Tetrahedron 67 (2011) 1589–1597

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An experimental and theoretical investigation of the regio- and stereoselectivity of the polar [3+2] cycloaddition of azomethine ylides to nitrostyrenes

Kamal Alimohammadi, Yaghoub Sarrafi *, Mahmood Tajbakhsh, Saeed Yeganegi, Mahshid Hamzehloueian

Department of Organic Chemistry, Faculty of Chemistry, Mazandaran University, Babolsar, Iran

ARTICLE INFO

Article history:
Received 16 September 2010
Received in revised form 23 November 2010
Accepted 13 December 2010
Available online 17 December 2010

Keywords:
1,3-Dipolar cycloaddition
Azomethine ylide
DFT calculations
Spiro compounds
Pyrrolizine

ABSTRACT

The regio- and stereochemical polar [3+2] cycloaddition of the azomethine ylides, which were generated in situ by the reaction of isatin derivatives and proline, with *trans*-β-nitrostyrene and (*E*)-1-phenyl-2-nitropropene were studied using experimental and theoretical methods. In comparison with *trans*-β-nitrostyrene, when the reactions were performed with (*E*)-1-phenyl-2-nitropropene, a remarkable inversion in the regioselectively was observed. The regioselectivity of the reactions was investigated using global and local reactivity indices and frontier molecular orbital (FMO) analysis at the B3LYP/6-31G(d,p) level of theory. The effects of the electronic and steric factors on the regioselectivity of the reactions were discussed. The inspection of geometries and energetics of transition states revealed the importance of weak interactions in regioselectivity of the cycloaddition reactions.

1. Introduction

1,3-Dipolar cycloaddition of azomethine ylides to electron-deficient alkenes is one of the most efficient and expedient synthetic protocols for the construction of highly substituted pyrrolidine and pyrrolizine rings.[1] The synthesis of pyrrolidine-based heterocycles has been the center of attraction for the past several decades because it constitutes an important class of substances with highly pronounced biological activities.[2] Nitropyrrolidines are the effective precursors for the synthesis of cephalotaxus alkaloids and potentially useful as sources of conformationally restricted analogues of dopamine.[3] In addition, oxindoles derivatives, in particular 3-spirooxindoles, are the central skeleton of numerous alkaloids and are elegant targets in organic synthesis due to their significant biological activities.[4]

In the past decades, in addition to the selectivity behavior, the understanding of the underlying principles in the polar [3+2] cycloaddition reactions has grown from a fruitful interplay between theory and experiment and continues to present as a real challenge.[5] The steric and electronic effects are two major factors can influence the selectivity of these reactions.[6] Their regio- and stereochemistry may be controlled either by choosing the appropriate dipole and dipolarophile or by controlling the reaction using a catalyst.[7] Herein we report the synthesis of nitropyrrolizines with spirooxindole moieties and theoretical investigation of all possible regio- and stereocycloaddition channels using global and local reactivity indices, frontier molecular orbital (FMO) analysis, and corresponding transition states calculations at the B3LYP/6-31G (d,p) level of theory.

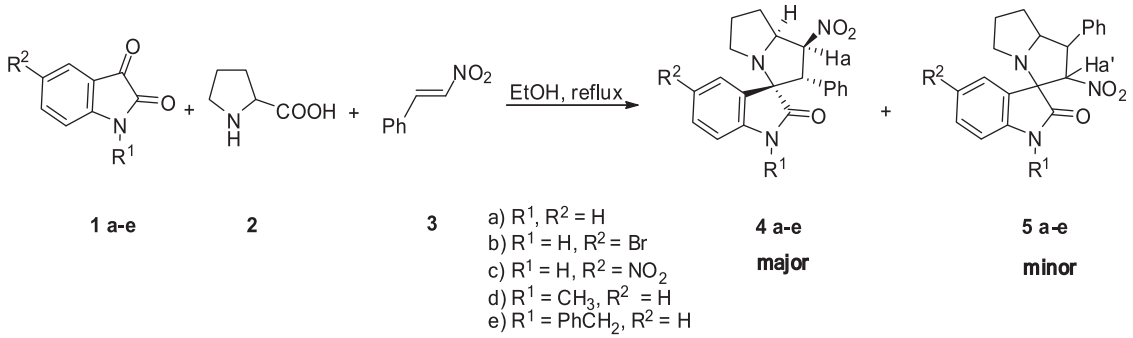
2. Results and discussion

1,3-Dipolar cycloaddition of azomethine ylides, which were generated in situ by the reaction of isatin derivatives **1a**–**e** and proline **2** in ethanol at reflux, with *trans*-β-nitrostyrene **3** afforded a mixture of the spirooxindolo nitropyrrolizines **4a**–**e** and **5a**–**e** in good to excellent yields (Scheme 1). The molar ratio of regioisomers was determined by ^{1}H NMR spectroscopy. The reaction was found to be relative regioselective and highly stereochemistry at the spiro centre. It is noted that regioisomers **4a**–**e** were obtained as major products in all cases (Table 1). Among isatin derivatives, *N*-methylisatin **1d** gave the cycloadduct **4d** as the sole product in 92% yield (Table 1, entry 4). While compounds **4a** and its regioisomer **5a** were separated by column chromatography, compounds **4b**, **4c**, **4e** and their corresponding regioisomers could not be separated due to their similar R_f values in different organic solvents. However, the pure regioisomers of **4a**–**e** were obtained by recrystallizing the crude reaction mixture from ethanol at room temperature.

The structures and the regiochemistry of the cycloadducts were confirmed by spectroscopic data. The ^{13}C NMR spectrum of **4d**, showed two peaks at δ 175.8 and 74.9 ppm for an oxindole carbonyl

* Corresponding author. Tel./fax: +98 1125342350; e-mail address: ysarrafi@umz.ac.ir (Y. Sarrafi).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.12.034



Scheme 1. Regioselective synthesis of spirooxindolo nitropyrrolizines **4a**–**e** and **5a**–**e**.

Table 1
1,3-Dipolar cycloaddition reaction of isatin derivatives **1a**–**e** and proline **2** with *trans*-β-nitrostyrene **3**

Entry	Reactants	Products	Yield[a] (%)	Regioisomer ratio[b] (**4**:**5**)
1	**1a**+**2**+**3**	**4a**+**5a**	87	88:12
2	**1b**+**2**+**3**	**4b**+**5b**	81	87:13
3	**1c**+**2**+**3**	**4c**+**5c**	83	60:40
4	**1d**+**2**+**3**	**4d**	92	100:0
5	**1e**+**2**+**3**	**4e**+**5e**	88	90:10

[a] Combined yield of isolated cycloadducts.
[b] Determined by ^{1}H NMR spectroscopy (Ha/Ha′).

group and the spiro carbon, respectively. In the ^{1}H NMR spectrum of the cycloadduct **4d**, a doublet at δ 4.49 ppm (J=10.5 Hz) corresponding to the benzylic proton consistent with the trans disposition with the $CHNO_2$ proton. A triplet and not a doublet at δ 6.30 ppm, attributed to the $CHNO_2$ proton, showing that the correct regiochemistry of the product **4d** is as shown in Scheme 1.

The stereochemical outcome of the cycloaddition was determined by a single X-ray crystal structure of 5-nitroisatin cycloadduct **4c** (Fig. 1).[8] The stereochemistry of cycloadducts is consistent with a *S*-shaped ylide and subsequent cycloaddition by an *endo*-transition state (pathway B, Scheme 2). However, the cycloadduct corresponding to *exo*-TS was not observed.

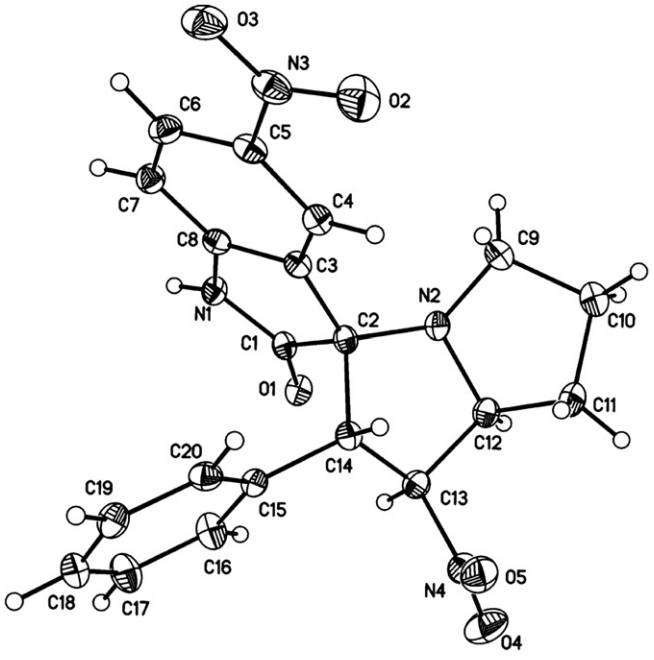


Fig. 1. ORTEP diagram of **4c**.

The ORTEP diagram of **4c** represents that, the *trans*-geometry of nitrostyrene is preserved in the product and also shows the relative configurations at all four chiral centers. However, to examine the issue of whether the reaction is concerted or proceeds via a stepwise diradical transition state, when benzoquinone as a radical scavenger was added to the reaction mixture under reaction conditions, the rate of reaction did not decrease. This is an anticipated result on the basis of a concerted cycloaddition reaction.

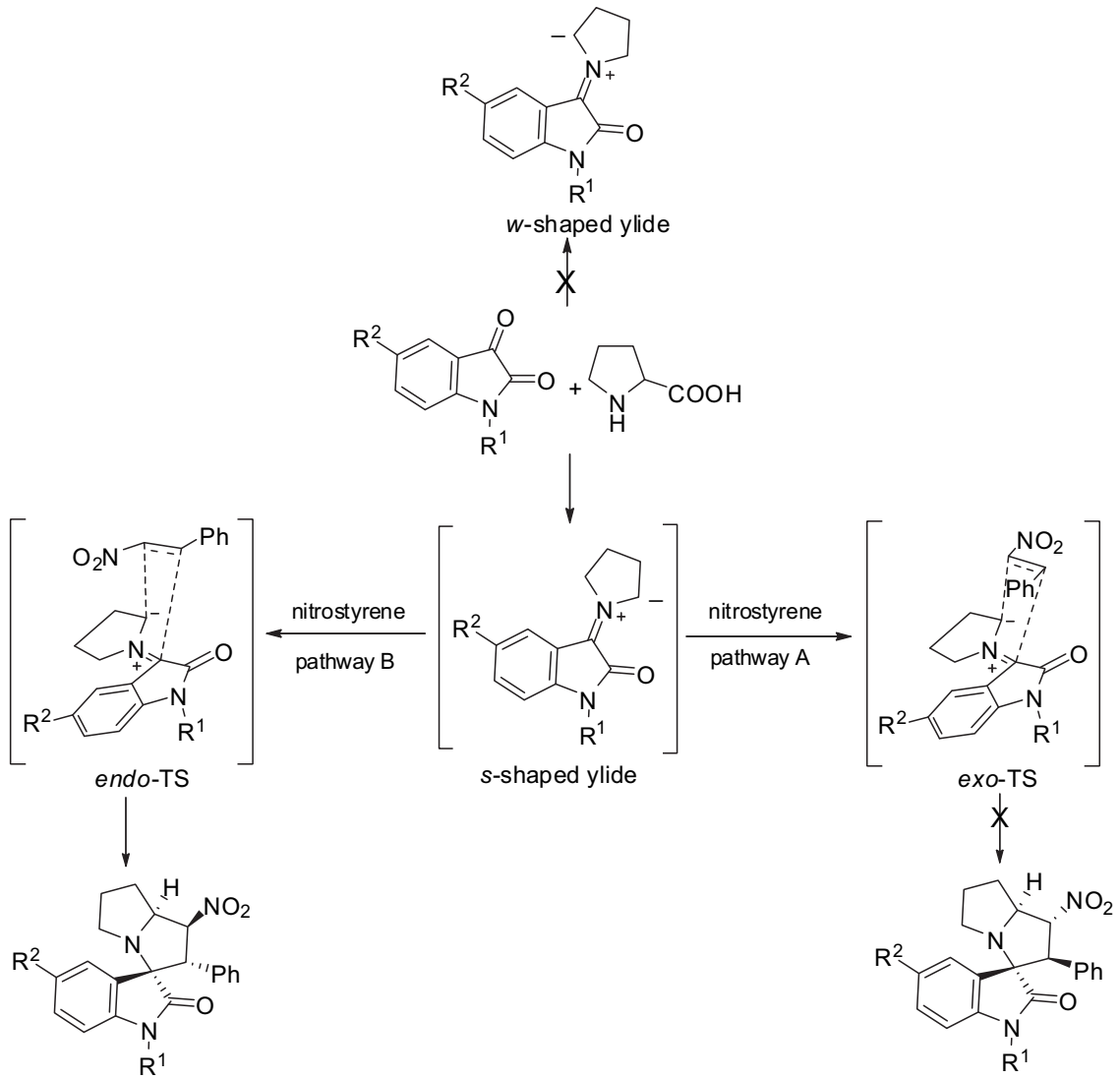
Similarly, the reaction of (*E*)-1-phenyl-2-nitropropene **6**, as a substituted precursor with an electron-donor group, with the azomethine ylide generated from **1a**–**e** and **2** afforded a mixture of the spirooxindolo nitropyrrolizines **7a**–**e** and **8a**–**e** in good yields (Scheme 3). The structures and the regiochemistry of the cycloadducts were confirmed by spectral analysis. Interestingly, the regioisomers **8a**–**d** were the main obtained products that their regiochemistry is in contrast to the major products **4a**–**d**. In compounds **4a**–**e** the carbon atom bearing the nitro group is bonded to the pyrrolidine ring, whereas in products **8a**–**e** it is bonded to the oxindole ring.

The ^{1}H NMR spectrum of **8a**–**e** exhibited a doublet for the benzylic proton, while it was observed as a singlet for the **7a**–**e**. The structure of **8a** was unequivocally established by X-ray single crystal analysis,[9] which further confirmed the stereochemistry (Fig. 2).

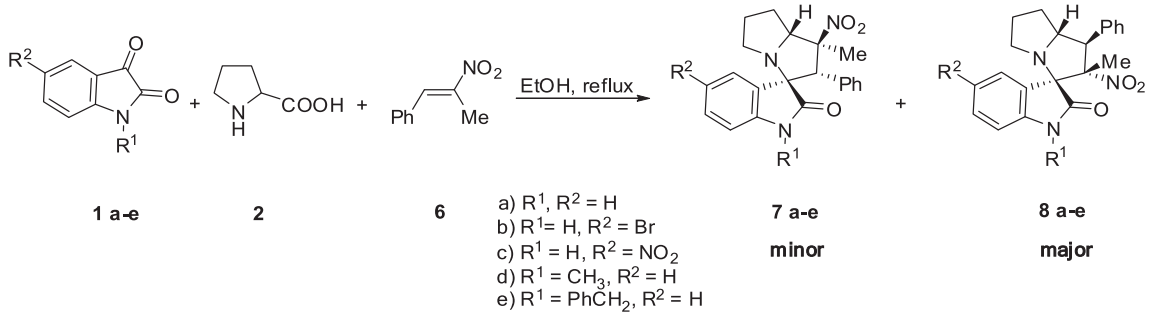
Notably, when **1e** and proline was treated with **6**, a sharp decrease in the regioselectivity was observed, and a 46:36:18 mixture of **8e**, *exo*-**7e** and *endo*-**7e** was obtained, respectively (Table 2, entry 5). The mixture of regio- and stereoisomers were separated and purified by column chromatography. The geometries of *exo*- and *endo*-isomers of **7e** were determined based on ^{1}H NMR chemical shift. A singlet at δ 5.30 ppm, attributed to the benzylic proton of *exo*-**7e**, appeared at lower field compared to *endo*-**7e** (δ 4.92 ppm) due to a deshielding effect of the carbonyl group of the oxindole ring.

3. Computational details

All calculations were performed using the Gaussian03[10] suit of programs. The full geometrical optimization of all structures and transition states (TSs) were carried out with Density Functional Theory (DFT) using non local B3LYP hybrid functional and 6-31G (d,p) basis set. No symmetrical restriction was applied during geometrical optimizations. The stability of the DFT wave functions for selected equilibrium geometries was tested using the keyword STABLE in Gaussian03. The nature of stationary geometries has been characterized by calculating the frequencies in order to verify that the transition states have one and only one imaginary frequency. Also, harmonic frequencies, zero-point energies and thermodynamic corrections were obtained using analytical force constants. Thermal corrections to enthalpy and entropy values were evaluated at 298.15 K.



Scheme 2. Proposed mechanism for the cycloaddition of the azomethine ylides with nitrostyrene.



Scheme 3. Regioselective synthesis of spirooxindolo nitropyrrolizines **7a**–**e** and **8a**–**e**.

4. FMO, global, and local electrophilicity/nucleophilicity analysis

Frontier Molecular Orbital (FMO) is one of the best methods to analyze reactions, which was mainly developed by Fukui.[11] Sustman[12] classified 1,3-dipolar cycloaddition reactions into three types on the basis of the relative FMO energies between the dipole and the dipolarophile. Group **I** includes the processes controlled by the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction (normal electron demand reactions), while group **III** is characterized by the $HOMO_{dipolarophile}$–$LUMO_{dipole}$ predominant interaction (inverse electron demand reactions), and the intermediate group **II** collects the reactions with significant involvement of both types of the HOMO–LUMO interactions. The HOMO–LUMO energy gap for the corresponding cases generally determines which interaction is the most important. The lower energy difference leads to the greater orbital interaction. In most cases, group **I** is dominating. However, this changes as the

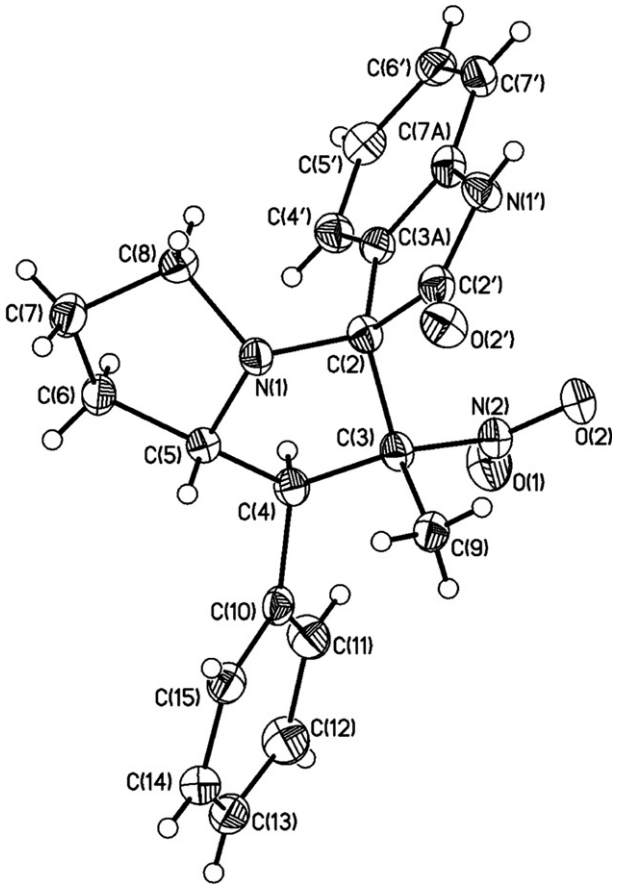


Fig. 2. ORTEP diagram of **8a**.

electron donating ability of the 1,3-dipole decreases or the donating ability of the dipolarophile increases.[1d,13]

The regio- and stereoselectivities of the reactions of azomethine ylide **9** with *trans*-β-nitrostyrene **3** and (*E*)-1-phenyl-2-nitropropene **6** as reactions **1** and **2** were investigated by theoretical methods (Scheme 4). The calculated HOMO and LUMO energies are presented in Table S2 in Supplementary data.

In this study, the HOMO–LUMO energy gaps suggest that the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction controls the cycloaddition

Table 2
1,3-Dipolar cycloaddition reaction of isatin derivatives **1a**–**e** and proline **2** with (*e*)-1-phenyl-2-nitropropene **6**

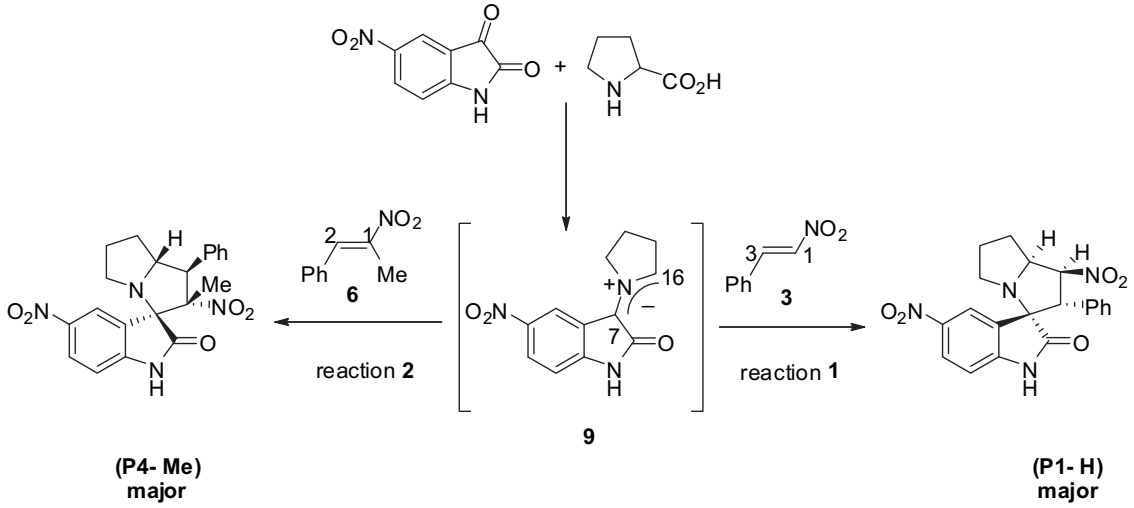
Entry	Reactants	Products	Yield[a] (%)	Regioisomer ratio[b] (**8**:**7**)
1	**1a**+**2**+**6**	**7a**+**8a**	86	88:12
2	**1b**+**2**+**6**	**7b**+**8b**	78	86:14
3	**1c**+**2**+**6**	**8c**	84	100:0
4	**1d**+**2**+**6**	**7d**+**8d**	88	84:16
5	**1e**+**2**+**6**	**7e**+**8e**	82	46:54[c]

[a] Combined yield of isolated cycloadducts.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Combined yield of the *exo*- and *endo*-**7e**.

reaction (normal electron demand reactions). To better visualize the FMO approach, the two possible interactions $HOMO_{dipolarophile}$–$LUMO_{dipole}$ and $HOMO_{dipole}$–$LUMO_{dipolarophile}$ for each reaction are shown in Fig. 3. Global properties of dipole **9** and dipolarophiles **3** and **6** and MO coefficients at the reactive sites for the reactants are shown in Tables S2 and S3 in Supplementary data, respectively.

As shown in, Fig. 3 for the dipolarophile **3** the LUMO coefficient of C3 is 0.297 and that of C1 is −0.199 and the HOMO coefficients of dipole **9** on the reactive sites C7 and C16 are 0.338 and −0.282, respectively. Therefore, the important orbital overlap should be between C3 and C7. The analysis of the regioselectivity of the reaction **2** by FMO theory shows that the most favored large–large interaction takes place between C2 of the alkene **6** and C7 of azomethine ylide **9** (Fig. 3). While for the reaction **1** DFT calculations predict the regioselectivity experimentally observed, for the reaction **2** it fails.

Recent studies have shown that the defined global and local indices in the context of density functional theory are powerful tools to understand the behavior of 1,3-DC reactions.[14] The charge transfer ability of a molecule in its ground state approximated by Koopmans' theorem[15] can be described by the electronic chemical potential, which is defined as the arithmetic mean of one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L as $\mu=(\varepsilon_H+\varepsilon_L)/2$. The chemical hardness η, which is a measure of the stability of a system, may be approached in terms of ε_H and ε_L as $\eta=\varepsilon_L-\varepsilon_H$.[14] The global electrophilicity index ω, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, was given the following simple expression, $\omega=(\mu^2/2\eta)$,[15] in terms of the electronic chemical potential and the chemical hardness. The calculated global properties μ, η, and ω are shown in Table S2 in Supplementary data. The electronic chemical potential, μ, of the dipole **9** is higher than the dipolarophile **3** also the electrophilicity of dipolarophiles is greater than that of the dipole, therefore the charge transfer takes place from the dipole to the dipolarophile.



Scheme 4. The regioselectivity channels for 1,3-DC of azomethine ylide **9** and *trans*-β-nitrostyrene **3** and (*E*)-1-phenyl-2-nitropropene **6**.

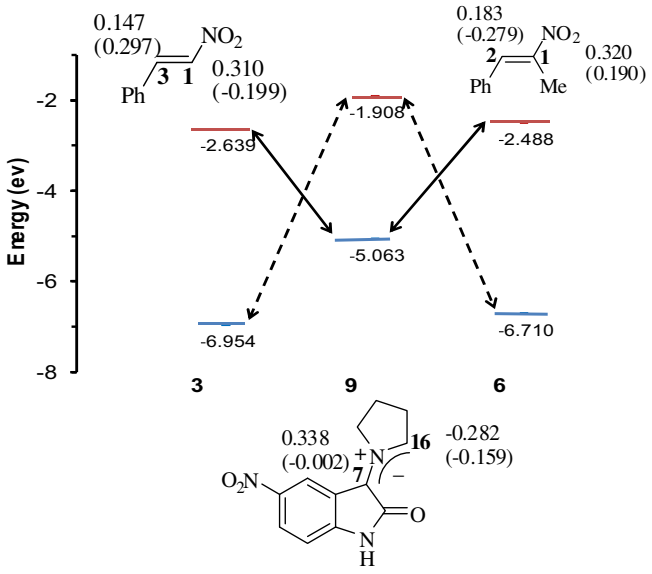


Fig. 3. Calculated FMO energies (eV) and HOMO and LUMO Coefficients at the reactive sites for the reactants obtained at B3LYP/6-31G(d,p).The LUMO Coefficients are given in parenthesis.

We used the DFT-based reactivity descriptors, such as Fukui functions and local electrophilicity indices for the interpretation of regioselectivity. These concepts have been found to be very useful for explaining regiochemistry in addition reactions.[16c–g] The local electrophilicity index, ω_k, can be measured by $\omega_k=\omega f_k^+$ in which f_k^+ is the Fukui function for a nucleophilic attack.[16] This expression shows that wherever f_k^+ has its maximum value, i.e., at the active site of the electrophile. For these polar cycloadditions the most favorable regioisomeric pathway corresponds to the bond-formation at the most electrophilic and nucleophilic sites of unsymmetrical reactants. The regioselectivity of these cycloaddition reactions can be explained using the local electrophilicity index ω_k, at the more electrophile reactant together with the nucleophilic Fukui functions, f_k^-, at the less electrophilic one.

The calculated local properties of dipole **9** and dipolarophiles **3** and **6** are summarized in Table 3. For the dipole **9**, C7 has a larger f_k^- value than C16, i.e., 0.109 and 0.088, respectively. The C3 site of dipolarophile **3** (the β-position) presents a larger local electrophilicity value than C1 site. Therefore, C3 will be the preferred position for a nucleophilic attack by C7 of the dipole **9**, which is in good agreement with the experimental observation.

It was found that the substitution pattern has a strong influence on the reaction profiles.[17] In comparison with **3**, **6** possess an electron releasing methyl group on C1 position that decreases the electrophilicity at C1 and C2 sites. As expected, the decrease of the electrophilicity at C1 is greater than C2. As indicated in Table 3, the C2 site represents a higher local electrophilicity value than C1. Therefore, C2 in **6** will be the preferred position for a nucleophilic attack by C7 of the dipole **9**. In contrast with the reaction **1** local electrophilicity failed to correctly predict the experimentally observed major product of the reaction **2**.

Table 3
Local properties of dipole **9** and dipolarophiles **3** and **6**

Reactant	Site	f_k^+	f_k^-	ω_k(eV)
3	C1	0.042	0.101	0.112
3	C3	0.071	0.013	0.189
9	C7	0.014	0.109	0.027
9	C16	0.085	0.088	0.164
6	C1	0.027	0.087	0.069
6	C2	0.072	0.022	0.185

5. Energies of transition structures

Although the FMO theory, which is based on electronic factors without consideration of steric factors, provides a good basis for understanding the regioselectivity of 1,3-DC reactions, in many cases steric factors control the regiochemistry of the reaction.[5] The regiochemistry of the reactions **1** and **2** can be explained by assuming both of electronic and steric factors.

Previous studies on related cycloadditions have predicted concerted transition structures.[18] Therefore, four possible transition structures for the reaction **1**, TS-1-H, TS-2-H, TS-3-H, and TS-4-H and for the reaction **2**, TS-1-Me, TS-2-Me, TS-3-Me, and TS-4-Me, and their corresponding cycloadducts have been optimized and characterized. The optimized geometries of *endo*-transition states in each cases TS-1-H, TS-4-H, TS-1-Me, and TS-4-Me are shown in Fig. 4 and related *exo* transition states TS-2-H, TS-3-H, TS-2-Me, and TS-3-Me are represented in Supplementary data. The activation energies, enthalpies, and Gibbs free energies as well as the reaction energies, enthalpies, and Gibbs free energies are reported in Table 4.

In the gas phase, the activation barriers associated with the reaction **1** are: 8.79 (Ts-1-H), 14.15 (Ts-2-H), 13.36 (Ts-3-H), and 7.76 kcal/mol (Ts-4-H). Substitution of the hydrogen atom by a methyl group on the nitrostyrene increases the activation energies of the cycloaddition reaction. The activation energies orders found for the transition structures in the reactions **1** and **2** are Ts-4-H<Ts-1-H<Ts-3-H<Ts-2-H, and Ts-4-Me<Ts-1-Me<Ts-3-Me<Ts-2-Me, respectively. The calculated activation barriers show that the energy of Ts-4-H is 1.03 kcal/mol lower than that of TS-1-H, favoring the formation of the P4-H regioisomer, and for the reaction between **6** and **9**, TS-4-Me is 4.09 kcal/mol lower than TS-1-Me, favoring the formation of the P4-Me regioisomer (Table 4). The B3LYP/6-31G(d,p) calculations for the reaction **2** successfully predict the experimentally observed regioselectivity, but it fails for the reaction **1**. Furthermore, previous theoretical studies on 1,3-DC reactions have pointed out that the predicted regioselectivity of this type of cycloadditions is strongly dependent on the computational level used.[19] It is well known that the DFT methods are unable to estimate the stabilization gained by weak interaction between aromatic rings.[20] However, realization of this interaction by ab initio methods requires a computationally demanding method, such as CCSD (T) (coupled cluster) with a very large basis set near saturation. Recently Tsuzuki et al. have studied the interaction energy between benzene dimer models at CCSD(T) with a very large basis set.[21] They found that the interaction energies of parallel, T-shaped, and slipped-parallel models are −1.48, −2.46, and −2.48 kcal/mol, respectively.

The energy of TSs with suitable geometry can be affected by π/π interaction. The optimized geometries of Ts-1-H, Ts-2-H, Ts-1-Me, and Ts-2-Me show that the two phenyl rings are in slipped-parallel configuration. Therefore, they can be stabilized by π/π interaction about −2.48 kcal/mol. Assuming the stabilization gained by π/π interaction makes the energy of Ts-1-H lower than that of Ts-4-H, in agreement with the experimentally observed major regioisomer (P1-H). However, this correction has no effect on the energy order of Ts-4-Me and Ts-1-Me.

In order to assess the aromaticity of the optimized TSs, the Nucleus-independent chemical shifts (NICS)[22] was computed using gauge invariant atomic orbital (GIAO)[23] approach at the B3LYP/6-31G(d,p). The calculated NICS values present in Table 5. 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. Therefore, it can be concluded that transition states associated with 1,3-dipolar reactions between azomethine ylides and nitroalkenes exhibit in-plane aromaticity and undergoing a concerted mechanism.

In conclusion, the regioselective polar [3+2] cycloaddition reactions of the azomethine ylides with *trans*-β-nitrostyrene and

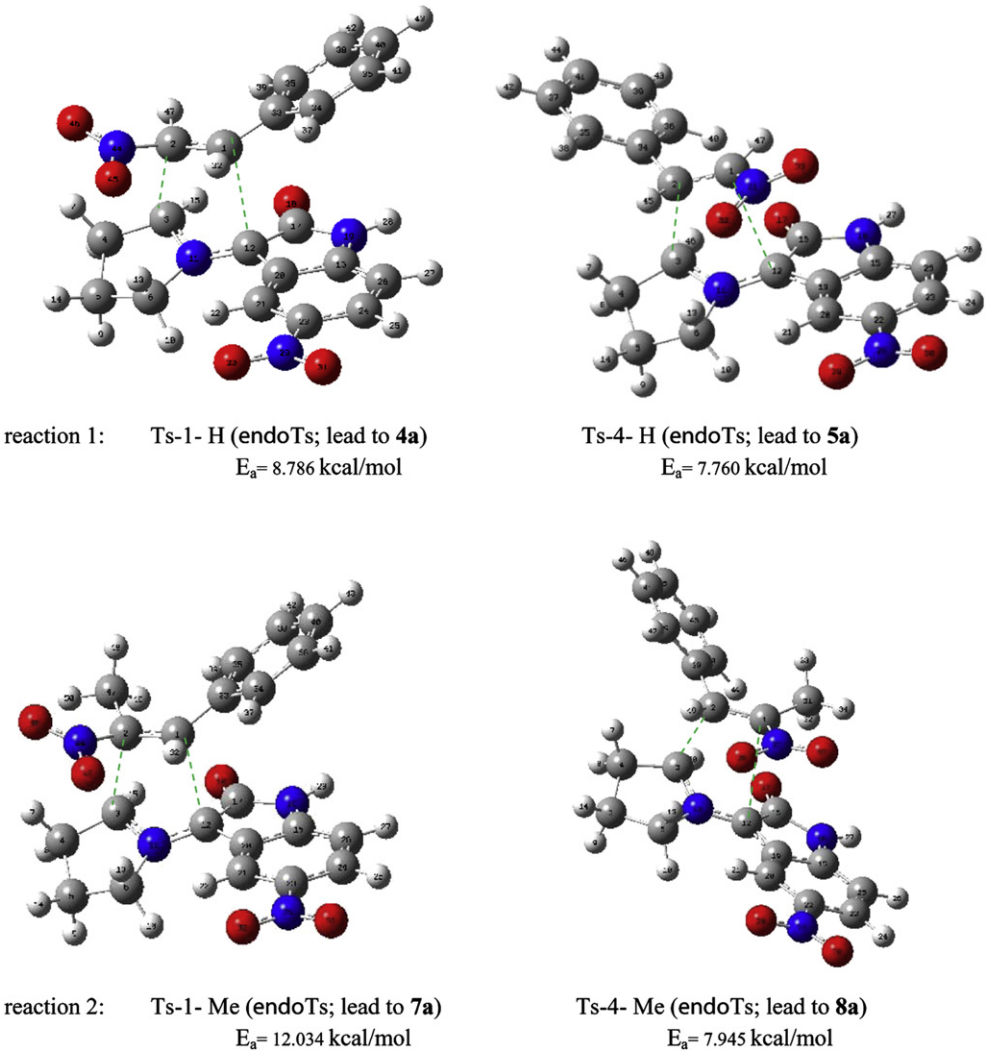


Fig. 4. Selected optimized transition structures at the B3LYP/6-31G(d,p) corresponding to the regiosomeric path of the 1,3-DC reactions **1** and **2**.

Table 4
Calculated electronic activation energies E_a, reaction Gibbs free energies ΔG, reaction enthalpies ΔH, reaction energies ΔE_{rxn}, activation Gibbs free energies $\Delta G^{\#}$, activation enthalpies $\Delta H^{\#}$, and reaction entropies ΔS (cal/molK) at the B3LYP/6-31G(d,p), all energies are in kcal/mol

Product	E_a	ΔG	ΔH	ΔE_{rxn}	$\Delta G^{\#}$	$\Delta H^{\#}$	ΔS
P1(TS-1)-H	8.786	−2.208	−17.045	−16.429	22.936	8.353	−43.768
P2(TS-2)-H	14.151	−0.902	−15.412	−14.814	26.113	12.152	−42.666
P3(TS-3)-H	13.360	−0.084	−15.247	−14.570	27.667	13.320	−44.858
P4(TS-4)-H	7.760	−2.870	−17.425	−16.871	22.716	7.324	−42.815
P1(TS-1)-Me	12.034	−0.070	−14.136	−14.026	25.825	12.161	−45.828
P2(TS-2)-Me	38.504	3.360	−10.786	−10.656	51.984	38.827	−44.129
P3(TS-3)-Me	15.757	4.552	−10.034	−9.753	29.004	16.041	−48.943
P4(TS-4)-Me	7.945	1.793	−12.710	−12.828	22.274	8.044	−48.643

Table 5
Nucleus-independent chemical shifts (NICS, ppm/mol)

Ts	NICS	Product	NICS
TS-1-H	−14.38	p-1-H	−4.60
TS-2-H	−13.96	p-2-H	−4.61
TS-3-H	−14.30	p-3-H	−8.68
TS-4-H	−15.67	p-4-H	−5.03
TS-1-Me	−14.49	p-1-Me	−4.87
TS-2-Me	−13.40	p-2-Me	−4.15
TS-3-Me	−12.87	p-3-Me	−4.41
TS-4-Me	−14.71	p-4-Me	−4.28

(*E*)-1-phenyl-2-nitropropene were carried out. Experimental results have shown that the regiochemistry in these reactions is sensitive to the substituent on the double bond of nitrostyrene. In comparison with *trans*-β-nitrostyrene, when the reactions were performed with (*E*)-1-phenyl-2-nitropropene, a remarkable inversion in the regioselectively was observed.

Mechanism and the regiochemistry of two reactions have studied in terms of global and local reactivity indices, FMO analysis and characterization of relevant transition states at the B3LYP/6-31G(d,p) level of theory. Inspection of theoretical results indicated that in the case of the reaction **1**, the electronic factors control the regiochemistry of the reaction and results of FMO analysis agree with experimentally favored product. While for the reaction **2** FMO analysis failed to predict the major product, analysis of transition states energies successfully explains the experimental results.

6. Experimental section

6.1. General procedure for preparation of spirooxindolo nitropyrrolizines 4a–e and 5a,b

A mixture of isatin (0.147 g, 1 mmol), proline (0.115 g, 1 mmol), and *trans*-β-nitrostyrene (0.149 g, 1 mmol) in ethanol (10 mL) was stirred at reflux for 1–2 h. After completion of the reaction, as indicated by TLC, to the solution was added water (25 mL), and the

precipitated solid was separated by filtration to afford the corresponding regioisomers of **4a**–**e** and **5a**–**e**. The molar ratio of **4a**–**e**/**5a**–**e** was determined by ^{1}H NMR spectroscopy. The pure cycloadducts **4a**–**e** were obtained by recrystallization from ethanol and the product **5a** was purified on a silica-gel plate (eluent dichloromethane/ethyl acetate 12:8). Notably, the products **4b** and **5b** could be separated by recrystallizing the crude reaction mixture in ethanol owing to their different crystalline shape.

*6.1.1. 1′-Nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**4a**).* Colorless solid (0.27 g, 77%), mp: 195–197 °C (Ref. Mp: 208–210 °C);[1f] IR (KBr, cm^{-1}) ν=3198, 1710, 1547, 1347; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.09 (s, 1H, NH), 7.59 (d, 1H, J=7.4 Hz, Ar–H), 7.27 (d, 1H, J=6 Hz, Ar–H), 7.11 (m, 6H, Ar–H), 6.71 (d, 1H, J=7.7 Hz, Ar–H), 6.32 (t, 1H, J=9.8 Hz, $CHNO_2$), 4.87 (q, 1H, J=8.2 Hz, N–CH), 4.53 (d, 1H, J=10.4 Hz, benzylic), 3.29 (m, 1H, pyrrolizine), 2.90 (t, 1H, J=7.2 Hz, pyrrolizine), 1.48–2.21 (m, 4H, pyrrolizine); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.9, 141.9, 132.4, 130.1, 128.6, 128.2, 128.0, 126.2, 125.1, 122.5, 110.4, 91.6, 75.2, 64.2, 53.2, 51.1, 27.8, 25.6. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.58; H, 5.39; N, 11.94.

*6.1.2. 5-Bromo-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**4b**).* Brown solid (0.30 g, 70%), mp: 201–202 °C; IR (KBr, cm^{-1}) ν=3244, 1726, 1548, 1373; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.22 (s, 1H, NH), 7.71 (s, 1H, Ar–H), 7.39 (d, 1H, J=7.8 Hz, Ar–H), 7.14 (m, 5H, Ar–H), 6.62 (d, 1H, J=8.1 Hz, Ar–H), 6.26 (t, 1H, J=9.8 Hz, $CHNO_2$), 4.87 (m, 1H, N–CH), 4.50 (d, 1H, J=10.1 Hz, benzylic), 1.51–3.23 (m, 6H, pyrrolizine); ^{13}C NMR (75 MHz, $CDCl_3$): δ=176.0, 141.0, 137.9, 133.1, 131.9, 129.0, 128.8, 128.2, 126.0, 115.0, 111.9, 91.3, 75.1, 64.2, 53.4, 51.1, 27.7, 25.6. Anal. Calcd for $C_{20}H_{18}BrN_3O_3$: C, 56.09; H, 4.24; N, 9.81. Found: C, 56.19; H, 4.15; N, 9.73.

*6.1.3. 1′,5-Dinitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**4c**).* Yellow solid (0.20 g, 50%), mp: 253–255 °C; IR (KBr, cm^{-1}) ν=3296, 1725, 1548, 1334; ^{1}H NMR (300 MHz, DMSO-d_6): δ=11.00 (s, 1H, NH), 8.95 (s, 1H, Ar–H), 8.17 (d, 1H, J=8.7 Hz, Ar–H), 7.17 (br s, 6H, Ar–H), 6.82 (d, 1H, J=8.6 Hz, Ar–H), 6.40 (t, 1H, J=10.1 Hz, $CHNO_2$), 4.85 (d, 1H, J=11 Hz, benzylic), 4.60 (q, 1H, J=8.1 Hz, N–CH), 3.43 (m, 1H, pyrrolizine), 2.62 (t, 1H, J=6 Hz, pyrrolizine), 1.44–2.01 (m, 4H, pyrrolizine); ^{13}C NMR (75 MHz, DMSO-d_6): δ=178.1, 149.9, 142.7, 133.3, 128.9, 128.6, 128.2, 127.6, 126.2, 123.8, 110.3, 90.3, 74.7, 63.7, 53.3, 51.0, 28.2, 25.6. Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 60.99; H, 4.71; N, 14.13.

*6.1.4. 1-Methyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**4d**).* Colorless solid (0.33 g, 92%), mp: 194–195 °C; IR (KBr, cm^{-1}) ν=1701, 1536, 1375; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.60 (d, 1H, J=7.4 Hz, Ar–H), 7.30 (m, 1H, Ar–H), 7.12 (m, 6H, Ar–H), 6.63 (d, 1H, J=7.8 Hz, Ar–H), 6.35 (t, 1H, J=9.9 Hz, $CHNO_2$), 4.95 (q, 1H, J=8.1 Hz, N–CH), 4.53 (d, 1H, J=10.5 Hz, benzylic), 3.30 (m, 1H, pyrrolizine), 2.95 (s, 3H, N–CH_3), 2.91 (m, 1H, pyrrolizine), 1.46–2.23 (m, 4H, pyrrolizine); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.8, 144.7, 132.4, 130.2, 128.4, 128.2, 127.9, 125.7, 124.5, 122.5, 108.6, 91.8, 74.9, 64.3, 53.2, 51.3, 27.8, 25.8, 25.6. Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.35; H, 5.89; N, 11.64.

*6.1.5. 1-Benzyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**4e**).* Cream solid (0.35 g, 79%), mp: 205–207 °C; IR (KBr, cm^{-1}) ν=1719, 1543, 1372; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.66 (d, 1H, J=7.4 Hz, Ar–H), 7.06–7.24 (m, 10H, Ar–H), 6.40–6.54 (m, 3H, Ar–H, 1H, $CHNO_2$), 5.12 (AB quartet, 1H, J=16.1 Hz, N–CH_AH$_B$), 4.99 (q, 1H, J=8.2 Hz, N–CH), 4.66 (d, 1H, J=10.3 Hz, benzylic), 4.31 (AB quartet, 1H, J=16.1 Hz, N–CH$_A$$H_B$), 3.36 (m, 1H, pyrrolizine), 2.95 (t, 1H, J=7.3 Hz, pyrrolizine), 1.53–2.27 (m, 4H, pyrrolizine); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.8, 143.9, 134.6, 132.4, 130.1, 128.7, 128.6, 128.4, 128.0, 127.2, 126.3, 125.9, 124.6, 122.5, 109.9, 91.5, 75.1, 64.4, 53.4, 51.2, 43.4, 27.8, 25.7. Anal. Calcd for $C_{27}H_{25}N_3O_3$: C, 73.78; H, 5.73; N, 9.56. Found: C, 73.84; H, 5.79; N, 9.51.

*6.1.6. 2′-Nitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5a**).* Colorless solid (0.04 g, 10%), mp: 189–191 °C; R_f (60% CH_2Cl_2/hexane) 0.38; IR (KBr, cm^{-1}) ν=3220, 1731, 1553, 1369; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.03 (s, 1H, NH), 7.48 (m, 2H, Ar–H), 7.40 (m, 2H, Ar–H), 7.33 (m, 3H, Ar–H), 7.11 (t, 1H, J=8.4 Hz, Ar–H), 6.94 (d, 1H, J=7.6 Hz, Ar–H), 5.78 (d, 1H, J=11.2 Hz, $CHNO_2$), 4.14 (dt, 1H, J=9.6, 6.4 Hz, N–CH), 3.97 (dd, 1H, J=10.8, 9.6 Hz, benzylic), 1.73–2.76 (m, 6H, pyrrolizine); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.3, 141.5, 138.6, 136.6, 130.8, 129.1, 128.0, 127.8, 126.1, 122.8, 110.9, 96.8, 73.4, 70.52, 53.5, 48.2, 31.3, 27.1. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.87; H, 5.55; N, 12.09.

*6.1.7. 5-Bromo-2′-nitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5b**).* Brown solid (0.04 g, 11%), mp: 194–196 °C; IR (KBr, cm^{-1}) ν=3244, 1726, 1548, 1373; ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.85 (s, 1H, NH), 7.75 (d, 1H, J=2.0 Hz, Ar–H), 7.56 (d, 2H, J=7.2 Hz, Ar–H), 7.51 (dd, 1H, J=6.4, 2.0 Hz, Ar–H), 7.39 (t, 2H, J=7.2 Hz, Ar–H), 7.30 (m, 1H, Ar–H), 6.86 (d, 1H, J=8.0 Hz, Ar–H), 5.78 (d, 1H, J=11.6 Hz, $CHNO_2$), 4.20 (dd, 1H, J=11.6, 9.6 Hz, benzylic), 3.70 (dt, 1H, J=9.6, 6.0 Hz, N–CH), 1.67–2.48 (m, 6H, pyrrolizine); ^{13}C NMR (100 MHz, DMSO-d_6): δ=177.5, 142.8, 137.5, 134.0, 129.2, 129.1, 128.1, 127.9, 125.5, 114.1, 112.8, 95.3, 73.1, 70.7, 51.5, 48.2, 30.1, 27.2. Anal. Calcd for $C_{20}H_{18}BrN_3O_3$: C, 56.09; H, 4.24; N, 9.81. Found: C, 56.01; H, 4.17; N, 9.76.

6.2. General procedure for preparation of spirooxindolo nitropyrrolizines 7a–e and 8a–e

A mixture of isatin (0.147 g, 1 mmol), proline (0.115 g, 1 mmol), and (*E*)-1-phenyl-2-nitropropene (0.163 g, 1 mmol) in ethanol (10 mL) was stirred at reflux for 1–2 h. After completion of the reaction, as indicated by TLC, to the solution was added water (25 mL), and the precipitated solid was separated by filtration, which contained mixture of two regioisomers **7a**–**e** and **8a**–**e**. The molar ratio of **8a**–**e**/**7a**–**e** was determined by ^{1}H NMR spectroscopy. However, the pure cycloadducts **8a**–**e** was obtained by recrystallization from ethanol and the products **7a**–**e** were purified on a silica-gel plate or column chromatography(eluent hexane/ethyl acetate 1:1).

*6.2.1. 1′-Methyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**7a**).* White solid (0.04 g, 10%), mp: 191–192 °C; R_f (50% ethyl acetate/hexane) 0.32; IR (KBr, cm^{-1}) ν=3241, 1719, 1543, 1345; ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.6 (s, 1H, NH), 7.59 (d, 1H, J=7.6 Hz, Ar–H), 7.11–7.23 (m, 6H, Ar–H), 6.97 (t, 3H, J=6.8 Hz, Ar–H), 5.24 (s, 1H, benzylic), 4.33 (dd, 1H, J=8.4, 5.6 Hz, N–CH), 1.83–3.30 (m, 4H, pyrrolizine), 1.75 (s, 3H, CH_3NO_2), 1.19–1.71 (m, 2H, pyrrolizine); ^{13}C NMR (100 MHz, DMSO-d_6): δ=178.5, 143.1, 131.0, 130.3, 130.1, 129.0, 128.6, 128.3, 126.0, 122.2, 110.2, 101.8, 73.9, 73.7, 59.1, 49.1, 27.6, 25.1, 23.8. Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.56; H, 5.75; N, 11.61.

*6.2.2. 5-Bromo-1′-methyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**7b**).* Cream solid (0.05 g, 11%), mp: 168–169 °C; R_f (50% ethyl acetate/hexane) 0.35; IR (KBr, cm^{-1}) ν=3214, 1719, 1554, 1361; ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.8 (s, 1H, NH), 7.84 (d, 1H, J=2 Hz, Ar–H), 7.38(dd, 1H, J=8.0, 2 Hz, Ar–H), 7.24 (m, 3H, Ar–H), 7.15 (m, 2H, Ar–H), 6.69 (d, 1H,

J=8.4 Hz, Ar–H), 5.22 (s, 1H, benzylic), 4.32 (dd, 1H, J=8.0, 6 Hz, N–CH), 1.67–3.32 (m, 4H), 1.74 (s, 3H, CH_3NO_2),1.23–1.70 (m, 2H, pyrrolizine); ^{13}C NMR (100 MHz, DMSO-d_6): δ=178.0, 142.4, 133.2, 133.1, 130.1, 129.1, 128.8, 128.4, 126.1, 114.0, 112.2, 101.3, 74.0, 73.7, 59.0, 48.9, 27.6, 25.1, 23.8. Anal. Calcd for $C_{21}H_{20}BrN_3O_3$: C, 57.02; H, 4.56; N, 9.50. Found: C, 56.91; H, 4.42; N, 9.58.

*6.2.3. 1,1′-Dimethyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**7d**).* Cream solid (0.05 g, 14%), mp: 168–170 °C; R_f (50% ethyl acetate/hexane) 0.40; IR (KBr, cm^{-1}) ν=1724, 1543, 1350; ^{1}H NMR (500 MHz, DMSO-d_6): δ=7.66 (d, 1H, J=7.5 Hz, Ar–H), 7.29 (t, 1H, J=7.7 Hz, Ar–H), 7.19 (m, 3H, Ar–H), 7.05 (m, 3H, Ar–H), 6.91 (d, 1H, J=7.8 Hz, Ar–H), 5.26 (s, 1H, benzylic), 4.36 (dd, 1H, J=8.0, 5.6 Hz, N–CH), 3.29 (m, 2H, pyrrolizine), 3.10 (s, 3H, N–CH_3), 1.84–2.19 (m, 2H, pyrrolizine), 1.76 (s, 3H CH_3NO_2), 1.23–1.74 (m, 2H, pyrrolizine); ^{13}C NMR (125 MHz, DMSO-d_6): δ=176.9, 144.8, 133.6, 130.8, 130.4, 129.5, 128.8, 126.3, 126.1, 123.4, 109.7, 102.2, 74.2, 74.0, 59.6, 49.7, 28.1, 26.7, 25.6, 24.2. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.14; H, 6.19; N, 11.22.

*6.2.4. 1-Benzyl-1′-methyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (exo-**7e**).* White solid (0.13 g, 30%), mp: 149–151 °C; R_f (25% ethyl acetate/hexane) 0.72; IR (KBr, cm^{-1}) ν=1715, 1534, 1358; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.69 (d, 1H, J=7.2 Hz, Ar–H), 7.02–7.33 (m, 12H, Ar–H), 6.84 (d, 1H, J=8.0 Hz, Ar–H), 5.3 (s, 1H, benzylic), 4.98 (AB quartet, 1H, J=15.6 Hz, N–CH_AH$_B$), 4.79 (AB quartet, 1H, J=15.6 Hz, N–CH$_A$$H_B$), 4.40 (dd, 1H, J=8.0, 6.0 Hz, N–CH), 1.87–3.28 (m, 4H, pyrrolizine), 1.82 (s, 3H, CH_3NO_2),1.24–1.77 (m, 2H, pyrrolizine); ^{13}C NMR (100 MHz, DMSO-d_6): δ=176.5, 143.6, 136.3, 133.0, 130.4, 129.1, 129.0, 128.4, 127.9, 127.8, 125.9, 123.1, 109.9, 101.5, 73.9, 73.8, 59.2, 49.1, 43.2, 27.7, 25.1, 23.9. Anal. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27. Found: C, 74.01; H, 5.89; N, 9.35.

*6.2.5. 1-Benzyl-1′-methyl-1′-nitro-2′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (endo-**7e**).* Cream solid (0.07 g, 15%), mp: 185–187 °C; R_f (25% ethyl acetate/hexane) 0.38; IR (KBr, cm^{-1}) ν=1709, 1539, 1347; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.60 (d, 1H, J=7.2 Hz, Ar–H), 7.03–7.27 (m, 12H, Ar–H), 6.64 (d, 1H, J=7.2 Hz, Ar–H), 4.92 (s, 1H, benzylic), 4.83 (AB quartet, 1H, J=15.6 Hz, N–CH_AH$_B$), 4.76 (AB quartet, 1H, J=15.6 Hz, N–CH$_A$$H_B$), 4.45 (dd, 1H, J=9.6, 6.0 Hz, N–CH), 2.03–2.63 (m, 4H, pyrrolizine), 1.98 (s, 3H, CH_3NO_2), 1.81–1.96 (m, 2H, pyrrolizine); ^{13}C NMR (100 MHz, DMSO-d_6): δ=176.5, 142.3, 136.2, 132.1, 131.0, 130.3, 129.6, 129.0, 128.7, 128.6, 127.8, 127.7, 124.2, 123.7, 109.6, 96.1, 76.3, 73.5, 65.3, 46.8, 43.4, 27.7, 27.6, 19.9. Anal. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27. Found: C, 74.09; H, 6.05; N, 9.24.

*6.2.6. 2′-Methyl-2′-nitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8a**).* White solid (0.27 g, 76%), mp: 196–198 °C; IR (KBr, cm^{-1}) ν=3246, 1732, 1547, 1352; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.54 (s, 1H, NH), 7.54 (d, 2H, J=7.6 Hz, Ar–H), 7.53 (d, 1H, J=7.6 Hz, Ar–H), 7.25–7.37 (m, 4H, Ar–H), 7.00 (t, 1H, J=7.6 Hz, Ar–H), 6.81 (d, 1H, J=7.7 Hz, Ar–H), 4.39 (d, 1H, J=10.2 Hz, benzylic), 4.18 (m, 1H, N–CH),1.74–2.50 (m, 5H, pyrrolizine), 1.74 (s, 3H, CH_3NO_2), 1.66 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=176.9, 143.5, 135.6, 131.5, 131.1, 129.0, 128.5, 127.4, 125.2, 122.2, 110.9, 102.3, 76.4, 67.5, 55.6, 47.9, 31.7, 28.3, 20.0. Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.54; H, 5.68; N, 11.64.

*6.2.7. 5-Bromo-2′-methyl-2′-nitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8b**).* Cream solid (0.30 g, 67%), mp: 177–179 °C; IR (KBr, cm^{-1}) ν=3193, 1729, 1543, 1345; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.71 (s, 1H, NH), 7.31–7.67 (m, 7H, Ar–H), 6.79 (d, 1H, J=6 Hz, Ar–H), 4.36 (d, 1H, J=8.5 Hz, benzylic), 4.18 (br s, 1H, N–CH), 2.40 (br s, 2H, pyrrolizine), 1.85 (br s, 2H, pyrrolizine), 1.72 (br s, 3H, CH_3NO_2, 2H, pyrrolizine); ^{13}C NMR (125 MHz, DMSO-d_6): δ=176.5, 142.8, 135.5, 134.1, 131.5, 129.6, 128.9, 128.5, 127.7, 114.2, 112.8, 102.6, 76.5, 67.4, 55.4, 48.0, 31.4, 28.3, 20.1. Anal. Calcd for $C_{21}H_{20}BrN_3O_3$: C, 57.02; H, 4.56; N, 9.50. Found: C, 57.21; H, 4.47; N, 9.41.

*6.2.8. 2′-Methyl-2′,5-dinitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8c**).* Yellow solid (0.34 g, 84%), mp: 186–188 °C; IR (KBr, cm^{-1}) ν=3191, 1737, 1541, 1338; ^{1}H NMR (500 MHz, DMSO-d_6): δ=11.37 (s, 1H, NH), 8.26 (dd, 1H, J=9.0, 2.0 Hz, Ar–H), 8.20 (d, 1H, J=1.5 Hz, Ar–H), 7.57 (d, 1H, J=7.5 Hz, Ar–H), 7.30–7.38 (m, 3H, Ar–H), 7.05 (d, 1H, J=8.6 Hz, Ar–H), 4.37 (d, 1H, J=10.2 Hz, benzylic), 4.26 (m, 1H, N–CH),1.80–2.57 (m, 5H, pyrrolizine), 1.73 (s, 3H, CH_3NO_2),1.67 (m, 1H, pyrrolizine); ^{13}C NMR (125 MHz, DMSO-d_6): δ=177.3, 149.9, 142.9, 135.0, 131.4, 129.1, 128.7, 128.5, 126.0, 122.2, 111.3, 102.9, 76.2, 67.4, 55.9, 47.9, 31.7, 28.3, 20.0. Anal. Calcd for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.93; H, 4.81; N, 13.58.

*6.2.9. 1,2′-Dimethyl-2′-nitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8d**).* Cream solid (0.28 g, 74%), mp: 173–175 °C; IR (KBr, cm^{-1}) ν=1711, 1534, 1352; ^{1}H NMR (500 MHz, DMSO-d_6): δ=7.60 (t, 3H, J=7.0 Hz, Ar–H), 7.29–7.39 (m, 4H, Ar–H), 7.08 (t, 1H, J=7.5 Hz, Ar–H), 7.02 (d, 1H, J=7.8 Hz, Ar–H), 4.41 (d, 1H, J=10.2 Hz, benzylic), 4.22 (m, 1H, N–CH), 3.16 (s, 3H, N–CH_3), 1.76–2.50 (m, 5H, pyrrolizine), 1.74 (s, 3H, CH_3NO_2),1.68 (m, 1H, pyrrolizine); ^{13}C NMR (125 MHz, DMSO-d_6): δ=175.2, 144.8, 135.6, 131.5, 131.2, 129.0, 128.5, 127.0, 124.5, 122.9, 109.8, 102.3, 76.3, 67.5, 55.6, 48.0, 31.6, 28.3, 27.3, 20.1. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.13; H, 6.29; N, 11.22.

*6.2.10. 1-Benzyl-2′-methyl-2′-nitro-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**8e**).* Yellow solid (0.17 g, 38%), mp: 85–87 °C; IR (KBr, cm^{-1}) ν=1715, 1534, 1364; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.63 (m, 3H, Ar–H), 7.26–7.40 (m, 9H, Ar–H), 7.07 (t, 1H, J=7.2 Hz, Ar–H), 6.86 (d, 1H, J=7.6 Hz, Ar–H), 5.02 (AB quartet, 1H, J=16 Hz, N–CH_AH$_B$), 4.89 (AB quartet, 1H, J=15.6 Hz, N–CH$_A$$H_B$), 4.46 (d, 1H, J=10.4 Hz, benzylic), 4.23 (m, 1H, N–CH), 1.86–2.52 (m, 4H, pyrrolizine), 1.83 (s, 3H, CH_3NO_2),1.73 (m, 2H, pyrrolizine); ^{13}C NMR (100 MHz, DMSO-d_6): δ=175.2, 143.4, 136.5, 135.1, 131.2, 130.7, 129.1, 128.6, 128.2, 127.9, 127.4, 126.8, 124.3, 122.6, 110.1, 101.8, 75.8, 67.2, 55.2, 47.5, 43.5, 31.2, 27.9, 19.9. Anal. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27. Found: C, 74.01; H, 6.17; N, 9.20.

Acknowledgements

The authors acknowledge the University of Mazandaran for financial support of this research.

Supplementary data

Experimental procedure, copies of ^{1}H and ^{13}C NMR spectra for all compounds, X-ray crystallographic data, Cartesian coordinates, total energy, and number of imaginary frequencies. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.034.

References and notes

1. (a) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984; Vol. 1, p 2; (b) Najera, C.; Sansano, J. M. *Angew. Chem.* **2005**, *117*, 6428; (c) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; pp 211–247; (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863; (e) Lakshmi, N. V.; Thirumurugan, P.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 1064; (f) Poornachandran, M.; Raghunathan, R. *Synth. Commun.* **2007**, *37*, 2507.

2. (a) Cordell, G. A. *The Alkaloids: Chemistry and Biology*; Academic: San Diego, 1998; (b) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651; (c) Xue, J.; Zhang, Y.; Wang, X.-I.; Fun, H. K.; Xu, J. H. *Org. Lett.* **2000**, *2*, 2583; (d) Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481.
3. (a) Fejes, I.; Toke, L.; Blasko, G.; Nyerges, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 8545; (b) Nyerges, M.; Bitter, I.; Kadas, I.; Toth, G.; Toke, L. *Tetrahedron* **1995**, *51*, 11489; (c) Rang, H. P.; Dale, M. M. *Pharmacology*; Churchill Livingstone: Edinburgh, 1991; (d) Song, C.; Leonard, B. E. *Fundamentals of Psychoneuroimmunology*; John Wiley: Chichester, UK, 2000; (e) Albert, A. *Selective Toxicity*; Chapman and Hall: London, 1985.
4. (a) Daly, J. W.; Spande, T. W. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, T.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265; (b) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639; (c) Liddel, J. R. *Nat. Prod. Rep.* **1996**, *13* 187 and 653; (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209; (e) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, *15*, 327; (f) Dounary, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261 and references therein.
5. (a) Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Saez, J. A.; Perez, P.; Chamorro, E.; Domingo, L. R.; Mongin, F. *J. Org. Chem.* **2009**, *74*, 2120; (b) Nacereddine, A. K.; Yahia, W.; Bouacha, S.; Djerourou, A. *Tetrahedron Lett.* **2010**, *51*, 2617; (c) Benchouk, W.; Mekelleche, S. M.; Aurell, M. J.; Domingo, L. R. *Tetrahedron* **2009**, *65*, 4644; (d) Bakavoli, M.; Moeinpour, F.; Davoodnia, A.; Morsali, A. *J. Mol. Struct. (THEOCHEM)* **2010**, *969*, 139; (e) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifinab, A.; Romeoc, G. *Tetrahedron* **2003**, *59*, 3581.
6. (a) Padwa, A. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Wiley: Hoboken, 2003; (b) Merino, P. In *Science of Synthesis*; Padwa, A., Ed.; George Thieme: New York, NY, 2004; Vol. 27; (c) Bakthadoss, M.; Sivakumar, N. *Synlett* **2009**, 1014.
7. (a) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979; (b) Li, W.; Shi, M. *J. Org. Chem.* **2008**, *73*, 4151; (c) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321; (d) Yamashita, Y.; Guo, X.-X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3262; (e) Ghandi, M.; Yari, A.; Rezaei, S. J. T.; Taheri, A. *Tetrahedron Lett.* **2009**, *50*, 4724.
8. Sarrafi, Y.; Alimohammadi, K. *Acta Crystallogr.* **2008**, *E64*, o1740.
9. (a) Sarrafi, Y.; Alimohammadi, K. *Acta Crystallogr.* **2008**, *E64*, o1490; (b) Crystallographic data for **4c** and **8a** have been deposited in the Cambridge Crystallographic Data Centre with the deposition numbers CCDC 691716 and 691717, respectively. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
10. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03*; Gaussian: Wallingford CT, 2004.
11. (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363; (b) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57; (c) Fukui, K. *Molecular Orbitals in Chemistry, Physics, and Biology*; Academic: New York, NY, 1964; p 525.
12. (a) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717; (b) Sustmann, R.; Trill, H. *Tetrahedron Lett.* **1972**, 4271; (c) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569; (d) Sustmann, R. *Tetrahedron Lett.* **1971**, 2721.
13. Rahm, M.; Brinck, T. *J. Phys. Chem. A* **2008**, *112*, 2456.
14. (a) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512; (b) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University: New York, NY, 1989.
15. Parr, R. G.; Szentpaly, L. V.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
16. (a) Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417; (b) Domingo, L. R.; Asensio, A.; Arroyo, P. *J. Phys. Org. Chem.* **2002**, *15*, 660; (c) Domingo, L. R.; Arno, M.; Contreras, R.; Perez, P. *J. Phys. Chem. A* **2002**, *106*, 952; (d) Domingo, L. R. *Tetrahedron* **2002**, *58*, 3765; (e) Domingo, L. R.; Aurell, M. J. *J. Org. Chem.* **2002**, *67*, 959; (f) Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 3884; (g) Domingo, L. R.; Andres, J. *J. Org. Chem.* **2003**, *68*, 8662.
17. Arrieta, A.; Otaegui, D.; Zubia, A.; Cossio, F. B.; Diaz-Ortiz, A.; Hoz, X.; Herrero, M. A.; Prieto, P.; Foces-Foces, C.; Pizarro, J. L.; Arriortua, M. I. *J. Org. Chem.* **2007**, *72*, 4313.
18. (a) Valentin, C. D.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 6112; (b) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.
19. (a) Cossio, F. P.; Morao, I.; Jiao, H.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737; (b) Carda, M.; Portoles, R.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragoza, R. J.; Roper, H. *J. Org. Chem.* **2000**, *65*, 7000.
20. Hagiwara, Y.; Tateno, M. *J. Phys.: Condens. Matter* **2009**, *21*, 245103.
21. Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104.
22. Schleyer, P. V. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. V. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.
23. Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.