Synthesis and transformations of (imidazolylimino)thiazolidinones

O. S. El´tsov, V. S. Mokrushin, N. P. Bel´skaya, and N. M. Kozlova*

Urals State Technical University,
19 ul. Mira, 620002 Ekaterinburg, Russian Federation.
Fax: +7 (343 2) 74 5483. E-mail: eltsov@htf.ustu.ru

The reaction of ethyl 5-phenylthioureido-3*H*-imidazole-4-carboxylate with bromoacetic acid afforded (imidazolylimino)thiazolidinones, which were transformed into the corresponding 5-arylidene-4-thiazolidinones by the reactions with aldehydes. Under the conditions of the Knoevenagel reaction, the thiazolidine ring in derivatives of 4-(4-oxothiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxamides was opened to form substituted guanidines.

Key-words: (imidazolylimino)thiazolidinone, aldehydes, α-haloalkanoic acids and their esters, imidazolylthiourea, imidazolylisothiourea, 5-arylidene-4-thiazolidinones, guanidines.

As part of our continuing studies of the synthesis of new heterocyclic compounds based on esters and amides of 5-phenylthioureidoimidazole-4-carboxylic acid, which are derivatives of imidazolyliminothiazolines[1] and 2-(imidazolylamino)benzothiazoles,[2] we reported on the preparation of previously unknown (imidazolylimino)thiazolidinones and characteristic features of their selected transformations.

The condensation of thiourea derivatives with α-haloalkanoic acids and their esters[3] serves as a convenient procedure for the construction of the thiazolidinone ring. The presence of several reactive nucleophilic centers in derivatives of 5-thioureido-3*H*-imidazole-4-carboxylic acid **1a—g** is favorable for the formation of different products. Thus, cyclization can proceed at one of the nitrogen atoms of the thioureido substituent (to form thiazolidines **2** and **2´**) or at the nitrogen atom of the imidazole ring (to form thiadiazepines **2″**) in the case of unsubstituted compounds.

The reactions of thioureas **1a—c** with bromoacetic acid and the reactions of thioureas **1e,f** with ethyl chloroacetate afforded heterocycles **2a—c,e,f**, respectively (Scheme 1). To confirm the structures of the resulting compounds, (imidazolylimino)thiazolidines **2d** and **2g** were prepared by the reactions of 5-methylthioureido derivatives of imidazole-4-carboxylic acid **1d,g** with bromoacetic acid. The structures of the latter compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy (Tables 1 and 2). In the ^{13}C NMR spectra, the signals for the C(2) atoms are observed as a triplet of quartets with similar spin-spin coupling constants with the protons of the methylene (^3J = 1.9—2.0 Hz) and methyl (^3J = 1.7—1.8 Hz) groups. In the ^{13}C NMR spectra, the signals for the carbonyl C(4) atom of the thiazolidine ring located at lower field are also observed as a triplet of quartets with ^2J (C(4)—CH_2) = 6.2—6.9 Hz and ^3J (C(4)—CH_3) = 2.4 Hz. In the case of alternative structure **2´**, the C(4)—CH_3 spin-spin coupling constant would have a much smaller value.[4] Structure **2″** is also highly improbable, because the ^{13}C NMR spectra show neither coupling between the C(6) atom and the proton at the C(2´) atom of the imidazole ring nor coupling between the C(2) atom of the assumed seven-membered ring and the proton of the NH group.

Then we compared the UV spectra of the heterocycles prepared based on methyl- and phenylthioureas. The presence of absorption maxima in the UV spectra of compounds **2a** and **2d** at 222, 298 nm (**2a**) and 225, 301 nm (**2d**) are indicative of the similarity of these compounds. The spectra of heterocycles **2e** and **2g** are also characterized by very similar absorption maxima observed at 227, 303, 310 nm (**2e**) and at 230, 301, 310 nm (**2g**). The chemical shifts in the ^{13}C NMR spectra of these bicyclic compounds differ by 0.1—1.7 ppm, which also confirms the identity of their heterocyclic systems.

The reactions of compounds **2a—c** with aldehydes in the presence of piperidine afforded 5-substituted (imidazolylimino)thiazolidinones **3a—d**. Their structures are confirmed by the facts that the ^{1}H NMR spectra of these compounds have signals for the protons of the inserted aldehyde fragment, whereas the signal for the protons of the CH_2 group of the thiazolidinone ring is absent. In the mass spectra of compounds **3a—d**, *m/z* for the molecular ion peaks correspond to the calculated values.

Unlike ester derivatives **2a—c**, methylamide of 5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylic acid (**2e**) reacted with bezaldehyde in the presence of piperidine to give a product devoid of the sulfur atom. The ^{1}H NMR spectrum of the resulting compound has no signals for the protons of the ylidene

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 440—445, February, 2003.

1066-5285/03/5202-461 $25.00

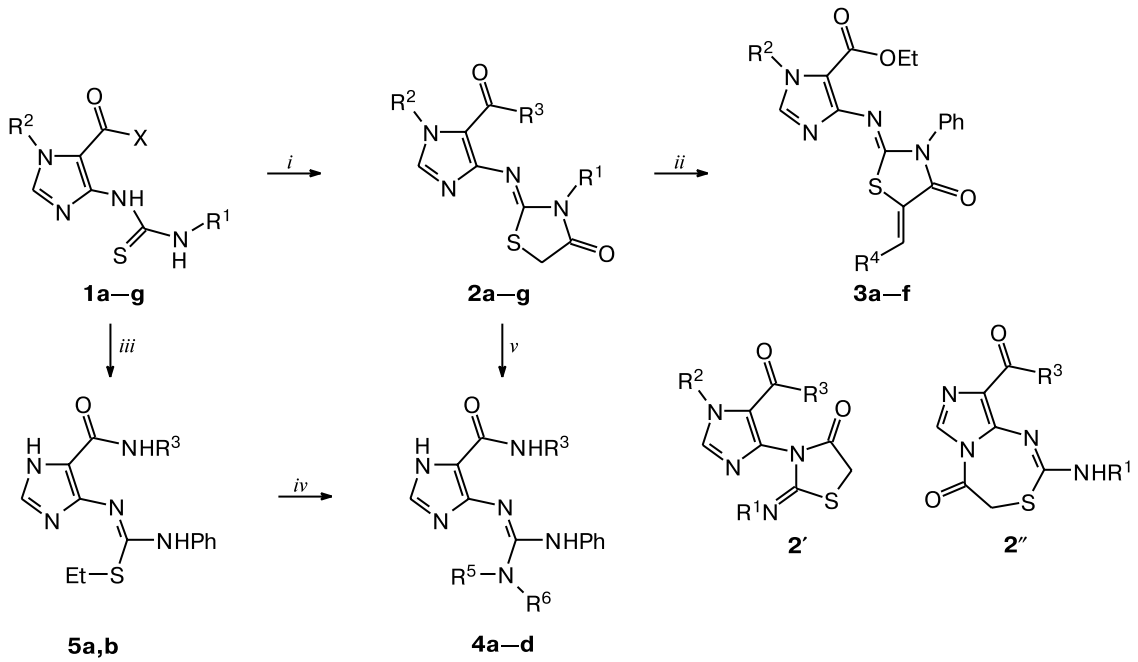
Table 1. Characteristics of the resulting compounds

Compound	Yield (%)	M.p. /°C	MS, m/z $[M]^+$	Found / Calculated (%)				Molecular formula	^{1}H NMR, δ (*J*/Hz)
				C	H	N	S		
2a	41	203—207	358	56.79 56.97	5.22 5.06	15.50 15.63	9.10 8.95	$C_{17}H_{18}N_4O_3S$	7.73 (s, 1 H, CH, Im); 7.50—7.32 (m, 5 H, Ph); 4.26 (q, 2 H, N$\underline{CH_2}CH_3$, *J* = 7.0); 4.03 (s, 2 H, CH_2); 4.00 (q, 2 H, O$\underline{CH_2}CH_3$, *J* = 7.0); 1.32, 1.00 (both t, 3 H each, $NCH_2\underline{CH_3}$, $OCH_2\underline{CH_3}$, *J* = 7.0)
2b	39	179—180	372	57.89 58.05	5.19 5.41	14.90 15.04	8.79 8.61	$C_{18}H_{20}N_4O_3S$	7.70 (s, 1 H, CH, Im); 7.50—7.32 (m, 5 H, Ph); 4.17 (t, 2 H, N$\underline{CH_2}CH_2CH_3$, *J* = 7.0); 4.03 (s, 2 H, CH_2); 3.99 (q, 2 H, O$\underline{CH_2}CH_3$, *J* = 7.0); 1.70 (m, 2 H, $NCH_2\underline{CH_2}CH_3$); 1.00 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 7.0); 0.84 (t, 3 H, $NCH_2CH_2\underline{CH_3}$, *J* = 7.3)
2c	44	243—244	386	56.11 55.95	4.54 4.70	14.33 14.50	8.46 8.30	$C_{18}H_{18}N_4O_4S$	7.64 (s, 1 H, CH, Im); 7.47—7.33 (m, 5 H, Ph); 5.08 (s, 2 H, N$\underline{CH_2}COCH_3$); 4.04 (s, 2 H, CH_2); 3.97 (q, 2 H, O$\underline{CH_2}CH_3$, *J* = 7.3); 2.14 (s, 3 H, $NCH_2CO\underline{CH_3}$); 0.97 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 7.3)
2d	35	149—150	296	48.81 48.65	5.25 5.41	18.70 18.92	11.00 10.81	$C_{12}H_{16}N_4O_3S$	7.77 (s, 1 H, CH, Im); 4.28, 4.26 (both q, 2 H each, N$\underline{CH_2}CH_3$, O$\underline{CH_2}CH_3$, *J* = 7.0); 3.87 (s, 2 H, CH_2); 3.21 (s, 3 H, NCH_3); 1.36, 1.34 (both t, 3 H each, $NCH_2\underline{CH_3}$, $OCH_2\underline{CH_3}$, *J* = 7.0)
2e	74	>300	315	53.49 53.32	4.00 4.16	22.10 22.21	9.99 10.17	$C_{14}H_{13}N_5O_2S$	12.79 (br.s, 1 H, NH, Im); 7.72—7.40 (m, 5 H, Ar, $\underline{NH}CH_3$); 7.65 (s, 1 H, CH, Im); 7.10—7.08 (m, 1 H, Ar); 4.15 (s, 2 H, CH_2); 2.37 (d, 3 H, $NH\underline{CH_3}$, *J* = 4.9)
2f	88	>300	391	61.21 61.37	4.28 4.38	17.74 17.89	8.29 8.19	$C_{20}H_{17}N_5O_2S$	12.93, 9.07 (both br.s, 1 H each, 2 NH); 7.70 (s, 1 H, CH, Im); 7.58—7.42 (m, 5 H, Ph); 6.95—6.53 (AA´BB´, 4 H, Ar, *J* = 8.2); 4.11 (s, 2 H, CH_2); 2.24 (s, 3 H, CH_3)
2g	44	292—293	253	42.84 42.69	4.17 4.35	27.50 27.67	12.82 12.65	$C_9H_{11}N_5O_2S$	12.80 (br.s, 1 H, NH, Im); 7.73 (br.s, 1 H, $\underline{NH}CH_3$); 7.52 (s, 1 H, CH, Im); 3.89 (s, 2 H, CH_2); 3.23 (s, 3 H, $N\underline{CH_3}$); 2.89 (d, 3 H, $NH\underline{CH_3}$, *J* = 4.6)
3a	55	232—233	446	64.72 64.56	4.80 4.97	12.39 12.55	7.01 7.18	$C_{24}H_{22}N_4O_3S$	7.83 (s, 1 H, CH, Im); 7.72 (s, 1 H, CH); 7.65—7.41 (m, 10 H, Ar); 4.30 (q, 2 H, N$\underline{CH_2}CH_3$, *J* = 7.3); 4.02 (q, 2 H, O$\underline{CH_2}CH_3$, *J* = 6.7); 1.35 (t, 3 H, $NCH_2\underline{CH_3}$, *J* = 7.3); 0.97 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 6.7)
3b	51	217—218	460	65.33 65.19	5.44 5.26	12.02 12.17	6.79 6.96	$C_{25}H_{24}N_4O_3S$	7.82 (s, 1 H, CH, Im); 7.72 (s, 1 H, CH); 7.66—7.42 (m, 10 H, Ar); 4.21 (t, 2 H, N$\underline{CH_2}CH_2CH_3$, *J* = 6.7); 4.02 (q, 2 H, O$\underline{CH_2}CH_3$, *J* = 7.0); 1.73 (m, 2 H, $NCH_2\underline{CH_2}CH_3$); 0.96 (t, 3 H, $NCH_2CH_2\underline{CH_3}$, *J* = 6.7); 0.87 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 7.0)
3c	43	212—213	478	62.58 62.74	4.68 4.85	11.90 11.71	6.88 6.70	$C_{25}H_{23}FN_4O_3S$	7.82 (s, 1 H, CH, Im); 7.72—7.66 (m, 3 H, Ar); 7.55—7.40 (m, 5 H, Ar, CH); 7.33—7.26 (m, 2 H, Ar); 4.21 (t, 2 H, N$\underline{CH_2}CH_2CH_3$, *J* = 7.0); 3.98 (q, 2 H, O$\underline{CH_2}CH_3$, *J* = 7.0); 1.67 (m, 2 H, $NCH_2\underline{CH_2}CH_3$); 0.96 (t, 3 H, $NCH_2CH_2\underline{CH_3}$, *J* = 7.0); 0.87 (t, 3 H, $OCH_2\underline{CH_3}$, *J* = 7.3)

3d	57	214—215	466	59.33 59.20	4.59 4.76	11.91 12.01	13.85 13.74	$C_{23}H_{22}N_4O_3S_2$	7.96 (s, 1 H, CH, Im); 7.86—7.21 (m, 9 H, Ar, CH, thienyl); 4.21 (t, 2 H, $N\underline{CH_2}CH_2CH_3$, J = 7.0); 4.02 (q, 2 H, $O\underline{CH_2}CH_3$, J = 7.0); 1.74 (m, 2 H, $NCH_2\underline{CH_2}CH_3$); 0.96 (t, 3 H, $NCH_2CH_2\underline{CH_3}$, J = 7.0); 0.87 (t, 3 H, $OCH_2\underline{CH_3}$, J = 7.3)
3e*	40	245—247	504	61.78 61.89	4.61 4.79	10.96 11.11	6.48 6.35	$C_{26}H_{24}N_4O_5S$	7.75, 7.69 (both s, 1 H each, CH, Im, CH); 7.64—7.06 (m, 9 H, Ar); 5.13, 5.08 (both s, 2 H, $N\underline{CH_2}COCH_3$); 4.04, 3.85 (both s, 3 H, OCH_3); 3.95 (q, 2 H, $O\underline{CH_2}CH_3$, J = 7.0); 2.16, 2.14 (both s, 3 H, $NCH_2CO\underline{CH_3}$); 0.94 (t, 3 H, $OCH_2\underline{CH_3}$, J = 7.0)
3f	31	203—204	426	59.39 59.15	4.99 5.16	13.28 13.15	7.40 7.51	$C_{21}H_{22}N_4O_4S$	7.67 (s, 1 H, CH, Im); 7.49—7.35 (m, 5 H, Ph); 6.85 (t, 1 H, $CH_3CH_2\underline{CH}$, J = 6.6); 5.10 (s, 2 H, $N\underline{CH_2}COCH_3$); 3.93 (q, 2 H, $O\underline{CH_2}CH_3$, J = 7.3); 2.32 (m, 2 H, $CH_3\underline{CH_2}CH$); 2.15 (s, 3 H, $NCH_2CO\underline{CH_3}$); 1.17 (t, 3 H, $\underline{CH_3}CH_2CH$, J = 6.7); 0.93 (t, 3 H, $OCH_2\underline{CH_3}$, J = 7.3)
4a	60	182—184	326	62.39 62.56	6.90 6.79	25.61 25.75	—	$C_{17}H_{22}N_6O$	12.51 (br.s, 1 H, NH, Im); 10.78, 8.63 (both br.s, 1 H each, 2 NH); 7.39 (s, 1 H, CH, Im); 7.34—7.12 (m, 5 H, Ph); 3.44—3.15 (m, 4 H, CH_2); 2.88 (d, 3 H, $NH\underline{CH_3}$, J = 4.6); 1.60—1.51 (m, 6 H, CH_2)
4b	52	181—183	302	55.49 55.62	6.19 6.00	27.63 27.80	—	$C_{14}H_{18}N_6O_2$	12.10 (br.s, 1 H, NH, Im); 8.90 (br.s, 2 H, 2 NH); 8.63 (br.s, 1 H, $\underline{NH}CH_3$); 7.32—7.01 (m, 6 H, CH, Im, Ph); 3.63, 3.41 (both m, 2 H each, $N\underline{CH_2}CH_2OH$, $NCH_2\underline{CH_2}OH$); 2.64 (d, 3 H, $NH\underline{CH_3}$, J = 4.7)
4c	30	230—231	404	65.19 65.32	6.10 5.98	20.89 20.78	—	$C_{22}H_{24}N_6O_2$	12.74 (br.s, 1 H, NH, Im); 11.03, 10.57 (both br.s, 1 H each, 2 NH); 7.51 (s, 1 H, CH, Im); 7.48—7.18 (m, 6 H, Ar); 7.11 (d, 2 H, Ar, J = 8.2); 7.03—6.96 (br.s, 1 H, Ar); 3.67—3.54 (m, 4 H, CH_2); 6.34—3.27 (s, 4 H, CH_2); 2.30 (s, 3 H, CH_3)
4d	42	222—223	424	70.59 70.73	5.55 5.70	19.62 19.80	—	$C_{25}H_{24}N_6O_2$	12.47, 10.63 (both br.s, 1 H each, 2 NH); 7.42—7.22 (m, 12 H, Ar, NH, CH, Im); 7.06—6.83 (m, 5 H, Ar); 4.67 (d, 2 H, $NH\underline{CH_2}$, J = 5.8); 2.22 (s, 3 H, CH_3)
5a	88	209—210	303	55.28 55.43	5.50 5.65	23.28 23.08	10.77 10.57	$C_{14}H_{17}N_5OS$	12.24, 11.76 (both br.s, 1 H each, 2 NH); 8.85 (br.s, 1 H, $\underline{NH}CH_3$); 7.49 (s, 1 H, CH, Im); 7.41—7.26 (m, 5 H, Ph); 3.03 (d, 3 H, $NH\underline{CH_3}$, J = 4.1); 2.96 (q, 2 H, $S\underline{CH_2}CH_3$, J = 7.6); 1.36 (t, 3 H, $SCH_2\underline{CH_3}$, J = 7.6)
5b	82	207—208	379	63.21 63.30	5.72 5.58	18.28 18.45	8.59 8.45	$C_{20}H_{21}N_5OS$	12.93, 12.07, 10.23 (all br.s, 1 H each, 3 NH); 7.58 (s, 1 H, CH, Im); 7.45—7.20 (m, 7 H, Ph, Ar); 7.10 (d, 2 H, Ar, J = 8.2); 3.14 (q, 2 H, $S\underline{CH_2}CH_3$, J = 7.3); 2.30 (s, 3 H, CH_3); 1.32 (t, 3 H, $SCH_2\underline{CH_3}$, J = 7.3)
6	55	250—252	330	54.80 54.55	4.15 4.24	17.21 16.97	9.80 9.69	$C_{15}H_{14}N_4O_3S$	12.09 (br.s, 1 H, OH); 8.11 (s, 1 H, CH, Im); 7.56—7.34 (m, 5 H, Ph); 4.32 (q, 2 H, $N\underline{CH_2}CH_3$, J = 7.0); 3.86 (s, 2 H, CH_2); 1.44 (t, 3 H, $NCH_2\underline{CH_3}$ J = 7.0)
7	42 (55)	141—142	193	60.26 55.96	3.80 3.65	7.48 7.25	16.25 16.59	$C_9H_7NO_2S$	7.49—7.24 (m, 5 H, Ph); 4.24 (s, 2 H, CH_2)

* A mixture of the *cis* and *trans* isomers.

Scheme 1



1, **2**	**a**	**b**	**c**	**d**	**e**	**f**	**g**
R^1	Ph	Ph	Ph	Me	Ph	Ph	Me
R^2	Et	Pr	CH_2Ac	Et	H	H	H
R^3	OEt	OEt	OEt	OEt	NHMe	NHTol-*p*	NHMe

3	**a**	**b**	**c**	**d**	**e**	**f**
R^2	Et	Pr	Pr	Pr	CH_2Ac	CH_2Ac
R^4	Ph	Ph	C_6H_4F-*p*	2-thienyl	C_6H_4OMe-*m*	Et

4	**a**	**b**	**c**	**d**
R^3	NHMe	OEt	NHTol-*p*	NHTol-*p*
R^5	—	H	—	H
R^6	—	$(CH_2)_2OH$	—	Bn
$R^5 + R^6$	$(CH_2)_5$	—	$(CH_2)_2O(CH_2)_2$	—

5	**a**	**b**
R^3	NHMe	NHTol-*p*

Reagents and conditions: *i*. $BrCH_2CO_2H$, EtOH, NaOAc (for **1a—d**); $ClCH_2CO_2Et$, DMF, Et_3N (for **1e—g**). *ii*. R^4CHO, EtOH, piperidine (for **2a—c**). *iii*. EtI, Et_3N, DMF (for **1e,f**). *iv*. $H_2N(CH_2)_2OH$ or H_2NBn. *v*. HNR^5R^6, DMF (for **2e,f**).

fragment. However, multiplets of the CH_2 groups of piperidine are observed at δ 3.44—3.15 and 1.60—1.51. We proposed that piperidine interacted with the C(2) atom of the thiazolidine ring, which was accompanied by the ring opening and elimination of the sulfur-containing fragment. Actually, the reactions of thiazolidines **2e,f** with amines also gave rise to guanidine derivatives **4a—d**.

Scheme 2

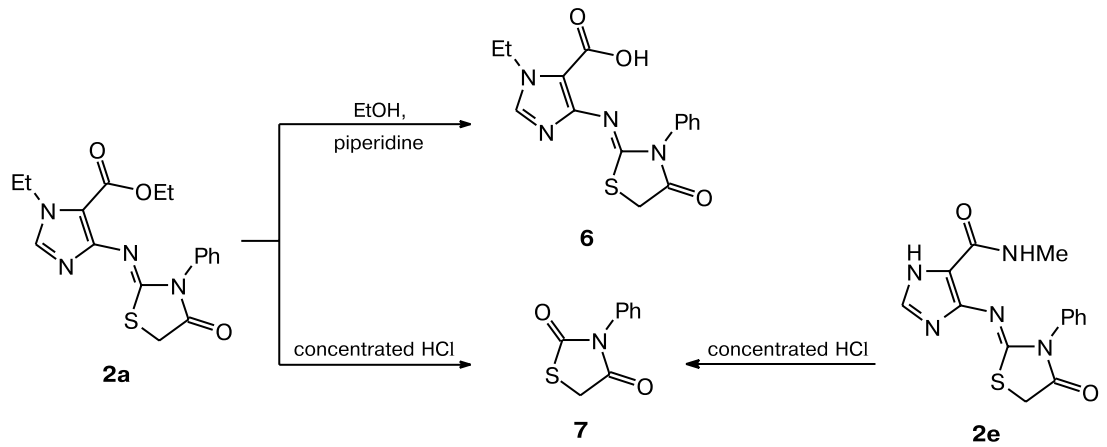
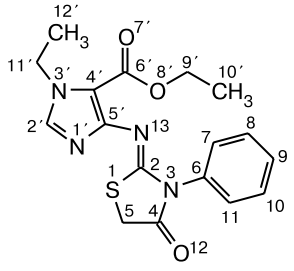
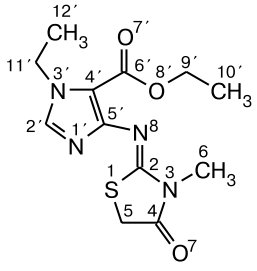


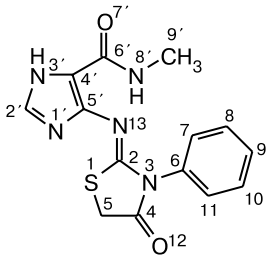
Table 2. Data from ^{13}C NMR spectroscopy* of compounds **2a,d,e,g**



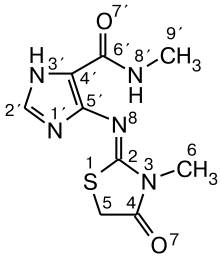
2a



2d



2e



2g

Compound	δ (*J*/Hz)
2a	171.6 (t, C(4), ^2J = 6.3); 159.7 (t, C(6′), ^3J = 4.4); 157.3 (t, C(2), ^3J = 1.7); 150.0 (d, C(5′), ^3J = 11.3); 138.7 (dt, C(2′), ^1J = 210.5, ^3J = 4.8); 135.5 (m, C(6)); 128.6 (dd, C(7), C(11), ^1J = 162.6, ^2J = 8.4); 128.4 (ddd, C(8), C(10), ^1J = 162.9, ^2J = 6.2, ^3J = 1.7); 128.1 (ddd, C(9), ^1J = 161.6, ^2J = 8.0, ^3J = 1.0); 110.9 (dt, C(4′), ^3J = 3.2, ^3J = 2.4); 59.4 (tq, C(9′), ^1J = 147.7, ^2J = 4.5); 41.8 (tqd, C(16′), ^1J = 142.2, ^2J = 4.5, ^3J = 1.3); 33.1 (t, C(5), ^1J = 147.1); 16.4 (qt, C(10′), ^1J = 127.7, ^2J = 3.3); 13.9 (qt, C(12′), ^1J = 126.8, ^2J = 2.6)
2d	171.9 (tq, C(4), ^2J = 6.2, ^3J = 2.4); 159.8 (t, C(6′), ^3J = 2.7); 156.8 (qt, C(2), ^3J = 1.9, ^3J = 1.7); 150.1 (d, C(5′), ^3J = 11.3); 138.7 (dt, C(2′), ^1J = 210.6, ^3J = 4.8); 111.3 (dt, C(4′), ^3J = 3.2, ^3J = 2.4); 59.6 (tq, C(9′), ^1J = 147.7, ^2J = 4.4); 41.9 (tqd, C(11′), ^1J = 141.8, ^2J = 4.6, ^3J = 1.3); 33.0 (t, C(5), ^1J = 146.8); 29.1 (q, C(6), ^1J = 141.5); 16.4 (qt, C(10′), ^1J = 127.6, ^2J = 3.4); 13.9 (qt, C(12′), ^1J = 126.7, ^2J = 2.6)
2e	171.2 (t, C(4), ^2J = 6.2); 159.5 (m, C(6′)); 157.3 (t, C(2), ^3J = 1.7); 143.6 (dd, C(5′), ^3J = 7.8, ^3J = 7.9); 135.8 (m, C(6)); 134.4 (dd, C(2′), ^1J = 210.7, ^2J = 1.6); 129.9 (dd, C(7), C(11), ^1J = 163.8, ^2J = 8.1); 128.8 (ddd, C(8), C(10), ^1J = 162.5, ^2J = 7.8); 128.1 (ddd, C(9), ^1J = 167.4, ^2J = 7.0); 115.9 (m, C(4′)); 33.8 (t, C(5), ^1J = 147.2); 24.8 (qd, C(9′), ^1J = 140.7, ^2J = 3.1)
2g	171.8 (tq, C(4), ^2J = 6.9, ^3J = 2.4); 159.9 (m, C(6′)); 157.4 (qt, C(2), ^3J = 2.0, ^3J = 1.8); 144.1 (dd, C(5′), ^3J = 8.4, ^3J = 11.2); 134.1 (dd, C(2′), ^1J = 209.6, ^2J = 3.4); 115.9 (m, C(4′)); 33.2 (t, C(5), ^1J = 146.9); 29.3 (q, C(6), ^1J = 141.6); 25.5 (qd, C(9′), ^1J = 137.8, ^2J = 3.0)

* The assignment of the chemical shifts was made and the spin-spin coupling constants were determined with the use of the BB and Gate techniques.

The thiazolidine-ring opening and the formation of guanidine structures were confirmed by the independent synthesis of compounds **4b,d** involving alkylation of thioureas **1e,f** with iodoethane to give isothioureas **5a,b** followed by the reactions of the latter compounds with amines.

Interestingly, the treatment of compound **2a** with piperidine in aqueous ethanol did not lead to the thiazolidine-ring opening. In the latter case, the ester group was hydrolyzed to form the derivative of imidazolecarboxylic acid **6** (Scheme 2). In our opinion, the difference in the behavior of bicyclic compounds **2a—c** and **2e,f** in the presence of amines is associated with the possibility of the formation of imidazolium salts in the case of compounds **2e,f** resulting in the redistribution of the electron density in the molecule and destabilization of the thiazole ring.

Acid hydrolysis of imidazolylthiazolidines **2a** and **2e** afforded 3-phenyl-2,4-thiazolidinedione (**7**) independently on the nature of the substituents at positions 1 and 5 of the imidazole ring.

The new imidazolylimino-substituted 5-arylidene-4-thiazolidinones, which are structurally similar to 5-arylidene-4-thiazolidinones exhibiting antimicrobial and pain-relieving activities,[5] and guanidine derivatives are of interest as potentially biologically active compounds.[6]

Experimental

The ^1H and ^{13}C NMR spectra were measured on a Bruker WM-250 instrument (250.13 and 100.00 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The course of the reactions and the purities of the resulting compounds were monitored by TLC on Sorbfil UV-254 plates in the 1 : 10 EtOH—$CHCl_3$ system. The UV spectra were recorded on a Specord-240 instrument. The concentration of the compounds in solutions in EtOH was $1.0 \cdot 10^{-5}$ mol L^{-1}. The mass spectra were measured on a Varian MAT 311A instrument; the accelerating voltage was 3 kV, the energy of ionizing electrons was 70 eV. The melting points were not corrected.

Compounds **1a—g** were prepared according to procedures described earlier.[1,7,8] The characteristics of the compounds are given in Tables 1 and 2.

Ethyl 3-ethyl-5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylate (2a), ethyl 5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3-propyl-3*H*-imidazole-4-carboxy-

late (2b), ethyl 3-(2-oxopropyl)-5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylate (2c), and ethyl 3-ethyl-5-(4-oxo-3-methylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylate (2d) (general procedure). Sodium acetate (3.45 mmol) and bromoacetic acid (1.38 mmol) were added to a solution of substituted thiourea **1a—d** (0.69 mmol) in EtOH (30 mL). The reaction mixture was refluxed for 2—3 h. Then water (30 mL) was added and the reaction mixture was cooled. The precipitate that formed was filtered off and purified by recrystallization from EtOH.

Methylamide of 5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylic acid (2e), *p*-tolylamide of 5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylic acid (2f), and methylamide of 5-(4-oxo-3-methylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylic acid (2g) (general procedure). Triethylamine (0.76 mmol) and ethyl chloroacetate (0.76 mmol) were added to a solution of substituted thiourea **1e—g** (0.69 mmol) in DMF (2 mL). The reaction mixture was kept at room temperature for 10 h and then H_2O (30 mL) was added. The precipitate that formed was filtered off, refluxed in EtOH (20 mL), filtered without cooling, and dried.

Ethyl 5-(5-benzylidene-4-oxo-3-phenylthiazolidin-2-ylideneamino)-3-ethyl-3*H*-imidazole-4-carboxylate (3a), ethyl 5-(5-benzylidene-4-oxo-3-phenylthiazolidin-2-ylideneamino)-3-propyl-3*H*-imidazole-4-carboxylate (3b), ethyl 5-[5-(4-fluorobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylideneamino]-3-propyl-3*H*-imidazole-4-carboxylate (3c), ethyl 5-[4-oxo-5-(2-thienylmethylene)-3-phenylthiazolidin-2-ylideneamino]-3-propyl-3*H*-imidazole-4-carboxylate (3d), ethyl 5-[(5-(3-methoxybenzylidene)-4-oxo-3-phenylthiazolidin-2-ylideneamino]-3-(2-oxopropyl)-3*H*-imidazole-4-carboxylate (3e), and ethyl 3-(2-oxopropyl)-5-[4-oxo-5-propylidene-3-phenylthiazolidin-2-ylideneamino]-3*H*-imidazole-4-carboxylate (3f) (general procedure). Compounds **2a—c** (0.70 mmol) were dissolved in EtOH (10—15 mL). Then aldehyde (0.77 mmol) and piperidine (7.00 mmol) were added. The reaction mixture was refluxed for 4—5 h and cooled. The precipitates of product **3a—f** that formed were filtered of and recrystallized from EtOH.

Methylamide of 5-(piperidino-*N*-phenylaminomethyleneamino)-3*H*-imidazole-4-carboxylic acid (4a), methylamide of 5-[(*N*-(2-hydroxyethyl)-*N*´-phenylguanidino]-3*H*-imidazole-4-carboxylic acid (4b), *p*-tolylamide of 5-(morpholino-*N*-phenylaminomethyleneamino)-3*H*-imidazole-4-carboxylic acid (4c), and methylamide of 5-[(*N*-benzyl-*N*´-phenylguanidino]-3*H*-imidazole-4-carboxylic acid (4d) (general procedure).

A. Dimethylformamide (2—3 mL) and amine (7.00 mmol) were added to compound **2e,f** (0.70 mmol). The reaction mixture was kept at 80 °C for 2—24 h and H_2O (30 mL) was added. Then 1 *N* HCl was added to pH 6—7, and the reaction mixture was kept for ~16 h. The precipitates of compound **4a—d** that formed were filtered off and purified by recrystallization from EtOH.

B. Isothiourea **5a,b** (0.70 mmol) was dissolved in EtOH (5 mL) and then amine (7.00 mmol) was added. The reaction mixture was refluxed for 6 h and then cooled. The precipitates of compounds **4b** and **4d** that formed were filtered off and crystallized from EtOH.

Methylamide of 5-(*S*-ethyl-1-phenylisothioureido)-3*H*-imidazole-4-carboxylic acid (5a) and *p*-tolylamide of 5-(*S*-ethyl-1-phenylisothioureido)-3*H*-imidazole-4-carboxylic acid (5b) (general procedure). Compound **1e,f** (0.69 mmol) was dissolved in DMF (2 mL), and then Et_3N (0.76 mmol) and EtI (0.76 mmol) were added. The reaction mixture was kept at room temperature for 10 h and then H_2O (30 mL) was added. The precipitate that formed was filtered off, recrystallized from EtOH, filtered off, and dried.

Synthesis of 3-ethyl-5-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-imidazole-4-carboxylic acid (6). A solution of compound **2a** (0.70 mmol) in EtOH (1 mL) and piperidine (7.00 mmol) was kept at 70—80 °C for 24 h. The resulting solution was neutralized with concentrated HCl to pH 6—7, H_2O (15 mL) was added, and the reaction mixture was cooled. The precipitate that formed was filtered off and purified by recrystallization from aqueous EtOH.

Synthesis of 3-phenyl-2,4-thiazolidinedione (7). Compound **2a** (or **2e**) (0.70 mmol) was dissolved in concentrated HCl (5 mL). The reaction mixture was kept at 70—80 °C for 0.5 h and then cooled. The precipitate that formed was filtered off and washed on a filter with water and EtOH.

This study was financially supported by the Russian Foundation for Basic Research (Project Nos. 01-03-32609 and 01-03-96433) and the US Civilian Research and Development Foundation (CRDF, Grant REC-005).

References

1. O. S. Eltsov, V. S. Mokrushin, T. V. Rybalova, Y. V. Gatilov, and A. V. Tkachev, *Mendeleev Commun.*, 2000, 233.
2. O. S. El´tsov and V. S. Mokrushin, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 506 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 547].
3. T. S. Griffin, T. S. Woods, and D. L. Klayman, *Adv. Heterocycl. Chem.*, 1975, **18**, 99.
4. *Spectroscopic Methods in Organic Chemistry*, Eds. M. Hesse, H. Meier, and B. Zeeh, Thieme, New York, 1997, 365 pp.
5. S. Mishra, S. K. Srivastava, and S. D. Srivastava, *Ind. J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1997, **36(B)**, 826.
6. K. Feichtinger, C. Zapf, H. L. Sings, and M. Goodman, *J. Org. Chem.*, 1998, **63**, 3804.
7. A. H. Cook, A. C. Davis, Sir Ian Heilbron, and G. H. Thomas, *J. Chem. Soc.*, 1949, 1071.
8. Y. Wang, P. R. Lowe, W. T. Thomson, J. Clark, and M. F. G. Stevens, *Chem. Commun.*, 1997, 363.

Received March 18, 2002;
in revised form October 8, 2002