Direct functionalization of BODIPY dyes by oxidative nucleophilic hydrogen substitution at the 3- or 3,5-positions†

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BODIPY dyes are shown to be susceptible to oxidative nucleophilic substitution of the α-hydrogens, incorporating nitrogen and carbon nucleophiles in a single, high yielding step. The reaction is an excellent alternative to conventional functionalization of this popular fluorophore.

The recent interest in direct functionalization rather than by functional group interconversion has opened up a rapidly expanding field of chemistry.[1] Several approaches have been developed to introduce functional groups, especially on aromatic systems and through transition metal catalysis.[2] As these methods alleviate the need for tedious introduction of substituents and greatly improve synthetic power, this approach will become increasingly important.

Application of such procedures to the popular boron dipyrromethene (BODIPY) fluorophores[3] is limited to palladium and iridium catalyzed double bond introduction at the 2,6-positions.[4] Up to now, no selective direct substitution of hydrogen at the spectroscopically interesting 3,5-positions has been reported. For derivatization of BODIPY dyes at these positions, chlorinated derivatives have recently been shown to be highly versatile.[5] The ease of introduction of nucleophiles *via* nucleophilic aromatic substitution (S_NAr) has been exploited in the synthesis, and subsequent functionalization, of several halogenated BODIPY dyes.[6]

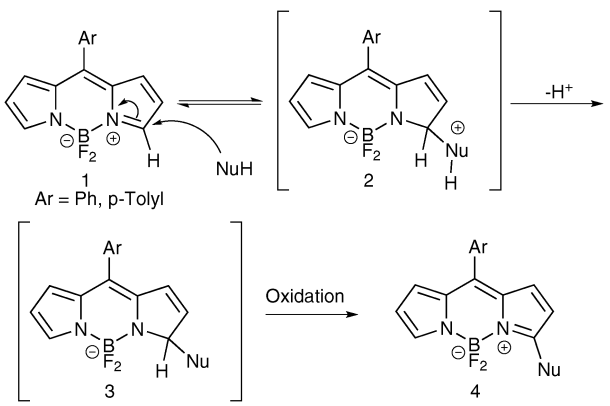
In contrast with S_NAr, the oxidative nucleophilic substitution of hydrogen (ONSH) is less well-known.[7] Generally, electron poor aromatic systems are susceptible to equilibrated nucleophilic attack at activated positions, forming a σ_H-adduct. Hydride does not act as a leaving group from this adduct, but an oxidation step is needed to re-establish aromaticity. We reasoned that the electron poor 3,5-positions of BODIPY dyes **1** could undergo this ONSH at the electron poor 3-carbon (Scheme 1). The resulting negative charge on the σ_H-adduct **2** would be stabilized by the boron complex, and oxidation of this intermediate could result in the substitution product.

Much to our delight we observed a reaction upon stirring a *meso*-phenyl model BODIPY **1**, in butylamine as the solvent, under air. The yield was rather low, and from an optimization of the reaction procedure (ESI†), it was clear that the reaction proceeded preferably in polar solvents. As for the oxidizing agent, DDQ, CAN, or permanganate were able to effect the reaction, but superior yields were obtained under oxygen atmosphere in DMF.

Aliphatic amine nucleophiles where highly reactive under the given conditions, and both primary (Table 1, entries 1–3) and secondary (entry 4) amines readily participated in the ONSH reactions. Due to the strong deactivation of the BODIPY dye by the amine substituent, no disubstituted product was formed. Aniline (entry 5) failed to substitute the model compounds under the given conditions, and this was presumably because of its lowered nucleophilicity.

Carbon nucleophiles showed excellent reactivity. Indeed, malonate addition resulted in the substituted ester **4e–f** in good yield (entries 6 and 7), and this under mildly basic conditions. By increasing the amount of malonate and the reaction time, the reaction goes to disubstituted **4g** in excellent yield (entry 8). Attesting to the generality of the reaction was the rapid and clean incorporation of nucleophiles such as enolates of ketones **4h** and esters **4i** (entries 9 and 10). All the substitutions proceeded at room temperature, both for amine and carbon nucleophiles. Heating only led to decreased yields.

Conversely, oxygen and sulfur centred nucleophiles did not lead to the formation of products. In the case of oxygen nucleophiles, butanoxide or phenoxide (entries 11 and 12), formation of substitution products could not be observed. Substitution with sulfur nucleophiles, such as butanethiol or thiophenol (entries 13 and 14), was very slow and resulted in inseparable mixtures of mono and disubstituted products. Prolonged reaction periods with excess of sulfur nucleophiles



Scheme 1 Direct oxidative substitution on a BODIPY dye.

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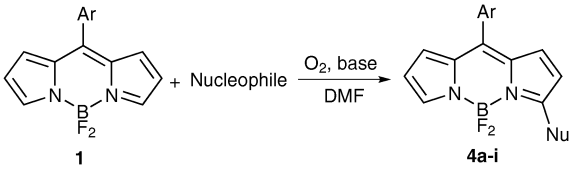
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data for the substrates and product. See DOI: 10.1039/c0cc00568a

Table 1 Condensation of halogenated pyrroles to the corresponding BODIPY dyes



Entry	Nucleophile	Base[a]	Reaction time	Product	Yield[b] (%)
1	$BuNH_2$	—	16 h	4a	65
2	$DodecylNH_2$	—	16 h	4b	75
3	$BnNH_2$	—	16 h	4c	85
4	Piperidine	—	16 h	4d	68
5	Aniline	—	7 days	—	—
6	$(MeOOC)_2CH_2$	K_2CO_3	20 h	4e	70
7	$(tBuOOC)_2CH_2$	K_2CO_3	36 h	4f	72
8	$(tBuOOC)_2CH_2$[c]	K_2CO_3	20 h	4g	80
9	$PhCOCH_3$	KOtBu	6 h	4h	59
10	$EtOOCCH_2Ph$	KHMDS	6 h	4i	63
11	BuOH	NaH	6 days	—	—
12	PhOH	K_2CO_3	6 days	—	—
13	BuSH	K_2CO_3	6 days	—	~10[d]
14	PhSH	K_2CO_3	6 days	—	~10[d]

[a] For amines, a second equivalent of amine is added. [b] Isolated yields for reactions at 0.5 mmol scale. [c] Product of double substitution, at both the 3- and 5-position. [d] No pure compound could be obtained.

only led to disappearance of the thiol *via* oxidative disulfide formation.

This low reactivity can be rationalized *via* the nucleophilic addition equilibrium (Scheme 1). In the case of thiolate and alkoxide, the σ_H-adduct **2** does not exist long enough to be efficiently oxidized. In the case of amine nucleophiles, removal of the proton from the σ_H-adduct **2** produces a stable intermediate **3** that can only decompose by releasing a poor amide leaving group, and thus the equilibrium is pushed towards the oxidation product. Similar considerations can be made for the carbon nucleophile adducts.

For carbon nucleophiles, products formed are present in the reaction mixture as their corresponding stabilized enolates, and a strong color change from purple to orange can be observed upon acidification of the mixtures after completion of the reaction.

The existence of such an enolate **5** was proven by an NMR study of dye **4h**. Under neutral, apolar conditions, this compound is present as the keto form. But, upon addition of a base, the concomitant color switch could be related to a disappearance of the carbonyl function and the appearance of a new double bond in **5** (ESI†). The process is fully reversible, and after addition of acid, the keto form **4h** was again the sole product.

This equilibrium can also be visualized by the solvent dependency of the absorption (Fig. 1). In an apolar solvent, like toluene or dichloromethane, the compound displays typical BODIPY absorbance around 510 nm. However, upon increasing the polarity of the solvent, a dramatic red shift takes place, giving an exceptionally large bathochromic shift of up to 100 nm in methanol. An intermediate situation can be observed for THF, where most of the compound is in the keto form, with a shoulder of the enol form around 570 nm. Also in methanol, a small portion of keto form can still be observed. Similar to the NMR-experiments, the gradual addition of base to the compound in THF induces a shift to the enol form. All compounds have rather low quantum yields (ESI†), attributed to free rotation of the *meso*-aryl substituent. The general photophysical studies of nitrogen and carbon substituted BODIPY dyes have been reported previously.[8]

In conclusion, α-unsubstituted BODIPY fluorophores are shown to be highly reactive towards the oxidative nucleophilic substitution of the α-hydrogen, introducing functionality in a single step. The novel method is an excellent alternative to the previously reported halogenated systems, and conveniently uses cheap and widely available chemicals. α-Unsubstituted BODIPY dyes, the starting products for these reactions, can be easily prepared in large amounts through acid catalyzed

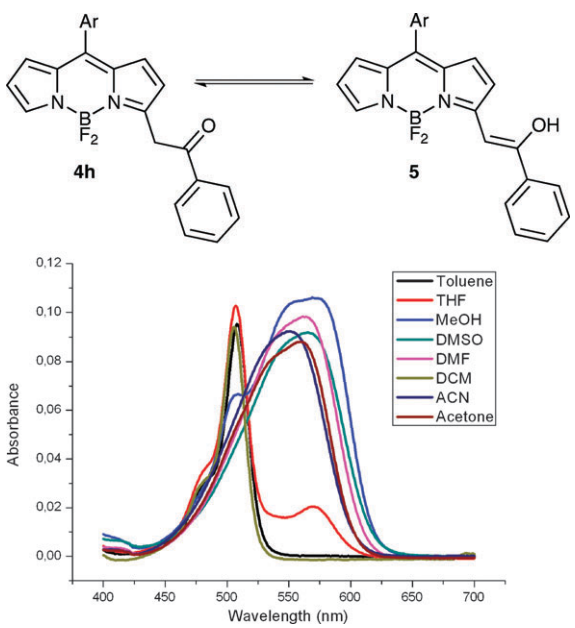


Fig. 1 Solvent polarity dependence of the acetophenone product.

condensation of aromatic aldehydes with pyrrole and subsequent oxidation and complexation.[9] We are currently determining the full scope of the reactions.

Notes and references

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