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Thiocyanation of 3-substituted and 3,5-disubstituted BODIPYs and its application for the synthesis of new fluorescent sensors

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ABSTRACT

Interest in BODIPYs (acronym of boron dipyrromethene) has skyrocketed in recent decades, mainly due to their favourable photophysical properties and the wide range of functionalization methods reported for these organic fluorescent dyes. In this context, a simple and straightforward method for the direct thiocyanation of 1,3,5,7-tetramethy-BODIPYs using ammonium thiocyanate and oxone was recently reported as an alternative for the preparation of thiocyanated and thioalkylated BODIPYs. Herein, we performed the thiocyanation of 3-substituted and 3,5-disubstituted BODIPY dyes, which were synthesized from the nucleophilic substitution of halogenated precursors with morpholine, propanethiol and sodium methoxide. There was a direct relation between the electron-donating character of the substituent and the yields of the thiocyanated BODIPYs, which gives support to a mechanism based on the electrophilic substitution by a thiocyanogen species formed *in situ*. Spectroscopic and photophysical characterization of these new fluorophores was performed and included bi-dimensional NMR, UV/vis absorption, fluorescence emission and fluorescence quantum yields. The photophysical properties are highly dependable on the structural features of each dye. While 3-morpholino-8-phenyl BODIPYs are virtually non-fluorescent, the fluorescence quantum yields of 3-(4-methoxybenzylamino)-8-methyl BODIPYs were close to 0.9. The thiocyanation of BODIPYs can result in interesting photophysical shifts that can be explored in the fine-tuning of fluorescent sensors. We also report the results of a preliminary qualitative analysis that indicates interesting bathochromic or hypsochromic shifts on the absorption and fluorescence emission spectra when some of the highly emissive dyes were treated with strong acid.

1. Introduction

Fluorescence-based analytical and imaging techniques are widely applied in several research areas due to their intrinsic high sensitivity and specificity [1]. Such techniques often require exogenous fluorescent probes, among which BODIPY (boron dipyrromethene) dyes (formally 4,4′-difluoro-4-bora-3a, 4a-diaza-*s*-indacene) have been found in several technological applications in recent decades [2]. The BODIPY core is a complex of a dipyrrin with a difluoroboryl unity and was first reported in 1968 by Treibs and Kreuzer [3]. The development of BODIPY-based chemosensors and labelling agents skyrocketed in the last 35 years due to their robustness and positive optical features, such as high quantum yields and molar absorptivity [4].

Despite their interesting photophysical properties, one may argue that the chemical versatility is the main advantage of BODIPY dyes. The growing application of this class of dyes was only possible due to the development of new ways to chemically modify the BODIPY core, aiming at its functionalization and optical diversification. In this sense, post-functionalization of BODIPY dyes has risen as a very interesting field of research with several practical applications. Currently, there are methods to functionalize every position of the BODIPY core including halogenations [5], nucleophilic substitutions [6], cross-coupling reactions [7], C-H activations [8], radical-mediated functionalizations [9] and dimerization [10]. The chemical manipulation of the BODIPY core is a vast field of research, and very good reviews have been published in recent years [4,11].

Aiming to explore the versatility of thiocyanato functionality, we have started a research programme on the direct thiocyanation of BODIPY dyes, and preliminary results were recently published [12]. In that publication, we presented a very simple and high yield method for

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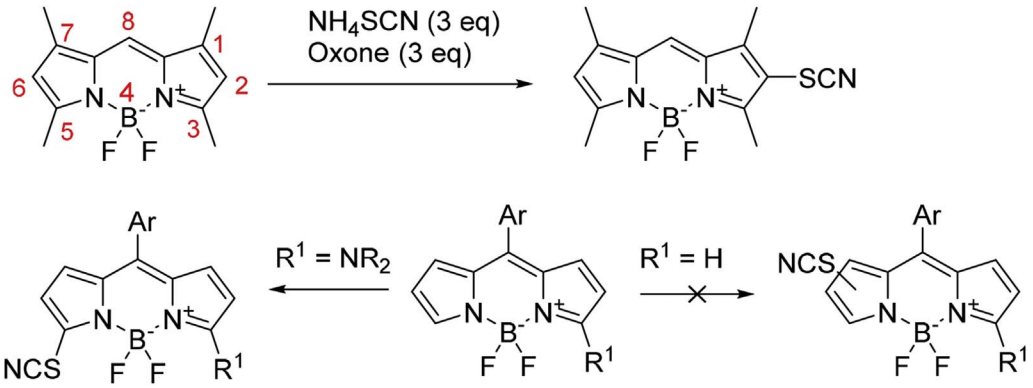

Scheme 1. Direct thiocyanation of BODIPY dyes previously reported and IUPAC numbering of the BODIPY core.

the thiocyanation of BODIPY dyes based on the use of ammonium thiocyanate and oxone. It was also reported that 1,3-dimethyl BODIPYs and 1,3,5,7 tetramethyl BODIPYs are good substrates for the thiocyanation reaction; however, non-methylated BODIPYs were not prone to such a conversion. Interestingly, the addition of a secondary amine (piperidine) group in the position 3 of the non-reactive BODIPY dye restored its reactivity, leading to a 5-thiocyanato substituted derivative (Scheme 1) [12].

Even though we could not exclude a radical mechanism, our data suggested that the electrophilic attack of a thiocyanogen species, formed *in situ* from the oxidation of thiocyanate anion, is a more likely mechanism [13]. The absence of reactivity of the non-methylated BODIPYs indicates that a radical reaction is less likely, since this kind of non-methylated dye was previously applied in other radical reactions [9]. The restored reactivity of the piperidino-substituted dye indicates that an electron-rich BODIPY core is necessary for the thiocyanation to proceed. Moreover, the 2-positions of the BODIPY core are usually prone to electrophilic attacks [4]. In this context, an in-depth analysis of the thiocyanation of electron-rich BODIPY dyes is required to better understand the scope of this reaction. In this paper, we report the reactivity of 3-substituted and 3,5-disubstituted BODIPYs towards the thiocyanation reaction and the application of this reaction to the preparation of acid-sensitive fluorescent probes.

2. Results and discussion

2.1. Nucleophilic substitutions

To synthesize the substituted BODIPYs needed for this study, we applied nucleophilic substitution reactions using nitrogen, oxygen and sulfur nucleophiles. For that, the monochlorinated BODIPY **1** and the dichlorinated BODIPY **2** were synthesized using previously published methods [5d,6a] and submitted to nucleophilic substitution reactions with morpholine, sodium methoxide and 1-propanethiol.

The substitution of monochlorinated BODIPY **1** with morpholine (2.5 equivalents) was performed in acetonitrile at room temperature, leading to the derivative **3** in 61% yield (Table 1, entry 1). A similar reaction with 2.5 equivalents of sodium methoxide in methanol yielded 58% of methoxy-BODIPY **4** (Table 1, entry 2). The alkylsulfanyl-substituted derivative **5** was synthesized in 62% yield using 2.5 equivalents of 1-propanethiol and trimethylamine in refluxing acetonitrile (Table 1, entry 3).

Harsher reaction conditions were necessary to carry the substitution reaction of dichlorinated BODIPY **2** to completion. While the substitution of the first chlorine atom could typically be achieved at room temperature, the second substitution was only possible when higher temperature and excess reagent were employed. The 3,5-disubstituted BODIPYs **6** (71% yield), **7** (37% yield) and **8** (62% yield) were synthesized *via* nucleophilic substitution with morpholine, sodium methoxide and 1-propanethiol, respectively (Table 1, entries 4–6).

2.2. Thiocyanation of 3-substituted BODIPYs

Monofunctionalized compounds **3**, **4** and **5** were submitted to our previously published thiocyanation protocol, based on the reaction of BODIPY with oxone and ammonium thiocyanate [12]. Similar to our previous results, 3-morpholino BODIPY **3** was thiocyanated at position 5, yielding 79% of BODIPY **9** (Table 2, entry 1). TLC control showed full conversion of the starting compound almost exclusively to the 5-thiocyanato substituted BODIPY **9**. We also observed a secondary spot on the TLC with different Rf value and optical features, probably a regioisomer; however, the amount was negligible, and no further characterization of this secondary compound was performed.

Interestingly, when a larger excess of the reagents was used, a second thiocyanato group was inserted (Table 2, entry 2). The insertion of a second thiocyanate group seems to be less favourable, as only a yield of 40% of the 2,5-dithiocyanated BODIPY **10** was achieved. In fact, no full conversion was observed, as a mixture of compounds **9** and **10** was obtained even when 15 equivalents of the reagents were employed in a 24-h reaction.

Thiocyanation of the 3-methoxy substituted dye **2** and the 3-propylsulfanyl substituted dye **3** also occurred at position 5, yielding respectively 74% of the BODIPY **11** and 47% of the BODIPY **12** (Table 2, entries 3 and 4). The reactivity of compounds **2** and **3** was lower than the reactivity of 3-morpholino compound **1**, probably due to the stronger donating effect of the latter. While for the methoxy compound **2**, it was necessary to employ 8 equivalents of ammonium thiocyanate and oxone in a 4-h reaction. Full conversion of 3-propylsulfanyl BODIPY **3** was not observed by TLC analysis, even after reacting for 24 h using 15 equivalents of the reactants. Higher temperatures were not used as our previous results indicated extensive degradation. Note that the insertion of a second thiocyanato group was not possible for BODIPYs **4** and **5**, which is feasibly also related to weaker donating effects.

2.3. Thiocyanation of 3,5-disubstituted BODIPYs

In the following experiments, we observed that compound **6**, in which positions 3 and 5 are substituted by a morpholino group, was readily thiocyanated at position 2, yielding compound **13** in 72% yield (Table 3, entry 1). Two equivalents of oxone and ammonium thiocyanate were enough for full conversion. When the amount of reagents was doubled to 4 equivalents, full conversion to the 2,6-dithiocyanated derivative **14** (65% yield) was observed (Table 3, entry 2).

The thiocyanation of the methoxy-substituted BODIPY **7** was also successfully performed, and the 2-thiocyanato derivative **15** was obtained in 72% yield (Table 3, entry 3). Due to the weaker donating effect of the methoxy group, a higher excess of oxone and ammonium