

## Spectral and Quantum-Chemical Study of the 1,3-Dipolar Cycloaddition Reaction of Phenyl Azide and Chalcone

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### Abstract

A study of 1,3-dipolar cycloaddition reaction of phenyl azide and chalcone was carried out theoretical and experimental in ethanol by DFT/B3LYP (3-21G) method, without and with CuCl as catalyst. The isolated and purified products were characterized by spectral methods, by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, Cosy and Dept-135. Theoretical study of the reaction was achieved using Gaussian03 program based on a density function method, DFT/B3LYP (3-21G) . The structural, electronic and spectral properties were calculated for the more probable product.

The experimental and theoretical results were consistent, the title was found to be nonspontaneous under standard conditions (T=298,15 K , P= 1 atm), but it took place in ethanol under reflux in the presence of CuCl, the reaction was completely regioselective and the expected product was formed in high yield 75%, formula C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O and m.p 164-165C<sup>0</sup>.

**Keywords:** Dipolar Cycloaddition, Phenyl Azide, Chalcone, activation energy, DFT.

### الخلاصة

تمّ دراسة تفاعل الضم الحلقي من نوع (3,1) ثنائي القطب لأزيدو فنييل مع الشالكون تجريبياً ونظرياً باستخدام طريقة DFT=B3LYP/(3-21G) عند غياب ووجود كلور النحاسي كحفاز. تمّ فصل الناتج بالاستخلاص ثمّ تنقيته؛ وحددت بنيته الجزيئية باستخدام أطياف الـ NMR (Cosy , Dept-135 , <sup>1</sup>H-NMR , <sup>13</sup>C-NMR) و طيف الأشعة تحت الأحمر (IR).

كما تمّ دراسة التفاعلات نظرياً باستخدام برنامج Gaussian03 بالاعتماد على طريقة الكثافة DFT=B3LYP/(3-21G) وقد تم حساب الخصائص البنوية والإلكترونية والطيفية للناتج الأكثر احتمالاً.

أثبتت النتائج العملية والنظرية أن تفاعل الضم الحلقي من نوع (3,1) ثنائي القطب لمركب أزيدو فنيبل مع الشالكون هو تفاعل غير تلقائي عند الشروط القياسية (T=298,15 K , P= 1 atm)، بينما يحدث التفاعل تلقائياً وذلك بالتسخين ويوجد CuCl كحفاز؛ حيث يتم الحصول على ناتج نقي بمرود 75% ، صيغته المجملة  $C_{21}H_{17}N_3O$  ودرجة انصهاره (164-165 °C).

## Introduction

Organic azides undergo 1,3-dipolar cycloaddition reactions with unsaturated compounds in particular, those activated by electron-withdrawing groups conjugated with the double or triple bond to form triazoline or triazole ring. The latter five-membered heterocycles are important from both synthetic and pharmaceutical point of view. Some triazole antibiotics, antiviral, anti-proliferative agents, and to act as potassium channel activators, exhibited an anti-HIV activity, has a cytostatic activity and were used as a radiosensitizer<sup>(1)</sup>.

Moreover, it has been found that saccharides combined with triazole rings through 1,3-dipolar cycloaddition, have significant effects on many biological events, including the cellular recognition in the processes of inflammation, immune response, tumor metastasis, and bacterial and viral infections<sup>(2)</sup>.

However, a lot of work has been done on the 1,3-dipolar cycloaddition reactions of organic azides to different dipolarophiles<sup>(3-8)</sup>. Acid catalysis has been used to accelerate these reactions<sup>(9-14)</sup>. For example copper (I) in the form of salt or cluster was used which led to significant reduction in reaction time as well as formation of selective products<sup>(10)</sup> suitable for biological testing<sup>(15)</sup>.

On the other hand theoretical studies were carried out. Density function method, (B3LYP/6-31G) was used to determine the structure of the triazole products<sup>(16)</sup>. (DFT/B3LYP) and (MP2)

were used to determine transitional active levels in the reaction of substituted organic azides with cycloalkenes and cycloalkynes.

It was found that the activation energy of cycloaddition to cycloalkynes decreased with the decreasing in ring size, and that cycloalkynes were more reactive than cycloalkenes<sup>(17)</sup>.

Furthermore, method (B3LYP (6-31G++)) was employed to calculate the tautomeric equilibrium, structure, vibrational frequencies, and ionization energies in similar reactions<sup>(18)</sup>.

## Materials & tolls :

\* NMR spectra were measured on 400MHz spectrometer and chemical shifts in ppm are and were used as a radiosensitizer<sup>(1)</sup>.

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However, a lot of work has been done on the 1,3-dipolar cycloaddition reactions of reported relative to internal Me4Si (CDCl<sub>3</sub>).

\* Melting points were determined by using a micro-melting point apparatus without any corrections.

\* Infra Read spectra pattern FT-IR-410 prduce Jasco – Japan . reported relative in KBr stretch bonds in cm<sup>-1</sup>

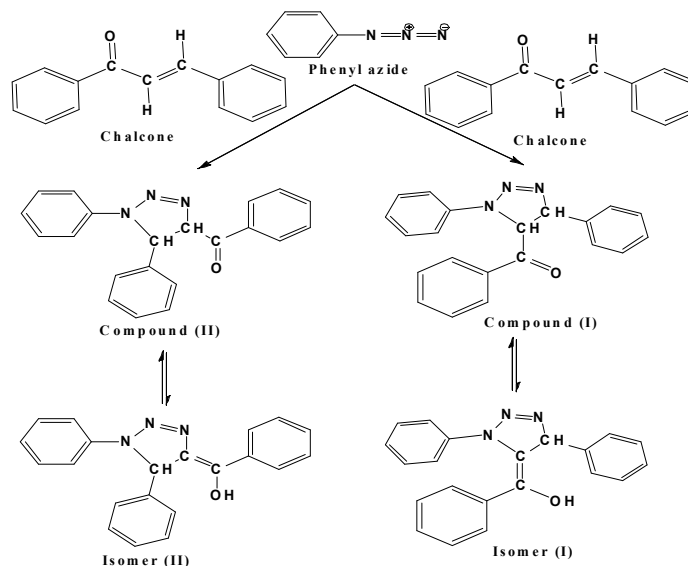
- \* rotary evaporator pattern 4.91 produce Normschiff – Germany.
- \* Thin chromatographic layer (aluminum and glass) covered with selicalgel60F254 20X 20 produced Merck – Germany.
- \* All chemical materials from Merck.

## Results and Discussion

### Synthesis and spectroscopic study

Phenyl azide and chalcone were prepared according to previous

methods<sup>(19-21)</sup>. Phenyl azide reacted with chalcone in absolute ethanol at reflux temperature for 54 hrs to yield two products. Product (I) (mp=164-165 °C, 61%) and product (II) (mp=157-158 °C, 23%). These products were isolated by filtration from reaction mixture and separated by column chromatography (silica gel, hexan: chloroform). The same reaction was run in the presence of CuCl, it took 16 hrs and gave product (I) as the only product in 75% yield. Figure 1



**Scheme 1:** reaction of Phenyl azide with chalcone

The structure of triazolone (I) was confirmed by IR and NMR spectroscopy. In <sup>1</sup>H-NMR, the aromatic protons (15H) appeared as a complex signal in the range  $\delta = 7.37-7.65$  ppm.

The protons at position 4 and 5 in the ketone tautomer appear as doublets at  $\delta = 8.30$  ppm and  $\delta = 7.54$  ppm respectively, whereas they show two singles at  $\delta = 8.32$  ppm for the 4-H and  $\delta = 1.66$  ppm for the hydroxylic proton in the enole form. Figure 2.

Moreover, the cosy spectrum shows the coupling between 4-H and 5-H in the ketone form. Figure 3.

Figure 4 shows the <sup>13</sup>C-NMR of compound (I). The signals at  $\delta = 186.8$ , 133.2, and 139.9 ppm are ascribed to carbonyl C-4 and C-7 respectively. The bands at  $\delta = 143.6$ , 141.2, 137.2, 126.1, and 125.3 ppm are assigned to C-18, C-5 (enole), C-6 (enole), C-7, C-19 and C-5 (ketone) in order. The aromatic carbons resonate in the range  $\delta = 128.3-130.7$  ppm.

Moreover, the Dept-135 spectrum displays the absence of secondary carbons and disappearance of the six quaternary carbons, C=O, C-19, C-18, C-7, C-6 (enole) and C-5 (enole). Figure 5.

Finally, the IR spectrum shows a strong absorption at  $1653\text{ cm}^{-1}$  (C=O) and absorption bands at 3448, 1595, 1494, 1415, 1222 and  $757\text{ cm}^{-1}$  ascribed to O-H (enole), C=C (alkene), aromatic rings, N=N, C-N and C-H bending benzene rings. These values are in good agreement with those calculated in the quantum study. Figure 6.

### Theoretical-chemical study

Gaussian 03 program based on a DFT/ B3LYP (3-21G) calculations were achieved for the two possible channels of cycloaddition reaction of phenyl azide with chalcone<sup>(22-24)</sup>. At first, the structural and electronic properties of reactants in the gas phase at  $T= 298.15\text{K}$  were calculated. Table1.

Figure 7 shows three dimensional optimized structures for reacted compound with elemental charges in (e) units and bond lengths in (Å) units.

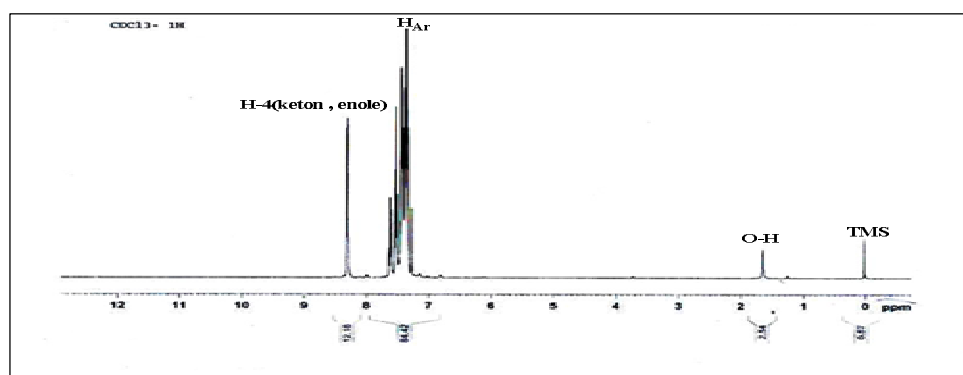


Figure 2:  $^1\text{H-NMR}$  spectrum of compound (I)

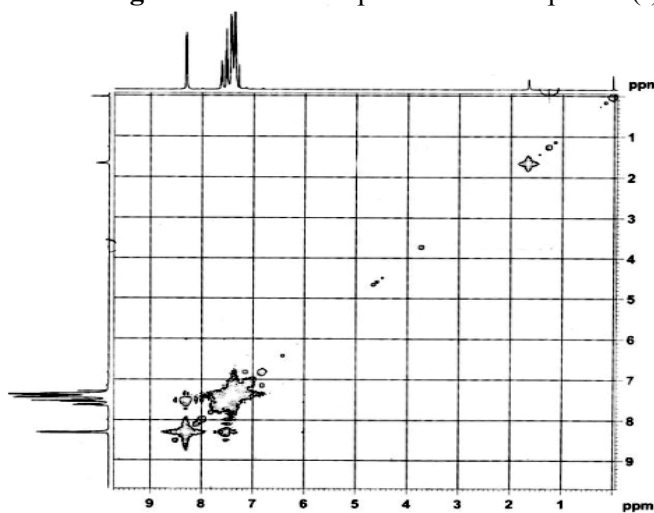


Figure 3: Cosy spectrum of compound (I)

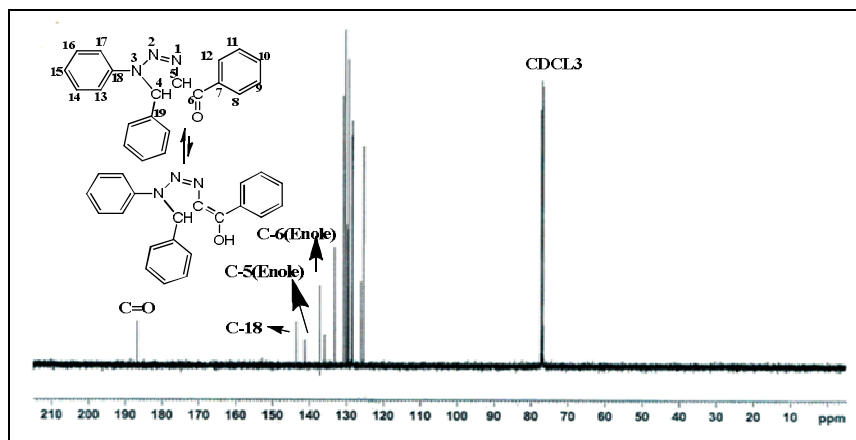


Figure 4:  $^{13}\text{C}$ -NMR spectrum of compound (I)

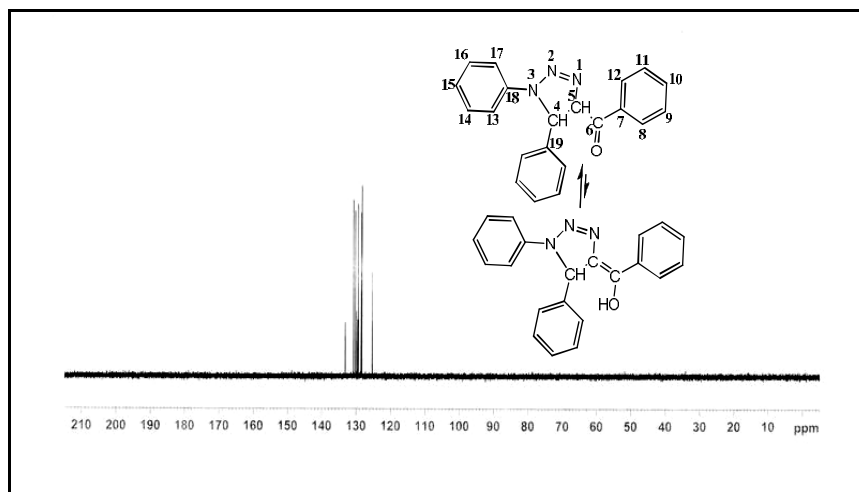


Figure 5: Dept-135 spectrum of compound (I)

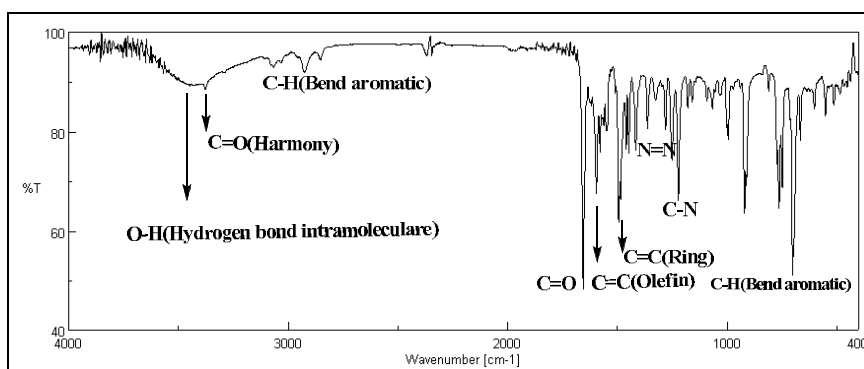


Figure 6: IR spectrum of compound(I)

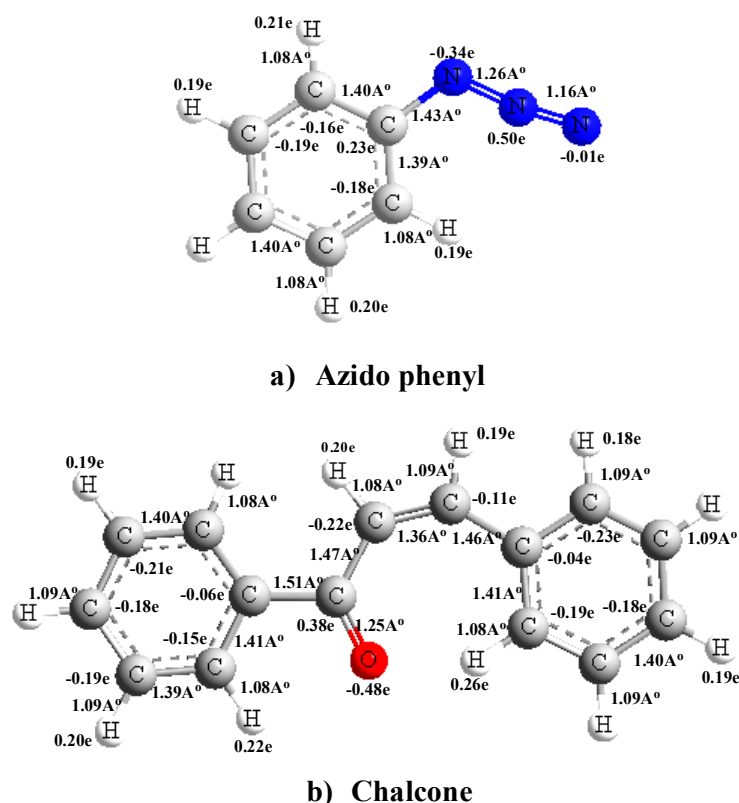


Figure 7: Three dimensional optimized structures for reacted compound with elemental charges and bond lengths

Table 1: Bonding energies and molecular orbital energies of reactants in the gas phase at T= 298.15K

Molecule	Molecular formula	Layout formula	$E_b$ (M) (KJ\Mol)	$\epsilon_{\text{HOMO}}$ (KJ\Mol)	$\epsilon_{\text{LUMO}}$ (KJ\Mol)
Chalcone	$C_{15}H_{12}O$		-13537.208	-608.779	-149.601
Azido phenyl	$C_6H_5N_3$		-6268.408	-585.153	-104.437

Summarizes the results, including bonding energies,  $E_b$ , and energies of highest occupied and lowest unoccupied molecular orbitals. Bonding energies were calculated according to equation(1).

$$E_b(M) = E_{\text{elec}}(M) - \sum_{A=1}^N E_{\text{elec}}(A) \quad \dots (1)$$

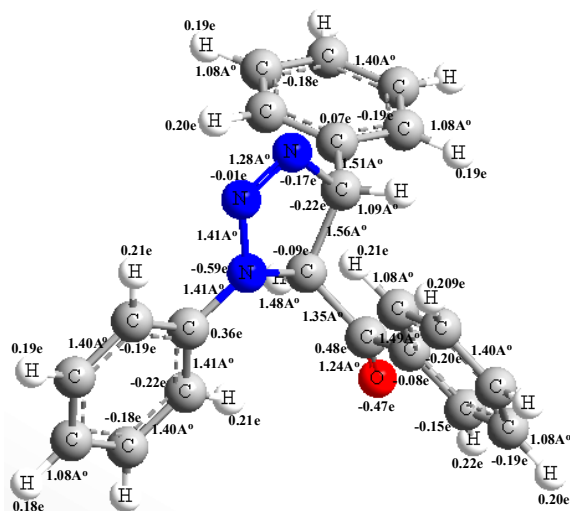
Then, the energies of the two possible cycloaddition reactions,  $\Delta_R E$ , and the bonding energies of the products in the gas phase at T = 298.15 K were calculated,  $\Delta_R E$  according to equation(2). Table 2 lists these values.

$$\Delta_R E = E_b(\text{products}) - \sum E_b(\text{reactives}) \dots\dots(2)$$

Figure 8 and 9 show three dimensional optimized structures for ketone and enole tautomers with elemental charges in (e) units and bond lengths in (Å) units.

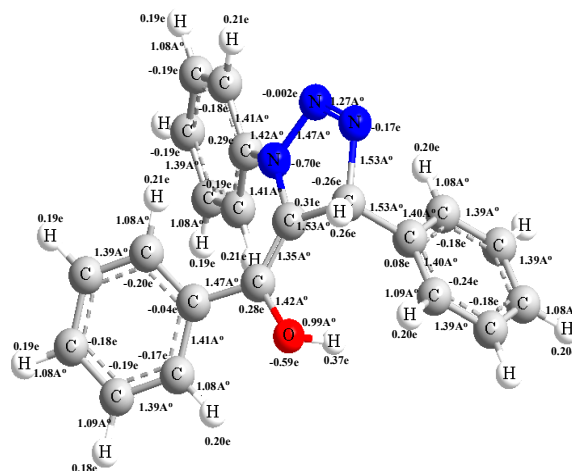
**Table 2: Bonding energies and molecular orbital energies of results in the gas phase at T= 298.15K**

Molecule	Molecular formula	$E_b$ (KJ/Mol)	$\Delta_R E$ (KJ/Mol)	$\epsilon_{\text{HOMO}}$ (KJ/Mol)	$\epsilon_{\text{LUMO}}$ (KJ/Mol)
Compound (I)	C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O	-19902.339	-96.722	-548.412	-175.218
Compound (II)	C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O	-19891.827	-86.211	-552.366	-173.675
Tautomer (I)	C <sub>21</sub> H <sub>17</sub> N <sub>3</sub> O	-19833.871	-28.254	-492.867	-130.377



**Figure 8: Three dimensional optimized structures for keton tautomer**

Based on the reaction and bonding energies in table 2, it is clear that the more likely reaction is the one leading to compound (I) which is the more stable. Moreover, the careful study of the molecular orbitals of chalcone, phenyl azide and product (I) in figure 10, shows that the energy difference between the LUMO in chalcone and the HOMO in phenyl azide is relatively large ( $\Delta_1 \epsilon = 4.05 \text{ eV}$ ) leading to a weak



**Figure 9: Three dimensional optimized structures for enole tautomer**

interaction ( $\Delta_2 \epsilon = + 0.381 \text{ eV}$ ). In addition, the dipole moment of chalcone (2.87 Debye) is bigger than that of phenyl azide (1.79 Debye) which means that the reaction is not spontaneous at 298.15 K in the liquid state clearly, activation energy,  $E_a$ , in the form of heat, is required where  $E_a \gg \Delta_2 \epsilon$ , in addition to a catalyst to reduce the difference between the LUMO of

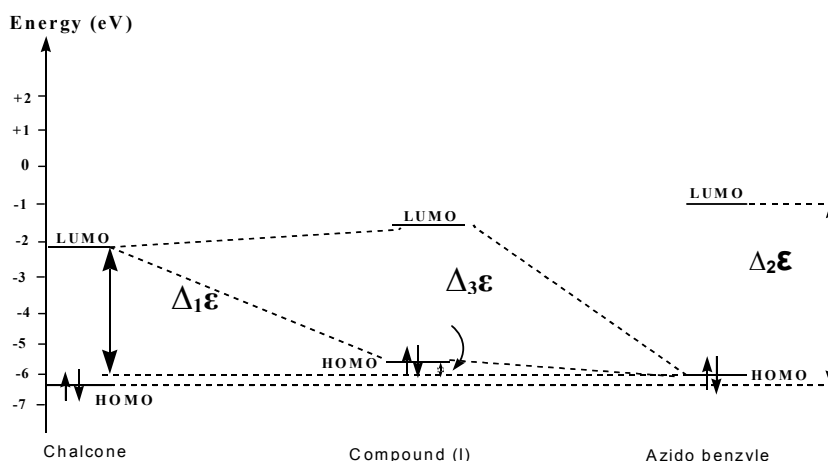
chalcone and HOMO of phenyl azide, and consequently to reduce the HOMO of compound (I). It is known that Lewis acids can play this role and this why CuCl was used as catalyst.

To compare the results of quantum and experimental the calculated absorption

frequencies in the IR spectra of the ketone and enole forms of compound (I) were compared with those found experimentally. Table 3 displays very good agreement.

**Table 3:** Comparison between theoretical and experimental values

Functional Group	Wave number [cm <sup>-1</sup> ]	
	Experimental	Computational
O-H(Enole)	3448	3450
C=O(Harmony)	3300	3271
C-H(Stretch aromatic)	3062	3064
C=O(Stretch)	1653	1652
C=C(Olefin)	1595	1592
C=C(Ring)	1494	1506
N=N	1417	1420
C-N	1222	1224
C-H(Bend)	757	755



**Figure 10:** Energy spectrum of reactants and results

### Conclusions

The 1,3-dipolar cycloaddition reaction of phenyl azide and chalcone is not spontaneous at 298.15 K in the liquid state. A theoretical study of the reaction was achieved using Gaussian03 program based on a density function method, DFT/B3LYP (3-21G). A catalyst was used to reduce the difference between the LUMO of

chalcone and HOMO of phenyl azide and consequently to reduce the HOMO of compound (I). It is known that Lewis acids can play this role and this why CuCl was used as catalyst. In the presence of CuCl, the reaction was completely regioselective and the expected product was formed in high yield. The practical and theoretical infrared spectrum shows very good agreement through the absorption bands.



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