Synthesis and characterisation of the unsubstituted dipyrrin and 4,4-dichloro-4-bora-3a,4a-diaza-s-indacene: improved synthesis and functionalisation of the simplest BODIPY framework. Groves, Brandon R.; Crawford, Sarah M.; Lundrigan, Travis; Matta, Cherif F.; Sowlati-Hashjinb, Shahin; Thompson, Alison. *Chem. Commun.*, 2013, **49**, 816-818. **DOI:** 10.1039/c2cc37480c
An improved and scalable synthesis of the unsubstituted 4,4-difluoro-4-bora-3a,4a-diaza-indacene framework facilitates access to the previously unreported parent dipyrrin HCl salt, as well as 4,4-dichloro-4-bora-3a,4a-diaza-indacene.

Within the unsubstituted family of dipyrrins (Fig. 1) only the 4,4-difluoro-4-bora-3a,4a-diaza-indacene (F-BODIPY 1) is known, whereas dipyrrins and BODIPYs substituted around the dipyrrinato scaffold are commonplace. Indeed, compound 1 was synthesised only recently vs. reports that have appeared for decades concerning a plethora of dipyrrins, dipyrrinato salts and BODIPYs substituted around the dipyrrinato backbone. We report herein an improved one-pot synthesis of 1, the first derivatisation of 3, generation of the unsubstituted dipyrrin 3 (C-BODIPY 2) and the first characterisation of the unsubstituted dipyrrin 3 as its HCl salt. We also describe the use of 1 and 2 as starting materials for BODIPYs substituted with carbon- and oxygen-based moieties at the boron atom (dubbed C- and O-BODIPYs), alongside supporting computational and NMR analysis. Collectively, these investigations provide an increased understanding of the reactivity of the fundamental core structure within this important class of fluorophore.

Our work began with the development of an improved synthesis of 1. Of the three syntheses published, two involve one-pot protocols that require trapping dipyrrin 3; this strategy is attractive in terms of atom economy and numbers of steps, but has reported yields <10%. The one-pot approach towards 1 relies upon the efficient oxidation of di(1H-pyrrol-2-yl)methane, and subsequent trapping of dipyrrin 3 upon the addition of BF3·OEt2 (Table 1). Using sterically hindered amine bases, and changing the oxidant from DDQ to p-chloranil, resulted in an increased yield of 1; however, the procedure still suffered from yields <30%. We then increased the oxidation time and the temperature, and allowed the mixture to slowly warm to room temperature after the addition of BF3·OEt2, which reproducibly obtained ∼70% yields of the target BODIPY 1; substantially increased yields compared to the initial attempts. Most trials were conducted on ∼0.5 mmol scales, whilst one trial was conducted on a 3.4 mmol scale to generate >450 mg of isolated product and demonstrate scalability.

Cognisant that the parent dipyrrin 3 has been described as unstable at temperatures above −40 °C, we sought to intercept and characterise this previously elusive compound. Our initial strategy relied upon isolating 3 after the oxidation of di(1H-pyrrol-2-yl)methane (first step in Table 1). To a slurry of p-chloranil in CH2Cl2 at −40 °C under nitrogen, a solution of di(1H-pyrrol-2-yl)methane in CH2Cl2 was added drop-wise. The solvent was removed
in vacuo at −40 °C after 3 hours: the $^1$H NMR spectrum of the resulting crude mixture in CDCl$_3$ (probe held at −45 °C) indicated a complex mixture of products. Visual inspection revealed decomposition at room temperature: the isolated yellow solid darkened to black over several minutes in an inert nitrogen atmosphere. A sample, held at −40 °C until just prior to dissolution in methanol and injection, was submitted for analysis using ESI$^+$ mass spectrometry. Although the [M + H]$^+$ molecular ion for 3 at 145.1 m/z exhibited very low intensity, the base peak at 289.1 m/z corresponded to a protonated dimer of 3, [2M + H]$^+$. Furthermore the presence of trimeric, tetrameric and pentameric ions clearly indicated the formation of the desired dipyrrin 3, as its free-base. Despite the successful formation of 3 this route, we were unable to attain satisfactory NMR data.

We then investigated the derivatization of 1 to prepare the first analogues at boron featuring the unsubstituted dipyrrinato framework. Having demonstrated$^{13}$ the quantitative replacement of fluorine atoms with chlorine on the boron atom of substituted 4,4-difluoroBODIPYs, we sought the 4,4-dichloroBODIPY 2$^{14}$ featuring the parent unsubstituted skeleton.$^{13}$ Gratifyingly, treatment of 1 with BCl$_3$ gave 2 in 99% isolated yield (Scheme 1). Notably, the characteristic triplet observed in the $^{13}$B NMR spectrum of 1 was replaced by a singlet for 2. Exposure of 2 to air lead to complete decomposition over several hours. The conversion of 1 to 2 is the first chemical transformation featuring the unsubstituted dipyrrinato framework.

To further explore the reactivity, we treated 1 with EtMgBr and obtained an inseparable fluorescent mixture of the BODIPYs 4 and 5 in 2:1 ratio according to $^1$H NMR analysis (Scheme 2). Previous reports state that the treatment of meso-unsubstituted 4,4-difluoroBODIPYs with allyl or aryl reagents generates the corresponding meso-allyl or meso-aryl substituted BODIPYs as major products,$^{14}$ and so the generation of 5 was unsurprising. Exposure of the product mixture to air resulted in decomposition over several hours, contrasting starkly with the generally high stability of 4,4-dialkylBODIPYs with substituted dipyrrinato frameworks. Substitutions at the boron centres of 4,4-dichloroBODIPYs require milder reaction conditions than those of substituted variants.$^{1–6}$ However, reaction of 1 with EtMgBr was no more successful than for 4,4-dimethoxyBODIPY ($^4$), as such reactions are insufficient to account for the extreme instability of the 4,4-dimethoxyBODIPY 6 (least stable experimentally) under both atmospheric and inert conditions, particularly since the calculated strengths of the B–N bond in these compounds. These descriptions demonstrate the relatively strong and short B–N bond$^{15}$ in compounds. These observations correlate well with our experimental results (i.e., the 4,4-difluoroBODIPY is most stable), but this data is insufficient to account for the extreme instability of the 4,4-dimethoxyBODIPY 6 (least stable experimentally) under both atmospheric and inert conditions, particularly since the calculated strengths of the B–N bonds in 4 and 6 are of approximately equal value.

To explore the formal loss of BX$_2$ for decomposition, the thermochemical properties of these compounds in their complexed and dissociated states were calculated (Table 3). As the B–N bond in the BODIPY 1 is chemically robust, the formal dissociation of BF$_2$.

<table>
<thead>
<tr>
<th>Boron substitution</th>
<th>Length (Å)</th>
<th>Frequency (cm$^{-1}$)</th>
<th>Force constant (millidyne per Å)</th>
<th>Ionicity (a.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoro (1)</td>
<td>1.392</td>
<td>1165.5</td>
<td>5.265</td>
<td>3.630</td>
</tr>
<tr>
<td>Ethyl (4)</td>
<td>1.599</td>
<td>1126.4</td>
<td>3.023</td>
<td>3.233</td>
</tr>
<tr>
<td>Methoxy (6)</td>
<td>1.603</td>
<td>1138.4</td>
<td>3.207</td>
<td>3.570</td>
</tr>
</tbody>
</table>

Ionicity of the bond is defined as: $q(B) - q(N)$, the difference in the charges of the boron and nitrogen atoms.
Table 3 Calculated energies of the hypothetical dissociation reactions of BODIPYS to their ionic boron-dipyrrin products

<table>
<thead>
<tr>
<th>Boron substitution (X)</th>
<th>ΔG (kcal mol⁻¹)</th>
<th>ΔH (kcal mol⁻¹)</th>
<th>ΔE (kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoro (1)</td>
<td>267.7</td>
<td>280.2</td>
<td>283.3</td>
</tr>
<tr>
<td>Ethyl (4)</td>
<td>183.7</td>
<td>201.0</td>
<td>205.9</td>
</tr>
<tr>
<td>Methoxy (6)</td>
<td>174.2</td>
<td>192.6</td>
<td>195.5</td>
</tr>
</tbody>
</table>

Calculated at the B3LYP/6-311++G(d,p) level of theory in the gas phase at 25°C.

Fig. 2 Top to bottom: partial ¹H NMR spectra in CDCl₃ obtained after step-wise addition of methanol to 2, to form 3 HCl.

Finally, methanol (5 eq.) was added to a solution of 2 in anhydrous CH₂Cl₂ under nitrogen. After 30 minutes, analysis using ¹H and ¹¹B NMR spectroscopy confirmed that decomposition had occurred, and that 3-HCl had again been formed. BCl₃ (5 eq.) was then added, and the reaction was stirred for an hour before work-up and analysis. The ¹H spectrum revealed two sets of pyrrolic signals: one for 4,4-dichloroBODIPY 2 and another for the dipyrrin salt 3-HCl. The ¹¹B spectrum featured the 4,4-dichloroBODIPY 2 at 2.26 ppm, alongside signals for B(OMe)Cl₂, B(OMe)₂Cl and B(OMe)₃, as well as two unassigned signals. This experiment demonstrates that, not only can the dipyrrin 3 be generated from 4,4-dichloroBODIPY 2, but that there is potential for the formation of other BODIPYS subsequent to the in situ formation of 3.

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC).

Notes and references