Synthesis of 2,1,3-Benzothiadiazolecarbonitriles

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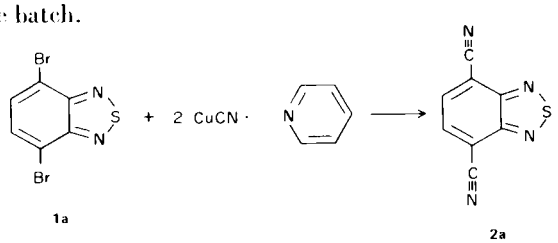
2,1,3-Benzothiadiazolecarbonitriles, **2**, have been prepared by two different methods. Reaction of bromo-2,1,3-benzothiadiazoles, **1**, with cuprous cyanide occurs advantageously in refluxing dimethylformamide to give **2**, complexed with curpous bromide. Hydrogen peroxide in hydrochloric acid at 30-40° is shown to be an effective reagent for efficient decomposition of these reactions complexes, **2**·CuBr, and subsequent isolation of **2**. Yields in the Sandmeyer method for preparing nitriles **2** were improved by diazotizing amino-2,1,3-benzothiadiazoles, **3**, with nitrosylsulfuric acid prior to reaction with the cuprous-sodium cyanide complex.

Certain 2,1,3-benzothiadiazoledicarbonitriles have been of recent interest due to their herbicidal activity (1) and because of their interesting defoliating properties (2). We have reported on a facile bromination of 2,1,3-benzothiadiazoles (3,4).

We have now examined an approach to the synthesis of 2,1,3-benzothiadiazolecarbonitriles, **2**, that utilizes readily available bromo-2,1,3-benzothiadiazoles, **1**, (3,4) and cuprous cyanide. Of the many procedures described in the literature for the preparation of aromatic nitriles (5), metathesis (**1** and metal cyanides) appeared to be the method of choice for the preparation of **2** (6).

Good results have been obtained by heating a mixture of 4,7-dibromo-2,1,3-benzothiadiazole, **1a**, with the pyridine-cuprous cyanide complex at 230° for three hours. Treatment of the crude product with 25% hydrochloric acid followed by extraction with benzene gave 2,1,3-benzothiadiazole-4,7-dicarbonitrile, **2a**, in 49% yield. The reaction was exothermic at about 210° and hazards may be involved in treating large quantities of starting materials in one batch.



1a 2a

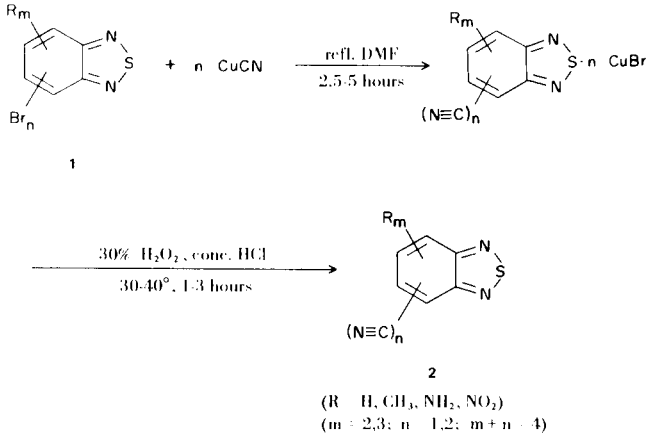
Reaction of the various **1** compound (Table I) with equimolar amounts of cuprous cyanide has been found to proceed rapidly (2.5 to 5 hours) and efficiently in refluxing dimethylformamide (7). As the reaction proceeds, the solution usually becomes dark brown. The isolation of nitriles, **2**, from these reactions initially posed problems as the **2** compounds are produced in form of stable complexes with the cuprous bromide formed in these reactions. Complex formation between cuprous halides and aromatic as well as allylic and acrylic nitriles is well-documented (7). In several instances, nitrile cuprous salt complexes have been isolated and identified (8,9).

Effective methods for the decomposition of nitrile-cuprous ion complexes with subsequent release of the nitrile have been developed and reviewed (7). Decomposition of the complex formed from **1a** and curpous cyanide with aqueous ammonia (10) followed by extraction with benzene is tedious and yields of **2a** were generally low (1). Aqueous sodium cyanide (7) is very effective in destroying the **2**·CuBr complexes as it forms strong complexes with curpous ions which are water soluble. However, extraction of these aqueous cyanide solutions proved difficult because of their tendency to form emulsions with the solvent. In the present study, a mixture of 30% hydrogen peroxide and concentrated hydrochloric acid at 30-40° has been found to destroy the nitrile-cuprous bromide complexes formed in the reactions of **1** with cuprous cyanide. Oxidation by hydrogen peroxide of cuprous to cupric ion is rapid and the nitriles, **2**, which do not complex with the cupric salts in solution, separate and may be conveniently collected by filtration or extraction techniques.

The results obtained with variously substituted bromo-2,1,3-benzothiadiazoles, **1a**-**1e**, and cuprous cyanide in refluxing dimethylformamide, which are summarized in Table I, demonstrate the synthetic versatility of the tech-

nique outlined in Scheme I. In the oxidation step, cuprous bromide is converted into cupric chloride with the simultaneous formation of bromine (11). From the reaction times listed in Table I, it is apparent that the methyl and amino substituents in **1** had little effect on the rate of the reaction. On the other hand, the nitro group in **1j** and **1k** markedly increased the reaction rate as would be expected from an aromatic *ortho*-nitrobromo compound.

Scheme I



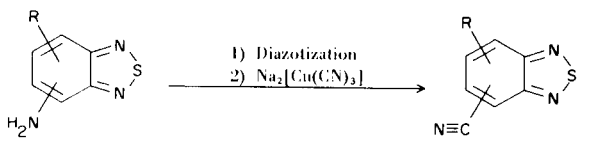
1

2

(R = H, CH_3, NH_2, NO_2)
(m = 2,3; n = 1,2; m + n = 4)

Interestingly, reaction of **1a** could not be effected with sodium or potassium cyanide under conditions that gave reaction with cuprous cyanide. Attempted reaction of silver cyanide and **1a** in refluxing acetonitrile was also unsuccessful. 4,7-Dichloro- and 4,5,7-trichloro-2,1,3-benzothiadiazole were stable when heated in refluxing dimethylformamide containing 2.2 molar equivalents of cuprous cyanide over a period of ten hours. Similarly, attempted reaction of these two chlorobenzothiadiazoles with cuprous cyanide at 200-230° in the absence of solvent led to the recovery of starting materials.

Although the decomposition of diazonium salt solutions with the watersoluble sodium cyanide-cuprous cyanide complex, $Na_2[Cu(CN)_3]$, is a standard method of introducing cyano groups into aromatic compounds (5), decomposition of diazonium salts derived from amino-2,1,3-benzothiadiazoles in the presence of cuprous cyanide-sodium or potassium cyanide has not been reported. As the amino-2,1,3-benzothiadiazoles **3a** (12), **3b** (12) and **3c** (13) were readily available to us, it was decided to diazotize **3a** and **3b** in 10% hydrochloric acid with sodium nitrite and treat



3

a: 4-NH_2, R = H
b: 5-NH_2, R = H
c: 4-NH_2, 5,7-Cl_2

2

l: 4-CN, R = H
m: 5-CN, R = H
n: 4-CN, R = 5,7-Cl_2

the resulting diazonium salt solution with sodium-curpous cyanide. The yield obtained by this method from **3a** was very poor (9%), whereas no product was obtained from diazotized **3b**. However, when the diazotization of **3b** was carried out with sodium nitrite in concentrated sulfuric acid, a 63% yield of **2m** was obtained. In this fashion, we were able to prepare 5,7-dichloro-2,1,3-benzothiadiazole-4-carbonitrile, **2n**, in 30% yield from **3c**. All carbonitriles showed a strong nitrile bond in the region between 2225 and 2238 cm^{-1} consistent with the assigned structure.

In conclusion, the preparation of 2,1,3-benzothiadiazolecarbonitriles from bromo-2,1,3-benzothiadiazoles and cuprous cyanide in refluxing dimethylformamide followed by oxidation of the resulting nitrile-cuprous bromide complex with hydrogen peroxide in hydrochloric acid has been shown to be an effective procedure. The ease of producing bromo-2,1,3-benzothiadiazoles by direct bromination (3) makes it a potentially useful preparative method. 2,1,3-Benzothiadiazole(mono)carbonitriles were also obtained by diazotization of the appropriate amino-2,1,3-benzothiadiazole with nitrosylsulfuric acid, followed by reaction with excess of aqueous sodium-cuprous cyanide.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Thomas-Hoover capillary apparatus.

5,6-Dibromo-2,1,3-benzothiadiazole, **1d**.

Catalytic reduction of 1,2-dibromo-4,5-dinitrobenzene (m.p. 114-115°) in tetrahydrofuran (56 lbs H_2 pressure, Raney-Nickel) gave the corresponding diamine in 92% yield. Reaction of the crude diamine with *N*-sulfinylaniline in refluxing toluene afforded **1d** in 35% yield, m.p. 132-134°.

Anal. Calcd. for $C_6H_2Br_2N_2S$: N, 9.5; S, 10.9. Found: N, 9.6; S, 10.8.

5-Amino-4,7-dibromo-2,1,3-benzothiadiazole, **1i**.

To a stirred solution of 7.55 g. (0.05 mole) of 5-amino-2,1,3-benzothiadiazole, **3b**, in 100 ml. of glacial acetic acid was added dropwise (20 minutes) 32.0 g. (0.2 mole) of bromine. The reaction mixture was poured into 800 ml. of cold 15% ammonium hydroxide and the product was filtered, washed with water and dried to give 12.7 g. (82%) of **1i**, a yellow crystalline solid, m.p. 155°.

Anal. Calcd. for $C_6H_3Br_2N_3S$: N, 13.6; S, 10.4. Found: N, 13.2; S, 10.4.

2,1,3-Benzothiadiazole-4,7-dicarbonitrile, **2a**.

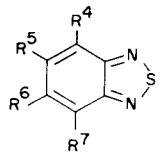
A) From 4,7-Dibromo-2,1,3-benzothiadiazole, **1a**, and C_5H_5·CuCN.

A powdered mixture of 5.9 g. (0.02 mole) of **1a** and 6.8 g. (0.04 mole) of the pyridine-cuprous cyanide complex (16) was heated for 3 hours at 230° (nitrogen blanket). There appeared to be an exothermic reaction at 210° and the temperature rose briefly to 235°. After cooling, the glassy reaction product was finely ground, taken up in 100 ml. of concentrated hydrochloric acid and 50 g. of ice, stirred for 1.5 hours and extracted with 150 ml. of benzene to give 2.0 g. (49%) of **2a**, a yellow brown solid, m.p. 179-181°. Recrystallization from benzene raised the melting point to 189-191°.

Table I

Reaction of Bromo-2,1,3-benzothiadiazoles with Cuprous Cyanide in Refluxing Dimethylformamide

Final Product,



No. of Bromo Compound	No.	R^4	R^5	R^6	R^7	Reaction Time (Hour)	Yield %	M.p., °C	Formula	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
1a (a)	**2a**	CN	H	H	CN	3-10	50-87	189-191	$C_8H_2N_4S$	30.1	29.7	17.2	17.2
1b (a)	**2b**	CN	CN	H	H	2.5-4	26-46	156-159	$C_8H_2N_4S$	30.1	29.6	–	–
1c (b)	**2c**	CN	H	CN	H	3.5-4	40-52	175-178	$C_8H_2N_4S$	30.1	29.7	17.2	16.7
1d	**2d**	H	CN	CN	H	4	29	201-203	$C_8H_2N_4S$	30.1	29.8	17.2	17.1
1e (a)	**2e**	CN	CH_3	H	H	5	63	150-153	$C_8H_5N_3S$	24.0	23.5	18.3	18.4
1f (a)	**2f**	CN	H	H	CH_3	2	79	168-173	$C_8H_5N_3S$	–	–	18.3	18.0
1g (a)	**2g**	CH	CH_3	H	CN	3.5	61	173-177	$C_9H_4N_4S$	28.0	27.6	16.0	15.5
1h (a)	**2h**	CN	CH_3	CH_3	CN	6.5	50	235-236	$C_{10}H_6N_4S$	26.2	25.8	15.0	15.1
1i	**2i**	CN	NH_2	H	CN	4	15	241-218	$C_8H_3N_5S$	34.8	35.2	15.9	16.4
1j (c)	**2j**	CN	NO_2	H	Br	2.5 (d)	43	190-193	$C_7HBrN_4O_2S$	19.6	19.2	11.2	11.2
1k (b)	**2k**	CN	H	CN	NO_2	3.5	7	224-228	$C_8HN_5O_2S$	–	–	13.9	14.1

(a) Reference 3. (b) Reference 14. (c) Reference 15. (d) Reaction temperature 75°; higher temperature led to extensive decomposition (see Experimental).

B) From **1a** and Cuprous Cyanide in DMF.

A mixture of 70 g. (0.238 mole) of **1a**, 43 g. (0.478 mole) of cuprous cyanide and 700 ml. of dimethylformamide was refluxed (10 hours) in a dry nitrogen atmosphere. After cooling, the dark reaction mixture was decanted into 1400 ml. of 10% amonium hydroxide, 700 ml. of benzene was added and the mixture was stirred for 10 minutes and phase separated. The extraction was repeated with an additional 700 ml. portion of benzene. The combined benzene extracts were washed with water, dried (magnesium sulfate), filtered and evaporated. Repeated recrystallization from benzene (2X) and xylene (1X) afforded 12 g. (44%) of **2a**, m.p. 187-189°.

Anal. Calcd. for $C_8H_2N_4S$: C, 51.6; H, 1.1; N, 30.1; S, 17.2. Found: C, 52.1; H, 1.5; N, 29.6; S, 17.2.

C) From **1a** and Cuprous Cyanide in DMF Followed by Oxidation of the Reaction Complex, **2a**-Cuprous Bromide, With Hydrogen Peroxide/Hydrochloric Acid Mixture.

A solution of 29.4 g. (0.1 mole) of **1a** and 20 g. (0.22 mole) of cuprous cyanide in 300 ml. of DMF was refluxed (10 hours), then concentrated under reduced pressure. The black residue was suspended in 50 ml. of concentrated hydrochloric acid and 25 ml. of 30% hydrogen peroxide was added dropwise with stirring. The addition was exothermic and the temperature was controlled at 40° by external cooling. The mixture was stirred for a total of 3 hours and filtered. Both filtrate and filter cake were extracted with 600 ml. of benzene. The combined benzene extracts were washed with water and concentrated to give 16.2 g. (87%) of **2a**, m.p. 189-191°.

7-Bromo-5-nitro-2,1,3-benzothiadiazole-4-carbonitrile, **2j**.

A solution of 17 g. (0.05 mole) of **1j** and 9 g. (0.1 mole) of cuprous cyanide in 200 ml. of dimethylformamide was heated at 75° for 2.5 hours. The black reaction mixture was concentrated under reduced pressure, taken up in 100 ml. of concentrated hydrochloric acid and 100 ml. of benzene. To this mixture was added dropwise (1.5 hours) 25 ml. of 30% hydrogen peroxide at 30-40°. The benzene layer was washed with water, dried (magnesium sulfate), filtered and concentrated to give 6 g. (43%) of **2j**, a tan solid, m.p. 190-193°.

When this reaction was carried out in refluxing dimethylformamide (4 hours), only a black tar was formed.

2,1,3-Benzothiadiazole-4-carbonitrile, **2l**.

A solution of 10 g. (0.066 mole) of 4-amino-2,1,3-benzothiadiazole in 150 ml. of 10% hydrochloric acid was diazotized with 4.7 g. (0.067 mole) of sodium nitrite. The dark red and muddy looking mixture was poured into a solution of 10 g. of sodium cyanide and 5 g. of cuprous cyanide in 200 ml. of water, heated on a steam bath (1.5 hours), cooled and filtered. Extraction of tje filter cake with ether gave 0.9 g. (8.5%) of **2l**, a reddish crystalline solid, m.p. 124-125° (from ether-hexane).

Anal. Calcd. for $C_7H_3N_3S$: N, 26.1. Found: N, 25.9.

2,1,3-Benzothiadiazole-5-carbonitrile, **2m**.

Sodium nitrite, 10.1 g. (0.146 mole), was added in small portions with stirring to 44 ml. of cold (0°) concentrated sulfuric acid. The mixture was briefly (5 minutes) heated to 55°. To the cooled (10°) solution was added dropwise (15 minutes) a solution of 11 g. (0.073 mole) of 5-amino-2,1,3-benzothiadiazole, **3b**, in 55 ml. of glacial acetic acid. The mixture was stirred for one hour and added slowly to a cold (5°) aqueous solution of the sodium cyanide-cuprous cyanide complex prepared from 21.5 g. (0.438 mole) of sodium cyanide and 13.1 g. (0.146 mole) of cuprous cyanide in 300 ml. of water. Sodium carbonate was added from time to time to keep the solution basic. After twelve hours, the mixture was filtered. Extraction with benzene of the filter cake gave 7.5 g. (63%) of **2m**, a yellow-orange crystalline solid, m.p. 112-113°.

Anal. Calcd. for $C_7H_3N_3S$: N, 26.1; S, 19.9. Found: N, 25.9; S, 20.0

5,7-Dichloro-2,1,3-benaothiadiazole-4-carbonitrile, **2n**.

This compound was prepared analogously in 30% yield from 4-amino-5,7-dichloro-2,1,3-benzothiadiazole, **3c**, and melted at 188-192°.

Anal. Calcd. for $C_7HCl_2N_3S$: Cl, 30.8; N, 18.2; S, 13.9. Found: Cl, 30.6; N, 18.1; S, 13.8.

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