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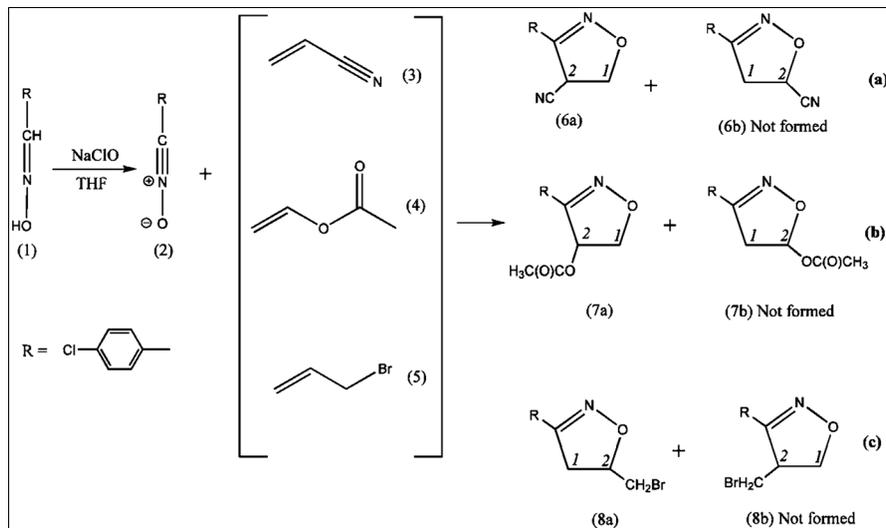
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Reaction of 4-chlorobenzonitrile oxide (**2**) which was generated *in situ* with acrylonitrile (**3**), vinyl acetate (**4**) and allyl bromide (**5**) as dipolarophile afforded the new cycloadducts **6a**, **7a**, and **8a** compounds, respectively. Reactivity and regiochemistry of these reactions were investigated using activation energy calculations and density functional theory-based reactivity indexes. The theoretical <sup>13</sup>C NMR chemical shifts of the cycloadducts which were obtained by gauge-invariant atomic orbital method were comparable with the observed values.

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## INTRODUCTION

The cycloaddition of 1,3-dipolar species to an alkene for the synthesis of five-membered rings is a classic and important reaction in organic chemistry [1]. These 1,3-dipolar cycloaddition (1,3-DC) reactions are used for both academia and industrial purposes [2]. These reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry. Current understanding of the underlying principles in the Diels–Alder reactions and the 1,3-DC has grown from a fruitful interplay between theory and experiment [2–4]. The stereochemistry of these reactions may be controlled either by choosing the appropriate substrates or by controlling the reaction using a metal complex acting as catalyst [5].

The 1,3-DC reactions possess several interesting characteristics, in particular, regioselectivity. Fleming [6] demonstrated that the Frontier molecular orbital model (FMO) seems to be able to explain the observed regioselectivity

and reactivity differences. Although transition state (TS) theory remains the most widely used and the most rigorous approach for the study of the mechanism and the regiochemistry of these reactions, the localization of TSs is not always easier.

Furthermore, transition-state calculations are often very time consuming when bulky substituents are present in reactive systems.

Recently, reactivity descriptors based on the density functional theory (DFT), such as Fukui indexes, local softnesses and local electrophilicity, have been extensively used for the prediction of the regioselectivity. For instance, several treatments of 1,3-DC reactions of nitrile oxides with various dipolarophiles can be found in the literature [7–9]. In this context, we became interested in the reactivity of nitrile oxide (**2**) as dipole towards acrylonitrile (**3**), vinyl acetate (**4**) and allyl bromide (**5**) as dipolarophiles to synthesize the new 3-(4-chlorophenyl)-4,5-dihydroisoxazole-5-carbonitrile (**6a**), 3-(4-chlorophenyl)-4,5-dihydroisoxazol-4-yl

acetate (**7a**) and 5-(bromomethyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole (**8a**) (Fig. 1). In addition, we found it worthwhile to analyze the regioselectivity of these 1,3-DC reactions by several theoretical approaches, namely, activation energy calculations and DFT-based reactivity indexes. Finally, the gauge-invariant atomic orbital (GIAO) method [10] was used to calculate NMR chemical shifts, to help the experimental cycloadduct determination, because it has shown to yield data comparable to those of the experiment [11].

**Regioselectivity criteria for two-center reactions.** A useful simplification for the study of the regioselectivity in reactions may be obtained by looking at those processes having a markedly polar character, where the transition structure associated with the rate-determining step mostly involves the formation of one single bond between the most electrophilic and other nucleophilic sites. According to the model recently proposed by Domingo [12,13], during an electrophile-nucleophile interaction process, The preferred interaction will be through the most electrophilic site of the former and the most nucleophilic site of the latter. Local philicity indexes (for definition, see computational details) are therefore expected to be useful descriptor of regional electrophilicity/nucleophilicity patterns that may account for the observed regioselectivity in two-center reactions with a significant polar character.

## COMPUTATIONAL METHODS

All calculations were performed with the Gaussian98 program suite [14]. For DFT calculations, the B3LYP/6-31G (d) level of theory was employed. The optimizations of equilibrium geometries of reactants and products were performed using the Bery analytical gradient optimization

method [15]. The TSs for the 1,3-DC reactions have been localized at the B3LYP/6-31G (d) level of theory. The stationary points were characterized by frequency calculations to verify that the TSs had one and only one imaginary frequency.

The global electrophilicity for dipole and dipolarophile was evaluated using Eq. 1 [16]:

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

In Eq. 1  $\mu$  and  $\eta$  are the electronic chemical potential and the chemical hardness of the ground state of atoms and molecules, respectively.

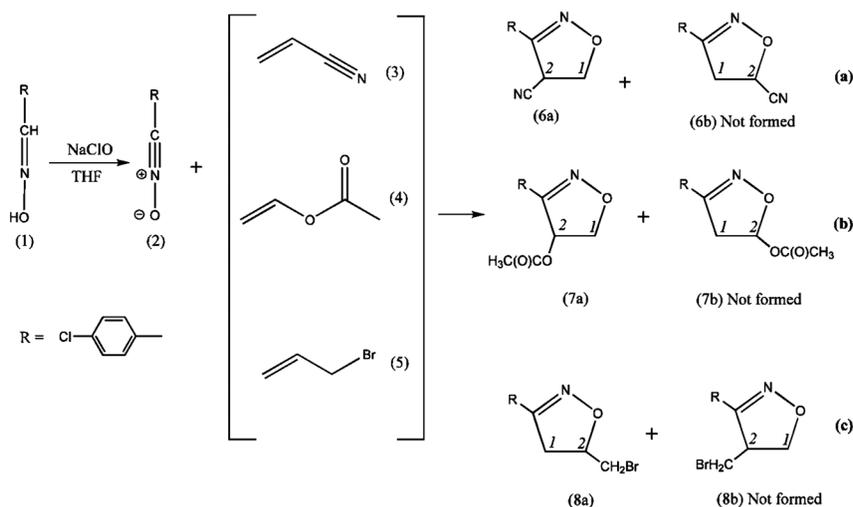
The electronic chemical potential  $\mu$  and chemical hardness  $\eta$  were evaluated in terms of the one electron energies of the FMOs, HOMO, and LUMO, using Eqs. 2 and 3, respectively [17,18]:

$$\mu \approx \frac{(\epsilon_H + \epsilon_L)}{2} \quad (2)$$

$$\eta \approx (\epsilon_L - \epsilon_H) \quad (3)$$

As usual, local indexes are computed in atomic condensed form [19]. The well-known Fukui function [20] for electrophilic ( $f^+$ ) and nucleophilic attack ( $f^-$ ) have been evaluated from single point calculations performed at the ground state of molecules at the same level of theory, using a method described elsewhere [21]. This method evaluates the Fukui functions using the coefficients of the FMOs involved in the reaction and the overlap matrix.

The local electrophilicity index,  $\omega_k$ , condensed to atom  $k$  is easily obtained by projecting the global quantity onto any atomic center  $k$  in the molecule by using the electrophilic Fukui function (i.e., the Fukui function for nucleophilic attack,  $f^-$  [22])



**Figure 1.** The regioisomeric pathways for 1,3-DC of benzonitrile oxide (2) and dipolarophiles (3–5).

$$\omega_k = \omega_k^{f^+} \quad (4)$$

Recently, Domingo *et al.* has introduced an empirical (relative) nucleophilicity index [23],  $N$ , based on the HOMO energies obtained within the Kohn–Sham scheme, [18] and defined as  $E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}$  (tetracyanoethylene). This nucleophilicity scale is referred to tetracyanoethylene taken as a reference.

Local nucleophilicity [24] index,  $N_k$ , was calculated using the following equation:

$$N_k = N_k^{f^-} \quad (5)$$

where  $f$  is the Fukui function for an electrophilic attack [20].

The  $^{13}\text{C}$  NMR chemical shifts were calculated by means of the GIAO method [10], using the tetramethylsilane as  $^{13}\text{C}$  reference, at the B3LYP/6-31G (d) level of theory (reference value of  $^{13}\text{C}$  184 5307 ppm).

## RESULTS AND DISCUSSION

Nitrile oxide **2** was generated *in situ* from the oxime **1** in a mixture of aqueous NaClO in THF. 1,3-DC of nitrile oxide **2** with the dipolarophiles acrylonitrile **3**, vinyl acetate **4** and allyl bromide **5** proceeded smoothly in a selective manner to give a single regioisomer of each pair **6a-b**, **7a-b**, and **8a-b** in very good yields (Fig. 1). It should be noted that the absence of the nitrile absorption band in the IR spectrum of the cycloadduct **6a**, is the reminiscent of the previously reported observations with the aliphatic nitriles which are activated by a nitrogen or an oxygen atom in their  $\beta$ -position [25–27]. The assignment of the regiochemistry of these products was based upon (i) comparing the theoretical  $^{13}\text{C}$  NMR spectral data obtained by GIAO method with the observed values for both regioisomers; (ii) activation energy calculations; and (iii) DFT-based reactivity indexes.

- i For further cycloadduct characterization, we obtained the theoretical  $^{13}\text{C}$  chemical shifts values for the products through the GIAO method and compared it with the observed values. As it can be seen in Table 1, the observed values for C1 and C2 in each of the isolated products (41.0, 66.8; 41.2, 96.0, and 39.5, 79.9 ppm in compounds **6**, **7**, and **8**, respectively) are in close proximity to the theoretical values for compounds **6a**, **7a**, and **8a**. It seems likely that the isolated regioisomers are structurally similar to **6a**, **7a** and **8a**. Further proofs came from activation energy and DFT studies as followings:
- ii Activation energy calculations: The TSs have been localized for both cyclization modes. The corresponding activation energies and structures are given in Table 2 and Figure 2, respectively. An analysis of the geometries at the TSs given in Figure 2 indicates that they

**Table 1**

The comparison of theoretical  $^{13}\text{C}$  NMR chemical shifts data ( $\delta$ , ppm) of C1 and C2 of each pair of regioisomers with those obtained from the experimental  $^{13}\text{C}$  NMR spectroscopy.

Compound	Atom number	Calculated chemical shift	Experimental chemical shift
<b>6a</b>	C1	41.3	41.0
	C2	70.9	66.8
<b>6b</b>	C1	56.4	
	C2	21.3	
<b>7a</b>	C1	42.3	41.2
	C2	98.1	96.0
<b>7b</b>	C1	60.8	
	C2	69.4	
<b>8a</b>	C1	39.4	39.5
	C2	77.6	79.9
<b>8b</b>	C1	35.1	
	C2	75.7	

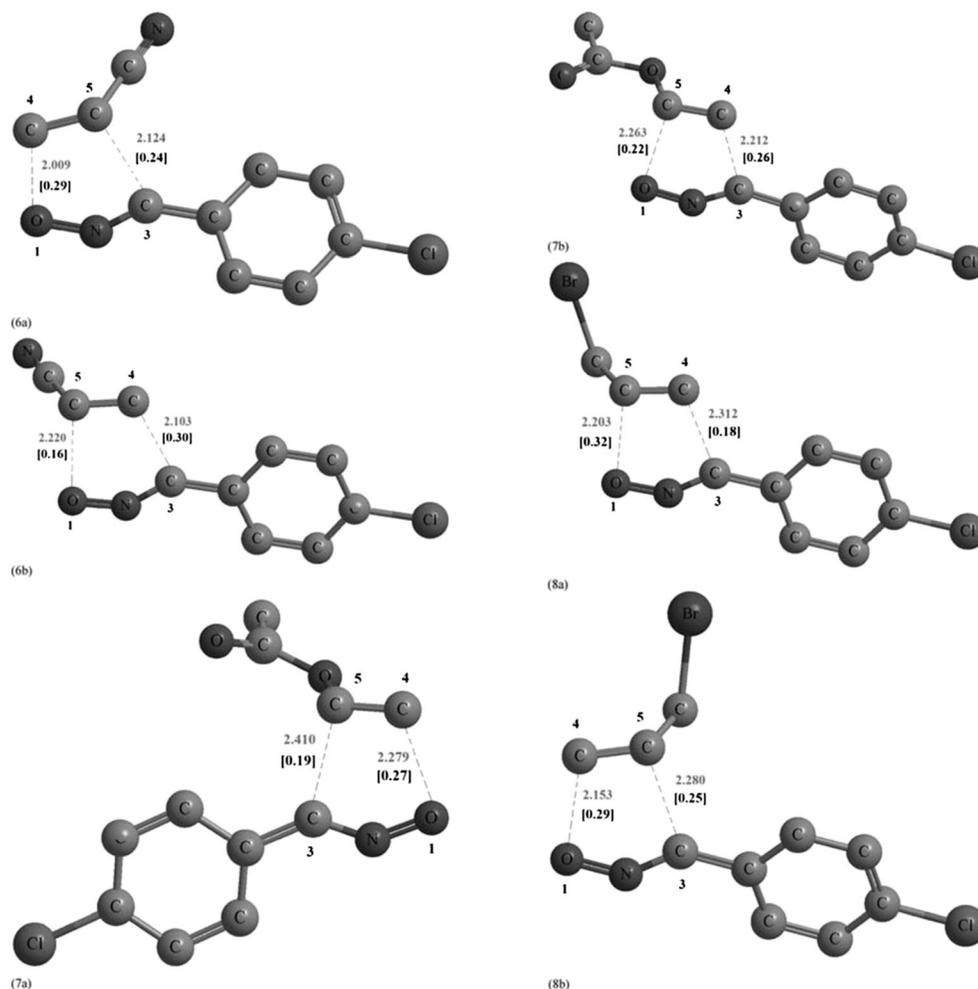
correspond to an asynchronous bond formation processes. The extent of bond formation along a reaction pathway is provided by the concept of bond order (BO) [28]. The BO (Wiberg indexes) values of the O-C and C-C forming bonds at TSs are shown in brackets in Figure 2. These values are within the range of 0.16 to 0.32. Therefore, it may be suggested that these TSs correspond to early processes. In general, the asynchronicity shown by the geometrical data is

**Table 2**

Energies of reactants, transition states and cycloadducts **6**, **7**, and **8**,  $E$  (hartree), relative activation energies  $\Delta E_a$  (kcal mol $^{-1}$ ) and relative energies between products and reactants,  $\Delta E_r$  (kcal mol $^{-1}$ ).

	$E$	$\Delta E_a^a$	$\Delta E_r^a$
Reaction b			
Nitrile oxide <b>2</b>	-859.23462		
Acrylonitrile <b>3</b>	-170.83155		
TS <b>6a</b>	-1030.04639	12.4	
TS <b>6b</b>	-1030.04560	12.9	
<b>6a</b>	-1030.12341		-35.9
<b>6b</b>	-1030.12172		-34.8
Reaction b			
Nitrile oxide <b>2</b>	-859.23462		
Vinyl acetate <b>4</b>	-306.47987		
TS <b>7a</b>	-1165.68492	18.6	
TS <b>7b</b>	-1165.67990	21.7	
<b>7a</b>	-1165.77693		-39.2
<b>7b</b>	-1165.76849		-33.9
Reaction c			
Nitrile oxide <b>2</b>	-859.23462		
Allyl bromide <b>5</b>	-2689.00537		
TS <b>8a</b>	-3548.22689	8.2	
TS <b>8b</b>	-3548.22220	11.2	
<b>8a</b>	-3548.31542		-47.3
<b>8b</b>	-3548.30911		-43.4

<sup>a</sup>To reactants;  $\Delta E_a = E_{\text{TS}} - (E_{\text{nitrile oxide}} + E_{\text{dipolarophile}})$ ;  $\Delta E_r = E_{\text{product}} - (E_{\text{nitrile oxide}} + E_{\text{dipolarophile}})$



**Figure 2.** Optimized geometries for transition state structures at the B3LYP/6-31G (d) level of theory. Hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms. The bond orders are given in brackets.

accounted for by the BO values. A qualitative reactivity can be estimated by applying Hammond's postulate [29]. All of the reactions proceeded exothermically with large  $\Delta E_r$  (relative energies between products and reactants) energy values. According to Hammond's postulate, the TSs should then be closer to the reactants. The activation energy values,  $\Delta E_a$ , also favor the formation of the cycloadducts **6a**, **7a**, and **8a** against their regioisomers **6b**, **7b**, and **8b**, respectively.

iii DFT-based reactivity indexes: The chemical hardnesses  $\eta$ , global electrophilicity  $\omega$  and global nucleophilicity  $N$  of the nitrile oxide and dipolarophiles are given in Table 3. The Fukui indexes for the atoms O1 and C3 of the dipole (nitrile oxide) and for the atoms C4 and C5 of the dipolarophiles (acrylonitrile, methyl methacrylate and allyl bromide), local electrophilicity  $\omega_k$  and local nucleophilicity  $N_k$  values are given in Table 4 (see Fig. 3 for atom numbering).

As it can be seen in Table 3, the electronic chemical potential of dipolarophiles vinyl acetate and allyl bromide is greater than that of nitrile oxide (dipole), which indicates the charge transfer is taking place from dipolarophiles to nitrile oxide. The electronic chemical potential of dipolarophile acrylonitrile is smaller than that of nitrile oxide which indicates the charge transfer is taking place from nitrile oxide to dipolarophile. Consequently, the nitrile oxide can act as electrophile in reactions a and c and in reaction b acts as nucleophile. In Figure 3, we have reported the values of local electrophilicities  $\omega_k$  for atoms O1 and C3 of the dipole (nitrile oxide) and the local nucleophilicities  $N_k$  for atoms C4 and C5 of dipolarophiles in **7** and **8**. For **6** the values of  $N_k$  for atoms O1 and C3 of dipole (nitrile oxide) and  $\omega_k$  for atom C4 and C5 of dipolarophile (acrylonitrile) were reported. As it can be seen in Figure 3, according to the Domingo's model [23,24], in the reaction between nitrile oxide **2** and acrylonitrile **3**, the most favorable two-center interaction takes place between C3 of acrylonitrile and O1 of the nitrile oxide leading to the formation

**Table 3**

HOMO, LUMO energies in a.u., electronic chemical potential ( $\mu$  in a.u.), chemical hardness ( $\eta$ , in a.u.), global electrophilicity ( $\omega$ , in eV) and global nucleophilicity ( $N$ , in eV) for dipole and dipolarophile systems.

	HOMO	LUMO	$\mu$	$\eta$	$\omega$	$N^{\text{el}}$
Dipole(nitrile oxide)	-0.238	-0.059	-0.148	0.178	1.68	2.65
Dipolarophil(acrylonitrile)	-0.289	-0.056	-0.173	0.233	1.74	1.25
Dipolarophile (vinyl acetate)	-0.249	-0.010	-0.130	0.239	0.96	2.33
Dipolarophile (allyl bromide)	-0.264	-0.004	-0.134	0.260	0.93	1.94

<sup>a</sup>The HOMO energy of tetracyanoethylene is -0.3351 a.u. at the same level of theory.

of the cycloadduct **6a**. It is noteworthy that during the reaction of nitrile oxide **2** with vinyl acetate **4** and allyl bromide **5**, the most favorable interactions take place between O1 of the nitrile oxide and C4 of the vinyl acetate and C5 of the allyl bromide, respectively. These results clearly indicate that the two-center polar model, based on electrostatic charges, predict correctly the experimental regioselectivity.

In conclusion, the regioselectivity for the 1,3-DC reactions of nitrile oxide **2** with acrylonitrile **3**, vinyl acetate **4** and allyl bromide **5** has been investigated using experimental and theoretical <sup>13</sup>CNMR studies together with the activation energy calculations and the DFT-based reactivity indexes at the B3LYP/6-31G(d) level of theory. The results obtained in this work clearly predict the regiochemistry of the isolated cycloadducts.

## EXPERIMENTAL

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The <sup>1</sup>H NMR (400 MHz) spectra were recorded on a Bruker AC 400 spectrometer. <sup>13</sup>C NMR spectra were determined using the Bruker AM-400 instrument operating at 100 MHz. NMR spectra were obtained on solutions in CDCl<sub>3</sub> using tetramethylsilane as internal standard. IR spectra were determined as KBr pellets on a Bruker model 470 spectrophotometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analyses were carried out on Eager CHNS-O 300 apparatus and were in good accordance

with theoretical data. Oxime **1** the precursor of nitrile oxide **2** is a known compound was prepared according to generally used methods [30].

**General procedure for the synthesis of cycloadducts.** To a mixture of 1 mmol of oxime and 1.5 mmol of dipolarophile in tetrahydrofuran (THF) (25 mL) was added aqueous NaOCl (11% Cl<sub>2</sub> content, 1.62 mL, 2.50 mmol) at 5°C. The reaction was stirred for 10 min, then at r.t. for 24 h. After that, H<sub>2</sub>O (30 mL) was added, the organic layer separated and remaining product extracted from the aqueous layer using CHCl<sub>3</sub> (15 mL). The combined organic layers were washed with H<sub>2</sub>O (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under reduced pressure. The crude product was purified by precipitation with cold Et<sub>2</sub>O to afford cycloadducts as white powders.

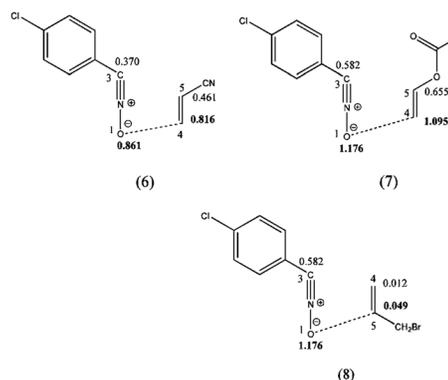
**3-(4-Chlorophenyl)-4,5-dihydroisoxazole-5-carbonitrile (6a).** This compound was obtained as white powder (80%). m.p. 126-128°C. IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1598. MS (EI, 70 eV)  $m/z$ : 206 ( $M^+$ ), 208 ( $M^+ + 2$ ). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  3.71(1H, dd, CH<sub>A</sub>H<sub>B</sub>,  $J = 6.40$  Hz,  $J = 10.40$  Hz), 3.78 (1H, dd, CH<sub>A</sub>H<sub>B</sub>,  $J = 6.00$  Hz,  $J = 10.80$  Hz), 5.41 (1H, dd, CH,  $J = 6.40$  Hz,  $J = 4.40$  Hz), 7.43 (2H, d, CH-Ar,  $J = 8.40$  Hz), 7.61 (2H, d, CH-Ar,  $J = 8.80$  Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>),  $\delta_{\text{C}}$ : 41.0, 66.8, 117.0, 125.9, 128.3, 129.4, 137.4, 155.5. Anal. Calcd for C<sub>10</sub>H<sub>7</sub>ClN<sub>2</sub>: C, 58.13; H, 3.41; N, 13.56%. Found: C, 58.23; H, 3.46; N, 13.37%.

**3-(4-Chlorophenyl)-4,5-dihydroisoxazol-4-yl acetate (7a).** This compound was obtained as white powder (85%). m.p. 90-91°C. IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1750, 1598. MS (EI, 70 eV)  $m/z$ : 239 ( $M^+$ ), 241

**Table 4**

Fukui indexes for the O1 and C3 atoms of the nitrile oxide, for atoms C4 and C5 of the dipolarophiles, local electrophilicities,  $\omega_k$ , (eV) and local nucleophilicities,  $N_k$ , (eV).

	Atom number	$f_k^+$	$f_k^-$	$\omega_k$	$N_k$
Nitrile oxide	O1	0.077	0.325	1.176	0.861
	C3	0.056	0.139	0.582	0.370
Acrylonitrile	C4	0.469		0.816	
	C5	0.265		0.461	
Vinyl acetate	C4		0.470		1.095
	C5		0.281		0.655
Allyl bromide	C4		0.006		0.012
	C5		0.025		0.049



**Figure 3.** Illustration of the favorable interactions using local nucleophilicities,  $N_k$ , for dipolarophile centers (in **7** and **8**); for **6** local electrophilicities  $\omega_k$  and local electrophilicities,  $\omega_k$ , for the nitrile oxide centers (for six local nucleophilicities,  $N_k$ ).

( $M^+ + 2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.10 (3H, s,  $\text{CH}_3$ ), 3.34 (1H, dd,  $\text{CH}_A\text{H}_B$ ,  $J = 1.60$  Hz,  $J = 16.40$  Hz), 3.61 (1H, dd,  $\text{CH}_A\text{H}_B$ ,  $J = 6.80$  Hz,  $J = 10.80$  Hz), 6.85 (1H, dd, CH,  $J = 1.60$  Hz,  $J = 5.20$  Hz), 7.42 (2H, d, CH-Ar,  $J = 8.40$  Hz), 7.66 (2H, d, CH-Ar,  $J = 8.40$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ),  $\delta_{\text{C}}$ : 21.0, 41.2, 96.0, 126.8, 128.3, 129.2, 136.9, 156.1, 169.7. Anal. Calcd for  $\text{C}_{11}\text{H}_{10}\text{ClNO}_3$ : C, 55.13; H, 4.21; N, 5.84%. Found: C, 54.73; H, 4.27; N, 6.73%.

**5-(Bromomethyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole (8a).** This compound was obtained as white powder (83%). m. p. 97-98°C. IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 1600. MS (EI, 70 eV)  $m/z$ : 273 ( $M^+$ ), 275 ( $M^+ + 2$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.31 (1H, dd,  $\text{CH}_A\text{H}_B$ ,  $J = 6.40$  Hz,  $J = 10.40$  Hz), 3.44 (1H, dd,  $\text{CH}_A\text{H}_B$ ,  $J = 8.40$  Hz,  $J = 2.40$  Hz), 3.51 (1H, dd,  $\text{CH}_A\text{H}_B$ ,  $J = 10.40$  Hz,  $J = 6.80$  Hz), 3.60 (1H, dd,  $\text{CH}_A\text{H}_B$ ,  $J = 4.40$  Hz,  $J = 6.00$  Hz), 5.04 (1H, m, CH), 7.40 (2H, d, CH-Ar,  $J = 8.80$  Hz), 7.62 (2H, d, CH-Ar,  $J = 8.80$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ),  $\delta_{\text{C}}$ : 33.4, 39.5, 79.9, 127.5, 128.0, 129.1, 136.4, 155.2. Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{BrClNO}$ : C, 43.75; H, 3.30; N, 5.10%. Found: C, 43.72; H, 3.30; N, 5.22%.

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