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Synthesis, Molecular Structure, and Applications of 2-Hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate to the Synthesis of Novel Heterocyclic Ring Systems

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2-Hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate (**1**) has been prepared by reacting 2-chloro-4,5-dihydroimidazole with hydroxylamine-*O*-sulfonic acid. Deprotonated compound **1a** containing both the nucleophilic endocyclic nitrogen atoms and electrophilic exocyclic nitrogen was used for the syntheses of 3-substituted 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]oxadiazoles **2**−**9** and 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione (**10**) by tandem nucleophilic addition−electrophilic amination reaction. The method promises utility in the synthesis of a variety of other heterocycles. On the other hand, the convenient routes to 7,8-dihydroimidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione (**16**) and 2,6,7,8-tetrahydroimidazo[1,2-*a*][1,3,5]triazine-4(3*H*)-thione derivative (**17**) are reported starting from compound **1**. The structures of the compounds prepared were established by elemental analyses, IR, NMR, and MS spectra, and in some instances X-ray analyses.

Introduction

Electronegatively substituted amine derivatives of general formula **A** (Figure 1) have received considerable attention due to the ability of the nitrogen atom bearing a good leaving group to behave as either a nucleophile ($^{\delta-}NH_2$ synthon) or electrophile ($^{\delta+}NH_2$ synthon) depending on the circumstances. Preparative methods and synthetic uses of *O*-alkyl-, *O*-acyl-, and *O*-sulfonylhydroxylamines **A** have been surveyed in several comprehensive reviews.[1−7]

The displacement of the leaving group on electrophilic nitrogen atoms by carbon, nitrogen, sulfur, or phosphorus nucleophiles leads to the formation of C−N, N−N, S−N, S═N, or P═N bonds, respectively.[8] Furthermore, the intramolecular version of this type of "*Umpolung*" amination has also been used for the preparation of pyrrolidine derivatives.[9]

In contrast, reports on the analogous hydroxyguanidine-*O*-sulfonic acids of type **B** (Figure 1) have been scarce. Hessing and co-workers reported the reaction of

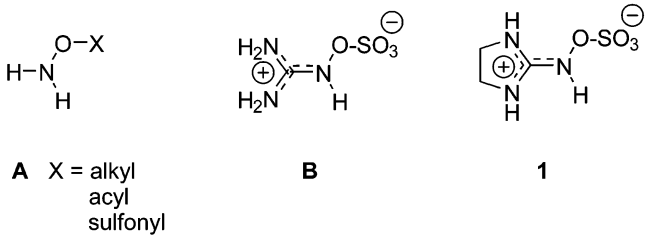

FIGURE 1.

N-hydroxyguanidine with chlorosulfonic acid to give the corresponding hydroxyguanidine-*O*-sulfonic acid (HGS),[10] which then was successfully used in the electrophilic guanidination of aromatic compounds under Friedel−Crafts conditions[11] and for the preparation of various semicarbazones by means of the reaction with aldehydes or cyclic ketones.[12]

Continuing our work in the field of 4,5-dihydroimidazole chemistry,[13] we describe in this paper the facile synthesis, molecular structure, and reactivity of 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate (**1**) (Figure 1).

Results and Discussion

Our research started with the reaction between 2-chloro-4,5-dihydroimidazole[14] and hydroxylamine-*O*-sulfonic acid

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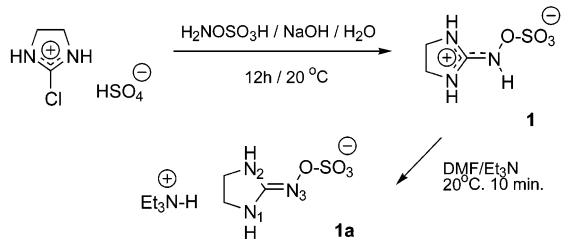
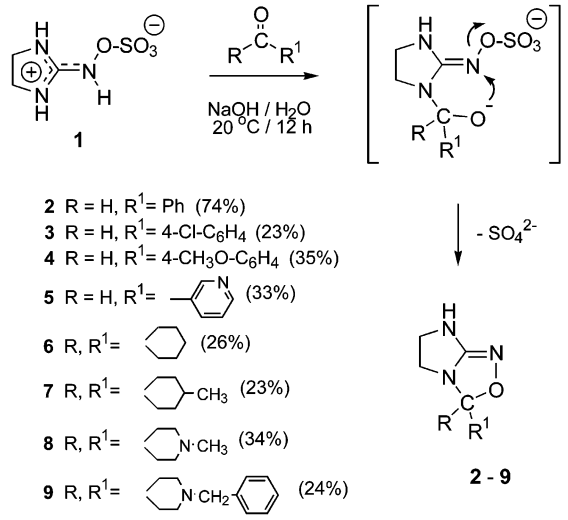
SCHEME 1. Preparation of Zwitterion 1 and the Deprotonated Compound 1a[a]



[a] Key: calculated[16] natural atomic charges (plain), charges from Mulliken population analysis (italic), and atomic charges from electrostatic potential (underlined) for the nitrogen atoms of **1a**.

SCHEME 2. Preparation of Imidazo[2,1][1,2,4]-oxadiazoles 2−9



in aqueous solution at room temperature, which gave the desired **1** in 69% yield (Scheme 1). In the ^{1}H NMR spectrum of the zwitterion **1** the four CH_2 protons of the imidazoline ring were seen as a singlet at 3.61 ppm, the signal of two protons attached to endocyclic nitrogen atoms appeared at 8.32 ppm, and the signal of the exocyclic NH appeared at 12.01 ppm. The structure of **1** was also confirmed by X-ray crystal structure analysis (Supporting Information), providing the molecular geometry for further molecular modeling studies.

The molecules of **1** exist in crystals as zwitterions with a proton transferred from the sulfate group to the guanidine moiety. The exocyclic C−N bond in the oxyguanidine moiety of **1** is 1.356 Å, whereas the two endocyclic C−N bonds are 1.318 and 1.320 Å and show more pronounced double-bond character. This is in contrast with the geometry of the natural oxyguanidine moiety of L-canavanine,[15] which exists in crystals in the imino tautomeric form with the C−N bond of its oxyimino fragment 1.302 Å and the two amino C−N bonds 1.347 and 1.361 Å.

We have generated and optimized the molecular structure of the zwitterion **1** in vacuo using ab initio (RHF/6-31G** and MP2/6-31G**) as well as density functional (B3LYP/6-31G**) computations[16] The inspection of the experimental and optimized calculated values of the most relevant geometrical parameters [bond distances (Å) and angles (deg)] (Supporting Information S8) indicates that none of the methods studied are suitable for geometric description of the zwitterionic structure **1**, as the geometric parameters calculated by these methods show differences with respect to the experimental values.

Deprotonation of the charged guanidine moiety of **1** (determined pK_a value 4.9[17]) upon treatment with triethylamine is predicted to occur at the exocyclic nitrogen atom, which is least able to support a positive charge, leading to the imino tautomer **1a** containing both the nucleophilic N1 and N2 nitrogen atoms and the electrophilic N3 nitrogen atom (Scheme 1). Further evidence for the predominant existence of the imino tautomer in solution was provided by a consideration of the chemical shift of the methylene protons of the 2-imidazolidine moiety in the ^{1}H NMR spectrum. Thus, the observed shift of 3.27 ppm for the imino tautomer **1a** (vide infra) is in agreement with those found for the formally related 2-iminoimidazolidine derivatives.[18]

Treatment of **1** with a range of aromatic aldehydes in aqueous NaOH solution gave the 3-substituted 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]oxadiazoles **2**−**5** (Scheme 2). The method also allowed the synthesis of spiro compounds **6**−**9** bearing the 6,7-dihydro-5*H*-imidazo[2,1-*c*]oxadiazole unit by reacting **1** with cyclic ketones. The yields of these processes were rather moderate (23−35%), except for benzaldehyde, which gave 74% of the product **2**. However, compound **1** under the conditions tried failed to give any detectable reaction with less reactive aliphatic aldehydes and open-chain ketones.

The reaction can be mechanistically explained by nucleophilic addition of the imidazoline NH group to the carbonyl group and subsequent abstraction of the proton from the hydroxyl group of the heminal initially formed, followed by intramolecular electrophilic amination of the anionic oxygen atom with simultaneous extrusion of the SO_4^{2-} moiety. A five-membered, oxadiazole ring is thus formed which is made up of the N−C=N substructure of **1a** and the carbonyl group of the reagent.

The mass spectrometric degradation pattern [M^+], [M^+ − NO] is in agreement with the proposed structures. The molecular structure of these compounds was further confirmed by X-ray crystal structure analysis of **7**.

It should also be pointed out that the previously described reaction of hydroxyguanidinium-*O*-sulfonate of type **B** with carbonyl compounds led to the formation of semicarbazone derivatives.[6]

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(16) The geometries of the zwitterionic structure **1** and compounds **10** and **15** were fully optimized using a molecular orbital ab initio method at the Hartree−Fock level of theory with the 6-31G** basis set, and a density functional B3LYP/6-31G** method. The ab initio calculations were carried out using the SPARTAN program distributed by Wavefunction Inc. and installed on a workstation. The density functional calculations were carried out using the TITAN program distributed by Wavefunction Inc. and installed on a PC computer.

(17) The pK_a value was determined at 25 °C by potentiometric titration with TiNet 2.5 software.

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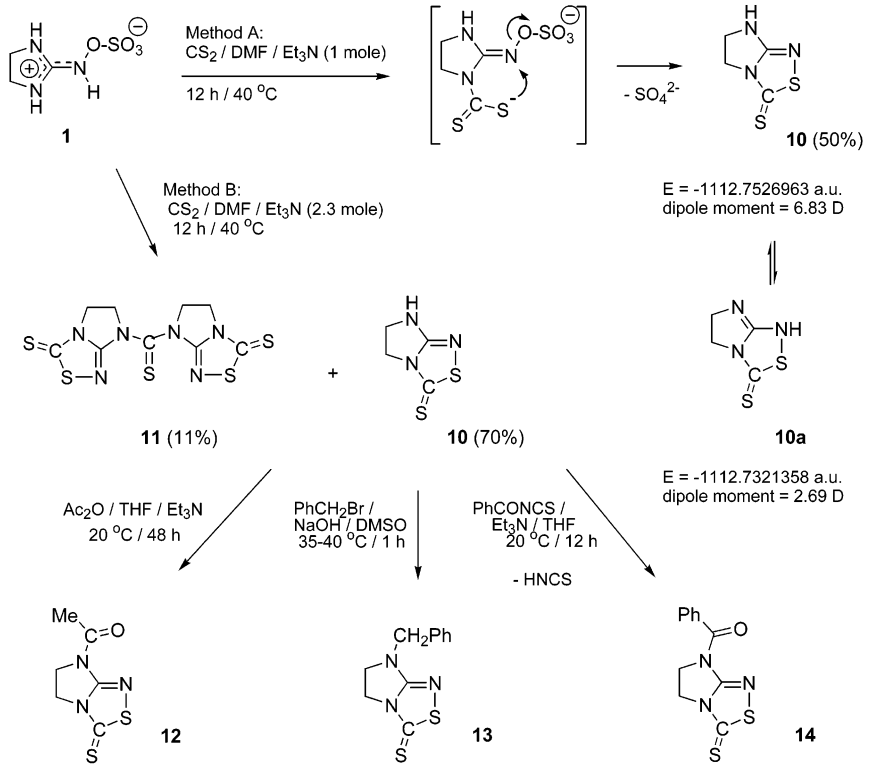
SCHEME 3. Reactions of 1 with Carbon Disulfide in DMF Solution



Encouraged by our success with imidazo[2,1-*c*][1,2,4]-oxadiazole synthesis, we decided to broaden the scope of these studies by examining the reactions of **1** with heterocumulenes such as carbon disulfide and phenyl isothiocyanate.

The reaction of **1** with carbon disulfide took two different courses, dependent on a base−solvent combination. Thus, when the reaction of **1** was performed in DMF in the presence of an equimolar amount of triethylamine, 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione (**10**) was produced in 50% yield as a result of tandem nucleophilic addition−electrophilic amination reaction (method A, Scheme 3), which mechanistically is related to those described above for the formation of oxadiazoles **2**−**9**. In the presence of excess triethylamine, compound **10** underwent subsequent reaction with a second molecule of carbon disulfide to give di(5,6-dihydro-7*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione-7-yl)-methanethione (**11**) (method B, Scheme 3). The resulting mixture contained **10** and **11** in a ratio of about 7:1, and the two products could easily be separated owing to a considerable difference in their solubility in hot methanol.

The imidazothiadiazole **10** can exist in two likely (i.e., low-energy) tautomeric forms, the N7−H tautomer **10** and N1−H tautomer **10a**, which can interconvert via a 1,3-prototropic shift. Calculations of the energy[16] indicated that **10** has a relative energy calculated to be 12.9 kcal/mol below that of **10a**. We were able to prove by NMR spectroscopy that the low-energy tautomer **10** is also present in DMSO-d_6 solution. The methylene groups of the imidazoline moiety are nonequivalent, and the NOE was observed (Supporting Information) between an upfield-shifted C6−H proton and the N−H proton.

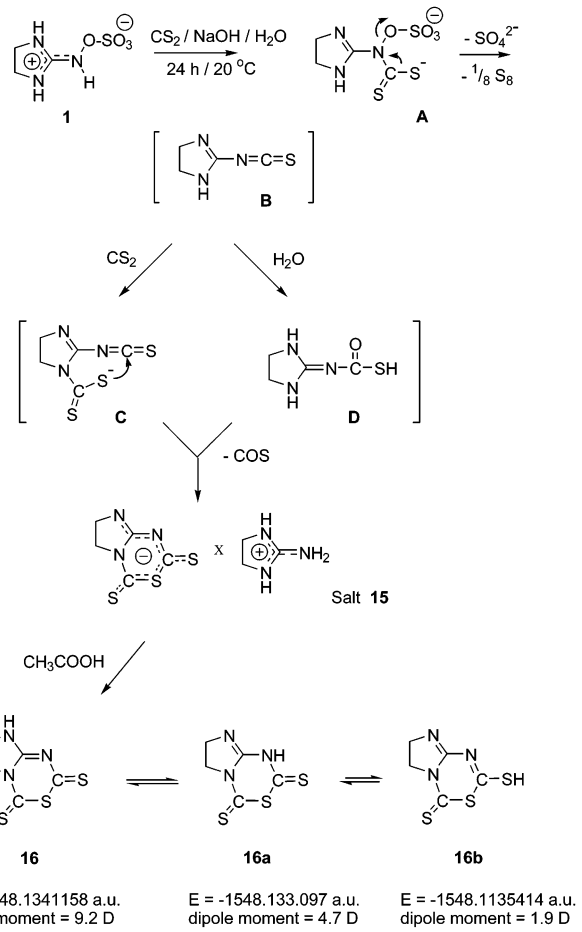
Compound **10** reacted in the normal manner with acetic anhydride and benzyl bromide as indicated in Scheme 3 to afford **12** and **13**, respectively. The structure of 7-benzyl-6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione (**13**) was confirmed by an X-ray crystallographic study (Supporting Information). On the other hand, the reaction of **10** with benzoyl isothiocyanate carried out in THF in the presence of Et_3N at room temperature led to the formation of the *N*7-benzoyl derivative **14** (Scheme 3).

In contrast to the above-described reactions of **1** with carbon disulfide in DMF, an analogous reaction performed in aqueous NaOH solution gave 7,8-dihydroimidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione in the form of a salt with 2-aminoimidazoline (**15**), together with a small amount of imidazothiadiazole **10**. We assume that the mechanism of the reaction leading to **10** is analogous to those described in Scheme 2, whereas a plausible route to the formation of **15** is shown in Scheme 4.

Apparently, when the reaction is carried out in water, which is more effective than DMF at solvating atoms with partial negative charges, the competing nucleophilic attack of the exocyclic nitrogen atom of **1a** at carbon disulfide may occur to give the intermediate **A**, which decomposes with the formation of elemental sulfur, sulfate anion, and 4,5-dihydroimidazol-2-yl isothiocyanate **B**. A portion of the transiently formed **B** reacts further with an excess carbon disulfide to give **C**, which then cyclizes to 7,8-dihydroimidazo[1,2-*c*][1,3,5]thiadiazine-2,4(6*H*)-dithione (**16**). Simultaneously, hydrolytic decomposition of the isothiocyanate **B** produces 2-iminoimidazoline, which combines with the dithione **16**, giving rise to the formation of the stable salt **15**.

Salt **15** isolated from the reaction mixture was recrystallized from DMF. The needle-shaped crystals were unstable when removed from the mother liquor, and all specimens checked were twinned (nonmehroedral axial

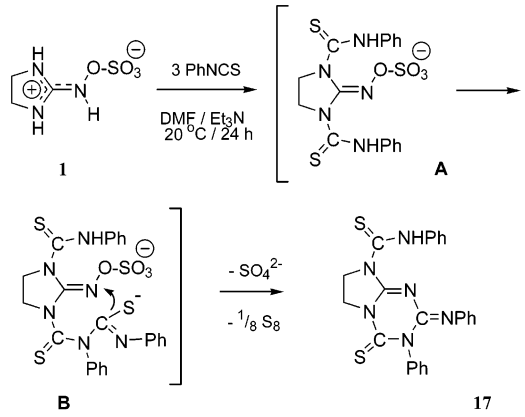
SCHEME 4. Reactions of 1 with Carbon Disulfide in Aqueous NaOH Solution



twins). These crystals were triclinic, space group $P\bar{1}$, $a = 6.847(1)$ Å, $b = 12.144(2)$ Å, $c = 12.939(2)$ Å, $\alpha = 79.03(2)°$, $\beta = 89.96(2)°$, $\gamma = 82.30(1)°$. For the crystal of **15** the intensity data were collected at 130 K, and the overlap of a large group of reflections was not taken into account when the data were processed from the CCD camera. However, despite errors in the experimental data set, the direct methods produced the electron-density map, which showed the asymmetric unit cell of the crystal consisting of a molecule of **16**, 2-aminoimidazoline, and two DMF molecules. All these structural units were hydrogen-bonded, forming discreet H-bonded assemblies. However, due to twinning refinement of the crystal structure stopped at R1 = 0.20 (Supporting Information). The structure of **16** was confirmed by X-ray analysis of the yellow blocklike crystals that precipitated when acetic acid was added to the solution of **15** in DMF (Supporting Information).

The ab initio geometry optimization at the HF/6-31G** level[16] was performed on the imidazothiadiazine-2,4-dithione **16** to examine its three possible tautomers **16**, **16a**, and **16b** as shown in Scheme 4. These computations showed that the tautomer **16** observed in its X-ray crystallographic analysis was the most stable among the three tautomers. Tautomer **16** was favored over **16a** by 0.6 kcal/mol, and **16b** was disfavored by 12.9 kcal/mol. However, the limited magnitude of the energy difference between **16** and **16a** suggests that both tautomers may occur in solution with solvent effects possibly governing their relative concentrations. On the basis of their calculated dipole moments, **16** (9.2 D) would be predicted to predominate over **16a** (4.7 D) in polar solvents.

SCHEME 5. Reaction of 1 with Phenyl Isothiocyanate



The reaction of **1** with phenyl isothiocyanate was carried out in DMF at room temperature in the presence of Et_3N to give 3-phenyl-2-(phenylimino)-8-(phenylthiocarbamoyl)-2,6,7,8-tetrahydroimidazo[1,2-*a*][1,3,5]triazine-4(3*H*)-thione (**17**) as the only isolable organic product (Scheme 5). We propose that the first step of the reaction sequence is the formation of thioureido derivative **A**, which then reacts with a third equivalent of phenyl isothiocyanate. This leads to the dianion **B**, which subsequently undergoes ring closure via a cyclodesulfurization process.

It is worth noting that compounds **10**, **12**, and **13** have been tested at the U.S. National Cancer Institute (Bethesda, MD) for their in vitro anticancer activity. Details of this test system and the information which is encoded by the activity pattern over all cell lines have been published.[19−21] Compounds **12** and **13** were inactive (log $GI_{50} > -4$), whereas the parent imidazothiadiazole-3-thione **10** exhibited moderate activity against the breast cancer T-47D cell line (log $GI_{50} = -6.07$).

Experimental Section

Melting points determined are not corrected. FT-IR spectra were recorded using a mixture of the compound and KBr. ^1H and ^{13}C NMR spectra were taken at 500 and 125 MHz, respectively, with an acquisition time of 1.8 s. Chemical shifts were measured relative to the residual solvent signal at 2.50 or 7.26 ppm and 39.5 or 77 ppm, respectively. MS spectra were recorded at 70 eV. All reagents were used directly as obtained commercially. 2-Chloro-4,5-dihydroimidazole[14] was prepared according to a previous literature procedure.

2-Hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate (1). To a solution of 2-chloro-4,5-dihydroimidazole (10 g, 0.05 mol) and hydroxylamine-*O*-sulfonic acid (7 g, 0.062 mol) in water (15 mL) was added a solution of NaOH (1.9 g, 0.0475 mol) in water (10 mL). The reaction mixture was kept at room

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temperature for 12 h, and then the product **1** that precipitated was filtered off, washed with cold water, and dried in a vacuum desiccator over P_2O_5: yield 6.2 g (69%); mp 226−228 °C dec (H_2O); ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 4H), 8.32 (s, 2H), 12.01 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 43.2, 160.3; IR (cm^{-1}) 3329, 3128, 3038, 2900, 1654, 1269. Anal. Calcd for $C_3H_7N_3O_4S$: C, 19.89; H, 3.89; N, 23.19. Found: C, 19.79; H, 3.64; N, 22.83.

Triethylaminium 2-Hydroxyliminoimidazolidine-*O*-sulfonate (1a). A suspension of compound **1** (1.81 g, 10 mmol) in DMF (15 mL) was treated with triethylamine (2.1 mL, 15 mmol) at room temperature. The reaction mixture was stirred until **1** had dissolved (ca 10 min), and then the reaction mixture was cooled to 15 °C. The solid that precipitated was collected by suction, washed with DMF and acetone, and dried in a vacuum desiccator: mp 193−195 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (t, 9H, CH_3), 3.04 (q, 6H, CH_2), 3.27 (s, 4H, CH_2), 6.30 (br s, 3H, NH); ^{13}C NMR (DMSO-d_6) δ 9.3, 43.2, 46.3, 163.4; IR (cm^{-1}) 3384, 3244, 3015, 2738, 2677, 1654, 1476, 1396, 1252, 1204, 1054. Anal. Calcd for $C_7H_{17}N_4O_4S$: C, 33.19; H, 6.77; N, 22.12. Found: C, 33.15; H, 6.69; N, 21.97.

Preparation of 6,7-Dihydro-5*H*-imidazo[2,1-c][1,2,4]-oxadiazoles 2−9. General Procedure. To a suspension of **1** (1.81 g, 10 mmol) and an equimolar amount of a suitable aldehyde or ketone in water (15 mL) was added a solution of NaOH (1.2 g, 0.03 mol) in water (15 mL) [in the case of *p*-chlorobenzaldehyde methanol (5 mL) was added to enhance solubility]. The reaction mixture was stirred vigorously at room temperature for 12 h. Then the product was extracted with dichloromethane (3 × 20 mL). Combined organic layers were dried with anhydrous Na_2SO_4, evaporated to dryness, and washed with diethyl ether, and the crude compound (**2**−**9**) thus obtained was purified by crystallization from a suitable solvent.

The following compounds were obtained according to the above procedure.

3-Phenyl-6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]-oxadiazole (2): yield 1.4 g (74%); mp 202−204 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 2.98−3.07 (m, 2H, CH_2), 3.73−3.80 (m, 2H, CH_2), 5.53 (s, 1H, CH), 6.71 (s, 1H, NH), 7.40−7.46 (m, 3H, CH), 7.52−7.57 (m, 2H, CH); ^{13}C NMR (DMSO-d_6) δ 45.4, 49.3, 96.1, 127.6, 128.5, 129.6, 135.7, 168.2; IR (cm^{-1}) 3198, 3060, 2819, 1645, 1380; EIMS *m*/*z* (relative intensity) 189 (M^+, 31.9), 159 (M^+ − NO, 100) 131 (29.5), 117 (33), 116 (46). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.15; H, 5.51; N, 21.87.

3-(4-Chlorophenyl)-6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]-oxadiazole (3): yield 0.48 g (23%); mp 192−193 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 3.08−3.18 (m, 2H, CH_2), 3.93−4.03 (m, 2H, CH_2), 5.07 (s, 1H, NH), 5.66 (s, 1H, CH), 7.40 (d, 2H, CH, J = 8.3 Hz), 7.55 (d, 2H, CH, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 45.8, 50.2, 96.7, 129.1, 129.4, 133.8, 136.2, 168.5; IR (cm^{-1}) 3205, 3060, 1643, 1597, 1417, 1374, 1276, 1088. Anal. Calcd for $C_{10}H_{10}N_3OCl$: C, 51.07; H, 4.76; N, 19.85. Found: C, 50.99; H, 4.71; N, 19.77.

3-(4-Methoxyphenyl)-6,7-dihydro-5*H*-imidazo[2,1-c]-[1,2,4]oxadiazole (4): yield 0.77 g (35%); mp 176−178 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 2.94−3.03 (m, 2H, CH_2), 3.74−3.86 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 5.48 (s, 1H, CH), 6.67 (s, 1H, NH), 6.97 (d, 2H, CH, J = 8.3 Hz), 7.47 (d, 2H, CH, J = 8.3 Hz); ^{13}C NMR (DMSO-d_6) δ 45.9, 49.9, 55.8, 96.6, 114.5, 128.2, 128.7, 160.9, 168.9; IR (cm^{-1}) 3207, 2955, 1646, 1610, 1252. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.54; H, 5.79; N, 19.44.

3-(Pyridin-3-yl)-6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]-oxadiazole (5): yield 0.63 g (33%); mp 184−185 °C (H_2O); ^{1}H NMR (DMSO-d_6) δ 3.06−3.11 (m, 2H, CH_2), 3.76−3.82 (m, 2H, CH_2), 5.62 (s, 1H, CH), 6.78 (s, 1H, NH), 7.47 (dd, 1H, CH, J = 4.8 Hz, J = 7.8 Hz), 7.96 (d, 1H, CH, J = 7.8 Hz), 8.63 (dd, 1H, CH, J = 1.5 Hz, J = 4.8 Hz), 8.71 (d, 1H, CH, J = 1.5 Hz); ^{13}C NMR (DMSO-d_6) δ 46.0, 50.00, 94.6, 124.5, 132.2, 136.0, 149.6, 151.6, 168.8; IR (cm^{-1}) 3201, 3056, 1644, 1595, 1370, 1179. Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.66; H, 5.15; N, 29.13.

6,7-Dihydro-3-spirocyclohexyl-5*H*-imidazo[2,1-c][1,2,4]-oxadiazole (6): yield 0.47 g (26%); mp 191−193 °C (methanol); ^{1}H NMR (DMSO-d_6) δ 1.09−1.16 (m, 1H, CH), 1.40−1.54 (m, 2H, CH), 1.56−1.60 (m, 5H, CH), 1.74 (d, 2H, CH, J = 11.7 Hz), 3.10 (t, 2H, CH_2, J = 6.3 Hz), 3.63 (t, 2H, CH_2, J = 6.3 Hz), 6.31 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 22.6, 24.5, 31.3, 41.5, 48.8, 95.2, 166.1; IR (cm^{-1}) 3159, 2925, 1651, 1486, 1440; EIMS *m*/*z* (relative intensity) 181 (M^+, 27.1), 164 (18.5), 151 (M^+ − NO, 35.5), 138 (100), 125 (28). Anal. Calcd for $C_9H_{16}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: 59.54; H, 8.12; N, 23.01.

6,7-Dihydro-3-spiro(4-methylcyclohexyl)-5*H*-imidazo-[2,1-c][1,2,4]oxadiazole (7): yield 0.45 g (23%); mp 212−214 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, CH_3 J = 5.8 Hz), 1.31−1.44 (m, 3H, CH), 1.51−1.57 (m, 2H, CH), 1.64 (d, 2H, CH, J = 10.7 Hz), 2.04 (d, 2H, CH, J = 12.2), 3.21 (t, 2H, CH_2, J = 6.8), 3.86 (t, 2H, CH_2, J = 6.8), 4.80 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 22.2, 31.3, 31.5, 31.8, 41,7, 49.8, 96.8, 166.8; IR (cm^{-1}) 3177, 2915, 1646, 1487, 1281. Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.15; H, 8.78; N, 21.52. Found: C, 61.01; H, 8.98; N, 21.12.

6,7-Dihydro-3-spiro(1-methylpiperidin-4-yl)-5*H*-imidazo[2,1-c][1,2,4]oxadiazole (8): yield 0.67 g (34%); mp 176−178 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 1.92−2.03 (m, 4H, CH), 2.33−2.48 (m, 2H, CH), 2.35 (s, 3H, CH), 2.82 (d, 2H, CH, J = 11.2 Hz), 3.22 (t, 2H, CH_2, J = 6.3 Hz), 3.86 (t, 2H, CH_2, J = 6.3 Hz), 4.71 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 31.1, 41.8, 45.9, 49.7, 52.3, 94.1, 167.0; IR (cm^{-1}) 3194, 2796, 1660, 1643, 1285. Anal. Calcd for $C_9H_{16}N_4O$: C, 55.08; H, 8.22; N, 28.55. Found: C, 55.16; H, 8.07; N, 55.22.

6,7-Dihydro-3-spiro(1-benzylpiperidin-4-yl)-5*H*-imidazo-[2,1-c][1,2,4]oxadiazole (9): yield 0.65 g (24%); mp 180−181 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 1.86−1.96 (m, 2H, CH), 1.99 (d, 2H, CH, J = 11.7 Hz), 2.40 (m, 2H, CH), 2.84 (m, 2H, CH), 3.22 (t, 2H, CH_2, J = 6.3 Hz), 3.55 (s, 2H, CH_2), 3.85 (t, 2H, CH_2, J = 6.3 Hz), 4.66 (br s, 1H, NH), 7.25−7.34 (m, 5H, CH); ^{13}C NMR ($CDCl_3$) δ 31.4, 41.9, 49.8, 50,3, 63.0, 95.2, 127.4, 128.5, 128.6, 129.5, 166.7; IR (cm^{-1}) 3207, 2938, 2815, 1640, 1488, 1448. Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 65.42; H, 7.18; N, 20.43.

Reaction of 1 with Carbon Disulfide. Method A: Preparation of 6,7-Dihydro-5*H*-imidazo[2,1-c][1,2,4]thiadiazole-3-thione (10). To a solution of **1** (1.8 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in DMF (15 mL) was added carbon disulfide (3 mL, 50 mmol), and the reaction mixture was stirred at 40 °C for 12 h. The volatile material was evaporated under reduced pressure, and the oily residue was triturated with water (20 mL). The precipitate thus obtained was filtered off and washed with water to give 0.8 g (50%) of **10**: mp 190−192 °C (H_2O); ^{1}H NMR (DMSO-d_6) δ 3.93−3.97 (m, 2H, CH_2), 3.98−4.03 (m, 2H, CH_2), 7.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 43.2, 47.9, 161.4, 193.4; IR (cm^{-1}) 3278, 3195, 1646, 1367. Anal. Calcd for $C_4H_5N_3S_2$: C, 30.17; H, 3.17; N, 26.39. Found: C, 30.01; H, 3.28; N, 26.79.

Reaction of 1 with Carbon Disulfide. Method B: Preparation of 6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]thiadiazole-3-thione (10) and Di(5,6-dihydro-7*H*-imidazo[2,1-c][1,2,4]-thiadiazole-3-thione-7-yl)methanethione (11). To a solution of **1** (1.8 g, 10 mmol) and Et_3N (3.2 mL, 23 mmol) in DMF (15 mL) was added carbon disulfide (3 mL, 50 mmol), and the reaction mixture was stirred at 40 °C for 12 h. The volatile material was evaporated under reduced pressure, and the oily residue was triturated with water (20 mL). The precipitate thus obtained was filtered off, washed with water, and then treated with hot methanol (150 mL). The insoluble material was separated by suction and crystallized from DMSO to give compound **11** (0.21 g, 11%): mp 250 °C dec (DMSO); ^{1}H NMR (DMSO-d_6) δ 4.06 (t, 4H, CH_2, J = 7.3 Hz)), 4.69 (br s, 4H, CH_2); IR (cm^{-1}) 1599, 1461, 1417, 1382, 1309, 1190; EIMS *m*/*z* (relative intensity) 360 (M^+, 100), 284 (M^+ − CS_2, 34), 208 (284

− CS_2, 9.9), 202 (25.2), 118 (35.7). Anal. Calcd for $C_9H_8N_6S_5$: C, 29.98; H, 2.24; N, 23.31. Found: C, 29.90; H, 2.29; N, 23.42.

The filtrate was evaporated to dryness under reduced pressure to give **10** (1.12 g, 70%), which was identical with the product obtained according to method A.

7-Acetyl-6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]thiadiazole-3-thione (12). A solution of imidazothiadiazole-3-thione **10** (0.25 g, 1.57 mmol), acetic anhydride (0.6 mL, 6.36 mmol), and Et_3N (0.9 mL, 6.5 mmol) in THF (10 mL) was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure, and the residue was treated with water. The product thus obtained was filtered off and purified by crystallization from methanol: yield 0.23 g (74%); mp 168−169 °C; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H, CH_3), 4.03−4.11 (m, 2H, CH_2), 4.49−4.57 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 25.8, 42.6, 51.1, 154.1, 170.2, 196.4; IR (cm^{-1}) 2966, 2913, 1702, 1608, 1302, 1199. Anal. Calcd for $C_6H_7N_3OS_2$: C, 35.80; H, 3.51; N, 20.88. Found: C, 35.49; H, 3.69; N, 20.49.

7-Benzyl-6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]thiadiazole-3-thione (13). To a mixture of imidazothiadiazole-3-thione **10** (0.5 g, 3.14 mmol) and finely powdered NaOH (0.5 g, 12.5 mmol) in DMSO (7 mL) was added dropwise benzyl bromide (0.41 mL, 3.45 mmol). The resulting solution was stirred at 35−40 °C for 1 h. Then water was added to the reaction mixture, and the solid that precipitated was collected by filtration. Product **13** thus obtained was purified by crystallization from ethanol: yield 0.64 g (82%); mp 127−129 °C; ^{1}H NMR ($CDCl_3$) δ 3.82−4.03 (m, 4H, CH_2), 4.49 (s, 2H, CH_2), 7.30−7.44 (m, 5H, CH); ^{13}C NMR ($CDCl_3$) δ 41.6, 49.4, 51.3, 128.3 (two overlapping signals), 128.90, 134.72, 158.90, 195.17; IR (cm^{-1}) 2913, 1631, 1381, 1258. Anal. Calcd for $C_{11}H_{11}N_3S_2$: C, 52.98; H, 4.45; N, 16.85. Found: C, 22.64; H, 4.15; N, 16.88.

7-Benzoyl-6,7-dihydro-5*H*-imidazo[2,1-c][1,2,4]thiadiazole-3-thione (14). A mixture of imidazothiadiazole-3-thione **10** (0.3 g, 1.875 mmol), Et_3N (0.26 mL, 1.87 mmol), and benzoyl isothiocyanate (0.25 mL, 1.87 mmol) in THF (4 mL) was stirred at room temperature for 12 h. Then the solvent was evaporated under reduced pressure, and the solid residue was treated with methanol (10 mL). The insoluble product **14** thus obtained was collected by filtration and purified by crystallization from DMF: yield 0.26 g (52%); mp 219−227 °C; ^{1}H NMR (DMSO-d_6) δ 4.01 (t, 2H, CH_2, J = 7.8 Hz) 4.53 (t, 2H, CH_2, J = 7.8 Hz), 7.47 (m, 2H, CH), 7.57 (m, 1H, CH, J = 7.3 Hz), 7.69 (d, 2H, CH, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 42.0, 51.7, 128.7, 129.1, 132.6, 134.1, 154.0, 167.8, 193.6; IR (cm^{-1}) 1661, 1601, 1469, 1415, 1326, 1316. Anal. Calcd for $C_{11}H_9N_3OS_2$: C, 50.17; H, 3.45; N, 15.96. Found: 49.87; H, 3.12; N, 3.01.

7,8-Dihydroimidazo[1,2-c][1,3,5]thiadiazine-2,4(6*H*)-dithione Imidazolidin-2-imine (15). To a solution of **1** (1.81 g, 10 mmol) and NaOH (1.6 g, 40 mmol) in water (12 mL) was added carbon disulfide (5.0 mL, 82 mmol), and the reaction mixture was stirred vigorously at room temperature for 24 h. The excess carbon disulfide was evaporated under reduced pressure, and the solid residue containing the salt **15** and traces of **10** (NMR evidence) was collected by filtration. Recrystallization of the crude product from DMF (elemental sulfur that crystallized first was separated by suction) gave pure salt **15**, which melted at 172−174 °C: yield 0.45 g (31%); ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 4H, CH_2), 3.66 (m, 2H, CH_2), 4.12 (m, 2H, CH_2), 7.88 (s, 4H, NH); ^{13}C NMR ($CDCl_3$) δ 42.5, 47.4, 49.6, 151.9, 160.0, 184.7, 187.8; IR (cm^{-1}) 3389, 2966, 1684, 1614, 1497, 1260, 1042. Anal. Calcd for $C_5H_5N_3S_3 \cdot C_3H_7N_3$: C, 35.98; H, 4.03; N, 32.02. Found: C, 36.17; H, 3.76; N, 31.88.

7,8-Dihydroimidazo[1,2-c][1,3,5]thiadiazine-2,4(6*H*)-dithione (16). Salt **15** (0.2 g) was dissolved in hot DMF (4 mL), treated with 3 drops of acetic acid, and left overnight at room temperature for crystallization. The pure product **16** (0.12 g) thus obtained melted at 249−251 °C: ^{1}H NMR (DMSO-d_6) δ 3.70 (t, 3H, CH_2, J = 8.8 Hz), 4.36 (t, 3H, CH_2, J = 8.8 Hz), 10.53 (s, 1H, NH); IR (cm^{-1}) 3056, 1641, 1406, 1406, 1338, 1277. Anal. Calcd for $C_5H_5N_3S_3$: C, 29.54; H, 2.48; N, 20.67. Found: C, 29.11; H, 2.36; N, 20.45.

3-Phenyl-2-(phenylimino)-8-(phenylthiocarbamoyl)-2,6,7,8-tetrahydroimidazo[1,2-a][1,3,5]triazine-4(3*H*)-thione (17). To a solution of **1** (1.81 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in DMF (15 mL) was added phenyl isothiocyanate (3.6.mL, 30 mmol), and the reaction mixture was kept at room temperature for 24 h. Elemental sulfur that precipitated was separated by suction, and the filtrate was treated with methanol (30 mL). The pale yellow solid thus obtained was separated by suction, washed with methanol, and purified by crystallization from ethanol: yield 1.7 g (37%); mp 279−282 °C; ^{1}H NMR (DMSO-d_6) δ 4.08 (t, 2H, CH_2, J = 7.8 Hz), 4.30 (t, 2H, CH_2, J = 7.8 Hz), 6.73 (d, 2H, CH), 6.95 (t, 1H, CH), 7.00 (d, 2H, CH), 7.16 (t, 3H, CH), 7.24 (t, 2H, CH), 7.33 (d, 2H, CH), 7.40 (t, 1H, CH), 7.52 (t, 2H, CH), 12.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.3, 46.8, 121.5, 121.6, 122.8, 126.1, 128.4, 128.7, 129.1, 129.3, 129.6, 137.8, 140.6, 145.5, 148.6, 148.8, 175.9, 176.1; IR (cm^{-1}) 2978, 1672, 1618, 1479, 1418. Anal. Calcd for $C_{24}H_{20}N_6S_2$: C, 63.13; H, 4.41; N, 18.41. Found: C, 63.02; H, 4.04; N, 18.12.

X-ray Structure Analyses. The intensity data for the crystals have been collected using a diffractometer. The crystal structures have been solved with SHELXS-97[22] and refined with SHELXL-97.[23]

Crystal data for $C_3H_7N_3O_4S$ (**1**): monoclinic, space group $P2_1/n$, a = 5.4594(3) Å, b = 12.0514(7) Å, c = 10.5212(6) Å, β = 102.393(5)°, V = 676.10(7) Å^3, Z = 4, λ = 0.71073 Å, T = 130 K, R1 = 0.0260, wR2 = 0.0672 for 1427 independent reflections with $I > 2\sigma(I)$.

Crystal data for $C_{10}H_{17}N_3O$ (**7**): monoclinic, space group $P2_1/c$, a = 10.6922(14) Å, b = 9.8340(13) Å, c = 10.9612(14) Å, β = 115.541(13)°, V = 1039.9(2) Å^3, Z = 4, λ = 0.71073 Å, T = 294 K, R1 = 0.0445, wR2 = 0.1123 for 1591 independent reflections with $I > 2\sigma(I)$.

Crystal data for $C_9H_8N_6S_5$ (**11**): orthorhombic, space group *Pbcn*, a = 6.2662(3) Å, b = 13.0714(7) Å, c = 17.4538(9) Å, V = 1429.61(13)Å^3, Z = 4, λ = 0.71073 Å, T = 140 K, R1 = 0.0290, wR2 = 0.0705 for 1750 independent reflections with $I > 2\sigma(I)$.

Crystal data for $C_{11}H_{11}N_3S_2$ (**13**): triclinic, space group $P\bar{1}$, a = 6.6652(5) Å, b = 8.1833(8) Å, c = 11.2460(8) Å, α = 83.311-(7)°, β = 77.601(6)°, γ = 69.863(8)°, V = 561.86(8) Å^3, Z = 2, λ = 0.71073 Å, T = 130 K, R1 = 0.0329, wR2 = 0.0837 for 2038 independent reflections with $I > 2\sigma(I)$.

Crystal data for $C_5H_5N_3S_3$ (**16**): monoclinic, space group $C2/c$, a = 22.7501(13) Å, b = 6.1929(4) Å, c = 15.6134(9) Å, β = 132.541(5)°, V = 1620.77(17) Å^3, Z = 8, λ = 0.71073 Å, T = 294 K, R1 = 0.0403, wR2 = 0.1053 for 1754 independent reflections with $I > 2\sigma(I)$.

Crystal data for $C_{24}H_{20}N_6S_2$ (**17**): monoclinic, space group $P2_1/c$, a = 9.9784(4) Å, b = 16.5446(6) Å, c = 13.1448(6) Å, β = 91.663(4)°, V = 2169.14(16) Å^3, Z = 4, λ = 0.71073 Å, T = 100 K, R1 = 0.0392, wR2 = 0.0947 for 3875 independent reflections with $I > 2\sigma(I)$.

Supporting Information Available: Crystallographic data for the structures **1**, **7**, **11**, **13**, **16**, and **17**, the asymmetric part of the crystal unit cell in **15**, a table showing selected theoretical and experimental bond distances (Å) and bond angels (deg) for zwitterionic compound **1**, and NMR spectra for compounds **6** and **10**. This material is available free of charge via Internet at http://pubs.acs.org.

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