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Recent advances of synthesis of Boron derivatives and their applications in bioimaging

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ABSTRACT

The increasing interest in the luminescent boron materials is due to their potential application in diverse areas such as solar cells, optoelectronic devices, and biological imaging materials. Continuous search for the compounds with better properties, luminescent organoboron materials have been gaining more importance, especially in the development of new technologies and novel techniques for bioimaging, which is a powerful tool to analyze the cellular organelles with important value into the cell biology and medical research. Synthesis, properties, and applications of luminescent boron compounds and their application in bioimaging are reviewed.

1. Introduction

An interesting alternative for the development of luminescent materials are the coordination compounds derived from main group elements. Recently, there has been great interest in the development of boron compounds, which display an important role in different fields such as supramolecular chemistry,[1] construction of organic light-emitting diodes (OLEDs),[2] photo-responsive materials,[3] sensing,[4] molecular rotors,[5] and in the development of new materials for fluorescent bioimaging (FBI).[6] The FBI is a practical technique to study the localization and movement of molecules in living cells by fluorescence.[7] Recently have been demonstrated that fluorescent compounds derived from boron have several advantages for this application. These benefits include their capability to penetrate into the cells, solubility and stability in biological media, which can be excited and emit non-damaging wavelengths.[8,9] This also reveals the photophysical properties and large Stokes shift for effective discrimination of excitation and emission wavelengths.

2. Synthesis of luminescent organoboron materials

Fluorescent organoboron compounds are significant and promising materials due to their photonic, biomedical, and optoelectronic applications.[2,10–18] By reviewing the synthetic routes of luminescent organoboron compounds, numerous methods have been carried out by conventional methods, for example simple reflux to open-flask can be isolated tetracoordinated fluorescent Boron compounds derived from Schiff bases and Ph_2BOH or $PhB(OH)_2$.[5,19–21] However, when starting materials of Boron are air-sensitive such as BPh_3,[22–24] $BF_3(OEt_2)$,[25–30] BBr_3,[31,32] and $(Mes)_2BF$ (Mes = 2,4,6-$Me_3C_6H_2$) [33] the synthesis must be carried out in special conditions due to their high toxicity and reactivity (Scheme 1). For example, it has been reported the synthesis of derived from quinolate,[34–38] smaragdyrins,[39] difluoroboron,[40,41] BODIPYs,[42–44] and three-coordinated molecules using Schlenk line,[45–47] with reaction time ranging from 2 to 18 hours, and other multi-step synthesis, which takes around 5 days.[48] Chan *et al.* have reported a green synthetic approach of fluorescent organoboron compounds derived from Schiff bases by microwave-assisted synthesis. They described the preparation of four organoboron compounds in acetonitrile and alumina (Al_2O_3) as a support, with reaction time of 5 minutes in both routes and with enough chemical yields (94-97%) with more solvent. The reaction time decreased about of 576 times less than conventional method previously reported.[49]

3. Fluorescent bioimaging by luminescent organoboron materials

Boron-dipyrromethene (BODIPY) derivatives have attracted great interest over the past years due to their high phosphorescence and their photophysical properties, including high stability toward light and chemical agents, large molar extinction coefficients in the higher-wavelength visible region, high fluorescence quantum yields, and relatively long fluorescence lifetimes.[50,51] All of these features make this family an excellent option for biological applications in disease therapies and cell imaging.[52,53] For bioimaging purpose, developing water soluble BODIPYs which present a far-red or NIR emission and large Stokes shift, is an important research topic and of particular interest due to the unique advantages of NIR in biological applications. The long-wavelength region would generate minimum photo-toxicity to biological components, deep tissue penetration and minimize auto-fluorescence background by bio-molecules.[8]

The solubility of these dyes in aqueous media can be greatly enhanced by introducing hydrophilic groups, such as quaternary ammonium, sulfonate, phosphonates and the symmetric functionalization of the boron-core, without changing their high fluorescence quantum yields.[58] We can find in the literature NIR BODIPY-based fluorescent compounds capable to penetrate the cell and localize in the cytoplasm[59] or organelles such as mitochondria and endoplasmic reticulum[60,61] also there are reports of fluorescent probes for specific molecules such as enzymes.[62]

Fluorescent molecular rotors of Boron compounds derived from Schiff bases has been reported as well, as favorable molecules to penetrate the cell membrane and stain the cytoplasm. These compounds demonstrate the quantum yield rise when solvent viscosity increases as well, property that is extremely functional in viscosity studies on cellular scale.[5]

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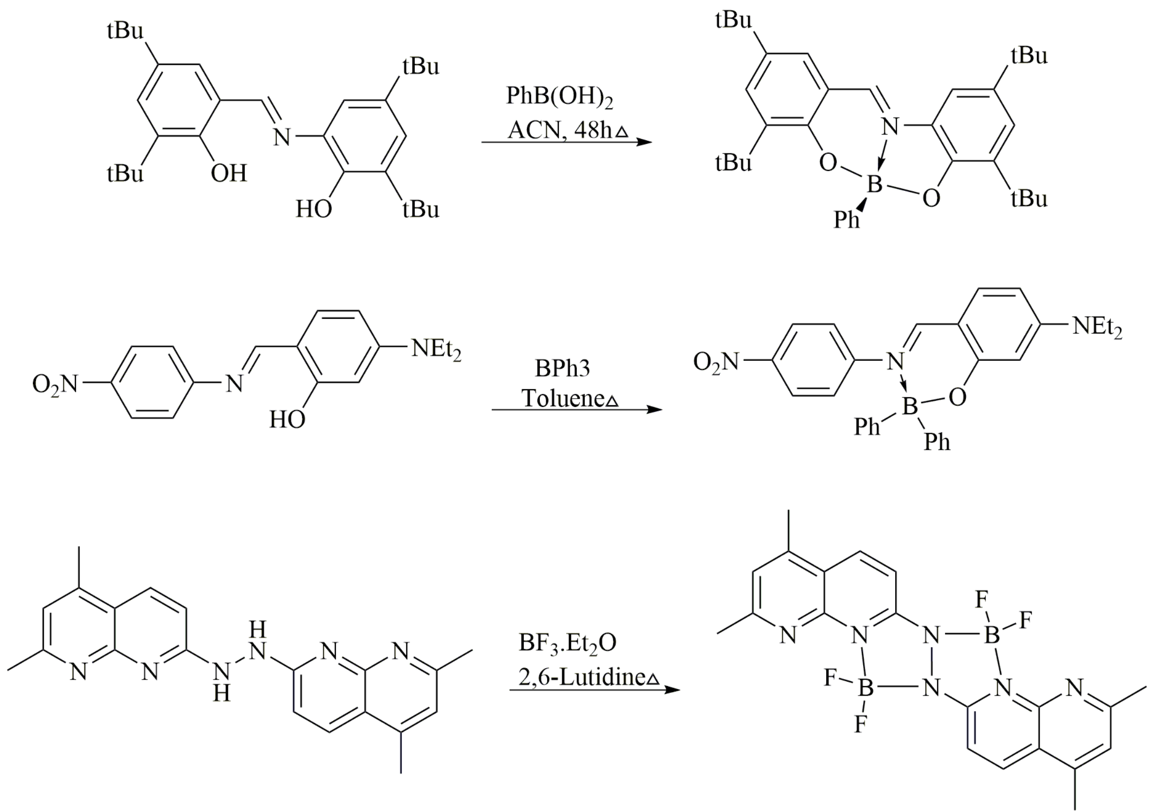

Scheme 1 - Routes for synthesis of boron compounds.

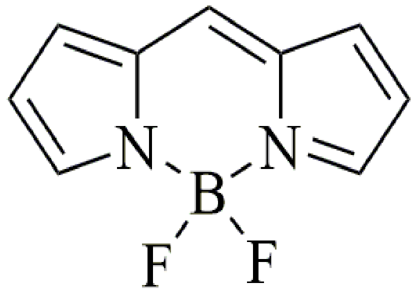

Figure 1 - Structure of a BODIPY fragment.

1) Generate a "*push–pull*" structure and to extend π-conjugation whit the functionalization at α-, β- and mesosites of the BODIPY core.[54,55]

(2) Employment of π-extended pyrrole units instead of the simple pyrrole or fusion of aromatic units to extend the π-conjugation at the [a] bond, [b] bond of the BODIPY.[56]

(3) Substitution of the meso-carbon by an imine type nitrogen atom.[57]

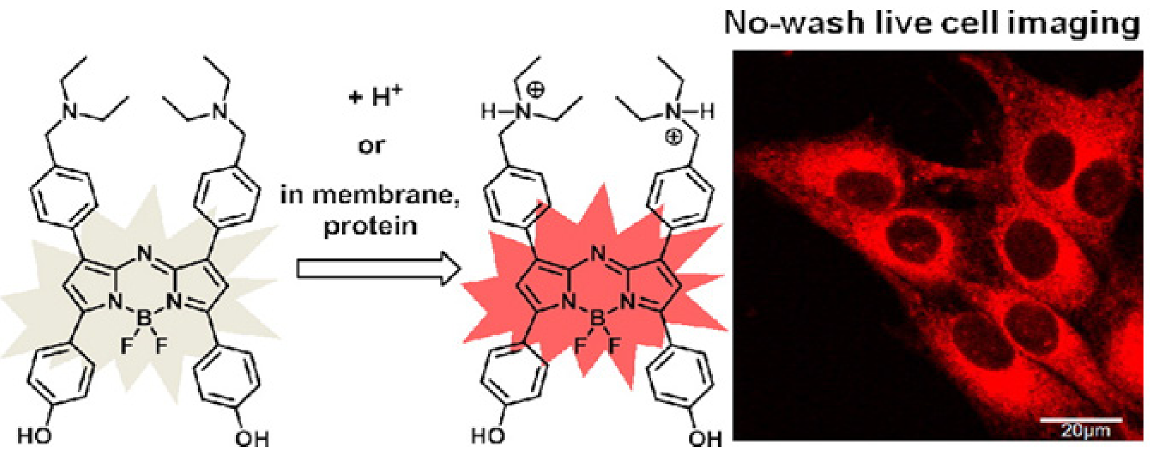

Figure 2 - NIR BODIPY dye displayed off-on at acidic pH and its live-cell image of dye after 3 h. Reprinted with permission from ref.[63] Copyright (2013) American Chemical Society.

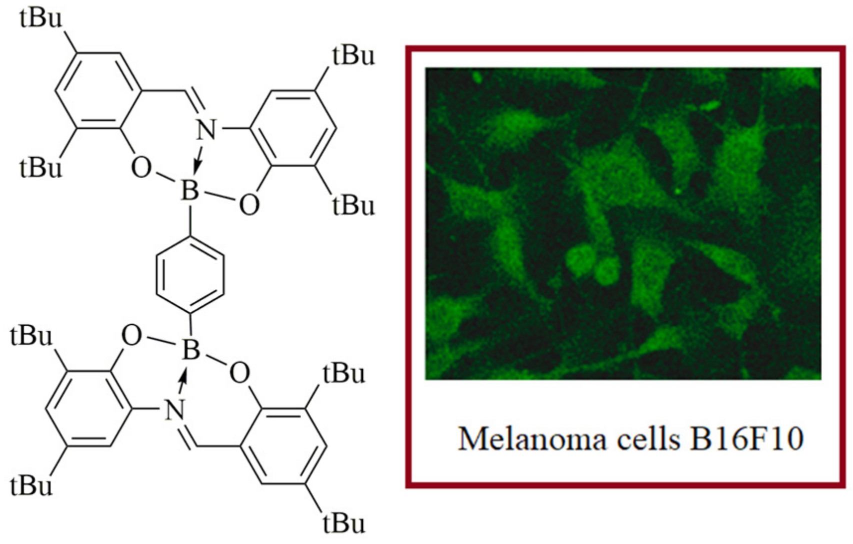

Figure 3 - Organoboron compound and its application as a fluorescent dye of melanoma cells B16F10 treated with 10 µg/mL of the compound for 2 h. Reprinted with permission from ref.[5] Copyright (2017) American Chemical Society.

4. Conclusion and outlook

Luminescent compounds derived from boron have been synthesized by different synthetic techniques, predominantly by conventional methods or using Schlenk techniques. Despite the immense advance in the green synthetic methods, only a few have been reported for the synthesis of these main group compounds, where the compounds of boron, aluminum, and bismuth, have been synthesized by microwaves, mechanosynthesis or via solvothermal respectively. It is therefore expected that future research can focus on greener synthetic methods due to the great advantages that this implies. Fluorescence bioimaging has become a potent and resourceful tool in pharmaceutical, biological, medical and associated sciences in recent years, due to their attractive facilities for studying, both *in vivo* and *in vitro*, living organisms and their live processes with rapid response and being weakly invasive. Nowadays, the design and synthesis of new metallic compounds with potential use as fluorescent imaging agents has become a dynamic research field. There are many reports on boron complexes used for this propose, especially BODIPY compounds, that has been demonstrated their potential use as cellular markers.

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