Organic LETTERS

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Straightforward Synthesis of Oligopyrroles through a Regioselective S_NAr Reaction of Pyrroles and Halogenated Boron Dipyrrins

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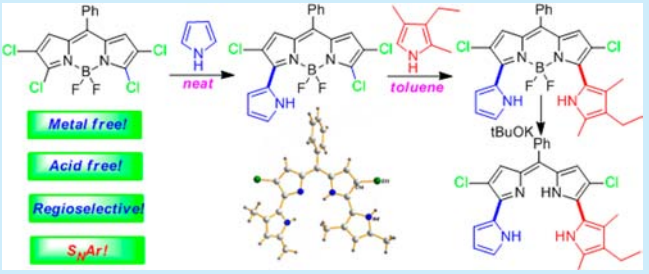
Supporting Information

ABSTRACT: A novel stepwise and regioselective nucleophilic aromatic substitution (S_NAr) reaction of halogenated boron dipyrrins (BODIPYs) with pyrroles has been developed under mild conditions with no catalyst needed and shown to be diversity oriented. The resultant pyrrole-substituted BODIPYs are interesting red and near-infrared (NIR) fluorescent dyes with absorption maxima up to 733 nm. Removal of the BF_2 protecting group of the 3-pyrrole or 3,5-dipyrrole-substituted BODIPYs provides a facial entry to oligopyrroles with direct 2,2′-bipyrrole linkages.



Short oligopyrroles,[1] such as dipyrrins, pyrrolyldipyrrin, tripyrrins, and tetrapyrroles, are versatile precursors for the synthesis of porphyrinoids and have also found wide applications in medicinal chemistry, material science, and supramolecular chemistry as anion-binding and cation-coordination reagents.[1,2] Among those, tetrapyrroles featuring with direct 2,2′-bipyrrole linkages are the core structure of many contracted and expanded porphyrins.[3−5] For example, they are key intermediates for the construction of isocorroles and isoporphycenes by Vogel et al.[3a,b] Sessler et al. reported oxidative dimerization of tetrapyrrole to [32]-octaphyrin(1.0.0.0.1.0.0.0).[3c] There is a very limited number of tetrapyrroles reported to date due to their lengthy total synthesis.[3] Reported tetrapyrroles were generally prepared with limited diversity through condensations of bipyrroles and triethyl orthoformate under acidic conditions[3] (Figure 1). However, construction of direct 2, 2′-bipyrrole linkages, especially unsymmetrical 2,2′-bipyrroles, are very difficult, although limited methods have been developed, including the Paal−Knorr cyclization,[4] the oxidative coupling of α-unsubstituted pyrroles,[5] Ullmann coupling,[6] and other metal-mediated coupling reactions.[7] It is thus highly desirable, and also of practical importance, to explore a new synthetic strategy toward tetrapyrrole framework.

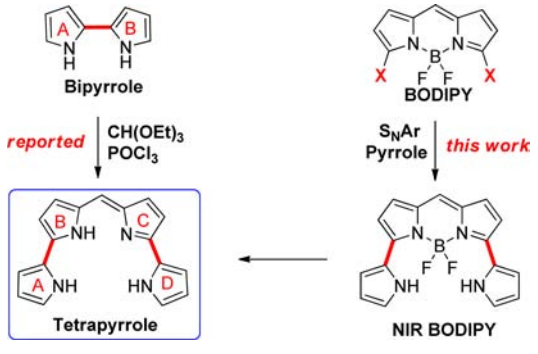


Figure 1. Existing method and our method for synthesis of tetrapyrrole fragments.

The α,ω-dihalogenated dipyrrins and their metal complexes, as old porphyrin precursors, have recently been widely used for the metal-promoted construction of porphyrinoids.[8−10] Bröring et al. synthesized 10-heterocorroles from α,ω-dibrominated dipyrrin with copper salt.[8] Shinokubo et al. reported syntheses of norcorrole, octaphyrin, azacorrole, and thioporphyrinoid from a series of metal dihalogenated dipyrrins.[9] The boron-coordinated α,ω-dihalogenated dipyrrins (known as BODIPY) with better stability than corresponding dipyrrin have shown good reactivity toward various nucleophiles[11a] and also been used to construct antiaromatic porphyrinoids by transition-metal-mediated synthesis.[11b] On the other hand, BODIPYs[12] are widely used as labeling dyes or fluorescence sensors in biological systems due to their excellent photophysical properties,[13] and development of near-infrared (NIR) derivatives of BODIPY has recently gained much attention.[14] For example, BF_2 complexes of pyrrole-containing BODIPYs such as BODIPY 576/589 and BODIPY 650/665 marketed by Invitrogen and their analogues have been widely used as red fluorescence dyes.[15]

Herein, we report a stepwise and regioselective aromatic substitution reaction of halogenated BODIPYs with pyrroles. The resultant pyrrole-substituted BODIPYs are interesting red

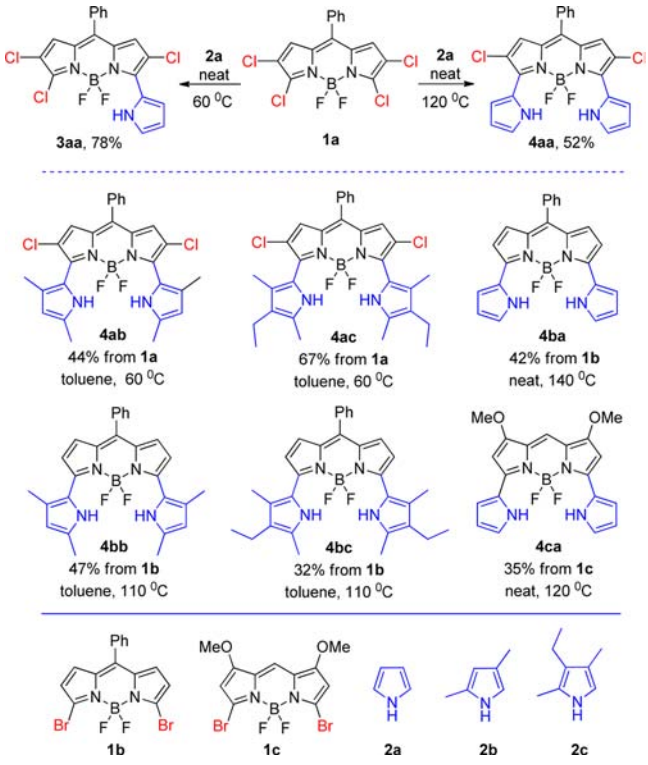
Received: February 17, 2014
Published: March 26, 2014

dx.doi.org/10.1021/ol500507f | Org. Lett. 2014, 16, 1952−1955

and NIR fluorescent dyes and also provide a facial entry to a series of novel tetrapyrroles through removal of BF_2 protecting group. The high efficiency in the preparation of pyrrole-substituted BODIPYs is rather remarkable, with no catalyst needed and being diversity oriented.

Initially, the reaction was performed by heating tetrachlorinated BODIPY **1a** with neat pyrrole under argon (Scheme 1),

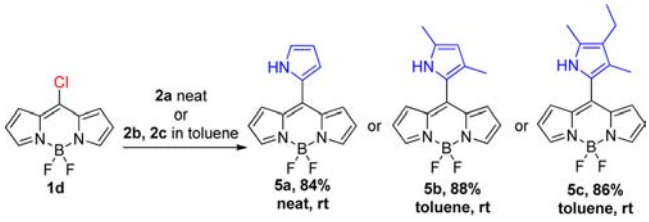
Scheme 1. Synthesis of Dyes 3 and 4 through S_NAr Reaction of Pyrroles



from which a new reddish spot (later identified as **3aa**) and a new greenish spot (later identified as **4aa**) were smoothly generated and detected by TLC. By optimizing the reaction temperature, we found that the reaction solely gave **3aa** at 60 °C, while **4aa** was selectively obtained at 120 °C with longer reaction time. More interestingly, **1a** showed higher reactivity toward 2,4-dimethylpyrrole **2b**. Simply mixing **1a** and **2b** in toluene at 60 °C gave **4ab** in 45% yield. Similar results were obtained with 2,4-dimethyl-3-ethylpyrrole **2c**. This S_NAr reaction reaction proceeded smoothly and gave similar results in the presence of 5 equiv of triethylamine as an acid scavenger. Subsequently, our synthetic strategy was extended to halogenated BODIPYs **1b,c**, from which the corresponding dyes **4ba–ca** were obtained in 32–47% isolated yields (Scheme 1). The presence of electron-withdrawing groups on the halogenated BODIPYs enhances their reactivity toward pyrroles as BODIPY **1a** exhibits higher reactivity than **1b**. Our method also provides a novel route to dyes **4ca** from BODIPY **1c**, which is a BF_2-coordinated derivative of a pyrrole antibiotic, a natural pigment possessing important biological properties.[1b,16]

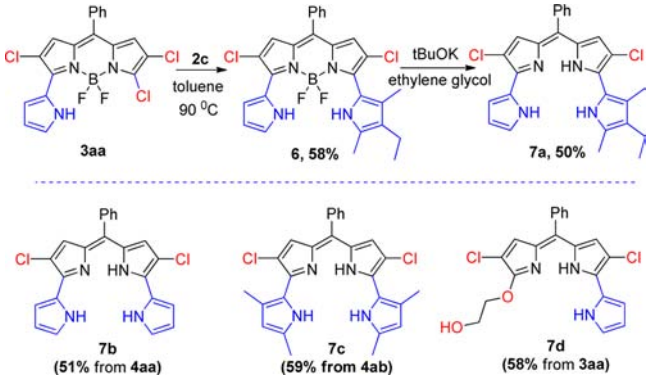
Next, *meso*-chlorinated BODIPY **1d**[17] also showed high reactivity and was reacted with pyrroles **2a–c** (Scheme 2) at room temperature, giving *meso*-pyrrole-substituted BODIPYs **5a–c** in 84–88% yields.

Scheme 2. Synthesis of Dyes 5a–c through S_NAr Reactions of Pyrroles



The pyrrole-substituted halogenated BODIPYs **3aa** are similarly well suited as starting materials for the synthesis of unsymmetrical tetrapyrrole dyes which were not previously obtainable. Reaction between **3aa** and 2,4-dimethyl-3-ethylpyrrole **2c** smoothly gave unsymmetrical tetrapyrrole **6** in 58% yield at 90 °C in toluene (Scheme 3).

Scheme 3. Synthesis of Dyes 6 and 7



Further removal of the BF_2 protecting group using *t*-BuOK in ethylene glycol[18] successfully gave unsymmetrical tetrapyrrole **7a** cleanly. Similarly, tetrapyrroles **7b** and **7c** were also easily obtained from the corresponding **4aa** and **4ab** in good yields (Scheme 3). By contrast, the pyrrole-substituted halogenated BODIPY **3aa** under the same conditions gave ethylene glycol substituted pyrrolyldipyrrin **7d** in 58% yield.

The structures of **4aa**, **6**, and **7c** have been confirmed by X-ray crystallographic analysis (Figures 2 and 3). These dyes all showed an almost planar structure for the dipyrrin core (dihedral angles of two pyrrole rings in dipyyrin core are all less than 12.2°; see the Supporting Information, Table S1). The 3,5-pyrrole substituents in **4aa** and **6** lie slightly out of the plane of the dipyrrin core, with deviations of 38.7°/38.6° and 24.7°/

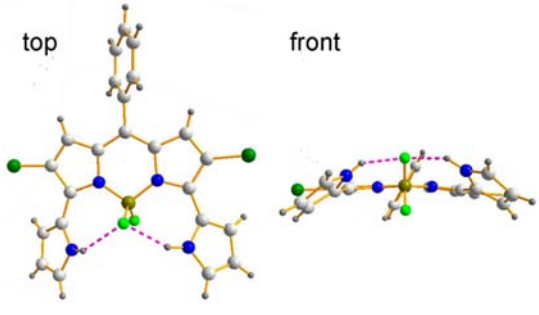


Figure 2. X-ray structure of **4aa**: C, light gray; H, gray; N, blue; B, dark yellow; F, bright green; Cl, green.

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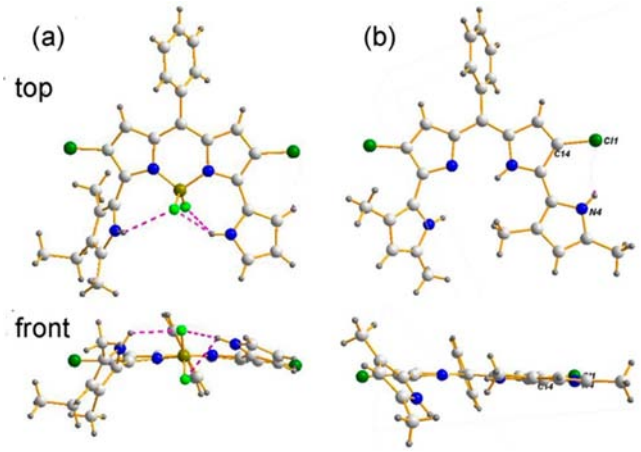

Figure 3. X-ray structures of **6** (a) and **7c** (b): C, light gray; H, gray; N, blue; B, dark yellow; F, bright green; Cl, green; Br, dark green.

58.9°, respectively. Intramolecular hydrogen bonds between the hydrogen attached to the uncoordinated pyrrolic nitrogen and the fluorine atoms in **4aa** and **6** were observed. The observed distances between N atoms of 3,5-substituted pyrroles and F atoms were around 2.81−3.42 Å. Multiple intermolecular C−H···F hydrogen bonds between F atoms and various hydrogen atoms are formed due to the strong electron negativity of the F atom. These strong intermolecular hydrogen bonds aid the establishment of the crystal packing structure and make **4aa** and **6** nearly parallel to each other in a slipped head-to-head orientation (Figures S1 and S2, Supporting Information).

The molar absorption coefficients, the absorption and emission maxima, fluorescence quantum yields, and Stokes shifts of compounds **3**−**6** are summarized in Table S2 (Supporting Information). Their UV−vis absorption and fluorescence spectra measured in hexane, dichloromethane, and methanol are shown in Figures S3−S12 (Supporting Information). Figure 4 shows the UV−vis absorption and fluorescence spectra of **4ba**, **4bb**, and **4bc** in CH_2Cl_2. In comparison with parent BODIPY **A** (Table S2, Supporting Information), significant spectral red-shifts (158 nm in absorption, 162 nm in emission, respectively) were observed for BODIPYs **4ba**, indicating the enhancement in the π-electron delocalization due to the existence of uncoordinated pyrrole units. The gradual red-shift of the absorption and emission has been observed with an increase of the alkyl substituents on the uncoordinated pyrrole unit. 2,4-Dimethyl-3-ethylpyrrole-substituted BODIPY **4bc** absorbs/emits at 718/760 nm in CH_2Cl_2, while 2,4-dimethylpyrrole-substituted BODIPY **4bb** and pyrrole-substituted BODIPY **4ba** absorb/emit at 700/739 and 658/689 nm, respectively. Adding halogen atoms on the BODIPY core gives further spectral red-shifts as BODIPYs **4aa**, **4ab**, and **4ac** absorb/emit at 685/719, 708/760, and 733/805 nm in CH_2Cl_2, respectively. 3-Pyrrole-substituted BODIPY **3aa** absorbs/emits at 617/648 nm in CH_2Cl_2, while BODIPY **6** with addition of another 2,4-dimethyl-3-ethyl-pyrrole absorbs/emits at 712/795 nm.

Tetrapyrroles **7a**−**c** show broad absorptions around 600 nm. The addition of TFA to the CH_2Cl_2 solution induced dramatic absorption spectral red-shifts to above 700 nm (Figures S13−16, Supporting Information). For example, absorption of **7c** red-shifts from 591 nm in CH_2Cl_2 to 771 nm after adding TFA (Figure 5), while pyrrolyldipyrrin **7d** red-shifts from 504 to 619 nm.

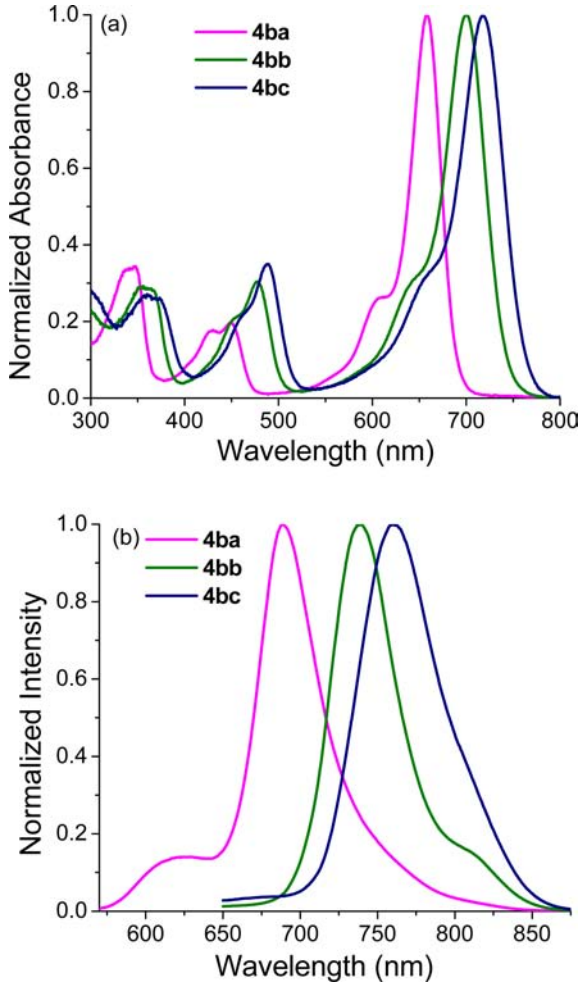

Figure 4. Normalized absorption (a) and fluorescence (b) spectra of **4ba**, **4bb**, and **4bc** in CH_2Cl_2.

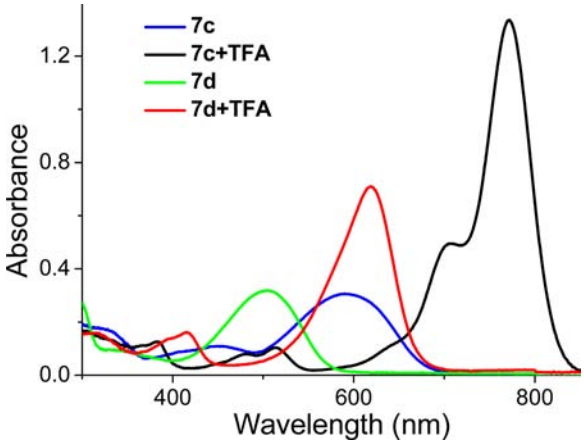

Figure 5. Absorption spectra changes of dyes **7c** and **7d** (1×10^{-5} M) in CH_2Cl_2 after addition of TFA.

The fluorescence quantum yields of those dyes can be finely tuned by the uncoordinated pyrroles at the 3/5-positions and the polarity of solvents (Table S2, Supporting Information). The fluorescence quantum yields were decreased from pyrrole and 2,4-dimethylpyrrole to 2,4-dimethyl-3-ethylpyrrole when installed at the 3/5-positions of the BODIPY core. Most of those dyes show strong fluorescence in hexane (fluorescence

dx.doi.org/10.1021/ol500507f | Org. Lett. 2014, 16, 1952−1955

quantum yields for **4ba**, **4bb**, and **bc** are 0.67, 0.37, and 0.31, respectively) but give decreased fluorescence in methanol, indicative of a possible intramolecular charge-transfer process.[19] Those dyes may be developed as a library of environment-sensitive fluorescence probes due to their strong solvent-dependent fluorescence.[20]

In summary, we have developed a new synthetic strategy for the facile preparation of a series of novel oligopyrrole derivatives featuring a regioselective substitution reaction of halogenated BODIPYs with pyrroles without the usage of any catalyst. The resultant pyrrole substituted BODIPYs are interesting tunable red to NIR-fluorescent dyes. Our methodology reported here may provide an efficient way for the facile synthesis of oligopyrroles with direct 2,2′-bipyrrole linkages.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR, additional photophysical data, and CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the National Nature Science Foundation of China (Grants Nos. 21072005, 21272007, and 21372011).

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