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Unprecedented One-Pot Sequential Thiolate Substitutions under Mild Conditions leading to a Red Emissive BODIPY Dye 3,5,8-tris(PhS)-BODIPY.

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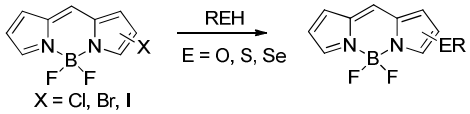
The simple reaction of phenylthiol with 8-MeS-BODIPY (1) in dichloromethane was readily accomplished to form 8-PhS-BODIPY (2). If the reaction is performed in THF 3,8-bis(phenylthio)-BODIPY (3) and 3,5,8-tris(phenylthio)-BODIPY (4) are sequentially formed in an unprecedented reaction. This provides a simple new methodology for the introduction of the phenylthio- moiety in the 3- and 5-positions. Alkyl thiols, do not form the multi-thiolated products under identical conditions, as exemplified using EtSH, where only 8-EtS-BODIPY (5) is formed.

Bright fluorescent dyes emitting in the red region have attracted wide research interest for biological applications because of their skin penetration and low phototoxicity properties.[1] Indeed, the "Nile Red" is a popular fluorophore used as membrane dye. On the contrary, blue and green emission dyes usually require UV light for the excitation process, which present a drawback since these wavelengths are scattered/absorbed by the medium which may present some phototoxicity for the biological samples.[2] Therefore, continuous research efforts are devoted to create new red emission dyes in high yields.

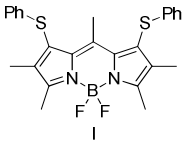
Boron dipyrromethenes (BODIPY) have been extensively studied due to their facile tunable optical properties.[3] The emission wavelength may be changed depending upon substitutions in the BODIPY core.[4-6] Due to these features, such molecules have found applications as metal sensors,[7] protein tags,[8] and laser dyes.[9] The ability to place a variety of substituents onto the BODIPY core is an active area of research and a wide range of such modified BODIPYs have been reported. In general, the expansion of the π-system conjugation causes a bathochromic shift in the absorbance and fluorescence resulting in red emissive dyes. However, some pyrrole reactants required to build these extended π-system BODIPYs are not readily. Therefore, the overall reaction yields are poor.[10] Another approach for the design of red emissive dyes involves the introduction of halogens in the BODIPY.[11] Then, a π-conjugated moiety may be introduced to the halogenated BODIPY *via* carbon-carbon bond formation through Stille,[12] Sonogashira,[13] and Suzuki[14] cross coupling reactions.

The halogenated-BODIPYs may also be used for the introduction of oxygen,[15] sulfur, [16] and selenium,[17] among other atoms *via* nucleophilic substitution, which significantly impacts their optical properties. However, the reaction conditions are harsh and, in some cases, the use of a base is crucial to form the alkoxide, thiolate, or selenate, Scheme 1.



Scheme 1 General nucleophilic substitution of halogenated BODIPYs

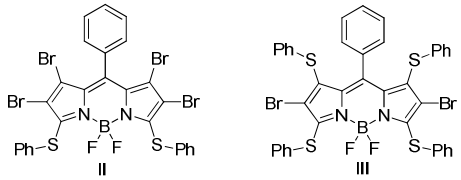
Using this synthetic methodology, the synthesis of 1,7-bis(phenylthio)-BODIPY (I) has been reported, Figure 1.[18] This material exhibits a bathochromic shift of ~30 nm compared to the unsubstituted BODIPY dye,[19] with absorption and emission maxima ranging from 550 nm to 570 nm, with emission quantum yields ranging from 0.30 in non-polar environments to 0.07 in polar media.



I

Figure 1 1,7-bis(phenylthio)-BODIPY

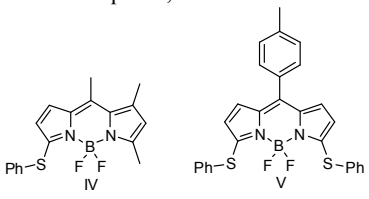
Jiao *et al*. reported two poly-phenylthio- BODIPYs, functionalized in the 3,5- (II) and 1,3,5,7- (III) positions, Figure 2.[20] The absorption and emission maxima for these molecules range from 600 nm to 630 nm. However, the fluorescence intensities for these fluorophores are barely detectable with quantum yields less than 0.003.



II III

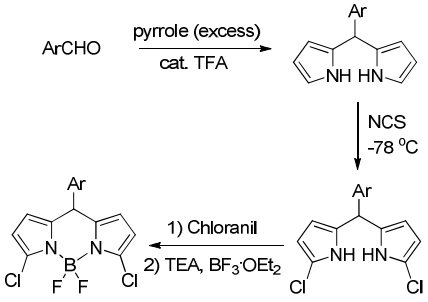
Figure 2 3,5- and 1,3,5,7- phenylthio-BODIPYs

The synthesis of phenylthio- functionalized BODIPYs in the 3- (IV), and 3,5- positions (V), Figure 3, have been reported by reacting the corresponding 3-chloro- or 3,5-dichloro-BODIPY with phenylthiol at high temperatures, ~ 50-70°C, in the presence of a base such as potassium carbonate.[21,17] It is important to note that in order to prepare the 3,5-dichloro-BODIPY precursor, a multi-step synthesis is required, Scheme 2.[21]



IV V

Figure 3 Phenylthio-BODIPYs functionalized at the 3- and 3,5- positions

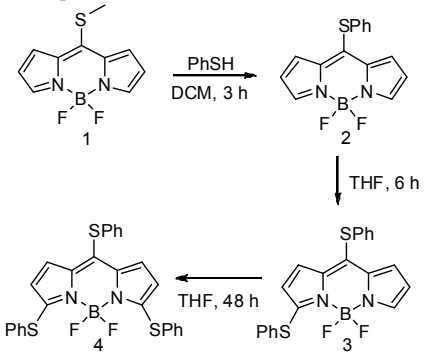


Scheme 2 Preparation of 3,5-dichloro-8-arylBODIPYs

BODIPY IV exhibits an absorbance maxima at ~530 nm and emission maxima at ~545 nm with quantum yields of 0.85. BODIPY V has a larger bathochromic shift in absorbance and emission maxima at ~580 nm and ~600 nm with a quantum efficiency of 0.84.

In general, the synthesis of the phenylthio- substituted BODIPYs depend upon the availability of halogenated BODIPYs. The reactions are carried out at high temperatures and in the presence of a base such as potassium carbonate or triethylamine. It is important to underscore the synthetic utility of thiolated BODIPY dyes. We, and others, have established that the methylthio group in 8-methylthio-BODIPY[16] (**1**) may be readily substituted to form carbon-carbon,[22] carbon-nitrogen,[23] and carbon-oxygen[15] bonds. Furthermore, Burgess *et al.*, have demonstrated that 3,5-bis-thiolated BODIPY dyes efficiently participated in transition-metal catalyzed C-C bond formation with organostannanes .[24]

We now describe a one-step synthetic pathway for the introduction of phenylthio- groups in the 8-, 3- and 5- sites under very mild and chemically simple reaction conditions resulting in highly fluorescent red emissive dye in the case of the tris-thiolated material. A thiol exchange reaction between **1** and PhSH that leads to 8-(phenylthio)-BODIPY, **2**, which can be readily isolated and purified. A further unprecedented transformation of this material sequentially to 3,8-bis(phenylthio)- and 3,5,8-tris(phenylthio)-BODIPYs, **3** and **4**, respectively, using PhSH, has been achieved, Scheme 3. Remarkably, the second and third stages of this reaction sequence occur only in THF; in DCM the formation of **2** occurs exclusively, regardless of either time or relative concentrations of PhSH used. If the reaction is performed initially in THF the transformation of **2** to **3** is very rapid and isolation of **2** is not feasible. This most facile process does not require stringent condition nor synthetically challenging procedures involving initially halogenated BODIPY precursors. This new methodology is a complement to a recent report by Dehaen *et al.* where an oxidative nucleophilic subsitution in the 3- and 5- sites of the BODIPY core was proposed. In their report, they were able to introduce thiols in the 3- and 5- positions. However, the reaction yields were approximately 10% after 6 days and no pure compound was obtained. This reaction, however, is a plausible pathway to introduce amines in the 3- and 5- sites.[25] To the best of our knowledge there is only one report in which the 3- and 5-positions have been arylated starting from an unsubstituted BODIPY analogue, however, the process displays selectivity issues, needs high temperatures (110 °C) and requires Pd-catalysis and the presence of an additive in order to work.[26]



Scheme 3 Sequential nucleophilic substitution of 1 by PhSH

It seems that the secondary substitution is 100% regiospecific for the 3- and 5- sites of the BODIPY core; i.e. no evidence for substitution at the 1-, 7- or 2, 6- sites was not observed even at longer times or with excess of thiophenol. Parenthetically, as with all BODIPY syntheses, trace amounts of fluorescent by-products can be observed during the chromatographic purification process. The spectroscopic data associated with the new materials, and typical synthetic procedures, are presented in the ESI. Their ^{13}C and ^{1}H NMR data exhibit no evidence for any restricted rotations about the S-C(8) bond which could be associated with delocalization of an S lone pair to the BODIPY core, as noted for the asymmetric amine derivatives 8-NHR-BODIPY.[23a]

Under oxygen atmosphere, the reaction occurs at a slower pace and only 40% of the starting material had converted to BODIPY **3** after 48 hours. BODIPY **4** was not observed even after reacting for one week. Furthermore, raising the temperature did not help to increase the reaction rate. Therefore, the nitrogen atmosphere seems to be critical for the reaction to proceed to the formation of BODIPY **4**, presumably by preventing disulphide formation. One can speculate that the first step for the formation of **3** and **4**, is the nucleophilic addition of the thiol to the electrophilic 3- and 5-positions of the BODIPY core. However, at present we are not clear as to the precise mechanism of this apparent oxidation. We are currently investigating this aspect of this new chemistry and for example note that the reaction also occurs in the absence of light.

The reaction of BODIPY **1** with several alkylthiols in tetrahydrofuran at room temperature in an inert atmosphere did not produce bis- and tris- substitution products. Instead, the substitution only occurs at the 8- position. The experimental details for the formation of 8-EtS-BODIPY from the reaction of **1** and EtSH are presented in the ESI, along with the characterization of this material, to illustrate this result.

The presence of the phenylthio- group in the 3- position induces a bathochromic shift in BODIPY **3**. The absorbance and emission maxima are ~50 nm higher in comparison to BODIPY **2**, an effect observed for other 3-arylthio-BODIPYs.[20]

Both BODIPYs **2** and **3** only exhibit detectable fluorescence in hexane. However, fluorophore **2** is non-emissive in polar solvents whereas **3** exhibits a weak emission in any other more polar common organic solvents tested, Figure 4. This effect was not observed, however, for 3-phenylthio-BODIPY,[21] therefore, it appears that the fluorescence dependence upon solvent polarity is directly associated to the phenylthio- substituent in the 8-position. This effect was also observed for asymmetric 8-amino-BODIPYs.[23]

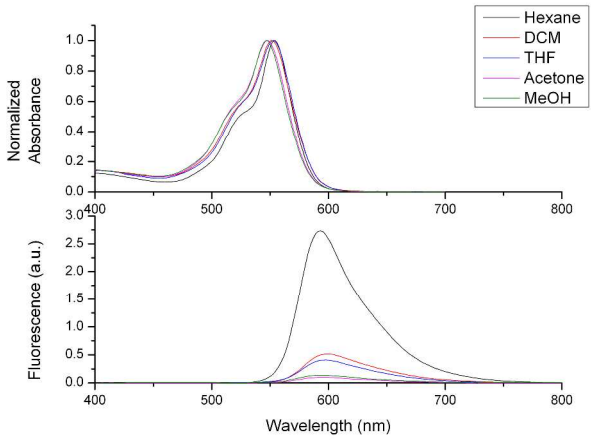


Figure 4 Absorbance (top) and emission spectra for 3 in different solvents

The introduction of the third phenylthio- moiety in the 5-position produces a further ~50 nm bathochromic shift in the absorbance and fluorescence maxima compared to BODIPY **3**, as noted in Figure 5. Since, the PhS- substituent in the 8- position induces a bathochromic shift of ~30 nm with respect to 3,5-bis(phenylthiol)-8-phenyl-BODIPY,[17] fluorophore **4** has the largest bathochromic shift compared to other thio-functionalized BODIPYs. The molar extinction coefficients are slightly lower for BODIPY **4** compared to **3**, but still within range for similar BODIPYs.[3] Also, the vibronic shoulder is more defined in **4**. This is also in concordance with other reported BODIPY fluorophores,

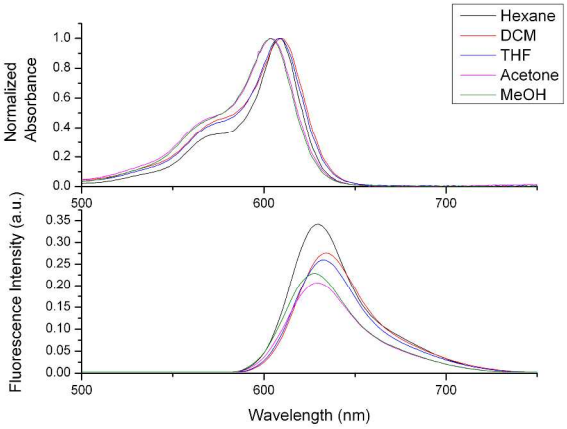


Figure 5 Absorbance (top) and emission spectra for 4 in different solvents

The emission intensity of BODIPY **4** is virtually unaffected by the solvent polarity. The quantum yields range from 0.22 in hexane to 0.18 in methanol.

The single crystal structures of the new PhS-BODIPY compounds **2**, **3**, and **4** have been solved; their CCDC #s are 959249, 959246 and 1004338, respectively. The various BODIPY cores deviate somewhat from planarity, exhibiting pyrrole-pyrrole ring dihedral angle of 16° (**2**), 9.6°(**3**) and 8.8° (**4**), Figure 6. Such deviations from planarity in the solid state have been recognized previously for, *inter alia*, 8-amino-BODIPYs; however, with exception of the diethylamino derivative which exhibited an angle >35°, such small deviations are generally associated with solid state packing issues and not any defined structural feature of the molecular species.[22a, 23a]

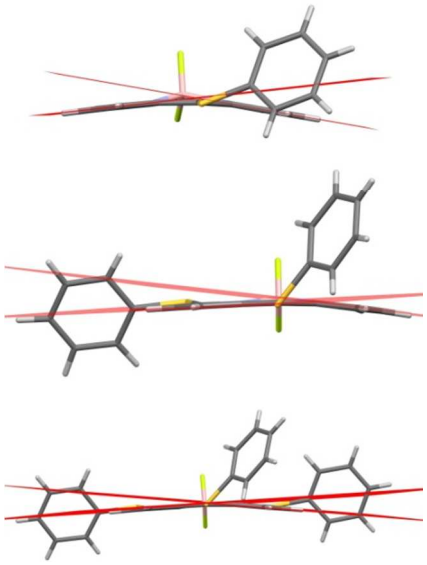


Figure 6 Distortion of BODIPY core geometry for 2 (top), 3, and 4 (bottom).

Positions 3 and 5 of the BODIPY core have a lower steric hindrance in comparison to the position 8, where the hydrogen atoms of positions 1 and 7 are important, resulting in an observed reduction in the length bond for C3-S and C5-S compared to that of C8-S in each molecule where comparisons are possible: i.e. C8-S = 1.759Å (**3**), 1.758Å (**4**); S-C3 =1.731Å (**3**), 1.726 (**4**) Å; and S-C5 = 1.744 Å(**4**). All the BODIPY C-S bond lengths are shorter than the corresponding phenyl C-S bond lengths, average phenyl C-S = 1.768(3)Å vs average BODIPY C-S = 1.743(3)Å. Such reduction in the BODIPY C-S bond lengths can suggest a limited but significant delocalization of the S lone pairs to the electron- deficient BODIPY core, sufficient for structural variation but not observable via NMR data associated with restricted rotation about this bond, *vide supra*.

In all structures the phenyl rings of the thiol substituents are twisted out of the BODIPY plane. Thus, the 8-PhS ring is twisted 57, 37° and 37°, in **2**, **3**, and **4**, respectively and in structures **3** and **4** the 3 and 5 substituents angles are 71 and 73° respectively.

The crystal packing of the new BODIPYs is of interest and the crystal data and Figures illustrating the various solid state packing motifs, and corresponding narrative, is included in the ESI. Thus, whereas **2** illustrates solid state chains and ribbons, primarily via hydrogen bonds between the fluorine atoms and two hydrogen atoms in the aromatic ring (F1···H13 [2.635 Å] and F2···H11 [2.395Å],(Figure 9, SM) the presence of the second phenyl ring on BODIPY **3** results in the predominant formation of dimers (Figure 10, SM), via a strong interaction between the F and S atoms of 3.054 Å, a distance significantly shorter than the sum of the Van der Waals S and F radii by 0.216 Å.

In the case of the tris-adduct, **4**, similar formation of dimers is observed, (Figures 11-14, SI). The distance between them (mean planes) is 3.531 Å, longer than for **3** due to the increased molecular volume.

In summary, via an unprecedented direct single step involving substitution of 8-MeS-BODIPY with PhSH we have successfully introduced a phenylthio- moiety in the 8 (**2**), 8,3 (**3**) and 8,3,5 (**4**) positions of the BODIPY core under simple and mild conditions in good yields. This synthetic pathway does not involve the need

of a halogenated BODIPY. The generality of the new chemistry is under study; however, to date we have not been able to observe significant multiple thiolation using 8-Ph-BODIPY and 8-NHR-BODIPY starting materials upon treatment with PhSH. A progressive bathochromic shift occurs, **2→3→4** for both absorbance (497 → 554 → 609 nm) and emission (542 → 593 → 630 nm) such that **4** exhibits largest bathochromic shift reported for thio-BODIPYs. It possesses a large quantum yield, comparable to other thio-BODIPYs, and its fluorescence intensity is only mildly impacted by solvent polarity. Further investigations are in progress to explore key conditions in the activation of the 3 and 5 carbons of the BODIPY core, to elucidate the reaction mechanism of the thiolation at the 3- and 5-position, and to exploit the scope and limitations of these new derivatives in transition metal-catalyzed C-C bond formation.

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Notes and References

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Electronic Supplementary Information (ESI) available: NMR characterization and Crystallographic data are available in the ESI file.

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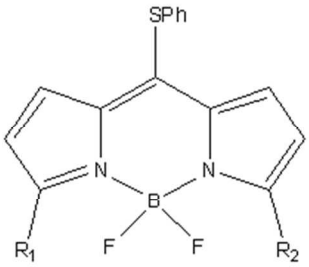
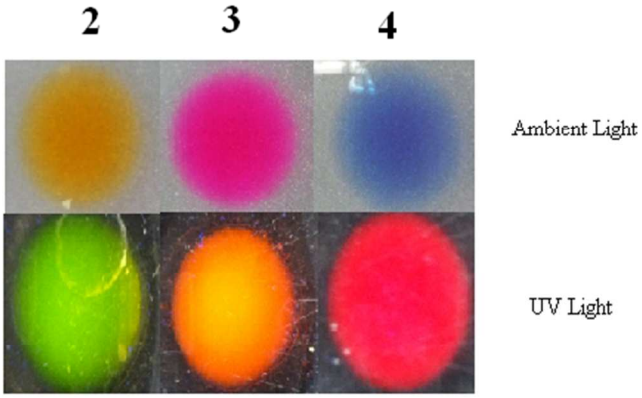


2 $= R_1 = H \quad R_2 = H$

3 $= R_1 = SPh \quad R_2 = H$

4 $= R_1 = SPh \quad R_2 = SPh$



Phenylthiol performs a thiol exchange with 8-MeS-BODIPY and activates/ substitutes the 3, 5 positions forming a tri-thiolated BODIPY.