SYNTHESIS OF HETERO[1,2,4]THIADIAZINE 1,1-DIOXIDES

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Abstract - The synthesis of several representatives of the new thieno- and pyrazolo[1,2,4]thiadiazine 1,1-dioxides ring systems is described. It was carried out by cyclization of the isocyanates (**4**) formed in the Curtius rearrangement of acyl azides (**3**). The reactivity of these new rings towards some electrophilic reagents was also explored.

The sulfonamide and sulfamoyl groups have been widely used as modifying substituents of the activity in a number of pharmacological drugs; but it is perhaps more important their participation as primary pharmacophores in the molecular structures of several antibacterial, hypoglucemiant, antiinflammatory, cardiovascular, psychotropic and antiviral agents.[1,2]

Among these structures are those belonging to the 1,2,4-benzothiadiazine 1,1-dioxides heterocyclic ring system, whose more significant representatives, Chlorothiazide and Diazoxide, have found clinical utility as diuretic and antihypertensive drugs respectively.[3-7] The discovery of the exceptional properties of these prototypes favored the preparation of a considerable number of benzothiadiazine analogues and the development of other therapeutic agents.

In marked contrast, the synthesis of 1,2,4-thiadiazine 1,1-dioxides fused to other aromatic heterocycles has been scarcely considered. Several pyrido[2,3-*e*]-,[8-13] pyrido[4,3-*e*]-[13-15] and pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxides[12] are known, but only two [2,3-*e*] derivatives of thieno[1,2,4]thiadiazine 1,1-dioxides structures have been described so far[16] and no pyrazolo[1,2,4]thiadiazine 1,1-dioxide seems to have been hitherto synthesized.

These antecedents and our interest in the search for useful active compounds of potential pharmaceutical development led us to synthesize the first examples of the 2*H*,4*H*-thieno[3,4-*e*], 2*H*,4*H*-thieno[2,3-*e*] and 2*H*,4*H*-pyrazolo[4,3-*e*][1,2,4]thiadiazine 1,1-dioxide ring systems. The preparation of these new compounds and their preliminary chemical behaviour in electrophilic reactions such as nitration and halogenation are the subject of the present paper.

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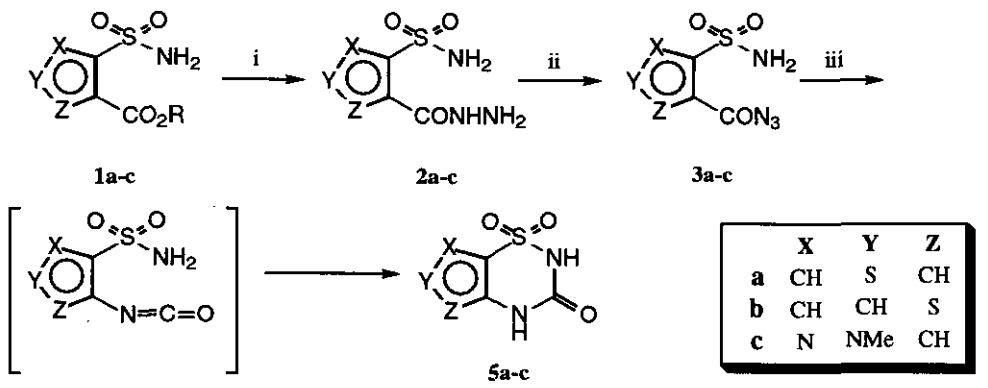
Most of the described synthetic methods of 1,2,4-benzothiadiazines start from aniline derivatives,[17] but they are not applicable to the formation of their thieno[1,2,4]thiadiazine isosteres because of the known instability of the required starting aminothiophenes.[18] Therefore an alternative approach (Scheme 1) which involves the cyclization of the methyl sulfamoylthiophenecarboxylates (**1a-b**) through a classical Curtius reaction was used.[19,20] The approach was successfully employed to prepare also the target pyrazolo[1,2,4]thiadiazine analogue from the ethyl sulfamoylpyrazolocarboxylate (**1c**).

The sulfamoylheterocarboxylates (**1a-c**) had been prepared previously by reaction of methyl 4-chlorosulfonylthiophene-3-carboxylate, methyl 3-chlorosulfonylthiophene-2-carboxylate and ethyl 3-chlorosulfonyl-1-methylpyrazole-4-carboxylate with ammonia[21]. These sulfamoyl esters were readily converted to the acyl azides (**3a-c**) by the action of nitrous acid on hydrazides (**2a-c**), which, in turn, were obtained by reaction of **1a-c** with hydrazine hydrate in ethanol. Acyl azides (**3a-c**) were obtained in 90-95% yields as white solids which, due to their potentially explosive nature, were not purified; however, they could be conveniently identified by the presence of the N_3 group characteristic band at 2130-2160 cm^{-1} in their IR spectra.

The synthesis of desired thieno- and pyrazolo[1,2,4]thiadiazines (**5a-c**) were achieved in good yields by spontaneous ring-closure of the intermediate isocyanates (**4a-c**) generated in the thermal rearrangement of acyl azides (**3a-c**) in dry toluene.

Structural assignments for these compounds were based on their elemental and spectral analyses. Thus, they exhibited in their IR spectra, in addition to the expected absence of the azide absorption, the characteristic strong bands of the SO_2 group at 1320-1295 and 1160-1120 cm^{-1}, as well as an intense and sharp band near 1700 cm^{-1} typical of stretching frequencies of CO bonds. Their ^{1}H-NMR spectra (DMSO-d_6) showed a broad signal at low field (12.50-10.50 ppm), corresponding to a proton exchangeable with deuterium by D_2O addition, which was assigned to one of the NH groups.

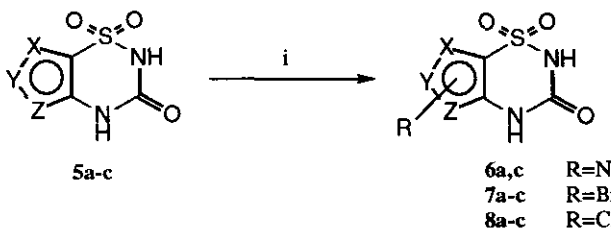


Scheme 1. (i) $N_2H_4.H_2O$/EtOH; (ii) HNO_3 (2N), $NaNO_2$, H_2O; (iii) Δ/toluene;

Compounds (**5a-c**) belong to practically unpublished ring systems, so that it was of interest to have at our disposal new derivatives of these heterocycles not only to investigate their general reactivity but also to assess their possible biological activity and study structure-activity relationships. Therefore, the chemical

behaviour of compounds (**5a-c**) in typical electrophilic substitution reactions such as nitration and halogenation was investigated .

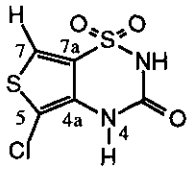
As expected, nitration of **5a** and **5c** with the mixture of nitric and sulfuric acids (Scheme 2, Method A) gave rise to the formation of monosubstituted nitro derivatives (**6a**) and (**6c**) in 90 and 41% yields respectively. Nitration of the thieno[2,3-*e*]thiadiazine (**5b**) under similar conditions led, however, to a complex mixture of products from which no nitro analogue (**6b**) could be isolated. This anomalous behaviour of **5b** can be attributed to a certain instability of its thiadiazine structure in the reaction medium, which was also detected in several reactions of this compound in other strong acidic conditions. The IR spectra of **6a** and **6c**, with bands at 1600-1500 and 1350-1300 cm^{-1} characteristic of the NO_2 group were consistent with the assigned structures. In addition, their ^{1}H-NMR spectra (DMSO-d_6) showed the disappearance of the doublet at low field due to the aromatic thiophene protons of **5a**, and the absence of the pyrazole proton signal of compound (**5c**).



	X	Y	Z
a	CH	S	C
b	CH	C	S
c	N	NMe	C

Scheme 2. (i) Method A: HNO_3:H_2SO_4; Method B: NBS or NCS, THF, 1,4-dioxane or DMF, Δ

Halogenation of heterothiadiazines (**5a-c**) was carried out with *N*-bromo- and *N*-chlorosuccinimide in refluxing tetrahydrofuran giving (Scheme 2, Method B) the corresponding monosubstituted bromo and chloro derivatives (**7a-c**) and (**8a-c**) in good yields. Changes of solvent were necessary for chlorination of the thienothiadiazine (**5b**) and for bromination and chlorination of the pyrazolothiadiazine (**5c**). In the first case, 1,4-dioxane was used instead of tetrahydrofuran, and in the second, *N,N*-dimethylformamide was found to be most suitable. The structures of the halogenated compounds were established according to analytical and spectroscopic data. Thus, the same ^{1}H-NMR parameters which were utilized to prove the introduction of nitro group into the aromatic ring of heterothiadiazines (**5a-c**) served to demonstrate that of the halogen atoms.



8a

C-4a: 130.5 (dd, $^3J_{CH}$=7.8 Hz, $^2J_{CH}$=2.1 Hz)
C-7a: 126.3 (dd, $^3J_{CH}$=4.7 Hz, $^2J_{CH}$=2.1 Hz)
C-7: 122.5 (d, $^1J_{CH}$=198.8 Hz)
C-5: 107.8 (dd, $^3J_{CH}$=2.0 Hz, $^3J_{CH}$=7.7 Hz)

Figure 1

The site of aromatic substitution in the thienothiadiazines (**6a-b**, **7a-b** and **8a-b**) was determined on the basis of their coupled ^{13}C-NMR spectra. For example, in the case of the chloro-thieno[3,4-*e*]thiadiazine (**8a**) (Figure 1) the C-7 signal at 122.5 ppm is a doublet with a $^{1}J_{CH}$ = 198.9 Hz, while the remaining thiophene carbon atoms appear as double doublets because of their long range couplings with the N-4 proton, thus clearly indicating that chlorine atom enters the position 5 of thieno[3,4-*e*]thiadiazine ring. No similar long range couplings were observed, however, in the ^{13}C-NMR spectra of both bromo- and chloro-thieno[2,3-*e*] derivatives (**7b**) and (**8b**), so that the site of halogenation in these compounds had to be elucidated by comparison of the C-H coupling constants of their thiophene CH groups with those of the starting thiadiazine **5b** (Figure 2).

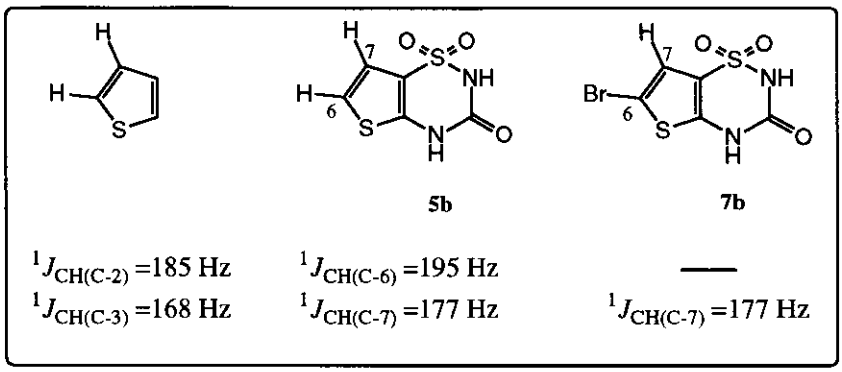


Figure 2

As is known, the C-H coupling constant value of carbon atoms at positions 2 and 5 in thiophene systems is, in general, larger than that of carbon atoms at positions 3 and 4. For thiophene, $^{1}J_{CH(C-2)}$ value is 185 Hz whereas $^{1}J_{CH(C-3)}$ is 168 Hz.[22] The starting thiadiazine (**5b**), for instance, showed in its ^{13}C-NMR spectrum C-H coupling constants of 195 and 177 Hz for the two carbon atoms of thiophene moiety. Consequently, the signal with $^{1}J_{CH}$ = 195 Hz was assigned to the carbon atom at position 6 of the heterocycle, and the signal with $^{1}J_{CH}$ = 177 Hz was ascribed to that at position 7. Bromothiadiazine (**7b**) only exhibits a coupled C-H signal with a $^{1}J_{CH}$ = 177 Hz which evidently corresponds to the carbon atom at position 7 of its structure and, consequently, confirms position 6 as the site of electrophilic substitution in the thieno[2,3-*e*]thiadiazines.

EXPERIMENTAL

All melting points were determined on Gallenkamp capillary apparatus and are uncorrected. IR spectra were recorded using a Shimadzu IR-435 instrument. ^{1}H-NMR spectra were measured with a Bruker AM-200 and a Varian XL-300 spectrometer. Chemical shift values are reported relative to tetramethylsilane (TMS) in appropriate solvents. The purity of compounds was verified by thin-layer chromatography (TLC) which was run on silica gel GF_{254} (E. Merck) with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v respectively) as eluents. Medium-pressure chromatography was performed using 230-400 mesh

silica gel purchased from E. Merck, Inc. Microanalysis were performed at the Centro Nacional de Química Orgánica on a Perkin-Elmer 2400 CHN analyzer.

Sulfamoylcarbohydrazides (2a-c). General Procedure: A solution of the sulfamoyl ester (**1**) (1 equiv.) and 98% hydrazine hydrate (3 equiv.) in ethanol (550 mL) was refluxed for 1 h. The precipitated solid was filtered off, washed with ethanol, dried and recrystallized from the appropriate solvent.

4-Sulfamoylthiophene-3-cabohydrazide (2a) White solid (86%) of mp 206-208°C (from water). IR (KB): ν_{max} (cm^{-1}) 3400-3200 (NH); 1690 (C=O); 1320, 1125 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 9.90 (s, 1H, exchanged with deuterium by D_2O addition, NH), 8.15 (d, 1H, J = 3.0 Hz, thiophene CH), 8.03 (d, 1H, J = 3.0 Hz, thiophene CH), 7.27 (s, 2H, exchanged with deuterium by D_2O addition, NH_2), 4.57 (s, 2H, exchanged with deuterium by D_2O addition, NH_2). *Anal.* Calcd for $C_5H_7N_3O_3S_2$: C, 27.15; H, 3.17; N, 19.00. Found: C, 26.85; H, 3.28; N, 18.75.

3-Sulfamoylthiophene-2-carbohydrazide (2b) Yellow solid (80%) of mp 141-143°C (from water). IR (KBr): ν_{max} (cm^{-1}) 3300-3200 (NH); 1660 (C=O); 1340, 1130 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 7.72 (AB, 1H, J = 5.1 Hz, thiophene CH), 7.33 (AB, 1H, J = 5.1 Hz, thiophene CH), 8.00-7.00 (br s, 3H, exchanged with deuterium by D_2O addition, CONH and SO_2NH_2), 4.00-5.00 (br s, 2H, exchanged with deuterium by D_2O addition, NH_2). *Anal.* Calcd for $C_5H_7N_3O_3S_2$: C, 27.15; H, 3.17; N, 19.00. Found: C, 27.27 H, 3.31; N, 18.99.

1-Methyl-3-sulfamoylpyrazole-4-carbohydrazide (2c) From **1c** (45 g, 0.19 mol) and 98% hydrazine hydrate (56.25 mL, 1.16 mol). Refluxing time 24 h. White solid (85%) of mp 216-218°C (from ethanol-water). IR (KBr) ν_{max} (cm^{-1}) 3400-3000 (NH); 1675 (C=O); 1345, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 9.60 (s, 1H, exchanged with deuterium by D_2O addition, NH), 8.30 (s, 1H, pyrazole CH), 7.60 (s, 2H, exchanged with deuterium by D_2O addition, NH_2), 4.55 (s, 2H, exchanged with deuterium by D_2O addition, NH_2), 3.90 (s, 3H, CH_3). *Anal.* Calcd for $C_5H_9N_5O_3S$: C, 27.39; H, 4.11; N, 31.95. Found: C, 27.57; H, 4.09; N, 31.68.

Sulfamoylcarboxy azydes (3a-c). General Procedure: To a solution of the sulfamoylcarbohydrazide (**2**) (1 equiv.) in 2N nitric acid (720 mL) was added dropwise a solution of sodium nitrite (1.2 equiv.) in water (200 mL), maintaining the reaction temperature below 10°C. The mixture was stirred at this temperature for 2 h and the precipitate was filtered, washed with water and dried. The compounds were pure enough to be used as such in the following step.

4-Sulfamoylthiophene-3-carboxy azyde (3a) White solid (90%). IR (KBr) ν_{max} (cm^{-1}) 3400, 3200 (NH); 2150, 1210 (N_3); 1660 (C=O); 1340, 1160 (SO_2).

3-Sulfamoylthiophene-2-carboxy azyde (3b) White solid (92%). IR (KBr) ν_{max} (cm^{-1}) 3350, 3250 (NH_2); 2130, 1230 (N_3); 1660 (C=O); 1335, 1175 (SO_2).

1-Methyl-3-sulfamoylpyrazole-4-carboxy azyde (3c) White solid (95%). IR (KBr) ν_{max} (cm^{-1}) 3250 (NH); 2150 (N_3); 1680 (C=O); 1335, 1170 (SO_2).

1,1,3-Trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazines (5a-c). General Procedure: A solution of the acylazide (**3**) (0.02 mol) in dry toluene (250 mL) was refluxed for 2-6 h. The precipitate was filtered off and recrystallized from the appropriate solvent.

1,1,3-Trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (5a) Compound (**3a**) was refluxed for 2.5 h to give **5a** as a white solid (85%) of mp 258-260°C (decomp) (from butanol). IR (KBr) ν_{max} (cm^{-1}) 3360 (NH); 1665 (C=O); 1320, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.12 (s, 1H, exchanged with deuterium by D_2O addition, NH), 8.45 (d, 1H, *J* = 2.9 Hz, thiophene CH), 6.98 (d, 1H, *J* = 2.9 Hz, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 150.3 (C=O), 133.6 (C-4a), 125.9 (C-7a), 125.2 (C-7), 106.1 (C-5). *Anal.* Calcd for $C_5H_4N_2O_3S_2$: C, 29.41; H, 1.96; N, 13.72; S, 31.43. Found: C, 29.30; H, 2.05; N, 13.57; S, 31.20.

1,1,3-Trioxo-2*H*,4*H*-thieno[2,3-*e*][1,2,4]thiadiazine (5b) Compound (**3b**) was refluxed for 3 h to give **5b** as a white solid (90%) of mp 233-235°C (from acetonitrile). IR (KBr) ν_{max} (cm^{-1}) 3250 (NH); 1700 (C=O); 1295, 1130 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.87 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 7.17 (AB, 2H, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 150.0 (C=O), 143.9 (C-4a), 118.9, 118.2 (C-6, C-7), 116.6 (C-7a). *Anal.* Calcd for $C_5H_4N_2O_3S_2$: C, 29.41; H, 1.96; N, 13.72; S, 31.40. Found: C, 29.70; H, 2.01;N, 14.00; S, 31.65.

6-Methyl-1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*][1,2,4]thiadiazine (5c) Compound (**3c**) was refluxed for 6 h to give **5c** as a yellow solid (90%) of mp 260-263°C (from ethanol-water). IR (KBr) ν_{max} (cm^{-1}) 3320 (NH); 1690 (C=O); 1320, 1120 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 10.80 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 7.65 (s, 1H, pyrazole CH), 3.90 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ 150.4 (C=O), 134.3 (C-7a), 121.7 (C-4a), 117.9 (C-5), 39.9 (CH_3). *Anal.* Calcd for $C_5H_6N_4O_3S$: C, 29.70; H, 2.97; N, 27.72; S, 15.84. Found: C, 29.82; H, 3.10; N, 27.80; S, 15.65.

Nitro-1,1,3-trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazines (6). General Procedure: To a suspension of the thiadiazine (**5**) (0.02 mol) in sulfuric acid 96% (12.5 mL) was added dropwise a mixture of nitric acid 40%:sulfuric acid 96% (1:1.1 v/v, 3.75 mL) at a temperature of 0-5°C. The reaction mixture was stirred for 2 h at this temperature and then was poured over ice-water. The precipitate was filtered and recrystallized from the appropriate solvent.

5-Nitro-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (6a) White solid (90%) of mp >220°C (decomp) (from ethanol). IR (KBr) ν_{max} (cm^{-1}) 3210 (NH); 1710 (C=O); 1590, 1340 (NO_2); 1170 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 10.42 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 8.72 (s, 1H, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 150.4 (C=O), 135.3 (C-4a), 131.7 (C-7), 129.3 (C-5), 126.2 (C-7a). *Anal.* Calcd for $C_5H_3N_3O_5S_2$: C, 24.09; H, 1.21; N, 16.86; S, 25,73. Found: C, 24.00; H, 1.12; N, 16.86; S, 25.96.

6-Methyl-5-nitro-1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*]thiadiazine (6c) White solid (41%) of mp 202-204°C (from ethyl acetate-hexane). IR (KBr) ν_{max} (cm^{-1}) 3345 (NH); 1705 (C=O); 1535, 1320 (NO_2); 1337, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 11.29 (s, exchanged with deuterium by D_2O addition, NH), 4.22 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ 151.3 (C=O), 132.8, 132.3 (C-7a, C-5), 121.0 (C-4a), 42.3 (CH_3). *Anal.* Calcd for $C_5H_5N_5O_5S$: C, 24.29; H, 2.04; N, 28.33; S, 12.97. Found: C, 24.50; H, 1.83; N, 28.10; S, 12.68.

Bromo and chloro-1,1,3-trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazine (7-8). General Procedure: To a solution of **5** (1.0 g, 5 mmol) in THF, DMF or 1,4-dioxane (40 mL) was added *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) (5 mmol). The reaction mixture was refluxed for 3-20 h. The

solvent was evaporated to dryness and the residue was treated with water. The solid was filtered, dried and recrystallized from the appropriate solvent.

5-Bromo-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (7a) Compound (**5a**) and NBS were refluxed in THF for 3 h to give **7a** as a brown solid (80%) of mp 273-275°C (decomp) (from acetonitrile). IR (KBr) ν_{max} (cm^{-1}) 3270 (NH); 1685 (C=O); 1330, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.06 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 8.52 (s, 1H, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 150.5 (C=O), 132.7 (C-4a), 126.9 (C-7a), 125.6 (C-7), 91.9 (C-5). *Anal.* Calcd for $C_5H_3N_2O_3BrS_2$: C, 21.21; H, 1.07; N, 9.90; S, 22.65. Found: C, 21.31; H, 1.04; N, 10.02; S, 22.79.

6-Bromo-1,1,3-trioxo-2*H*,4*H*-thieno[2,3-*e*][1,2,4]thiadiazine (7b) Compound (**5b**) and NBS were refluxed in THF for 20 h to give **7b**, as a yellow solid (67%) of mp >300°C (decomp). IR (KBr) ν_{max} (cm^{-1}) 3450 (NH); 1615 (C=O); 1360, 1145 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 10.08 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 7.03 (s, 1H, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 152.0 (C=O), 145.6 (C-4a), 122.8 (C-7), 116.8 (C-7a), 98.4 (C-6). *Anal.* Calcd for $C_5H_3N_2O_3BrS_2$: C, 21.21; H, 1.07; N, 9.90; S, 22.65. Found: C, 21.46; H, 0.86; N, 10.03; S, 22.91.

5-Bromo-6-methyl-1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*][1,2,4]thiadiazine (7c) Compound (**5c**) and NBS were stirred in DMF at 80°C for 7 h to give **7c** as a yellow solid (64%) of mp >240 (decomp) (from acetonitrile). IR (KBr) ν_{max} (cm^{-1}) 3275 (NH); 1710 (C=O); 1330, 1140 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.29 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 3.91 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ 150.9 (C=O), 134.8 (C-7a), 121.7 (C-4a), 100.0 (C-5), 38.8 (CH_3). *Anal.* Calcd for $C_5H_5N_4O_3BrS$: C, 21.36; H, 1.79; N, 19.93; S, 11.41. Found: C, 21.52; H, 1.82; N, 20.01; S, 11.71.

5-Chloro-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (8a) Compound (**5a**) and NCS were refluxed in THF for 4 h to give **8a** as a white solid (90%) of mp 187-189°C (from ethanol-water). IR (KBr) ν_{max} (cm^{-1}) 3275 (NH); 1685 (C=O); 1325, 1160 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.25 (s, 2H, exchanged with deuterium by D_2O addition, NH), 8.37 (s, 1H, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 150.6 (C=O), 130.6 (C-4a), 126.4 (C-7a), 122.6 (C-7), 107.9 (C-5). *Anal.* Calcd for $C_5H_3ClN_2O_3S_2$: C, 25.16; H, 1.27; N, 11.74; S, 26.87. Found: C, 25.40; H, 1.24; N, 11.57; S, 26.58.

6-Chloro-1,1,3-trioxo-2*H*,4*H*-thieno[2,3-*e*][1,2,4]thiadiazine (8b) Compound (**5b**) and NCS were refluxed in 1,4-dioxane for 20 h to give **8b** as a white solid (62%) of mp 284-286°C (from acetone). IR (KBr) ν_{max} (cm^{-1}) 3270 (NH); 1700 (C=O); 1318, 1140 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.90 (s, 1H, exchanged with deuterium by D_2O addition, NH), 7.43 (s, 1H, thiophene CH). ^{13}C-NMR (DMSO-d_6) δ 150.0 (C=O), 141.6 (C-4a), 120.7 (C-6), 118.7 (C-7), 115.6 (C-7a). *Anal.* Calcd for $C_5H_3N_2O_3ClS_2$: C, 25.16; H, 1.27; N, 11.74; S, 26.87. Found: C, 25.30; H, 1.19; N, 11.60; S, 26.63.

5-Chloro-6-methyl-1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*][1,2,4]thiadiazine (8c) Compound (**5c**) and NCS were stirred in DMF at 80°C for 7 h to give **8c** as a white solid (65%) of mp >240°C (decomp) (from acetonitrile). IR (KBr) ν_{max} (cm^{-1}) 3275 (NH); 1710, 1675 (C=O); 1330, 1150 (SO_2). ^{1}H-NMR (DMSO-d_6) δ 11.41 (br s, 1H, exchanged with deuterium by D_2O addition, NH), 3.89 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ 150.8 (C=O), 134.3 (C-7a), 118.7, 112.7 (C-4a, C-5), 37.7 (CH_3). *Anal.* Calcd for $C_5H_5N_4O_3ClS$: C, 25.37; H, 2.13; N, 23.68; S, 13.55. Found: C, 25.52; H, 2.10; N, 23.57; S, 14.94.

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