

INVESTIGATION INTO THE REGIOCHEMISTRY OF SOME PYRAZOLES DERIVED FROM 1,3-DIPOLAR CYCLOADDITION OF ACRYLONITRILE WITH SOME NITRILIMINES: THEORETICAL AND EXPERIMENTAL STUDIES

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ABSTRACT

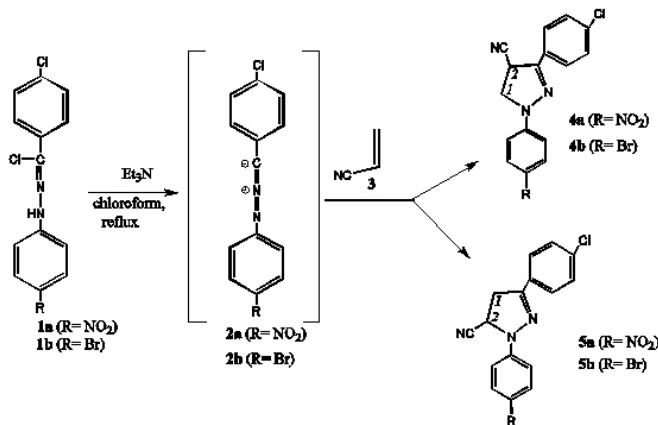
1,3-dipolar cycloaddition between acrylonitrile and two N-(4-substituted)phenyl-C-(4-chlorophenyl)nitrilimines which were generated in situ afforded the new pyrazoles. The regiochemistry and reactivity of these reactions has been investigated on the basis of density functional theory (DFT) -based reactivity indexes and activation energy calculations. The theoretical ¹³C NMR chemical shifts of the cycloadducts which were obtained by GIAO method were comparable with the observed values.

INTRODUCTION

1,3-Dipolar cycloaddition reactions of nitrilimines with dipolarophiles containing a carbon-carbon double bond represent an important synthetic route to substituted pyrazoles and pyrazolidines¹. These reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry². Current understanding of the underlying principles in the Diels-Alder (DA) reactions and the 1,3-DCs has grown from a fruitful interplay between theory and experiment²⁻⁴. Two major factors i.e. the steric and electronic effects can influence the regioselectivity of these reactions². Although transition state 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 transition states 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 nitrilimines with various dipolarophiles can be found in the literature⁵⁻⁸. In this context, we became interested in the reactivity of acrylonitrile **3** as dipolarophile towards two N-(4-substituted)phenyl-C-(4-chlorophenyl)nitrilimines **2** as dipoles which were generated in situ by base treatment of the corresponding hydrazoneyl chlorides **1** in order to synthesize the new 3-(4-chlorophenyl)-1-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-4-carbonitrile **4a** and 1-(4-bromophenyl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-5-carbonitrile **5b** (Scheme1). 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) method⁹ 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 experiment¹⁰.

Regioselectivity criteria for two-center reactions

According to the model recently proposed by Domingo^{11, 12}, the regioselectivity of a polar cycloaddition reaction could be explained by the most favorable two-center interactions between the highest nucleophilic and electrophilic sites of the reagents. The corresponding reaction channel favors the maximum CT from the nucleophilic to the electrophilic reagent in the course of the polar cycloaddition reaction. Local electrophilicity and nucleophilicity indexes¹³⁻¹⁵ (for definition, see Eqs. 6 and 7) are 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.



Scheme 1. The regioisomeric pathways for 1,3-DC of nitrilimines **2** and dipolarophile **3**.

3. COMPUTATIONAL DETAILS

All calculations were performed with the Gaussian98 program suite¹⁶. 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 method¹⁷. The transition states (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 in order to verify that the TSs had one and only one imaginary frequency. The atomic electronic populations were evaluated according to Merz-Kollman scheme (MK option)^{18,19}. The global electrophilicity w for dipoles and dipolarophile was evaluated using Eq. (1)²⁰:

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

In Eq. (1) μ and η are the electronic chemical potential and the chemical hardness of the ground state (GS) of atoms and molecules, respectively.

The electronic chemical potential μ and chemical hardness η were evaluated in terms of the one electron energies of the HOMO and LUMO, using Eqs. (2) and (3), respectively^{21,22}:

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

$$\eta \approx (\varepsilon_L - \varepsilon_H) \quad (3)$$

As usual, local indexes are computed in atomic condensed form²³. The well-known Fukui function^{24,25} for electrophilic (f_k^-) and nucleophilic attack (f_k^+) can be written as

$$f_k^- = [\rho_k(N) - \rho_k(N-1)] \quad (4)$$

$$f_k^+ = [\rho_k(N+1) - \rho_k(N)] \quad (5)$$

Where $\rho_k(N)$, $\rho_k(N-1)$ and $\rho_k(N+1)$ are the gross electronic populations of the site k in neutral, cationic, and anionic systems, respectively.

The local electrophilicity index¹⁴, ω_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_k^+)¹⁴

$$\omega_k = \omega f_k^+ \quad (6)$$

Recently, Domingo et al. has introduced an empirical (relative) nucleophilicity index¹³, N_k , based on the HOMO energies obtained within the Kohn–Sham scheme²², and defined as $E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{TCE})$. This nucleophilicity scale is referred to tetracyanoethylene (TCE) taken as a reference. Local nucleophilicity index²⁶, N_k , was evaluated using the following equation²⁶:

$$N_k = N f_k^- \quad (7)$$

where f_k^- is the Fukui function for an electrophilic attack²⁵.

The ¹³C NMR chemical shifts were calculated by means of the GIAO method⁹, using the tetramethylsilane (TMS) as ¹³C reference, at the B3LYP/6-311+G (d) level of theory (reference value of ¹³C = 184.5307 ppm).

EXPERIMENTAL

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The ¹H NMR (400 MHz) spectra were recorded on a Bruker AC 400 spectrometer. ¹³C NMR spectra were determined using the Bruker AM-400 instrument operating at 100 MHz. IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Hydrazonoyl chlorides (**1**) the precursors of nitrilimines (**2**) are known compounds and were prepared according to generally used methods²⁷.

Typical experimental procedure for **4a** and **5b**

To a solution of acrylonitrile **3** (5 mmol) and hydrazonoyl chlorides **1a,b** (5 mmol) in chloroform (20 ml) was added triethylamine (0.7 ml, 5 mmol). The reaction mixture was refluxed for 8-10 h till the hydrazonoyl chloride disappeared as indicated by TLC analysis. The solvent was evaporated and the residue was treated with methanol. The solid that formed was collected and crystallized from suitable solvent to afford the pure products **4a** and **5b** respectively in good yields.

3-(4-chlorophenyl)-1-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-4-carbonitrile (4a): This compound was obtained as brown solid (90%). m.p. 182 °C. IR (KBr) ($n_{\text{max}}/\text{cm}^{-1}$): 1395, 1493, 1597 cm^{-1} . MS (EI, 70 eV) m/z : 326 (M^+), 328 ($M^+ + 2$). ¹H NMR (400 MHz, CDCl₃) d_H : 3.88 (1H, d, J = 16 Hz, CH_AH_B), 4.01 (1H, d, J = 16 Hz, CH_AH_B), 5.92 (1H, t, CH, J = 8 Hz), 7.39 (2H, dd, CH, J = 8 Hz, 4-nitrophenyl ring), 7.58 (2H, dd, CH, J = 8 Hz, 4-chlorophenyl ring), 7.85 (2H, dd, CH, J = 8 Hz, 4-chlorophenyl ring), 8.27 (2H, dd, CH, J = 8 Hz, 4-nitrophenyl ring). ¹³C NMR (100 MHz, CDCl₃) d_C : 39.0 (CH), 48.7 (CH₂), 115.9 (C \equiv N), 113.0, 127.6, 128.2, 128.5, 129.3, 136.8, 147.2 (C, phenyl rings), 149.9 (C = N). Anal. Calcd for C₁₆H₁₁N₄O₂: C, 58.82; H, 3.39; N, 17.15. Found: C, 58.85; H, 3.43; N, 17.19.

1-(4-bromophenyl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-5-carbonitrile (5b): This compound was obtained as light pink solid (88%). m.p. 165 °C. IR (KBr) ($n_{\text{max}}/\text{cm}^{-1}$): 1336, 1558, 1580 cm^{-1} . MS (EI, 70 eV) m/z : 359 (M^+), 361 ($M^+ + 2$), 363 ($M^+ + 4$). ¹H NMR (400 MHz, CDCl₃) d_H : 3.64 (1H, d, J = 12 Hz, CH_AH_B), 3.66 (1H, d, J = 12 Hz, CH_AH_B), 4.98 (1H, t, CH, J = 8 Hz), 7.13 (2H, dd, CH, J = 8 Hz, 4-bromophenyl ring), 7.42 (2H, dd, CH, J = 8 Hz,

4-bromophenyl ring), 7.48 (2H, dd, CH, J = 8 Hz, 4-chlorophenyl ring), 7.64 (2H, dd, CH, J = 8 Hz, 4-chlorophenyl ring); ¹³C NMR (100 MHz, CDCl₃) d_C : 38.8 (CH₂), 50.0 (CH), 116.7 (C \equiv N), 114.1, 115.1, 127.3, 129.1, 132.2, 135.9, 142.5 (C, phenyl rings), 147.7 (C = N). Anal. Calcd for C₁₆H₁₁Br ClN₃: C, 53.29; H, 3.07; N, 11.65. Found: C, 53.33; H, 3.09; N, 11.67.

RESULTS AND DISCUSSION

Nitrilimines **2** were generated in situ from base treatment of corresponding hydrazonoyl chlorides **1** by refluxing in chloroform. 1,3-DC of nitrilimines **2** with the dipolarophile proceeded smoothly in a selective manner to give a single regioisomer of each pair **4a-5a** and **4b-5b** in 90% and 88% yields respectively (scheme 1). For each one of these cycloaddition reactions, two cyclization modes have been investigated. They are related to the two regioisomeric approaching modes of nitrilimines **2** to the acrylonitrile **3** mentioned as **4a-5a** and **4b-5b**. The assignment of the regiochemistry of these products was based upon *i*) comparing the theoretical ¹³C 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 ¹³C 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 and Scheme 1, the observed values for C1 and C2 in each of the isolated products (48.7 and 39.0, 38.8 and 50.0 ppm in compounds **4** and **5**, respectively) are in closer proximity to the theoretical values for compounds **4a** and **5b**. It seems likely that the isolated regioisomers are structurally similar to **4a** and **5b**. Further proofs came from activation energy and DFT studies as followings:

Table 1. The comparison of theoretical ¹³C NMR chemical shifts data (δ , ppm) of C-1 and C-2 of each pair of regioisomers with those obtained from the experimental ¹³C NMR spectroscopy.

Experimental chemical shift	Calculated chemical shift	Atom number	Compound
48.7	48.4	C-1	4a
39.0	38.7	C-2	
	33.2	C-1	5a
	47.5	C-2	
	45.2	C-1	4b
	31.3	C-2	
38.8	38.5	C-1	5b
50.0	49.4	C-2	

ii) Activation energy calculations

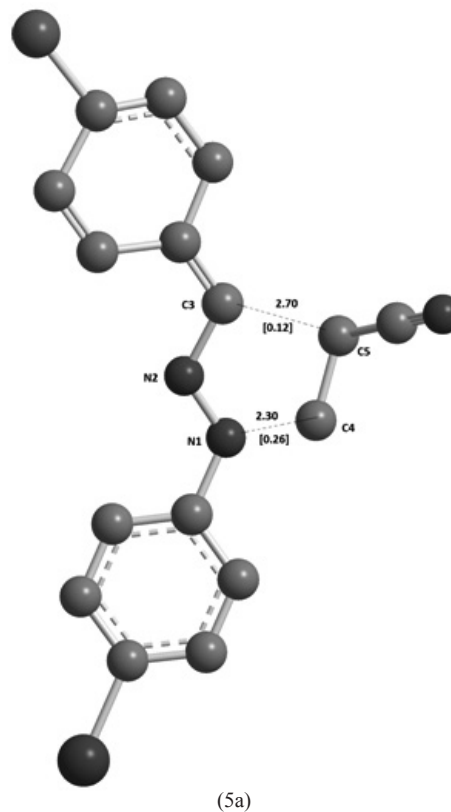
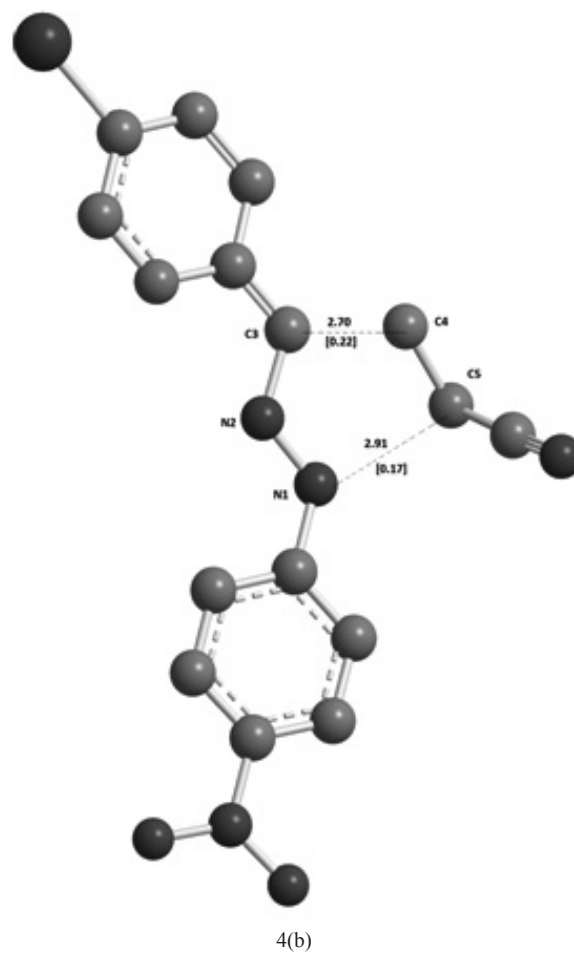
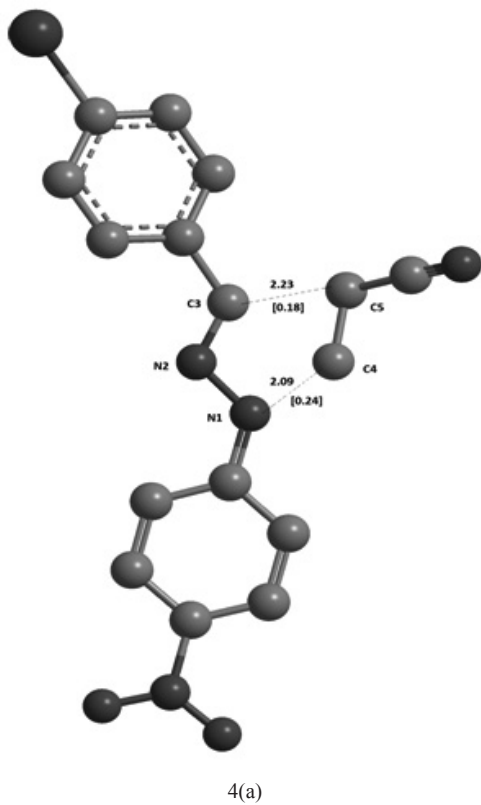
The transition states have been localized for both cyclization modes. The corresponding activation energies and structures are given in Table 2 and Figure 1 respectively. As it can be seen in Table 2, in the reaction between **2a** and **3**, TS **4a** is located 1.6 kcal below TS **5a** and in the reaction between **2b** and **3** TS **5b** is located 0.5 kcal below TS **4b**. The activation energies corresponding to the two cyclization modes of the reactions are: 8.5, 10.1 for **2a+3**, and 7.9, 7.2 for **2b+3**. Thus, in **2a+3** reaction pathway, **4a** regioisomer is kinetically more favored than the **5a**. In reaction between **2b + 3**, **5b** regioisomer is kinetically more favored than the **4b**. The presence of the nitro group in nitrilimine **2a** not only changes the regioselectivity but also slightly increases the barrier. An analysis of the geometries at the TSs given in Figure 1 indicates that they 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 N–C and C–C forming bonds at TSs are shown in brackets in Figure 1. These values are within the range of 0.17 to 0.26. Therefore, it may be suggested that these TSs correspond to early processes. In general, the asynchronicity shown by the geometrical data is accounted for by the BO values. A qualitative reactivity can be estimated by applying Hammond's postulate²⁹. All the reactions proceeded exothermically with large ΔE_r (relative energies between products and reactives) energy values which make them irreversible processes (see Table 2). According to Hammond's postulate, the TSs should then be closer to the reactives. The activation energy values, ΔE_a , also favor the formation of the cycloadducts **4a** and **5b** against their regioisomers **5a** and **4b** respectively. The polar nature of the two cyclization modes can be estimated by a charge transfer (CT) analysis at the TSs. The CT from nitrilimine **2a** to acrylonitrile **3** is 0.19 e at TS **4a** and 0.16 e at TS **5a**. Therefore the CT calculations show a NED (normal electron demand) character for this reaction. For **2b + 3**, The CT from nitrilimine **2b** to

acrylonitrile **3** is 0.13 e at TS **4b** and 0.17 e at TS **5b**. Thus the CT calculations show a NED character for this process.

Table 2. Energies of reactives, transition states and cycloadducts **4** and **5**, E (a.u.), relative activation energies ΔE_a (kcal mol⁻¹) relative energies between products and reactives, ΔE_r (kcal mol⁻¹) and charge transfer (CT, in e) at TSs

Reaction	System	E	ΔE_a^a	ΔE_r^a	CT
2a+3	Nitrilimine 2a	-3386.446204			
	Acrylonitrile 3	-170.831848			
	TS 4a	-3357.264112	8.5		0.19
	TS 5a	-3357.261021	10.1		0.16
	4a	-3357.337234		-37.3	
	5a	-3357.336012		-36.7	
2b+3	Nitrilimine 2b	-3641.523112			
	Acrylonitrile 3	-170.831848			
	TS 4b	-3812.342220	7.9		0.13
	TS 5b	-3812.343012	7.2		0.17
	4b	-3812.431102		-47.9	
	5b	-3812.432241		-48.5	

^a to reactives



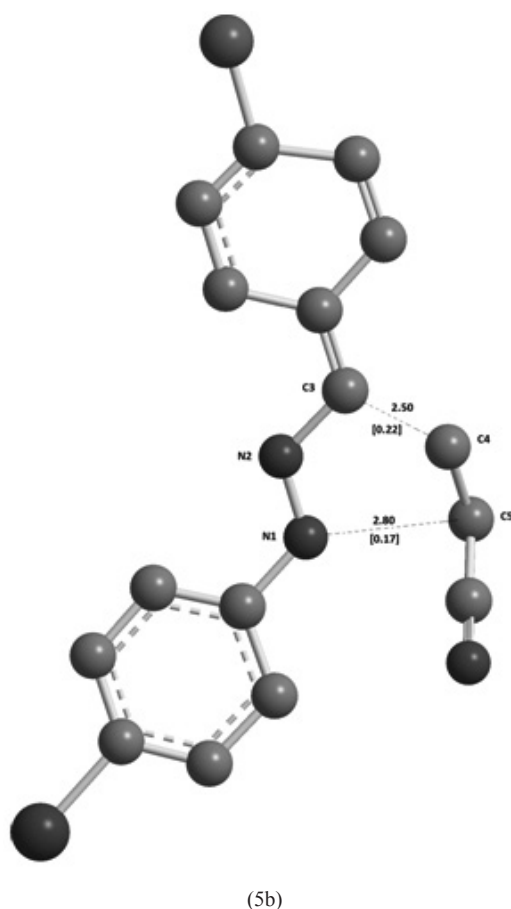


Figure 1. Optimized geometries for transition state structures at the B3LYP/6-31G(d) level of theory. Hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms. The bond orders are given in brackets.

iii) DFT-based reactivity indexes

Prediction of regiochemistry by using DFT-based reactivity indexes

The chemical hardnesses η , global electrophilicity w and global nucleophilicity N of the nitrilimines and dipolarophile are given in Table 3. The Fukui indexes for the atoms N1 and C3 of the dipoles (nitrilimines) and for the atoms C4 and C5 of the dipolarophile (acrylonitrile), calculated with MK population analysis, are given in Table 4 (see Scheme 2 for atom numbering).

Table 3. HOMO, LUMO energies in a.u., electronic chemical potential (μ in a.u.), chemical hardness (η , in a.u.), global electrophilicity (ω , in eV) and global nucleophilicity (N , in eV) for dipole and dipolarophile systems.

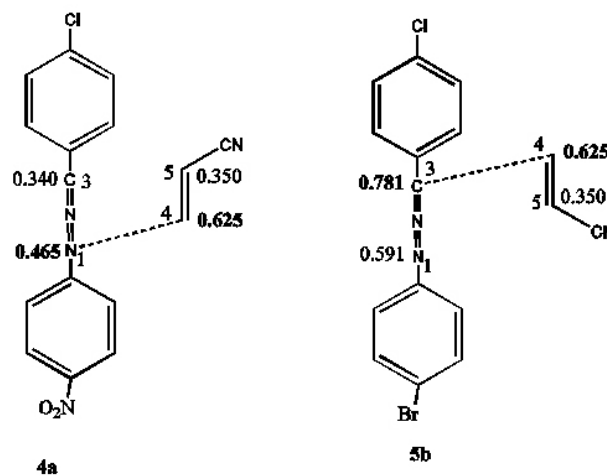
N^a	ω	η	μ	LUMO	HOMO	Reactants
3.416	2.309	0.126	-0.146	-0.083	-0.210	2a
3.625	1.891	0.133	-0.136	-0.069	-0.202	2b
1.250	1.744	0.233	-0.173	-0.056	-0.289	3

^a The HOMO energy of tetracyanoethylene is -0.33514 a.u. at the same level of theory.

Table 4. Fukui indexes for the N1 and C3 atoms of the nitrilimines and for atoms C4 and C5 of the acrylonitrile

System	Atom number	f_k^+	f_k^-	ω_k	N_k
Nitrilimine 2a	N1		0.136		0.465
	C3		0.100		0.340
Nitrilimine 2b	N1		0.163		0.591
	C3		0.215		0.781
Acrylonitrile 3	C4	0.359		0.625	
	C5	0.201		0.350	

As it can be seen in Table 3, the electronic chemical potentials of nitrilimines (dipoles) **2a** and **2b** are greater than that of acrylonitrile **3** (dipolarophile), which indicates the charge transfer is taking place from nitrilimines to acrylonitrile. Note that even though nitrilimine **2a** has a larger electrophilicity value w than acrylonitrile **3**, the latter has a lower chemical potential, which is the index that determines the direction of the electronic flux along the cycloaddition. These results are in agreement with CT calculations at the TSs. For better visualization we have depicted these interactions in Scheme 2. In the reaction between **2a** and **3**, the most favorable two-center interaction takes place between N1 of nitrilimine **2a** and C4 of the acrylonitrile **3** leading to the formation of the **4a** regioisomer. In the reaction between **2b** and **3**, the most favorable two-center interaction takes place between C3 of nitrilimine **2b** and C4 of the acrylonitrile **3** leading to the formation of the **5b** regioisomer. The replacement of Br group in **2b** (or **5b** in Scheme 2) by NO₂ in **2a** (or **4a** in Scheme 2) changes the N1 and C3 values. This fact is the responsible for the changes in the calculated regioselectivity. As it can be seen in Scheme 2, the local philicity indexes (ω_k , N_k) seem to be a reliable tool for the prediction of the most favored interaction in a two-center polar process. It turns out that the two-center polar model, based on electrostatic charges, predicts correctly the experimental regioselectivity.



Scheme 2. Illustration of the favorable interactions using Local nucleophilicities, N_k , for dipole centers and local electrophilicities, ω_k , for the acrylonitrile centers calculated with MK population analysis.

In conclusion the regioselectivity for the 1,3-DC reactions of nitrilimines **2** with acrylonitrile **3** has been investigated using experimental and theoretical ¹³C NMR 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.

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