Synthesis of 8-substituted 4, 4-difluoro-4-bora-3a,4a-diaza-s-indacene Dyes (BODIPY)

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Summary: 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes are important in synthetic and applied chemistry. The reaction of pyrrolomethane **1** with acetyl chloride and boron trifluoride etherate in the presence of triethylamine afforded the 4,4-Difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **2a**. When benzoylchloride and chloroacetyl chloride were used, phenyl **2b** and chloromethyl **2c** derivatives formed. The treatment of pyrrolomethane **1** with 3- (phenylthio)propanal **3** in the presence of ytterbium (III) trifluoromethanesulfonate hydrate in catalitic amount yielded the 5-(2-thiophenyl ethane)-1,9-dimethyldipyrromethane **4**, which was reacted with DDQ and boron trifluoride etherate in the presence of triethylamine formed 8-(2-thiophenylethan) 4,4-difluoro-3,5dimethyl-4-bora-3a,4a-diaza-3-indacene **5**. The oxidation of 8-(thiomethyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **6** with m-CPBA gave methylsulfonyl product **7.** Bromination of 4,4-difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **2a** yielded 1,2,6,7-tetrabromo-4,4-difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **8.**

Introduction

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes have attracted much attention due to the excellent applications in many areas such as fluorescent switches [1-2], supramolecular polymers [3-5], labeling reagents [6-8], chemosensors [9-11], near-IR absorbing/emitting dyes [12-14], nonlinear optical materials [15-16], photodynamic therapy [17-19], chromogenic probes [20], laser dyes [21], light-harvesters and sensitizers for solar cell applications [22]. BODIPY dyes tend to be strongly UV-absorbing small molecules that emit relatively sharp fluorescence peaks with high quantum yields. Small modifications to their structures enable tuning of their fluorescence characteristics; consequently, these dyes are widely used to label proteins [23] and DNA [24].

Herein, we report the synthesis of substituted BODIPY compounds under mild reaction conditions in reasonable yield. The structures of synthesised compounds were identified by spectroscopic techniques, including ^{1}H-, ^{13}C-NMR, IR, MS, micro analysis.

Result and Discussion

The treatment of pyrrolomethane **1** with acetyl chloride and boron trifluoride etherate in the presence of triethylamine gave 4,4-Difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **2a**. The ^{1}H-spectrum of **2a** displayed the signals at δ 2.48 which belonged to methyl bonded to C-8 carbon. On the other hand, the singlet observed at δ 2.58 which belonged to methyl groups attached to C-3 and C-5 carbons. The characteristic doublet appeared at δ 6.24 with a coupling constant as 4.3 Hz assigned to the methine protons (H-1 and H-7) and the other methine protons (H-2 and H-6), resonated at δ 7.06, coupled with H-1 and H-7 as the same coupling constant. In the ^{13}C-spectrum, the observation of seven peaks is fully in agreement with the 4,4-Difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **2a.** When benzoylchloride and chloroacetyl chloride were used instead of acetyl chloride, corresponding 4,4-Difluoro-8-phenyl-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **2b** and 4,4-difluoro-8-chloromethyl-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **2c** were formed, respectively. The ^{1}H-spectrum of compound **2b** resembled the spectrum of compound **2a** but compound **2b** consisted of phenyl instead of methyl that the compound **2a** contained. In ^{1}H-spectrum, phenyl protons resonated at δ 7.45 as multiplet, H-1 and H-7 gave the signal at δ 6.90 as doublet (J = 3.7), and the signal observed at δ 6.24 as doublet (J = 3.7) could be attributed to the H-2 and H-6. The appearance of ten lines in ^{13}C spectrum was also accordance with the proposed structure, compound **2b**. The ^{1}H spectrum of compound **2c** showed the singlet at aliphatic region as δ 4.56 and other signals looked like the compound **2a** and **2b**. The seven lines in ^{13}C spectrum and other spectroscopic data confirmed the proposed structure. The reaction of pyrrolomethane **1** with 3- (phenylthio)propanal **3** in the presence of ytterbium (III) trifluoromethanesulfonate hydrate in catalytic amount

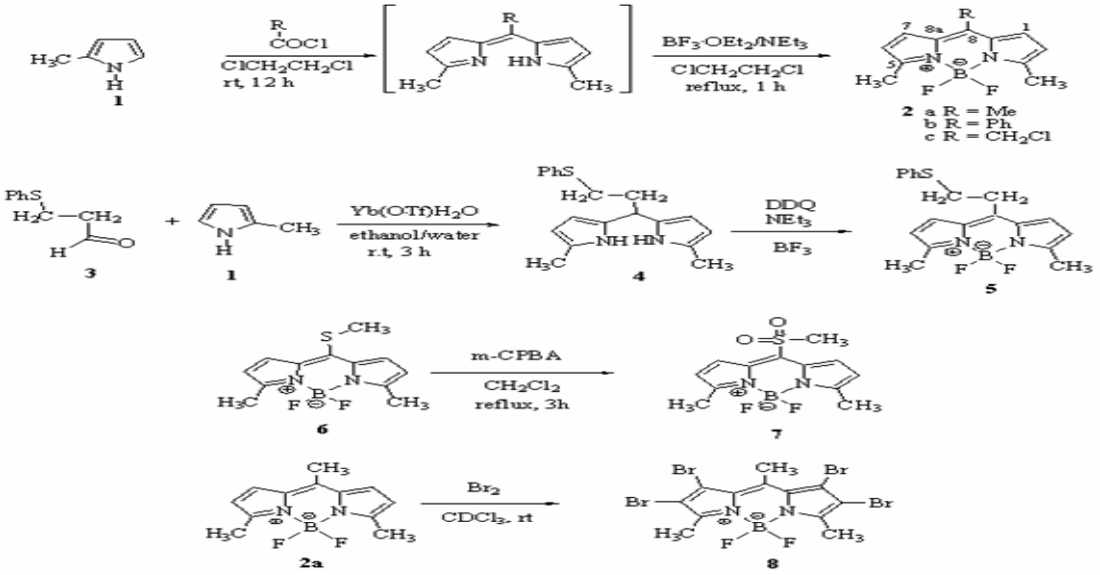
gave the 5-(2-thiophenyl ethane)-1,9-dimethyldipyrromethane **4**, which was treated with DDQ and boron trifluoride etherate in the presence of triethylamine yielded 8-(2-thiophenylethan) 4,4-difluoro-3,5dimethyl-4-bora-3a,4a-diaza-3-indacene **5**. In ^{1}H spectrum of compound **4**, the signals appeared at δ 7.52 as broad singlet that belonged to the proton attached to nitrogen. While the phenyl protons resonated at δ 7.30-7.12, the methyl groups gave the signal at δ 2.19. The appearance of the other protons in expected location confirmed the structure of compound **4**. In the ^{1}H spectrum of compound **5**, The aromatic protons gave the signals at δ 7.36-7.24. The signal of H-1 and H-7 appeared at δ 6.86 as doublet (J = 4.2 Hz) and the resonance appeared at δ 6.21 as doublet (J = 4.2) could be ascribed to H-2 and H-6. The aliphatic protons gave rise to AA' and BB' at δ 3.15 and δ 3.0 and methyls signal appeared at 2.57 as singlet. The observation of twelve lines in ^{13}C spectrum verified the proposed structure. 8-(thiomethyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **6** was synthesised according to the study carried out by Biellmann et al [25]. The oxidation of 8-(thiomethyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **6** with m-CPBA gave methylsulfonyl product **7** in a yield of 10%. The bromination reactions are prominent in synthetic chemistry [26-28]. Due to the importance of brominated compounds as precursors in the preparation of organometallic reagents [29] and metal mediated coupling reactions [30], we brominated 4,4-difluoro-3,5,8-trimethyl-4-bora-3a,4a-d

iaza-s-indacene **2a** in tube to yield 1,2,6,7-tetrabromo-4,4-difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **8** (scheme). In ^{1}H spectrum of compound **8**, the appearance of only methyl peaks at δ 3.09 and δ 2.60 indicated that addition-elimination reaction took place and four bromines were bonded to the compound **2a**. In addition, seven lines in ^{13}C spectrum were in accordance with the proposed structure.

Experimental

General Procedure

Commercial reagents were purchased from standard chemical suppliers and purified if needed. Flash column chromatography was carried out on Silica Gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F_{254} (0.25 mm, E. Merck), detection was done by spraying with a solution of Ce(NH4h(N03)6, (NH4)6M07024, and H2S04 in water or ninhydrin and acetic acid solution in n-butanol and subsequent heating on a hot plate. Melting points were determined with a Biichi B-540 apparatus and are uncorrected. ^{1}H and ^{13}C spectra were recorded with Bruker 300 MHz instruments. Chemical shifts are in ppm from TMS as internal standard; generated from the $CDCl_3$. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Elemental analysis was done with a Perkin-Elmer 2400CHN instrument. Mass spectra were obtained with a FAB JMS-700 double focusing mass spectrometer (JEOL, Tokyo, Japan).



Scheme: Synthesis of 8-substituted 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene dyes

Synthesis of 4,4-Difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **2a** *(BODIPY-2a)*

To a solution of 2-Methylpyrrole **1** (1.9 g, 23 mmol) in $C_2H_4Cl_2$ (10 mL) was dropwise added a solution of acetyl chloride (2.33 mL, 32 mmol) in $C_2H_4Cl_2$ (10 mL) at room temperature for 30 min under nitrogen. After addition, the solution was stirred at room room temperature for 12 h under nitrogen. The solution was cooled to 0 ºC ice-water bath, triethylamine (7 ml, 50 mmol) was then added dropwise at 0 ºC for 10 min, and the mixture was stirred for 10 min. The ice-water bath was removed. After reaction mixture was reached to room temperature, then BF_3 etherate (11 mL, 90 mmol) was added, and the mixture was stirred at room temperature for 1h. After removal of solvent, the residue was passed through a silica gel column using 10% EtOAc in hexanes to give **4** as a deep purple needles crystalline product after removal of solvent (0.57 g, 21%). mp 121-123 ^oC. υ_{max} IR $(CH_2Cl_2)/cm^{-1}$ 705, 752, 1151, 1270, 1497, 1581. δ_H ($CDCl_3$, 300 MHz) 7.06 (d, *J* 4.3 Hz, 2H), 6.24 (d, *J* 4.3 Hz, 2H), 2.58 (s, 6H), 2.48 (s, 3H). δ_C ($CDCl_3$, 75 MHz) 156.5, 140.1, 134.9, 126.9, 118.7, 15.1, 14.7. MS (FAB^+, NBA) *m/z* 234.2 (M^+). Anal. Calcd. For $C_{12}H_{13}BF_2N_2$; C, 61.58; H, 5.60; N, 11.97. Found; C, 61.22; H, 5.82; N, 11.21.

Synthesis of 4,4-Difluoro-8-phenyl-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **2b** *(BODIPY-2b)*

To a solution of 2-methylpyrrole **1** (1.81 g, 22 mmol in $C_2H_4Cl_2$ (10 mL) was added a solution of benzoylchloride (3.14 g, 22 mmol) in $C_2H_4Cl_2$ (10 mL) dropwise at room temperature for 30 min under nitrogen. After addition, the solution was refluxed for 12 h under nitrogen. A black solution was formed. The solution was cooled to room temperature, then triethylamine (7 mL, 50 mmol) was added dropwise at room temperature for 10 min under nitrogen. After the addition, the dark solution was further stirred for 10 min at room temperature. Then BF_3 etherate (11 ml, 90 mmol) was added, and the mixture was refluxed for 1 h under nitrogen. The solvent was removed, and the residue was passed through a silica gel column using 10% EtOAc in hexanes to give **2b** as a deep purple needles crystalline product after removal of solvent (1.7 g, 53%). mp 131-132 ºC. υ_{max} IR $(CH_2Cl_2)/cm^{-1}$ 440, 705, 1011, 1153, 1269, 1499, 1560). δ_H ($CDCl_3$, 300 MHz) 7.45 (m, 5H), 6.90 (d, *J* 3.7 Hz, 2H), 6.24 (d, *J* 3.7 Hz, 2H), 2.64 (s, 6H). δ_C ($CDCl_3$, 75 MHz) 157.5, 142.5, 134.5, 134.0, 130.4, 130.3, 129.9, 128.1, 119.3, 14.8. MS (FAB^+, NBA) *m/z* 296.1 (M^+). Anal. Calcd. For $C_{17}H_{15}BF_2N_2$; C, 68.95; H, 5.11; N, 9.46. Found; C, 68.65; H, 5.13; N, 9.08.

Synthesis of 4,4-Difluoro-8-chloromethyl-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **2c** *(BODIPY-2c)*

To a solution of 2-Methylpyrrole **1** (2.48 g, 30.6 mmol) in $C_2H_4Cl_2$ (10 mL) was added dropwise a solution of chloroacetyl chloride (2.50 mL, 30.6 mmol) in $C_2H_4Cl_2$ (10 mL) at room temperature for 30 min under nitrogen. After addition, the solution was stirred at room temperature for 12 h under nitrogen. A black solution was formed. Triethylamine (8.5 mL, 60.2 mmoL was then added dropwise at 0 ºC for 10 min under nitrogen, and the mixture was stirred for 10 min. Then BF_3 etherate (15.4 mL, 122.4 mmol) added, and the mixture was stirred at room temperature for 1h. After removal of solvent, the residue was passed through a silica gel column using 10% EtOAc in hexanes to give **2c** as a black fine solid after removal of solvent (0.87, 21%). mp 155-157 ºC. δ_H ($CDCl_3$, 300 MHz) 7.12 (d, *J* 4.2 Hz, 2H), 6.28 (d, *J* 4.2 Hz, 2H), 4.56 (s, 2H), 2.59 (s, 6H). δ_C ($CDCl_3$, 75 MHz) 159.2, 135.6, 134.1, 127.1, 119.9, 37.4, 15.0. MS (FAB^+, NBA) *m/z* 268.1 (M^+). Anal. Calcd. For $C_{12}H_{12}BClF_2N_2$; C, 53.68; H, 4.50; N, 10.43. Found; C, 53.45; H, 4.53; N, 10.18.

Synthesis 5-(2-thiophenyl ethane)-1,9-dimethyldipyrromethane **4**

To a 0.1 M ytterbium (III) trifluoromethanesulfonate hydrate (0.62 g) in solution of ethanol/water (7 mL/3 mL) was added 2-methylpyrrole (1.62 g, 20 mmol) and 3-(phenylthio)propanal (0.83 g, 5 mmol). The reaction mixture was stirred 3 h at room temperature. After stirring, to the reaction mixture was added saturated $NaHCO_3$ (50 mL), extracted three times with ether (totally 75 mL). The combined organic layer was washed with brine. The extract was then dried over $MgSO_4$ and purified by flash column chromatograpy (silica gel 60, 70-230 mesh). The pyrromethane **4** was otained as yellow liquid (0.71g, 46%). δ_H ($CDCl_3$, 300 MHz) 7.52 (brd s, 2H, NH) 7.30-7.12 (m, 5H), 5.93 (d, *J* 4.8 Hz, 2H), 5.80 (d, *J* 4.8 Hz, 2H), 4.11 (t, *J* 7.8 Hz 1H), 2.93 (t, *J* 7.5 Hz 2H) 2.22 (dt, 2H) 2.19 (s, 6H). Anal. Calcd. For $C_{19}H_{22}N_2S$; C, 73.51; H, 7.14; N, 9.02. Found; C, 73.31; H, 7.02; N, 9.23.

Synthesis of 8-(2-thiophenylethan) 4,4-difluoro-3,5dimethyl-4-bora-3a,4a-diaza-3-indacene **5** *(BODIPY-5)*

A 0,65 g sample (2.1 mmol) of 1,9-dimethyl-5-(thiophenylethane)dipyrromethane was

dissolved in 10 mL toluene at room temperature in a 25 mL one-neck round flask. DDQ (470 mg, 2.1 mmol) was added at once and the reaction mixture was stirred at room temperature. After 5 min, triethylamine (2 mL, 14 mmol) was added to the black reaction mixture followed immediately by BF_3-etherate (4 mL, 31.8 mmol) under nitrogen at room temperature. After 1 h, the reaction mixture was rotary evaporated to a black viscous material. Column chromatography (silica gel, ethyl acetate/hexanes, 1/9) gave the desired product, which eluted as the first component. Removal of the solvent gave 210 mg (28%) of the title compound as a deep red oily liquid. δ_H ($CDCl_3$, 300 MHz) δ 7.36-7.24 (m, 5H), 6.86 (d, *J* = 4.2 Hz, 2H), 6.21 (d, *J* = 4.2 Hz, 2H), 3.15 (AA' part of AA'BB', 2H), 3.00 (BB' part of AA'BB', 2H) 2.57 (s, 6H). δ_C ($CDCl_3$, 75 MHz) 157.2, 141.4, 134.8, 134.3, 130.4, 129.1, 126.9, 126.6, 119.0, 36.8, 30.3, 14.7. Anal. Calcd. For $C_{19}H_{19}BF_2N_2S$; C, 64.06; H, 5.38; N, 7.86. Found; C, 63.91; H, 5.25; N, 7.91.

Oxidation 8-(thiomethyl) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **6** *(BODIPY-6) to Sulfone* **7**

A mixture of BODIPY-**6** (87 mg, 0.3 mmol) and m-CPBA (0.172 g, 0.9 mmol) in dry CH_2Cl_2 (5 mL) was heated to reflux for 3 h under nitrogen atmosphere. After cooling, the reaction mixture was washed with a mixture of saturated $NaHCO_3$ and 10% $NaHSO_3$ solution and extracted with CH_2Cl_2. The solution was dried and chromatographed and SiO_2 column. Elution with n-hexane and ethyl acetate (4:1) provided 8-(sulfone) 4,4-difluoro-3,5-dimethyl-4-bora-3a,4a-diaza-s-indacene **7** in 10% yield (8.9 mg). δ_H ($CDCl_3$, 300 MHz) 7.76 (A part of AB system, 2H, *J* = 4.4 Hz), 6.37 (B part of AB system, 2H, *J* = 4.4 Hz), 2.72 (s, 3H), 2.57 (s, 6H). MS (EI+) *m/z* 298.1 $[M]^+$.

Bromination of BODIPY-2a: Synthesising of tetrabromo-4,4-difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **8**

A solution of a trace of 2a in $CDCl_3$ in tube was added 1-2 drops bromine at room temperature. The ^{1}H-and ^{13}C-spectra were recorded. Spectral data indicated the formation of 1,2,6,7-tetrabromo-4,4-difluoro-3,5,8-trimethyl-4-bora-3a,4a-diaza-s-indacene **8** as the sole product. Mp188-190 ºC. δ_H ($CDCl_3$, 300 MHz) 3.09 (s, 3H), 2.60 (s, 6H). δ_C ($CDCl_3$, 75 MHz) 153.5, 129.0, 120.4, 114.2, 105.5, 17.2, 14.2. MS (FAB^+, NBA) *m/z* 545.8 (M^+). Anal. Calcd. For $C_{12}H_9BBr_4F_2N_2$; C, 26.22; H, 1.65; N, 5.11. Found; C, 26.11; H, 1.37; N, 5.22.

Conclusion

Due to the many application area of BODIPY, synthesising of 8-substituted 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene dyes (BODIPY) under mild reaction conditions in reasonable yield could be the significant for applied chemistry. In addition, Brominated BODIPY could be the valuable precursor for functionalisation of the BODIPY core by coupling reactions.

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