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REACTION OF 2-ARYLHYDRAZONO-2-CYANO-N-CYCLOHEXYLTHIOACETAMIDES WITH HALOCARBONYL COMPOUNDS

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The reaction of arylhydrazonocyanothioacetamides containing an N-cyclohexyl fragment with chloroacetone, phenacyl bromide, ethyl chloroacetate, and chloroacetonitrile was investigated. It was shown that a substituent with a large steric effect in the thioamide group alters the direction of intramolecular cyclization of the thioimidate intermediate. In contrast to the Hantsch reaction, which usually leads to the formation of thiazoles under these conditions, the only products are 3-amino-4-arylhydrazono-4,5-dihydrothiophenes.

Keywords: arylhydrazonothioacetamides, halocarbonyl compounds, thiazoles, thioamide group, thioimidates, thiophenes, alkylation, cyclization.

Unsubstituted thioamides react with biselectrophiles with the participation of the nitrogen and sulfur atoms [1-3]. When α-halocarbonyl derivatives are used in this reaction a thiazole ring is formed (the Hantsch reaction). Arylhydrazonothioacetamides are not an exception in this respect and, as shown by our investigations [4, 5], readily give high yields of 1,3-thiazoles in reaction with halo ketones. However, the introduction of a phenyl group at the nitrogen atom of the thiocarbamoyl radical leads to the result that, depending on the substituent in the aromatic ring and also on the structure of the halo ketone, the products of this reaction may also include 4,5-dihydrothiophenes in addition to the 3H-thiazol-2-ylidenes [5]. On the basis of the electronic effects of the cyclohexyl group the exclusive formation of (3H-thiazol-2-ylidene)arylazoacetonitriles **3** could be expected for 2-arylhydrazono-2-cyano-N-cyclohexylthioacetamides **1** in reaction with the halocarbonyl compounds **2** (scheme 1). However, in the case of the reaction of 2-cyano-2-[(4-methoxyphenyl)hydrazono]-N-cyclohexylthioacetamide **1a** with chloroacetone **2a** we showed in a brief communication [6] that the reaction product was 4,5-dihydrothiophene (**4a**) [6]. The aim of the present work was to make a more detailed study of the effect of the substituent in the aromatic ring of the initial hydrazono derivatives **1a-d** and the structure of the halocarbonyl reagent **2a-d** on the direction of intramolecular cyclization of the thioimidic esters [5].

* Dedicated to Prof. Dr. E. Lukevics on his 70th birthday

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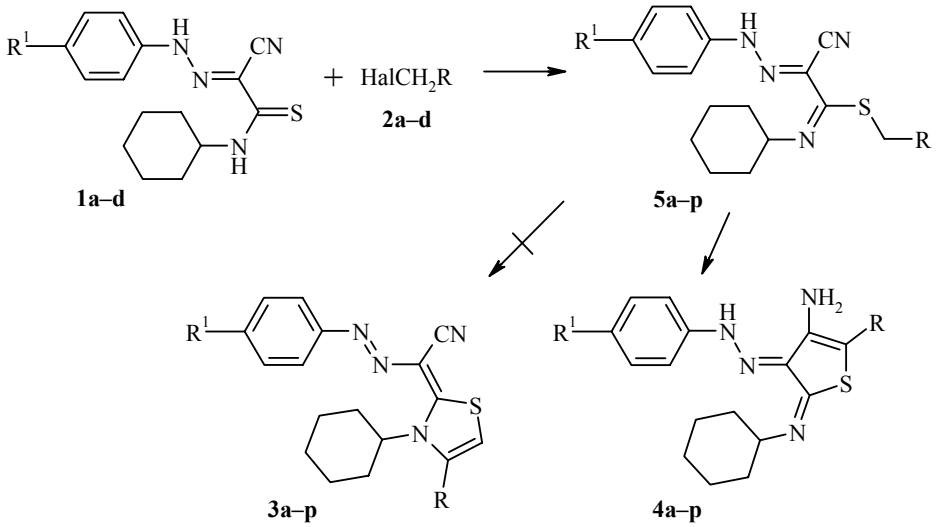
Scheme 1



1 a R^1 = OMe, **b** R^1 = H, **c** R^1 = Cl, **d** R^1 = NO_2; **2 a**, **c**, **d** Hal = Cl, **b** Hal = Br; **a** R = COMe, **b** R = 4-$MeOC_6H_4CO$; **c** R = COOEt, **d** R = CN; **3–5 a–d** R = COMe, **e–h** R = 4-$MeOC_6H_4CO$, **i–l** R = COOEt, **m–p** R = CN; **a**, **e**, **i**, **m** R^1 = OMe, **b**, **f**, **j**, **n** R^1 = H, **c**, **g**, **k**, **o** R^1 = Cl, **d**, **h**, **l**, **p** R^1 = NO_2

The reaction of 2-arylhydrazono-2-cyano-N-cyclohexylthioacetamides **1a-d** with the halo derivatives **2a-d** was conducted in DMFA in the presence of a base at room temperature or with heating. The reaction products were isolated with yields of 50-90% (Table 1) and were yellow or brown crystalline substances. The *m*/*z* values of the molecular ion in the mass spectra of the compounds (Table 1) showed unambiguously that a water molecule is not eliminated during the condensation process. The absence of the stretching vibrations of the cyano group shows that intramolecular interaction with the cyano group occurred and that the reaction products were 3-amino-4-(4-arylhydrazono)-5-cyclohexylimino-4,5-dihydrothiophenes **4a-p** (Table 2). The IR spectra of the obtained compounds contained absorption bands for the stretching vibrations of the amino group in the region of 3280-3480 cm^{-1} and absorption bands for the C–H bonds of the cyclohexyl fragment in the regions of 2860 and 2940 cm^{-1}. In addition, for compounds **4a-h** there was a strong band in the region of 1610-1640 cm^{-1} and for **4i-l** in the region of 1650-1640 cm^{-1}, characteristic of the C=O group with an intramolecular hydrogen bond. For compounds **4m-p** there was an absorption band in the region of 2180-2185 cm^{-1} (the CN group).

The ^{1}H NMR spectra of the reaction products (Table 2) contain signals for the protons of the aromatic ring, the cyclohexyl group, and the proton-containing groups of the substituent R^1 and broad singlets for the NH and NH_2 groups in the regions of 10.4-12.8 and 5.1-8.4 ppm respectively. Here, the signal of the amino group for compounds **4i-p** is shifted upfield, and its intensity is increased in comparison with the analogous signals of the thiophenes **4a-h**. This may be due to weakening of the intramolecular hydrogen bond between the amino group and the carbonyl fragment in the transition from the derivatives of the ketones **4a-h** to the esters **4j-l** and the nitriles **4m-p**. In addition, it should be noted that the signal for the proton of the NH group in the ^{1}H NMR spectrum of 4-nitrophenylhydrazono-4,5-dihydrothiophene (**4d)** takes the form of a doublet with spin-spin coupling constant J = 5.6 Hz, which may result from the existence of this compound in the form of the tautomer **B** (scheme 2).

TABLE 1. The Characteristics of the Synthesized Compounds **4a-p**, **5m-o**, and **8a-c**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	*m/z* (I_{real}, %)	Yield, %
		C	H	N	S			
1	2	3	4	5	6	7	8	9
4a	$C_{19}H_{24}N_4O_2S$	61.45 / 61.27	6.22 / 6.49	14.92 / 15.04	8.40 / 8.61	165-168	372 (81)	80
4b	$C_{18}H_{22}N_4OS$	63.16 / 63.13	6.43 / 6.48	16.47 / 16.36	9.36 / 9.36	162-164	342 (100)	91
4c	$C_{18}H_{21}ClN_4OS$	57.11 / 57.36	5.54 / 5.62	14.33 / 14.86	8.46 / 8.51	245-246	376 (54)	94
4d	$C_{18}H_{21}N_5O_3S$	55.61 / 55.80	5.43 / 5.46	18.29 / 18.07	8.17 / 8.28	235-236	387 (100)	68
4e	$C_{25}H_{28}N_4O_3S$	64.81 / 64.63	6.13 / 6.07	12.37 / 12.06	6.77 / 6.90	196-198	464 (86)	76
4f	$C_{24}H_{26}N_4O_2S$	66.36 / 66.33	5.99 / 6.03	12.90 / 12.89	6.90 / 7.38	211-213	434 (78)	88
4g	$C_{24}H_{25}ClN_4O_2S$	61.27 / 61.46	5.29 / 5.37	11.68 / 11.95	6.65 / 6.84	208-209	469 (20)	77
4h	$C_{24}H_{25}N_5O_4S$	60.30 / 60.11	5.32 / 5.25	14.71 / 14.60	6.48 / 6.69	234-235	479 (58)	85
4i	$C_{20}H_{26}N_4O_3S$	59.39 / 59.68	6.33 / 6.51	13.78 / 13.92	7.75 / 7.97	130-132	402 (63)	63
4j	$C_{19}H_{24}N_4O_2S$	61.42 / 61.27	6.50 / 6.49	15.31 / 15.04	8.85 / 8.61	182-184	372 (80)	60

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
4k	$C_{19}H_{23}ClN_4O_2S$	56.30 56.08	5.69 5.70	13.55 13.77	7.65 7.88	141-142	406 (73)	94
4l	$C_{22}H_{24}N_6O_2$	54.39 54.66	5.30 5.55	16.96 16.77	7.45 7.68	179-180	417 (60)	65
4m	$C_{18}H_{21}N_5OS$	60.85 60.82	5.92 5.95	19.72 19.70	9.01 9.02	174-176	355 (91)	80
4n	$C_{17}H_{19}N_5S$	62.57 62.74	5.65 5.88	21.74 21.52	9.95 9.85	173-174	325 (100)	71
4o	$C_{17}H_{18}ClN_5S$	56.95 56.74	5.09 5.04	19.68 19.46	8.61 8.91	186-187	359 (58)	68
4p	$C_{17}H_{18}N_6O_2S$	55.34 55.13	4.83 4.86	22.35 22.70	8.39 8.65	196-198	370 (79)	58
5m	$C_{18}H_{21}N_5OS$	61.05 60.82	6.22 5.95	19.92 19.70	9.25 9.02	190 (p)	355 (78)	54
5n	$C_{17}H_{19}N_5S$	62.47 62.74	5.73 5.88	21.68 21.52	9.25 9.55	196-198	325 (53)	65
5o	$C_{17}H_{18}ClN_5S$	56.55 56.74	5.22 5.04	19.62 19.46	9.20 8.91	203-206	359 (65)	61
8a	$C_{12}H_{16}N_2S$	65.59 65.41	7.35 7.32	12.62 12.71	14.65 14.55	98-100	220	50
8b	$C_{18}H_{20}N_2OS$	69.38 69.20	6.50 6.45	8.68 8.97	10.47 10.26	163-165	312	80
8c	$C_{11}H_{14}N_2OS$	61.38 61.08	7.30 7.13	14.25 13.90	15.57 15.90	148-149	222	58

TABLE 2. The Spectral Characteristics of the Aminothiophenes **4a-p**

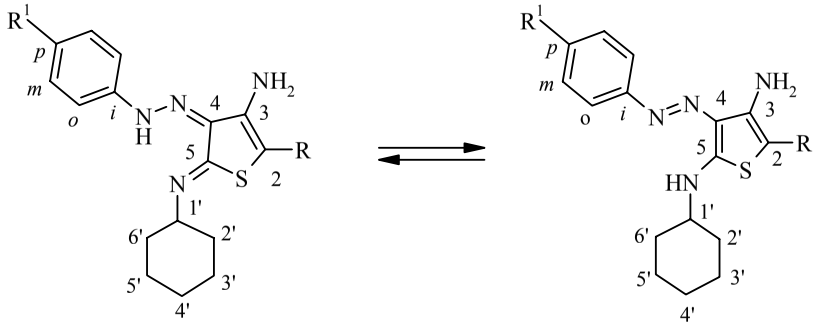
Com-pound	IR spectrum, ν, cm^{-1}			NMR spectrum ^1H, δ ppm. (SSCC, *J*, Hz)					
	NH	CH_{Alk}	C=O	NH (1H, br. s)	NH_2 (2H, br. s)	S_6H_{11}-*cyclo*	R^1	R	Ar_H
1	2	3	4	5	6	7	8	9	10
4a	3450, 3320	2930, 2850	1600	10.40	7.0-8.0	3.35 (1H, m, CH–NH); 1.50-2.10 (10H, m, SH_2)	3.79 (3H, s, OCH_3)	2.09 (3H, s, $COCH_3$)	6.94 and 7.72 (AA'BB', 4H, *J* = 9.0)
4b	3400 3300	2970	1610	10.55	7.2-7.6	3.33 (1H, m, CH–NH); 1.50-2.20 (10H, m, SH_2)	—	2.23 (3H, s, $COCH_3$)	7.20-7.50 (3H, m); 7.64 (2H, d, *J* = 7.7)
4c	3480, 3420, 3325	2940, 2860	1600	11.00	7.0-8.0	3.33 (1H, m, CH–NH); 1.30-2.15 (10H, m, SH_2)	—	2.22 (3H, s, $COCH_3$)	7.56 and 7.57 (AA'BB', 4H, *J* = 8.8)
4d	3475, 3340	2940, 2860	1610	12.34*	7.5-8.5	3.42 (1H, m, CH–NH), 1.3-2.20 (10H, m, SH_2)	—	2.12 (3H, s, $COCH_3$)	7.89 and 8.23 (AA'BB', 4H, *J* = 8.2)
4e	3450, 3320	2940, 2860	1600	10.30	7.6-8.2	3.28 (1H, m, CH–NH), 1.25-2.10 (10H, m, SH_2)	3.84 (3H, s, OCH_3)	6.96 and 7.75 (AA'BB', 4H, *J* = 8.8); 3.84 (3H, s, OCH_3)	6.94 and 7.61 (AA'BB', 4H, *J* = 8.8)
4f	3470, 3310	2935, 2860	1600	11.00	7.5-8.4	3.29 (1H, m, CH–NH); 1.30-2.10 (10H, m, SH_2)	—	6.96 and 7.60 (AA'BB', 4H, *J* = 8.6); 3.84 (3H, s, OSH_3)	7.25-7.35 (1H, m); 7.35-7.50 (2H, m); 7.77 (2H, d, *J* = 7.32)
4g	3450, 3300	2920, 2830	1600	10.65	7.5-8.2	3.31 (1H, m, CH–NH); 1.35-2.10 (10H, m, SH_2)	—	6.95 and 7.41 (AA'BB', 4H, *J* = 8.2); 3.83 (3H, s, OSH_3)	7.61 and 7.81 (AA'BB', 4H, *J* = 8.5)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
4h	3480, 3320	2910, 2840	1610	12.00	7.8-8.3	3.29 (1H, m, CH–NH); 1.25-.00 (10H, m, SH_2)	—	7.96 and 7.61 (AA'BB', 4H, J = 8.2); 3.87 (3H, s, OSH_3)	8.25 and 6.98 (AA'BB', 4H, J=8.8)
4i	3480, 3360	2920, 2850	1660	10.60	6.69	3.27 (1H, m, CH–NH); 1.30-2.15 (10H, m, SH_2)	—	4.16 (q, 2H, J = 7.1); 1.28 (3H, t, J = 7.1, CH_3)	7.69 and 6.93 (AA'BB', 4H, J = 8.9)
4j	3460, 3440	2930, 2850	1675	11.50	6.70	3.30 (1H, m, CH–NH); 1.30-2.00 (10H, m, SH_2)	—	4.18 (q, 2H, J = 7.2, CH_2); 1.25 (3H, t, J = 7.1, CH_3)	8.26 and 7.93 (AA'BB', 4H, J = 8.8)
4k	3490, 3340	2935, 2860	1680	12.50	6.70	3.28 (1H, m, CH–NH); 1.30-2.20 (10H, m, SH_2)	—	4.17 (2H, q, J = 7.2, CH_2); 1.30 (3H, J = 7.1, CH_3)	7.68 (d, 2H, J = 7.6), 7.39 (t, 2H, J = 7.5), 7.22 (t, 1H, J = 7.5)
4l	3470, 3340	2930, 2860	1685	12.80	6.8	3.35 (1H, m, CH–NH); 1.20–2.00 (10H, m, SH_2)	–	4.20 (2H, q, J = 7.0, CH_2); 1.27 (3H, t, J = 7.0, SH_3)	8.20 and 7.8 (AA'BB', 4H, J = 9.0)
4m	3460, 3330	2920, 2845	2180 (CN)	10.95	6.50	3.19 (1H, m, CH–NH); 1.35-2.10 (10H, m, SH_2)	3.83 (s, 3H, OCH_3)	—	7.66 and 6.93 (AA'BB', 4H, J = 9.3)
4n	3460, 3330	2920, 2845	2180 (CN)	12.35	6.55	3.10 (1H, m, CH–NH); 1.30–2.05 (10H, m, SH_2)	—	—	7.65 (2H, d, J = 7.8); 7.33–7.45 (2H, m,); 7.15–7.25 (1H, m,)
4o	3470, 3340	2930, 2860	2180 (CN)	11.50	5.10	3.22 (1H, m, CH–NH); 1.30-2.20 (10H, m, SH_2)	—	—	7.53 and 7.35 (AA'BB', 4H, J = 8.8)
4p	3480, 3340	2940, 2865	2185 (CN)	12.80	6.80	3.20 (1H, m, CH–NH); 1.30-2.00 (10H, m, SH_2)	—	—	7.63 and 8.35 (AA'BB', 4H, J = 9.0)

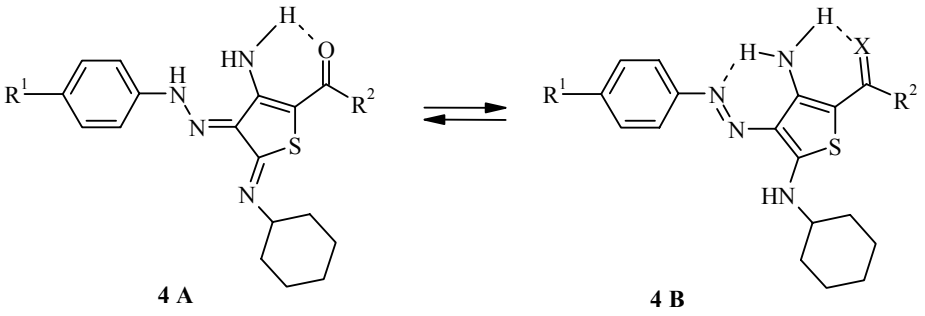
*Doublet, J = 5.6 Hz.

TABLE 3. The ^{13}C NMR Spectra of the Aminothiophenes



Compound	Chemical shifts δ, ppm (*J*, Hz)										
	C(2), m	C(3)	C(4)	C(5)	C_6H_{11}-*cyclo*	C(*i*)	C(*o*), dd	C(*m*), dd	C(*p*)	R^1, q	R^2
4a	94.88	153.1 (br)	121.73 (m)	154.3 (br)	56.34 (d, ^1J = 135.1, C(1')); 32.15 (t, ^1J = 129.3, C(2',6')); 25.3 (t, ^1J = 130.6, C(4')); 24.0 (t, ^1J = 125.9, C(3',5'))	146.44 (tt, ^3J = 5.6, ^2J = 2.5)	122.19 (^1J = 159.9, ^2J =6.1)	114.25 (^1J = 159.1, ^2J = 5.7)	160.1 (m)	55.49 (^1J = 142.9)	187.9 (q, ^2J = 5.3, CO); 27.56 (q, ^1J = 126.3, CH_3)
4d	96.72	151.02 (s)	125.95 (m)	156.08 (d, ^3J= 5.7)	59.12 (d, ^1J = 135.4, C(1')); 32.16 (t, ^1J = 129.2, C(2',6')); 25.27 (t, ^1J = 129.0, C(4')); 24.0 (t, ^1J = 127.0, C(3',5'))	145.67 (tt, ^3J = 9.4, ^2J = 3.8)	119.44 (^1J = 165.2, ^2J = 5.9)	125.12 (^1J = 168.4, ^2J = 4.7)	154.62 (t, ^2J = 8.0)		189.51 (q. t, ^2J = 5.4, ^4J = 1.1, CO), 27.92 (q, ^1J = 126.9, CCH_3)
4e	94.03	155.11 (br)	121.65 (m)	155.82 (br)	56.16 (t, ^1J = 136.1, C(1')); 32.2 (t, ^1J = 127.0, C(2',6')); 25.29 (t, ^1J = 129.0, C(4')); 23.97 (t, ^1J = 127.7, C(3',5'))	146.59 (tt, ^3J = 8.0, ^2J =2.3)	122.3 (^1J = 160.7, ^3J = 6.4, C(12,16))	114.27 (^1J = 160.0, ^3J = 5.1)	160.14 (tq, ^3J = 8.5, ^2J = 4.0)	55.52 (^1J = 144.2)	185.26 (t, ^3J = 3.7, CO); 161.18 (tq, ^3J = 8.7, ^2J = 4.3, C(R-*p*)); 134.11 (tq, ^3J = 7.1 C(R-*i*)); 129.21 (dd, ^1J = 159.7, ^2J = 7.4, C(R-*o*)); 113.46 (dd, ^1J = 160.3, ^2J = 4.7 C(R-*m*)); 55.29 (q, ^2J = 144.2)
4i	82.19	152.35 (br)	122.41 (s)	154.36 (br)	56.61 (d, ^1J = 134.8, C(1')); 32.24 (t, ^1J = 125.7, C(2',6')); 25.42 (t, ^1J = 127.1, C(4')); 24.11 (t, ^1J = 127.1, C(3',5'))	146.27 (m)	121.94 (^1J = 159.2, ^2J = 5.8)	114.92 (^1J = 159.0, ^2J = 4.9)	159.83 (m)	55.56 (^1J = 143.1)	164.73 (m, CO); 59.53 (t, ^1J = 149.0, CH_2); 14.77 (q. t, ^1J = 126.1, ^2J = 2.3, CH_3)
4m	61.99	152.89 (m)	120.94 (m)	153.22 (br)	57.09 (t, ^1J = 134.4, C(1')), 32.14 (t, ^1J = 127.7, C(2',6')); 25.30 (t, ^1J = 133.3, C(4')); 23.90 (t, ^1J = 129.6, C(3',5'))	145.68 (tt, ^3J = 8.3, ^2J = 3.3)	121.93 (^1J = 159.6, ^3J = 6.2)	114.34 (^1J = 159.1, ^3J = 5.0)	160.06 (m)	55.54 (^1J = 143.0)	116.91 (s, CN)

Scheme 2

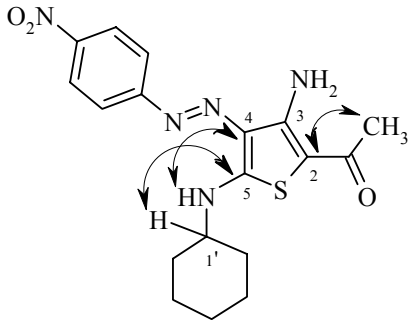


4 A **4 B**

4 a–h R^2 = 4-$MeOC_6H_4$, **i–l** R^2 = Me, **m–p** R^2 = OEt

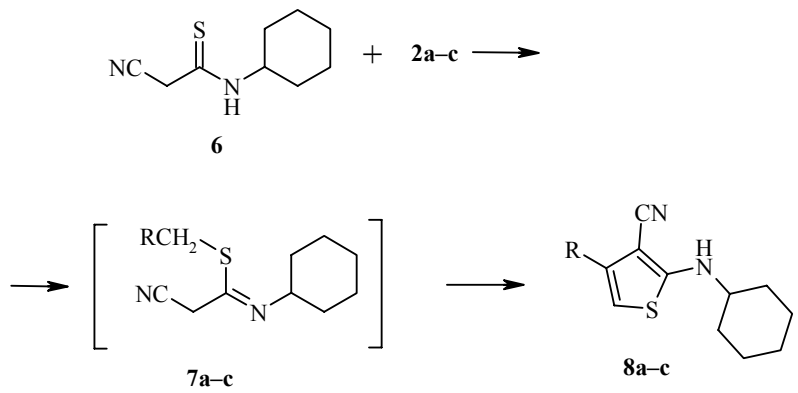
The presence of the tautomeric equilibrium and the strong intramolecular hydrogen bond affects the ^{13}C NMR spectra of the synthesized compounds **4a-p** and makes it difficult to interpret them by the usual methods. Thus, the signals of the C(3) (at 151.02-155.11) and C(5) (at 153.22-155.82 ppm) of the thiophene ring are significantly broadened and have lower intensity compared with the other signals in the spectrum (Table 3), and the multiplicity of the other signals is distorted. A more accurate assignment of the signals of the protonated quaternary carbon atoms was therefore made on the basis of HSQC ($^1J_{CH}$) and HMBC ($^{2\text{-}3}J_{CH}$) 2D experiments. Thus, the presence of long-range coupling between the C(2) atoms and the protons of the methyl group and also between C(4) and NH and between C(5) and C(1') was established for 4-nitrophenylhydrazonothiophene (**5d)** (scheme 3).

Scheme 3



In the reaction of arylhydrazonothioacetamides **1a-c** with chloroacetonitrile at room temperature we were able to isolate the intermediate S-cyanomethylthioimidic esters **5m-o**, which may result from their lower solubility compared with the esters **5a-l**. These compounds are characterized by a strong band for the cyano group in the region of 2200 cm^{-1} in the IR spectra and a two-proton singlet for the CH_2 group at 3.8 ppm in the ^1H NMR spectra.

In order to find the determining factor in the intramolecular cyclization of the thioimidates formed at the first stage of the process we studied the reaction of 2-cyano-N-cyclohexylthioacetamide (**6**) with the halo-derivatives **2a-c** under analogous conditions. According to the ^1H NMR, IR, and mass spectra and elemental analysis, the reaction products in all cases were 2-cyclohexylaminothiophene-3-carbonitriles **8a-c** (scheme 4).



7 a R = COMe , **b** R = 4-MeOC$_6$H$_4$CO, **c** R = COOEt;

8 a R = Me , **b** R = 4-MeOC$_6$H$_4$, **c** R = OH

Thus, it was shown that in contrast to the corresponding N-phenyl-substituted thioamides the concluding stage of cyclization for the reaction of 2-arylhydrazono-2-cyano-N-cyclohexylthioacetamides with the halocarbonyl compounds is mainly determined by the steric effect arising from the presence of the bulky substituent next to one of the nucleophilic centers. The steric hindrances created by the cyclohexyl group make any kind of interaction with the nitrogen atom of the thioamide group and the formation of 1,3-thiazoles impossible. In this case too the only reaction products are 4,5-dihydrothiophenes, irrespective of the structure of the initial 4,5-dihydrothiophenes.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 instrument (400 and 100 MHz respectively) in chloroform solution with TMS as internal standard. The signals in the ^{13}C NMR spectra were assigned on the basis of HSQC and HMBC 2D experiments. The IR spectra were recorded on a UR-20 spectrometer for tablets in potassium bromide. The reactions and the individuality of the products were monitored by TLC on Sorbfil UV-254 plates in the 1:1 ethyl acetate–hexane system. The mass spectra were recorded on a Varian MATT 311A instrument with accelerating potential 3 kV and ionization energy 70 eV. The melting points were not corrected.

The initial arylhydrazonocyanothioacetamides **1a-d** were obtained from the corresponding arenediazonium chlorides and cyanocyclohexylthioacetamide by the known method [7].

Reaction of Arylhydrazonocyanothioacetamides 1a-d with Compounds 2a-d. A. To a solution of the arylhydrazonocyanothioacetamide **1a-d** (1 mmol) in DMFA (5 ml) we added the respective halocarbonyl compound **2a-c** (1 mmol) and *t*-BuONa (2 mmol). The reaction mass was kept at 80°C until the initial substances had disappeared (TLC) and was then poured into water. The precipitate that separated was filtered off and crystallized from ethanol.

B. To a solution of the compound **1a-c** (1 mmol) in DMFA (5 ml) we added (0.6 ml) 10% solution of potassium hydroxide and chloroacetonitrile (**2d**) (1 mmol). The reaction mass was kept at room temperature for 1 h. The precipitate was filtered off and crystallized from a mixture of hexane and chloroform.

S-Cyanomethyl 2-Cyano-2-(4-methoxyphenyl)hydrazono-N-cyclohexylthioimidate (5m). This compound was obtained by method B. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (1H, m, CH_2); 1.60 (3H, m, CH_2); 1.90 (4H, m, CH_2); 2.68 (2H, m, CH_2); 3.79 (2H, s, CH_2,); 3.86 (3H, s, OCH_3); 4.87 (1H, m, CH); 6.92 and 7.70 (4H, AA′BB′, J = 8.5 Hz, H_{Ar}); 8.15 (1H, s, NH).

S-Cyanomethyl 2-Cyano-2-phenylhydrazono-N-cyclohexylthioimidate (5n). This compound was obtained by method B. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (1H, m, CH_2); 1.48 (3H, m, CH_2); 1.90 (4H, m, CH_2); 2.65 (2H, m, CH_2); 3.81 (2H, s, CH_2); 4.85 (1H, m, CH); 7.06 (1H, t, *J* = 7.70, H_{Ar}); 7.32 (2H, t, *J* = 7.60, H_{Ar}); 7.60 (2H, d, *J* = 7.70, H_{Ar}), 8.15 (1H, s, NH).

S-Cyanomethyl 2-(4-Chlorophenyl)hydrazono-2-cyano-N-cyclohexylthioimidate (5o). This compound was obtained by method B. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (1H, m, CH_2); 1.52 (3H, m, CH_2); 1.90 (4H, m, CH_2); 2.67 (2H, m, CH_2); 3.81 (2H, s, CH_2); 2.17 (3H, s, CH_3); 4.87 (1H, m, CH); 7.35 and 7.64 (4H, AA′BB, *J* = 8.5, H_{Ar}); 8.16 (1H, s, NH).

2-Cyclohexylamino-4-methylthiophene-3-carbonitrile (8a). This compound was obtained by method A from 2-cyano-N-cyclohexylthioacetamide (**6**) and chloroacetone at room temperature for 30 min. $_1$H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (5H, m, CH_2); 1.55 (1H, m, CH_2); 1.80 (2H, m, CH_2); 2.08 (2H, m, CH_2); 2.17 (3H, s, CH_3); 3.15 (1H, m, CH); 4.77 (1H, d, *J* = 7.4, NH); 5.90 (1H, s, CH).

2-Cyclohexylamino-4-(4-methoxyphenyl)thiophene-3-carbonitrile (8b). This compound was obtained by method A from compound (**6**) and 4-methoxyphenacyl bromide (**2b**) at room temperature for 2 h. ^{1}H NMR spectrum, δ ppm (*J*, Hz): 1.32 (5H, m, CH_2); 1.66 (1H, m, CH_2); 1.82 (2H, m, CH_2); 2.14 (2H, m, CH_2); 2.17 (3H, s, CH_3); 3.18 (1H, m, CH); 4.95 (1H, d, *J* = 8.0, NH); 6.20 (1H, s, CH); 6.94 and 7.52 (4H, AA′BB′, *J* = 8.8, H_{Ar}).

2-Cyclohexylamino-4-hydroxy-4,5-dihydrothiophene-3-carbonitrile (8c). This compound was obtained by method A from compound (**6**) at room temperature for 2 h. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (5H, m, CH_2); 1.65 (1H, m, CH_2); 1.83 (2H, m, CH_2); 2.3 (2H, m, CH_2); 3.90 (1H, m, CH); 3.93 (2H, s, NH+OH); 5.37 (1H, s, CH).

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