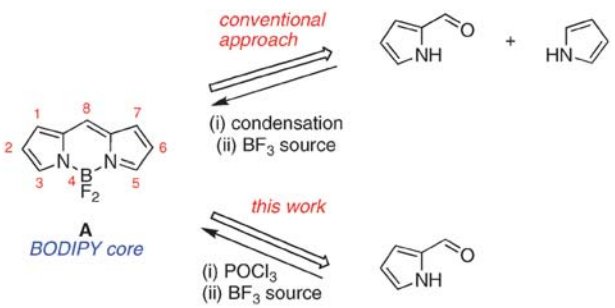
A new synthesis of symmetric boraindacene (BODIPY) dyes†

Liangxing Wu and Kevin Burgess*

Received (in Austin, TX, USA) 23rd June 2008, Accepted 26th July 2008
First published as an Advance Article on the web 19th September 2008
DOI: 10.1039/b810503k

BODIPY dyes were synthesized from pyrrole-2-carbaldehyde derivatives in high yields; this constitutes a new approach to this dye framework.

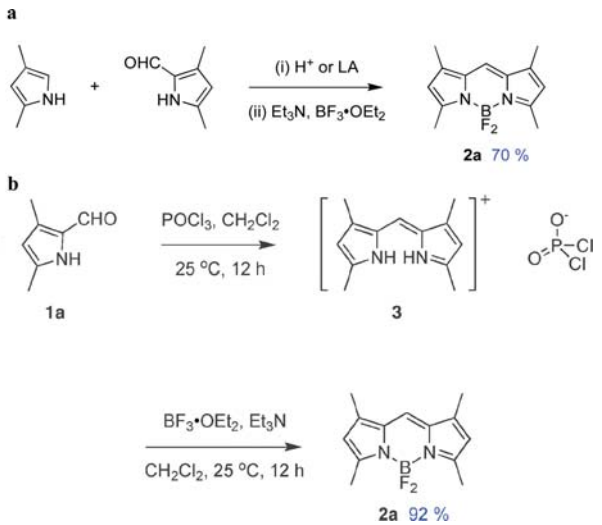
4,4-Difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene, or BODIPY® (hereafter abbreviated to BODIPY) dyes are important probes for biotechnology and other applications.[1,2] They share the framework **A**, though many simple alkylated derivatives have never been prepared. This is partially because there are relatively few methods to access these systems. Usually, BODIPY dyes without an 8-substituent are obtained *via* condensation of a pyrrole-2-carbaldehyde with a pyrrole,[3–5] as illustrated below. This communication describes the serendipitous discovery that this same product can be prepared from the aldehyde component alone. Further, the yields can be superior for this new approach, as indicated in Scheme 1.



When 3,5-dimethylpyrrole-2-carbaldehyde (0.2 M in dichloromethane) was treated with 1.2 equivalents of $POCl_3$ as indicated in Scheme 1b, a yellow solution resulted, and evolution of gas was observed. ^1H, ^{13}C, ^{31}P NMR and MS analyses of the crude reaction mixture showed that it contained the known[3–5] dipyrromethenium cation **3** and the dichlorophosphate counterion. Intermediate **3** was converted to the BODIPY product **2a** without isolation by adding $BF_3{\cdot}OEt_2$ to the reaction mixture.

The process in Scheme 1b (but in $CDCl_3$, at 0.2 M of substrate) was followed by ^1H, ^{13}C, and ^{31}P NMR over 10 min intervals at room temperature. More than 95% conversion was observed in less than 20 min, and no by-products were observed by NMR (see ESI†). Gas evolution occurred, possibly due to loss of CO and HCl from the system.

The reaction shown in Scheme 1b was also followed *via* continual UV measurements. This experiment required a considerably more dilute solution (6.7×10^{-5} M). Excess phosphorus oxychloride was used in this experiment, so the concentration of that reagent was effectively invariant throughout the transformation. Absorbance peaks for phosphorus oxychloride, the pyrrole-2-carbaldehyde and the product **3** were well resolved under these conditions (Fig. 1). As the reaction progressed, the concentration of the pyrrole **1a** declined and the dipyrromethene **3** was formed. No intermediates or byproducts were detected.



Scheme 1 (a) Conventional synthesis of tetramethyl-BODIPY **2a**; and (b) the new approach described here.

Kinetic data extracted from the UV experiment are plotted in Fig. 1c. Over the first 20 min of the transformation, it is second order with respect to the pyrrole (6.43 L mol^{-1} s^{-1}). This analysis assumes that there were no intermediates having coincident UV absorption characteristics.

Table 1 outlines how the new reaction conditions were used to prepare a series of BODIPY dyes **2b–2g**. Product yields tended to be good, except where there were steric issues from a C^3-substituent (compare **2b** and **2d**), where the pyrrole was less electron rich (compare **2e** and **2h**), or for reasons that cannot be explained simply (**2f** and **2g**). Characteristically, all the new BODIPY dyes emit bright, sharp fluorescent signals (Table 2 and Fig. 2). Various substituents were tolerated in the synthesis, hence probes could be prepared that emit in the range 516–662 nm.

The data collected on this reaction type were quite extensive, but still no clearly favored mechanism emerges. All the evidence indicates that phosphorus oxychloride seems to be intimately involved in this reaction; when this reagent is

Department of Chemistry, Texas A&M University, P. O. Box 30012, College Station, TX 77842, USA. E-mail: burgess@tamu.edu
† Electronic supplementary information (ESI) available: Procedures for syntheses and spectral data for characterization. See DOI: 10.1039/b810503k

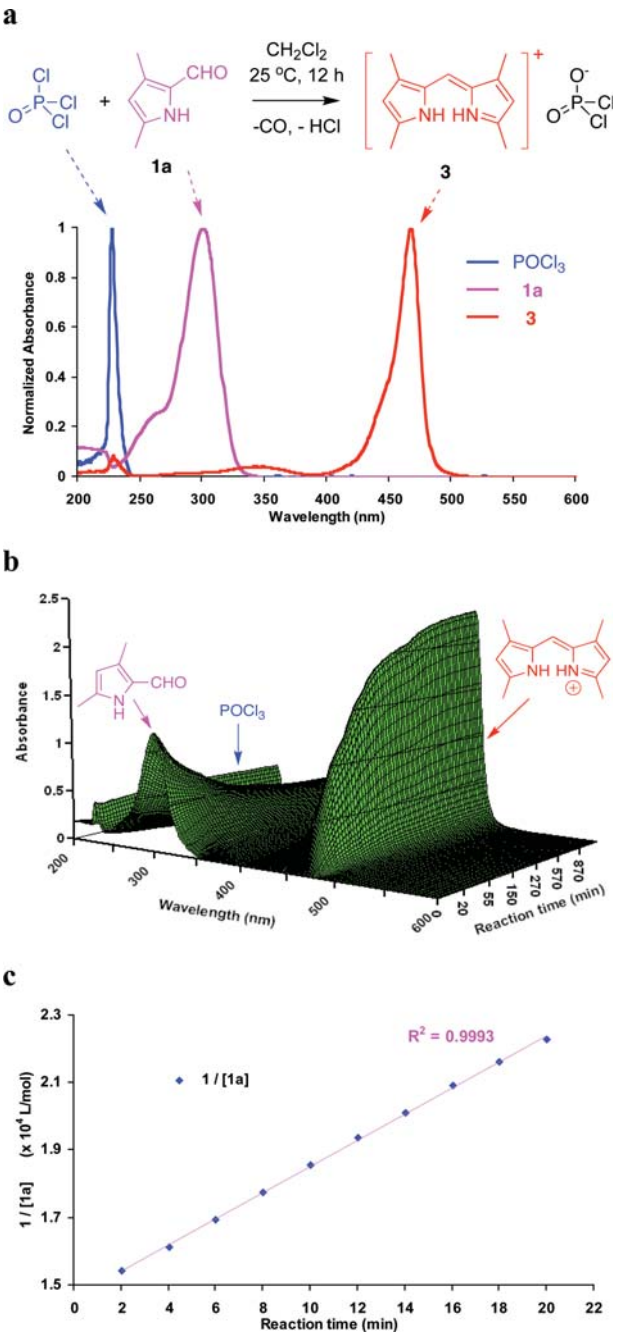
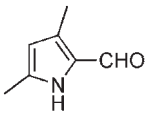
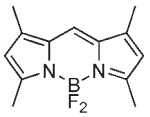
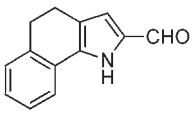
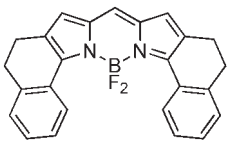
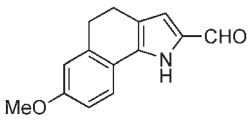
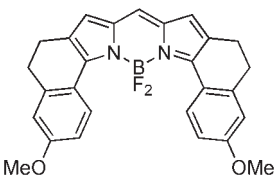
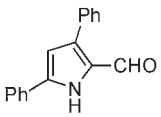
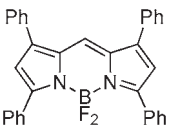
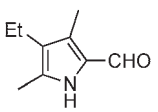
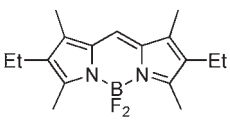
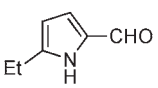
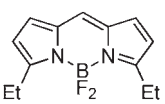
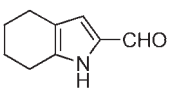
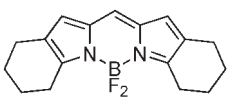
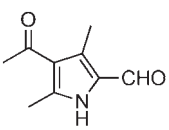
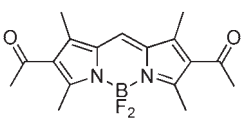


Fig. 1 UV study of the self-condensation reaction shown in CH_2Cl_2 at 25 °C, and 6.7×10^{-5} M of pyrrole **1a**. (a) Reaction components and their UV spectra; (b) UV profile for the reaction; (c) plot used to deduce the rate of the reaction.

replaced with another Lewis acid (specifically, TFA or $BF_3{\cdot}OEt_2$), the dipyrromethenium cation **3** did not form. One possibility is that $POCl_3$ reacts with pyrrole-2-carboxyaldehyde to give a vinylogous Vilsmeyer–Hack reagent (Fig. 3, where alternatively the chloride could be a *P*-based leaving group). Formation of the product then relies on electrophilic attack of this reagent on the C^2-atom of another pyrrole-2-carbaldehyde molecule. However, it is somewhat surprising if this is the regioselectivity of the attack in that step for some of the substrates.

Table 1 Synthesis of symmetric BODIPYs

Entry	Substrate **1**	Product **2**	Yield (%)
a			92
b			91
c			85
d			21
e			75[a]
f			28
g			22
h			0[b]

[a] Literature reported yield was 45%.[6,7] [b] Complex mixtures, trace amount product.

Table 2 Photophysical properties of BODIPYs **2** in CH_2Cl_2

	$\lambda_{max\ abs}$/nm	ε/M^{-1} cm^{-1}	$\lambda_{max\ emiss}$/nm	fwhm[a]/nm	Φ_{fl}
2a	505	83 200	516	—	0.80[b]
2b	629	161 500	637	23	0.78 ± 0.03[c]
2c	651	149 100	662	27	0.71 ± 0.04[c]
2d	564	78 000	593	—	1.00[d]
2e	531	87 000	538	21	0.86 ± 0.03[e]
2f	512	110 200	516	17	0.96 ± 0.02[e]
2g	547	92 000	553	20	0.90 ± 0.02[e]

[a] Full width at half maximum height of fluorescence (fwhm). [b] Data were obtained from reference.[8] [c] Nile blue (Φ 0.27 in EtOH) was used as a standard.[9] [d] Data were obtained from ref. 10. [e] Rhodamine 6G (Φ 0.94 in EtOH) was used as a standard.[11]

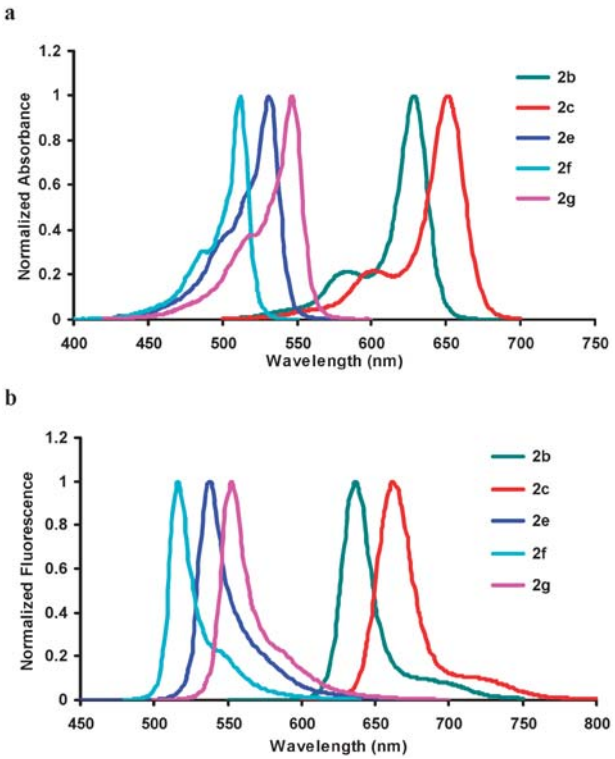


Fig. 2 Spectra of BODIPY **2** in CH_2Cl_2: (a) absorbance (10^{-6} M); (b) fluorescence (10^{-7} M, excited at $\lambda_{max\ abs}$).

In summary, the new route to BODIPYs described here allows for efficient preparation of materials, in some cases in good yields, with a diversity of alkyl and aryl substituents.

We thank Mr Cliferson Thivierge for the preparation of 2,4-diphenylpyrrole, the National Institutes of Health (GM72041) and The Robert A. Welch Foundation for financial support, and the TAMU/LBMS-Applications Laboratory directed by Dr Shane Tichy for assistance with mass spectrometry.

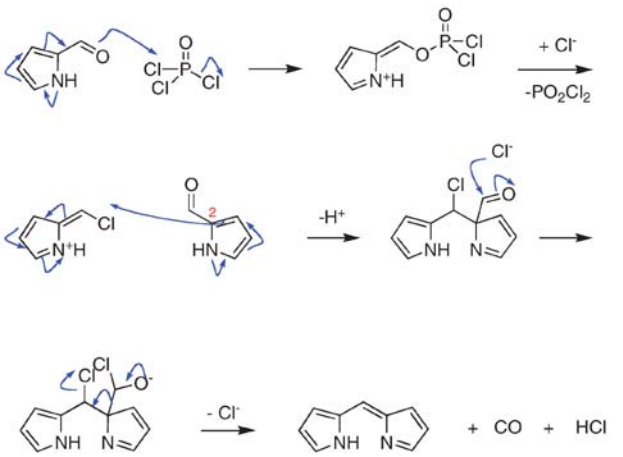


Fig. 3 A possible mechanism for the formation of dipyrromethene.

Notes and references

1 A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891–4932.
2 G. Ulrich, R. Ziessel and A. Harriman, *Angew. Chem., Int. Ed.*, 2008, **47**, 1184–1201.
3 J. A. Van Koeveringe and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, 1977, **96**, 55–58.
4 E. Vos de Wael, J. A. Pardoen, J. A. Van Koeveringe and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, 1977, **96**, 306–309.
5 H. J. Wories, J. H. Koek, G. Lodder, J. Lugtenburg, R. Fokkens, O. Driessen and G. R. Mohn, *Recl. Trav. Chim. Pays-Bas*, 1985, **104**, 288–291.
6 T. E. Wood, B. Berno, C. S. Beshara and A. Thompson, *J. Org. Chem.*, 2006, **71**, 2964–2971.
7 H. Falk, O. Hofer and H. Lehner, *Monatsh. Chem.*, 1974, **105**, 169–178.
8 M. Shah, K. Thangaraj, M. L. Soong, L. Wolford, J. H. Boyer, I. R. Politzer and T. G. Pavlopoulos, *Heteroat. Chem.*, 1990, **1**, 389–399.
9 R. Sens and K. H. Drexhage, *J. Lumin.*, 1981, **24–25**, 709–712.
10 B. P. Wittmershaus, J. J. Skibicki, J. B. McLafferty, Y.-Z. Zhang and S. Swan, *J. Fluoresc.*, 2001, **11**, 119–128.
11 D. Magde, R. Wong and P. G. Seybold, *Photochem. Photobiol.*, 2002, **75**, 327–334.