Reactivity of cyclic alkoxyguanidines: experimental and theoretical studies

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Abstract

Cyclic alkoxyguanidines such as 2-methoxyiminoimidazolidine, 2-benzyloxyiminoimidazolidine and 6',7'-dihydro-5'*H*-spiro[cyclohexane-1,3'-imidazo[2,1-*c*][1,2,4]oxadiazole react with isocyanates and isothiocyanates to give the corresponding urea and thiourea derivatives, which under basic reaction conditions undergo an intramolecular $S_N2\sigma$ nucleophilic substitution reaction at the sp^2 nitrogen atom of the alkoxyimine moiety with simultaneous extrusion of the alkoxy anion leading to the formation of imidazo[2,1-*c*][1,2,4]triazol-3-one and imidazo[2,1-*c*][1,2,4]thiadiazole with new N-N and N-S bonds, respectively. The above extensions of the Boulton–Katritzky rearrangement were studied theoretically with the DFT B3LYP-6-31+G* method and SM8 solvation model.

Keywords: Cyclic alkoxyguanidines, nucleophilic addition, electrophilic amination, Boulton–Katritzky rearrangement, DFT calculations

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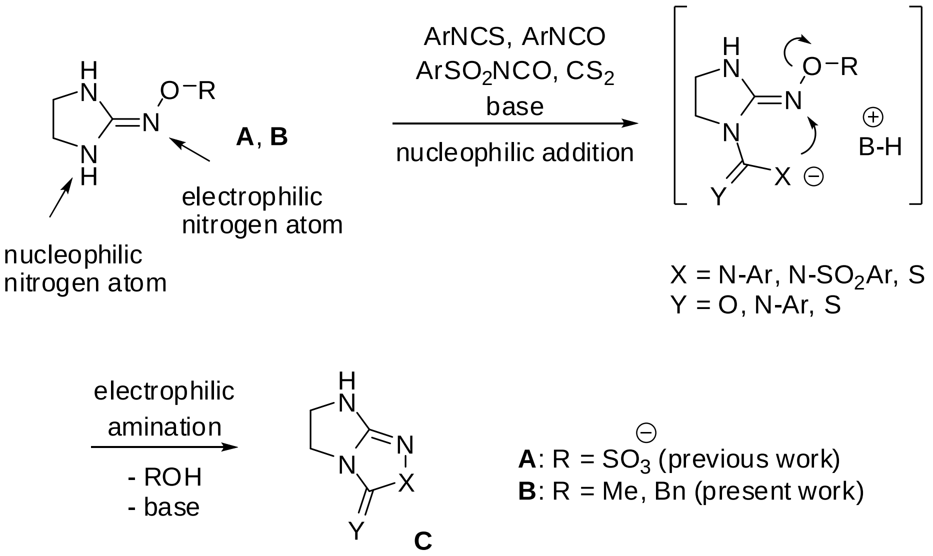
Introduction

Alkoxyguanidine compounds exhibit interesting biological properties including hypoglycemic,[1] antitumor, anti-inflammatory and anti-ischemic[2] as well as antithrombotic activity.[3] Thus far, however, the chemical properties of alkoxyguanidine functionality have been poorly investigated and are limited to the scission of the N–O bond.[4,5]

Recently, we have described a series of tandem nucleophilic addition – electrophilic amination reactions of the cyclic sulfonyloxyguanidine derivative **A** with a variety of heterocumulenes such as isocyanates and isothiocyanates (Scheme 1). The above reactions proceed smoothly due to the presence of both the nucleophilic endocyclic and electrophilic exocyclic nitrogen atoms and lead to the formation of novel imidazoline-containing heterocyclic ring systems of type **C**.[6-9] However, poor solubility of the substrate **A** in most organic solvents required the use of dimethylformamide (DMF) as the reaction medium. Although DMF is commonly used in many industrial processes, it is hazardous in case of skin and eye contact, ingestion or inhalation. Therefore, DMF use should be avoided due to its hepatotoxicity and because it has been found to be associated with testicular cancer.[10,11] Thus, the next logical step in the development of this chemistry was to study the reactivity of highly soluble cyclic alkoxyguanidines (**B**) in other solvents (Scheme 1).



Scheme 1. Nucleophilic addition – electrophilic amination reactions of cyclic sulfonyloxyguanidines (**A**) and alkoxyguanidines (**B**) with heterocumulenes.

Results and Discussion

As shown in Scheme 2, the reaction of monocyclic alkoxyguanidines such as 2-methoxyiminoimidazolidine (**1a**) and 2-benzyloxyiminoimidazolidine (**1b**) with *p*-tolyl isocyanate and tosyl isocyanate in acetonitrile led to the formation of corresponding arylureas (**2a**, **2c**) and arylsulfonylureas (**2b**, **2d**), respectively, in high yields. The structures of compounds **2** bearing an urea functionality were confirmed by elemental analysis, IR and NMR spectroscopy (Experimental section) as well as by X-ray diffraction analysis of compound **2b** (Figure 1).

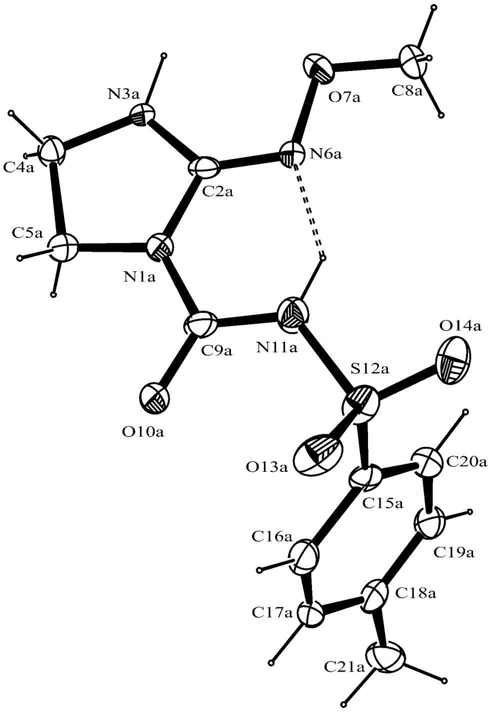
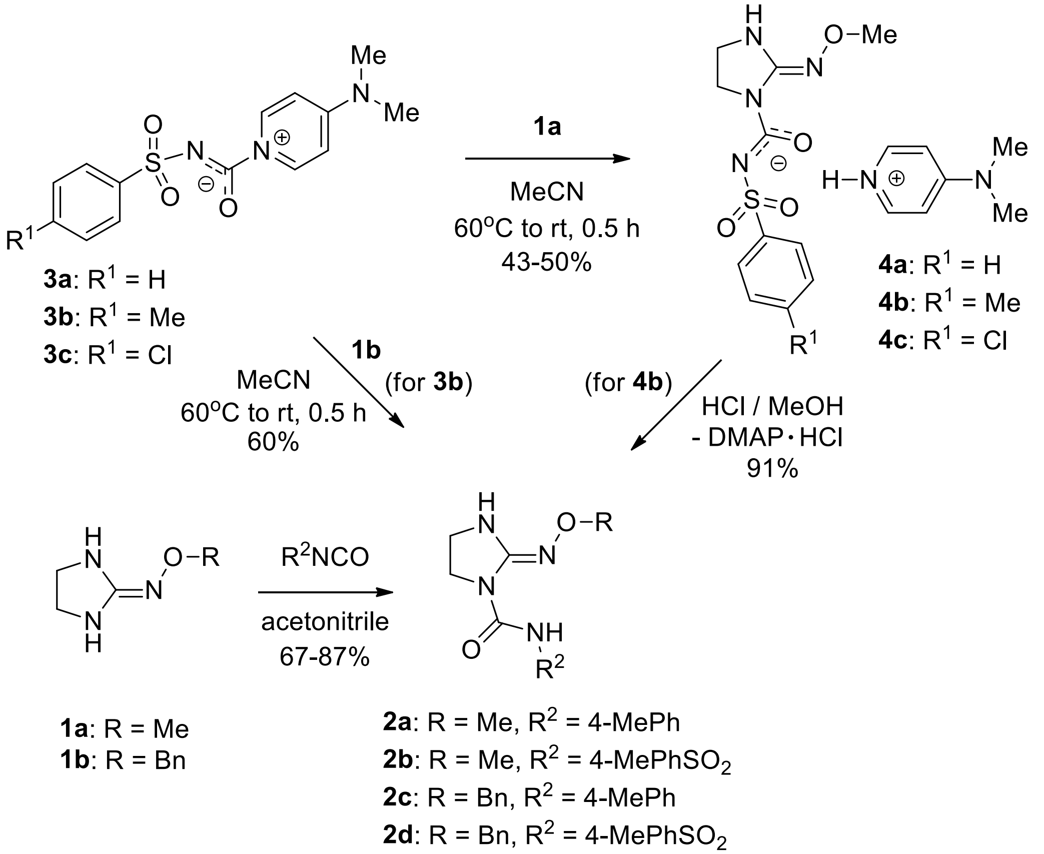


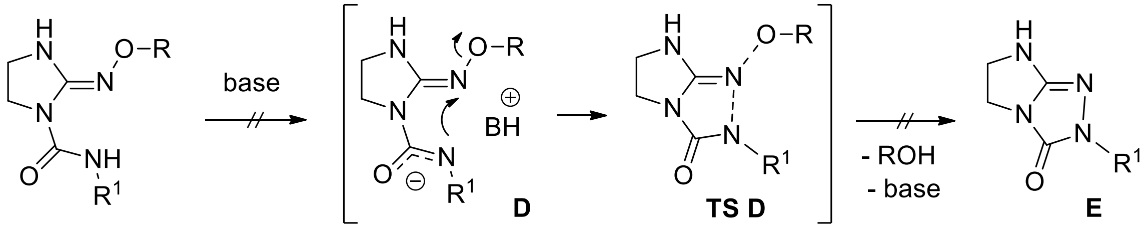
Figure 1. X-ray structure of **2b**.



Scheme 2. Reaction of monocyclic alkoxyguanidines with aryl isocyanates and carbamoylides.

In order to fully explore the reactivity pattern of cyclic alkoxyguanidines we have subjected compounds **1a** and **1b** to reactions with 4-(dimethylamino)pyridinium arylsulfonyl carbamoylides **3a**–**c**, stable substitutes for the arylsulfonyl isocyanates prepared previously in our laboratories.[17,18] Interestingly enough, 2-methoxyiminoimidazolidine (**1a**) reacted with **3a**-**c** giving rise to the formation of the arylsulfonylurea derivatives in the form of corresponding 4-(dimethylamino)pyridinium salts **4a**-**c**, which upon acidification with dilute hydrochloric acid were transformed into the free arylsulfonylureas **2** (Scheme 2). On the other hand, the reaction of 2-benzyloxyiminoimidazolidine (**1b**) with carbamoylide **3b** gave directly the sulfonylurea **2d** (Scheme 2). Apparently an equilibrium between pyridinium salt **4** and free sulfonylurea **2** exists, and the less soluble benzyloxy derivative **2d** precipitates from the reaction mixture.

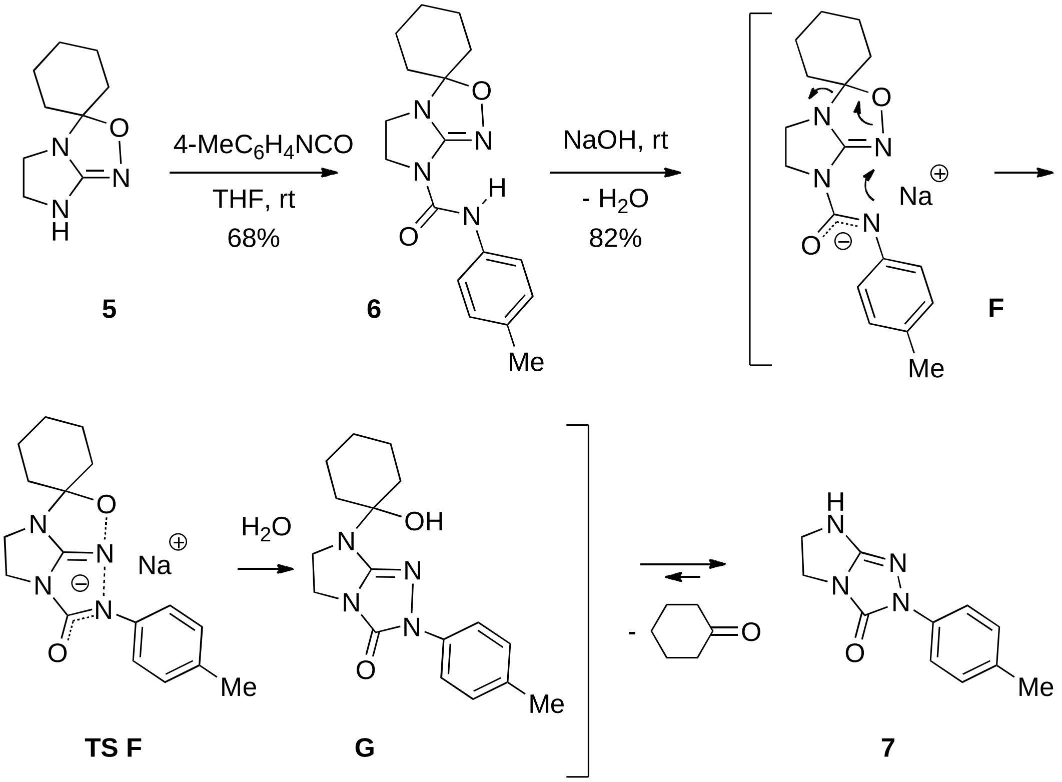
It should be noted that analogous reactions of 2-(hydroxyimino)imidazolidine *O*-sulfonate (**A**) with arylsulfonyl isocyanates and carbamoylides gave 2-(arylsulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (**E**) throgh tandem nucleophilic addition – electrophilic amination reaction, while the use of aryl isocyanates provided urea derivatives susceptible to intramoecular amination reaction upon treatment with a base.[7] Therefore, the nucleophilic addition products **2a**-**d** were treated with a strong base to form the ambident carboximidate anions **D**, which, we expected, would undergo intramolecular electrophilic amination[12-14] with simultaneous extrusion of methoxide or benzyloxide anion (Scheme 3). However, we found that treatment of **2a**-**d** with bases such as sodium hydroxide, triethylamine or pyrrolidine did not provide the desired imidazo[2,1-*c*][1,2,4]triazol-3-ones (**E**), which indicated that the anions **D** are rather weak nucleophiles, unable to induce the intramolecular electrophilic amination reactions at the sp^2-hybridized nitrogen atom of the exocyclic alkoxyimino group.



2a: R = Me, R^1 = 4-MePh
2b: R = Me, R^1 = 4-MePhSO$_2$
2c: R = Bn, R^1 = 4-MePh
2d: R = Bn, R^1 = 4-MePhSO$_2$

Scheme 3. The intramolecular electrophilic amination reaction attempts.

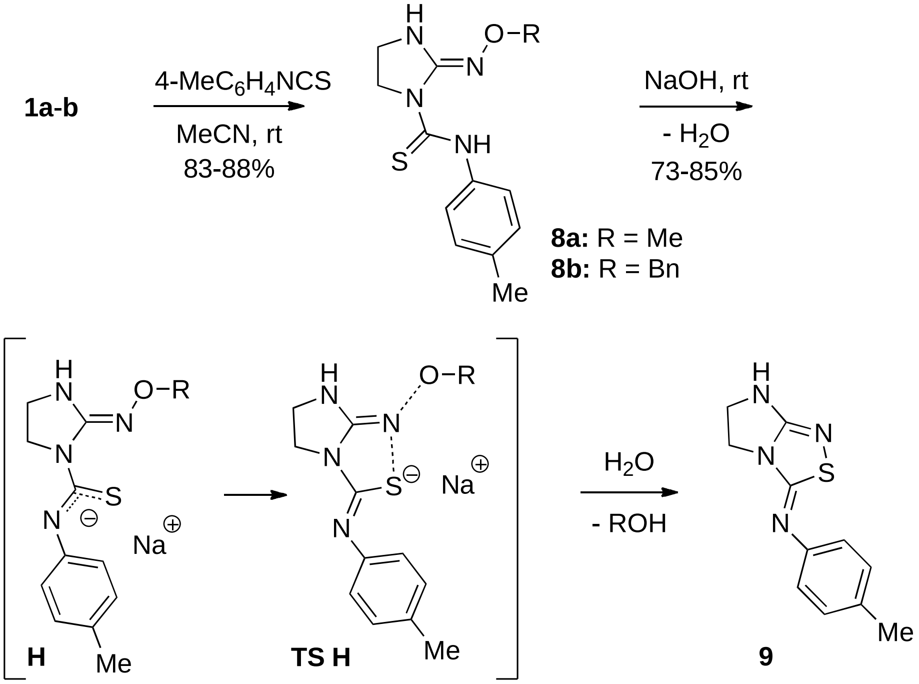
Therefore we further examined the reaction of *p*-tolyl isocyanate with 6',7'-dihydro-5'*H*-spiro[cyclohexane-1,3'-imidazo[2,1-*c*][1,2,4]oxadiazole (**5**), a bicyclic alkoxyguanidine analogue bearing an alkoxy group incorporated into the fused oxadiazole ring system. The reaction of **5** with *p*-tolyl isocyanate was carried out in THF at ambient temperature and it gave the expected urea derivative **6**, which was converted into the desired imidazo[2,1-*c*][1,2,4]triazol-3-one (**7**) using sodium hydroxide (Scheme 4). The observed reaction sequence involving initial nucleophilic addition of the NH group to the isocyanate moiety followed by intramolecular nucleophilic substitution at the sp^2-hybridized nitrogen atom via transition state **TS F** and hemiaminal **G**, can the regarded as an extension of the Boulton–Katritzky rearrangement.[15,16] The above results demonstrated that the ambident carboxamidate anion can displace the internal alkoxy group in the constrained bicyclic alkoxyguanidine **6**, while its nucleophilicity towards the external alkoxyimino group of **2** is insufficient.



Scheme 4. Reaction of bicyclic alkoxyguanidine with *p*-tolyl isocyanate.

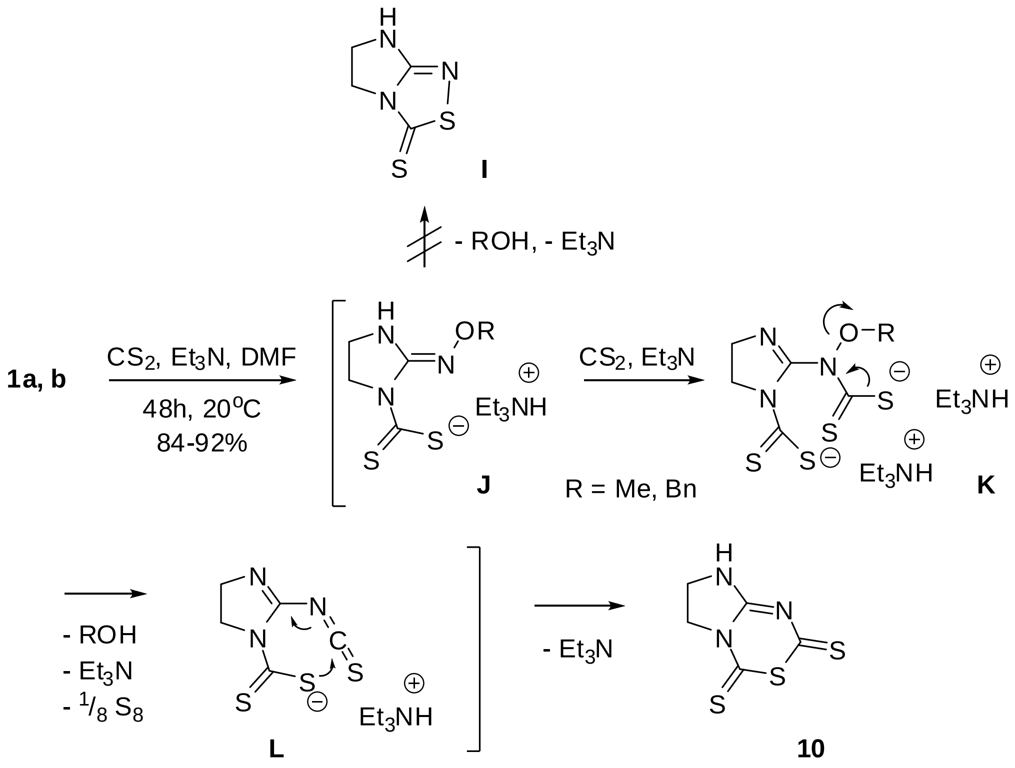
Next, we turned our attention to the reaction of alkoxyguanidines **1a**,**b** with less reactive aryl isothiocyanates. The reaction was carried out in acetonitrile at ambient temperature and led to the formation of the expected thiourea derivatives **8a**,**b** (Scheme 5). These products proved to be stable in the presence of aliphatic amines such as triethylamine or pyrrolidine, however, upon treatment with sodium hydroxide a facile conversion into imidazo[2,1-*c*][1,2,4]thiadiazole **9** was observed. Presumably the above reaction proceeded through the initially formed salt **H** followed by an intramolecular nucleophilic substitution at the sp^2-hybridized nitrogen atom via the transition state **TS H** (Scheme 5).

The observed difference in reactivity of ureas **2** and thioureas **8** in the presence of the strong bases may result from superior nucleophilic character of the sulfur atom of the thioimidate anion **H** (Scheme 5) compared to the nitrogen atom of amidate anion **D** (Scheme 3). Note, in the previously investigated reactions of 2-(hydroxyimino)imidazolidine *O*-sulfonate (**A**) with aryl isothiocyanates furnishing imidazo[2,1-*c*][1,2,4]thiadiazoles **9**, the intermediate thiourea derivatives of type **8**[7] could not be isolated.



Scheme 5

Encouraged by the above results, we attempted the reaction of cyclic alkoxyguanidines **1a**,**b** with CS_2 in the presence triethylamine or sodium methoxide. Surprisingly, no reaction was observed when acetonitrile or methanol was used as a solvent. However, compounds **1a**,**b** reacted smoothly with CS_2 in DMF solution at room temperature in the presence of triethylamine giving rise to the formation of imidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione **10** as the sole product (Scheme 6). Apparently, the transiently formed addition product **J** reacted with a second CS_2 molecule to form **K**, which underwent desulfurization[19,20] to isothiocyanate **L** with simultaneous extrusion of the alkoxy anion. Finally, nucleophilic addition of the thiolate anion to isothiocyanate group in **L** gave the final product **10**. A similar reaction was observed when cyclic sulfonyloxyguanidine **A** (Scheme 1) was reacted with CS_2 in aqueous sodium hydroxide solution.[6] It is worth noting that the expected intramolecular electrophilic amination reaction in **J** leading to 6,7-dihydroimidazo[2,1-*c*][1,2,4]thiadiazole-3(5*H*)-thione (**I**) did not take place.



Scheme 6

To gain insight into the base-induced transformations of cyclic alkoxyguanidines described above, we have undertaken theoretical studies with use of DFT methods. Our attention focused on the base-induced transformations of the ureas **2a** and **6** as well as of thiourea **8a**. In all cases the corresponding ambident anions **D**, **F** and **H** (Figure 2), generated by the treatment of amides or thioamides with strong bases, attack the electron-deficient pivotal nitrogen atom (either exocyclic or annular) and the reaction proceeds with the formation and destruction of σ-bonds. Mechanistically such transformation can be considered as an intramolecular electrophilic amination reaction with simultaneous extrusion of the alkoxide anion, $S_N2\sigma$ nucleophilic substitution at the sp^2-hybridized nitrogen atom of the oxime[21-23] or as a particular case of the base-induced Boulton–Katritzky rearrangement.[24-27]

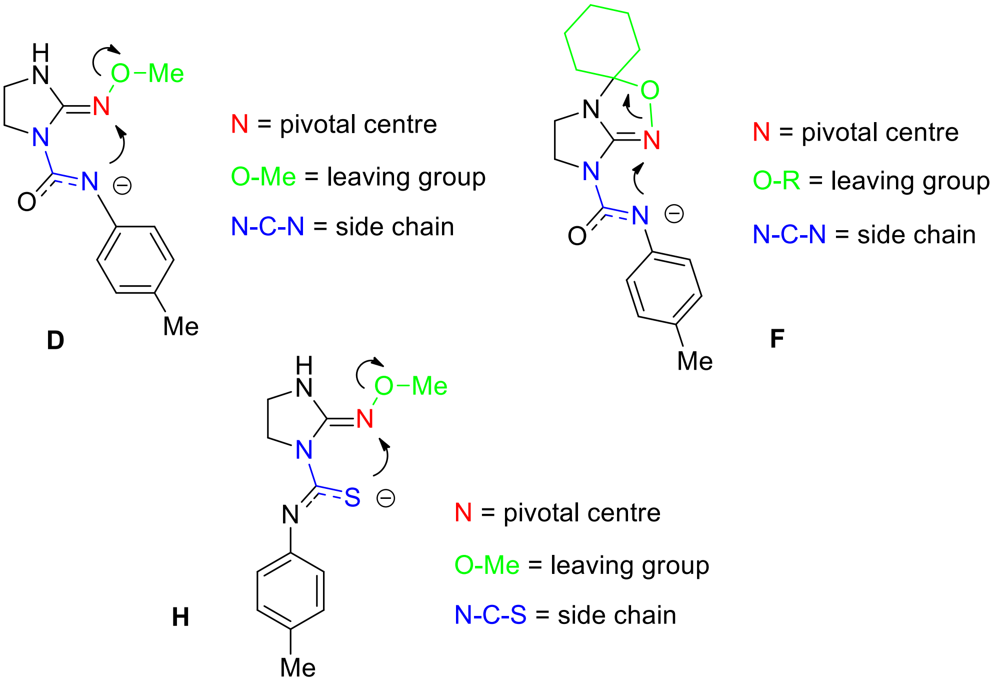


Figure 2. Possible base-induced rearrangements of alkoxyguanidines.

As shown in Figure 3, in the ambident carboxamidate anions **D**, **F** and carboxthioamidate anion **H** the absolute HOMO values are greater at the nitrogen and sulfur atoms than at the oxygen and nitrogen atoms, respectively. Also the lowest natural negative charges in the carboximidates are located on the nitrogen atoms, while in the carboxthioimidate the negative charge is distributed equally. These observations indicate that the nucleophilic substitutions of the alkoxy leaving groups by the amidate and thioimidate anions involve HOMO orbitals.

The theoretical studies of the transformations of **D**, **F** and **H** to the fused bicyclic compounds **7** and **9** provided the structures of the planar in-plane $S_N2\sigma$ transition states **TS D**, **TS F** and **TS H**, respectively (Figure 4), all of which bear resemblance to vinylic S_N2-type reactions at carbon atoms[28-30] and Boulton–Katritzky rearrangements.[31-33] The in-plane displacement of the alkoxy anion occurs in a nearly linear manner and the nucleophiles interact with the σ* orbital of the imino nitrogen of the N–O bond. The stretch of these transition states correlates with the activation barriers, that is, the higher the barrier for the intramolecular concerted S_N2-type reaction, the larger the stretching of the N–O bond in the transition-state structures (Table 1). If fact, the most constrained transition state **TS D** marked with the highest energy barrier of 16.0 kcal/mol corresponds to the reaction that did not occur under conditions tested. The lowest energy barrier of 1.8 kcal/mol was computed for the Boulton–Katritzky transformation of **6** (**TS F**) and this reaction is considerably more exothermic than the corresponding cyclizations of the urea **2a** and thiourea **8a** derivatives.

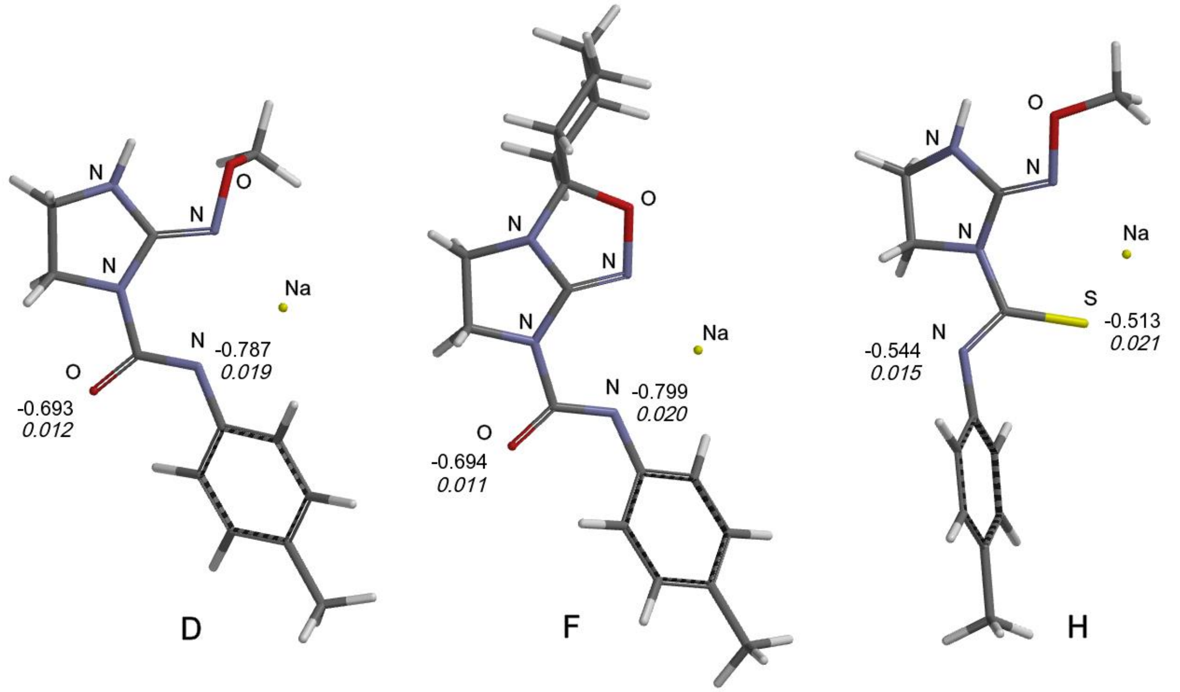


Figure 3. Natural charges [e] (regular) and the HOMO absolute values [square root of e/au^3] mapped on the isodensity surface (0.002 e/au^3) (*italics*) for slats **D**, **F**, and **H** calculated with B3LYP 6-31+G* method.

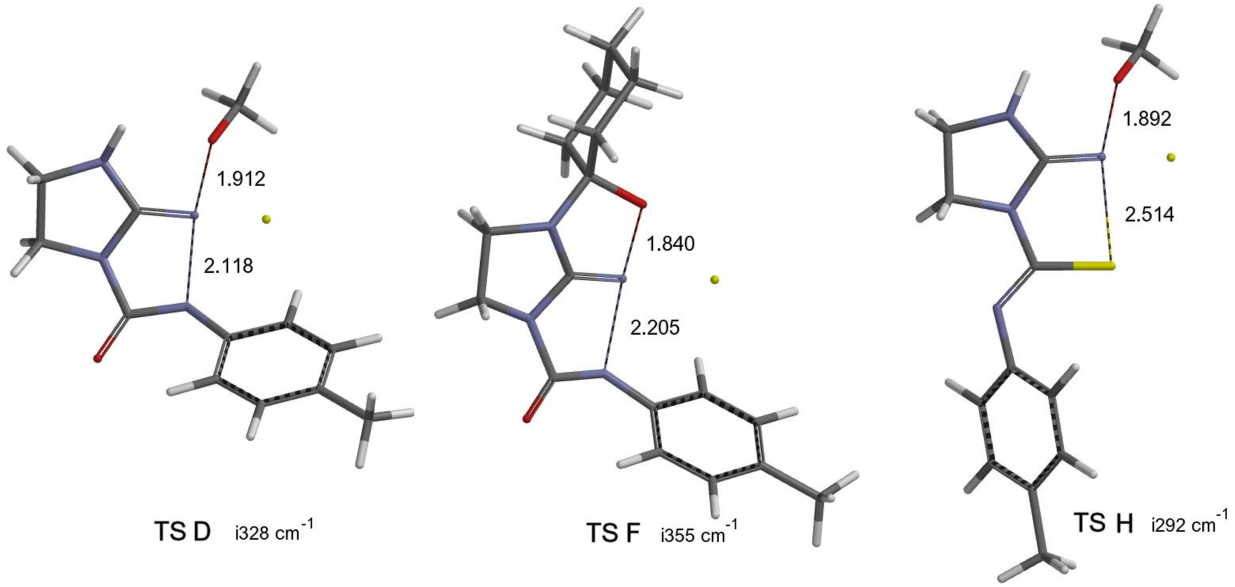


Figure 4. N-N, N-S and N-O atoms distances for transition states **TS D**, **TS F** and **TS H** calculated with B3LYP 6-31+G* method.

Table 1. Electronic energy and Gibbs free energy profiles (298.15 K) for the intramolecular amination reactions calculated with B3LYP 6-31+G* method using SM8[34] MeOH solvation model[a]

Relative energy	**2a**, NaOH	**D**, H_2O	**TS D**, H_2O	**7** (**E**), NaOH, MeOH
ΔE_e	0	-12.3	16.6	-9.5
ΔG	0	-11.8	16.0	-21.3
Relative energy	**6**, NaOH	**F**, H_2O	**TS F**, H_2O	**7**, NaOH, cyclohexanone
ΔE_e	0	-17.4	5.3	-22.9
ΔG	0	-17.8	1.8	-39.2
Relative energy	**8a**, NaOH	**H**, H_2O	**TS H**, H_2O	**9**, NaOH, MeOH
ΔE_e	0	-12.3	10.2	-14.7
ΔG	0	-12.5	8.7	-27.5

[a] Relative energies (ΔE_e and ΔG) given in kcal/mol

Conclusions

The monocyclic alkoxyguanidines such as 2-methoxyiminoimidazolidine (**1a**) and 2-benzyloxyiminoimidazolidine (**1b**) incorporate both the nucleophilic endocyclic and electrophilic exocyclic nitrogen atom. These properties can be utilized in stepwise nucleophilic addition-electrophilic amination reactions with heterocumulenes such as isocyanates, isothiocyanates and carbon disulfide leading to the formation of bicyclic imidazoline-containing heterocycles. Thus, alkoxyguanidines of type **B** bear resemblance to the previously studied sulfonyloxyguanidine (**A**). However, the alkoxy group appears to be a rather poor leaving group and requires the generation of strong nucleophiles for its displacement. On the other hand, a constrained bicyclic alkoxyguanidine such as 6',7'-dihydro-5'*H*-spiro[cyclohexane-1,3'-imidazo[2,1-*c*][1,2,4]oxadiazole (**5**), proved to be more reactive and underwent a facile base-induced Boulton–Katritzky rearrangement upon generation of a weakly nucleophilic carboxamidate ambident anion. The intramolecular S_N2-type reaction at the imine sp^2-hybridized nitrogen atom was investigated with the use of DFT calculations and was found to proceed according to an $S_N2\sigma$ mechanism, i.e. the in-plane backside attack of nucleophiles relative to alkoxy leaving group.

Experimental Section

General. Melting points were determine on a Boetius melting point apparatus they are not corrected. The IR spectra were recorded on Thermo Scientific Nicolet FT-IR spectrometer using KBr tablet method. ^1H and ^{13}C NMR spectra were acquired using Varian Gemini 200 or Varian Unity Plus 500. The chemical shifts were measured relative to the residual solvent signals at 2.50 or 7.26 ppm and 39.50 or 77 ppm, respectively. All reagents were used directly as obtained commercially. 2-(Methoxyimino)imidazolidine[9] (**1a**) 2-(benzyloxyimino)imidazolidine[9] (**1b**), the 4-dimethylaminopyridinium *N*-(arylsulfonyl)carbamoylides[17,18] (**4a-c**), and 6',7'-dihydro-5'*H*-spiro[cyclohexane-1,3'-imidazo[2,1-*c*][1,2,4]oxadiazole] (**5**)[6] were prepared according to the previous literature procedures.

The diffraction data were collected with a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software.[35] The crystal structures were solved by direct methods with the program SHELXS-97[36] and refined by full-matrix least-squares method on F^2 with SHELXL-97.[37]

All the calculations presented were carried out with the Spartan 08 program package supplied by Wavefunction, Inc. All the geometries were fully optimized in vacuum with DFT B3LYP method using diffuse functions 6-31+G* basis set. Frequency calculations were performed for all structures to prove their energy minima. The geometries of the transition states found showed a single imaginary frequencies pertaining to N–N or N–S bond formation and N–O bond breakage. The $S_N2\sigma$ reaction energy profiles were derived from DFT B3LYP/6-31+G* calculations with application of the methanol SM8[34] solvation models. The Gibbs free energies were obtained from the electronic energies corrected with the zero-point vibrational energies (ZPE), thermal energies involving temperature increase from 0 to 298.15 K and entropies. Relative energies were obtained by subtracting the energy of the lowest-energy structures from the energies of all the other geometries and converting these differences into kcal/mol^{-1}.

General procedure for the synthesis of amides and sulfonamides (2a-d). 2-(Methoxyimino)imidazolidine (**1a**) or 2-(benzyloxyimino)imidazolidine (**1b**) (2 mmol) and the corresponding isocyanate (2.1 mmol) were reacted at room temperature in acetonitrile (3 mL) for 0.5 h. Then, the solvent was evaporated under reduced pressure and the residue was treated with methanol. The precipitated product was filtered off, washed with small amount of methanol and dried in vacuum.

According to the above procedure the following compounds were obtained:

2-(Methoxyimino)-*N*-(4-methylphenyl)-imidazolidine-1-carboxamide (2a). Yield 0.41 g (83%); mp 168-170 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.50 (t, 2H, CH_2, *J* 7.7 Hz), 3.80 (s, 3H, CH_3), 4.02 (t, 2H, CH_2, *J* 7.7 Hz), 5.19 (bs, 1H, NH), 7.11 (d, 2H, CH, *J* 8.3 Hz), 7.38 (d, 2H, CH, *J* 8.3 Hz), 10.10 (bs, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 40.4, 44.9, 62.9, 120.3, 129.9, 133.4, 136.3, 151.3, 153.6. IR (KBr, cm^{-1}) 3358, 3068, 2929, 1691, 1648, 1612, 1561, 1479, 1428, 1329, 1255, 1075, 814. $C_{12}H_{16}N_4O_2$ (248.28): calcd. C 58.05, H 6.50, N 22.57; found C 57.91, H 6.74, N 22.33.

2-(Methoxyimino)-*N*-(4-methylphenylsulfonyl)imidazolidine-1-carboxamide (2b). Yield 0.43 g (69%); alternative synthesis: the salt (**4b**) (0.23 g, 0.53 mmol) was dissolved in methanol (10 mL) and the methanolic hydrogen chloride (0.53 mmol) was added to the solution. The solvent was evaporated under reduced pressure and the residue was treated with water (10 mL) and extracted with methylene chloride (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated. The solid obtained was crystallized from mixture of water and methanol; yield 0.15 g (91%); mp 146-148 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H, CH_3), 3.49 (t, 2H, CH_2, *J* 6.8 Hz), 3.80 (s, 3H, CH_3), 3.87 (t, 2H, CH_2, *J* 6.8 Hz), 5.15 (bs, 1H, NH), 7.34 (d, 2H, CH, *J* 7.8 Hz), 7.98 (d, 2H, CH, *J* 7.8 Hz), 11.00 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 40.1, 44.1, 62.9, 128.7, 129.7, 136.5, 144.9, 148.2, 151.8. IR (KBr, cm^{-1}) 3364, 2992, 2936, 1697, 1667, 1481, 1428, 1354, 1274, 1166, 1090, 865, 664. $C_{12}H_{16}N_4O_4S$ (312.34): calcd. C 46.14, H 5.16, N 17.94; found C 45.85, H 5.25, N 17.71. Crystal data for $C_{12}H_{16}N_4O_4S \cdot H_2O$ (**2b**): orthorhombic, space group $Pna2_1$, a = 7.6571(4), b = 29.8679(16), c = 13.5816(8) Å, V = 2393.07(7) Å^3, Z=8, d_x = 1.413 g.cm^{-3}, T = 150K. Data were collected for a crystal with dimensions 0.5x0.08x0.05 mm. Final R indices for 4349 reflections with $I>2\sigma(I)$ and 402 refined parameters are: R_1=0.0632, wR_2=0.1608 (R_1=0.0778, wR_2=0.1682 for all 5485 data). The structure is pseudocentrosymmetric with the inversion center symmetry broken exclusively by the arrangement of water molecules; CCDC 742649.[37]

2-(Benzyloxyimino)-*N*-(4-methylphenyl)imidazolidine-1-carboxamide (2c). Yield 0.56 g (87%); mp 188-189 ºC. ^{1}H NMR (200MHz, DMSO-d_6) δ 2.23 (s, 3H, CH_3), 3.33 (t, 2H, CH_2, *J* 7.4 Hz), 3.79 (t, 2H, CH_2, *J* 7.4 Hz), 4.92 (s, 2H, CH_2), 7.03-7.15 (m, 4H, CH), 7.17 (s, 1H, NH), 7.31-7.46 (m, 5H, CH), 10.28 (s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.3, 39.3, 43.8, 75.1, 118.4, 127.5, 128.1, 128.2, 129.2, 131.6, 136.0, 138.5, 150.1, 152.5. IR (KBr, cm^{-1}) 3343, 3061, 2915, 1686, 1651, 1612, 1561, 1516, 1481, 1431, 1324, 1301, 1256, 1049. $C_{18}H_{20}N_4O_2$ (324.38): calcd. C 66.65, H 6.21, N 17.27; found C 66.53, H 6.35, N 17.02.

2-(Benzyloxyimino)-*N*-(4-methylphenylsulfonyl)imidazolidine-1-carboxamide (2d). Yield 0.52 g (67%); alternative synthesis: 2-(benzyloxyimino)imidazolidine (**1b**) (0.31 g, 1.62 mmol) and the carbamoylide (**3b**) (0.52 g, 1.62 mmol) were added to acetonitrile (3 mL). The resulting suspension was heated at 60 ºC with stirring for 10 minutes. Subsequently, the solvent was evaporated under reduced pressure and the residue was crystallized from methanol. The precipitated product (**2d**) was filtered off, washed with methanol and dried in vacuum; yield 0.38 g (60%); mp 140-142 ºC. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.37 (s, 3H, CH_3), 3.33 (t, 2H, CH_2, *J* 7 Hz), 3.70 (t, 2H, CH_2, *J* 7 Hz), 4.86 (s, 2H, CH_2), 7.33-7.43 (m, 7H, CH), 7.71 (d, 2H, CH), 7.85 (bs, 1H, NH), 11.73 (bs, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.9, 39.8, 44.1, 76.1, 127.4, 128.1, 128.3, 128.9, 129.3, 136.8, 137.5, 143.4, 148.9, 152.5. IR (KBr, cm^{-1}) 3376, 2914, 1710, 1669, 1597, 1477, 1434, 1349, 1166, 1086, 1023, 858, 820. $C_{18}H_{20}N_4O_4S$ (388.44): calcd. C 55.66, H 5.19, N 14.42; found C 55.48, H 5.47, N 14.20.

General procedure for the synthesis of 4-(dimethylamino)pyridinium (2-(methoxyimino)imidazolidine-1-carbonyl)(arylsulfonyl)amides (4). 2-(Methoxyimino)-imidazolidine (**1a**) (0.1 g, 0.87 mmol) and the corresponding carbamoylide[17,18] (**3**) (0.87 mmol) were added to acetonitrile (3 mL). The resulting suspension was heated at 60 °C with stirring for 10 minutes. Subsequently, the solvent was evaporated under reduced pressure and the sticky residue was crystallized from methanol. The precipitated salt (**4**) was filtered off, washed with acetone and dried in vacuum.

4-(Dimethylamino)pyridinium (2-(methoxyimino)imidazolidine-1-carbonyl)(phenyl-sulfonyl)amide (4a). Yield 0.18 g (50%); mp 140-142 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.03 (s, 6H, CH_3), 3.32 (t, 2H, CH_2, *J* 7.8 Hz), 3.56 (s, 3H, OCH_3), 3.77 (t, 2H, CH_2, *J* 7.8 Hz), 6.72-6.75 (m, 2H, CH), 7.43-7.48 (m, 3H, CH), 7.79-7.84 (m, 2H, CH), 8.07-8.11 (m, 2H, CH), 6.00-9.00 (bs, 2H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.0, 42.3, 45.9, 62.1, 106.7, 127.0, 128.0, 130.8, 144.1, 145.4, 153.5, 154.7, 155.0. IR (KBr, cm^{-1}) 3167, 3055, 2937, 2893, 1652, 1574, 1556, 1444, 1332, 1263, 1140, 1089, 1076. $C_{18}H_{24}N_6O_4S$ (420.49): calcd. C 51.41, H 5.75, N 19.99; found C 51.17, H 6.03, N 19.61.

4-(Dimethylamino)pyridinium (2-(methoxyimino)imidazolidine-1-carbonyl)(4-methyl-phenylsulfonyl)amide (4b). Yield 0.16 g (43%); mp 143-147 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.33 (s, 3H, CH_3), 3.03 (s, 6H, CH_3), 3.30 (t, 2H, CH_2, *J* 7.8 Hz), 3.57 (s, 3H, OCH_3), 3.75 (t, 2H, CH_2, *J* 7.8 Hz), 6.73 (d, 2H, CH, *J* 5.4 Hz), 7.25 (d, 2H, CH, *J* 7.8 Hz), 7.72 (d, 2H, CH, *J* 7.8 Hz), 8.10 (d, 2H, CH, *J* 5.4 Hz), 6.00-9.00 (bs, 2H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 21.2, 39.2, 40.0, 45.8, 62.3, 107.0, 127.5, 128.9, 140.9, 141.5, 145.8, 152.9, 154.7, 155.3. IR (KBr, cm^{-1}) 3365, 2926, 2815, 1660, 1643, 1568, 1440, 1396, 1333, 1257, 1206, 1131, 1087, 1047, 859, 810, 768. $C_{19}H_{26}N_6O_4S$ (434.51): calcd. C 52.52, H 6.03, N 19.34; found C 52.40, H 6.29, N 19.13.

4-(Dimethylamino)pyridinium (2-(methoxyimino)imidazolidine-1-carbonyl)(4-chloro-phenylsulfonyl)amide (4c). Yield 0.18 g (45%); mp 148-152 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.06 (s, 6H, CH_3), 3.34 (t, 2H, CH_2, *J* 7.8 Hz), 3.57 (s, 3H, OCH_3), 3.79 (t, 2H, CH_2, *J* 7.8 Hz), 6.76 (d, 2H, CH, *J* 5.4 Hz), 7.48 (d, 2H, CH, *J* 7.8 Hz), 7.79 (d, 2H, CH, *J* 7.8 Hz), 8.11 (d, 2H, CH, *J* 5.4 Hz), 6.00-9.00 (bs, 2H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.1, 40.8, 46.3, 62.1, 106.8, 127.8, 128.9, 135.0, 144.0, 144.2, 154.6, 155.1, 155.4. IR (KBr, cm^{-1}) 3013, 2930, 2805, 1643, 1559, 1437, 1394, 1331, 1258, 1212, 1144, 1085, 857, 775, 748. $C_{18}H_{23}ClN_6O_4S$ (454.93): calcd. C 47.52, H 5.10, N 18.47; found C 47.42, H 5.36, N 18.19.

***N*-*p*-Tolyl-5'*H*-spiro[cyclohexane-1,3'-imidazo[2,1-*c*][1,2,4]oxadiazole]-7'(6'*H*)-carboxamide (6).** 6',7'-Dihydro-5'*H*-spiro[cyclohexane-1,3'-imidazo[2,1-*c*][1,2,4]oxadiazole] (**5**)[6] (0.15 g, 0.83 mM) and 4-methylphenyl isocyanate (0.12 mL, 0.95 mM) were added at room temperature to anhydrous THF (1.5 mL) with stirring. After 24 h the solvent was evaporated and the white residue was washed with small amount of diethyl ether, filtered off and dried in vacuum. Yield 0.177 g (68%); mp 135-138 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19-1.22 (m, 1H, CH_2), 1.50-1.72 (m, 7H, CH_2), 2.05-2.11 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 3.34 (t, 2H, CH_2, *J* 7 Hz), 4.32 (t, 2H, CH_2, *J* 7 Hz), 7.10 (d, 2H, CH, *J* 8.3 Hz), 7.35 (m, 2H, CH, *J* 8.3 Hz), 8.37 (bs, 1H, NH),).

^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 23.2, 25.2, 32.6, 40.7, 51.0, 99.9, 120.2, 129.9, 134.0, 135.6, 149.7, 160.4. IR (KBr, cm^{-1}) 3312, 3287, 2937, 2899, 2846, 1702, 1655, 1609, 1552, 1514, 1484, 1452, 1327, 1287, 1250, 1190, 814. $C_{17}H_{22}N_4O_2$ (314.38): calcd. C 64.95, H 7.05, N 17.82; found C 64.71, H 7.17, N 17.60.

2-*p*-Tolyl-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-one (7). Compound **6** (0.05 g, 0.16 mM) and NaOH (0.15g, 3.75 mM) were dissolved in methanol (4 mL). After 24 h the solvent was evaporated and the reaction mixture was quenched with water (5 mL), neutralized with hydrochloric acid, and extracted with methylene chloride (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was washed with acetone and diethyl ether. Yield 0.028 g (82%); mp 196-200 ºC (lit. 208-209 ºC).[7] IR (KBr, cm^{-1}) 3234, 2927, 1697, 1614, 1512, 1367, 1293, 818.

General procedure for the synthesis of thioamides (8a-b). 2-(Methoxyimino)imidazolidine (**1a**), or 2-(benzyloxyimino)imidazolidine (**1b**) (2 mmol) and the 4-methylphenyl isothiocyanate (2.1 mmol) were added at room temperature to acetonitrile (3 mL). After 6 h the solvent was evaporated under reduced pressure and the crude product was purified on silica gel with use of chromatotron (CH_2Cl_2).

***N*-(4-Methylphenyl)-2-(methoxyimino)imidazolidine-1-carbothioamide (8a).** Yield 0.44 g (83%); mp 124-127 ºC. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3), 3.52 (t, 2H, CH_2, *J* 7.5 Hz), 3.77 (s, 3H, OCH_3), 4.41 (t, 2H, CH_2, *J* 7.5 Hz), 5.17 (bs, 1H, NH), 7.20 (d, 2H, CH, *J* 8.3 Hz), 7.40 (d, 2H, CH, *J* 8.3 Hz), 11.65 (bs, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 39.9, 50.1, 62.9, 125.7, 129.8, 136.6, 136.9, 154.1, 178.2. IR (KBr, cm^{-1}) 3346, 2934, 2815, 1672, 1563, 1513, 1473, 1415, 1395, 1317, 1300, 1063, 957, 817. $C_{12}H_{16}N_4OS$ (264.35): calcd. C 54.52, H 6.10, N 21.19; found C 54.31, H 6.31, N 21.02.

***N*-(4-Methylphenyl)-2-(benzyloxyimino)-imidazolidine-1-carbothioamide (8b).** Yield 0.60 g (88%); mp 120-122 ºC. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3), 3.49 (t, 2H, CH_2, *J* 7.5 Hz), 4.38 (t, 2H, CH_2, *J* 7.5 Hz), 4.93 (s, 2H, CH_2), 5.20 (bs, 1H, NH), 7.16 (d, 2H, CH, *J* 8.3 Hz), 7.29-7.36 (m, 7H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 39.9, 50.0, 77.0, 125.3, 128.7, 129.0, 129.1, 129.7, 136.4, 136.8, 137.8, 154.0, 177.9. IR (KBr, cm^{-1}) 3345, 2927, 2850, 1684, 1604, 1565, 1471, 1410, 1316, 1301, 1247, 1021, 957, 820, 749, 699. $C_{18}H_{20}N_4OS$ (340.44): calcd. C 63.50, H 5.92, N 16.46; found C 63.38, H 6.18, N 16.25.

***N*-(6,7-dihydroimidazo[2,1-*c*][1,2,4]thiadiazol-3(5*H*)-ylidene)-4-methylaniline (9).** Thioamide **8a** or **8b** (0.3 mM) and NaOH (0.36 g, 9.0 mM) were dissolved in mixture of chloroform (4 mL) and methanol (2 mL). After 24 hours the reaction mixture was quenched with water (5 mL), neutralized with hydrochloric acid, and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The crude product was purified on silica gel with use of a chromatotron (AcOEt). Yield 0.05 g (73%) and 0.06 g (85%), respectively; mp 216-218 ºC (lit. 208-209 ºC).[7] IR (KBr, cm^{-1}) 3195, 2922, 1650, 1628, 1598, 1506, 1483, 1472, 1442, 1237, 1110, 822.

7,8-Dihydro-2*H*-imidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione (10). To the solution of 2-(methoxyimino)imidazolidine (**1a**) (0.05 g, 0.26 mM) or 2-(benzyloxyimino)imidazolidine (**1b**)

(0.03 g, 0.26 mM) in DMF (1 mL) triethylamine (0.05 g, 0.49 mM) and carbon disulfide (0.40 g, 5.2 mM) were added. The reaction mixture was stirred at room temperature for 24 h. Then, the solvent was evaporated under reduced pressure and the solid residue was treated with water (5 mL). The resulting precipitate was filtered off and dried in vacuum. Yield 0.038 g (92%) and 0.035 g (84%) of 7,8-dihydro-2H-imidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione (**10**), respectively; mp 250-251 °C (lit. 249-251 °C).[6] ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.70 (t, 3H, CH_2, *J* 8.5 Hz), 4.36 (t, 3H, CH_2, *J* 8.5 Hz), 10.60 (s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 38.6, 48.9, 153.4, 190.9, 197.9. IR (KBr, cm^{-1}) 3059, 1646, 1471, 1443, 1435, 1408, 1363, 1339, 1279, 1159, 1057, 993, 707.

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37. CCDC 742649 (compound **2b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.