Synthesis of BODIPY Chromophores Bearing Fused-Carbocycles

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Dipyrrometheneboron difluoride (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) known as the trademark BODIPY shows many intriguing chemical and physical properties such as high absorption coefficient and fluorescence quantum yield, long wavelength emission, photochemical stability and insensitivity toward changes of the polarity, acidity and oxygen content of the medium.[1] BODIPY chromophores have been conjugated to diverse biomolecules such as proteins,[1] DNA,[2] carbohydrates[3] and cholesterols.[4] BODIPY dyes have been used in fluorescent switches,[5] probes for protons,[6] mercuric ion[7] and nitric oxide,[8] biological labeling and syntheses of molecular devices.[9] Therefore, synthesis of various BODIPY dyes and their application to biomolecules are of current interest. Recently, efficient synthetic methods of BODIPY chromophores were reported.[10] Burgess *et al.* developed many efficient synthetic methods of BODIPY dyes possessing 2,5-diaryl groups[10a,10c] and 2-keto-pyrrole-BF$_2$ complexes.[10d] Boenes *et al.* found synthetic method of new BODIPY dyes having phenolic or naphtholic subunits as fluorescent pH probes.[10g] On the basis of initial results of Burgess, we prepared recently some tunable BODIPY dyes by introducing new aryl substituents at C-3 and C-5 positions.[11] Although aryl substituents on the BODIPY chromophores would generally red-shift the absorption and emission spectra, they did not significantly improve the extinction coefficients of these molecules. In addition, the fluorescence quantum yields of BODIPY dyes possessing 2,5-diaryl groups were remarkably lower than that of BODIPY having alkyl groups. Because free rotation of aryl substituents on the BODIPY chromophore resulted in the reduced quantum yields and fluorescence, the rigid BODIPY restricted bond rotations have been required to improve physical and chemical properties. Despite this recent progress in fluorescent dyes, synthesis of BODIPY derivatives bearing alkyl-, aryl- or cyclic moieties is still needed because their fluorescence maxima depend on substituents on the BODIPY chromophore. In this paper, we synthesized various BODIPY dyes **3** restricted bond rotations by introducing new carbocycles on the BODIPY (Scheme 1).[10e,11]

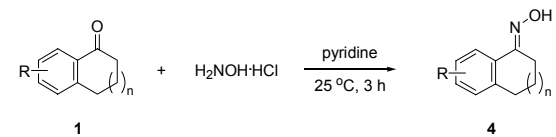A variety of oximes were required for synthesis of the BODIPY chromophores **3** restricted bond rotations through introduction of carbocycles. Treatment of α-tetralone (1 equiv) with hydroxylamine hydrochloride (1.5 equiv) in pyridine (25 °C, 3 h) as a solvent gave 5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one oxime (**4a**) in quantitative yield (entry 1). Similarly, reaction of α-tetralone possessing methoxy or methyl groups with hydroxylamine hydrochloride produced the desired compounds (**4b**, **4c**, and **4d**) in good to excellent yields (entries 2-4). 1-Benzosubernon was treated with hydroxylamine hydrochloride to afford the corresponding oxime **4e** in 97% yield under the present conditions (entry 5).
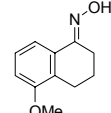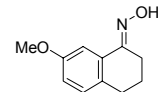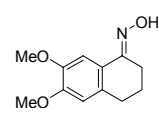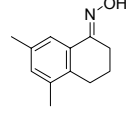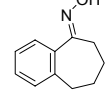
Next, we try to prepare pyrrole derivatives **2** from the reaction of oximes **4** with acetylene.[12] After acetylene gas was bubbled to a solution of oxime **4a** (1 equiv) and lithium hydroxide monohydrate (4.4 equiv) in DMSO for 3 h, the reaction mixture was refluxed at 140 °C for 8 h under the nitrogen atmosphere, affording the corresponding pyrrole **2a** in 57% yield (entry 1, Table 2). However, the oximes **4b** and **4c** provided pyrroles **2b** and **2c** in 22% and 18% yields, respectively, under the present conditions (entries 2 and 3). In the case of 5,7-dimethyl-1-tetralone (**4d**), the corresponding pyrrole **2d** was obtained in 53% yield (entry 4). We were pleased to obtain **2e** in 54% yield from the treatment of **4e** with acetylene (entry 5).
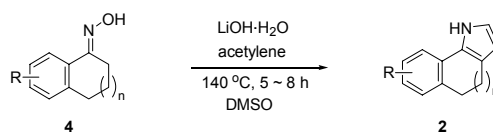
Next, we carried out the reaction of pyrroles **2** with 4-iodobenzoyl chloride to obtain BODIPY dyes *via* dipyrromethane and the results are summarized in Table 3. 4-Iodobenzoyl chloride was used due to further functionalization *via* transition metal-catalyzed cross-coupling reactions. Because yields of BODIPY chromophore **3** through dipyrromethane were low, condensation reactions and subsequent treatment of boron trifluoride etherate were carried out in one-pot procedure without separation of dipyrromethane. Yield of **3** in one-pot procedure is better than one in two-pot procedure. Pyrrole **2a** (2 equiv) was treated with 4-iodobenzoyl chloride (1 equiv) in refluxing dichloroethane (83 °C) for 48 h. After the reaction mixture was cooled to 25 °C, it was treated with triethylamine (4.2 equiv) for 5 min. Finally, boron trifluoride etherate (5.7 equiv) was added to the reaction mixture, affording BODIPY dye **3a** in
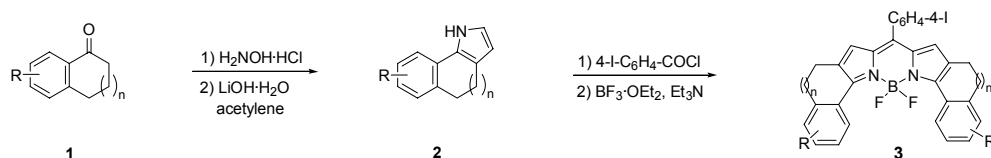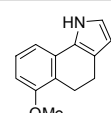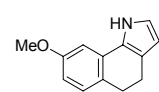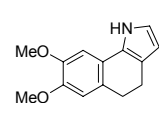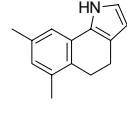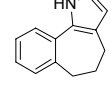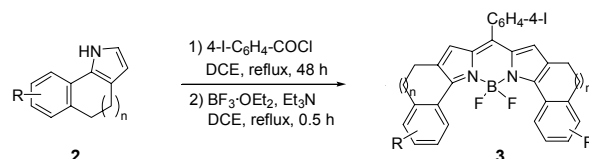

Scheme 1. Preparation of BODIPY
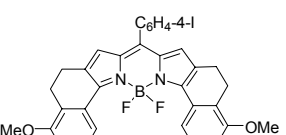
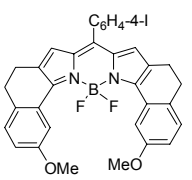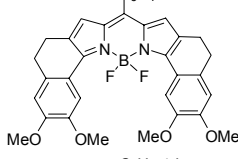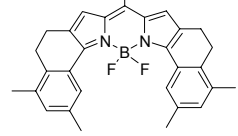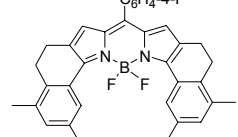**Table 1.** Preparation of oximes from cyclic ketones and hydroxylamine

Entry	Oxime		Yield (%)
1		**4a**	99
2		**4b**	94
3		**4c**	93
4		**4d**	95
5		**4e**	97

Table 2. Preparation of pyrroles from oximes and acetylene

Entry	Pyrroles		Yield (%)
1		**2a**	57
2		**2b**	22
3		**2c**	18
4		**2d**	53
5		**2e**	54

Table 3. Preparation of BODIPY chromophores

Entry	Products		Yield (%)
1		**3a**	34
2		**3b**	29
3		**3c**	19
4		**3d**	19
5		**3e**	45

34% yield (entry 1). Exposure of pyrroles **2b** and **2c** to 4-iodo-benzoyl chloride followed by triethylamine and boron trifluoride etherate resulted in the formation of **3b** and **3c** in 29% and 19% yields, respectively (entries 2 and 3). Under the optimum reaction conditions, pyrrole **2d** having dimethyl group was converted to BODIPY chromophore **3d** in 19% yield (entry 4). Pyrrole **2e** possessing cycloheptyl ring turned out to be compatible with the present reaction conditions, producing BODIPY dye **3e** in 45% yield (entry 5).

Reaction of **3a** with 5-hexynoic acid (**5**) catalyzed by (Ph$_3$P)$_4$ Pd and CuI in the presence of piperidine in THF gave the desired cross-coupling product **6** in 52% yield (Scheme 2). BODIPY **6** was treated with EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride] and *N*-hydroxysuccinimide to provide **7** in 64% yield in DMF.

The spectroscopic data for five BODIPY dyes **3** in chloroform was listed in Table 4. Although four methyl substituted BODIPY system D-2190[13] shows λ_{max} (absorption) = 495 nm and $\varepsilon = 8.7 \times 10^4$ M^{-1}cm^{-1}, wavelength for absorption of the BODIPY **3b** restricted bond rotations is 646 nm (red-shifted) and its extinction coefficient (ε) obtained is 9.8×10^4 M^{-1}cm^{-1}.

Scheme 2. Introduction of linker to **3a**

λ_max = 495 nm
ε = 8.7 x 10⁴ M⁻¹cm⁻¹
Stokes shift = 8 nm

D-2190

λ_max = 589 nm
ε = 5.3 x 10⁴ M⁻¹cm⁻¹
Stokes shift = 32 nm
(558 nm, 590 nm)

λ_max = 602 nm
ε = 6.5 x 10³ M⁻¹cm⁻¹
Stokes shift = 37 nm
(565 nm, 602 nm)

λ_max = 646 nm
ε = 9.8 x 10⁴ M⁻¹cm⁻¹
Stokes shift = 30 nm
(646 nm, 676 nm)

3b

In addition, these BODIPY dyes restricted bond rotations exhibit larger Stokes shifts (18 ~ 51 nm) than the methyl substituted systems (8 nm for D-2190). Although the fluorescence intensities of BODIPY **3a**, **3c**, and **3e** are smaller than those of methyl substituted BODIPY, the fluorescence intensities of BODIPY **3b** and **3d** are larger than those of D-2190 and 3,5-diaryl BODIPY dyes.

In conclusion, various pyrroles were prepared from the reaction of α-tetralone or 1-benzosubernon with hydroxylamine hydchloride followed by treatment with acetylene. These compounds reacted with 4-iodobenzoyl chloride to give dipyrromethane. Then, subsequent treatment with triethylamine and boron trifluoride diethyl etherate produced the new BODIPY chromophores restricted bond rotations through introduction of carbocycles whose emission wavelength are shifted to red compared with alkyl substituted BODIPY dyes.

Experimental Section

5-Methoxy-3,4-dihydro-2*H*-naphthalen-1-one oxime (4a). 5-Methoxy-1-tetralone (**1a**) (352.0 mg, 2.0 mmol) was added to a solution of hydroxylamine hydrochloride (209.0 mg, 3.0 mmol) in pyridine (4.8 mL) under N₂ atmosphere. After being stirred at 25 °C for 3 h, the reaction mixture was quenched with HCl (2 M aqueous solution, 50 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combine organic layers were washed with brine. The resulting organic layers were dried over MgSO₄, filtered and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:hexane = 1:5) to give **4a** (380.0 mg, 99%). ¹H NMR (400 MHz, CDCl₃) δ 8.40 (s, 1H), 7.52 (d, *J* = 7.99 Hz, 1H), 7.18 (t, *J* = 8.05 Hz, 1H), 6.83 (d, *J* = 8.08 Hz, 1H), 3.84 (s, 3H), 2.80 (t, *J* = 6.63 Hz, 2H), 2.74 (t, *J* = 6.16 Hz, 2H), 1.85 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 156.7, 155.7, 131.6, 128.9, 126.5, 116.2, 110.3, 55.5, 23.1, 22.2, 20.8.

Table 4. Spectroscopic data for BODIPY dyes **3** in CHCl₃

Entry	BODIPY	Absorption (nm)	Emission (nm)	ε (M⁻¹cm⁻¹)	Stokes Shift (nm)[a]
1	**3a**	634	657	4.9×10^4	23
2	**3b**	646	676	9.8×10^4	30
3	**3c**	590	641	1.0×10^4	51
4	**3d**	641	668	1.0×10^5	27
5	**3e**	584	602	5.2×10^4	18

[a]Stokes shift = emission − absorption

7-Methoxytetralone oxime (4b). ¹H-NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 7.43 (d, *J* = 2.74 Hz, 1H), 7.06 (d, *J* = 8.44 Hz, 1H), 6.86 (dd, *J* = 8.42, 2.69 Hz, 1H), 3.81 (s, 3H), 2.79 (t, *J* = 6.67 Hz, 2H), 2.70 (t, *J* = 6.09 Hz, 2H), 1.89-1.82 (m, 2H).

6,7-Dimethoxytetralone oxime (4c). ¹H-NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 37.34 Hz, 1H), 7.40 (s, 1H), 6.61 (s, 1H), 3.89 (s, 6H), 2.78 (t, *J* = 6.64 Hz, 2H), 2.70 (t, *J* = 5.98 Hz, 2H), 1.90-1.84 (m, 2H).

5,7-Dimethyltetralone oxime (4d). ¹H-NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.60 (s, 1H), 7.00 (s, 1H), 2.79 (t, *J* = 6.68 Hz, 2H), 2.65 (t, *J* = 6.14 Hz, 2H), 2.30 (s, 3H), 2.24 (s, 3H), 1.90-1.84 (m, 2H).

Benzosuberone oxime (4e). ¹H-NMR (400 MHz, CDCl₃) δ 9.92 (s, 1H), 7.41 (d, *J* = 7.19 Hz, 1H), 7.29 (t, *J* = 7.06 Hz, 1H), 7.22 (t, *J* = 7.13 Hz, 1H), 7.12 (t, *J* = 7.15 Hz, 1H), 2.76-2.71 (m, 4H), 1.78-1.73 (m, 2H), 1.66-1.62 (m, 2H).

6-Methoxy-4,5-dihydro-1*H*-benz[*g*]indole (2a). After acetylene gas was bubbled to the solution of oxime **4a** (240.0 mg, 1.3 mmol) and lithium hydroxide monohydrate (241.0 mg, 5.75 mmol) in DMSO (3 mL) for 3 h, the reaction mixture was refluxed at 140 °C for 8 h under nitrogen atmosphere. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combine organic layers were washed with brine. The resulting organic layers were dried over MgSO₄, filtered and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂:hexane = 1:1) to give **2a** (148.0 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.11 (t, *J* = 7.89 Hz, 1H), 6.76 (d, *J* = 7.59 Hz, 1H), 6.70-6.66 (m, 2H), 6.10 (t, *J* = 2.30 Hz, 1H), 3.82 (s, 3H), 2.94 (t, *J* = 7.80 Hz, 2H), 2.72 (t, *J* = 7.81 Hz, 2H).

8-Methoxy-4,5-dihydro-1*H*-benz[*g*]indole (2b). ¹H-NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.10 (d, *J* = 8.20 Hz, 1H), 6.75 (t, *J* = 2.65 Hz, 1H), 6.72 (d, *J* = 2.51 Hz, 1H), 6.60 (dd, *J* = 8.19, 2.55 Hz, 1H), 6.12 (t, *J* = 2.38 Hz, 1H), 3.81 (s, 3H), 2.86 (t, *J* = 7.54 Hz, 2H), 2.72 (t, *J* = 7.52 Hz, 2H).

7,8-Dimethoxy-4,5-dihydro-1*H*-benz[*g*]indole (2c). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.33 (s, 1H), 6.78 (s,1H), 6.74 (s, 1H), 6.71 (t, *J* = 2.58 Hz, 1H), 6.11 (t, *J* = 2.36 Hz, 1H), 3.87 (s, 6H), 2.86 (t, *J* = 7.61 Hz, 2H), 2.72 (t, *J* = 7.71 Hz, 2H).

6,8-Dimethyl-4,5-dihydro-1*H*-benz[*g*]indole (2d). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.22 (s, 1H), 6.84 (s, 1H), 6.78 (s, 1H), 6.72 (t, *J* = 2.61 Hz, 1H), 6.10 (s, 1H), 2.84 (t, *J* = 7.52 Hz, 2H), 2.73 (t, *J* = 7.56 Hz, 2H), 2.29 (s, 3H), 2.27 (s, 3H).

1,4,5,6-Tetrahydro-1-aza-benzo[*e*]azulene (2e). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.16 (s, 1H), 7.33 (d, *J* = 7.79 Hz, 1H), 7.21 (td, *J* = 7.45, 1.35 Hz, 1H), 7.15 (d, *J* = 6.69 Hz, 1H), 7.08 (td, *J* = 7.28, 0.69 Hz, 1H), 6.83 (t, *J* = 2.73 Hz, 1H), 6.16 (t, *J* = 2.68 Hz, 1H), 2.90 (t, *J* = 6.88 Hz, 2H), 2.82 (t, *J* = 4.75 Hz, 2H), 2.04-1.98 (m, 2H).

Preparation of BODIPY (3a). 4-Iodobenzoyl chloride (40.0 mg, 0.16 mmol) was added to a solution of 6-methoxy-4,5-dihydro-1*H*-benzo[*g*]indole (**2a**) (64.0 mg, 0.32 mmol) in 1,2-dichloroethane (5.0 mL). The reaction mixture was refluxed to 83 °C for 48 h and it was cooled to 25 °C. After addition of triethylamine (68.0 mg, 0.67 mmol) to the reaction mixture, it was stirred at 25 °C for 5 min. Then, boron trifluoride diethyl etherate (130.0 mg, 0.91 mmol) was added to the reaction mixture. After being refluxed to 83 °C for 0.5 h, the solvent was removed under the reduced pressure. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$:hexane = 1:1) followed by basic alumina column chromatography (CH$_2$Cl$_2$:hexane = 1:1) to give **3a** (36 mg, 34%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (d, *J* = 8.11 Hz, 2H), 7.85 (dd, *J* = 6.67 Hz, 1.58 Hz, 2H), 7.40 (t, *J* = 8.16 Hz, 2H), 7.28 (dd, *J* = 6.67, 1.61 Hz, 2H), 6.96 (d, *J* = 8.18 Hz, 2H), 6.51 (s, 2H), 3.86 (s, 2H), 2.93 (t, *J* = 7.15 Hz, 4H), 2.63 (t, *J* = 7.12 Hz, 4H).

BODIPY (3b). The neutral alumina was used in 2nd column chromatography (CH$_2$Cl$_2$:hexane = 1:1). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.47 (s, 2H), 7.86 (d, *J* = 8.20 Hz, 2H), 7.29 (d, *J* = 8.19 Hz, 2H), 7.17 (d, *J* = 8.32 Hz, 2H), 6.89 (dd, *J* = 8.25, 2.47 Hz, 2H), 6.53 (s, 2H), 3.93 (s, 6H), 2.84 (t, *J* = 6.95 Hz, 4H), 2.67 (t, *J* = 6.95 Hz, 4H).

BODIPY (3c). The neutral alumina was used in 2nd column chromatography (CH$_2$Cl$_2$:hexane = 1:1). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.78 (d, *J* = 8.27 Hz, 2H), 7.41 (s, 2H), 7.28 (d, *J* = 8.31 Hz, 2H), 6.80 (s, 2H), 6.28 (s, 2H), 3.96 (s, 6H), 3.94 (s, 6H), 2.90 (t, *J* = 7.04 Hz, 4H), 2.75 (t, *J* = 7.07, 4H).

BODIPY (3d). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.58 (s, 2H), 7.84 (d, *J* = 8.18 Hz, 2H), 7.30 (d, *J* = 8.31 Hz, 2H), 7.05 (s, 2H), 6.49 (s, 2H), 2.80 (t, *J* = 7.53 Hz, 4H), 2.65 (t, *J* = 7.54 Hz, 4H), 2.42 (s, 6H), 2.31 (s, 6H).

BODIPY (3e). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.06-8.04 (m, 2H), 7.88 (d, *J* = 8.32 Hz, 2H), 7.36 (d, *J* = 8.28 Hz, 2H), 7.32-7.28 (m, 4H), 7.24-7.22 (m, 2H), 6.62 (s, 2H), 2.61 (t, *J* = 6.83 Hz, 4H), 2.34 (s, 4H), 2.06-1.99 (m, 4H).

Preparation of 7. 5-Hexynoic acid (**5**) (23.0 mg, 0.21 mmol) and piperidine (70.0 mg, 0.83 mmol) was added to a solution of (Ph$_3$P)$_4$Pd (5.0 mg, 0.004 mmol) and copper iodide (1.0 mg, 0.004 mol) in THF (3 mL). After being stirred at 65 °C for 12 h, the solvent was removed under the reduced pressure and then, the residue was purified by silica gel column chromatography (CH$_2$Cl$_2$:MeOH = 9:1) to give **6** (18.0 mg, 52%). Because compound **6** is unstable, it (55.0 mg, 0.085 mmol) was treated with EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride] (18.0 mg, 0.094 mmol) and *N*-hydroxysuccinimide (11.0 mg, 0.094 mmol) in DMF (2 mL). After being stirred at

25 °C for 12 h, the reaction mixture was extracted with chloroform (3 × 20 mL). The combine organic layers were washed with NaHCO$_3$ (20 mL). The resulting organic layers were dried over MgSO$_4$, filtered and concentrated under the reduced pressure. The residue was purified by silica gel column chromatography (CH$_2$Cl$_2$:MeOH = 9:1) to give **7** (40.0 mg, 64%). NMR (400 MHz, CDCl$_3$) δ 8.46 (d, *J* = 8.12 Hz, 2H), 7.50 (dd, *J* = 12.48, 8.22 Hz, 1.58 Hz 2H), 7.39 (t, *J* = 8.14 Hz, 2H), 6.96 (d, *J* = 8.13 Hz, 2H), 6.54 (s, 2H), 3.85 (s, 6H), 2.92 (t, *J* = 6.67 Hz, 4H), 2.87-2.82 (m, 6H) 1H), 2.65-2.59 (m, 6H), 2.08 (dd, *J* = 7.17, 7.19 Hz, 2H).

References and Notes

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