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Direct sulfonylation of BODIPY dyes with sodium sulfinates through oxidative radical hydrogen substitution at the α-position†

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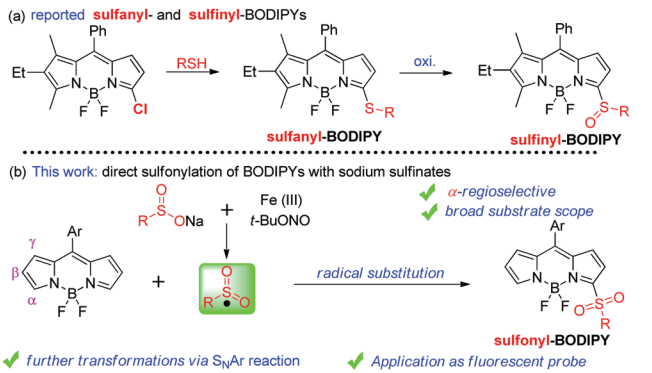
An efficient and convenient protocol for the direct sulfonylation of BODIPY dyes with sodium sulfinates *via* a radical process is described for the first time. This transformation presented wide substrate scope and high regioselectivity, providing a series of α-sulfonylated BODIPYs. Meaningfully, the sulfonyl group, as a good leaving group, allowed the facile introduction of a variety of functionalities on the BODIPY core. Moreover, a 2,4-dinitrobenzenesulfonyl (DBS) group substituted BODIPY showed dramatically quenched fluorescence *via* the photo-induced electron transfer (PET) pathway, and was demonstrated as a new fluorescent probe for selective biothiol detection.

BODIPY (4,4′-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene) dyes,[1] as an important class of emerging fluorophores, have received increasing attention due to their highly favourable and tunable photophysical properties.[2] Continuing efforts in developing efficient and modular synthesis and postfunctionalization methods for BODIPYs to increase their structural diversities will be of importance for their diverse applications as bioimaging reagents, sensors, photosensitizers, *etc.*[3,4]

Sulfonylated heterocycles typically exhibit unique bioactivities and chemical properties, and have found a wide range of applications in medicinal chemistry and organic synthesis.[5] Sulfonylation on BODIPYs can be a nice tool to tune their photophysical properties, to further introduce functional groups and to induce interesting bioactivities. Recently, sulfanyl-substituted BODIPY dyes were reported from nucleophilic substitution of α-halogenated BODIPY or C–H/S–H crosscoupling reaction.[6] From them, sulfinyl-substituted BODIPY dyes were obtained *via* oxidation (Scheme 1a).[6a] However, direct sulfonyl-substituted BODIPYs were not obtained and have not been reported yet.

More recently, a radical reaction has been used as a mild and powerful method for regioselective functionalization of BODIPY dyes.[7,8] As part of our continuing efforts on developing efficient postfunctionalization methods for BODIPY dyes,[2b] herein we report an oxidative hydrogen substitution reaction for the synthesis of sulfonylated BODIPYs from sodium sulfinates in the presence of *tert*-butyl nitrite (*t*-BuONO) as an oxidant (Scheme 1b). Such a direct sulfonylation strategy uses easily accessible starting materials and allows us to generate structurally diverse sulfonylated BODIPYs *via* the radical pathway.

Since sodium sulfonates are regarded as a green sulfonyl source, we started our investigation by taking BODIPY **1a** and *p*-toluensulfinate **2a** as model substrates to identify the optimized reaction conditions, as summarized in Table S1 (ESI†). The combination of *t*-BuONO and sodium sulfinates was reported to generate sulfonyl and NO radicals;[5] thus, we first utilized *t*-BuONO as an oxidant in this reaction. The reaction



Scheme 1 (a) Reported synthesis of sulfanyl- and sulfinyl-BODIPYs. (b) Oxidative radical sulfonylation of BODIPY with sodium sulfonates reported in this work.

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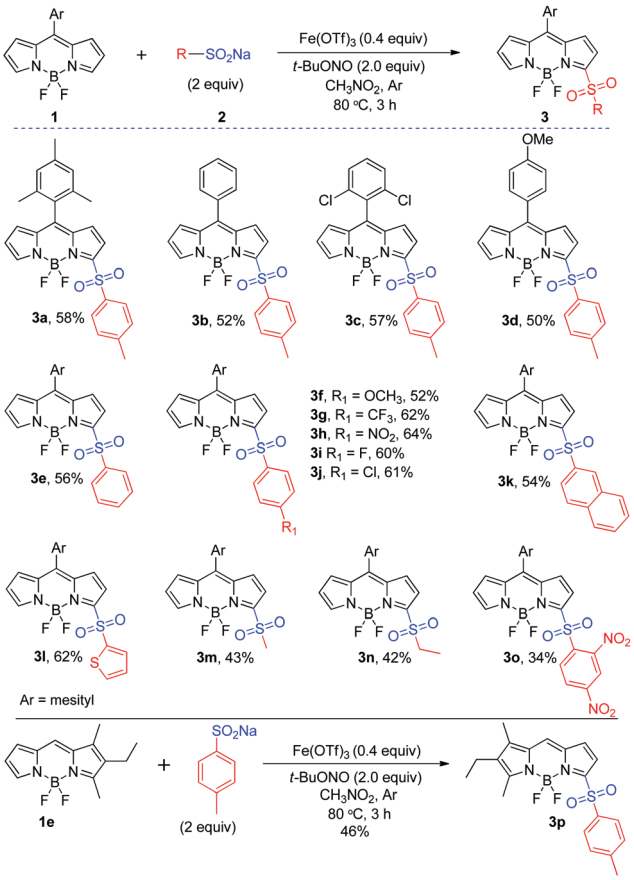
between BODIPY **1a** and *p*-toluensulfinate **2a** in the presence of *t*-BuONO in acetonitrile at 80 °C for 3 h under argon indeed afforded the desired sulfonylated BODIPY **3a** in 34% yield despite the fact that 60% yield of starting BODIPY **1a** was recycled (Table S1, ESI,† entry 1). NMR and HRMS characterization clearly indicated that the monosulfonylation exclusively took place at the α-position of the BODIPY core. To further investigate the reaction conditions, a series of catalysts including $Cu(OAc)_2$, $AgNO_3$, $FeCl_3$, $Fe(NO_3)_3$ and $Fe(OTf)_3$ were applied under identical reaction conditions (entries 2–6). The best yield for **3a** is 57% when $Fe(OTf)_3$ was used as the catalyst (entry 6). Other oxidants, including *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), *tert*-butylperoxy benzoate (TBPB) and $K_2S_2O_8$, were less effective than *t*-BuONO for this reaction (entries 7–10). Solvent selection is also a very important factor in this reaction. Other common organic solvents like *N*,*N*-dimethylformamide (DMF), acetonitrile, toluene, and 1,2-dichloroethane (DCE) all gave inferior results (entries 11–14). The amounts of *t*-BuONO and $Fe(OTf)_3$ as well as the reaction temperature (entries 15–20) were briefly screened. The optimal reaction conditions for obtaining **3a** were 0.5 equiv. of $Fe(OTf)_3$, and 2 equiv. of *t*-BuONO at 80 °C in 3 h under argon (Table S1, ESI,† entry 6).

To test the versatility of this sulfonylation reaction, BODIPYs **1b–d** (Chart S1, ESI†) bearing different electron-withdrawing or electron-donating groups at the *meso*-position were reacted with *p*-toluensulfinate **2a** under the optimized conditions, giving the targeted sulfonylated BODIPYs **3b–d** in 50–57% yields (Scheme 2). Next, the scope of this sulfonylation was further expanded to a range of sodium sulfinate salts. A wide range of sodium sulfinates (Chart S1, ESI†) bearing aryl and alkyl groups worked well in this reaction, affording the corresponding sulfonylated BODIPYs with yields up to 64%. Generally, phenylsulfonates with electron-withdrawing groups at the *para*-position, including CF_3, NO_2, F and Cl groups, provided the desired products **3g–j** in slightly higher yields than those of *para*-methoxylphenylsulfonate (giving **3f**). Moreover, sodium naphthalen-2-sulfinate (**2h**) and sodium thiophene-2-sulfinate (**2i**) could also participate in the coupling, furnishing the desired products in 54% and 62% yield, respectively. Other alkyl sodium sulfinates could also be used in this reaction and gave the sulfonylation BODIPYs **3m** and **3n** in 43% and 42% yields, respectively. Importantly, the reaction between BODIPY **1a** and sodium 2,4-dinitrobenzenesulfinate successfully gave BODIPY **3o** bearing a DBS group. The highly electron deficient DBS group was expected to quench the fluorescence of **3o** *via* the PET process from the BODIPY motif to a DBS group. Finally, *meso*-H BODIPY **1e** was also reacted with *p*-toluensulfinate to regioselectively afford the corresponding α-sulfonylated BODIPY **3p** in 46% yield. No disulfonylated BODIPYs were obtained in all the above reactions, indicating that monosulfonylated BODIPYs are not reactive enough for further reaction toward electron-deficient sulfonyl radicals. Single crystals for **3e** (Fig. S1, Tables S2 and S3, ESI†) unambiguously revealed the high regioselectivity of this sulfonylation. The newly formed C–S bond has a length of 1.75 Å, which is similar to previously reported C–S bond length of thioether substituted BODIPYs.[6c]

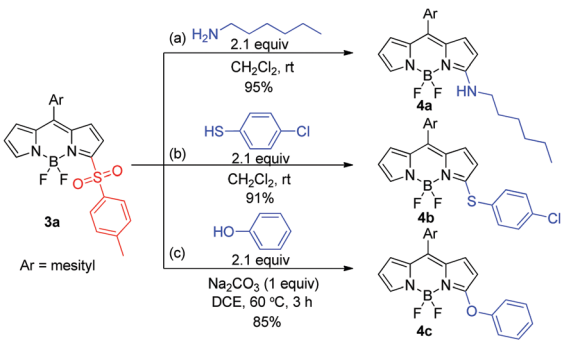
Finally, we demonstrated that these sulfonylated BODIPYs are nice intermediates for further diversifications of the BODIPY structure. Diverse transformations of the sulfonyl group were



Scheme 2 Synthesis of sulfonylated BODIPYs **3a–p** from BODIPYs **1** and various sodium sulfinates.

performed to introduce new functional groups (Scheme 3). Typical nucleophiles of hexamine and *p*-chlorophenylthiol were smoothly reacted with BODIPY **3a** in dichloromethane at rt for only 5 min to give the corresponding BODIPYs **4a** and **4b** in 95% and 91% yields, respectively (Scheme 3b and c). Phenol was also reacted with **3a** in the presence of base Na_2CO_3, giving BODIPY **4c** in 85% yield (Scheme 3c).

To gain insight into the mechanism of this direct sulfonylation, radical inhibitors TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (butylated hydroxytoluene) were added into the standard reactions between BODIPY **1a** and *p*-toluensulfinate (Scheme S1, ESI†). Both reactions were inhibited with the recovery of starting



Scheme 3 Synthesis of BODIPYs **4a–c** from BODIPY **3a**.

BODIPY **1a**, indicating that radical intermediates might be involved. Combined with the above results and previous reports,[5,7c] a plausible mechanism is proposed. First, sulfinate sodium was transformed to the sulfonyl radical by the oxidation of *t*-BuONO. The sulfonyl radical then added to BODIPY **1** to from the radical α-complex **B**, which was oxidized by Fe(III) followed by deprotonation to afford the sulfonylated BODIPY **3**.

The photophysical properties of these sulfonylated BODIPYs were studied in dichloromethane (Fig. S3–S12 and Table S4, ESI†). In comparison with the starting BODIPYs **1**, aryl sulfonylated BODIPYs gave slightly red-shifted absorption and emission maxima, while alkyl sulfonylated BODIPYs (**3m** and **3n**) showed 3 nm blueshifts in absorption maxima and 6–7 nm blueshifts in emission maxima. Most of these sulfonylated BODIPY dyes maintain good fluorescence quantum yields, while **3b** and **3d** have low fluorescence quantum yields similar to their corresponding starting BODIPYs **1b** and **1d** due to the free rotation of a *meso*-phenyl group (Table S4, ESI†). Interestingly, BODIPY **3p** derived from highly electron rich unsymmetrical *meso*-H BODIPY **1e** exhibits a decreased quantum yield of 0.12, indicating a possible PET process from an electron donating BODIPY core to an electron deficient toluenesulfoyl group. Finally, as expected, BODIPY **3o** also shows very low quantum yields due to a similar PET pathway after installation of a highly electron deficient DBS group and the solvatochromic effects of BODIPY **3o** were also investigated (Fig. S2 and Table S5, ESI†). With increasing solvent polarity, obvious blueshifts of absorption maxima from 508 nm (in cyclohexane) to 481 nm (in DMSO) and a lowest fluorescent quantum yield of 0.003 in DMSO were observed.

Encouraged by the high reactivity of sulfonylated BODIPYs toward nucleophiles and the extremely weak fluorescence of BODIPY **3o**, we turned our attention to the possibility of fluorescence sensing of biological thiols using sulfonylated BODIPY **3o**. Biological thiols, such as cysteine (Cys) and glutathione (GSH), play a critical role in keeping appropriate redox status in biosystem and only a few probes could differentiate between Cys and GSH due to their similar reduction property.[9,10] Interestingly, similar to previously reported α-halogenated BODIPYs,[9] **3o** is able to distinguish Cys and GSH due to their different reaction pathways (giving amino-substituted BODIPY or the sulfur-substituted BODIPY, Fig. 1a). Importantly, due to the excellent leaving property of a DBS group, **3o** showed much higher reactivity than α-halogenated BODIPYs toward both Cys and GSH, and gave immediate responses at room temperature upon addition of thiols. Intense "turn-on" emissions (Fig. 1c and e) were observed because of blocking the PET process from the BODIPY donor to DBS acceptor. With increasing Cys amounts up to 12.5 equiv. during titration of **3o** in PBS buffer solution, the absorption spectra indicated the formation of a new species (Fig. 1b), while the emission maximum at 529 nm increased significantly and immediately (Fig. 1c). In contrast, in the case of GSH addition to the solution of **3o**, the absorption maximum at 480 nm decreased and a new band at 532 nm formed (Fig. 1d). In the meantime, the emission peak at 550 nm increased rapidly with the addition of GSH (Fig. 1e). Notably, **3o** could differentiate between Cys and GSH by the naked eye. The solution of **3o** in the presence of Cys emitted brilliant green light (Fig. 1c, inset picture); in contrast, **3o** in the presence of GSH exhibited bright yellow fluorescence (Fig. 1e, inset picture) under ultraviolet light.

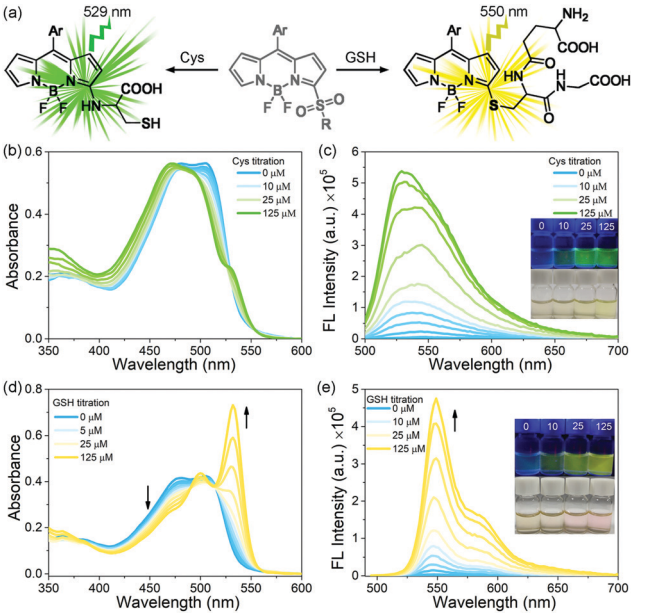


Fig. 1 (a) A schematic illustration of the fluorescence response to Cys and GSH by **3o**. UV-vis absorption (b and d) and fluorescence (c and e) titration spectra of **3o** (10 μM, V_{DMSO}/V_{PBS}: 1/3, pH 7.4) solution upon additions of Cys or GSH. The spectra were recorded immediately after the addition of Cys or GSH (excited at 480 nm). Inset picture: photos of the above solutions under 365 nm light (top) or daylight (bottom).

Inspired by the highly sensitive distinction between Cys and GSH, we further studied the imaging performance of **3o** in cells. The standard CCK-8 assay was conducted first to evaluate the cytotoxicity of **3o**, which indicated negligible cytotoxic effect under imaging concentration (5 μM, Fig. S13, ESI†). HeLa cells incubated with **3o** (5 μM) for 0.5 h showed bright fluorescence in two emission channels, green (500–520 nm) and red (550–650 nm), indicating that **3o** is cell-permeable and can react with cellular intrinsic biological thiols (Fig. 2a). In contrast, when the cells were pretreated with *N*-ethylmaleimide (NME), a scavenger of biological thiols, and further incubated with **3o**, fluorescence from the green channel and especially the red channel significantly decreased (Fig. 2b). To increase the GSH concentration inside cells, the cells were first treated with 20 mM GSH then replaced with **3o**. The fluorescence from the red channel dramatically improved (Fig. 2c) and the ratio of the emissions from the red and green channels was ~2.8 (Fig. S14c, ESI†), confirming that **3o** was sensitive to cellular GSH. Similarly, green channel fluorescence significantly enhanced after being pretreated with Cys (Fig. 2d) and the ratio of the emissions was ~0.9 (Fig. S14a, ESI†). These results demonstrated that **3o** showed excellent membrane permeability and good biocompatibility and could competently differentiate variations of GSH and Cys levels in living cells by the changes of fluorescence intensity.

In conclusion, we have developed an efficient and convenient protocol for the direct α-sulfonylation of BODIPY dyes with

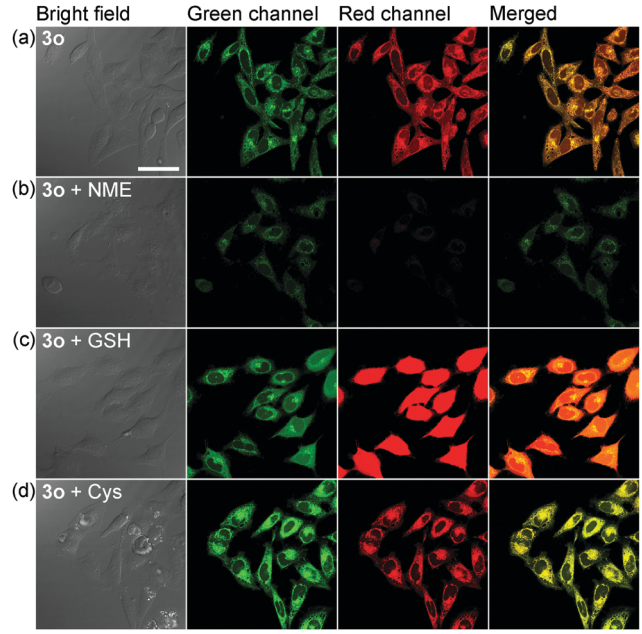


Fig. 2 Confocal fluorescence images of **3o** to sense Cys and GSH in HeLa cells. Cells were only incubated with **3o** (5 μM, 0.5 h) and then imaged (a); cells were pretreated with 20 mM NEM (b), or 20 mM GSH (c) or 20 mM Cys (d), and subsequently incubated with **3o** (5 μM, 0.5 h), and then imaged. Green channel at 500–530 nm; red channel at 550–650 nm, excited at 488 nm. Scale bar = 50 μm.

sodium sulfinatesal. Moreover, a sulfonated BODIPY based probe was developed for rapid and selective detection of Cys and GSH, and was successfully applied for live cell imaging.

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Conflicts of interest

There are no conflicts to declare.

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