Synthesis of 2-iminoimidazolidin-4-one derivatives by cyclization of 2-aryl-1-(4,6-dimethylpyrimidin-2-yl)guanidines with ethyl bromoacetate, dimethyl acetylenedicarboxylate, and maleic anhydride

A. S. Shestakov, O. E. Sidorenko, and Kh. S. Shikhaliev★

Voronezh State University,
1 Universitetskaya pl., 394006 Voronezh, Russian Federation.
Fax: +7 (473 2) 55 6890. E-mail: chocd261@chem.vsu.ru

Derivatives of 2-iminoimidazolidin-4-one, (*E*)-methyl (2-imino-5-oxoimidazolidin-4-ylidene)acetate, and (2-imino-5-oxo-imidazolidin-4-yl)acetic acid were synthesized by the cyclization of 2-aryl-1-(4,6-dimethylpyrimidin-2-yl)guanidines with ethyl bromoacetate, dimethyl acetylenedicarboxylate, and maleic anhydride, respectively.

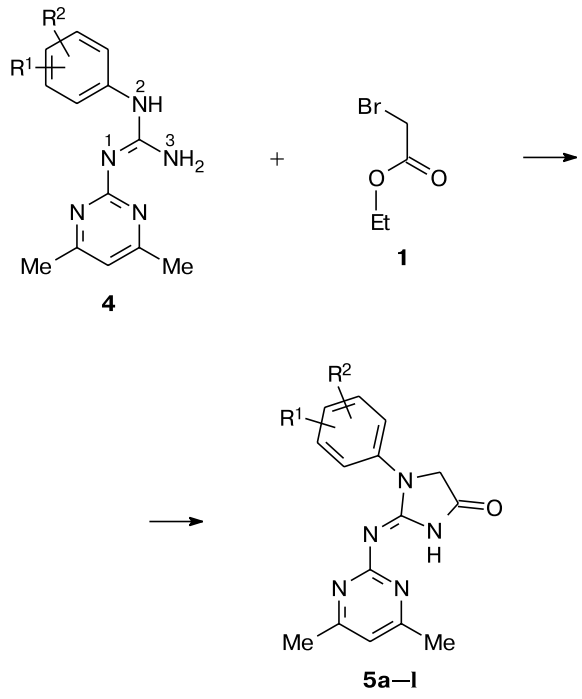
Key words: 2-aryl-1-(4,6-dimethylpyrimidin-2-yl)guanidines, ethyl bromoacetate, dimethyl acetylenedicarboxylate, maleic anhydride, imidazole, NOESY, dielectrophiles, cyclization.

Guanidines serve as convenient building blocks for the formation of heterocyclic moieties with two nitrogen atoms. The heterocyclization proceeds with the involvement of the N—C—N fragment of guanidine. The condensation of the latter with the bis-electrophilic two-carbon fragment affords the imidazole system.[1] α-Halo- or α-hydroxycarbonyl compounds are most often used as dielectrophiles. In the present study, we investigated the heterocyclization of unsymmetrical guanidines with commercially available ethyl bromoacetate **1**, dimethyl acetylenedicarboxylate (DMAD) **2**, and maleic anhydride **3**. Guanidines **4** were synthesized from pentane-2,4-dione, dicyanodiamide, and anilines.[2]

It was found that the reaction of ethyl bromoacetate **1** with guanidines **4** regioselectively produces 1-aryl-2-[(4,6-dimethylpyrimidin-2-yl)imino]imidazolidin-4-ones **5** (Scheme 1). Excess guanidine acts as an acceptor of hydrobromic acid that is eliminated in the reaction.

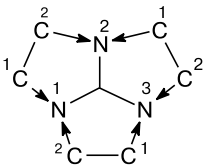
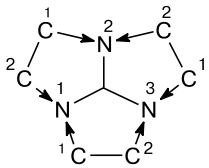
Ester **1** is an unsymmetrical two-carbon electrophile, which can form two regioisomeric imidazolones in reactions with the unsymmetrical bis-nucleophilic R—NH—C—NH—R′ fragment of guanidines **4**. Taking into account that guanidines **4** contain three 1,3-bi-nucleophilic moieties sharing the carbon atom, the number of possible regioisomeric cyclization products equals six. Strictly speaking, the involvement of the pyrimidine nitrogen atom in the reaction cannot be ruled out as well. This reaction was described for 2-aminopyrimidine and ethyl bromoacetate.[3] However, in the case under consideration, this reaction is hardly probable taking into account the presence of the nucleophilic guanidine fragment. All possible cyclization products do not differ in the elemental composition, and the ^{1}H NMR spectrum contradicts none of these structures. The data considered below suggest that the cyclization affords compound **5**.

Scheme 1



5	R^1	R^2	5	R^1	R^2
a	H	H	**g**	H	3-F
b	H	2-Me	**h**	H	4-F
c	3-Me	4-Me	**i**	H	4-Ph
d	3-MeO	4-MeO	**j**	H	4-Bu
e	H	4-EtO	**k**	3-Cl	4-Cl
f	H	4-Et	**l**	H	2-MeO

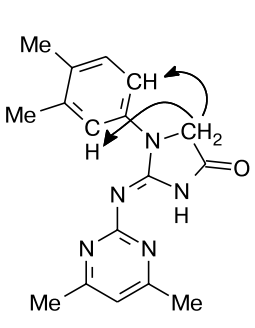
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1372—1378, July, 2007.

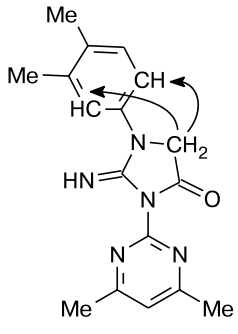



Preliminarily, we performed quantum chemical calculations for the geometric parameters and the electronic structures of guanidines **4** with the use of the GAUSSIAN-03 program package.[4] The calculations were carried out by the density functional theory using the B3LYP functional. The full geometry optimization of the molecule was performed with the 3-21G* basis set. The electronic structures were calculated using the 6-31G* basis set. The choice of the basis set and the calculation method was substantiated by the fact that a further increase in the accuracy of calculations did not lead to substantial changes in the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

The calculations demonstrated that the region, where the wave function of the HOMO differs from zero, is located on the nitrogen atoms N(2) and N(3). Therefore, these atoms should be involved in the ring formation in orbital-controlled reactions.

The structures of the heterocycles were confirmed by the NOESY experiment. The spectrum of compound **5c** shows intense correlation peaks at δ 4.44/7.47 and 4.44/7.63, which correspond to the interactions between the methylene protons of iminoimidazolidinone **5** and the *ortho* protons of the phenyl group. These interactions are possible only for two regioisomers, *viz.*, **5c** and **5´c**. However, the formation of compound **5´c** assumes that the most easily accessible N(3) atom is not involved in cyclization despite the fact that this atom, unlike the N(1) and N(2) atoms, is involved in the reactions with such electrophiles as isocyanates, acid chlorides, and sulfochlorides.[2] The formation of a product analogous to **5c** was detected in the reaction of mixed anhydride of acetic and chloroacetic acids with symmetrical diarylguanidines.[5] Structure **5´c** contradicts the above-considered calculations of the electron distribution on HOMO. In addition,


5c


5´c

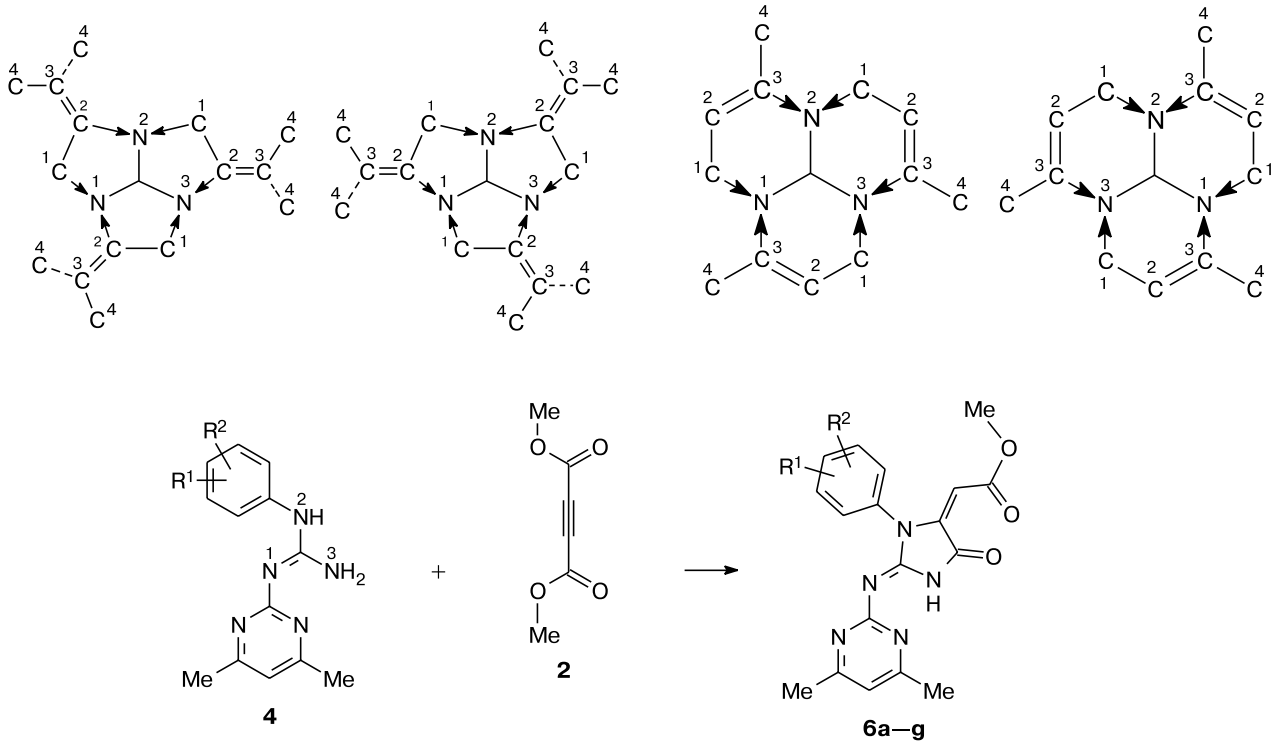
cross-peaks between the proton of the free imino group and the *ortho* protons of the phenyl group are absent in the NOESY spectrum. Hence, the reaction of ethyl bromoacetate **1** with guanidines **4** produces compounds of general formula **5**. These compounds can undergo keto-enol tautomerism. The fact that the ^{1}H NMR spectrum in DMSO-d_6 shows a singlet at δ 4.44 is indicative of the almost complete shift of the equilibrium toward the ketone form.

Dimethyl acetylenedicarboxylate was used as another cyclizing agent. Guanidines **4** actively react with this compound in chloroform at room temperature, and these reactions are also regioselective.

Ester **2** contains four electrophilic centers (two carbonyl and two acetylenic carbon atoms). The reaction of DMAD with guanidines would be expected to yield both six-membered pyrimidin-4-ones and five-membered imidazolin-4-ones. In this case, the number of possible regioisomers is 12. Taking into account the *E*,*Z* isomerism in the case of the exocyclic position of the double bond in imidazolin-4-ones, it can easily be seen that the number of possible isomers increases to 18. Therefore, in the case under consideration, the formation of heterocycles corresponding to structure **6** (Scheme 2) was not apparent.

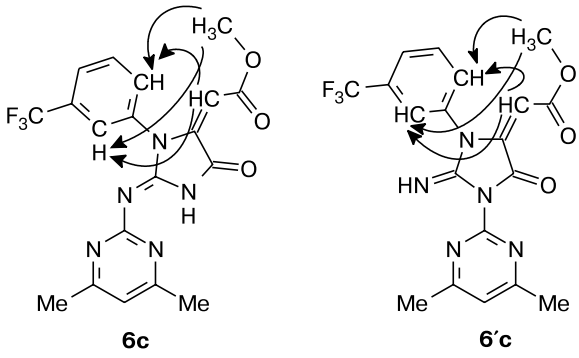
Both the five- and six-membered reaction products of DMAD with 1,3-binucleophiles were described in the literature. X-ray diffraction data show that triphenylguanidine forms five-membered imidazolidinone,[6] whereas 2-aminobenzothiazole gives six-membered pyrimidinone.[7] The reactions of 2-aminobenzothiazoles with derivatives of hex-3-yne-2,5-dione, which is a ketone analog of DMAD, also produce pyrimidinone.[8] Depending on the number of substituents and the reaction conditions, the reactions of aminoguanidine derivatives with DMAD give both imidazolidinones and pyrimidinones.[9] In the ^{1}H NMR spectra of the five-membered cyclization products, the signal for the β-enamine proton is shifted upfield (δ ~5.9) compared to the analogous signal in the spectra of the six-membered compounds (δ ~6.6). Based on this fact, it was concluded that DMAD reacts with unsubstituted guanidine to give the five-membered heterocycle.[6] The position of the signal for this proton (δ 5.54—5.71) in the spectra of the reaction products suggests that the reactions afford one of 12 possible imidazolidinones. The ultimate choice was made based on the NOESY data. The spectra were measured for compound **6c**. It appeared that the β-enamine proton (δ 5.74) and the protons of the —OCH_3 group (δ 3.15) give cross-peaks with the *ortho* protons of the phenyl group (δ 7.79 and 7.81). This is possible only for two of 18 probable cyclization products, *viz.*, **6c** and **6´c**. Based on the above-considered evidence in favor of structure **5** assigned to the cyclization product of guanidines **4** and ester **1**, it can be concluded that the reactions of compounds **4** and **2** produce compounds **6**, whose structures are presented in

Scheme 2



6	R^1	R^2	6	R^1	R^2
a	H	H	**e**	3-Cl	4-Cl
b	H	4-Me	**f**	H	3-Me
c	H	3-CF_3	**g**	H	3-EtO
d	H	4-Cl			

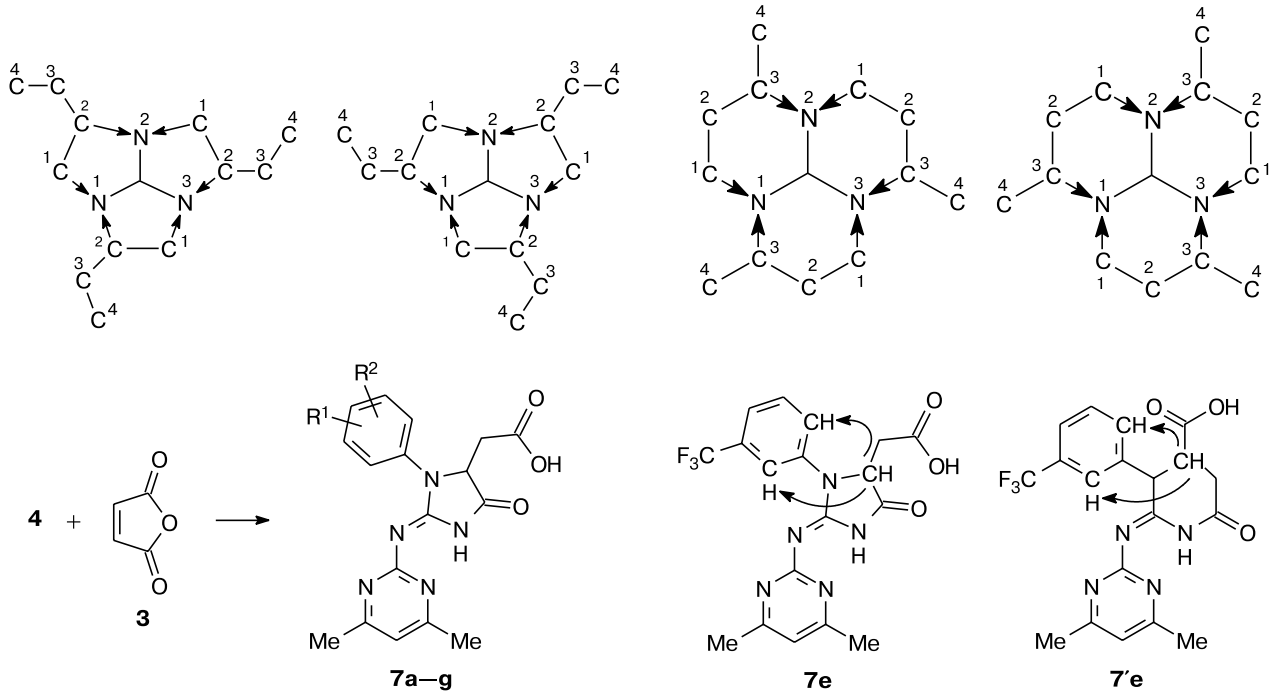
Scheme 2. The presence of the above-mentioned correlation peaks at δ 5.74/7.79 and 3.15/7.79 is evidence that compounds **6** exist as *Z* isomers. Actually, the analysis of the interatomic distances, which were estimated by the quantum chemical calculations for compound **6c**, shows that the distances between these protons in the *E* isomer are longer than 6 Å, which does not allow the observation of the nuclear Overhauser effect.



We performed the analogous cyclization by heating maleic anhydride **3** with guanidines **4** in dioxane (Scheme 3). As in the above-considered case, the number of possible regioisomers is 12. In the reactions of disubstituted guanidines with strong electrophiles, including anhydrides, the attack occurs on the N(3) atom of guanidine.[2] Hence, four regioisomers, in which this nitrogen atom remains unsubstituted, can be excluded from consideration. Based on the analysis of the NOESY spectrum for compound **7e**, six other possible structures can be rejected. Hence, two structures, **7e** and **7′e**, should be considered. For these structures, the correlation peaks between the methine proton of the heterocycle and the *ortho* protons of the phenyl group can be observed. These cross-peaks are actually present in the spectrum at δ 5.19/7.84 and 5.19/7.79.

The absence of cross-peaks between the phenyl *ortho* protons and either the protons of the carboxy group, the presence of which would be evidence in favor of structure **7′e**, or the methylene protons, which would be evidence for structure **7e**, does not allow us to decide between these structures based only on the NOESY spectrum. However, the data published in the literature show that structure **7e** is more favorable. It is known that the cyclization products with N,S-binucleophiles are often

Scheme 3



7	R^1	R^2	7	R^1	R^2
a	H	4-MeO	**e**	H	3-CF_3
b	H	3-Cl	**f**	2-MeO	5-MeO
c	H	3-Me	**g**	2-Cl	4-Cl
d	3-Me	4-Me			

analogous to those formed by N,N-binucleophiles.[6] For example, the reactions of maleic anhydride with thiocarbamides[10,11] and thioamides[12] produce five-membered thiazolines. The X-ray diffraction study showed that the reactions of amidines with arylmaleinimides afford five-membered oxoimidazole rather than oxopyrimidine derivatives.[13]

Experimental

The ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz) at 20 °C in DMSO-d_6 with Me_4Si as the internal standard. The 2D ^{1}H NMR spectra were measured on a Bruker DRX-500 instrument (500 MHz) at 20 °C in DMSO-d_6. The purity of the compounds and the course of the reactions were monitored by TLC on Merck UV-254 plates (chloroform—methanol, 20 : 1, as the eluent).

2-Iminoimidazolidin-4-ones 5 (general procedure). Ester **1** (1.2 mL, 11 mmol) was added dropwise to a solution of guanidine **4** (20 mmol) in dioxane (40 mL), and the reaction mixture was heated at 90 °C for 5 h. The precipitate of guanidine hydrobromide that formed upon cooling of the reaction mixture was filtered off, and the filtrate was concentrated. The residue was twice recrystallized from isopropyl alcohol. (*E*)-2-[(4,6-Dimethylpyrimidin-2-yl)imino]-1-phenylimidazolidin-4-one (**5a**), (*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-*o*-tolylimidazolidin-4-one (**5b**), (*E*)-1-(3,4-dimethylphenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]imidazolidin-4-one (**5c**), (*E*)-1-(3,4-dimethoxyphenyl)imidazolidin-2-[(4,6-dimethylpyrimidin-2-yl)imino]-4-one (**5d**), (*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-(4-ethoxyphenyl)imidazolidin-4-one (**5e**), (*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-(4-ethylphenyl)imidazolidin-4-one (**5f**), (*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-(3-fluorophenyl)imidazolidin-4-one (**5g**), (*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-(4-fluorophenyl)imidazolidin-4-one (**5h**), (*E*)-1-(biphenyl-4-yl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]imidazolidin-4-one (**5i**), (*E*)-1-(4-butylphenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]imidazolidin-4-one (**5j**), (*E*)-1-(3,4-dichlorophenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]imidazolidin-4-one (**5k**), and (*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-1-(2-methoxyphenyl)imidazolidin-4-one (**5l**) were prepared. The yields, melting points, elemental analysis data, and ^{1}H NMR spectroscopic data for compounds **5a—l** are given in Table 1.

(*E*)-Methyl (2-imino-5-oxoimidazolidin-4-ylidene)acetates 6 (general procedure). Dimethyl acetylenedicarboxylate (1.35 mL, 11 mmol) was added dropwise to a solution of guanidine **4** (10 mmol) in chloroform (20 mL), during which the reaction mixture warmed up and rapidly turned dark-red. After 1 h, the solution was concentrated to a minimum volume and passed through an alumina column. The eluate was concentrated, and the residue was recrystallized from isopropyl alcohol. (*E*)-Methyl 2-{(*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxo-3-phenylimidazolidin-4-ylidene}acetate (**6a**), (*E*)-methyl

Table 1. Characteristics of 2-iminoimidazolidin-4-ones **5a—l**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N		
5a	48	176	64.17 64.06	5.41 5.34	24.79 24.91	$C_{15}H_{15}N_5O$	2.39 (s, 6 H, 2 Me); 4.50 (s, 2 H, CH_2); 6.72 (s, 1 H, H(5), pyrimidine); 7.19 (t, 1 H, H arom., *J* = 7.5); 7.40 (t, 2 H, H arom., *J* = 7.3); 7.90 (d, 2 H, H arom., *J* = 7.5); 9.80 (br.s, 1 H, NH)
5b	41	151	65.16 65.08	5.68 5.76	23.86 23.73	$C_{16}H_{17}N_5O$	2.21 (s, 3 H, Me); 2.35 (s, 6 H, 2 Me); 4.45 (s, 2 H, CH_2); 6.70 (s, 1 H, H(5), pyrimidine); 7.12 (d, 1 H, H arom., *J* = 8.9); 7.28 (t, 1 H, H arom., *J* = 8.9); 7.46 (d, 1 H, H arom., *J* = 8.9); 7.73 (t, 1 H, H arom., *J* = 7.2); 9.21 (br.s, 1 H, NH)
5c	42	153	65.89 66.02	6.04 6.15	22.69 22.65	$C_{17}H_{19}N_5O$	2.20, 2.23 (both s, 3 H each, 2 Me); 2.34 (s, 6 H, 2 Me); 4.44 (s, 2 H, CH_2); 6.78 (s, 1 H, H(5), pyrimidine); 7.14 (d, 1 H, H arom., *J* = 8.5); 7.47 (s, 1 H, H arom.); 7.63 (d, 1 H, H arom., *J* = 8.0); 11.44 (br.s, 1 H, NH)
5d	62	198	59.64 59.82	5.50 5.57	20.41 20.53	$C_{17}H_{19}N_5O_3$	2.34 (s, 6 H, 2 Me); 3.75, 3.81 (both s, 3 H each, 2 OMe); 4.18 (s, 2 H, CH_2); 6.71 (s, 1 H, H(5), pyrimidine); 6.78 (d, 1 H, H arom., *J* = 7.4); 7.12 (d, 1 H, H arom., *J* = 8.4); 7.62 (s, 1 H, H arom.); 11.20 (br.s, 1 H, NH)
5e	46	156	62.70 62.77	5.85 5.85	21.61 21.54	$C_{17}H_{19}N_5O_2$	1.35 (t, 3 H, $CH_2\underline{Me}$, *J* = 7.2); 2.36 (s, 6 H, 2 Me); 4.31 (s, 2 H, CH_2); 4.45 (q, 2 H, $C\underline{H}_2Me$, *J* = 7.2); 6.63 (s, 1 H, H(5), pyrimidine); 7.08 (d, 2 H, H arom., *J* = 7.3); 7.54 (d, 2 H, H arom., *J* = 8.6); 10.80 (br.s, 1 H, NH)
5f	52	166	66.08 66.02	6.19 6.15	22.51 22.65	$C_{17}H_{19}N_5O$	1.12 (t, 3 H, $CH_2\underline{Me}$, *J* = 7.4); 2.32 (s, 6 H, 2 Me); 2.64 (q, 2 H, $C\underline{H}_2Me$, *J* = 7.4); 4.42 (s, 2 H, CH_2); 6.75 (s, 1 H, H(5), pyrimidine); 7.12 (d, 2 H, H arom., *J* = 7.3); 7.62 (d, 2 H, H arom., *J* = 8.6); 11.10 (br.s, 1 H, NH)
5g	64	201	60.12 60.20	4.75 4.68	23.59 23.41	$C_{15}H_{14}FN_5O$	2.32 (s, 6 H, 2 Me); 4.35 (s, 2 H, CH_2); 6.84 (s, 1 H, H(5), pyrimidine); 7.05 (s, 1 H, H arom.); 7.12 (d, 1 H, H arom., *J* = 8.2); 7.26 (t, 1 H, H arom., *J* = 8.2); 7.41 (d, 1 H, H arom., *J* = 8.3); 10.40 (br.s, 1 H, NH)
5h	61	221	59.91 60.20	4.56 4.68	23.36 23.41	$C_{15}H_{14}FN_5O$	2.31 (s, 6 H, 2 Me); 4.32 (s, 2 H, CH_2); 6.88 (s, 1 H, H(5), pyrimidine); 7.25 (d, 2 H, H arom., *J* = 7.6); 7.41 (d, 2 H, H arom., *J* = 8.5); 10.40 (br.s, 1 H, NH)
5i	58	212	70.83 70.59	5.30 5.32	19.70 19.61	$C_{21}H_{19}N_5O$	2.30 (s, 6 H, 2 Me); 4.36 (s, 2 H, CH_2); 6.82 (s, 1 H, H(5), pyrimidine); 6.94 (d, 2 H, H arom., *J* = 8.6); 7.21 (t, 1 H, H arom., *J* = 7.3); 6.33 (t, 2 H, H arom., *J* = 7.4); 6.52 (d, 2 H, H arom., *J* = 7.9); 7.75 (d, 2 H, H arom., *J* = 8.5); 10.60 (br.s, 1 H, NH)
5j	52	113	67.81 67.66	6.74 6.82	20.56 20.77	$C_{19}H_{23}N_5O$	0.95 (t, 3 H, $CH_2\underline{Me}$, *J* = 7.0); 1.39 (m, 2 H, $CH_2C\underline{H}_2Me$); 1.60 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.38 (s, 6 H, 2 Me); 2.61 (t, 2 H, $ArC\underline{H}_2CH_2$, *J* = 7.5); 4.48 (s, 2 H, CH_2); 6.71 (s, 1 H, H(5), pyrimidine); 7.19 (d, 2 H, H arom., *J* = 7.6); 7.74 (d, 2 H, H arom., *J* = 8.5); 11.60 (br.s, 1 H, NH)
5k	50	242	51.29 51.43	3.68 3.71	19.87 20.00	$C_{15}H_{13}Cl_2N_5O$	2.31 (s, 6 H, 2 Me); 4.35 (s, 2 H, CH_2); 6.68 (s, 1 H, H(5), pyrimidine); 7.42 (d, 1 H, H arom., *J* = 8.5); 7.53 (s, 1 H, H arom.); 7.56 (d, 1 H, H arom., *J* = 8.5); 9.85 (br.s, 1 H, NH)
5l	58	175	65.18 65.08	5.64 5.76	23.73 23.73	$C_{16}H_{17}N_5O$	2.35 (s, 6 H, 2 Me); 3.89 (s, 3 H, OMe); 4.27 (s, 2 H, CH_2); 6.61 (s, 1 H, H(5), pyrimidine); 7.00 (t, 1 H, H arom., *J* = 8.5); 7.10 (d, 1 H, H arom., *J* = 8.5); 7.32 (t, 1 H, H arom., *J* = 8.0); 7.44 (d, 1 H, H arom., *J* = 8.5); 11.60 (br.s, 1 H, NH)

Table 2. Characteristics of (*E*)-methyl (2-imino-5-oxoimidazolidin-4-ylidene)acetates **6a—g**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N		
6a	29	198	61.73 61.54	4.76 4.84	20.15 19.94	$C_{18}H_{17}N_5O_3$	2.35 (s, 6 H, 2 Me); 3.15 (s, 3 H, OMe); 5.71 (s, 1 H, —CH=); 6.80 (s, 1 H, H(5), pyrimidine); 7.16 (d, 2 H, H arom., *J* = 8.0); 7.36 (t, 2 H, H arom., *J* = 7.5); 7.42 (t, 1 H, H arom., *J* = 7.6); 11.80 (br.s, 1 H, NH)
6b	38	193	62.28 62.47	5.16 5.21	19.25 19.18	$C_{19}H_{19}N_5O_3$	2.12 (s, 3 H, Me); 2.33 (s, 6 H, 2 Me); 3.22 (s, 3 H, OMe); 5.62 (s, 1 H, —CH=); 6.74 (s, 1 H, H(5), pyrimidine); 7.21, 7.53 (both d, 2 H each, H arom., *J* = 8.2); 11.60 (br.s, 1 H, NH)
6c	41	195	54.54 54.42	3.80 3.82	16.70 16.71	$C_{19}H_{16}F_3N_5O_3$	2.32 (s, 6 H, 2 Me); 3.15 (s, 3 H, OMe); 5.74 (s, 1 H, —CH=); 6.70 (s, 1 H, H(5), pyrimidine); 7.71 (d, 1 H, *J* = 8.0); 7.74 (t, 1 H, H arom., *J* = 7.9); 7.79 (d, 1 H, *J* = 8.0); 7.81 (s, 1 H, H arom.); 11.50 (br.s, 1 H, NH)
6d	42	202	56.10 56.02	4.12 4.15	18.08 18.15	$C_{18}H_{16}ClN_5O_3$	2.34 (s, 6 H, 2 Me); 3.14 (s, 3 H, OMe); 5.71 (s, 1 H, —CH=); 6.89 (s, 1 H, H(5), pyrimidine); 7.30, 7.60 (both d, 2 H each, H arom., *J* = 8.2); 11.80 (br.s, 1 H, NH)
6e	43	177	51.48 51.43	3.62 3.57	16.61 16.67	$C_{18}H_{15}Cl_2N_5O_3$	2.32 (s, 6 H, 2 Me); 3.18 (s, 3 H, OMe); 5.58 (s, 1 H, —CH=); 6.72 (s, 1 H, H(5), pyrimidine); 7.19, 7.54 (both d, 1 H each, H arom., *J* = 8.1); 8.10 (s, 1 H, H arom.); 11.50 (br.s, 1 H, NH)
6f	65	159	62.36 62.47	5.32 5.21	19.06 19.18	$C_{19}H_{19}N_5O_3$	2.36 (s, 6 H, 2 Me); 2.52 (s, 3 H, Me); 3.17 (s, 3 H, OMe); 5.70 (s, 1 H, —CH=); 6.82 (s, 1 H, H(5), pyrimidine); 7.95 (d, 1 H, H arom., *J* = 7.8); 7.32 (d, 1 H, H arom., *J* = 8.1); 7.61 (t, 1 H, H arom., *J* = 7.7); 7.81 (s, 1 H, H arom.); 11.70 (br.s, 1 H, NH)
6g	44	160	60.84 60.76	5.46 5.32	17.61 17.72	$C_{20}H_{21}N_5O_4$	1.33 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7.2); 2.34 (s, 6 H, 2 Me); 3.16 (s, 3 H, OMe); 3.90 (q, 2 H, $OC\underline{H}_2Me$, *J* = 7.2); 5.70 (s, 1 H, —CH=); 6.83 (s, 1 H, H(5), pyrimidine); 7.10, 7.50 (both d, 2 H each, H arom., *J* = 8.2); 11.50 (br.s, 1 H, NH)

Table 3. Characteristics of (2-imino-5-oxoimidazolidin-4-yl)acetic acids **7a—g**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N		
7a	44	224	58.46 58.54	5.23 5.15	19.06 18.97	$C_{18}H_{19}N_5O_4$	2.45 (s, 6 H, 2 Me); 2.87 (dd, 1 H, CH_2, *J* = 4.4, *J* = 17.9); 3.13 (dd, 1 H, CH_2, *J* = 5.6, *J* = 17.9); 3.79 (s, 1 H, OMe); 4.64 (t, 1 H, CH, *J* = 6.8); 6.92 (s, 1 H, H(5), pyrimidine); 6.98 (d, 2 H, H arom., *J* = 7.2); 7.24 (d, 2 H, H arom., *J* = 7.7); 12.15 (br.s, 1 H, COOH); 12.33 (s, 1 H, NH)
7b	36	305	54.44 54.60	4.29 4.28	18.63 18.74	$C_{17}H_{16}ClN_5O_3$	2.39 (s, 6 H, 2 Me); 2.69 (dd, 1 H, CH_2, *J* = 4.8, *J* = 18.3); 2.94 (dd, 1 H, CH_2, *J* = 5.8, *J* = 18.3); 4.93 (t, 1 H, CH, *J* = 6.6); 6.97 (s, 1 H, H(5), pyrimidine); 7.37 (d, 1 H, H arom., *J* = 7.4); 7.53 (t, 1 H, H arom., *J* = 8.4); 7.72 (d, 1 H, H arom., *J* = 7.6); 8.12 (s, 1 H, H arom.); 12.2 (br.s, 1 H, COOH); 12.41 (s, 1 H, NH)

(*to be continued*)

Table 3 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N		
7c	29	302	61.25 61.19	5.30 5.38	19.80 19.83	$C_{18}H_{19}N_5O_3$	2.28 (s, 3 H, Me); 2.45 (s, 6 H, 2 Me); 2.82 (dd, 1 H, CH_2, J = 4.5, J = 18.1); 3.08 (dd, 1 H, CH_2, J = 5.7, J = 18.1); 4.69 (t, 1 H, CH, J = 6.8); 6.85 (s, 1 H, H(5), pyrimidine); 7.10 (d, 1 H, H arom., J = 7.5); 7.22 (d, 1 H, H arom., J = 7.8); 7.38 (t, 1 H, H arom., J = 7.5); 7.52 (s, 1 H, H arom.); 12.23 (br.s, 1 H, COOH); 12.46 (s, 1 H, NH)
7d	29	235	62.23 62.12	3.78 5.72	18.98 19.07	$C_{19}H_{21}N_5O_3$	2.26 (s, 3 H, 2 Me); 2.31 (s, 3 H, Me); 2.49 (s, 6 H, Me); 2.89 (dd, 1 H, CH_2, J = 4.3, J = 18.3); 3.16 (dd, 1 H, CH_2, J = 5.2, J = 18.3); 4.61 (t, 1 H, CH, J = 7.1); 6.99 (s, 1 H, H(5), pyrimidine); 7.12 (d, 1 H, H arom., J = 8.1); 7.41 (d, 1 H, H arom., J = 8.3); 7.50 (s, 1 H, H arom.); 12.12 (br.s, 1 H, COOH); 12.34 (s, 1 H, NH)
7e	32	273	52.96 53.07	3.88 3.93	17.10 17.20	$C_{18}H_{16}F_3N_5O_3$	2.32 (s, 6 H, 2 Me); 2.69 (dd, 1 H, CH_2, J = 4.8, J = 18.0); 2.84 (dd, 1 H, CH_2, J = 5.8, J = 18.0); 5.19 (t, 1 H, CH, J = 6.6); 6.89 (s, 1 H, H(5), pyrimidine); 7.59 (d, 1 H, H arom., J = 7.3); 7.68 (t, 1 H, H arom., J = 8.6); 7.84 (d, 1 H, H arom., J = 7.4); 7.79 (s, 1 H, H arom.) 11.00—13.00 (br.s, 2 H, NH, COOH)
7f	42	241	57.16 57.14	5.35 5.26	17.50 17.54	$C_{19}H_{21}N_5O_5$	2.48 (s, 6 H, 2 Me); 2.78 (dd, 1 H, CH_2, J = 4.6, J = 18.2); 3.04 (dd, 1 H, CH_2, J = 5.9, J = 18.2); 3.74, 3.82 (both s, 3 H each, OMe); 4.62 (t, 1 H, CH, J = 7.0); 6.67 (s, 1 H, H(5), pyrimidine); 6.86, 6.97 (both d, 1 H each, H arom., J = 7.7); 7.06 (s, 1 H, H arom.); 12.41 (br.s, 1 H, COOH); 12.69 (s, 1 H, NH)
7g	25	257	50.36 50.00	3.61 3.68	17.08 17.16	$C_{17}H_{15}Cl_2N_5O_3$	2.41 (s, 6 H, 2 Me); 2.93 (dd, 1 H, CH_2, J = 4.5, J = 18.2); 3.21 (dd, 1 H, CH_2, J = 5.9, J = 18.2); 4.76 (t, 1 H, CH, J = 6.9); 7.10 (s, 1 H, H(5), pyrimidine); 7.52 (d, 1 H, H arom., J = 7.8); 7.72 (s, 1 H, H arom.); 8.59 (d, 1 H, H arom., J = 7.8); 12.17 (br.s, 1 H, COOH); 12.62 (s, 1 H, NH)

2-{(*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxo-3-*p*-tolylimidazolidin-4-ylidene}acetate (**6b**), (*E*)-methyl 2-{(*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxo-3-[3-(trifluoromethyl)phenyl]imidazolidin-4-ylidene}acetate (**6c**), (*E*)-methyl {2-(*E*)-3-(4-chlorophenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxoimidazolidin-4-ylidene}acetate (**6d**), (*E*)-methyl 2-{(*E*)-3-(3,4-dichlorophenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxoimidazolidin-4-ylidene}acetate (**6e**), (*E*)-methyl 2-{(*E*)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxo-3-*m*-tolylimidazolidin-4-ylidene}acetate (**6f**), and (*E*)-methyl 2-{(*E*)-2-[(4,6-dimethylpyrimidin-2-ylimino]-3-(2-ethoxyphenyl)-5-oxoimidazolidin-4-ylidene}acetate (**6g**) were prepared. The yields, melting points, elemental analysis data, and ^{1}H NMR spectroscopic data for compounds **6a—g** are given in Table 2.

(2-Imino-5-oxoimidazolidin-4-yl)acetic acids 7 (general procedure). A solution of guanidine **4** (10 mmol) and anhydride **3** (10 mmol) in dry dioxane (15 mL) was kept at 70 °C for 3 h. The precipitate that formed was filtered off and recrystallized from dioxane. An additional amount (20—30%) of the somewhat less pure product can be isolated from the filtrate by pouring the latter into cold water followed by recrystallization of the precipitate that formed from dioxane. (*E*)-2-{2-[(4,6-Dimethylpyrimidin-2-yl)imino]-3-(4-methoxyphenyl)-5-oxoimidazolidin-4-yl}acetic acid (**7a**), (*E*)-2-{3-(3-chlorophenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxoimidazolidin-4-yl}acetic acid (**7b**), (*E*)-2-{2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxo-3-*m*-tolylimidazolidin-4-yl}acetic acid (**7c**), (*E*)-3-(3,4-dimethylphenyl)-2-{2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxoimidazolidin-4-yl}acetic acid (**7d**), (*E*)-2-{2-[(4,6-dimethylpyrimidin-2-yl}imino]-5-oxo-3-[3-(trifluoromethyl)phenyl]imidazolidin-4-yl}acetic acid (**7e**), (*E*)-2-{3-(2,5-dimethoxyphenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxoimidazolidin-4-yl}acetic acid (**7f**), and (*E*)-2-{3-(2,4-dichlorophenyl)-2-[(4,6-dimethylpyrimidin-2-yl)imino]-5-oxoimidazolidin-4-yl}acetic acid (**7g**) were prepared. The yields, melting points, elemental analysis data, and ^{1}H NMR spectroscopic data for compounds **7a—g** are given in Table 3.

References

1. M. R. Grimmet, *Imidazole and Benzimidazole Synthesis*, Academic Press, New York, 1997, p. 134.

2. D. V. Kryl´skii, Kh. S. Shikhaliev, A. S. Shestakov, and M. M. Liberman, *Zh. Obshch. Khim.*, 2005, **75**, 331 [*Russ. J. Gen. Chem.*, 2003, **75** (Engl. Transl.)].
3. B. E. Mandrichenko, I. A. Mazur, and P. M. Kochergin, *Khim. Geterotsikl. Soedin.*, 1974, 1140 [*Chem. Heterocycl. Compd.*, 1974 (Engl. Transl.)].
4. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven, Jr., J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cros, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Paghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komafomi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Faanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, *GAUSSIAN-03, Revision C. 02*, Gaussian, Inc., Wallingford CT, 2004.
5. Yu. V. Svetkin and A. N. Minlibaeva, *Zh. Org. Khim.*, 1971, **7**, 1299 [*Russ. J. Org. Chem.*, 1971, **7**, 1339 (Engl. Transl.)].
6. R. M. Acheson and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1981, 415.
7. Ch. K. Chan, J. C. N. Ma, and Th. C. W. Mak, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1070.
8. G. Trapani, A. Caretti, M. Franco, A. Latrofa, G. Genehi, and G. Liso, *Eur. J. Med. Chem.*, 1993, **28**, 13.
9. Y. Miyamoto and C. Yamazaki, *J. Heterocycl. Chem.*, 1994, **31**, 1445.
10. V. Balasubramaniyan, P. Balasubramaniyan, and M. J. Wani, *Ind. J. Chem.*, 1990, **29B**, 1092.
11. H.-G. Hahn, K. D. Nam, and H. Mah, *Heterocycles*, 2001, **55**, 1283.
12. T. Takido, S. Tamura, K. Sato, H. Kamijo, T. Nakazawa, T. Hata, and M. Seno, *J. Heterocycl. Chem.*, 1998, **35**, 437.
13. D. V. Kryl´skii, Kh. S. Shikhaliev, Yu. A. Kovygin, and A. Yu. Potapov, *Geterotsiklicheskie sistemy na osnove proizvodnykh guanidina i ego strukturnykh analogov* [*Heterocyclic Systems Based on Guanidine and Its Structural Analogs*], Voronezh. Gos. Un-t, Voronezh, 2006, p. 80 (in Russian).

Received January 29, 2007;
in revised form April 11, 2007