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General Route to Symmetric and Asymmetric *meso*-CF_3-3(5)-Aryl(hetaryl)- and 3,5-Diaryl(dihetaryl)-BODIPY Dyes

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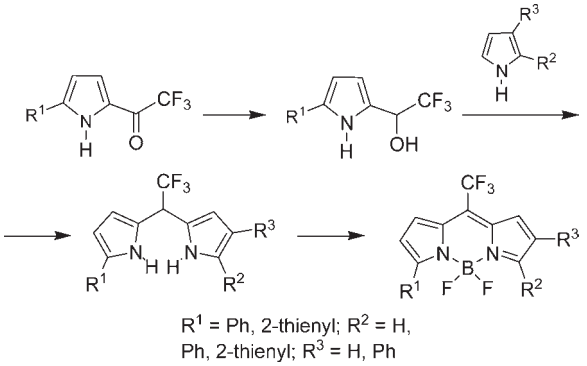
ABSTRACT



A general efficient route to hitherto inaccessible symmetric and asymmetric *meso*-CF_3-BODIPY dyes has been developed. The key stages include the reduction of available 2-trifluoroacetylpyrroles to the corresponding alcohols which are further condensed with pyrroles. The method allows the BODIPY with 3(5)aryl(hetaryl) and 3,5-diaryl(hetaryl) substituents to be readily assembled. The BODIPY dyes synthesized fluoresce (Φ_f = 0.56−1.00) in the 560−680 nm region.

BODIPY dyes (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) possess many distinctive and desirable properties such as high molar absorption coefficient, fluorescence quantum yields, and long wavelength emission.[1] Photochemical and chemical stabilities of the boron dipyrromethene chromofore are higher than those of many other dyes, and extended π-electron conjugation can be modified by introduction of substituents, affording red-shifted BODIPY derivatives.

Applications of BODIPY to optical chemosensors,[2] fluorescent biolabeling reagents,[3] light-harvesting materials,[4] nanotechnology,[5] optoelectronic devices,[6] and photodynamic therapy reagents[7] have been studied extensively. Biochemical application of BODIPY includes conjugation with a variety of biomolecules such as lipids,[8] proteins,[9] DNA,[10] carbohydrates,[11] and cholesterol.[12]

BODIPY's absorption and emission properties can be tuned by introducing appropriate substituents onto the BODIPY framework.[13] The *meso*-aryl group and the BODIPY framework interact weakly since the two moieties are almost orthogonal to each other.[14] Hence, any modifications to the *meso*-aryl group do not noticeably influence the position of absorption and fluorescence

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bands. A more appropriate way to modulate the properties of the BODIPY chromophore is the introduction of different aryl substituents to the 3- and 5-positions of the BODIPY core. However, in the single publication on the *meso*-CF_3-substituted BODIPY derivative it was shown that this strongly electron-withdrawing group caused a deep (~30 nm) bathochromic shift compared to that of the congeners with aryl substituents in this position.[15]

Meanwhile, the BODIPY dyes with a *meso*-CF_3-group are desirable targets because they might have at least two benefits as a biochemical probe. First, the probe is small. Second, the CF_3-group is known to be useful as an NMR marker.[15]

The combination of a CF_3 group, aryl or hetaryl moieties, and BODIPY scaffold in one molecule may result in synergism of their properties and, hence, to higher performance optical materials.

Herein, we describe a general synthetic strategy for preparation of symmetric and asymmetric *meso*-CF_3-substituted BODIPY dyes having aryl or hetaryl substituents. The thiophene substituent was chosen for its known[16] ability to enhance fluorescence properties owing to its easier electron delocalization compared to benzene. This narrows optical band gaps due to a better effective π-conjugation. This usually leads to a bathochromic shift of the absorption and emission wavelengths. Until now, only a few such BODIPY dyes have been synthesized,[17] mostly due to the difficulty in preparation of the necessary thiophene functionalized starting materials.

To the best of our knowledge, so far BODIPY dyes with a *meso*-CF_3-group and 3,5-diaryl substituents are unknown. The known *meso*-CF_3-BODIPY dyes have been synthesized via the intermediate, di(pyrrol-2-yl)trifluoromethane, which in turn, was obtained by condensation of pyrrole and 2,2,2-trifluoro-1-methoxyethanol in 48% yield.[15]

A promising general strategy for the synthesis of symmetric and asymmetric BODIPY dyes with a *meso*-CF_3-group and 3,5-diaryl(hetaryl) substituents could be based on the reaction of 2-trifluoroacetylpyrroles **1**,**2** with pyrroles having a vacant α-position of the pyrrole ring.

However, we have found that pyrroles **1**,**2** (as opposed to 2-acetylpyrroles[1c]) in this reaction (CF_3COOH, rt, 1 h or P_2O_5, rt, 15−16 h) proved to be inactive. Taking into account that pyrrolcarbinols condense with pyrroles in acidic media to give corresponding dipyrromethanes[18] we used 2,2,2-trifluoro-1-(pyrrol-2-yl)-1-ethanols **3**,**4**, products of reduction of pyrroles **1**,**2** with $NaBH_4$, as a key intermediate for the synthesis of the dipyrromethanes **9a**−**e**, Table 1.

The reaction of ethanols **3**,**4** with pyrroles **5**−**8** in the presence of P_2O_5 (equimolar quantity) gave dipyrromethanes **9a**−**e** in high (85−97%) yields. The similar symmetric *meso*-trifluoromethyldipyrromethanes, synthesized from pyrrole and trifluoroacetaldehyde methyl hemiacetal in the 50−70% yield, was used as the major intermediate in the synthesis of *trans*-trifluoromethylporphyrins as well as of *meso*-tetrakis(trifluoromethyl)porphyrin.[19]

Oxidation of dipyrromethanes **9a**−**e** with DDQ and the following complexation of formed dipyrromethenes with $BF_3 \cdot$etherate were realized as a one-pot procedure to afford the target BODIPY dyes in a yield up to 84% (Table 1).

Thus, we have developed a general effective route to a novel family of the *meso*-CF_3-3,5-diaryl(hetaryl)-BODIPY dyes, prospective fluorophores, based on easily available 2-aryl- and 2-hetarylpyrroles. These pyrroles, including 2-(2-thienyl)pyrrole, are readily obtained from

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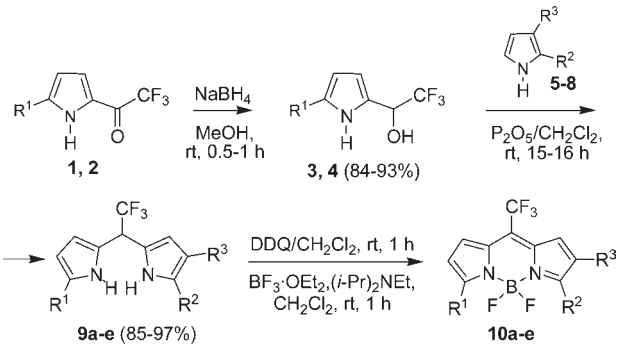
Table 1. Synthesis of Meso-CF_3-BODIPY **10a**–**e**



pyrrole **3, 4**	pyrrole **5-8**	BODIPY **10a-e**, yield
3	**5**	**10a**, 50%
3	**6**	**10b**, 57%
4	**5**	**10c**, 61%
4	**7**	**10d**, 39%
3	**8**	**10e**, 84%

alkylaryl(hetaryl)ketones and acetylene (through the corresponding ketoximes)[20] by Trofimov reaction[21] in a one-pot procedure. In contrast, the introducing of thienyl substituent to the BODIPY core was previously realized by the multistep synthesis involving 3,5-dichlorosubstituted dipyromethanes via the Suzuki coupling.[17c]

Pyrroles **1** and **2** were obtained by trifluoroacetylation of corresponding pyrroles **6** and **7** with trifluoroacetic anhydride in high yields.[22]

The absorption and fluorescence spectra of the synthesized BODIPYs (*n*-hexane, rt) in the region of wavelengths >450 nm are shown in Figure 1. In all cases, the spectra of excitation of fluorescence fully complied with the absorption ones. The only reported representative of the BODIPY series with *meso*-CF_3-substituent displays the following spectral characteristics: $\lambda_{max,abs} = 548$ nm, $\lambda_{max,f} = 554$ nm, $\varepsilon = 89000\ M^{-1}\cdot cm^{-1}$, $\Phi_f = 1.00$ in CH_2Cl_2.[15] Among the synthesized BODIPYs, very close quantum yield and molar extinction coefficient are observed for compound **10d** (Table 2), but its absorption and fluorescence bands are strongly shifted to red area (similar to the spectral properties of aza-BODIPY dyes[1b]) owing to a greater extent of the π-system and donor abilities of the thiophene ring.

As seen from Table 2, the Φ_f value increases from mono- to disubstituted representatives and is highest (1.00) for dithienyl derivative **10d**. Generally, thienyl-substituted BODIPYs absorb and fluoresce at a longer wavelengths then the corresponding phenyl congeners. The lengthing of the conjugation by the introduction of the second phenyl or thienyl moiety expectedly leads to the intensity enhancement and bathochromic shifts of the absorption and fluorescence bands (Figure 1). The thienyl derivatives **10c**,**d** have fairly narrow absorption and fluorescence bands with well-defined vibrational structure and small $\Delta\nu_{St}$ ($\sim 200\ cm^{-1}$). Their fluorescence bands almost mirror the corresponding absorption bands. The most intensive vibronic transition is always the 0–0 one. All this evidence that the geometry of the BODIPY **10c**,**d** in the ground (S_0) and the first electronically excited state (S_1) is close to planar. This conclusion is supported by the observation that the $\Delta\nu_{St}$ of BODIPY **10c**,**d** coincide with $\Delta\nu_{St}$ of flat 3,5-dichloro-8-trifluoromethyl-BODIPY ($\Delta\nu_{St} = 200\ cm^{-1}$).[15]

Replacement of thienyl rings by the bulkier phenyl substituent (BODIPY **10a**,**b**) augment the $\Delta\nu_{St}$ value and broadens and smears the thin structure of the absorption and fluorescence bands so that 0–1 vibronic transitions appears only as shoulders (Figure 1). These spectral changes correspond to a more significant deviation of the phenyl rings from the BODIPY plane as compared to the thienyl derivatives **10c**,**d** (calculated dihedral angles $\sim 40°$ for **10a**,**b** and $\sim 20°$ for **10c**,**d**, respectively; see the Supporting Information).This is predicted result of a greater steric hindrance exerted by ortho-hydrogen atoms of the phenyl rings. The compound **10e** has a substantially lower Φ_f and largest $\Delta\nu_{St}$, in comparison with **10a**–**d**. This is probably due to the strong violation of the planarity of the π-system (calculated dihedral angles $\sim 39°$, $\sim 56°$, and $\sim 35°$ for 2-, 3-, and 5-phenyls of **10e**, correspondingly; see the Supporting Information) and a more significant change in molecular geometry upon excitation.

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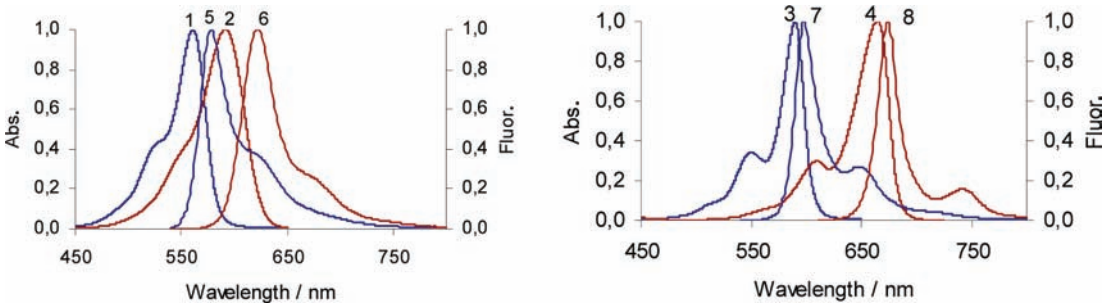

Figure 1. Normalized absorption and fluorescence spectra of BODIPY **10a**–**d** in *n*-hexane: 1,5- (**10a**), 2,6- (**10b**), 3,7- (**10c**), 4,8- (**10d**).

Table 2. Photophysical Data of BODIPY **10a**–**e** Recorded in *n*-Hexane

BODIPY	$\lambda_{max,abs}$ (nm)	absorption coefficient (ε, M^{-1} cm^{-1})	$\lambda_{max,f}$ (nm)	$\lambda_{max,ex}$ (nm)	Stokes shift ($\Delta\nu_{St}$, cm^{-1})	τ_f (ns)	fluorescence quantum yield (Φ_f)
10a	561	36000	578	561	520	4.5	0.56[a]
10b	592	48000	622	591	820	6.4	0.74[a]
10c	589	63000	597	589	230	5.6	0.67[a]
10d	665	85000	674	665	200	5.5	1.00[b]
10e	613	31000	653	616	1000		0.06[b]

[a] Rhodamine 6G as standard (Φ_f = 0.95, ethanol).[23] [b] Nile blue as standard [(Φ_f = 0.27, 0.5% (v/v) 0.1 M HCl in ethanol].[24]

Like thienyl derivatives **10c**,**d**, the phenyl substituted BODIPY **10a**,**b** have an approximate mirror symmetry of absorption and fluorescence spectra; 0–0 vibronic transition remaining as the strongest one. Consequently, the shape of phenyl-containing BODIPY molecules changes just slightly upon excitation, being relatively nonplanar in the S_1 state.

These inferences are in accordance with DFT/BP86/def2-TZVP and TD-BP86/def2-TZVP quantum-chemical calculations (see the Supporting Information).

In conclusion, a general route to a new family of the BODIPY fluorophores with the *meso*-trifluoromethyl moiety has been devised. The original features of the new methodology involve the reduction of the available 2-trifluoroacetylpyrroles followed by the condensation of the alcohols, thus produced, with pyrroles.

The methodology for the first time allows both symmetric and asymmetric BODIPY dyes with *meso*-trifluoromethyl moieties to be easily assembled. All BODIPYs are highly fluorescent (with the exception of compound **10e**) with $\Phi_f > 0.5$ and small Stokes shifts.

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Supporting Information Available. Detailed experimental procedures, ^{1}H, ^{11}B, ^{13}C, ^{15}N, and ^{19}F NMR spectra for all new compounds, and DFT calculation data. This material is available free of charge via the Internet at http://pubs.acs.org.