Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 547-304.4+547.538.141+ 547.775+519.688

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The Theoretical and Experimental Study of Diazomethane-Styrene [3+2]-Cycloadditions

Abstract

Pyrazolines are an important class of heterocyclic compounds known for their biological activities, making them attractive objects for medicinal chemistry. This study investigated the regioselective [3+2]-cycloaddition of diazomethane with *para*-substituted styrenes featuring electron-withdrawing (EWG) and electron-donating (EDG) groups. Experimental results have demonstrated that the electronic properties of substituents significantly affect the reaction efficiency and regioselectivity, as well as the product stability. At the same time, EWG provided lower activation barriers and higher reaction yields. Calculations performed by the density functional theory (DFT) method confirmed the experimental data allowing us to understand in detail the reaction mechanism, activation energy values, and thermodynamic parameters. This integrated experimental and theoretical approach improves understanding of the effects of substituents, contributing to the rational design of substituted pyrazolines.

Keywords: diazomethane; styrene; pyrazoline; cycloaddition; DFT calculations

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Теоретичне та експериментальне дослідження реакції [3+2]-циклоприєднання діазометану до стиренів

Анотація

Піразоліни є важливим класом гетероциклічних сполук та відомі своєю біологічною активністю, що робить їх привабливими об'єктами для медичної хімії. У цій роботі досліджено регіоселективне [3+2]-циклоприєднання діазометану до *пара*-заміщених стиренів, які містять електроноакцепторні (EWG) та електронодонорні (EDG) групи. Експериментальні результати продемонстрували, що електронні властивості замісників помітно впливають на ефективність і регіоселективність реакції, а також стабільність продукту. Із цим EWG забезпечували нижчі бар'єри активації та вищі виходи реакції. Розрахунки, виконані методом теорії функціоналу густини (DFT), підтвердили експериментальні дані, давши змогу детально зрозуміти механізм реакції, значення енергії активації і термодинамічні параметри взаємодії. Інтегрований експериментально-теоретичний підхід покращує розуміння впливу замісників, сприяючи раціональному дизайну заміщених піразолінів.

Ключові слова: діазометан; стирен; піразолін; циклоприєднання; теорія функціоналу густини

Citation: Ivonin, S. P.; Shuvakin, S. I. The Theoretical and Experimental Study of Diazomethane-Styrene [3+2]-Cycloadditions. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (1), 49–55.
https://doi.org/10.24959/ophcj.25.326552
Supporting information: Details of experiments and synthesis; spectral and analytical data for the compounds synthetized; copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra. Details of calculations.
Received: *29 December 2024*; **Revised:** *24 March 2025*; **Accepted:** *25 March 2025*

Funding: The work was supported by the National Reseach Foundation of Ukraine (grant No. 0124U003838).
Conflict of interests: The authors have no conflict of interests to declare.

Introduction

Pyrazolines, five-membered nitrogen-containing heterocycles, are widely recognized for their significant biological activities, including antimicrobial, anti-inflammatory, analgesic, antidepressant, and anticancer properties, making them valuable scaffolds in medicinal chemistry [1].

The regioselective [3+2] cycloaddition between diazomethane (CH_2N_2) and styrene derivatives is an important synthetic method for preparing substituted pyrazolines [2]. Despite its established importance, practical applications have historically been limited due to safety and operational challenges associated with diazomethane handling [3, 4]. However, recent advancements, particularly through flow chemistry techniques, have improved the safety and reproducibility of these reactions [5].

Previous studies have shown that substituents in styrene significantly affect the reaction efficiency, regioselectivity, and stability of the products. Electron-withdrawing groups generally enhance reactivity, while electron-donating groups reduce it [6]. However, isolation and thorough characterization of intermediate Δ^1-pyrazolines remain scarce despite their synthetic potential as precursors for various valuable derivatives [7].

In this study, using flow chemistry for safer handling of diazomethane, we investigated the regioselective cycloaddition of diazomethane with *para*-substituted styrenes featuring different electronic properties. By integrating experimental results and calculations based on density functional theory (DFT), we aim to gain an understanding of the effect of substituents and increase the practical synthetic utility of pyrazoline derivatives for medicinal chemistry applications.

Results and discussion

Styrenes containing substituents of different electronic nature in position 4 of the benzene ring were introduced into the reaction with diazomethane (**Figure 1**). By doing so, we found that 1-fluoro-4-vinylbenzene (**1a**), methyl 4-vinylbenzoate (**1b**), and 4-vinylbenzonitrile (**1c**) reacted regioselectively with diazomethane, forming the corresponding Δ^1-pyrazolines (**Figure 1**). Analysing crude reaction mixtures by ^{1}H NMR method evidenced that the reaction of **1b,c** with an excess of diazomethane (3 equiv.) led to 60% conversion of products **2b,c**, while the conversion of **1a** to **2a** was only 30%. After purification by chromatography on silica gel, pure products **2a–c** were isolated with the yields of 24–47%. It is worth noting that the use of a larger amount of diazomethane or increased reaction time (more than 2 days) did not improve the conversion to pyrazoline **2a–c**.

The interaction of **1d** with diazomethane occurred almost quantitatively, as evidenced by the absence of the olefin proton signals in the ^{1}H NMR spectrum of the crude reaction mixture and the TLC data of the reaction mixture. However, it was not possible to isolate the product of the [3+2]-cycloaddition **2d** due to the polymerization of the reaction mixture content upon the evaporation of the solvent at temperatures below 0°C.

The interaction of alkenes **1e–f** with diazomethane under the standard conditions did not lead to the formation of pyrazolines, and the starting alkenes were isolated unchanged from the reaction mixture (**Figure 1**). For **1f**, we observed the formation of a small amount (5–7% according to ^{1}H NMR data) of the cyclopropanation product – 1-cyclopropyl-4-methylbenzene (**4f**). Diazomethane ntroduced into the reaction mostly formed a polymer. Additionally, using 4-vinylpyridine (**1g**) as a substrate in the reaction with diazomethane resulted in only the polymerization of **1g**.

The treatment of ethereal solutions of pyrazolines **2a,b** with HCl in a dry diethyl ether led to the isomerization into the corresponding Δ^2-pyrazolines **3a,b** (**Figure 1**).

A cursory analysis of the experimental data suggests that the introduction of an acceptor substituent into the aromatic fragment increases the activity of styrene in the reaction, while a donor substituent causes the opposite effect. Therefore, it became necessary to investigate this reaction by quantum-chemical calculations in the DFT approximation. As the study objects, we chose parent styrene undergoing a [3+2]-cycloaddition reaction with CH_2N_2, as well as *p*-F, *p*-CO_2Me-substituted derivatives, and, additionally, we employed three styrenes that did not react with diazomethane.

The reaction of styrenes **1** with diazomethane proceeded as a typical [3+2]-cycloaddition (**Figure 2**, *A*). In the structure of the transition state **TS-1h** (**Figure 2**, *B*), the interatomic distances C···C and C···N preceding the formation of the corresponding bonds in the cyclic product **2h** were 2.144 and 2.342 Å, respectively, therefore the process was quite synchronous. As shown by quantum chemical calculations, the values of the Gibbs free energies of activation of the cyclization

ISSN 2308-8303 (Print) / 2518-1548 (Online)

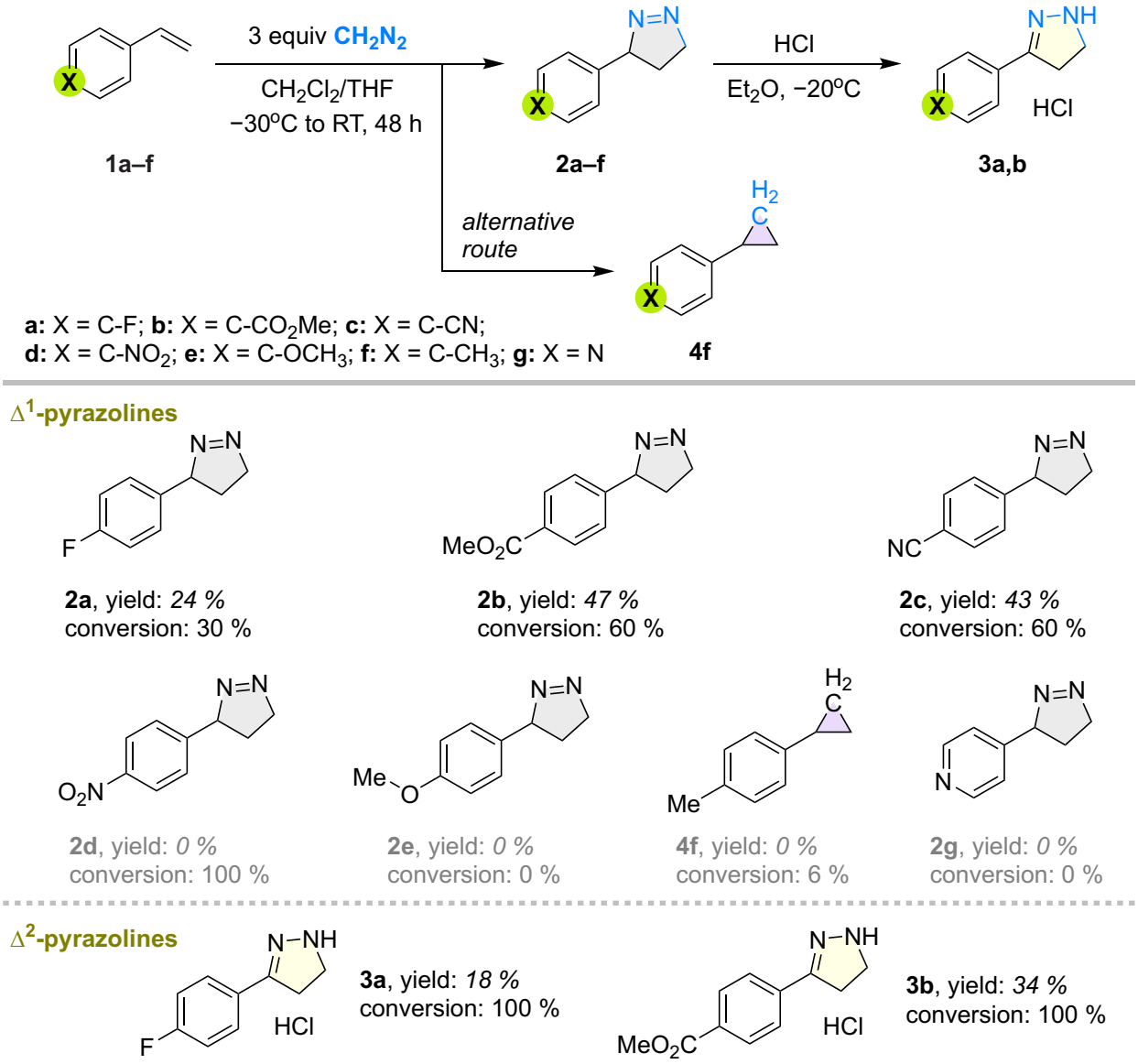
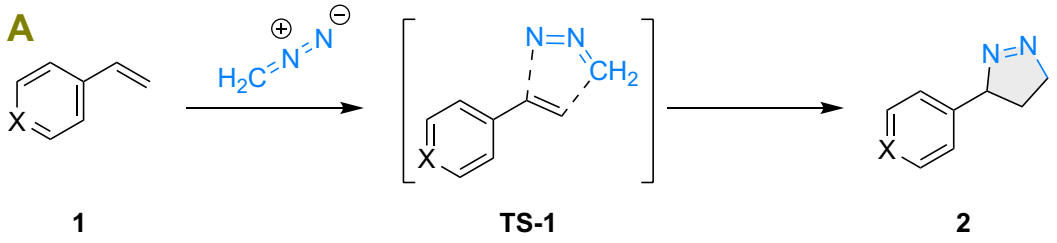


Figure 1. The synthesis of Δ¹-/Δ²-pyrazolines from *p*-substituted styrenes: scope and limitations

process (**Table 1**, $DG^{\neq}$) significantly exceeded the corresponding values of the thermally corrected energy and enthalpy values ($DE^{\neq}$ and $DH^{\neq}$); it was the result of the entropic component effect in the addition reaction. All the values were slightly dependent on the nature of the substitution in the benzene ring. However, in the case of styrenes with electron-withdrawing substituents in the aromatic moiety (**1b** and **1g**), the activation barrier values were somewhat lower than in the remaining compounds. However, there was no clear correlation between the results of calculations and the experiment. The cycloaddition products **2a,b,f–h** were significantly more favorable than the sum of the energies of the starting compounds **1a,b,f–h** and diazomethane, i.e., in all cases considered, the reaction was exothermic and exergonic. Therefore, the possibility of occurring a reverse reaction could be excluded.

■ Conclusions

This work presents an experimental and theoretical analysis of the regioselective [3+2]-cycloaddition of diazomethane with *para*-substituted styrenes. The application of the flow chemical approach made it possible to ensure safe handling of hazardous diazomethane and its controlled use, offering reproducible access to substituted pyrazolines. Experimental results have clearly demonstrated how substituent electronic effects significantly affect the reaction efficiency and regioselectivity, as well as the product stability, with electron-withdrawing groups facilitating cycloaddition. Calculations performed by the density functional theory (DFT) method confirmed these observations, providing valuable mechanistic insights and clarifying the energetic and structural aspects of reaction intermediates and transition states.



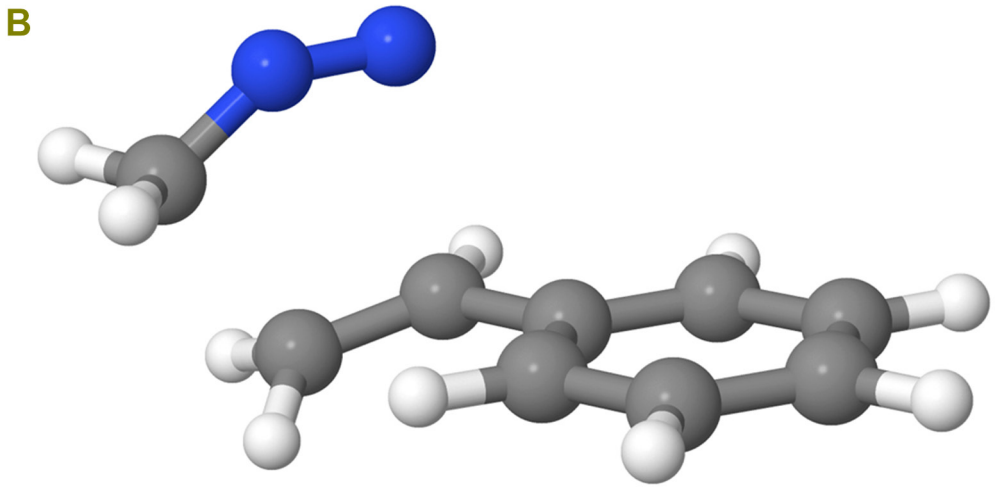


Figure 2. The model reaction used for quantum chemical studies (*A*); Jmol [8, 9] graphical representation of the transition state structure of **TS-1h** optimized in the M06-2X/def2-TZVP level of approximation (*B*)

Table 1. Calculated values of thermally corrected energies, enthalpies and Gibbs free energies of activation ($\Delta E^{\neq}$, $\Delta H^{\neq}$ та $\Delta G^{\neq}$, respectively, kcal mol^{-1}), corresponding to the transition state structures **TS-1a,b,f–h**, and energies, enthalpies and Gibbs free energies of forming **2a,b,f–h** (ΔE, ΔH and ΔG, respectively, kcal mol^{-1}) calculated in the CPCM(CH_2Cl_2)//M06-2X/def2-TZVP approximation

Structure	$\Delta E^{\neq}$	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔE	ΔH	ΔG
TS-1h	14.2	13.6	26.6	-32.9	-33.5	-19.6
TS-1f	14.7	14.1	27.1	-33.3	-33.9	-20.5
TS-1a	14.4	13.8	26.8	-33.1	-33.6	-19.8
TS-1b	12.5	11.9	24.6	-33.1	-33.7	-19.8
TS-1g	12.0	11.5	24.8	-32.9	-33.5	-19.3

This integrated experimental and theoretical study improves understanding of the effects of substituents in diazomethane-based cycloadditions, contributing to the rational design and synthesis of structurally diverse pyrazolines for further applications in medicinal chemistry and organic synthesis.

■ Experimental part

All starting compounds and solvents were obtained from Enamine Ltd. and used without additional purification. Diazomethane was generated in-flow as it was reported previously [5]. The composition of hydrochloride salts was determined by the acid-base titration method. NMR experiments were performed on a Bruker Avance III (at 302 MHz for ^{1}H NMR, 188 MHz for ^{19}F NMR, and 76 MHz for ^{13}C NMR) in the DMSO-d_6 or D_2O solution. NMR chemical shifts are reported in ppm units with the use of the δ scale and referenced using the residual solvent peaks. Mass spectra were taken on an Agilent LC/MSD SL 1100 instrument (atmospheric pressure electrospray ionization (ES-API)). Elemental analyses were performed at the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

Details of calculations

All calculations were carried out using the ORCA (version 5.03) [10, 11] program package. First, the geometry optimization was performed using the BP86/TZVP level of approximation [12, 13] in combination with the Resolution of

ISSN 2308-8303 (Print) / 2518-1548 (Online)

the Identity (RI) [14–17] routine. Then the structures were re-optimized using the same program at the M06-2X/def2-TZVP level of theory [18]. The TZVP and def2-TZVP basis sets were the TZV triple-zeta basis sets [19] extended by adding polarization functions, as implemented in the ORCA program. The RI – "chain of spheres" approximation (RIJCOSX) [20] was utilized in the case of the M06-2X functional to increase the calculation speed and efficiency. The solvent effects were taken into account, calculating the single-point energy values using the empirical CPCM procedure developed by Cammi and Tomasi [21]. In order to find the best approximation to transition state structures, the relaxed scanning of potential energy surfaces was performed at the RI-BP86/SV(P) level of approximation using the ORCA program package. The SV(P) basis sets were Ahlrichs split-valence basis sets [22] with one set of polarization d-functions for non-hydrogen atoms. Vibration frequencies and corrections for calculation of relative energies (ΔE) and relative free Gibbs energies (ΔG) were derived analytically at the BP86/TZVP level of theory and numerically for the M06-2X/def2-TZVP approach. For the structures corresponding to local energy minima, no imaginary frequencies were detected by the vibration analysis. The Jmol [8, 9] program was used for the graphical presentation of **TS-1h**.

The general procedure for the synthesis of pyrazolines 2a–c

0.01 mol of 4-substituted styrene was dissolved in 20 mL of a dry methylene chloride. A solution of diazomethane (0.03 mol, 3 equiv.) generated by a flow reactor at a rate of 0.40 mol h^{-1} was added dropwise to the styrene solution cooled to -30 °C over 4.5 min. The reaction mixture was left to stir in an ice bath for 4 h and allowed to stir for two days at ambient temperature in the darkness. The reaction mixture was evaporated under reduced pressure, redissolved in 50 mL of MTBE and filtered through cotton wool to remove the polymer formed by decomposition of diazomethane. The filtrate was evaporated, and chromatography on silica gel (hexane-MTBE, 70:30) gave the pyrazolines **2a–c**.

The general procedure for the synthesis of pyrazolines 3a,b

0.01 mol of 4-substituted styrene was dissolved in 20 mL of a dry methylene chloride. A solution of diazomethane (0.03 mol, 3 equiv.) generated by a flow reactor at a rate of 0.40 mol h^{-1} was added dropwise to the styrene solution cooled to -30 °C over 4.5 min. The reaction mixture was left to stir in an ice bath for 4 h and allowed to stir for two days at ambient temperature in the darkness. The reaction mixture was evaporated under reduced pressure, redissolved in 50 mL of a dry diethyl ether and filtered through a layer of cotton wool. The filtrate was cooled to -20 °C, and 5 mL of a saturated solution of HCl in diethyl ether was added dropwise. The reaction mixture was stirred vigorously for 10 min, and the precipitate formed was filtered off. The precipitate was collected and further dried in an oil pump vacuum, giving pyrazolines **3a,b**.

3-(4-Fluorophenyl)-4,5-dihydro-3H-pyrazole (**2a**)

A yellow oil. Yield – 390 mg (24%). Anal. Calcd for $C_9H_9FN_2$, %: C 65.84, H 5.53, N 17.06. Found, %: C 65.99, H 5.41, N 17.11. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 1.23–1.44 (1H, m), 2.00–2.26 (1H, m), 4.16–4.38 (1H, m), 4.72–4.88 (1H, m), 5.29–5.46 (1H, m), 7.12–7.25 (2H, m), 7.25–7.35 (2H, m). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 25.63, 76.66, 89.55, 115.48 (d, J = 21.3 Hz), 129.41 (d, J = 8.2 Hz), 135.88, 161.62 (d, J = 243.5 Hz). ^{19}F NMR (188 MHz, DMSO-d_6), δ, ppm: -114.96. MS (ES-API), m/z: 165 $[M+H]^+$.

Methyl 4-(4,5-dihydro-3H-pyrazol-3-yl)benzoate (**2b**)

An easily fusible solid. Yield – 960 mg (47%). Anal. Calcd for $C_{11}H_{12}N_2O_2$, %: C 64.69, H 5.92, N 13.72. Found, %: C 64.78, H 5.87, N 13.64. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 1.44–1.31 (1H, m), 2.14–2.26 (1H, m), 3.86 (3H, s), 4.26–4.38 (1H, m), 4.79–4.90 (1H, m), 5.49 (1H, t, J = 9.0 Hz), 7.43 (2H, d, J = 8.1 Hz), 7.99 (2H, d, J = 8.1 Hz). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 25.48, 52.20, 76.92, 89.91, 127.76, 128.82, 129.62, 144.94, 166.04. MS (ES-API), m/z: 205 $[M+H]^+$.

4-(4,5-Dihydro-3H-pyrazol-3-yl)benzonitrile (**2c**)

A yellow oil. Yield – 736 mg (43%). Anal. Calcd for $C_{10}H_9N_3$, %: C 70.16, H 5.30, N 24.54. Found, %: C 70.02, H 5.38, N 24.50. ^{1}H NMR (302 MHz, DMSO-d_6), δ, ppm: 1.20–1.54 (1H, m), 2.03–2.36 (1H, m), 4.15–4.46 (1H, m), 4.65–5.03 (1H, m), 5.48 (1H, t, J = 9.0 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.85 (2H, d, J = 8.2 Hz). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 25.38, 77.03, 89.77, 110.47, 118.77, 128.44, 132.70, 145.03. MS (ES-API), m/z: 172 $[M+H]^+$.

3-(4-Fluorophenyl)-4,5-dihydro-1H-pyrazole hydrochloride (**3a**)

A brown solid. Yield – 360 mg (18%). Anal. Calcd for $C_9H_{10}ClFN_2$, %: C 53.88, H 5.02, N 13.96. Found, %: C 53.81, H 5.10, N 14.04. ^{1}H NMR

(302 MHz, DMSO-d_6), δ, ppm: 3.46–3.68 (4H, m), 7.34–7.46 (2H, m), 7.90–8.02 (2H, m), 12.20–12.88 (1H, br. s). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 35.26, 42.42, 116.31 (d, J_{C-F} = 22.1 Hz), 125.37, 131.27 (d, J_{C-F} = 9.2 Hz), 164.66 (d, J_{C-F} = 251.3 Hz), 173.26. ^{19}F NMR (188 MHz, DMSO-d_6) δ, ppm: -106.52. MS (ES-API), *m/z:* 165 $[M+H]^+$.

Methyl 4-(4,5-dihydro-1H-pyrazol-3-yl)benzoate hydrochloride (**3b**)

A yellow solid. Yield – 818 mg (34%). Anal. Calcd for $C_{11}H_{13}ClN_2O_2$, %: C 54.89, H 5.44, N 11.64. Found, %: C 55.05, H 5.37, N 11.56. ^{1}H NMR (302 MHz, D_2O), δ, ppm: 3.55–3.71 (2H, m), 3.84 (5H, s + m), 7.82 (2H, d, J = 8.2 Hz), 7.89 (2H, d, J = 8.5 Hz). ^{13}C NMR (76 MHz, D_2O), δ, ppm: 36.43, 43.75, 53.49, 129.35, 130.40, 132.50, 134.78, 168.50, 177.84. MS (ES-API), *m/z:* 205 $[M+H]^+$.

Aknowledgments

The work would not be possible without the National Reseach Foundation of Ukraine, which kindly provided funding for creating a computer cluster at the Taras Shevchenko National University of Kyiv used for the quantum-chemical calculations in this work. The authors also thank Prof. Dr. Alexander B. Rozhenko, Institute of Organic Chemistry, NAS of Ukraine, for performing the DFT calculations.

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ISSN 2308-8303 (Print) / 2518-1548 (Online)

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