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A General Synthetic Strategy for the Design of New BODIPY Fluorophores Based on Pyrroles with Polycondensed Aromatic and Metallocene Substituents

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4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene known as the trademark BODIPY shows many intriguing optical and chemical properties like high absorption coefficient and fluorescence quantum yield, long wavelength emission, and photochemical stability.[1] BODIPY moieties have been conjugated to a variety of biomolecules such as proteins,[2] DNA,[3] carbohydrates,[4] and cholesterol.[5] Furthermore, BODIPY derivatives have been used in fluorescent switches;[6] probes for protons,[7] mercuric ion,[8] and nitric oxide;[9] biological labeling; and syntheses of molecular devices.[10] Thus, the synthesis of diverse BODIPY derivatives and their application to biomolecules are of current interest. Despite this recent progress, synthesis of BODIPY derivatives that have aryl groups remains an important research objective, because the fluorescence maxima of BODIPY strongly depend on the structure of aryl substituents. Generally, fused aromatic and heteroaromatic compounds are intensively studied[11] because the narrow HOMO–LUMO gap enables high lability of their π-electrons, and consequently they exhibit a strong optical response to manifold chemical and physical effects.

The integration of condensed aromatic moieties with the BODIPY scaffold in one molecule has been shown to lead to synergism of their properties and to high-performance optical materials.[12] Therefore, the design of molecules combining the pyrrole moiety and condensed aromatic frameworks represents a long-standing challenge in BODIPY chemistry.

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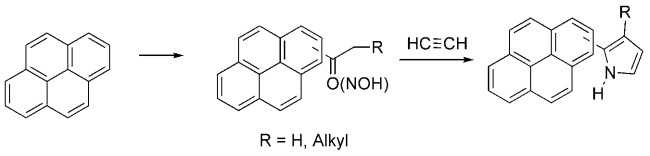
To the best of our knowledge, just a few syntheses of pyrroles linked with polycondensed aromatics have been reported. Most recently, a series of pyrrole–polycyclic-aromatic ensembles obtained by a two-stage synthetic strategy was published.[13] Their central 2,5-diaryl-3,4-dinaphthyl-substituted pyrrole core was constructed by a Paal–Knorr reaction. Furthermore, to introduce the condensed aromatic substituents, a Suzuki–Miyaura reaction was employed in the cross-coupling of the corresponding boronic acids with the triflated sites of the core. Most of the synthesized pyrroles were blue-light emitters and exhibited high quantum efficiencies.[13] Previously, microwave-assisted synthesis of 2,3-diphenyl-5-naphthylpyrrole from the corresponding 1,4-dione and ammonium formate has been reported.[14] Also, 2-naphthylpyrroles were prepared by the cross-coupling of *N*-protected-2-bromopyrrole with naphthylboronic acid.[15] The functionalized pyrroles with condensed aromatic substituents, such as 4-methyl-3-(2-methoxy-1-naphthyl)pyrrole-2-carboxylate and 4-ethyl-3-(10-methoxy-9-phenanthryl)pyrrole-2-carboxylate, were synthesized from the corresponding nitroalkenes and ethyl isocyanoacetate.[16] The synthesis of 2-(9-anthrylvinyl)pyrroles was achieved by a Wittig reaction of 9-anthrylmethyltriphenylphosphonium bromide and the corresponding aldehyde.[17]

As the above concise overview shows, no approach general enough to design pyrroles with condensed aromatic substituents so far exists. A promising general strategy for the synthesis of these pyrrole systems could be the reaction of acylated polyaromatic compounds and acylated metallocenes (via their oximes) with acetylene in the presence of MOH/DMSO (M = Li, Na, K, Cs) superbase systems (the Trofimov reaction).[18] Indeed, in accordance with this assumption, we reported the first example of such synthesis; 1-vinyl-2-naphthylpyrroles were synthesized from acetylnaphthalenes and acetylene in 61–71% yield.[19] Herein, we further develop the modification of the above reaction to create a general strategy for the synthesis of polycondensed aromatic and metallocene–pyrrole ensembles of wide diversity, starting from accessible polycondensed hydrocarbons and metallocenes.

We have devised a synthesis to enable the preparation of polycondensed aromatic and metallocene–pyrrole ensembles, such as 2-(anthr-2-yl)-, 2-(phenanthr-2-yl)-, 2-(pyren-1-yl)-, and 2-(ferrocen-1-yl)pyrroles, in just two steps. The corresponding hydrocarbons are acylated and the resulting ketones further react (as ketoximes) with acetylene in the presence of a superbase suspension MOH/DMSO (Scheme 1, only one example is given).



Scheme 1. From condensed aromatics or metallocenes to pyrroles in two steps.

Our initial experiments have shown that for the pyrrole synthesis, the reaction of oximes **1a**–**1e** with acetylene needs to be modified. For example, in the NaOH/DMSO system, under common widely varied conditions[19,20] (100–140 °C, 1–5 h, acetylenic pressure from atmospheric to 12–14 atm), none of the anticipated pyrroles were formed. Also, in the KOH/DMSO system, oximes **1a**–**1c** gave only trace amounts of the expected pyrroles, despite the wide variation of the reaction conditions. Instead, the deoximation of ketoximes **1a**–**1c** occurred to give the starting ketones as the major products.

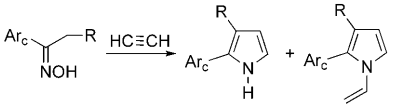
Pyrroles **2d**, **2e**, and their 1-vinyl derivatives **3d** and **3e** were obtained from oximes **1d** and **1e** in 29–46 % and 16–30 % yields, respectively, under atmospheric pressure at 120 °C for 5 h in the KOH/DMSO system (Table 1).

To synthesize pyrroles **2b**, **2c**, **3b,** and **3c** another modification was elaborated. For this, the system LiOH/CsF/DMSO was chosen as a catalyst precursor and the cesium salts of the ketoximes (instead of free ketoximes **1b** and **1c**) were used. The Cs-oximates were generated in situ, by removal of water from the reaction mixture under vacuum.

The Cs-oximates **1b** and **1c** were then treated with excess acetylene in DMSO at 100 °C for 1 h under pressure (initial pressure was 14 atm at RT, which reached 25–30 atm at the reaction temperature) to give the anticipated pyrroles **2b** and **2c** (in 32 and 37 % yields, respectively) and 1-vinyl pyrroles **3b** and **3c** (in 30 and 29 % yields, respectively, Table 1). Notably, pyrroles and their 1-vinyl derivatives are easily separated by column chromatography (Al_2O_3, diethyl ether/*n*-hexane).

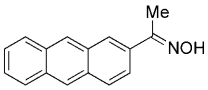
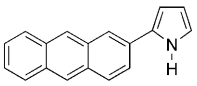
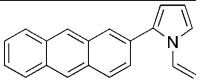
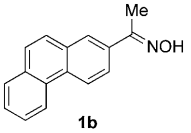
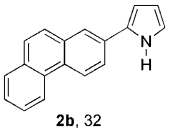
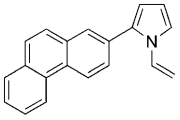
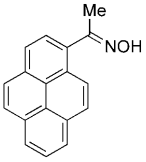
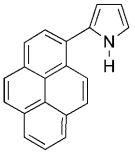
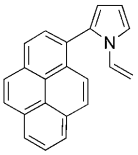
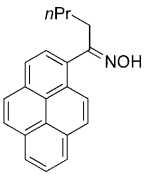
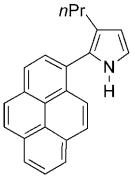
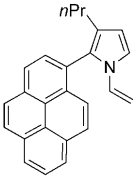
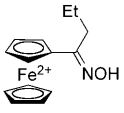
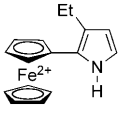
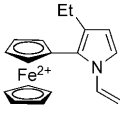
However, these conditions (100 °C, 1 h, 12–14 atm) appeared to be invalid for the transformation of anthracene to anthrylpyrrole through the corresponding oxime **1a** (Table 1). The reaction of oxime **1a** with acetylene proceeded with intense tar formation and deoximation to acetylanthracene. Under milder conditions (80 °C, 5 min, other reaction parameters remained as above), the only product formed was the *O*-vinyloxime **4**, isolated in 45 % yield (Scheme 2).

Table 1. Synthesis of pyrroles and 1-vinyl pyrroles from oximes and acetylen.

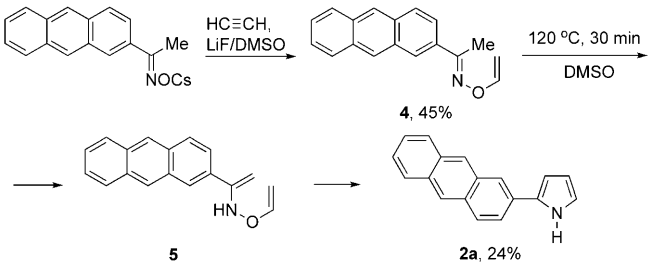


1a-e **2a-e** **3a-e**

Ar$_c$ = Condensed aryl or ferrocenyl; R = H, Et, *n*Pr

Oxime	Reaction conditions	Pyrrole (Yield [%])[a]	1-Vinyl pyrrole (Yield [%])[a]
 **1a**	CsF/LiOH; 12–14 atm; 90–100 °C, 5 min–1 h	 **2a**, traces	 **3a**, traces
 **1b**	CsF/LiOH; 14 atm; 100 °C, 1 h	 **2b**, 32	 **3b**, 30
 **1c**	CsF/LiOH; 14 atm; 100 °C, 1 h	 **2c**, 37	 **3c**, 29
 **1d**	KOH; 1 atm; 120 °C, 5 h	 **2d**, 46	 **3d**, 16
 **1e**	KOH; 1 atm; 120 °C, 5 h	 **2e**, 29	 **3e**, 30

[a] Yields of products isolated.



Scheme 2. Synthesis of *O*-vinyloxime **4** and its rearrangement to pyrrole **2a**.

O-Vinyloximes were proven to be key intermediates in the pyrrole synthesis from ketoximes and acetylene.[21] According to the established mechanism, a [3,3] sigmatropic rearrangement of a tautomeric form of *O*-vinyloxime **5** leads to pyrrole **2a** (Scheme 2). Indeed, rearrangement of **4** upon heating in DMSO (120 °C, 30 min) occurred to give pyrrole **2a** in 24 % yield.

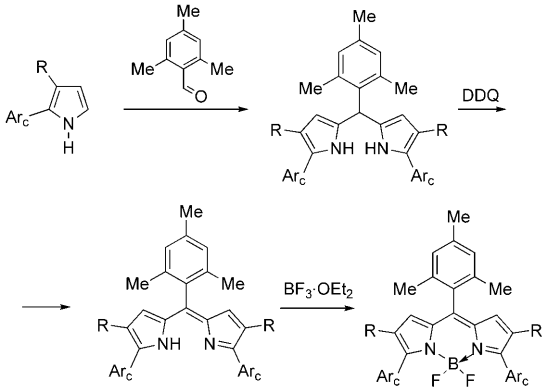
All the pyrroles synthesized are meltable, faintly to brightly colored powders or crystals that are soluble in common organic solvents (benzene, diethyl ether, chloroform, ethyl acetate), but are scarcely soluble in hexane. The corresponding *N*-vinyl pyrroles **3a**–**3e** can be considered as protected NH-pyrroles because they can be easily deprotected by treatment with the $Hg(OAc)_2/NaBH_4$ system in aqueous MeCN according to known procedures.[20b]

The pyrroles **2b**–**2d**, together with 2-(naphth-1-yl)- and 2-(naphth-2-yl)pyrroles (synthesized previously by devinylation of the corresponding *N*-vinyl derivatives[19]), were further used to assemble the novel 4,4-difluoro-3,5-diaryl-8-mesityl-4-bora-3a,4a-diaza-*s*-indacenes (BODIPY derivatives) **6**–**9** as prospective fluorophores.

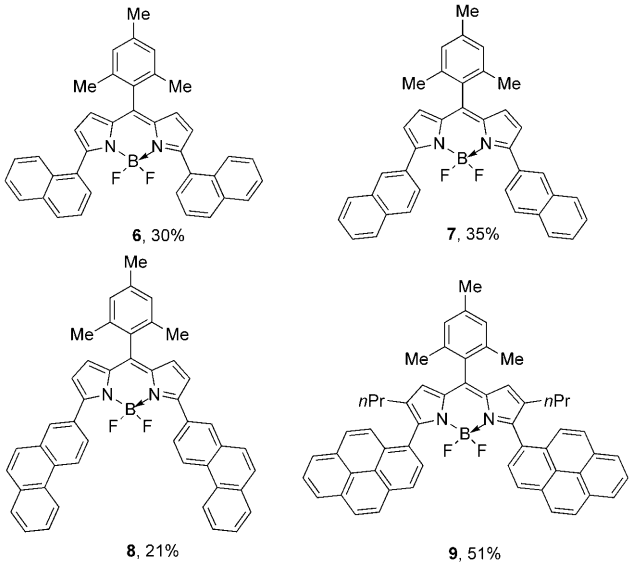
The assembly was achieved by using a one-pot procedure involving condensation of the pyrroles with mesityl aldehyde in the presence of trifluoroacetic acid to give dipyrromethanes, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the corresponding dipyrromethenes, which then underwent complexation with boron trifluoride etherate (Scheme 3). Scheme 4 presents the chemical structure and yields of the novel boron dipyrromethene dyes with polycondensed aromatic frameworks at the C3 and C5-positions.

The introduction of the mesityl group at the *meso* 8-position of the BODIPY derivatives was carried out to impart additional constraints on the molecules to ensure a higher fluorescence quantum yield. Commonly, the BODIPY fluorescence emission is known to be deactivated by free rotation of the aryl group at the *meso* position.[22] Therefore, the additional methyl groups were introduced into the benzene ring (mesityl substituent) to hinder this rotation.

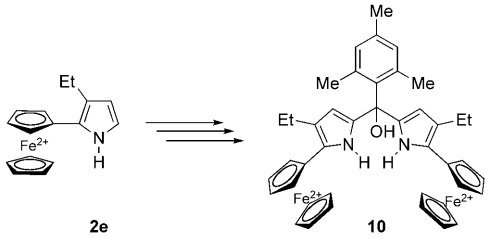
Our attempt to synthesize the corresponding BODIPY from 3-ethyl-2-ferrocenylpyrrole **2e** and mesityl aldehyde failed. From the reaction mixture obtained by using the above conditions, only dipyrrolylhydroxymethane **10** (Scheme 5), an unexpected adduct of the intermediate dipyrromethene with water molecules, was detected (by analysis of NMR data and MS).



Scheme 3. One-pot synthesis of BODIPY derivatives; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



Scheme 4. Chemical structures and yields of the novel BODIPY derivatives with polycondensed aromatic frameworks.



Scheme 5. Attempted synthesis of BODIPY from pyrrole **2e**, resulting in the formation of the unexpected adduct **10**.

All the new BODIPY dyes are violet crystals with no melting point (decomposed upon heating above 250 °C) and are soluble in chloroform, light petroleum, and dichloromethane.

The photophysical properties of the BODIPY derivatives have been investigated in dichloromethane (Figure 1). All the derivatives displayed an intense, sharp absorption band in the visible spectra between 538 and 580 nm. Other bands are observed in the UV range, which result from the overlap

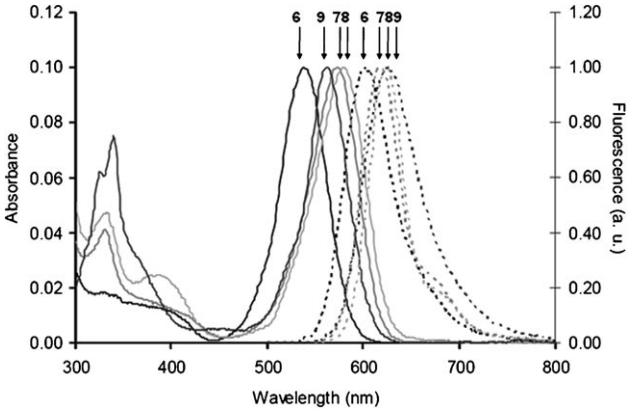


Figure 1. Normalized absorption (full lines) and emission (broken lines) spectra of BODIPY derivatives **6**, **7**, **8**, and **9** recorded in dichloromethane.

of the second absorption of the BODIPY and those of the appended aromatics. For example, an intense band can be noted for **9** at 340 nm, arising from the pyrene moiety.

Interestingly, increasing the size of the aromatic substituent does not yield an automatic red shift of the absorption band (Table 2). Indeed, the maximum absorption for **9** (1-pyrenyl) is centered at 562 nm, whereas for **7** (2-naphthyl) and **8** (2-phenanthryl) it is found at 573 and 579 nm, respectively. In addition, compared with **6**, compound **7** produces a 35 nm shift of the absorption band just by a simple change of the attachment position by one carbon. At first glance this result can seem strange but can be rationalized by performing a geometry optimization of the BODIPY derivatives (Figure 2). The relative orientation of the planes of the BODIPY and the attached aromatics is driven by the size of the substituent, which cannot be coplanar when it is too large because of constraints imposed by the BF_2 moiety

Table 2. Photophysical data (recorded in dichloromethane) and the calculated angle between the BODIPY and appended aromatic planes.

Compound	λ_{abs} [nm]	$\varepsilon \times 10^3$ [$L\,mol^{-1}\,cm^{-1}$]	λ_{em}[a] [nm]	Stokes shift [cm^{-1}]	Φ_{fluo}[b]	τ_{fluo}[c] [ns]	Calculated angle[d] [°]
6	538	66.3	601	1948	0.95	5.5	60
7	573	105.1	618	1271	0.95	5.5	42
8	579	69	624	1246	0.77	4.8	42
9	562	51	626	1819	0.64	4.5	58

[a] Excitation was set equal to the maximum of absorption. [b] Sulforhodamine 101 in ethanol $\Phi_{fluo} = 0.9$[23] was used as the reference. [c] Excitation at 495 nm. [d] Calculations were performed at the B3LYP/6-31+G(d) level of theory.[24]

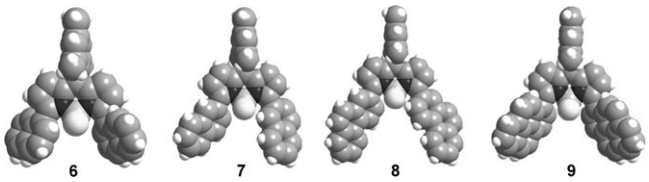


Figure 2. Space orientation of the BODIPY derivatives based on B3LYP/6-31+G(d) calculations.

(Figure 2). Hence, planarity is better achieved in **7** and **8** than in **6** and **9** (see calculated angle in Table 2). This result correlates well with the position of the absorption maxima.

All the BODIPY derivatives are highly fluorescent (Φ_{fluo} up to 0.95) with a lifetime around 5 ns and have modest Stokes shifts, which are typical for this type of fluorophore. The largest Stokes shifts are observed for compounds **6** and **9**, which implies that in the excited state of **6** and **9**, the substituents are more coplanar with the BODIPY core than in the ground state. The emission spectra of **8** and **9** have also been recorded after excitation in the absorption band of the aromatic substituent (310 and 340 nm respectively). Interestingly, no fluorescence signal arising from the phenanthrene or the pyrene could be detected (See Figures S1 and S2 in the Supporting Information). It can then be inferred that a very efficient excited-state energy transfer (EET) takes place from the attached aromatic to the BODIPY.

In conclusion, a general and convenient strategy for the design of novel BODIPY fluorophores based on pyrroles with polycondensed aromatic and metallocene substituents has been developed. The pyrroles synthesized, due to the long-range conjugation in their molecules and size variation of the attached aromatics, proved to be promising building blocks for assembling BODIPY fluorophores with enhanced quantum yield and red emission in solution. Current work is focused on the study of the spectroscopic and electrochemical properties of the novel BODIPY dyes and their structure–performance relationship as potential solid state fluorophores. These results will be disclosed in due course.

Experimental Section

For experimental details, see the Supporting Information.

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Keywords: BODIPY · condensed aromatics · fluorescence · pyrroles · synthetic methods

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