# 1,2,4-THIADIAZINO[3,4-*b*]BENZOTHIAZOLE: A NEW CYCLIC SULPHENIMINE

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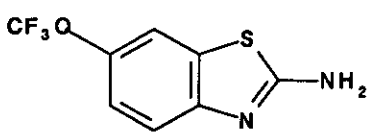
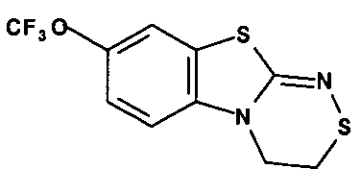
**Abstract-** 3,4-Dihydro-8-trifluoromethoxy-1,2,4-thiadiazino[3,4-*b*]benzothiazole (**2**) was prepared in five steps from 6-trifluoromethoxy-2-benzothiazolamine (riluzole, **1**). The key final step consisted of an original N-S bond forming reaction between unsubstituted imine and thiol groups, using chloramine-T as reagent (75% yield).

The therapeutically useful activities of riluzole (**1**) (Scheme 1), an indirectly-acting excitatory amino acid antagonist,[1] as well as the need for new pharmaceutical tools to elucidate its mechanisms of action, prompted us to synthesize analogs of this lead compound.[2] As part of this work, we describe herein an efficient and simple synthesis of 3,4-dihydro-8-trifluoromethoxy-1,2,4-thiadiazino[3,4-*b*]benzothiazole (**2**) (Scheme 1),[3] and a new convenient synthetic approach for the preparation of the cyclic sulphenimine moiety.




**1 riluzole**



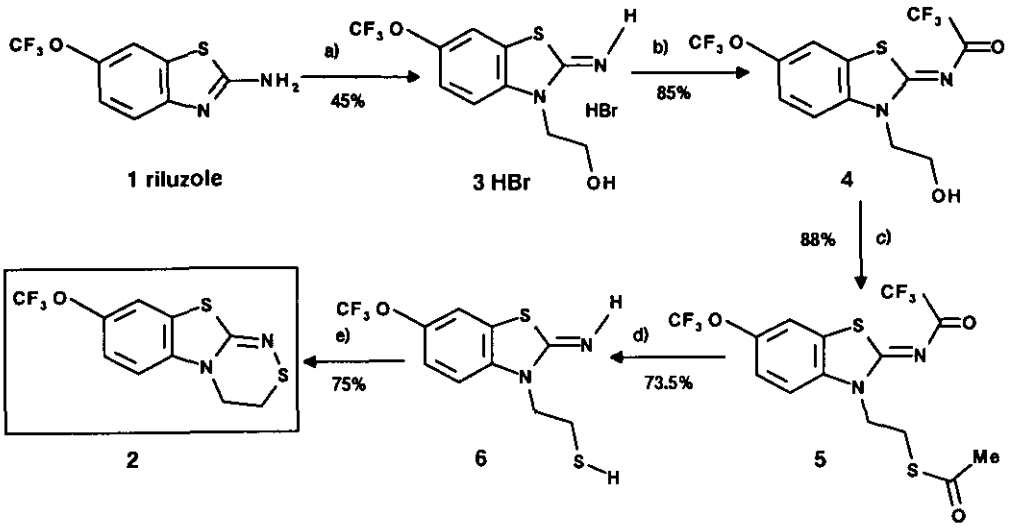

**2**

**Scheme 1**

Compound (2) was synthesized in a straightforward fashion from riluzole[4] as shown in Scheme 2. 3-(2-Hydroxyethyl)-2-trifluoroacetylimino-6-trifluoromethoxybenzothiazoline (4) was first prepared by reaction of 2-bromoethanol with riluzole in refluxing ethanol followed by trifluoroacetylation of the imino group using ethyl trifluoroacetate. The position of the alkyl chain on the 2-aminothiazole nucleus was confirmed by $^1$H-nmr, where a positive n.O.e. interaction between the N-C$\underline{H}_2$ group and the hydrogen in position 4 of the benzothiazoline moiety was observed (qualitative 1D n.O.e. difference experiment); this positive n.O.e. interaction would not be observed with the hydroxyethyl chain in position 2. Compound (4) was then treated with thiolacetic acid at room temperature under Mitsunobu reaction conditions to give the acetylthiobenzothiazoline (5) in 88% yield. Simultaneous *N*-trifluoroacetyl and *S*-acetyl group hydrolyses were achieved by treatment with a methanolic solution of potassium carbonate under mild conditions (room temperature, 72 h) to afford the thiol derivative (6) with 73.5% yield. This compound was easily converted to the expected heterocycle (2) by reaction with chloramine-T trihydrate[5] at room temperature in methanol (75% yield).[6] To the best of our knowledge, such a direct cyclization reaction between imino and thiol groups to give the sulphenimine skeleton has never been described in the literature.[7]

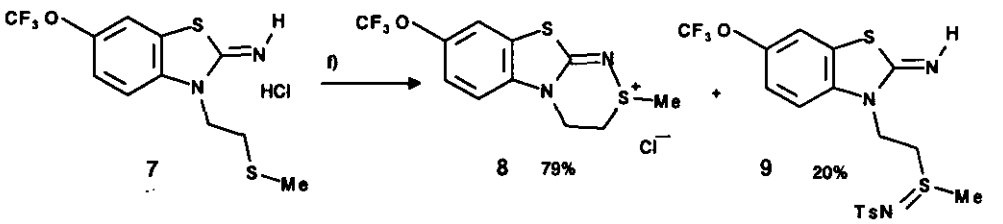
The main pathways reported for the general preparation of sulphenimines[7] are: a) condensation reactions such as, *N*-chloro imines or *O*-acyl oximes with thiols, sulphenyl chlorides or aryl disulphides with imines, sulphoxides with $\alpha$-halogeno isocyanates, *N*-unsubstituted sulphenamides or disulphides with aldehydes or ketones, b) Pummerer reactions of unsubstituted sulphenamides or c) oxidation reactions of sulphenamides. Consequently, the new procedure described above provide an easy and convenient method for the preparation of sulphenimines using chloramine-T as activating reagent, and thus avoiding the preparation of sulphenyl halides or *N*-chloro imines.

Further extension of this reaction was performed with 3-(2-methylthioethyl)-6-trifluoromethoxy-benzothiazoline (7)[8] following the same procedure: addition of chloramine-T to the benzothiazoline (7) (methanol, 50°C, 30 min) gave mainly the stable cyclic sulpheniminium (8) in 79% yield (Scheme 3). In addition, the previously expected sulphimide (9) was isolated in 20% yield. The position of the methyl group in compound (8) was confirmed by the presence of positive n.O.e. interactions between the S-C$\underline{H}_3$ and SC$\underline{H}_2$CH$_2$N or SCH$_2$-C$\underline{H}_2$N groups (qualitative 1D n.O.e. difference experiment).




**Scheme 2**

a) $BrCH_2CH_2OH$, EtOH, 80°C, 95 h b) $CF_3CO_2Et$, EtOH, room temperature, 16 h then 40°C, 4 h c) AcSH, $P(C_6H_5)_3$, DEAD, THF, room temperature, 15 h d) $Na_2CO_3$, MeOH, room temperature, 72 h e) Chloramine-T trihydrate, MeOH, room temperature, 2 h




f) Chloramine-T trihydrate, MeOH, 50°C, 30 min

**Scheme 3**

Concerning the pharmacological properties, the sulphenimine (2) displayed an unexpectedly high level of in vivo antiglutamate activity, close to the activity observed for riluzole.[9]

In conclusion, the above reported synthesis represents a convenient preparation of the unknown 1,2,4-thiadiazino[3,4-*b*]benzothiazole ring system under mild laboratory conditions. Furthermore, we describe a direct and efficient synthesis of the sulphenimine moiety from the corresponding unsubstituted imine and thiol using chloramine-T as activating agent; this procedure should allow the synthesis of a variety of (cyclic) sulphenimines.

## ACKNOWLEDGMENT

We were indebted to Mrs C. Do Huu and Mr P. Ganil for technical assistance and Mr M. Vuilhorgne and coworkers for structural determination.

## EXPERIMENTAL

Commercially available reagents were used as received from suppliers. The progress of the reactions was monitored by tlc. on silica gel plates (Merck Kieselgel $60F_{254}$). Melting points were determined using a Reichler-Kofler apparatus and are uncorrected. $^{1}$H-Nmr spectra and $^{13}$C-nmr spectra were recorded on WP 200, WM 250 and WP 300 Brucker spectrometers. Ir spectra were recorded on a 983G Perking-Elmer spectrophotometer. Ms were obtained on a Finnigan quadrupolar 3300 apparatus (electron impact: EI; 70 ev), on a Nermag R10-10B (desorption chemical ionization: DCI, reactant gas: $NH_3$) or on a Kratos MS50 (fast atom bombardment: FAB). The combustion analyses were performed at Centre de Recherche de Vitry-Alfortville (Rhône-Poulenc Rorer). Flash chromatographies were performed on silica gel (Merck Kieselgel, 230 mesh).

### 3-(2-Hydroxyethyl)-6-trifluoromethoxy-2-benzothiazoline hydrobromide (3).

To a magnetically stirred solution of riluzole (9.4 g, 40 mmol) in ethanol (30 ml) at room temperature was added 2-bromoethanol (10 g, 80 mmol). The reaction mixture was heated under reflux for 95 h, then cooled to room temperature. The white solid thus formed was filtered, washed with ether (100 ml), to afford pure (3) as white needles; 6.4 g (45%): mp 219°C; $^{1}$H-nmr (DMSO-$d_6$, 250 MHz) δ 3.79 (t, J=5 Hz,

2H, $CH_2O$-), 4.43 (t, J=5 Hz, 2H, $NCH_2$), 7.6 (br d, 1H, 5-ArH), 7.86 (d, J=9 Hz, 1H, 4-ArH), 8.22 (br s, 1H, 7-ArH), 9.7-11.0 (m, 2H, =NH.HBr); ms(EI), m/z (relative intensity) 278 (M+), 234 (100), 220 (30), 165 (60); ir (KBr) 3400-2700, 1640, 1570, 1485, 1280-1125, 1080-1050 $cm^{-1}$. Anal. Calcd for $C_{10}H_9N_2O_2F_3S$. HBr: C, 33.44; H, 2.81; N, 7.80; Br, 22.25; F, 15.87; S, 8.93. Found: C, 33.21; H, 2.82; N, 8.04; Br, 22.23; F, 15.92; S, 9.17.

**3-(2-Hydroxyethyl)-2-trifluoroacetylimino-6-trifluoromethoxy-2-benzothiazoline (4).**

To a stirred suspension of the hydrobromide of **(3)** (36.0 g, 0.1 mol) in ethanol (200 ml) was added at room temperature triethylamine (22.0 g, 0.22 mol) followed by ethyl trifluoroacetate (17.0g, 0.12 mol), and the mixture stirred for 4 h. The solvent was then evaporated under reduced pressure to afford 37.4 g of a white solid. This crude product was recrystallized in hot water/ethanol (1/1 mixture) to yield **(4)** as white needles; 32 g (85%, Rf = 0.4 in ethyl acetate/cyclohexane 1/1 mixture): mp 141°C; $^1$H-nmr (DMSO-$d_6$, 200 MHz) δ 3.85 (br q, J=5 Hz, 2H, -$CH_2O$-), 4.60 (br t, J=5 Hz, 2H, $NCH_2$-), 5.00 (br t, 1H, -OH), 7.66 (br d, J=8.5 Hz, 1H, 5-ArH), 8.03 (d, J=8.5 Hz, 1H, 4-ArH), 8.25 (br s, 1H, 7-ArH); ms(EI), m/z (relative intensity) 374 (M+, 10), 330 (20), 305 (20), 261 (60), 69 (55), 45 (100); ir (KBr) 3395, 3100, 3075, 2950, 2890, 1660, 1630, 1500, 1485, 1285-1135 $cm^{-1}$.

**3-(2-Acetylthioethyl)-2-trifluoroacetylimino-6-trifluoromethoxy-2-benzothiazoline (5).**

To a solution of triphenylphosphine (21.0 g, 80 mmol) in tetrahydrofuran (150 ml) at 5°C under nitrogen was added dropwise a solution of diethyl azodicarboxylate (12.8 ml, 80 mmol) in tetrahydrofuran (100 ml). The reaction mixture was stirred for 1 h at this temperature. Then, a solution of **(4)** (14.2 g, 40 mmol) and thiolacetic acid (5.6 ml, 80 mmol) in tetrahydrofuran (250 ml) was added dropwise over a period of 30 min at 0°C. The solution was then warmed to room temperature and stirred for an additional 15 h. The reaction mixture was evaporated under reduced pressure to afford 58 g of a yellow solid. Flash chromatography on silica gel of this residue using an ethyl acetate/cyclohexane 95/5 mixture as eluent gave **5** as white needles; 15.3 g (88%, Rf = 0.3 in ethyl acetate/cyclohexane 95/5 mixture): mp 120°C; $^1$H-nmr ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H, -$SCOCH_3$), 3.26 (t, J=7.5 Hz, 2H, -$CH_2S$-), 4.60 (t, J=7.5 Hz, 2H, N-$CH_2$), 7.46 (br d, J=8.5 Hz, 1H, 5-ArH), 7.65 (br s, 1H, 7-ArH), 7.89 (d, J=8.5 Hz, 1H, 4-ArH); ms(EI), m/z (relative intensity) 432 (M+, 28); 389 (25); 330 (25); 261 (10); 103 (23); 69 (30); 43 (100); ir (KBr)

3100, 3075, 1680, 1635, 1505, 1485, 1280-1125 $cm^{-1}$. Anal. Calcd for $C_{14}H_{10}N_2O_3F_6S_2$: C, 38.90; H, 2.33; N, 6.48; F, 26.36; S, 14.83. Found: C, 38.67; H, 2.33; N, 6.51; F, 25.91; S, 14.64.

**2-Imino-3-(2-mercaptoethyl)-6-trifluoromethoxy-2-benzothiazoline (6).**

To a solution of compound **(5)** (15.1 g, 35 mmol) in methanol (550 ml) at room temperature under nitrogen, was added a 7% aq. $Na_2CO_3$ solution (75 ml). This solution was stirred overnight at room temperature. The solvent was then evaporated under reduced pressure, and the reaction mixture was triturated with water (500 ml) to give a white solid which was filtered and washed with water (2 x 100 ml). This crude product was purified by flash chromatography on silica gel using ethyl acetate as eluent to afford **(6)** as white needles after evaporation; 6.3 g (74%, Rf = 0.3 in ethyl acetate): mp 110°C; $^1$H-nmr (DMSO-$d_6$, 200 MHz) δ 3.04 (t, J=6.5 Hz, 2H, -$CH_2$S-), 4.17 (t, J=6.5 Hz, 2H, N-$CH_2$), 7.10 (d, J=8.5 Hz, 1H, 4-ArH), 7.20 (br d, J=8.5 Hz, 1H, 5-ArH), 7.58 (br s, 1H, 7-ArH); ms(EI), m/z (relative intensity) 294 (M+, 55); 261 (25); 234 (100); 165 (60); 69 (35); ir (KBr) 3350, 2940, 2480, 2440, 1610, 1585, 1485, 1440, 1280-1120 $cm^{-1}$.

**8-Trifluoromethoxy-3,4-dihydro[1,2,4]thiadiazino[3,4-*b*]benzothiazole oxalate (2).**

To a solution of chloramine-T trihydrate (1.2 g, 4 mmol) in methanol (15 ml) at room temperature was added portionwise compound **(6)** (1.2 g, 4 mmol), and the reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure, and the white solid thus obtained (2.4 g) was dissolved in water (50 ml). The aqueous solution was extracted with ether (2 x 30 ml), and the combined organic layers were washed with water (2 x 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford 1.2 g of a white foam. Flash chromatography on silica gel of this residue using an ethyl acetate/cyclohexane 3/2 mixture as eluent gave pure **(2)** as a colourless oil after evaporation; 0.9 g (75%, Rf = 0.2 in ethyl acetate) which was characterized as its oxalate salt: white needles: mp 178°C; $^1$H-nmr (DMSO-$d_6$, 200 MHz) δ 3.15 (br t, J=7 Hz, 2H, -$CH_2$S-), 4.35 (br t, J=7 Hz, 2H, N$CH_2$-), 5.30 (br s, $HO_2CCO_2H$ and DOH), 7.38 (br s, 2H, 4-ArH and 5-ArH), 7.80 (br s, 1H, 7-ArH); ms(EI), m/z (relative intensity).292 (M+, 50); 264 (25); 234 (100); 165 (55); 69 (25); ir (KBr) 3400-2250, 1725, 1650, 1625, 1570, 1485, 1280-1125 $cm^{-1}$; Anal. Calcd for $C_{10}H_7N_2OF_3S_2$. $C_2H_2O_4$. 0.9 $H_2O$: C,37.70; H, 2.37; N, 7.33; F, 14.91; S, 16.77. Found: C, 37.69; H, 2.39; N, 7.22; F, 15.27; S, 16.84.

**2-Methyl-8-trifluoromethoxy-3,4-dihydro[1,2,4]thiadiazino[3,4-*b*]benzothiazolium, chloride (8).**

To a solution of 2-imino-3-(2-methylthioethyl)-6-trifluoromethoxy-2-benzothiazoline hydrochloride **(7)** (1.7 g, 5.0 mmol) in methanol (10 ml) was added portionwise chloramine-T trihydrate (1.9 g, 5.5 mmol) at room temperature. The solution was stirred for 30 min at room temperature, then 30 min at 50°C. During the evolution of the reaction, compound **(9)** precipitated as white needles (0.5 g, 20% yield, Rf = 0.7 in ethyl acetate). Partial evaporation of the methanolic solution under reduced pressure afforded a white solid which was filtered and triturated with ethyl acetate (50 ml) to afford the heterocycle **(8)** as white needles; 1.3 g (79%, Rf = 0.16 in methanol/ethyl acetate 3/7 mixture): mp 145°C; $^1$H-nmr (DMSO-d$_6$, 250 MHz) δ 3.23 (s, 3H, -SCH$_3$), 3.98 (m, 2H, -CH$_2$S-), 4.52 and 4.87 (two m, 1H each, NCH$_2$-), 7.57 (br d, J=8.5 Hz, 1H, 5-ArH), 7.70 (d, J=8.5 Hz, 1H, 4-ArH), 8.10 (br s, 1H, 7-ArH); $^{13}$C-nmr (DMSO-d$_6$, 75 MHz) δ 168 (C-10a), 145 (C-8), 139 (C-5a), 124 (C-9a), 121 (C-6), 121 (OCF$_3$), 113 (C-7), 38 (C-4), 32 (SCH$_3$), 31.7 (C-3); ms(EI), m/z (relative intensity) 292 (100); 264 (50); 238 (50); 69 (25); ms(FAB), m/z 307 (M+); ir (KBr) 2980, 2910, 1540, 1485, 1280, 1120 cm$^{-1}$.

Compound (9): white needles, mp 200°C (decomp.); $^1$H-nmr (DMSO-d$_6$, 250 MHz) δ 2.37 (s, 3H, SCH$_3$), 2.78 (s, 3H, CH$_3$), 3.40 (m, 2H, CH$_2$S), 4.30 (m, 2H, NCH$_2$-), 7.30 (d, J = 8 Hz, 2H, 3'-ArH and 5'-ArH), 7.38 (br s, 2H, 4-ArH and 5-ArH), 7.64 (d, J = 8 Hz, 2H, 2'-ArH and 6'-ArH), 7.90 (m, 1H, 7-ArH); ms(EI), m/z (relative intensity) 259 (100); 234 (25); 91 (70); ms(FAB), m/z 478 (MH+).

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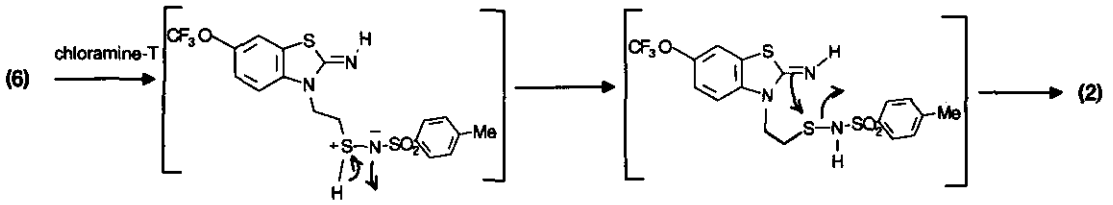
4. L. M. Yagupolskii and L. Z. Gandelsman, *J. Gen. Chem. USSR*, 1963, **33**, 2240 (*Chem. Abstr.*, 1991, **60**, 692a).

5. For a review, see: M.M. Campbell and J. Graham, *Chem. Rev.*, 1978, **78**, 65.

6. Synthesis of **2** from **6** could be explained following the chemical process represented in the scheme shown below:




The intramolecular reaction between the imino group and the *N*-tosyl sulphenamide could be deduced by analogy with the reaction of sulphenamides with amines (see reference 7, Chap. 10, pp. 490-492.)

7. For a review, see: S. Patai, "The Chemistry of Sulphenic Acids and their derivatives", Chap. 17, ed. John Wiley and Sons, 1990, pp. 723 - 741.

8. Compound **(7)** was prepared by condensation of 2-chloroethyl methyl sulphide with riluzole (butan-2-one, 110°C, 72 h, 54.5% yield): mp 208°C; $^1$H-nmr (DMSO-d$_6$, 200 MHz) δ 2.20 (s, 3H, -SCH$_3$), 2.90 (t, J=7 Hz, -SCH$_2$-), 4.60 (t, J=7 Hz, 2H, NCH$_2$-), 7.60 (br dd, J=8.5 and 2.5 Hz, 1H, 5-ArH), 7.82 (d, J=8.5 Hz, 1H, 4-ArH), 8.20 (br d, J=2.5 Hz, 1H, 7-ArH), 11.00 (br s, 2H, C=NH$_2$+); ms(EI), m/z (relative intensity) 308 (M+, 5); 234 (100); 165 (55); ir (KBr) 3350-2500, 1635, 1595, 1575, 1485, 1280-1125 cm-1. Anal. Cald for $C_{11}H_{11}N_2OF_3S_2$.HCl: C, 38.31; H, 3.50; N, 8.12; Cl, 10.28; F, 16.53; S, 18.59. Found: C, 38.09; H, 3.44; N, 7.95; Cl, 10.28; F, 16.38; S, 18.37.

9. In vivo antiglutamate activity of compound **(2)** was determined as described in reference 2b ($ED_{50}$ = 2.5 mg/kg i.p.).

Received, 21st June, 1993