Preparation of Diverse BODIPY Diesters

Sewwandi Abeywardana, Annabelle L. Cantu, Teodora Nedic, Michael P. Schramm

PII: S0040-4039(18)30935-3
DOI: https://doi.org/10.1016/j.tetlet.2018.07.054
Reference: TETL 50163

To appear in: *Tetrahedron Letters*

Received Date: 25 May 2018
Accepted Date: 23 July 2018

Please cite this article as: Abeywardana, S., Cantu, A.L., Nedic, T., Schramm, M.P., Preparation of Diverse BODIPY Diesters, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.07.054

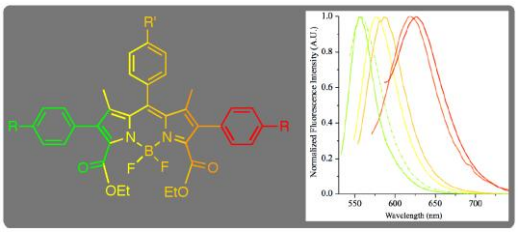
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Preparation of Diverse BODIPY Diesters

Sewwandi Abeywardana, Annabelle L. Cantu, Teodora Nedic and Michael P. Schramm

Leave this area blank for abstract info.



Tetrahedron Letters
journal homepage: www.elsevier.com

Preparation of Diverse BODIPY Diesters

Sewwandi Abeywardana, Annabelle L. Cantu, Teodora Nedic and Michael P. Schramm[a,]*

[a]*Department of Chemistry and Biochemistry, California State University Long Beach, 1250 Bellflower Blvd, Long Beach, CA, U.S.A.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Dipyrrolemethane
BODIPY
fluorophores
Fluorescence
combinatorial

ABSTRACT

The synthesis and properties of a variety of substituted BODIPY diesters is presented. We find that certain substitution patterns afford appreciable yields of the target compounds and that electronic effects result in predicable differential fluorescent behavior. Challenges to further water solubilize these dyes and/or provide new points of attachment for biological tagging remain, these strategies are discussed.

The synthesis of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (after referred to as BODIPY) dyes has a rich history with room for further exploration. Improvement to existing synthetic strategies as well as peripheral modification to provide means of attachment to biological molecules are a central focus to their further deployment towards pressing areas. BODIPY dyes have numerous favorable properties that make them suitable for biological applications.[1-2] They are small molecules that absorb light in the UV-visible range, their absorbance and emission peaks are relatively sharp and they have high molar extinction coefficients as well as typically high quantum yields of fluorescence.[3] BODIPY dyes are uncharged, relatively insensitive to solvent polarity and reasonably stable under physiological conditions.

To our knowledge BODIPY **2** was first reported in 1968 (Figure 1)[4] and reviews demonstrate its extensive study[5] including tuning from green to near-IR.[6] In general the dipyrrolemethane scaffold 1 provides a facile retrosynthetic target, subsequent oxidation and insertion of BF_2 completes the forward sequence. These final steps, however are not without peril. Advances continue despite synthetic challenges as this motif has potential as a near-infrared emitter **3**[7] as well as a selective chemical sensor compatible with cells **4**.[8] Most applicable to the work we present include BODIPYS with carboxy groups attached to the pyrrole components (e.g. **5**).[9-11]

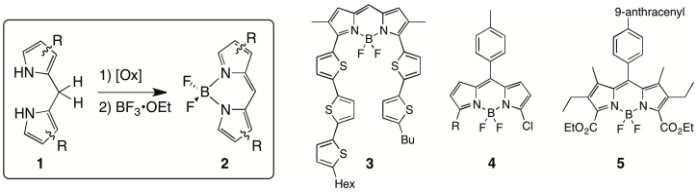


Figure 1: The dipyrrolemethane precursor 1 and BODIPY motif 2 and selected examples 3-5 (description of utility discussed in text).

Additionally, we are very interested in applications where BODIPYs are directly applied to biological problems. Several compelling examples exist that utilize some of the above mentioned features.[12-13] We previously published a report *en route* to BODIPYS as we developed a modular methodology of diverse dipyrrolemethane preparation.[14] Within this initial study we recognized that modular routes afforded critical modifications around the core that would ultimately allow for photochemical tuning should the dipyrrolemethanes be converted to BODIPY, some examples are shown (Figure 2). Of the three scaffolds shown, we produced several variations for each. The final condensation of 2 pyrrole molecules with an aldehyde was universal, but the syntheses of the pyrroles was different for each substitution pattern.

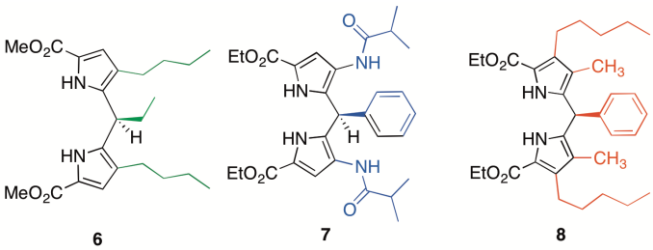


Figure 2: 3 variations on a theme, dipyrrolemethanes prepared from the condensation of pyrrole with aldehyde. For **6**, **7** and **8** however, the individual pyrrole building blocks required different routes.

Knowing that BODIPYS posses low toxicity, directed us towards conversion of these dipyrrolemethanes into functional BODIPYS, as we envisioned points of attachment allowing for the development of new probes for biological applications. The modular synthesis also provides options to improve water solubility. Currently, there are only a few BODIPY dyes commercially available to use as imaging probes and thus the development of new chemistry remains relevant to fully utilize these molecules.

Results and Discussion

We began our study with dipyrrolemethanes based on compounds **6** and **7** and their analogs. A variety of conditions were unsuccessful in converting these compounds into their BODIPY counterparts. Standard conditions for oxidation include DDQ or chloranil, conventional or microwave heating, stepwise isolation of dypprolemethenes or direct addition of BF_3. A vast screen of these reactions never gave promising results, even though starting material was consumed by TLC. We decided to examine the more heavily substituted scaffolds such as found in compound **8**. The fully substituted pyrrole components ultimately provided a course for development. We describe in detail exclusively the results with this scaffold.

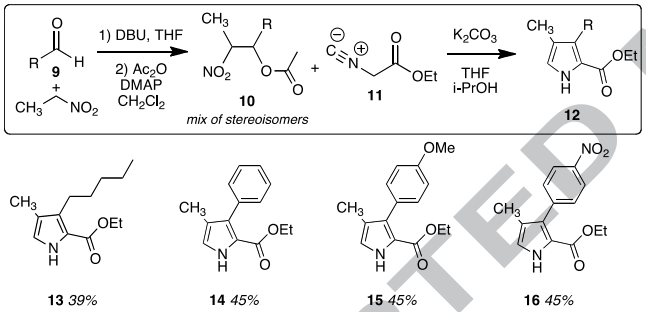


Figure 3: Preparation of tri-substituted pyrrole building blocks used in this study. Yields are reported for the overall process starting from a variety of aldehydes, production of 10 grams of compound via this route is straightforward.

We began by preparing tri-substituted pyrroles. Using a procedure[15] that we previously employed for the preparation of **13** and **14**,[14] we were able to vary the electronics of the pyrrole building block with the preparation of new p-methoxy (**15**) and p-nitro (**16**) pyrroles (Figure 3). Starting with a variety of aliphatic and aromatic aldehydes, reaction with nitroethane and subsequent reaction with acetic anhydride produces a mix of nitro-acetate stereoisomers **10**. Additionally, the presence of (E)-alkene isomers (via loss of acetate) were sometimes noted as previously reported.[15] These details, while complicating characterization of **10** didn't interfere with subsequent steps. After reaction with ethylisocyanoacetate, pyrroles **12** were easily isolated on 10 gram scale. Pyrroles **15** and **16** were newly prepared for this work and demonstrate that the yields are consistent across a variety of motifs. While low yielding for a two step process, the ready availability and variability of aldehydes **9** makes this an incredibly powerful strategy for the rapid preparation of diverse pyrroles **12**.

Having completed the preparation of a series of pyrroles, we next condensed them with aldehydes to construct the BODIPY precursor, dipyrrolemethanes (Figure 4). The reaction of tri-substituted pyrroles with aldehydes in DCM with catalytic p-toluenesulfonic acid provides a reliable and high-yielding route to these compounds (Figure 4).[14, 16] Of the six permutations we report (**19-24**), they range in yield from 72% to quantitative. Dipyrrolemethanes **19** and **20** we previously reported.[14] These reactions yield material that is very pure, typically extraction followed by either evaporation of excess aldehyde or trituration with diethyl ether gives compounds with greater than 95% analytical purity. The compounds are also readily purified by silica gel chromatography. For this work benzaldehyde and 4-formyl benzoic acid were employed. Other aldehydes work with similar efficacy. Of note at this stage is that 4-formyl benzoic acid[17] after condensation places a carboxylic acid group onto our BODIPY framework. This group survives subsequent steps and ultimately could provide a means of covalent attachment to biological molecules via well-known amide coupling reactions. A similar functional group with an alkyl tether has been used to attach cholesterol.[18]

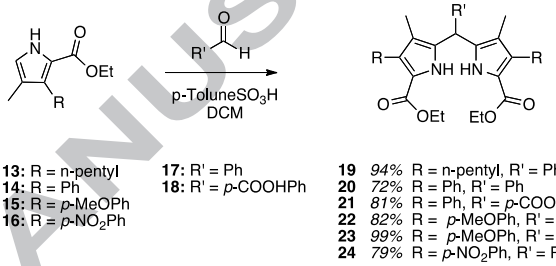


Figure 4: Preparation of dipyrrolemethanes from tri-substituted pyrrole building blocks and isolated yields .

The subsequent conversion to BODIPYs **25-30**, is more perilous however (Figure 5). The conditions that we explored revealed one combination that was better than the rest. For certain scaffolds a two-step procedure where the dipyrrolemethene (not illustrated) is isolated before insertion of boron was reported to be preferable.[19] We find that combination of dipyrrole with DDQ in degassed DCM under microwave irradiation gave clean conversion of dipyrrolemethane to dipyrrolemethene after 5-7 minutes. TLC was used after 5 minutes and if starting material remained, an additional 2 minutes was sufficient to exhaust it. Isolation of the dipyrrolemethene was desirable to us, but in practical terms was not possible due to resulting degradation on chromatography. We thus proceeded by adding TEA and BF_3 and allowing the mixture to stir overnight. Under these conditions, the resulting TLCs showed lots of colored and streaking material, but in all cases, one clean and fluorescent spot was observed. Subsequent silica gel chromotography afforded adducts in 90% or higher analytical purity as determined by H NMR. Isolated yields vary tremendously for these compounds, but in all cases enough material was isolated to fully characterize UV and fluorescent properties. It remains to be understood why substitution of the phenyl group R (which is attached to the pyrrole ring) would have such a drastic effect on yield. Indeed both p-methoxy (**28**, **29**) and p-nitro (**30**) groups for now are not well tolerated. The reported yields are after several attempts. Pentyl was acceptable (**25**) but phenyl was superior (**26, 27**).

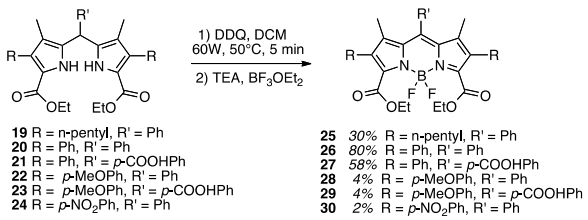


Figure 5: Preparation of diverse BODIPY diesters.

We carried out uv-visible and fluoresce measurement of newly synthesized BODIPY in order to understand photophysical properties in relation to their structure. It is found that electron donating groups generally shift the absorbance and emission maxima of BODIPY to higher wavelength (red shift) while electron withdrawing groups shifts those to lower wavelength (blue shift).

Table 1: Absorbance and Fluorescent maxima (in Chloroform)

Compound	λabs (nm)	λems (nm)
25	537	557
26	535	576
27	538	586
28	541	620
29	547	628
30	530	558

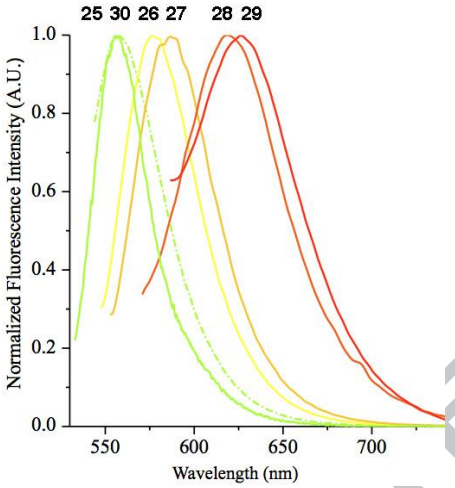


Figure 6: Normalized emission spectra for compounds **25-30**. Excitation was carried out at compounds' absorbance maxima.

First we replaced the pentyl substituent in **25** with phenyl groups in **26**. While absorbance maxima remain the same (Table 1), we see a slight red shift in emission consistent with the increased donating ability of phenyl into the BODIPY core (Table 1, Figure 6). We followed with addition of a carboxylic acid group to the central phenyl ring **27**. Absorbance remained largely insensitive throughout the whole series, but with **27** further red shift occurred. **28** and **29** were prepared and p-methoxy groups were now introduced and gave the most drastic red-shifts to the emission spectra. Indeed both donation in the form of the para-methoxy AND incorporation of a para-carboxylic acid group on the central ring gave **29** with our highest emissions of 628 nm. The remaining compound with para-nitro groups, **30** displayed expected blue shifts, further to the left of the phenyl variant **26**.

Conclusion

Having completed the preparation and characterization of these compounds we again confirm the clear challenges to isolating large quantities of BODIPYs. The one pot method of converting dipyrrole to BODIPY proved the best in our group, and though it produced good yields for three compounds, the remaining three yields were stark (Figure 5). Nevertheless, in this series, compound **27** was isolated in 58% yield and interesting has a carboxylic acid group incorporated into the back of the BODIPY core. This should provide ample peptide coupling opportunities for this compound to be added to biological molecules of importance. This work also aimed to convert the flanking ester groups into carboxylic acids; after which coupling to other molecules would be possible. As has been reported, BODIPY is very sensitive to strong base, and in our hands neither base nor acid could give the corresponding BODIPY diacids that we originally desired. When we took a dipyrrolemethane precursor and prepared a diacid from it, the subsequent oxidation and incorporation of BF_2 failed. With think other protecting group strategies could lead to BODIPYS with free carboxylic acids flanking the core, but for now other researchers can contemplate those challenges. We have presented methods to produce a variety of dipyrrolemethanes that will lead to BODIPYS. The challenging yields in the later stages remain empirical. The dipyrrolemethane syntheses using heavily substituted pyrroles like **13-16** however are very robust. Additionally, the preparation of **13-16** is also versatile, straightforward and economical. When these building blocks are crossed with either benzaldehyde or its para-carboxylic acid analog, many new compounds can be prepared and isolated with ease. Having mapped out a small set of 6 compounds' absorbance and emissions properties provides a straightforward path for subsequent work in the area. Our ultimate goal to deploy compounds **27** and **29** towards bio-labeling is undergoing.

Acknowledgments

We would like to thank Research Corporation for a Single Investigator Cottrell College Science Award that made this work possible. We also thank Woman and Philanthropy (A.C.) and NIH RISE (NIH 2R25GM071638-09A1) (A.C., T.N.) for significant student support. NMR instrumentation was provided by the National Science Foundation (MRI CHE-1337559). The content is solely the responsibility of the authors and does not necessarily represent the views of Research Corporation, the National Institutes of Health nor the National Science Foundation.

Supplementary Material

Experimental procedures for the preparation of all new compounds as well as H, C, MS, UV-Vis Absorbance and Fluorescence spectra are included .

References and notes

1. Karolin, J.; Johansson, L. B. A.; Strandberg, L.; Ny, T., Fluorescence and Absorption Spectroscopic Properties of Dipyrromethene boron Difluoride (BODIPY) Derivatives in Liquids, Lipid Membranes, and Proteins. *J. Am. Chem. Soc.* **1994,** *116* (17), 7801-7806.
2. Yee, M.-c.; Fas, S. C.; Stohlmeyer, M. M.; Wandless, T. J.; Cimprich, K. A., A Cell-permeable, Activity-based Probe for Protein and Lipid Kinases. *J. Biol. Chem.* **2005,** *280* (32), 29053-29059.
3. Ulrich, G.; Ziessel, R.; Harriman, A., The Chemistry of Fluorescent Bodipy Dyes: Versatility Unsurpassed. *Angew. Chem. Int. Ed.* **2008,** *47* (7), 1184-1201.
4. Treibs, A.; Kreuzer, F.-H., Difluorboryl-Komplexe von Di- und Tripyrrylmethenen. *Justus Liebigs Annalen der Chemie* **1968,** *718* (1), 208-223.
5. Loudet, A.; Burgess, K., BODIPY Dyes and Their Derivatives: Syntheses and Spectroscopic Properties. *Chem. Rev.* **2007,** *107* (11), 4891-4932.

6. Ziessel, R.; Ulrich, G.; Harriman, A., The chemistry of Bodipy: A new El Dorado for fluorescence tools. *New J. Chem.* **2007,** *31* (4), 496-501.
7. Poirel, A.; De Nicola, A.; Ziessel, R., Oligothienyl-BODIPYs: Red and Near-Infrared Emitters. *Org. Lett.* **2012,** *14* (22), 5696-5699.
8. Niu, L.-Y.; Guan, Y.-S.; Chen, Y.-Z.; Wu, L.-Z.; Tung, C.-H.; Yang, Q.-Z., BODIPY-Based Ratiometric Fluorescent Sensor for Highly Selective Detection of Glutathione over Cysteine and Homocysteine. *J. Am. Chem. Soc.* **2012,** *134* (46), 18928-18931.
9. Kollmannsberger, M.; Gareis, T.; Heinl, S.; Daub, J.; Breu, J., Electrogenerated Chemiluminescence and Proton-Dependent Switching of Fluorescence: Functionalized Difluoroboradiaza-s-indacenes. *Angewandte Chemie International Edition in English* **1997,** *36* (12), 1333-1335.
10. Gossauer, A.; Nydegger, F.; Kiss, T.; Sleziak, R.; Stoeckli-Evans, H., Synthesis, Chiroptical Properties, and Solid-State Structure Determination of Two New Chiral Dipyrrin Difluoroboryl Chelates. *J. Am. Chem. Soc.* **2004,** *126* (6), 1772-1780.
11. Uppal, T.; Hu, X.; Fronczek, F. R.; Maschek, S.; Bobadova-Parvanova, P.; Vicente, M. G. H., Synthesis, Computational Modeling, and Properties of Benzo-Appended BODIPYs. *Chemistry - A European Journal* **2012,** *18* (13), 3893-3905.
12. Xie, S.-X.; Petrache, G.; Schneider, E.; Ye, Q.-Z.; Bernhardt, G.; Seifert, R.; Buschauer, A., Synthesis and pharmacological characterization of novel fluorescent histamine H2-receptor ligands derived from aminopotentidine. *Bioorg. Med. Chem. Lett.* **2006,** *16* (15), 3886-3890.
13. Middleton, R. J.; Briddon, S. J.; Cordeaux, Y.; Yates, A. S.; Dale, C. L.; George, M. W.; Baker, J. G.; Hill, S. J.; Kellam, B., New Fluorescent Adenosine A1-Receptor Agonists That Allow Quantification of Ligand−Receptor Interactions in Microdomains of Single Living Cells. *J. Med. Chem.* **2007,** *50* (4), 782-793.
14. Pham, C. C.; Park, M. H.; Pham, J. Y.; Martin, S. G.; Schramm, M. P., Modular Preparation of Diverse Dipyrrolemethanes. *Synthesis* **2013,** *45* (09), 1165-1173.
15. Stępień, M.; Donnio, B.; Sessler, J. L., Supramolecular Liquid Crystals Based on Cyclo[8]pyrrole. *Angew. Chem. Int. Ed.* **2007,** *46* (9), 1431-1435.
16. Garrido Montalban, A.; Herrera, A. J.; Johannsen, J.; Beck, J.; Godet, T.; Vrettou, M.; White, A. J. P.; Williams, D. J., Synthesis and reactions of dipyrromethane-2,10-dicarboxylates. *Tetrahedron Lett.* **2002,** *43* (9), 1751-1753.
17. Matvey, G.; Ulyana, C.; Natalia, B.; Arkadiy, K., Synthesis and Optical Properties of BODIPY with Active Group on meso-Position. *Letters in Organic Chemistry* **2016,** *13* (10), 718-725.
18. Li, Z.; Mintzer, E.; Bittman, R., First Synthesis of Free Cholesterol−BODIPY Conjugates. *The Journal of Organic Chemistry* **2006,** *71* (4), 1718-1721.
19. Burghart, A.; Kim, H.; Welch, M. B.; Thoresen, L. H.; Reibenspies, J.; Burgess, K.; Bergström, F.; Johansson, L. B. Å., 3,5-Diaryl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) Dyes: Synthesis, Spectroscopic, Electrochemical, and Structural Properties. *The Journal of Organic Chemistry* **1999,** *64* (21), 7813-7819.

The synthesis and properties of a 6 different substituted BODIPY diesters is presented.
Examples provide points of attachment for biomolecules.
Combinatorial approach to dipyrrolemethane and BODIPY preparations gives access to many new scaffolds.
UV-Vis and Fluorescent data adds to knowledge of this important fluorophore.