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REGULAR ARTICLE

Highly efficient *endo'*- selective synthesis of (dispiro 3,2′-pyrrolidinyl) bisoxindoles containing three contiguous chiral stereocenters with two contiguous quaternary spirostereocenters

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Abstract. An efficient, atom economical, one-pot synthesis of *endo'*- selective (dispiro 3,2′-pyrrolidinyl) bisoxindole containing three contiguous chiral stereocenters with two contiguous quaternary spirostereo centers have been achieved by three-component reaction of isatins, malononitrile (cyanoacetic ester) and 1,3-dicarbonyl compounds in water in the presence of L-proline. One-pot, azomethine ylide cycloaddition with a dipolarophile without using any catalyst have also been achieved in good yields. This new methodology offers many advantages of catalyst-free, mild reaction conditions, shorter reaction time, environmental friendliness, regio- and stereoselective processes in higher yields.

Keywords. 1,3-Dipolar cycloaddition; *Endo*-Selectivity; Dispiro-bis-oxindoles; HOMO-LUMO interaction.

1. Introduction

Spirocyclic oxindole has been an elegant target of a synthetic chemist owing to prevalence in several natural alkaloids.[1] Spirotryprostatin A has been isolated from the fermentation broth of aspergillus fumigates and identified as a novel inhibitor of microtubule assembly, muscarinic serotonin receptors as well as medicinally relevant compounds.[2] Among the different, the spirooxindoles,[3] the pyrrolidinyl spirooxindole framework has recently drawn the attention of a synthetic chemist because of its significant bioactivities such as anti-microbial, anti-tumour, anti-inflammatory and acetylcholinesterase (AChE) inhibitory activities (Figure 1).[4] Particularly, stereocontrolled synthesis of such compounds installing the spiro-quaternary stereocenter at 3- position, poses a great synthetic challenge.[5] A few venerable asymmetric transformations such as cycloaddition or Heck reaction are only known to achieve this challenging goal.[6]

Multi-step synthesis poses many drawbacks such as decreased yield, time-consuming and use of toxic solvents. To overcome these hurdles, 1, 3 dipolar cycloaddition reactions are considered as the most widely used methodology for the construction of many biologically active heterocyclic systems. It also offers many advantages such as atom economical, eco-friendly solvent, less time consuming, stereospecificity, stereoselectivity and regioselectivity.[7,8] The reaction pathway concludes that the cycloaddition reactions proceed *via* a concerted mechanism. The mechanism was first suggested by Huisgen,[9] and it has been specified as one pot, five-centre, and involves 4π electrons from the 1,3-dipole and 2π electrons from the dipolarophile.

In the continuation of our previous reports to synthesize spirooxindoles[10] *via* 1,3-dipolar cycloaddition

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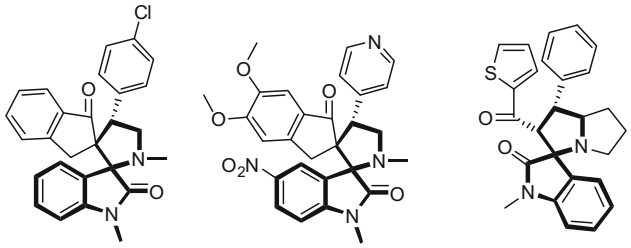


Figure 1. Bioactive compounds containing 3,2′-pyrrolidinyl spirooxindoles framework.

reaction, we wish to accomplish the synthesis of 3,2′-pyrrolidinyl spirooxindoles *via* more convenient 1,3-dipolar cycloaddition reaction. It is noteworthy to mention that the method reported herein appears to be excellent for the construction of a series of complex bis-spirooxindole derivatives with three contiguous stereocenters including two spiro-quaternary chiral carbon atoms. Moreover, the method reported herein is an effective extension of the Huisgen synthesis for dispiroheterocycles[11,12] without using any catalyst.

2. Experimental

2.1 *Materials and Physical measurements*

All chemicals and solvents required for the reactions were purchased from Sigma-Aldrich, Merck, and used without further purification. All reactions were carried out in oven-dried glassware. Progress of reactions was monitored by thin-layer chromatography (TLC), while column chromatography was utilized for purification of crude compounds by using silica gel (100–200 mesh). ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz and 125 spectrometers respectively in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in ppm and coupling **constants are given in Hz. The data for 1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; m = multiplet; br = broad), coupling constant (Hz), integration. Mass spectra were recorded using 6495C Triple Quadrupole LC/MS.

2.2 *Synthesis of (dispiro 3,2′-pyrrolidinyl) bisoxindoles*

A mixture of isatin (**1a-k**) (1.0 mmol), sacrosine **2** (1.5 mmol) and 2-oxindole-3-ylidene **3** (1.1 mmol) in acetonitrile was refluxed until the completion of the reaction as monitored by TLC and then cooled to room temperature. The solid formed in the reaction mixture was filtered and dried under vacuum. The solid crude product was purified by preparative HPLC and the pure products (**4a-k**) and (**5a-k**) obtained in good yields (80–99%).

For **4a**: White solid. M.p.: 240–243 °C. *Rf 0.25* (50% EtOAc/Petroleum ether). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.96 (s, 3H), 3.27 (s, 3H), 3.51 (t, J = 18 Hz, 1H), 3.98 (t, J = 17 Hz, 1H), 4.38 (t, J = 18 Hz, 1H), 6.55–6.59 (m, 2H), 6.83 (t, J = 14.5 Hz, 1H), 6.82 (t, J = 14.5 Hz, 1H), 7.12–7.14 (m, 2H), 7.30 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H) and 7.70 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): 26.4, 29.8, 36.3, 48.6, 51.5, 54.1, 61.7, 107.6, 109.5, 122.2, 122.5, 124.5, 125.1, 126.6, 126.9, 129.0, 129.8, 141.6, 143.8, 170.6 and 177.1. **LC-MS:** Calcd. for $C_{22}H_{21}N_3O_4$ is m/z = 391.14 [M+1]. Found: m/z = 392.2.

For **5a**: White solid. M.p.: 238–240 °C. *Rf* 0.25 (50% EtOAc/Petroleum ether). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.21 (s, 3H), 3.00 (s, 3H), 3.17 (s, 3H), 3.71 (t, J = 20 Hz, 1H), 3.98–4.01 (m, 1H), 4.71–4.72 (m, 1H), 6.16 (d, J = 8 Hz, 1H), 6.52 (t, J = 15 Hz, 1H), 6.66 (t, J = 14.5 Hz, 2H), 7.00 (t, J = 15 Hz, 1H), 7.12 (t, J = 15.5 Hz, 1H), 7.29 (t, J = 15.5 Hz, 1H), 7.57 (s, 1H) and 7.66 (d, J = 7.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): 26.3, 35.3, 49.5, 51.5, 54.5, 62.5, 77.4, 107.4, 109.6, 121.1, 121.8, 122.3, 123.3, 126.0, 126.6, 127.7, 129.2, 129.7, 141.9, 144.0, 170.6 and 176.5. **LC-MS:** Calcd. for $C_{22}H_{21}N_3O_4$ is m/z = 391.14 [M+1]. Found: m/z = 392.2.

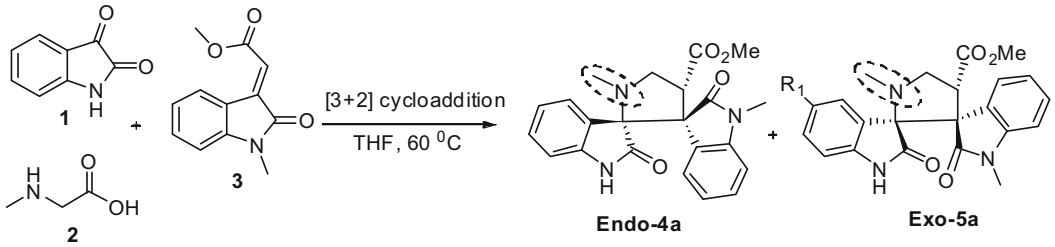
3. Results and Discussion

3.1 *Synthesis and characterization*

Primarily, investigation of isatin **1**, sacrosine **2** and 2-oxindole-3-ylidene **3** in THF as a solvent at 60 °C affords the functionalized dispiropyrrolidine bis-oxindole **4a** and **5a** with two spirocentres in 55% combined yields (Scheme 1). This strategy would provide access to a fast, one-pot synthesis of dispiroheterocycles, which are otherwise accessible only through multi-step synthesis.

3.2 *Structure of compounds **4a** and **5a***

The structure of the two regioisomers **4a** and **5a** were confirmed by various spectroscopic analyses such as ^{1}H, ^{13}C, and DEPT-135 and mass spectroscopy. The ^{1}H NMR spectrum of compound **4a** exhibited four characteristic singlets at δ 2.21, 2.96, 3.23 and 7.70 due to the presence of – NCH_3 protons of pyrrolidine, –NCH_3 protons of oxindoles, –OCH_3 protons of methyl ester and –NH proton of oxindole, respectively. The ^{1}H NMR data confirm the incorporation of two spiro oxindole rings. In ^{13}C NMR spectrum, the spirocarbon atoms appeared at δ 54.0 and 61.6 ppm, respectively. The shifts at δ 170.6 and 177.0 ppm representing ester carbonyl and amide carbonyl



Scheme 1. Synthesis of dispiropyrrolidine oxindoles **4a** and **5a**.

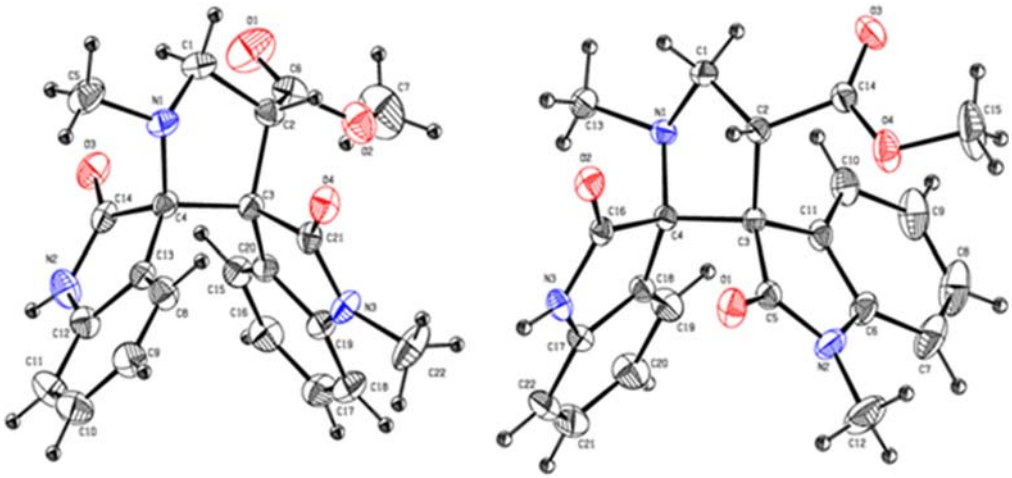


Figure 2. ORTEP view of compounds **4a**[13] and **5a**[14].

groups, respectively. The DEPT-135 spectrum showed a chemical shift at 54.1 ppm corresponds to one -CH_2 carbon atom. These observed chemical shift values are in accordance with the structure of the compound **4a**. Moreover, the presence of a molecular ion peak at m/z 391 (M+1) in the mass spectrum confirmed the structure of the bisoxindole **4a**. The relative stereochemistry of the product **4a** was established through single-crystal X-ray analysis (Figure 2).

Table 1. Optimization of the reaction conditions.

Entry	Solvent	Temp (°C)	Yield (%)[a,b,c]
1	THF	60	55(46/9)
2	Toluene	60	60(50/10)
3	MeOH	60	70(61/9)
4	EtOH	60	65(55/10)
5	H_2O	60	NR
6	CH_3CN	60	85(76/9)
7	**CH_3CN**	**85**	**99(91/8)**

[a]Isolated yield. [b]The ratio was determined by ^{1}H NMR and preparative mass. NR-No reaction. [c]All the reactions were performed in 5 ml of CH_3CN at reflux condition.

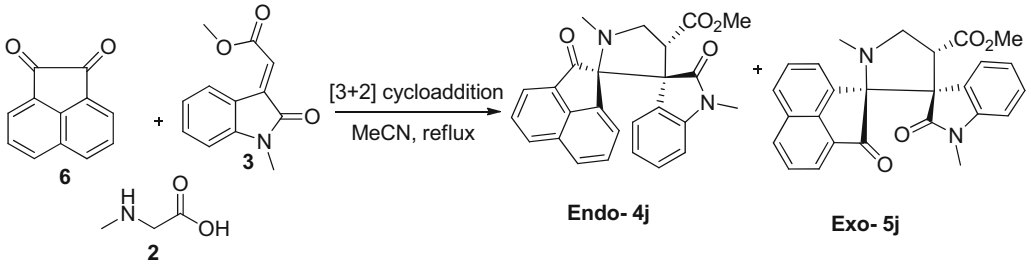
The ^{1}H NMR spectrum of compound **5a** exhibited characteristic four singlets appeared at δ 2.22, 3.00, 3.18 and 7.57 representing –NCH_3 protons of pyrrolidine, –NCH_3 protons of oxindole, –OCH_3 protons of methyl ester and –NH proton of oxindole, respectively. The ^{13}C NMR spectrum spirocarbon atoms of two oxindole rings show chemical shifts at δ 54.5 and

Table 2. Synthesis of dispiropyrrolidine bis-oxindoles derivatives **4a-i** and **5a–i**.

Entry	R^1	R^2	*Endo*(P_1)[a,b]	*Exo*(P_2)[a,b]	P_1/P_2
1	H	H	4a[c]	5a[c]	91/8
2	Cl	H	4b	5b	80/8
3	Br	H	4c	5c	78/10
4	F	H	4d	5d	75/10
5	NO_2	H	4e	5e	79/9
6	H	Cl	4f	5f	80/10
7	H	Br	4g	5g	78/9
8	H	F	4h	5h	81/8
9	H	NO_2	4i	5i	79/10

[a]The products were characterized by ^{1}H and ^{13}C NMR spectra and LC-MS.

[b]Isolated yield after purification. [c]X-ray diffraction analysis.



Scheme 2. Synthesis of dispiropyrrolidine oxindoles **4j** and **5j.**

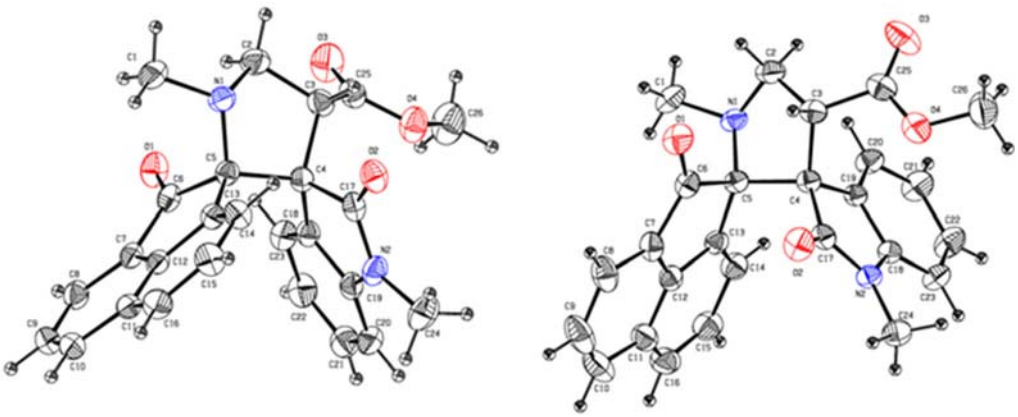
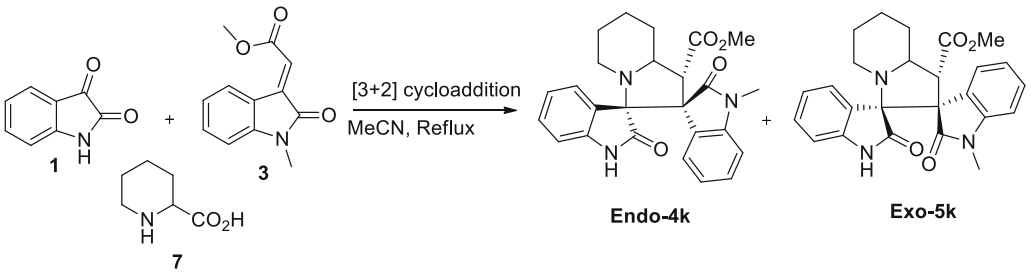


Figure 3. ORTEP view of compounds **4J**[15] and **5J**[16].



Scheme 3. Synthesis of dispiropyrrolidine oxindoles **4j** and **5j.**

62.5 ppm. The chemical shifts at δ 170.7 and 176.5 ppm are due to the presence of ester carbonyl and oxindole carbonyl carbon, respectively. The DEPT-135 spectrum showed a chemical shift at δ 52.1 corresponding to one -CH_2 carbon atom. The NMR data clearly confirms the structure of the compound **5a**. Moreover, the presence of a molecular ion peak at m/z 391 (M+1) in the mass spectrum has also confirmed the structure of the bisoxindole **5a**. The relative stereochemistry of the product **5a** was established through single-crystal X-ray analysis (Figure 2).

To improve the yield of the reaction, many efforts were made to optimize the reaction condition by varying solvent and reaction temperature. Solvent plays a key role in improving the reaction yield; therefore, various solvents such as THF, toluene, CH_3CN, CH_3OH and EtOH were screened for the reaction optimization. In general, aprotic polar solvents provided cycloaddition product in good to high yields, whereas protic polar solvents provided moderate to good yields. Thus, the optimum condition was observed with acetonitrile as a solvent led to the 99% desired product in quantitative yield (Table 1, entry **7**). The reason may be due to the good solubility of the dipolarophile in acetonitrile rather than protic solvents. However, methanol as a solvent gave the product only 70% yield (Table 1, entry **3**). On the other hand, when water was employed as a solvent, no product formation was detected (Table 1, entry **5**).

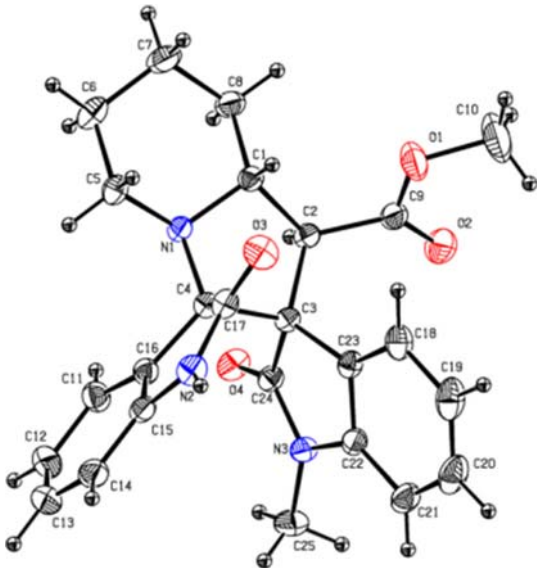
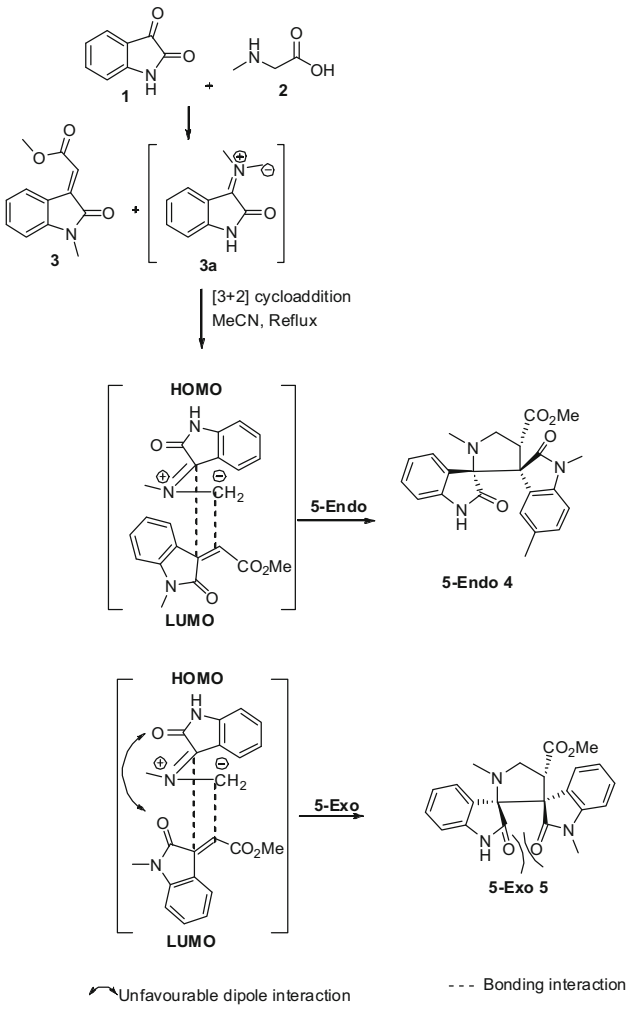


Figure 4. ORTEP view of compound **4K.**[17]



Scheme 4. Proposed models for *endo*/*exo* cycloaddition.

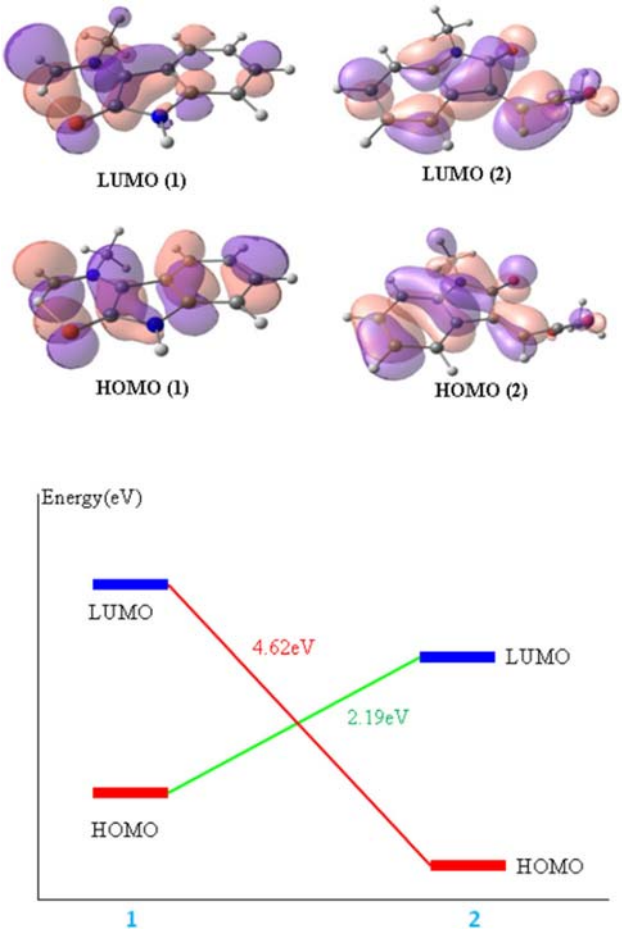


Figure 5. Frontier Molecular Orbitals (FMOs) of dipole **1** and dipolarophile **2**.

The reason may be due to poor solubility of dipolarophile in water. The effect of temperature also significantly influences the reaction yield. It was observed that acetonitrile as a solvent at 60 °C afforded 85% yield (entry **6**). When the temperature of the reaction was increased to 85 °C in acetonitrile, the yield of the products was improved to 99% (entry **7**), however, no appreciable change in the yield beyond the optimized temperature of 85 °C. Based on the comprehensive consideration of reaction temperature and yield, the optimal reaction condition was established in acetonitrile.

To establish the wider scope of the reaction, the effect of changing different substituents in isatin **1** and 2-oxindole-3-ylidene **3** with sacrosine 2 were attempted under the optimized conditions (Table 2). All the reactions underwent smoothly to generate the desired *endo'*- selective diastereo isomers **4** and **5** in good to excellent yields (Table 2). For instance, 2-oxindole-3-ylidene **3** with isatin **1** under the optimized conditions and the reaction accomplished desired *endo'*- selective

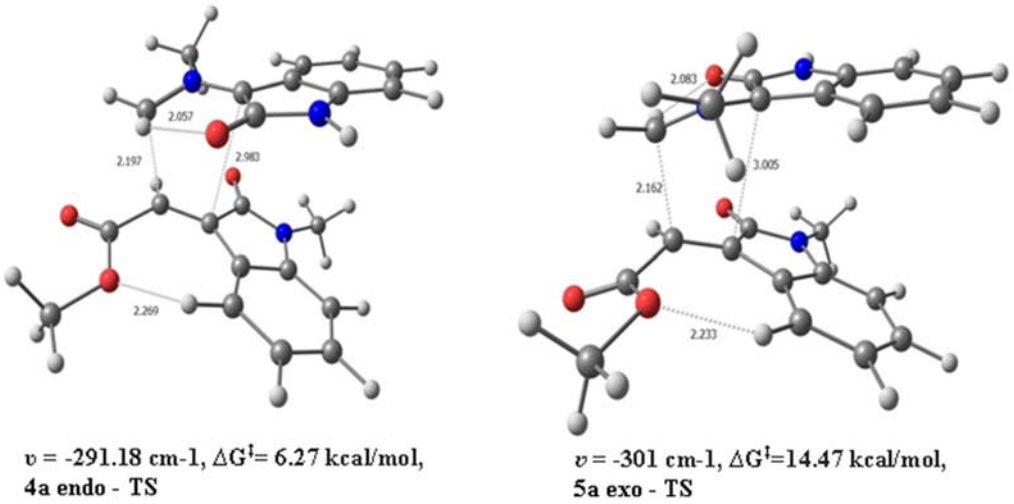


Figure 6. TS structures of dipolarophile **3** and dipole **3a** and their relative energies (kcal/mol).

diastereo isomers **4a** (91%) and **5a** (8%) in good yields (Table 2, entry **1**). When isatin **1** substituted at 5-position with an electron-withdrawing group such as fluoro, chloro, bromo and nitro group under the standard conditions and the reaction furnished desired *endo'*- selective diastereo isomers (**4b-4e)** and (**5b-5e**) in slightly reduced yields (Table 2, entries **2**–**5**). The reason may be due to electron-withdrawing group at 5-position of isatin **1** destabilizing the dipole during cyclo-addition. Similar yields were isolated when 2-oxindole-3-ylidene **3** bearing electron-withdrawing group at 5-position such as chloro, fluoro, bromo and nitro with unsubstituted isatin **1** (Table 2, entries **6**–**9**).

To extend the scope of the cycloaddition, we have performed the reaction by refluxing 2-oxindole-3-ylidene, sacrosine and acenaphthene quinine **6** under the optimized condition to afford respective dispiropyrrolidine bis-oxindoles **4j** and **5j** in good combined yields (Scheme 2).

The structures of **4j** and **5j** were confirmed by the single-crystal X-ray analysis (Figure 3).

Likewise, a reaction of isatin, 2-oxindole-3-ylidene and DL-pipecolinic acid under the optimized condition provided the products **4k** and **5k** in good combined yields (Scheme 3). The structure of **4k** was confirmed by the single-crystal X-ray analysis (Figure 4).

Based on the observed products, we have proposed a possible mechanism, as shown in Scheme 4. The factors determining the stereoselectivity of the 1,3-dipolar cycloaddition reaction as reported in the literature are complex. In the classic case, stereochemistry was governed by secondary orbital interactions (SOI) analogous to those directions the *exo*/*endo* approach in the Diels-Alder reaction. When secondary orbital interactions are negligible, the major product has been observed to be the *exo* **5**. However, in the present work, we obtained exo product only as a minor product. This may be due to the unfavorable formation of the *exo* product that leads to an adverse dipole-dipole interaction, in the transition state, between the carbonyl group of the dipole and dipolarophile.

Although the detailed mechanism of the above reaction is not fully clarified, the formation of *exo* and *endo* products could be explained. Decarboxylative condensation of isatin **1** with sacrosine **2** gives the azomethineylide (dipole **3a**) which then undergoes 1,3-dipolar cycloaddition reaction *endo*-selectively with the dipolarophile **3** as shown in Figure 5.

Frontier Molecular Orbitals (FMO) calculations have been analyzed to understand the observed selectivity. The FMO calculation revealed that the HOMO of dipole and LUMO of dipolarophile

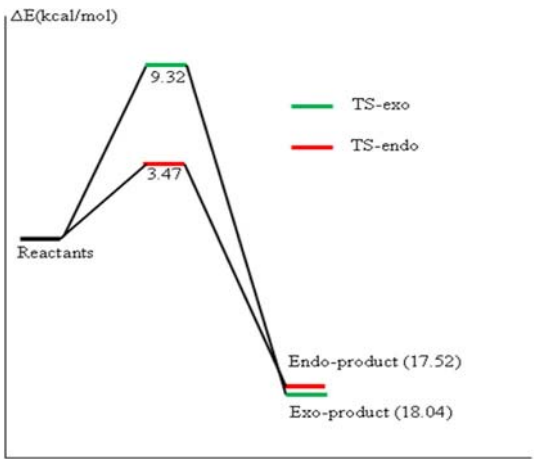


Fig. 7. Energy profile diagram for TSs. Energies (in kcal/mol) and computed at B3LYP/6-31g (d) level.

interaction is more feasible than the HOMO of dipolarophile and LUMO of dipole as shown in Figure 6.

Transition state (TS) analysis revealed that the ***endo*-TS** shows less energy of activation favoured than ***exo*-TS** by 8.23 kcal/mol (Figure 3). The reason due to the steric nature of the methyl group in isatin, which attacks through less hindered side in *endo*-TS. Thus, one can assume that ***endo*-TS** should have a lower energy of activation implies that ***endo*** should be the major product of the cycloaddition reaction. This observation is in good agreement with the experimentally observed selectivity. All geometry optimizations and frequency calculations were carried out on the reactants, transition states (TS) and products using the B3LYP/6-31G (d) level of theory. All gas-phase-optimized stationary points were verified as minima or first-order saddle points by the frequency calculations. All calculations were performed with the GAUSSIAN 09[18] program package, as shown in Figure 7.

4. Conclusions

In summary, 1,3 dipolar cycloaddition has been utilized for accessing a new series of spirooxindole derivatives in an efficient atom economical and one-pot multicomponent reaction. This approach promises good suitability in preparing numerous analogues that may prove to generate potential anticancer derivatives of this class of unique spirooxindole alkaloids. The methodology is a valuable contribution towards the synthesis[19] of novel *endo*'-selective spiropyrrolidine bis-oxindole frameworks. This methodology offers numerous advantages over the others that include accessible starting materials, mild reaction conditions, regio- and stereoselective methods along with high yield (up to 99%) without any side products.

Supplementary Information (SI)

Spectral data of all the synthesized compounds are available at www.ias.ac.in/chemsci.

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