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SHORT COMMUNICATION

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Rapid and Selective Electrophilic Trifluoromethylation of the 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) Scaffold

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This report deals with the rapid functionalization of the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) scaffold by means of electrophilic trifluoromethylation. Subjecting dye **2** to the disclosed protocol led to the successful isolation of 3-trifluoromethylated derivative **9**. Subsequent comparison of structural and electronic properties allowed for the characterization of changes imparted by the CF_3 group. A diminution in the quantum yield [$\Phi_F(\mathbf{2})_{MeOH} = 0.15$, $\Phi_F(\mathbf{9})_{THF} = 0.024$] was accompanied by a larger Stokes shift [$\Delta S(\mathbf{2})_{MeOH} = 12$ nm, $\Delta S(\mathbf{9})_{THF} = 54$ nm], whereas the molar extinction coefficient at the global absorbance maximum remained largely unaffected [$\varepsilon(\mathbf{2})_{MeOH} = 40 \times 10^3$ M^{-1} cm^{-1}, $\varepsilon(\mathbf{9})_{THF} = 30 \times 10^3$ M^{-1} cm^{-1}].

Introduction

Since the initial preparation of the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) core in 1968 by Treibs and Kreuzer in the form of structure **1** (Figure 1),[1] the central motif has emerged as a privileged framework for designing stable fluorescent dyes.[2] Usually, this development is attributed to several factors including largely solvent-independent fluorescence quantum yields, large molecular extinction coefficients up to 320000 M^{-1} cm^{-1}, and, typically, small Stokes shifts (ca. 10 nm).[3] Consequently, these intriguing structures have found numerous applications. For instance, they have been used as chemodosimeters for fluoride-ion detection, and their implementation as on-site singlet oxygen generators applicable in photodynamic therapy was considered.[4] Furthermore, ^{18}F analogs have been created for hybrid optical and positron emission tomography imaging.[5] Generally, these molecules are accessed by relying on the condensation of prefunctionalized pyrrole starting materials and suitable aldehydes or carboxylic acid derivatives rather than subjecting an abundant BODIPY framework to further derivatization strategies.[6] In this regard, one of the most remarkable developments in recent years was the introduction of Biellmann's BODIPY derivative **2**, the *meso* position of which could be further derivatized by means of Liebeskind–Srogl cross-coupling methodology.[7] Moreover, Tang and Peña-Cabrera showcased in 2009 for the first time that a palladium-catalyzed reduction of the thioether functionality granted access to parent BODIPY **3**,[8] which paralleled the more conventional syntheses reported at the same time by Tram et al. and Schmitt et al.[9] Other rapid diversification strategies are based on nucleophilic aromatic substitution reactions (S_NAr) performed on 3-chloro or 3,5-dichloro precursors.[10] In this context, also the incorporation of the strongly electron-withdrawing CF_3 group ($\sigma_{para} = 0.54$)[11] at the *meso* carbon atom was considered, which thereby rendered 3,5-dichloro scaffold **4** more susceptible to exchange reactions.[12] Accordingly, functionalization of Avidin with **4** was achieved under mild, aqueous conditions. Additionally, in these bioconjugates the CF_3 group was envisaged as a small ^{19}F NMR reporter probe. Most recently, congener **5** was

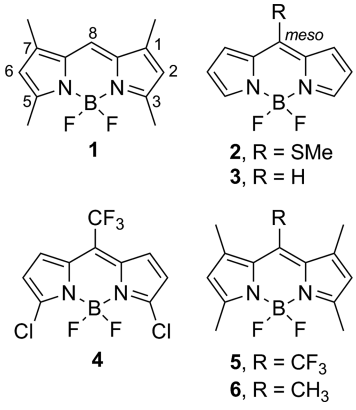

Figure 1. The first reported BODIPY dye **1**, Biellmann's derivative **2**, and trifluoromethylated congeners **4**–**6**.

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found to display aggregation-induced emission enhancement contrasting the photophysical behavior of methylated derivative **6**.[13]

Correspondingly, the incorporation of the CF_3 group into the BODIPY platform can lead to highly desirable modifications of inherent reactivity and electronic properties and, hence, demands further attention. However, to the best of our knowledge the feasibility of the late-stage trifluoromethylation of the pyrrole subunits of the BODIPY scaffold has not yet been addressed.[14] Herein, a synthetic protocol providing access to the desired motif is reported, the salient features of which include operational simplicity and very short reaction times. Furthermore, structural and electronic changes resulting from the trifluoromethylation are discussed.

Results and Discussion

Since the advent of 3,3-dimethyl-1-(trifluoromethyl)-3*H*-1λ^3,2-benziodaoxole (**7**) and 1-(trifluoromethyl)-3*H*-1λ^3,2-benziodaoxol-3-one (**8**),[15] a plethora of methods for generating an electrophilic trifluoromethyl radical ($CF_3^{\cdot}$) through reduction of these structures have sprouted (Figure 2). Notably, modification of a broad variety of electron-rich and electron-deficient aromatic systems has been reported by utilizing **8** in conjunction with catalytic amounts of $MeReO_3$ (MTO) at elevated temperatures.[16] Additionally, the desired reactive intermediate was also observed in the presence of photoredox catalysts,[17] copper sources[18] and deprotonated oximes.[19] More recent examples have employed tetrabutylammonium iodide (TBAI) as a an initiator.[20] In accordance, thiols, with typical reduction potentials ranging from 0.8 to 1 V,[21] were also envisioned to provide $CF_3^{\cdot}$ from **7** and **8**.[22] Specifically, upon treatment of **7** with a prototypical thiol RSH at ambient temperature the occurrence of the corresponding disulfide byproduct $(RS)_2$ alongside the desired $RSCF_3$ was noted, which thereby hinted towards the involvement of radical species.[23] As a logical consequence, the functionalization of suitable nucleophiles, namely, a BODIPY derivative, by interception of these electrophilic radicals was conceived. Therefore, in consideration of the previously outlined versatility of derivative **2**, the applicability of the rationale to effect the trifluoromethylation of this structure was tested.

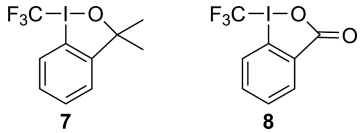
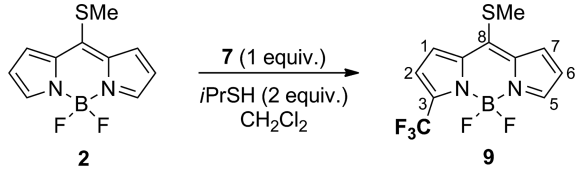


Figure 2. Electrophilic trifluoromethylating agents.

To our delight, treatment of a mixture of **2** and **7** with *i*PrSH furnished new BODIPY dyes, as suggested by ^{19}F NMR spectroscopy. Particularly, the occurrence of triplet-like signals around δ = –62.0 ppm with coupling constants J = 11–13 Hz was noted. These patterns most likely arise from through-space ^{19}F–^{19}F coupling between the CF_3 and BF_2 moieties and, hence, suggest functionalization of the 3,5-positions. In addition, the chemical shifts were in good agreement with values reported for 2-(trifluoromethyl)-1*H*-pyrrole (–59.2 ppm).[24] Unsurprisingly, the use of an excess amount of **2** (2–4 equiv.) led to increased selectivity for the presumably monofunctionalized product. Hence, a mixture of **2** (4 equiv.) and **7** (1 equiv.) in CH_2Cl_2 at ambient temperature was treated with *i*PrSH (2 equiv.) in CH_2Cl_2 (Scheme 1). Subsequent chromatographic purification over silica gel afforded the newly formed product as a red crystalline solid in 37% yield. Generally, these reactions went to completion over the course of minutes. In stark contrast, the MTO-based protocol performed by employing reagent **8** only led to degradation of the starting materials. TBAI catalysis with **7** furnished the same product; however, chromatographic purification was more tedious, and therefore, the whole procedure was less practical.

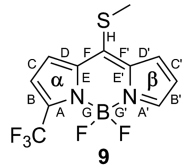


Scheme 1. Radical trifluoromethylation of BODIPY **2**.

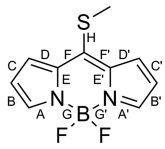
^1H NMR spectroscopy revealed the presence of five aromatic signals between δ = 6.50 and 7.77 ppm attributable to two individual sets of coupling partners by correlation spectroscopy (COSY). The ^{19}F NMR spectrum revealed a triplet at δ = –60.3 ppm (J_{FF} = 11.4 Hz, 3 F) and a pseudoquartet of quartets at δ = –145.1 ppm ($^1J_{BF}$ = 27.9 Hz, J_{FF} = 11.7 Hz, 2 F), and accordingly, ^{11}B NMR spectroscopy furnished a triplet at δ = 0.0 ppm ($^1J_{BF}$ = 27.8 Hz). Finally, HRMS (ESI) showed $[M + H]^+$ at m/z = 307.0498, which is in line with the calculated mass of m/z = 307.0496 for protonated **9**. Gratifyingly, also single crystals suitable for solid-state structure analysis were obtained by vapor diffusion of pentane into a saturated solution of **9** in acetone at 4 °C. The most important bond lengths for dye **9** and parent compound **2** are given in Table 1. An ORTEP representation of **9** is found in Figure 3.

A bond length comparison between the substituted (α) and the unfunctionalized pyrrole subunit (β) in **9** uncovers small differences, ΔXX′, on average of 0.019 Å. In symmetric parent compound **2**, the same consideration reveals less distinct variations (0.005 Å), which are mostly attributable to measurement uncertainties and packing effects. Therefore, if ΔXX′ ≥ 0.01 Å, then this difference ΔXX′ is presumably a direct consequence of pyrrole functionalization. Judged by this criterion, bonds A/A′–F/F′ in the pyrrole α and β subunits of compound **9** are dissimilar and are clearly distinguishable as a result of the introduction of the CF_3 moiety. In addition, the C^8–SMe bond lengths indicate a shortening of 0.019 Å upon modifying dye **2** (Table 1, entry H). Thus, the substitution of hydrogen for the trifluoromethyl group furthered electron donation through lone pairs of electrons on the sulfur atom, which thereby lends

Table 1. Comparison of X-ray-derived bond lengths for compounds **9** and **2**.



9



2

Bond[a]	**9** [Å]	ΔXX′ [Å][b]	**2** [Å][b][7]	ΔXX′ [Å]
A	1.3603(16)	+0.0181	1.346	+0.005
A′	1.3422(17)		1.341	
B	1.3835(18)	–0.0178	1.378	–0.008
B′	1.4013(19)		1.386	
C	1.3937(19)	+0.0257	1.374	+0.005
C′	1.3680(20)		1.369	
D	1.4022(18)	–0.0215	1.405	–0.004
D′	1.4237(18)		1.409	
E	1.3852(16)	–0.0146	1.392	+0.005
E′	1.3998(16)		1.387	
F	1.4370(17)	+0.0346	1.408	+0.003
F′	1.4024(18)		1.405	
G	1.5439(18)	+0.0012	1.542	+0.004
G′	1.5427(17)		1.538	
H	1.7112(13)	n/a	1.730	n/a

[a] For **9**, ΔXX′ is the difference in bond length between the functionalized α-pyrrole subunit and the unfunctionalized β-pyrrole subunit, e.g., A–A′. For **2**, it is the difference between the left and the right subunit. [b] Asymmetric unit contains two independent molecules.

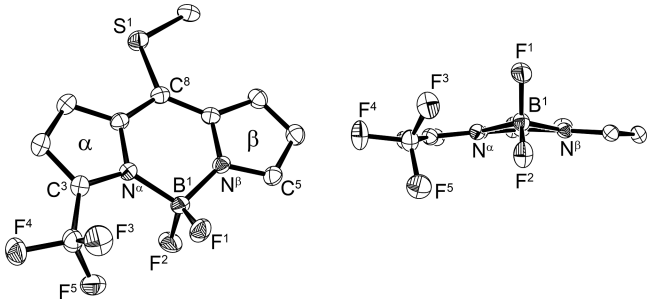
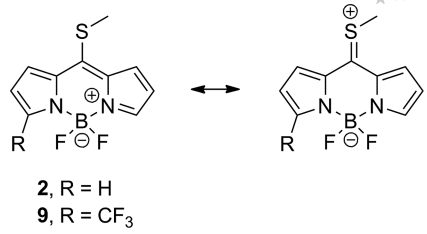


Figure 3. ORTEP representation of **9**. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are set to 50% probability. Deviation from perfect planarity is indicated by an angle of 9.56° between the two pyrrole α and β subunits.

increased weight to a resonance structure bearing a formal positive charge at the chalcogen atom (Figure 4). Markedly, however, the BF_2 unit is complexed symmetrically in both **9** and **2** with comparable B–N bonds G/G′ of 1.544/1.543 Å and 1.542/1.538 Å, respectively. Therefore, similar electron densities at the α- and β-nitrogen atoms were expected, a fact that was further substantiated by the ^{15}N NMR chemical shifts (see below).

Finally, in compound **2**, the deviation from perfect planarity of the ligand, as defined by the angle between planes parallel to the pyrrole moieties, is 6.11°, whereas in **9** a slightly larger angle of 9.56° is calculated. This deviation is likely to cause a quantum yield for **9** that is slightly diminished relative to that of **2**. Electronic differentiation as a direct consequence of the trifluoromethylation is also ob-



2, R = H
9, R = CF_3

Figure 4. BODIPY resonance structures.

served in the ^{13}C NMR spectrum, in that the carbon atoms belonging to the α subunit are shielded between 0.2 and 19.5 ppm relative to the corresponding carbon atoms belonging to the β-pyrrole unit (see the Experimental Section). In addition, for the pyrrole nitrogen N^{α} and N^{β} atoms the ^{15}N NMR chemical shifts of δ = 181.3 and 201.9 ppm, respectively, could be derived by means of $^{1}H/^{15}N$ HSQC spectroscopy, which substantiates the electronic similarity of the heteroatoms found in the crystal structure (the ^{15}N chemical shift range is roughly 800 ppm). Furthermore, stronger $^{1}H/^{13}C$ HMBC contacts between the methyl thioether and the proton at C^7 are indicative of a solution-phase orientation that is comparable to the one found in the solid state. Lastly, a very pronounced effect of the CF_3 group on the electronic structure of the dye is observed as well, as evidenced by the UV/Vis spectrum of **9** obtained in THF (Figure 5). The spectrum exhibits two well-separated maxima at λ_{max} 387 ($\varepsilon = 14.9 \pm 0.2 \times 10^3$ M^{-1} cm^{-1}) and 470 nm ($\varepsilon = 30.1 \pm 0.2 \times 10^3$ M^{-1} cm^{-1}), which give rise to a hypsochromic shift of $\Delta\lambda_{max}$ = 21 nm relative to the λ_{max} of **2** [λ_{max}(THF) = 491 nm; λ_{max}(MeOH) = 527 nm, $\varepsilon_{MeOH} = 40 \times 10^3$ M^{-1} cm^{-1}]. Subsequent irradiation of a 4.7 μM THF solution of **9** at 470 nm resulted in fluorescence emission around λ_{em} = 524 nm with an associated Stokes shift of ΔS = 54 nm, which is roughly four times larger than the value reported for **2** in MeOH (ΔS = 12 nm).

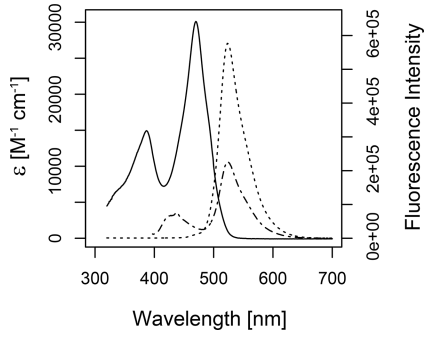


Figure 5. UV/Vis absorption spectrum (solid) and fluorescence spectra for λ_{ex} = 470 nm (dashed) and λ_{ex} = 387 nm (dot-dashed) of dye **9** in THF.

In addition, fluorescence quantum yields of $\Phi_F(\mathbf{9})_{THF}$ = 0.0244 and 0.0237 against the standards 9,10-diphenylanthracene and perylene, respectively, were obtained, which contrast the reported value of $\Phi_F(\mathbf{2})_{MeOH}$ = 0.15 of the parent structure. Indeed, this result further corroborates the electron-deficient nature of **9**, as quenching of the excited state by intramolecular charge transfer from the *meso*

heteroatom is expected to become more favorable.[25] Finally, in agreement with Kasha's rule,[26] if the excitation wavelength was set to 387 nm, the main emission was still centered around 524 nm, which corresponds to a pseudo-Stokes shift of ΔS = 137 nm. In light of recent endeavors to access dyes with large Stokes shifts for applications as molecular imaging probes, the findings delineated above are topical and are currently of high interest. Studies directed towards further conjugation of product **9** by means of cross-coupling methodology are ongoing and will be reported in due time.

Conclusions

In summary, the direct trifluoromethylation of the BODIPY scaffold was achieved through interception of reactive intermediates generated by treatment of reagent **7** with a thiol. The salient features of the protocol include no requirement for dried solvents, an inert atmosphere, or rigorous temperature control, and generally, short reaction times (<10 min) are observed. Application of the protocol to dye **2** resulted in novel derivative **9**, which features a Stokes shift that is approximately four times larger than that of **2** and a fluorescence quantum yield of $\Phi_F(\mathbf{9})_{THF}$ = 0.024.

Experimental Section

4,4-Difluoro-8-(thiomethyl)-3-(trifluoromethyl)-4-bora-3a,4a-diaza-*s*-indacene (9): 3,3-Dimethyl-1-(trifluoromethyl)-3*H*-1λ^3,2-benziodaoxole (**7**; 88 mg, 0.27 mmol, 1 equiv.) was added to a solution of BODIPY-SMe (**2**; 0.25 g, 1.05 mmol, 3.94 equiv.) in CH_2Cl_2 (5 mL), and the mixture was stirred for 5 min. Then, a solution of *i*PrSH (40 mg, 0.5 mmol, 1.97 equiv.) in CH_2Cl_2 (0.85 mL) was added dropwise over the course of 2 min. After 1 h at ambient temperature, the mixture was concentrated under reduced pressure. Chromatographic purification (silica gel, hexane/EtOAc = 8:1 to 2:1, R_f = 0.04 in hexane/EtOAc = 8:1) was followed by a second chromatographic purification (silica gel, pentane/ether = 1:1, R_f = 0.19), which afforded the pure product (30 mg, 37%) as a red crystalline solid, m.p. 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H, C^5H), 7.55 (d, J = 4.6 Hz, 1 H, C^7H), 7.30 (d, J = 4.0 Hz, 1 H, C^1H), 6.73 (d, J = 4.2 Hz, 1 H, C^2H), 6.70 (d, J = 4.6 Hz, 1 H, C^6H), 2.97 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4 (C^8), 145.8 (C^5), 137.9 (q, J = 40.2 Hz, C^3), 134.7 (C^8CN^{β}), 134.5 (C^8CN^{α}), 131.2 (m, C^7), 122.8 (m, C^1), 120.9 (dd, J = 5.1, 2.5 Hz, C^6), 120.44 (q, J = 270.0 Hz, C^3CF_3), 116.1 (td, J = 3.9, 2.1 Hz, C^2), 20.6 (C^8SCH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –60.3 (t, J = 11.5 Hz, 3 F, CF_3), –145.1 (Ψqq, J = 27.9, 11.7 Hz, 2 F, BF_2) ppm. ^{11}B NMR (128 MHz, $CDCl_3$): δ = 0.1 (t, J = 27.8 Hz, BF_2) ppm. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ = 181.4 (N^{α}), 202.0 (N^{β}) ppm. HRMS (ESI): calcd. for $C_{11}H_8BF_5N_2NaS$ 329.0316 [M + Na^+]; found 329.0316. $C_{11}H_8BF_5N_2S$ (306.06): calcd. C 43.17, H 2.63, N 9.15; found C 42.90, H 2.92, N 8.87.

CCDC-1011443 contains the supplementary crystallographic data for compound **9**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Synthesis of compound **2**, copies of the NMR spectra and quantum yield determination for compound **9**.

Acknowledgments

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