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Controlling Vilsmeier-Haack processes in *meso*-methylBODIPYs: A new way to modulate finely photophysical properties in boron dipyrromethenes

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ABSTRACT

In the herein work we report the fine and selective control of competitive processes when submitting *meso*-methylBODIPYs to Vilsmeier-Haack reaction conditions. These competitive processes generate BODIPYs with opposed photophysical properties, from highly fluorescent dyes enabling laser emission, to non-fluorescent singlet-oxygen photosensitizers. The synthetic control is exerted on the basis of the structure of the starting BODIPY, as well as the electrophilic character (hard or soft) of the formylating reagent.

1. Introduction

There is a growing interest in the development and applications of materials based on boron dipyrromethene (BODIPY) dyes. This is due to the unique properties of BODIPYs as photoactive systems, as well as their remarkably high chemical versatility [1]. Thus, the distinct ability of the BODIPY scaffold to undergo selective functionalization allows the design and synthesis of "tailor-made" dyes with optimized properties for specific advanced applications in photonics and biomedicine [2]. However, in order to exploit their full potential, further progress is required to improve the control of synthetic protocols involving potentially competitive pathways with respect to the BODIPY carbon scaffold.

One of these protocols concerns the formylation of BODIPYs with activated dimethylformamide (Vilsmeier-Haack reaction). This popular transformation has been successfully applied to formylate BODIPYs at their β-positions [3]. The so-obtained formyl derivatives (general structure **1** in Fig. 1) have been used, among other applications, as key synthetic intermediates to further advanced dyes, including interesting multichromophoric systems [4]. However, this protocol can be applied only to certain BODIPYs where the probability and extent of competitive reactions with electrophilic activated DMF is low (e.g., Mannich-like condensations involving acidic-enough methyl groups). It is known that certain *meso*-methylBODIPYs can react preferably at the acidic *meso*-methyl group with activated DMF, to generate *meso*-enamine-substituted BODIPYs (general structure **2** in Fig. 1) instead of β-formylated *meso*-methylBODIPYs [5]. Nonetheless, these

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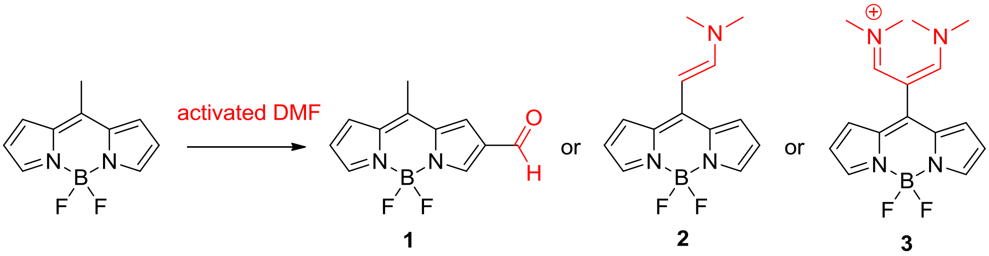

Fig. 1. General Vilsmeier-Haack reaction of BODIPYs, including potential competing reaction by-products.

enamines are also interesting BODIPY dyes and, indeed, an alternative procedure has been recently developed for their preparation from different BODIPY precursors [6]. On the other hand, it is also known that these BODIPYs bearing enamines can undergo further condensation with activated DMF, to yield charge-delocalized *meso*-iminiumenamine salts (general structure **3** in Fig. 1) [5].

Therefore, treating *meso*-methylBODIPYs with electrophilically activated DMF can afford electron-rich BODIPYs (BODIPY *meso*-enamines) or electron-poor BODIPYs (β-formylBODIPYs and BODIPY *meso*-iminium/enamine salts). Taking into account that the photophysical signatures of BODIPYs are highly sensitive to the electronic effects exerted by functional groups located at key positions [1d,1e,7], it is obvious that controlling the selective formation of the said compounds (aldehydes, enamines and iminiumenamine salts) by simple treatment of *meso*-methylBODIPYs with activated DMF, would establish a powerful synthetic protocol to finely modulate the photonic properties of BODIPY dyes. However, the control of these competitive processes has not been addressed to date, neither has the comparative photophysical study of the corresponding final dyes been conducted.

Along these lines, herein we report a systematic study on the reactivity of *meso*-methylBODIPYs with activated DMF as electrophilic reagent, as well as a study on the photophysical (and laser when available) properties, aided with computational calculations and electrochemistry, of the obtained compounds. This research has allowed the establishment of synthetic protocols to achieve selectively BODIPYs substituted with β-formyl, *meso*-enamine or *meso*-iminium/enamine, as a new way tune the photophysical properties of BODIPYs, including the synthesis of highly fluorescent dyes, able to act as laser dyes or bioimaging probes, and nonfluorescent single oxygen photosensitizers.

2. Experimental

2.1. General methods

2.1.1. Synthesis

All starting materials and reagents were commercially obtained, unless indicated otherwise, and used without further purifications. Common solvents were dried and distilled by standard procedures. Flash chromatography was performed using silica gel (230–400 mesh) or neutral activated aluminium oxide, Brockmann I (~150 mesh). Melting points were determined on a melting point apparatus and are uncorrected. NMR spectra were recorded at 20 °C in $CDCl_3$. ^1H chemical shifts are reported in ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) as internal reference. ^{13}C chemical shifts are reported in ppm with $CDCl_3$ ($\delta = 77.04$ ppm) as the internal standards. DEPT 135 experiment was used to determine the type of carbon nucleus (C *vs.* CH *vs.* CH_2 *vs.* CH_3). FTIR spectra were obtained from neat samples using the ATR technique. Mass spectrometry (MS) was performed using EI or FAB techniques. High resolution mass spectrometry (HRMS) was conducted using the EI technique in combination with electrostatic sector and magnetic sector mass analyzers.

2.1.2. Photophysical properties

The photophysical properties were measured in diluted solutions (around 2×10^{-6} M), which were prepared by adding the corresponding solvent to the residue from the adequate amount of a concentrated stock solution in acetone evaporated under vacuum. UV–Vis absorption and fluorescence spectra were recorded on a Varian model CARY 4E spectrophotometer and a SPEX Fluorolog 3-22 spectrofluorimeter, respectively. The fluorescence spectra were corrected from the wavelength dependence of the detector sensibility. Fluorescence quantum yield (ϕ) was obtained using a methanolic solution of PM567 as reference ($\phi^r = 0.91$). Radiative decay curves were registered with the time correlated single-photon counting technique (Edinburgh Instruments, model FL920) using a microchannel plate detector (Hamamatsu C4878), with picosecond time resolution (~20 ps). Fluorescence emission was monitored at the maximum emission wavelength after excitation at 410, 440 and 470 nm by means of diode lasers (PicoQuant, model LDH410, 440 and 470, respectively) with 150 ps FWHM pulses. The fluorescence lifetime (τ) was obtained from the slope after the deconvolution of the instrumental response signal from the recorded decay curves by means of an iterative method. The goodness of the exponential fit was controlled by statistical parameters (chi-square, Durbin-Watson and the analysis of the residuals). The radiative (k_{fl}) and non-radiative deactivation (k_{nr}) rate constants were calculated by means of: $k_{fl} = \phi/\tau$ and $k_{nr} = (1\text{-}\phi)/\tau$, respectively.

2.1.3. Electrochemical measurements

Cyclic voltammograms (Metrohm Autolab) were recorded using a three-electrode set up with a platinum disk (diameter 3 mm) working electrode, platinum wire as counter electrode and Ag/AgCl as reference electrode. The potential scan rate was 0.2 V/s starting in positive direction. A 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) in dry acetonitrile was used as the electrolyte solvent in which the compounds were dissolved to achieve a concentration of 1 mM. All redox potentials were reported *vs* ferrocene as internal standard. The solutions were purged with argon and all the measurements were performed under such inert atmosphere.

2.1.4. Singlet oxygen generation

The production of $^1O_2$ was determined by direct measurement of the luminescence at 1270 nm with a NIR detector integrated in the spectrofluorimeter (InGaAs detector, Hamamatsu G8605-23). The $^1O_2$ signal was registered in front configuration (front face), 40° and 50° to the excitation and emission beams, respectively and leaned 30° to the plane formed by the direction of incidence and registration in cells of 1 cm. The signal is filtered by a low cut-off of 850 nm. $^1O_2$-generation quantum yield (ϕ_Δ) was determined using