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Synthesis and Characterization of 1-(2-Methyl-4-(4-methylbenzoyl)-7-thioxo-5-*p*-tolylpyrazolo[1,5-f]pyrimidin-1(7*H*)-yl)propan-2-one

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Abstract

1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidin-2(1*H*)-thione (**1**) was prepared in two steps by the reaction of furan-2,3-dione and acetophenon thiosemicarbazone. 1-(2-Methyl-4-(4-methylbenzoyl)-7-thioxo-5-*p*-tolylpyrazolo[1,5-f]pyrimidin-1(7*H*)-yl)propan-2-one (**2**) was synthesized from compound **1** with α-chloracetone. The structure of new compound **2** was verified by FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. The theoretical properties of compound **2** was also calculated using Gaussian 09 program.

Keywords: Aminopyrimidine, α-chloracetone, pyrazolo[1,5-f]pyrimidin.

Introduction

Compounds containing pyrimidine ring attract researchers' attention due to their different properties. For example, Ishida et al. synthesized Cu(II) complexes having pyrimidine ring, and investigated their magnetic properties [1]. By Wiśniewski et al., Ru(III), Rh(III), Pd(II) and Pt(II) metal complexes containing pyrimidine ring were designed and tested as *in vitro* against A549, LS-180 and MCF-7 cell lines for learning their cell proliferation activities [2]. In the conducted study by Kökbudak et al., a series of various metal complexes were prepared from a Schiff base having pyrimidine core, and the cytotoxic activity properties of the complexes were

screened against human lung cell line [3]. In the study conducted by Semenov et al, some compounds including pyrimidine ring were reported and their antibacterial activities were tested [4].

In this study, compound **1** was synthesized in two steps from furan-2,3-dione derivative and acetophenon thiosemicarbazone [5]. Targeted product (**2**) was prepared in 64% yield via cyclocondensation reaction of starting material **1** with α-chloroacetone. This new molecule **2** was characterized by elemental analysis, FT-IR, ^{1}H NMR and ^{13}C NMR. The theoretical study of the relative compound was done with Gaussian 09 software.

Experimental section

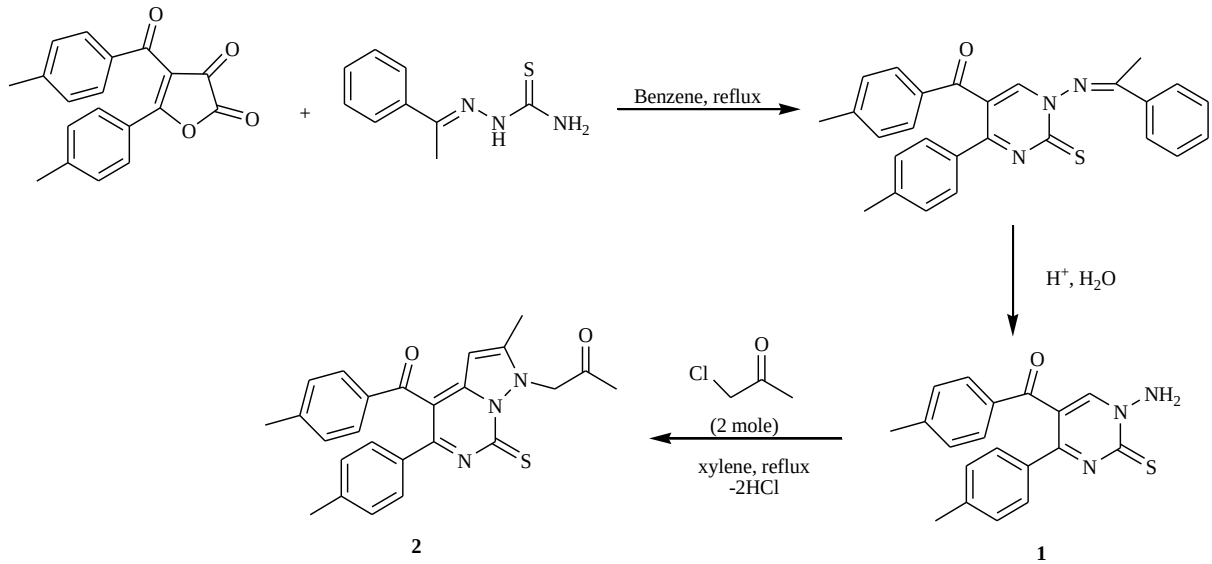
Reagents and solvents used were commercially purchased. Melting point of compound was determined using a digital melting point apparatus (Electrothermal 9100). Microanalysis study was performed on a Leco CHNSO-932 Elemental Analyzer. IR spectra were recorded on a Shimadzu Model 8400 FT-IR spectrophotometer. The ^{1}H (^{13}C) NMR spectra were recorded on a Bruker 400 (100) MHz Ultra Shield instrument.

1-(2-Methyl-4-(4-methylbenzoyl)-7-thioxo-5-*p*-tolylpyrazolo[1,5-f]pyrimidin-1(7*H*) yl)propan-2-one, (2)

Yield: 64%; m.p. 174-176 ^{o}C. FT-IR: 3051.2 (aromatic C-H), 2920.0 and 2896.9 (aliphatic C-H), 1726.2 and 1652.9 (C=O), 1598.9 (C=N), 1485.1 (C=C), 740-660 cm^{-1} (pyrimidine ring skeleton vib.). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ= 8.69 (s, H, -CH=), 7.71-7.10 (m, 8 H, Ar-H), 3.53 (s, 2 H, -CH_2-), 2.58, 2.44, 2.40 and 2.31 (s, 12 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 192.56, 160.90, 158.40, 149.03, 145.05, 140.26, 136.37, 134.58, 133.84, 130.22, 129.43, 129.17, 129.10, 120.93, 97.89, 45.71, 27.96, 21.77, 21.37 and 13.13. Anal. cald. for: $C_{25}H_{23}N_3O_2S$: C, 69.91; H, 5.40; N, 9.78; S, 7.47. Found: C, 69.77; H, 5.37; N, 9.65; S,7.31.

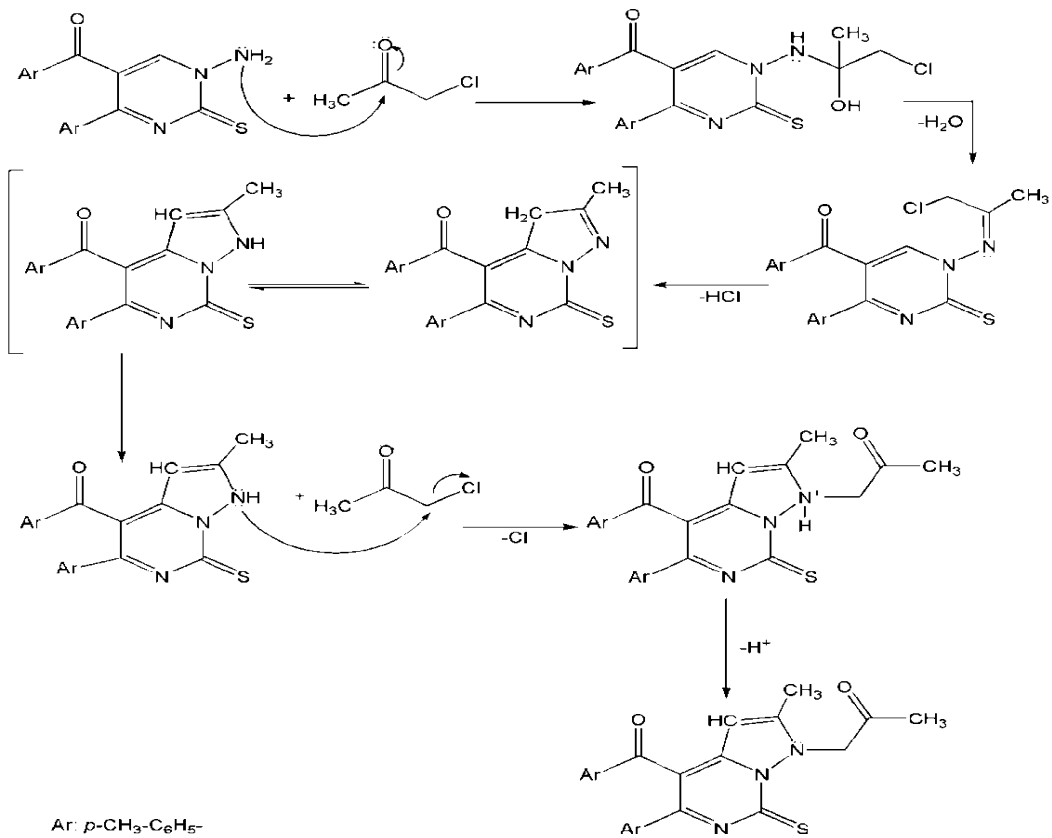
Synthesis

In this study, according to the literature procedure, a new compound **2** was synthesized by the cyclization reaction of **1** with α-chloracetone in xylene under reflux for 2 h [6-9]. The compound was characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and elemental analysis. The general synthesis outline of the targeted product is shown in Scheme 1.



Scheme 1. Synthesis of compound **2**.

The proposed mechanism for the synthesis of compound 2 is depicted in scheme 2.



Scheme 2. Mechanistic proposal for the formation of **2.**

The reaction starts with a nucleophilic attack of the nitrogen atom lone pair electrons of compound 1 to the carbonyls' carbon of α-chloracetone [10, 11]. At first step, Schiff base occurs by the condensation reaction of 1 and α-chloracetone. The cyclization reaction occurs via elimination of a molecule of hydrogen chloride by refluxing in xylene and product 2 was obtained in 64% yield.

Results and Discussion

Spectroscopic Analysis of a Pyrimidine Based Compound

The structure of **2** was verified using analytic and spectroscopic methods. The IR spectrum of **2** showed that the characteristic NH group bands found in the starting material **1** were disappearance. The absorption bands were obtained at ν = 3051.2 for CH aromatic, 2920.0 and 2896.9 for CH aliphatic, and 1726.2, 1652.9 cm^{-1} for carbonyl (C=O), respectively.

Methyl protons (C*H*$_3$-) in the structure of compound **2** resonated as singlet signal at δ 2.58, 2.44, 2.40 and 2.31 ppm in ^{1}H NMR spectra. The methylene' (-CH_2-) protons resonated as singlet at δ 3.53 ppm. The signals belong to the protons in aromatic rings were seen as multiple at δ 8.69-7.10 ppm.

In the ^{13}C NMR spectra, the characteristic carbonyl group signal was observed at δ 192.56 ppm. The methylene carbon (CH_2) signal was seen to be resonated at δ 45.71 ppm. The carbon in the methyl group (CH_3-) were found to be resonated at δ 27.96, 21.77, 21.37 and 13.13 ppm in ^{13}C NMR. On the other hand, the aromatic carbon signals were obtained between δ 120.93 and 160.90 ppm. As result, the spectroscopic data verified the structure of the synthesized new organic compound **2**.

Electrostatic Potential Map

The molecular electrostatic potential (MEP) value is related to regional charge distribution, electronegativity, dipole moment and chemical activity. On the other hand, electrostatic potential (ESP) maps provide valuable information on many features such as size, charge density, chemical activity zones. Electrostatic potential values on the molecular surface are expressed in different colors. Red: the highest electron density- blue: the highest positive potential (low electron density) characterizes areas suitable for nucleophilic attacks. The ESP map of compound **2** is given in Figure 1.

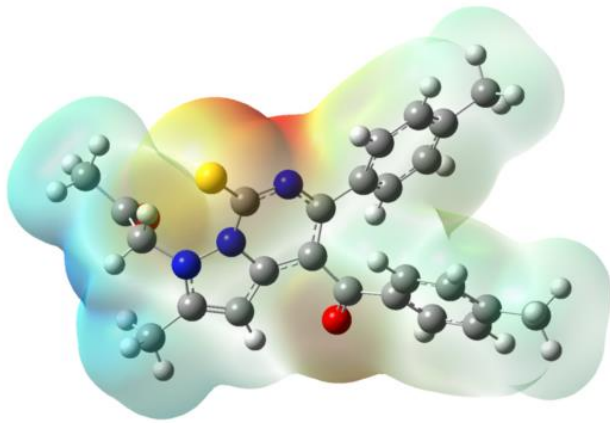


Figure 1. ESP map of compound **2**.

Relative compound was optimized using hybrid functional B3LYP of DFT with 6.311 (d, p) basis set. The highest electron density in molecule was seen around the nitrogen and sulfur atom in pyrimidine ring. This region can be seen as a suitable area for chemical interaction. The blue areas on the ESP map show lower electron density areas.

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) values were further calculated and found as -5.671 eV and -2.246 eV, respectively. The HOMO-LUMO gap value was calculated as 3.425 eV. Since this value is greater than 1.5 eV, it cannot be said that relative molecule is very active chemically.

Conclusion

In this study, a new compound was synthesized and the structure of it was verified by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. Using Gaussian 09 program, the theoretical calculation of molecule **2** was done.

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