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Reaction of *N*-Alkyl-6(4)-bromo-2,1,3-benzoxadiazol-4(6)-amines with Terminal Alkynes

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Abstract—*N*-Alkyl-6(4)-bromo-2,1,3-benzoxadiazol-4(6)-amines reacted with terminal alkynes to give amino-substituted 2,1,3-benzoxadiazoles containing acetylenic fragments directly attached to the carbocycle.

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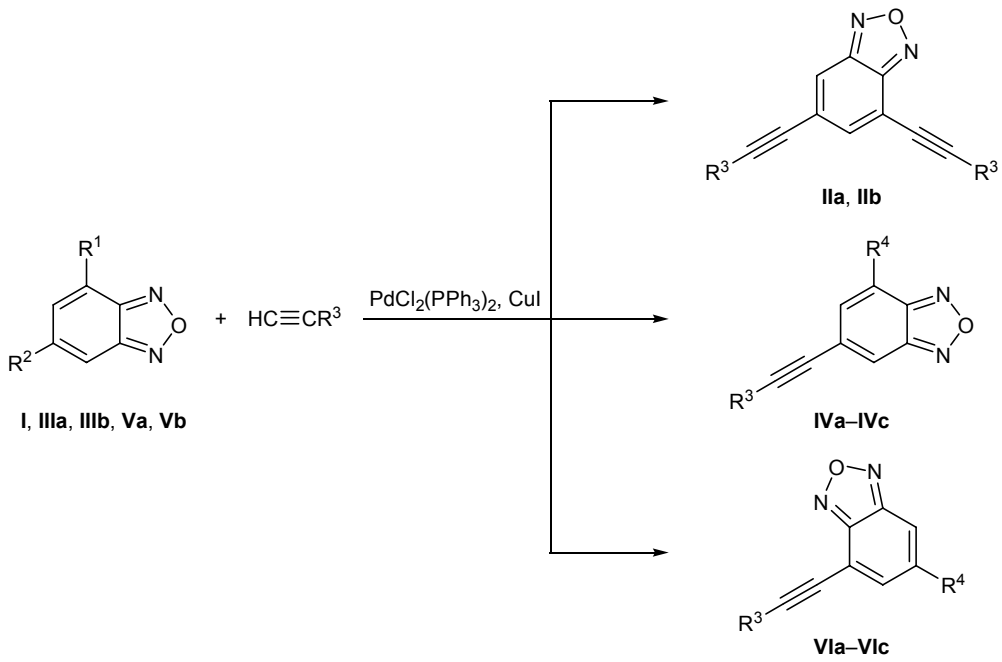
2,1,3-Benzoxadiazoles (benzofurazans) containing a dialkylamino group in the carbocycle exhibit luminescent properties and are suitable for use as fluorescent labels in biochemical studies [1]. Derivatives of benzofurazans having an acetylenic fragment with the triple bond considerably distant from the carbocycle can also be used as fluorescent labels [2]; acetylenic benzofurazan derivatives in which the triple-bonded carbon atom is directly attached to the carbocycle were not reported previously.

The goal of the present work was to study cross-coupling of bromobenzofurazans **I**, **III**, and **V** with terminal alkynes according to Sonogashira [3]. 2,1,3-Benzoxadiazoles **III** and **V** having a bromine atom in position *4* or *6*, as well as 4,6-dibromo derivatives **I**, reacted with phenylacetylene and 2-methylbut-3-yn-2-ol in boiling benzene in the presence of triphenylphosphine, palladium(II) chloride, copper(I) iodide, and triethylamine under argon to give the corresponding alkynylbenzofurazans **II**, **IV**, and **VI**,

Scheme 1.



I, **IIIa**, **IIIb**, **Va**, **Vb**

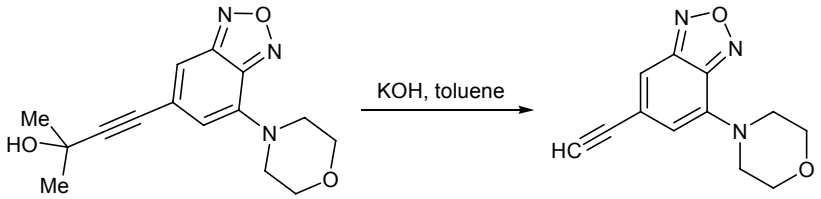
IIa, **IIb**

IVa–IVc

VIa–VIc

I, $R^1 = R^2 = Br$; **II**, R^3 = Ph (**a**), $HOCMe_2$ (**b**); **III**, R^2 = Br, R^1 = morpholino (**a**), Me_2N (**b**); **V**, R^1 = Br, R^2 = morpholino (**a**), Me_2N (**b**); **IV**, **VI**, R^3 = Ph, R^4 = morpholino (**a**), Me_2N (**b**); $R^3 = HOCMe_2$, R^4 = morpholino (**c**).

Scheme 2.



which were isolated by conventional methods (Scheme 1). The reactions involved replacement of either both bromine atoms (**I** → **II**) or one bromine atom in position *6* (**III** → **IV**) or *4* (**V** → **VI**). Using compound **IVc** as an example we showed that such compounds may be converted into terminal ethynylbenzofurazans (Scheme 2).

The structure of the newly synthesized compounds was confirmed by their ^{1}H NMR and mass spectra and elemental analyses. The positions of the long-wave absorption maxima in the electronic absorption spectra of initial compounds **I**, **III**, and **V** and final products **II**, **IV**, and **VI** differ insignificantly. Compounds **IV** and **VI** showed luminescence, and the position of their emission maxima differed insignificantly from those typical of the corresponding initial compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) using tetramethylsilane as internal reference. The progress of reactions and the purity of products were monitored by thin-layer chromatography on Silufol UV-254 plates. The melting points were determined on a Boetius melting point apparatus. The luminescence spectra were measured on a Cary Eclipse scanning spectrofluorimeter from solutions in acetonitrile (cell path length 1 cm, concentration 2×10^{-4} M). The mass spectra were obtained on a Finnigan MAT 8200 mass spectrometer. The electronic absorption spectra were recorded on an Evolution 300 spectrophotometer from solutions in THF (cell path length 1 cm, concentration 1×10^{-4} M).

4,6-Dibromo-2,1,3-benzoxadiazole (**I**) was synthesized according to the procedure reported in [4], and amino derivatives **III** and **V** were prepared as described in [5].

4-Bromo-6-morpholino-2,1,3-benzoxadiazole (Va) [5]**.** Electronic absorption spectrum, λ_{max}, nm (logε): 253 (4.09), 294 (3.79), 386 (3.58). Luminescence spectrum: λ_{max} 546 nm.

4,6-Bis(phenylethynyl)-2,1,3-benzoxadiazole (IIa). A solution of 0.70 g (2.5 mmol) of dibromobenzofurazan **I**, 0.82 ml (7.5 mmol) of phenylacetylene, and 2 ml of triethylamine in 10 ml of benzene was heated for 20 min under reflux in an argon atmosphere. A catalytic mixture consisting of 0.02 g (2 mol %) of $PdCl_2(PPh_3)_2$ and 0.009 g (2 mol %) of CuI was added, and the mixture was heated for 1 h under reflux in a stream of argon. The precipitate of triethylamine hydrobromide was filtered off and washed on a filter with 5–10 ml of boiling benzene. The filtrate was concentrated to a volume of 2 ml, the residue was ground with 7–10 ml of heptane, and the greenish precipitate was filtered off and recrystallized from heptane. Yield 0.67 g (84%), mp 121–123°C. Electronic absorption spectrum, λ_{max}, nm (logε): 256 (4.39), 299 (4.37), 356 (4.24). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.49–7.53 m (6H, H_{arom}), 7.66–7.69 m (4H, H_{arom}), 7.97 d (1H, 5-H, J = 1 Hz), 8.38 d (1H, 7-H, J = 1 Hz). Mass spectrum, m/z (I_{rel}, %): 320 (100) $[M]^+$, 288 (18.32), 264 (39.24), 160 (16.52), 105 (51.15), 77 (60.46). Found, %: C 81.79; H 3.75; N 8.58. $C_{22}H_{12}N_2O$. Calculated, %: C 82.50; H 3.75; N 8.75.

Compounds **IIb**, **IVa**–**IVc**, and **VIa**–**VIc** were synthesized in a similar way.

4,4′-(2,1,3-Benzoxadiazol-4,6-diyl)bis(2-methylbut-3-yn-2-ol) (IIb) was synthesized from 0.70 g (2.5 mmol) of compound **I** and 0.73 ml (7.5 mmol) of 2-methylbut-3-yn-2-ol using 10 ml of benzene, 2 ml of triethylamine, 0.02 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.009 g (2 mol %) of CuI. Yield 0.50 g (70%), colorless powder, mp 108–111°C. Electronic absorption spectrum, λ_{max}, nm (logε): 246 (4.34), 279 (3.65), 332 (3.89). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.49 s (6H, CH_3), 1.51 s (6H, CH_3), 5.65 s (1H, OH), 5.71 s (1H, OH), 7.53 d (1H, 5-H, J = 2 Hz), 8.10 d (1H, 7-H, J = 2 Hz). Mass spectrum, m/z (I_{rel}, %): 284 (8.21) $[M]^+$, 269 (13.51), 251 (14.31), 127 (10.51), 43 (100). Found, %: C 66.96; H 5.58; N 9.65. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.60; H 5.60; N 9.80.

4-Morpholino-6-(phenylethynyl)-2,1,3-benzoxadiazole (IVa) was synthesized from 0.54 g (1.9 mmol) of compound **IIIa** and 0.31 ml (2.85 mmol) of phenylacetylene using 10 ml of benzene, 0.5 ml of triethylamine, 0.016 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.0072 g (2 mol %) of CuI. Yield 0.31 g (53%), yellow powder, mp 117–119°C. Electronic absorption spectrum, λ_{max}, nm (log ε): 248 (4.31), 299 (4.25), 331 (3.91), 413 (3.60). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.60 t (4H, CH_2N, J = 5 Hz), 3.83 t (4H, CH_2O, J = 5 Hz), 6.60 s (1H, 5-H), 7.47–7.49 m (3H, H_{arom}), 7.62–7.65 m (2H, H_{arom}), 7.64 m (1H, 7-H). Mass spectrum, m/z (I_{rel}, %): 305 (100) $[M]^+$, 247 (29.33), 217 (28.53), 190 (21.42). Found, %: C 70.75; H 4.84; N 13.63. $C_{16}H_{15}N_3O_2$. Calculated, %: C 70.82; H 4.92; N 13.63.

***N*,*N*-Dimethyl-6-(phenylethynyl)-2,1,3-benzoxadiazol-4-amine (IVb)** was synthesized from 0.24 g (1 mmol) of compound **IIIb** and 0.16 ml (1.5 mmol) of phenylacetylene using 10 ml of benzene, 0.3 ml of triethylamine, 0.009 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.004 g (2 mol %) of CuI. Yield 0.16 g (61%), orange powder, mp 89–91°C. Electronic absorption spectrum, λ_{max}, nm (log ε): 250 (4.35), 302 (4.29), 437 (3.69). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.38 s (6H, CH_3), 6.16 s (1H, 5-H), 7.29 s (1H, 7-H), 7.41 m (3H, H_{arom}), 7.59 m (2H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 263 (100) $[M]^+$, 220 (24.02), 190 (12.61), 126 (12.71), 77 (13.71). Found, %: C 72.32; H 4.85; N 15.79. $C_{16}H_{13}N_3O$. Calculated, %: C 73.00; H 4.94; N 15.97.

2-Methyl-4-(7-morpholino-2,1,3-benzoxadiazol-5-yl)but-3-yn-2-ol (IVc) was synthesized from 0.28 g (1 mmol) of compound **IIIa** and 0.14 ml (1.5 mmol) of 2-methylbut-3-yn-2-ol using 10 ml of benzene, 0.3 ml of triethylamine, 0.009 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.004 g (2 mol %) of CuI. Yield 0.20 g (70%), yellow powder, mp 123–125°C. Electronic absorption spectrum, λ_{max}, nm (log ε): 250 (4.24), 312 (3.44), 408 (3.54). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.50 s (6H, CH_3), 3.55 t (4H, CH_2N, J = 5 Hz), 3.81 t (4H, CH_2O, J = 5 Hz), 5.59 s (1H, OH), 6.40 s (1H, 5-H), 7.43 s (1H, 7-H). Mass spectrum, m/z (I_{rel}, %): 287 (84.98) $[M]^+$, 214 (100), 184 (36.14), 43 (74.67). Found, %: C 62.63; H 5.74; N 14.51. $C_{15}H_{17}N_3O_3$. Calculated, %: C 62.70; H 5.90; N 14.60.

6-Morpholino-4-(phenylethynyl)-2,1,3-benzoxadiazole (VIa) was synthesized from 0.54 g (1.9 mmol) of compound **Va** and 0.31 ml (2.85 mmol) of phenylacetylene using 10 ml of benzene, 0.5 ml of triethylamine, 0.016 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.0072 g (2 mol %) of CuI. Yield 0.48 g (83%), orange powder, mp 144–145°C. Electronic absorption spectrum, λ_{max}, nm (log ε): 243 (4.22), 290 (4.15), 329 (4.08), 390 (3.69). Luminescence spectrum: λ_{max} 545 nm. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.39 t (4H, CH_2N, J = 5 Hz), 3.76 t (4H, CH_2O, J = 5 Hz), 6.92 d (1H, 5-H, J = 2 Hz), 7.49–7.52 m (3H, H_{arom}), 7.63–7.66 m (2H, H_{arom}), 7.99 d (1H, 7-H, J = 2 Hz). Mass spectrum, m/z (I_{rel}, %): 305 (100) $[M]^+$, 290 (15.52), 247 (12.91), 105 (10.81). Found, %: C 70.15; H 4.81; N 13.47. $C_{16}H_{15}N_3O_2$. Calculated, %: C 70.82; H 4.92; N 13.63.

***N*,*N*-Dimethyl-7-(phenylethynyl)-2,1,3-benzoxadiazol-5-amine (VIb)** was synthesized from 0.50 g (2 mmol) of compound **Vb** and 0.32 ml (3 mmol) of phenylacetylene using 10 ml of benzene, 0.50 ml of triethylamine, 0.017 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.0076 g (2 mol %) of CuI. Yield 0.30 g (57%), yellow powder, mp 98–100°C. Electronic absorption spectrum, λ_{max}, nm (log ε): 246 (4.19), 305 (4.10), 429 (3.64). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.50 s (6H, CH_3), 6.50 d (1H, 5-H, J = 2 Hz), 7.48–7.50 m (3H, H_{arom}), 7.63–7.65 m (2H, H_{arom}), 7.80 d (1H, 7-H, J = 2 Hz). Mass spectrum, m/z (I_{rel}, %): 263 (67.57) $[M]^+$, 190 (24.42), 164 (17.92), 126 (31.83), 105 (39.54), 77 (56.26), 63 (29.53), 51 (31.83), 42 (100), 39 (38.64). Found, %: C 72.77; H 5.07; N 15.93. $C_{16}H_{13}N_3O$. Calculated, %: C 73.00; H 4.94; N 15.97.

2-Methyl-4-(6-morpholino-2,1,3-benzoxadiazol-4-yl)but-3-yn-2-ol (VIc) was synthesized from 0.54 g (1.9 mmol) of compound **Va** and 0.28 ml (2.85 mmol) of 2-methylbut-3-yn-2-ol using 10 ml of benzene, 0.5 ml of triethylamine, 0.016 g (2 mol %) of $PdCl_2(PPh_3)_2$, and 0.0072 g (2 mol %) of CuI. Yield 0.33 g (62%), yellow powder, mp 136–138°C. Electronic absorption spectrum, λ_{max}, nm (log ε): 256 (4.01), 311 (3.88), 389 (3.55). Luminescence spectrum: λ_{max} 541 nm. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.51 s (6H, CH_3), 3.33 t (4H, CH_2N, J = 5 Hz), 3.72 t (4H, CH_2O, J = 5 Hz), 5.66 s (1H, OH), 6.83 s (1H, 5-H), 7.73 s (1H, 7-H). Mass spectrum, m/z (I_{rel}, %): 287 (100) $[M]^+$, 272 (25.23), 214 (15.62), 43 (75.68). Found, %: C 62.70; H 5.90; N 14.60. $C_{15}H_{17}N_3O_3$. Calculated, %: C 62.70; H 5.90; N 14.60.

6-Ethynyl-4-morpholino-2,1,3-benzoxadiazole (VII). Powdered potassium hydroxide, 0.56 g (10 mmol), was added to 0.41 g (1.4 mmol) of compound **IVc** in 30 ml of toluene. The mixture was stirred for 10 min on heating under reflux, the precipitate was filtered off and washed on a filter with 15–

20 ml of boiling toluene, and the filtrate was washed with water, dried over calcium chloride, and concentrated to a volume of 2 ml. The residue was ground with 7–10 ml of diethyl ether, and the yellow precipitate was filtered off and recrystallized from heptane–diethyl ether, 4:1. Yield 0.25 g (80%), mp 98–100°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.57 t (4H, CH_2N, J = 5 Hz), 3.81 t (4H, CH_2O, J = 5 Hz), 4.55 s (1H, ≡CH), 6.49 d (1H, 5-H, J = 2 Hz), 7.70 d (1H, 7-H, J = 2 Hz). Mass spectrum, m/z (I_{rel}, %): 229 (80.88) $[M]^+$, 171 (76.18), 141 (100), 114 (37.04), 87 (35.04), 64 (14.61), 63 (25.52), 62 (19.82), 52 (15.72), 42 (26.53). Found, %: C 61.57; H 4.76; N 18.05. $C_{12}H_{11}N_3O$. Calculated, %: C 62.88; H 4.80; N 18.34.

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