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β-Formyl-BODIPYs from the Vilsmeier−Haack Reaction

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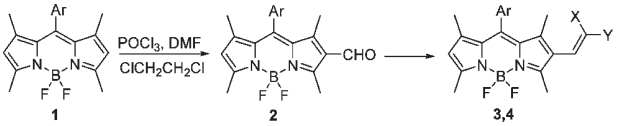

A series of β-formyl-BODIPYs **2** were synthesized in high yields from tetramethyl-BODIPYs **1** via the Vilsmeier−Haack reaction and were further functionalized using a Knoevenagel condensation to generate novel BODIPYs **3** and **4**.

Boradiazaindacenes, known as BODIPY dyes, are strongly UV-absorbing small molecules with high fluorescence quantum yields, sharp fluorescence emissions, high photophysical stability, and low sensitivity to the polarity and pH of their environment.[1,2] Their fluorescence profiles can be easily tuned by way of small modifications to the structures. Consequently, these molecules have found wide applications as fluorescent labels for DNA[3] and proteins[4] and have attracted renewed research interests[2] in highly diverse fields as labeling reagents,[3−5] fluorescent switches,[6] chemosensors,[7,8] laser dyes,[9] photosensitizers,[10] energy transfer cassettes,[11] supramolecular fluorescent gels,[12] and harvesting arrays.[13] Currently, their further application is hampered by the limited availability associated with synthetic limitations, especially for those compounds with extended conjugation.

BODIPY itself is intrinsically electron-rich and has several positions available for functional modification, but most of the functionalization methods are not straightforward.[2] Among these, functionalization at the 8-(meso) position (Figure 1) is relatively easy compared with the pyrrolic positions via the condensation of various aryl aldehydes (Lindsey's method)[14a] or acyl chlorides with pyrroles;[14] many functional groups such as ligands or biomolecules are often introduced via this method. However, the meso substituents and the BODIPY chromophore are almost perpendicular to each other, resulting in poor electronic conjugation between the two moieties. Thus, functionalization at the pyrrolic positions is more desirable.[2,15] Typical approaches include (1) de novo syntheses from appropriately substituted pyrroles if accessible and (2) the direct introduction of pyrrolic substituents to a ready-made partially unsubstituted BODIPY chromophore;[2] this latter method is efficient, and substitution can be performed at both α- and β-positions of the chromophore (Figure 1). Methods available for functionalization at the α-position include Knoevenagel condensations of 3,5-dimethyl-BODIPYs using aryl aldehyde,[16] nucleophilic substitutions,[17a,b] or organometallic couplings[18] of 3,5-dichloro-BODIPYs[17a,b] and analogues.[17c]

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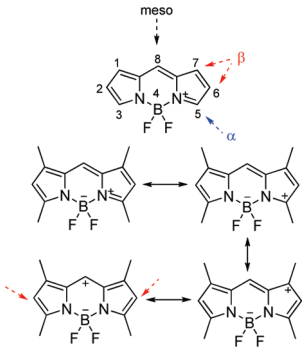


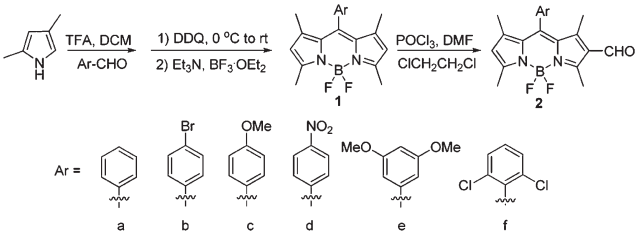
FIGURE 1. IUPAC numbering system for BODIPY and the most susceptible positions on tetramethyl-BODIPY for electrophilic substitution reactions.[2a]

In the mesomeric structures[2a] of BODIPY as shown in Figure 1, the 2,6-(β-)positions of the BODIPY core bear the least positive charge and should be most susceptible to electrophilic attack. Surprisingly, only limited electrophilic reactions have been reported at these positions, including (1) halogenation,[10] (2) sulfonation,[19] (3) nitration,[20] and (4) palladium-catalyzed C−H functionalization.[21] There are no reports of common electrophilic substitution reactions such as the Vilsmeier−Haack reaction.

The Vilsmeier−Haack reaction of pyrroles[22] using DMF/$POCl_3$ has been extended to thiophenes,[23] indoles,[24] bipyrroles,[25] porphyrins,[26] chlorins,[26] and dipyrromethanes[27] and represents highly efficient approaches to the introduction of various substituents into specific positions of these molecules. For example, formylporphyrins, in general, and β-formylporphyrins, in particular, are valuable precursors in the synthesis of porphyrin derivatives with important applications in biomedical and natural sciences.[28] The introduction of formyl groups into a BODIPY core is an important method for the further elaboration of BODIPYs. We wondered if the same strategy could be used for the particular case of BODIPYs to generate the desired β-formyl-BODIPYs.

Herein we report in detail the syntheses of a series of β-formyl-BODIPYs **2** via the Vilsmeier−Haack reaction on BODIPYs **1** as shown in Scheme 1 and their photophysical properties. BODIPY **2a** was further functionalized using a

SCHEME 1. Syntheses of BODIPYs 2



Knoevenagel condensation as shown in Scheme 2 to demonstrate the ready transformation of these β-formyl-BODIPYs. The formylation procedure was extended to aza-BODIPY **5** as shown in Scheme 3 to exemplify the versatility of this reaction.

BODIPYs **1a**−**f** were chosen because they were easily available via Lindsey's method[14a] from the condensation of 2,4-dimethylpyrrole with the corresponding aryl aldehydes. 2,4-Dimethylpyrrole was chosen to limit possible reaction positions for the formylation reaction and to thus avoid the generation of complex mixtures. The standard Vilsmeier−Haack reaction required stoichiometric amounts of Vilsmeier reagent prepared via interaction between $POCl_3$ and DMF for 1 h at room temperature. Initially, a standard condition was used for the formylation of BODIPY **1a** in DCM at room temperature, but no reaction occurred over 1 week. Simply raising the temperature to refluxing or increasing the Vilsmeier reagent to an excess amount (up to 200 equiv) made no difference. With the combination of these two factors, BODPY **2a** was generated slowly and in low yield, and most of the starting BODIPY **1a** was recovered. Influenced by the formylation conditions used for the porphyrin system, in which the refluxing 1,2-dichloroethane is generally used as solvent, the formylation of BODIPY **1a** was also carried out in refluxing 1,2-dichloroethane instead of DCM. In this case, in the presence of an excess amount of Vilsmeier reagent, BODIPY **1a** was completed consumed within 2 h. After hydrolysis of the intermediate iminium salts, followed by the usual workup and column chromatographic isolation, BODIPY **2a** was obtained in 89% yield.

BODIPYs **1b**−**f** exhibited similar reactivity under the same reaction conditions as shown in Scheme 1 and are also completely consumed within 2 h. After workup and column chromatographic isolation, BODIPYs **2b**−**f** were obtained in 87−93% yields, as summarized in Table 1. The ^{1}H NMR spectra give a typical singlet one-proton signal between 9.99 and 10.03 ppm for the formyl protons for most of the β-formyl-BODIPYs, with the exception of **2e**, which has the appropriate signal at 9.80 ppm. Crystals of BODIPY **2c** suitable for X-ray analysis were obtained via slow evaporation of a DCM solution. It has a planar BODIPY framework as shown in Figure 2. The dihedral angle between the phenyl and the BODIPY core is 60°, which is different from the 78° dihedral angle reported in BODIPY **1d**.[29] The plane defined by the F−B−F atoms is perpendicular to that of the BODIPY core, similar to previous reported results.[29,30]

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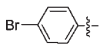
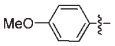
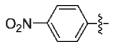
TABLE 1. Isolated Yields and Characteristic ^{1}H NMR Signals for BODIPY 2a−f from Mono-β-formylation of the Corresponding BODIPY 1a−f

BODIPY **2**	Ar-	Isolated yield (%)	^{1}H NMR of CHO
2a		89%	10.00
2b		93%	10.01
2c		91%	10.01
2d		87%	9.99
2e		90%	9.80
2f		85%	10.03

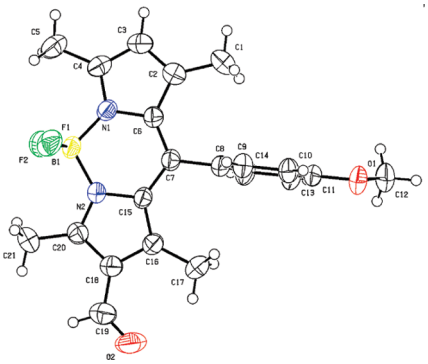
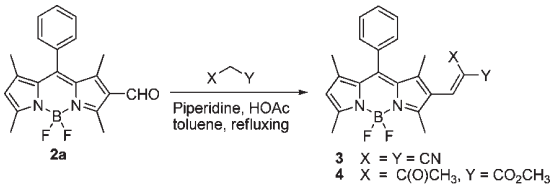


FIGURE 2. Perspective view of compound **2c**, including atom numbering.

SCHEME 2. Synthesis of BODIPY 3 and 4



By further extending the reaction time, a mixture of mono- and diformylated BODIPYs was obtained according to TLC monitoring. The diformylated BODIPYs failed to survive the subsequent hydrolysis conditions and led to unidentified polar complex mixtures. Variation of the hydrolysis conditions, such as changing the base, lowering the temperature, and performing under argon, gave similar results, and no diformylated BODIPYs were isolated.

With the efficient generation of β-formyl-BODIPYs **2** in high yields, and to demonstrate the easy structural modification of these β-formyl-BODIPYs, BODIPY **2a** was further functionalized via Knoevenagel condensations with malononitrile or methyl acetoacetate as shown in Scheme 2. After column separation, BODIPY **3** was obtained in 80% yield, while BODIPY **4** was obtained in lower yield as a mixture of two regioisomers (1.3:1). Crystals of BODIPY **3** suitable for

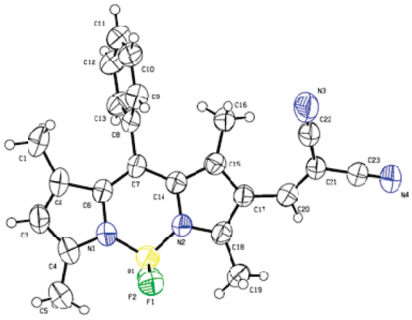


FIGURE 3. Perspective view of compound **3**, including atom numbering.

X-ray analysis were obtained via slow evaporation of a DCM solution. BODIPY **3** has a planar BODIPY framework as shown in Figure 3. The dihedral angle between the phenyl and the BODIPY core is 60°, similar to that of BODIPY **2c**. The plane defined by the F−B−F atoms is also almost perpendicular with that of the BODIPY skeleton with a dihedral angle of about 82°, which is only slightly different from that of BODIPY **2c**. Thus, BODIPY **3** shows only a small distortion of the structure compared with that of β-formyl-BODIPY **2a**.

With several new BODIPYs in hand, we further studied the photophysical properties of these compounds. BODIPYs **1**−**3** are colorful to the eye, and most of them are brilliant upon irradiation. Similar to the starting BODIPYs **1**, these new BODIPYs gave good dispersion of UV absorbance and fluorescence emission and were insensitive to the polarity of the media as exemplified for BODIPY **2a** in Figure S1 in the Supporting Information. Their spectral data in DCM are compared with those of the starting BODIPYs **1** in Table 2.

The molar absorptivities of BODIPYs **2** are comparable to those of BODIPYs **1**. There are small blue-shifts (2−6 nm) of the absorption and emission bands for BODIPYs **2**, with the exception of BODIPY **2f** in which a relatively larger (14 nm) blue-shifted band is observed. Most of BODIPYs **2** have good fluorescence quantum yields, with the exception of BODIPYs **1d** and **2d**. This is attributed to the strong electron-withdrawing effect of the nitro-substituted benzene moiety at the 8-position, which leads to photoinduced electron-transfer processes and reduces the fluorescence quantum yield as described in the literature.[31] With the increased conjugation on BODIPY **3**, the spectra become slightly broader and are red-shifted (20 nm for absorption and 27 nm for fluorescence emission) compared with those of BODIPY **2a**.

To test the versatility of this formylation reaction, we further extended the reaction procedure to aza-BODIPY **5**[32] as shown in Scheme 3, from which β-formylaza-BODIPY **6** was obtained in 74% yield. The resulting BODIPY **6** shows a good fluorescence quantum yield and has blue-shifted absorption (22 nm) and emission (17 nm) bands compared with those of the starting BODIPY **5**, as shown in Table 2. Aza-BODIPYs generally have long-wavelength absorption and

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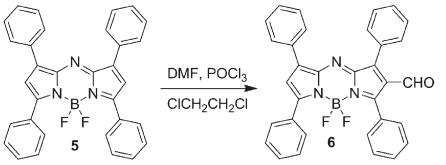
TABLE 2. Photophysical Properties of BODIPY 1a−f, 2a−f, 3, 5, and 6 in DCM

BODIPY	λ_{max} (nm)	log (ε_{max})	λ_f (nm)	Stokes shift (nm)	Φ_f
1a	500	5.02	520	20	0.36
2a	494	4.81	516	22	0.41
1b	502	4.77	522	20	0.29
2b	498	4.79	519	21	0.37
1c	500	4.92	519	19	0.38
2c	494	4.70	516	22	0.40
1d	504	4.94	527	23	< 0.01
2d	500	4.77	528	28	0.08
1e	500	4.64	520	20	0.46
2e	496	4.81	518	22	0.64
1f	510	4.74	532	22	0.51
2f	496	4.81	518	22	0.51
3	514	4.74	543	29	0.45
5	646	4.90	680	34	0.34
6	624	4.73	663	39	0.45

SCHEME 3. Synthesis of Aza-BODIPY 6



emission properties but suffer from limited potential for their synthetic modification because functionalization at the 8-position is not possible. Thus, our formylation reaction provided a useful approach for the efficient modification of aza-BODIPYs.

In summary, modified Vilsmeier−Haack reactions using excess amounts of DMF/$POCl_3$ in refluxing 1,2-dichloroethane have been successfully applied for the formylation of the BODIPY core at its β-position, from which a series of BODIPYs **2** have been obtained in high yields. The further functionalization of **2a** via the Knoevenagel condensation generates novel BODIPYs **3** and **4** with extended conjugation. The formylation procedure was further extended to aza-BODIPY **5** and smoothly produced β-formylaza-BODIPY **6** in good yield.

Experimental Section

BODIPY 2a. A mixture of DMF (6 mL) and $POCl_3$ (6 mL) was stirred in an ice bath for 5 min under argon. After being warmed to room temperature, it was stirred for additional 30 min. To this reaction mixture was added **1a** (158 mg, 0.5 mmol) in dichloroethane (60 mL), the temperature was raised to 50 °C, and the mixture was stirred for an additional 2 h. The reaction mixture was cooled to room temperature and slowly poured into saturated aqueous $NaHCO_3$ (200 mL) under ice-cold conditions. After being warmed to room temperature, the reaction mixture was further stirred for 30 min and washed with water (2 × 150 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was further purified using column chromatography (silica gel, EtOAc/hexane = 1:4, v/v) to give BODIPY **2a** (157 mg, 89%) as a reddish-brown powder: mp > 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.53 (s, 3H), 7.29 (s, 2H), 6.15 (s, 1H), 2.83 (s, 3H), 2.62 (s, 3H), 1.65 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 161.7, 156.5, 147.4, 143.6, 142.9, 134.1, 129.6, 129.5, 127.7, 126.3, 124.1, 15.1, 14.9, 13.0, 11.6; ESI-MS 351.2 $[M - H]^-$, 374.4 $[M + Na]^+$. Anal. Calcd for $C_{20}H_{19}BF_2N_2O$: C, 68.21; H, 5.44; N, 7.95. Found: C, 68.34, H 5.51, N 7.12.

BODIPY 3. To a mixture of **2a** (130 mg, 0.4 mmol) and malononitrile (106 mg, 1.6 mmol) in toluene (20 mL) were added one drop of piperidine and a catalytic amount of HOAc under argon. The reaction mixture was stirred at refluxing conditions under argon for 10 h and then washed with water (2 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified using column chromatography (silica gel, DCM) to give BODIPY **3** (128 mg, 80%) as an orange powder: mp 213-216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.53−7.55 (m, 3H), 7.26−7.29 (m, 2H), 6.18 (s, 1H), 2.63 (s, 3H), 2.61 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 153.5, 152.6, 148.2, 142.8, 139.1, 134.5, 133.7, 130.9, 129.7, 127.6, 124.7, 123.0, 114.4, 113.2, 81.9, 15.2, 14.9, 14.3, 14.2; ESI-MS 399.2 $[M - H]^-$. Anal. Calcd for $C_{23}H_{19}BF_2N_4$: C, 69.02; H, 4.78; N, 14.00. Found: C, 68.89, H 4.68, N 14.21.

Aza-BODIPY 6. A mixture of DMF (3 mL) and $POCl_3$ (3 mL) was stirred in an ice bath for 5 min under argon. After being warmed to room temperature, it was stirred for an additional 30 min. To this reaction mixture was added BODIPY **5**[32] (90 mg, 0.18 mmol) in dichloroethane (6 mL); the mixture was raised to 70 °C and stirred for an additional 20 h. The mixture was then cooled to room temperature and slowly poured into saturated aqueous $NaHCO_3$ (200 mL) under ice-cold conditions. After being warmed to room temperature, the mixture was stirred for 1 h. The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was further purified using column chromatography (silica gel, hexane/CH_2Cl_2 = 3:2, v/v) to give BODIPY **6** (70 mg, 74%) as a dark blue greenish powder: mp > 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.99 (d, J = 7.4 Hz, 4H), 7.79 (d, J = 7.0 Hz, 2H), 7.66 (d, J = 4.2 Hz, 2 H), 7.44−7.33 (m, 12 H), 7.13 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 186.2, 166.3, 159.3, 148.8, 147.5, 143.2, 142.1, 132.7, 132.0, 130.9, 130.8, 130.7, 130.3, 130.21, 130.16, 129.8, 129.7, 129.6, 128.9, 128.8, 128.6, 128.0, 127.8, 126.1, 121.5; ESI-MS 526.2 $[M + H]^+$. Anal. Calcd for $C_{33}H_{22}BF_2N_3O$: C, 75.44; H, 4.22; N, 8.00. Found: C, 75.65, H, 4.18, N 8.24.

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Supporting Information Available: General experimental methods, experimental procedures, compound characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, crystallographic information files (CIFs) for compound **2c** and **3**, and UV−vis and fluorescence spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.