α-Ureidoalkylation of thiosemicarbazide and aminoguanidine

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Optimum conditions for the targeted synthesis of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones, 4,5-bis(3-thiosemicarbazido(guanidinoamino))imidazolidin-2-ones, and 1,3-dialkyl-4-(guanidinoimino)imidazolidin-2-ones by α-ureidoalkylation of thiosemicarbazide or aminoguanidine were found. A novel conglomerate in the series of imidazolidin-2-one derivatives was detected: 4,5-bis(guanidinoamino)-1,3-dimethylimidazolidin-2-one dihydrochloride dihydrate.

Key words: α-ureidoalkylation, thiosemicarbazide, aminoguanidine, 4,5-dihydroxyimidazolidin-2-ones, targeted synthesis, 4,5-bis(3-thiosemicarbazido(guanidinoamino))imidazolidin-2-ones, 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones, 1,3-dialkyl-4-(guanidinoimino)imidazolidin-2-ones, conglomerates.

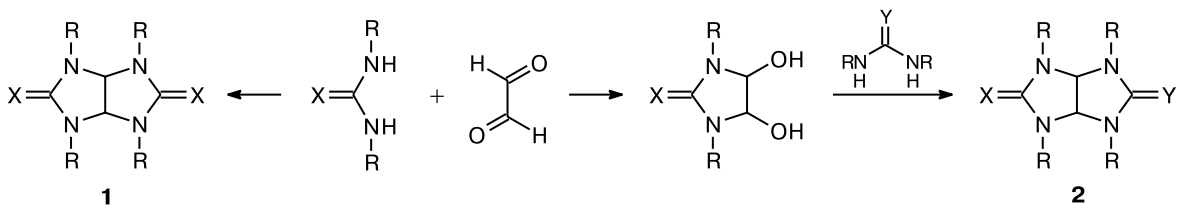
It is known[1—5] that α-ureidoalkylation reactions of glyoxal with some ureas or their heteroanalogs afford 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (glycolurils) and their heteroanalogs **1**. In addition, glycolurils and their heteroanalogs **2** are obtained by α-ureidoalkylation of ureas, thioureas, and nitro- and cyanoguanidines[1—5] with 4,5-dihydroxyimidazolidin-2-ones (2-thiones, 2-nitroimines, or 2-cyanoimines) (Scheme 1).

Recently, we have much investigated the α-ureidoalkylation of ureas,[3] sulfamides,[6,7] ureido alcohols,[8] and ureido acids[8] and developed general methods for the targeted synthesis of various *N*,*N*′-disubstituted glycolurils and their sulfur analogs. α-Enantiomerically pure glycolurils have been obtained for the first time by diastereoselective or diastereospecific ureidoalkylation of optically pure *N*-carbamoyl-*S*(*R*)-α-amino acids.[9,10] The conditions for the aforementioned reactions are commonly as follows: acid catalysis, pH 1—2, water or aqueous methanol as a solvent, 60—100 °C, 0.5—3 h (see Refs 1—10).

The goal of the present work was to study the α-ureidoalkylation of urea heteroanalogs containing the hydrazine fragment (thiosemicarbazide or aminoguanidine) with various *N*,*N*′-disubstituted 4,5-dihydroxyimidazolidin-2-ones (DHI) **3a—f** as ureidoalkylating reagents.

First, we carried out the α-ureidoalkylation of thiosemicarbazide with compounds **3b,c** (the ratio of the reagents was 1 : 1) in water in the presence of catalytic amounts of HCl (pH 2) at 80 °C for 1 h. The resulting mixture of compounds was separated by fractional crystallization into products of two types. The ^{1}H NMR spectra of products of one type show a singlet at δ 3.82—4.19 corresponding the CH—CH protons characteristic of DHI (Table 1). Signals for the N—Me(Et) groups of the imidazolidine fragment appear in their usual ranges (singlets for N—Me at δ 2.49—2.59; triplets and multiplets for the N-ethyl groups at δ 0.95—0.98 and 3.02—3.45, respectively). Signals for the OH protons of the starting DHI are absent, while broadened singlets appear at δ 5.53—8.65 in the intensity ratio 1 : 1 : 1 : 1. According to

Scheme 1



1 **2**

R = H, Alk, Ar; X = O, S, NNO_2, NCN
2: X, Y = O, NNO_2, NCN, S(X=O)

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Table 1. ^{1}H NMR spectra ([$^2H_6$]DMSO) of the compounds obtained

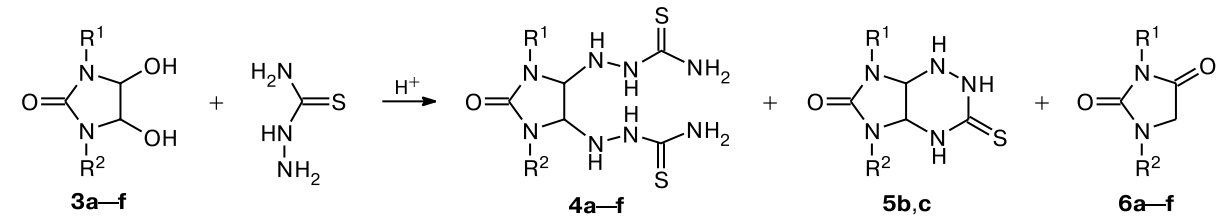
Product	δ (*J*/Hz)
4a	4.07 (s, 2 H, 2 CH); 5.67 (s, 2 H, 2 NH); 6.75 (s, 2 H, $NH_{imidazole}$); 7.53 (br.s, 4 H, 2 NH_2); 8.52 (s, 2 H, 2 NH)
4b	2.59 (s, 6 H, 2 Me); 3.82 (s, 2 H, 2 CH); 5.98 (s, 2 H, 2 NH); 7.59 and 7.83 (both br.s, 2 H each, 2 NH_2); 8.61 (s, 2 H, 2 NH)
4c	0.98 (t, 6 H, 2 Me, ^3J = 7.2); 3.02 (m, 2 H, CH_2); 3.45 (m, 2 H, CH_2); 4.16 (s, 2 H, 2 CH); 5.79 (br.s, 2 H, 2 NH); 7.45 and 7.68 (both br.s, 2 H each, 2 NH_2); 8.28 (br.s, 2 H, 2 NH)
4d	2.49 (s, 2 H, NCH_2); 4.03 (br.s, 2 H, H(2) + H(6)); 5.53 (br.s, 1 H, H(3)); 5.92 (s, 1 H, H(7)); 6.72 (s, 1 H, H(1)); 7.50 (br.s, 2 H, H(5) + H(9)); 7.82 (br.s, 2 H, H(5) + H(9)); 8.50 (s, 1 H, H(4)); 8.65 (s, 1 H, H(8))
4e	0.95 (t, 3 H, CMe, ^3J = 7.0); 3.19 (m, 2 H, NCH_2); 4.09 (br.s, 1 H, H(2)); 4.19 (br.s, 1 H, H(6)); 5.57 (br.s, 1 H, H(3)); 5.90 (s, 1 H, H(7)); 6.68 (s, 1 H, H(1)); 7.50 (br.s, 2 H, H(5) + H(9)); 7.83 (br.s, 2 H, H(5) + H(9)); 8.49 (s, 1 H, H(4)); 8.55 (s, 1 H, H(8))
4f	0.86 (t, 3 H, CMe, *J* = 6.71); 2.61 (s, 3 H, NMe); 2.96 and 3.30 (both m, 1 H each, NCH_2); 3.86 (br.s, 1 H, H(2)); 3.99 (br.s, 1 H, H(6)); 5.92 (br.s, 1 H, H(3)); 5.98 (br.s, 1 H, H(7)); 7.67 (br.s, 2 H, H(5) + H(9)); 7.84 (br.s, 2 H, H(5) + H(9)); 8.53 (s, 1 H, H(4)); 8.61 (s, 1 H, H(8))
5b	2.59 (s, 3 H, Me); 2.61 (s, 3 H, Me); 4.61 and 4.79 (both d, 1 H each, CHCH, ^3J = 8.5); 5.66 (br.s, 1 H, CHN<u>H</u>C=S); 8.77 (br.s, 1 H, CHN<u>H</u>NH); 9.41 (br.s, 1 H, NHN<u>H</u>C=S)
5c	0.99 (t, 3 H, Me, ^3J = 7.3); 1.01 (t, 3 H, Me, ^3J = 7.3); 3.05 (m, 2 H, CH_2); 3.14 (m, 2 H, CH_2); 4.73 (dd, 1 H, CH, ^3J = 8.6, ^3J = 1.8); 4.91 (dd, 1 H, CH, ^3J = 8.8, ^3J = 2.4); 5.59 (d, 1 H, CHN<u>H</u>C=S, ^3J = 2.4); 8.67 (d, 1 H, CHN<u>H</u>NH, ^3J = 1.8); 9.38 (br.s, 1 H, NHN<u>H</u>C=S)
6e	1.06 (t, 3 H, Me, *J* = 6.2); 3.30 (m, 2 H, NCH_2); 3.91 (s, 2, CH_2); 11.47 (s, 1 H, NH)
6f	1.04 (t, 3 H, Me, *J* = 6.5); 2.78 (s, 3 H, NMe); 3.27 (m, 2 H, NCH_2); 4.03 (s, 2 H, CH_2)
7a	4.21 (s, 2 H, 2 CH); 5.89 (br.s, 2 H, 2 NH); 6.89 (s, 2 H, NHCONH); 7.00—7.85 (br.m, 8 H, 2 NH_3^+, 2 NH); 9.02 (br.s, 2 H, 2 NH)
7b	2.67 (s, 6 H, 2 Me); 3.98 (s, 2 H, 2 CH); 6.32 (s, 2 H, 2 NH); 6.85—7.98 (br.m, 8 H, 2 NH_3^+, 2 NH); 9.08 (s, 2 H, 2 NH)
7c	0.94 (t, 6 H, 2 Me, ^3J = 6.7); 3.05 (m, 2 H, CH_2); 3.32 (m, 2 H, CH_2); 4.10 (s, 2 H, 2 CH); 6.29 (s, 2 H, 2 NH); 6.87—7.95 (br.m, 8 H, 2 NH_3^+, 2 NH); 8.89 (s, 2 H, 2 NH)
8b	2.85 (s, 3 H, NMe); 2.96 (s, 3 H, NMe); 4.25 (s, 2 H, CH_2); 7.40 (br.s, 4 H, NH_3^+, NH); 11.05 (s, 1 H, NH)
8c	1.05 (m, 6 H, 2 CMe); 3.07 (m, 4 H, NCH_2); 4.24 (s, 2 H, CH_2); 7.50 (br.s, 4 H, NH_2 + NH_2^+); 11.00 (s, 1 H, NH)

the literature data on the chemical shifts in thiosemicarbazide,[11] these signals can be assigned to the hydrazine NH (δ 5.67—5.98 and 8.28—8.61) or amide NH_2 groups (two singlets at δ 7.52—7.83) of the thiosemicarbazide residues. Our spectroscopic data allow these compounds to be identified as 4,5-bis(thiosemicarbazido)imidazolidin-2-one derivatives **4b,c**. Their yields from compounds **3b,c** were 25—32%.

The ^{1}H NMR spectra of products of the second type show signals attributable to bicyclic structures, *viz.*, 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones **5b,c**. This assumption is supported by the presence of signals for the protons at the bridgehead methine C atoms (δ 4.61—4.79, AB system) and double signals for the alkyl substituents at the N atoms of the imidazolidine ring. The signals for the protons of three NH groups (δ 5.59—5.60, 8.67—8.77, and 9.38—9.41) are consistent with the presence of the triazine ring in structures **5** (see Table 1). The yields of bicyclic products **5b,c** from the starting reagents **3b,c** were 3—5%. The ^{1}H NMR data were confirmed by ^{13}C NMR spectra. The structures of compounds **5** were finally proved[12] by X-ray diffraction analysis of bicyclic product **5b**.

A reaction of thiosemicarbazide with compound **3a** under the same conditions gave exclusively monocyclic product **4a**.

Scheme 2



	a	b	c	d	e	f
R^1	H	Me	Et	H	H	Me
R^2	H	Me	Et	Me	Et	Et

In all cases, nonconsumed thiosemicarbazide[11] and hydantoins **6a—c** were isolated from mother liquors after the fractional crystallization (see Refs 13—15). The latter are products of a pinacol-type rearrangement[16] of DHI (Scheme 2).

In a search for reaction conditions for the selective formation of compounds **4** or **5**, we varied pH (from 2 to 6), the solvent (water, H_2O—MeOH, and MeOH), and the ratio of **3a—c** to thiosemicarbazide (1 : 1 or 1 : 2). The ratios of mono- and bicyclic products **4** and **5** were estimated from the integral intensities of the most informative signals for the CH—CH protons in the ^{1}H NMR spectra of the reaction mixtures evaporated to dryness. The results obtained are summarized in Table 2 (entries *1—15*). The indicated yields refer to the isolated compounds.

It is obvious from Table 2 that the optimum conditions for the formation of monocyclic products **4a—c** are as follows: water as a solvent, pH 2, reaction temperature 80 °C, reaction duration 1 h, and ratio of **3a—c** to thiosemicarbazide 1 : 2. The yields were 80—90% (entries *1*, *4*, and *13*). With the reaction of thiosemicarbazide with compound **3b** as an example, we studied the effects of pH, the ratio of the reagents, and the solvent nature on the yields of both mono- (**4b**) and bicyclic products (**5b**). An increase in pH from 2 to 6 lowered the yield of product **4b** (entries *4—6*). The reaction in aqueous methanol changed the **4b**/**5b** ratio: the yield of compound **5b** increased, while that of compound **4b** remained virtually unchanged (78—82%; entries *7—9*). In methanol alone, the fraction of compound **5b** was higher since the yield of compound **4b** decreased to 34% (entry *10*). All reactions

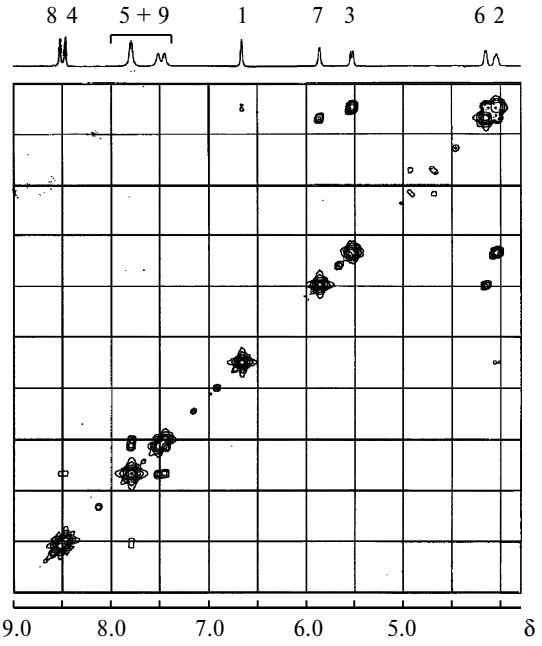
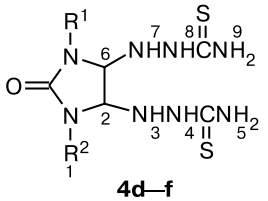


Fig. 1. COSY NMR experiment for compound **4e**.

in methanol were catalyzed by conc. HCl. The fraction of compound **5b** in the reaction products was also increased when the ratio of the reagents was changed from 1 : 2 to 1 : 1 (*cf.* entries *7* and *11*). The highest yield (96%) of product **5b** was reached in methanol with portionwise addition of an equimolar amount of thiosemicarbazide (entry *12*). A similar pattern was obtained with compound **3c** (entries *13—15*). At the same time, the α-ureidoalkylation of thiosemicarbazide with *N*-unsubstituted compound **3a** yielded only product **4a** (entries *1—3*), which suggests that the α-ureidoalkylation pathway depends on the DHI structure.

To further study the effect of the DHI structure on the regioselectivity of the α-ureidoalkylation of thiosemicarbazide, we used *N*-monosubstituted compounds **3d,e** and unsymmetrically substituted DHI **3f** in this reaction. Under the optimum conditions for the synthesis of monocyclic imidazolidin-2-one derivatives **4a—c**, we obtained monocyclic products **4d—f** in 78—87% yields (entries *16*, *18*, and *20*).



4d—f

	d	**e**	**f**
R^1	Me	Et	Me
R^2	H	H	Et

Since compounds **4d—f** are asymmetric, their ^{1}H NMR spectra show double signals for the CH—CH protons and for the thiosemicarbazide fragments. Refined assignments of the ^{1}H NMR signals for these compounds were obtained from the COSY data for compound **4e** (Fig. 1).

α-Ureidoalkylation of thiosemicarbazide with compounds **3d—f** under the optimum conditions for the synthesis of bicyclic products **5b,c** only resulted in decreasing yields of the corresponding monocyclic products **4d—f** (entries *17*, *19*, and *21*). The ^{1}H NMR spectra of the mother liquors evaporated to dryness show only signals for the protons of thiosemicarbazide and hydantoins **6d—f**. Hydantoins **6d—f** have been documented;[3,13—15] however, spectroscopic characteristics have been reported only for compound **6d** (see Refs 13, 14). For this reason, we characterized compounds **6e,f** by ^{1}H NMR spectroscopy (see Table 1).

To ascertain that compounds **4** and **5** are produced in two parallel reaction pathways, we studied the possibility of a hydrolytic transformation of monocyclic compound **4b** into bicyclic product **5b** by refluxing its suspension in water at pH 2 for 3 h. However, compound **4b** remained intact under these conditions, which confirmed our assumption of different formation mechanisms for structures **4** and **5**.

Thus, the α-ureidoalkylation of thiosemicarbazide with compounds **3d—f** (as with **3a**) yields only monocyclic

Table 2. Effects of various parameters on the selectivity of the formation of mono- (**4**) and bicyclic compounds (**5**) in the α-ureidoalkylation of thiosemicarbazide

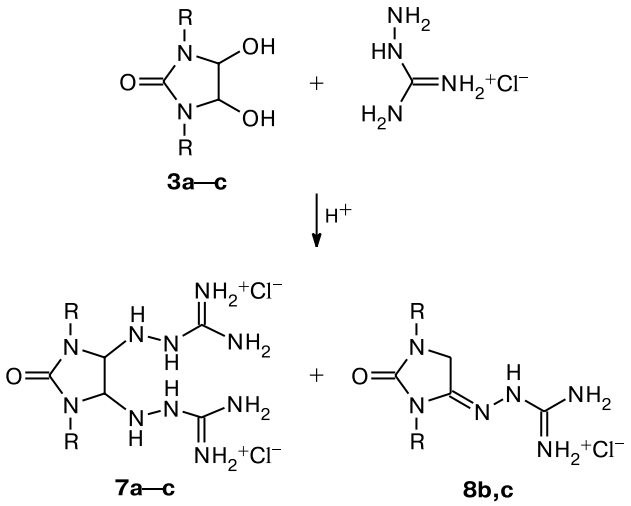
Entry	Starting DHI	Solvent (proportion)	Ratio of the reagents	pH	Yield (%) (ratio of the products)[a]
1	**1a**	H_2O	1 : 2	2	**4a** — 80
2	**1a**	H_2O/MeOH (5 : 1)	1 : 1	2	**4a** — 38 [b]
3	**1a**	MeOH(suspension)	1 : 1	[c]	**4a** — 30
4	**1b**	H_2O	1 : 2	2	**4b/5b** (12 : 1) **4b** — 90
5	**1b**	H_2O	1 : 2	4	**4b** — 62 [b]
6	**1b**	H_2O	1 : 2	6	**4b** — 12 [b]
7	**1b**	H_2O/MeOH (1 : 1)	1 : 2	2	**4b/5b** (6 : 1) **4b** — 78
8	**1b**	H_2O/MeOH (1 : 2.5)	1 : 2	[c]	**4b/5b** (5 : 1) **4b** — 82
9	**1b**	H_2O/MeOH (1 : 5)	1 : 2	[c]	**4b/5b** (4 : 1) **4b** — 80
10	**1b**	MeOH	1:2	[c]	**4b/5b** (2 : 1) **4b** — 34
11	**1b**	H_2O/MeOH (1 : 1)	1 : 1	2	**4b/5b** (1.5 : 1) **5b** — 28
12	**1b**	MeOH	1 : 1	[c]	**5b** — 96
13	**1c**	H_2O	1 : 2	2	**4c/5c** (9 : 1) **4c** — 85
14	**1c**	MeOH	1 : 2	[c]	**4c/5c** (1 : 5) **5c** — 52
15	**1c**	MeOH	1 : 1	[c]	**5c** — 90
16	**1d**	H_2O	1 : 2	2	**4d** — 87
17	**1d**	MeOH	1 : 1	[c]	**4d** — 30 [b]
18	**1e**	H_2O	1 : 2	2	**4e** — 85
19	**1e**	MeOH	1 : 1	[c]	**4e** — 29 [b]
20	**1f**	H_2O	1 : 2	2	**4f** — 78
21	**1f**	MeOH	1 : 1	[c]	**4f** — 20 [b]

[a] From the ^{1}H NMR spectra.
[b] Nonconsumed thiosemicarbazide was recovered and hydantoins were obtained.
[c] Concentrated HCl (2 mol.% with respect to DHI) was added.

products **4d—f**. The reactions with compounds **3b,c** in water at pH 2 also give mainly monocyclic products **4b,c**. The exclusive formation of bicyclic products **5** is possible only if the reaction is carried out in acidified methanol with symmetrically substituted DHI **3b,c** as ureidoalkylating reagents.

To extend the area of application of this new line in α-ureidoalkylation yielding monocyclic imidazolidin-2-one derivatives **4**, we studied α-ureidoalkylation of aminoguanidine hydrochloride with compounds **3a—c** under the same conditions as for products **4** and found that the major reaction products obtained in 50—68% yields are analogous compounds, *viz.*, 4,5-bis(guanidinoamino)imidazolidin-2-ones **7a—c**. The ^{1}H NMR spectra of products **7a—c** are similar to those of compounds **4a—c**, differing only in the character and integral intensities of the signals for the terminal NH protons (Scheme 3; Table 1).

Scheme 3



R = H (**a**), Me (**b**), Et (**c**)

In the reaction of aminoguanidine hydrochloride with compound **3a**, the sole product **7a** was obtained in 75% yield; however, reactions with DHI **3b,c** gave novel compounds in low yields. Their structures escaped unambiguous determination by ^{1}H NMR spectroscopy. Based on the chemical shifts and integral intensity ratio of the signals, one could assume that these are bicyclic analogs of imidazotriazines **5**: 5,7-dialkyl-3-iminoperhydroimidazo[4,5-*e*][1,2,4]-triazin-6-ones. However, the ^{1}H NMR spectra shows no AB system at δ 4.24—4.25 for the CH—CH protons characteristic of bicyclic compounds; instead, singlets appear that can be assigned to signals for the CH_2 protons (see Table 1). These data, as well as data from gated decoupling ^{13}C NMR spectroscopy, allowed the products obtained to be formulated as 1,3-dialkyl-4-(guanidinoimino)imidazolidin-2-ones **8b,c**. Earlier,[7] we have discovered an analogous pathway of α-ureidoalkylation in reactions of sulfamides with DHI.

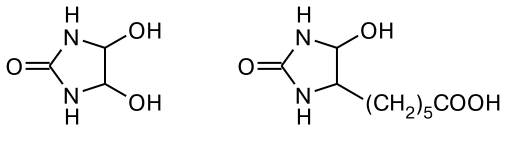
Our study of the α-ureidoalkylation of aminoguanidine hydrochloride with DHI **3a—c** under the conditions for the formation of bicyclic products **5** revealed that the reaction with DHI **3a** gives 4,5-bis(guanidinoamino)imidazolidin-2-one **7a** in 75% yield (with respect to amino-

guanidine) as the sole product. In two other cases, the reaction products were 1,3-dialkyl-4-(guanidinoimino)imidazolidin-2-ones (**8b,c**). The ^{1}H NMR spectra of the mother liquors evaporated to dryness show signals for 4,5-bis(guanidinoamino)imidazolidin-2-ones **7b,c**, which were not isolated because of their small amounts.

The formation of hydrazones **8** through the corresponding hydantoins **6** seems to be quite plausible. However, no products **8** were detected (even by TLC) in reactions of aminoguanidine with independently synthesized hydantoins **6b,c**. Therefore, hydantoin is not an intermediate of this reaction.

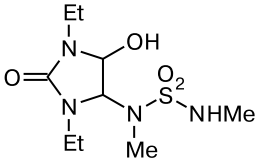
It was interesting to study the possibility of crystallization of compounds **7** as conglomerates, because imidazolidin-2-one derivatives belong to classes of compounds that form crystal conglomerates. For instance, conglomerates have been found for DHI **3a**,[17,18] 6-(5-hydroxy-2-oxoimidazolidin-4-yl)hexanoic acid (**9**),[19] and *N*-(1,3-diethyl-5-hydroxy-2-oxoimidazolidin-4-yl)-*N*,*N*′-dimethylsulfamide (**10**) (see Ref. 20).

Single-crystal X-ray diffraction analysis of products **7b,c** revealed that compound **7b** form a crystal conglomerate (space group $P6_1$), while compound **7c** crystallizes in a racemic space group (space group *P*).[21]



3a

9



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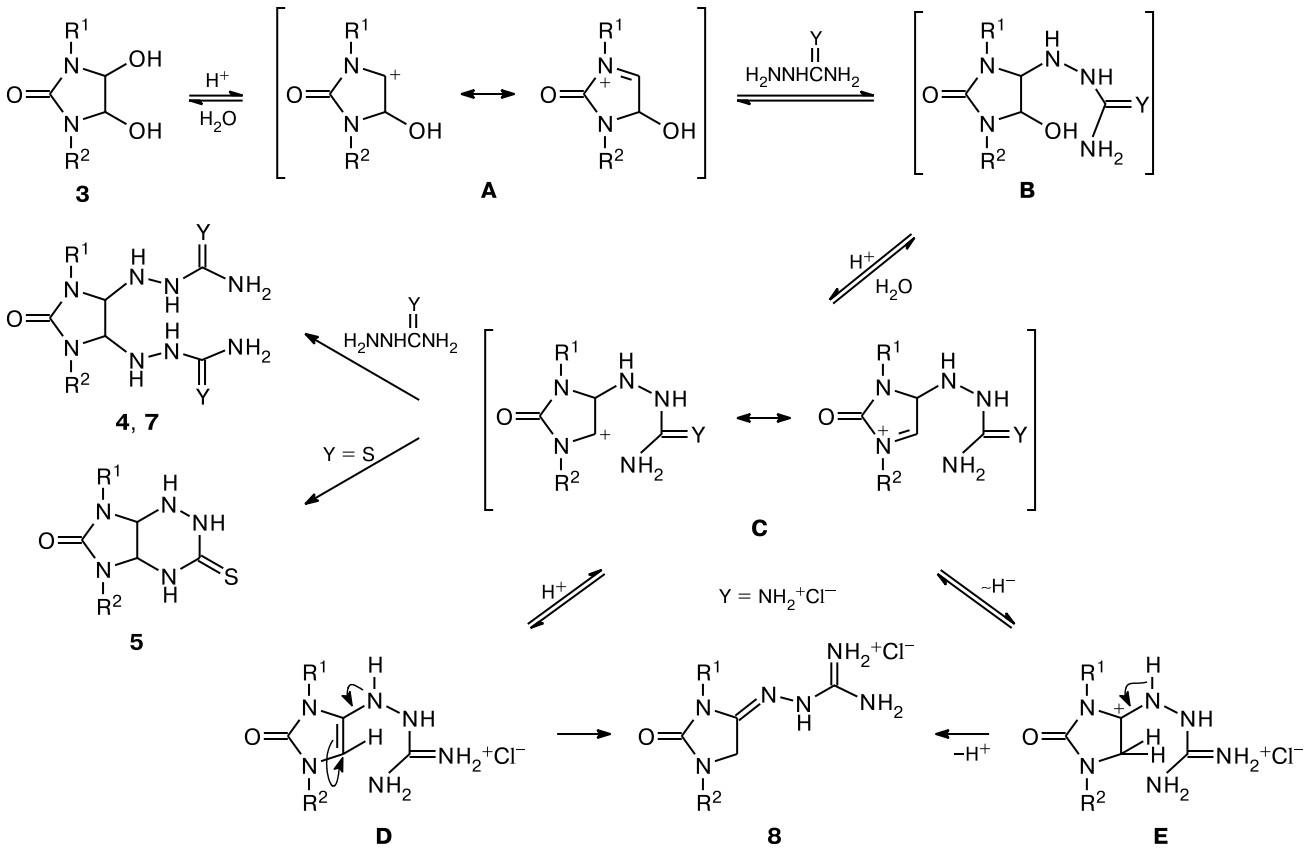
The aforesaid new pathways of α-ureidoalkylation yielding earlier unknown mono- (**4**, **7**, and **8**) and bicyclic products (**5**) agree with classical concepts of the mechanism of acid-catalyzed α-amino-, amido-, and ureidoalkylation.[1,22,23] The first step involves generation of carbenium-immonium ion **A** (depicted as two resonance structures), which undergoes condensation with a thiosemicarbazide (or aminoguanidine) molecule. The resulting intermediate **B** is dehydrated to form carbenium-immonium ion **C**. This is followed by either intramolecu-

Scheme 4



lar cyclization into bicyclic product **5** or condensation with another thiosemicarbazide (or aminoguanidine) molecule to give compound **4** (Scheme 4).

Based on the known mechanisms of formation of hydantoins from DHI[16] and 1,3-dialkyl-4-(arylsulfonylimino)imidazolidin-2-ones synthesized by α-ureidoalkylation of monoarylsulfamides with DHI,[7] we propose two probable pathways for the formation of hydrazones **8** (Scheme 4). The generation of carbenium-immonium ion **C** is followed by either 1,2-hydride shift (giving rise to cation **E**), which precedes deprotonation, or deprotonation yielding (guanidinoamino)imidazolin-2-one **D**. Either pathway finally leads to compound **8**.

Thus, we studied the acid-catalyzed α-ureidoalkylation of thiosemicarbazide and aminoguanidine with 1,3-unsubstituted, 1-alkyl-, and 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones. We also specified the structural factors and found the reaction conditions that favor the formation of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones, 4,5-bis[3-thiosemicarbazido(guanidinoamino)]imidazolidin-2-ones, or 1,3-dialkyl-4-(guanidinoimino)imidazolidin-2-ones. 4,5-Bis(guanidinoamino)-1,3-dimethylimidazolidin-2-one dihydrochloride dihydrate was found to crystallize as a conglomerate.

Experimental

Commercial urea, dimethylurea, diethylurea, thiosemicarbazide, aminoguanidine hydrochloride, aqueous 40% glyoxal, and glyoxal trimer dihydrate (Acros) were used. 1-Methyl-, 1-ethyl-, and 1-ethyl-3-methylureas were prepared by reactions of the corresponding amine with KOCN or MeNCO as described earlier.[24,25] 4,5-Dihydroxyimidazolidin-2-ones **3** were synthesized by reactions of appropriate ureas with glyoxal according to known procedures.[7,26,27]

^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-250 (250 MHz) and Bruker AM-300 spectrometers (75.5 MHz), respectively. Chemical shifts on the δ scale are referenced to Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT CH-6 mass spectrometer (70 eV). Melting points were determined on a GALLENKAMP instrument (Sanyo).

Table 3. Yields and selected physicochemical characteristics of the compounds obtained

Compound	Yield (%)	Melting point/°C	Found* / Calculated (%)					Molecular formula
			C	H	N	S	Cl	
4a	80	250—251 (decomp.)	22.65 22.72	4.51 4.58	42.31 42.39	6.11 6.05	—	$C_5H_{12}N_8OS_2$
4b	90	238—240 (decomp.)	28.69 28.75	5.45 5.52	38.41 38.32	22.01 21.93	—	$C_7H_{16}N_8OS_2$
4c	85	223—225	33.79 33.73	6.20 6.29	35.02 34.97	20.09 20.01	—	$C_9H_20N_8OS_2$
4d	87	194—196	25.81 25.89	5.15 5.07	40.18 40.26	23.12 23.04	—	$C_6H_{14}N_8OS_2$
4e	85	183—184	28.78 28.75	5.47 5.52	38.26 38.32	22.00 21.93	—	$C_7H_{16}N_8OS_2$
4f	78	179—180	31.40 31.36	5.85 5.92	36.51 36.57	20.99 20.93	—	$C_8H_{18}N_8OS_2$
5b	96	234—235	35.77 35.81	5.47 5.51	34.84 34.80	15.86 15.93	—	$C_6H_{11}N_5OS$
5c	90	216—218	41.95 41.90	6.64 6.59	30.49 30.54	13.91 13.98	—	$C_8H_{15}N_5OS$
7a	68	230—231 (decomp.)	19.80 19.81	5.37 5.32	46.14 46.20	—	23.43 23.39	$C_5H_{16}Cl_2N_{10}O$
7b	57	222—224 (decomp.)	25.34 25.38	6.01 6.09	42.34 42.29	—	21.36 21.41	$C_7H_{20}Cl_2N_{10}O$
7c	50	213—214 (decomp.)	30.13 30.09	6.68 6.73	38.91 38.99	—	19.79 19.74	$C_9H_{24}Cl_2N_{10}O$
8b	78	227—228	32.71 32.66	5.99 5.94	38.02 38.09	—	16.03 16.07	$C_6H_{13}ClN_6O$
8c	72	205—206	38.68 38.63	6.81 6.89	33.75 33.79	—	14.30 14.25	$C_8H_{17}ClN_6O$

* All the compounds obtained were dried to constant weights in order to remove nonstoichiometric amounts of crystallization water.

Synthesis of 4,5-bis(3-thiosemicarbazido)imidazolidin-2-ones 4a—f (general procedure). A solution of an appropriate DHI **3a—f** (0.02 mol) in water (20 mL) was acidified with conc. HCl (0.2 mL) and then thiosemicarbazide (0.04 mol) was added. The reaction mixture was stirred at 80 °C for 1 h. The precipitates that formed were filtered off and washed with hot methanol—water (1 : 1) to give 4,5-bis(3-thiosemicarbazido)imidazolidin-2-one (**4a**), 1,3-dimethyl-4,5-bis(3-thiosemicarbazido)imidazolidin-2-one (**4b**), 1,3-diethyl-4,5-bis(3-thiosemicarbazido)imidazolidin-2-one (**4c**), 1-methyl-4,5-bis(3-thiosemicarbazido)imidazolidin-2-one (**4d**), 1-ethyl-4,5-bis(3-thiosemicarbazido)imidazolidin-2-one (**4e**), and 3-ethyl-1-methyl-4,5-bis(3-thiosemicarbazido)imidazolidin-2-one (**4f**). Their yields and selected physicochemical characteristics are summarized in Table 3. Their ^{1}H NMR spectra are given in Table 1. The mass and ^{13}C NMR spectra of compound **4b** are given in Tables 4 and 5, respectively.

Synthesis of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones 5b,c (general procedure). A solution of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-one **3b,c** (0.02 mol) in MeOH (50 mL) was acidified with conc. HCl (0.2 mL) and heated to 50 °C. Then thiosemicarbazide (0.02 mol) was slowly added in portions for 0.5 h. The reaction mixture was stirred at 70—75 °C for 1 h and kept at 4 °C for 16 h. Crystalline precipitates of compounds **5b,c** that formed were filtered off and recrystallized from MeOH. The yields of 5,7-dimethyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-one (**5b**) and 5,7-diethyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-one (**5c**) were 96 and 90%, respectively.

Their yields and selected physicochemical characteristics are summarized in Table 3. Their ^{1}H NMR spectra are given in Table 1. The mass and ^{13}C NMR spectra of compound **5b** are given in Tables 4 and 5, respectively.

Synthesis of 4,5-bis(guanidinoamino)imidazolidin-2-ones 7a—c (general procedure). A solution of an appropriate DHI **3a—c** (0.02 mol) in water (20 mL) was acidified with conc. HCl (0.2 mL) and heated to 80 °C. Aminoguanidine hydrochloride (0.04 mol) was added thereto. The reaction mixture was kept at 80 °C for 1 h and then at 4 °C for 16 h. The precipitates that formed were filtered off and crystallized from MeOH to give 4,5-bis(guanidinoamino)imidazolidin-2-one dihydrochloride (**7a**), 4,5-bis(guanidinoamino)-1,3-dimethylimidazolidin-2-one dihydrochloride (**7b**), and 1,3-diethyl-4,5-bis(guanidinoamino)imidazolidin-2-one dihydrochloride (**7c**).

Their yields and selected physicochemical characteristics are summarized in Table 3. Their ^{1}H NMR spectra are given in Table 1. The mass spectrum of compound **7c** is given in Table 4. The ^{13}C NMR spectrum of compound **7b** is given in Table 5.

Synthesis of 1,3-dialkyl-4-(guanidinoimino)imidazolidin-2-ones 8b,c (general procedure). A solution of an appropriate DHI **3b,c** (0.02 mol) in MeOH (50 mL) was acidified with conc. HCl (0.2 mL) and heated to 60 °C. Aminoguanidine hydrochloride (0.02 mol) was slowly added in portions for 15 min. The reaction mixture was stirred at 70—75 °C for 1 h and then kept at 4 °C for 16 h. The crystalline precipitates that formed were filtered off and recrystallized from MeOH. The yields of 4-(guanidinoimino)-1,3-dimethylimidazolidin-2-one hydrochloride (**8b**) and 1,3-diethyl-4-(guanidinoimino)imidazolidin-2-one hydrochloride (**8c**) were 78 and 72%, respectively.

Their yields and selected physicochemical characteristics are summarized in Table 3. Their ^{1}H NMR spectra are given in Table 1. The ^{13}C NMR spectrum of compound **8b** is given in Table 5.

Table 4. Mass spectra of compounds **4b**, **5b**, and **7c**

Product	MS, *m/z* (*I* (%))
4b	201 (30) [$M^+ - NH_2NHC(S)NH_2$], 184 (19), 170 (19), 144 (19), 112 (100), 91 (58), 82 (25), 60 (48), 58 (97)
5b	201 (38) [M^+], 184 (4), 170 (30), 144 (13), 126 (7), 112 (100), 97 (4), 89 (12), 83 (11), 69 (11), 58 (31)
7c	212 (90) [$M^+ - NH_2NHC(NH)NH_2$], 180 (12), 168 (25), 155 (26), 153 (28), 141 (50), 140 (63), 116 (63), 114 (47), 98 (85), 97 (56), 69 (63), 58 (81), 56 (100)

Table 5. ^{13}C NMR spectra ([$^2H_6$]DMSO) of compounds **4b**, **5b**, **7b**, and **8b**

Product	δ
4b	33.4 (2 Me), 78.5 (2 CH), 163.7 (C=O), 187.8 ($C=NH_2^+$)
5b	27.1 (Me), 27.4 (Me), 63.7 (CH), 69.0 (CH), 158.0 (C=O), 184.0 (C=S)
7b	28.422 (2 Me), 73.359 (2 CH), 158.455 (C=O), 159.443 ($C=NH_2^+$)
8b	26.1 (Me), 29.7 (Me), 47.8 (CH_2), 151.7 (C=O), 155.7 (C=N), 156.6 (C=N)

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