# A NEW ROUTE FOR THE SYNTHESIS OF 6-SUBSTITUTED IMIDAZO[4,5-c]-1,2,6-THIADIAZINE 2,2-DIOXIDES: NMR STUDY AND CRYSTAL STRUCTURE OF A COMPLEX WITH DIMETHYLFORMAMIDE

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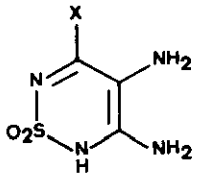
Abstract-The synthesis of 6-substituted imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxides from 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide and aldehydes is described. $^{1}H$- and $^{13}C$-nmr studies of the synthesized compounds have been carried out. The crystal structure of the complex formed by the 6-(p-methoxyphenyl) derivative and dimethylformamide has been studied. The imidazo-thiadiazine ring has an envelope conformation in a packing by hydrogen interactions.

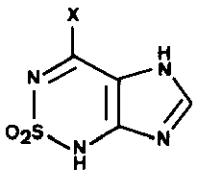
Reaction of 3,4-diaminothiadiazine 1,1-dioxides 1 with potassium dithioformate or formic acid/acetic anhydride affords the corresponding 4-thioformamido or mido or 4-formamido derivatives, respectively, which cyclize on heating to imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxides 2.[1,2,3]




1

1a , X = $NH_2$

1b , X = OH

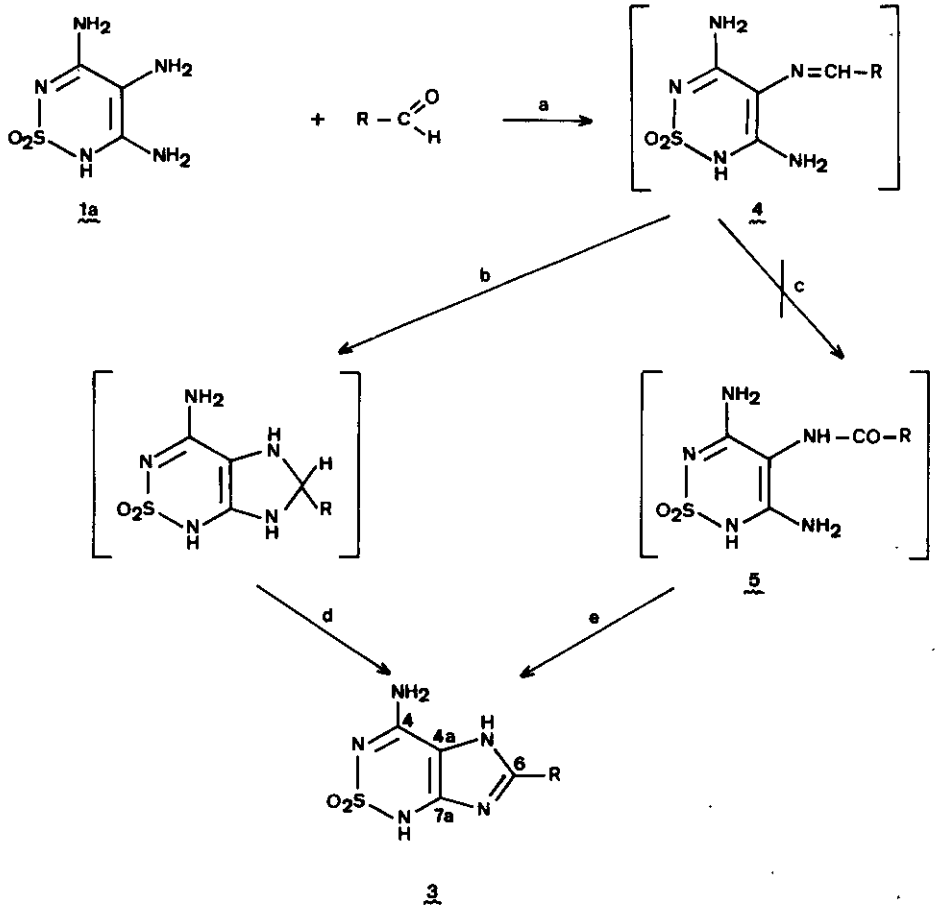



2

2a , X = $NH_2$

2b , X = OH

In this paper, we report a novel synthetic route to 6-substituted imidazothiadiazine 2,2-dioxides by the reaction of triamino derivative 1a and aldehydes. Thus, the reaction of 3,4,5-triaminothiadiazine 1,1-dioxide (1a) with a number of aromatic aldehydes, in aqueous acetic acid or aqueous dimethylformamide, at room temperature, afforded the correponding 6-substituted 4-aminoimidazothiadiazine 2,2-dioxide 3, as only product. The yield was independent of the acidity of the solvent used (runs 2 and 3 in Table 1). The first reaction step (a) must be the formation of the Schiff base of the most reactive 4-amino group, which in no case could be isolated (Scheme 1). The conversion to the imidazothiadiazine requires oxidation and ring closure (c and e, or b and d).




SCHEME 1

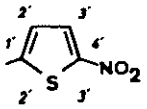
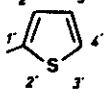
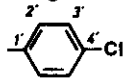
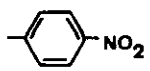
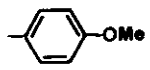
The enhanced reactivity of the thiadiazine Schiff bases 4 in comparison with those of related pyrimidines[4] is shown by the impossibility to isolate the former ones. Pathway c may be discarded, since cyclization of benzoyl derivative 5 (R=$C_6H_5$)[5] is only possible under forcing conditions (dimethylformamide at 160 °C) and in a lower yield (40%).

In order to extend the synthetic route to the 6-alkylated compounds 3, the reaction of 1a and acetaldehyde was carried out at room temperature. The corresponding 6-methylimidazothiadiazine derivative 3g was isolated in moderate yield (Table 1), whilst, no cyclized compound 3g was obtained from the acetyl derivative 4 (R=Me)[5], even at reflux temperature.

A similar pathway has been described in the synthesis of related 8-arylpurines. However, in these cases high temperature together with oxidant agents such as ferric chloride[4] or boiling nitrobenzene[6] have been used. In our case, the atmospheric oxygen or perhaps the aldehyde itself (an increment in its molar ratio enhances the yield) acts as dehydrogenating agent.

The imidazothiadiazine derivatives and the reaction conditions are shown in Table 1.

TABLE 1. 4-AMINO-1H,5H-IMIDAZO[4,5-c]-1,2,6-THIADIAZINE 2,2-DIOXIDES (3)

| Run | Comp. | R | Solvent | Temperature | 1a/aldehyde molar ratio | Yield % |
|---|---|---|---|---|---|---|
| 1 | 3a |  | $AcOH/H_2O$ | 25 °C | 1/2 | 48 |
| 2 | 3b |  | $AcOH/H_2O$ | 25 °C | 1/2 | 67 |
| 3 | 3b | | $DMF/H_2O$ | 25 °C | 1/2 | 70 |
| 4 | 3c |  | $AcOH/H_2O$ | 25 °C | 1/2 | 63 |
| 5 | 3d |  | $AcOH/H_2O$ | 25 °C | 1/2 | 67 |
| 6 | 3d | | $AcOH/H_2O$ | 25 °C | 1/3 | 92 |
| 7 | 3d | | EtOH | reflux | 1/2 | 25 |
| 8 | 3e |  | $DMF/H_2O$ | 25 °C | 1/3 | 95 |
| 9 | 3f |  | $AcOH/H_2O$ | 25 °C | 1/3 | 67 |
| 10 | 3g |  | $AcOH/H_2O$ | 25 °C | 1/3 | 45 |

The data shown in Table 1 point out that the yields of compounds rise with the molar ratios of the aldehydes (runs 5 and 6) and with the change from electron-releasing to electron-withdrawing substituents at the 6 position, except for the 5-nitrofuryl substituent, in which case the lower yield can be due to decomposition of starting aldehyde.

Compound 3a crystallizes with a molecule of water whilst all 6-aromatic substituted derivatives crystallize with a molecule of dimethylformamide (DMF) when they are recrystallized from DMF/water. On dissolving the complex of DMF and 3 in aqueous sodium hydroxide and by acidifying, compounds 3 crystallized without solvent molecule.

On the other hand, 6-unsubstituted (2) and 6-alkylsubstituted (3g) imidazothiadiazines do not crystallize with DMF.

In order to gain further knowledge on the complex formed by arylimidazothiadiazines and DMF, its $^{1}H$- and $^{13}C$-nmr spectra and X-ray crystallographic study of the complex [3g. DMF], have been carried out.

## Nmr studies

In Table 2 $^{1}H$-nmr data of the imidazothiadiazine derivatives 3 are shown. The assignments were straightforward. The value of $^{3}J_{H-2',H-3'}$ of 3a is similar to that found in the literature[7] for 5-nitrofurfural. The assignment of H-2' and H-4' signals of 3b were made on the basis of the value of both $^{3}J$.

TABLE 2. $^{1}H$-NMR[a] CHEMICAL SHIFTS (ppm) AND COUPLING CONSTANTS (Hz) OF 3[b]

| Comp. | $NH_2$, NH | H-2' | H-3' | H-4' | Coupling constants |
|---|---|---|---|---|---|
| 3a | 8.0,7.7 | 7.25(d) | 7.82(d) | - | $^{3}J_{H-2',H-3'}$=4.0 |
| 3b | 7.9,7.4 | 7.76(dd) | 7.33(dd) | 7.85(dd) | $^{3}J_{H-2',H-3'}$=3.6 |
| | | | | | $^{3}J_{H-3',H-4'}$=5.1 |
| | | | | | $^{4}J_{H-2',H-4'}$=1.2 |
| 3c | 7.8,7.6 | 8.02(d) | 7.69(d) | - | $^{3}J_{H-2',H-3'}$=8.7 |
| 3d | 7.9 | 7.90(m) | 7.50(m) | 7.50(m) | - |
| 3e | 7.3 | 8.13(d) | 8.38(d) | - | $^{3}J_{H-2',H-3'}$=9.0 |
| 3f | 8.0,7.6,6.3 | 7.90(d) | 7.13(d) | 3.83(s)(OMe) | $^{3}J_{H-2',H-3'}$=9.0 |
| 3g | 7.4 | 2.32(s)(Me) | - | - | - |

a) In DMSO-$d_6$ at 90 MHz. b) For numbering see Table 1 and structure 3.

TABLE 3. $^{13}$C-NMR CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz) OF COMPOUNDS 3[a,b]

| Comp. | C-4 | C-4a | C-6 | C-7a | C-1' | C-2' | C-3' | C-4' | DMF carbons |
|---|---|---|---|---|---|---|---|---|---|
| 3a[c] | 153.9 | 107.6 | 135.2 | 148.3 | 146.4(t)<br>$^2J_{C-1',H-2'}$=8.8<br>$^3J_{C-1',H-3'}$=8.8 | 115.2(d)<br>$^1J$=186.1 | 112.3(d)<br>$^1J$=186.1 | 151.4(m) | - |
| 3b | 153.5 | 104.9 | 128.5 | 149.3 | 145.5(d)<br>$^2J_{C-1',H-2'}$=6.6 | 128.3(dd)<br>$^1J$=174.0<br>$^3J_{C-2',H-4'}$=4.0 | 126.3(dq)<br>$^1J$=168.9<br>$^2J_{C-3',H-4'}$=9.4<br>$^2J_{C-3',H-2'}$=5.8 | 132.2(m) | - |
| 3c | 153.9 | 105.7 | 145.9(m) | 149.6 | 128.0(t)<br>$^3J_{C-1',H-3'}$=7.0 | 129.3(dd)<br>$^1J$=164.4<br>$^2J_{C-2',H-3'}$=6.0 | 127.6(dd)<br>$^1J$=168.4<br>$^2J_{C-3',H-2'}$=4.2 | 134.9(m) | - |
| 3d[d] | 153.6 | 104.8 | 146.9 | 149.6 | 128.8 | 128.4(d) | 129.0(d) | 130.0(d) | - |
| 3e[c] | 153.9 | 107.2 | 143.8 | 148.7 | 134.7(t)<br>$^3J_{C-1',H-3'}$=6.9 | 126.4(dd)<br>$^1J$=166.5<br>$^2J_{C-2',H-3'}$=5.7 | 124.1(dd)<br>$^1J$=171.0<br>$^2J_{C-3',H-2'}$=3.4 | 147.5(t)<br>$^3J_{C-4',H-2'}$=6.8 | - |
| 3f | 153.1 | 103.9 | 147.1(m) | 149.8 | 121.2(t)<br>$^3J_{C-1',H-3'}$=7.6 | 127.1(dd)<br>$^1J$=163.3<br>$^2J_{C-2',H-3'}$=6.4 | 114.4(m)<br>$^1J$=163.4 | 161.7(m)<br>55.5(q,OMe) | - |
| [3f.DMF] | 153.2 | 103.9 | 147.3(t)<br>$^3J_{C-6,H-2'}$=3,5 | 149.9 | 121.1(t)<br>$^3J_{C-1',H-3'}$=7.7 | 126.5(dd)<br>$^1J$=161.3<br>$^2J_{C-2',H-3'}$=7.2 | 114.6(dd)<br>$^1J$=162.8<br>$^2J_{C-3',H-2'}$=4.5 | 161.0(m)<br>55.3(q,OMe) | 163.2(d,CHO)<br>$^1J$=189.1<br>35.6(N-Me)<br>30.7(N-Me) |
| 3g | 153.5 | 103.5 | 146.7(q)<br>$^2J_{C-6,Me}$=7.0 | 148.6 | 14.1(q,Me)<br>$^1J$=129.2 | - | - | - | - |

a) In DMSO-$d_6$ at 20.15 MHz.

b) For numbering see Table 1 and structure 3.

c) DMSO-$d_6$+TFA at 60 °C.

d) Multiplicity from off-resonance spectrum.

Some differences between $^{1}H$- and $^{13}C$-nmr spectra of free 3f and [3f.DMF] complex were found. The differences are not justifyed by the presence of the little amount of DMF in the solvent but much more probably by the complex formation. Thus, in the $^{1}H$-nmr spectrum of the complex [3f. DMF] the NH signal appears 2 ppm shifted to lower field in comparison to that of 3f (6.3 ppm).

In Table 3 $^{13}C$-nmr data of compounds 3 and complex [3f.DMF] are gathered. Owing to the prototropic tautomerism that exists in thiadiazine dioxide derivatives,[8] C-4, C-4a and C-7 signals appear broadened and in some cases, it is necessary to add drops of TFA and to record the spectra at 60°C.

Chemical shift assigments were made by intercomparison with the data of reported thiadiazine derivatives[8] and related aromatic compounds.[7,9-11] The signals corresponding to C-2' and C-3' of compound 3c were assigned by comparison of both $^{2}J$ with the corresponding ones unequivocally assigned for 3e. Long-range couplings of C-1' and C-4' when its signals are triplets were assigned as $^{3}J$ on the bases of $^{3}J > {}^{2}J$ in aromatic compounds.[12]

The main differences of $^{13}C$ chemical shifts between 3f and complex [3f.DMF] spectra is the shielding shown by the signals corresponding to C-4' (0.7 ppm) and C-2' (0.6 ppm) in the spectrum of the complex.

## X-ray analysis of complex [3f.DMF]

The main geometrical characteristics are given in Table 4. The thiadiazine ring adopts a distorted envelope conformation flapping at S(2) and, together with fused five-membered ring, is twisted around C(6)-C(8) by 22.0 (1)° with respect to the phenyl ring.

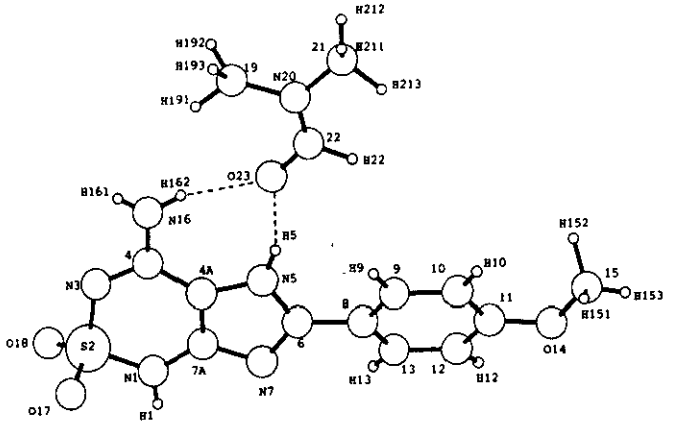



Fig. 1. The DMF molecule corresponds to the symmetry operator iii *(see Table 4)*

TABLE 4. SELECTED GEOMETRICAL PARAMETERS (Å, °).

| | | | | | |
|---|---|---|---|---|---|
| N1-S2 | 1.633(3) | N1-C7A | 1.369(5) | S2-N3 | 1.587(4) |
| S2-O17 | 1.452(5) | S2-O18 | 1.381(7) | N3-C4 | 1.331(5) |
| C4-C4A | 1.419(5) | C4-N16 | 1.338(5) | N5-C4A | 1.391(5) |
| C4A-C7A | 1.379(5) | N5-C6 | 1.345(4) | C6-N7 | 1.354(5) |
| C6-C8 | 1.458(5) | N7-C7A | 1.364(4) | C15-O14 | 1.414(7) |
| C19-N20 | 1.439(10) | N20-C21 | 1.462(9) | N20-C22 | 1.307(6) |
| C22-O23 | 1.232(6) | | | | |
| | N1-S2-O18 | 110.0(3) | N1-S2-O17 | 105.5(4) | |
| | N1-S2-N3 | 109.3(3) | O17-S2-O18 | 114.2(6) | |
| | N3-S2-O18 | 112.3(4) | N3-S2-O17 | 106.3(3) | |
| S2-N1-C7A-C4A | | -10.0(10) | C7A-N1-S2-N3 | | 17.3(8) |
| N1-S2-N3-C4 | | -17.2(8) | S2-N3-C4-C4A | | 7.7(10) |
| N3-C4-C4A-C7A | | 3.4(10) | C4-C4A-C7A-N1 | | -1.9(11) |
| N5-C6-C8-C9 | | 22.0(10) | C10-C11-O14-C15 | | -8.7(11) |
| C19-N20-C22-O23 | | -0.6(13) | | | |
| C22-H22 | 1.03(9) | C22-O18(i) | 3.291(10) | H22-O18(i) | 2.58(10) |
| C22-H22...O18(i) | | 126(6) | | | |
| C13-H13 | 0.96(6) | C13-O17(ii) | 3.480(8) | H13-O17(ii) | 2.65(5) |
| C13-H13...O17(ii) | | 144(4) | | | |
| *N1-H1 | 0.82(7) | N1-N7(ii) | 2.943(5) | H1-N7(ii) | 2.13(7) |
| N1-H1.....N7(ii) | | 174(7) | | | |
| *N5-H5 | 0.86(5) | N5-O23(iii) | 2.747(5) | H5-O23(iii) | 1.93(5) |
| N5-H5.....O23(iii) | | 159(4) | | | |
| C9-H9 | 0.93(5) | C9-O18(iii) | 3.331(7) | H9-O18(iii) | 2.58(5) |
| C9-H9.....O18(iii) | | 138(4) | | | |
| *N16-H162 | 0.85(7) | N16-O23(iii) | 2.927(6) | H162-O23(iii) | 2.10(7) |
| N16-H162..O23(iii) | | 165(6) | | | |
| *N16-H161 | 0.78(7) | N16-N3(iv) | 3.051(5) | H161-N3(iv) | 2.28(6) |
| N16-H161..N3(iv) | | 173(6) | | | |

Symmetry operation: i; x,y,z ii; 1-x,1-y,1-z iii; x,1+y,z iv; 1-x,1-y,-z

The molecule of dimethylformamide is attached through hydrogen bonds to the imidazothiadiazine molecule in which O(23) of DMF, H(5) and H(162) of imidàzo-thiadiazine are involved (see Figure 1) the packing is built through hydrogen interactions (see Table 4) some of which are considered as hydrogen bonds[13] and are marked with an asterisk.[14]

## EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. $^{1}$H-Nmr spectra were recorded at 90 MHz on a Varian EM-390 spectrometer. $^{13}$C-NMR spectra were recorded at 20.15 MHz on a Bruker WP 80 spectrometer. Chemical shifts are reported as $\delta$ values (part per million) relative to tetramethylsilane as internal standard. Ir and uv spectra were recorded in a Perkin Elmer 257 and a Perkin Elmer 550 SE spectrometers respectively.

### X-ray Crystallography

$(C_{11}H_{12}N_5O_5S)(C_3H_7NO)$. Yellow plated transparent sample, 0.60 x 0.24 x 0.12 mm. triclinic, $P\bar{1}$; 25 *reflections between 9 and 13° in θ used for the least-squares* fit of the unit cell constants: 7.271(6), 9.684(13), 12.582(5)Å, 88.46(6), 100.56(8) and 104.67 (10)°, with Z=2. Nonius CAD-4 diffractometer, $MoK_\alpha$ radiation, graphite monochromated, bisecting geometry, 1+0.35 tan θ° scan width, [2+0.35 tan θ] mm apertures, 4 deg./min of speed and θ between 2 and 30° for the data collection of 4845 intensities, with no variation in the two standard reflexions monitored every 100 other ones. 2950 Oberved data ($3\sigma(I)$)were used with direct methods[15,16] for the solution, and for the least-squares refinement on Fobs and one block[17] of 298 parameters. Hydrogen atoms from difference synthesis and empirical weighting scheme as to even the trends. Final shift/error 0.05, final maximum thermal factor U11(0.18)=0.23(1)Å$^2$ and maximum peak in the difference synthesis of 1.4 eÅ$^{-3}$ near the S atom. R and Rw factors are 0.074, 0.091 respectiviely with atomic scattering factors taken from reference.[18]

### General Synthetic Method

To a mixture of 34 ml of water and 7 ml of acetic acid or dimethylformamide (DMF) 1 g (5.6 mmol) of 3,4,5-triamino-2H-1,2,6-thiadiazine 1,1-dioxide (1a) was added. In the case of run 7 in Table 1, 50 ml of EtOH as solvent was used. The mixture

was boiled until the majority of 1a was dissolved. Then 11.2 or 16.8 mmol of aldehyde were added and stirred at room temperature for 3 h. The resulting precipitate was separated by filtration, washed with water and recrystallized in each case.

4-Amino-6-[2'-(5'-nitrofuranyl)]-1H,5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (3a)

Mp > 350°C ($H_2O$). Ir (KBr) ν: 3380, 3320 ($NH_2$), 3120 (NH), 1635 (C=N), 1510, 1350 ($NO_2$), 1315, 1170-1090 ($SO_2$) $cm^{-1}$. Uv ($H_2O$) $\lambda$max (log$\varepsilon$ ): 222 (sh) (3.58), 270 (3.44), 307 (3.43), 442 nm (3.58). Anal. Calcd. for $C_8H_6N_6O_5S.H_2O$: C, 30.38; H, 2.55; N, 26,57; S, 10.14. Found: C, 30.35; H, 2.46; N, 26.55; S, 10.47.

4-Amino-6-(2-thienyl)-1H,5H-imidazo[4,5-c]1,2,6-thiadizine 2,2-Dioxide (3b)

Mp 313°C (decomp.) (MeOH/$H_2O$). Ir (nujol) ν: 3440, 3300 ($NH_2$), 3190 (NH), 1630 (C=N), 1290, 1140 ($SO_2$) $cm^{-1}$. Uv ($H_2O$) $\lambda$max (log$\varepsilon$ ): 249 (3.8), 280 (3.70), 341 nm (4.1). Anal. Calcd. for $C_8H_7N_5O_2S_2$: C, 35.68; H, 2.62; N, 26.00; S, 23.81. Found: C, 35.50; H, 2.52; N, 26.15; S, 23.75.

4-Amino-6-(4'-clorophenyl)-1H,5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (3c)

Mp 292-293°C (MeOH/$H_2O$). Ir (nujol) ν: 3400, 3300 ($NH_2$), 3200 (NH), 1640 (C=N), 1280, 1140 ($SO_2$) $cm^{-1}$. Uv (MeOH/$H_2O$: 1/1) $\lambda$max (log$\varepsilon$ ): 244 (4.4), 331 nm (4.4). Anal. Cald. for $C_{10}H_8N_5O_2Cl$: C, 40.34; H, 2.71; N, 23.52; S, 10.77; Cl, 11.91. Found: C, 39.98; H, 3.00; N, 23.30; S, 10.90, Cl, 11.90.

4-Amino-6-phenyl-1H,5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (3d)

Mp 320-321°C ($H_2O$). Ir (nujol) ν: 3485, 3420 ($NH_2$), 3360 (NH), 1635 (C=N), 1290, 1140 ($SO_2$) $cm^{-1}$. Uv (MeOH) $\lambda$max (log$\varepsilon$ ): 238 (4.66), 290 (sh) (4.36) 334 nm (4.65). Anal. Calcd. for $C_{10}H_9N_5O_2S$: C, 45.62; H, 3.45; N, 26.60; S, 12.18. Found: C, 45.48; H, 3.48; N, 26.54; S, 12.12.

4-Amino-6-(4'-nitrophenyl)-1H,5H-imidazo[4,5-c]-1,2,6-thiadizine 2,2-Dioxide (3e)

Mp 310°C (decomp.)[19]. Ir (nujol) ν: 3450, 3310 ($NH_2$), 3210 (NH), 1630 (C=N), 1510, 1350 ($NO_2$), 1295, 1160 ($SO_2$) $cm^{-1}$. Uv (MeOH) $\lambda$max (log$\varepsilon$ ): 220 (sh) (3.96), 249 (sh) (3.83), 363 nm (3.97). Anal. Calcd. for $C_{10}H_8N_6O_4S$: C, 38.96; H, 2.62; N, 20.76. Found: C, 38.82; H, 2.70; N, 20.73.

4-Amino-6-(4'-methoxyphenyl)-1H,5H-imidazo[4,5-c]1,2,6-thiadiazine 2,2-Dioxide (3f)
Mp 283-284 °C.[19] Ir (nujol) ν: 3370, 3300 ($NH_2$), 3200 (NH), 1615 (C=N), 1470 ($OCH_3$), 1290, 1090 ($SO_2$) $cm^{-1}$. Uv (MeOH) λmax (log ε): 250 (4.18), 325 nm (4.28). Anal. Calcd. for $C_{11}H_{11}N_5O_3S$: C, 45.04; H, 3.78; N, 23.88. Found: C, 45.24; H, 3.80; N, 23.58.

Complex[3f. DMF]
Mp 268 °C (DMF/$H_2O$). Ir (nujol) ν: 3330-3180 (br.) ($NH_2$, NH), 1665 (C=O), 1600 (C=N), 1315, 1160 ($SO_2$) $cm^{-1}$. Uv (MeOH) λmax (log ε): 250 (4.2), 287 (4.05) 332.5 nm (4.36). Anal. Cald. for $C_{14}H_{18}N_6O_4S$: C, 45.89; H, 4.95; N, 22.94. Found: C, 46.11; H, 5.01; N, 23.24.

4-Amino-6-methyl-1H,5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (3g)
Mp 296-298 °C ($H_2O$). Ir (nujol) ν: 3410, 3320 ($NH_2$), 3150 (NH), 1630 (C=N), 1260, 1090 ($SO_2$) $cm^{-1}$. Uv (MeOH) λmax (log ε): 218 (3.6), 290 nm (3.5). Anal. Calcd. for $C_5H_7N_5O_2S$: C, 27.40; H, 4.14; N, 31.95; S, 14.63. Found: C, 27.60; H, 4.24; N, 31.72; S, 14.56.

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