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Long range $^{1}H-^{19}F$ coupling through multiple bond in thienopyridines, isoquinolines and 2-aza-carbazoles derivatives

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ABSTRACT

Long range ^{5}J and ^{6}J ($^{1}H-^{19}F$) spin-spin coupling constants for a set of nine biarylic fluorinated derivatives were determined by ^{1}H NMR experiments. The quantitation of these long-range ^{5}J and ^{6}J ($^{1}H-^{19}F$) coupling can be found through the measure of the residual coupling-signals obtained after the selective decoupling process. The information obtained for the NMR spectra was confirmed through computational studies.

1. Introduction

The biological activity of organic compounds can be substantially affected by substitution of fluorine atoms at specific sites of the molecule [1–5]. Data derived from X-ray crystallography and molecular orbital calculations indicates that the change in activity may be ascribed to alterations in their conformation and/or functional group activity [6,7]. In solution, the relationship between a fluorinated compound and its biological activity could be established by NMR spectroscopy detecting conformational changes; this would yield a large number of stereochemical data about fluorine substituent effects on the chemical shifts of neighboring nuclei [8,9].

Additional information about the fluorinated compounds could also be deducted from 19F spin coupling constants measurements in either 1H or 13C NMR spectra [9,10]. Long-range coupling between protons and 19F nuclei has been of interest from both a stereochemical and a theoretical point of view [11,12]. Because of this, the long-range 1H–19F and 13C–19F couplings have been the object of numerous studies [13–15].

Work in our laboratory has focused on the synthesis and conformational study of biarylic derivatives, with varying substitution pattern. During this work, we observed the NOESY NMR spectra for several of these derivatives, which displayed different substituent at the *ortho* and *ortho′* positions on the aryl group.

This revealed that spatial orientation of biaryl heteroaromatic units around the pivotal bond depends on both steric and electronic phenomena. Previously, the most significant results showed that biaryl derivatives adopt two characteristic situations: one where both aromatic units displayed a free rotation and one where this move was blocked by the presence of unshared electron pairs in the *ortho* positions on nitrogen atom of both heteroaromatic units [16]. Moreover, the literature indicates that the motion of the aromatic rings around the single bond – or pivotal bond connecting two aromatic units – depends on the size of the substituent *ortho* to the link, generating – in the case of this hindered rotation – an atropisomerism [17].

Because of the interest in preparing new biologically active pyridine analogs, we used a modification of the TAWERS procedure, [18–21] combining the iminophosphorane intermediate with fluorinated aldehydes to produce biaryl compounds, which would

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possess these interesting conformational properties. In this paper, we describe the synthesis of novel fluorinated thienopyridines, isoquinolines, and 2-aza-carbazoles, as well as their $^{1}H-^{19}F$ nuclear spin-spin long-range coupling by NMR, crystallographic and computational analysis.

2. Experimental

The NMR ^{1}H and ^{13}C spectra were recorded on a Varian Unity 300 spectrometer operating at observation frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C. The ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the tetramethylsilane (TMS). High resolution spectra were recorded on a Varian Unity 500 operating at frequency of 500 MHz for ^{1}H and 125 MHz for ^{13}C. The experiments were performed using an inverse detection 5 mm probe. The COSY, NOESY, HMQC and HMBC spectrum were recorded using usual Varian Unity software. Mass spectra were recorded on instruments using standard FAB or CI/EI sources in glycerol or with Nicolet FX-SX and Nicolet 55-X in film mode. The rotational barriers were calculated through Density Functional Theory (DFT) methods at the B97D/6-31 + G (*d*,*p*) level of theory. Geometry optimizations of all molecules were performed until the lowest energy conformations were found as assessed by the Hessian matrix in which no imaginary frequencies were present, confirming the arrival to an energy minimum. Subsequently, the dihedral angle around the pivotal bond was scanned in 30° increments until a full 180° turn was achieved.

3. Results and discussions

3.1. Synthesis

New fluorinated heteroaromatic biaryl compounds (**1**–**9**) (Fig. 1) were obtained in moderated yields (42–56%) through a tandem aza-Wittig electrocyclic ring closure methodology (TAWERS) [18–21] which has previously been used by our research group [22].

3.2. NMR analysis

To perform this NMR study of the biarylic derivatives (**1**–**9**), we chose compounds based on their increased electronic demand, and therefore on the increased rotational barriers of both biarylic units. For this reason, we decided to synthesize biarylic fluorinated heterocyclic compounds, supposing that the fluorine atom could affect the conformational behavior of these molecules. Indeed, for some derivatives, the position of the fluorine atom was planned to be *ortho* to the pivotal bond with the aryl moiety. For the heterocyclic moiety, this distance was variable because the value of the coupling constant was affected by the distance to the hydrogen that was nearest to the pivotal bond (Fig. 1).

With this in mind, we performed three conformational NMR studies of fluorinated thienopyridines, isoquinolines, and 2-aza-carbazoles derivatives: (i) spectral assignment of the chemical shift difference; and (ii) long-range $^{1}H-^{19}F$ and $^{13}C-19F$ coupling constant evaluations.

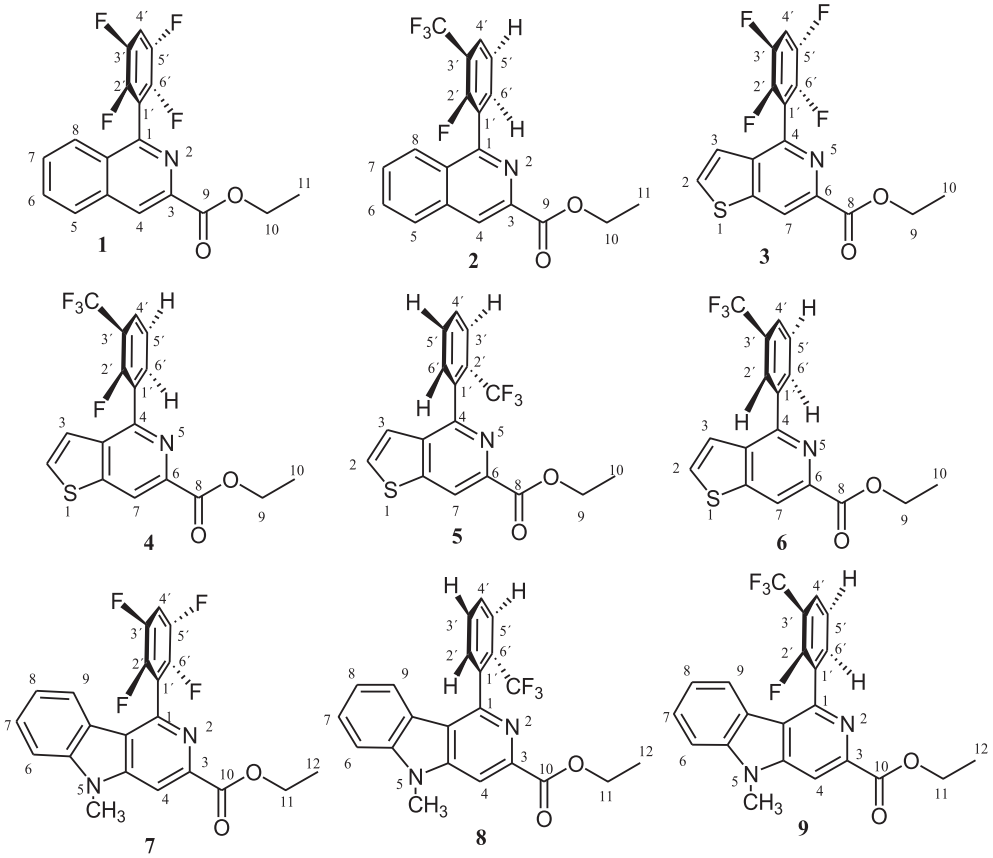

Fig. 1. Fluorinated biarylic compounds.