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Versatile Methods for the Synthesis of 2-Amino-6-trifluoromethoxy-(nitro)benzothiazoles

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VERSATILE METHODS FOR THE SYNTHESIS OF 2-AMINO-6-TRIFLUOROMETHOXY-(NITRO)BENZOTHIAZOLES

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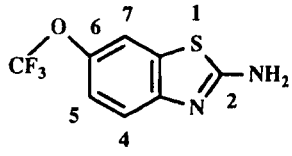
ABSTRACT

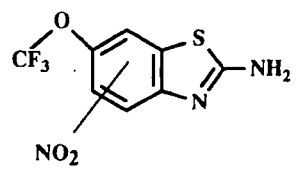
Convenient and regioselective syntheses of all three isomers of mononitro-6-trifluoromethoxy-benzothiazoles, starting from 2-amino-6-trifluoromethoxy-benzothiazole (riluzole) are described.

2-Aminobenzothiazoles have been widely used as starting materials for the synthesis of monoazo dyes[1] and pharmacological properties were discovered for some of them[2]. Recently, it was shown that 2-amino-6-trifluoromethoxy-benzothiazole (riluzole) possesses potent anticonvulsant and neuroprotective activities due to its action as an antagonist to excitatory aminoacid neurotransmission[3].

As part of our research program on riluzole derivatives, we developed a synthetic method for the preparation of nitrated analogs. This paper describes new convenient synthetic methods for the regioselective introduction of a nitro group in riluzole (Scheme I), leading to compounds **1-3**[4].



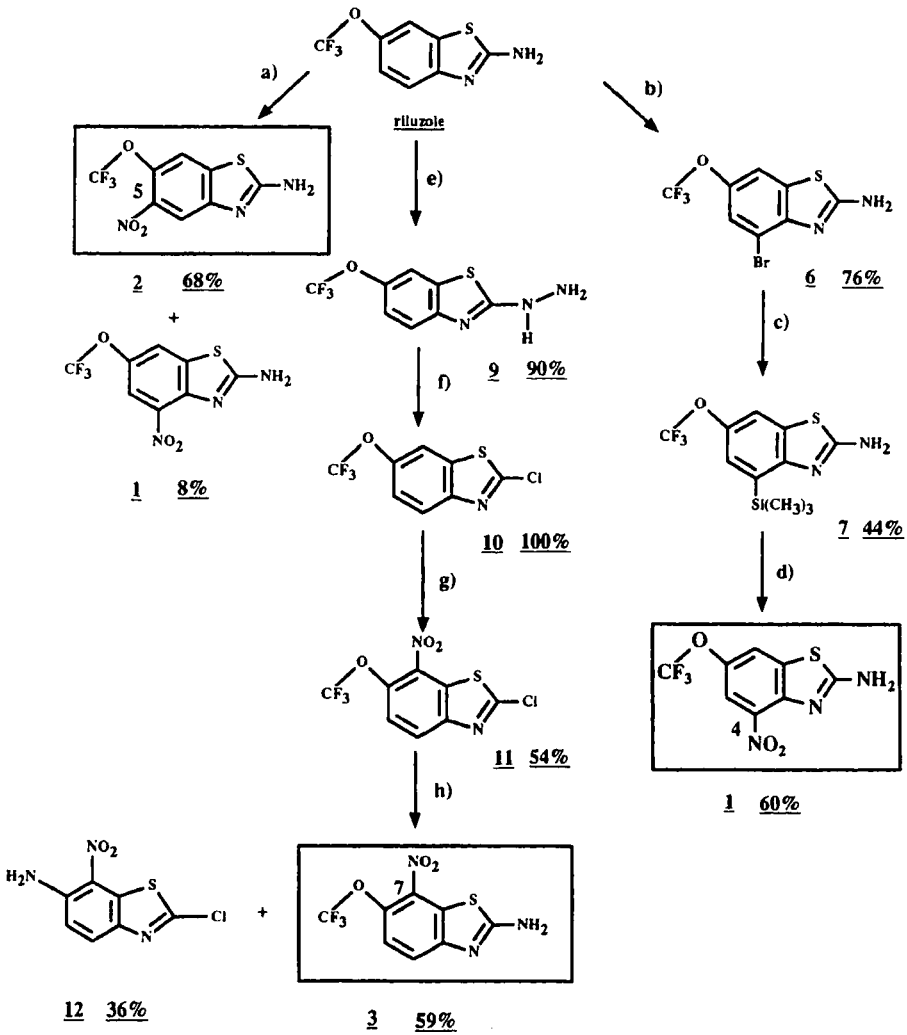
riluzole



1 4-NO_2 **2** 5-NO_2 **3** 7-NO_2

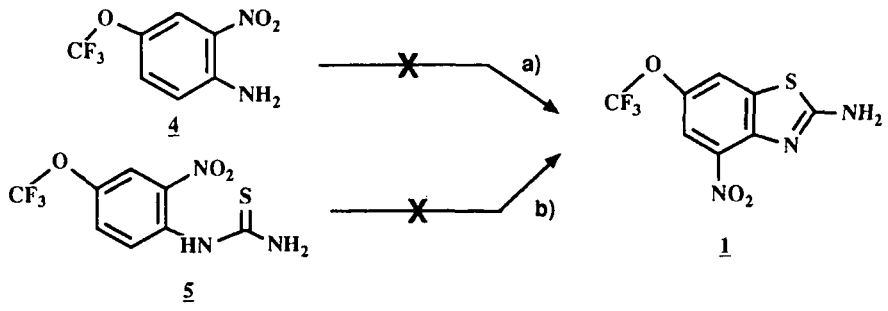
* To whom correspondence should be addressed.

Scheme I



a) conc.HNO_3-conc.H_2SO_4, 35 minutes, 0°C; b) Br_2, CH_3CO_2H, 12 hours, 50°C; c) 1. 3 eq. n-BuLi, THF, 45 minutes, -78°C 2. $(CH_3)_3SiCl$, THF, 1 hour, 0°C; d) NO_2BF_4, CH_3CN, 12 hours, rt; e) H_2N-$NH_2.H_2O$, H_2N-$NH_2.HCl$, ethylene glycol, 2 hours, 140°C; f) $SOCl_2$, 2 hours, 50°C; g) conc.HNO_3-conc.H_2SO_4, 1 hour, 10°C and 1 hour 60°C; h) NH_4OH (33%), C_2H_5OH, 5 hours, 110°C (autoclave).

Scheme II.



a) Br_2, KSCN, CH_3CO_2H, 18 hours, rt b) Br_2, $CHCl_3$, 10 hours , reflux

2-Amino-5-nitro-6-trifluoromethoxy-benzothiazole 2.

To our knowlege, there is only one precedent dealing with the direct nitration of 2-benzothiazolamine[5].

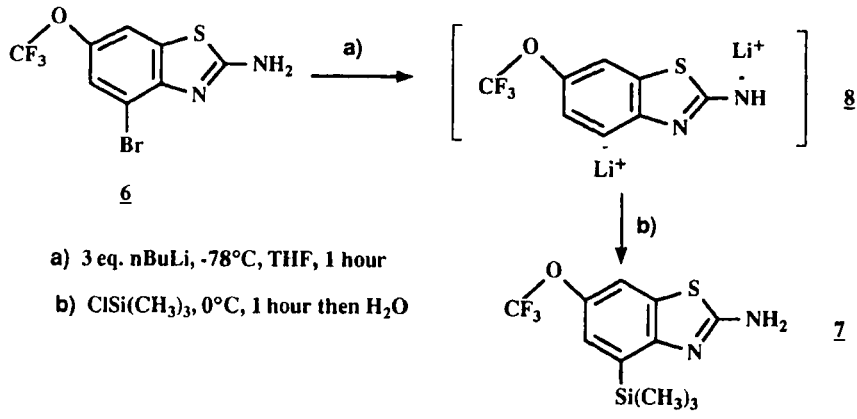
Nitration of riluzole by conc.HNO_3-conc.H_2SO_4 at low temperature (5°C, 30 minutes) led to a mixture of 2-amino-4-nitro- and 2-amino-5-nitro-6-trifluoromethoxy-benzothiazole 1 and 2, respectively. The final products were isolated by flash chromatography on silica gel and pure samples of 2 (68%) and 1 (8%) were obtained.^{1}H.NMR data are in agreement with the structures for 1 and 2: the coupling constants J(H-H) found were 2 Hz (*meta*) and 0 Hz (*para*), respectively. Under these conditions, neither the 2-amino-7-nitro-6-trifluoromethoxy-benzothiazole 3 nor the dinitro derivatives were isolated. We did not succeed in the nitration of riluzole with nitronium tetrafluoroborate at room temperature under Lynch's conditions[6] and only starting material was recovered.

2-amino-4-nitro-6-trifluoromethoxy-benzothiazole 1

We first attempted to synthesize 2-amino-4-nitro-6-trifluoromethoxy-benzothiazole 1 by cyclization of 4-trifluoromethoxy-2-nitroaniline 4[7] with bromine and potassium thiocyanate (acetic acid, 18 hours, room temperature)[8] or by cyclization of 2-nitro-4-trifluoromethoxy-benzenethiourea 5[9], using bromine as oxidizing agent (chloroform, 10 hours, reflux)[10](Scheme II). Although both reactions are known methods for the synthesis of 2-amino-(nitro)benzothiazoles[11], we could not obtain the desired product 1, and only 20-40% of starting material was recovered. The trifluoromethoxy group (*ortho-para* directing influence)[12] deactivates electrophilic substitution in the *meta* position , therefore electrophilic-type cyclizations cannot occur.

Finally, we succeded in the preparation of 1 using the 4-trimethylsilyl derivative 7 as starting material.

Scheme III.



Remarkably, only 2-amino-4-nitro-6-trifluoromethoxy-benzothiazole **1** was obtained by nitration of 2-amino-4-trimethylsilyl-6-trifluoromethoxy-benzothiazole **7** using nitronium tetrafluoroborate[13] under mild conditions[6] (acetonitrile, 12 hours, room temperature). The yield of this *ipso*-electrophilic-substitution reaction[14] was 60%. To the best of our knowledge, such reactions have not yet been described on benzothiazole derivatives; and this method should allow the introduction of a variety of substituents (e.g. Br, I, Cl etc.) into the benzene ring of 2-amino benzothiazole via the corresponding silylated derivative[15]. The position of the silyl group was confirmed by the presence of positive n.O.e. between H^5 and H (trimethylsilyl) and the coupling $^5J(H\text{-}F)$ = 1Hz of the protons H^5 and H^7. The trimethylsilyl derivative **7** was prepared as follows: metalation of 2-amino-4-bromo-6-trifluoromethoxy-benzothiazole **6** with 3 equivalents of *n*-butyllithium at -78°C in THF produced the dilithiated intermediate **8**[16] which reacted with trimethylchlorosilane to give compound **7** in 44% yield after hydrolysis (Scheme III).
2-Amino-4-bromo-6-trifluoromethoxy-benzothiazole **6** was obtained by direct bromination of riluzole in 76% yield (bromine, glacial acetic acid). Thus bromination occurs selectively at position 4, whereas nitration occurs predominantly at position 5.

2-Amino-7-nitro-6-trifluoromethoxy-benzothiazole **3**

Nitration of 2-chloro-6-trifluoromethoxy-benzothiazole **10** (conc.HNO_3-conc.H_2SO_4, 60°C, 1 hour) led predominantly to required 2-chloro-7-nitro-6-trifluoromethoxy-benzothiazole **11** in 54% yield[17] (Scheme I). The chlorine substituent in the 2-position of compound **10** is responsible for this remarkable change in the selectivity of the nitration reaction and position 7 becomes the preferred reaction site.

Treatment of compound **11** with an ethanolic solution of 33% ammonium hydroxide in an autoclave (110°C, 5 hours) afforded the expected 2-amino-7-nitro-6-trifluoromethoxy-benzothiazole **3** in 59% yield and 6-amino-2-chloro-7-nitro-benzothiazole **13**[18] in 36% yield. The structure of **3** was established by ^{1}H-NMR measurements: a J(H-H) coupling constant of 9Hz confirms the *ortho* disposition of the two aromatic protons.
Compound **9** was obtained in 90% yield by treatment of riluzole with hydrazine hydrate and hydrazine dihydrochloride (2 \ 1) (140°C, 2 hours)[19]. Compound **10** was then prepared quantitatively by chlorination of **9** with thionyl choride (50°C, 2 hours)[20].

In conclusion, this work presents simple synthetic routes to 4-, 5- and 7-nitro-riluzole derivatives by direct nitration of riluzole or its derivatives, and utilisation of an original *ipso*-electrophilic-substitution reaction to introduce nitro or bromine group in the 2-benzothiazolamine moiety.

EXPERIMENTAL SECTION

Solvents (tetrahydrofuran, acetonitrile, ethylene glycol) were dried over 4Å molecular sieves.
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 Reicher-Kofler apparatus and are uncorrected.
^{1}H Nuclear Magnetic Resonance (^{1}H-NMR) spectra and ^{13}C Nuclear magnetic Resonance (^{13}C-NMR) spectra were recorded on 200 WP, 250WP or AM400 Brucker spectrometers with Me_4Si as internal standard (unless otherwise noted).
Infrared (IR) spectra were recorded on a 983G Perkin-Elmer spectrophotometer or a 60SXR Nicolet spectrophotometer.
Ultraviolet spectra (UV) were determined using a UV2100 Shimadzu spectrophotometer.
Mass spectra (MS) were obtained on a Finigan 3000 apparatus (electron impact: EI; 70ev).
Elemental analysis (Anal) were performed at Centre de Recherches de Vitry-Alfortville (Rhône-Poulenc Rorer)
Flash column chromatography was performed on silica gel (Merck kieselgel, 230-400 mesh).

2-Amino-5-nitro-6-trifluoromethoxy-benzothiazole **2**.
A mixture of concentrated nitric acid (d=1.42, 10ml) and concentrated sulphuric acid (d=1.83, 20ml) was cooled to 0°C and added over 35 minutes to riluzole[21] (11.7g, 50mmol) with mechanical stirring at such a rate that the temperature did not rise above 5°C. The resulting mixture was stirred at -2°C for 30 minutes, then poured with **caution** to a water-ice mixture (1\1). The reaction mixture was basified with ammonium hydroxide (28%, 75ml) and the yellow solid thus obtained was filtered, dried and purified by flash chromatography using cyclohexane-ethyl acetate mixture (3 \ 2) as eluent giving 2-amino 4-nitro-6-trifluoromethoxy-benzothiazole **1** (1.15g, 8%, yellow solid, m.p. 260°C) R_f=0.25 and 2-amino-5-nitro -6-trifluoromethoxy-benzothiazole **2** (9.45g, 68%, yellow solid, m.p. 260°C) R_f=0.15 in cyclohexane-ethylacetate mixture 3 \ 2.

2 ^{1}H-NMR (DMSO-d_6, 200MHz) δ: 8.0 (s, 1H, H^4), 8.1 (brd, 2H, NH_2), 8.2 (m, 1H, H^7).
MS (EI) m/z(%): 279(38, $M^{+\cdot}$); 249(3, -NO); 221(14, 249-CO); 167(75); 140(100, 167-HCN); 69(25, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3405 and 3300 (NH), 3100 (NH), 1640 (C=N), 1605;1575;1505 and 1455 (aromatic benzothiazole ring), 1535 (NO_2), 1330 (NO_2), 1300-1150 (C-O and C-F), 840 (CH) cm^{-1}.
Anal.Calc. for $C_8H_4F_3N_3SO_3$: C, 34.42; H, 1.44; F, 20.41; N, 15.05; O, 17.11; S, 11.48. Found: C, 34.3; H, 1.2; F, 20.3; N, 14.7; S, 11.4.
U.V.(Methanol) λ max(nm), ε(cm^{-1}.mol^{-1}.l) 345.0(2309), 259.4(27820),215.7(14786)

Spectra data of 1 are given below.

2-Amino-4-bromo-6-trifluoromethoxy-benzothiazole 6 (hydrobromide)
Bromine (2.4g, 0.77ml, 15mmol) in glacial acetic acid (6ml) was added dropwise over a period of 15 minutes to a stirred solution of riluzole (3.51g, 15 mmol) in glacial acetic acid (30ml) at 50°C. Stirring and heating were continued for 12 hours. After cooling, the white solid was filtered off, and the crude product was recrystallized from ethanol to provide 4.5g (76%) of the hydrobromide salt 6 as colourless needles(m.p. 300°C).

^{1}H-NMR (DMSO-d_6, 250MHz) δ: 7.5 (dm, ^{4}j(H-H)= 2Hz, 1H, H^7), 7.9 (dm, ^{4}J(H-H)= 2Hz, 1H, H^5), 8.1 (brd, 3H, NH_2+HBr).
MS (EI) m/z(%): 312 and 314(22, $M^{+\cdot}$); 243 and 245 (28, -CF_3); 215 and 217 (8, 243 and 245 -CO); 206 (20); 80 and 82 (40); 69 (100, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3300-2600 (N^+-H), 1650 and 1630 (N-C=N), 1605;1580;1565 and 1475 (aromatic benzothiazole ring), 1300-1150 (C-F and C-O) cm^{-1}.
Anal.Calc. for $C_8H_5BrF_3N_2OS$: C, 24.39; H, 1.28; Br, 40.56; F, 14.46; N, 7.11; O, 4.06; S, 8.14.
Found: C, 24.4; H, 1.3; Br, 40.3; F, 14.2; N, 7.1; S, 8.5.

2-Amino-4-trimethylsilyl-6-trifluoromethoxy-benzothiazole 7
n-Butyllithium (1.6M in hexane, 18.7ml, 30 mmol) was added dropwise during 1 hour into a solution of 6 in the form of its free base[22] (3.13g ,10 mmol) in dry tetrahydrofuran (50ml) under nitrogen. An exothermic reaction was observed and a green coloration appeared within a few minutes. The solution was stirred for 45 minutes at -78°C. Trimethylchlorosilane (6.5g, 7.6ml, 60 mmol) was then added dropwise during 15 minutes at this temperature and the resulting yellow mixture was stirred 1 hour at 0°C. Water (100ml) was then added and the reaction mixture was extracted with ethyl acetate (2 x 100ml). The organic solution was washed with water, dried over anhydrous magnesium sulphate and the solvent was removed on a rotary evaporator. Flash chromatography on silica gel using a cyclohexane-ethyl acetate mixture (92 \ 8) as eluent afforded 1.6g (44%) of 7 as pale yellow needles (m.p. 76°C, R_f=1.4 in dichloromethane-methanol mixture 95 \ 5).

^{1}H-NMR ($CDCl_3$, 200MHz) δ: 0.3 (s, 9H, $Si(CH_3)_3$), 5.0 (s, 2H, NH_2), 7.1 (q, ^{5}J(H-F)=1Hz, 1H, H^5), 7.4 (q, ^{5}J(H-F)=1Hz, 1H, H^7).
^{13}C-NMR (DMSO-d_6, 50MHz) δ: -0.8, 115, 121, 123, 129, 132, 142, 156, 167.
MS (EI) m/z(%): 306(28, $M^{+\cdot}$); 305 (30, -H); 291 (100, -CH_3); 222 (15, 291-CF_3); 69 (70, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3500 and 3310 (NH), 3150 (NH), 2875-3000 (CH_3), 1645 (N-C=N), 1595;1565;1535 and 1435 (aromatic benzothiazole ring), 1275-1145 (C-O; C-F and Si-CH_3), 875-825 (Si-C; CH_3 and CH) cm^{-1}.
Anal.Calc. for $C_{11}H_{13}F_3N_2OSSi$: C, 43.12; H, 4.28; F, 18.60; N, 9.14; O, 5.22; S, 10.47; Si, 9.17. Found: C, 43.3; H, 4.3; F, 18.7; N, 9.0; S, 10.6.

2-Amino-4-nitro-6-trifluoromethoxy-benzothiazole **1**

To a solution of **7** (0.76g, 2.5mmol) in acetonitrile (20ml), nitronium tetrafluoroborate (0.68g, 5mmol) was added in small portions at 0°C, then stirring was continued for 12 hours at room temperature. The resulting solution was diluted with water (50ml) and extracted with ethyl acetate (2 x 100ml). The organic layer was dried over anhydrous magnesium sulphate and concentrated in rotary evaporator. The residue was purified by flash chromatography on silica gel using a cyclohexane-ethyl acetate mixture (7 \ 3) as eluent to give 0.3g (43%) of **1** as yellow solid (m.p. 260°C, R_f=0.25 in cyclohexane-ethyl acetate mixture 3 \ 2).

^{1}H-NMR (DMSO-d_6, 200MHz) δ: 8.0 (m, ^{4}j(H-H)=2Hz, 1H, H^5), 8.3 (m, 1H, H^7), 8.6 (brd, 2H, NH_2).
MS (EI) m/z(%): 279(100, $M^{+\cdot}$); 249(10, -NO); 236(55); 206(50, 236-NO); 193(40, -CF_3OH); 189(48, 236-HNO_2); 69(60, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3400 and 3300 (NH), 3100 (NH), 1640 (C=N), 1575 and 1440 (aromatic benzothiazole ring), 1520 (NO_2), 1350 (NO_2), 1300-1150 (C-O and C-F), 870 and 840 (CH) cm^{-1}.
Anal.Calc. for $C_8H_4F_3N_3SO_3$: C, 34.42; H, 1.44; F, 20.41; N, 15.05; O, 17.11; S, 11.48. Found: C, 34.4; H, 1.3; F, 20.2; N, 14.8; S, 11.2.
U.V.(Methanol) λ max(nm), ε(cm^{-1}.mol^{-1}.l) 366.9(5150), 259.1(13501),217.5(25676)

2-Hydrazino-6-trifluoromethoxy-benzothiazole **9**

To a suspension of riluzole (93.6g, 0.4mol) in ethylene glycol (420ml) under nitrogen were added, hydrazine hydrate (48g, 0.8mol) and hydrazine dihydrochloride (42.0g, 0.4mol). The mixture was heated in an oil bath at 140°C for 2 hours. After cooling, the precipitate was filtered and triturated in water-diethyl ether mixture (1 \ 1) to afford 89.9g (90%) of desired **9** as a white powder (m.p. 208°C, R_f=0.2 in ethyl acetate).

^{1}H-NMR (DMSO-d_6, 200MHz) δ: 5.1 (brd, 2H, NH_2), 7.2 (dq, ^{3}J(H-H)=9 Hz, ^{5}j(H-F)=1 Hz, 1H, H^5), 7.4 (d, ^{3}J(H-H)=9Hz, 1H, H^4), 7.8 (q, ^{5}J(H-F)=1Hz, 1H, H^7), 9.2 (brd, 1H, NH-N).
MS (EI) m/z(%): 249 (100, $M^{+\cdot}$); 232 (36, -NH_3); 180 (12, -CF_3); 69 (65, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3350-2880 (NH), 1660 (C=N), 1610;1565 and 1460 (aromatic benzothiazole ring), 1300-1120 (C-F and C-O), 825 and 815 (CH) cm^{-1}.

2-Chloro-6-trifluoromethoxy-benzothiazole **10**

The hydrazino-compound **9** (49.4g, 0.2mol) was added during 1 hour to thionyl chloride (97.9g, 61.2ml, 0.8mol) heated at 50°C. The mixture was stirred for one more hour at the same temperature. The solution was then cooled to 0°C. After addition of a water-ice mixture (200ml, 1 \ 1), the precipitated solid was filtered off and washed with water (2 x 50ml) to afford **10** (54.5g, 100%, m.p. 50°C, R_f=0.7 in ethyl acetate) which was used in the next step without further purification.

^{1}H-NMR (DMSO-d_6, 200MHz) δ: 7.5 (dq, ^{5}J(H-F)=1Hz, ^{3}j(H-H)=9 Hz, 1H, H^5), 8.1 (d, ^{3}J(H-H)= 9 Hz, 1H, H^4), 8.2 (q, ^{5}J(H-F)=1 Hz, 1H, H^7).
MS (EI) m/z(%): 253 (100, $M^{+\cdot}$); 255 (255, $M^{+\cdot}$); 184 (90, -CF_3); 186 (30, -CF_3); 156 (75); 158 (25); 69 (25, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3100-3080 (CH), 1605;1560;1485 and 1450 (aromatic benzothiazole ring), 1300-1150 (C-F and C-O), 825 and 815 (CH) cm^{-1}.

2-Chloro-7-nitro-6-trifluoromethoxy-benzothiazole **11**

The chloro-compound **10** (10.0g, 39mmol) was added dropwise to a mixture of concentrated sulphuric acid (d=1.83, 50ml) and concentrated nitric acid (d=1.42, 25ml) over a period of 1 hour at 10°C and the solution was then heated at 60°C for 1 hour. After cooling, the reaction mixture was poured with **caution** into a water-ice mixture (1 \ 1) and extracted with chloroform (3 x 100ml). The organic layer was dried over anhydrous magnesium sulphate and concentrated. The residue was purified by flash chromatography using a chloroform-cyclohexane mixture (4 \ 6) as eluent to give **11** as a yellow solid (6.4g, 54%, m.p. 64°C, R_f=0.4 in chloroform-cyclohexane mixture 35 \ 65).

^{1}H-NMR ($CDCl_3$, 400MHz) δ: 7.9 (d, ^{3}J(H-H)=9 Hz, 1H, H^5), 8.5 (d, ^{3}J(H-H)=9 Hz, 1H, H^4)
^{13}C-NMR (DMSO-d_6, 50MHz) δ: 120, 123, 130, 134, 135, 140, 150, 158.
MS (EI) m/z(%): 297(30, M^+-H), 268(6, M-NO), 262(7, M-HCl), 239(11), 151(35), 69(100, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3100-3000 (CH), 1610;1555;1480 and 1445 (aromatic benzothiazole ring), 1525 (NO_2), 1320 (NO_2), 1260;1205 and 1165 (C-F and C-O), 820 (CH) cm^{-1}.
Anal.Calc. for $C_8H_2ClF_3N_2O_3S$: C, 32.18; H, 0.68; Cl, 11.87; F, 19.09; N, 9.38; O, 16.07; S, 10.74; Found: C, 32.5; H, 0.5; Cl, 11.9; F, 18.9; N, 9.3; S, 10.7.

2-Amino-7-nitro-6-trifluoromethoxy-benzothiazole **3** and 6-amino-2-chloro-7-nitro-benzothiazole **12**.

A mixture of 2-chloro-7-nitro-6-(trifluoromethoxy)benzothiazole **11** (0.4g, 1.3mmol) and aqueous ammonium hydroxyde solution (10ml, 33%) in ethanol (30ml) was heated at 110°C in an autoclave for 5 hours. The mixture was cooled to room temperature and the solvent was evaporated. The reaction mixture was purified by flash chromatography with a cyclohexane-ethyl acetate mixture (4 \ 6) as eluent, to give the desired 2-amino-7-nitro-6-trifluoromethoxy-benzothiazole **3** (0.22g, 59%, orange solid, m.p. 180°C, R_f=0.3 in cyclohexane-ethyl acetate 4 \ 6) and 6-amino-2-chloro-7-nitro-benzothiazole **12** (0.13g, 36%, red solid, m.p. 200°C (sublimation), R_f=0.45 in cyclohexane-ethyl acetate 4 \ 6)

3 ^{1}H-NMR (DMSO-d_6, 200MHz) δ: 7.5 (d, ^{3}J(H-H)=9Hz, 1H, H^5), 7.7 (d, ^{3}J(H-H)=9Hz, 1H, H^4), 8.1 (brd, 2H, NH_2).
MS (EI) m/z(%): 279(80, $M^{+\cdot}$), 253 (10, M-CN), 194 (15, M-OCF_3), 167 (80, 194-HCN), 140 (100, 167-HCN), 69(80, CF_3^+).
IR (KBr) υ max: 3470 and 3300 (NH), 3200-2700 (NH), 1655 (C=N), 1605;1570;1540 and 1445 (aromatic benzothiazole ring), 1525 (NO_2), 1310 (NO_2), 1275-1550 (C-F and C-O), 845 and 830 (CH) cm^{-1}.
Anal Calcd for $C_8H_4F_3N_3O_3S$: C, 34.42; H, 1.44; F, 20.41; N, 15.05; O, 17.20; S, 11.48; Found: C, 34.6; H, 1.4; F, 20.4; N, 14.6; S, 11.8.
U.V.(Methanol) λ max(nm), ε(cm^{-1}.mol^{-1}.l) 311.6(4403), 267.8(14553),214.4(31979)

12 ^{1}H-NMR (DMSO-d_6, 200MHz) δ 7.2(d, ^{3}J(H-H)=9Hz, 1H, H^5), 8.0 (d, ^{3}J(H-H)=9Hz, 1H, H^4), 8.4 (brd, 2H, NH_2).
^{13}C-NMR ($CDCl_3$-CH_3OD, 50MHz) δ 153, 147,142,132,129,114 (C^2 not observed).
MS (EI) m/z(%): 229(80, $M^{+\cdot}$), 199 (15, M-NO), 183 (55, M-NO_2), 148 (100, 183-Cl), 121 (30, 148-HCN), 69(25, CF_3^+).
IR (KBr) υ max: 3445 and 3000 (NH), 3100-3000 (CH), 1625 (C=N), 1585;1535;1510 and 1460 (aromatic benzothiazole ring), 1250-1225 (NO_2), 830 (CH) cm^{-1}.

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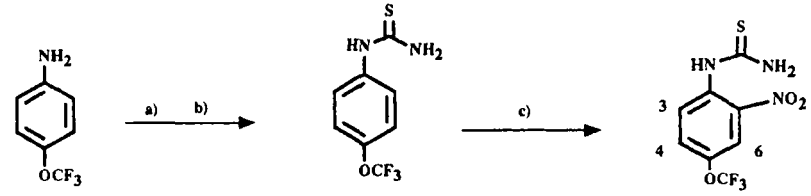
9). 2-Nitro-4-trifluoromethoxy-benzenethiourea **5** (yellow crystals, m.p. 110°C) was synthesized in low yield (10%) by nitration of 4-trifluoromethoxy-benzenethiourea **14** (cream-coloured solid, m.p. 140°C). The latter was obtained by a two-step synthesis from 4-trifluoromethoxy-aniline **13** (commercially available from ALDRICH) in 58% overall yield.



13 **14** **5**

a) NH_4SCN, C_6H_5COCl, acetone, rt, 12 hours b) NaOH (50%), 80°C, 12 hours

c) conc.H_2SO_4-conc.HNO_3, -10°C, 10 hours

5 ^{1}H-NMR (DMSO-d_6, 200MHz) δ: 9.8 (m, 1H, NHCS), 8.4-7.6 (m, 2H, NH_2), 8.0 (dt, J=2Hz, 1H, H^6), 7.7 (ddt, J=8.5 and 2Hz, 1H, H^4), 7.9 (dt, J=8.5Hz, 1H, H^3).
MS (EI) m/z(%): 281(5, $M^{+\cdot}$), 235(100, M-NO_2), 176(10), 149(10), 69(10, $CF_3^{+\cdot}$).
IR (KBr) υ max: 3370, 3300 and 3200 (NH), 1650 and 1625 (aromatic benzothiazole ring and NH_2), 1525 (NO_2), 1355 (NO_2), 1325-1125 (C-F and C-O) cm^{-1}.

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11) To our knowledge, few examples were described in the literature:
a. 2-amino-5-nitro-benzothiazole was prepared in high yields by cyclization of 2,4-dinitrochlorobenzene or 2,4-dinitrophenyl thiocyanate with thiourea in pyridine or ammonium thiocyanate in sulpholane. R. Hamprech, U. S. Patent. 4,808,723, **1989** (Chem. Abstr. 101 211131).

b. 2-amino-4-nitro-benzothiazole was prepared by cyclization of 2-nitro-phenylthiourea with sulphur dichloride (S. Claude, R. Tabacchi, L. Duc, J-F. Marrel, Helv. Chem. Acta, **1981**, 64(5), 1545) or lead(IV)-phosphate complexe (S. A. Von Mahmoud, S.A. Mohamed, J. Prakt. Chem., **1974**, 316(1), 154.

c. 2-amino-6-nitro-benzothiazole was prepared by cyclisation of 4-nitro-phenylthiourea with lead(IV)-phosphate complexe (S. A. Von Mahmoud, S. A. Mohamed, J. Prakt. Chem., **1974**, 316(1), 154), by reduction of 2,4-dinitro-phenylthiocyanate (J. Schulze, H. Tannerberg, H. Matschiner, Z. Chem., **1980**, 20(12), 436) or by direct nitration of 2-benzothiazolamine (See reference 5).

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13). The treatment of silylated riluzole 7 with conc.HNO_3-conc.H_2SO_4 at low temperature (0°C, 1 hour) produced a mixture of 2-amino-4,5-dinitro-6-trifluoromethoxy-benzothiazole and 2-amino-4,7-dinitro-6-trifluoromethoxy-benzothiazole with 72% overall yield.

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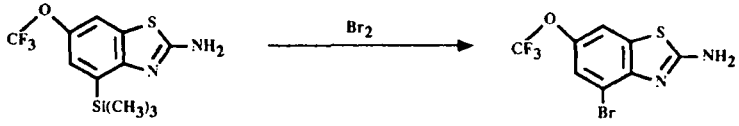
15). Another example of a regioselective-*ipso*-electrophilic-substitution reaction on compound 7, is the action of bromine (glacial acetic acid, 70°C, 3 hours) which produces specifically 2-amino-4-bromo-6-trifluoromethoxy-benzothiazole 6 with 64% yield.



7 6

16). a. Hydrolysis of the dilithiated species 8 with dilute HCl produced riluzole quantitatively.
b. Under similar conditions (2.5 equivalents of *n*-butyllithium, -78°C, THF), the metalation of 2-amino-6-bromo-benzothiazole followed by the addition of trimethylchlorosilane afforded 2-amino-6-trimethysilyl-benzothiazole in very low yield (6%, white crystals, m.p.140°C).

17). In addition, 1% of 2-chloro-5-nitro-6-trifluoromethoxy-benzothiazole was isolated after flash-chromathography [yellow solid, m.p.125°C, R_f=0.3 in chloroform-cyclohexane mixture as eluent 35 \ 65, ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 7.9 (q, ^{5}J(H-F)=1 Hz, 1H, H^7), 8.6 (s, 1H, H^4)]

18). This nucleophilic aromatic substitution of the trifluoromethoxy group (which acts as an halogen, see W. A. Sheppard, J.Am. Chem. Soc., **1963**, 85, 1314) was activated by the presence of a nitro group in *ortho* position. The anionic intermediate termed Meisenheimer complex (T. J. Broxton, R. P. T. Chung, J. Org. Chem., **1990**, 55, 3886 and references cited therein) was stabilized by conjugaison in the benzothiazole ring.

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22). To prepare the free base, a solution of **6**.(HBr) in dichloromethane was treated with 10 equivalents of sodium hydroxide, the free base was obtained after normal work up.

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