A New Method for the Synthesis of 4*H*-1,3,4-Thiadiazino[5,6-*b*]quinoxalines

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The reaction of 6-chloro-2-[1-methyl-2-(*N*-methylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **5** with acetic anhydride or trifluoroacetic anhydride resulted in dehydrative cyclization to give 2-(*N*-acetyl)-methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **6** or 8-chloro-2-(*N*-trifluoro-acetyl)methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **9**, respectively. The oxidation of compound **6** or **9** with 2-fold molar amount of *m*-chloroperbenzoic acid afforded the 4*H*-1,3,4-thiadiazino-[5,6-*b*]quinoxaline 1,1-dioxide **8** or **13**, respectively. The acetyl group of compound **6** was hardly hydrolyzed, but the trifluoroacetyl group of compound **9** was easily hydrolyzed to change into 8-chloro-4-methyl-2-methylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **10**. The acylation of compound **10** with acetic anhydride, trifluoroacetic anhydride, phenyl isocyanate, and chloroacetyl chloride furnished the 2-(*N*-acetyl)methylamino **6**, 2-(*N*-trifluoroacetyl)methylamino **9**, 2-(1-methyl-3-phenylureido) **11**, and 2-(*N*-chloroacetyl)methylamino **12** derivatives, respectively.

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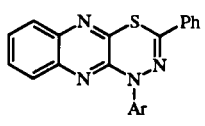
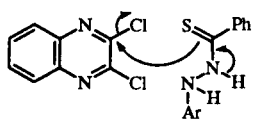
Some of 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **1** have been synthesized by the reaction of 2,3-dichloro-quinoxaline **2** with thioacylhydrazines [1,2] (Chart 1) *via* the Smiles rearrangement [3]. The synthesis of the condensed 4*H*-1,3,4-thiadiazines **3** *via* 1,4-disubstituted thiosemicarbazides **4** [4,5] is essentially same as the above. These methods for the synthesis of the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **1** and condensed 4*H*-1,3,4-thiadiazines **3** are classified into the cyclization method I shown in Chart 2. However, there have been few reports on the synthesis of the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **1** by the cyclization method II *via* an acylated quinoxaline *N*-oxides. Accordingly, we undertook the synthesis of 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines from the quinoxaline *N*-oxide **5** (Scheme 1), wherein the α-carbon of quinoxaline *N*-oxides easily undergoes the nucleophilic attack after the acylation of the *N*-oxide moiety [6] (Chart 2). This paper describes a new method for the synthesis of novel 4*H*-1,3,4-thiadiazino[5,6-*b*]-quinoxalines **6-13** from the 2-(thiocarbamoylhydrazino)-quinoxaline 4-oxide **5** (Scheme 1).

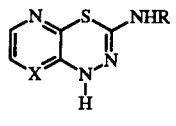
Chart 1



1

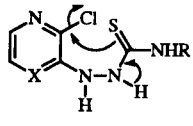


2



3

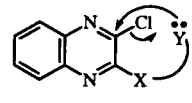
X = N, CH



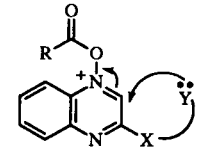
4

X = N, CH

Chart 2



Cyclization Method I

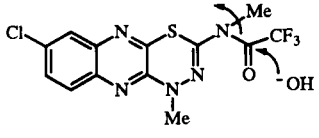


Cyclization Method II

The reaction of compound **5** [7] with acetic anhydride gave 2-(*N*-acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **6** (61%), whose yield was improved by the reaction in acetic anhydride/acetic acid (81%). The oxidation of compound **6** with an equimolar or 2-fold molar amount of *m*-chloroperbenzoic acid afforded 2-(*N*-acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1-oxide **7** or

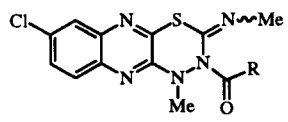
1,1-dioxide **8** [8], respectively. Further oxidation of the 1-oxide **7** with an equimolar amount of *m*-chloroperbenzoic acid provided the 1,1-dioxide **8.** Since an attempt for the deacetylation of compounds **6-8** was unsuccessful under several acidic or alkaline conditions, a different method was devised to obtain the deacetylated 2-methylamino compound **10** so as to produce some novel derivatives. The direct cyclization of compound **5** to the 2-methylamino derivative **10** with phosphoryl chloride was not convenient because of low yield, and hence trifluoroacetic anhydride was employed as an annelation agent in consideration of a facile hydrolytic elimination of the trifluoroacetyl group which would be formed in the side chain (Chart 3).

Chart 3

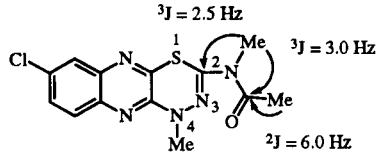


The reaction of compound **5** with trifluoroacetic anhydride under reflux in dioxane furnished 8-chloro-2-(*N*-trifluoroacetyl)methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **9**, whose trifluoroacetyl group was easily hydrolyzed with triethylamine/water to furnish 8-chloro-4-methyl-2-methylamino-4*H*-1,3,4-thiadiazino-[5,6-*b*]quinoxaline **10**. The reaction of compound **10** with

Chart 4



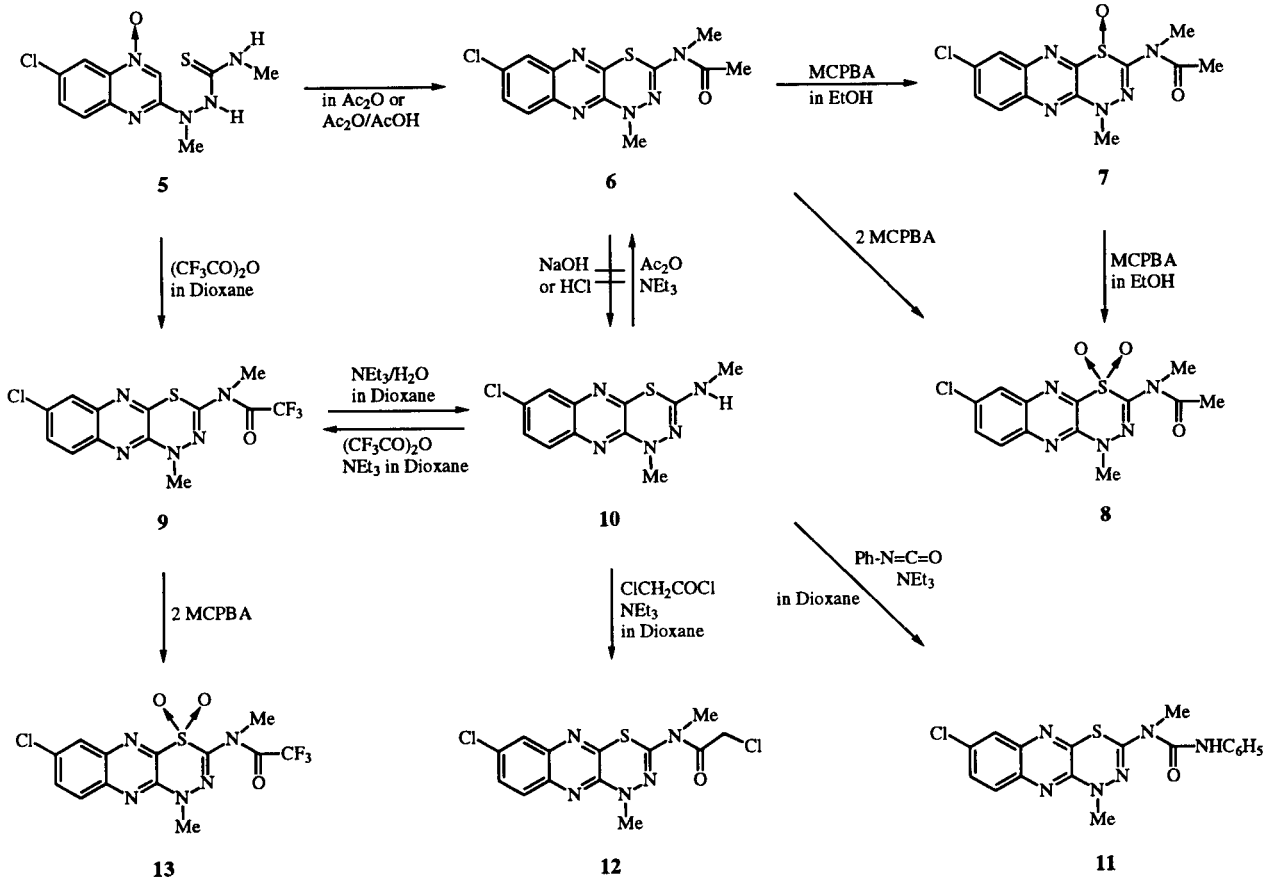
A



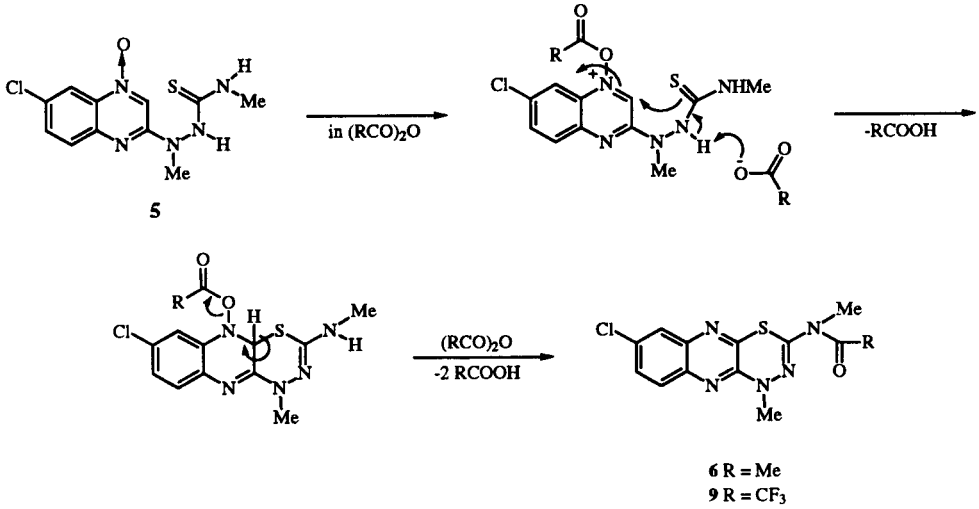
6

Carbon	δ in CF_3COOD
C_2	146.7
C_2-NMe	35.3
C=O	177.9

Scheme 1



Scheme 2



6 R = Me
9 R = CF_3

acetic anhydride, trifluoroacetic anhydride, phenyl isocyanate, or chloroacetyl chloride gave compound **6**, compound **9**, 8-chloro-4-methyl-2-(1-methyl-3-phenylureido)-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **11**, or 8-chloro-2-(*N*-chloroacetyl)methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **12**, respectively. The oxidation of compound **9** with a 2-fold molar amount of *m*-chloroperbenzoic acid provided 8-chloro-2-(*N*-trifluoroacetyl)-methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]-quinoxaline 1,1-dioxide **13**. The mechanism for the acylative cyclization of compound **5** to compounds **6** and **9** is shown in Scheme 2.

The structural assignment of novel compounds **6-13** was based on the analytical and spectral data. In the nmr spectra of compound **6**, the ^3J coupling between the C_2-NCH_3 protons and acetyl C=O carbon excluded the 3-acetyl-2-methylimino structure A (Chart 4). Moreover, compound **7** was found to be composed of α- and β-oxides from the nmr spectral data. The ratio of the major to minor isomer was 78 *versus* 22.

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

2-(*N*-Acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **6**.

Method A.

A solution of compound **5** (5 g) in acetic anhydride (150 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol/water to provide yellow needles (3.3 g, 61%). Recrystallization from ethanol gave yellow needles **6**, mp 186-187°; ir: ν cm^{-1} 1680, 1590, 1520; ms: m/z 321 (M^+), 323 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 7.69 (d, J = 2.0 Hz, 1H, C_9-H), 7.57 (d, J = 8.5 Hz, 1H, C_6-H), 7.52 (dd, J = 2.0, 8.5 Hz, 1 H, C_7-H), 3.36 (s, 3H, N_4-CH_3), 3.21 (s, 3H, C_2-NCH_3), 2.21 (s, 3H, C_2-$NCOCH_3$).

Anal. Calcd. for $C_{13}H_{12}ClN_5OS$: C, 48.52; H, 3.76; Cl, 11.02; N, 21.77; S, 9.96. Found: C, 48.50; H, 3.77; Cl, 11.16; N, 21.72; S, 9.68.

Method B.

A solution of compound **5** (10 g) in acetic anhydride (150 ml)/acetic acid (150 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol/water to provide yellow needles **6** (8.73 g, 81%). Recrystallization from ethanol gave yellow needles.

2-(*N*-Acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1-Oxide **7**.

A solution of compound **6** (5 g, 15.6 mmoles) and *m*-chloroperbenzoic acid (50% purity) (5.90 g, 1.1 equivalent) in ethanol (250 ml) was refluxed on a boiling water bath for 4 hours. The solution was allowed to stand overnight to precipitate yellow scales of **7**, which were collected by suction filtration and washed with ethanol to give an analytically pure sample (2.09 g, 40%), mp 199-200°; ir: ν cm^{-1} 3040, 2930, 1650, 1590, 1520; ms: m/z 337 (M^+), 339 (M^+ + 2); pmr (deuteriotrifluoroacetic acid): [major *S*-oxide (78%)] 8.20 (d, J = 1.5 Hz, 0.78H, C_9-H), 7.91 (d, J = 9.0 Hz, 0.78H, C_6-H), 7.74 (dd, J = 1.5, 9.0 Hz, 0.78H, C_7-H), 3.96 (s, 2.34H, N_4-CH_3), 3.37 (s, 2.34H, C_2-NCH_3), 2.31 (s, 2.34H, C_2-$NCOCH_3$); [minor *S*-oxide (22%)] 8.50 (d, J = 1.5 Hz, 0.22H, C_9-H), 8.40 (d, J = 9.5 Hz, 0.22H, C_6-H), 4.24 (s, 0.66H, N_4-CH_3), 3.67 (s, 0.66H, C_2-NCH_3), 2.42 (s, 0.66H, C_2-$NCOCH_3$). The C_7-H proton signal of the minor *S*-oxide was overlapped with other signals.

Anal. Calcd. for $C_{13}H_{12}ClN_5O_2S$: C, 46.22; H, 3.58; Cl, 10.49; N, 20.73; S, 9.49. Found: C, 46.19; H, 3.68; Cl, 10.28; N, 20.56; S, 9.35.

2-(*N*-Acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1,1-Dioxide **8**.

From compound **6**.

A solution of compound **6** (10 g, 31.1 mmoles) and *m*-chloroperbenzoic acid (purity, 50%) (26.83 g, 2.5 equivalents) in ethanol (500 ml) was refluxed on a boiling water bath for 4 hours to precipitate yellow needles of **8**. After the reaction mixture was cooled to room temperature, the yellow needles **8** were collected by suction filtration and washed with ethanol to give an analytically pure sample (6.31 g, 57%), mp 258-259°; ir: ν cm^{-1} 1680, 1590, 1520; ms: m/z 353 (M^+), 355 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 8.45 (d, J = 2.0 Hz, 1H, C_9-H), 8.16 (d, J = 9.0 Hz, 1H, C_6-H), 8.09 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 3.94 (s, 3H, N_4-CH_3), 3.26 (s, 3H, C_2-NCH_3), 2.16 (s, 3H, C_2-$NCOCH_3$).

Anal. Calcd. for $C_{13}H_{12}ClN_5O_3S$: C, 44.13; H, 3.42; Cl, 10.03; N, 19.80; S, 9.07. Found: C, 44.11; H, 3.49; Cl, 9.91; N, 19.90; S, 8.88.

From the 1-Oxide **7**.

A solution of the 1-oxide **7** (1 g, 2.96 mmoles) and *m*-chloroperbenzoic acid (purity, 50%) (1.53 g, 1.5 equivalents) in ethanol (50 ml) was refluxed on a boiling water bath for 1 hour to precipitate yellow needles of **8**, which were collected by suction filtration and washed with ethanol to give an analytically pure sample (0.74 g, 71%).

8-Chloro-2-(*N*-trifluoroacetyl)methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **9**.

A solution of compound **5** (10 g, 33.6 mmoles) in trifluoroacetic anhydride (20 ml)/dioxane (400 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol/water to provide yellow needles of **9** (11.10 g, 88%). Recrystallization from dioxane/ethanol gave yellow needles, mp 151-152°; ir: ν cm^{-1} 1710, 1660, 1685, 1520; ms: m/z 375 (M^+), 377 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 7.72 (dd, J = 2.0, 0.5 Hz, 1H, C_9-H), 7.61 (dd, J = 0.5, 9.0 Hz, 1H, C_6-H), 7.57 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 3.37 (s, 3H, N_4-CH_3), 3.25 (s, 3H, C_2-NCH_3).

Anal. Calcd. for $C_{13}H_9ClF_3N_5OS$: C, 41.55; H, 2.41; N, 18.64; S, 8.53. Found: C, 41.57; H, 2.51; N, 18.57; S, 8.61.

8-Chloro-4-methyl-2-methylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]-quinoxaline **10**.

A solution of compound **9** (10 g) in triethylamine (5 ml)/water (50 ml)/dioxane (150 ml) was refluxed in an oil bath for 30 minutes. Evaporation of the solvent *in vacuo* gave orange needles of **10**, which were triturated with ethanol/water and then collected by suction filtration (7.19 g, 87%). Recrystallization from ethanol/water afforded orange needles, mp 147-148°; ir: ν cm^{-1} 3240, 1620, 1590, 1520; ms: m/z 279 (M^+), 281 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 7.65 (dd, J = 2.0, 1.0 Hz, 1H, C_9-H), 7.52 (dd, J = 9.0, 1.0 Hz, 1H, C_6-H), 7.48 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 6.92 (q, J = 4.5 Hz, 1H, C_2-NH),3.31 (s, 3H, N_4-CH_3), 2.72 (d, J = 4.5 Hz, 3H, C_2-NCH_3).

Anal. Calcd. for $C_{11}H_{10}ClN_5S$: C, 47.23; H, 3.60; Cl, 12.67; N, 25.04; S, 11.46. Found: C, 47.07; H, 3.59; Cl, 12.56; N, 24.77; S, 11.21.

8-Chloro-4-methyl-2-(1-methyl-3-phenylureido)-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **11**.

A solution of compound **10** (5 g, 17.9 mmoles) and phenyl isocyanate (3.19 g, 26.8 mmoles) in triethylamine (1 ml)/dioxane (50 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent *in vacuo* afforded an oily residue, which was crystallized from ethanol/water to provide yellow crystals of **11** (4.60 g, 65%). Recrystallization from dioxane/ethanol/water gave yellow needles of **11**, mp 183-184°; ir: ν cm^{-1} 1690, 1600, 1590, 1545, 1515; ms: m/z 398 (M^+), 340 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 9.30 (s, 1H, NH), 7.63 (dd, J = 2.5, 1.0 Hz, 1H, C_9-H), 7.53 (dd, J = 1.0, 8.5 Hz, 1H, C_6-H), 7.48 (dd, J = 8.5, 2.5 Hz, 1H, C_7-H), 7.47 (m, J = 7.5, 7.5, 1.0, 1.0 Hz, 2H, o-H), 7.30 (m, J = 7.5, 7.5, 1.0, 1.0 Hz, 2H, m-H), 7.05 (m, J = 7.5, 7.5, 1.0, 1.0 Hz, 1H, p-H), 3.36 (s, 3H, N_4-CH_3), 3.31 (s, 3H, C_2-NCH_3).

Anal. Calcd. for $C_{18}H_{15}ClN_6OS$: C, 54.20; H, 3.79; Cl, 8.89; N, 21.07; S, 8.04. Found: C, 54.20; H, 3.83; Cl, 8.90; N, 21.09; S, 8.01.

8-Chloro-2-(*N*-chloroacetyl)methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **12**.

A solution of compound **10** (1 g), chloroacetyl chloride (0.5 ml), and triethylamine (1 ml) in dioxane (30 ml) was refluxed in an oil bath for 30 minutes. Evaporation of the solvent *in vacuo* gave brown crystals of **12**, which were triturated with ethanol/water and then collected by suction filtration (970 mg, 76%). Recrystallization from dioxane/ethanol/water afforded yellow needles, mp 168-169°; ir: ν cm^{-1} 1710, 1685, 1600; ms: m/z 355 (M^+), 357 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 7.66 (d, J = 2.0 Hz, 1H, C_9-H), 7.55 (d, J = 9.0 Hz, 1H, C_6-H), 7.51 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 4.67 (s, 2H, CH_2), 3.34 (s, 3H, N_4-CH_3), 3.20 (s, 3H, C_2-NCH_3).

Anal. Calcd. for $C_{13}H_{11}C_{12}N_5OS$: C, 43.88; H, 3.11; Cl, 19.91; N, 19.66; S, 9.00. Found: C, 43.54; H, 3.24; Cl, 19.82; N, 19.63; S, 8.89.

8-Chloro-2-(*N*-trifluoroacetyl)methylamino-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1,1-Dioxide **13**.

A solution of compound **9** (10 g, 26.5 mmoles) and *m*-chloroperbenzoic acid (purity, 50%) (22.9 g, 2.5 equivalents) in ethanol (250 ml) was refluxed on a boiling water bath for 3 hours. The hot solution was immediately filtered to precipitate orange needles of **13**, which were collected by suction filtration and washed with ethanol to provide an analytically pure sample (6.35 g, 59%), mp 206-207°; ir: ν cm^{-1} 1690, 1680, 1650, 1510; ms: m/z 407 (M^+), 409 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 8.51 (dd, J = 2.0, 0.8 Hz, 1H, C_9-H), 8.20 (dd, J = 0.8, 9.0 Hz, 1H, C_6-H), 8.14 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 3.94 (s, 3H, N_4-CH_3), 3.49 (s, 3H, C_2-NCH_3).

Anal. Calcd. for $C_{13}H_9ClF_3N_5O_3S$: C, 38.29; H, 2.22; N, 17.18; S, 7.86. Found: C, 38.47; H, 2.32; N, 17.33; S, 8.10.

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