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**REARRANGEMENT OF 2-(2,5-DIOXOPYRROLIDIN-1-YL)GUANIDINE:
AN EFFICIENT SYNTHESIS AND STRUCTURE OF
3-(5-AMINO-1*H*-1,2,4-TRIAZOL-3-YL)PROPANOIC ACID AND
DERIVATIVES**

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Abstract – The reaction between aminoguanidine and succinic acid in water under acid catalysis yields a mixture of guanyl- and diguanylhydrazides of succinic acid, which turns into a poorly separable mixture of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanoic acid (**3**) and 3,3'-(ethane-1,2-diyl)bis(1*H*-1,2,4-triazol-5-amine) (**5**) in basic media. The fusion of aminoguanidine hydrochloride with succinic anhydride at 150-170 °C results in the regioselective formation of 2-(2,5-dioxopyrrolidin-1-yl)guanidine hydrochloride (**11**). Compound **11** upon heating in an aqueous solution in the presence of alkali quantitatively rearranges into 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanoic acid (**3**). This reaction represents a new rearrangement in the 2,5-dioxopyrrolidine series. Investigations by pK_a determination, IR, NMR and X-ray revealed that compound **3** exists both in unionized and zwitterionic forms.

INTRODUCTION

Substituted azoles containing amino and carboxyl groups as substituents (so-called “azoleamino acids”)¹ are valuable building blocks in medicinal chemistry. These compounds are used for the preparation of heteroaromatic oligopeptides, which are promising candidates for controlling gene expression² and inhibiting protein-protein interactions.³ The best application in the 1,2,4-triazole series involves 5-amino-1*H*-1,2,4-triazole-3-carboxylic acid (**1**), which has been used for producing ribavirin and

derivatives, which have anti-HCV and anti-HIV activities,⁴ antibiotics,⁵ water soluble azo dyes⁶ and metal-organic hybrid frameworks.⁷ Therefore, we hypothesize that homologues of compound **1**, such as 2-(5-amino-1*H*-1,2,4-triazol-3-yl)acetic acid (**2**) and 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanoic acid (**3**), are also of great interest (Figure 1). The structural fragment of compound **2** is a constituent of semisynthetic cephalosporin antibiotics,⁵ and acyl derivatives of the ethyl ester of compound **2** exhibit anti-inflammatory activity.⁸

A general approach for the preparation of compounds **1-3** is the acylation of aminoguanidine by dicarboxylic acids in aqueous solutions and subsequent cyclization of the formed 2-guanylhazides in alkaline media.^{8,9} This method produces compound **1** from aminoguanidine and oxalic acid in high yields,^{9b} but less favorable results are obtained with other dicarboxylic acids.¹⁰ For example, the reaction of aminoguanidine with malonic acid proceeds slowly and nonselectively relative to that with oxalic acid and gives a mixture of guanylhazide and diguanylhazide, which then form the desired compound **2** and by-product **4** upon alkaline cyclization (Figure 1).¹⁰ After kinetic and thermodynamic investigation of the reaction between aminoguanidine and malonic acid, we improved the synthetic procedure and enhanced the yield of compound **2** to 44%-51%.¹⁰ An analogous reaction of aminoguanidine with succinic acid has not been well studied. To the best of our knowledge, synthesis of compound **3** was described only in a patent,¹¹ and the structural and chemical properties of this substance have not been investigated.

Herein, we report the effective synthesis and structure of compound **3** and some of its derivatives.

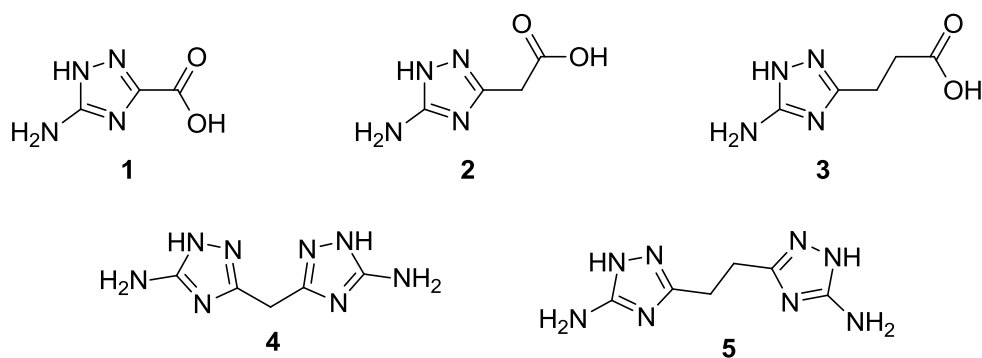
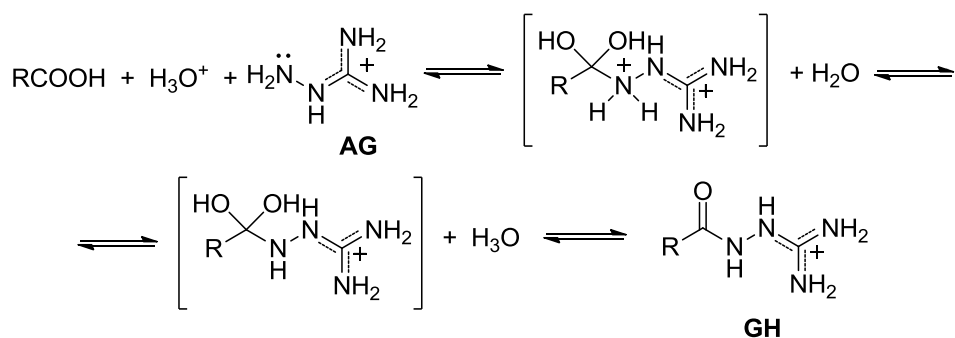


Figure 1. (5-Amino-1*H*-1,2,4-triazol-3-yl)substituted carboxylic acids and bis(5-amino-1*H*-1,2,4-triazol-3-yl)alkanes

RESULTS AND DISCUSSION

Refluxing a mixture of aminoguanidine hydrogen carbonate and succinic acid in water for 8 h according to the described procedure¹¹ yielded a white crystalline substance with a melting point (mp) of 183-185 °C (lit.¹¹ 184-185 °C). Elemental and spectral analyses as well as mp determination of a mixture with an authentic sample revealed that the obtained substance was the starting succinic acid rather than

compound **3**. Because of the absence of any spectral data in the cited patent,¹¹ we assume that the structure of the desired product **3** was erroneously assigned to succinic acid. Iodometric titration of the reaction mixture after synthesis according to the described procedure revealed that the conversion of aminoguanidine was only 2-4%, i.e., the reaction rate was very low. In accordance with kinetic investigations,^{10a} the mechanism of an analogous reaction between aminoguanidine and malonic acid is similar to that of the acylation of amines by carboxylic acids via acid catalysis,¹² but monoprotonated aminoguanidine (**AG**) is the nucleophile (Scheme 1).



Scheme 1. The mechanism of the reaction between aminoguanidine and carboxylic acids^{10a}

The reaction rate is in direct proportion to the concentration of H_3O^+ and can be expressed by equation (1),^{10a}

$$\frac{dc_{\text{GH}}}{dt} = k_1 c_{\text{AG}} c_{\text{RCOOH}} c_{\text{H}_3\text{O}^+} - k_{-1} c_{\text{GH}} c_{\text{H}_2\text{O}} c_{\text{H}_3\text{O}^+} \quad (1)$$

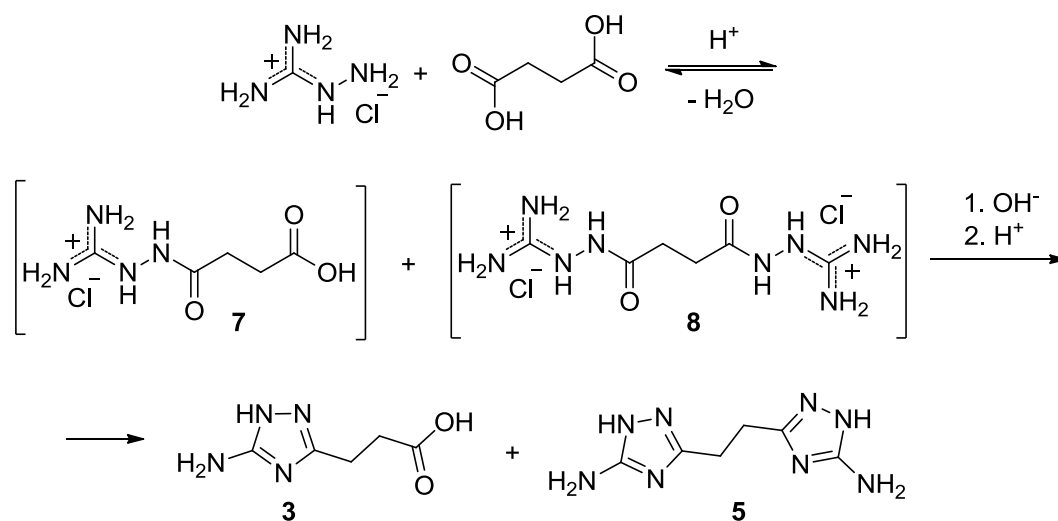
where k_1 and k_{-1} are the rate constants of the forward and reverse reactions, respectively; c_{AG} is the concentration of aminoguanidine cation (**AG**); c_{RCOOH} is the concentration of the unionized form of carboxylic acid; and c_{GH} is the concentration of 2-guanylhydrazide.

It seems that the reaction for the formation of succinic acid 2-guanylhydrazide follows the same mechanism. We previously determined that an acceptable reaction rate is reached at a $\text{pH} \leq 2$.^{10b} However, because succinic acid is a weak acid ($\text{p}K_a = 4.21$),¹³ the pH of the aminoguanidine succinate solution, which forms at the dissolution of aminoguanidine hydrogen carbonate and succinic acid in water, is only 4.2-4.3 even with 15% excess succinic acid. Therefore, the insufficient acidity of the reaction mixture is responsible for the very low reaction rate and failure of the synthesis according to the described procedure.¹¹

To accelerate the synthesis of succinic acid 2-guanylhydrazide, we used an approach analogous to that described in our previous work.^{10b} Hydrochloric acid was employed as a catalyst and the reaction was carried out in highly concentrated solutions to enhance the equilibrium yield. Analysis of the reaction

mixtures revealed that equilibrium was reached within 70-90 min and that 86-87% of aminoguanidine was converted. Similar to the reaction between aminoguanidine and malonic acid,¹⁰ a mixture of compounds **7** and **8** formed, with yields of 65% and 22%, respectively, according to HPLC analysis (Scheme 2).

A mixture containing ~ 69% of compound **3** (yield ~45%) and ~ 19% of compound **5** (yield ~20%) was obtained after treatment of the guanylylhydrazides **7** and **8** solution with NaOH and subsequent acidification. It is preferable to isolate compounds **3** and **5** at pH 4-5, this interval is limited by the ionization constants of compound **3**. We determined by potentiometric titration that compound **3** has a pK_a of 5.19 ± 0.04 for the elimination of a proton and pK_a of 3.67 ± 0.05 for the addition of a proton in water at 20 °C. Considerable losses of compounds **3** and **5** were observed during their separation by crystallization from water due to comparable solubility (Table 1). However, at pH ~7, acid **3** formed a readily soluble sodium salt, while compound **5** was non-ionizable and almost insoluble at 0-5 °C and thus was separated by filtration. Unfortunately, due to losses within separation and crystallization, the pure compounds **3** and **5** were obtained in yields of only 27-32% and 8-11%, respectively.



Scheme 2. Synthesis of compounds **3** and **5** from aminoguanidine and succinic acid

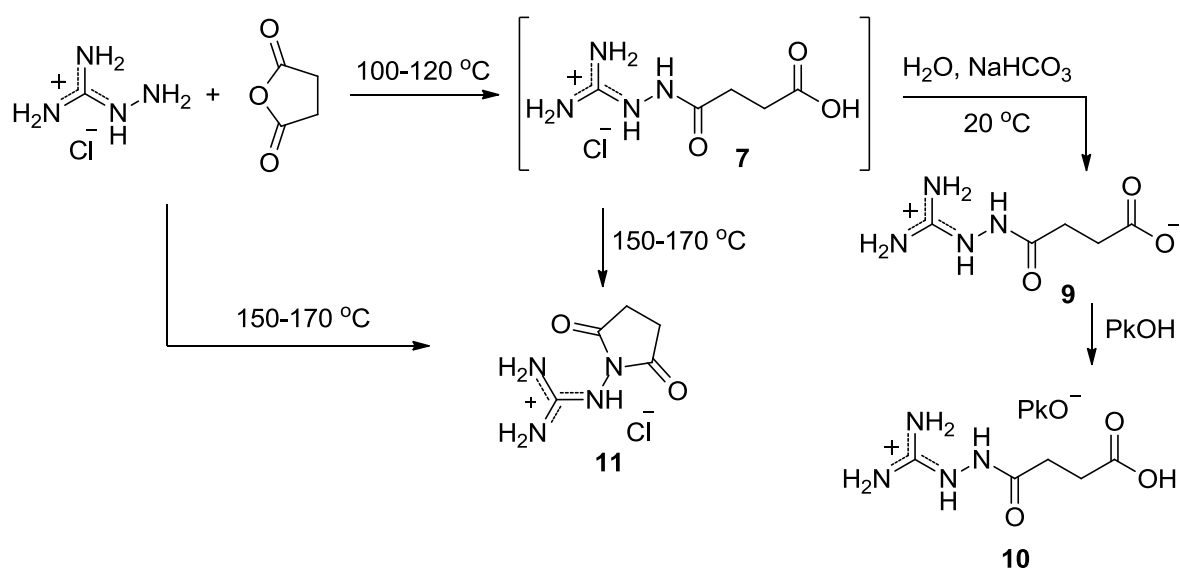
Table 1. Solubility of compounds **3** and **5** in water

Compound	Solubility, g per 100 g of H ₂ O			
	6 °C	25 °C	65 °C	96.5 °C
3	0.194±0.007	0.51±0.01	2.23±0.02	7.55±0.04
5	0.006±0.002	0.197±0.002	1.76±0.02	1.90±0.01

Because the reaction between aminoguanidine and succinic acid did not produce compound **3** in satisfactory yields, we needed a more selective method for preparation of compound **3**.

For the selective synthesis of compound **3** from aminoguanidine, the guanylylhydrazide **7** (or equivalent compound) must be a main product at the first stage. We hypothesized that it is possible in the reaction between aminoguanidine and succinic anhydride (**SAH**), which should be a more selective acylating agent than succinic acid. Successful synthesis of 2-guanylylhydrazide of benzoic acid by fusion of aminoguanidine hydrochloride with benzoic anhydride has been described in the literature.^{9b} Therefore, we investigated a reaction between aminoguanidine hydrochloride (**AGH**) and **SAH** in melt.

We established that the hydrochloride of 2-guanylylhydrazide of succinic acid (**7**) is formed selectively upon fusion of the reagents at 110-130 °C (Scheme 3). Compound **7** crystallizes from a melt during its formation, preventing the development of a side reaction for the formation of compound **8**. Our attempts to isolate pure compound **7** were unsuccessful, because of decomposition during recrystallization, instead yielding compound **8** and succinic acid according to the NMR ¹H and HPLC analyses. However, free guanylylhydrazide **9** was successfully obtained by neutralization of an aqueous solution of the reaction mixture with NaHCO₃ at room temperature (Scheme 3). Picrate **10** was prepared by rapid interaction of compound **9** with picric acid.



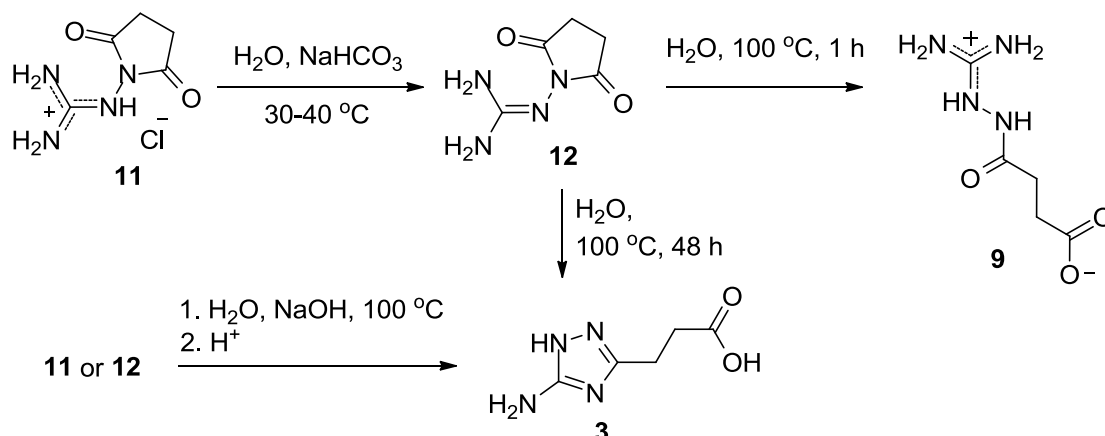
Scheme 3. Synthesis of compounds **9-11**

After fusion of **AGH** with **SAH** at 150 °C and higher or by heating the reaction mixture obtained at 110-130 °C to 150-155 °C, a highly exothermic reaction began and hydrochloride of 2-(2,5-dioxopyrrolidin-1-yl)guanidine (**11**) was formed in high yields (Scheme 3). Notably, the observed reaction is different from the similar reaction of the amidrazones of benzoic and pyridinecarboxylic acids with anhydrides of maleic and *cis*-1,2-cyclohexanedicarboxylic acids, at which substituted carboxyalkyl-1,2,4-triazoles are formed.^{14a,b} In our case, the cyclization of compound **7** into compound **3** does not occur because the guanidine fragment of compound **7** is protonated and its nucleophilicity is

very low.

Compound **9** cyclizes rapidly under heating in an alkaline water solution to produce triazole **3** in quantitative yield. The cyclization also takes place by refluxing **3** in water in the absence of an alkali, according to the recently reported procedure;¹⁵ however, the reaction occurs very slowly and is accompanied by the formation of sparingly soluble unidentified compounds. The reaction proceeds slowly because of the low nucleophilicity of the protonated guanidine fragment of compound **9**, whose predominant tautomer probably has a zwitterionic structure (Scheme 3). Sparingly soluble by-products can result from side reactions of oligomerization due to the presence of a reactive carboxylic group in compound **9**.

Compound **11** is sufficiently stable in water. Free 2-(2,5-dioxopyrrolidin-1-yl)guanidine (**12**) is formed with the addition of an equimolar amount of NaHCO₃ to an aqueous solution of **11**. Both compounds **11** and **12** can be converted quantitatively into the triazole **3** by short-term heating in an alkaline water solution (Scheme 4).

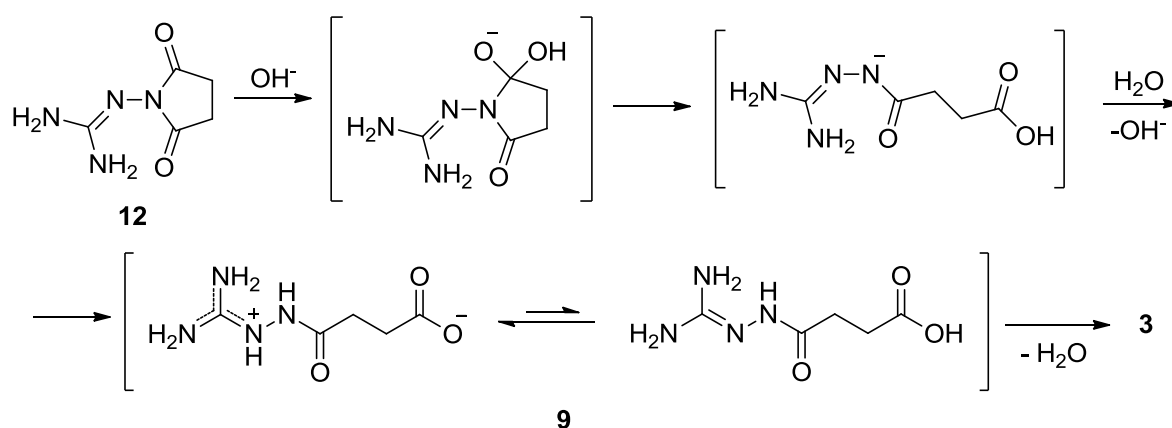


Scheme 4. Reactions of compounds **11** and **12**

The observed rearrangement follows the ANRORC mechanism. The pyrrolidine-2,5-dione ring opens when exposed to hydroxide ions to give guanylylhydrazide **9**, which then cyclizes into triazole **3** (Scheme 5). This mechanism was corroborated by guanylylhydrazide **9** being obtained by refluxing of compound **12** for 1 h in water (Scheme 4). Apparently, the hydroxide ion acts as a nucleophile instead of a water molecule, even in the absence of alkali. Because compound **12** is a weak base ($pK_a = 5.75 \pm 0.03$ at 20 °C), its water solution has a slightly alkaline pH (8-9), thus providing the necessary concentration of hydroxyl ions. If a water molecule served as a nucleophile, the splitting of the pyrrolidine-2,5-dione ring would occur faster upon refluxing of compound **11** instead of **12** due to the negative inductive effect of the protonated guanidine fragment. However, compound **11** is hydrolyzed slowly in boiling water.

The transformation of compound **12** into triazole **3** represents a new rearrangement in the series of

2,5-dioxopyrrolidine. According to the Babaev-Zefirov ring-bond-redistribution (RBR) graphs classification of heterocyclic ring transformations (Figure 2), this rearrangement relates to the relatively rare (a)(d)-class of the simple heterocyclic ring transformations and has a code 552-(a)(d).¹⁶ The majority of other rearrangements of five-membered heterocycles involving a side chain of three atoms have the code 552-(a)(a), i.e. fission of an old bond and formation of a new bond occur at one pivotal atom, instead of at two, as in the case of the observed rearrangement.^{16,17} This rearrangement is topologically similar to the rearrangement of the methyl ester of 2-(2-(2,5-dioxopyrrolidin-1-yl)phenyl)acetic acid into 3-(3-(methoxycarbonyl)-1*H*-indol-2-yl)propanoic acid under the action of bases,¹⁸ which has the same type, class and sort, but relates to another family.¹⁶



Scheme 5. Proposed mechanism of the rearrangement of compound **12**

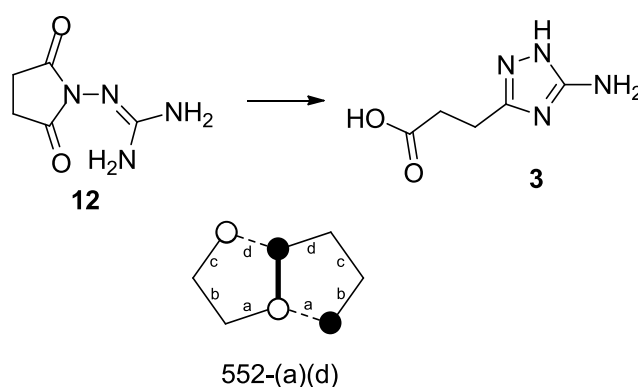


Figure 2. Ring-bond-redistribution graph (G_2) and code for the observed rearrangement according to the Babaev-Zefirov classification¹⁶

Thus, two approaches for the preparation of compound **3** from **AGH** and **SAH**, which differ in the first step, are possible. The first method implies the synthesis of guanylhyaide **7** at 110-130 °C, while the second includes the formation of compound **11** at temperatures higher than 150 °C. At the second step of both approaches, the intermediate product **7** or **11** is readily converted into compound **3** by heating in an

alkaline water solution and subsequent acidification. Therefore, both approaches can be used for one-pot synthesis, i.e., without isolation of intermediate compound **7** or **11**.

As determined by iodometric titration, the conversion of **AGH** at 115-120 °C increased to ~ 60% within 15-20 min. Then, the reaction mixture began to crystallize and the reaction proceeded slowly due to diffusion limitation, reaching 93% conversion of **AGH** within only 2 h. At 160-170 °C the reaction was completed within 10 min with 96-97% conversion of **AGH**. Thus, the second approach for the preparation of compound **3** (through the intermediate compound **11**) is more advantageous because it requires less time and provides greater conversion of the starting compounds. According to HPLC analysis, a small amount of diguanylhydrazide **8**, which subsequently cyclizes to give by-product **5**, is still formed with an equimolar ratio of reagents in the first stage of the synthesis. However, the use of a small excess (20-30%) of **SAH** relative to **AGH** allows for almost complete suppression of by-product formation (Table 2) and for obtaining pure compound **3** in 85% to 90% yield after one recrystallization from water.

Table 2. Optimization of the molar ratio of **AGH:SAH** at the first stage of the one-pot synthesis of compound **3** (fusion of the reagents at 160 °C within 10 min)

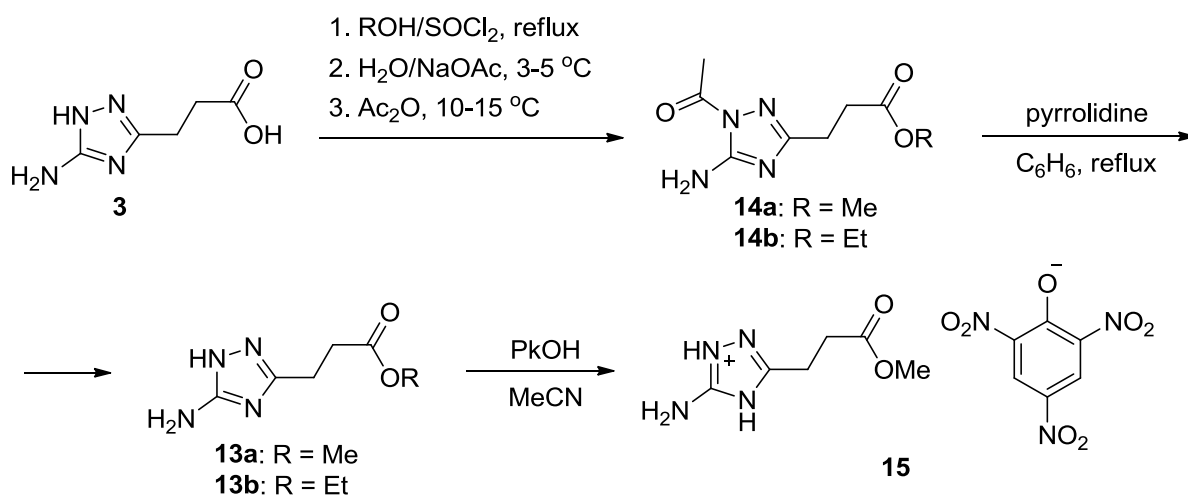
Molar ratio of AGH:SAH	Conversion of AGH , % ^{a)}	Yield of 3 , % ^{b)}	Yield of 5 , % ^{b)}	Selectivity, %
1:1.0	96	85	11	88
1:1.1	99	93	6	94
1:1.2	99	95	4	96
1:1.3	100	≥98	2	≥98
1:1.5	100	≥98	0	≥98

a) According to iodometric titration. b) The yield in the reaction mixture according to HPLC.

Because we needed esters of compound **3** to investigate the tautomerism, methyl (**13a**) and ethyl (**13b**) esters were obtained by esterification of compound **3** with alcohols in the presence of thionyl chloride according to the previously described procedure for the preparation of the esters of acids **1** and **2**.¹⁹ However, due to very high solubility in water and polar organic solvents, compounds **13a,b** could not be isolated from the reaction mixtures by common methods with reasonable yields. Therefore, the esters were isolated in the form of acylated derivatives **14a,b**, which were sparingly soluble in cold water and easily crystallized. Compounds **13a,b** were obtained by deacetylation of **14a,b** with pyrrolidine in benzene (Scheme 6). The picrate of the methyl ester of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanoic acid (**15**), which is required for investigation of the tautomerism of compound **3**, was obtained by rapid mixing

of solutions of compound **13a** and picric acid in acetonitrile (Scheme 6).

The structures of the synthesized compounds were determined by elemental analysis, MS, IR, NMR spectra and finally corroborated by X-ray diffraction studies of compounds **3** and **11**. Signal assignments in the NMR ^{13}C spectra were performed based on proton-coupled ^{13}C spectra and ^1H - ^{13}C HMBC spectra. Compound **3** can presumably exist in the tautomeric forms **A-F** (Figure 3). Imino forms are not considered because they are recognized as being thermodynamically unstable compared to the amino forms and have not been detected so far.²⁰ The form **F** was also excluded, because according to the quantum chemical calculations for protonated 3-amino-1,2,4-triazole and its *N*-methyl derivatives, the tautomer analogous to the form **F** is 8-9 kcal/mol less stable than the tautomers corresponding to the **D** and **E** forms.²¹



Scheme 6. Synthesis of compounds **12a,b**, **13a,b** and **15**

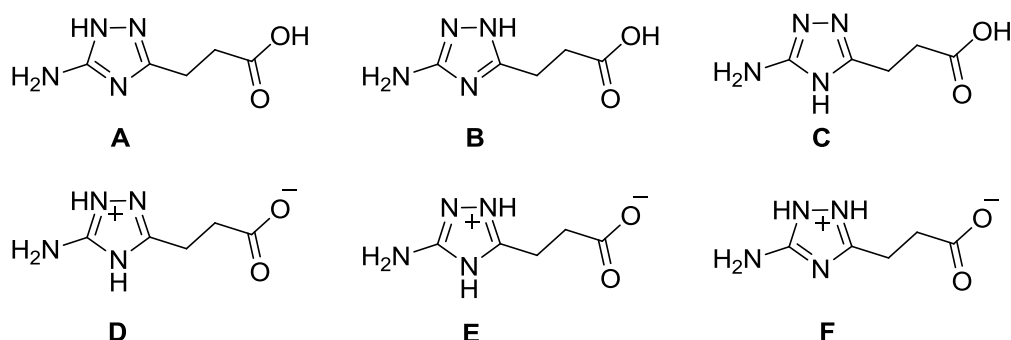


Figure 3. Possible tautomeric forms of compound **3**

NMR spectroscopy is one of the most informative methods for investigation of the tautomerism of *C*-amino-1,2,4-triazoles in solutions.^{15,22} The ^1H and ^{13}C NMR spectra of compound **3** did not show doubling of signals characteristic for 3(5)-substituted 5(3)amino-1,2,4-triazoles,¹⁵ which could be

accounted for either by the coalescence of signals of different tautomers or the predominance of one tautomer and a very low concentration (or absence) of the other tautomers.²² Comparison of the ¹H and ¹³C NMR spectra of compound **3** with the spectra of esters **13a,b**, picrate **15** and literature data for tautomeric forms **A-C**^{1,15,21,23} and salts **D,E**^{1,21,24} (Figures 4 and 5) suggests that compound **3** in DMSO exists predominately in the **A** and **B** tautomeric forms, but with the prevalence of tautomer **A**. Other tautomers are absent or present in low concentrations insufficient to be detected by NMR.

In the presence of tautomers **D** or **E** (Figure 3) in significant concentrations, the signals of NH₂ protons should be observed at lower field (as for picrate **15**), and the signals of the triazole carbons would be at higher field (Figures 4 and 5). In tautomer **C**, the carbon connected to the carboxyethyl group should give a signal at a considerably higher field, such as in 3-amino-4,5-dimethyl-1,2,4-triazole and 3-amino-4-methyl-5-phenyl-1,2,4-triazole (151.3 and 152.1 ppm, respectively).^{23b} The proton spectra of the esters **13a,b** at 0.1 M concentration show two sets of signals corresponding to tautomers **A** and **B** (Figures 4 and 5). However, the ¹³C NMR spectra of these compounds at 0.4 M concentration exhibit only one set of signals, apparently due to coalescence. The ratio of the integral intensities of NH₂ protons of tautomers **A** and **B** gives $K_T = [A]/[B] \sim 3.2$ at 27 °C. The NH₂ protons of compound **3** exhibit an average shift between the corresponding signals of tautomers **A** and **B** of esters **13a,b**. In addition, the ¹³C NMR spectrum of compound **3** is very similar to that of esters **13a,b**, in which coalescence of the signals of tautomers **A** and **B** is observed. Therefore, we concluded that compound **3** in DMSO exists predominately as both tautomers **A** and **B**. The averaging of the NMR chemical shifts of the tautomers arises from coalescence due to accelerated proton exchange (in comparison with esters **13a,b**) catalyzed by carboxyl group. Taking over as model signals the chemical shifts of NH₂ protons of tautomers **A** and **B** of compound **13a** we calculated by interpolation²² $K_T = 3.3$ for compound **3**. This value is very close to the K_T of the esters **13a,b**.

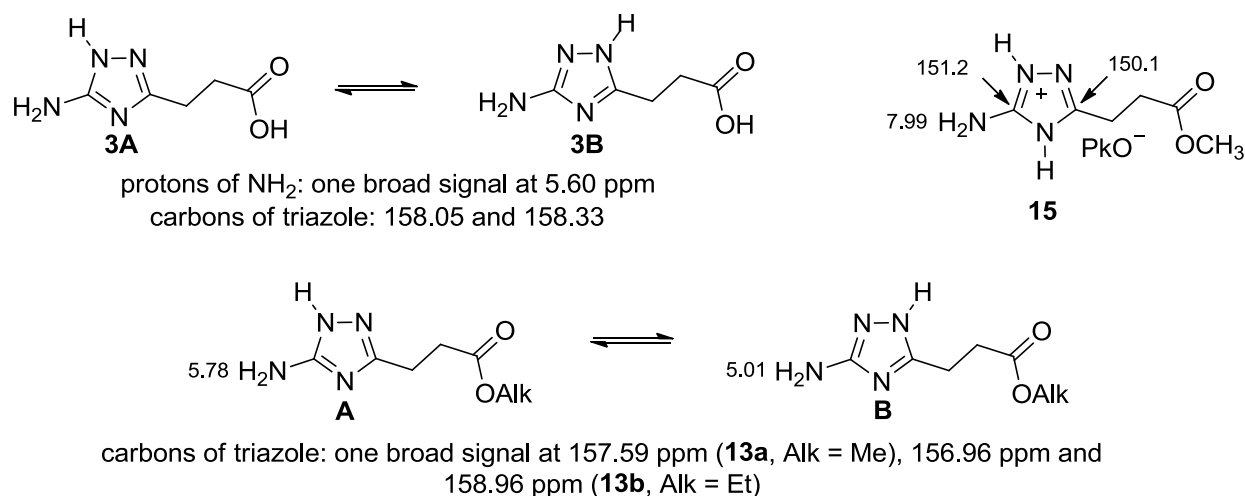


Figure 4. The characteristic signals (ppm) in the ¹H and ¹³C NMR spectra of compounds **3**, **13a,b** and **15**

To estimate the tautomeric equilibrium of compound **3** in water and detect the existence¹³ of zwitterionic forms, we compared its acid-base properties with those of ester **13b**. By potentiometric titration of **13b** with 0.1 M hydrochloric acid at 20 °C, we determined a pK_a of 4.32 ± 0.05 , which is an approximately average value between the pK_a obtained by titration of compound **3** with acid (3.67 ± 0.05) and base (5.19 ± 0.04). Therefore, we concluded that an equilibrium exists between the neutral (apparently predominately **A**) and zwitterionic (probably **D**) forms of compound **3** and determined a ratio, $R = [\text{zwitterion}]/[\text{neutral molecule}]$ calculated from the Ebert formula,¹³ of 3.47.

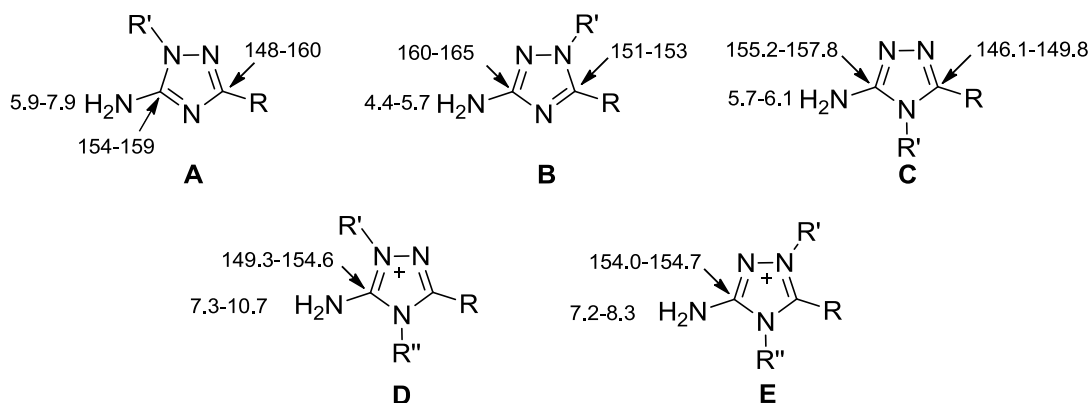


Figure 5. The characteristic signals (ppm) in the ^1H and ^{13}C NMR spectra of various tautomeric forms of C-amino-1,2,4-triazoles^{1,15,21,23} and triazolium salts^{1,21,24}

The structure of **3** in the crystal was investigated by FTIR spectroscopy and X-ray analysis. The FTIR spectrum of the sample obtained by crystallization of compound **3** from water contains a very broad band of the OH stretching absorption in the region of $3300\text{--}2500\text{ cm}^{-1}$, which is typical for carboxylic acids.²⁵ An intensive band of a C=O stretching at 1674 cm^{-1} indicates the presence of an unionized tautomer, most likely tautomer **A**, based on the literature data for other 3-substituted 5-amino-1,2,4-triazoles.^{1,15,20,23h} The stretching vibrations of the zwitterionic tautomers **D** and **E**, which have ionized carboxyl groups, should be observed in the region of $1610\text{--}1550\text{ cm}^{-1}$.²⁵ Although the spectrum shows an intensive band at 1553 cm^{-1} , this band can also be assigned to the valence vibrations of C=N of the triazole ring.^{20c} For example, the analogous band presents in the FTIR spectra of compounds **14a,b**. Because it was difficult to draw conclusions about the presence or absence of the zwitterionic forms of compound **3** based on the FTIR spectrum, we conducted X-ray crystallography.

A single crystal for X-ray analysis was obtained by crystallization of compound **3** from DMF. In the crystal, compound **3** exists as a solvate with DMF with a composition of 1:1. For subsequent discussion of the structure, the crystallographic numbering system will be used (Figure 6). The carboxyl group of **3** is partially deprotonated and a proton is disordered between O1 and N4 (site occupancy factors are 0.72 and 0.28, correspondingly). These observations likely result because the crystal consists of 72% of neutral

(tautomer **A**) and 28% of zwitterionic (tautomer **D**) forms of compound **3**. The bond lengths and angles in the aminotriazole fragment are close to those reported for other 5-amino-1,2,4-triazoles.^{1b,15a,23g,h} The triazole fragment of the molecule is planar, with maximal deviations of atoms from the mean-square plane not exceeding 0.011(8) Å. A planar amino group is almost coplanar to the triazole ring (dihedral angle between the NH₂ and triazole planes is 4(2)°). Conjugation between the unshared electron pair of N5 and the π system of the triazole cycle leads to shortening of the C5—N5 bond (1.342(1) Å) relative to the standard length of a purely single N_{sp²}—C_{sp²} bond (1.43–1.45 Å).²⁶ The C5—N1 and C5—N4 bonds have almost equal lengths of 1.336(1) and 1.337(1) Å, respectively. In DMF, one of the methyl group (C11) is disordered in two positions, which differ in rotation about the C11—N6 bond. In the crystal, the molecules of **3** are linked together by hydrogen bonds: N5—H5A···O2 [N···O 2.937(1) Å, O···H 2.08(2) Å, N—H 0.89(2) Å, angle NHO 162(1)°], O1—H1o···N4 [O···N 2.574(1) Å, H···N 1.71(2) Å, O—H 0.86(2) Å, angle OHN 173(1)°] and N4—H4···O1 [H···O 1.78(8) Å, N—H 0.80(6) Å, angle NHO 173(3)°] (Figure 6). Molecules of DMF are hydrogen-bonded to **3** via N1—H1···O3 [N···O 2.802(1) Å, H···O 1.95(2) Å, N—H 0.86(2) Å, angle NHO 168(1)°] and N5—H5B···O3 [N···O 2.896(1) Å, H···O 2.07(2) Å, N—H 0.84(2) Å, angle NHO 170(1)°].

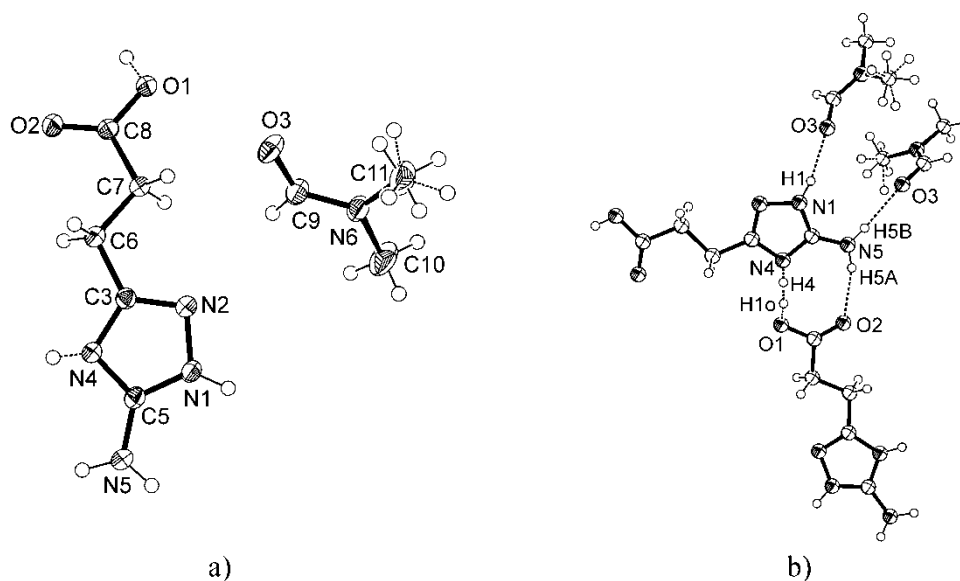


Figure 6. The molecular structure of the crystallosolvate of compound **3** with DMF (a) and its hydrogen-bonding scheme (b)

The ¹H NMR spectrum of compound **9** shows the broadening of NH signals and the appearance of an additional very broad peak at 7.03 ppm, indicating the presence of at least two different tautomers in DMSO. The structure and purity of **9** were also confirmed by elemental analysis, which is in good agreement with the chemical formula proposed for the monohydrate, and by the ¹³C NMR spectrum,

which exhibits only one set of coalesced signals. In addition, the ^1H NMR spectrum of picrate **10** is analogous to spectra of other salts of 2-guanylhydrazides of carboxylic acids.²⁷ The pK_a , determined by the potentiometric titration of **9** with 0.1 M hydrochloric acid in water and corresponding to the addition of a proton, is 3.95 ± 0.02 (at 27 °C), which is considerably lower than the corresponding pK_a of 2-guanylhydrazide of 4-chlorobenzoic acid (7.85 ± 0.04 at 24 °C). By contrast, the pK_a , determined by the titration of **9** with KOH and corresponding to the elimination of a proton, is 9.23 ± 0.03 (at 30 °C). These data indicate that compound **9** in water exists in the zwitterionic form. The FTIR spectrum of **9** also indicates the presence of an ionized carboxyl group showing bands at 1568 and 1591 cm^{-1} . Based on these data, the zwitterionic structure in Scheme 5 was assigned to compound **9**, though its structural features and tautomerism demand more thorough investigation.

The proposed structures of compounds **11** and **12** are in good agreement with spectral data and were confirmed unambiguously by X-ray crystal analysis of compound **11**. A single crystal for X-ray investigation was obtained by crystallization of **11** from 80% ethanol.

The structure of compound **11** (Figure 7) is somewhat similar to that of 2-guanylhydrazides of carboxylic acids and aminoguanidinium salts.²⁸ The pyrrolidine-2,5-dione ring and N2N3N4C5 fragment of the molecule are planar and nearly perpendicular to each other, with a dihedral angle of $81.95(4)^\circ$. The bonds C5—N3 and C5—N4 have lengths of 1.313(1) and 1.329(1) Å, respectively, close to the analogous bonds in the aminoguanidine cation, though C5—N2 bond is somewhat longer (1.355(1) Å instead of 1.325-1.341 Å).²⁸ All nitrogen atoms have a trigonal pyramidal configuration (sums of valence angles are 358.6 at N(1), 353.9 at N(2), 356.6 at N(3) and 357.3 at N(4)). The bond lengths and angles in pyrrolidine-2,5-dione cycle are in agreement with those reported for similar compounds.²⁹

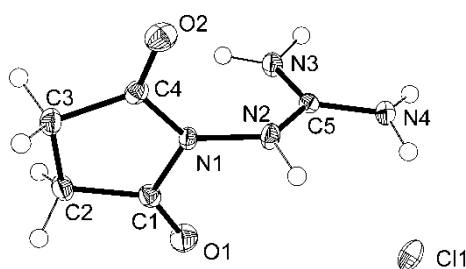


Figure 7. Molecular structure of compound **11**

The spectra of compounds **14a,b** are analogous to the ones described for other 1-acyl-5-amino-1,2,4-triazoles.^{1a,8,23f}

In conclusion, we described the selective one-pot synthesis of compound **3** by fusion of aminoguanidine hydrochloride with succinic anhydride and subsequent rearrangement of the produced hydrochloride of

2-(2,5-dioxopyrrolidin-1-yl)guanidine (**11**) in an aqueous alkaline solution. The rearrangement is new for the 2,5-dioxopyrrolidine series and is related to a relatively rare (a)(d)-class of simple heterocyclic ring transformations. Compound **3** exhibits tautomerism and exists as tautomers **A**, **B** and zwitterion **D** depending on the conditions. Further analysis is needed to elucidate the structural features of compound **9**.

EXPERIMENTAL

General. The melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. The IR spectra were recorded on a Varian Excalibur 3100 FT-IR spectrometer using a single reflection ATR system as a sampling accessory. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 instrument at 500 MHz and 125 MHz, respectively, and a Bruker Avance 600 instrument at 600 MHz (150 MHz for ^{13}C) or Varian Unity 300 at 300 MHz in $\text{DMSO-}d_6$ using TMS as an internal standard. Mass spectra were recorded in the form of m/z (intensity relative to base 100) on a Finnigan MAT INCOS 50 instrument using electron impact ionization. Elemental analyses were determined with a Perkin-Elmer 2400 Elemental Analyzer. HPLC analyses were performed on a Milichrom-5 chromatograph equipped with a Separon- C_{18} column (0.025 M solution of KH_2PO_4 as the mobile phase) and a UV detector (220 nm) according to a described procedure.^{10a} The concentration of aminoguanidine in solutions was analyzed by iodometric titration.^{10a} The pK_a values of compounds **3**, **9**, **12** and **13b** were determined by potentiometric titration¹³ in water using a Mettler Toledo S40-KS instrument equipped with an InLab[®]Expert Pro combined electrode.

Single-crystal X-ray diffraction experiments were carried out with a Bruker SMART 1000 CCD area detector (for compound **3**) and Bruker APEX II CCD area detector (for compound **11**) using graphite monochromated Mo K_α radiation at 120 and 100 K, respectively. The structures were solved by the direct method and refined by a full-matrix least-squares method against F^2 in anisotropic (for no-hydrogen atoms) approximation. For compound **3**, all H(N) and H(O) hydrogen atoms were located from the difference Fourier syntheses and were refined in isotropic approximation. The H(C) atoms were placed in geometrically calculated positions and were refined in isotropic approximation in riding model with the $U_{\text{iso}}(\text{H})$ parameters equal to $1.2 U_{\text{eq}}(\text{Ci})$, where $U(\text{Ci})$ are the equivalent thermal parameters of the atoms to which corresponding H atoms are bonded. For compound **11**, the H(N) hydrogen atoms were located from the difference Fourier syntheses, and the H(C) atoms were placed in geometrically calculated positions. All hydrogen atoms were refined in isotropic approximation in a riding model with the $U_{\text{iso}}(\text{H})$ parameters equal to $1.2 U_{\text{eq}}(\text{Ci})$, where $U(\text{Ci})$ are the equivalent thermal parameters of the atoms to which the corresponding H atoms are bonded. All calculations were performed on an IBM PC/AT using SHELXTL (G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI-53719, USA).

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC), with deposition numbers 783902 and 783901 for **(3)** and **(11)**, respectively.

3-(5-Amino-1*H*-1,2,4-triazol-3-yl)propanoic acid (3) and 3,3'-(ethane-1,2-diyl)bis(1*H*-1,2,4-triazol-5-amine) (5). A mixture of succinic acid (4.31 g, 37 mmol), aminoguanidine hydrogen carbonate (5.00 g, 37 mmol) and 36% aqueous solution of hydrochloric acid (4.31 g, 43 mmol) was heated at 97 °C for 1.5 h. Then 30 mL (183 mmol) of 6.1 molar aqueous solution of NaOH was added and the reaction mixture was additionally heated at 97 °C for 1 h, acidified to pH 4-5 with conc. HCl, cooled to 3-5 °C and stored at this temperature for one day. The precipitate formed was filtered off and dried at 120 °C to give 3.77 g of a mixture, which, according to HPLC, contained 69% of compound **3** (45% yield) and 19% of compound **5** (20% yield). The mixture obtained was slurred in water (7 mL) and alkalified to pH 7-8 with 20% aqueous solution of NaOH. The slurry was heated at stirring to boiling and then cooled to 3-5 °C and kept at this temperature for one day. A precipitate formed was filtered off and dried to give 0.68 g (19% yield) of crude compound **5** as white solid. After one recrystallization from water the yield of pure compound **5** amounted to 0.4 g (11%), mp 310 °C (mp 310-312 °C³⁰); ¹H NMR, δ: 2.68 (br s, 4H, 2CH₂), 5.00 (br s, 4H, 2NH₂ of tautomer B), 5.77 (br s, 4H, 2NH₂ of tautomer A), 11.54 (br s, 2H, 2NH of tautomer A), 12.32 (br s, 2H, 2NH of tautomer B); MS, *m/z*: 194 (M⁺, 72), 136 (12), 111 (20), 98 (100), 69 (10), 57 (27), 43 (86). *Anal.* Calcd for C₆H₁₀N₈: C, 37.11; H, 5.19; N, 57.70. Found: C, 37.00; H, 5.31; N, 58.01.

The filtrate after separation of compound **5** was acidified with 20% HCl to pH 4.4-4.7 and cooled to 3-5 °C. A precipitate formed was filtered off to give 2.1 g (36% yield) of crude compound **3** as white solid. After one recrystallization from water the yield of pure compound **3** amounted to 1.56 g (27%), mp 219-220 °C; ¹H NMR, δ: 2.54 (t, *J* = 7.4 Hz, 2H, CH₂COOH), 2.62 (t, *J* = 7.4 Hz, 2H, CH₂), 5.60 (s, 2H, NH₂), 11.89 (br s, 2H, NH and COOH); ¹³C NMR, δ: 23.01 (CH₂CH₂COOH), 31.82 (CH₂CH₂COOH), 158.05 (C³ of triazole), 158.36 (C⁵ of triazole), 174.10 (COOH); IR (ATR), ν (cm⁻¹): 3224, 3107, 2933, 2730, 2500, 1674 (CO), 1553, 1407; MS, *m/z*: 156 (M⁺, 23), 111 (100), 69 (10), 57 (40), 43 (48). *Anal.* Calcd for C₅H₈N₄O₂: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.50; H, 5.18; N, 35.69.

Selective one-pot synthesis of 3-(5-amino-1*H*-1,2,4-triazol-3-yl)propanoic acid (3). A magnetically stirred mixture of finely ground aminoguanidine hydrochloride (30 g, 0.271 mol) and succinic anhydride (30 g, 0.300 mol) was gradually heated in an oil bath at stirring. The mixture melted at 95-100 °C and an exothermal reaction began at about 150-155 °C. At this point temperature of the reaction mixture rose to 160-170 °C and the melt solidified. The mixture was heated at 160-170 °C for 10 min and then cooled to 40-50 °C. A solution of NaOH (32 g, 0.8 mol) in water (80 mL) was added gradually at stirring. The resulted mixture was heated at 95-100 °C and stirring to complete homogenization and then additionally

for 30 min, then cooled to 50-60 °C and acidified with 20% HCl to pH 4.4-4.7, causing precipitation of compound **3**. The resulted slurry was cooled to 3-5 °C and kept at this temperature for 1 h. The precipitate formed was filtered off, washed with cold water and dried in vacuum at 120 °C to give 43.6-44.5 g of white solid, which contained, according to HPLC, 95-97% of compound **3** (yield ~ 100%). This product was crystallized from water to give 36.5-37.2 g (86-88% yield) of pure compound **3**. Its mp, MS and ¹H NMR spectra were identical with those prepared by the method, described above.

4-[2-(Diaminomethylidene)hydrazinyl]-4-oxobutanoic acid hydrate (**9**).

Method A. A mixture of finely ground aminoguanidine hydrochloride (6.00 g, 54.3 mmol) and succinic anhydride (5.43 g, 54.3 mmol) was heated in an oil bath at 120-130 °C and stirring for 20 min, then cooled to 20 °C and dissolved in 20 mL of water. Sodium hydrogen carbonate (4.56 g, 54.3 mmol) was added in a few portions to the resulted solution at stirring. The mixture was stirred for 20 min at 20 °C then cooled to 5 °C. The precipitate formed was filtered off, washed with ice-cold water and dried at 100 °C to give 5.96 g (57% yield) of title compound. White solid (from water), mp 181 °C (dec.); ¹H NMR, δ: 2.08-2.11 (m, 2H, CH₂), 2.31 (m, 2H, CH₂), 7.03 (br s, 1H, NH), 7.67 (br s, 1H, NH), 9.31 (br s, 1H, NH), 9.98 (br s, 1H, NH), 10.47 (br s, 1H, NH); ¹³C NMR, δ: 29.42 (CH₂), 32.45 (CH₂), 159.52, 173.25 (CO), 177.17 (CO); IR (ATR), ν (cm⁻¹): 3465, 3324, 3125, 2935, 2623, 1693, 1656, 1591, 1568, 1497; MS, *m/z*: 156 ([C₅H₁₀N₄O₃ - H₂O]⁺, 20), 111 (20), 55 (22), 43 (100). *Anal.* Calcd for C₅H₁₂N₄O₄: C, 31.25; H, 6.29; N, 29.15. Found: C, 31.30; H, 6.39; N, 29.38.

Method B. A solution of compound **12** (1.00 g, 6.4 mmol) in 6 mL of water was refluxed for 1 h, then cooled to 5 °C. The precipitate formed was filtered off, washed sequentially with cold water and EtOH, then dried at 100 °C to give 0.84 g (68% yield) of title compound. Its mp, ¹H NMR and IR spectra were identical with those prepared by method A.

4-[2-(Diaminomethylidene)hydrazinyl]-4-oxobutanoic acid picrate (10**).** A warm solution of picric acid (474 mg, 2.06 mmol) in EtOH (2 mL) was added at stirring to a warm solution of compound **9** (300 mg, 1.72 mmol) in water (1 mL). After cooling to room temperature, the precipitate formed was filtered off, washed with acetonitrile and dried in vacuum at 120 °C to give 395 mg (57% yield) of title compound. Yellow filaments, mp 180 °C (dec.); ¹H NMR, δ: 2.41-2.43 (m, 2H, CH₂), 2.47-2.49 (m, 2H, CH₂), 7.39 (br s, 4H, 2NH₂), 8.58 (s, 2H, arom.), 9.44 (s, 1H, NH), 10.04 (s, 1H, NH), 12.25 (s, 1H, OH); ¹³C NMR, δ: 27.16 (CH₂), 28.64 (CH₂), 124.57 (C⁴ of PkO⁻), 125.33 (C³ of PkO⁻), 141.82 (C² of PkO⁻), 158.49, 160.95 (C¹ of PkO⁻), 171.85 (CO), 173.88 (CO); IR (ATR), ν (cm⁻¹): 3367, 3305, 3221, 3117, 1720, 1693, 1674, 1611, 1565, 1548, 1519. *Anal.* Calcd for C₁₁H₁₃N₇O₁₀: C, 32.76; H, 3.25; N, 24.31. Found: C, 32.40; H, 3.39; N, 24.68.

2-(2,5-Dioxopyrrolidin-1-yl)guanidine hydrochloride (11**).** A mixture of finely ground aminoguanidine hydrochloride (10 g, 90.5 mmol) and succinic anhydride (10 g, 100.0 mmol) was gradually heated in an

oil bath at stirring. The mixture melted at 95-100 °C and an exothermal reaction began at about 150-155 °C. At this point temperature of the reaction mixture rose to 160-170 °C and the melt solidified. The mixture was heated at 160-170 °C for 30 min, cooled to room temperature and then dissolved in 15 mL of hot water. The solution obtained was diluted with EtOH (40 mL) and cooled to 3-5 °C. The precipitate formed was filtered off, recrystallized from water-EtOH mixture and dried at 120 °C to give a white solid (15.2 g, 87%). Mp 270-272 °C; ¹H NMR, δ: 2.70 (s, 4H, 2CH₂), 7.89 (br s, 2H, NH₂), 8.09 (br s, 2H, NH₂), 10.06 (br s, 1H, NH); ¹³C NMR, δ: 27.14 (2CH₂), 157.97, 174.65 (2CO); IR (ATR), ν (cm⁻¹): 3409, 3325, 3107, 2949, 1735, 1677, 1617, 1586; MS, *m/z*: 156 (C₅H₈N₄O₂⁺, 47), 114 (48), 101 (16), 85 (22), 55 (25), 43 (100). *Anal.* Calcd for C₅H₉ClN₄O₂: C, 31.18; H, 4.71; N, 18.41. Found: C, 31.16; H, 4.28; N, 18.55.

2-(2,5-Dioxopyrrolidin-1-yl)guanidine hydrate (12). Sodium hydrocarbonate (4.38 g, 52.1 mmol) was added gradually to a solution of compound **11** (10.00 g, 52.1 mmol) in 15 mL of water at 30-40 °C and stirring. Resulted mixture was cooled to 15-20 °C and stirred at this temperature for 20 min. The precipitate formed was filtered off, washed with cold water (10 mL) and dried at 100 °C to give 10.34 g (85% yield) of compound **12**, pure enough for further synthesis. Analytical sample was obtained by crystallization of crude **12** from water. White plates, mp > 300 °C; ¹H NMR, δ: 2.50 (s, 4H, 2CH₂), 5.23 (s, 2H, NH₂), 5.57 (s, 2H, NH₂); ¹³C NMR: δ 26.90 (2CH₂), 160.03, 175.64 (2CO); IR (ATR), ν (cm⁻¹): 3433, 3344, 3167, 1683, 1667, 1644, 1569, 1498; MS, *m/z*: 156 (M⁺, 76), 114 (82), 101 (23), 85 (29), 43 (100). *Anal.* Calcd for C₅H₁₀N₄O₃: C, 34.48; H, 5.79; N, 32.17;. Found: C, 34.65; H, 5.55; N, 32.33.

Methyl 3-(1-acetyl-5-amino-1H-1,2,4-triazol-3-yl)propanoate (14a). Thionyl chloride (5.59 g, 47 mmol) was added drop by drop within 10 min to a stirred suspension of compound **3** (7.34 g, 47 mmol) in 25 mL of absolute MeOH. The resulted mixture was refluxed for 1 h. Then 5.59 g (47 mmol) of thionyl chloride was additionally added drop by drop and the reaction mixture was refluxed for 3 h. The excess of MeOH was distilled off in vacuum. The semisolid residue was cooled to 3-5 °C and neutralized to pH 5-6 by addition of cold saturated aqueous solution of sodium acetate at stirring. Then acetic anhydride 5.8 g (57 mmol) was added drop by drop to the neutralized solution and the reaction mixture was stirred for 20 min at 10-15 °C. The precipitate formed was filtered off, washed with cold water and dried to give 6.69 g (67% yield) of white solid. Mp 157-158 °C (from MeOH); ¹H NMR, δ: 2.48 (s, 3H, CH₃CO), 2.65-2.68 (m, 2H, CH₂COOMe), 2.70-2.74 (m, 2H, CH₂), 3.60 (s, 3H, CH₃O), 7.43 (s, 2H, NH₂); ¹³C NMR, δ: 23.04 (CH₃CO), 23.30 (CH₂), 30.58 (CH₂), 51.42 (MeO), 157.07 (C⁵ of triazole), 161.65 (C³ of triazole), 171.14 (CH₃CO), 172.48 (COOMe); IR (ATR), ν (cm⁻¹): 3395, 3303, 3211, 3140, 2940, 1737 (CO), 1715 (CO), 1653, 1553; MS, *m/z*: 212 (M⁺, 11), 170 (47), 139 (23), 111 (100), 43 (45). *Anal.* Calcd for C₈H₁₂N₄O₃: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.18; H, 6.00; N, 26.22.

Ethyl 3-(1-acetyl-5-amino-1H-1,2,4-triazol-3-yl)propanoate (14b). This compound was prepared

analogously to compound **13a**, yield 8.29 g (78% yield), white solid. Mp 130-131 °C (from water); ^1H NMR, δ : 1.16 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.47 (s, 3H, CH_3CO), 2.65 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 4.07 (q, $J = 7.1$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 7.39 (s, 2H, NH_2); ^{13}C NMR, δ : 14.11 ($\text{CH}_3\text{CH}_2\text{O}$), 22.99 (CH_3CO), 23.35 (CH_2), 30.81 (CH_2), 59.91 ($\text{CH}_3\text{CH}_2\text{O}$), 157.07 (C^5 of triazole), 161.71 (C^3 of triazole), 171.13 (CH_3CO), 171.96 (COOEt); IR (ATR), ν (cm^{-1}): 3391, 3301, 3211, 3142, 2960, 2940, 1737 (CO), 1718 (CO), 1652, 1550; MS, m/z : 226 (M^+ , 13), 184 (55), 139 (45), 111 (100), 54 (17), 43 (99). *Anal.* Calcd for $\text{C}_9\text{H}_{14}\text{N}_4\text{O}_3$: C, 47.78; H, 6.24; N, 24.77. Found: C, 48.01; H, 6.02; N, 24.51.

Methyl 3-(5-amino-1H-1,2,4-triazol-3-yl)propanoate (13a). Pyrrolidine (0.40 g, 5.6 mmol) was added to a suspension of compound **14a** (1.00 g, 4.7 mmol) in benzene (3 mL) and the resulted mixture was refluxed for 30 min. After cooling to room temperature the precipitate formed was filtered off, crystallized from MeCN and dried. Yield 0.68 g (85%), white solid, mp 137-138 °C (from MeCN). ^1H NMR, δ : 2.61-2.63 (m, 2H, CH_2COOMe), 2.66-2.68 (m, 2H, CH_2), 3.56 (s, 3H, CH_3O), 5.02 (s, 2H, NH_2 of tautomer B), 5.78 (s, 2H, NH_2 of tautomer A), 11.56 and 12.30 (both br s, 1H, NH of tautomers A and B, accordingly); ^{13}C NMR, δ : 22.97 ($\text{CH}_2\text{CH}_2\text{COOMe}$), 31.30 ($\text{CH}_2\text{CH}_2\text{COOMe}$), 51.27 (CH_3O), 157.59 (C^3 and C^5 of triazole), 172.68 (CO); IR (ATR), ν (cm^{-1}): 3383, 3108, 2956, 2930, 1722 (CO), 1659, 1591, 1533; MS, m/z : 170 (M^+ , 21), 139 (16), 111 (100), 57 (12), 43 (13). *Anal.* Calcd for $\text{C}_6\text{H}_{10}\text{N}_4\text{O}_2$: C, 42.35; H, 5.92; N, 32.92. Found: C, 42.56; H, 6.08; N, 32.76.

Ethyl 3-(5-amino-1H-1,2,4-triazol-3-yl)propanoate (13b). This compound was prepared from **14b** analogously to compound **13a**. Yield 0.71 g (87%), white solid, mp 104-105 °C (from EtOAc); ^1H NMR, δ : 1.15 (t, $J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.59-2.66 (m, 4H, 2 CH_2), 4.03 (q, $J = 7.1$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 5.01 (s, 2H, NH_2 of tautomer B), 5.78 (s, 2H, NH_2 of tautomer A), 11.55 and 12.30 (both br s, 1H, NH of tautomers A and B, accordingly); ^{13}C NMR: δ 14.01 ($\text{CH}_3\text{CH}_2\text{O}$), 23.03 ($\text{CH}_2\text{CH}_2\text{COOEt}$), 31.52 ($\text{CH}_2\text{CH}_2\text{COOEt}$), 59.74 ($\text{CH}_3\text{CH}_2\text{O}$), 156.96 and 158.96 (carbons of triazole), 172.13 (CO); IR (ATR), ν (cm^{-1}): 3387, 3310, 3150, 2987, 2920, 1719 (CO), 1655, 1585, 1532; MS, m/z : 184 (M^+ , 21), 139 (31), 111 (100), 78 (10), 57 (14), 43 (21). *Anal.* Calcd for $\text{C}_7\text{H}_{12}\text{N}_4\text{O}_2$: C, 45.65; H, 6.57; N, 30.42. Found: C, 45.71; H, 6.42; N, 30.57.

Picrate of methyl 3-(5-amino-1H-1,2,4-triazol-3-yl)propanoate (15). A solution of 444 mg (1.94 mmol) of picric acid in MeCN (2 mL) was added at stirring to a hot solution of compound **13a** (300 mg, 1.76 mmol) in MeCN (2 mL). The resulted mixture was cooled to 20 °C and precipitate formed was filtered off, washed with cold MeCN and dried at 100 °C. Yield 569 mg (71%), yellow solid, mp 177-178 °C (from MeCN); ^1H NMR, δ : 2.71 (t, $J = 6.8$ Hz, 2H, CH_2), 2.84 (t, $J = 6.8$ Hz, 2H, CH_2), 3.59 (s, 3H, CH_3O), 7.99 (s, 2H, NH_2), 8.58 (s, 2H, arom.), 13.26 (br s, 2H, 2NH); ^{13}C NMR: δ 20.60 (CH_2), 29.59 (CH_2), 51.60 (OCH_3), 124.52 (C^4 of PkO^-), 125.31 (C^3 of PkO^-), 141.83 (C^2 of PkO^-), 150.10 (C^3 of triazole), 151.17 (C^5 of triazole), 160.95 (C^1 of PkO^-), 171.95 (CO); IR (ATR), ν (cm^{-1}): 3393, 3195, 3081,

2961, 2831, 1710, 1689, 1642, 1567, 1546, 1501. *Anal.* Calcd for C₁₂H₁₃N₇O₉: C, 36.10; H, 3.28; N, 24.56. Found: C, 36.29; H, 3.17; N, 24.79.

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REFERENCES AND NOTES

- (a) A. Dzygiel, B. Rzeszotarska, E. Masiukiewicz, P. Cmoch, and B. Kamiński, *Chem. Pharm. Bull.*, **2004**, *52*, 192; (b) E. Masiukiewicz, B. Rzeszotarska, I. Wawrzycka-Gorczyca, and E. Kołodziejczyk, *Synth. Commun.*, **2007**, *37*, 1917.
- (a) H.-Ch. Gallmeier and B. König, *Eur. J. Org. Chem.*, **2003**, 3473; (b) P. G. Baraldi, D. Preti, F. Fruttarolo, M. A. Tabrizi, and R. Romagnoli, *Bioorg. Med. Chem.*, **2007**, *15*, 17; (c) G. Kashiwazaki, T. Bando, K. Shinohara, M. Minoshima, S. Nishijima, and H. Sugiyama, *Bioorg. Med. Chem.*, **2009**, *17*, 1393.
- N. Fantò, G. Gallo, A. Ciacci, M. Semproni, D. Vignola, M. Quaglia, V. Bombardi, D. Mastroianni, M. P. Zibella, G. Basile, M. Sassano, V. Ruggiero, R. Santis, and P. Carminati, *J. Med. Chem.*, **2008**, *51*, 1189.
- (a) M. V. Chudinov, I. D. Konstantinova, O. I. Ryzhova, R. S. Esipov, A. M. Yurkevich, V. I. Shvets, and A. I. Miroshnikov, *Pharm. Chem. J.*, **2005**, *39*, 212; (b) M. Uenaka, K. Kawata, M. Nagai, and T. Endoh, US Patent 6831177, 2004 (*Chem. Abstr.*, **2005**, *134*, 29421); (c) Q. Wu, F. Qu, J. Wan, X. Zhu, Y. Xia, and L. Peng, *Helv. Chim. Acta*, **2004**, *87*, 811; (d) J. Wan, Y. Xia, Y. Liu, M. Wang, P. Rocchi, J. Yao, F. Qu, J. Neyts, J. L. Iovanna, and L. Peng, *J. Med. Chem.*, **2009**, *52*, 1144.
- H. Ohnishi, H. Kosuzume, M. Mizota, Y. Suzuki, and E. Mochida, Eur. Patent 150507A2, 1985 (*Chem. Abstr.*, **1985**, *104*, 68678y).
- (a) W. Shimizu, US Patent 7097700, 2006 (<http://www.freepatentsonline.com/7097700.html>); (b) G. Wright and P. Gregory, US Patent 7238228, 2007 (<http://www.freepatentsonline.com/7238228.html>).
- H. Park, G. Krigsfeld, S. J. Teat, and J. B. Parise, *Cryst. Growth. Des.*, **2007**, *7*, 1343.
- A. M. Abdel-Megeed, H. M. Abdel-Rahman, G.-E. S. Alkaramany, and M. A. El-Gendy, *Eur. J. Med. Chem.*, **2009**, *44*, 117.
- (a) J. Thiele and W. Manchot, *Liebigs Ann. Chem.*, **1898**, *303*, 33; (b) G. Chipen and V. Grinstein, *Latv. PSR Zinatnu Akad. Vestis Kim. Ser.*, **1965**, 204 (*Chem. Abstr.*, **1965**, *63*, 13243f).
- (a) A. V. Chernysheva, V. M. Chernyshev, P. V. Korolenko, and V. A. Taranushich, *Russ. J. Appl.*

- [Chem.](#), 2008, **81**, 1813; (b) V. M. Chernyshev, A. V. Chernysheva, and V. A. Taranushich, [Russ. J. Appl. Chem.](#), 2009, **82**, 276.
11. V. A. Lopyrev, T. N. Vereschagina, G. G. Kononenko, V. V. Makarskii, and K. L. Krupin, USSR Patent 320496, 1971 (*Chem. Abstr.*, 1972, **76**, 126990k).
 12. (a) R. S. Brown, A. J. Bennet, and H. Slebocka-Tilk, [Acc. Chem. Res.](#), 1992, **25**, 481; (b) A. M. Aman and R. S. Brown, [J. Am. Chem. Soc.](#), 1999, **121**, 4598.
 13. A. Albert and E. P. Serjeant, 'The Determination of Ionization Constants. A laboratory manual,' 3rd ed., Chapman and Hall, London, 1984, p. 218.
 14. (a) B. Modzelewska-Banachiewicz, J. Banachiewicz, A. Chodkowska, E. Jagiełło-Wójtowicz, and L. Mazur, [Eur. J. Med. Chem.](#), 2004, **39**, 873; (b) M. Ziegler-Borowska, M. Ucherek, J. Kutkowska, L. Mazur, B. Modzelewska-Banachiewicz, D. Kędziera, and A. Kaczmarek-Kędziera, [Tetrahedron Lett.](#), 2010, **51**, 2951.
 15. (a) A. V. Dolzhenko, G. Pastorin, A. V. Dolzhenko, and W. K. Chui, [Tetrahedron. Lett.](#), 2009, **50**, 2124; (b) A. V. Dolzhenko, A. V. Dolzhenko, and W. K. Chui, [Heterocycles](#), 2007, **71**, 429.
 16. (a) E. V. Babaev and N. S. Zefirov, [Chem. Heterocycl. Compd.](#), 1992, **28**, 671; (b) E. V. Babaev and N. S. Zefirov, [J. Math. Chem.](#), 1992, **11**, 65; (c) E. V. Babaev, D. E. Lushnikov, and N. S. Zefirov, [J. Am. Chem. Soc.](#), 1993, **115**, 2416; (d) H. C. Van der Plas, 'Advances in Heterocyclic Chemistry: Degenerate Ring Transformations of Heterocyclic Compounds,' Vol. 74, ed. by A. R. Katritzky, Academic Press, Inc., London, 1999, pp. 1-9.
 17. (a) G. L'abbé, [J. Heterocycl. Chem.](#), 1984, **21**, 627; (b) N. Vivona, S. Buscemi, V. Frenna, and G. Cusmano, 'Advances in Heterocyclic Chemistry: Ring Transformations of Five-Membered Heterocycles,' Vol. 56, ed. by A. R. Katritzky, Academic Press, Inc., London, 1993, pp. 49-154; (c) F. D'Anna, V. Frenna, S. Guernelli, G. Z. Lanza, G. Macaluso, S. Marullo, and D. Spinelli, *ARKIVOC*, 2009, **viii**, 125.
 18. G. Kim and G. Keum, [Heterocycles](#), 1997, **45**, 1979.
 19. V. M. Chernyshev, A. V. Chernysheva, and V. A. Taranushich, [Russ. J. Appl. Chem.](#), 2006, **79**, 783.
 20. (a) V. I. Minkin, A. D. Garnovskii, J. Elguero, A. R. Katritzky, and O. V. Denisko, 'Advances in Heterocyclic Chemistry: The Tautomerism of Heterocycles: Five-Membered Rings with Two or More Heteroatoms,' Vol. 76, ed. by A. R. Katritzky, Academic Press, Inc., London, 2000, pp. 157-323; (b) G. Karpińska and J. Cz. Dobrowolski, *J. Mol. Struct. THEOCHEM*, 2008, **853**, 7; (c) M. Pagacz-Kostrzewa, R. Bronisz, and M. Wierzejewska, [Chem. Phys. Lett.](#), 2009, **473**, 238.
 21. E. Anders, K. Wermann, B. Wiedel, and J.-J. Vanden Eynde, *Liebigs. Ann./Recueil*, 1997, 745.
 22. (a) J. Elguero, A. R. Katritzky, and O. V. Denisko, 'Advances in Heterocyclic Chemistry: Prototropic Tautomerism of Heterocycles: Heteroaromatic Tautomerism – General Overview and Methodology,'

- Vol. 76, ed. by A. R. Katritzky, Academic Press, Inc., London, 2000, pp. 1-84; (b) R. M. Claramunt, C. López, M. D. Santa María, D. Sanz, and J. Elguero, [Prog. Nucl. Magn. Reson. Spectrosc.](#), **2006**, **49**, 169.
23. (a) R. N. Butler, T. McEvoy, E. Alcalde, R. M. Claramunt, and J. Elguero, [J. Chem. Soc., Perkin Trans. 1](#), **1979**, 2886; (b) T. Winkler and H. Kristinsson, [Helv. Chim. Acta](#), **1983**, **66**, 694; (c) P. Dvortsák, J. Reiter, T. Somorai, and P. Sohár, [Magn. Reson. Chem.](#), **1985**, **23**, 194; (d) J. Reiter, L. Pongó, T. Somorai, and P. Dvortsák, [J. Heterocycl. Chem.](#), **1986**, **23**, 401; (e) L. Salazar, M. Espada, C. Avendaño, and J. Elguero, [J. Heterocycl. Chem.](#), **1990**, **27**, 1109; (f) A. Dzygiel, E. Masiukiewicz, and B. Rzeszutarska, [J. Agric. Food. Chem.](#), **2002**, **50**, 1383; (g) V. M. Chernyshev, V. A. Rakitov, V. V. Blinov, V. A. Taranushich, and Z. A. Starikova, [Chem. Heterocycl. Compd.](#), **2009**, **45**, 436; (h) M. Bichay, J. W. Fronabarger, R. Gilardi, R. J. Butcher, W. B. Sanborn, M. E. Sitzmann, and M. D. Williams, [Tetrahedron. Lett.](#), **2006**, **47**, 6663.
24. H. Xue, S. W. Arritt, B. Twamley, and J. M. Shreeve, [Inorg. Chem.](#), **2004**, **43**, 7972.
25. (a) E. Pretsch, P. Bühlmann, and M. Badertscher, 'Structure Determination of Organic Compounds: Tables of Spectral Data,' 4th ed, Springer, Berlin, 2009, p. 436; (b) R. M. Silverstein, F. X. Webster, and D. J. Kiemle, 'Spectrometric identification of organic compounds,' 7th ed., Wiley, New York, 2005, p. 502.
26. (a) M. Burke-Laing and M. Laing, [Acta. Cryst. B](#), **1976**, **32**, 3216; (b) F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, [J. Chem. Soc., Perkin Trans. 2](#), **1987**, S1-S19.
27. According to our unpublished results, for hydrochloride of 4-chlorobenzoic acid 2-guanylhydrazide, ¹H NMR (300 MHz, DMSO-*d*₆), δ: 7.57 (br s, 2H, NH₂), 7.64 (d, *J* = 8.6 Hz, 2H, arom.), 7.87 (br s, 2H, NH₂), 7.97 (d, *J* = 8.6 Hz, 2H, arom.), 9.75 (s, 1H, NH), 10.78 (s, 1H, NH); for hydrochloride of acetic acid 2-guanylhydrazide, ¹H NMR (600 MHz, DMSO-*d*₆), δ: 1.87 (s, 3H, CH₃), 7.57 (br s, 4H, 2NH₂), 9.53 (s, 1H, NH), 10.10 (s, 1H, NH).
28. V. M. Chernyshev, A. V. Chernysheva, E. V. Tarasova, V. V. Ivanov, and Z. A. Starikova, *Acta Cryst.*, **2010**, **E66**, o1152.
29. (a) A. K. Tripathi, C. Bruhn, S. Flock, and H. Frauenrath, *Acta Cryst.*, **2005**, **61C**, o705; (b) G.-L. Zhao, R. Rios, J. Vesely, L. Eriksson, and A. Córdova, [Angew. Chem. Int. Ed.](#), **2008**, **47**, 8468.
30. R. N. Shreve and R. K. Charlesworth, US Patent 2744116, 1956 (*Chem. Abstr.*, 1957, **51**, 489h).