ORGANIC LETTERS

2008
Vol. 10, No. 14
2991−2993

Near-Infrared Fluorophores Containing Benzo[*c*]heterocycle Subunits

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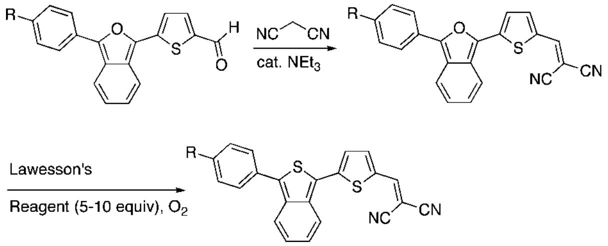
Received April 30, 2008

ABSTRACT



The syntheses and spectroscopic properties of eight new push−pull-type near-infrared fluorophores that contain either isobenzofuran or isothianaphthene subunits are presented. The isobenzofuran dyes demonstrate significantly red-shifted absorption compared with their isothianaphthene counterparts, which is attributed to isobenzofuran's more potent pro-quinoidal character.

In vivo near-infrared (NIR) fluorescence imaging is rapidly emerging as a powerful diagnostic method.[1] In the NIR region (650−900 nm) biological chromophores exhibit low absorption and autofluorescence,[2] thus allowing photons to pass through the tissue and rendering this technique relatively noninvasive. With applications such as vascular mapping of the heart[3] and brain[4] and visualization of various pathologies including tumors,[5] atherosclerosis,[6] and β-amyloid plaques,[7] the demand for new NIR fluorescent contrast agents is ever increasing.

Our group recently reported the synthesis and *in vivo* imaging properties of NIAD-4 (**1**), NIM-1 (**2**), and NIM-2 (**3**), all donor−acceptor type dyes (Figure 1).[7a,8] In the case of **2** and **3**, it was found that the incorporation of benzo[*c*]heterocycle isothianaphthene (ITN) into the conjugated bridge red-shifted both the absorption and emission substantially. Herein we explore the use of benzo[*c*]heterocycle isobenzofuran (IBF) in place of ITN as a molecular component in this class of dyes.

Isothianaphthene has a relatively long history as a component in functional materials, with examples in fluorophores,[9] OLEDs,[10] photovoltaics,[11] and low band gap polmyers, of which polyisothianaphthene (PITN)[12] is the progenitor. The smaller band gap of these ITN-containing materials over similar

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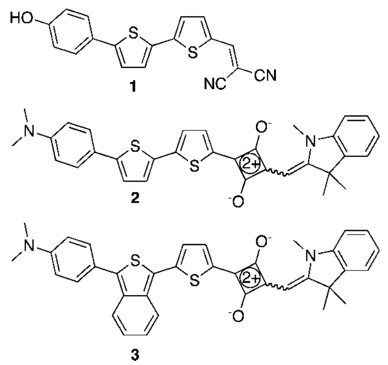


Figure 1. Structures of NIAD-4, NIM-1, and NIM-2.

thiophene-containing materials is a result of the increased contribution of the quinoid resonance structure (Figure 2) due to the stabilization achieved by aromatization of the benzene ring.[13]

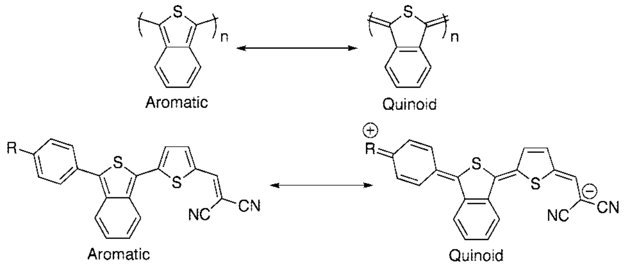
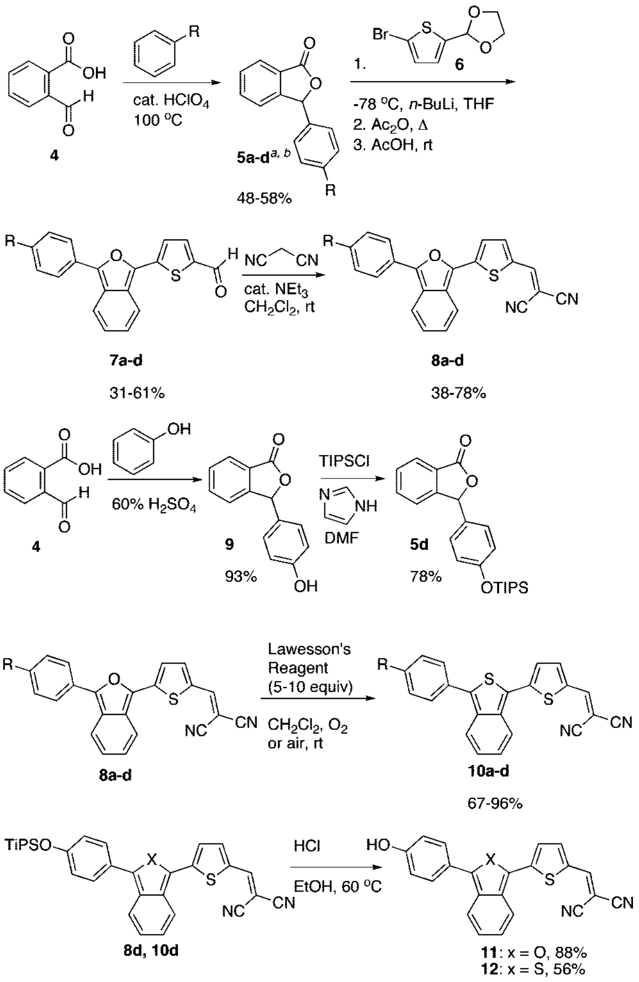


Figure 2. Aromatic and quinoid resonance structures of PITN and ITN donor−acceptor dyes.

In contrast, only a few examples[14] of functional materials containing isobenzofuran are reported in the literature, presumably because of its reduced stability.[15] For this reason, we predicted that IBF would prove even more pro-quinoidal and that its incorporation into donor−acceptor dyes would further reduce the band gap of these materials.

To test this principal, we synthesized a series of IBF and ITN dyes similar to NIAD-4 (Scheme 1). Four different electron-donating (R) groups, H-, MeO-, HO-, and Me_2N-, were incorporated in order to span a range of wavelengths. Appropriately substituted aryl-lactones **5a−d** were either purchased or synthesized via acid-mediated condensation[16] of 2-carboxybenzaldehyde and substituted benzenes. In the case of the phenol group (R = OH), TiPS protection was employed. Initially, the IBF framework was constructed with a free 5 position on the thiophene, which was subsequently lithiated and then formylated with DMF.

Scheme 1. Synthesis of IBF and ITN Dyes



[a]a: R = H-. b: R = MeO-. c: R = Me_2N-. d: R = TIPSO-. [b]**5a** is comercially available, **5d** synthesized as above.

However, these unsubstituted intermediate compounds proved relatively difficult to isolate and purify, resulting in poor yields for the formylation. Exploiting the acetal-protected aldehydes allowed us to bypass these troublesome intermediates. Protected aldehydes **7a−d** were produced in one step by reaction of the lactones with the lithio-derivative of **6**[17] followed by dehydration with acetic anhydride and deprotection with aqueous acetic acid. Knoevenagal condensation of the aldehydes with malonitrile installed the dicyanomethylene electron-withdrawing group to afford dyes **8a−d** in moderate yields. Deprotection of **8d** was achieved under acidic conditions as fluoride was found to revert the dicyanovinyl group to the aldehyde.

To access the ITN counterparts to dyes **10a−d**, we decided to explore methods by which the IBF dyes could be converted directly. It was found that such a transformation could be accomplished with good yields, in one pot, using a

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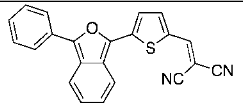
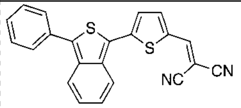
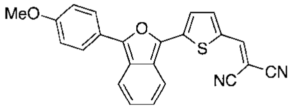
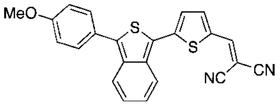
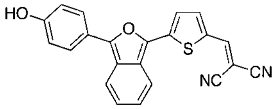
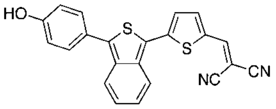
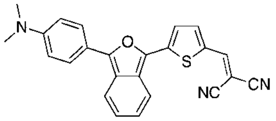
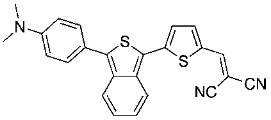
Table 1. Spectroscopic Properties of IBF and ITN Dyes[a]

IBF dye	λ_{max} abs (nm)	λ_{max} em (nm)	Φ^b	ITN dye	λ_{max} abs (nm)	λ_{max} em (nm)	Φ^b
 **8a**	556^c	658^c	.077^c	 **10a**	525^c	637^c	.061^c
	578^d	635^d	.075^d		544^d	629^d	.079^d
 **8b**	578^c	686^c	.078^c	 **10b**	537^c	672^c	.046^c
	599^d	675^d	.16^d		559^d	663^d	.099^d
 **11**	584^c	696^c	.049^c	 **12**	545^c	684^c	.023^c
	600^d	679^d	.12^d		559^d	667^d	.071^d
 **8c**	637^c	790^c	.0055^c	 **10c**	579^c	785^c	.0015^c
	656^d	762^d	.046^d		604^d	743^d	.021^d

[a] Spectra available in Supporting Information. [b] Quantum yields calculated by comparison to standards; see Supporting Information. [c] MeOH as solvent. [d] $CHCl_3$ as solvent.

5−10-fold excess of Lawesson's reagent in the presence of air or anhydrous oxygen. A possible mechanism includes the formation of an endoperoxide upon reaction of the IBF and oxygen, which in turn rearranges into to a diketone[18] followed by conversion of the diketone to the dithioketone with Lawesson's reagent and cyclization to form the ITN.[19] In the case of **8c**, the dicyanovinyl group was cleaved during the procedure, presumably to a thioaldehyde by Lawesson's reagent,[20] and thus treatment with excess malonitrile and base was necessary to obtain **10c**. Dye **10d** was deprotected under acid conditions in a similar manner as **8d**.

The spectroscopic properties of **8a−c**, **10a−c**, **11**, and **12** are listed in Table 1. In all cases, the IBF dyes exhibited markedly red-shifted absorption from the corresponding ITN moieties, thus demonstrating the narrower band gaps of the IBF compounds. The degree of this effect increases as the efficacy of the electron-donating group increases. The degree of red shift in the emission proved only modest, especially in the case of **8c** and **10c**, indicating that perhaps the quinoid resonance structure stabilization does not factor as heavily into the excited-state energies of these molecules.

In conclusion, we have demonstrated the greater effectiveness of isobenzofuran over isothianaphthene as a red-shifting component in donor−acceptor-type dyes, an effect attributable to the great pro-quinoidal nature of IBF. Currently, these compounds are being screened as NIR contrast agents for biomedical applications, and future investigations will explore the use alternate electron-withdrawing groups and the incorporation of different heterocycles into this fascinating class of compounds.

Acknowledgment. This work was supported by a NIH BRP grant (R01 AG026240-01A1).

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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