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Facile synthesis of boronic acids on a BODIPY core with promising sensitivity towards polyols†

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An efficient strategy for the synthesis of *o*-((ethyl)aminomethyl) phenyl boronic acid anchored on a BODIPY core is reported. Kinetic studies highlight the association with diols and fructose; BODIPY fluorescence is quenched upon substrate binding, showing an unusual turn-off response.

Monitoring of the concentration of sugars is essential in clinical and industrial applications, and the instrumental analysis is often based on information outputs processed at the molecular level.[1]

Chemical sensors are single molecules of particular interest, able to recognize signal analytes in real time; fluorescent molecules, due to their easily detected fluorescence output, are particularly suitable in this regard. They can be configured to be used as chemical and biochemical active indicators specifically designed to detect certain analytes, for example carbohydrates.[2]

The interest towards some kind of molecular apparatus that contains a boronic-acid group, able to bind to the unit through the formation of stable glycosidic esters,[3] is widely recognized but not many studies are described in combination with borodiazaindacene (BODIPY).[4] In the design of boronic acid based sensory systems, it has been established that suitable receptor, linker and fluorophore sub-units are required if selectivity for specific saccharides is to be achieved.[5] The most popular class of the fluorescent boronic acid-based sensors utilizes an amine group proximal to boron. The Lewis acid–base interaction between the boronic acid and the neighboring amine has a dual role. First, it enables molecular recognition to occur at neutral pH; moreover, it can be used to communicate binding by modulating the intensity of fluorescence emission of the conjugate fluorescent unit through changes in photoinduced electron transfer (PET) efficiency, introducing an optical response, including BODIPYs,[6] sensitive to environment changes.[7] It is well-established that B–N interaction, either direct or H-mediated, is essential for the binding of polyols with boronic acid sensor. Without this B–N interaction, the binding will be very weak, or binding can only occur in basic solution (OH binding to the B center will stabilize the binding complex).[8]

In this paper, the synthesis of new molecular systems containing boronic groups connected to BODIPY fluorophores is described, furthermore spectroscopic studies highlight the association with diols and fructose. The BODIPY-based fluorescence of the new boronic acid systems is quenched upon esterification, revealing the occurring of the process by an unusual turn-off fluorescence response.

Scheme 1 reports an efficient and improved two-steps synthesis of *o*-phenyl boronic acid derivatives, combined with BODIPY separated by an aminomethyl backbone as the linker.

The catalytic reduction of the nitro-BODIPY derivatives **1a**, **1b** (Scheme 1) in acetonitrile/ethanol has provided the expected products amines **2**, **3** according to the procedure described in the literature.[9] The optimization of the reaction allowed, through an easy chromatographic separation, to isolate in a 1 : 1 ratio the two amino derivatives **2**, **3** in very good overall yields. The secondary amine alkylation was obtained from benzyl bromide derivative, whereas from the primary amine reductive amination was required. In either case a preliminary treatment of the crude with silica and methanol, then filtration and subsequent separation in the chromatography column, allowed to isolate directly the boronic acid derivatives **4**, **5**. The combination of two different one-pot procedures avoids synthetic steps much more laborious and less efficient, such as the mono-alkylation of aromatic amines and especially the hydrolysis of the ester of the boronic acids. Evidences of association of **4a** with diols were obtained by absorption and luminescence measurements; also NMR and MALDI-TOF

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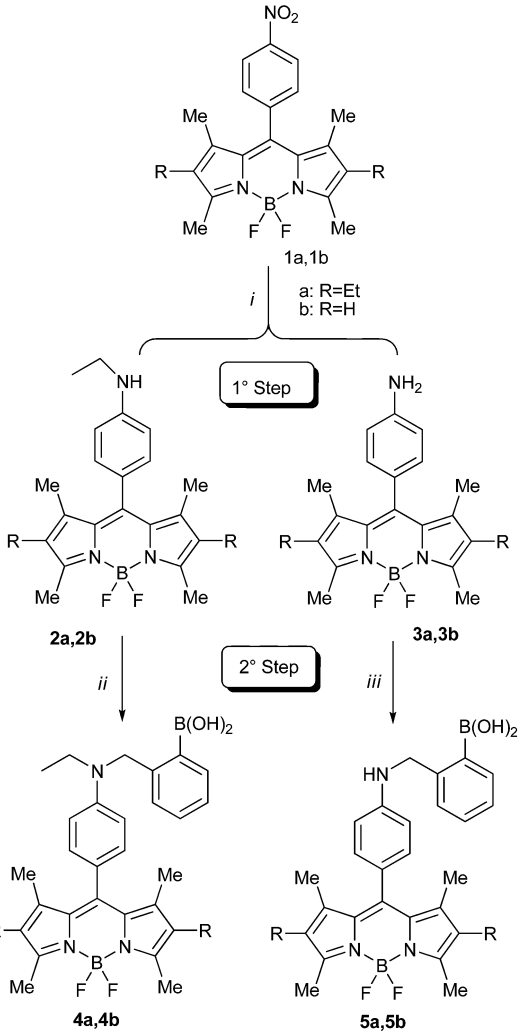

i: 10%Pd/C; H_2/EtOH/MeCN; *ii*: 1) 2-(2-(Bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Cs_2CO_3, 2) SiO_2/MeOH; *iii*: 1) 2-formylphenylboronic acid pinacol ester, 2) $NaBH_3CN$, 3) SiO_2/MeOH;

Scheme 1 Description of the synthetic procedure.

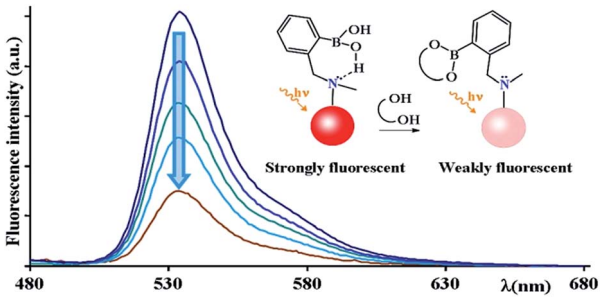

Fig. 1 Evidence of fluorescence quenching of the BODIPY in the formation of boronic ester with aliphatic diols.

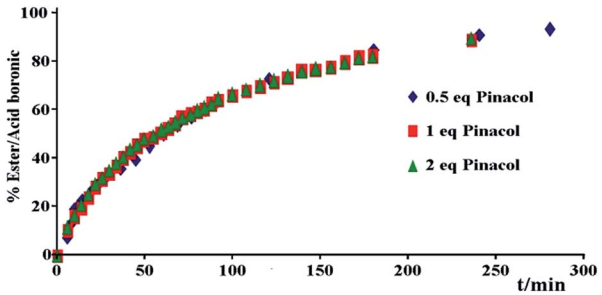

Fig. 2 Rating of formation of the ester of **4a** in $CDCl_3$, varying pinacol concentration.

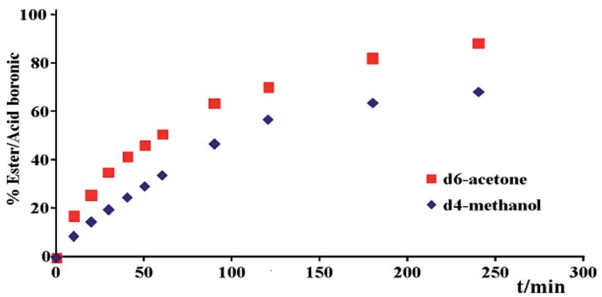

Fig. 3 Rating of formation of the ester of **4a** in CD_3COCD_3 and CD_3OD, with 1 eq. of pinacol.

analysis confirm the formation of boronic esters, simply mixing them together in organic solvent.

The molecules are soluble in organic solvents and the rate of association with diols is dependent on the solvent polarity used. Preliminary and qualitative UV-Vis analysis with some aliphatic diols showed no evidence of variations in the absorption spectra, when the fluorimetric analysis showed an unusual quenching of fluorescence (Fig. 1).

In parallel, the kinetic studies of association of the boronic acid **4a** were performed varying the concentration of the diol (pinacol) (Fig. 2) and the deuterated solvent (chloroform, acetone, methanol) (Fig. 3). It showed the formation of the ester, monitoring by ^{1}H-NMR analysis the specific benzilic protons peaks related to acid (4.4 ppm) and ester (4.9 ppm) species, and plotting their integral ratio. The results (Fig. 2) show that in aprotic solvent ($CDCl_3$ and CD_3COCD_3) the rate of formation of the ester is independent of the concentration of diol. Instead, in CD_3OD the process is clearly slower (Fig. 3). Plausibly, the formation of a reaction intermediate is assumed, as well known in aqueous media, which regulates the rate of the process and that intermediate is influenced by the presence of protic solvents. The reaction of boronic acid with diols consists of two steps: fast nucleophilic attack of the hydroxy group (I step) is followed by the rate-determining step at which chelate ring closure occurs with water molecules release (II step), according to kinetic studies reported in the literature.[10]

Therefore, the methanol could be competitive in the formation of the intermediate, slowing down the overall process of formation of the more stable cyclic boronic ester.

Similar experiments in association with monosaccharides were carried out. Nevertheless, the poor water solubility of the derivatives **4**, **5** and the impossibility of using alcohols as

solvents, for interaction problems mentioned above, have provided noticeable results with fructose using acetone as solvent. Even in the latter experiment, the fluorimetric analysis showed an emission quenching compared to the acid derivative. These measures have also allowed to determine the stoichiometry of the adduct BODIPY–fructose (1 : 1) and its thermodynamic stability. The equilibrium constant calculated ($K_{eq} = 7.4 \times 10^4$) from the experimental data (see ESI†) agrees with the constants reported in the literature of similar systems.[11] As a further confirmation, also the analysis by means of MALDI-TOF mass spectrometry highlights the association with diols and fructose (see ESI†).

Although many examples in the literature of similar molecules show a different photochemical response,[11] we can justify our results as follows, considering the photoinduced electron transfer from the amino group to the BODIPY part (Fig. 1).

The possible intramolecular interaction between the aminic nitrogen and the hydrogen of one of the two hydroxyl groups of the boronic acid (Fig. 1), with the consequent engagement of the lone pair on the nitrogen was reported in a recent paper.[12] This intramolecular interaction is apparently not possible in the ester derivative of **4** and **5**, which leaves the electron doublet of nitrogen to quench the fluorescence of the chromophore BODIPY. This hypothesis confirms the predictions from the calculations that the fluorescence quenching trend, as reported,[12] for boronate ester formation, will be reversed in aprotic polar solvents, respect to the trend in polar protic solvents. In other words, the calculation indicates that boronate ester formation will have a lower fluorescence quantum yield than that of the corresponding acid in aprotic polar solvents.[13] Differently in aqueous solutions, the mechanism of electron transfer is necessarily correlated with the protonation rather than a change of the interaction B–N, to be considered for the development of new systems.

Conclusion

We obtained **4a**, **4b**, **5a**, **5c** with a very efficient two steps synthetic strategy, in good overall yields. This strategy, compared to known procedures for the synthesis of similar systems, has significantly reduced preparation times and offers a useful alternative to the synthesis of analogous molecules. The esterification of these chromophoric systems showed an unusual fluorescence quenching which was justified taking into account previous results reported in the literature. These studies add further information to the understanding of the mechanism of interaction of boronic systems with diols.

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