Synthesis of 4(6)-aryloxy- and 4-arylthio-2,1,3-benzoxadiazoles

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Reactions of 4,6-dibromo-2,1,3-benzoxadiazole with phenols or arenelthiols lead to 4-aryloxy-6-bromo-2,1,3-benzoxadiazoles or 4-arylthio-6-bromo-2,1,3-benzoxadiazoles, respectively. Isomeric 6-aryloxy-4-bromo-2,1,3-benzoxadiazoles were synthesized by replacement of the fluorine atom in 2,6-dibromo-4-fluoro-1-nitrosobenzene with phenols and treatment of the resulting 4-aryloxy-2,6-dibromo-1-nitrosobenzene with sodium azide.

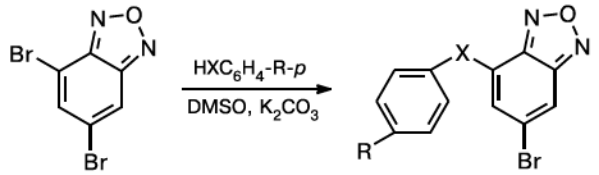
Key words: 4,6-diboromo-2,1,3-benzoxadiazole, 4(6)-aryloxy-2,1,3-benzoxadiazoles, 4-arylthio-2,1,3-benzoxadiazoles.

2,1,3-Benzoxadiazoles are biologically active and can find application as antileukemic agents.[1] Moreover, luminescent properties of some amino-2,1,3-benzoxadiazoles (benzofurazans) have attracted much interest due to their possible usage as fluorescent markers for biochemical objects.[2] Functionalized 2,1,3-benzoxadiazoles were prepared using amination,[3] alkynation,[4] and arylation reactions under Suzuki—Miyaura conditions.[5]

In the current work, we investigated synthetic pathways to benzofurazan derivatives having aryloxy and arylthio groups in position 4, and cyclic amino groups in position 6.

Treatment of 4,6-dibromo-2,1,3-benzoxadiazole (**1**) with phenols or arenethiols in DMSO in the presence of potassium carbonate gave the corresponding 4-aryloxy- or 4-arylthio-2,1,3-benzoxadiazoles **2a—f** (Scheme 1).

Scheme 1



1 **2a—f**

X = O, R = H (**a**), Me (**b**), Bu^t (**c**), Cl (**d**); X = S, R = H (**e**), Me (**f**)

Structures **2a—f** were confirmed by analytic methods including ^{1}H NMR and mass spectroscopy. In addition, particular replacement of the 4-positioned bromine atom by aryloxy or arylthio group was proved using two-dimensional NMR spectroscopy NOESY, with compounds **2c**,**f** being the examples. In a 2D NOESY spectrum of compound **2c**, correlation between the protons in positions 2 and 6 of the 4-*tert*-butylphenoxide substituent (δ_H 7.26), and protons in position 5 of the benzoxadiazole ring (δ_H 6.65) is clearly visible. For arylthiofurazan **2f**, correlation is observed between the protons in positions 2 and 6 of the 4-methylphenylthio substituent (δ_H 7.58), and protons in position 5 (δ_H 6.73) of benzofurazan.

It should be noted that reaction of dibromofurazan (**1**) with phenol and arylthio compounds was similar to its reaction with secondary aliphatic amines.[3]

Regioselectivity of bromine atom replacement in position 4 rather than 6 was ensured by our original synthesis of isomeric 6-aryloxy-4-bromo-2,1,3-benzoxadiazoles (**3a**,**b**) starting from 2,6-dibromo-4-fluoro-1-nitrosobenzene (**4**) (Scheme 2).

It is known that reaction of nitrosobenzene and its simpliest analogs with naphthols proceeds via nitroso group direct interaction and subsequent formation of azomethines[6] (Scheme 3).

In our case, high fugacity of the fluorine atom together with the bromine atom *ortho*-positioned to a nitro group in nitroarene **4** ensures fluorine atom substitution instead of condensation onto nitroso group. Nucleofugacity of the remaining bromine atom in benzofurazans **2** is reduced compared to the initial 4,6-dibromo-2,1,3-benzoxadiazole (**1**). For instance, amination of the compounds **2** with pyrrolidine and morpholine proceeds

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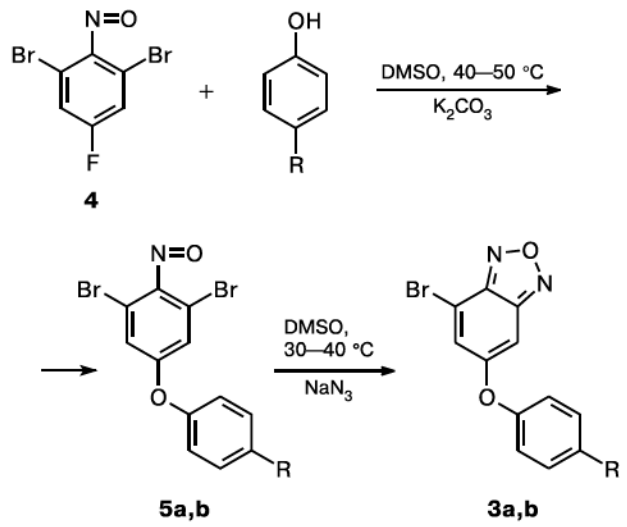
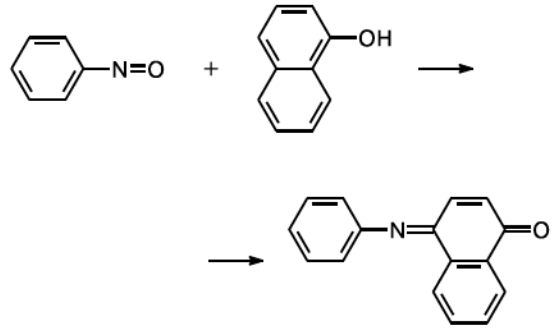
Scheme 2



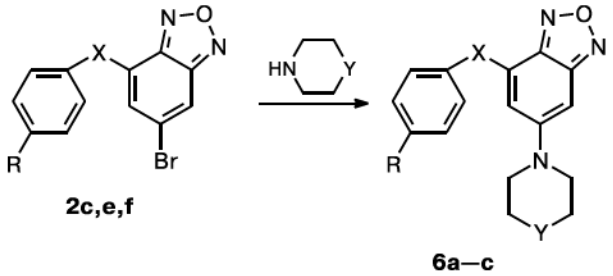
R = Me (**a**), Bu^t (**b**)

Scheme 3



only on heating to 80—90 °C, while monoamination of dibromofurazan (**1**) in position 4 (Scheme 4) proceeds at 20 °C.[3]

Scheme 4



X = O, R = Bu^t, Y = O (**a**); X = S, R = H, Y = O (**b**);
X = S, R = H, Y = σ-bond (**c**)

The resulting products **6a—c** possess luminescent properties which makes them promising as fluorescent markers.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) spectrometer in DMSO-d_6 using $SiMe_4$ as the internal standard, and on «Bruker AV-300» (300 MHz) in $CDCl_3$, the internal standard $SiMe_4$. Reaction course was monitored by TLC on Silufol UV-254 plates. Melting points were measured using Boetius melting point apparatus. The mass spectra were recorded on a Finnigan MAT 8200 spectrometer. High resolution mass spectra were recorded on a DFC High Resolution GC/MS mass spectrometer.

4,6-Dibromo-2,1,3-benzoxadiazole (1) and **2,6-dibromo-4-fluoronitrosobenzene (4)** were prepared using the existing methods.[3,7]

Synthesis of 4-aryloxy-6-bromo-2,1,3-benzoxadiazoles 2 (general procedure). Phenol (6 mmol) and K_2CO_3 (0.83 g, 6 mmol) were added to a solution of 4,6-dibromo-2,1,3-benzoxadiazole (**1**) (1.39 g, 5 mmol) in DMSO (10 mL). The reaction mixture was stirred for 10—11 h at 55—60 °C. The resulting solution was cooled in an ice bath. The precipitate was filtered, washed with water, and dried.

6-Bromo-4-phenoxy-2,1,3-benzoxadiazole (2a). Yield 1.11 g (76%), m.p. 93—94 °C (EtOH). Found (%): C, 49.24; H, 2.40; N, 9.85. $C_{12}H_7N_2O_2Br$. Calculated (%): C, 49.48; H, 2.40; N, 9.62. ^{1}H NMR, δ: 6.65 (s, 1 H, H(5)); 7.35 (m, 3 H, H(2′), H(4′), H(6′)); 7.54 (t, 2 H, H(3′), H(5′), J = 7.7 Hz); 8.15 (s, 1 H, H(7)). MS, m/z (I_{rel} (%)): 292 [M$^+$] (100), 290 (96), 262 (66), 260 (67), 211 (37), 153 (40), 76 (86), 65 (48), 51 (36).

6-Bromo-4-(4-methylphenoxy)-2,1,3-benzoxadiazole (2b). Yield 1.33 g (87%), m.p. 88—89 °C (EtOH). Found (%): C, 51.19; H, 2.94; N, 9.12. $C_{13}H_9N_2O_2Br$. Calculated (%): C, 51.14; H, 2.95; N, 9.18. ^{1}H NMR, δ: 2.36 (s, 3 H, Me); 6.60 (d, 1 H, H(5), J = 1.2 Hz); 7.24 (d, 2 H, H(2′), H(6′), J = 8.5 Hz); 7.33 (d, 2 H, H(3′), H(5′), J = 8.5 Hz); 8.17 (d, 1 H, H(7), J = 1.2 Hz). MS, m/z (I_{rel} (%)): 306 [M]$^+$ (17), 276 (18), 274 (19), 167 (26), 104 (18), 91 (100), 89 (22), 79 (20), 77 (59), 65 (90), 63 (31), 51 (31), 39 (36).

6-Bromo-4-(4-*tert*-butylphenoxy)-2,1,3-benzoxadiazole (2c). Yield 1.46 g (84%), m.p. 110—112 °C (EtOH). Found (%): C, 55.35; H, 4.09; N, 7.75. $C_{16}H_{15}N_2O_2Br$. Calculated (%): C, 55.33; H, 4.32; N, 8.06. ^{1}H NMR, δ: 1.32 (s, 9 H, Bu^t); 6.65 (d, 1 H, H(5), J = 1.2 Hz); 7.26 (d, 2 H, H(2′), H(6′), J = 8.8 Hz); 7.55 (d, 2 H, H(3′), H(5′), J = 8.8 Hz); 8.20 (d, 1 H, H(7), J = 1.2 Hz). MS, m/z (I_{rel} (%)): 347 [M]$^+$ (14), 334 (17), 235 (12), 207 (17), 179 (22), 117 (24), 107 (26), 91 (50), 76 (43), 65 (21), 55 (38), 51 (17), 43 (47).

6-Bromo-4-(4-chlorophenoxy)-2,1,3-benzoxadiazole (2d). Yield 1.40 g (86%), m.p. 89—90 °C (EtOH). Found (%): C, 44.14; H, 1.83; N, 8.69. $C_{12}H_6N_2O_2ClBr$. Calculated (%): C, 44.23; H, 1.84; N, 8.60. ^{1}H NMR, δ: 6.87 (d, 1 H, H(5), J = 1.2 Hz); 7.39 (d, 2 H, H(2′), H(6′), J = 8.9 Hz); 7.56 (d, 2 H, H(3′), H(5′), J = 8.9 Hz); 8.24 (d, 1 H, H(7), J = 1.2 Hz). MS, m/z (I_{rel} (%)): 326 [M]$^+$ (12), 296 (11), 289 (10), 261 (15), 259 (15), 180 (15), 152 (14), 127 (15), 111 (44), 99 (44), 76 (42), 75 (100), 63 (30), 50 (43).

6-Bromo-4-phenylthio-2,1,3-benzoxadiazole (2e). Thiophenol (0.27 mL, 2.5 mmol) and K_2CO_3 (0.34 g, 2.5 mmol) were

added to a solution of 4,6-dibromo-2,1,3-benzoxadiazole (**1**) (0.70 g, 2.5 mmol) in DMSO (10 mL). The mixture was stirred in room temperature for 6 h. The resulting solution was cooled in an ice bath. The precipitate was filtered, washed with water, and dried. Yield 0.60 g (78%), m.p. 92—93 °C (EtOH). Found (%): C, 46.70; H, 2.22; N, 9.08; S, 10.65. $C_{12}H_7N_2OBrS$. Calculated (%): C, 46.90; H, 2.28; N, 9.12; S, 10.42. ^{1}H NMR, δ: 6.85 (s, 1 H, H(5)); 7.57 (m, 3 H, H(3´), H(4´), H(5´); 7.67 (m, 2 H, H(2´), H(6´); 8.32 (c, 1 H, H(7)). MS, *m/z* (I_{rel} (%)): 308 [M]$^+$ (47), 306 (48), 278 (33), 276 (32), 197 (62), 196 (77), 109 (76), 93 (16), 88 (17), 77 (88), 69 (45), 65 (47), 51 (100), 50 (31), 39 (24).

6-Bromo-4-(4-methylphenylthio)-2,1,3-benzoxadiazole (2f) was obtained similarly from 4,6-dibromo-2,1,3-benzoxadiazole (**1**) (1.39 g, 5 mmol) in DMSO (15 mL), 4-methylthiophenol (0.58 g, 5 mmol) and K_2CO_3 (0.82 g, 6 mmol). Yield 1.25 g (78%), m.p. 100—101 °C (EtOH). Found (%): C, 48.80; H, 2.76; N, 8.76; S, 10.05. $C_{13}H_9N_2OBrS$. Calculated (%): C, 48.59; H, 2.80; N, 8.72; S, 9.96. ^{1}H NMR, δ: 2.40 (s, 3 H, Me); 6.73 (d, 1 H, H(5), *J* = 1.3 Hz); 7.40 (d, 2 H, H(3´), H(5´), *J* = 8.1 Hz); 7.58 (d, 2 H, H(2´), H(6´), *J* = 8.1 Hz); 8.28 (d, 1 H, H(7), *J* = 1.3 Hz). MS, *m/z* (I_{rel} (%)): 322 [M]$^+$ (50), 320 (53), 292 (35), 290 (36), 211 (36), 210 (35), 196 (47), 123 (84), 120 (31), 91 (81), 77 (66), 71 (50), 69 (53), 65 (100), 63 (100), 51 (39), 45 (76), 39 (74).

4-(4-*tert*-Butylphenoxy)-6-morpholino-2,1,3-benzoxadiazole (6a). Morpholine (1 mL, 11.6 mmol) was added to a solution of compound **2c** (1 g, 2.9 mmol) in DMSO (7 mL). The mixture was stirred at 70—80°C for 20 h, followed by cooling in an ice bath. The precipitate was filtered, washed with water, and dried. The product was purified by column chromatography using benzene for elution. Yield 0.50 g (50%), m.p. 120—121 °C (EtOH). Found (%): C, 67.75, H, 6.26, N, 11.80. $C_{20}H_{23}N_3O_3$. Calculated (%): C, 67.98; H, 6.51; N, 11.82. ^{1}H NMR, δ: 1.30 (s, 9 H, Bu^t); 3.33 (t, 4 H, $\underline{CH_2}$N, *J* = 4.8 Hz); 3.70 (t, 4 H, $\underline{CH_2}$O, *J* = 4.8 Hz); 6.67 (s, 1 H, H(5)); 7.0 (s, 1 H, H(7)); 7.1 (d, 2 H, H(2´), H(6´) *J* = 8.5 Hz); 7.45 (d, 2 H, H(3´), H(5´), *J* = 8.5 Hz). MS, *m/z* (I_{rel} (%)): 353 [M]$^+$ (100), 324 (26), 323 (58), 296 (10), 266 (14), 43 (30), 42 (20).

Synthesis of 6-R-amino-4-phenylthio-2,1,3-benzoxadiazoles (6b,c) (general procedure). Amine (3.6 mmol) was added to a solution of compound **2e** (1 mmol, 0.30 g) in DMSO (5 mL). The mixture was stirred at 80—90 °C for 20 h. The resulting solution was cooled in an ice bath. The precipitate was filtered, washed with water and dried.

6-Morpholino-4-phenylthio-2,1,3-benzoxadiazole (6b). Yield 0.23 g (73%), m.p.151—153 °C (EtOH). Found (%): C, 60.91; H, 4.51; N, 13.29. $C_{16}H_{15}N_3O_2S$. Calculated (%): C, 61.34; H, 4.79; N, 13.41 ^{1}H NMR, δ: 3.24 (t, 4 H, $\underline{CH_2}$N, *J* = 4.8 Hz); 3.70 (t, 4 H, $\underline{CH_2}$O, *J* = 4.8 Hz); 6.80 (d, 1 H, H(5), *J* = 1.9 Hz); 7.37 (d, 1 H, H(7), *J* = 1.9 Hz); 7.41 (m, 1 H, H(4´); 7.44 (m, 2 H, H(3´), H(5´); 7.50 (m, 2 H, H(2´), H(6´)). MS, *m/z* (I_{rel} (%)): 313 [M]$^+$ (100), 283 (14), 77 (15).

6-Pyrrolidino-4-phenylthio-2,1,3-benzoxadiazole (6c). Yield 0.21 g (71%), m.p. 128—130 °C (EtOH). Found (%): C, 64.36; H, 4.93; N, 14.12. $C_{16}H_{15}N_3OS$. Calculated (%): C, 64.60; H, 5.05; N, 14.14. ^{1}H NMR, δ: 1.92 (m, 4 H, CH_2); 3.27 (m, 4 H, $\underline{CH_2N}$); 6.18 (d, 1 H, H(5), *J* = 1.8 Hz); 6.92 (d, 1 H, H(7), *J* = 1.8 Hz); 7.44—7.49 (m, 3 H, H(3´), H(4´), H(5´)); 7,56 (m, 2 H, H(2´), H(6´)). MS, *m/z* (I_{rel} (%)): 297 [M]$^+$ (100), 267 (38), 188 (25), 158 (25), 109 (20), 77 (52), 65 (16), 51 (32), 41 (32), 39 (24), 32 (65).

Synthesis of 4-aryloxy-2,6-dibromo-1-nitrobenzenes 5 (general procedure). Phenol (2 mmol) and K_2CO_3 (0.28 g, 2 mmol) was added to a solution of 2,6-dibromo-4-fluoro-1-nitrosobenzene (**4**) (0.56 g, 2 mmol) in DMSO (7 mL). The mixture was stirred at 40—50 °C for 30—40 min. The resulting solution was cooled in an ice bath. The precipitate was filtered, washed with water, and dried.

2,6-Dibromo-4-(4-methylphenoxy)nitrosobenzene (5a). Yield 0.61 g (83%), m.p. 113—115 °C (EtOH). Found (%): C, 42.34; H, 2.29; N, 3.60. $C_{13}H_9NO_2Br_2$. Calculated (%): C, 42.04; H, 2.42; N, 3.77. ^{1}H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, Me); 6.99 (d, 2 H, H(2´), H(6´), *J* = 8.5 Hz); 7.24 (s, 2 H, H(3), H(5)); 7.25 (d, 2 H, H(3´), H(5´), *J* = 8.5 Hz). HR MS: *m/z* 368.8995 [M]$^+$. $C_{13}H_9NO_2Br_2$, calculated: *M* = 368.8992. MS, *m/z* (I_{rel} (%)): 371 [M]$^+$ (100), 340 (14), 262 (16), 181 (31), 153 (90), 91(41), 65 (34).

2,6-Dibromo-4-(4-*tert*-butylphenoxy)nitrosobenzene (5b). Yield 0.70 g (85%), m.p. 130—132 °C (EtOH). Found (%): C, 46.66; H, 3.49; N, 3.34. $C_{16}H_{15}NO_2Br_2$. Calculated (%): C, 46.48; H, 3.63; N, 3.38. ^{1}H NMR, δ: 1.32 (s, 9 H, Bu^t); 7.21 (d, 2 H, H(2´), H(6´), *J* = 8.7 Hz); 7.41 (s, 2 H, H(3), H(5)); 7.55 (d, 2 H, H(3´), H(5´), *J* = 8.7 Hz). MS, *m/z* (I_{rel} (%)): 413 [M]$^+$ (100), 411 (31), 398 (39), 368 (53), 287 (29), 91(33), 77 (28), 74 (23), 57 (21), 44 (32), 30 (100).

Synthesis of 6-aryloxy-4-bromo-2,1,3-benzoxadiazoles 3 (general procedure). Sodium azide (0.13 g, 2 mmol) was added to a solution of compound **5** (2 mmol) in DMSO (10 mL). The reaction mixture was kept at room temperature for 60—70 min followed by cooling in an ice bath. The precipitate was filtered, washed with water, and dried.

4-Bromo-6-(4-methylphenoxy)-2,1,3-benzoxadiazole (3a). Yield 0.49 g (81%), m.p. 113—115 °C (EtOH). Found (%): C, 50.72; H, 2.75; N, 8.92. $C_{13}H_9N_2O_2Br$. Calculated (%): C, 51.14; H, 2.95; N, 9.18. ^{1}H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, Me); 6.73 (d, 1 H, H(5), *J* = 1.7 Hz); 7.00 (d, 2 H, H(2´), H(6´), *J* = 8.5 Hz); 7.28 (d, 2 H, H(3´), H(5´), *J* = 8.5 Hz); 7.56 (d, 1 H, H(7), *J* = 1.7 Hz). HR MS, found: *m/z* 303.9842 [M]$^+$; $C_{13}H_9N_2O_2Br$; calculated: *M* = 303.9841. MS, *m/z* (I_{rel} (%)): 304 [M]$^+$ (100), 276 (32), 248 (12), 208 (20), 195 (40), 167 (20), 158 (47), 115 (15), 91 (43), 77 (38), 65 (60), 63 (15), 51 (15), 39 (20).

4-Bromo-6-(4-*tert*-butylphenoxy)-2,1,3-benzoxadiazole (3b). Yield 0.50 g (75%), m.p. 95—97 °C (EtOH). Found (%): C, 55.26; H, 4.20; N, 8.04. $C_{16}H_{15}N_2O_2Br$. Calculated (%): C, 55.33; H, 4.32; N, 8.06. ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 9 H, Bu^t); 6.76 (d, 1 H, H(5), *J* = 1.7 Hz); 7.05 (d, 2 H, H(2´), H(6´), *J* = 8.8 Hz); 7.46 (d, 2 H, H(3´), H(5´), *J* = 8.8 Hz); 7.56 (d, 1 H, H(7), *J* = 1.7 Hz). HR MS, found: *m/z* 346.0311 [M]$^+$; $C_{16}H_{15}N_2O_2Br$; calculated: *M* = 346.0306. MS, *m/z* (I_{rel} (%)): 347 [M]$^+$ (20), 331 (100), 165 (2), 118 (5), 91 (12), 91(33), 78 (3), 77 (8), 41 (10).

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