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Computational study in Regioselectivie Synthesis of New Spiro-oxindolopyrrolidines

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ABSTRACT: One-pot, four-component procedure for the synthesis of a small library of new chiral spiro- oxindolopyrrolidines with high regio-, diastereo- (>99:1 dr), and enantioselectivity (up to 80% ee) is described. In this process, the regio- and stereochemical 1,3-dipolar cycloaddition of azomethine ylides, which were generated insitu by the reaction of isatin derivatives and sarcosin,with optically active chiral menthyl cinnamate studied on the basis of the assignment of the absolute configuration of the cycloadducts, and on theoretical calculations. In comparison with active cinnamoyl oxazolidinone, when the reactions were performed with active chiral menthyl cinnamate as dipolarophile, a remarkable unexpected inversion in the regioselectively was observed. The regioselectivity of the reactions was investigated using global and local reactivity indices at the B3LYP/6-311G(d,p) level of theory. The effects of the electronic and steric factors on the regioselectivity of the reactions were discussed. The electronic structures of critical points were studied by the natural bond orbital (NBO) method.

Keywords: *Asymmetric 1,3-dipolar, Chiral auxiliaries, chiral non-racemic menthol, Chiral spiro-oxindolopyrrolidines*

INTRODUCTION

Compounds that differ in the position of a substituent are known as regioisomers. Although the regioisomers look very alike, they might possess different properties. Since Padwa and co-workers performed the first diastereoselectivity of 1,3-dipolar cycloaddition reaction in 1985, by applying a chiral non-racemic azomethine ylide, (Daly, *et al.*, 1986) their applications has been developed as a cornerstone in organic synthesis (Carroll and Grieco 1993). One of today's challenges in this field is to control the regio-, diastereo- and enantioselectivities of these reactions. For many years the chiral auxilliary was the only way of asymmetric induction in synthetic organic chemistry. The different types chiral auxiliary were applied in asymmetric synthesis of chiral structure. Two of the most important chiral auxiliary are menthol (in both enantiomer) and chiral oxazolidinone derivatives, which have frequently been used in various asymmetric reactions as reliable method of creating new stereogenic centers Rosenmond, *et al.*, 1994). In compare with oxazolidinones, chiral non-racemic menthol or p-menthan-3-ol have not been as extensively used as chiral auxiliaries in 1,3-dipolar cycloaddition reactions. Better results were achieved by

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Grigg *et al.* using menthyl acrylate for the construction of substituted pyrrolidines starting from azomethine ylides (Grigg, 1995). Asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides offer an effective means to access chiral pyrrolidines substructures containing up to four new stereogenic centres that found in many biologically active compounds (Shi, *et al.*, 2009, Li, *et al.*, 2011, Suresh Babu, *et al.*, 2009).

Systematic investigation has shown that spirooxindolopyrrolidines systems, formed from joining spirooxindole and pyrrolidine rings at C-3 (spiro carbon), provide more opportunities for the development of a wide spectrum of biologically active compounds (Rajkumar, *et al.*, 2012). In 2002, Ganguly and co-workers synthesized spirooxindolopyrrolidines 1 with high regioselectivity via stereocontrolled 1,3-dipolar cycloaddition reactions of isatin derivative 2, sarcosine and chiral cinnamoyl oxazolidinone as dipolarophile 3 (Scheme 1).

According to the above facts and in continuation of our previous work on the synthesis of spirooxindoles, (Faraji, *et al.*, 2010) herein, we report a facile synthesis of a small library of novel spirooxindolopyrrolidines 4 with the help of menthol as a chiral auxiliary in an asymmetric three-component 1,3-dipolar cycloaddition reaction of azomethine ylides derived from isatin.

Interestingly, in contrast Ganguly's report (Ganguly, *et al.*, 2002) and in a same reaction condition when chiral menthyl cinnamate 5 (menthol derived dipolarophile) was utilized in this reaction as dipolarophile, inversion in the regioselectivity was observed and corresponding spirooxindolopyrrolidines 4 was obtained as a sole product in high yield, high diastereo- (>99:1 dr) and enantioselectivity (up to 80% ee) (Scheme 1). This means that the reaction pathways for this reaction probably proceed through different intermediate. Thus, the molecular mechanism of this reaction has been investigated by means of a density functional theory (DFT) method.

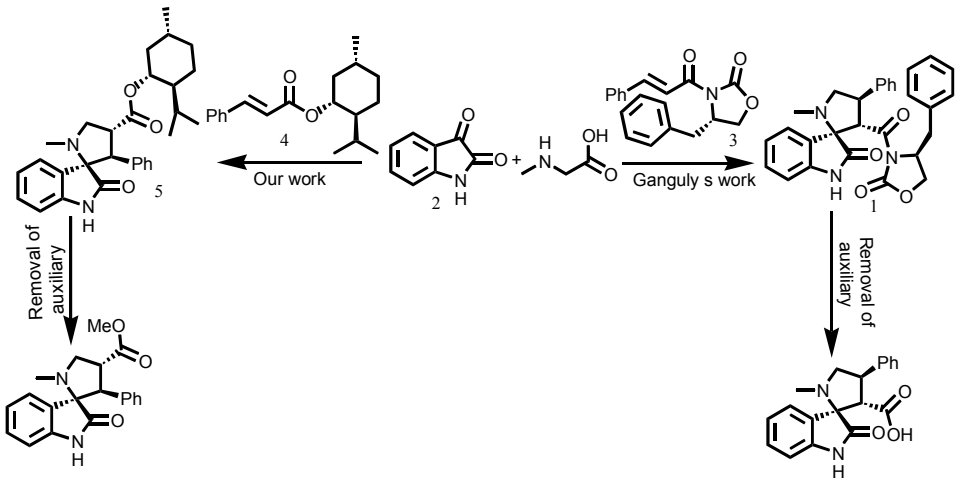
MATERIALS AND METHODS

Experimental

General melting point were recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a mattson 1000 FTIR. ^{1}H, $^{13}CNMR$ spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 MHz. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an electron energy of 70 eV. isatin derivatives, proline, were obtained from Fluka (Buchs, Switzerland) and were used without further purification, and trans-cinnamic acid derived from the menthol were obtained via synthesized.

General procedure

To a magnetically stirred solution of aisatin derivatives (2) (1 mmol), sarcosine (6) (1 mmol) and trans-cinnamic acid derived from the menthol (5) (1 mmol), as chiral auxiliaries in 10 mL EtOH was added dropwise at reflux temperature. Then, the reaction mixture



Scheme 1: Synthesis of chiral spirooxindolopyrrolidines 1, 5.

Table 1: Synthesis of chiral spirooxindolopyrrolizidines 4, 8.

Entry	R	X	Product	4[a]		8	
				Yield (%)[b]	$[\alpha]_D^{25c}$	Yield (%)[b]	$[\alpha]_D^{25c}$
1	H	H	A	70	-5.4	65	-4.2
2	H	Br	B	75	-6.2	72	-4.3
3	H	NO_2	C	72	-5.8	65	-4.7
4	Me	H	D	65	-5.4	60	-4.4
5	Me	Br	E	70	-5.2	65	-4.5
6	Me	NO_2	F	67	-5.7	60	-4.4
7	Et	H	G	65	-5.2	60	-4.2
8	Et	Br	H	65	-5.7	62	-4.7
9	Et	NO_2	I	72	-5.1	65	-4.3

[(a)] The reaction was carried out in the ratio of 1/2/3/ 1:1: 1; [(b)] Isolated yield based on substituted isatins; [(c)] [α] D25 (c 1, CH_2Cl_2).

was stirred for 12 h. The solvent was then removed under reduced pressure and the residue was separated by column chromatography (silica gel, Merck 230–400 mesh) using n-hexane–ethyl acetate (90:10) as eluent. To a magnetically stirred solution of a 4 derivatives (1 mmol), sodium methoxide (3 mmol) and 10 (mol%) BF_3. OEt_2 in 10 mL THF at room temperature. Then, the reaction mixture was stirred for 1 h. The solution was quenched with HCl (1N). Then the solution was extracted with 20 mL of EtOAc and the organic phase was separated, washed with 20 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The solvent was then removed under reduced pressure.

RESULTS AND DISCUSSION

Chiral menthyl cinnamate 5 is conveniently prepared from the corresponding cinnamoyl chloride (usually obtained from the cinnamic acid after treatment with $SOCl_2$) and chiral with commercially available (E)-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl after deprotonation of this with a base such as BuLi (Ennis and Womack, 1955). The one-pot three component reaction was carried out by stirring a mixture of 1 equiv of isatin 2 and 1 equiv of sarcosine 6 for 10 min in 10 mL of aqueous ethanol followed by addition of 1 equiv of chiral menthyl cinnamate 5. The [3+2] cycloaddition of chiral dipolarophile 5 with azomethine ylide 7 resulted in the formation of new chiral spirooxindolopyrrolidines 4 which contains four contiguous stereogenic centers. Despite the fact that sixteen different stereoisomers could be prepared theoretically, only diastereoisomer 4 was obtained (Scheme 1).

In order to investigation of solvent effect in stereoselectivity of the products, the one-pot four component reaction was also carried out in toluene and aqueous dioxane, similar solvent with Ganguly's report, for the dipolarophiles 3 and it was found that even under refluxing condition, there was no effect on regioselectivity and no improvement in result reaction even reaction in toluene, led to a decrease in the isolated yield of the cycloadducts. This is attributed to the poor solubility of reactantin toluene specially the amino acid, sarcosine 6 which is responsible for the formation of azomethine ylide with isatin derivatives 2.

The structures of cycloadducts were characterized on the basis of spectroscopic data. Thus, the IR spectrum of spirooxindolopyrrolidines 4a showed two absorption at 1613 cm^{-1} and 1714 cm^{-1} indicating the presence of two carbonyl group. In ^{1}HNMR spectrum of the product 7d, the pyrrolidin ring proton attached to the phenyl ring appeared as a multiplet at δ= 4.02. The pyrrolidin $–NCH_2$ proton appeared as a multiplet at δ= 3.66 whereas the pyrrolidin proton attached to the menthyl moiety is more deshielded and exhibited a multiplet at δ= 4.35 (H_{20}). The aromatic protons appeared as a multiplet in the region δ= 6.96–7.63.

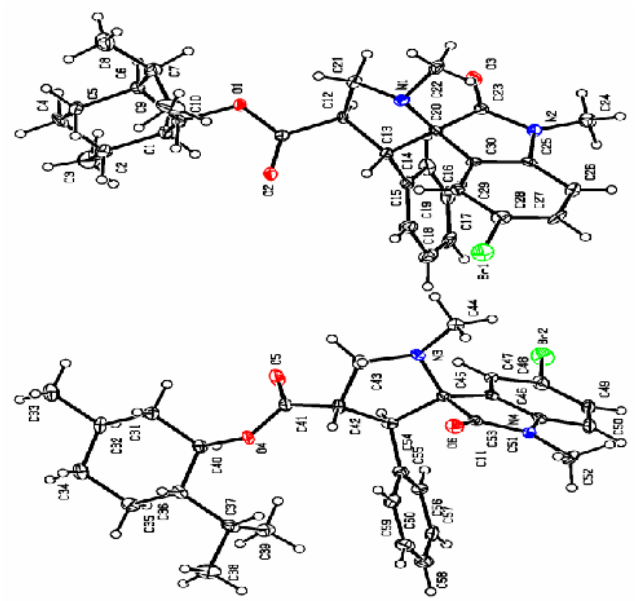
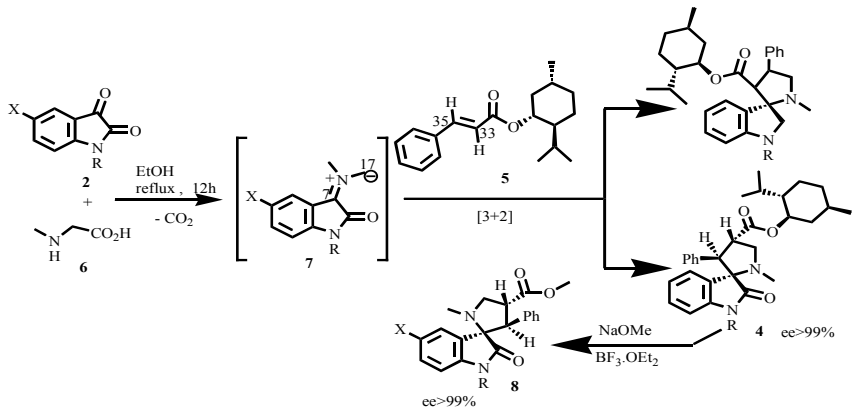


Fig. 1: The ORTEP diagram of one of the two crystallographic independent molecules in the asymmetric unit of 4g is shown. Thermal ellipsoids are at 30% probability level.

The off resonance decoupled ^{13}CNMR spectra of 4d exhibited characteristic peaks for the spiro carbon and carbonyl group attached to the menthyloxy moiety at 74.2 and 179.9 ppm respectively and the signals for all other carbons are located at appropriate chemical shifts in agreement with the proposed structure. The formation of the product was confirmed by mass spectral and elemental analyses. The mass spectrum of 4d showed a peak at m/z 553 (M+).

We also were able to obtain suitable crystals of the 4e for crystallography to confirm the assigned stereochemistry and regionselectivity of products 4, as suggested by NMR spectroscopy. The absolute configuration of chiral spirooxindolopyrrolidines 4e was also determined by single crystal as 5R (spiro carbon C7), 6S (C21), 7R (C14), 8R (C13) (Fig. 1). Particularly noteworthy is the fact that all of the covalently attached azomethine ylide auxiliaries require destructive removal. It was in this context that we initiated studies whose goal was to develop a recoverable chiral auxiliary. Interestingly, for compounds 6, the chiral auxiliary was removed easily with sodium methoxide and BF3.OEt$_2$ in THF and provides access to a variety of enantiomerically pure products 8a–i in excellent to quantitative yields (Scheme 2). Note that the auxiliary was recovered from this reaction in high yield.

The stereochemistry and the structure of resulted cycloadduct 4a were carried out using ^{1}HNMR and ^{13}CNMR and also ^{2}DNMR spectroscopy techniques. The ^{13}CNMR spectrum displays 30 signals, which are classified into four methylene, sixteen methines, and ten quaternary carbons including to spiro carbon by the DEPT 135° experiments. In the HMQC spectrum of product 4a, the positions of three protons (Ha, Hb, and Hc) that were directly bonded to these carbon atoms (CH) were assigned. The ^{1}HNMR spectrum displays two signals at δ= 4.02 and δ= 4.35 ppm (Hc, Hb respectively); the Hb could be trans to Hc, because of absence of any correlation between them in the ROESY spectrum. This is also confirmed from the weak NOE pattern between them. To determine the exact regioselectivity, the connectivity of the carbons in the molecular structure was obtained by using the analysis of the HMBC spectra. Based on the HMBC spectrum, there is no correlation between Hc and the signal of carbonyl group, which confirms presence of the carbonyl group at C-2′ position in 4a (instead of C-1′)



Scheme 2: Synthesis of chiral spirooxindolopyrrolizidines 4, 8.

(Scheme 2).

It is known that chiral cinnamoyl oxazolidinone, in the absence of Lewis acids, prefer a low energy Z-conformer of S-Cis. So, on the basis of the absolute configuration of the four stereogenic centers in the pyrrolizidine ring, it is assumed that the azomethine ylide approaches endo to the si-face of the dipolarophile as a Z-conformer of S-Cis (Scheme 3).

COMPUTATIONAL STUDY

All calculations were performed using Gaussian09 (Frisch, 2009), suite 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 6-311G(d,p) basis set in the gas-phase. No symmetrical restriction was applied during geometrical optimizations. 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. The electronic structures of critical points were studied by the natural bond orbital (NBO) method (Reed, *et al.*, 1988). Furthermore, Zero-point vibrational energies and thermodynamic corrections at 298.15 K were calculated at the same level as the geometry optimization.The atomic Cartesian coordinates of optimized structures for all transition states are included in supporting information.

Prediction of regiochemistry

FMO, Global and Local Electrophilicity/Nucleophilicity Analysis

The regio- and stereoselectivity of the reaction of azomethine ylide 7 with chiral non-racemic menthyl cinnamate 1 was investigated by theoretical methods (Scheme 2). The FMO approach provides the most reliable general explanation of regiochemistry of the cycloaddition reactions (Fukui, 1981). The HOMO-LUMO energy gap for the reactants generally determines the most significantinteraction. Then the regiochemical preferences of these reactions can be predicted in terms of the maximum overlap of the largest coefficients of the HOMO and LUMO orbitals at the reaction sites (Wang, *et al.*, 2005). According to Houk's rule, the regioselectivity of 1,3-dipolar cycloaddition reactions can be explained on the basis that the large-large and small-small FMO interactions are more favoured than the large-small and small-large FMO interactions (Wang, *et al.*, 2005). The calculated frontier orbital energies and the coefficients of 5 and 7 (at DFT/B3LYP/6-311G(d,p) level of theory) are given in Tables 2 and 3, respectively. Obviously, the electron density transfer takes place from the HOMO orbital of azomthine ylide 7 to LUMO orbital of menthyl cinnamate 5, as a result of the small energy gap (normal electron demand character). The FMO analysis was suggested that C_7 of the azomethine ylide 7 reacts preferentially with the β-enone carbon atom C_{35} of the alkene, which is in good agreement with the experimental observation (Scheme 2).

The chemical potential, hardness, softness, global and local electrophilicity and nucleophilicity have been computed for the reagents (Tables 2 and 3). The electronic chemical potential μ is usually associated with the charge transfer ability of the system in its ground state geometry and it can be defined as the mean value of HOMO and LUMO energies [$\mu=(\varepsilon_H+\varepsilon_L)/2$] (Politzer, *et al.*, 1983, Sanderson, 1983). The chemical hardness η which is describes the resistance to this charge transference is the difference between LUMO and HOMO energies. The chemical softness parameter S is strictly related to the chemical hardness and it is due to the inverse of 2η. The global electrophilicity index ω, which measures the stabiliza-

Table 2: Global properties of dipole 7 and dipolarophile 5.

Reactant	HOMO (eV)	LUMO (eV)	μ (a.u)	η (a.u)	ω (eV)	S(a.u.)
5	-6.584	-1.952	-0.1568	0.1702	1.965	2.938
7	-4.924	-1.637	-0.1206	0.1193	1.660	4.190

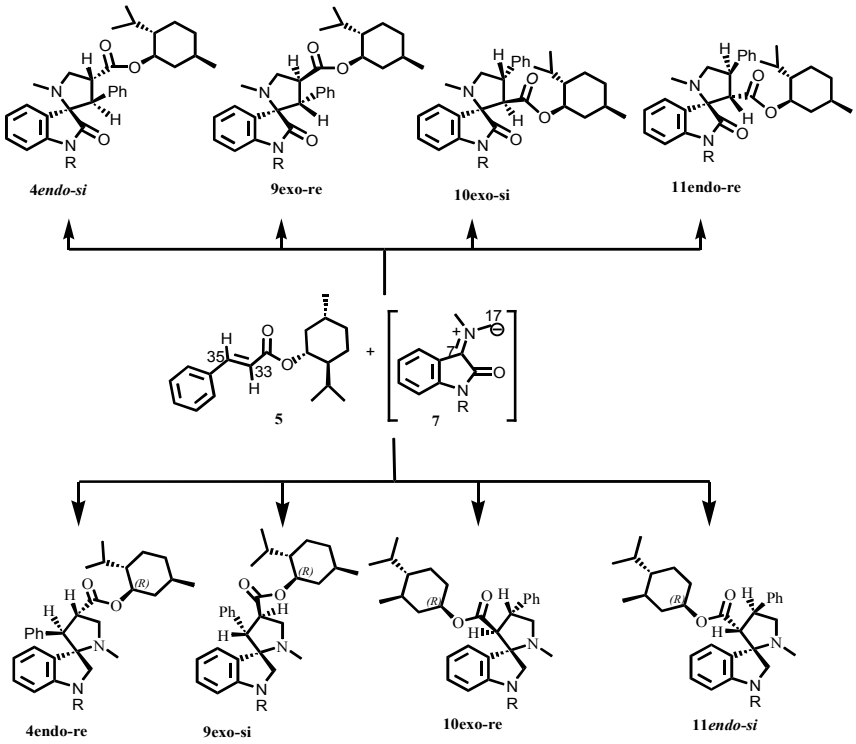
Table 3: Local properties of dipolarophile 5 and dipole 7.

Reactant	Site	MO coefficient (HOMO)	MO coefficient (LUMO)	f_k^+	f_k^-	s^+	s^-	ω_K (eV)
dipolarophile 5	C_{33}	0.128	-0.108	0.0750	0.2153	0.2202	0.6324	0.15
dipolarophile 5	C_{35}	0.076	0.122	0.0709	0.0118	0.2084	0.0345	0.14
dipole 7	C_7	0.144	0.057	0.0062	0.1083	0.0261	0.4537	0.01
dipole 7	C_{17}	-0.134	0.184	0.1729	0.1373	0.7246	0.5753	0.29

tion in energy when the system acquires an additional electronic charge ΔN from the environment, was given the following simple expression, $\omega = \mu^2/2\eta$, in terms of the electronic chemical potential and the chemical hardness (Parr, 1999).

The electronic chemical potentials, μ, of the azomethine ylide 7, -0.1206 a.u., is higher than those for menthyl cinnamate 5, -0.1568 a.u., indicatesa net charge transfer from the azomethine ylide to menthyl cinnamate. The electrophilicity of menthyl cinnamate 5 in Table 2 is greater than 1.5 eV (ω= 1.965), thus according to the classification of electrophilicity, this compound can be classified as a strong electrophile (Domingo and Andres 2003). Azomethine ylide 7 also has a large electrophilicity value, ω= 1.660. Since, the electrophilicity of menthyl cinnamate 5 (dipolarophile) is greater than that of the azomethine ylide (dipole), the electrondensity transfer takes place from dipole 7 to dipolarophile 5.

After considering the global properties, a local analysis was carried out through Fukui indices calculation. The atomic condensed Fukui functions,based on Mulliken population analysis and depending on the type of electron transfer, are defined as $f^-(r)=q_k(N)-q_k(N-1)$ and $f^+(r)=q_k(N+1)-q_k(N)$ (Li and Evans 1995). Then the electrophilicity local indexis calculated from Fukui index f^+ as $\omega=\omega f_k^+$. The analysis of the local electrophilicity index, ω_k at the electrophilic reagent and the nucleophilic Fukui function, f_k^- at the nucleophilic compound allows one to explain the observed regi-



Scheme 3: Possible transition structures for the concerted reaction of azomethine ylide

oselectivity (Domingo and Andres 2003). Thementhyl cinnamate 5 has the largest electrophilic activation at the C_{33} carbon atom, ω_k= 0.15 eV, whereas the azomethine ylide 7 has the largest nucleophilic activation at the C_{17} carbon atom, f_k^- = 0.1373 (Table 3). Therefore, C_{33} of menthyl cinnamate 5 will be the preferred position for a nucleophilic attack by C_{17} of the dipole 7, which is in good agreement with the experimental observation (Scheme 2). Regioselectivity can be studied in terms of the softness matching index, defined by the following relationship (Chandra and Nguyen 2002).

$$S = 1/2\eta \quad (1)$$

where i and j are the atoms of a molecule A involved in the formation of a cycloadduct with atoms k and l of a molecule B, and s_is are the appropriate type of atomic softness. s_i and s_j are electrophilic where s_k and s_l are nucleophilic and they calculated as:

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

where S is the global softness and computed as (Chermette, 1999):

$$s_k^{\pm} = f_k^{\pm} S \quad (3)$$

According to local HSAB concept, the reaction associated with a lower Δ value (equation 1) will be the preferred one (Pearson, 1995). In the case of cycloaddition reaction of 7 to 5, Δ_{ij}^{kl} for the generation of 4 (0.1861) is smaller than that of the generation of other regioisomer (0.1891). (Table 3, Scheme 2) and hence agrees well with the experimental results.

Energies of transition state structures

Possible transition structures for the concerted reaction of azomethine ylide 7 with dipolarophile 5 and their corresponding cycloadducts for both re and si faces of the chiral non-racemic menthyl cinnamate 5 have been optimized and characterized (Scheme 3). The activation energies, enthalpies and Gibbs free energies as well as the reaction energies, enthalpies and Gibbs free energies are reported in Table 4. For each transition state, the most stable conformation has been chosen. The naming symbols are coined according to a particular highlighted combination endo/exo and re/si faces attack at the C_{33} and C_{35} of menthyl cinnamate 5.

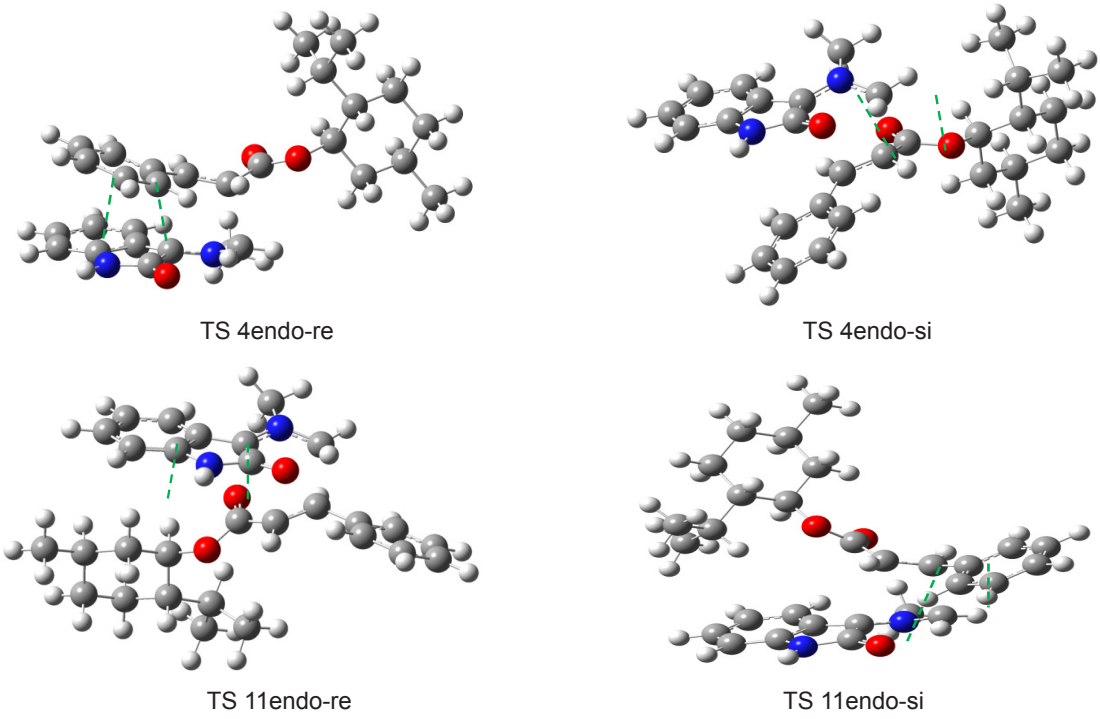


Fig. 2: Selected optimized transition structures at the B3LYP/6-311G(d,p) corresponding to the regiosomeric path of the 1,3-dipolar cycloaddition reaction 5 and 7.

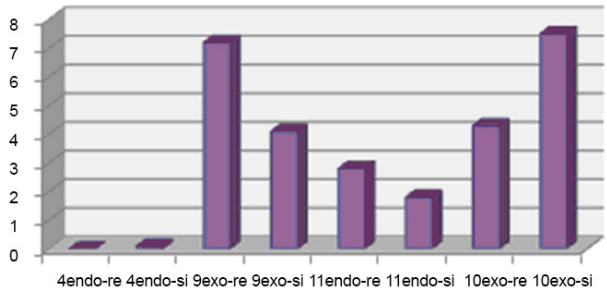


Fig. 3: Relative energy of possible transition structures.

The relative activation energies of the transition states in Fig. 3 show that azomethine ylide 7 should undergo 1,3-dipolar cycloadditions with menthyl cinnamate 5 very easily, as predicted by the low activation energy of 8.1 kcal/mol and 8.2 kcal/mol, obtained at the Becke3LYP/6-311G(d,p) level for the 4 endo-re and 4 endo-si channels. The cycloaddition reaction between 5 and 7 is favored in the endo reaction channels. The optimized geometries of endo transition states are shown in Fig. 2.

A theoretical preference for regioisomers 4, Where the carbon bearing the phenyl group attached to the Spiro Center, is observed and the predominance of endo adducts are correctly predicted with a difference of more than 4.0 kcal/mol. The theoretical preference for re and si faces is less pronounced,especially for 4 endo adifference of only 0.1 kcal/mol is observed. Preference based on this energy difference is very weak and not reliable. Rate constants were calculated according with the Eyring transition state theory: $k=TK_B/h\times e^{-\Delta G^{\#}/RT}$ where k_B is Boltzmann's constant; h is Planck's constant; R is the ideal gas constant; T is the temperature (25°C), and, $\Delta G^{\#}$ is the activation Gibbs free energy of the transition state structures. The unequal new C–C bonds in transition states are consistent with anasynchronous concerted cycloaddition mechanism.

CONCLOUSIONS

Because of wide distribution in nature and variegated biological activities, chiral pyrrolizidines alkaloids are very attractive synthetic targets. Since a pyrrolizidine can be viewed as a fused pyrrolidine, the method employed for the formation of pyrrolidine rings can be used to construct the pyrrolizidine ring system. So, the asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides, including pyrrolidine derivatives with olefins, can be the useful method for the synthesis of chiral pyrrolizidines. On the other hand, oxindoles are also structural key moieties in many bioactive substances and it is interesting that systematic investigation has shown that if this moiety is joined to the pyrrolizidine or pyrrolidine ring through a spiro atom at C-3, the resulting compounds show an increased spectrum of biological activity. As a result, we have found a tri- component synthetic method for the prepration of some oxindoles derivatives of potential synthetic interest. The present method carries the advantage that

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 Rate constants at the B3LYP/6-311G(d,p), all energies are in kcal/mol.

Structure	E_a	$\Delta H^{\#}$	$\Delta G^{\#}$	ΔE_{rxn}	ΔH	ΔG	$k_{(25)}$
4 endo-re	8.1	7.6	21.6	-25.3	-25.8	-11.4	8.85×10^{-4}
4 endo-si	8.2	8.0	22.4	-25.6	-26.5	-11.3	2.29×10^{-4}
9 exo-re	15.3	15.1	28.4	-21.1	-21.9	-6.0	9.09×10^{-9}
9 exo-si	12.2	12.1	26.1	-22.1	-22.6	-8.0	4.42×10^{-7}
11 endo-re	10.9	10.5	26.1	-22.8	-23.3	-8.0	4.42×10^{-7}
11 endo-si	9.9	9.5	25.2	-25.1	-26.0	-9.9	2.02×10^{-6}
10 exo-re	12.4	12.1	25.5	-24.7	-25.3	-9.8	1.22×10^{-6}
10 exo-si	15.6	15.3	30.2	-21.7	-22.4	-6.6	4.34×10^{-10}

not only the reaction is performed under neutral conditions, but also the starting materials and the reagents can be mixed without any activation or modification. The regioselectivity of the reactions was investigated using global and local reactivity indices at the B3LYP/6-311G(d,p) level of theory. The effects of the electronic and steric factors on the regioselectivity of the reactions were discussed. The electronic structures of critical points were studied by the NBO method.

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