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Synthesis and Heterocyclization of 3-Aryl-2-methyl-2-thiocyanatopropanamides

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Abstract—Reactions of arenediazonium tetrafluoroborates with methacrylamide in the presence of potassium thiocyanate in aqueous acetone (1:2.5) or aqueous dimethyl sulfoxide (1:4) gave the corresponding 3-aryl-2-methyl-2-thiocyanatopropanamides which underwent heterocyclization in boiling acetic anhydride to produce difficultly accessible 2-(acetyl)amino-5-benzylthiazol-4(5*H*)-ones.

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α,β-Unsaturated carboxylic acid amides exhibit enhanced reactivity due to considerable electron-withdrawing effect of the amide group on the double carbon–carbon bond and are promising substrates in Meerwein reactions and conjugate additions [1–3].

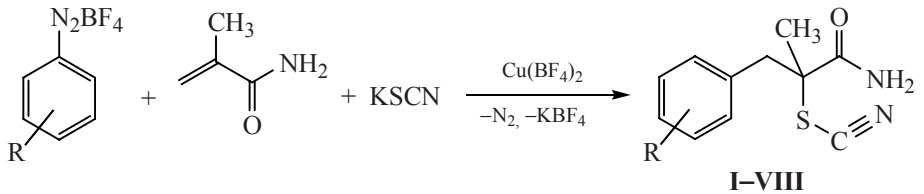
For example, acrylamide reacts with arenediazonium chlorides to give up to 70% of the corresponding 3-aryl-2-chloropropanamides as a result of addition of the aryl radical and chloride ion at the double C=C bond. The adducts undergo dehydrochlorination to arylacrylamides by the action of triethylamine [4].

We previously showed [5] that reactions of arenediazonium tetrafluoroborates with acrylamide in the presence of alkali metal or ammonium thiocyanates involve evolution of nitrogen and lead to the formation of 3-aryl-2-thiocyanatopropanamides. A necessary conditions for the reaction to occur is the presence of copper or iron salt as catalyst.

In continuation of these studies, in the present work we examined for the first time analogous reaction with methacrylamide; the expected adducts attract interest from the viewpoint of their subsequent heterocyclization to thiazol-4-one derivatives [6].

We found that, like acrylamide, methacrylamide reacted with arenediazonium tetrafluoroborates in the presence of thiocyanate ion with evolution of nitrogen to give products of addition of the aryl radical and thiocyanato group at the double C=C bond, 3-aryl-2-methyl-2-thiocyanatopropanamides **I–VIII** (Scheme 1).

Scheme 1.



I–VIII

I, R = H; **II**, R = 2-Me; **III**, R = 3-Me; **IV**, R = 4-Me; **V**, R = 2-MeO; **VI**, R = 4-MrO; **VII**, R = 4-Br; **VIII**, R = 2,5-Cl_2.

The reactions were carried out in aqueous acetone (1:2.5) at –15 to –10°C using potassium thiocyanate and a catalytic amount of copper(II) tetrafluoroborate. The optimal reactant ratio diazonium salt–methacrylamide–potassium thiocyanate–copper(II) tetrafluoroborate was 1.1:1:1.2:0.12, and the yields of compounds **I–VIII** ranged from 59 to 83%. The reaction was accompanied by side formation of up to 10% of

the corresponding aryl thiocyanates and aryl isothiocyanates. The yield of the target products increased (by 5–10%), while the amount of by-products decreased, when the reaction was performed in aqueous dimethyl sulfoxide at –20 to –15°C.

The yields, melting points, elemental analyses, and ^{1}H NMR spectra of 3-aryl-2-methyl-2-thiocyanatopropanamides **I**–**VIII** are given in Tables 1 and 2.

The IR spectra of **I**–**VIII** contained absorption bands belonging to stretching vibrations of the carbonyl, thiocyanato, and amide NH groups in the regions 1716–1728, 2152–2164, and 3412–3424 cm^{-1}, respectively. Compounds **I**–**VIII** displayed in the ^{1}H NMR spectra signals from protons in the aromatic ring (δ 7.5–6.8 ppm, m), methylene groups adjacent to the aromatic fragment (two doublets at δ 3.5–3.3 and 3.2–3.0 ppm, J = 7.4–7.0, 7.8–7.1 Hz, respectively), and methyl group (δ 1.85–1.80 ppm, s).

Thus the reaction with methacrylamide takes a way similar to the reactions of other methacrylic acid

Table 1. Yields, melting points, and elemental analyses of 3-aryl-2-methyl-2-thiocyanatopropanamides **I**–**VIII**, *N*-(5-benzyl-5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)acetamides **IX**–**XVI**, and 2-amino-5-benzyl-5-methylthiazol-4(5*H*)-ones **XVII**–**XXIV**

Compound no.	Yield,[a] %	mp,[b] °C	Found, %		Formula	Calculated, %	
			N	S		N	S
I	85 (77)	123	12.59	14.39	$C_{11}H_{12}N_2OS$	12.72	14.56
II	73 (70)	108	11.91	13.69	$C_{12}H_{14}N_2OS$	11.96	13.68
III	68 (59)	119	11.87	13.61	$C_{12}H_{14}N_2OS$	11.96	13.68
IV	84 (83)	117	11.89	13.61	$C_{12}H_{14}N_2OS$	11.96	13.68
V	71 (64)	138	11.02	12.86	$C_{12}H_{14}N_2O_2S$	11.19	12.81
VI	83 (80)	109	11.24	12.78	$C_{12}H_{14}N_2O_2S$	11.19	12.81
VII	86 (82)	167	9.38	10.66	$C_{11}H_{11}BrN_2OS$	9.36	10.72
VIII	79 (74)	177	9.61	11.02	$C_{11}H_{10}Cl_2N_2OS$	9.69	11.09
IX	80	198	10.49	12.09	$C_{13}H_{14}N_2O_2S$	10.68	12.22
X	65	171	10.19	11.81	$C_{14}H_{16}N_2O_2S$	10.14	11.60
XI	68	162	10.24	11.55	$C_{14}H_{16}N_2O_2S$	10.14	11.60
XII	74	172	10.08	11.66	$C_{14}H_{16}N_2O_2S$	10.14	11.60
XIII	79	165	9.61	11.02	$C_{14}H_{16}N_2O_3S$	9.58	10.97
XIV	67	213	9.72	10.89	$C_{14}H_{16}N_2O_3S$	9.58	10.97
XV	71	184	8.07	9.31	$C_{13}H_{13}BrN_2O_2S$	8.21	9.40
XVI	75	167	8.29	9.73	$C_{13}H_{12}Cl_2N_2O_2S$	8.46	9.68
XVII		225	12.66	14.50	$C_{11}H_{12}N_2OS$	12.72	14.56
XVIII		238	11.88	13.75	$C_{12}H_{14}N_2OS$	11.96	13.68
XIX		247	11.99	13.84	$C_{12}H_{14}N_2OS$	11.96	13.68
XX		253	12.01	13.70	$C_{12}H_{14}N_2OS$	11.96	13.68
XXI		249	11.07	12.69	$C_{12}H_{14}N_2O_2S$	11.19	12.81
XXII		240	11.16	12.93	$C_{12}H_{14}N_2O_2S$	11.19	12.81
XXIII		257	9.40	10.85	$C_{11}H_{11}BrN_2OS$	9.36	10.72
XXIV		260	9.65	11.17	$C_{11}H_{10}Cl_2N_2OS$	9.69	11.09

[a] In parentheses are given the yield of **I**–**VIII** in aqueous acetone. [b] From methanol.

Table 2. ^{1}H NMR spectra of 3-aryl-2-methyl-2-thiocyanatopropanamides **I**–**VIII**, *N*-(5-benzyl-5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)acetamides **IX**–**XVI**, and 2-amino-5-benzyl-5-methylthiazol-4(5*H*)-ones **XVII**–**XXIV**

Comp. no.	Chemical shifts δ, ppm					
	H_{arom}	NH_2 (NH)	CH_3	$C(O)CH_3$	CH_2Ar	R
I	7.38–7.21 m (5H)	8.16 s, 7.89 s	1.83 s	–	3.46 d, 3.10 d	–
II	7.25–7.08 m (4H)	8.03 s, 7.88 s	1.82 s	–	3.38 d, 3.24 d	2.34 s
III	7.24–7.00 m (4H)	8.14 s, 7.90 s	1.81 s	–	3.40 d, 3.04 d	2.28 s
IV	7.21–7.10 m (4H)	8.12 s, 7.86 s	1.81 s	–	3.40 d, 3.04 d	2.27 s
V	7.16–6.82 m (4H)	8.08 s, 7.91 s	1.82 s	–	3.40 d, 3.22 d	3.76 s
VI	7.18–6.86 m (4H)	8.11 s, 7.86 s	1.80 s	–	3.38 d, 3.03 d	3.73 s
VII	7.46–7.18 m (4H)	8.06 s, 7.79 s	1.85 s	–	3.43 d, 3.07 d	–
VIII	7.49–7.28 m (3H)	7.99 s, 7.91 s	1.85 s	–	3.50 d, 3.44 d	–
IX	7.32–7.14 m (5H)	12.48 s	1.51 s	2.11 s	3.06 s	–
X	7.14–7.06 m (4H)	12.50 s	1.56 s	2.10 s	3.10 d.d	2.29 s
XI	7.17–6.95 m (4H)	12.49 s	1.50 s	2.11 s	3.02 s	2.24 s
XII	7.05 s (4H)	12.47 s	1.50 s	2.11 s	3.01 s	2.24 s
XIII	7.25–6.81 m (4H)	12.50 s	1.46 s	2.11 s	3.26 d, 2.88 d	3.76 s
XIV	7.08 d, 6.81 d (4H)	12.46 s	1.50 s	2.11 s	2.99 s	3.70 s
XV	7.45 d, 7.11 d (4H)	12.37 s	1.53 s	2.11 s	3.06 d.d	–
XVI	7.48–7.20 m (3H)	12.62 s	1.57 s	2.12 s	3.36 d, 3.21 d	–
XVII	7.29–7.08 m (5H)	8.67 s	1.52 s	–	3.03 d.d	–
XVIII	7.18–6.99 m (4H)	8.81 s, 8.57 s	1.56 s	–	3.09 d.d	2.29 s
XIX	7.19–6.93 m (4H)	8.82 s, 8.60 s	1.50 s	–	2.98 d.d	2.26 s
XX	7.06 s (4H)	8.75 s, 8.56 s	1.50 s	–	2.97 d.d	2.25 s
XXI	7.21–6.85 m (4H)	8.91 s, 8.62 s	1.46 s	–	3.29 d, 2.86 d	3.78 s
XXII	7.10 d, 6.81 d (4H)	8.84 s, 8.60 s	1.49 s	–	2.96 d.d	3.72 s
XXIII	7.44 d, 7.12 d (4H)	8.81 s, 8.62 s	1.53 s	–	3.02 d.d	–
XXIV	7.52–7.16 m (3H)	8.96 s, 8.69 s	1.58 s	–	3.31 d, 3.18 d	–

derivatives, which is consistent with the mechanism proposed previously [7]. The reactivity of methacrylamide is higher than that of methacrylic acid esters [8], indicating stronger activation of the double C=C bond by amide group as compared to ester. Slightly increased yields of the adducts obtained from methacrylamide relative to acrylamide derivatives [5] may be attributed to more effective stabilization of intermediate fatty–aromatic radical [7].

Molecules **I**–**VIII** contain both thiocyanato and amide groups, and they may be regarded as convenient starting compounds for the synthesis of 5-benzyl-substituted thiazol-4-one derivatives. In fact, heating of 3-aryl-2-methyl-2-thiocyanatopropanamides **I**–**VIII** in boiling acetic anhydride promoted their intramolecular cyclization with formation of *N*-(5-benzyl-5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)acetamides **IX**–**XVI** which readily underwent alkaline hydrolysis to give 2-amino-

5-benzyl-5-methylthiazol-4(5*H*)-ones **XVII**–**XXIV** (Scheme 2).

The yields of *N*-(5-benzil-5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)acetamides **IX**–**XVI** were 65–80%, and their transformation into aminothiazoles **XVII**–**XXIV** was quantitative. The yields, melting points, elemental analyses, and ^{1}H NMR spectra of compounds **IX**–**XXIV** are collected in Tables 1 and 2.

In the IR spectra of **IX**–**XVI** we observed absorption bands due to stretching vibrations of two carbonyl groups (1690–1740 cm^{-1}); unlike initial 3-aryl-2-methyl-2-thiocyanatopropanamides **I**–**VIII**, no band typical of thiocyanato group (2152–2164 cm^{-1}) was present. The ^{1}H NMR spectra of **IX**–**XVI** contained signals from aromatic protons in the region δ 7.48–6.81 ppm (as multiplets for unsymmetrical substitution in the benzene ring or as singlets or doublets for *para*-substitution). Protons in the methyl and NH groups of the acetamide fragment resonated as singlets at δ 2.12–2.10 and 12.62–12.37 ppm, respectively. The 5-methyl group gave a singlet at δ 1.575–1.46 ppm, and signals from methylene protons in the benzyl fragments appeared as singlets or doublets in the region δ 3.36–2.88 ppm.

Thus 3-aryl-2-methyl-2-thiocyanatopropanamides **I**–**VIII** are convenient starting compounds for the synthesis of difficultly accessible 5-benzylthiazol-4(5*H*)-ones which attract interest as potential biologically active substances [9, 10].

EXPERIMENTAL

The IR spectra were recorded on IKS-29 and Specord M80 spectrometers from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured from solutions in DMSO-d_6 on a Varian Mercury instrument (400 MHz) using tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using methanol–acetone (5 : 2) as eluent.

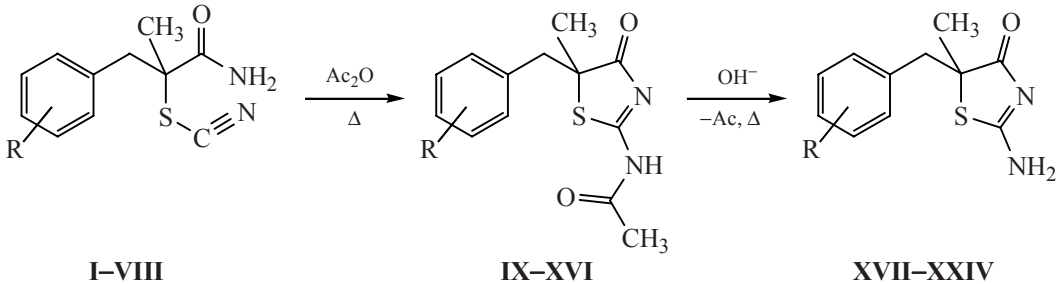
2-Methyl-3-phenyl-2-thiocyanatopropanamide (I). Benzenediazonium tetrafluoroborate, 20 g, was added in portions over a period of 1 h to a mixture of 6.8 g of methacrylamide, 2.8 g of copper(II) tetrafluoroborate hexahydrate, and 11.7 g of potassium thiocyanate in 250 ml of a 1 : 4 water–DMSO mixture under stirring at –20°C. When nitrogen no longer evolved (1.5 h), the mixture was diluted with 150 ml of water and extracted with diethyl ether (200 ml). The extract was washed with water, dried over anhydrous calcium chloride, and evaporated, and the solid residue was recrystallized from methanol. Yield 14.9 g (85%). The reaction in aqueous acetone (1 : 2.5) was performed in a similar way. Following an analogous procedure, we obtained compounds **II**–**VIII**.

***N*-(5-Benzyl-5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)acetamide (IX).** A solution of 2 g of compound **I** in 15 ml of acetic anhydride was heated for 6 h under reflux. The mixture was concentrated under reduced pressure to a volume of 5 ml and cooled to –20°S, and the colorless crystals were filtered off and purified by recrystallization from methanol. Yield 1.9 g (80%).

Compounds **X**–**XVI** were synthesized in a similar way.

2-Amino-5-benzyl-5-methylthiazol-4(5*H*)-one (XVII). Compound **IX**, 1.5 g, was dissolved in 8 ml of ethanol, a solution of 0.9 g of potassium hydroxide in 1.5 ml of water was added, and the mixture was heated for 4 h under reflux. The mixture was cooled and extracted with 15 ml of diethyl ether. The extract was washed with water, dried over anhydrous calcium

Scheme 2.



I–VIII **IX–XVI** **XVII–XXIV**

IX, **XVII**, R = H; **X**, **XVIII**, R = 2-Me; **XI**, **XIX**, R = 3-Me; **XII**, **XX**, R = 4-Me; **XIII**, **XXI**, R = 2-MeO; **XIV**, **XXII**, R = 4-MrO; **XV**, **XXIII**, R = 4-Br; **XVI**, **XXIV**, R = 2,5-Cl_2.

chloride, and evaporated, and the residue was recrystallized from methanol. Yield 1.35 g (96%).

Compounds **XVIII**–**XXIV** were synthesized in a similar way.

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REFERENCES

1. Dombrovskii, A.V., *Usp. Khim*., 1984, vol. 53, no. 10, p. 1625.
2. Grishchuk, B.D., Gorbovoi, P.M., Ganushchak, N.I., and Dombrovskii, A.V., *Usp. Khim*., 1994, vol. 63, no. 3, p. 269.
3. Grishchuk, B.D., Gorbovoi, P.M., and Baranovskii, V.S., Abstracts of Papers, *XXI Ukrainskaya konferentsiya po organicheskoi khimii* (XXIst Ukrainian Conf. on Organic Chemistry), Chernigov, 2007, p. 29.
4. Shkol'nik, Ya.S., Dombrovskii, A.V., and Rogovik, L.I., *Zh. Org. Khim*., 1967, vol. 4, no. 2, p. 229.
5. Grishchuk, B.D., Gorbovoi, P.M., Ganushchak, N.I., and Kudrik, E.Ya., *Zh. Obshch. Khim*., 1993, vol. 63, no. 10, p. 1620.
6. Zimmermann, T., Fischer, G.W., and Oik, B., *J. Prakt. Chem*., 1990, vol. 332, no. 4, p. 540.
7. Grishchuk, B.D., Gorbovoi, P.M., Baranovskii, V.S., and Ganushchak, N.I., Abstracts of Papers, *6 Rossiiskaya konferentsiya "Mekhanizmy kataliticheskikh reaktsii"* (6th Russian Conf. "Mechanisms of Catalytic Reactions"), Moscow, 2002, vol. 2, p. 105.
8. Grishchuk, B.D., Gorbovoi, P.M., and Ganushchak, N.I., *Zh. Obshch. Khim*., 1989, vol. 59, no. 5, p. 1969.
9. Hui-Ling Liu, Zong-cheng Li, and Anthonsen, T., *Molecules*, 2000, vol. 5, no. 9, p. 1055.
10. Vicini, P., Geronikaki, A., Anastasia, K., Incerti, M., and Zani, F., *Bioorg. Med. Chem*., 2006, vol. 4, no. 11, p. 3859.