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Authors: Xindong Jiang, Tingjiang Zhang, Changliang Sun, Yanqiu Meng, Linjiu Xiao

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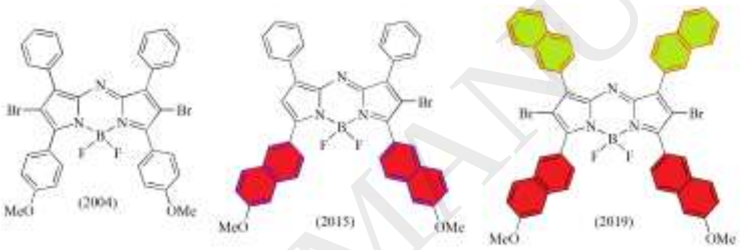
Communication

Synthesis of aza-BODIPY dyes bearing the naphthyl groups at 1,7-positions and application for singlet oxygen generation

Xindong Jiang [a,b,∗], Tingjiang Zhang [a], Changliang Sun [c], Yanqiu Meng [d], Linjiu Xiao [a]

[a] *College of Applied Chemistry, Key Laboratory of Rare-earth Chemistry and Applying of Liaoning Province, Shenyang University of Chemical Technology, Shenyang 110142, China*
[b] *Department of Chemistry, Graduate School of Science, Hiroshima University, Higashi-Hiroshima 739-8526, Japan*
[c] *Center of Physical and Chemistry Test, Shenyang University of Chemical Technology, Shenyang 110142, China*
[d] *College of Pharmaceutical and Biological Engineering, Shenyang University of Chemical Technology, Shenyang 110142, China*

Graphical Abstract



Near-infrared absorbing aza-BODIPYs with the naphthyl groups at 1,7-positions were prepared for the first time. The singlet oxygen generation of aza-BODIPY with the naphthyl groups at 1,7-positions was more effective than that of the corresponding aza-BODIPY with the phenyl groups at 1,7-positions.

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ABSTRACT

Using 2-vinylnaphthalene, aza-BODIPYs with the naphthyl groups at 1,7-positions were prepared and their photophysical properties were characterized. Due to attachment of the naphthyl groups at 1,7-positions, aza-BODIPYs show long-wavelength absorption and emission in the near-infrared region. The singlet oxygen generation of the dibromo substituted aza-BODIPY with the naphthyl groups at 1,7-positions as a photosensitizer was more effective than that of the corresponding aza-BODIPY with the phenyl groups at 1,7-positions. No photobleaching of the naphthyl-containing aza-BODIPY was observed and such NIR aza-BODIPY could be used for the singlet oxygen generation.

Photodynamic therapy (PDT) was usually advocated as a non-invasive medical technique for a damage of tumor tissues [1-3]. Because photosensitizers (PS) transfer energy from light to the molecular oxygen to produce the singlet oxygen ($^1O_2$), which can cause oxidative damage of lipids, proteins and DNA in tumor tissues during PDT process [4-7]. Therefore, the singlet oxygen is an important cytotoxic agent in the PDT therapeutic process, and the investigation of generation of the singlet oxygen has attracted increasing interest [8-11]. Generally speaking, the singlet oxygen generation from a PS is controlled by the spin-forbidden electronic transition from a singlet to a triplet state upon irradiation [12]. Introduction of the heavy atom to the fluorescent molecules was

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∗ Corresponding author.
E-mail address: xdjiang@syuct.edu.cn

found to efficiently increase intersystem crossing (ISC) to generate the singlet oxygen [13-15].

Borondipyrromethenes (BODIPYs) are the classical fluorescent dyes with intense absorption, high quantum yields, and tunable emission wavelength [16-21]. Such dyes and their derivatives were widespreadly applied for biological imaging, fluorescent probes, dye-sensitized solar cells and supramolecular chemistry and so forth [22-28]. Take advantage of the attachment of the heavy atoms to the BODIPY core, the modifications could provide the outstanding efficiency of the singlet oxygen generation by increasing the S1→T1 transition [29]. The pioneer work reported by O'Shea indicated that aza-BODIPY **1Br** (λ_{abs} = 679 nm) is an excellent PS (Fig. 1a) [30], but the reserved topic is to be develop NIR-absorbing (>700 nm) aza-BODIPY-based PS. Recently, our group reported aza-BODIPYs **2H** and **2Br** with the naphthyl group at 3,5-positions (Fig. 1a) [31]. In this work, using of the heavy atom effect, we reported synthesis and photophysical properties including the singlet oxygen generation of NIR-absorbing dyes **3Br** and **4Br** (λ_{abs} = 705 nm) with the naphthyl group at 1,7-positions in aza-BODIPY system for the first time (Fig. 1b).

Synthesis of NIR-absorbing dye aza-BODIPY **4Br** with four naphthyl groups at 1,3,5,7-positions was outlined in Scheme 1. Utilizing 2-vinylnaphthalene as the starting material, the snuffcolored oil 3-(naphthalen-2-yl)-2*H*-azirine **5** was obtained in 53% yield in the mild condition, comparing to the relatively rigorous condition for the synthetic of analogue (Scheme 1) [32]. For the preparation of the naphthyl-containing pyrrole, 1-(6-methoxynaphthalen-2-yl)ethanone was employed to react with **5** to providess 2-(6-methoxynaphthalen-2-yl)-4-(naphthalen-2-yl)-1*H*-pyrrole **6** in 37% yield in the presence of NaH (Scheme 1) [33]. The dinaphthyl-containing pyrrole **6** showed a typical hydrogen signal δ 8.72 (br s, $1H_{N\text{-}H}$) in the ^{1}H NMR spectrum (Supporting information), which is in agreement with that of the reported pyrrole (δ 8.56 (br s, $1H_{N\text{-}H}$) [31,34-37]. aza-BODIPY **4H** was successfully synthesized from pyrrole **6** in 36% combined yield under HOAc, Ac_2O and $NaNO_2$, followed by complexation with $BF_3{\cdot}Et_2O{-}Et_3N$ (Scheme 1). Moreover, aza-BODIPY **4H** reacted with *N*-bromosuccinimide to provide the dibromo substituted aza-BODIPY **4Br**. To our knowledge, this aza-BODIPY structure is the first to bear a naphthyl group at 1,7-positions in aza-BODIPY system.

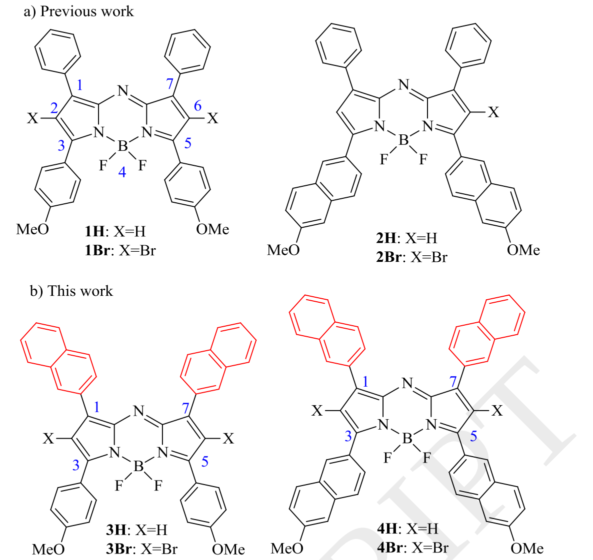
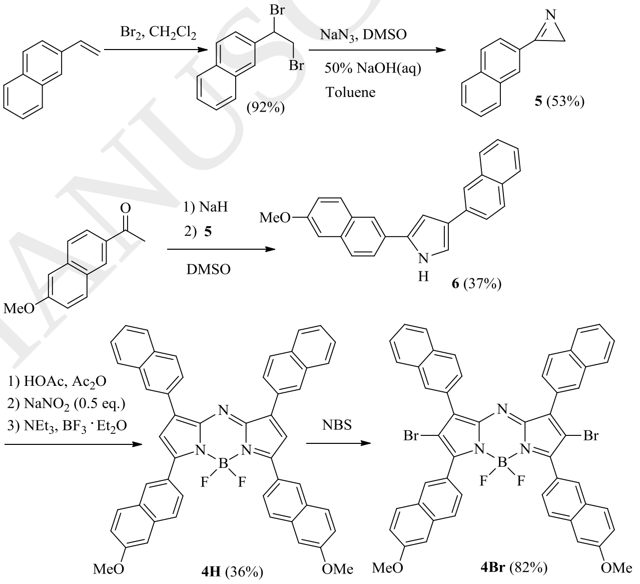
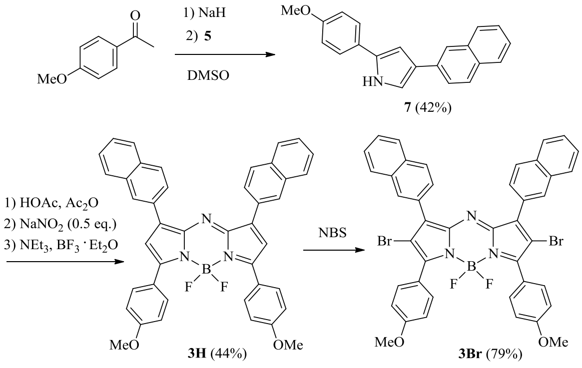


Fig. 1. The design strategies for the naphthyl-containing aza-BODIPYs at 1,7-positions.



Scheme 1. Synthesis of aza-BODIPY **4Br**.

To severely compare with the photophysical properties, as shown in Scheme 2 aza-BODIPYs **3H** and **3Br** were synthesized too.



Scheme 2. Synthesis of aza-BODIPY **3Br**.

The spectra of absorption and fluorescence of **3** and **4** are shown and outlined in Fig. 2 and Table 1, and the excitation wavelength (λ_{ex}) is 700 nm. Due to the heavy atom effect, both compounds **3Br** (Φ_f < 0.01) and **4Br** (Φ_f = 0) are very weakly fluorescent, in comparison with **3H** (Φ_f = 0.34) and **4H** (Φ_f = 0.29). Dye **3H** absorbs and emits at 704 and 733 nm, respectively. Changing the phenyl to naphthyl group at 3,5-positions in **3H**, aza-BODIPY **4H** shows long-wavelength absorption and emission waves ($\lambda_{abs}/\lambda_{em}$ = 718/754 nm). The absorption maximum of **4Br** is blue-shifted to 698 nm comparing to that of the corresponding parent aza-BODIPY **4H** (λ_{abs} = 718 nm). NIR-absorbing Dyes **3** and **4** have high extinction coefficients (ε = 88000-95000 L mol^{-1} cm^{-1}). Attaching of the naphthyl group at 3,5-positions provides a broader full width at half maximum for **4Br** (FWHM = 76 nm) compared with **3Br** (FWHM = 64 nm).

In comparison with the maximum absorption of aza-BODIPY **2H** bearing the phenyl groups at 1,3-positions (λ_{abs} = 706 nm) [31], a substituent change from phenyl to naphthyl group in dye **4H** (λ_{abs} = 718 nm) leads to be 12 nm of bathochromic shift. However, only attaching naphthyl groups at 1,7-positions or 3,5-positions in **1H**, their photophysical properties **2H** and **3H** are nearly same, except the FWHM. Additionally, the molecular geometries of aza-BODIPYs **1H**, **2H** and **4H** were optimized by using density functional theory (DFT) at the B3LYP/6-31G(d) level of theory [38]. The calculated HOMO and LUMO orbital energy levels are summarized in Fig. 3. The HOMO and LUMO were mainly localized in the aza-BODIPY core. Changing the substituent from phenyl to naphthyl group resulted in a remarkable bathochromic shift (λ_{abs} = 688 nm for **1H**, λ_{abs} =706 nm for **2H**, λ_{abs} =718 nm for **4H**), owing to a narrowing of the HOMO–LUMO band gap for the lowest-energy absorption bands in dye **4H** (1.95 eV) relative to those of dye **1H** (2.06 eV) or dye **2H** (1.97 eV), according to MO calculations (Fig. 3).

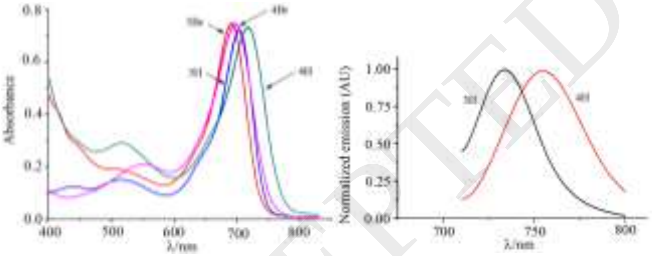


Fig. 2. Absorption and fluorescence spectra of **3** and **4** in CH_2Cl_2 at 298 K. λ_{ex} = 700 nm for **3** and **4**.

Table 1
Photophysical properties of aza-BODIPYs **3** and **4** in CH_2Cl_2 at 298 K.

Dye	λ_{max} for absorption and emission (nm)	FWHM (nm)	ε (L mol^{-1} cm^{-1})	Φ_f
1H[30]	688/715	55	85000	0.36
1Br[30]	679/714	57	75000	0.1
2H[31]	706/733	67	89000	0.33
2Br[31]	695/728	69	82000	0.12
3H	704/733	58	90000	0.34
3Br	692/734	64	88000	<0.01
4H	718/754	79	95000	0.29
4Br	698/NA	76	92000	0

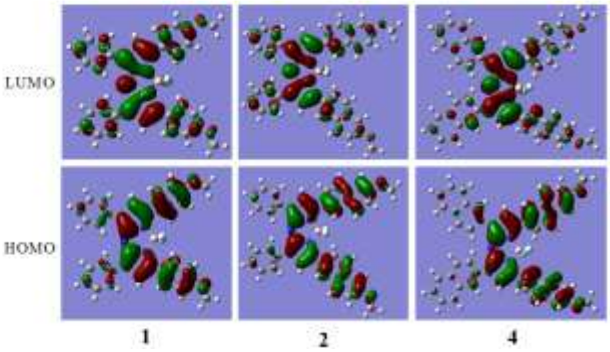


Fig. 3. Frontier molecular orbitals of aza-BODIPYs **1**, **2** and **4** at the B3LYP/6-31G(d) level with Gaussian 09. For **1**, **2** and **4**, HOMO/LUMO (eV) = –5.33/–3.27, –4.99/–3.02, and –4.99/–3.04, respectively.

The investigation of the singlet oxygen generation was performed to assess the ability of naphthyl-containing aza-BODIPYs **3Br** and **4Br** as a PS in toluene. To simulate a deep tissue penetration and to reduce the normal cell-damage, the monochromatic light [39-41] at 690 nm by using a 150 W xenon lamp at 0.5 mW/cm^2 was selected to irradiate the toluene solution. Singlet oxygen generation was estimated by 1,3-diphenylisobenzofuran (DPBF), a singlet oxygen indicator [42]. The experiments were performed at initial concentrations of 6.5 × 10^{-6} mol/L of **3** and **4**, and 6 × 10^{-5} mol/L of DPBF. When the oxidation of DPBF with the reactive singlet oxygen happened, the absorption maximum of DPBF at 416 nm was found to be decreased. The results demonstrate that the singlet oxygen generation of **4Br** with the dibromo groups at 2,6-positions (Figs. 4 and 5) was more effective than that of **4H**. A 14.5-fold rate enhancement is observed for **4Br** compared to **4H** (Fig. 5 and Fig. S1 in Supporting inforamtion). And, the singlet oxygen generation of **4Br** (4.2-fold rate) is more effective than that of **3Br** (Fig. 5 and Fig. S1). Moreover, one notices that aza-BODIPY **4Br** with the naphthyl groups at 1,7-positions is a stronger PS than **2Br** with the phenyl groups at 1,7-positions, having a 2.2-fold rate enhancement for generating the singlet oxygen (Fig. S2 in Supporting information) [31]. Additionally, no photobleaching of **4Br** was found during this experiment, based on the absorption intensity (λ_{abs} = 705 nm in toluene) (Fig. 4). These results indicated that the NIR PS **4Br** was able to be used for the generation of the singlet oxygen.

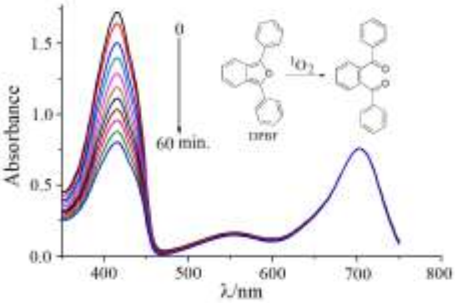


Fig. 4. DPBF (initial concentration at 6 × 10^{-5} mol/L) degradation profile in toluene by aza-BODIPY **4Br** (6.5 × 10^{-6} mol/L) under the light. Monochromatic light (690 nm at 0.5 mW/cm^2) was used. The figure displays time-dependent decrease (0, 1, 3, 5, 10, 15, 20, 25, 30, 40, 50 and 60 min) of the absorbance at 416 nm by oxidation of DPBF with **4Br**.

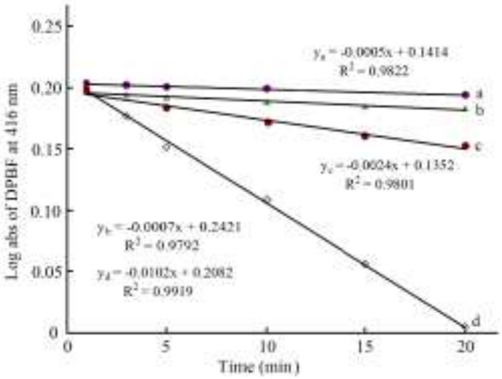


Fig. 5. Time-dependent decrease (0, 1, 3, 5, 10, 15 and 20 min) of log absorbance at 416 nm by oxidation of DPBF with aza-BODIPY **3H** (line a), **4H** (line b), **3Br** (line c) and **4Br** (line d).

In summary, utilizing 2-vinylnaphthalene as the starting material, aza-BODIPYs bearing the naphthyl groups at 1,7-positions were prepared. To attaching naphthyl group at 1,7-positions, aza-BODIPYs show long-wavelength absorption (λ_{abs} > 692 nm) and emission (λ_{em} > 733 nm) in the near-infrared region. NIR naphthyl-containing aza-BODIPYs possess high extinction coefficients. The singlet oxygen generation of the dibromo substituted aza-BODIPY as a PS was more effective and had about 14.5-fold rate enhancement compared to the parent aza-BODIPY. No photobleaching of naphthyl-containing aza-BODIPY was observed and such NIR aza-BODIPY could be used for the singlet oxygen generation.

Acknowledgments

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