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Synthesis of 5-Arylsubstituted Thiazol-4-one Acetyl and Amino Derivatives by the Heterocyclization of the Products of Acrylamide Thiocyanatoarylation

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Abstract—The heterocyclization of 2-thiocyanato-3-arylpropionamides in acetic anhydride followed by the deacylation of the intermediates formed in an alkaline medium afforded the otherwise difficultly accessible 2-amino-5-benzylthiazol-4-ones.

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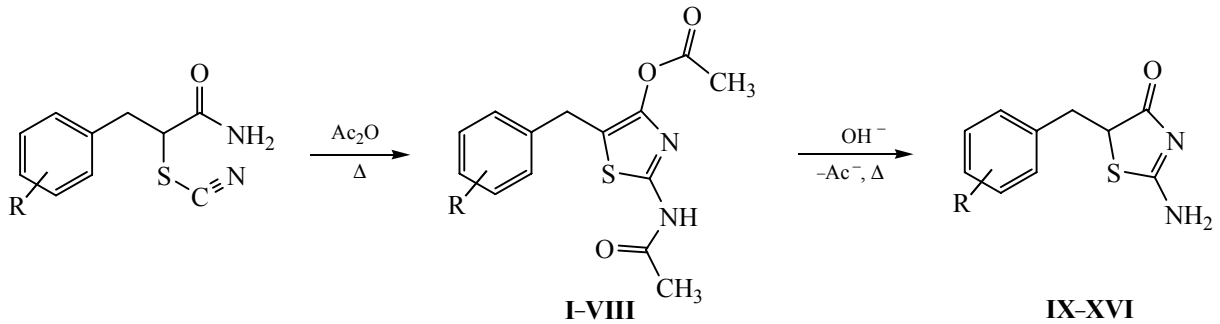
Owing to the presence of the sulfur atom in combination with a nitrile group in the molecule, the organic thiocyanates are widely used in the synthesis of heterocyclic compounds [1]. A convenient method of obtaining such thiocyanates is the anion-arylation of unsaturated compounds with aromatic diazonium salts [2, 3].

Recently the products of acrylonitrile thiocyanatoarylation and allylisothiocyanate chloroarylation were used to obtain some substituted thiazoles [4, 5]. By the example of 2-thiocyanato-2-methyl-3-arylpropanamides, the methacrylamide thiocyanatoarylating products, a possibility was demonstrated of their cyclization to form *N*-(5-benzyl-5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)acetamides. The latter are easily converted into 2-amino-5-benzyl-5-methylthiazol-4-ones in an alkaline medium [6].

Continuing these investigations, in the present work we examined the heterocyclization of acrylamide thiocyanatoarylation products [7] into the thiazol-4-one acetyl and amino derivatives, which are of interest as potential biologically active substances [8, 9].

We found that boiling 2-thiocyanato-3-arylpropanamides in acetic anhydride yielded 2-acetamido-5-benzylthiazol-yl acetates **I**–**VIII**, which transformed readily in an alkaline medium into the 2-amino-5-benzylthiazol-4-ones **IX**–**XVI** as follows:



I–**VIII** **IX**–**XVI**

R = H (**I, IX**), 2-CH_3 (**II, X**), 3-CH_3 (**III, XI**), 4-CH_3 (**IV, XII**), 2-CH_3O (**V, XIII**), 4-CH_3O (**VI, XIV**), 4-Br (**VII, XV**), 2,5-Cl_2 (**VIII, XVI**).

Table 1. Yields, melting points, and elemental analysis data of compounds **I–XVI**

Comp. no.	Yield, %[a]	mp, °C (methanol)	Found, %		Formula	Calculated, %	
			N	S		N	S
I	77	173	9.74	11.22	$C_{14}H_{14}N_2O_3S$	9.65	11.04
II	70	154	9.01	10.43	$C_{15}H_{16}N_2O_3S$	9.20	10.54
III	74	114	9.27	10.65	$C_{15}H_{16}N_2O_3S$	9.20	10.54
IV	85	168	9.09	10.49	$C_{15}H_{16}N_2O_3S$	9.20	10.54
V	65	129	8.59	9.90	$C_{15}H_{16}N_2O_4S$	8.74	10.01
VI	74	156	8.68	10.07	$C_{15}H_{16}N_2O_4S$	8.74	10.01
VII	77	94	7.41	8.80	$C_{14}H_{13}BrN_2O_3S$	7.59	8.68
VIII	82	204	7.86	8.88	$C_{14}H_{12}Cl_2N_2O_3S$	7.80	8.93
IX	–	192	13.64	15.41	$C_{10}H_{10}N_2OS$	13.58	15.55
X	–	218	12.64	14.39	$C_{11}H_{12}N_2OS$	12.72	14.56
XI	–	244	12.81	14.69	$C_{11}H_{12}N_2OS$	12.72	14.56
XII	–	215	12.79	14.45	$C_{11}H_{12}N_2OS$	12.72	14.56
XIII	–	226	11.99	13.70	$C_{11}H_{12}N_2O_2S$	11.86	13.57
XIV	–	245	11.77	13.61	$C_{11}H_{12}N_2O_2S$	11.86	13.57
XV	–	231	9.72	11.06	$C_{10}H_9BrN_2OS$	9.82	11.24
XVI	–	251	10.23	11.84	$C_{10}H_8Cl_2N_2OS$	10.18	11.65

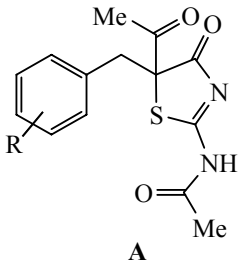
[a] Yields are quantitative for compounds **IX–XVI**.

The yields of derivatives **I–VIII** are 65–85%, and they convert into the 2-aminothiazol-4-ones **IX–XVI** quantitatively. Tables 1, 2 list the yields, melting points, elemental analysis, and ^{1}H NMR spectral data of the synthesized compounds **I–XVI**.

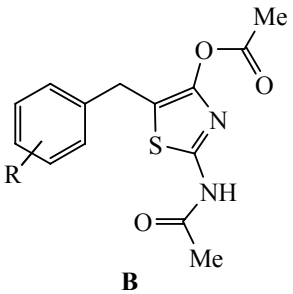
The ^{1}H NMR spectrum of acetamide **I** contains the multiplet signals of phenyl protons at 7.33–7.20 ppm and the singlet signals of the methylene protons of benzyl fragment at 3.88 ppm and the methyl protons of acetyl fragments at 2.27 and 2.09 ppm. The NH-proton of acetamide moiety is shifted downfield to 7.12 ppm. In the spectrum of aminothiazole **IX** there are no signals of the methyl protons of acetyl fragments. The amino protons resonate upfield at 8.85 ppm.

The presence in the ^{1}H NMR spectrum of the cyclization product **I** of a double number of the signals of methyl protons in comparison with the heterocycles based on methacrylamide [7] is due to the fact that it includes two acetyl fragments, one of which forms the acetamide moiety.

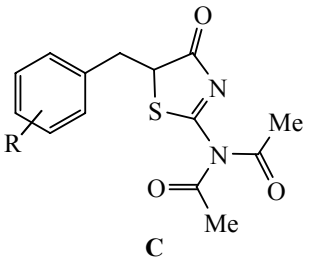
Thus, the cyclization of 2-thiocyanato-3-arylpropanamides can results in the products of different structures containing two acetyl fragments.



A



B



C

To determine the structure of the heterocyclization products we recorded the ^{13}C NMR spectrum of compound **IV** whose analysis allowed us to exclude structure **A.** To choose between structures **B** and **C** we performed a comprehensive analysis of the heteronuclear correlation (HMBC and HMQC) spectra. The

Table 2. ^{1}H NMR spectral parameters of compounds **I–XVI**

Comp. no.	Chemical shift, δ, ppm					
	Ar	N<u>H</u> (N<u>H</u>$_2$)	C<u>H</u>	C(O)C<u>H</u>$_3$	C<u>H</u>$_2$Ar	R
I	7.33–7.20 m (5H)	12.07s	–	2.27 s, 2.09 s	3.88 s	–
II	7.15 s (4H)	12.08 s	–	2.22 s, 2.08 s	3.86 s	2.23 s
III	7.21–6.99 m (4H)	12.06 s	–	2.24 s, 2.10 s	3.85 s	2.22 s
IV	7.09 s (4H)	12.09 s	–	2.25 s, 2.08 s	3.82 s	2.27 s
V	7.31–6.94 m (4H)	12.01 s	–	2.26 s, 2.08 s	3.81 s	3.75 s
VI	7.13 d, 6.86 d (4H)	12.00 s	–	2.27 s, 2.09 s	3.80 s	3.73 s
VII	7.87 d, 7.66 d (4H)	12.11 s	–	2.26 s, 2.10 s	3.87 s	–
VIII	7.56–7.27 m (3H)	12.12 s	–	2.24 s, 2.10 s	4.00 s	–
IX	7.32–7.18 m (5H)	8.85 br.s.	4.58 d.d	–	3.38 d.d, 2.88 d.d	–
X	7.28–7.00 m (4H)	8.99 br.s, 8.75 br.s	4.55 d.d	–	3.46 d.d, 2.81 d.d	2.30 s
XI	7.25–6.97 m (4H)	8.91 br.s	4.54 d.d	–	3.35 d.d, 2.81 d.d	2.27 s
XII	7.21–6.99 m (4H)	8.92 br.s, 8.70 br.s	4.55 d.d	–	3.32 d.d, 2.85 d.d	2.26 s
XIII	7.28–6.89 m (4H)	8.94 br.s, 8.62 br.s	4.57 d.d	–	3.38 d.d, 2.84 d.d	3.75 s
XIV	7.11 d, 6.82 d (4H)	8.88 br.s, 8.65 br.s	4.54 d.d	–	3.37 d.d, 2.91 d.d	3.74 s
XV	7.47 d, 7.19 d (4H)	8.92 br.s, 8.76 br.s	4.59 d.d	–	3.31 d.d, 2.93 d.d	–
XVI	7.67–7.31 m (3H)	8.96 br.s	4.62 d.d	–	3.48 d.d, 3.02 d.d	–

full assignment of the signals to the protons and carbon atoms allowed us to exclude structure **B**. The found correlations are listed in Table 3.

Thus, the heterocyclization of 2-thiocyanato-3-arylpropanamides is accompanied by the acylation at the position 4 of thiazole ring, which is possible due to the migration of the hydrogen atom from the position 5 by the mechanism of keto-enol tautomerization. For this reason the cyclization products **I–VIII** contain two acetyl fragments. Their structures differ from those of the heterocycles derived from 2-thiocyanato-2-methyl-3-arylpropanamides [7] where the hydrogen migration at their formation is impossible owing to the presence of a methyl group in the position 5.

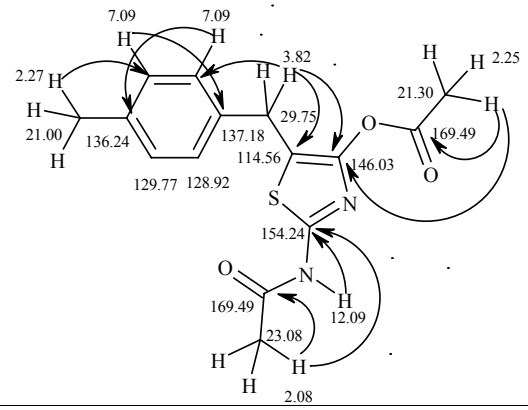
These results confirm the usefulness of the fatty-aromatic α-thiocyanatoamides as convenient synthons for the preparation of difficultly accessible 5-aryl-substituted 2-aminothiazol-4-ones. The latter are of interest for the design of new heterocyclic systems and as biologically active substances of a broad activity range.

EXPERIMENTAL

The IR spectra of compounds **I–XXIV** were recorded on IKS-29 and Specord M80 instruments from mulls in mineral oil. The ^{1}H NMR spectra were obtained on a Varian Mercury instrument (400 MHz) from DMSO-d_6 solutions with external reference TMS. The individuality of the synthesized compounds was established by the TLC on Silufol UV-254 plates eluting with a methanol–acetone mixture (5:2). 2-Thiocyanato-3-arylpropanamides were obtained by the procedure [7].

2-Acetamido-5-benzylthiazol-4-yl acetate (I). A solution of 1.5 g (7.3 mmol) of 2-thiocyanato-3-phenylpropanamide in 20 ml of acetic anhydride was boiled for 4 h, then evaporated in a vacuum to a volume of 5 ml, and cooled. The reaction product was

Table 3. HMBC and HMQC spectral analysis of 2-acetamido-5-(4-methylbenzyl)thiazol-4-yl acetate **IV**



Chemical shift, δ, ppm

^{1}H	^{13}C	
	HMQC	HMBC
2.27	21.00	129.77
7.09	129.77	136.24
7.09	128.92	137.18
3.82	29.75	128.92, 114.56, 146.03
2.25	21.30	169.49
12.09		154.24
2.08	23.08	169.49, 154.24

filtered off and recrystallized from methanol. Yield 1.6 g (77%), mp 173°C.

Compounds **II**–**VIII** were obtained similarly.

2-Amino-5-benzylthiazol-4-one (IX). To a solution of 1 g (3.4 mmol) of 2-acetamido-5-benzylthiazol-4-yl acetate **I** in 15 ml of 96% ethanol was added a solution of 1.8 g (30 mmol) of KOH in 3 ml of water. The mixture was boiled for 2 h, then cooled to room temperature and extracted with 15 ml of diethyl ether. The organic extract was washed with water and dried with $CaCl_2$. The solvent was evaporated in a vacuum, the solid residue was recrystallized from methanol. Yield 0.67 g (95%), mp 192°C.

Compounds **X**–**XVI** were obtained similarly.

REFERENCES

1. Erian, A.W. and Sherif, S.M., *Tetrahedron*, 1999, vol. 55, p. 7957.
2. Grishchuk, B.D., Gorbovoi, P.M., Ganushchak, N.I., and Dombrovskii, A.V., *Usp. Khim.,* 1994, vol. 63, p. 269.
3. Grishchuk, B.D., Gorbovoi, P.M., Baranovskii, V.S., and Ganushchak, N.I., *Zh. Org. Farm. Khim.,* 2008, vol. 6, no. 3(23), p. 16.
4. Obushak, N.D., Matijchuk, V.S., Ganushchak, N.I., and Martyak, R.I., *Khim. Geterotsikl. Soed*., 1997, vol. 33, no. 8, p. 1142.
5. Karpyak, V.V., Obushak, N.D., and Ganushchak, N.I., *Khim. Geterotsikl. Soed*., 1997, vol. 33, no. 9, p. 1278.
6. Baranovskii, V.S., Simchak, R.V., and Grishchuk, B.D., *Zh. Obshch. Khim.*, 2009, vol. 79, no. 2, p. 280.
7. Grishchuk, B.D., Gorbovoi, P.M., and Ganushchak, N.I., *Zh. Obshch. Khim.,* 1993, vol. 63, no. 10, p. 2335.
8. Schneider, G., Steinhilber, D., Franke, L., and Hofmann, B., Patent WO/2009/027077; *http://www.wipo.int/pctdb/en/wo.jsp?WO= 2009027077.*
9. Zalisko, N.I., Atamanyuk, D.V., and Lesik, R.B., *Zh. Org. Farm. Khim.,* 2009, vol. 7, no. 1(25), p. 42.