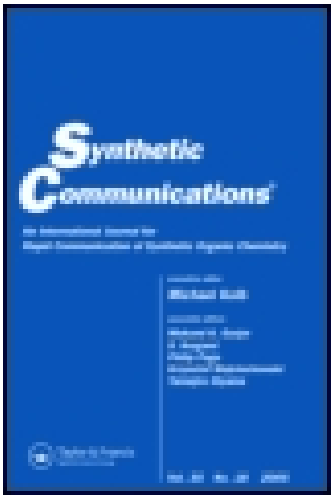

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PYRROLIDYLSUBSTITUTED AZADIPYRROMETHENE WITH FULLY CHELATED BORON ATOM

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A difluorosubstituted aza-boron–dipyrromethene derivative with fully chelated boron atom was synthesized by the reaction of $BF_3 \cdot Et_2O$ with 3,3,5,5-tetraarylazadipyrromethene, which was easily prepared from 1,3-diaryl-4-nitro-butan-1-one and ammonium acetate. One fluorine atom of the dye was substituted by pyrrolidine residue. This resulted in a significant bathochromic effect. Ultraviolet absorption and fluorescence emission spectra were recorded, and quantum yields of the obtained compounds were calculated.

Keywords: BODIPY; boradiaza-s-indacene; long-wavelength dye

The popularity of boron–dipyrromethene dyes (4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes, BODIPY, BDP) has steadily increased over the past two decades. Their excellent thermal, chemical, and photochemical stability, high molar absorptivity, fluorescence quantum yields, insensitivity to solvent polarity and pH, relatively long excited-state lifetimes, a large two-photon cross-section for multiphoton excitation, lack of ionic charge, and good solubility all have added to the general attractiveness of these materials.[1] Recently, special attention has been paid to long-wave compounds of this type[2] caused by practical applications of near infrared (NIR) dyes.[3]

There are a number of approaches to shift BODIPY absorption bands to longer wavelengths. For example, the substitution of a carbon at the *meso* position of dipyrromethene by the nitrogen atom results in a bathochromic shift of an absorption band (compound of **A** type aza-BODIPY).[4] Modification of this basic core by electron-donating groups at the *para* position of 5-aryl substituents leads to a further red shift. The introduction of dialkylamino groups has been observed to cause especially high bathochromic effect (structures of **B** type, 150 nm shift).[5] Finally, the complete chelation of boron atoms not only induces a red shift of 80 nm and increases the fluorescence but also produces the spiral chirality (compounds of **C** type).[6] Our goal was to combine all three factors in a target structure, **E**.

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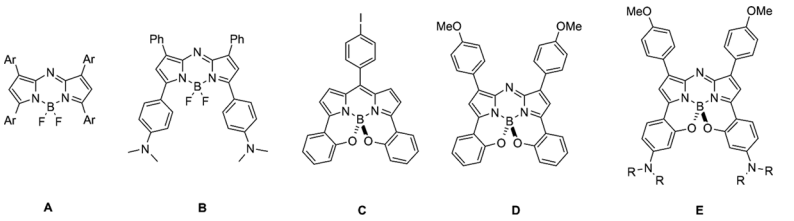
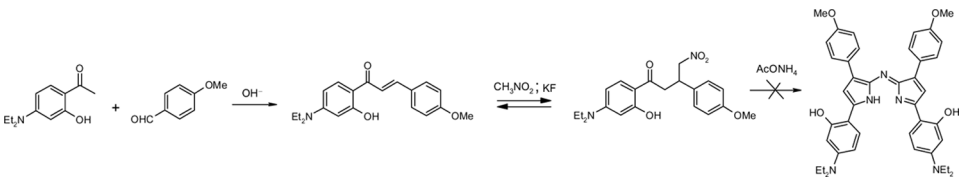


Partially, this task has been already realized. Recently, we reported the synthesis of azadipyrromethene dye with fully chelated boron atom (structure **D**).[7] As expected, this dye is a quite intensive long-wave luminophore. Almost simultaneously, the dye and its close analogs were obtained by joint efforts of the groups of Burgess and O'Shea.[8] However, their attempt to obtain the dye of **E** type failed, presumably because of the instability of the latter. Independently, we performed our own investigations and obtained some promising results, although we could not reach the goal of synthesizing compound **E** as well.

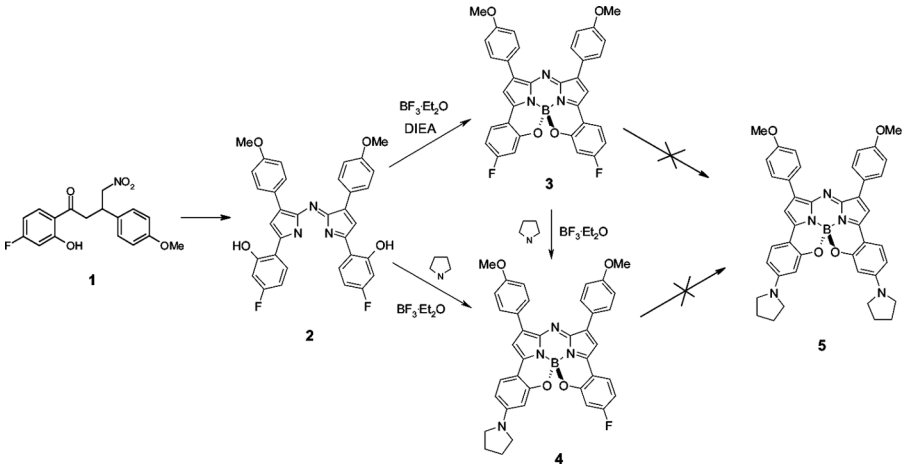
We used a well-known approach[4b,7–9] for the synthesis (Scheme 1). By starting from 2-hydroxy-4-diethylaminoacetophenone[10] and anisaldehyde chalcone, it was obtained, although in a quite poor yield (25–35%). The next step, addition of nitromethane, also proceeded with considerable difficulties because of the cleavage of the nitromethane molecule from nitrobutanone under basic conditions (retro-Michael reaction). Apparently, for the same reason, the attempts to obtain the desired azadipyrromethene were not successful (elimination of nitromethane from nitrobutanone in the presence of ammonium acetate is faster than its cyclization).

We therefore decided to use another approach starting from 2-hydroxy-4-fluoroacetophenone,[11] with the aim of substituting fluorine atoms with dialkylamino groups. As expected, in this case we faced no special difficulties in the synthesis of the corresponding azadipyrromethene. Chalcone and 1,3-diaryl-4-nitrobutan-1-one (**1**) were prepared with yields of 80% and 65%, respectively (reactions were performed just as shown in Scheme 1[4,7–9]). The cyclization of compound **1** (Scheme 2) led to the desirable azadipyrromethene (**2**) (27% yield, which is quite good for this reaction).

Azadipyrromethene then reacted with an excess of $BF_3 \cdot Et_2O$ in the presence of diisopropylethylamine (DIEA) in toluene under short reflux to form the expected complex (**3**) with 63% yield. However, when pyrrolidine was used as a base under the same conditions, the substitution of one of the fluorine atoms by amine occurred simultaneously with chelating to give the complex (**4**) with 61% yield. The same



Scheme 1. Approach to the synthesis of diethylamino-substituted azadipyrromethene.



Scheme 2. Synthesis of NIR dyes **3** and **4**.

complex can be also obtained by refluxing compound (**3**) with pyrrolidine in the presence of BF_3 etherate, though the first method seems to be more attractive for the preparative synthesis. Nevertheless, only mono-pyrrolidine substituted complex (**4**) was formed in the latter case as well. Also, numerous efforts to substitute the second fluorine atom to obtain the dye (**5**) failed. A variety of attempts to employ less basic amines such as morpholine and diethylamine in the reaction were not successful.

The spectral properties of difluorosubstituted dye (**3**) are very similar to those of nonsubstituted analog **D**, which has a narrow and quite intensive absorption band (Table 1, Fig. 1). When going from **3** to compound **4**, the expected bathochromic shift (69 nm) was observed with some intensity decrease and broadening of the absorption band. Changing CH_2Cl_2 for DMF resulted in minor bathochromic shifts of 4 and 2 nm for **4** and **3**, respectively.

Fluorescent properties of the dyes are shown in Table 1. The small Stokes shift (17 nm) is observed for **3**; its fluorescent quantum yield is 0.2 and is not affected by the solvent polarity. Unlike that dye, compound **4** has a significantly greater Stokes shift (56 nm). Its fluorescence quantum yield is only 0.02 because of PET as in the cases described in Refs. 2a, 2e, and 5. In contrast to their close analogs, the BF_2 complexes,[5] dye **4** cannot be fully protonated. The reason for this is the strong

Table 1. Optical properties of compounds **2**, **3**, and **4**

	CH_2Cl_2				DMF			
Dye	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$, $M^{-1} \cdot cm^{-1}$)	λ_{em} (nm)	fwhm (cm^{-1})	Φ_f	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$, $M^{-1} \cdot cm^{-1}$)	λ_{em} (nm)	fwhm (cm^{-1})	Φ_f
2	621 (41)	—	2062	—	629 (50)	—	2181	—
3	725 (67)	742	689	0.204	727 (67)	743	705	0.20
4	794 (55)	850	1034	0.02	798 (52)	854	1173	0.025

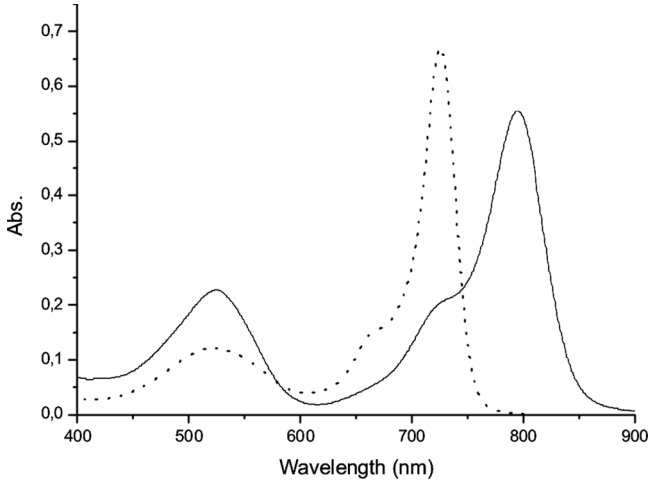


Figure 1. Absorption spectra of the dyes **3** (dotted line) and **4** (solid line) in CH_2Cl_2.

conjugation between the terminal nitrogen atom and π-system of BODIPY, owing to a rigid molecular structure.

EXPERIMENTAL

General

Absorption spectra were recorded on a Shimadzu UV-3100 spectrophotometer. ^{1}H NMR [300 MHz, 25 °C, tetramethylsilane (TMS) as internal standard] spectra were obtained on a Varian VXR-300 instrument. Liquid chromatography/mass spectral (LC/MS) measurements were performed with an LC/MS system consisting of an Agilent 1100 Series HPLC instrument equipped with a diode matrix detector and Agilent LC/MSD SL mass-selective detector. Atmospheric pressure chemical ionization (APCI) with detection of positive ions was used. Fluorescence spectra were recorded on a Solar CM 2203 fluorescence spectrophotometer. Fluorescence quantum yields (ϕ) for compounds were determined relative to pentamethine dioxaborinate ($\phi = 0.57$, CH_2Cl_2).[12]

Synthesis

1-(4-Fluoro-2-hydroxypenyl)-3-(4-methoxyphenyl)-4-nitrobutan-1-one (1). A mixture of 1-(4-fluoro-2-hydroxpenyl)-3-(4-methoxyphenyl)-propenone (5.44 g, 0.02 mol), nitromethane (12.2 g, 0.2 mol), dry KF (0.23 g, 0.004 mol), and 18-crown-6 (0.264 g, 0.001 mol) in dry acetonytrile was heated under reflux for 2 h. The acetonitrile was removed, and the resulting oil was portioned between CH_2Cl_2 (50 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2×25 mL), and the combined organic fractions were dried over sodium sulfate. The solvent was removed, and the resulting material was recrystallized from a mixture of *i*-PrOH-hexane in a 1:1 ratio (4.5 g, 67%), mp 93–95 °C. ^{1}H NMR ($CDCl_3$,

300 MHz): δ 3.41 (dd, $J = 5.1$ CH_2), 3.79 (s, 3H, CH_3), 4.12–4.21 (m, 1H, C*H*), 4.62–4.81 (m, 2H, CH_2), 6.57–6.68 (m, 2H, Ar*H*), 6.89 (d, $J = 9$ Hz, 2H, Ar*H*), 7.20 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.74 (dd, $J = 6.3$, 6.0 Hz, 1H, Ar*H*), 12.31 (s, 1H, O*H*). LC-MS: m/z 334 ($[M + H]^+$). Elemental analysis: calcd. for $C_{17}H_{16}FNO_5$: C, 61.26; H, 4.80; N, 4.20. Found: C, 61.41; H, 4.71; N, 4.29.

[5-(4-Fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrol-2-yl]-[5-(4-fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-pyrrol-2-ylidene] amine (2). $AcONH_4$ (19 g, 0.245 mol) was added to 1-(4-fluoro-2-hydroxpenyl)-3-(4-methoxyphenyl)-4-nitrobutan-1-one **1** (2.1 g, 6.3 mmol) in AcOH (20 mL), and the reaction mixture was heated at 110 °C for 5 h. After cooling, the mixture was kept overnight at room temperature. Crude product **2** was filtered off and washed with AcOH. Yield 0.5 g, 27%, mp > 250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.87 (s, 6H, CH_3), 6.77–6.83 (m, 4H, Ar*H*), 7.03 (d, $J = 8.1$, 4H, Ar*H*), 7.56 (s, 2H, pyrrole *H*), 7.99 (d, $J = 8.4$, 4H, Ar*H*), 8.12 (dd, $J = 7.2$, 2H, Ar*H*). LC-MS: decomposition. Elemental analysis: calcd. for $C_{34}H_{25}F_2N_3O_4$: C, 70.71; H, 4.33; N, 7.28. Found: C, 70.52; H, 4.49; N, 7.43.

Boron chelated [5-(4-fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrol-2-yl]-[5-(4-fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-pyrrol-2-ylidene]amine (3). The mixture of compound **2** (0.173 g, 0.3 mmol), $BF_3 \cdot Et_2O$ (0.64 g, 4.5 mmol), and DIEA (0.39 g, 3 mmol) in dry toluene (30 mL) was stirred under reflux for 1 h. After cooling, the reaction mixture was washed with water (4 × 50 mL), and the organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on Al_2O_3 (eluent CCl_4–EtOAc 98:2). Yield 0.11 g, 63%, mp > 250 °C. ^{1}H NMR ($CDCl_3$): δ 3.84 (s, 6H, CH_3), 6.65 (dd, $J = 10.5$, $J = 2.1$, 2H, AR*H*), 6.78 (ddd, $J = 10.5$, $J = 6.6$, $J = 2.1$, 2H, Ar*H*), 6.93 (d, $J = 8.4$, 4H, Ar*H*), 7.00 (s, 2H, pyrrole*H*), 7.73 (dd, $J = 6.6$, $J = 2.1$, 2H, Ar*H*), 8.03 (d, $J = 8.4$, 4H Ar*H*). LC-MS: $m/z = 587$ ($[M + H]^+$). Elemental analysis: calcd. for $C_{34}H_{23}BF_2N_3O_4$: C, 69.64; H, 3.95; N, 7.17. Found: C, 69.82; H, 4.19; N, 7.05.

Boron chelated [5-(4-pyrolidyl-2-hydroxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrol-2-yl]-[5-(4-fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-pyrrol-2-ylidene]amine (4).

Method A. The mixture of compound **2** (0.12 g, 0.2 mmol), $BF_3 \cdot Et_2O$ (0.57 g, 4 mmol), and pyrrolidine (0.15 g, 2 mmol) in dry toluene (10 mL) was stirred for 1 h at 110 °C. Pyrrolidine (0.5 mL) was added to this mixture, and stirring continued for 30 min. Then the mixture was evaporated to dryness, and the residue was diluted with CH_2Cl_2. The mixture was washed with water (4 × 50 ml), and organic layer was separated and dried over Na_2SO_4. The dye **4** was isolated by flash-column chromatography on silica gel (eluent CH_2Cl_2). Yield 0.08 g, 61%.

Method B. The mixture of compound **3** (0.12 g, 0.2 mmol), $BF_3 \cdot Et_2O$ (0.57 g, 4 mmol), and pyrrolidine (0.45 g, 6 mmol) in dry toluene (15 mL) was stirred under reflux for 30 min. After cooling, the reaction mixture was washed with water (4 × 25 mL), and organic layer was separated, dried over Na_2SO_4 and evaporated

to dryness. The residue was chromatographed on silica gel (eluent CH_2Cl_2) to give pure dye **4**. Yield 0.1 g, 75%.

Mp 204–206 °C. ^{1}H NMR ($CDCl_3$): δ 2.01 (q, 4H, pyrrolidine*H*), 3.37 (q, 4H, pyrrolidine*H*), 3.87 (s, 3H, C*H*$_3$), 3.88 (s, 3H, C*H*$_3$), 6.12 (d, $J = 2.1$, 1H), 6.38 (dd, $J = 7$, $J = 2.1$, 1H, Ar*H*), 6.65–6.78 (m, 2H, Ar*H*), 6.88 (s, 1H, pyrrole*H*), 6.96 (d, $J = 4.2$, 2H, Ar*H*), 6.99 (d, $J = 4.2$, 2H, Ar*H*), 7.09 (s, 1H, pyrrole*H*), 7.58 (d, $J = 9$, 1H, Ar*H*), 7.69 (dd, $J = 6.6$, $J = 1.5$, 1H, Ar*H*), 8.05 (d, $J = 8.7$, 2H, Ar*H*), 8.12 (d, $J = 8.7$, 2H, Ar*H*). LC-MS: $m/z = 638$ ($[M + H]^+$). Elemental analysis: calcd. for $C_{38}H_{31}BFN_4O_4$: C, 71.60; H, 4.90; N, 8.79. Found: C, 71.82; H, 4.79; N, 8.95.

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