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Proceeding Paper

Experimental and Theoretical Study of a New Functionalized Derivative of 3-Methyl-2-Trifluoromethyl Chromone [†]

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Abstract: The investigation of new chemical compounds with medicinal potential is essential for addressing a wide range of diseases and pathogens. Among these compounds, chromones and their functionalized derivatives stand out for their biological activity. In this study, a nitro-substituted derivative of 3-methyl-2-pentafluoroethylchromone was synthesized through a nitration reaction with a 79% yield. The product was characterized using spectroscopic techniques such as vibrational (IR) and electronic (UV-Visible) spectroscopy, and ^{1}H and ^{13}C nuclear magnetic resonance (NMR). Additionally, quantum chemical calculations at different theoretical levels were performed to complement the interpretation of the experimental results.

Keywords: chromone derivative; theoretical calculations

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1. Introduction

Diseases represent a significant challenge to human health and the optimal functioning of society [1]. Research on medicinal plants has highlighted the high medicinal value of heterocycles [2]. Among these, chromones, which are a class of oxygen-containing heterocyclic compounds [3,4], have been used pharmacologically for a long time [2]. Both synthetic and natural chromones exhibit a wide range of biological functions as well as pharmacological activities [3,5], including antibacterial [2], antifungal [4], antiviral [5], antimicrobial [6], antiallergic [7], and antitumor activities [8].

The incorporation of halogen substituents is an effective way to increase biological activity [9–11]. However, halogen-containing chromones are rare in nature [3]. As a result, several studies on the chemistry of halochromones and haloalkylchromones have been published in recent years. These compounds are characterized by the presence of halogen atoms attached directly to carbon atoms or to side chains, respectively [12]. Among the substituents, difluoromethylene (-CF_2-) and trifluoromethyl (-CF_3) groups are particularly attractive [13,14] because of their relevant properties for drug development, such as high electronegativity, lipophilicity, metabolic stability, and bioavailability [14].

Based on the above, new functionalized derivatives of 3-methyl-2-polyhaloalkylchromones were synthesized and studied experimentally and theoretically, as they could have antimicrobial activity. This study describes the synthesis of a new functionalized derivative of 3-methyl-2-pentafluoroethylchromone with a nitro group via a nitration reaction, resulting in a 79% yield. The experimental results were complemented by quantum chemical calculations at several levels of theory.

2. Materials and Methods

2.1. General

All solvents and reagents were purchased from Sigma-Aldrich (St. Louis, MI, USA) and used without further purification. Melting points were determined using a Büchi Melting Point M-560 apparatus, without correction. FTIR spectra were recorded using a JASCO FT/IR-4600 equipped with attenuated total reflectance (ATR), with a resolution of 4.0 cm^{-1}, over a spectral range of 4000 cm^{-1} to 650 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded at 298 K on a Bruker Advance 500 MHz spectrometer, equipped with a triple resonance cryoprobe (^{1}H, ^{13}C, ^{15}N) with z-gradient, using $CDCl_3$ as solvent. Chemical shifts are reported in ppm with tetramethylsilane (TMS, δ = 0 ppm) as the internal reference. Theoretical studies were conducted using the Gaussian 09 software package [15], and results were visualized with the Gauss View 6.0 interface.

The precursor 3-methyl-2-pentafluoroethylchromone **1** was prepared as previously reported [16]. Reactions were monitored by thin-layer chromatography (TLC) on silica gel using ethyl acetate/hexane mixtures as eluent, and compounds were visualized under UV light. The reported yield corresponds to purified material and has not been optimized.

2.2. Synthesis of 3-Methyl-6-Nitro-2-Pentafluoroethylchromone (2)

The synthesis of 3-methyl-6-nitro-2-pentafluoroethylchromone **2** was adapted from a procedure reported by Avendaño [17]. In an ice bath, a solution of 3-methyl-2-pentafluoroethylchromone (**1**) (0.5 mmol) in concentrated H_2SO_4 (0.6 mL) was prepared. A nitrating mixture of concentrated H_2SO_4 (0.5 mmol) and HNO_3 (7.5 mmol) was carefully added while maintaining continual stirring. After the addition, the reaction mixture was removed from the ice bath and allowed to come to room temperature. The mixture was then heated to 75 °C for one hour. The progress of the reaction was monitored by TLC in an EtOAc/Hexane (10:1) mixture. Following completion, ice water was added to the reaction mixture while constantly stirring and next stored at 4 °C overnight. The solid was filtered, washed with cold water, and dried under vacuum. Compound **2** was obtained as a white crystalline solid with a 79% yield. Mp 75–76 °C; ^{1}H NMR (500 MHz, *$CDCl_3$*) δ (ppm) 9.03 (d, *J* = 2.7 Hz, 1H, H-5), 8.55 (dd, *J* = 9.2 and *J* = 2.7 Hz, 1H, H-7), 7.66 (d, *J* = 9.2 Hz, 1H, H-8), 2.26 (q, *J* = 3.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) 176.22 (C-4), 157.81 (C-8a), 147.89 (t, $^{2}J_{C,F}$ = 27.2 Hz, C-2), 145.21 (C-6), 128.85 (C-7), 124.34 (C-3 or C-4a), 122.84 (C-5), 121.96 (C-4a or C-3), 119.98 (C-8), 118.45 (qt, $^{1}J_{C,F}$ = 287.6, $^{2}J_{C,F}$ = 36.4 Hz, CF_3), 110.01 (tq, $^{1}J_{C,F}$ = 260.4, ^{2}J_C,F = 40.3 Hz, CF_2), 8.75 (t, $^{4}J_{C,F}$ = 4.8 Hz, CH_3); ^{19}F NMR (56 MHz, $CDCl_3$) δ (ppm) −82.82 (t, J = 2.2 Hz, 3F, $CF_2C\underline{F_3}$), −115.36 (t, J = 2.4 Hz, 2F, $C\underline{F_2}CF_3$); FTIR (cm^{-1}): 3040, 1630, 1625, 1613, 1178, 758; UV (nm): 301, 242, 218, 193.

2.3. Theoretical Study

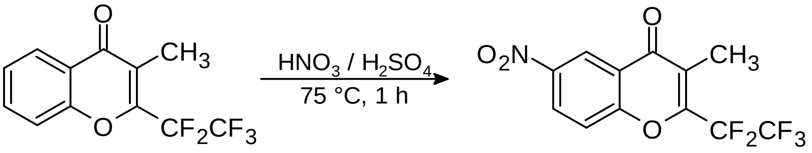
A molecular model of compound **2** was constructed and optimized using the semiempirical PM6/ZDO level of theory. The DFT B3LYP/6-311++G(d,p) level of theory [15] was used to simulate IR spectrum, conformational analysis, natural bond orbital (NBO) analysis, and frequency calculations. UV-Vis spectrum was predicted using the CPCM model at the DFT B3LYP/6-311++G(d,p) level of theory [15], and chemical shift calculations at the B3LYP/6-311+G(2d,p) level of theory were done using the GIAO (Gauge Including Atomic Orbital) approach. This correlation coefficient was used to compare the theoretical chemical shifts with experimental data.

3. Results and Discussion

3.1. Synthesis

The precursor 3-methyl-2-pentafluoroethylchromone **1** was synthesized as previously reported [16], with a modification in the reaction time to 11 days, which increased the yield from 5% to 67.2%. The reaction of the precursor with a nitrating mixture of concentrated H_2SO_4 and HNO_3, under constant stirring at 75 °C, yielded compound **2** with good efficiency (Scheme 1).

The nitration of the aromatic ring occurs at C6, positioned meta to the carbonyl and para to the ether, facilitating the production of compound **2** in high yields. Due to the proximity of the aryl-vinyl ether group, nitration at C8 could present higher steric hindrance, and there was no evidence of obtaining this regioisomer.



1 2

Scheme 1. Synthesis of 3-methyl-2-pentafluoroethylchromone substituted with a nitro group.

3.2. Experimental and Theoretical Study

3.2.1. Conformational Analysis

Relative potential energy curves for compound **2** were generated, and the lowest energy structure (most stable conformer) was identified (Figure 1). This conformational isomer had a dihedral angle ϕ (C3-C2-CF_2-CF_3) of 88°, suggesting a synclinal conformation relative to the C2=C3 bond. The -CF_2CF_3 group is located on one side of the chromone ring plane, while the fluorine atoms adopt the classic alternating conformation to minimize repulsion.

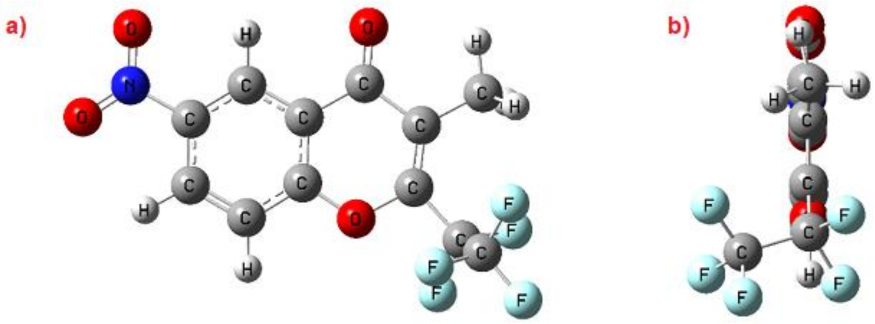


Figure 1. Most stable conformer of compound **2**, (**a**) front view and (**b**) side view.

3.2.2. NBO Analysis

Theoretical calculations using population analysis and the NBO approximation were used to evaluate donor → acceptor interactions. The most important interactions involve the lone pair (LP) electrons on the fluorine atoms (LP(F)) of the pentafluoroethyl group (CF_2CF_3) and the lone pairs on oxygen (LP(O)). The lowest energy conformation had a stabilization interaction in CF_2 due to a donation of the type of LP(F) → $\sigma^*(C_2\text{-}O_1)$ (Figure 2), which contributed to stability with 0.72 kcal/mol.

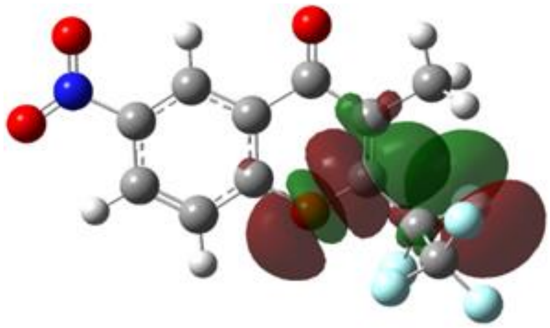


Figure 2. NBO of compound **2**. Interaction LP(F) → σ*(C_2-O_1).

3.2.3. IR Spectroscopy

The experimental and theoretical vibrational spectra of compound **2** show signals for the main functional groups (Figure 3). Weak absorption bands are observed due to symmetric and asymmetric C-H stretching from the methyl group (CH_3) and the aromatic ring. There is also an intense band attributed to carbonyl stretching, as well as another band corresponding to pyran ring double bond stretching. A medium-intensity band associated with the nitro group is also seen. Characteristic bands for the trifluoromethyl group are visible, corresponding to both symmetric and asymmetric stretches.

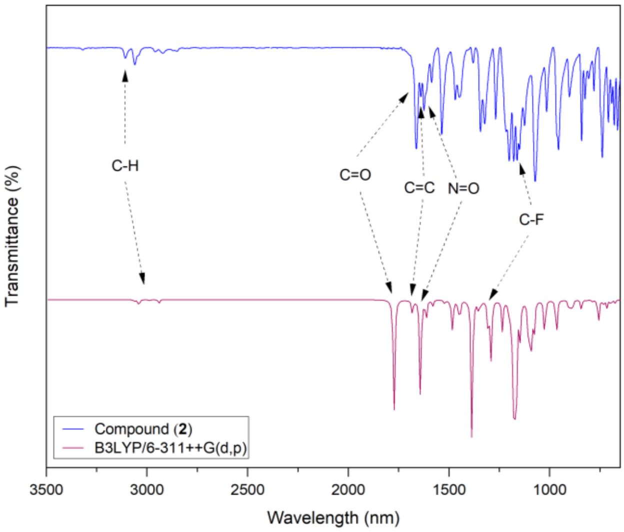


Figure 3. Infrared spectrum of compound **2**.

3.2.4. UV-Visible Spectroscopy

Compound **2** has three absorption bands, with a shoulder adjacent to the second band (Figure 4). The absorption bands at 193 nm (calc. 201 nm), 242 nm (calc. 261 nm), and the shoulder at 218 nm (calc. 231 nm) correspond to $\pi \rightarrow \pi^*$ transitions between the orbitals of both rings, i.e., the heterocycle and benzene ring's double bonds. The nitro group also causes an electronic transition from $\eta \rightarrow \pi^*$. The lower-intensity band at 301 nm (calc. 330 nm) is attributed to $\pi \rightarrow \pi^*$ transitions in the chromone backbone and $\eta \rightarrow \pi^*$ transitions from oxygen atoms.

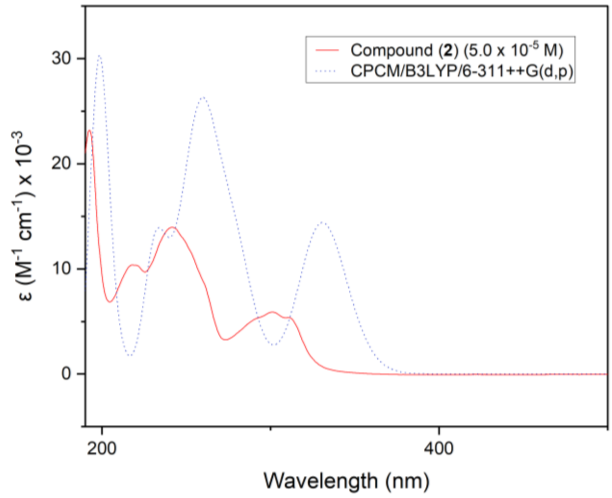


Figure 4. Experimental (solid line) and calculated (dashed line) electronic spectra of compound **2** in acetonitrile.

3.2.5. NMR Spectroscopy

A linear regression of chemical shifts for ^1H and ^{13}C nuclei was used to correlate experimental and theoretical data. The correlation coefficients for ^1H and ^{13}C were 0.9971 and 0.9921, respectively. The theoretical and experimental ^1H NMR spectra showed a good correlation (variation range: 0.15–1.17 ppm). The ^{13}C NMR spectrum showed a good correlation, with a variation range of −12.5–2.5 ppm. The CF_2CF_3 group's carbons showed the greatest difference between experimental and calculated values, with values ranging from 8–11 ppm.

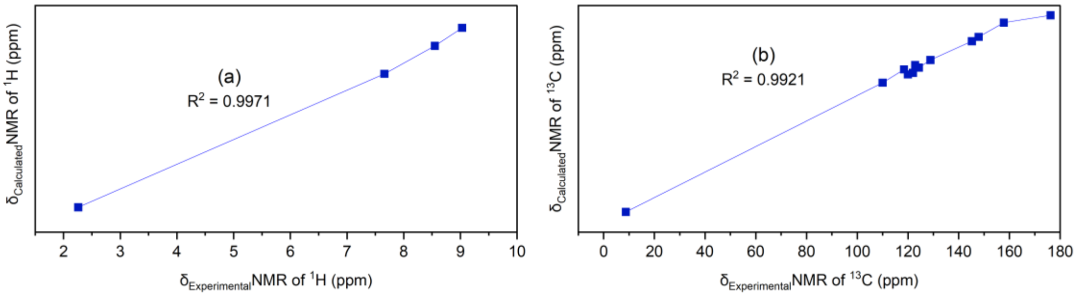


Figure 5. Linear regression of (**a**) ^1H NMR and (**b**) ^{13}C NMR.

4. Conclusions

In this study, a nitro-substituted derivative of 3-methyl-2-pentafluoroethylchromone **2** was synthesized with a 79% yield using a nitration reaction. The compound was studied experimentally and theoretically using spectroscopic techniques such as vibrational (IR), electronic (UV-Visible), and nuclear magnetic resonance (NMR) of ^1H and ^{13}C. Quantum chemical calculations were also performed at various theoretical levels to help interpret the results.

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