Experimental and Theoretical DFT Study on Synthesis of Novel 5-Chloroisatin Derivatives via 1, 3-Dipolar Cyclo Addition Reactions between Allyl-5-chloroindoline-2, 3-dione and 4-Chlorobenzaldoxime

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Abstract

*this work deals about 1,3-Dipolar cycloaddition reactions between 1-allyl-5-chloroindoline-2,3-dione **2** and 4-Chlorobenzaldoxime **3** proceed under mild conditions, with complete regioselectivity. A DFT study was conducted by GAUSSIAN 09W software using the B3LYP functional and a 6-31G basis set elucidated the reactivity, selectivity, and mechanisms of such direct synthesis. The present study demonstrates that the theoretically obtained results were found to be consistent with the experimental data reported.*

Keywords: *1,3-Dipolar cycloaddition, DFT, 1-allyl-5-chloroindoline-2,3-dione, 4-Chlorobenzaldoxime,^{1}H NMR, ^{13}C NMR.*

I. INTRODUCTION

In recent years, the chemistry of heterocycles or heteroatoms has developed remarkably, and the majority of compounds developed in the fields of biological and industrial pharmaceutical chemistry are based on this family of molecules [1, 2]. Indeed, it should be noted that two thirds of the compounds known in the literature are heterocycles [3, 4]. It is therefore not surprising that this class of compounds has become the focus of a large community of experimental chemists and theorists. Generally, Isatin and its derivatives constitute a class of heterocyclic compounds which have interesting pharmacological and biological properties [5-8]. They are used in a very broad way for their anxiolytic [9, 10], anticonvulsant[11-13], muscle relaxant, antiviral, anti-inflammatory[13-19], anticancer [20-23], anticorrosive[24, 25] and analgesic [26, 27] action.

The study of the reactivity of aromatic heterocycles can be directly related to the study of their electrophilic substitution reaction [28, 29], because these systems are very rich in electrons.

Moreover, due to the conjugation possessed by these systems, they can participate in cycloaddition reactions of the 1,3-type dipolar cycloaddition [30]. The cycloaddition reaction between alkynes and nitrous oxide provided one of the simplest methods for producing synthetically useful cycloadducts of isoxazoline and dioxazoline types. The quantum theory of reactivity allows us not only to elaborate the reaction mechanisms and the energy profiles but also to justify and predict the experimental chemoselectivities [31], stereoselectivities [32] and regioselectivities [33]. Several theories have been developed for the study of chemical reactivity, functional density theory (DFT) has emerged as the most popular in recent decades. Slater's [34] simplification of the Hartree–Fock [35, 36] method, the theorems by Hohenberg and Kohn [37], and the orbital-based Kohn–Sham [38] equations mark the beginning of practical DFT calculations. Kohn–Shambased DFT calculates the energy of a non-interacting reference system and approximates the difference to the real system using the exchange and correlation functionals. The first exchange and correlation functionals depend only on the electron density itself [39].

In this paper, we undertake a systematic study of DFT calculation to recognize the operative mechanism that occurs in the 1,3-dipolar cycloaddition reaction between allyl 5-chloroisatian and chlorobenzaldehyde, by powerful tools for prediction of reactive sites of systems Molecules [40]. Some of these concepts are well known by chemists as electronic chemical potential (m) and electronegativity (c). New concepts such as electrophilicity (ω) and hardness (η) have been derived from the fundamental equations of the DFT [41].

In our work, we used the B3LYP method which is the most successful variant of the DFT (Density Functional Theory) methods [42-44]. Our choice of

this method is justified by the fact that it takes into account the electronic correlation on the one hand and by the fact that it is less costly in computation time by comparing with the other correlation methods as CI Interaction) or MP2 (Moller-Plesset of order 2).

The calculation of the atomic loads was carried out using Mulliken's natural and electrostatic population analyzes (Chelp, Chelpg and MK (Merz-Kollman).) All the calculations were carried out using the GAUSSIAN program 09W [45-46].

II. RESULTS AND DISCUSSION

A. Synthesis and spectra:

The mechanism of 1,3-dipolar cycloaddition reactions [47] is characterized by a nucleophilic/electrophilic interaction. In this work we have studied the reactivity of nitrile oxide on the dipolarophile. First, 5-Chloroisatin was condensed with propargyl bromide in the presence of potassium carbonate as the base, was carried out in dimethylformamide with stirring at 25°C, under the conditions of phase transfer catalysis. It thus leads to the formation of 1-allyl-5-chloroindoline-2,3-dione **2**(Scheme 1).
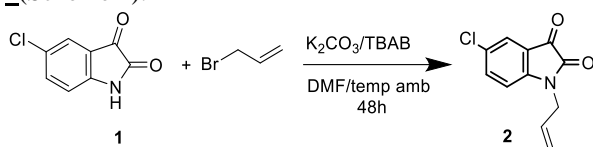
Scheme 1

Then, the action of 4-Chlorobenzaldoxime **3** on 1-allyl-5-chloroindoline-2,3-dione **2**dissolved chloroform in the presence of sodium hypochlorite (NaOCl) at a temperature between 0°C leads to compounds possessing the isoxazoline nucleus where the electron-attracting or electron donor substituent of the dipolarophile and also a dioxazoline nucleus (Scheme 2). Regioisomer structures were established on the basis of ^{1}H NMR, ^{13}C NMR spectral data.
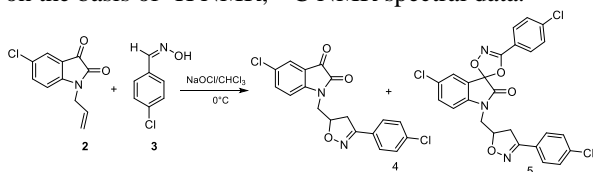
Scheme 2

B. DFT Calculation:

A theoretical study was also carried out in order to define the regiochemistry of the dipolar-1,3-cycloaddition of 4-Chlorobenzaldoxime**3** and the dipolarophile [48]. The optimized structures and the HOMO and LUMO energies of the compound **2** and 4-Chlorobenzaldoxime **3** are represented according to the figures below.
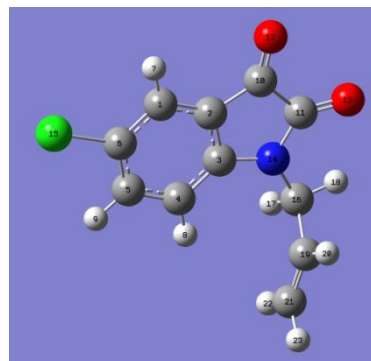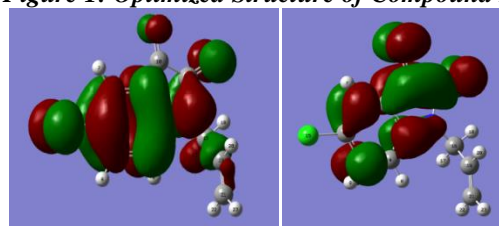
Figure 1: Optimized Structure of Compound 2

HOMO   *LUMO*

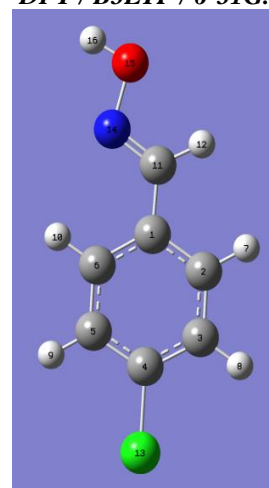**Figure 2: The molecular orbitals of compound 2 by DFT / B3LYP / 6-31G.**
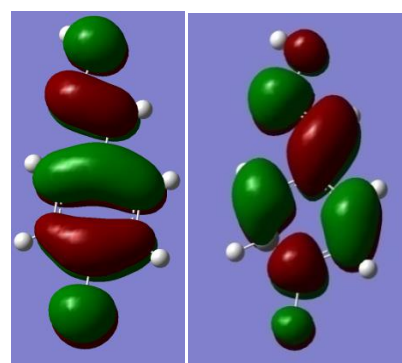
Figure 3: Optimized structure of 4-Chlorobenzaldehyde 3

HOMO   *LUMO*

Figure 4: the molecular orbitals of 4-Chlorobenzaldoxime 3 by DFT

C. Prediction of the character (NED or IED) of the reaction

We calculated the HOMO/LUMO gaps for the two possible combinations as well as the electronic chemical potential and the electrophilicity index ω of the reagents in order to demonstrate the NED (Electronic Normal Demand) or Reverse Electronic Demand the reaction. In our case and granting the analysis of FMO boundary molecular orbitals, the HOMO oxime - LUMO Alcene and HOMO Alcene - LUMO oxime energy differences are respectively 3.32 eV and 5.02 eV. These results suggest that the reaction is controlled by the interaction HOMO oxime - LUMO Alkene. This reaction was analyzed using the local and global indexes defined in the context of the functional density theory [49, 50]. The calculation parameters already mentioned are shown in Table 1 below.

Table 1: Quantum chemical parameters of dipole and dipolarophile in eV

molecules	$E_{(HOMO)}$	$E_{(LUMO)}$	EA	PI	χ	η	S	ω	μ	$\Delta\mu$
2	-6,6598	-3,1817	3,1817	6,6598	4,9208	1,7390	0,5750	6,9620	-4,9208	-
3	-6,5099	-1,6342	1,6342	6,5099	4,0721	2,4378	0,4102	3,4010	-4,0721	0,8487

Recent studies have shown that these indices are useful and powerful tools for studying nucleophilic and electrophilic reactions for a wide variety of systems. If the difference in chemical potential between 4-Chlorobenzaldehydoxime and alkyne is calculated, the direction of charge transfer can be determined. The result (Δ (μ_{oxime}-μ_{2}) = 0.848 eV) indicates that the net charge transfer will occur from the nitrile oxide to the alkene.4-Chlorobenzaldoxime acts as a nucleophile and the alkene as an electrophile. Considering the values ω of the overall electrophilicity, the largest value corresponds to 1-allyl-5-chloroindoline-2,3-dione, which implies that the dipolarophile acts as an electrophile.

In conclusion, the three theoretical approaches ($Gaps_{HOMO/LUMO}$, electronic chemical potentials μ, values of the electrophilicity indices ω) of the 1,3-dipolar cycloaddition reaction between the dipole and the dipolarophile have a NED character (normal electronic request) .

Use of Fukui indices:

The Fukui nucleophilic indexes f⁻ (and local softness S⁻) for dipolarophile **2** and electrophilic f⁺ (and local softness S ⁺) for the dipole are summarized in the table below:

Table 2: Relative indices of electrophilicity, nucleophilicity (in eV) and values of the Fukui f_k condensed function for dipole and dipolarophile junction atoms [51].

	Atomes	f^+_k	f^-_k	S^+_k/S^-_k	S^-_k/S^+_k
2	C19	-0,0011	-0,0017	0,6816	1,4669
	C21	0,0898	0,0803	1,1178	0,8945
3	C11	0,1067	0,1739	0,6138	1,6291
	O15	0,1747	0,1290	1,3542	0,7384

From a local point of view, the relative electrophilicity indexes S^+_k/S^-_k (S^-_k/S^+_k) describe the electrophilicity of an atomic center compared with its own nucleophilicity .The site with the largest S^+_k/S^-_k ratio is the most likely site for nucleophilic attack and the one with the largest S^-_k/S^+_k, most likely to interact with an electrophile. According to Table 6, the most favored electrophilic/nucleophilic interaction will take place between the **C21** carbon of the dipolarophile which is the most electrophilic site and the **C11** carbon of the dipole which is the most nucleophilic site.

III. EXPERIMENTAL SECTION

A. Analytical techniques

Melting points were determined via the use of open capillaries with an Electrothermal melting point apparatus. The ¹H and ¹³C NMR data were obtained on a Bruker Avance 300 MHz (¹H) and 75 MHz (¹³C) NMR in CDCl₃ solution. Chemical shifts for proton NMR are reported in δ (ppm) downfield from tetramethylsilane as an internal standard. Coupling constants (**J**) are in Hz. The following abbreviations are used to describe peak patterns where appropriate: **s,**

singlet; **d**, doublet; **dd**, double doublet; **t**, triplet; **q**, quartet; **dt**, double triplet; **m**, multiplet. Flash column (Silica Gel, Premium R$_f$, 200-400 mesh, Sorbent Technologies) and thin layer chromatography reactions were performed on silica gel with indicated solvent systems.

B. Synthesis
1. Synthesis of dipolarophile

5-Chloro-1*H*-indole-2,3-dione (0.4 g, 2.20 mmol), potassium carbonate (0.5 g, 3.3 mmol) and tetra-n-butylammonium catalyst (0,1g, 0,3mmol) was dissolved in DMF (15 mL), then, 3-bromoprop-1-ene (0.34 mL, 2.97 mmol) was added dropwise with stirring at room temperature for 48 hours. The product was obtained in 89% yield after a simple decantation and column purification.

1-allyl-5-chloroindoline-2,3-dione (2) : Yield: 97%; mp: 140-142; R_f=0.78 (Ethyl acetate / hexane: 1/2). ^{1}H NMR (CDCl$_3$; 300MHz) δppm 7.52-7.58 (m, 2H, H_{Ar}); 6.89 (d, H, H_{Ar}, $^3J_{H-H}$=9Hz); 5.77-5.90 (m, 1H, CH); 5.30-5.35 (m, 2H, CH$_2$); 4.38 (d, 2H, CH$_2$, $^4J_{H-H}$=3Hz). ^{13}C NMR (CDCl$_3$; 75MHz) δppm: 182.18 (C=O); 157.34 (N-C=O); 149.07, 129.67, 118.93 (Cq); 137.64, 130.02, 112.00 (CH$_{Ar}$); 125.25 (C=CH); 118.41 (C=CH$_2$); 42.63 (CH$_2$).

2. General procedure for preparation of cycloadduts:

0.2 g (0.903 mmol) of dipolarophile **2** and 1.2 equivalent of 4-Chlorobenzaldoxime **3** was added to a solution of chloroform (12 mL), when the mixture reaches 0°C, 4 mL of sodium hypochlorite (NaOCl) was putted and the mixture is left to stir for 4 hours, the reaction is followed by TLC and the compound obtained purified and recrystallized from ethanol.

5-chloro-1-((3-(4-chlorophenyl)-4,5dihydroisoxazol-5-yl)methyl)indoline-2,3-dione: Yield: 75% ; mp: 210-215; R_f=0.55; (Ethyl acetate/Hexane (5:1)). ^{1}H NMR(CDCl$_3$; 300MHz) δppm 7.55-7.61 (m, 4H, H_{Ar}); 7.40 (d, 2H, H_{Ar}, $^3J_{H-H}$=9Hz); 7.21 (d, 1H, H_{Ar},$^3J_{H-H}$=6Hz); 5.04-5.14 (m, H, CH); 3.92-4.09 (qd, 2H, CH$_2$,$^3J_{H-H}$ =18Hz , $^4J_{H-H}$=6Hz); 3.21-3.56 (qd, 2H, CH$_2$, $^3J_{H-H}$ =12Hz, $^4J_{H-H}$ =6Hz);^{13}C NMR (CDCl$_3$; 75MHz) δppm: 181.55 (C=O); 158.57 (NC=O),149.45, 145.81, 136.69, 130.03, 127.12, 116.76 (Cq); 138.03, 129.16, 128.08, 125.07, 113.16 (CH$_{Ar}$); 79.39 (CH), 44.02, 38.05 (CH$_2$).

5-chloro-3'-(4-chlorophenyl) -1-((3-(4-chlorophenyl) - 4,5-dihydroisoxazol-5 yl)methyl) spiro [indoline-3,5'-[1,4,2]dioxazol]-2-one: Yield : 55%; mp : 224-228; R_f=0.53 (Ethyl acetate/Hexane (4: 1)). ^{1}H NMR (CDCl$_3$; 300MHz). (CDCl$_3$) δppm 7.80 (d, 2H, H_{Ar}, $^3J_{H-H}$ =6Hz =8.4Hz); 7.50 (d, 2H, H_{Ar}, $^4J_{H-H}$ =6Hz =3.6Hz); 7.48-7.45 (m, 6H, H_{Ar}); 7.19 (d, H, H_{Ar}, $^3J_{H-H}$ = 9Hz, $^4J_{H-H}$ =6Hz); 5.12-5.05 (m, H, CH); 3.87-4,06 (qd, H, CH$_2$, $^3J_{H-H}$= 15Hz,$^4J_{H-H}$= 6Hz); 3.21-3.55 (qd, H, CH$_2$,$^3J_{H-H}$= 15Hz,$^4J_{H-H}$= 6Hz). ^{13}C NMR (CDCl$_3$; 75MHz) δppm: 168.12 (NC=O); 166.03, 162.00 (C=N); 141.45, 138.63, 136.51,130.20, 122.62, 120.05 (Cq); 133.39, 128.52, 128.10, 126.77, 126.65, 126.62, 111.11 (CH$_{Ar}$); 79.39 (CH); 44.06, 35.71 (CH$_2$).

3. Computational methods

All calculations were performed using Gaussian09 suite of programs. The full geometrical optimization of all structures and transition states (TSs) was realized with the Density Functional Theory (DFT) using non-local B3LYP hybrid functional and the 6-31G basis set [52].

In particular, For an element A, the (first) ionization potential is defined as the energy necessary to tear an electron from an A atom isolated in the gaseous state:

$$IP = -E_{HOMO}$$

This quantity is generally positive (negative ΔU): the fixation of an electron releases energy. This is predictable from the orbital interpretation of the phenomenon:

$$EA = -E_{LUMO}$$

The electronic chemical potentials (μ) and chemical hardness (η) of the reactants under study were evaluated in terms of the one-electron energies of the frontier molecular orbital, using the following equations [53, 54]:

$$μ = (E_{HOMO} + E_{LUMO})/2$$

$$η = \frac{IP - EA}{2}$$

Softness S is defined as the inverse of the hardness.

$$σ = \frac{1}{η}$$

The electrophilicity index ω is related to electronegativity by the following relation [55]:

$$ω = χ^2/2η$$

The Positive and Negative Fukui functions are defined using the left and right drifts. The condensed form of Fukui functions in a molecule with N electrons has been proposed by Yang and Mortier [56]:

• For nucleophilic attack

$$f^+ = q_{(N+1)} - q_N$$

• For electrophilic etching

$$f^- = q_N - q_{(N-1)}$$

• For free radical attack

$$f° = (q_{N+1} + q_{N-1})/2$$

$q_{(N)}$: electron population of the atom k in the neutral molecule.

$q_{(N+1)}$: electronic population of the atom k in the anionic molecule.

$q_{(N-1)}$: electronic population of the atom k in the cationic molecule.

IV. LOCAL SOFTNESS S_K

The condensed local softnesses $S_k^±$ can be easily calculated from the condensed Fukui functions $S_k^±$ and the overall softness S:

$$S_k^+ = S[q_{k(N+1)} - q_{k(N)}] = S f^+_k$$

$$S_k^- = S[q_{k(N)} - q_{k(N-1)}] = S f^-_k$$

V. CONCLUSION

In this work, we used a systematic theoretical study on the regioselectivity in 1,3-dipolar cycloaddition reactions of 1-allyl-5-chloroindoline-2,3-dione **2** using DFT method that, was conducted with the B3LYP method as implemented with the Gaussian 09 program package, in order to understand the mechanism and reactivity between dipolarophile and 4-Chlorobenzaldoxime. This theoretical study enabled us to confirm the results obtained experimentally

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