

4,7-Disubstituted 2,1,3-Benzothiadiazoles

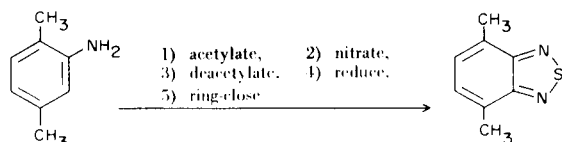
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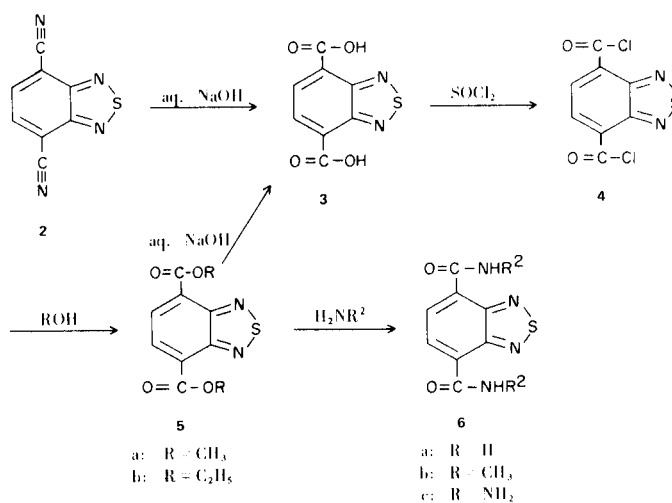
During an investigation of the relationships governing the herbicidal activity of 2,1,3-benzothiadiazolecarbonitriles, it was established that highest activity is associated with the 4,7-dicyano isomer, **2**, whereas other dicyano isomers are less active (**1**). In order to arrive at definite conclusions with regard to structure-activity relationships existing in this class of heterocycles, the preparation of a number of 4,7-disubstituted 2,1,3-benzothiadiazoles was undertaken.

Although it is convenient to base the preparation of 4,7-disubstituted 2,1,3-benzothiadiazoles on the respective 3,6-disubstituted *o*-phenylenediamines, preparation of the latter is often long and difficult. The main limitation in the preparation of 4,7-dialkyl-2,1,3-benzothiadiazoles is the difficulty in preparing dialkyl *o*-nitroanilines with the alkyl groups in the required 3,6-orientation. The preparation of such compounds usually involves a separation of mixtures of isomers and yields are often poor. For example, synthesis of 4,7-dimethyl-2,1,3-benzothiadiazole, **1**, from *p*-xylydine was achieved in a multi-step synthesis in very low (3.7%) overall yield as follows:

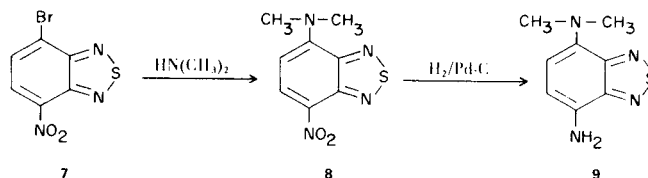


It is obvious that the preparation of homologs of **1** as well as other 4,7-disubstituted 2,1,3-benzothiadiazoles in this manner is not attractive.

Attention was turned to the hydrolysis of 2,1,3-benzothiadiazole-4,7-dicarbonitrile (**2**), **2**, to 2,1,3-benzothiadiazole-4,7-dicarboxylic acid, **3**, which contains the carboxy groups in the desired positions. Treatment of **2** with aqueous alkali followed by acidification produced **3** melting at 325-329°. This acid showed normal reactivity and was thus a suitable intermediate for a number of 2,1,3-benzothiadiazole-4,7-dicarboxylic acid derivatives. As expected, the acid chloride, **4** obtained by warming **3** with thionyl chloride formed the esters, **5a** and **5b**, on treatment with methanol and ethanol, respectively. Treatment of **5b** with ammonia, methylamine and hydrazine proceeded smoothly to give the dicarboxamides, **6a** and **6b**, and the hydrazide, **6c**, in high yield.

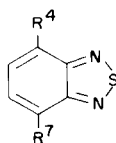


Substitution reactions of 4-bromo-7-nitro-2,1,3-benzothiadiazole (**3**), **7**, were briefly investigated so that 4,7-diamino derivatives could be prepared. Halogen atoms in *ortho*- or *paranitro*haloaromatics normally possess high reactivity, easily entering in nucleophilic displacement reactions. It was therefore surprising that reaction of **7** with ammonia in methanol was sluggish at 130-140° (8 hours, 200 lbs pressure), though no definite product could be isolated from the tarry products. In a similar manner (80°, 20 hours, 50 lbs pressure), however, dimethylamine and **7** produced the dark red 4-dimethylamino-7-nitro-2,1,3-benzothiadiazole, **8**, in 76% yield. Catalytic reduction of **8** (5% Pd on C, 5 hrs, 40 lbs H₂-pressure) in glacial acetic acid at 80° provided the red-brown 4-amino-7-dimethylamino-2,1,3-benzothiadiazole, **9**, in 58% yield.



The reduction of 4-alkyl-7-nitro-2,1,3-benzothiadiazoles, **11**, to 4-alkyl-7-amino-2,1,3-benzothiadiazoles, **12**, was investigated so that acylated and carbamoylated derivatives **13**, could be prepared. Nitration in concentrated sulfuric

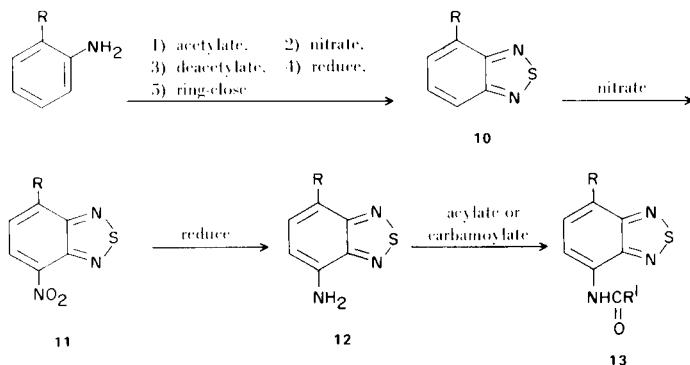
Table I
4,7-Disubstituted 2,1,3-Benzothiadiazoles



No.	R ⁴	R ⁷	% Yield	M.p., °C	Nitrogen		Sulfur	
					Calcd.	Found	Calcd.	Found
1	CH ₃	CH ₃	3.7	59	17.1	16.8	19.5	19.9
3	CO ₂ H	CO ₂ H	53	325-329	12.5	12.1	112 (a)	114 (a)
5a	CO ₂ CH ₃	CO ₂ CH ₃	11	163-164	11.1	11.0	126 (b)	135 (b)
5b	CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	62	65	10.0	9.8	11.4	11.7
6a	CONH ₂	CONH ₂	82	308-310	25.2	25.1	14.4	14.7
6b	CONHCH ₃	CONHCH ₃	100	227-228	22.4	22.1	12.8	13.1
6c	CONHNH ₂	CONHNH ₂	98	220-223	-	-	12.4	12.7
8	N(CH ₃) ₂	NO ₂	76	234-235	25.0	25.1	14.2	14.6
9	N(CH ₃) ₂	NH ₂	58	80-81	28.8	28.8	16.5	16.5
11b	C ₂ H ₅	NO ₂	84	103-105	20.1	19.8	-	-
11c	C ₃ H ₇	NO ₂	55	65-66.5	18.8	18.5	14.3	13.9
12b	C ₂ H ₅	NH ₂	50	63-64	-	-	17.9	17.9
13a	CH ₃	NHCONHCH ₃	42	195-196	25.2	25.0	14.4	14.3
13b	CH ₃	NHCON(CH ₃) ₂	85	295-296	23.7	23.9	-	-
13d	C ₂ H ₅	NHCONHCH ₃	68	171-172	23.3	23.5	13.6	13.6
13e	C ₂ H ₅	NHCOCH ₃	86	134-136	19.0	19.0	14.5	14.5
13f	C ₂ H ₅	NHCOCH ₂ Cl	87	102-103	16.5	16.4	-	-

(a) Neutralization equivalent. (b) Methoxy equivalent.

acid at 0.5° of 4-methyl-2,1,3-benzothiadiazole (4), **10a** (R = CH₃), took place at both position 5 and 7 to give **11a** (53%) and the 5-nitro isomer (12%), which were separated by silica chromatography. By contrast, nitration of 4-ethyl-2,1,3-benzothiadiazole (4), **10b** (R = C₂H₅), and 4-propyl-2,1,3-benzothiadiazole, **10c** (R = C₃H₇), proceeded smoothly under the same conditions to give exclusively the 7-nitro analogs, **11b** and **11c**, in 84% and 55% yield. Sodium dithionite reduction of **11b** (R = C₂H₅) gave 4-amino-7-ethyl-2,1,3-benzothiadiazole, **12b**, in 50% yield. Acylation and carbamoylation of the **12** compounds produced the amides and ureas of general formula **13** in high yield (Table I).



C. W. Bird *et al.* (5) have recently drawn attention to the need for 3,6-disubstituted *o*-phenylenediamines in heterocyclic synthesis. Certain 4,7-disubstituted 2,1,3-benzothiadiazoles (Table I) would seem to offer promise as precursors of 3,6-disubstituted *o*-phenylenediamines as judged by the effects of strong reducing reagents on 2,1,3-benzothiadiazoles leading to *o*-phenylenediamines (6).

EXPERIMENTAL

4,7-Dimethyl-2,1,3-benzothiadiazole, **1**.

2,5-Dimethylaniline, 60.5 g. (0.5 mole), was added portionwise to a mixture of acetic anhydride (700 ml.) and chloroform (100 ml.). The resulting slurry was cooled to 10° and nitrated by the dropwise addition of 30 ml. of 90% nitric acid. Chloroform and excess acetic anhydride was removed under reduced pressure. The concentrated reaction mixture was diluted with 19% hydrochloric acid (1000 ml.) and distilled with steam. The distillate (2,5-dimethyl-6-nitroaniline) was dissolved in methanol (500 ml.) and reduced in the presence of Raney-Nickel (3 g.) by the dropwise addition of 100 ml. of 85% hydrazine hydrate to the refluxing mixture. Filtration followed by concentration afforded the crude diamine which was dissolved in toluene (800 ml.) containing *N*-sulfinylaniline, 69.5 g. (0.5 mole), and heated to reflux for four hours. After hydrolysis of excess *N*-sulfinylaniline (250 ml. of 15% hydrochloric acid, one hour reflux), the toluene layer was washed with water, dried and concentrated. The residual solid was decolorized with charcoal in methanol and crystallized to give 9.0 g. (3.7%) of light yellow crystalline solid, m.p. 59°.

2,1,3-Benzothiadiazole, 4,7-dicarboxylic Acid Diethyl Ester, **5b**.

A mixture of 50 g. (1.345 moles) of **2** in 1000 ml. of 25% aqueous sodium hydroxide was heated to reflux until evolution of ammonia had ceased (15 hours). Acidification with hydrochloric acid afforded a brown solid which was air-dried and treated with refluxing thionyl chloride (2000 ml.) for 15 hours. After cooling and filtering, evaporation of the filtrate gave 130 g. (35.8%) of the crude dicarboxylic acid dichloride.

A portion, 30 g. (0.083 mole), of the crude acid chloride was added to a solution of 18.2 g. of pyridine in 300 ml. of ethanol. The mixture was refluxed for 2 hours, poured into water, and the product was filtered and dried. Recrystallization from hexane with the aid of charcoal afforded 20.0 g. (62%) of colorless crystalline solid, m.p. 65°; nmr (deuteriochloroform): δ 1.5 (3, t, CH₃), 4.6 (2, q, CH₂), and 7.48 ppm (2, s, CH=); ir (potassium bromide): 1725 (C=O), and 1272, 1178 cm⁻¹ (C-O-C).

2,1,3-Benzothiadiazole-4,7-*N,N'*-dimethyldicarboxamide, **6b**.

Methylamine was introduced into a solution of **5a**, 5.0 g. (19.8 mmoles), in 100 ml. of methanol. A colorless solid precipitated; yield, 4.5 g. (100%); m.p. 227-228°; ir (potassium bromide): 3320 (NH), 1640 (C=O), and 1540 cm⁻¹ (amide II).

2,1,3-Benzothiadiazole-4,7-dicarboxylic Acid **3**.

A mixture of 25.2 g. (0.1 mole) of the ester **5a** and 11.2 g. (0.2 mole) of potassium hydroxide in 250 ml. of ethanol and 10 ml. of water was refluxed for 12 hours, cooled, and concentrated to dryness under reduced pressure. The brown dipotassium salt was dissolved in 300 ml. of water and acidified with concentrated hydrochloric acid. Filtration afforded 11.8 g. (52.8%) of tan solid; m.p. 325-329° dec.

4-Dimethylamino-7-nitro-2,1,3-benzothiadiazole, **8**.

A slurry of 50.0 g. (0.19 mole) of **7** in 200 ml. of methanol and 90 g. (2.0 mole) of dimethylamine was heated at 80° with stirring in a pressurized (25-5 lbs) autoclave for twenty hours. After cooling, the reaction mixture was concentrated to dryness, and the product was washed with water and recrystallized from dimethylformamide (450 ml.) to give 32.7 g. (75.8%) of dark red crystalline solid, m.p. 234-235°.

4-Amino-7-dimethylamino-2,1,3-benzothiadiazole, **9**.

A solution of 4.4 g. (0.02 mole) of **8** in 200 ml. of glacial acetic

acid containing 1.5 g. of 10% palladium on charcoal was placed in a Parr bomb and heated at 80° under a hydrogen pressure of 35 to 40 lbs. After five hours, the reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. Recrystallization of the residual solid from hexane (200 ml.) and ethanol (15 ml.) with the aid of charcoal gave 2.2 g. (58%) of dark red crystalline solid; m.p. 80-81°; ir (potassium) 3450, 3119 (NH₂) and 1618 cm⁻¹ (C=).

4-Ethyl-7-nitro-2,1,3-benzothiadiazole, **11b**.

To a solution of 16.4 g. (0.1 mole) of **10** (R = C₂H₅) in 150 ml. of concentrated sulfuric acid was added dropwise with stirring, at 0°, 7.2 ml. of 70% nitric acid. After 30 minutes, the mixture was poured into ice water and filtered. The light yellow crystalline solid was recrystallized from 150 ml. of ethanol to give 17.5 g. (83.7%) of **11**; m.p. 103-105°; nmr (deuteriochloroform): δ 1.35 (3, t, CH₃), 3.15 (2, q, CH₂), 7.55 (1, s, CH=), and 7.7 ppm (1, s, CH=); ir: 1354 and 1520 cm⁻¹ (NO₂).

4-Amino-7-ethyl-2,1,3-benzothiadiazole, **12b**.

A mixture of 15.0 g. (0.072 mole) of **11b** and 150 g. (0.86 mole) of sodium dithionite was gradually added to 1000 ml. of boiling water. After the addition was completed, the reaction mixture was cooled to 5° and filtered. Recrystallization from hexane gave 6.0 g. (49.6%) of yellow-brown solid; m.p. 63-64°; ir: 3462, 3362 and 1618 cm⁻¹ (NH₂); nmr (deuteriochloroform): δ 1.25 (3, t, CH₃), 2.9 (2, q, CH₂), 5.85 (2, s, NH₂), and 6.6, 7.15 ppm (2, q, CH=).

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