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Vicarious Nucleophilic Substitution of α-Hydrogen of BODIPY and Its Extension to Direct Ethenylation

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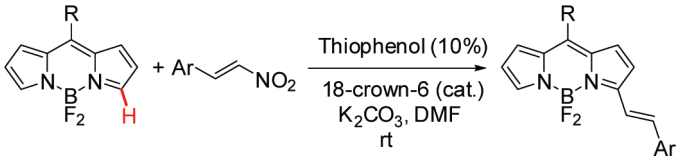
ABSTRACT

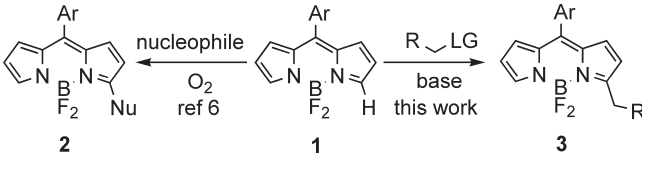


Direct, oxidizer-free substitution of the 3-hydrogen of BODIPY derivatives has been established through a vicarious nucleophilic substitution procedure. This methodology has been combined with a reversible Michael addition on nitrostyrenes to provide a novel, highly efficient entry to the valuable 3-styrylated BODIPY dyes.

In recent years, the BODIPY (*bo*ron *dipy*rromethene or boradiazaindacene) class of fluorophores has emerged as an exceedingly versatile and popular category of fluorescent dyes.[1,2] Their outstanding properties, such as excellent stability, high fluorescence quantum yields, large molar absorption coefficients, and narrow absorption and emission bands located in the visible wavelength range have led to an impressive increase in research on these dyes. However, perhaps most advantageous to the promotion of these fluorophores has been the enormous synthetic potential. The chemical robustness of BODIPY combines with a rich chemistry to allow the development of new fluorescent probes and fluorescent devices.[3]

In our contributions to this research, we have focused on halogenated BODIPY scaffolds that are amenable to fast and diverse substitution to permit rapid construction of complex fluorophores.[4] As such, the synthesis of several 3,5-dihalogenated systems has led to the preparation of new probes for biological applications, fluorescent sensors, and fluorescent polymers.[5]

Recently, we extended this reactivity to oxidative nucleophilic substitution (ONSH) of the 3,5-hydrogens of α-unsubstituted BODIPY derivatives **1**.[6] This methodology allows the direct introduction of nitrogen and carbon centered substituents, easily yielding multigram amounts of functionalized dyes **2** from commercial starting materials. While this reaction proceeds according to an ONSH mechanism, and hence needs an external oxidizer, a second option is available to effect a similar substitution affording compounds **3**.[7] This second reaction type, vicarious nucleophilic substitution (VNS) of hydrogen, can take place if the nucleophile carries a leaving group (LG).



(1) Treibs, A.; Kreuzer, F.-H. *Liebigs Ann. Chem.* **1968**, *718*, 208–223.
(2) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891–4932.
(3) Ulrich, G.; Ziessel, R.; Harriman, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1184–1201.
(4) (a) Rohand, T.; Baruah, M.; Qin, W.; Boens, N.; Dehaen, W. *Chem. Commun.* **2006**, 266–268. (b) Rohand, T.; Qin, W.; Boens, N.; Dehaen, W. *Eur. J. Org. Chem.* **2006**, 4658–4663. (c) Leen, V.; Braeken, E.; Luckermans, K.; Jackers, C.; Van der Auweraer, M.; Boens, N.; Dehaen, W. *Chem. Commun.* **2009**, *30*, 4515–4517.
(5) (a) Dilek, O.; Bane, S. *Tetrahedron Lett.* **2008**, *49*, 1413–1416. (b) Li, L.; Nguyen, B.; Burgess, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3112–3116. (c) Yin, S.; Leen, V.; Van Snick, S.; Boens, N.; Dehaen, W. *Chem. Commun.* **2010**, *46*, 6329–6331. (d) Yin, S.; Leen, V.; Jackers, C.; Van der Auweraer, M.; Smet, M.; Boens, N.; Dehaen, W. *Dyes Pigm.* **2011**, *88*, 372–377.
(6) Leen, V.; Zaragozí Gonzalvo, V.; Deborggraeve, W. M.; Boens, N.; Dehaen, W. *Chem. Commun.* **2010**, *46*, 4908–4910.
(7) Mąkosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631–2666.

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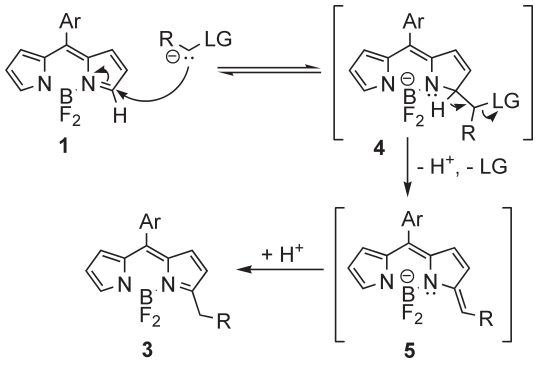
Scheme 1. Mechanism of the VNS of the 3-Hydrogen of a BODIPY Dye



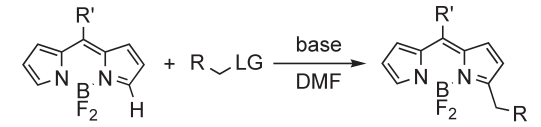
As demonstrated previously, nucleophiles rapidly attack α-unsubstituted BODIPY dyes at the 3-carbon, forming σ_H-adducts, but due to the reversibility of this addition, there is no net conversion unless oxidation can take place.[6] Conversely, in the vicarious hydrogen substitution mechanism, outlined in Scheme 1, the placement of a leaving group on the nucleophile favors a base-mediated elimination/rearomatization from intermediate **4** to the substitution product **3**.

From the initial VNS reactions, it became clear that a sufficiently strong base could affect the elimination, and optimized procedures were rapidly reached. The VNS of hydrogen allows introduction of several carbon nucleophiles in good yield, and as such BODIPY dyes substituted with acetate esters (**3a** and **3b**), malonate ester (**3e**), and ketones (**3c** and **3d**) were prepared in a single step (Table 1). The leaving group can be varied, and even thioethers derived from thiophenol and 2-mercaptobenzothiazole act as leaving groups. Often, the reactions are particularly fast, and after only a few minutes of stirring the mixture in DMF with base, all the starting material is consumed to yield the substituted products **3**.

As an illustration of the generality of the method, VNS of hydrogen with a phenacyl nucleophile was also applied to BODIPY dyes with a phenyl or thiomethyl group at the *meso* position (**3f** and **3g**). The latter is of particular interest as palladium catalyzed substitution of the reactive thioether handle has been shown to be a powerful method for further elaboration.[8]

While examining the scope of the reaction we realized that the addition of nitronate nucleophiles could provide an entry to the prevalent styrylated BODIPY fluorophores. Such styrylated BODIPY dyes can be prepared from adequately substituted pyrroles, but this linear synthesis had only limited synthetic applications.[9] Other routes to these interesting long-wavelength absorbing dyes are transition metal catalyzed

Table 1. Direct VNS of the 3-Hydrogen of BODIPY



R' = 2,6-dichlorophenyl, phenyl or -SCH_3

product	LG[a]	R	base	time[b]	yield [%][c]
3a	Br	COOMe	KO*t*Bu	30 min	56
3a	Br	COOMe	DBU[d]	1 h	67
3b	Br	COO*t*Bu	KO*t*Bu	30 min	54
3a	Cl	COOMe	KO*t*Bu	1 h	43
3b	SPh	COO*t*Bu	DBU[d]	14 h	55
3b	Mbzt[e]	COO*t*Bu	DBU[d]	15 min	69
3c	Br	COMe	DBU[d]	14 h	42
3d	Br	COPh	DBU[d]	15 min	65
3d	Br	COPh	K_2CO_3	14 h	63
3e	[f]	[f]	DBU[d]	15 min	74
3f[g]	Br	COPh	DBU[d]	15 min	65
3g[h]	Br	COPh	DBU[d]	15 min	65

[a] LG = leaving group. [b] Reaction time at room temperature. [c] Yields are isolated yields for a single reaction at 0.2 mmol of **1** scale. [d] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [e] Mbzt = 2-Mercaptobenzothiazole. [f] 2-Bromodiethyl malonate, EtOOCCH(Br)COOEt, was used as the leaving group carrying the nucleophile. [g] R′ = Phenyl. [h] R′ = *S*-Thiomethyl.

cross-coupling reactions on halogenated[4b] and borylated BODIPY dyes,[10] but the direct condensation of activated methyl substituents with aromatic aldehydes in a Knoevenagel type reaction is by far the most used.[11] Products prepared in this fashion have found use as chemosensors, sensitizers for solar cells, and novel fluorescent materials.[12]

Despite this widespread use, the relatively harsh conditions generally used for the Knoevenagel type reaction, i.e., reflux in toluene with buffered acetic acid or base, often lead to lowered yields. Conversely, the synthesis of styrylated pyrroles as starting materials for the corresponding BODIPY dyes requires several steps.[13]

In search of a solution to this problem, it was reasoned that a reversible nucleophilic Michael type addition to nitrostyrene should form a stabilized nitronate anion **7** (Scheme 2). Reminiscent of the Baylis−Hillman reaction,[14] this anion could then attack the BODIPY dye at the 3-carbon, to yield σ_H-adduct **8**. Completing the VNS of hydrogen, nitrous acid is eliminated from this σ_H-adduct under the influence of a base. The resulting intermediate **9** subsequently eliminates the nucleophile, and from

(8) Peña-Cabrera, E; Aguilar-Aguilar, A.; Gonzalez-Dominguez, M.; Lager, E.; Zamudio-Vazquez, R.; Godoy-Vargas, J.; Villanueva-Garcia, F. *Org. Lett.* **2007**, *9*, 3985–3988.

(9) Kang, H.; Haugland, R. P. Ethenyl-substituted dipyrromethene-boron difluoride dyes, US 5187288 A, 1993.

(10) Chen, J.; Mizumura, M.; Shinokubo, H.; Osuka, A. *Chem.—Eur. J.* **2009**, *15*, 5942–5949.

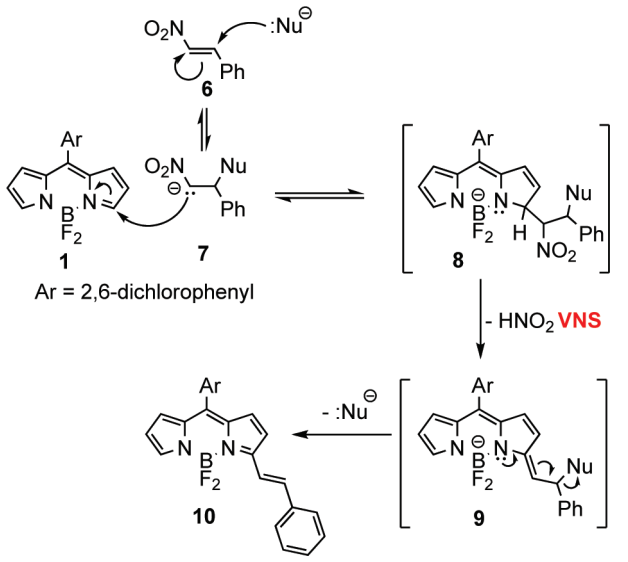
(11) (a) Rurack, K.; Kollmannsberger, M.; Daub, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 385–387. (b) Atilgan, S.; Ozdemir, T.; Akkaya, E. U. *Org. Lett.* **2008**, *10*, 4065–4067.

(12) Rousseau, T.; Cravin, A.; Bura, T.; Ulrich, G.; Ziessel, R.; Roncali, J. *Chem. Commun.* **2009**, 1673–1675.

(13) (a) Smith, J. R.; Campbell, S. A.; Ratcliffe, N. M.; Dunleavy, M. *Synth. Met.* **1994**, *63*, 233–243. (b) Smith, J. R.; Ratcliffe, N. M.; Campbell, S. A. *Synth. Met.* **1995**, *73*, 171–182.

(14) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147–150.

Scheme 2. Proposed Mechanism for a Tandem Reversible Michael Addition/VNS of Hydrogen with Nitrostyrene at the 3-Position of BODIPY, Resulting in the 3-Styrylated Product



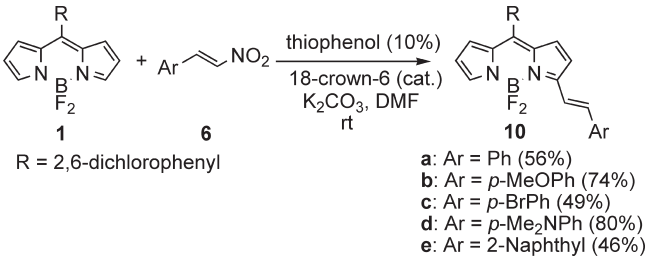
rearomatization through retro-Michael addition, the styrylated product **10** arises. Fortunately, the nitrostyrene starting materials are readily available as crystalline and stable solids from the Henry reaction between nitromethane and aromatic aldehydes.[15]

Much to our delight, initial tests of this new reaction showed fast formation of the desired product under a wide range of conditions. For example, diazabicyclooctene (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triphenylphosphine, *N*,*N*-dimethylpyridine (DMAP), and thiol (thiophenol and butane-1-thiol) all acted as activating nucleophilic organocatalysts in the equilibrated Michael addition. This range of nucleophiles could be combined with several bases such as triethylamine, DBU, 1,8-bis-(dimethylamino)naphthalene (proton sponge), and (sodium, potassium and cesium) carbonates to provide the styrene in various degrees of conversion. However, in all of these cases, the reaction failed to reach completion, and this is presumably due to autocondensation of nitrostyrenes as a competing pathway. When applying fluoride as a base, in the form of tetrabutylammonium fluoride in tetrahydrofuran solution, the reaction proceeded to completion in mere minutes, and the products were isolated in yields ranging from 14 to 60%. Nonetheless, eradication of trace impurities was difficult and time-consuming.

Optimized conditions were finally reached when it was observed that potassium carbonate, combined with a catalytic amount of 18-crown-6 and thiophenol in DMF, rapidly leads to the target products in excellent yields (Scheme 3). Other potassium containing bases, such as K_3PO_4 and KF, could also be combined with 18-crown-6 leading to improved yields in individual cases (**10c**).

(15) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.

Scheme 3. Results of the Reversible Michael Addition on Nitrostyrenes in Tandem with VNS of 3-Hydrogen



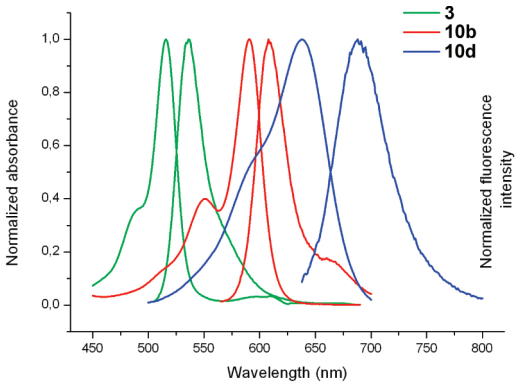


Figure 1. Normalized absorption and fluorescence emission profiles of **1**, **10b**, and **10d** in toluene.

Like the VNS itself, the tandem reaction has a particular selectivity for monosubstitution, and in most cases, the disubstituted product was only observed in trace amounts. All attempts to push the reaction to disubstitution failed, and this is presumably due to a lowered tendency to form the σ_H-adduct after the first hydrogen substitution.

The products **3a** and **3b** with acetate substituents obtained via the classic VNS have absorption and emission maxima comparable to those of the starting compound **1** (Figure 1). The enol tautomer of BODIPY derivative **3d** is prevalent in methanol solution whereas the phenyl ketone is the prevailing form in the aprotic solvents acetonitrile, toluene, and THF. This keto−enol tautomerism has been reported for an analogous BODIPY derivative.[6] The keto−enol tautomerism is also observed in the absorption and emission spectra which show contrary to other BODIPY analogues a strong red shift from acetonitrile to methanol (two solvents of similar dielectric constant). In analogy to what was observed for other BODIPY compounds in which the conjugation is extended to the 3-position by an electron donor substituent,[16]

(16) (a) Qin, W.; Baruah, M.; Sliwa, M.; Van der Auweraer, M.; De Borggraeve, W. M.; Beljonne, D.; Van Averbeke, B.; Boens, N. *J. Phys. Chem. A* **2008**, *112*, 6104–6114. (b) Qin, W.; Leen, V.; Rohand, T.; Dehaen, W.; Dedecker, P.; Van der Auweraer, M.; Robeyns, K.; Van Meervelt, L.; Beljonne, D.; Van Averbeke, B.; Clifford, J. N.; Driesen, K.; Binnemans, K.; Boens, N. *J. Phys. Chem. A* **2009**, *113*, 439–447.

Table 2. Spectroscopic Data of Products from the Vicarious Substitution of Hydrogen and the Tandem Double Bond Formation

BODIPY	solvent	λ_{abs} [nm]	λ_{em} [nm]	$\Delta\bar{\nu}$ [cm^{-1}]	Φ_f
3a	CH_3OH	513	527	518	0.60
	CH_3CN	509	527	671	0.61
	THF	516	533	618	0.86
	Toluene	519	536	611	0.88
3d	CH_3OH	562	618	1612	0.04
	CH_3CN	514	528	516	0.34
	THF	518	534	578	0.61
	Toluene	521	538	606	0.87
10a	CH_3OH	568	580	364	1.00
	CH_3CN	567	581	425	1.00
	THF	572	585	389	1.00
	Toluene	577	591	411	1.00
10b	CH_3OH	580	603	658	0.74
	CH_3CN	580	605	712	0.81
	THF	585	604	538	0.99
	Toluene	590	608	502	1.00
10c	CH_3OH	570	585	445	0.36
	CH_3CN	570	585	445	0.40
	THF	576	589	388	0.46
	Toluene	580	595	421	0.42
10d	CH_3OH	626	783	3205	0.009
	CH_3CN	631	831	3824	0.004
	THF	631	747	2476	0.17
	Toluene	638	695	1276	0.90
	CH_3CN+H^+	566	581	456	0.90

this red shift can be attributed to the extended conjugation of the BODIPY core with the electron-donating enol function.

It is well-known that the introduction of 3-styryl and 3,5-distyryl substituents in BODIPY produces very large bathochromic shifts of their absorption and fluorescence emission maxima.[17] These large styryl-induced red shifts have been crucial for the increase in use of such BODIPY dyes in sensors and novel materials. Indeed, while the unsubstituted starting BODIPY **1** displays strong green fluorescence, all of the 3-styryl substituted products **10** fluoresce at substantially longer wavelengths (Figure 1 and Table 2). As described previously, this bathochromic shift is accompanied by a high fluorescence quantum yield in **10a** and **10b**, while the reduced quantum yield for brominated product **10c** can be attributed to the heavy atom effect.

In the case of the *p*-*N*,*N*-dimethylanilino substituted product **10d**, the red shift of the emission spectrum compared to **1** extends over nearly 200 nm in apolar solvents to nearly 300 nm in polar solvents, caused by a contribution of the lone pair of the nitrogen into the conjugation. Furthermore, one should note also the strong decrease of the fluorescence quantum yield Φ_f of **10d** upon increasing the solvent polarity. Such a red shift and solvent dependence of Φ_f was also observed for other BODIPY analogues carrying a conjugated electron-donating substituent at the 3-position.[15,16] Protonation or quaternization reduces this effect, leading to a hypsochromic shift and a strong increase in fluorescence (Table 2, final entry), and this principle has been used extensively in the preparation of fluorescent chemosensors.[18]

In conclusion, the VNS of the α-hydrogen of BODIPYs is a facile method for the introduction of diverse carbon nucleophiles in a single step. This strategy has obvious applications in fluorescent labeling and the construction of fluorescent building blocks. Furthermore, we have extended the reactivity into a novel tandem double bond formation. The preliminary results of tandem VNS with reversibly activated nitronate anions indicate that 3-styrylated BODIPYs are easily accessible *via* this new synthetic methodology. In addition, the aforementioned procedure, which to the best of our knowledge has not been previously described, makes use of easily attainable starting materials. As several other (hetero)aromatics have been shown to be susceptible to VNS of hydrogen,[7] this method may find broad application there.

Presently we are applying this approach to the synthesis of novel fluorescent chemosensors with absorption and fluorescence spectra extending into the near-infrared region. The full scope of this promising reaction is currently under investigation.

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Supporting Information Available. Detailed experimental procedures, additional spectroscopic data and NMR spectra of all the synthesized BODIPY compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) (a) Qin, W.; Baruah, M.; De Borggraeve, W. M.; Boens, N. *J. Photochem. Photobiol. A: Chem.* **2006**, *183*, 190–197. (b) Yu, Y.-H.; Descalzo, A. B.; Shen, Z.; Rohr, H.; Liu, Q.; Wang, Y.-W.; Spieles, M.; Li, Y.-Z.; Rurack, K.; You, X.-Z. *Chem.—Asian J.* **2006**, *1*, 176–187.

(18) (a) Baruah, M.; Qin, W.; Flors, C.; Hofkens, J.; Vallée, R. A. L.; Beljonne, D.; Van der Auweraer, M.; De Borggraeve, W. M.; Boens, N. *J. Phys. Chem. A* **2006**, *110*, 5998–6009. (b) Ziessel, R.; Ulrich, G.; Harriman, A.; Alimary, M. A. H.; Stewart, B.; Retailleau, P. *Chem.—Eur. J.* **2009**, *15*, 1359–1369. (c) Deniz, E.; Isbasar, G. C.; Bozdemir, Ö. A.; Yildirim, L. T.; Siemiarczuk, A.; Akkaya, E. U. *Org. Lett.* **2008**, *10* (16), 3401–3403.