Research Article

Synthesis of Some Pyrimidine, Pyrazole, and Pyridine Derivatives and Their Reactivity Descriptors

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Received 2 September 2018; Revised 9 October 2018; Accepted 22 October 2018; Published 13 November 2018

Academic Editor: Pedro M. Mancini

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A series of novel pyrimidine (2, 3), pyrazole (4, 5), and pyridine (6) derivatives were synthesized using a chalcone-bearing thiophene nucleus (1). The target compounds were synthesized by reaction of compound (1) with urea, thiourea, malononitrile, hydrazine hydrate, and 2,4-dinitrophenyl hydrazine, respectively. Molecular electronic structures have been modeled within density functional theory framework (DFT). Reactivity indices and electrostatic surface potential maps (ESP maps) allow us to establish trends that enable making predictions about chemical characteristics of the newly synthesized molecules and their proton transfer tautomers. Proton transfer is generally more favored in solution than in the gas phase. In acetonitrile, keto-form tautomers and thione-form tautomers become more energetically stable than the corresponding enol or thiol tautomers due to solvent-induced enhancement in the molecular polarity identified by computed dipole moment.

1. Introduction

Chalcone derivatives from natural sources or synthetic origin exhibit diverse pharmacological activities, such as antimicrobial [1], anticancer [2], antioxidant [3], antitumor [4], anti-inflammatory [5], and antitubercular [6].

Heterocyclic compounds particularly five- or six-membered ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities. These compounds possess diverse chemotherapeutic and pharmacological activities. Pyrimidine and their derivatives have been found to possess a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, analgesic, antiviral, and anticancer activities [7].

Pyrazolines are well-known important nitrogen-containing five-membered heterocyclic compounds. It is also worthy to mention that pyrazoline derivatives have been known to possess widespread pharmacological activities, such as anti-inflammatory [8], anticonvulsant [9, 10], antimicrobial [11, 12], anticancer [13], antiviral [14], and hypotensive [15] activities.

In the present work, a chalcone-bearing thiophene nucleus (1) was prepared and used as a key starting material for obtaining the desired pyrimidine, pyrazoline, and pyridine derivatives (2–6) (Figure 1). Experimentally obtained physical and spectroscopic properties will be presented and validated by theoretical parameters related to the molecular reactivities (such as, electrophilicity, nucleophilicity, chemical potential, and hardness), which are obtained by quantum chemical computations using DFT approximations. ESP maps of the energetically optimized new molecules will also be reported. The ESP map surfaces that enable exploration of molecular reactive sites will be discussed. Moreover, the reliably identified lowest energy tautomers will be explored in the gas phase as well as in acetonitrile (aprotic solvent).

2. Experimental Section

2.1. Synthesis

2.1.1. General Procedure for the Preparation of Compounds (2 and 3). A mixture of chalcone (1) (2.5 g, 10 mmol) and different nucleophilic reagents, namely, urea and thiourea
(10 mmol), was dissolved in ethanolic sodium hydroxide (4 g NaOH and 10 mL ethanol) and was stirred for about 2-3 hours with a magnetic stirrer. This was then poured into 400 mL of cold water with continuous stirring for an hour, and after that, we kept the mixture in a refrigerator for 24 hours. The precipitate obtained was filtered, washed, and recrystallized (mostly in ethanol).

4-(4-Nitrophenyl)-6-(thiophen-2-yl)pyrimidin-2-ol (2). Yields 80%, m.p. 252–255°C, yellow powder; IR (KBr, $\nu$/cm$^{-1}$): 3434 (3877) cm$^{-1}$ ($\nu$OH); 3096 (3242) cm$^{-1}$ 

Figure 1: Optimized geometries (best view) of chalcone (1) and newly synthesized molecules (left side) as well as nomenclature (right side). Hydrogen atoms are removed from some molecules for clarity.
(\textnormal{C-H}), 7.1 (\textnormal{singlet}, 1H, pyrimidine), 7.9–7.2 (\textnormal{multiplet}, 3H, thiophene), 7.1 (\textnormal{singlet}, 1H, NH), 7.0 (\textnormal{multiplet}, 3H, pyrazole), 4.0 (\textnormal{triplet}, 1H, pyrazole), 3.1 (\textnormal{doublet}, 2H, ArH), 2.1 (\textnormal{doublet}, 2H, ArH, J = 6.8 Hz), 7.5 (\textnormal{doublet}, 2H, ArH, J = 6.8 Hz).

**2.2. Instrumentation.** The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. \(^1\text{H-}\)NMR spectra were run at 300 MHz, on a Varian Mercury VX-300 NMR spectrometer using TMS as an internal standard in deuterated dimethylsulfoxide. The microanalytical data were measured in the Central Lab of Cairo University, Egypt; the Ministry of Defense Chemical Laboratories, Egypt; and the Microanalytical Center of Ain Shams University, Egypt. All the chemical reactions were monitored by TLC. Melting points measured were uncorrected.

**2.3. Computations.** Computations were performed using Gaussian 16 revision A.03 package [18] and/or Spartan’16 parallel QC program (Wavefunction, Inc., USA). Optimized structures and spectroscopic data were obtained within DFT by employing the widely used wB97X-D/6-31G(d,p) model. Long-range corrected hybrid density functional, the wB97X-D functional [19], includes empirical damped atom-atom dispersion corrections. wB97X-D is significantly more accurate than the commonly used functional B3LYP. Harmonic vibrational frequencies of the optimized geometries were calculated with the same model in order to verify that they are true minima (with zero imaginary frequencies). Tight SCF convergence (energy change 1.0e–08 au) and larger integration grids are used. The list of the convergence criteria followed is 5e–9 for RMS density change, 1e–7 for maximum density change, 5e–7 for direct inversion in the iterative subspace (DII) error convergence, and 1e–5 for orbital gradient convergence. Finally, we used successfully a less-expensive computational model wB97X-D/6-31G (d) without any change in the trends obtained from the basis set 6-31G(d,p).

**3. Results and Discussion**

**3.1. Synthesis and Spectroscopic Properties.** New pyrimidine derivatives are prepared by reaction of the chalcone (1) with urea and thiourea in ethanolic sodium hydroxide to produce 4-(4-nitrophenyl)-6-(thiophen-2-yl) pyrimidin-2-ol molecule (2) and 4-(4-nitrophenyl)-6-(thiophen-2-yl) pyrimidine-2-thiol (3), respectively. The structure of the products was confirmed by IR which showed OH group stretching at 3434 cm\(^{-1}\) (calculated 3675) cm\(^{-1}\). The \(^1\text{H-}\)NMR showed singlet of the SH group at 2362.37 (2689 calculated) cm\(^{-1}\).

**2.1. General Procedure for the Preparation of Compounds (4 and 5).** We dissolved a mixture of chalcone (1) (2.5 g, 10 mmol) and different nucleophilic reagents, namely, hydrazine hydrate and 2,4-dinitrophenyl hydrazine (10 mmol), using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. \(^1\text{H-}\)NMR spectra were run at 300 MHz, on a Varian Mercury VX-300 NMR spectrometer using TMS as an internal standard in deuterated dimethylsulfoxide. The microanalytical data were measured in the Central Lab of Cairo University, Egypt; the Ministry of Defense Chemical Laboratories, Egypt; and the Microanalytical Center of Ain Shams University, Egypt. All the chemical reactions were monitored by TLC. Melting points measured were uncorrected.

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The IR of compound 4 showed stretching vibration of the NH group at 3427.85 cm\(^{-1}\), and its \(^1\)H-NMR showed singlet of the pyrazole protons at \(\delta\) 4.061 (3.2) ppm. The \(^1\)H-NMR of compound 5 shows a singlet due to pyrazole protons at \(\delta\) 5.105 ppm. Finally, reaction of chalcone (1) with malononitrile in presence of ethanol and ammonium acetate produced the corresponding pyridine derivatives 2-amino-6-(4-nitrophenyl)-4-(thiophen-2-yl) nicotinonitrile (6). The IR spectrum of compound 6 exhibits stretching vibrations of the NH group at 3363.25 cm\(^{-1}\) and CN group at 2197.49 cm\(^{-1}\). Unfortunately, the computed IR spectra of these compounds in gaseous phase were not in good agreement with the experimentally measured IR spectra in the solid phase. It seems that the difference in the phase has influence in these molecules, whereas the computed (using the same model) \(^1\)H-NMR shifts (given between parentheses in the Experimental Section 2.1.) are in a fair agreement with experimentally measured values.

3.2. Molecular Reactivities. Chemical reactivity theory quantifies the reactive propensity of isolated species through the introduction of a set of reactivity indices or descriptors. Its roots go deep into the history of chemistry, as far back as the introduction of such fundamental concepts as acid, base, Lewis acid, and Lewis base. It pervades almost all of chemistry.

Theoretical reactivity indices based on the conceptual density functional theory (DFT) have become a powerful tool for the semiquantitative study of organic reactivity, and the most relevant indices defined within the conceptual DFT [20] are reviewed and discussed elsewhere [21–26]. Molecular reactivity indices [20–26] such as chemical potential (\(\mu\)), hardness (\(\eta\)), and electrophilicity (\(\omega\)) were computed from the energies of frontier orbitals (graphically represented in Figure 2 and summarized in Table 1) and defined in terms of ionization energy (I) and electron affinity (A) as follows:

\[
\mu \approx -\frac{1}{2} (I + A) \approx \frac{1}{2} (\varepsilon_L - \varepsilon_H),
\]

or simply \(\mu = 0.5(LUMO + HOMO)\).

Chemical potential is the link between structure and reactivity. The greater a structure’s chemical potential, the greater is its reactivity. The most important factors that contribute to the chemical potential are low-energy LUMO indicating strong acid behavior (reactive electrophile) and high-energy HOMO reflecting strong base behavior (reactive nucleophile). However, the defined index of chemical...
Figure 2: HOMO-LUMO frontier orbital of the newly synthesized molecules and the starting molecule (red color represents negative phase while the blue color points to the positive one). All molecules containing one or three nitro groups are of noticeable charge transfer character showing larger contribution of the orbitals localized on the nitro groups in the LUMOs.

Table 1: The structure-properties relationships in gas phase reflecting the effect of molecular structure on the associated energy and thermodynamic parameters, which are important for molecular characterization (HOMO-LUMO values of geometry-optimized molecules in acetonitrile (ACN) are also given).

<table>
<thead>
<tr>
<th>Molecule label</th>
<th>Energy (kcal/mol)</th>
<th>$E_{\text{HOMO}}$ (eV)</th>
<th>$E_{\text{LUMO}}$ (eV)</th>
<th>$E_{\text{HOMO}}$ (eV)</th>
<th>$E_{\text{LUMO}}$ (eV)</th>
<th>Dipole (debye)</th>
<th>$H^\circ$ (kcal/mol)</th>
<th>$G^\circ$ (kcal/mol)</th>
<th>$S^\circ$ (J/mol·K)</th>
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<td>$-867646$</td>
<td>$-867690$</td>
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potential takes into account the mean value of HOMO and LUMO.

\( \eta = \frac{1}{2} (I - A) = \frac{1}{2} (\epsilon_L - \epsilon_H), \) 

or simply \( \eta = 0.5 (\text{LUMO} - \text{HOMO}). \)

The chemical hardness \( \eta \) can be thought as a resistance of a molecule to exchange electron density with the environment.

(3) Electrophilicity. Parr (in 1999) defined the electrophilicity index \( \omega = \mu^2 / 2\eta \), which measures the total ability to attract electrons. The electrophilicity index gives a measure of the energy stabilization of a molecule in case it acquires an additional amount of electron density from the environment. The electrophilicity index shows the tendency of an electrophile to acquire an extra amount of electron density, given by \( \mu \), and the resistance of a molecule to exchange electron density with the environment, given by \( \eta \). Therefore, a good electrophile exhibits a high absolute \( \mu \) value and a low \( \eta \) value. The electrophilicity index is considered an important facility for the study of the reactivity of organic molecules [21].

(4) Nucleophilicity (N). Domingo and his coworkers [21–25] suggested that a simple index chosen for the nucleophilicity, \( N \), based on the HOMO energy, within DFT, could be employed to explain the reactivity of the organic material towards electrophiles.

The nucleophilicity index is defined as \( N = E_{\text{HOMO}}(\text{ev}) + 9.12(\text{ev}) \), where \(-9.12\) is the energy of the HOMO of tetra- 

cyanoethylene (TCE). Thus, this nucleophilicity scale is referred to TCE and taken as a reference because TCE exhibits the lowest HOMO energy \((-9.12\text{eV})\) in a large series of molecules investigated [22].

Inspecting molecule’s ESP surface is probably a good start for considerations of the molecule’s reactivity since this is where two approaching molecules would first interact. ESP maps are depicted in Figure 3. The results should point to the binding sites, which are of potential influence in chemical reactivities and medical applications.

Table 1 shows a compilation of some thermodynamic parameters and dipole moment values reflecting molecular polarities. All molecules are fairly polar and should be soluble in polar solvents. The computed total energy and thermodynamic parameters reflect the stability of the molecules. Solvent effect induced by acetonitrile (aprotic solvent) is reflected in destabilization of HOMO. LUMO energy levels are almost unaffected except in case of molecule 4 where its LUMO is stabilized by about 0.23 eV. This is reflected in the difference in reactivity indices given in Table 2. Nucleophilicity is markedly enhanced, while chemical potential and hardness values are lowered in presence of the solvent. Electrophilicity shows irregular behavior relative to the gas phase values. It seems that the more simple indices of chemical potential, hardness, and nucleophilicity are more reliable than the electrophilicity parameter, which is defined as the square of chemical potential divided by double of the hardness (Section 3.2).

Inspection of Table 2 reveals the reactivities of the new molecules; molecule 4 is the most susceptible molecule to electrophilic attack due to its large \( N \) value of 1.21 eV and smaller \( \omega \) value of 2.49 eV, whereas molecule 3 is the most likely attacked by a nucleophile. Molecule 6 is of highest chemical potential \((-4.77\text{eV})\), lowest nucleophilicity \( N = 0.60\text{eV} \), and of considerable high electrophilicity \( =3.02\text{eV} \). Thus, molecule 3 is the most chemically reactive among the related molecules (2, 4–6) and is seeking for electrons. However, in presence of a solvent such as acetonitrile, molecule 5 is of highest nucleophilic character. Nucleophilicity decreases in the order 5 > 4 > 1 > 6 > 2 > 3. More will be discussed later.

Spartan codes enabled identification of tautomers (due to proton transfer) through tautomer search. Each of molecules 2 and 3 has two tautomers, whereas molecule 6 has only one tautomer. Geometry optimized (employing wB97X-D/6-31G (d,p) model) tautomer’s information is summarized in Table 3, and their optimized geometries are depicted in Figure 4. It seems that the lowest energy (most stable) tautomers are the genuine 2, 3, and 6 molecules themselves. Proton transfer to form other tautomers (Figure 4) results in energy destabilization. Relative energy is reported for comparing relative energy of tautomers of individual compounds (Table 3). Largest destabilization could be seen in case of proton transfer in tautomer 6-1.

The reactivities of the tautomers in the gas phase are tabulated in Table 3 and could be easily seen by inspection of Figure 5. However, it should be mentioned that solvent nature could be of influential effect on the stability of a tautomer. Thus, we tried geometry optimization in the acetonitrile solvent (aprotic solvent) using the wB97X-D/6-31G(d,p) model and CPCM solvation model [27] and found a drastic effect on the relative stability of the tautomers as can be seen from the data summarized in Table 4. Proton transfer is generally more favored in solution than in the gas phase. Moreover, keto-form tautomers and thione-form tautomers become more energetically stable than the corresponding enol (2) or thiol (3) tautomers most probably because of the increase in conjugation. However, although solvent induces tiny stability relative to that of the gas phase, proton transfer in 6 is still a less-favored process. Understanding how reactivity descriptors of these polar molecules and their tautomers are modified in going from the gas phase into solution can be understood with the solvent-induced increase in the dipole moment value (Table 4) as well as thermodynamic parameters. The more polar the molecule is the more it is energetically stabilized as could be seen from the dipole moment data summarized in Table 4 for the gas and solvent phases. Furthermore, from thermodynamics point of view (Table 5), enhancements in the computed enthalpy and Gibbs free energy are noticed in acetonitrile. The values verify the conclusions drawn from Table 4.
Figure 3: Solid surface (8 bands) of ESP maps and color codes. The color code reflects electrostatic potential energy values in kJ/mol. The redder the area is, the higher the electron density is susceptible to electrophilic attack and the bluer the area is, the lower the electron density is that could easily bind with a nucleophile.

Table 2: Effect of the solvent on computed reactivity indices in eV sorted according to descending nucleophilicity in the gas phase.

<table>
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<tr>
<th>Molecule</th>
<th>Gas</th>
<th>Acetonitrile</th>
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<tbody>
<tr>
<td></td>
<td>μ</td>
<td>η</td>
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<tr>
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</table>
Reactivity indices also altered significantly. Nucleophility increases for 2 and its tautomers as well as for 3 and 6 because the solvent has a noticeable effect on HOMO stabilization. The solvent has smaller effect on stabilizing the HOMO of the thione tautomers of 3 and on 6-1 tautomer. Chemical potential and hardness markedly decrease except for thione tautomers of 3, whereas it increases in acetonitrile due to influential

<table>
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<tr>
<th>Tautomer</th>
<th>Relative energy (kJ/mol)</th>
<th>$E_{\text{HOMO}}$ (eV)</th>
<th>$E_{\text{LUMO}}$ (eV)</th>
<th>$\mu$</th>
<th>$\eta$</th>
<th>$\omega$</th>
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destabilization of LUMO. Electrophilicity dominantly decreases in acetonitrile.

More about the reactivities of other molecules could be predicted by inspection of Figure 5. It is of interest to visualize (Figure 5) the structure-properties relationship in the gaseous phase. Systematic increase in nucleophilicity while changing from molecule/tautomer 2-1 (of lowest nucleophilicity index) to 6-1 (of highest nucleophilic
property) could be suggested as a measure of tuning molecular properties. One can quickly predict any reactivity descriptor of a molecule or a tautomer by a glimpse of Figure 5. One can easily correlate all reactivity indices of a molecule to each other.

4. Conclusion

We synthesized five new products of pyrimidine, pyrazole, and pyridine derivatives using a chalcone substituted with a thiophene nucleus. Spectroscopic data were introduced as well as reactivity indices.

The wB97X-D/6-31G (d,p) model within the DFT is used to optimize the structures and predict the structure-properties relationships. Reactivity parameters calculated from the frontier orbitals help in prediction of nucleophilicity, electrophilicity, and hardness as well as chemical potential of the molecules synthesized. Proton transfer from functional groups in some molecules results in presence of several tautomers. In the gas phase, proton transfer destabilizes the tautomer molecules. Proton transfer is generally more favored in solution than in the gas phase due to solvent-induced enhancement of the molecular polarity identified by the computed dipole moment values. In particular, keto-form tautomers and thione-form tautomers become more energetically stable than the corresponding enol (2) or thiol (3) tautomers. However, proton transfer in 6 is still a less-favored process since the solvent induced small increase in the dipole moment value. Additionally, thermodynamic parameters verify the conclusions drawn from the molecular polarity.

Computed and visualized ESP map surfaces enable exploration of molecular reactive sites.

Generally, based on the relative nucleophilicity index N, nucleophilicity increases in the order 3 < 2 < 6 < 1 < 5 < 4 in the gas phase, while the order in acetonitrile is slightly different 3 < 2 < 6 < 1 < 4 < 5. Generally, all reactivity indices computed could be easily predicted for a compound by a glimpse of a reactivity indices-molecule graph.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest in publishing this manuscript.

References


