Bromination of 2,1,3-Benzothiadiazoles

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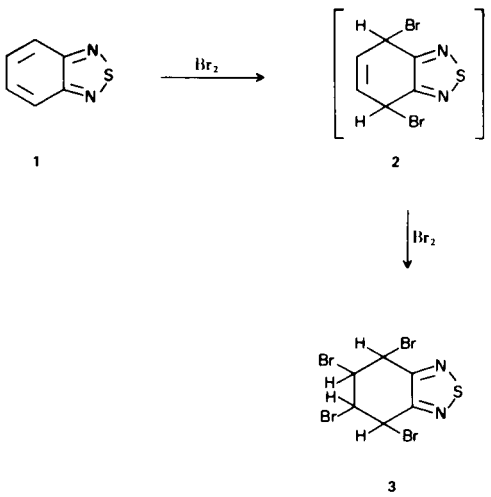
Contribution from the Biological Sciences Research Center
Shell Development Company

The bromination of 2,1,3-benzothiadiazoles in 47% hydrobromic acid at elevated temperature has led to a general preparative method for the synthesis in high yield of otherwise difficulty accessible brominated 2,1,3-benzothiadiazoles. The typical addition reaction is apparently eliminated under these reaction conditions and substitution takes place exclusively. Bromination of 2,1,3-benzothiadiazole occurs successively at positions 4 and 7. 4-Substituted 2,1,3-benzothiadiazoles are selectively brominated at position 7. 5-Bromo- and 5-methyl-2,1,3-benzothiadiazole are brominated consecutively at positions 4 and 7.

As a part of a program designed to study the herbicidal properties of 2,1,3-benzothiadiazolecarbonitriles (1), certain 4-bromo- and 4,7-dibromo-2,1,3-benzothiadiazoles were required for conversion to the corresponding carbonitriles by displacement of bromine with cuprous cyanide. Although *o*-phenylenediamines are important intermediates in the synthesis of 2,1,3-benzothiadiazoles (2,3) and it is convenient to base the preparation of the derivatives on *o*-phenylenediamine itself, this route leads only to 1,2-diamino-4,5-dibromobenzene (4) and, consequently, to 5,6-dibromo-2,1,3-benzothiadiazole. A route to 4,7-dibromo-2,1,3-benzothiadiazole was noted by Pesin, et. al., (5), who found that bromination of 2,1,3-benzothiadiazole (**1**) leads to the addition of four atoms of bromine and the formation of 4,5,6,7-tetrabromo-4,5,6,7-tetrahydro-2,1,3-benzothiadiazole (**3**). The literature data (5) imply that the first step here is 1,4-addition of bromine to the quinoid system with a shift of the double bond to give the

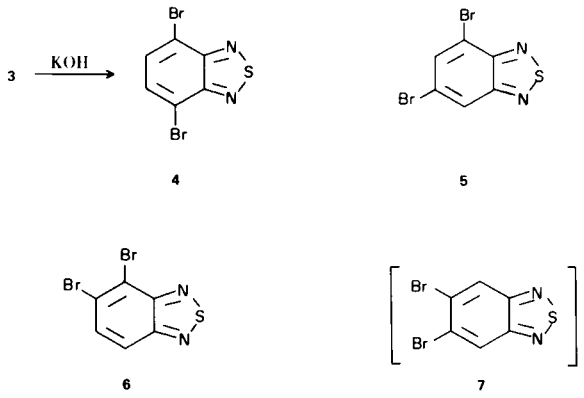


1 2 3

hypothetical 4,7-dibromo-4,7-dihydro-2,1,3-benzothiadiazole (**2**) as an intermediate. When treated with potassium hydroxide, **3** was converted into 4,7-dibromo-2,1,3-benzothiadiazole (**4**).

The above result was confirmed by carrying out the reaction of **1** with excess bromine at 65-75° followed by isolation of **3**. However, treatment of **3** with potassium hydroxide in ethanol as given by Pesin gave in our hands an almost quantitative yield of a mixture of **4** and its 4,6-dibromo analog (**5**) in the approximate molar proportion of 4:1. When a suspension of **3** in methanol was allowed to react with potassium hydroxide the product obtained was shown by thin-layer chromatography (TLC) and gas-liquid chromatographic analysis (GLC) to be a mixture of **4**, **5**, and a third component (**6**) which could be isolated in crystalline form either by fractionated crystallization or by preparative TLC. This compound was indistinguishable from an authentic sample of **6** on the basis of comparisons of thin-layer gas chromatograms. A mixture melting point with an authentic (6) sample of **6** was undepressed. The amounts of **6** obtainable from several experiments were variable and small (0.5-3%). The structure of **5** and **6** was confirmed by an unambiguous synthesis. The 5,6-dibromo analog (**7**) may have formed as well in these reactions, but would not be detected by TLC and GLC because its R_4-value and retention time in different solvent systems and on different columns proved to be identical to that of **5**.

When a mixture of **1** and excess bromine in constant boiling hydrobromic acid (47% hydrobromic acid, b.p. 126°) was heated at reflux for several hours, a colorless crystalline product was formed. This product was a mixture of **3** and **4** in the approximate proportion of 3:7. Prolonged heating did not change this ratio indicating that



3 was not the precursor of **4** under these reaction conditions.

When bromine was added dropwise at 126-130° to a mixture of **1** in 47% hydrobromic acid, 4-bromo-2,1,3-benzothiadiazole, **8**, was formed exlcusively at first (see Figure 1). Towards the half-way point of the addition, GLC indicated that the 4,7-dibromo analog (**4**) began to form. After completion of the bromination, **4** was isolated in almost quantitative yield. The failure to observe any of the addition product **3** under these reaction conditions indicates that **8** and **4** have been formed by electrophilic substitution. Moreover, the absence of 5 (and 6)-bromo-2,1,3-benzothiadiazoles such as **5**, **6**, **7** and **9** in the reaction mixture can be rationalized on the basis that attack of Br^+ at position 4 (or 7) which involves a σ-bond intermediate, is energetically favored over the attack of Br^+ at position 5 (or 6).

Hydrogen bromide, formed during the brominations with elemental bromine, does not dissolve in the already constant boiling hydrobromic acid and so escapes from the reaction flask. To avoid loss of hydrogen bromide from the reaction mixture, hydrogen peroxide which converts hydrogen bromide to bromine, was used in place of the latter. Thus, when a mixture of **1** in 47% hydrobromic acid was allowed to react with excess 90% hydrogen peroxide at 126-130°, **4** was isolated in 95% yield from the reaction mixture.

Some bromination reactions of 5-bromo-, (**9**), 5-methyl-, (**10**), 4,6-dibromo-, (**5**) and 5,6-dimethyl-, (**15**), 2,1,3-benzothiadiazole in refluxing 47% hydrobromic acid were also examined since these compounds can be prepared from commercially available *o*-nitroanilines. Electrophilic substitutions in these 5-substituted 2,1,3-benzothiadiazoles follow a simple pattern. The thiadiazole framework and the substituent in position-5 direct the bromine first to position-4 followed by substitution at position-7, if these positions are unoccupied. For example, 4-bromo-5-methyl-2,1,3-benzothiadiazole (**11**) is formed smoothly by reaction of **10** with one molar equivalent of bromine in refluxing 47% hydrobromic acid. Continued addition of bromine leads to formation of the 4,7-dibromo analog (**12**) in high yield. Steric and electronic effects are clearly operating in this reaction as evidenced by the more sluggish reaction of **9** with one molar equivalent of bromine under the same conditions to give **6** as the major (90%) product along with the tribromo (**14**) analog (5%) and some starting material (**9**). Formation of the 4,6-dibromo analog (**5**) was not observed. Again, excess bromine led to formation of **14** in almost quantitative yield. The same tribromo-2,1,3-benzothiadiazole (**14**) was obtained from **5** and must therefore be the 4,5,7-tribromo derivative. This confirms the structure assigned to the products of mono- and dibromination of **9**.

Analogous results were obtained with 5,6-dimethyl-2,1,3-benzothiadiazole (**15**). Bromine and **15** gave the 4,7-dibromo analog (**16**) in high yield.

Bromination of 4-methyl-2,1,3-benzothiadiazole (**17**) with one molar equivalent of bromine in 47% hydrobromic acid at 65-70° gave the expected 7-bromo derivative (**18**). The 4-(bromomethyl)-7-bromo compound (**19**) was formed in 80% yield when excess bromine was allowed to react with **17** in 47% hydrobromic acid at 126°. The structure of **19** was verified by its NMR spectrum, which showed the signals characteristic of a bromethyl compound at δ 4.95 ppm.

Similar results were obtained with 4-ethyl-2,1,3-benzothiadiazole (**20**). This thiadiazole gave the 7-bromo analog (**21**) in 75% yield in addition to starting material (15%) and two higher brominated materials (10%) by reaction with equimolar quantities of bromine in 47% hydrobromic acid at 80°. Higher reaction temperature and excess bromine led to extensive bromination in the side chain.

These results (summarized in Table 1) show that bromination of 2,1,3-benzothiadiazoles in 47% hydrobromic acid at elevated temperature is a convenient synthesis of brominated 2,1,3-benzothiadiazoles particularly when the corresponding *o*-phenylenediamine is not readily available for ring closure with *N*-thionylaniline or thionyl chloride.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Thomas-Hoover capillary apparatus. The NMR spectra were determined on a Varian A-60 spectrometer.

2,1,3-Benzothiadiazole (**1**).

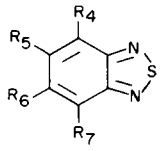
Reaction of *o*-phenylenediamine with thionyl chloride in benzene in the presence of pyridine afforded **1** in 89% yield, m.p. 44°, lit. (9,10) m.p. 44°.

4,6-Dibromo-2,1,3-benzothiadiazole (**5**).

This compound was prepared in 98% yield from 1,2-diamino-3,5-dibromobenzene and *N*-thionylaniline in refluxing toluene; m.p. 127°, lit (10) m.p. 127°.

TABLE I

Bromination Data of 2,1,3-Benzothiadiazoles in 47% Hydrobromic Acid at 126°



No. of Compd. Brominated	Final Product No.	R^4	R^5	R^6	R^7	% Yield	Mp, °C	Lit., Mp, °C	Formula	Analyses, % Bromine Calcd.	Bromine Found	Nitrogen Calcd.	Nitrogen Found
1	8	Br	H	H	H	62	80-81	83-85 (6)	$C_6H_3BrN_2S$	37.2	37.8	13.0	12.9
1	4(a)	Br	H	H	Br	98	188-189	184-185 (5)	$C_6H_2Br_2N_2S$	54.4	54.5	9.5	9.2
9	6	Br	Br	H	H	90.4	134-136	134-136 (6)	$C_6H_2Br_2N_2S$	54.4	54.4	9.5	9.1
9	14	Br	Br	H	Br	96.5	165-166	---	$C_6HBr_3N_2S$	64.4	64.7	7.5	7.5
5	14	Br	Br	H	Br	97	165-166	---	$C_6HBr_3N_2S$	64.4	64.6	7.5	7.6
10	11	Br	CH_3	H	H	94.4	92-95	96.4-97.5 (7)	$C_7H_5BrN_2S$	34.9	35.0	12.2	12.1
10	12	Br	CH_3	H	Br	88.3	147-148	145.5-146.5 (7)	$C_7H_4Br_2N_2S$	52.0	52.0	9.1	9.0
15	16	Br	CH_3	CH_3	Br	93.7	170-172	161-162 (8)	$C_8H_6Br_2N_2S$	49.7	49.4	8.7	8.7
17(b)	18	CH_3	H	H	Br	89.5	138-139	136-138 (8)	$C_7H_5BrN_2S$	34.9	34.6	12.2	11.8
17	19(c)	CH_2Br	H	H	Br	78.1	137-138	141.4-142.2 (7)	$C_7H_4Br_2N_2S$	52.0	51.9	9.1	9.2
20(d)	21	C_2H_5	H	H	Br	51.4	40-41	---	$C_8H_7BrN_2S$	32.9	33.2	11.5	11.8

(a) Sulfur, calcd.: 10.9; fd.: 11.1%. (b) Brominated at 65-70°. (c) Sulfur, calcd.: 10.4; fd.: 10.9%. (d) Brominated at 80°.

5-Methyl-2,1,3-benzothiadiazole (**10**).

This compound was prepared analogously from 3,4-diaminotoluene and *N*-thionylaniline and melted at 28-30°, lit. (9,10) m.p. 34°.

5-Bromo-2,1,3-benzothiadiazole (**9**).

This compound was prepared in 56% yield from 1,2-diamino-4-bromobenzene and *N*-thionylaniline and had m.p. 59-61°.

5,6-Dimethyl-2,1,3-benzothiadiazole (**15**).

Reaction of 1,2-diamino-4,5-dimethylbenzene with *N*-thionylaniline in refluxing toluene gave **15** in 61% yield, m.p. 81-82°.

Anal. Calcd. for $C_8H_8N_2S$: N, 17.1; S, 19.5. Found: N, 17.3; S, 19.4.

4-Methyl-2,1,3-benzothiadiazole (**17**).

This compound was obtained analogously from 2,3-diaminotoluene and *N*-thionylaniline in 73% yield, b.p. 76-78° (14 mm).

Anal. Calcd. for $C_7H_6N_2S$: N, 18.7; S, 21.3. Found: N, 18.9; S, 21.2.

4-Ethyl-2,1,3-benzothiadiazole (**20**).

The product obtained in 66% yield from 1,2-diamino-3-ethylbenzene and *N*-thionylaniline in refluxing benzene was (**20**), b.p. 83-84° (14 mm).

Anal. Calcd. for $C_8H_8N_2S$: N, 17.1; S, 19.5. Found: N, 16.9; S, 19.2.

4-Bromo-2,1,3-benzothiadiazole (**8**).

A mixture of 40.8 g. (0.3 mole) of **1** and 300 ml. of 47% hydrobromic acid was heated to reflux with stirring while bromine, 14 ml., was added dropwise. The reaction was closely followed by GLC (see Figure 1). After one hour, GLC indicated that the reaction was incomplete and consisted of about 33% of **1** (starting material), 62% of **8** (desired product) and 5% of **4** (4,7-dibromo analog). Steam distillation of the reaction mixture afforded **1** and **8** which were separated by crystallization from ethanol, yield, 26.9 g. (41.8%) of **8**, m.p. 80-81°, lit. (6) m.p. 83-85°. Filtration of the residue from the steam distillation gave **4**, m.p. 184-185° (from acetone), lit. (5) m.p. 184-185°.

4,7-Dibromo-2,1,3-benzothiadiazole (**4**).

(a) From **1** and Bromine in 47% Hydrobromic Acid.

A mixture of 136 g. (1.0 mole) of **1** in 200 ml. of 47% hydrobromic acid was heated under reflux with stirring, while 480 g. (3.0 moles, 165 ml.) of bromine was added slowly within 3.25 hours. Towards the half-way point of the addition, GLC indicated the following composition of the reaction mixture: *ca*, 30% of **1**, 60% of **8**, and 10% of **4**. A peak corresponding with **3** was not present in the gas chromatogram. Towards the end of the addition, the reaction mixture became a suspension of solid in the hydrobromic acid. In order to facilitate stirring, 100 ml. of 47% hydrobromic acid was added and the mixture was heated under reflux for 2.5 hours after completion of the bromine addition.

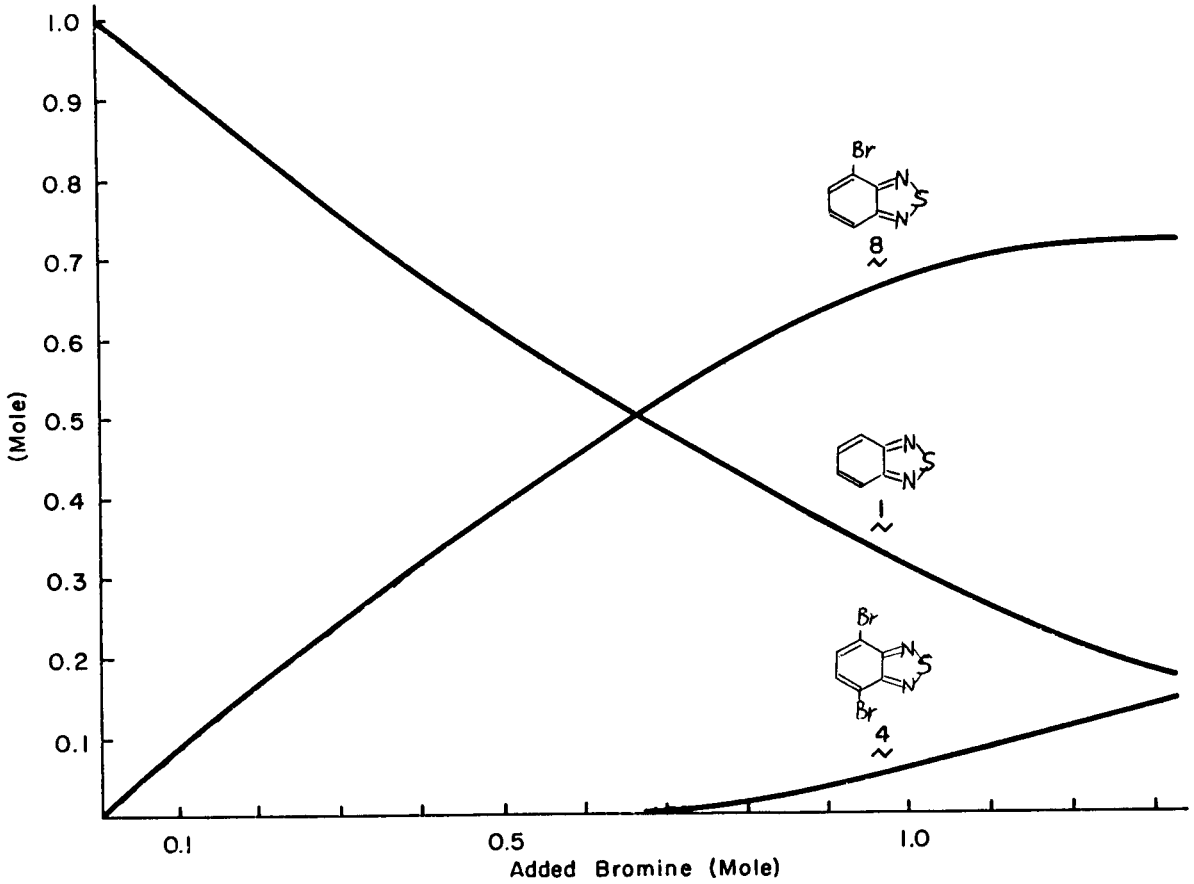


Figure 1. BROMINATION OF 2,1,3-BENZOTHIADIAZOLE (1) IN 47% HYDROBROMIC ACID AT 126°.

The mixture was filtered while hot, cooled, filtered again, washed well with water and dried to give 305 g. (98%) of **4** melting at 188-189°, lit. (5) m.p. 184-185°.

(b) From **1** and Hydrogen Peroxide in 47% Hydrobromic Acid.

A mixture of 27.2 g. (0.2 mole) of **1** and 250 ml. of 47% hydrobromic acid was heated under reflux while 50 ml. of 90% hydrogen peroxide was added dropwise. The only detectable product after six hours was **4** (by GLC). The reaction mixture was quenched in ice water, filtered, washed with water and dried to give 55.6 g. (95%) of **4**.

4,5-Dibromo-2,1,3-benzothiadiazole (**6**).

To a mixture of 71.0 g. (0.33 mole) of **9** in 470 ml. of boiling 47% hydrobromic acid, bromine, 20 ml., was added gradually within two hours. GLC indicated that the reaction was incomplete and contained about 65% of **9** and 35% of **6**. Bromine, 20 ml., was added again and heating was continued for an additional five hours. At this point, GLC indicated that only traces of **9** were present in the reaction mixture. However, the tribromo analog (**14**) started to build up. The reaction mixture was poured into ice water, filtered, washed well with water and dried. Recrystallization from methanol afforded 87.7 g. (90.4%) of **6**, melting at 134-136°, lit. (6) m.p. 134-136°.

4-Bromo-7-Methyl-2,1,3-benzothiadiazole (**18**).

Twenty g. (0.133 mole) of **17** and 200 ml. of 47% hydrobromic acid was heated with stirring at 65-70° while bromine, 9.0 ml., was added slowly over a period of 30 minutes. The mixture was heated for one additional hour, poured into 500 ml. of ice water and filtered. The crystalline solid was recrystallized from methanol to give 27.3 g. (89.5%) of **18**, melting at 138-139°, lit. (8) m.p. 136-138°; nmr, δ 2.65 (CH_3), 7.2 + 7.65 (aromatic H, J = 7.5 Hz).

4-Bromo-7-Bromomethyl-2,1,3-benzothiadiazole (**19**).

A mixture of 15.0 g. (0.1 mole) of **17** and 30 ml. of bromine in 100 ml. of 47% hydrobromic acid was heated under reflux for 4.5 hours, poured into ice water, and filtered. The brown solid was recrystallized from 150 ml. of acetone to give 25.0 g. (81.2% of **19** melting at 137-138°, lit. (7) m.p. 141.2-142.2°; nmr, δ *ca.* 7.7 (aromatic H) and 4.95 ppm (CH_2).

5,6-Dibromo-2,1,3-benzothiadiazole (**7**).

A mixture of 4,5-dibromo-*o*-phenylenediamine, 24.0 g. (0.09 mole), obtained by the reduction of 4,5-dibromo-1,2-dinitrobenzene (11), 25.0 g. (0.18 mole) of thionylaniline and 100 ml. of toluene was heated under reflux for 24 hours. The reaction mixture was acidified by addition of 150 ml. of 25% hydrochloric acid, filtered, and phase separated. The benzene layer was washed with water (3 x 150 ml.), dried (magnesium sulfate), charcoaled,

filtered and evaporated to dryness. Recrystallization of the residual solid from acetone afforded 9.0 g. (35%) of **7** melting at 132-134°.

Anal. Calcd. for $C_6H_2Br_2N_2S$: N, 9.5; S, 10.9. Found: N, 9.2; S, 10.8.

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