Synthesis of imidazolyl dithiocarbamates and their reactions with phenacyl bromides*

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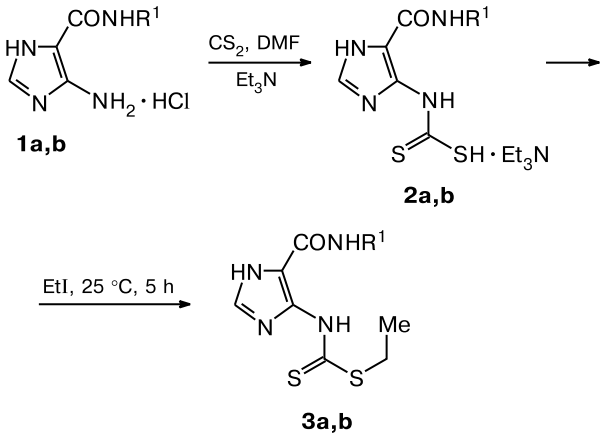
The reactions of ethyl (5-carbamoyl-3*H*-imidazol-4-yl)dithiocarbamate with phenacyl bromides afford the S-alkylation products as a mixture of *E*/*Z*-isomers, which undergo cyclization to 5-(2-oxo-4-arylthiazol-3-yl)-1*H*-imidazole-4-carboxamides under the action of a base.

Key words: imidazolyldithiocarbamates, alkylation, intramolecular heterocyclization, 5-(2-oxo-4-arylthiazol-3-yl)-1*H*-imidazole-4-carboxamides.

Earlier, we have shown that 5-aminoimidazole amides **1a,b** afford *S*-ethyldithiocarbamates **3a,b** in high yields upon sequential treatment with carbon disulfide and ethyl iodide without isolation of the intermediate imidazolyl-5-dithiocarbamic acid salt **2** (Scheme 1). The latter transform easily into the corresponding thioureas under the action of amines and results in imidazo[1,5-*c*][1,3,5]-thiadiazines in the reactions with dimethyl acetylenedicarboxylate.[1,2]

Scheme 1



R^1 = H (**a**), Me (**b**)

It is known that the reaction of 5-amino-4-imidazole(pyrazole)carboxamides with carbon disulfide results in the mercaptopurine[3] and pyrazolopyrimidine derivatives,[4] respectively, or pyrazolyldithiocarbamic acids, which undergo subsequently heterocyclization without their isolation.[5]

The present work is aimed at the synthesis and study of the reactions of 1*H*-imidazol-4-yldithiocarbamate **2a** and esters **3a,b** with phenacyl bromides.

Results and Discussion

Performing the reaction of 5-aminoimidazoles **1a,b** with carbon disulfide under mild conditions allowed isolation of triethylammonium 5-carbamoyl-1*H*-imidazol-4-yldithiocarbamate (**2a**) in a high yield (see Scheme 1), whose alkylation with ethyl iodide resulted in *S*-ethyl dithiocarbamate **3a**. We synthesized also the analogous methylamide derivative **3b**, but without isolation of the intermediate salt of imidazolyldithiocarbamic acid **2b**.

The presence of several nucleophilic centers in the molecule of substrate **2a** contemplates ambiguousness of the reaction pathway with aromatic haloketones.

In the reaction of triethylammonium 5-imidazolyldithiocarbamate **2a** with bromoacetophenones, the formation of several products with close chromatographic mobilities was observed, which made impossible the use of chromatography for separation and purification of substances. In attempting to crystallize compounds, they decomposed.

The reactions of 5-aminoimidazoles **1a**,**b** with carbon disulfide and aromatic haloketones as alkylating agents were performed analogously to the reaction with ethyl iodide.

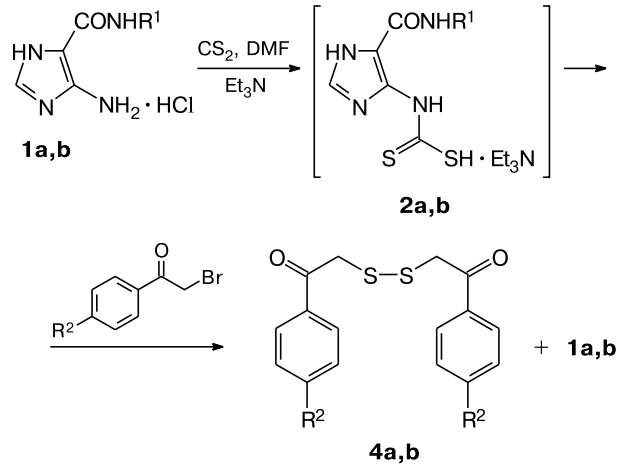
However, these reactions resulted in no alkylation products or subsequent cyclization products; after dilution of the reaction mixture with water, the symmetric aromatic disulfides **4a**,**b** (according to the data from ^{1}H, ^{13}C NMR, and mass spectrometry and elemental analy-

* Dedicated to Academician V. N. Charushin on the occasion of his 60th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 862—868, May, 2011.

sis) were isolated (Scheme 2). In addition, the starting aminoimidazoles **1a**,**b** were fixed chromatographically.

Scheme 2

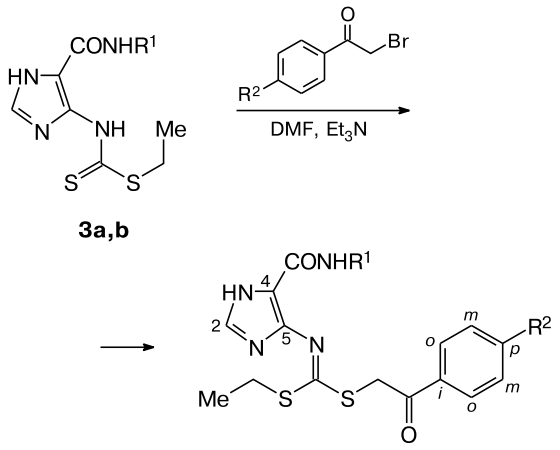


4: R^2 = Cl (**a**), NO_2 (**b**)

The ^{1}H NMR spectra of the isolated products **4a,b** contain no signals for the imidazole ring and its substituents and contain signals for the aromatic protons and CH_2 group. The peak values of molecular ion and fragment ions in the mass spectrum suggest also the formation of disulfides **4a,b**.

Further, we studied the reactions of ethyl imidazolyldithiocarbamates **3a,b** with bromoacetophenones. When performing this reaction in DMF in the presence of triethylamine, dialkylated imidazolyldithiocarbamates **5a—i** were produced (Scheme 3, Tables 1 and 2).

Scheme 3



(mixture of *E*/*Z*-isomers)

	R^1	R^2		R^1	R^2		R^1	R^2
a	H	H	**d**	H	NO_2	**g**	Me	OMe
b	H	Cl	**e**	Me	H	**h**	Me	NO_2
c	H	OMe	**f**	Me	Cl	**i**	Me	Me

Table 1. Yields, melting points, data from elemental analysis, ^{1}H NMR spectroscopy and mass spectrometry of compounds **2a**, **4a,b**, **5a—i**, and **6a—h**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR, δ (*J*/Hz)	$[M^+]$, *m*/*z*
2a	91	120	43.76 43.56	7.50 6.93	23.52 23.10	$C_{11}H_{21}N_5OS_2$	13.54, 11.02 (both s, 1 H each, NH); 7.19 (s, 1 H, CH_{Im}); 7.10 (br.s, 2 H, $CONH_2$); 3.06 (q, 6 H, $C\underline{H}_2CH_3$, *J* = 7.6); 1.18 (t, 9 H, $CH_2C\underline{H}_3$, *J* = 7.6)	303
4a	70	141	51.90 51.76	3.40 3.26	—	$C_{16}H_{12}O_2S_2Cl_2$	7.98—7.59 (AA´BB´ system, 4 H, H_{Ar}); 4.41 (s, 2 H, CH_2)	371
4b	75	122	48.65 48.97	2.75 3.08	7.55 7.14	$C_{16}H_{12}N_2O_6S_2$	8.35—8.17 (AA´BB´ system, 4 H, H_{Ar}); 4.50 (s, 2 H, CH_2)	392
5a	75	188	52.20 51.72	4.55 4.60	16.15 16.09	$C_{15}H_{16}N_4O_2S_2$	12.92, 12.76 (s, 1 H, NH_{Im}); 8.02—7.60 (m, 5 H, H_{Ar}); 7.69, 7.28 (br.s, 2 H, $CONH_2$); 7.32 (s, 1 H, CH_{Im}); 4.86 (s, 2 H, CH_2); 3.13, 3.08 (q, $C\underline{H}_2CH_3$, 2 H, *J* = 7.0); 1.29, 1.23 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.0)	348
5b	81	231	46.83 47.05	4.25 3.95	14.21 14.63	$C_{15}H_{15}ClN_4O_2S_2$	12.80, 12.66 (s, 1 H, NH_{Im}); 8.03—7.36 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.5); 7.32 (s, 1 H, CH_{Im}); 7.29, 6.99 (br.s, 2 H, $CONH_2$); 4.79, 4.73 (s, 2 H, CH_2); 3.15, 3.08 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.2); 1.38, 1.34 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.2)	382

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR, δ (*J*/Hz)	[M$^+$], *m/z*
5c	71	219	51.05 50.79	4.65 4.79	14.55 14.81	$C_{16}H_{18}N_4O_3S_2$	12.70, 12.65 (s, 1 H, NH_{Im}); 7.97—6.99 (AA´BB´ system, 4 H, H_{Ar}, *J* = 9.0); 7.52, 7.44 (s, 1 H, CH_{Im}); 7.34, 6.88 (br.s, 2 H, $CONH_2$); 4.69, 4.67 (s, 2 H, CH_2); 3.87 (s, 3 H, OCH_3); 3.14, 3.05 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.5); 1.35, 1.33 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.5)	378
5d	59	242	45.99 45.79	4.05 3.84	17.33 17.80	$C_{15}H_{15}N_5O_4S_2$	12.77, 12.65 (s, 1 H, NH_{Im}); 8.40—8.32 (AA´BB´ system, 4 H, H_{Ar}, *J* = 9.0); 7.52, 7.43 (br.s, 1 H, CH_{Im}); 7.23, 6.81 (br.s, 2 H, $CONH_2$); 4.85 (s, 2 H, CH_2); 3.06 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.5); 1.37 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.5)	393
5e	55	171	53.20 53.04	5.34 5.01	15.20 15.46	$C_{16}H_{18}N_4O_2S_2$	12.84, 12.68 (br.s, 1 H, NH_{Im}); 8.02—7.62 (m, 5 H, Ph); 7.78, 7.24 (q, 1 H, NH, *J* = 4.6); 7.61, 7.41 (s, 1 H, CH_{Im}); 4.77, 4.75 (s, 2 H, CH_2); 3.14, 3.10 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.2); 2.88, 2.68 (d, 3 H, $NHC\underline{H}_3$, *J* = 4.6); 1.35 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.2)	362
5f	70	175	48.05 48.42	4.01 4.32	14.10 14.12	$C_{16}H_{17}ClN_4O_2S_2$	12.51, 12.34 (br.s, 1 H, NH_{Im}); 7.71—7.19 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.7); 7.43, 6.91 (q, 1 H, NH, *J* = 4.3); 4.42, 4.40 (s, 2 H, CH_2); 2.80, 2.70 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.3); 2.54, 2.39 (d, 3 H, $NHC\underline{H}_3$, *J* = 4.3); 1.01 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.3)	396
5g	65	188	52.19 52.04	5.02 5.14	14.13 14.27	$C_{17}H_{20}N_4O_3S_2$	12.84, 12.68 (br.s, 1 H, NH_{Im}); 8.02—7.00 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.8); 7.78, 7.30 (q, 1 H, NH, *J* = 4.5); 7.51, 7.42 (s, 1 H, CH_{Im}); 4.70, 4.68 (s, 2 H, CH_2); 3.88 (s, 3 H, OCH_3); 3.16, 3.10 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.3); 2.88, 2.72 (d, 3 H, $NHC\underline{H}_3$, *J* = 4.5); 1.35 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.3)	392
5h	51	183	47.50 47.16	4.01 4.21	17.00 17.19	$C_{16}H_{17}N_5O_4S_2$	12.86, 12.70 (s, 1 H, NH_{Im}); 8.35—8.24 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.5); 7.75, 7.23 (q, 1 H, NH, *J* = 5.5); 7.51, 7.42 (s, 1 H, CH_{Im}); 4.84, 4.82 (s, 2 H, CH_2); 3.14, 3.11 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.5); 2.87, 2.73 (d, 3 H, $NHC\underline{H}_3$, *J* = 5.5); 1.35 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.5)	407
5i	40	168	53.98 54.23	5.21 5.35	14.97 14.89	$C_{17}H_{20}N_4O_2S_2$	12.84, 12.68 (s, 1 H, NH_{Im}); 7.93—7.31 (AA´BB´ system, 4 H, H_{Ar}, *J* = 9.5); 7.77, 7.26 (q, 1 H, NH, *J* = 4.3); 7.51, 7.42 (s, 1 H, CH_{Im}); 4.73 (br.s, 2 H, CH_2); 3.16, 3.12 (q, 2 H, $CH_2C\underline{H}_3$, *J* = 7.3); 2.87, 2.69 (d, 3 H, $NHC\underline{H}_3$, *J* = 4.3); 2.43 (s, 3 H, CH_3); 1.39 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7. 3)	376
6a	38	189	54.30 54.55	3.55 3.52	20.20 19.57	$C_{13}H_{10}N_4O_2S$	12.81 (s, 1 H, NH_{Im}); 7.74 (m, 2 H, Ph); 7.58 (s, 1 H, CH_{Im}); 7.44—7.33 (m, 5 H, Ph, $CONH_2$); 7.22 (s, 1 H, CH)	286
6b	46	200	48.32 48.67	3.02 2.83	17.13 17.47	$C_{13}H_9ClN_4O_2S$	12.81 (s, 1 H, NH_{Im}); 7.77—7.42 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.8); 7.57 (s, 1 H, CH_{Im}); 7.34—7.31 (m, 3 H, $CONH_2$, CH)	320
6c	51	242	47.38 47.13	3.10 2.74	20.85 21.14	$C_{13}H_9N_5O_4S$	12.85 (s, 1 H, NH_{Im}); 8.30—8.00 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.8); 7.73 (s, 1 H, CH_{Im}); 7.60 (s, 1 H, CH); 7.35, 7.32 (br.s, 2 H, $CONH_2$)	331
6d	38	177	55.80 56.00	4.32 4.03	18.35 18.65	$C_{14}H_{12}N_4O_2S$	12.85 (s, 1 H, NH_{Im}); 7.76 (m, 2 H, Ph); 7.70 (q, 1 H, NH, *J* = 4.3); 7.55 (s, 1 H, CH_{Im}); 7.44 (m, 3 H, Ph); 7.24 (s, 1 H, CH); 2.95 (d, 3 H, $NHC\underline{H}_3$, *J* = 4.3)	300

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	^{1}H NMR, δ (*J*/Hz)	[M^+], *m/z*
6e	45	165	50.10 50.23	3.65 3.31	16.82 16.74	$C_{14}H_{11}ClN_4O_2S$	12.86 (s, 1 H, NH_{Im}); 7.79—7.44 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.8); 7.67 (q, 1 H, NH, *J* = 4.7); 7.55 (s, 1 H, CH_{Im}); 7.33 (s, 1 H, CH); 2.95 (d, 3 H, $NHCH_3$, *J* = 4.7)	334
6f	65	250	49.01 48.70	3.03 3.21	20.01 20.29	$C_{14}H_{11}N_5O_4S$	12.90 (s, 1 H, NH_{Im}); 8.31—8.02 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.8); 7.74 (s, 1 H, CH_{Im}); 7.65 (q, 1 H, NH, *J* = 5.0); 7.57 (s, 1 H, CH); 2.96 (d, 3 H, $NHCH_3$, *J* = 5.0)	345
6g	59	205	53.02 53.16	3.56 3.82	18.08 17.71	$C_{14}H_{12}N_4O_3S$	12.92 (s, 1 H, NH_{Im}); 7.75 (s, 1 H, CH_{Im}); 7.65—7.27 (AA´BB´ system, 4 H, H_{Ar}, *J* = 8.3); 7.49, 7.36 (s, 2 H, $CONH_2$); 7.18 (s, 1 H, CH); 3.80 (s, 3 H, OCH_3)	316
6h	68	215	55.86 56.00	4.00 4.03	18.90 18.65	$C_{14}H_{12}N_4O_2S$	12.92 (s, 1 H, NH_{Im}); 7.75 (s, 1 H, CH_{Im}); 7.69—7.01 (AA´BB´ system, 4 H, H_{Ar}, *J* = 9.5); 7.49, 7.38 (s, 2 H, $CONH_2$); 7.12 (s, 1 H, CH); 3.33 (s, 3 H, CH_3)	300

Table 2. ^{13}C NMR spectral data for compounds **4a,b**, **5a—i**, and **6a—h**

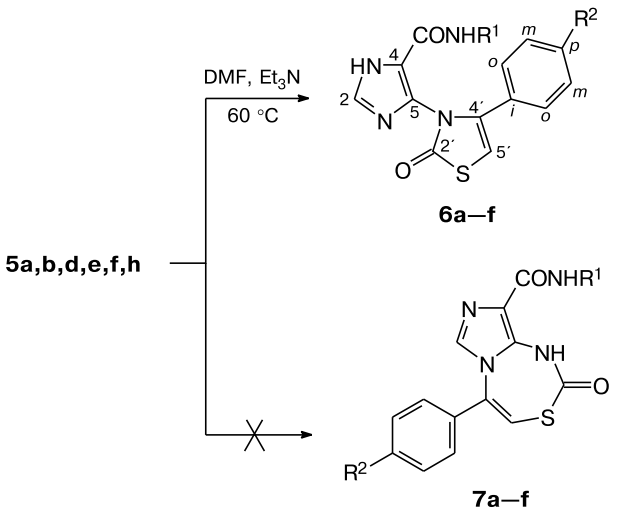
Compound	^{13}C NMR, δ
4a	193.00 (CO); 138.84, 133.68, 130.33, 128.53 (all C_{Ar}); 95.77 (CH_2)
4b	193.98 (CO); 150.40, 140.22, 130.06, 124.01 (all C_{Ar}); 44.50 (CH_2)
5a	193.81 (CO); 164.12 (CS); 163.33 ($CONH_2$); 145.05 (C(5)); 135.78 (C_i); 134.19 (C(2)); 130.12, 128.89, 128.86 (C_o, C_p, C_m); 115.91 (C(4)); 39.90 (CH_2); 26.91 ($\underline{C}H_2CH_3$); 14.47 ($CH_2\underline{C}H_3$)
5b	192.74 (CO); 163.87 (CS); 160.67 ($CONH_2$); 145.05 (C(5)); 135.69 (C(2)); 134.74 (C_p); 134.19 (C_m); 128.63 (C_o); 120.28 (C_i); 115.91 (C(4)); 39.90 (CH_2); 26.91 ($\underline{C}H_2CH_3$); 14.67 ($CH_2\underline{C}H_3$)
5c	191.25 (CO); 163.69 (CS); 160.24 ($CONH_2$); 145.15 (C(5)); 138.19 (C_i); 135.37 (C_p); 134.03 (C(2)); 123.89 (C_o, C_m); 115.48 (C(4)); 55.35 (OCH_3); 39.19 (CH_2); 26.47 ($\underline{C}H_2CH_3$); 14.30 ($CH_2\underline{C}H_3$)
5d	192.17 (CO); 160.54 (CS); 160.63 ($CONH_2$); 144.9 (C(5)); 140.18 (C_i); 130.71 (C(2)); 129.63, 125.98, 123.80 (C_m, C_o, C_p); 95.80 (C(4)); 39.99 ($\underline{C}H_2CH_3$); 26.72 ($\underline{C}H_2CH_3$); 14.36 ($CH_2\underline{C}H_3$)
5e	194.06 (CO); 163.87 (CS); 159.62 ($CONH_2$); 144.79 (C(5)); 135.53 (C_i); 134.19 (C(2)); 133.22 (C_p); 128.89, 127.58 (C_o, C_m); 115.91 (C(4)); 39.90 ($\underline{C}H_2CH_3$); 26.91 ($CH_2\underline{C}H_3$); 25.31 (CH_3)
5f	193.05 (CO); 163.60 (CS); 159.62 ($CONH_2$); 144.80 (C(5)); 138.97 (C_i); 134.47 (C_p); 130.48 (C(2)); 128.85 (C_o, C_m); 116.18 (C(4)); 39.90 ($\underline{C}H_2CH_3$); 26.91 ($CH_2\underline{C}H_3$); 25.31 (CH_3)
5g	192.20 (CO); 164.12 (CS); 159.62 ($CONH_2$); 145.05 (C(5)); 144.19 (C_p); 131.28 (C(2)); 128.37 (C_i); 127.60, 124.62 (C_o, C_m); 115.91 (C(4)); 55.79 (OCH_3); 39.62 ($\underline{C}H_2CH_3$); 26.91 ($CH_2\underline{C}H_3$); 25.06 (CH_3)
5h	193.26 (CO); 163.60 (CS); 159.89 ($CONH_2$); 150.61 (C(5)); 142.79 (C_p); 140.55 (C_i); 129.69 (C(2)); 125.55, 124.12 (C_o, C_m); 116.18 (C(4)); 39.90 ($\underline{C}H_2CH_3$); 26.91 ($CH_2\underline{C}H_3$); 25.31 (CH_3)
5i	193.84 (C(9)); 164.23 (C(7)); 163.59 (C(6)); 145.85 (C(5)); 135.80 (C_i); 134.19 (C(2)); 130.22 (C_p); 128.89, 128.86 (C_o, C_m); 115.91 (C(4)); 39.90 ($\underline{C}H_2CH_3$); 26.91 ($CH_2\underline{C}H_3$); 14.47 (CH_3)
6a	164.46 (C(2´)); 161.22 ($CONH_2$); 146.69 (C(4´)); 143.76 (C(5)); 134.32 (C(2)); 130.42, 129.34, 125.05 (C_o, C_m, C_p); 127.45 (C_i); 115.45 (C(4)); 102.35 (C(5´))
6b	164.26 (C(2´)); 161.22 ($CONH_2$); 145.17 (C(4´)); 143.43 (C(5)); 134.54 (C(2)); 134.11 (C_p); 129.55, 126.95 (C_m, C_o); 126.90 (C_i); 115.45 (C(4)); 102.87 (C(5´))
6c	163.33 (C(2´)); 160.95 ($CONH_2$); 147.18 (C(4´)); 144.53 (C(5)); 142.67 (C_p); 134.72 (C(2)); 133.39 (C_i); 125.72, 124.12 (C_m, C_o); 115.12 (C(4)); 106.38 (C(5´))
6d	164.12 (C(2´)); 159.89 ($CONHCH_3$); 146.11 (C(4´)); 142.40 (C(5)); 129.42 (C(2)); 130.55, 129.50, 124.66 (C_o, C_m, C_p); 127.83 (C_i); 115.12 (C(4)); 101.08 (C(5´)); 25.85 (CH_3)
6e	164.21 (C(2´)); 158.14 ($CONHCH_3$); 148.00 (C(4´)); 144.33 (C(5)); 140.52 (C_p); 135.40 (C(2)); 133.37 (C_i); 123.12, 121.88 (C_m, C_o); 115.03 (C(4)); 103.15 (C(5´)); 25.75 (CH_3)
6f	163.60 (C(2´)); 160.16 ($CONHCH_3$); 147.70 (C(4´)); 144.53 (C(5)); 142.14 (C_p); 134.47 (C(2)); 133.39 (C_i); 125.72 (C_m); 124.12 (C_o); 115.66 (C(4)); 106.65 (C(5´)); 25.31 (CH_3)
6g	163.92 (C(2´)); 160.59 ($CONHCH_3$); 145.95 (C(4´)); 143.03 (C_p); 138.85 (C_i); 129.66, 125.06 (C_o, C_m); 115.03 (C(4)); 99.57 (C(5´)); 55.32 (OCH_3)
6h	164.53 (C(2´)); 160.95 ($CONH_2$); 146.11 (C(4´)); 140.04 (C_p); 125.91, 124.66 (C_o, C_m); 120.54 (C_i); 115.17 (C(4)); 98.29 (C(5´)); 20.60 (CH_3)

It should be noted that, due to the presence of the —C=N bond, products **5** form as a mixture of *E*/*Z*-isomers, which is evidenced by the ^{1}H NMR spectral data where all signals are either broadened or appear as a double set of signals (in a ration of 1 : 2). Compared to the ^{1}H NMR spectra of the starting ethyl thioesters **3a**,**b**, the ^{1}H NMR spectra of compounds **5a—i** display the signals for the CH_2 groups and aromatic protons in the absence of the downfield signals for the NH group.

Taking into account the possibility of intramolecular cyclization involving the electrophilic carbonyl carbon atom and one of the nucleophilic centers in the molecules of imidazolyldithiocarbamates **5a**,**b**,**d**,**e**,**f**,**h**, we treated them with triethylamine in DMF at 60 °C.

Based on the data from ^{1}H, ^{13}C NMR, and mass spectrometry of isolated individual compounds, it was established that either imidazolylthiazolines **6a—f** or condensed seven-membered imidazothiadiazines **7a—f** can form as a result of heterocyclization (Scheme 4).

Scheme 4



	R^1	R^2		R^1	R^2		R^1	R^2
a	H	H	**c**	H	NO_2	**e**	Me	Cl
b	H	Cl	**d**	Me	H	**f**	Me	NO_2

However, the compounds **6** and **7** have identical molecular formulas, molecular weights, and the number of proton and carbon atoms with a low-informative multiplicity in the ^{1}H and ^{13}C NMR spectra, which makes difficult to assign the structures of isolated compounds by the above-mentioned methods.

To establish exactly the structures of compound obtained, the HMBC spectra were recorded, which allowed us unambiguously to make choice in favor of imidazolylthiazolidines **6a—f**. The presence of the cross peaks between the C(2) atom of the imidazole ring and the NH proton, which is typical of compounds **6**, as well as the absence of the proposed cross peaks between the signals for the carbon atom bound to the aromatic substituent and two heterocyclic CH protons (of the imidazole and thiadiazepine rings) for the condensed imidazothiadiazepines **7** are the most informative data.

The peak values of molecular ions in the mass spectra of compounds **6a—f** corresponds to the calculated ones. One can note an identical type of fragmentation: four most intensive fragment ions caused by destruction of the thiazolidine ring are distinguished in all mass spectra with the exception of nitro derivatives (Scheme 5, Table 3).

Scheme 5

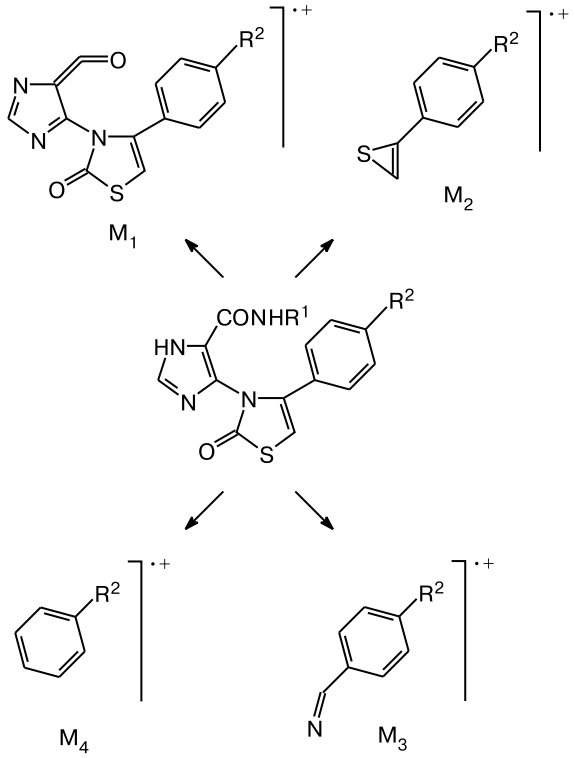
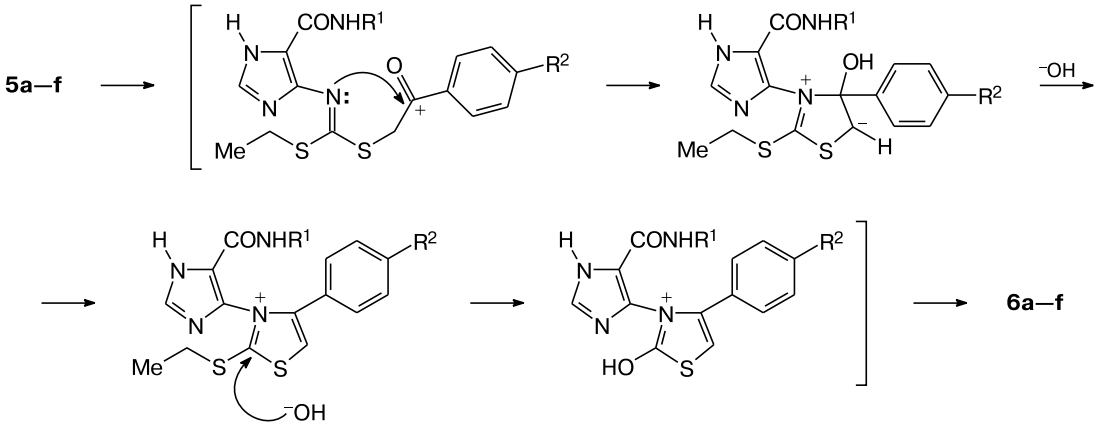


Table 3. Peaks of the main fragment ions in the mass spectra of compounds **6a—h**

Compound	m/z (I_{rel} (%))			
	M_1	M_2	M_3	M_4
6a	269 (44.87)	134 (47.22)	105 (100)	77 (53.47)
6b	303 (19.86)	168 (23.07)	139 (100)	111 (34.46)
6c	314 (61.63)	179 (8.73)	150 (65.30)	—
6d	269 (12.42)	134 (40.06)	105 (100)	77 (36.54)
6e	303 (12.35)	168 (36.20)	139 (100)	111 (28.78)
6f	314 (25.89)	179 (12.08)	150 (86.16)	—
6g	299 (4.40)	168 (11.31)	135 (100)	107 (6.78)
6h	283 (8.52)	152 (14.33)	116 (89.63)	91 (7.89)

Scheme 6



Note that cyclization found proceeded only in the case where the aromatic ring is unsubstituted or contains electron-withdrawing substituents (R^2 = Cl, NO_2). In the case where the substituent R^2 is electron-donating (R^2 = OMe, Me), the reaction did not proceed under the analogous conditions. Application of more severe conditions (temperature increase, use of stronger bases) resulted in resinification of the reaction mixture.

Such a behavior can be explained by the mechanism proposed for the synthesis of products **6a**—**f** (Scheme 6).

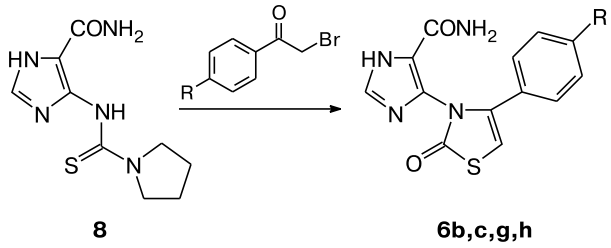
At the first step, the electron lone pair of the nitrogen atom of the dithiocarbamate fragment, which is most likely activated by triethylamine, attacks the positively charged carbon atom of the carbonyl group to form the thiazole ring. The readiness of this reaction depends on the nature of the substituent in the *para*-position of the phenyl ring. When the substituent is electron-donating (methyl or methoxy) group, the positive charge is insufficitent for the closure of a novel ring.

In the case when the phenyl ring is unsubstituted (R^2 = H) or substituted with electron-withdrawing groups (R = Cl, NO_2), the positive charge on the carbon atom increases, which promotes the reaction. The addition of the hydroxyl group to a new ring is possible only where there is a charge in the structure. This causes subsequent elimination of the S-ethyl fragment and proton, which form leaving ethanethiol.

To prove the above-given cyclization pathway, the trisubstituted thiourea **8** was chosen as the starting substrate.[1,2] It was assumed that the presence of the pyrrolidine fragment would considerably activate the electron lone pair of the nitrogen atom, which, in turn, would facilitate heterocyclization and the formation of the thiazole ring. In this case, the nature of the substituent in the aromatic ring will not influence the course of the reaction.

The reactions of imidazolylthiourea **8** with phenacyl bromides afforded compounds identical to the earlier synthesized imidazolylthiazolines **6b**,**c** by their physicochemical parameters, as well as compounds **6g**,**h**. Consequently, the formation of the thiazole ring was observed in the case of both electron-withdrawing and electron-donating substituents in the aromatic ring (Scheme 7).

Scheme 7



6: R = Cl (**b**), NO_2 (**c**), OMe (**g**), Me (**h**)

Thus, we found that alkylation of ethyl imidazolyldithiocarbamates **3a**,**b** with aromatic haloketones resulted in the dialkylated imidazolyldithiocarbamates **5a**—**i** as a mixture of *E*/*Z*-isomers, which can undergo intramolecular cyclization in the presence of base to form imidazolylthiazolidines **6a**—**f**. The latter are produced only in the presence of electron-withdrawing substituents in the aromatic ring. The analogous compounds can be obtained from the substituted imidazolylthiourea **8** by the reactions with bromoacetophenones containing both electron-withdrawing and electron-donating substituents in the aromatic ring.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVANCE II 400 (400.00 and 100.00 MHz, respectively) instrument in DMSO-d_6 using Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT-311A instrument

(EI, the energy of ionizing electrons is 70 eV). IR spectra were recorded on a Bruker Alpha FT-IR spectrometer with an ATR adapter (ZnSe crystal). TLC was performed on Silufol UV-254 plates in the chloroform—ethanol (3 : 1) system, compounds on TLC were visualized using UV light or iodine vapor.

Triethylammonium (5-carbamoyl-3*H*-imidazol-4-yl)dithiocarbamate (2a). To a solution of 5-aminoimidazole **1a** (2.83 mmol) in DMF (3 mL) and Et_3N (0.83 mL, 0.60 g, 5.95 mmol), carbon disulfide (0.2 mL, 0.25 g, 3.34 mmol) was added and the reaction mixture was kept for 24 h with stirring at room temperature. The mixture was diluted with chloroform (10 mL). The precipitate that formed was filtered off and purified by recrystallization from ethanol.

Ethyl (5-carbamoyl-3*H*-imidazol-4-yl)dithiocarbamate (3a). To a solution of dithiocarbamate **2a** (0.495 mmol) in DMF (1 mL), ethyl iodide (0.1 g, 0.641 mmol) was added and the reaction mixture was kept for 5 h at room temperature. The mixture was diluted with chloroform (25 mL). The precipitate that formed was filtered off and purified by recrystallization from ethanol.

Bis(4-chlorophenacyl) disulfide (4a), bis(4-nitrophenacyl) disulfide (4b) (general procedure). To a solution of 5-aminoimidazole **1a,b** (1.23 mmol) in DMF (1 mL) and Et_3N (0.4 mL), carbon disulfide (0.11 mL) was added and the reaction was kept for 24 h with stirring at room temperature. Bromoacetophenone (0.302 g, 1.29 mmol) was added. The mixture was kept for additional 1—2 h at room temperature and diluted with ice water (25 mL). The precipitate that formed was filtered off and purified by recrystallization from ethanol.

5-{[Ethylsulfanyl(phenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-carboxamide (5a), 5-{[ethylsulfanyl-(4-chlorophenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-carboxamide (5b), 5-{[ethylsulfanyl-(4-methoxyphenacylsulfanyl)methylidene]-amino}-1*H*-imidazole-4-carboxamide (5c), 5-{[ethylsulfanyl-(4-nitrophenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-carboxamide (5d), 5-{[ethylsulfanyl(phenacylsulfanyl)methylidene]-amino}-1*H*-imidazole-4-(*N*-methyl)carboxamide (5e), 5-{[ethylsulfanyl-(4-chlorophenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-(*N*-methyl)carboxamide (5f), 5-{[ethylsulfanyl-(4-methoxyphenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-(*N*-methyl)carboxamide (5g), 5-{[ethylsulfanyl-(4-nitrophenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-(*N*-methyl)carboxamide (5h), 5-{[ethylsulfanyl-(4-methylphenacylsulfanyl)methylidene]amino}-1*H*-imidazole-4-(*N*-methyl)carboxamide (5i) (general procedure). To a solution of ethyl dithiocarbamate **3a**,**b** (0.65 mmol) and haloketone (0.68 mmol) in DMF (1.5 mL), Et_3N (0.14 mL) was added and the reaction mixture was kept for 2 h with stirring at room temperature. The mixture was diluted with water (15 mL). The precipitate that formed was filtered off and purified by recrystallization from ethanol.

5-[2-Oxo-4-phenylthiazol-3-yl]-1*H*-imidazole-4-carboxamide (6a), 5-[2-oxo-4-(4-chlorophenyl)thiazol-3-yl]-1*H*-imidazole-4-carboxamide (6b), 5-[4-(4-nitrophenyl)-2-oxothiazol-3-yl]-1*H*-imidazole-4-carboxamide (6c), 5-[2-oxo-4-phenylthiazol-3-yl]-1*H*-imidazole-4-(*N*-methyl)carboxamide (6d), 5-[2-oxo-4-(4-chlorophenyl)thiazol-3-yl]-1*H*-imidazole-4-(*N*-methyl)carboxamide (6e), 5-[4-(4-nitrophenyl)-2-oxothiazol-3-yl]-1*H*-imidazole-4-(*N*-methyl)carboxamide (6f), 5-[4-(4-methoxyphenyl)-2-oxothiazol-3-yl]-1*H*-imidazole-4-carboxamide (6g), 5-[2-oxo-4-(*p*-tolyl)thiazol-3-yl]-1*H*-imidazole-4-carboxamide (6h) (general procedure *A*). To a solution of imidazolylthiazoline **5a**,**b**,**d**,**e**,**f**,**h** (0.28 mmol) in DMF (1 mL), Et_3N (0.2 mL) was added and the reaction mixture was kept for 5 (**6c**,**f**), 10 (**6b**,**e**), or 12 h (**6a**,**d**) at 60 °C. In the case of compounds **6c**,**f**, the mixture was diluted with water (20 mL). The precipitate that formed was filtered off. In the case of compounds **6a**,**b**,**d**,**e**, the reaction mixture was concentrated and the products were purified by recrystallization from an ethanol—acetonitrile (1 : 3) mixture.

Synthesis of compounds 6b,c,g,h (general procedure *B*). A solution of compound **8** (0.42 mmol) and haloketone (0.44 mmol) in acetonitrile (10 mL) was refluxed for 2 h. The precipitate that formed was filtered off and recrystallized from ethanol.

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Received February 3, 2011;
in revised form March 30, 2011