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Synthesis, crystal structure, computational study of 1-(6-chloro-pyridin-2-yl)-5-hydroxy-1*H*-pyrazole-3-carboxylic acid methyl ester and its 5-acetoxy analogs

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ABSTRACT

Two new pyrazole derivatives of 1-(6-chloro-pyridin-2-yl)-5-hydroxy-*1H*-pyrazole-3-carboxylic acid methyl ester **1a** and 5-acetoxy-1-(6-chloro-pyridin-2-yl)-*1H*-pyrazole-3-carboxylic acid methyl ester **2** were synthesized and characterized by ^{1}H, ^{13}C NMR, IR spectroscopies and HRMS analyses. The molecular structure of **1a** and **2** were studied by X-ray diffraction and compared to density-functional-theory (DFT) calculations. The gauge-including atomic orbital (GIAO) method for calculating ^{1}H and ^{13}C NMR nuclear magnetic shielding tensors at the DFT method with 6-31+G* basis set were applied to the compounds **1a** and **2**. Additionally, thermodynamic properties of the cyclization of the compound **3** to these compounds (**1a, 1b, 1c, 4**) were investigated by theoretical calculations. These theoretical calculations was shown that the compound **1a** was readily formed and was the most stable one. Tautomeric forms of the compound **1a** were optimized at the same methods and basis set. The calculated relative Gibbs free energies of the tautomeric forms of **1a** were used to estimate the equilibrium constants. It was shown that the **1a** was the most stable than tautomer of **1b** and **1c** in the gas phase.

1. Introduction

The reactions of α-hydrazino-azaheterocycles with dimethyl acetylenediccarboxylate (DMADC) have been studied extensively for the past decades due to biological importance and tautomeric forms of its product [1–6]. Theoretically, the cyclization of the hydrazones such as **3**, prepared from 6-chloro-2-hydrazionopyridine derivatives and (DMADC), could have occurred either on the hydrazine nitrogen atom with the formation of a 5-membered pyrazole ring **1a** or on the nitrogen atom of pyridine with the formation of 1,2,4-triazine-5-ones **4** (Scheme 1) [7,8]. Five-membered pyrazole ring **1a** exists in three possible tautomeric structures **1a, 1b** and **1c** [9–12] (Scheme 2). However, in the present paper, we reported the cyclization of the hydrazone **3** that only **1a** was obtained in the solid state. Prior to our studies, a synthesis of pyrido [2,1-c] [1,2,4] triazine-5-one was reported in acetic anhydride by LeCount and Greer in 1974 [13]. While heating the hydrazone **3** in acetic anhydride also failed to give the triazinone product, OH-acetylpyrazole **2** was isolated in good yield (Scheme 1). Herein, we have investigated the synthesis, spectroscopic characterization, X-ray crystal structures and quantum chemical calculations of two new pyrazole derivatives **1a** and **2**. We also reported thermodynamic properties of the cyclization of the compound **3** and the equilibrium constants for tautomerizations of **1a** by theoretical calculation. The experimental data were supplemented by using DFT quantum chemical calculations. We wanted to these calculations gave results allow us to rationalize and explain the experimental observations that the compound **1a** was readily formed and was the most stable tautomer.

2. Experimental and computational details

2.1. Materials and analyses

All chemicals were of reagent grade and used as commercially purchased without further purification. All solvents were dried and distilled before use. For TLC analysis, pre-coated plates of silica gel 60 F_{254} were used. Melting points were determined using a WRS-1B apparatus and were uncorrected. The IR spectra were recorded in the range of 400–4000 cm^{-1} with a Magna 550 FT-IR spectrometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV600 spectrometer, using tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent. High resolution mass (HRMS) spectra were obtained in ESI mode on a Finnigan MAT95XP HRMS system (Thermo Electron Corporation).

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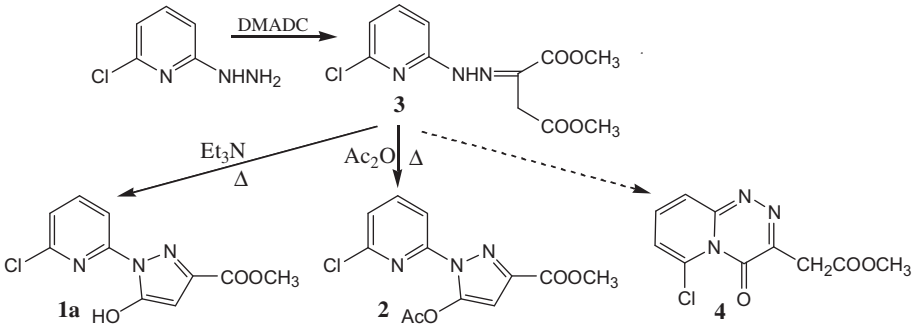
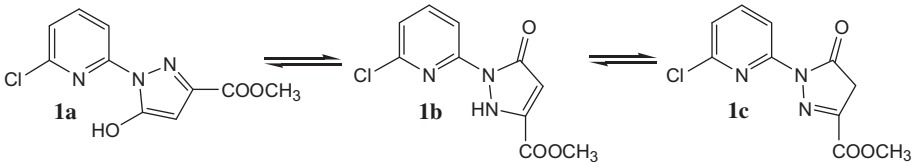


Scheme 1. Synthesis of compounds **1a**, **2** and **3**.



Scheme 2. Tautomeric forms of compounds **1a**.

2.2. Synthesis

2.2.1. Dimethyl -2-[(6-chloror-pyridin-2-yl)-hydrazono]succinate **3**

Dimethyl acetylenedicarboxylate (DMADC) (6.00 mL, 48.9 mmol) in methanol (60 mL) was added dropwise to a solution of (6-chloro-pyridin-2-yl)-hydrazine (5.00 g, 34.8 mmol) in methanol (50 mL) and the mixture was stirred vigorously for 5 h at 0 °C. The resulting suspension was filtered and the filter cake was washed thoroughly with cold methanol. The filter cake recrystallised from acetone to obtain the product (8.67 g, 87.1%) as a yellow solid. mp: 141–143 °C. ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 2H), 3.75 (s, 3H), 3.89 (s, 3H), 6.95 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.60–7.63 (m, 1H), 9.13 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 31.7, 52.8, 52.9, 106.7, 117.8, 130.9, 140.7, 149.3, 155.5, 164.5, 168.2 ppm; IR (KBr): 3305, 3037, 1741, 1706, 1612, 1591, 1574, 1018, 427 cm^{-1}.

2.2.2. 1-(6-chloro-pyridin-2-yl)-5-hydroxy-1H-pyrazole-3-carboxylic acid methyl ester ***1a***

To a solution of dimethyl -2-[(6-chloror-pyridin-2-yl)-hydrazono]succinate (**3**)(5.00 g, 17.5 mmol) in methanol (100 mL) was added Et_3N (1 mL). The reaction was refluxed for 1 h, then cooled to 0 °C, and quenched with water. The suspension was filtered and the filter cake was washed thoroughly with cold methanol. The filter cake recrystallised from acetone to obtain the product (3.60 g, 81.1%) as a white solid. mp: 174–176 °C. ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 3H), 6.12 (s, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.87–7.90 (m, 1H), 8.01 (d, J = 8.4 Hz, 1H), 11.41 (s, 1H). ppm. ^{13}C NMR ($CDCl_3$): δ 52.4, 90.6, 111.3, 121.6, 142.3, 144.9, 147.7, 153.5, 156.2, 162.4 ppm; HRMS ($M + H^+$) calcd for $C_{10}H_9O_3N_3Cl_1$ 254.0336, found 254.0338. IR (KBr): 3147, 3013, 1746, 1624, 1594, 1574, 1484, 1444, 1068, 1187, 422 cm^{-1}.

2.2.3. 5-Acetoxy-1-(6-chloro-pyridin-2-yl)-1H-pyrazole-3-carboxylic acid methyl ester ***2***

A solution of dimethyl-2-[(6-chloror-pyridin-2-yl)-hydrazono]succinate (**3**)(5.00 g, 17.5 mmol) in acetic anhydride (60 mL) was heated under reflux for 10 h, The resulting solution was evaporated to dryness, methanol (12 mL) was added, and the suspension was cooled to −10 °C and filtered. Recrystallisation from methanol to obtain the product (3.54 g, 68.0%). mp: 133–135 °C. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H), 3.96 (s, 3H), 6.65 (s, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.79–7.81 (m, 1H), 7.95(d, J = 7.8 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.8, 52.4, 101.3, 113.7, 122.8, 141.0, 143.6, 146.0, 149.1, 150.9, 161.9, 167.8 ppm. HRMS ($M + H^+$) calcd for $C_{12}H_{11}O_4N_3Cl_1$ 296.0433, found 296.0436; IR (KBr): 3095, 1791, 1721, 1581, 1484, 1457, 1424, 1065, 419 cm^{-1}.

2.3. X-ray crystallography

Diffraction experiments for **1a** and **2** were carried out on with *Mo* K_a radiation (λ = 0.71073 Å) using a bruker SMART APEX CCD diffractometer at 296 K. Raw frame data were integrated with the SAINT program. The structures were solved by direct methods and refined with full-matrix least-squares on F^2 using SHELXS-97 and SHELXL-97 [14]. All the non-hydrogen atoms were refine anisotropically. The hydrogen atoms were set in the calculated positions and refined by riding model. The crystallographic and refinement data of **1a** and **2** are shown in Table 1.

2.4. Computational methods

The Gaussian 03 package [15]was used to carry out all calculations. All geometries were optimized using DFT(B3LYP) [16,17] with the 6-31+G* [18] basis set. The energy was also calculated at DFT(B3LYP)/6-31+G* level of theory, and the single point frequency calculations based on the optimized geometries in order to ensure the energy minimum structure. ^{1}H and ^{13}C NMR chemical shifts were calculated within the GIAO approach [19,20] applying the same methods and basis set as used for geometry optimization. The ^{1}H and ^{13}C NMR chemical shifts were converted to the TMS scale by subtracting the calculated absolute chemical shielding of TMS, with values of 32.1 and 190.7 ppm for B3LYP/6-31+G*, respectively. The effect of solvent on the theoretical NMR parameters was included using the default model IEF-PCM provided by Gaussian 03. Trichloromethane ($CHCl_3$) was used as solvent.