Synthesis of Benzofurazancarbonitriles

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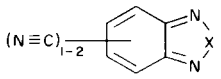
Carbonitriles of general structure I containing the group VI elements oxygen and sulfur offer an excellent series to investigate the influence of the heteroatom on a variety of chemical and biological properties. In the preceding article (1), it was shown that bromo-2,1,3-benzothiadiazoles undergo reaction with cuprous cyanide to give 2,1,3-benzothiadiazolecarbonitriles, Ib, in good yield. In conjunction with our interest in carbonitriles of aromatic heterocyclic



I

a: X = O
b: X = S

compounds as potential herbicides (2), it was noted that synthesis routes to benzofurazancarbonitriles, Ia, were not available. We now wish to report the synthesis of members of this class of heterocyclic carbonitriles employing the techniques previously reported for Ib.

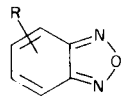
In an earlier study, it was shown that bromine in refluxing 47% hydrobromic acid was a particularly efficient route for the synthesis of a variety of bromo-2,1,3-benzothiadiazoles (3). In the present work, the dropwise addition of bromine to a mixture of benzofurazan, Ia, in refluxing (126°) 47% hydrobromic acid led to extensive degradation of the heterocycle. At ambient temperature, treatment of **1a** with bromine in 47% hydrobromic acid produced exclusively and quantitatively tetrabromotetrahydrobenzofurazan which proved to be stable in refluxing 47% hydrobromic acid.

Bromination of 4-methylbenzofurazan, **1b**, with bromine in 47% hydrobromic acid at 65-70°, resulted in extensive side chain bromination, with the formation of 4-bromo-7-(bromomethyl)benzofurazan, **2b**, along with about 12% of the dibromomethyl analog. Analytical and spectral data were consistent with the assigned structure showing the signals characteristic of a bromomethyl (δ 4.8 ppm) compound in addition to two aromatic protons at 7.6 ppm.

Reaction of 5-methylbenzofurazan, **1c**, in 47% hydrobromic acid occurred readily at 80-90° to give 4-bromo-5-methylbenzofurazan, **2c**, in 85% yield along with 5% of the 4,7-dibromo analog and 10% of starting material, **1c**.

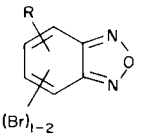
5-Bromobenzofurazan, **1d**, reacted analogously to give 4,5-dibromobenzofurazan, **2d**. Bromination of **1d** proceeded smoothly also in the presence of catalytic amounts of iron filings at 85-90° (2 hours) in the absence of aqueous hydrobromic acid. Under the latter conditions, **2d** was isolated in 64% yield in addition to 10% of starting material, **1d**. Continued bromination at elevated temperature (90-130°), led to the formation of 4,5,7-tribromobenzofurazan, **2e**.

Treatment of 5,6-dimethylbenzofurazan, **1e**, with bromine in refluxing 47% hydrobromic acid gave 4,7-dibromo-5,6-dimethylbenzofurazan, **2f**, in 78-85% yield. Analytical and spectral data were consistent with the assigned structure.



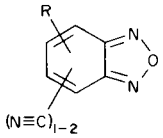
1

a: R = H
b: R = 4-CH_3
c: R = 5-CH_3
d: R = 5-Br
e: R = 5,6-$(CH_3)_2$



2

a: 4,7-Br_2, R = H
b: 4-Br, R = 7-CH_2Br
c: 4-Br, R = 5-CH_3
d: 4,5-Br_2, R = H
e: 4,5,7-Br_3, R = H
f: 4,7-Br_2, R = 5,6-$(CH_3)_2$



3

a: 5-CN, R = H
b: 4-CN, R = 5-CH_3
c: 4,5-$(CN)_2$, R = H
d: 4,7-$(CN)_2$, R = H

Replacement of bromine atoms in **1d**, **2a**, **2c**, and **2f** with cuprous cyanide occurred readily in dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMA) at elevated temperature within 1.5-5 hours to give the corresponding carbonitriles **3a**, **3b**, **3c** and **3d**, respectively, in moderate yields. Analytical and spectral data (ν C≡N 2225-2235 cm^{-1}) were again consistent with the assigned structure.

Benzofurazancarbonitrile-cuprous bromide complexes appear to be less stable than corresponding 2,1,3-benzothiadiazolecarbonitrile - cuprous bromide complexes (1). For example, all four carbonitriles, **3a**, **3b**, **3c**, and **3d**, could be extracted from their reaction mixtures with boiling benzene or xylene. Consequently, oxidation of cuprous to cupric ion prior to extraction of the nitrile proved unnecessary.

EXPERIMENTAL

4-Bromo-7-(bromomethyl)benzofurazan, **2b**.

To a refluxing mixture of 33.0 g. (0.246 mole) of 4-methylbenzofurazan (5), **1b**, and 175 ml. of 47% hydrobromic acid was added dropwise over six hours 30 ml. of bromine. At this point, glc indicated the presence of four compounds, one major component and three impurities. The reaciton mixture was diluted with water and extracted with methylene chloride. After removal of solvent, the residual oil crystallized from 75 ml. of methanol to give 27.5 g. (38%) of **2b** containing *ca.* 12% of the dibromomethyl analog; m.p. 60-62°; nmr (deuteriochloroform): δ 4.8 (2, s, CH_2), and 7.6 ppm (2, q, J = 7 Hz, CH=).

Anal. Calcd. for $C_7H_4BrN_2O$: Br, 54.8; N, 9.6. Found: Br, 55.9; N, 8.9.

4-Bromo-5-methylbenzofurazan, **2c**.

A mixture of 44.2 g. (0.335 mole) of 5-methylbenzofurazan (4), **1c**, 35 ml. of bromine and 200 ml. of 47% hydrobromic acid was stirred and heated at 80-90°. After two hours, glc indicated the following composition of the reaction mixture: 10% of starting material, **1c**, 85% of **2c** (desired product), and 5% higher brominated material. A sample taken 30 minutes later indicated an increase in the amount of dibromo derivative. The mixture was cooled and filtered, and the solid product was recrystallized from acetone to give 42.2 g. (60%) of **2c**; m.p 121.5-124°.

Anal. Calcd. for $C_7H_5BrN_2O$: Br, 37.1; N. 13.1. Found: Br, 37.1; N, 13.1.

5-Methylbenzofurazan-4-carbonitrile, **3b**.

A solution of 21.3 g. (0.1 mole) of **2c** and 20.0 g. (0.22 mole) of cuprous cyanide in 150 ml. of *N,N*-dimethylacetamide was heated at 150-155° for five hours and concentrated under reduced pressure. The residue was extracted with boiling xylene (5 x 200 ml.), the solvent was removed, and the residual oil was extracted with 1000 ml. of hexane. The extract was concentrated to 150 ml. and cooled to give 2.3 g. (14.5%) of **3b**, an orange crystalline solid; m.p. 97-99°.

Anal. Calcd. for $C_8H_5N_3O$: N, 26.4; Br, 0.0. Found: N, 25.9; Br, <0.5.

4,5-Dibromobenzofurazan, **2d**.

Fifteen g. (0.075 mole) of **1d** (5) and 0.5 g. of iron filings were mixed and heated. Bromine, 5 ml. was added slowly at 85-90° with sitrring. Reaction was closely followed by glc and as soon as glc indicated that dibromination took place (2 hours), addition of bromine was discontinued. The reaction mixture still contained about 19% of **1d**. On cooling, the melt solidified. Recrystallization from methanol with the aid of charcoal afforded 13.2 g. (64%) of **2d**; m.p. 118-121° (lit (6) m.p. 123-124°); nmr (deuteriochloroform): δ 7.7 ppm (q, J = 9 Hz).

Anal. Calcd. for $C_6H_2Br_2N_2O$: N, 10.0. Found: N, 9.6.

Benzofurazan-4,5-dicarbonitrile, **3c**.

A solution of 32.0 g. (0.115 mole) of **2d** and 23 g. (0.259 mole) of cuprous cyanide in 200 ml. of DMF was heated at 135-140° for three hours. The mixture was concentrated under reduced pressure. The black residual solid was purified by silica chromatography to give 1.7 g. (8.5%) of **3c**, m.p. 110-112°; nmr (deuteriochloroform): δ 7.7 and 8.5 ppm (2, CH=).

Anal. Calcd. for $C_8H_2N_4O$: N, 32.9; Br, 0.0. Found: N, 32.6; Br, <0.2.

4,5,7-Tribromobenzofurazan, **2e**.

5-Bromobenzofurazan (5), **1d**, 21.5 g. (0.104 mole), and 1 g. of iron filings were heated, with stirring, until the organic material melted. Bromine, 20 ml., was added dropwise over a two hour period. Glc indicated that the reaction mixture consisted of *ca.* 60% of dibrominated product, **2d**, and *ca.* 40% of tribromo analog.

The reaction mixture was heated to 130° and an additional 10 ml. of bromine was added dropwise over a two hour period. At this time, glc indicated the absence of **2d**. The reaction mixture was cooled, dissolved in warm aqueous ethanol, cooled and filtered. The crude solid was recrystallized from acetone to give 12.1 g. (29%) of brownish crystalline solid, m.p. 121-125°.

Anal. Calcd. for $C_6HBr_3N_2O$: N, 7.2. Found: N, 7.3.

4,7-Dibromo-5,6-dimethylbenzofurazan, **2f**.

A mixture of 5,6-dimethylbenzofurazan (4), **1e**, 22.5 g. (0.152 mole), 200 ml. of 47% hydrobromic acid and 40 ml. of bromine was heated to reflux for six hours, cooled and poured into cold water. The yellow precipitate was suction-filtered, washed with water and cold methanol to give 46.8 g. (84%) of **2f**, m.p. 144-146°.

Anal. Calcd. for $C_8H_6Br_2N_2O$: N, 9.2. Found: N, 9.1.

5-Benzofurazancarbonitrile, **3a**.

A solution of 10.0 g. (0.05 mole) of **1d** (5) and 5 g. (0.055 mole) of cuprous cyanide in 50 ml. of *N,N*-dimethylacetamide was stirred and heated at 160-170° for five hours. Glc indicated that all of **1d** had reacted. The solvent was removed under reduced pressure and the residue was extracted with boiling xylene. The combined xylene extracts were evaporated to dryness and the crude product was recrystallized from hexane to give 2.6 g. (36%) of yellow crystalline solid; m.p. 81°; ir (potassium bromide): 2225 cm^{-1} (C≡N).

Anal. Calcd. for $C_7H_3N_3O$: N, 28.9; Br, 0.0. Found: N, 28.4; Br, <0.2.

4,7-Benzofurazandicarbonitrile, **3d**.

A solution of 45.0 g. (0.162 mole) of 4,7-dibromobenzofurazan (6), **2a**, and 30 g. (0.5 mole) of cuprous cyanide in 200 ml. of dimehtylformamide was stirred and heated at 150-155° for 1.5 hours. Dimethylformamide was removed under reduced pressure and the residue was extracted several times with boiling xylene. After evaporation of the xylene, the crude dinitrile was recrystallized from ethanol (charcoal) to give 12.0 g. (43%) of yellow-brown crystals; m.p. 185-188°; ir (potassium bromide): 2230 cm^{-1} (C≡N).

Anal. Calcd. for $C_8H_2N_4O$: N, 32.9; Br, 0.0. Found: N, 32.9; Br, <0.2.

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