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Design of novel *meso*-CF_3-BODIPY dyes with isoxazole substituents

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ABSTRACT

The two approaches for the synthesis of *meso*-CF_3 substituted BODIPY dyes bearing isoxazole substituents at the position 3 of boradiazaindacene core have been developed. The key stages of the approaches are cycloaddition of hydroxylamine to the triple bond of available ethynyldipyrromethanes (1) and synthesis of isoxazoles from ethynylpyrrole and their further condensation with 2,2,2-trifluoro-1-(pyrrol-2-yl)-1-ethanols (2). The novel BODIPY dyes exhibit prospective optical features and fluorescence in the 611–646 nm with high (up to 0.94) quantum yield. Spectroscopic results have been rationalized with quantum mechanics calculation.

1. Introduction

Rapid interlaced evolution of science and industry requires new high technology materials, which could meet the totally new requirements of medicine, chemistry, optics and ecology. Boron dipyrromethenes (BODIPYs) are among such materials due to their application as probes in biotechnology [1,2], metals cations [3–5] and fluoride anion detectors [6], solar concentrators components [7], for photo-catalytic hydrogen generation [8] etc. The low sensitivity (in certain cases) to the polarity and basicity of the medium, as well as the relative stability under physiological conditions allow the BODIPY fluorophores to be applied as fluorescent probes, including fluorescent labels of proteins, lipids and DNA [9–11], as detectors of biological thiols in living cells [12]. BODIPY dyes are one of the most effective photosensitizers in photodynamic anticancer therapy [13–16]. Over last years BODIPY-based photosensitizers are widely used for the photodynamic antimicrobial, antifungal and antibacterial inactivation [17–21].

BODIPY chromophore photophysical characteristics are very sensitive to electronic and steric effects of functional groups attached to *meso*-position of the BODIPY core. The modification of BODIPY structure to the dipyrromethene core as well as functionalization of the *meso*-position enable tuning of their fluorescence characteristics, providing very sensitive methods for detection of various targets, including biomolecules (*e.g.* proteins, DNA, RNA, hormones) [9,22–24]. For example, *meso*-CF_3-BODIPY dyes which cause a deep bathochromic shift compared to that of the congeners with alkyl or aryl substituents in this position [25–29] are employed as fluorescent sensors for *in vivo* imaging systems and in photodynamic therapy due to confirmed singlet oxygen generation [29–35]. Quantum chemical calculations evidence that *meso*-CF_3 group significantly stabilizes the LUMO of such BODIPY, decreasing the HOMO-LUMO energy gap and explaining the bathochromic shift of the visible absorption band [28,36].

Although the importance of *meso*-CF_3-BODIPY is undisputed, compounds of this class containing heterocyclic, in particular, isoxazole substituents in their pyrrole moieties (C-3 or C-3,5 positions) are still unknown, though isoxazoles are well known biologically active fragments [37], common in natural compounds, their synthetic analogs and commercial drugs. For example, a number of well-marketed medicines are based on isoxazole scaffold [38,39]. Also, isoxazole containing compounds possess anti-tuberculosis [40], anti-inflammatory [41], cytotoxic [42], fungicidal [43] and antihypertensive properties [44]. Moreover, these compounds combined with fluorophore core are capable of deactivating multidrug-resistance protein (P-glycoprotein 1) that pumps many foreign substances out of cells [45]. Photosensitizer molecule, bearing isoxazole pharmacophore units, could strongly improve efficiency of PDT procedures, thus allowing a new class of highly effective medicines perspective for solving a multidrug-resistance problem to be designed.

Thus, the development of concise and expedient methods for the construction of BODIPY with *meso*-CF_3 and isoxazole substituents represents a one of the challenges for synthetic chemistry.

2. Results and discussion

Here we report the synthesis of *meso*-CF_3-BODIPY dyes with 3- or 5-phenylisoxazole substituents in the position C-3 of boradiazaindacene

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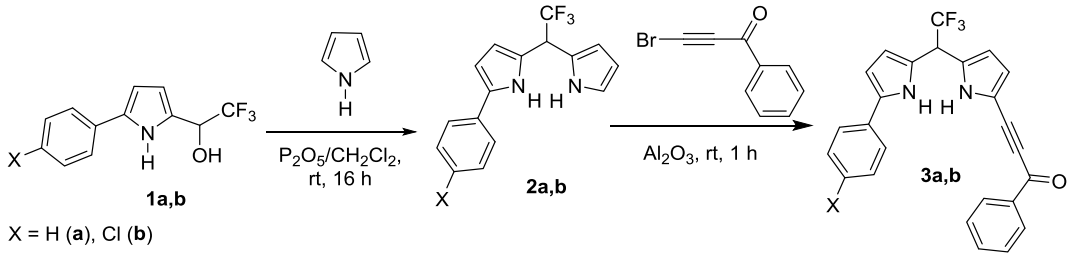
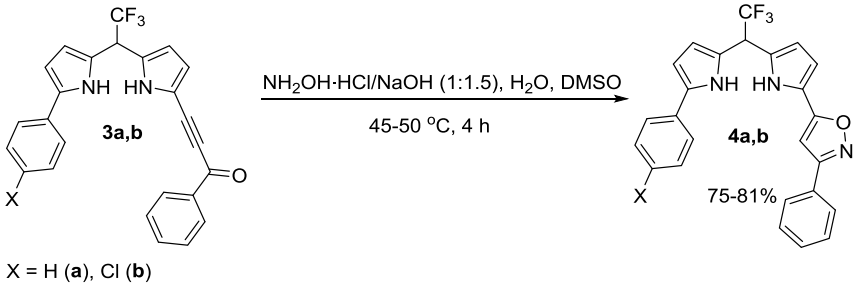
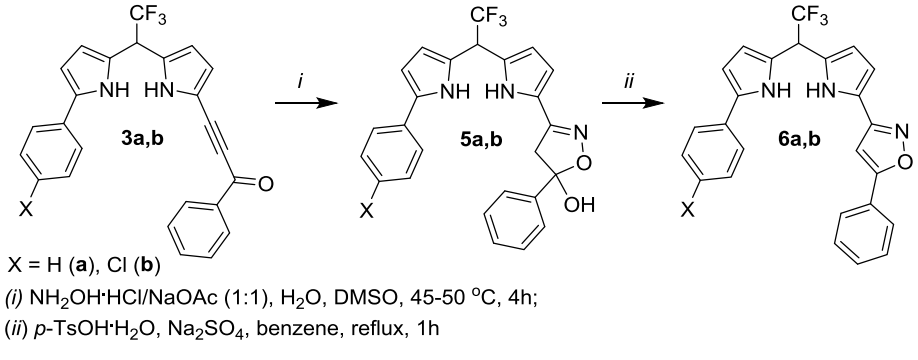


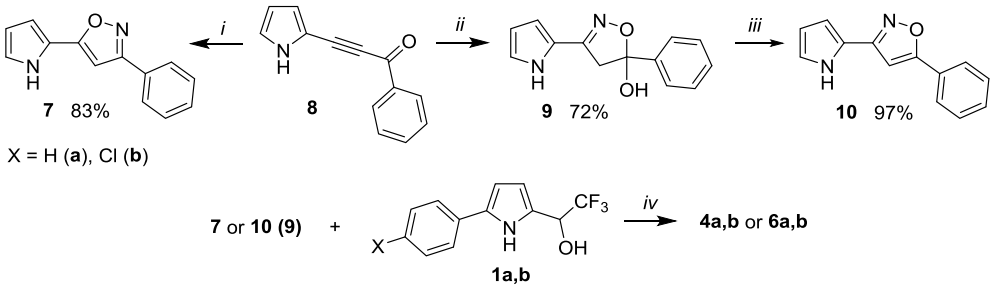
Scheme 1. Previous work.



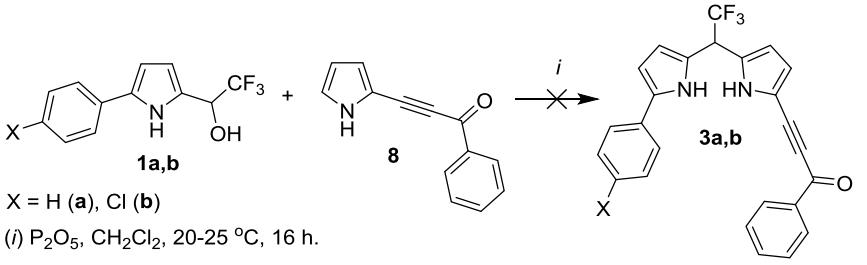
Scheme 2. Synthesis of (3-phenylisoxazol-5-yl)dipyrromethanes **4a,b** from ethynyldipyrromethanes **3a,b.**



Scheme 3. Synthesis of (5-phenylisoxazol-3-yl)dipyrromethanes **6a,b** from ethynyldipyrromethanes **3a,b.**



Scheme 4. Alternative synthesis of (3- or 5-phenylisoxazolyl)dipyrromethanes **4a,b** and **6a,b.**



Scheme 5. Synthesis of dipyrromethanes **3a,b** from 2,2,2-trifluoro-1-(pyrrol-2-yl)-1-ethanols **1a,b** and ethynylpyrrole **8.**