Synthesis and Quantum Chemical Study of Novel Pyridine Derivative Derived from N-Substituted Coumarin.

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Abstract: This work includes a synthesis of 3-acetyl-7-hydroxy-2H-chromen-2-one (1) through the reaction of 2,4-dihydroxybenzaldehyde with ethyl acetoacetate, then reacted with 4-(dimethylamino) benzaldehyde to produce Coumarinyl Chalcone (2). And cyclization of Coumarinyl Chalcones (2) with malononitrile in the presence of ammonium acetate to produce 2-amino-4-(4-(dimethylamino) phenyl)-6-(7-hydroxy-2-oxo-2H-chromen-3-yl) nicotinonitrile (3). Prepared compounds were diagnosed through melting point, TLC, FT-IR Spectroscopy analysis and ¹H-NMR. Quantum chemical parameters like highest occupied molecular orbital energy, lowest unoccupied molecular orbital energy (E_HOMO while ELUMO), while dipole moment (μ) was interpretation.

Keywords: 2H-chromen-2-one, chalcone, pyridine, Isotherm.

1. Introduction

Coumarin (1, 2H-chromen-2-one or 2H-1-benzopyran-2-one) Coumarin consists of a double ring; one of the rings is heterogeneous. The compound includes the benzene ring plus the pyrone ring, and the coumarin compound is an important compound because it has high efficacy in the pharmaceutical industry [1], like antithrombotic, anti-carcinogenic, anti-inflammatory, antioxidant, hepatoprotective, antiviral, antimicrobial, antituberculosis, antihyperlipidemic, monoamine oxidase-B inhibitors and anticholinesterase activities [2-5]. Pyridine ring is considered one of the important compounds for its overuse over the years [6]. Pyridine is one of the most common compounds for its widespread use in the field of pharmaceutical preparations such as cyan pyridines (nicotinonitriles) for different alkyl while aryl groups which contains biological activity such as antihypertensive [7] anti-inflammatory, analgesic, antipyretic properties [8] antimicrobial [9], cardiotonic [10] while anticancer activity [11,12].

In this study, the beginning of coumarin (3-acetyl-7-hydroxy-2H-chromen-2-one (1)) (considered as a basic substance in the preparation of other compounds 2 and 3) was prepared as shown in...
figure 1, and the chemical composition of the compounds was determined, diagnosed and its physical properties were studied.

![General Scheme of synthesis](image)

2- Experimental
The melting point was measured by open capillaries that were not corrected and the purity of the compounds prepared by them was measured via thin-layer chromatography (TLC). The spots were visualized by exposure to iodine vapors. The IR spectra (KBr disc) which measure within a Pye Unicam Sp-3-300 while a Shimadzu FTIR 8101 PC infrared optical Spectrometer. The \(^1\)H NMR spectra that count for JEOL-JNM-LA 400 while 500 MHz Spectrometer. The chemical transformation was represented within the δ (ppm) gauge. This is done by using TMS as a measured source.

3-acetyl-7-hydroxy-2H-chromen-2-one (1):
A solution from 2, 4-dihydroxybenzaldehyde (2 gm, 0.01 moles), piperidine (1.00 ml), and ethyl acetoacetate (1.3g, 0.01 mole) with ethanol (20 ml) is reflux for 8 hrs. The reaction was followed up through TLC. The precipitates was filtered and recrystallize the sediment with ethanol solvent,
brawn precipitate, yield 82%, M.P (244-246) °C. The FTIR Spectroscopic measurements showed the absorbance peaks within (1720 cm\(^{-1}\), Back to \(\nu\)C=O, ketone), (1662 cm\(^{-1}\), belonging to \(\nu\)C=O, coumarin), (1616, 1581 and 1485 cm\(^{-1}\), correlated to \(\nu\)C=C, Ar.), (3049 cm\(^{-1}\), belonging to \(\nu\)C-H, Ar.), while (2991 cm\(^{-1}\), belonging to \(\nu\)C-H, alpha.). \(^1\)H-NMR Spectroscopic measurements showed signal within 2.3 (s, 3H, CH3) and 6.9-8.5 (m, 4H, Ar-H and C=CH) and 10 (s, 1H, OH).

3-(3-(4-(dimethylamino) phenyl) acryloyl)-7-hydroxy-2H-chromen-2-one (2)

A13 gm., 0.05 mole of the compound (1) was dissolved with ethanol (10 ml), and 0.05 mole of 4-N,N-dimethylaminobenzaldehyde was added to the solution with four drops of piperidine, and with continuous stirring for one hour, then heated the mixture to three hours. The completion of the reaction was monitored by TLC and then the mixture is left to cool down, after that the sediment is filtered and the material is re-purified with ethanol: water. A red precipitate, yield 63%, M.P (213-216) °C. The FTIR spectroscopic measurements showed the absorbance peaks within (1699 cm\(^{-1}\), back to \(\nu\)C=O, chalcone), (1666 cm\(^{-1}\), related to \(\nu\)C=O, coumarin), (1610, 1595 and 1487 cm\(^{-1}\), belonging to \(\nu\)C=C, Ar.), (3043 cm\(^{-1}\), corresponding to \(\nu\)C-H, Ar.), (2906 cm\(^{-1}\), 2866 cm\(^{-1}\) and 2825 cm\(^{-1}\), for \(\nu\)C-H, alph.). And (3232 cm\(^{-1}\), for \(\nu\)OH). \(^1\)H-NMR Spectroscopic measurements showed signal within 3s (s,6H,2CH\(_3\)) and 6.6-7.8 (m,9H,Ar-H and HC=CH), 8.5(S,1H,C=CH, comarin) and 10 s (s,1H,OH).

2-amino-4-(4-(dimethylamino)phenyl)-6-(7-hydroxy-2-oxo-2H-chromen-3-yl)nicotinonitrile (3)

A 0.005 mole of Coumarinyl Chalcones (2) was dissolved with ethanol (10 ml); 0.005 mole of malononitrile and ammonium acetate (0.04 mole) were added to the mixture \[13, 14\]. The mixture was heated for two hours and the reaction was tracked TLC. The formed sediment was filtered while then washing for water and the material was re-purified from ethanol, orange precipitate, yield 61%, M.P (281-283) °C. The FTIR Spectroscopic measurements showed peaks within (1666 cm\(^{-1}\), belonging to \(\nu\)C=O, coumarin), (1610, 1595 cm\(^{-1}\), for \(\nu\)C=C, Ar.), (3045 cm\(^{-1}\), for \(\nu\)C-H, Ar.), (2212 cm\(^{-1}\), for \(\nu\)CN), (3365, 3295 for \(\nu\)NH\(_2\)) and (3232 cm\(^{-1}\), for \(\nu\)OH). \(^1\)H-NMR Spectroscopic measurements exhibited signal within 3s (s,6H,2CH\(_3\)), 6.6 (s,2H,NH\(_2\)), 6.8-7.8(m,8H,Ar-H), 8.7(s,1H,C=CH, comarin) and 10 s (s,1H,OH).

| No. | M.F            | M.W gm/mol | M.P °C  | Yield | Rf (7:3) Hexane.: Eth.acetate | Color   |
|-----|----------------|------------|---------|-------|-------------------------------|---------|
| 1   | C\(_{11}\)H\(_8\)O\(_4\) | 204        | 244-246 | 82    | 0.67                          | brawn   |
| 2   | C\(_{20}\)H\(_{17}\)NO\(_4\) | 335        | 213-216 | 63    | 0.73                          | red     |
| 3   | C\(_{23}\)H\(_{16}\)NO\(_3\) | 354        | 281-283 | 61    | 0.71                          | orange  |
3- Results and Discussion

3-1 Chemistry

3-(3-(4-(dimethylamino)phenyl)acryloyl)-7-hydroxy-2H-chromen-2-one (2) in general contain an enone (an α,β-unsaturated carbonyl) That is, an effective group (nucleophilic center). This potent group has the ability to bind to electrophilic groups and form a ring of pyridine derivative (3) (see figure 2).

![Figure 2. The synthetic approach of pyridine derivative (3)](image)

2-amino-4-(4-(dimethylamino)phenyl)-6-(7-hydroxy-2-oxo-2H-chromen-3-yl)nicotinonitrile (3) was synthesized by following the previous methods [15-17], by condensing 3-(3-(4-(dimethylamino)phenyl)acryloyl)-7-hydroxy-2H-chromen-2-one (2) with malononitrile.

The resultant IR spectrum from pyridine derivative 3 and that is there NH2 within the region 3365, 3295 cm⁻¹, and CN function within 2212 cm⁻¹ through putting until the coumarin carbonyl absorption band within 1666 cm⁻¹.

Measurements from ¹H-NMR showed signal within 6.8-7.8 ppm for aromatic protons and C=CH, the proton shows the pyridine derivative from a singlet at 6.6 ppm during addition to NH₂.

3-2 Computational Studies

3.2.1. Atomic Charges and Stabilities
The theoretical study of particles 1, 2 and 3 showed that the charges of the compound are influenced through the presence of compensating sums on the ring. And the geometry of the compounds appeared as in figure 3, the theoretical calculation of atomic charges of compounds 1, 2 and 3 have been shown. The highest atomic charge was compound 1 [O (14) −0.73] while the next shipment appeared within [C (11) −0.2]. And these results proved that the three atoms represent the most effective sites for interactions and calculate a family length and angles while 3D-geometrical structure, Proved that this molecule is not in a plane while should be added to the stereochemistry C (9)-C (8): (Z). The C (10)-C (11) bond length was 1.5090; C (13)-C (9) is 1.3791 and C (4)-O (7) is 1.3550.

Its highest the atomic charge was compound 2 [O (12) −0.920] while [O (14) −0.729] while the next shipment appeared within [C (11) −0.233]. And these results were proved that these atoms represent the most effective sites for interactions and calculate a family length and angles while 3d-geometrical structure, Proved that this molecule is not in a plane; it should be added to the stereochemistry C(9)-C(8): (Z) while C(11)-C(15):E. The N (23)-C (25) bond length was 1.4700; N (23)-C (24) is 1.4700; C (13)-C (9) is 1.3791 while C (4)-O (7) is 1.3550.

Its highest the atomic charge was compound 3 [O (12) −0.697], [N (20) −0.697]) while the next shipment appeared within [C (15) −0.232]. And these results proved that these atoms represent the most effective sites for interactions and calculate a family length and angles while 3d-geometrical structure, proved that this molecule is not in a plane; it should be added to the stereochemistry C(9)-C(8): (Z). The N (27)-C (29) bond length was 1.4700; N (27)-C (28) is 1.4700; C (2)-O (30) was 1.3550 while C (9)-C (10) is 1.3370.

![Figure 3. 3D-geometrical structures for components 1, 2 and 3.](image-url)
3.2.2. Density Function Theory (DFT)

The calculations of the Density Function Theory of compound 3 showed the stable molecular structures and the total energy of the most stable form as in Table 1 and the orbital calculations of the molecule showed through the description of the spatial characteristics, nodal patterns while individual atom contributions of the nodal patterns and the contribution of the individual atom. Diagram 4 shows the boundary orbits of the compounds 1, 2 while 3, comprising the Highest Occupied Molecular Orbital (HOMO) while the Lowest Unoccupied Molecular Orbital (LUMO). And it notices from this theoretical study that the orbits are distributed in a plane for coupling, as in Figure 3. HOMO orbitals were found within the compensating molecule while LUMO orbitals are similar to an uncompensated molecule, so the substitution of the molecule has the ability to give an electron, but its effect is small. [16–18]. The orbital energy levels from HOMO while LUMO from compound 1, 2 while 3 as shown in table 2. It can see the energy gaps through HOMO while LUMO was 4.0099 eV, 5.0178 eV while 3.4615eV belonging to compound 1, it is considered an important value and represents the energy required to move an electron for HOMO till the LUMO orbit, which represents the energy needed to move an electron.
Figure 4. The optimum structures of the compounds 1, 2, and 3 by B3LYP/6-31G.

Table 2. Total Energy (a.u), HOMO while LUMO energies from 1, 2 while 3 (eV)

| Total energy   | HOMO  | LUMO  | ΔE       | HOMO-1  | LUMO+1  | ΔE       |
|----------------|-------|-------|----------|---------|---------|----------|
| -724.674826    | -6.6502 | -2.6403 | 4.0099   | -6.9876 | -0.9934 | 5.9942   |
| -1127.69312    | -5.0814 | -2.3513 | 2.7301   | -6.2912 | -1.2734 | 5.0178   |
| -1330.90471    | -5.2645 | -2.6963 | 2.5682   | -5.7350 | -2.2735 | 3.4615   |
Conclusions

Compounds 1, 2, and 3 were prepared and diagnosed through various spectroscopic measurements and theoretical study of these compounds by estimating the charge of atoms, calculating the formation temperature and steric chemistry; it was found that the compounds are uneven.

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