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Multinuclear NMR spectroscopy, photophysical, electrochemical and DNA-binding properties of fluorinated 1,8-naphthyridine-based boron heterocycles

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ABSTRACT

This paper reports the results of the synthesis and structural elucidation by multinuclear NMR spectroscopy and single crystal X-ray diffraction of a new series of four examples of 1,1-difluoro-3-methyl-9-(aryl/heteroaryl)-7-(trifluoromethyl)-1*H*-[1,3,5,2]oxadiazaborinino[3,4-*a*][1,8]naphthyridin-11-ium-1-uides, which were obtained, at good yields (60–66%), from the reaction of 7-substituted *N*-(5-(trifluoromethyl)-1,8-naphthyridin-2-yl)acetamides — in which the 7-substituents are C_6H_5, 4-$CH_3C_6H_4$, 4-FC_6H_4, and 2-Thienyl — with $BF_3{\cdot}Et_2O$ solution. One-dimensional multinuclear NMR spectroscopy (^1H, ^{13}C, ^{19}F, and ^{11}B) and two-dimensional ^1H–^{15}N HMBC are presented as powerful tools for an easy and secure NMR chemical shift assignments and structural characterization of fluorinated 1,8-naphthyridine-based boron complexes. Additionally, investigations of photophysical, electrochemical and DNA-binding properties were done.

1. Introduction

Naphthyridines and their derivatives are an important class of heterocyclic compounds, and they have excellent biochemical and pharmacological properties. In this field, 1,8-naphthyridine-BF_2 complexes are an important heterocycle class — they are known as fluorescent dyes with high chemical stability [1] and high fluorescence quantum yields [2]. Additionally, organoboron complexes are widely used as agents in photodynamic therapy, [3] chemosensors, [4] and sensitizers in solar cells [5]. Some examples of these complexes can be seen in Fig. 1.

However, some of these compounds, such as the traditional BODIPY (boron-dipyrromethene) core, are inherently lipophilic and not very water soluble — this characteristic can be troublesome because it significantly biases cellular distribution of labeled small molecules to membranes, which is often confused for specific target binding.

Due to this, in 2017, Bumagina determined that the introduction of methyl substituents and other hydrocarbon chains into BODIPYs resulted in a change in the

physicochemical proprieties, electronic absorption, and the fluorescence spectra of these BF_2 complexes [6].

On the other hand, it has been recognized that the insertion of a trifluoromethyl group into heterocycles can be used to modulate the physical, chemical and biological properties. It is well documented that the influence of the trifluoromethyl substituent on physiological activity also causes greater cell permeability [7].

In 2012, Wu described the synthesis of 1,8-naphthyridine-based BF_2 complexes, using very simple 1,3-dicarbonyl compounds as limited synthons in order to obtain the 1,8-naphthyridine precursors [8]. Recently, upon amplifying the scope of the substituents, our research group [9] reported a similar synthesis of these complexes. In both studies, the push-pull effect of various substituents and their effect on the spectroscopy and photophysical properties were evaluated.

Thus, with interest in the design and synthesis of new naphthyridine-based BF_2 complexes, because of their intriguing luminescence properties and promising biological activities, we decided to synthesize new organoboron complexes from 1,8-naphthyridines — which would have a methyl substituent at the 3-position, a CF_3 group at the 5-position, and aryl(heteroaryl)substituents at the 7-position — and perform the NMR study of various nuclei present in the new structures (^1H, ^{13}C, ^{19}F, ^{11}B, and ^{15}N). The structural characterization — via ^{15}N-NMR — of these complexes has not yet been published, and to the best of our

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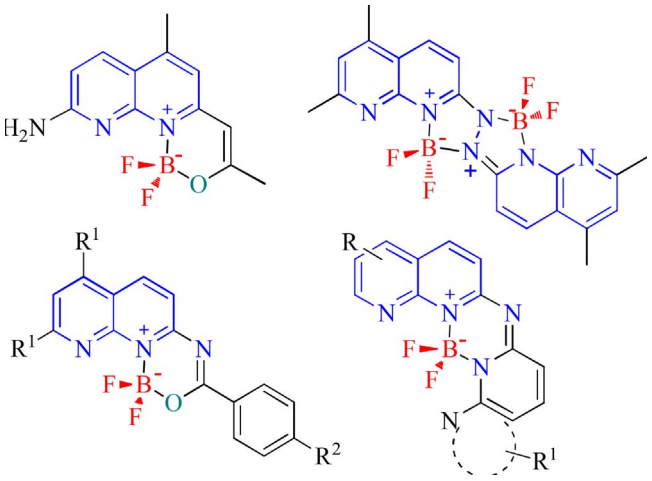


Fig. 1. Examples of 1,8-naphthyridine-based BF_2 complexes.

knowledge, ^{15}N-NMR for 1,8-naphthyridines is rare, [10] and there is little in the literature about the use of multinuclear NMR spectroscopy for easy structural characterization of this important fluorinated tri-heterocyclic class. In addition, absorption/emission (photophysical) and electrochemical experiments were carried out to investigate the behavior of these derivatives in solution, as well as their interactivity with biomolecules (DNA).

2. Results and discussion

Initially, a series of 2-acetamide derivatives (**1a–d**) were obtained according to the procedure described in the literature [11]. After purification and full characterization of the 2-acetamide derivatives, these compounds were employed in the synthesis of the respective BF_2 complexes (**2a–d**) — see Scheme 1. Subsequently, for the optimization of the reaction conditions for the synthesis of compounds **2a–d**, the molar ratio and reaction time were evaluated in tests using 1 mmol of acetamide **1a**. The reactions were done at room temperature, because when the reaction was done at reflux temperature, degradation of the product and a decrease in yield were observed. The change in the $BF_3{\cdot}Et_2O$:Et_3N ratio from 1:1 (v/v) to 1:0.6 (v/v) was evaluated — there was no reduction in yield. The reaction time was initially 24 h, and when tests were conducted at 16 and 30 h, a decrease in the yield was observed. Thus, the best reaction condition was used for the synthesis of the other compounds of the series, and it furnished the desired fluorine-boron complexes **2a–d** at good yields (60–66%).

It can be seen that there were no significant changes in the reaction yields when comparing the complexes containing a substituent possessing a typical electron-donating effect (+I) — there was a 61% yield for **2b**, in which R = 4-$CH_3C_6H_4$ — with the compound containing an electron-withdrawing group (–I) — there was a 60% yield for **2c**, in which R = 4-FC_6H_4.

The new structures were confirmed and characterized by ^{1}H-, ^{13}C-, ^{11}B-, ^{19}F-, and ^{1}H-^{15}N HMBC NMR, and their purity was evaluated from CHN elemental analysis.

The structural assignments for complexes **2a–d** are consistent with the ^{1}H- and ^{13}C NMR spectra described in the literature for similar compounds [8,9]. The ^{1}H NMR spectra of all the complexes **2a–d** showed: a doublet for the H-6 proton, in the 8.61–8.52 ppm range; a singlet for the H-8, in the 8.31–8.07 ppm range; and the signals of the aromatic hydrogen atoms, in the 8.44–7.26 ppm range. Furthermore, a singlet was also observed for the methyl group, in the 2.49–2.46 ppm range.

The ^{13}C NMR spectra of all compounds **2a–d** showed, on average, chemical shifts: at 176.6 ppm for C-3 and at 136.1 ppm for C-7 as a quartet with a $^2J_{CF}$ of 31 Hz; and at 122.6 ppm for the CF_3 group, as a quartet with a $^1J_{CF}$ of 275 Hz. The signals of the aromatic carbon and the naphthyridine ring carbon atoms were observed as singlets, in the 142.5–114.5 ppm range. Finally, a singlet was recorded for the methyl carbon, in the 24.6–23.9 ppm range.

Thus, in order to demonstrate the formation of the BF_2 complexes, analysis of the ^{11}B NMR and ^{19}F NMR data was also performed. As expected, from the literature [12] using chloroform-*d* as the solvent for compounds **2a–d**, the ^{11}B NMR spectra showed only singlet signals, in the 0.64–0.76 ppm range. The ^{19}F NMR spectra showed a singlet for the fluorine atoms of the CF_3 group, in the −60.69 to −60.83 ppm range; and a distorted quartet for fluorine atoms connected to the boron atom, in the −129.81 to −130.18 ppm range, as described in the literature [9,13].

In order to correctly identify the nitrogen atoms for compounds **1a–d** and **2a–d**, the 2D-NMR experiments were performed using the ^{1}H–^{15}N HMBC technique.

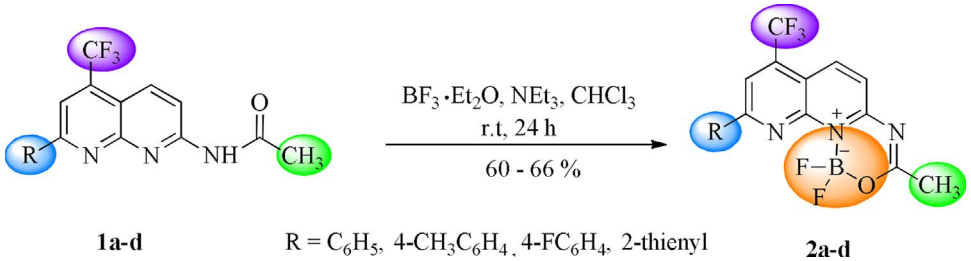
The 2D ^{1}H-^{15}N HMBC NMR spectra showed three ^{15}N-signals as singlets for each compound, with chemical shifts from: 188.57–188.34 ppm for N-11, 208.60–208.94 ppm for N-4, and 272.72–297.13 ppm for N-10. It is important to mention that the chemical shift values for the nitrogen atoms obtained for complexes **2a–d** are closely related to other similar heterocycles described in the literature [10]. It is important to mention that we did not perform direct ^{15}N-NMR experiments due to the low receptivity at natural abundance of nitrogen-15, but it was possible easy to obtain the respective chemical shifts indirectly performing ^{1}H-^{15}N HMBC NMR experiments.

For each compound, the 2D ^{1}H–^{15}N HMBC NMR spectrum in chloroform-*d* showed the following simultaneous correlations: (i) NH with the H-3 atom and the methyl group (**1a–d**) or N-4 with the H-5 atom and the methyl group attached at C-3 (**2a–d**); (ii) N-8 with the H-6 atom (**1a–d**) or N-10 with the H-8 atom (**2a–d**); and (iii) N-1 with the H-3 atom (**1a–d**) or N-11 with the H-5 atom (**2a–d**) — see Fig. 2.

The chemical shift values observed for the **2a–d** series — via NMR analysis of the ^{11}B-, ^{19}F-, and ^{15}N from ^{1}H-^{15}N HMBC — are summarized in Table 1.

For a better comparison, the ^{15}N-NMR data of the 2-acetamide precursors **1a–d** were also recorded and analyzed. The chemical shift values observed for the **1a–d** series — via ^{19}F- and ^{15}N-NMR analyses — are shown in Table 2.

In compounds **1a–d**, the ^{15}N NMR spectra displayed deshielded chemical shifts in the 266.18–264.13 ppm range for N-1, as opposed to 188.57–188.34 ppm in compounds **2a–d**. This large difference (approx. 86 ppm) in the chemical shifts of both series is due to the existence of a nitrogen-boron interaction only in the respective boron complexes **2**. In



1a-d R = C_6H_5, 4-$CH_3C_6H_4$, 4-FC_6H_4, 2-thienyl **2a-d**

Scheme 1. Synthetic route to obtain 1,8-naphthyridine-BF_2 complexes (**2a–d**).