. After cooling water (15 mL) was added to the mixture. The precipitate was filtered, air dried and recrystallized from the appropriate solvent.

*2-(2-Caproylhydrazino)-5-benzyl-2-thiazoline (3a)*; yield 86%, m.p. 156–157°C (from benzene – cyclohexane, 3:1); Found: C, 62.80; H, 7.70; S, 10.61; C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>OS requires C, 62.92; H, 7.59; S, 10.50%; <sup>1</sup>H-NMR: δ 0.90 (t, 3H, CH<sub>3</sub>), 1.18–1.38 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.42–1.60 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>C=O), 2.02 (t, 2H, CH<sub>2</sub>C=O), 2.92 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 9.2 Hz, J<sub>12</sub> 14.4 Hz), 3.04 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 6.8 Hz), 3.37 (dd, 1H, CH<sub>2</sub>N, J<sub>13</sub> 6.6 Hz, J<sub>12</sub> 8.0 Hz), 3.62 (dd, 1H, CH<sub>2</sub>N, J<sub>13</sub> 6.4 Hz), 3.94 (m, 1H, CH), 7.19–7.35 (m, 5H, C<sub>6</sub>H<sub>5</sub>).

*2-(2-Benzoylhydrazino)-5-benzyl-2-thiazoline (3b)*; yield 56%, m.p. 143–144°C (from toluene); Found: C, 65.41; H, 5.35; S 10.11; C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>OS requires C, 65.57; H, 5.50; S, 10.30%; <sup>1</sup>H-NMR: δ 2.93 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 8.6 Hz, J<sub>12</sub> 14.0 Hz), 3.06 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 6.0 Hz), 3.40 (dd, 1H, CH<sub>2</sub>N, J<sub>13</sub> 6.4 Hz, J<sub>12</sub> 11.2 Hz), 3.66 (dd, 1H, CH<sub>2</sub>N, J<sub>13</sub> 7.0 Hz), 3.98 (m, 1H, CH), 7.10–7.33 (m, 5H, C<sub>6</sub>H<sub>5</sub>), 7.38–7.48 (m, 3H, C<sub>6</sub>H<sub>5</sub>), 7.77–7.87 (m, 2H, C<sub>6</sub>H<sub>5</sub> – *o*-H).

*2-(2-Caproylhydrazino)-5-(3-chlorobenzyl)-2-thiazoline (3c)*; yield 69%, m.p. 149–150°C (from petroleum ether – benzene, 1:5); Found: C, 56.74; H, 6.68; S, 9.33; C<sub>16</sub>H<sub>22</sub>ClN<sub>3</sub>OS requires C, 56.54; H, 6.52; S, 9.43%; <sup>1</sup>H-NMR: δ 0.89 (t, 3H, CH<sub>3</sub>), 1.21–1.37 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.45–1.60 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>C=O), 2.03 (t, 2H, CH<sub>2</sub>C=O), 2.88 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 8.2 Hz, J<sub>12</sub> 13.6 Hz), 3.05 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 6.4 Hz), 3.38 (dd, 1H, CH<sub>2</sub>N, J<sub>13</sub> 5.4 Hz, J<sub>12</sub> 10.4 Hz), 3.63 (dd, 2H, CH<sub>2</sub>N, J<sub>13</sub> 6.6 Hz), 3.97 (m, 1H, CH), 7.16–7.36 (m, 4H, C<sub>6</sub>H<sub>4</sub>).

*2-(2-Benzoylhydrazino)-5-(3-chlorobenzyl)-2-thiazoline (3d)*; yield 56%, m.p. 176–177°C (from toluene); Found : C, 59.21; H, 4.44; S, 9.37; C<sub>17</sub>H<sub>16</sub>ClN<sub>3</sub>OS requires C, 59.04; H, 4.66; S, 9.27%; <sup>1</sup>H-NMR: δ 2.92 (dd, 1H, CH<sub>2</sub>Ar, J<sub>13</sub> 8.0 Hz, J<sub>12</sub> 14.4 Hz), 3.08 (dd, 2H, CH<sub>2</sub>Ar, J<sub>13</sub> 6.2 Hz), 3.41 (dd,

1H, CH<sub>2</sub>N, J<sub>13</sub> 5.6 Hz, J<sub>12</sub> 10.2 Hz), 3.66 (dd, 1H, CH<sub>2</sub>N, J<sub>13</sub> 5.8 Hz), 4.01 (m, 1H, CH), 7.15–7.50 (m, 7H, Ar), 7.78–7.88 (m, 2H, C<sub>6</sub>H<sub>5</sub> – o-H).

## References and Notes

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*Sample Availability:* Compounds **1-3** are available from the authors.