ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 816

Received 13th October 2012,
Accepted 14th November 2012

DOI: 10.1039/c2cc37480c

www.rsc.org/chemcomm

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†

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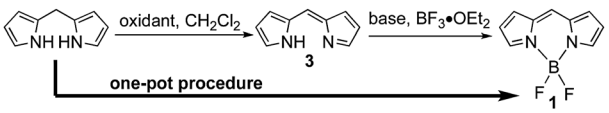
An improved and scalable synthesis of the unsubstituted 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene framework facilitates access to the previously unreported parent dipyrrin HCl salt, as well as 4,4-dichloro-4-bora-3a,4a-diaza-*s*-indacene.

Within the unsubstituted family of dipyrrins (Fig. 1) only the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY **1**) is known, whereas dipyrrins and BODIPYs substituted around the dipyrrinato scaffold are commonplace.[1–6] Indeed, compound **1**[7] was synthesised only recently[8–10] *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 **1**, generation of the 4,4-dichloro-4-bora-3a,4a-diaza-*s*-indacene (*Cl*-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%.[9,10] The one-pot approach towards **1** relies upon the efficient oxidation of di(1*H*-pyrrol-2-yl)methane,[11] and subsequent trapping of dipyrrin **3** upon the addition of $BF_3{\cdot}OEt_2$ (Table 1). Using sterically hindered amine bases, and changing the oxidant from DDQ to *p*-chloranil, resulted in an increased yield[10] of **1**:[12] 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 $BF_3{\cdot}OEt_2$. We 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,[7] we sought to intercept and characterise this previously elusive compound. Our initial strategy relied upon isolating **3** after the oxidation of di(1*H*-pyrrol-2-yl)-methane (first step in Table 1). To a slurry of *p*-chloranil in CH_2Cl_2 at −40 °C under nitrogen, a solution of di(1*H*-pyrrol-2-yl)-methane in CH_2Cl_2 was added drop-wise. The solvent was removed

Table 1 Optimization of the synthesis of BODIPY **1**



Entry	Oxidation conditions: Oxidant	Temp. (°C)	Time (h)	*F*-BODIPY formation conditions: Base	Temp. (°C)	Time (h)	Isolated yield of **1** (%)
1	DDQ	−78	**1**	DBU	−78 to 40	1	5–10[a]
2	*p*-Chloranil	−78	**1**	DIPEA	−78 to −30	3	29[b]
3	*p*-Chloranil	−40	**3**	DIPEA	−40 to 22	18	76,[b,d] 72[c,e]

[a] Reported literature result.[10] [b] 0.5 mmol scale. [c] 3.4 mmol scale. [d] Repeat in toluene, 78% isolated yield. [e] Repeat in toluene, 67% isolated yield.

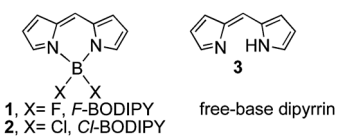


Fig. 1 Unsubstituted BODIPYs **1** and **2**, plus dipyrrin **3**.

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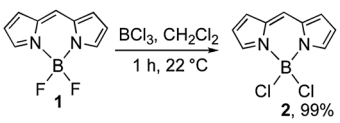
† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra. See DOI: 10.1039/c2cc37480c

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** *via* this route, we were unable to attain satisfactory NMR data.

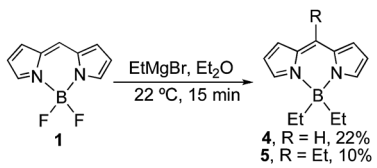
We then investigated the derivatization of **1** to prepare the first analogues at boron featuring the unsubstituted dipyrrinato framework. Having demonstrated[13] the quantitative replacement of fluorine atoms with chlorine on the boron atom of substituted 4,4-difluoroBODIPYs, we sought the 4,4-dichloroBODIPY **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 ^{11}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 alkyl or aryl reagents generates the corresponding *meso*-alkyl 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 4,4-difluoroBODIPYs, and are high yielding.[14] However, reaction of **2** with EtMgBr was no more successful than for **1**, presumably due to the instability of the unsubstituted dipyrrinato framework. Attempts to synthesise B-aryl analogs, using PhLi, were equally fruitless.

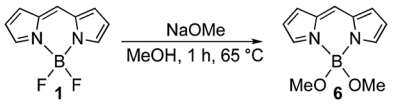
We then investigated using **1** and **2** for the synthesis of the 4,4-dimethoxyBODIPY (*O*-BODIPY) **6** as such reactions are



Scheme 1 Synthesis of 4,4-dichoroBODIPY **2**.



Scheme 2 Alkyl substitution of BODIPY **1**.



Scheme 3 Attempted alkoxy substitution of BODIPY **1**.

straightforward using 4,4-difluoroBODIPYs featuring substituted dipyrrinato units.[15] A solution of **1** in methanol was treated with NaOMe (Scheme 3). At room temperature the reaction did not progress, but heating to 65 °C resulted in complete consumption of the starting material within an hour. The product mixture contained highly unstable material that rapidly decomposed. In one case, the reaction mixture was quickly concentrated and filtered through a plug of alumina to give a mixture of **6** (as verified using ^{1}H NMR and ^{11}B NMR spectroscopy, and low resolution ESI mass spectrometry) and two unidentifiable products. As before, analogous experiments were conducted using the 4,4-dichloroBODIPY **2**. The addition of NaOMe to **2** in CH_2Cl_2 at room temperature was sufficient for reaction to occur (heat not required), further demonstrating the increased reactivity of 4,4-dichloroBODIPYs over 4,4-difluoroBODIPYs.[14] However, we were unable to obtain a sample of **6**.

To summarise our experimental findings, BODIPYs of the unsubstituted dipyrrinato skeleton are significantly less stable than those of substituted variants:[1–6] our experimental work indicates a relative stability of F > Cl > C > O with respect to substitution at boron. Although the decomposition of BODIPYs is documented,[16] theoretical studies for potential decomposition mechanisms are limited.[17] We therefore employed[18] theoretical methods to examine the B–N bonds, as well as pathways through which decomposition might occur. Several descriptors of the B–N bond strength in BODIPYs **1**, **4** and **6** were calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of density functional theory (Table 2).

These descriptors demonstrate the relatively strong and short B–N bond in **1** *cf.* within the other derivatives: the symmetric stretch vibrational frequencies (ν) reflect this trend. In addition, the force constants associated with these stretches indicate that the B–N bond in **1** is substantially more rigid (less deformable) than in the other 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 2 Calculated B–N bond descriptors of BODIPYs

Boron substitution	Length (Å)	Frequency (cm^{-1})	Force constant (millidyne per Å)	Ionicity (a.u.)
Fluoro (**1**)	1.392	1165.5	5.265	3.630
Ethyl (**4**)	1.599	1126.4	3.023	3.233
Methoxy (**6**)	1.603	1138.4	3.207	3.570

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

Boron substitution (X)	ΔG (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔE (kcal mol^{-1})
Fluoro (**1**)	267.7	280.2	283.3
Ethyl (**4**)	183.7	201.0	205.9
Methoxy (**6**)	174.2	192.6	195.5

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

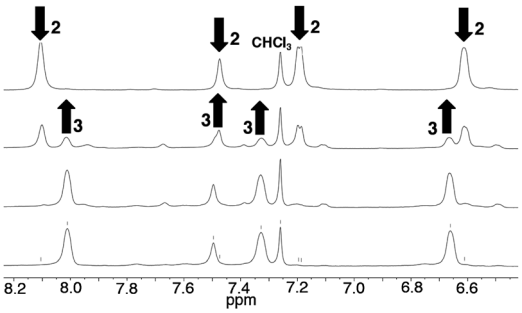
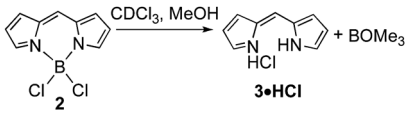


Fig. 2 Top to bottom: partial ^{1}H NMR spectra in $CDCl_3$ obtained after step-wise addition of methanol to **2**, to form **3·HCl**.

from **1** would be expected to be highly unfavoured. Indeed, the energy of dissociation is >80 kcal mol^{-1} higher for **1** than for **4**. Notably, the calculated trend indicates that the dimethoxy variant **6** exhibits the lowest energies of dissociation and that the 4,4-diethyl-BODIPY **4** is intermediate in stability: thus F > C > O, which matches our experimental observations. While further studies are required to fully understand potential mechanism(s) of decomposition, these preliminary investigations offer rationale for our synthetic work.

To monitor the decomposition of 4,4-dimethoxyBODIPY **6**, with hopes of attaining satisfactory NMR data for **3**, a series of spectra were acquired using a solution of **2** (^{11}B singlet at 2.26 ppm) in $CDCl_3$. Methanol (5 eq.) was added in three aliquots, at five minute intervals, and ^{1}H, ^{11}B spectra were acquired immediately (Fig. 2). The ^{1}H signals for **2** decreased as a new set of peaks formed in the aromatic region, accompanied by the emergence of an N–*H* signal at 14.6 ppm integrating for two protons. The signal at 14.6 ppm is consistent[19,20] with those for N–*H* units within dipyrrin salts. Concomitantly, a ^{11}B singlet for $B(OMe)_3$ at 18.5 ppm appeared as the ^{11}B singlet singlet at 2.26 ppm for **2** disappeared. A new set of peaks in the ^{13}C NMR spectrum were also obtained (see ESI† for ^{11}B stack plot and ^{13}C spectrum). Notably, these results were reproducible through the single addition of five equivalents of methanol to **2** with stirring for 30 minutes. These new signals are indicative of the unsubstituted dipyrrin salt **3·HCl**, presumably formed after the 4,4-dichloroBODIPY **2** was converted to the 4,4-dimethoxyBODIPY **6** which then decomplexed[21] to form **3**. Under these conditions **3** was protonated to give the hydrochloride salt. Such salts are more stable than the corresponding free-base dipyrrins,[20,22] and NMR characterisation was enabled for the first time. After 24 hours there were no dipyrrinato-type signals in the ^{1}H NMR spectrum: decomposition had occurred. However, ESI$^+$ mass spectral analysis after 30 minutes revealed a base peak at 289.1 *m*/*z* corresponding to the protonated dimer $[2M + H]^+$ of **3**, plus signals for monomeric, trimeric and tetrameric ions. These results matched those obtained for the highly unstable free-base sample of **3** prepared *via* oxidation of di(1*H*-pyrrol-2-yl)-methane. Methanol thus decomplexes **2** to enable the synthesis and characterisation of the HCl salt of the unsubstituted dipyrrin **3**, which is sufficiently stable to enable characterisation in solution.



Finally, methanol (5 eq.) was added to a solution of **2** in anhydrous CH_2Cl_2 under nitrogen. After 30 minutes, analysis using ^{1}H and ^{11}B NMR spectroscopy confirmed that decomplexation had occurred, and that **3·HCl** had again been formed. BCl_3 (5 eq.) was then added, and the reaction was stirred for an hour before work-up and analysis. The ^{1}H spectrum revealed two sets of pyrrolic signals: one for 4,4-dichloroBODIPY **2** and another for the dipyrrin salt **3·HCl**. The ^{11}B spectrum featured the 4,4-dichloroBODIPY **2** at 2.26 ppm, alongside signals for $B(OMe)Cl_2$, $B(OMe)_2Cl$ 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).

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