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8-Functionalization of Alkyl-Substituted-3,8-Dimethyl BODIPYs by Knoevenagel Condensation

Eduardo Palao,[†] Antonia R. Agarrabeitia,*[,†] Jorge Bañuelos-Prieto,[‡] Teresa Arbeloa Lopez,[‡] Iñigo Lopez-Arbeloa,[‡] Diego Armesto,[†] and Maria J. Ortiz*[,†]

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040 Madrid, Spain, and Departamento de Química Física, Universidad del País Vasco/EHU, Apartado 644, 48080 Bilbao, Spain

mjortiz@quim.ucm.es

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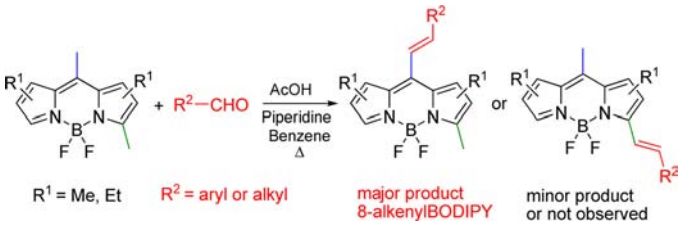
ABSTRACT



New 8-alkenylBODIPYs have been synthesized by Knoevenagel condensation between a series of alkyl-substituted-3,8-dimethylBODIPYs and aromatic or aliphatic aldehydes. This is in clear contrast with literature precedents, which indicate that this reaction occurs exclusively on the methyl group at C-3. The change in hybridization of the carbon at the 8-position (from sp^3 to sp^2) determines the fluorescence emission of the BODIPY, while the presence of electron-donating or -withdrawing groups leads to intramolecular charge transfer processes.

Among organic dyes, the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes, commonly known as BODIPYs, are a very interesting family of dyes with unique properties that have attracted increasing interest for their technological and/or biomedical applications,[1] as shown by more than 600 articles published in this area during the past year.

Many of their applications require derivatization of the *meso*-position to obtain new BODIPY dyes with interesting photophysical properties.

Various approaches have been described in the literature for the functionalization of the *meso*-position in BODIPYs. Thus, the synthesis of BODIPYs using suitably substituted pyrroles and aromatic aldehydes, or acid chlorides, allows the incorporation of different substituents at the 8-position, although this route has some limitations.[1]

Peña-Cabrera et al. have successfully prepared new 8-substituted BODIPY dyes, with emission from the blue to red spectral region, by nucleophilic aromatic substitution,[2] or by a direct Liebeskind–Srolg cross-coupling[3] with the boronic acid of 8-methylthioBODIPY.

Recently, Dehaen et al.[4] have described the versatile synthesis of new *meso*-functionalized BODIPYs by nucleophilic substitution of 8-halogenated BODIPYs by nitrogen, oxygen, or sulfur nucleophiles as well as transition metal-catalyzed cross-coupling reactions (Suzuki, Stille, and Sonogashira).

[†] Universidad Complutense.
[‡] Universidad del País vasco/EHU.

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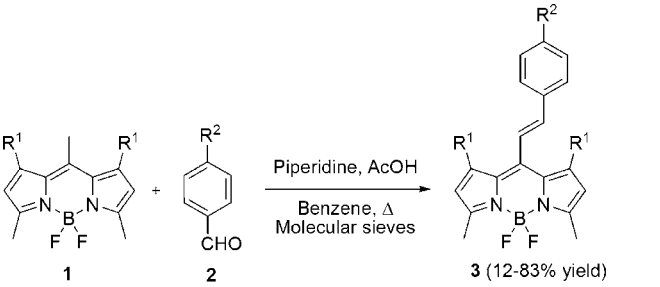
On the other hand, the Knoevenagel reaction using aromatic aldehydes is a facile and versatile route to effectively tune BODIPY dyes for near-infrared emission. According to literature precedents, this reaction takes place usually on the methyl groups in positions 3 and/or 5, yielding mono- and distyryl-BODIPYs.[1,5] The syntheses of 3,5,7-tristyryl- and 1,3,5,7-tetrastyryl-derivatives by this route have been also reported.[6] In all the cases studied of BODIPYs with an aryl group in the 8-position, the results show that the methyl groups in positions 3 and 5 are the most acidic.[5,6] Even in the case of the 1,3,5,7,8-pentamethylBODIPY, literature precedents show that the reaction takes place regioselectively at the C-3 and C-5 methyl groups.[7] As far as we are aware, there is only one report[8] of *meso*-styryl derivatives that were synthesized by regioselective Knoevenagel-type condensation of two commercially available BODIPYs (PM597 and PM567). This unusual reactivity was justified due to the presence of two methyl groups at positions 1 and 7, in addition to ethyl or *tert*-butyl groups at positions 2 and 6 of the BODIPY. Thus, the reaction at the *meso*-position could relieve the structural strain of these highly substituted BODIPYs, overriding the anticipated lower acidity of the *meso*-methyl protons.

Within the research done in our group, we were interested in carrying out the Knoevenagel condensation between BODIPY **1a** (PM546) and 4-acetamidobenzaldehyde (**2a**). Based on literature precedents the condensation product at the methyl group in position 3 was expected. However, contrary to these expectations, the 8-styryl derivative **3a** was obtained, exclusively (Scheme 1). No 3-styryl product was formed in this reaction. The structure of **3a** was confirmed by X-ray diffraction analysis (Figure S1).

The formation of **3a** cannot be justified by steric factors[8] due to the absence of alkyl groups at the 2- and 6-positions. Furthermore, this result implies that the methyl group at the 8-position of **1a** is the most acidic, in clear contrast with earlier observations in studies on the condensation of **1a** with other aldehydes that indicated that the corresponding 3-styryl derivative is always obtained.[7] Therefore,

Scheme 1. Knoevenagel Condensation of BODIPYs **1a** and **1b**



1: **1a**: R^1 = Me; **1b**: R^1 = H

2: **2a**: R^2 = NHCOMe; **2b**: R^2 = CN; **2c**: R^2 = NO_2; **2d**: R^2 = OMe; **2e**: R^2 = $N(Me)_2$

3 (12-83% yield): **3a**: R^1 = Me; R^2 = NHCOMe; **3b**: R^1 = Me; R^2 = CN; **3c**: R^1 = Me, R^2 = NO_2; **3d**[a]: R^1 = Me; R^2 = OMe; **3e**[a]: R^1 = Me; R^2 = $N(Me)_2$; **3f**: R^1 = H; R^2 = NHCOMe; **3g**: R^1 = H; R^2 = NO_2; **3h**: R^1 = H; R^2 = OMe; **3i**: R^1 = H; R^2 = $N(Me)_2$

[a]3-styryl derivative was also isolated (c.a. 10%)

this result was totally unexpected and prompted us to investigate the possible extension of this unusual regioselectivity to 8-methylBODIPYs **1a** and **1b** using different aromatic aldehydes (Scheme 1). BODIPY **1b** has been synthesized for the first time in this work.

Knoevenagel reaction of **1a** with aldehydes **2b** and **2c** in the presence of piperidine and AcOH, using benzene as solvent, afforded the 8-styryl derivatives **3b** (24%) and **3c** (23%), respectively, as the only products. These results are in clear contrast with literature precedents that suggest that the condensation only occurs on the methyl at C-3.

The Knoevenagel condensation of **1a** was extended to aldehydes **2d** and **2e**. Again in these instances, the corresponding 8-styryl products **3d** (25%) and **3e** (12%), respectively, were obtained as the major products, althought the 3-styryl analogues **4a** (11%) and **4b** (8%) were also formed in lower yields. This results is in clear contrast with literature precedents that indicated that **4a** and **4b** are the only products formed in these reactions.[7a,c] The main difference between our reaction conditions and those reported in the literature is the solvent used in the reactions. Therefore, in order to clarify this discrepancy, the reactions of **1a** with aldehydes **2d** and **2e** were reinvestigated under the same conditions described in the literature, using chlorobenzene and toluene as solvents, instead of benzene. Under these conditions, compounds **3d**, **3e**, **4a**, and **4b** are formed in the same percentage as in the herein reported study, demonstrating that the condensation takes place preferentially on the methyl group at C-8.

These results demonstrated that the 8-Knoevenagel reaction could be extended to BODIPYs unsubstituted at the 2- and 6-positions and suggests that other 8-methylBODIPYs with different substitution patterns could also undergo this reaction. Thus, 3,5,8-trimethylBODIPY **1b** was studied in order to determine whether this reaction could also occur with substrates without any steric hindrance around position 8. Thus, the condensation of **1b**

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with **2a**, **2c**, **2d**, and **2e** afforded the *meso*-styryl derivatives **3f**–**i**, respectively, in 43% to 83% yield. Compound **1b** proved to be more reactive than **1a** affording the corresponding *meso*-styryl derivatives after shorter reaction times and in higher yields than in the case of BODIPY **1a**. This is probably due to less steric hindrance for the attack at the methyl at position 8 in **1b** than in **1a**.

We extended the study to asymmetric BODIPY dyes **1c**[9] and **1d**. BODIPY **1d** has been synthesized for the first time in this work. The reaction of these compounds with the aldehyde **2a** produced the expected *meso*-styryl products **3j** and **3k**, exclusively, in 49% and 55% yields, respectively (Figure 1).

At this point, we were interested in checking the possibility of extending the 8-Knoevenagel reaction to aliphatic aldehydes. Thus, the reaction of BODIPY **1b** with isobutyraldehyde (**2f**) takes place smoothly at the *meso*-position yielding the corresponding condensation product **3l** in 71% yield (Figure 1). These additional examples add further support to the proposal that *meso*-methyl BODIPY dyes are more prone to undergo the 8-Knoevenagel reaction that the corresponding 3-methyl derivatives, contrary to previous reports.[7]

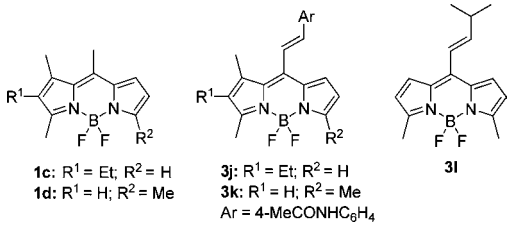

Figure 1. Structures of asymmetric BODIPYs **1c**–**d** and 8-alkenyl derivatives **3j**–**l**.

Such regioselectivity, especially in compound **1b**, can be understood by means of theoretical calculations. Other authors have justified the reactive sites to Knoevenagel reaction identifying the most acid protons by the charge distribution.[6a,8] We make use of the potential electrostatic maps as an intuitive way to localize the most susceptible methyls to undergo such a reaction. The results obtained in this study show that the positive charge density (blue color) is placed at the upper part of the molecule, in line with the dipole moment orientation (Figure 2).

Accordingly, the methyl group at 8-position should undergo the condensation reaction more readily than those at positions 3 and 5. Moreover, in compound **1b** the positive charge density is more concentrated around the 8-methyl than in compound **1a**, supporting the higher reactivity toward Knoevenagel condensation for the former compound observed experimentally.

At this point, it was considered necessary to obtain additional evidence on the higher acidity of the hydrogens

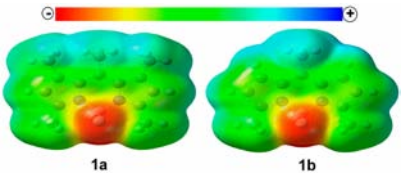

Figure 2. Electrostatic potential mapped onto the electronic density (b3lyp/6-31++g**) for compounds **1a** and **1b**.

on the methyl group in the 8 position. Thus, the reaction of **1a** in the presence of acetic acid-d_4 and piperidine-d_{11} was followed by NMR spectroscopy. The results obtained show that the hydrogens on the methyl group at C-8 are replaced by deuterium at a much faster rate than the hydrogens of the methyl groups at positions 3 and 5 (Supporting Information) clearly demonstrating that the hydrogens of the methyl group at C-8 are more acidic than those at positions 3 and 5.

Finally, 3,5,8-tristyryl BODIPYs can be easily synthesized by the strategy reported herein. Thus, condensation of **1a** with a large excess of aromatic aldehyde **2d** yields the corresponding 3,5,8-tristyryl dye **5a** (35%). Similarly, condensation of the 8-styryl derivative **3g** with isobutyraldehyde (**2f**) affords compound **5b** in 53% yield (Figure 3).

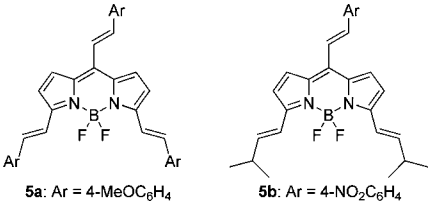

Figure 3. Structures of trialkenyl-BODIPYs **5a**–**b**.

The regioselectivity observed in this reaction allows an easy and direct synthetic route for the preparation of 8-alkenyl BODIPYs, of which only a few examples are reported in the literature.[3c,8,10] The new alkenyl BODIPYs derivatives are suitable substrates for subsequent functionalization.

Alkylated BODIPYs **1a**, **1b**, and **1d** show very high fluorescence emissions (approaching 100% in Table S1). The only exception is compound **1c** (ϕ = 0.70), where just one pyrrole ring is alkylated and the induced asymmetry in the charge distribution enhances the nonradiative pathways. The spectral band positions depend on the degree of alkylation and on the position in which they are attached to the BODIPY core (Table S1). The addition of a vinyl group at the 8 position (**3l**) leads to a bathochromic shift in terms of a resonant interaction. However, such electronic

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coupling drastically drops the fluorescence efficiency (from 1 to 0.12). This effect caused by the change of hybridization of the carbon at the *meso* position from sp^3 to sp^2 was related to a marked increase in the nonradiative deactivation pathways.[3c] Recently, it has been theoretically proposed that such relaxation is due to an increase of the vibrational motion out of plane of the pyrroles.[11] This structural flexibility enhances the internal conversion and is reflected in its high Stokes shift (1550 cm^{-1}).

Besides, the attachment of electron donor ($N(Me)_2$ $\sigma_p^+ = -1.711$, OMe −0.648 and NHCOMe −0.249) or electron acceptor (NO_2 $\sigma_p^+ = 0.740$ and CN 0.74) groups at the *para* position of the 8-styryl moiety leads to a considerable decrease in the fluorescence efficiency, due to the population of an intramolecular charge transfer (ICT) state. Indeed, the BODIPY moiety can behave as an electron donor or acceptor depending on the attached functionalization. In some compounds a broad and weak red band (assigned to the ICT emission) has been detected, following that from the locally excited state, which is drastically quenched (Figure 4). In the rest of the 8-styryl derivatives, the ICT is so favored that its fluorescence emission is negligible and almost no emission was detected.[12]

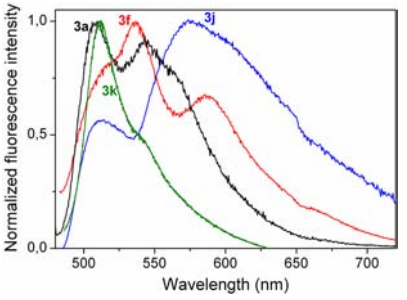

Figure 4. Fluorescence spectra of the 8-*p*-acetamidostyryl derivatives (**3a**, **3f**, **3j**, **3k**) in acetonitrile.

In the trialkenyl derivatives **5a** and **5b**, the spectral bands are significantly shifted toward the red part of the visible spectra (Table S1). Furthemore, the fluorescence efficiency is very low, due to the sp^2 hybridization of the carbon atom at position 8 and also to the ICT process from the methoxy or nitro groups, as stated above.

Electrochemical measurements of the reference compound **1b** reveal an irreversible oxidation at 1.377 V and a reversible reduction at −0.958 V (Figure 5). Further addition of vinyl (**3l**) brings the cathodic wave closer to the anodic reducing the energy gap. The presence of amino (**3i**) makes the compound easier to oxidize (0.893 V), while the presence of nitro groups (**3g** and **5b**) makes it easier to reduce (−0.549 V). These results confirm the electron donating and withdrawing ability of each moiety and support the presence of an ICT process (where the BODIPY core acts as an acceptor or donor respectively) as the main nonradiative pathway.

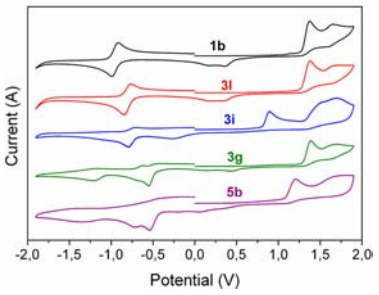

Figure 5. Cyclic voltammograms for 8-alkenyl derivatives of dye **1b**, bearing vinyl (**3l**), amine (**3i**), or nitro (**3g** and **5b**) groups, in acetonitrile.

In summary, previous studies have led to the conclusion that the Knoevenagel condensation in methyl-substituted BODIPYs takes place usually on the methyl groups in positions 3 and/or 5, yielding mono- and distyryl-BODIPYs. In contrast with these observations, the results of the current study show that alkyl-substituted-3,8-dimethyl BODIPYs undergo Knoevenagel condensation at the 8-position using aromatic and aliphatic aldehydes. These results allow an easy strategy for the *meso* functionalization of the BODIPY core using this condensation reaction. These results open the possibility of incorporating other functionalizations at the *meso*-position based on the acidity of the methyl groups at this position. Further work in this area is in progress.

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Supporting Information Available. Detailed experimental procedures, NMR spectra. Photophysical, electrochemical, X-ray crystal, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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