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An experimental and theoretical study on the regioselective synthesis of a new class of spiropyrrolothiazoles with quinoxalines motifs via 1,3-dipolar cycloaddition reaction. An evaluation of DFT methods

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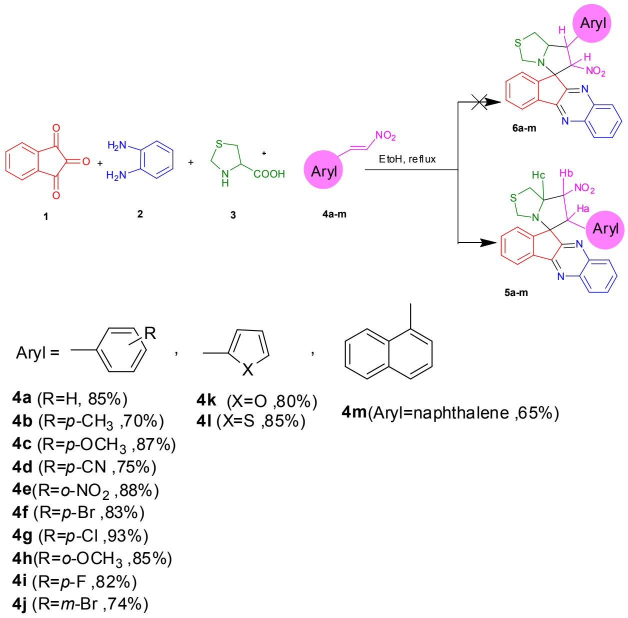
A series of novel spiropyrrolothiazoles with quinoxalines motifs have been synthesized by four-component 1,3-dipolar cycloaddition reaction of various derivatives of trans-β-nitrostyrene and an azomethine ylide, generated in situ from 1,3-thiazolane-4-carboxylic acid, ninhydrine and 1,2-phenylenediamine. The stereochemistry of the products has been confirmed by single crystal X-ray structure and spectroscopic techniques. Theoretical calculations have been carried out using DFT methods at the B3LYP/6-31G(d,p), wB97xD/6-31G(d,p) and M06-2X/6-31G(d,p) levels. The regio- and stereoselectivity have been explained on the basis of transition states stabilities and global and local reactivity indices of the reactants. The assessment of geometries and energetics of transition states revealed the importance of π/π interactions between aromatic rings in regioselectivity of the cycloaddition reaction. The B3LYP functional is unable to deal with this weak interactions in the proposed TSs and it leads to an incorrect conclusion about the reaction regioselectivity. In this report, we successfully employed wB97xD and M06-2X functionals to calculate the transition states relative energies.

Introduction

1,3-Dipolar cycloaddition (1,3-DC) reaction of azomethine ylides with dipolarophiles is an efficient method for the construction of nitrogen-containing five membered heterocycles in a highly regio- and stereo-selective manner.[1] Azomethine ylides can be produced by a number of methods, of which the decarboxylation route is a facile manner and investigated extensively by Grigg and co-workers. [2] Among the various nitrogen containing heterocycles, pyrrolidines, pyrrolizidines and pyrrolothiazoles have gained much consideration due to their unique biological activities, i.e. antimicobacterial, [3] hepatoprotective, [4] antibiotic, [5] antidiabetic [6] and anticonvulsant actions [7]. They also form the central skeleton of many natural products and alkaloids.[8] Spiropyrrolothiazoles have shown diverse biological activities such as antimicrobial,[9] antidiabetic,[10] anticancer [11] and acetylcholinesterase-inhibitory properties.[12] It is interesting to note from chemical literature that benzopyrazines (quinoxalines) and their derivatives also exhibit spectrum of biological activities like antimicrobial, antifungal, anticancer and antihelmentic propertities.[13] The other applications of this important motif includes dying, synthesis of pharmaceuticals and organic semi-conductors.[14]

Based on the biological activities of these derivatives and in continuation of our previous theoretical and experimental research program on the spiro heterocycles, [15] we became interested in the synthesis of a novel class of spiro-pyrrolothiazoles with quinoxalines motifs via the one-pot, four-



Scheme 1. Regioselective synthesis of spiropyrrolothiazole **5a-n**.

component condensation of trans-β-nitrostyrene derivatives with an azomethine ylide, generated in situ from 1,3-thiazolane-4-carboxylic acid, ninhydrine and 1,2-phenylenediamine. In particular, we focused our attention to study of mechanism and regioselectivity of this 1,3-DC reaction from a theoretical point of view by means of the Density Functional Theory (DFT).

Results and discussion

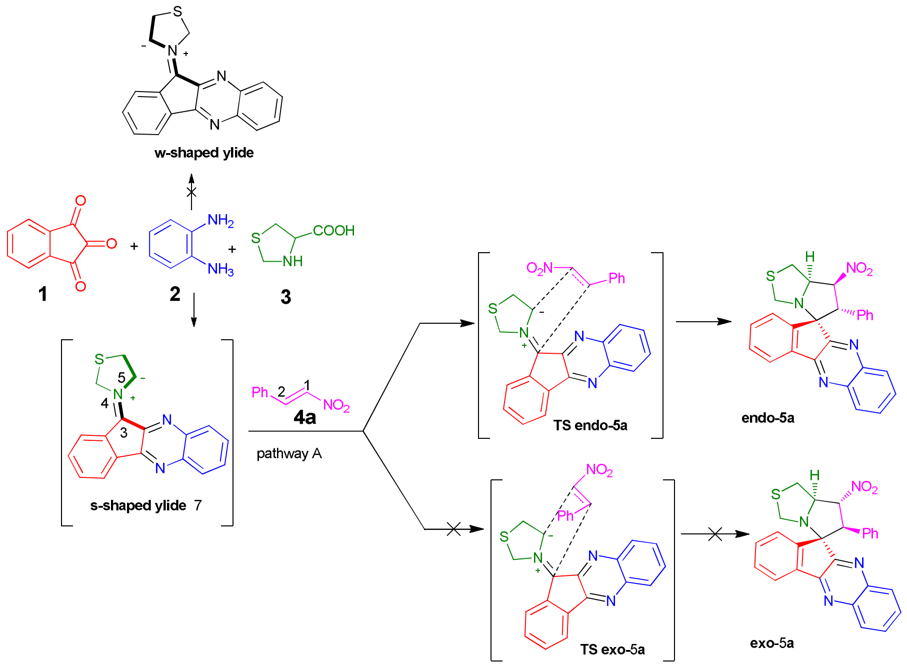
In our initial endeavor, we have investigated a four-component reaction of trans-β-nitrostyrene **4a** as dipolarophile with a non-stabilized azomethine ylide, generated in situ by the decarboxylative condensation of 1,3-thiazolane-4-carboxylic acid **3**, ninhydrine **1** and 1,2-phenylenediamine **2** in refluxing ethanol to give a single cycloadduct **5a** (Scheme 1). The extent of reaction was monitored by TLC and the pure cycloadduct was obtained by recrystallization from ethanol. This protocol was applied to a series of various derivatives of nitroalkene **4b–n** with both electron-withdrawing and electron-releasing substituents under similar conditions (Scheme 1). We found no spectroscopic evidence for a competing formation of isomeric compounds **6**.

The structure and regiochemistry of the cycloadducts were determined by various spectroscopic techniques. So, the IR spectrum of **5c** demonstrated absorption at 1338 and 1543 cm^{-1} indicating the presence of a Nitro group. The ^{1}H NMR spectrum of **5c** exhibited a singlet at δ =3.5 for the methoxy protons, a doublet at δ=4.69 ppm (*J*= 11.2Hz) for H_a, a doublet of doublet and not a doublet at δ = 6.82 ppm (*J*= 11.4, 7.4 Hz) for H_b (CHNO2) and a quartet at δ = 4.86 ppm (*J*= 7.2 Hz) for $H_{c.}$. This suggests that the correct regiochemistry of the product is **5c** as shown in Scheme 1. The ^{13}C NMR of **5c** showed a peak at δ =75.28 ppm owing to the spiro carbon and a peak at δ =86.06 ppm for the carbon attached to the Nitro group. The formation of the product was also confirmed by mass spectral. The mass spectrum of **5c** showed a molecular ion peak at 482 (M^{+}). Identical consequence were obtained for other products.

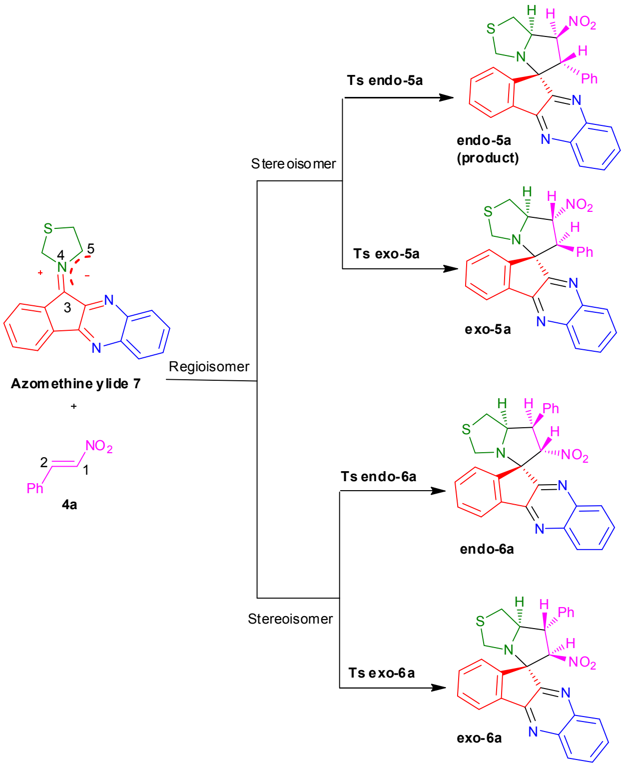
The ORTEP view of single crystal X-ray analysis of **5c** is indicated in Figure1. [16] The stereochemistry of cycloadducts is compatible with an S-shaped ylide and following cycloaddition by an *endo*-transition state (pathway B, Scheme 2).

Computational details

DFT calculations were done using the B3LYP, wB97xD and M06-2X functionals and the 6-31G(d,p) basis set, in the Gaussian 09 [17] environment. The electronic structures of critical points were surveyed by the natural bond orbital (NBO) way [18]. The nature of stationary geometries has been characterized by calculating the frequencies in order to verify that the transition states have only one imaginary frequency with the corresponding eigenvector involving the formation of the newly created C–C bonds. Also, zero-point energies and thermodynamic modifications were obtained using analytical force stable. Thermal modifications to enthalpy and entropy values were measured at 298.15 K.



Scheme 2. Proposed mechanism for the cycloaddition of the azomethine ylide **7** with nitrostyrene **4a**.



Scheme 3. Regio- and stereoisomeric pathways for a 1,3-DC reaction between azomethine ylide **7** with trans-β-nitrostyrene **4a**.

Prediction of regiochemistry

Due to the asymmetry of both the dipole and dipolarophile, the 1,3-dipolar cycloaddition reaction between nitrostyrene **4a** and azomethine ylide **7** can yield four isomeric products. First, we investigated the reaction energy path using B3LYP/6-31G(d,p). Four possible transition structures and related products have been optimized and characterized. They are related to two regioisomeric and two stereoisomeric approaches (Scheme 3).

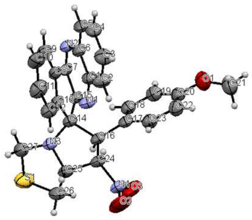


Figure 1. ORTEP diagram of **5c**.

The optimized geometries of transition states are represented in Figure 2. The activation energies, enthalpies and Gibbs free energies as well as the reaction energies, enthalpies, and Gibbs free energies are reported in Table S1.

In recent years, nucleus independent chemical shift (NICS) [29] values have been extensively used to assess aromaticity. [26-30] In order to evaluate the aromaticity of the optimized transition states, NICS was computed using gauge invariant atomic orbital (GIAO) [31] approach at the B3LYP/6-31G(d,p). As shown in Figure 2, all of the considered transition structures have large negative NICS values that indicate the aromatic characters of TSs due to the six electrons undergoing bond changing. In contrast, all cycloadducts have small negative NICS values (Table S2). Therefore, it can be concluded that possible transition states associated with 1,3-DC reaction between azomethine ylide **7** and β-nitrostyrene **4a** exhibit in-plane aromaticity.

As displayed in Figure 2, in the gas phase, the energy of **TS *endo*-6a** is 1.65 kcal/mol lower than that of **TS *endo*-5a**, favoring the formation of the ***endo*-6a** regioisomer as a product. One can see that the B3LYP functional fails to estimate the observed regioselectivity of the reaction. We find that the benzene ring in nitrostyrene and aromatic part of azomethine ylide are stacked in **TS *endo*-5a**, therefore there could be a dispersion π/π weak interaction between them which can be the reason of making the **TS *endo*-5a** more energy favorable.

The role of dispersion is very important in controlling stereo-selectivities of many reactions. [32] In our previous theoretical study, [15b] we reported that π/π interactions play a major role in the regiochemistry of a 1,3-DC reaction. It is well known that B3LYP is not able to estimate the stabilization gained by π/π interactions, [33] so we were encouraged to study the regiochemistry with more appropriate functional.

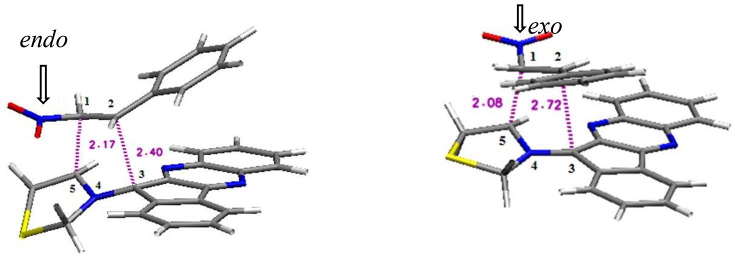
There are two approaches to deal with the weak interactions. One rout involves using post Hartree-Fock methods such as Møller-Plesset perturbation (MP2, MP4), Coupled Cluster and Configuration Interaction (CI) methods. All of this methods require huge computational resources which is not readily available at this time for molecules as large as studied here. The other popular strategy is to augment conventional DFT functionals with ad-hoc addition of non-bonded pairwise interaction namely DFT-D methods which contain a large number of free parameters in the functional form which are semiempirically fit using diverse data sets that include thermochemistry, noncovalent interactions and kinetics data.[34] So, the deficiency of hybrid functionals in the treatment of dispersion, can be minimized. The long-range van der Waals interaction will be included through the semi-empirical Grimme correction which does not attempt to describe the actual source of the interaction (fluctuating dipoles) but rather its effect on the DFT mean-field effective potential. The wB97xD and M06-2x functionals are two of the most popular meta GGA functionals in computational chemistry. The functional wB97xD is a version of Grimme's D2 dispersion model which is the latest functional from Head-Gordon and coworkers [35]. According to Zhao and Truhlar, the M05 and M06 series of functionals implicitly account for "medium-range" electron correlation because of the way they are parametrized, and this is sufficient to describe the dispersion interactions within many complexes.[36]

It is worth mentioning that, theoretical investigations to understand the accuracy of these functionals in the prediction of regioselectivity in cycloaddition reactions is rare. [37] Four possible transition structures have been optimized and characterized using wB97xD/6-31G(d,p) and M06-2X/6-31G(d,p). As shown in Table 1 in both level of theories, **TS *endo*-5a** has the lowest energy compared to other transition state isomers as a result of the π/π interaction, in accordance with experiment. Both method estimate that the relative stabilization of possible stationary points are: **TS *endo*-5a** > **TS *endo*-6a** > **TS *exo* 5a** > **TS *exo*-6a** (Figure 3).

The calculated activation energies with respect to the sum of the energies of the separated dipole **7** and dipolarophile **4a** are negative (Table 2). It is well understood that as two separated reactants are approached, a van der Waals pre-complex which is energetically more stable than the separated reactants, is initially formed between them in an appropriate distance and TS is formed from this pre-complex instead of separated reactants.[38]

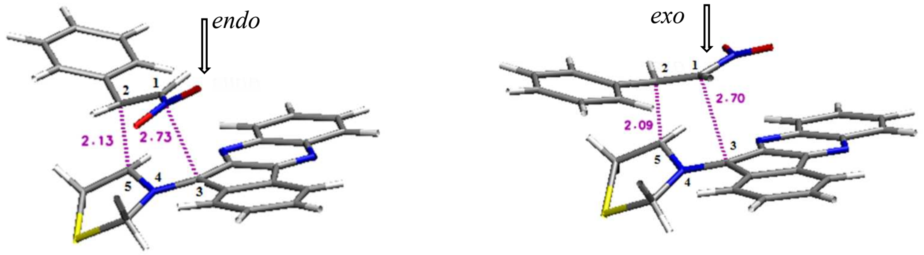
The charge transfer (CT) was calculated for all the optimized TSs, in terms of the residual charge on the azomethine ylide **7**, using Natural Population Analysis (NPA) at B3LYP, M06-2X and wB97xD levels (see Tables S1 and 1). The positive values are indicative of an electron flow from the HOMO of the azomethine ylide **7** to the LUMO of the nitrostyrene **4a.** These values indicate that these TSs have some zwitterionic character. The CT for the most favourable TSs, **TS *endo*-5a** at M06-2X (wB97xD) and **TS *endo*-6a** at B3LYP, is higher than the others.

The B3LYP/6-31G(d,p) lengths of the C2-C3 and C1-C5 forming-bonds are 2.40 and 2.17 Å at the **TS *endo*-5a** and 2.72 and 2.08 Å at **TS *exo*-5a**, respectively, while the lengths of the C1-C3and C2-C5 forming bonds are 2.73 and 2.13 Å at **TS *endo*-6a** and 2.70 and 2.09 Å at **TS *exo*-6a**, respectively (Figure 2). The M06-2x/6-31G(d,p) geometries of the TSs involved in this 1,3-DC reaction are given in Figure 3. The M06-2x/6-31G(d,p) lengths of the C2-C3 and C1-C5 forming-bonds are 2.18 and 2.35 Å at the **TS *endo*-5a** and 2.51 and 2.16 Å at **TS *exo*-5a**, respectively, while the lengths of the C1-C3 and C2-C5 forming bonds are 2.59 and 2.19 Å at **TS *endo*-6a** and 2.60 and 2.14 Å at **TS *exo*-6a**, respectively. A comparison of the B3LYP and M06-2X geometries for the 1,3-DC reaction, indicates that both functionals yield similar bond-formation processes except for the **TS *endo*-5a**. Different results are obtained where the M06-2X functional affords earlier bond-formation processes in the spiro center. Thus, the length of the C2-C3 is smaller than C1-C5 at M06-2X while the revers was the case for B3LYP. The wB97xD results are similar with M06-2X. This can be related to proper position of aromatic rings to allow the π/π interaction.



E$_{rel}$= 1.65
NICS= -13.74
TS *endo*-5a

E$_{rel}$= 3.66
NICS= -13.20
TS *exo*-5a



E$_{rel}$= 0.00
NICS= -14.00
TS *endo*-6a

E$_{rel}$= 5.38
NICS= -13.07
TS *exo*-6a

Figure 2. Transition structures corresponding to the regioisomeric and stereoisomeric path of the 1,3-DC reaction channels at B3LYP/6-31G(d,p). The bond lengths directly involved in the reaction are given in angstroms. The relative energies with respect to **TS *endo*-6a** are given under the structures.

Table 1. M06-2X/6-31G(d,p)(wB97xD/6-31G(d,p)) relative energies* (in kcal/mol), charge transfer (CT and forming bond length difference, ΔR (Å), of the stationary points involved in the 1,3-DC of nitrostyrene **4a** and azomethine ylide **7** and Average Bond Index Changes (δB_{av}), Synchronicities (Sy) and enthalpies ΔH (in kcal/mol) of the possible pathways of the reaction.

Structure	E_{rel} [a]	E_{rel} [b]	CT	ΔR	δB_{av}	*Sy*	ΔH
TS *endo*-5a	0.00	-12.75	0.2580	0.168	0.32	0.78	-52.18
	(0.00)	(-13.89)	(0.2729)	(0.289)	(0.31)	(0.75)	(-56.76)
TS *exo*-5a	4.86	-7.89	0.1749	0.348	0.24	0.51	-46.80
	(5.01)	(-8.89)	(0.1669)	(0.379)	(0.24)	(0.51)	(-50.55)
TS *endo*-6a	2.34	-10.41	0.2293	0.395	0.16	0.27	-49.36
	(3.77)	(-10.12)	(0.2195)	(0.403)	(0.15)	(0.18)	(-52.87)
TS *exo*-6a	7.20	-5.55	0.1953	0.468	0.21	0.21	-50.08
	(8.33)	(-5.56)	(0.1989)	(0.420)	(0.19)	(0.16)	-53.28

[a] relative to the most stable TS (**TS *endo*-5a**)

[b] relative to reagents (**4a**+**7**)

The difference between lengths of forming bonds in each TSs, ΔR, provides an estimate for the synchronicity of the bond-formation process. The calculated ΔR of TSs in Table 1 showed that reaction is asynchronous and **TS *endo*-5a** is more synchronous than other TSs.

The synchronicity (Sy) index of the cycloaddition reactions is estimated by the equation [39]

$$Sy = 1 - (2n-2)^{-1}\sum_{i=1}^{n}\frac{\left|\delta B_i - \delta B_{av}\right|}{\delta B_{av}} \qquad (1)$$

where *n* is the number of bonds directly involved in the reaction and δB_i is the relative variation of the Wiberg bond indices [40] for the ith bond in the TS, which is calculated by the equation:

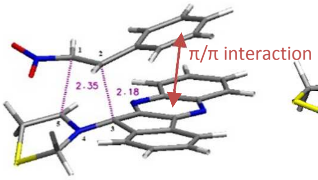
$$\delta B_i = \frac{B_i^{Ts} - B_i^{R}}{B_i^{P} - B_i^{R}} \qquad (2)$$

Here, superscript indices P, R, and TS correspond to the product, reactant, and transition state. The average variation δB_{av}, in eq 1 is detetmind by:

$$\delta B_{av} = n^{-1}\sum_{i=1}^{n}\delta B_i \qquad (3)$$

According to eq 1, for a perfectly synchronous process, *Sy*=1 and for fully asynchronous process synchronicity is zero. Based on eqs 2 and 3, early and late transition structures will be characterized by δB_{av} <0.5 and δB_{av} >0.5, respectively.[34g] The computed synchronicities (*Sy*) for four possible channels at M06-2X/6-31G(d,p) show that synchronicities order is **TS *endo*-5a> TS *exo*-5a** > **TS *endo*-6a > TS *exo*-6a**. The δB_{av}s are in all cases indicative of an early transition state which is in agreement with the exothermic nature of the reactions (Table 1).

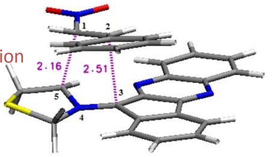
To predict the regioselectivity of cycloaddition reaction, a study using FMO analysis [19] and the global and local indices [20] for electrophilic/nucleophilic was also carried out at M06-2X/6-31G(d,p). Two types of azomethine ylide, anti (s-shape) and syn (w-shape) can be resulted from the reaction of ninhydrine **1**, 1,2-phenylenediamine **2** and 1,3-thiazolane-4-carboxylic acid **3** (Scheme 2). The s-shape azomethine ylide energy is lower than the w-shape by 1.41 kcal/mol which is in line with the product structure. In this study, the HOMO–LUMO energy gaps suggest that the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction controls the cycloaddition reaction within a normal electron demand reaction [21] (Figure 4). Inspection of the LUMO coefficients of the nitrostyrene **4a** and the HOMO coefficients of azomethine ylide **7** on the reactive sites in Table 3, revealed that the most favored large-large interaction takes place between C2 of the nitrostyrene and C3 of the azomethine ylide, which is in good agreement with the experimental observation.



E_{rel}= 0.00

NICS= -15.95

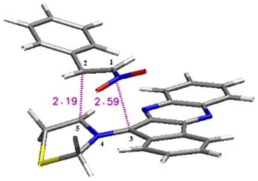
TS *endo*-5a



E_{rel}= 4.86

NICS= -16.11

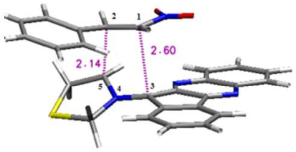
TS *exo*-5a



E_{rel}= 2.34

NICS= -16.08

TS *endo*-6a



E_{rel}= 7.20

NICS= -14.95

TS *exo*-6a

Figure 3. Transition structures corresponding to the regioisomeric and stereoisomeric path of the 1,3-DC reaction channels at M06-2X/6-31G(d,p). The bond lengths directly involved in the reaction are given in angstroms. The relative energies with respect to **TS *endo*-5a** are given under the structures.

Electronic chemical potential is defined as the mean value of HOMO and LUMO energies [μ= (E_{HOMO}+E_{LUMO})/2] and is a relative measure of the molecular capacity to donate electron density, while the global electrophilicity index is the ratio ω= μ^2 /(2η), which measures the total ability to attract electrons. η is the chemical hardness, and is the difference between the HOMO and LUMO energies [η=(E_{LUMO}-E_{HOMO}).[22]

The calculated global properties of dipole **7** and dipolarophile **4a** are shown in Table 2. The global reactivity indices also supported $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction. The electrophilicity of nitrostyrene at M06-2X /6-31G(d,p) in Table 2 is greater than 1.5 eV, thus according to the classification of electrophilicity, these compounds can be classified as strong electrophiles [23a]. However, the electrophilicity of nitrostyrene (1.82 eV) is greater than that of the azomethine ylide (1.10 eV). The electronic chemical potentials, μ, of the azomethine ylide **7** (-0.121 a.u.) is higher than those for the nitrostyrene **4a**, (-0.182 a.u.) indicating that along this 1,3-DC, azomethine ylide acts as a nucleophile whereas nitrostyrene acts as an electrophile and consequently the electronic flux is from dipole **7** to dipolarophile **4a**. As shown in Table 2, the B3LYP results are in agreement with M06-2X.

Studies of the regioselectivity of 1,3-DC reactions have demonstrated that the analysis of the local electrophilicity, ω_k, at the electrophile, together with the analysis of the nucleophilic Fukui functions, f_k^-, at the nucleophile, permit prediction of the regioselectivity in these competitive cycloadditions. [23-24] To reveal the most favorable reactive site, the DFT-based local chemical reactivity Fukui function for nucleophilic (f_k^+) and electrophilic (f_k^-) attacks, have been calculated through the NBO (Natural Bond Orbital) and Mulliken charges analysis using eqs (4) and (5), respectively.

$$f_k^+ = \rho_k^{N+1} - \rho_k^N = q_k^N - q_k^{N+1} \quad (4)$$

$$f_k^- = \rho_k^N - \rho_k^{N-1} = q_k^{N-1} - q_k^N \quad (5)$$

with k, N, ρ and q, corresponding to the index of the atom, the number of electrons, the population number and the net charge stemming from calculations, respectively.[25]

As shown in Table 3, nitrostyrene **4a** has the largest electrophilic activation at the C2 carbon atom, ω_k = 0.14 eV, whereas the azomethine ylide **7** has the largest nucleophilic activation at the C3 carbon atom, f_k^- =0.123. Therefore, C2 of nitrostyrene will be the preferred position for a nucleophilic attack by C3 of the azomethine ylide **7**, which is in good agreement with the observed regioselectivity. The B3LYP results are in accordance with M06-2X (see Table 3).

Table 2. The calculated global properties of dipolarophile **4a** and dipole **7** at M06-2X/6-31G(d,p) and B3LYP/6-31G(d,p) given in parenthesis.

Structure	*μ* (a.u)	*η* (a.u)	*ω* (eV)	*s*
nitrostyrene **4a**	-0.182 (-0.176)	0.247 (0.158)	1.82 (2.66)	2.028 (3.152)
Azomethine ylide **7**	-0.121 (-0.119)	0.183 (0.111)	1.10 (1.73)	2.732 (4.474)

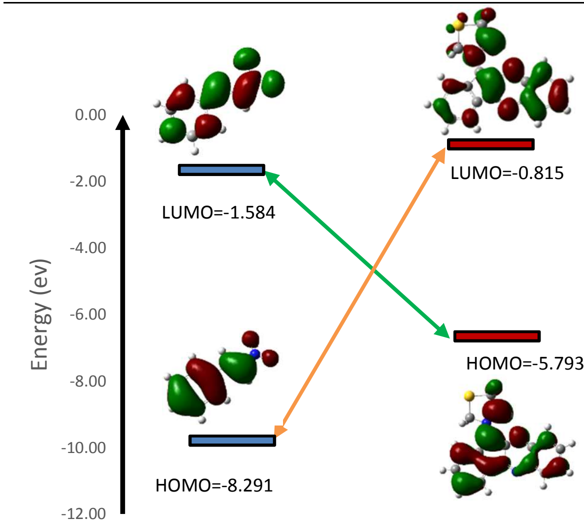


Figure 4. HOMO and LUMO energies of dipolarophile **4a** and azomethine ylide **7** calculated at the M06-2X /6-31G(d,p) level

Local softness, especially in conjunction with the hard and soft acids and bases (HSAB) principle, used successfully in predicting the regioselectivity of several cycloaddition reactions. [26] This principle states that the most favorable interaction results when the reactants have equal softness. Local softness and the HSAB principle thus provide a way to predict the favored product on the basis of the electronic properties of the isolated reactants. Predominance of one regioisomer over the other can be quantified by softness matching index *Δ*.[27]

$$\Delta_{ij}^{kl} = (s_i^- - s_k^+)^2 + (s_j^- - s_l^+)^2 \quad (6)$$

where atoms i and j of the nucleophile interact with atoms k and l of the electrophile to give rise to the preferred regioisomer; s_i^-, s_k^+, s_j^-, and s_l^+ are the respective local softnesses of the reactive sites and they calculated as:

$$s_k^{\pm} = f_k^{\pm} S \quad (7)$$

where *S* is the global softness and computed as [28]

$$S = \frac{1}{2\eta} \quad (8)$$

The reaction pathway involving a lower value of Δ_{ij}^{kl} will be the favored one. For 1,3-DC of azomethine ylide **7** and nitrostyrene **4a**, Δ_{ij}^{kl} for the generation of **5a** is smaller compared to that for **6a** (0.102 vs. 0.122). This suggests a preference for the generation of **5** along the cycloaddition reaction and hence agrees well with the regioselectivity experimentally observed. The B3LYP results are in agreement with M06-2X (0.117 vs. 0.130 for regioisomer **5a** compared with **6a**).

Conclusions

In summary, we have developed an efficient and simple method to regioselective synthesis of novel spiropyrrolothiazoles with quinoxalines motifs via a one pot four-component 1,3-DC of an azomethine ylide with trans-*β*-nitrostyrene derivatives. The pure products were isolated by recrystallization without requiring a further purification step. Mechanism and the regiochemistry of the reaction have been studied in terms of global and local reactivity indices, FMO analysis and characterization of relevant transition states at the B3LYP, wB97xD and M06-2X level of theories. The calculated global and local reactivity indices, FMO analysis and HSAB results at wB97xD and M06-2X are in line with the B3LYP's one. Although, popular B3LYP functional failed to predict the observed regioselectivity from the calculated energy paths of possible channels, wB97xD and M06-2X functionals were applied successfully. So, one can conclude that application of DFT dispersion corrected methods is essential in examining the regioselectivities of reactions by energies of transition states.

Table 3. Local properties of dipolarophile **4a** and azomethine ylide **7** at M06-2X/6-31G(d,p) and B3LYP/6-31G(d,p) given in parenthesis.

Reactant	Site	HOMO coefficients	LUMO coefficients	f_k^-	f_k^+	s^+	s^-	ω_k
nitrostyrene **4a**	C1	0.2909 (0.3090)	0.2208 (0.1994)	0.112 (0.100)	0.002 (0.042)	0.0041 (0.1325)	0.2272 (0.3180)	0.01 (0.11)
	C2	0.1458 (0.1475)	0.2904 (0.2971)	0.004 (0.013)	0.079 (0.070)	0.1602 (0.2235)	0.0081 (0.0437)	0.14 (0.18)
Azomethine ylide **7**	C3	0.3434 (0.3415)	0.0263 (0.0543)	0.123 (0.102)	0.015 (0.013)	0.0409 (0.0600)	0.3361 (0.4563)	0.016 (0.02)
	C5	0.2883 (0.3092)	0.2325 (0.3011)	0.099 (0.086)	0.042 (0.075)	0.1148 (0.3375)	0.2705 (0.3848)	0.046 (0.13)

Experimental

General procedure for preparation of spiropyrrothiazole 5(a–n)

A mixture of ninhydrin **1** (0.178 g, 1 mmol), 1,2-phenylenediamine **2** (0.108 g, 1 mmol), thiazolidin-4-carboxycilic acid **3** (0.133 g, 1 mmol) and trans-β-nitrostyrene **4a** (0.149 g, 1 mmol) was heated under reflux for about 5 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitated solid was washed with 3 mL cold ethanol (70%) to afford pure product **5a-n**.

General information and apparatus

Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) with CDCl3 as solvent. IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried with a Perkin-Elmer 2400II CHNS/O Elemental Analyzer.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI:

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An experimental and theoretical study on the regioselective synthesis of a new class of spiropyrrolothiazoles with quinoxalines motifs via 1,3-dipolar cycloaddition reaction. An evaluation of DFT methods

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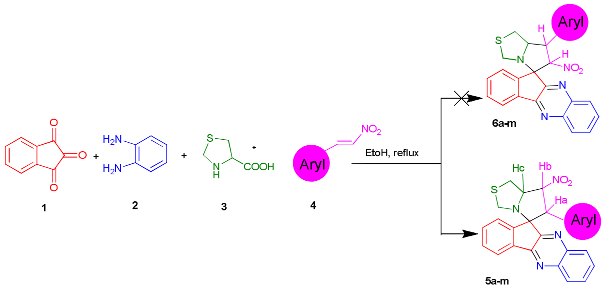

Evaluation of B3LYP/6-31G(d,p), wB97xD/6-31G(d,p) and M06-2X/6-31G(d,p) methods revealed the importance of π/π interactions in regio- and stereoselectivity of cycloaddition reactions.