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Substituents modification of *meso*-aryl BODIPYs for tuning photophysical properties

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ABSTRACT

We successfully synthesized eight *meso*-aryl BODIPYs with 2,6-diethyl- or 1,2,6,7-tetraethyl substituents and characterized their photophysical properties. The steric hindrance resulting from the phenolic group in the *meso*-aryl moiety and the ethyl groups on the BODIPY core affected the synthesis of dipyrromethanes as an intermediate as well as the UV–Vis absorption and fluorescence emission of the BODIPYs due to the constrained rotation of the aryl ring. The potential use of the *meso*-hydroxyphenyl BODIPY as a pH sensor was also shown by the pH-dependent fluorescence emissions.

1. Introduction

Fluorescence dyes, typically bearing π-conjugated bonds, have widely been studied in various areas because of fundamental interest in photo-chemical and -physical processes as well as technological applications such as analytical sensors, photovoltaic cells, light-emitting diodes, biomedical imaging, and biomarkers.[1–4] For example, cyanine dyes are used to label biomolecules such as proteins, antibodies, and peptides due to their fluorescence brightness, photostability, and low nonspecific binding.[5] To extend the use of fluorophores in technologically important fields, the first step will be to understand photophysical properties depending on the molecular structures and environmental conditions (e.g., solvent polarity and ions). However, it is difficult to systematically investigate the structure effect of most organic fluorophores because of limited structural modifications and poor solubility in common organic solvents.[6] 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) has recently received considerable attention due to its favorable photophysical properties, for example, narrow absorption and emission bands, high molar extinction coefficients, negligible triplet-state formation, and excellent photostability.[7] Furthermore, its facile structural modification[8] and high solubility in organic solvents make it easy to use in various areas such as molecular probes,[2,7,9] photosensitizers,[10–12] and chemical sensors.[13,14] To date, there are numerous BODIPY derivatives with different electronic and steric effects on the *meso*-position and periphery of boradiazaindacenes.[15–22] For example, electron-withdrawing substituents at the *meso*-position lowered the LUMO level leading to bathochromic shifts with respect to analogues with electron donating substituents. Additionally, the steric pressure at the 1,3,5,7-substituted BODIPY leads to the loss of its planarity resulting in increased non-radiative deactivation rates and lower quantum yields compared to the 3,5-substituted counterparts.[14] Though there has been many literature precedents for the BODIPYs with electron donating methyl groups in positions 3 and 5 on BODIPY core,[14,23–25] diethyl carboxylate substituents in positions 3 and 5[16] was employed in this work. The introduction of the diethyl carboxylate ester groups enables BODIPYs to increase water solubility after hydrolysis of the ester group, leading to facile biological applications. In addition, the carboxylate group can be converted to amide functional group for further applications, e.g.

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metal detection.

In particular, *meso*-hydroxyphenyl substituted BODIPYs have shown fluorescence on/off switching through deprotonation and protonation processes.[23–27] The emission intensity is attributed to the photoinduced electron transfer (PET) from the phenolate to the excited-state indacene acceptor moiety. Thus, it is important to systematically study how photophysical properties are affected by substituents at the periphery of *meso*-hydroxyphenyl substituted BODIPYs. Herein, we investigated the feasibility of synthesizing highly substituted *meso*-hydroxyphenyl/phenyl BODIPYs with di- or tetra-ethyl groups on the boradiazaindacenes as well as their photophysical properties. We successfully synthesized eight *meso*-aryl BODIPYs with 2,6-diethyl- or 1,2,6,7-tetraethyl substituents and characterized their quantum yield including the pH-dependent fluorescence emission.

2. Results and discussion

2.1. Design and synthesis of BODIPYs

To compare its photophysical properties with BODIPYs having aryl units in the *meso* position, *meso*-unsubstituted BODIPY **1** was synthesized. The periphery of the dipyrromethene is substituted with different electron driving forces. The 1, 2, 6, and 7 positions are functionalized with ethyl groups, and the 3 and 5 positions are substituted with carboxylate units. First, ethyl 3,4-diethyl-5-formyl-1*H*-pyrrole-2-carboxylate was synthesized from ethyl 3,4-diethyl-1*H*-pyrrole-2-carboxylate with $POCl_3$ in DMF with a known procedure (Scheme 1). Then, the aldehyde was condensed with ethyl 3,4-diethyl-1*H*-pyrrole-2-carboxylate in the presence of $POCl_3$, Et_3N followed by treatment with $BF_3{\cdot}OEt_2$ to yield BODIPY dye **1.**[18,28–30]

After the successful synthesis of *meso*-unsubstituted BODIPY **1** from ethyl 3,4-diethyl-1*H*-pyrrole-2-carboxylate, we then synthesized a series of *meso*-aryl-substituted BODIPYs **3a-d** with ethyl substituents at the 1, 2, 6, and 7 positions and carboxylate groups at the 3 and 5 positions on the boradiazaindacenes (Scheme 2). The dipyrromethanes **2a-d**, which are key intermediates, were prepared by condensation between the corresponding benzaldehyde and ethyl 3,4-diethyl-1*H*-pyrrole-2-carboxylate in the presence of trifluoroacetic acid (TFA) as a catalyst. Whereas **2a** was synthesized in CH_2Cl_2 (DCM), **2b-2d** were prepared in THF, a polar solvent, due to the limited solubility of the hydroxybenzaldehydes in CH_2Cl_2 (DCM). Products **2a-d** were further reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), a base, and $BF_3{\cdot}OEt_2$ to yield BODIPYs **3a-d**. While Et_3N was used in the preparation of **3a** and **3c**, *N,N*-diisopropylethylamine (DIPEA) was used as a base for the **3b** and **3d** preparation.

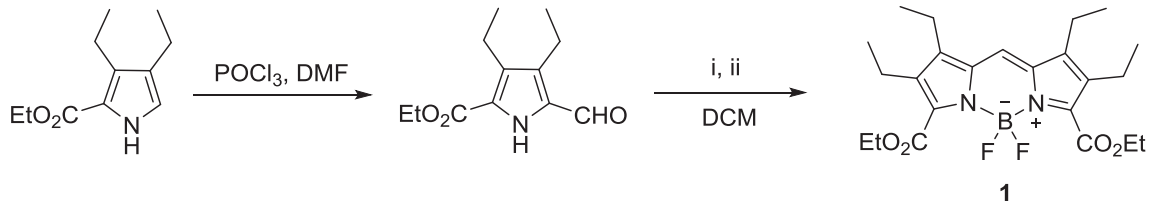
As shown in Scheme 2, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde and 3,5-dihydroxybenzaldehyde were successfully condensed with ethyl 3,4-diethyl-1*H*-pyrrole-2-carboxylate. However, 2-hydroxybenzaldehyde was unable to produce dipyrromethane. It was speculated that the steric interference between the 2-hydroxy group of benzaldehyde and the β-substituent of pyrrole prohibited the formation of dipyrromethane. Because the steric interference between the 2-hydroxy group of benzaldehyde and the β-substituent of pyrrole imposes a challenge on the formation of dipyrromethane, the elimination of the steric hindrance could facilitate the formation of dipyrromethane and BODIPY, sequentially, from 2-hydroxybenzaldehyde. In this sense, the synthesis of BODIPYs bearing ethyl substituents on the 2 and 6 positions was tried from ethyl 3-ethyl-1*H*-pyrrole-2-carboxylate (Scheme 3). Ethyl 3-ethyl-1*H*-pyrrole-2-carboxylate was prepared according to a previously reported method.[24] Unfortunately, the condensation of ethyl 3-ethyl-1*H*-pyrrole-2-carboxylate and benzaldehyde in the presence of TFA not only suffered from a low yield of **4a** but also produced α,β-connected dipyrromethane **5a** resulting in a poor yield (Table 1, entry 1) of the corresponding BODIPY. Though it was already reported that the yield of dipyrromethane from the condensation between benzaldehyde and ethyl 3-ethyl-1*H*-pyrrole-2-carboxylate was negligible,[31] we optimized the reaction condition to improve the yield of **4a**. As shown in Table 1, the only desired product **4a** was obtained using 10 or 1 equiv. of TFA (entry 2 and 3), while the condensation with excess TFA produced **5a** as a side product (entry 1). 0.5 equiv. of methanesulfonic acid (MSA) in CH_2Cl_2 (DCM) could produce **4a** in an optimized yield of 25% without **5a** (entry 8). However, *p*-toluene sulfonic acid (*p*-TSA), trichloroacetic acid (TCA), and $BF_3{\cdot}OEt_2$ were not effective for the formation of **4a** (entry 4, 5, and 6).

With these optimized conditions on hand, a series of dipyrromethane **4a-d** were prepared from 2-, 3- and 4-hydroxybenzalydehyde and subsequently converted to BODIPY **6a-d** using DIPEA as a base (Scheme 4). It is worth mentioning that the 2-hydroxyphenyl group in the *meso* position of BODIPY **6d** is compatible with the 2,6-diethyl units on dipyrromethene due to the reduction of the steric interference.

The one-pot synthesis for BODIPYs[32] was also tried, but we observed numerous by-products spots on TLC, which led to extremely low yield after column separation (<5%). Though we do not have the general hypothesis for the relatively low yields for BODIPY **1**, **3d**, and **6d** compared to other BODIPYs (*vide infra*), we suggest that the low yield is generally attributed to the formation of quite a few byproducts and several purification processes.

2.2. Photophysical properties of BODIPYs

The photophysical properties of the synthesized BODIPYs were investigated in CH_2Cl_2 solution. As shown in Fig. 1 and Table 2, BODIPY **1**, **3a-d**, and **6a-d** have narrow absorption bands with two absorption maxima. The main absorption at 534–554 nm resulted from the 0-0 band of a strong S_0-S_1 transition. The 0–1 vibrational band of the same transition generated the second maximum or shoulder at a short wavelength around 500 nm. In addition, a considerably weak broad absorption band is found at around 400 nm for the measured BODIPYs attributed to the S_0-S_2 transition. The emission spectra of the BODIPYs exhibit mirror symmetry with the absorption and Stokes-shifted band. Compared with the absorption spectra of **3a-d**, the absorption spectra of **6a-d** are red-



1

Scheme 1. Synthesis of *meso*-unsubstituted BODIPY **1**. Reagents and conditions: (i) Ethyl 3,4-diethyl-1*H*-pyrrole-2-carboxylate, $POCl_3$, Et_3N; (ii) $BF_3{\cdot}OEt_2$.