A versatile, modular synthesis of monofunctionalized BODIPY dyes†

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A careful choice of the pyrrole building blocks allows the synthesis of a wide range of monohalogenated BODIPY dyes with excellent reactivity in palladium catalyzed coupling reactions.

In recent years, there has been increasing interest in the use of fluorescent dyes, largely due to their potential applications in molecular recognition, as labels and probes in biotechnology, analytical chemistry, medical diagnostics, and materials science.[1] One of the most intensively studied and used fluorescent systems is 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene, better known as BODIPY.[2] Derivatives of this compound display many highly desirable properties, such as large molar absorption coefficients, good photostability and relatively high fluorescence quantum yields. Among the many applications are sensors for ions,[3] pH[4] and various optoelectronic devices.[5]

Recent work in our group is focused on the synthesis (Scheme 1) and reactivity of 3,5-dichloro-BODIPY **3**.[6] These particular compounds are readily substituted by several nucleophiles, allowing both mono and disubstitution by changing the reaction conditions. Further exploration of these reactive dyes showed that they can be used in palladium catalyzed cross-coupling reactions, such as Suzuki, Stille, Heck and Sonogashira reactions.[7] Combination of these reactions provides access to several highly interesting products from a single platform.[8]

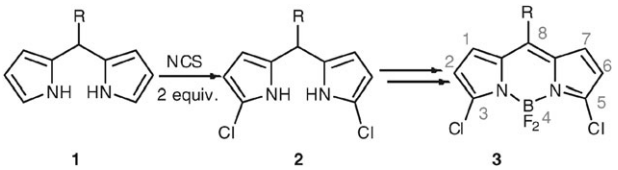
Drawbacks of the dichlorinated system are the need for disubstitution to avoid a reactive position remaining vacant and problems occurring during some palladium catalyzed coupling reactions. Notably in the Sonogashira reaction, the selectivity for monosubstitution is low and the resulting products are hard to isolate in pure form. Also, Suzuki reactions only proceed at an acceptable rate under microwave irradiation. We are convinced that part of these problems can be solved by the synthesis of monohalogenated BODIPY dyes. However, expanding the previously reported methods[6] to monohalogenation of the dipyrromethane precursors **1** resulted only in complex reaction mixtures.

Since the acid catalyzed condensation of an acylpyrrole and a second pyrrole is a well-known method for preparing dipyrromethenes,[9] the precursors of BODIPY, we reasoned that the synthesis of the desired products could be reduced to the preparation of 2-acyl-5-halopyrroles **5**.

Contrary to the well-known isomeric 2-acyl-4-halopyrroles **6**,[10] synthetic routes towards the compounds **5** are few. Although direct halogenation of acylpyrroles[11] may lead to derivatives **5**, this method has limitations. Due to the electron withdrawing nature of the acyl substituent, direct halogenation always produces a mixture of isomers. The amount of the desired isomer **5** varies with the reaction conditions, but it is never the sole product. Furthermore, it is often hard to separate the isomers chromatographically. After a review of the reported syntheses[11] and a laborious optimization study, we concluded that a general and selective method for the syntheses of derivatives **5** would not be easy to establish based on halogenation of 2-acylpyrroles.

Another option would be to halogenate pyrrole first, followed by acylation. The strong α-selectivity of pyrrole then ensures the correct regiochemistry.[12] However, 2-halogenated pyrrole **4** is notoriously unstable and decomposes violently upon isolation. This seriously reduces the scope of the literature procedure. It is only after several attempts that a one-pot procedure could be developed (Scheme 2). Careful temperature control proved crucial to ensure selective and complete halogenation prior to *in situ* acylation. Fortunately, both the Vilsmeier–Haack reaction and trifluoroacetylation proceed smoothly in THF, furnishing the targeted 5-halogenated acylpyrroles **5** on a large scale (up to 50 mmol) and with fair-to-good yields (33–64%).

Once a selective synthesis of monohalogenated pyrroles **5** was established, they were converted to the BODIPY dyes (Table 1). This was accomplished by adding one equivalent of phosphorus oxychloride to a mixture of acylpyrrole **5** and pyrrole **7**. The intermediate dipyrromethene was not isolated but was complexed *in situ* by adding excess triethylamine and boron trifluoride etherate to yield BODIPY dyes **8**. The BODIPY derivatives were then purified by column chromatography and were obtained in reasonable total yields. Since the 4-halogenated pyrroles **6** were available from our optimization study, they were also subjected to this condensation. Similar 2-halogenated BODIPY dyes have been prepared before, both



Scheme 1 Synthesis of 3,5-dichloro-BODIPY from dipyrromethane precursors.

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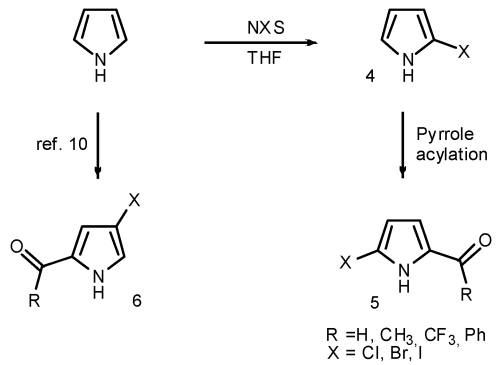
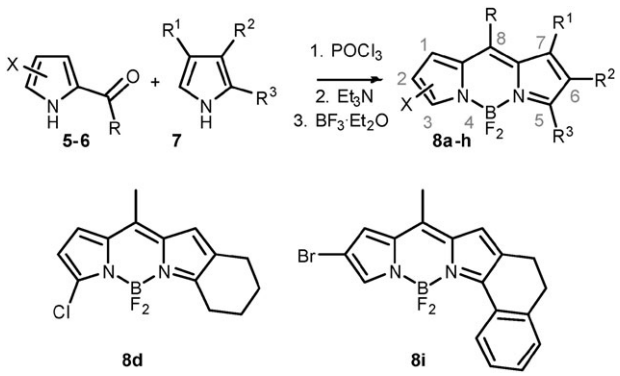


Scheme 2 Selective synthesis of halogenated acylpyrroles.

Table 1 Condensation of halogenated pyrroles to the corresponding BODIPY dyes



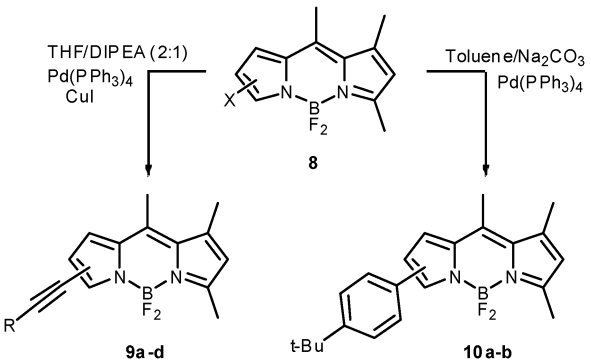
X(position)	R	R^1	R^2	R^3	Yield[a] (%)	Product
Cl (3)	H	CH_3	H	CH_3	90	**8a**
Cl (3)	CH_3	CH_3	H	CH_3	72[b]	**8b**
Cl (3)	CH_3	H	H	Ph	36	**8c**
Cl (3)	CH_3	H	Cyclohexyl		31	**8d**
Cl (3)	Ph	CH_3	H	CH_3	43	**8e**
Br (3)	CH_3	CH_3	H	CH_3	62	**8f**
Cl (2)	CH_3	CH_3	H	CH_3	36	**8g**
Br (2)	CH_3	CH_3	H	CH_3	57	**8h**
Br (2)	CH_3	H	DHBI[c]		59	**8i**
I (2)	CH_3	H	H	Ph	25	**8j**
I (2)	CH_3	CH_3	H	CH_3	40	**8k**

[a] Non-optimized yields for a single 0.5 mmol experiment. [b] Non-optimized yield for a single 5 mmol experiment. [c] DHBI stands for 4,5-dihydro-1*H*-benzo[*g*]indole.

by a condensation approach and halogenation of BODIPY,[13] but they always had multiple other substituents to ensure selective halogenation. In our modular approach one can choose between several widely available pyrroles as the second moiety of the target BODIPY and this selection will significantly affect the properties of the resulting dye. For example, replacing the commercially available 3,5-dimethylpyrrole with the conformationally restricted 4,5-dihydro-1*H*-benzo[*g*]indole results in dye **8i** with red-shifted spectra. Moreover, selection of the halogen allows tuning of the reactivity of the resulting BODIPY.

Finally, the *meso*-substituent of the BODIPY results from standard pyrrole acylation chemistry, most notably the Vilsmeier–Haack reaction. This reaction generally gives high

Table 2 Reactivity of the obtained dyes in palladium catalyzed coupling reactions



Reaction Type	X (position)	R	Yield (%)	Product
	Cl (3)	Ph	46	**9a**
	Br (3)	Ph	74	**9a**
Sonogashira	Br (2)	Ph	64	**9b**
	I (2)	Ph	75	**9b**
	Cl (3)	TMS	59	**9c**
	I (2)	TMS	81	**9d**
	Cl (3)	—	93	**10a**
Suzuki	Br (3)	—	86	**10a**
	I (2)	—	79	**10b**

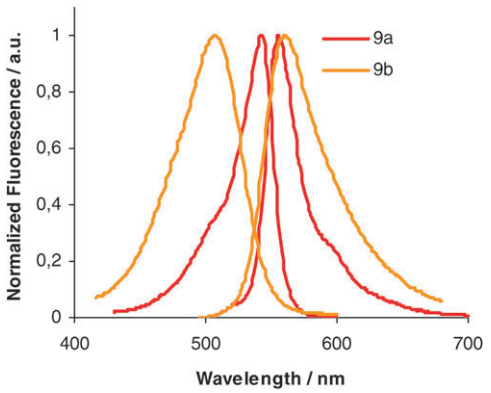
yields and is well established for pyrrole,[14] allowing for a large number of substituents to be introduced.

After successful synthesis of the desired monohalogenated dyes, they were subjected to palladium catalyzed reactions (Table 2). Indeed, both the 2- and 3-halogenated products react with acetylenes under standard Sonogashira conditions. Reaction of the 2-chlorinated dyes resulted in very low yields, even under forcing conditions. The 2-brominated compounds reacted in high yield, while the 2-iodinated molecules reacted even at room temperature. All 3-halogenated dyes were reactive in the Sonogashira reaction. The substituents on the second pyrrole moiety decrease the reactivity of the halogen, and the reaction is slower than observed for the dichloro-BODIPY **3**, but this could be circumvented by adapting our reported procedure.[7] Favorably, the Suzuki reaction proceeded under conventional heating, relieving the need for microwave irradiation. As expected, the reactivity increased when changing from chlorine to bromine and iodine, with excellent yields obtained in all cases.

As the Suzuki and Sonogashira coupling reactions lead to excellent probes, and are of great synthetic importance for the application of halogenated BODIPY dyes, these compounds could be a solution to the aforementioned problematic reactivity of the dichlorinated BODIPY dyes **3**.

Although all the resulting dyes are strongly fluorescent, one can see striking differences between the 2- and 3-substituted dyes (Table 3). The 3-alkynated dyes **9a** and **9c** show very high fluorescence quantum yields Φ_f, which decrease slightly upon increasing solvent polarity. Conversely, the corresponding 2-alkynated dyes **9b** and **9d** have lower Φ_f which decrease significantly with increasing solvent polarity, especially in acetonitrile. Moreover, the absorption maxima of the 3-alkynyl substituted dyes **9a** and **9c** are red shifted compared with those

Table 3 Absorption and emission profiles of **9a** (red) and **9b** (orange) in toluene spectroscopic data (absorption maxima λ_{abs}, emission maxima λ_{em}, Stokes shift $\Delta\bar{\nu}$) and fluorescence quantum yield (Φ_f) of selected substituted compounds in different solvents



BODIPY	Solvent	λ_{abs}/nm	λ_{em}/nm	$\Delta\bar{\nu}$/cm^{-1}	Φ_f
9a	Toluene	542	556	465	0.93
	THF	535	551	543	0.93
	MeOH	530	548	620	0.85
	MeCN	525	545	699	0.77
9b	Toluene	521	561	1369	0.61
	THF	513	569	1918	0.50
	MeOH	507	566	2056	0.37
	MeCN	503	566	2213	0.25
9c	Toluene	524	535	392	0.92
	THF	518	530	437	0.93
	MeOH	515	526	406	0.93
	MeCN	512	525	484	0.80
9d	Toluene	516	536	723	0.85
	THF	507	540	1205	0.78
	MeOH	502	533	1159	0.74
	MeCN	498	533	1319	0.55
10a	Toluene	527	553	892	0.83
	THF	522	549	942	0.86
	MeOH	517	545	994	0.79
	MeCN	513	543	1077	0.85
8i	Toluene	567	583	484	0.87
	THF	560	577	526	0.74
	MeOH	556	574	564	0.79
	MeCN	556	574	564	0.58

of the respective 2-alkynyl isomers **9b** and **9d**. In contrast, in solvents of intermediate and high polarity, the emission maxima of **9a** and **9c** are blue-shifted in comparison with those of **9b** and **9d**, respectively, resulting in small Stokes shifts for the 3-alkynyl isomers **9a** and **9c**.

Compound **10a** has relatively high Φ_f values, which are much higher than those reported for 3,5-diphenyl and 3-chloro-5-phenyl substituted BODIPY dyes.[11] The methyl group at the 5-position apparently has a significant fluorescence enhancement effect.

As an example of the versatility of our approach, one can see that the conformationally restricted dye **8i** has strongly red-shifted absorbance and fluorescence emission maxima, even without the presence of an alkynyl substituent. It is also noticeable that Φ_f of **8i** remains high, even though bromination at the 2-position has been used in the literature to induce triplet state formation for photodynamic therapy.[15] This example thus shows that a correct choice of the starting pyrroles can have a profound effect on the properties of the resulting products.

In conclusion, through an easy and selective synthesis of halogenated acylpyrroles, we have been able to prepare several new reactive BODIPY dyes in good total yields. These dyes show a range of tunable properties making the possibilities of this approach numerous. We are currently performing a detailed study of the reactivity of these halogenated dyes as well as a full spectroscopic/photophysical characterization. The results hereof will be reported in due course.

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