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Stereo, Regio and Chemoselective [3+2]-Cycloaddition of (2E,4E)-Ethyl 5-(Phenylsulfonyl) Penta-2,4-Dienoate with Various Azomethine Ylides, Nitrones and Nitrile Oxides - Synthesis of Pyrrolidine, Isoxazolidine and Isoxazoline Derivatives and A Computational Study

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Stereo, Regio and Chemoselective[3+2]-Cycloadditionof (2*E*,4*E*)-Ethyl 5-(Phenylsulfonyl)Penta-2,4-Dienoatewith Various Azomethine Ylides, Nitrones and Nitrile Oxides- Synthesis of Pyrrolidine,Isoxazolidine and IsoxazolineDerivatives and A Computational Study

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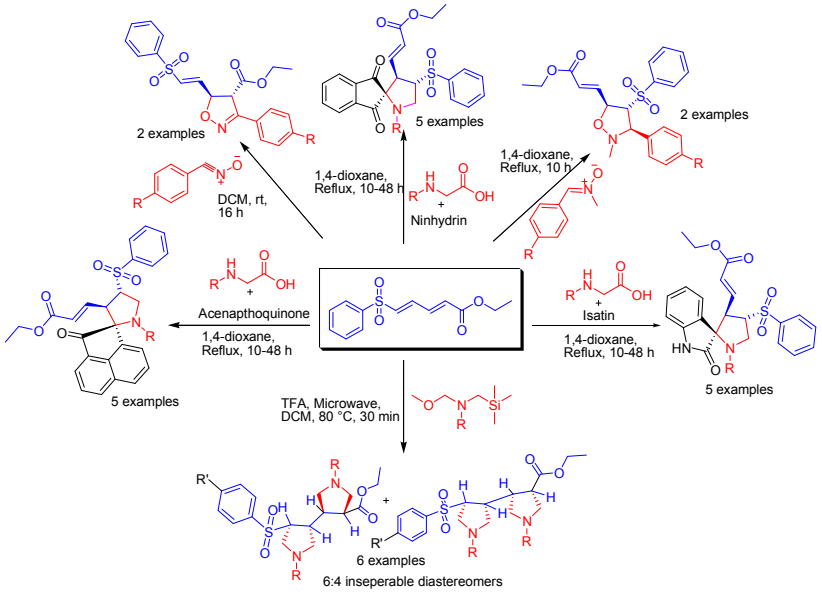
ABSTRACT: One pot chemo, regio and stereoselective synthesis of series of heterocyclic and spiroheterocyclic compounds were accomplished through mono and bis[3+2]-cycloaddition reaction of (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2, 4-dienoate as a dipolarophile with azomethine ylides,nitrones and nitrile oxides in good yields. The structure of the products were established by spectroscopic techniques as well as by single crystal XRD study and DFT calculation was performed to further understand the mechanism ofthis[3+2]-cycloaddition reaction.



INTRODUCTION

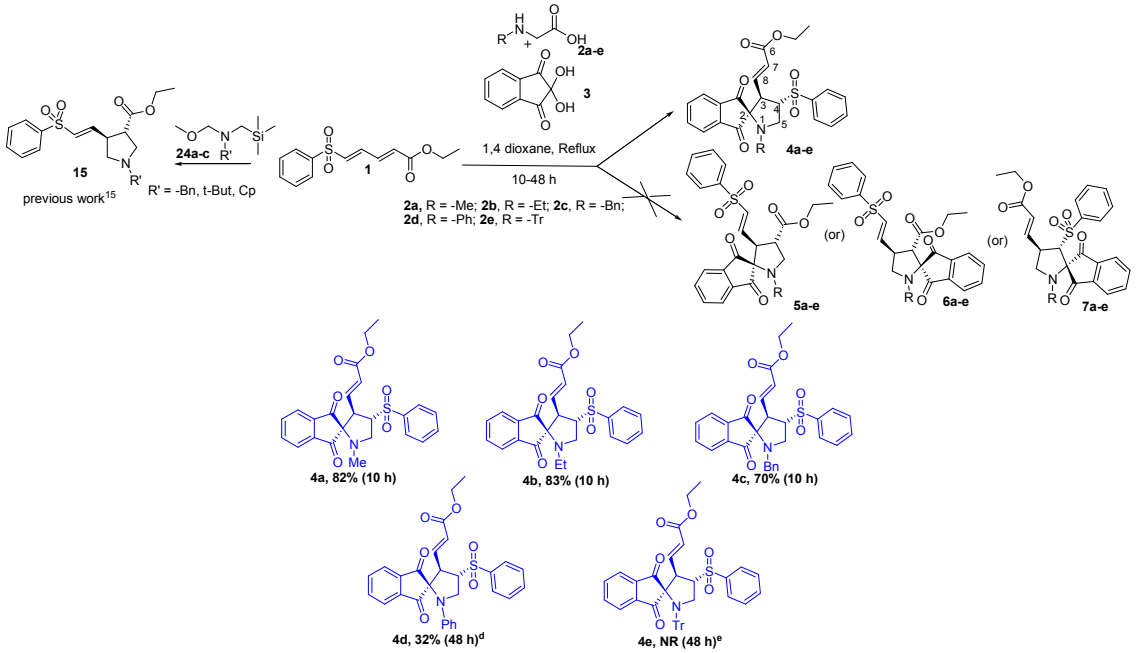
The [3+2]-cycloaddition, also known as the Huisgen cycloaddition,[1a] is a classical and fundamental reaction in organic chemistry, involving the reaction of 1,3-dipoles with olefinic or acetylenic dipolarophiles leading to production of various heterocyclic scaffolds which are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening.[1–5]There has been tremendous activity in this area since the discovery of clickreaction.[5f]Functionalized pyrrolidines, isoxazolidines and pyrrolizidines with spirooxindoles ring systems are the central skeletons for numerous alkaloids and pharmacologically important compounds.[6]Isoxazolidine unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds and displays a wide range of biological activity. Isoxazolidines are masked *γ*-amino alcohols. The N-O bond in isoxazolidines can be reductively cleaved to *γ*- amino alcohols which are present in a wide range of biologically active compounds.[7]Spiroheterocyclic compounds represent an

important class of naturally occurring substances characterized by highly pronounced biological properties. **Gelesmine**, **pseudotabersonine**, **isoformosanine**, and **mitraphylline** are some of the alkaloids containing spirooxindole ring systems.[8]Of particular interest, spiropyrrolidinyloxindole ring systems are also found in a number of alkaloids such as **horsifiline**, **spirotryprostatine A** and **B**, and **elacomine** etc.[9]Derivatives of spirooxindoles find very wide biological applications as anti-microbial, anti-inflammatory, anti-tumourals, anti-biotic agents and inhibitors of human NK-1 receptors.[10]Hence, there has been renewed interest in the synthesis of spirooxindoles.[11]

RESULTS AND DISCUSSION

Sulfonyl dienes like 1-arylsulphonyl 4-substituted-*E,E*-1,3-dienes have attracted considerable attention as dipolarophiles and in many cases they have been transformed into synthetically useful cycloadducts via chemoselective[3+2]-cycloaddition.[12a-c]Amalraj*et al*[13a]and Rusil*et al*[13b] have reported the [3+2]-cycloaddition of various azomethine ylides to dipolarophiles containing exocyclic double bonds.Recently Tanmaya*et al*[13c]reported the DFT calculations of regioselective [3+2]-cycloaddition of vinyl sulfones with sugarazides. Houk*et al*[14] have reported the HOMO-LUMO calculation for a number of electronegative alkenes. According to their FMO theory of calculation, the orbital coefficient of LUMO for ethyl acrylate is larger than that of phenyl vinyl sulfone, and carboxylate is a more powerful electron withdrawing group compared to that of phenyl sulphonyl group. Based on this, one can expect that in the case of the mono cycloaddition reaction of 1-arylsulphonyl 4-substituted-*E, E*-1, 3-dienes to azomethine ylides, might exhibit high chemoselectivity and that the reaction would occur at the acrylate double bond rather than at the vinyl sulphone double bond. In fact we had observed this chemo selectivity in the case of [3+2]-cycloaddition of simple acyclic azomethine ylides[15]to 1-arylsulphonyl 4-substituted-*E, E*-1, 3-dienes. We have recently observed that the chemo selectivity is dictated by the nature as well as by the steric bulk of the ylide (**Scheme 1**). In the case of azomethine ylides, the chemoselectivity could be tuned in favour of the vinyl sulphonyl double bond by changing its size which is also predicted by our DFT calculations.

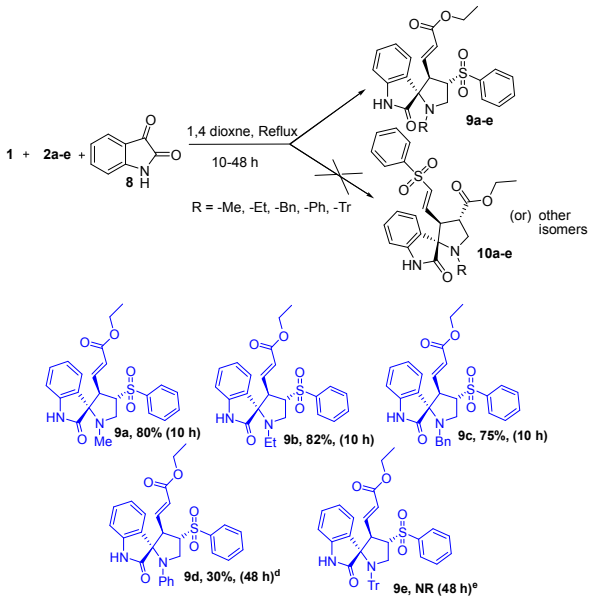
Scheme 1.Synthesis of spiropyrrolidines (4a-e)[a,b,c] via [3+2]-cycloaddition of diene 1and ninhydrin3 with various *N*-substituted glycine2a-e.



[a]All reactions were carried out with**1**(1 mmol), **3** (1 mmol) and **2a-e**(1 mmol) in 1, 4-dioxane (10 mL) at reflux for 10-48 h. [b]Isolated yield of the pure product. [c]All the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [d]crude LC-MS yield. [e]Noreaction.

In this publication, we describe a stereo and regioselective route for the synthesis of highly functionalized pyrrolidines based on chemoselective [3+2]-cycloaddition of azomethine ylides generated from *N*-alkyl-*α*-amino acids and cyclic ketones to (2*E*, 4*E*)-ethyl 5-(phenylsulphonyl)penta-2,4-dienoate and present also the conclusions derived from the DFT calculations of this cycloaddition reaction. Azomethine ylides can be generated a number of methods[16]among which the decarboxylation route offers a convenient method for the synthesis of pyrrolidines. We first investigated the one pot [3+2]-cycloaddition reaction of (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2,4-dienoate **1**[15] with dipoles generated *insitu* from sarcosine **2** and ninhydrin**3** as outlined in **Scheme 1**. A clean reaction was observed when **1** was refluxed in 1,4 dioxane for 10 h with sarcosine and ninhydrin without any catalyst, affording **4a** as the only cycloaddition productin very good yield (**Scheme 1**). LC-MS analysis of the crude product did not indicate the presence of any isomeric products like **5a, 6a** and **7a(Scheme 1).** The cycloadduct **4a** was characterized by ^{1}H NMR,^{13}C NMR spectra, HRMS, and X-ray single crystal analysis.[17] The reaction of **1** with *insitu*generated azomethine ylides from ninhydrin and ethylglycine orbenzylglycine orphenylglycine ortritylglycine (**2b-e**) in refluxing 1,4 dioxane (10-48 h) afforded the corresponding cycloadduct, viz., of (*E*)-ethyl 3-(1'-alkyl-1,3-dioxo-4'-(phenylsulfonyl)-1,3-dihydro spiro [indene-2,2'-pyrrolidine]-3'-yl)acrylate **4b-e** (**Scheme 1**) in good yield.We couldnotdetect the presence of the other regioisomers**5a-e, 6a-e** and **7a-e**, in any of the cases when the crude products were analysed by LC-MS. While it was easy to rule out the alternative structures from ^{1}H, ^{13}C, DEPT, COSY andHMBC spectral data, the relative stereochemistry at the spirocentre**C2** in the cases of **4a-e** could not be deduced from the NMR data. However, it could be fixed from the single crystal X-ray data of **4a**(Refer in supporting information (SI)).

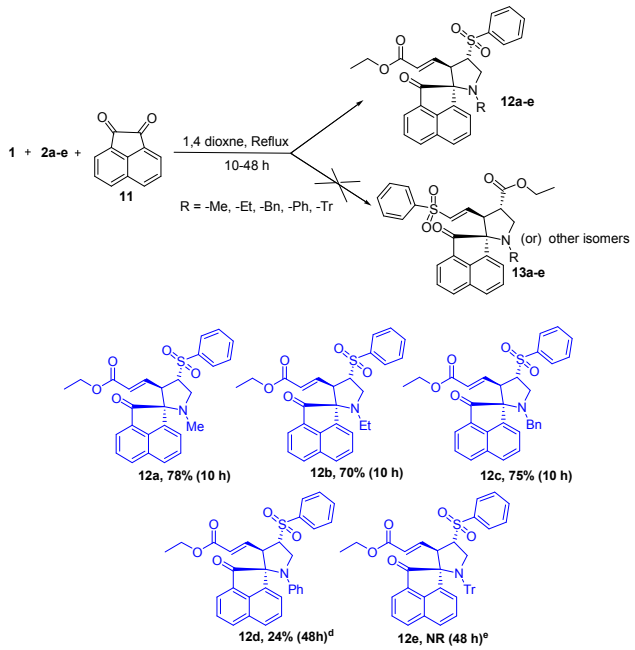
Scheme 2.Substrate scope forsynthesis of Spirooxindoles(9a-e)[a,b,c]



[a]All reactions were carried out with**1**(1 mmol), **8** (1 mmol) and **2a-e**(1 mmol) in 1, 4-dioxane (10 mL) at reflux for 10-48 h.[b]Isolated yield of the pure product. [c]All the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [d]crude LC-MS yield. [e]Noreaction.

Similarly the reaction of **1** with *insitu* generated azomethine ylides from isatin **8** and sarcosine orethylglycine or benzylglycine or phenylglycine or tritylglycine (**2a-e**) in refluxing 1, 4 dioxane furnished respectively the cycloadducts**9a-e**,[17] in good yield (**Scheme 2**). The reaction was highly chemo, stereo and regio selective in all cases, occurring only at the vinylsulphone double bond.Similarly, azomethine ylides generated from acenaphthenequinone reacted smoothly and yielded the spiropyrrolidine **12a-e**in good yields (**Scheme 3**). The chemo selectivity observed in the present case is in contrast to that observed in the case of acyclic azomethine ylide generated through desilylative method.[15]

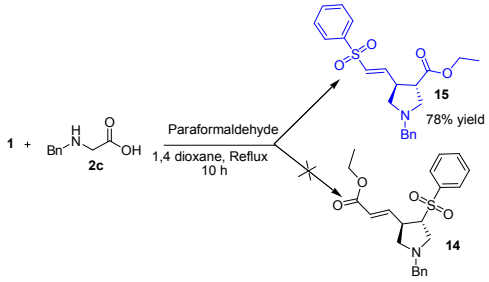
Scheme 3.Substrate scope for synthesis ofspiropyrrolidines(12a-e)[a,b,c]



[a]All reactions were carried out with**1** (1 mmol), **11** (1 mmol) and **2a-e** (1 mmol) in 1, 4-dioxane (10 mL) at reflux for 10-48 h.[b]Isolated yield of the pure product. [c]All the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS). [d]crude LC-MS yield. [e]Noreaction.

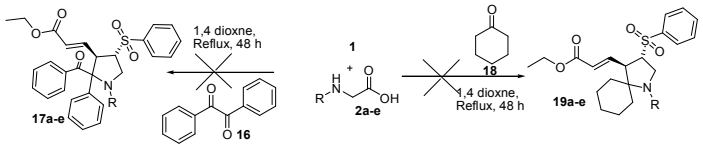
The chemo selectivity in the case of acyclic azomethine ylides generated by the desilylative method[15]was not altered when the same ylide was generated by the decarboxylative method (**Scheme 4**), indicating that the chemo selectivity is not influenced by the mode of generation of the ylide but is purely governed by the steric factors associated with the azomethine ylides. This inference has been supported by DFT calculations also which clearly reveals that chemo selectivity of cycloaddition is determined by the steric bulk of azomethine ylide.

Scheme 4.Synthesis of pyrrolidine15[a]via [3+2]-cycloaddition of diene 1 and *N*-benzyl glycine 2c with paraformaldehyde



[a]A reaction was carried out on **1** (1 mmol), paraformaldehyde (2 mmol) and **2c** (1 mmol) in 1,4-dioxane (10 mL) atreflux for 10 h. [b]The product was fully characterized by its spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

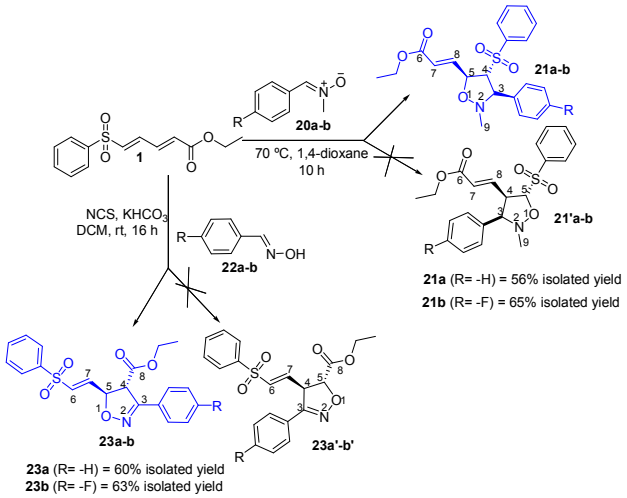
Scheme 5.Attempted Synthesis of spiropyrrolidines (17a-e, 19a-e)[a] via [3+2]-cycloaddition of diene 1 and *N*-alkyl glycine2a-e with benzil 16 or cyclohexanone 18.



[a]All the reactions were carried out with diene **1** (1 mmol), benzil**16**orcyclohexanone **18**(1 mmol)and **2a-e**(1 mmol)in 1,4-dioxane (10 mL) at reflux for 10-48 h.

We studied the reaction of **1** with *insitu* generated azomethine ylides from ninhydrin**3** and sarcosine **2a**in various solvents viz., toluene, methanol, 1, 4-dioxane and acetonitrile. 1, 4-dioxane was found to be the best in terms of yield, chemo, regio and stereoselectivity. Strangely there was no reaction in the case of tritylglycine even after 48 h and in the case of phenylglycine the yields of the cycloadduct **4d**, **9d** and **12d** were rather low (20-24%). While isatin, ninhydrin and acenaphthenequinone showed good reactivity, cyclohexanone and benzil, did not react under these conditions (**Scheme 5**). An attempt to react the mono cycloadduct **4a** with one more or excess equivalent of the azomethine ylide to get the bisadduct was in vain even after prolonged heating (48 h).With a view to explore the scope of this [3+2]-cycloaddition and also to find out whether the same chemoselectivity will be encountered in the case of other kinds of 1,3-dipoles, we investigated the reactionof **1**with nitrones**20a-b**and nitrile oxides precursor **22a-b**.[18a] In the event, we were surprised to note that while the cycloaddition in the case of nitrones occurred at the vinyl sulphonyl double bond, in the case of nitrile oxides it was the acrylate double bond that participated in the cycloaddition as outlined in **Scheme 6**.

Scheme 6.Substrate scope for synthesis of Isoxazolidines21a-b[a,b] and Isoxazolines23a-b[a,b]



[a]**Reaction condition for nitrone cycloaddition:**All the reactions were carried out on diene **1 (**1 mmol) with nitrone **20a-b** (1 mmol)in 1,4-dioxane(10 mL) at 70 ºC for 10 h. [b]All the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

[a]**Reaction condition for nitrile oxide cycloaddition:**All the reactions were carried out diene **1 (**1 mmol), Oxime **22a-b**(1 mmol), NCS (1.1 mmol) and $KHCO_3$(1.5 mmol) in DCM(10 mL) at rt for 16 h. [b]All the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

Nitrones (**20a-b**) were prepared according to literature procedure.[18b]A smooth reaction was observed when **1** was refluxed with nitrones **20a**in 1,4 dioxane for 10 h without any catalyst, affording isoxazolidine derivative **21a** in 56% yield (**Scheme 6**). LC-MS analysis of the crude productdid not indicate the presence of any isomeric products**.**Similarlytreatment of **1** with nitrone **20b**afforded the isoxazolidine**21b**.Structural elucidation of the isoxazolidine **21b** was accomplished using 1D, 2D NMRspectroscopy andHRMS. We have observed in our earlier work[15] that the olefinic protons of the vinyl sulphonyl moiety in the mono [3+2]-cycloadducts resonate in the regionof δ 6.6 and 6.9 asdoubletand doublet of doublet respectively. In the case of the adduct **21b**the signals of olefinic protons appeared at δ 5.9 and 6.8, indicating that the cycloaddition has occurred on the vinylsulphonyl double bond. This was further evident from the HMBC spectrum which showed a correlation between the olefinic proton**H7** at δ 5.93 (1H, d, J = 15.5 Hz) and the ester carbonyl at 165.91(Ref Page **S59**–**S63**in SI).In the ^{1}H NMR spectrum of **21b**the **H4** and **H3** proton of the isoxazolidine moiety resonated as doublet of doublet at δ 3.85 (J = 7.6, 4.4 Hz) and doublet at δ 3.95 (J = 7.2 Hz) respectively.The **H5** proton of the ring appeared as triplet at δ 5.19 (J = 5.5 Hz). The **H7** alkene proton appeared as doublet at δ 5.93 (J = 15.50 Hz) and the **H8** alkene protonresonated atδ 6.86 as a multiplet.The H,H-COSY spectrum revealed a correlation between **H4** proton at δ 3.85 ppm with **H3** proton at δ 3.95 ppm while there was no correlation between **H5** proton at δ 5.19 ppm with **H3**proton at δ 3.95 ppmwhich is consistent with the

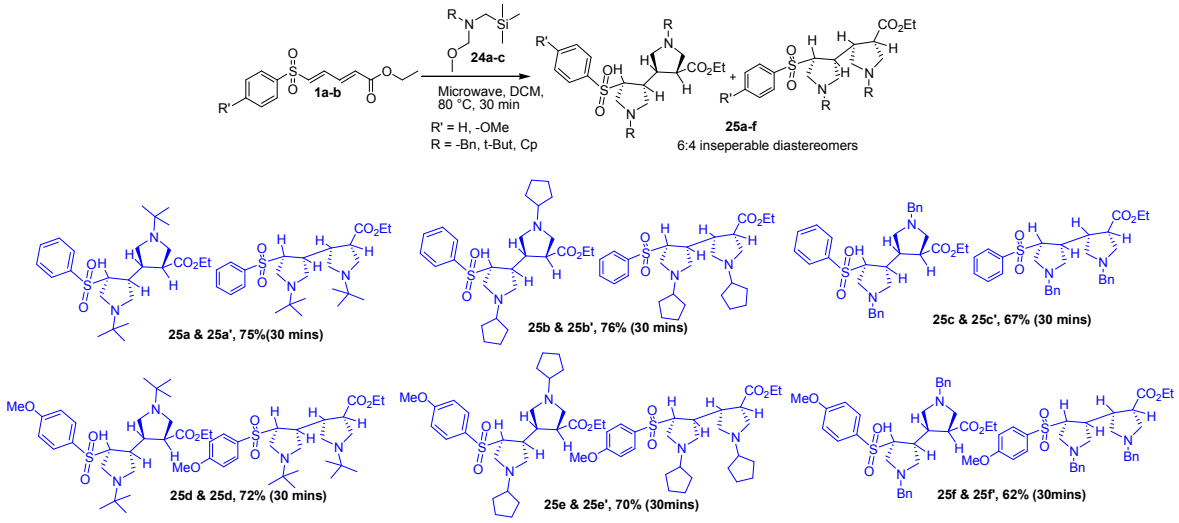
observed regioselectivity of cycloaddition. The NOESY NMR spectrum was also informative. It showed a correlation between the**H3**and **H5** proton indicating a cis relationship. A correlation between **H4** with **H8**proton was also noticed in the NOESY spectrum. Thus the relative stereochemistry between the three centres, viz. 3, 4 and 5 have been fixed. The chemoselectivity observed in the case of nitrones was also predicted by DFT calculations. The regiochemistry observed in the present study was similar to what has been reported in literature for nitrone [3+2]-cycloaddition to electron deficient olefins.[18c-f]

The reaction of **1** with nitrile oxides[18g] generated*insitu*from benzaldoxime(**22a-b)**, furnished respectively the 2-isoxazolines derivatives**23a-b** in good yield (**Scheme 6**). Interestingly the chemo selectivity observed in the caseof nitrile oxide cycloaddition was opposite to that of the nitrone cycloaddition reaction.This was evident from a glance of the ^{1}H NMR spectrum, particularly that of the olefinic region (Ref Page **S64-S68**in SI). One of the alkeneprotons, viz.,**H6**appeared as a doublet at δ 6.76 (J = 14.9 Hz) and the otherproton **H7** as a doublet of doublet at δ 6.96 (J = 14.9 Hz, J = 4.4 Hz).The ^{1}H NMR spectrum of **23a**exhibited a doublet at δ 4.36 (J = 5.6 Hz) for **H4**proton of the 2-isoxazoline moiety.While the**H5**proton resonated as triplet at δ 5.62 (J = 5.8 Hz). The H,H-COSY spectrum of **23a** showed correlation between the olefinic proton **H7** at δ 6.96 ppm with the proton at **H5** δ 5.62 ppm which in turn showed correlation with the proton **H4**at δ 4.36 ppm, establishing the regioselectivity,as well chemoselectivity. The correlation observed in the HMBC spectrum was in accordance with the assigned structure.

BIS [3+2]-CYCLOADDITION:

Next we explored the feasibility of synthesisofbis pyrrolidine by bis [3+2]-cycloaddition of azomethine ylides (**24a-c**) to the dienes(**1a-b**).

Scheme 7.Substrate scope for synthesis of bis pyrrolidines 25a-f[a,b,c] via[3+2]-cycloaddition of dienes1with*N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl) alkylamine24a-c.

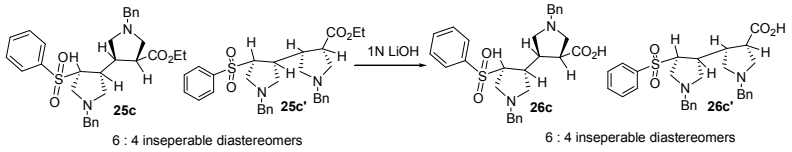


[a]All reactions were carried out on **1a-b**(1 mmol), **24a-c**(3 mmol) and TFA (0.2 mmol) in DCM (5 mL), microwave at 80 °C for30 min. [b]Isolated yield after flash column chromatography.[c]All the compounds were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS).

Literature survey[19,20]shows that [3+2]-cycloaddition of azomethine ylides with conjugated dienes leads to a mixture of mono and bis pyrrolidines. In the present work, bis[3+2]-cycloaddition reaction of azomethine ylides generated *insitu* by desilylation of synthons **24a-c**with 1-arylsulfonyl-4-ethoxycarbonyl 1, 3-dienes (**1a-b**) under microwave condition was investigated. Initially *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)benzylamine (**24c**) was selected as the dipole for the bis[3+2]-cycloaddition of diene**1a** as outlined in **Scheme-7**.All the azomethine precursors(**24a-c**) were prepared by the

known literature procedure[21] and were characterized thoroughly by spectral means. When **1a** reacted with **24a-c**in the absence of microwave irradiation, it led to a mixture of mono and bisadduct onlyeven under prolonged heating condition (24 h) in various solvents. However, under microwave condition, the bisadducts were obtained in good yield as a mixture of two inseparable diastereomers in all the examples studied. In a typical experiment, microwave irradiation of a solution ofTFA azomethine ylide precursor **24c** and the dipolarophile **1a** in dry dichloromethane in the presence of TFA at 80 °C in microwave for 30 minled to clean reaction, affording the bis cycloadduct as an inseparable mixture of diasteromers **25c**and **25c'**in 67% yield. Under these conditions, the mono adduct was not observed. By adopting this method a number ofbis pyrrolidine derivatives **25a-f** (**Scheme-7**) were synthesized in good yields.In all the cases the products appeared to be homogeneous on TLC and the complexity could not be deciphered from ^{1}H and ^{13}CNMR spectra. HPLC analysis of the bisadducts from reaction of **24a-b**, showed only a single peak in several solvent systems studied. However in the case of the bisadduct from the reaction of **24c,**HPLC showed two peaks with retention times of 21.927 & 22.069 min in the ratio of 6:4(Page **S85**inSI) and revealed it to be a mixture of two products. LC-MS revealed them to be isomeric, suggesting that they are diasteromers. When the mono pyrrolidine adduct **15**, independently synthesized[15], was reacted with anotherequivalent of the same azomethine ylide**24c**under microwave irradiation condition, it afforded the same bisadduct**25c**as was obtained from the direct reaction.It was hoped that hydrolysis of the ester functionality in **25c** would furnish the diasteromeric acids which would show different TLC mobility and thus facilitate their separation by column chromatography. With this intention, hydrolysis of the bisadduct **25c** was carried outunder mild basic conditions to ensure that in this process, the stereocentres at the sulphonyl end and ester end would not undergo epimerization. Exposure of the mixture of diatstereomeic esters **25c** and **25c'** to a 1N solution of LiOH at rt for 16 h, lead to a smooth saponification and furnished a mixture of the diasteromeric acids **26c** and **26c'** as depicted in **Scheme 8**.

Scheme 8.



The diasteromeric ratio of the carboxylic acids **26c** and **26c'** was determined by reverse phase HPLC analysis, and found to be nearly the same (6 : 4) (Page **S86** in SI)as that of the starting esters **25c** and **25c'**. Esterification of these diasteromeric mixture carboxylic acids **26c** and **26c'** with ethanol and oxalylchloride furnished a product which exhibited the same diasteromeric ratio and retention time in HPLC as that of the original ester **25**c and **25c'** obtained in the direct bis cycloaddition reaction, thus confirming that the in the course of the basic hydrolysis, the chiral centres were not epimerised and were intact. Since the [3+2]-cycloaddition is a concerted synprocess the stereochemistry at canters **2**and 5as well as at **6** and **9** can be fixed as *trans*. Both the two cycloadditions can occur on the same phase of the 1, 3-diene π frame work or they can occur on the opposite phases of 1,3-diene π frame work. Thus the two diasteromers should differ only in the configuration at the 3,4 carbons of one of the pyrrolidines rings as visualized in **Figure 1**.

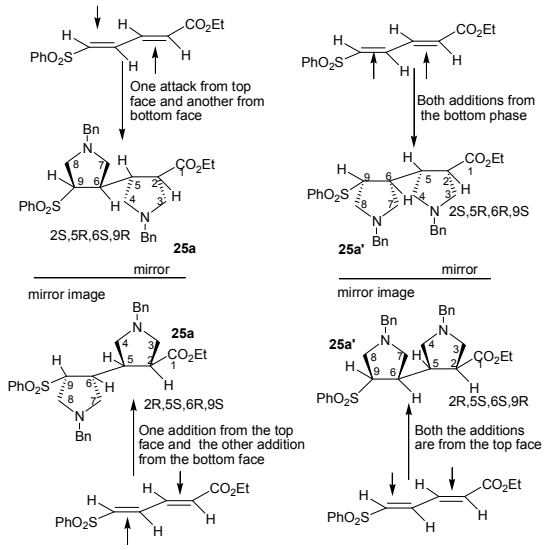


Figure 1. Mode of bis dipolar cycloaddition of dipole **24c** with diene **1**.

COMPUTATIONAL DETAILS

The geometries of reactants, products and all the transition states (TSs) were optimized using Density Functional Theory (DFT) based Becke's three parameter hybrid functional and Lee-Yang-Parr's[22] correlation functional (B3LYP) method employing 6-31G(d)[23]basis set. All these calculations were performed using Gaussian 09 suite of programs.[24]All gas-phase-optimized geometries were verified as minima or first-order saddle points by the frequency calculations. As in the standard practise, the presence of one imaginary frequency criteria was used for the characterization of TSs. Further, the transition states were also verified by the intrinsic reaction coordinate (IRC) calculations.[25,26]The fragment distortion and interaction energies were computed at M06-2X/6-311G(d,p) level of theory by single point energy calculations on B3LYP/6-31G(d) optimized geometries.

The global reactivity indices were estimated using the standard working equations proposed by Parr and Yang.[27] The global hardness (η) and electronic chemical potentials (μ) were evaluated using the energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The Hirschfeld charges were calculated using B3LYP/dnd method implemented in DMOL^3 programme. These charges were used to calculate the local reactivity descriptors such as condensed Fukui functions of reactants.

The aim of the computational calculation performed is to understand the mechanism of cycloaddition reaction. The nature of the reactants and their feasibility to undergo reaction upon substitution on ylides with different groups was also investigated. First of all, we examined the regioselectivity between **1** and the ylides. Overall reactivity and site selectivity of reactants and their individual atoms can be explained using global and local reactivity indices. The global nucleophilicity (N)[28]was calculated by using the equation (1)

$$N = E_{HOMO(nucleophile)} - E_{HOMO(TCE)} \qquad (1)$$

Where tetracyanoethelene (TCE), is taken as a reference as it has lowest HOMO energy and large electrophilicity value (ω = 5.90 eV).

The local reactivity indices such as, local electrophilicity (ω^+_k)[29] and the local nucleophilicity (N_k)[30]condensed to a particular atom k were calculated from nucleophilic and electrophilic Fukui Functions[31]using equations (2) and (3).

$$\omega^+_k = \omega f^+_k \qquad (2) \text{ and}$$

$$N_k = N f^-_k \qquad (3) \text{ where } f^+_k \text{ and } f^-_k \text{ are Fukui functions.}$$

Reactants

The reactant (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2, 4-dienoate (**1**) is an acyclic conjugated diene. The double bond which is next to the ester group is denoted as C1-C2 and double bond adjacent to phenyl sulphonyl group is referred to as C3-C4. **1** prefers to exist in the s-*trans* conformation for steric reasons but during the [2+ 3] cycloaddtion reaction, it reacts with its counter parts in the s-*cis* conformation. The s-*cis* conformation is less stable than s-*trans* conformation only by 3.31 kcal/mol due to the steric interaction between hydrogens of C1 and C4 atoms. We have carried out the calculations for the reaction of s-*trans* diene with all the dipoles. However, we could locate the transition states only for the reaction outline in Scheme 1. For the[2+3] cycloaddition reaction outline in the scheme 1, the calculated energy of activation in the case of reaction involving the diene 1 in s-*trans* confirmation is quite appreciably high when compared to that of s-*cis* diene ($\Delta G^{\ddagger}_{s\text{-}trans}$-$\Delta G^{\ddagger}_{s\text{-}cis}$ ~6.0 kcal/mol). Under the reaction conditions (reflux in dioxane) **1** is easily converted from s-*trans* into the more reactive s-*cis* conformation and tries to achieve a flat planar structure, before it reacts with the dienophile. The energy profile for s-*trans* to s-*cis* transformation is shown in **Figure 2**.

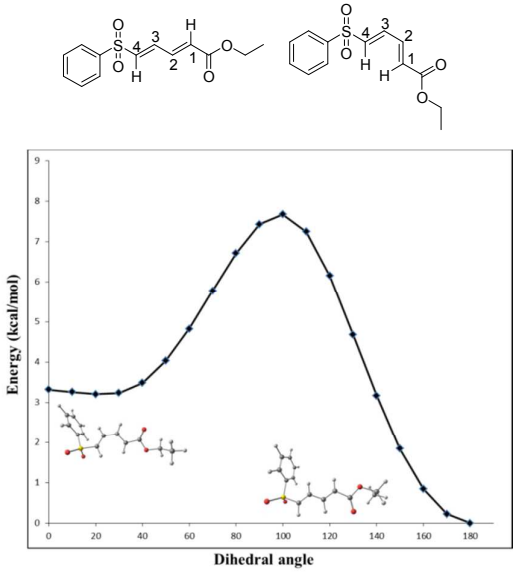


Figure 2.Structures of s-cis, s-trans conformations and S-trans to S-cis transformation of **1**.

Global and Local Properties

In order to rationalize the chemoselectivity and regioselectivity, we calculated conceptual density functional theory based global and local reactive descriptors. The calculated reactivity descriptors are listed in supporting information (SI) (**Table S1** and **S2** respectively). The analysis of global reactive indices suggests that, electronic chemical potential of dipoles (azomethine ylides, nitrones and nitrile oxides) (-0.110 to -0.135 a.u.) is higher than that of dipolarophile (**1**) (-0.173 a.u.) indicating that, the charge transfer will take place from the dipole towards dipolarophile. **1** has strong electrophilic character with large global electrophilicity (ω) value of 2.35 eV. The chosen dipoles are nucleophilic in nature due to their low ω values (0.4 to 2.1 eV) and high global nucleophilicity values (N). The dipoles of **18** (**18a-e**) have large ω values compared to other dipoles. Thus, the dipoles of **18** may react slowly with **1**. It can be seen from the results for **Schemes 1-5**, the nucleophilic nature of ylides increases graduallywith substitution of alkyl groups on nitrogen which is due to the electron releasing nature of alkyl group. On the other hand, for **Scheme 6**, the nucleophilic nature of dipole decreases due to the substitution of electronegative fluorine atom. On the whole, diene **1** will act as electrophile and dipoles will act as nucleophile.

The diene **1** has highest electrophilic activation (ω_k^+ =0.25 eV) at C4 in contrast to other three active carbons C1, C2 and C3. The C1 has more nucleophilic character (N_k = 0.26 eV) when compared to C4 (N_k =0.21 eV). In other words, even though, the electrophilic nature of C1 is nearly as same as C4, nucleophilic character of C1 atom dominates its electrophilic character, making C4 atom, a preferable electrophilic site in diene **1** for nucleophilic attack. The electrophilicity at C4 can be attributed due to the presence of strong electron withdrawing phenyl sulphonyl group at C4. On the other hand at C1, the ester group which is also an electron withdrawing but not as strong as phenyl sulphonyl. It is clear from the results that C3-C4 is more favourable double bond for 1, 3-dipolar cycloaddition reaction than C1-C2 double bond, and C4 be the preferable electrophilic site for nucleophilic attack. The dipoles have the largest nucleophilic activation at C7 (O7 for nitrone and nitrile oxide). Thus, C7 and O7 are the nucleophilic sites in dipoles. These findings reveal that C4 of **1** is preferred electrophilic site for nucleophilic attack (C7/O7) of dipoles which confirms the regioselectivity of 1,3-dipolar cycloaddition reactions.

Geometries of TSs

The geometries of TSs and the respective energy profile for the **Schemes 1-6**are depicted in **Figure 3-10** respectively. The TS structures are named according to their corresponding ylide/nitrone labelling (numbering). The careful examination of geometrical parameters of various TSs reveals that, for the **Scheme 1**, the newly forming C-C bonds for TS1 are longer than the forming C-C bonds of TS2, TS3 and TS4. The longer forming C-C bonds of TS1 implying lesser steric repulsion between reacting groups. The geometrical parameters of this transition state (TS1) resemble reactants indicating early transition state nature. On the other hand, the shorter forming C-C bonds of TS2, TS3 and TS4, reveal that there is a considerable increase in the steric repulsion between the reacting groups which leads to the destabilization of the corresponding transition states. The similar reactivity trend as of **Scheme 1** is also observed in the case of **Schemes 2 and 3**.It is interesting to note different trend in the reactivity for **Scheme 4**. The newly forming C-C bonds in TS1 are shorter than that of corresponding C-C bonds in TS2. In all the transition states of all the Schemes, the incoming bonds (C-C bonds in **Schemes 1-5** and C-O and C-C bonds in **Scheme 6**) form with unequal bond lengths showing the asynchronous nature of transition states. The degree of synchronicity can be measured by the difference between the ratios of the forming bond lengths in the TS and the corresponding bond lengths in the product ($\Delta\mathbf{d}_{TS/P}$).[32]The bond lengths of newly forming bonds and $\Delta\mathbf{d}_{TS/P}$ values are listed in SI (**Table S3)**. For **Schemes 1-6**, $\Delta\mathbf{d}_{TS/P}$ values indicate TSs areasynchronous nature. However, **Scheme 5**, $\Delta\mathbf{d}_{TS/P}$for TSs in Scheme 5 is higher (> 0.70) which indicates that, the reactions are strongly asynchronous.

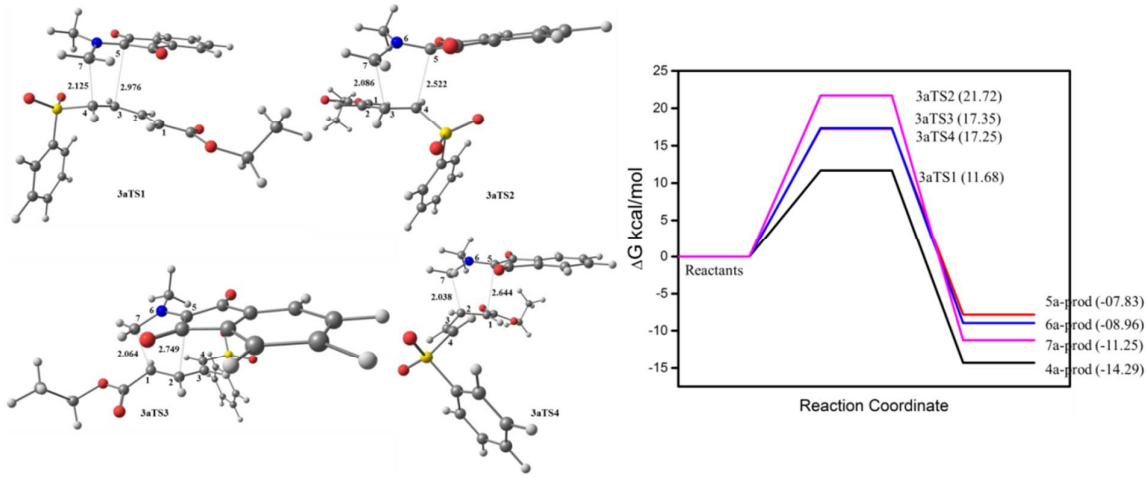


Figure 3 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **3a (Scheme 1)**, computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen)

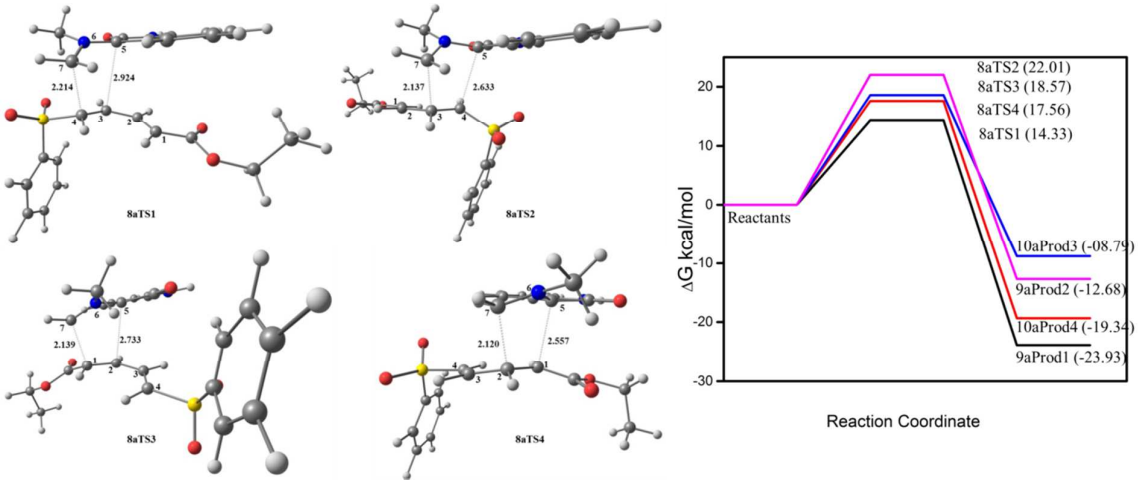


Figure 4 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **8a** (**Scheme 2**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

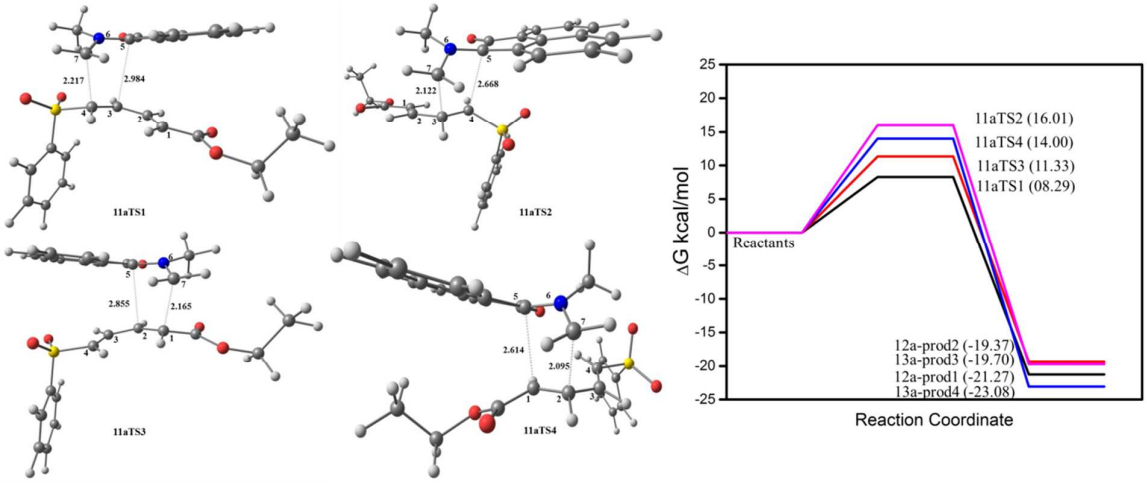


Figure 5 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **11a** (**Scheme 3**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

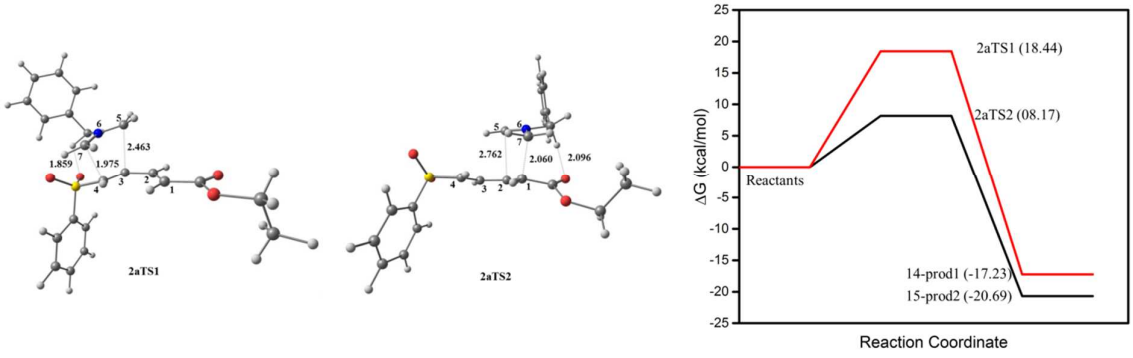


Figure 6 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **2a** (**Scheme 4**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

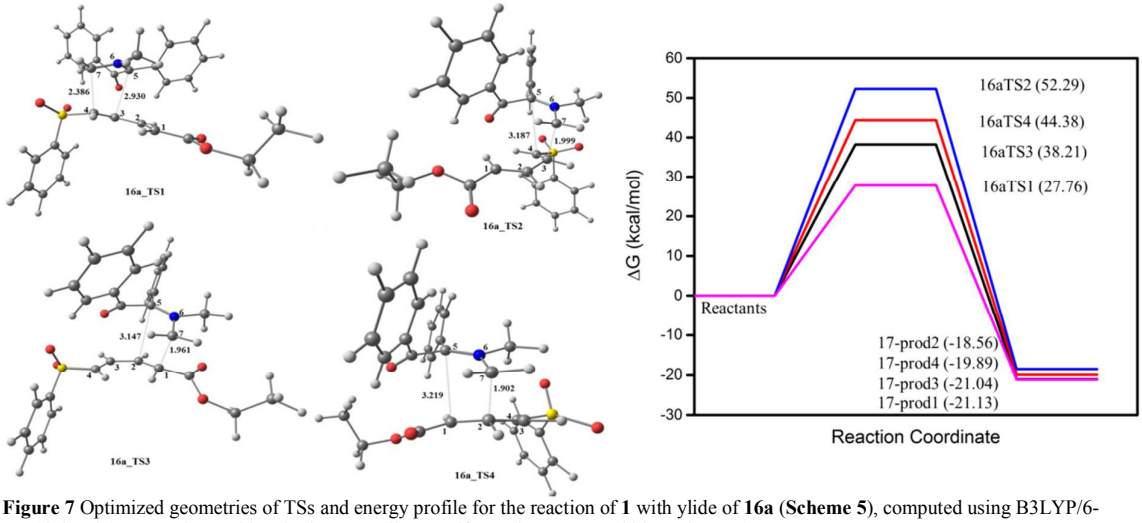


Figure 7 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **16a** (**Scheme 5**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

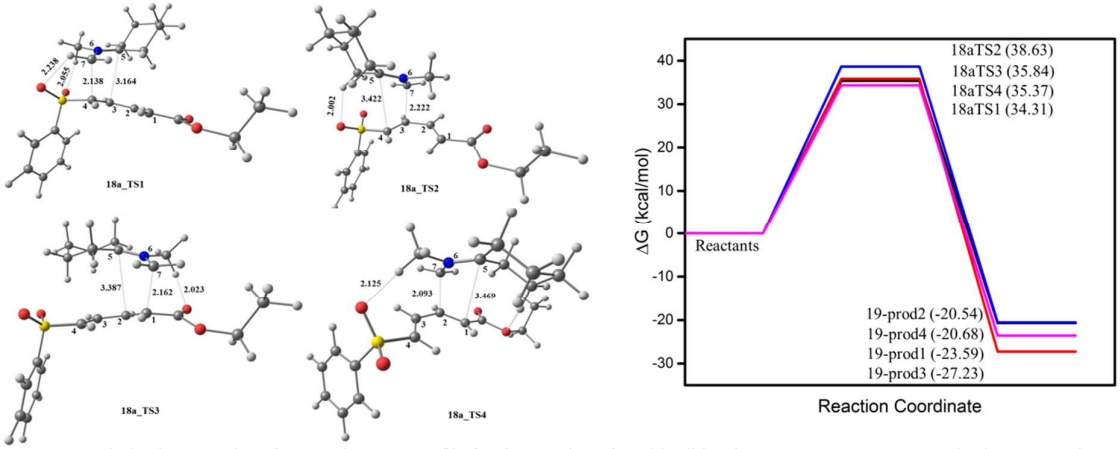


Figure 8 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **18a** (**Scheme 5**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

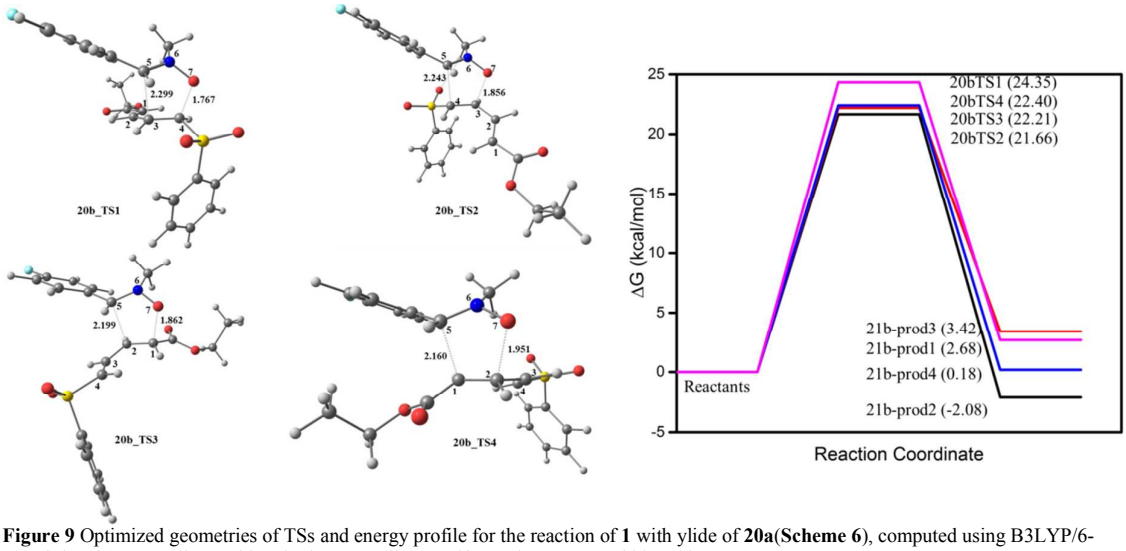


Figure 9 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **20a**(**Scheme 6**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

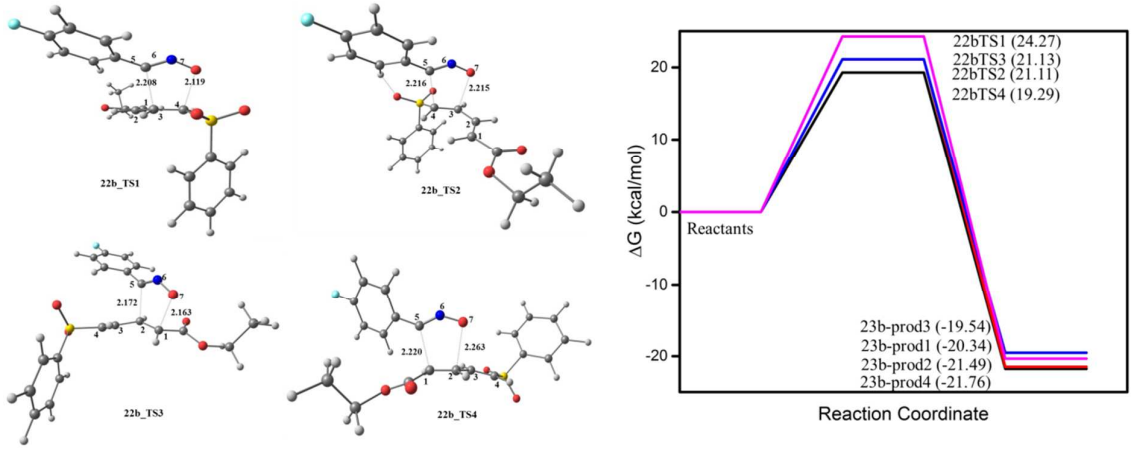


Figure 10 Optimized geometries of TSs and energy profile for the reaction of **1** with ylide of **22a** (**Scheme 6**), computed using B3LYP/6-31g(d) level (grey- carbon, white– hydrogen, yellow– sulfur, red- oxygen and blue- nitrogen).

Distortion/Interaction Analysis:

The distortion/interaction transition state model developed by Ess and Houk is a highly insightful method for understanding reactivity and activation barriers in cycloadditions[33]. The energy of activation ($\Delta E^{\ddagger}$) is divided into two major components called distortion energy ($\Delta E^{\ddagger}_{dist}$) and interaction energy ($\Delta E^{\ddagger}_{int}$). Distortion energy is calculated as the difference in energy of the reactants between distorted geometry and the fully optimized ground state geometry. The interaction energy is the energy difference between the energy of the geometry on the reaction coordinate and the energy of the corresponding distorted diene and dienophile parts. The $\Delta E^{\ddagger}_{dist}$ is the energy utilized for distorting reactant geometry to form product. Higher value of $\Delta E^{\ddagger}_{dist}$signifies requirement of considerable activation barrier.

The calculated distortion and interaction energies are tabulated in SI (**Table S4 and S5**). It is evident from the results that the TS which has low distortion energy and high interaction energy, has low activation barrier. In the case of **Schemes 1, 2 and 3**, TS1 and TS3 have low and comparable distortion energies. Thus, the reactivity is governed by interaction energy. $\Delta E^{\ddagger}_{int}$ is highest for TS1 which confirms the requirement of low activation barrier. For **Scheme 4**, TS2 has less distortion and more interaction energies and hence lowest activation barrier.

In the case of **Scheme 5**, the reaction is completely controlled by the distortion energy of reactants. It can be seen that there is no appreciable contribution from the $\Delta E^{\ddagger}_{int}$. Since $\Delta E^{\ddagger}_{dist}$ is high, the activation barriers are also high. On the other hand, for **Scheme 6**, in the case of nitrones, TS2 exhibits less activation energy, which is controlled by $\Delta E^{\ddagger}_{int}$ as distortion energy is similar for all the TSs. As compared with nitrones in **Scheme 6**, nitrile oxide dipoles have high $\Delta E^{\ddagger}_{dist}$. This is may be due to the presence of triple bond in nitrile oxide which requires more energy for distortion. As a consequence, the activation barriers are high.

The distortion/interaction analysis also suggest the stereo selectivity of 1,3 dipolar cycloaddition reaction. For all the schemes, Exo TSs exhibit low $\Delta E^{\ddagger}_{dist}$which is responsible for low activation barrier than endo TS. The $\Delta E^{\ddagger}_{int}$values also suggest that, the reaction pathway involving TS_{ex} is feasible.

Energies of TSs

The reaction energies and activation barriers associated with TSs of all schemes are compiled in SI (**Table S6)**. In the case of **Schemes 1-3**, the reaction pathway associated with TS1 is more favourable as the activation barriers are low. Accordingly, it can be predicted that the product associated with TS1 of these schemes will be dominating, in agreement with the experimental observations. In the case of **Scheme 4**, TS2 has lowest activation barrier compared to TS1. Hence, the reaction at C1-C2 is favourable for **Scheme 4**. In the case of **Scheme 5**, the activation barriers are very high (30-50 kcal/mol). This may be due to the steric repulsions exerted by bulky groups. It requires more energy to cross the activation barrier. Thus, the reaction may not undergo further in normal reaction conditions. In the case of **Scheme 6**, for dipoles of nitrone**20b**, the activation barrier for TS2 is low, which means nitrone (**20b**) reacts with C3-C4 double bond by bonding the most

nucleophilic O7 with C3 whereas for nitrileoxide the reaction happens at C1-C2 double bond through TS4. In this case, most nucleophilic O7 bonded with C1.

The stereoselectivity of [3+2]-cycloaddition reactions can be explained by reaction energies of exo-endo isomers. The reaction involved TS_{ex} is the most favourable reaction pathway due to its low activation barrier and formation of stable product. The TSs of exo and endo pathways for [3+2]-cycloaddition reaction of **1** with dipole **3a** (**Scheme-1**) and their corresponding energy profileare shown in **Figure 11** (geometries and energy profiles of all other schemes are given in SI as **Figure S3- S12**). The activation energies of endo and exo attacks for all the schemes are tabulated in SI (**Table S7**).

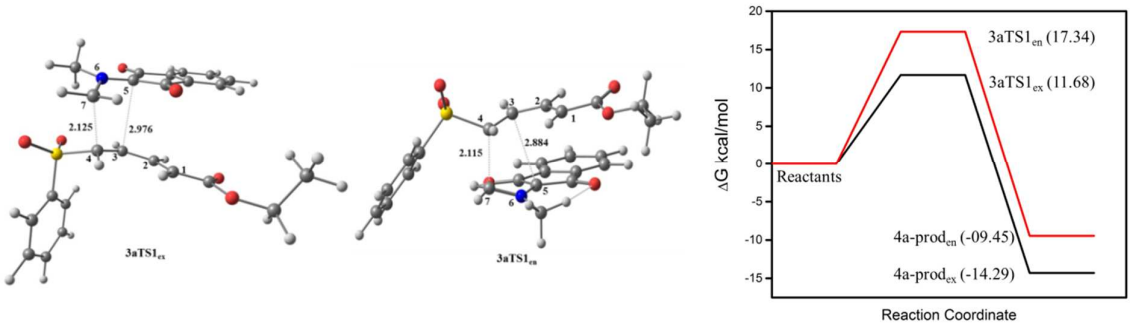


Figure 11 Optimized geometries and energy profile of exo and endo TSs for the reaction of **1** with ylide of **3a** (**Scheme 1**).

Scheme 7 illustrates theaddition of dipole at free double bond to form a *bis*product. The two possible reaction path ways for bisaddition of dipole were investigated. The TSs and corresponding energy profiles for *bis*addition are shown in **Figure 12**. The reaction energies are given in SI (**Table S8)**. The TSs associated with the two pathways have high activation barriers (34-35 kcal/mol) which elucidate that, the reaction may be possible on heating. The TSs and products of both pathways are separated by 1.0 kcal/mol each. Thus, the reaction is possible via both the pathways which may lead to the formation of racemic mixture of products (**25c** and **25c'**).

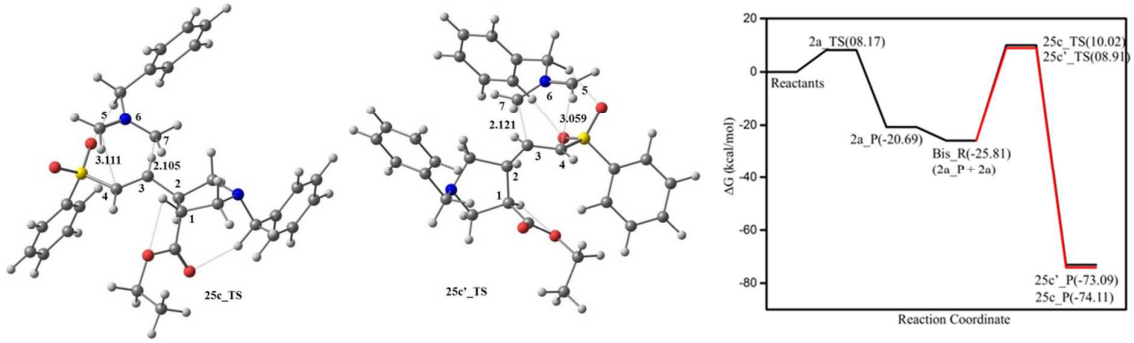


Figure 12 Optimized geometries and energy profile for TSs of bis reaction (**Scheme 7**).

CONCLUSIONS

In conclusion, we have demonstrated that the chemoselectivity of the cycloaddition of azomethine ylides to (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2, 4-dienoate is dependent upon the nature of the dipole as well as by its steric bulk. While simple azomethine ylides underwent the [3+2]-cycloaddition preferentially at the acrylate double bond, sterically bulky azomethine ylides exhibited opposite chemoselectivity, reacting at the vinylsulphonyl double bond. In the case of nitrones the cycloaddition occurred at the vinyl sulphonyl double bond, whereas in the case of nitrile oxides it took place at the acrylate double bond. The analysis of activation barriers, global and local reactive indices has been studied in order to rationalize the regioselectivity. The nucleophilic and electrophilic sites involved in the reaction and the effect of substitution on ylides are

explained using global and local reactive descriptors. The regioselectivity is also revealed by the reaction energies. Geometrical parameters and bond lengths of newly forming bonds indicate that the cycloaddition reactions follow a concerted mechanism with asynchronous transition states. The failure of the diene **1** to undergo the [2+3]-cycloaddtion with the 1,3-dipoles generated from benzil **16**/ cyclohexanone **18** and *N*-alkylglycines **2a-e**, outlined in **Scheme 5** is also explained by the high activation barriers of the transition states.

EXPERIMENTAL SECTION

General considerations: All reactions were carried out under an atmosphere of dry nitrogen. All reagents were purchased from commercial sources and used without further purification. Solvents were distilled prior to use. Column chromatography was performed on flash silica gel (230-400 mesh).**^{1}H NMR** (300 MHz or 400 MHz) and **^{13}C NMR** (75 MHz or 100 MHz) were recorded using $CDCl_3$ or DMSO as solvent and TMS as an internal standard (Chemical shift in (δ) ppm). High resolution mass spectrometry (**HRMS**) data were obtained using Electron ionization (EI) and the quadruple double focusing mass analyser was used. Melting points were determined on a melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using commercially available silica gel coated aluminium plate were visualized using iodine vapour and short wave UV lamp. All microwave reactions were performed on **Biotage® Initiator+**microwave reactor. Operating high frequency microwave 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300W maximum power.

General procedure for synthesis of spiropyrrolidnes 4a-e, 9a-e, 12a-e:

A mixture of (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2,4-dienoate **1**(1 mmol),ninhydrin**3** orisatin **8**oracenaphthenequinone **11** (1 mmol) and sarcosine or ethylglycine or benzylglycine or phenylglycine or tritylglycine **2a-e** (1 mmol) was refluxed in 1,4-dioxane (10 mL) for 10-48 h. The progress of the reaction wasmonitored by TLC. After completion of reaction,the solvent was evaporated underreduced pressure. Purification of the residue on a silica gel (230-400 mesh)columnchromatography using 30-40% of ethyl acetate in petroleum ether as eluent furnishedanalytically pure (*E*)-ethyl 3-(1'-alkyl-1,3-dioxo-4'-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2'-pyrrolidine]-3'-yl)acrylate (**4a-e)**, (*E*)-ethyl 3-(1'-alkyl-2-oxo-4'-(phenylsulfonyl)spiro[indoline-3,2'-pyrrolidine]-3'-yl)acrylate **(9a-e)** and (*E*)-ethyl 3-(1'-alkyl-2-oxo-4'-(phenylsulfonyl)-2H-spiro[acenapthylene-1,2'-pyrrolidine]-3'-yl)acrylate (**12a-e**).

(*E*)-ethyl 3-(1'-methyl-1,3-dioxo-4'-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2'-pyrrolidine]-3'-yl)acrylate (4a).

Colorless solid (377 mg, 82%); mp 158.1–159 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.97-7.86 (m, 6H), 7.60-7.53(m, 3H), 6.20 (dd, *J*=15.5,5.7 Hz, 1H), 5.50 (d, *J*=15.5 Hz, 1H), 4.18 (m, 1H), 3.95 (q, *J*=7.1 Hz, 2H), 3.80 (dd, *J*=10.4, 4.8 Hz, 1H), 3.70 (t, *J*=9.5 Hz, 1H), 3.51 (t, *J*=10.0 Hz 1H), 2.20 (s, 3H), 1.13 (t, *J*=7.1 Hz, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 202.5, 198.3, 164.4, 141.6, 140.5, 139.4, 137.9, 136.9, 136.8, 134.1, 129.4, 128.7, 126.1, 123.5, 122.9, 76.7, 65.6, 60.3, 54.0, 49.8, 35.9, 14.0 ppm. **HRMS(EI)** m/z calculated for $C_{24}H_{23}NO_6S$ $(M)^+$: 453.1246, found: 453.1245.

(*E*)-ethyl 3-(1'-ethyl-1,3-dioxo-4'-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2'-pyrrolidine] -3'-yl)acrylate (4b).

Pale yellow solid(393 mg, 83%); mp 148.8–150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ*7.86-7.79 (m, 6H), 7.53-7.45 (m, 3H) 6.07 (dd, *J*=15.5, 5.7 Hz, 1H), 5.41 (d, *J*=15.5 Hz, 1H), δ 4.16 (m, 1H**)**, 3.86 (q, *J*=7.0 Hz, 2H), 3.80 (dd,*J*=5.0, 5.3 Hz, 1H), 3.59 (t,*J*=9.6 Hz, 1H), 3.41 (t, *J*=10.0 Hz, 1H), 2.32 (m, 2H), 1.04 (t, *J*=7.0 Hz, 3H), 0.85 (t, *J*=7.1 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 202.7, 198.7, 164.3, 141.6, 140.3, 139.2, 137.8, 136.8, 136.7, 134.0, 129.3, 128.7, 126.2, 123.3, 122.8, 65.3, 60.2, 51.2, 50.0, 44.4, 14.4, 13.9 ppm; **HRMS(EI)** m/z calculated for $C_{25}H_{25}NO_6S$ $(M)^+$: 467.1402, found : 467.1401.

(*E*)-ethyl 3-(1'-benzyl-1,3-dioxo-4'-(phenylsulfonyl)-1,3-dihydrospiro[indene-2,2'-pyrrolidine]-3'-yl)acrylate (4c).

Pale yellow solid (419 mg, 78%); mp 179.5–179.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.87-7.79 (m, 6H), 7.60 (m, 1H), 7.53 (m, 2H), 7.14 (m, 3H), 7.06 (m, 2H), 6.21 (dd, *J*=15.5, 5.8 Hz, 1H), 5.54 (d, *J*=15.5 Hz, 1H), 4.23 (m, 1H), 3.94 (q, *J*=7.1 Hz, 2H), 3.67 (m, 2H), 3.49 (m, 3H), 1.12 (t, *J*=7.1 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 200.6, 196.6, 162.8,

140.1, 138.6, 137.7, 135.9, 135.1, 135.06, 134.8, 132.5, 127.7, 127.3, 127.1, 126.6, 126.0, 124.7, 121.6, 121.3, 63.9, 58.7, 52.7, 50.4, 48.4, 12.4 ppm; **HRMS(EI)** m/z calculated for $C_{30}H_{27}NO_6S(M)^+$: 529.1559, found : 529.1558.

(*E*)-ethyl 3-(1'-methyl-2-oxo-4'-(phenylsulfonyl)spiro[indoline-3,2'-pyrrolidine]-3'-yl)acrylate (9a).

Colorless solid (357 mg, 80%); mp177.4 – 178.5 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.76 (m, 1H), 7.64-7.52 (m, 3H), 7.29 (m, 2H), 7.09 (m, 1H), 6.78 (d,*J*= 7.5 Hz, 1H), 6.41 (dd, *J*=15.6, 6.9 Hz, 1H), 5.38 (d, *J*= 15.6 Hz, 1H), 4.25 (m, 1H), 4.01 (q, *J*=7.2 Hz, 2H), 3.73 (m, 1H), 3.58 (m, 2H), 2.1 (s, 3H), 1.16 (t, *J*=7.2 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.7, 165.0, 141.2, 140.5, 138.2, 133.9, 130.0, 129.3, 128.6, 125.8, 125.6, 124.4, 123.4, 109.9, 64.7, 60.3, 52.5, 51.6, 34.9, 14.0 ppm; **HRMS(EI)** m/z calculated for $C_{23}H_{24}N_2O_5S$ $(M)^+$: 440.1405, found : 440.1404.

(*E*)-ethyl 3-(1'-ethyl-2-oxo-4'-(phenylsulfonyl)spiro[indoline-3,2'-pyrrolidine]-3'-yl)acrylate (9b).

Colorless solid (378 mg, 82%); mp 141.7–142.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=2.8 Hz, 2H), 7.60-7.52 (m, 3H), 7.52 (b, 1H), 7.20-7.26 (m, 2H), 7.07 (m, 1H), 6.73 (d, *J*=7.6 Hz, 1H), 6.33 (dd, *J* = 15.6,6.8 Hz,1H), 5.32 (d, *J*=15.6 Hz,1H), 4.22 (m, 1H), 4.00 (q, *J*=7.2 Hz, 2H), 3.85 (m, 1H), 3.51 (m, 2H), 2.29 (m, 2H), 1.16 (t, *J*=7.2 Hz, 3H), δ 0.94 (t, *J*=7.2 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.0, 164.9, 141.1, 140.2, 138.1, 133.9, 129.8, 129.3, 128.7, 126.4, 125.6, 124.3, 123.4, 109.8, 64.4, 60.3, 51.8, 49.7, 43.2, 14.0, 13.7 ppm; **HRMS(EI)** m/z calculated for $C_{24}H_{26}N_2O_5S$ $(M)^+$: 454.1562, found : 454.1560.

(*E*)-ethyl 3-(1'-benzyl-2-oxo-4'-(phenylsulfonyl)spiro[indoline-3,2'-pyrrolidine]-3'-yl)acrylate (9c).

Colorless solid (393 mg, 75%); mp 206.6–207.7 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (s, 1H, -NH), 7.85 (d, *J*=7.9 Hz, 2H), 7.62 (m, 1H), 7.52 (m, 2H), 7.30-7.07 (m, 8H), 6.80 (d, 1H, *J*=7.7 Hz), 6.47 (dd, *J*=15.6, 6.7 Hz, 1H), 5.45 (d, *J*=15.6 Hz, 1H), 4.31 (m, 1H), 4.01 (q, *J*=7.1 Hz, 2H), 3.57 (m, 3H), 3.47 (d, *J*=13.2 Hz, 1H), 3.31 (d, *J*=13.1 Hz, 1H), 1.16 (t, *J*=7.1 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.1, 165.0, 141.5, 140.4, 137.6, 137.5, 133.9, 130.1, 129.3, 128.9, 128.3, 128.0, 127.2, 126.1, 125.7, 124.2, 123.6, 110.2, 64.7, 60.4, 52.8, 51.8, 50.0, 14.1 ppm; **HRMS(EI)** m/z calculated for $C_{29}H_{28}N_2O_5S$ $(M)^+$: 516.1718, found : 516.1715.

((*E*)-ethyl 3-(1'-methyl-2-oxo-4'-(phenylsulfonyl)-2H-spiro[acenapthylene-1,2'-pyrrolidine]-3'-yl) acrylate (12a).

Yellow solid (376 mg, 78%); mp 133.1-134.3 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.10(d,*J*=8.0 Hz, 1H), 7.96 (d, *J*=6.8 Hz, 2H),7.90 (d, *J*=8.4 Hz, 1H), 7.80 (d, *J*=6.8 Hz, 1H), 7.73-7.2 (m, 6H), 6.19 (dd, *J*=15.6,6.4 Hz, 1H), 5.24 (d, *J*=15.6 Hz, 1H), 4.37 (m, 1H), 3.89–3.67 (m, 5H), 2.00 (s, 3H), 1.06 (t, *J*=7.2 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.7, 164.8, 143.1, 140.7, 138.4, 136.2, 134.1, 132.4, 131.6, 130.6, 129.5, 129.0, 128.8, 128.4, 125.9, 125.3, 120.9, 120.9, 80.1, 65.3, 60.2, 53.3, 52.2, 35.1, 14.1 ppm; **HRMS(EI)** m/z calculated for $C_{27}H_{25}NO_5S$ $(M)^+$: 475.1453, found : 475.1450.

((*E*)-ethyl 3-(1'-ethyl-2-oxo-4'-(phenylsulfonyl)-2H-spiro[acenapthylene-1,2'-pyrrolidine]-3'-yl) acrylate (12b).

Yellow solid (347 mg, 70%); mp 155.9 – 156.4 °C;**^{1}H NMR** (400 MHz, $CDCl_3$) δ8.08(d,*J*=8.0 Hz, 1H), 7.95 (d, *J*=5.6 Hz, 2H),7.88 (d, *J*=8.4 Hz, 1H), 7.78 (d, *J*=6.4 Hz, 1H), 7.71-7.26 (m, 6H), 6.16 (dd, *J*=15.6 , 6.4 Hz, 1H), 5.16 (d, *J*=15.6 Hz, 1H), 4.41 (m, 1H), 3.95 (d, *J*=10.6 Hz, 1H), 3.84 (q, *J*=7.2 Hz, 2H), 3.72 (m, 1H), 3.63 (t, *J*=10.4 Hz, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.05 (t, *J*=7.2 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.8, 164.6, 142.8, 140.3, 138.1, 136.5, 133.9, 132.2, 131.3, 130.3, 129.3, 129.2, 128.9, 128.8, 128.3, 125.6, 125.7, 120.8, 120.6, 80.0, 64.9, 60.1, 52.2, 50.3, 43.0, 14.0, 13.9 ppm; **HRMS(EI)** m/z calculated for $C_{28}H_{27}NO_5S(M)^+$: 489.1609, found : 489.1605.

((*E*)-ethyl 3-(1'-benzyl-2-oxo-4'-(phenylsulfonyl)-2H-spiro[acenapthylene-1,2'-pyrrolidine]-3'-yl) acrylate (12c).

Yellow solid (420 mg, 75%); mp207.3 – 207.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=8.0 Hz, 1H), 7.88 (m, 4H), 7.74-7.52 (m, 6H), 7.23 (m, 3H), 7.13 (d, *J*=6.6 Hz, 2H), 6.27 (dd, *J*= 15.6, 6.5 Hz, 1H), 5.28 (d, *J*=15.6 Hz, 1H), 4.23 (m, 1H), 3.90 (q, *J*=7.1 Hz, 2H), 3.82 (m, 1H), 3.68 (m, 2H), 3.29 (d, 1H), 3.23 (d, 1H), 1.09 (t, *J*=7.1 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.1, 164.7, 143.04, 140.3, 137.7, 136.3, 133.9, 132.3, 131.3, 130.4, 129.3, 129.0, 128.9, 128.4, 128.3, 128.2, 127.8, 127.8, 127.2, 125.8, 125.3, 121.1, 120.6, 79.8, 65.2, 60.2, 52.7, 52.2, 50.7, 14.0 ppm; **HRMS(EI)** m/z calculated for$C_{33}H_{29}NO_5S$ $(M)^+$: 551.1766, found : 551.1765.

Synthesis of 1,3,4tri substituted pyrrolidine 15:

A mixture of (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2,4-dienoate **1**(1 mmol), paraformaldehyde (2 mmol) and benzylglycine **2c**(1 mmol) was refluxed in 1,4-dioxane (10 mL) for 10 h. The progress of the reaction wasmonitored by TLC. After completion of reaction,the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel (230-400 mesh) column chromatography using 30-40% of ethyl acetate in petroleum ether as eluent furnished analytically pure(*E*)-ethyl 1-benzyl-4-(2-(phenylsulfonyl)vinyl)pyrrolidine-3-carboxylate **15**.

(*E*)-ethyl 1-benzyl-4-(2-(phenylsulfonyl)vinyl)pyrrolidine-3-carboxylate (15).

Colorless syrup (271 mg, 67%); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.86 (m, 2H), 7.62-7.51 (m, 3H), 7.31-7.24 (m, 5H), 7.01 (dd,*J*=15.2, 8.2 Hz,1H), 6.39 (d, *J*=15.2 Hz, 1H), 4.11 (q,*J*= 7.2 Hz, 2H), 3.61 (s, 2H), 3.27 (m, 1H), 2.84 (m, 4H), 2.50 (m, 1H), 1.18 (t, *J*= 7.2Hz,3H) ppm;**^{13}CNMR** (75 MHz, $CDCl_3$) *δ* 172.8, 147.0, 140.3, 138.1, 133.2, 130.7, 129.3, 128.7, 128.4, 127.1, 126.9, 60.9, 59.3, 58.2, 56.1, 48.3, 42.9, 14.1 ppm; **HRMS(EI)** m/z calculated for $C_{22}H_{25}NO_4S$ $(M)^+$: 399.1504, found: 399.1503.

General procedure for isoxazolidines 21a-b:

A mixture of (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2,4-dienoate **1**(1 mmol) and nitrones **20a-b** (1 mmol) was heated at 70 ºC in 1,4-dioxane (10 mL) for 10 h. The progress of the reaction wasmonitored by TLC. After completion of reaction,the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel (230-400 mesh)columnchromatography using 40-50% of ethyl acetate in petroleum ether as eluent furnishedanalytically pure (*E*)-ethyl 3-(2-methyl-3-phenyl-5-(phenylsulfonyl)isoxazolidin-4-yl)acrylate **21a** and (*E*)-ethyl 3-(3-(4-fluorophenyl)-2-methyl-5-(phenylsulfonyl)isoxazolidin-4-yl)acrylate **21b.**

(*E*)-ethyl 3-(2-methyl-3-phenyl-5-(phenylsulfonyl)isoxazolidin-4-yl)acrylate (21a).

Pale yellow solid (228 mg, 56%);mp132.5–133 °C;**^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.75 (m, 2H), **7**.56 (m,1H), 7.43 (m, 2H), 7.21 (m, 3H), 7.08 (m, 2H), 6.93 (dd, *J*=15.6, 5.6 Hz, 1H), 5.99 (d, *J*=15.6 Hz, 1H), 5.18 (t, *J*=4.0 Hz, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 3.91 (m,2H), 2.56 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 166.0, 145.0, 137.8, 135.8, 134.3, 129.5, 128.8, 128.6,128.5, 128.0, 122.5, 80.0, 75.9, 74.3, 60.8, 42.6, 14.3 ppm. **HRMS(EI)** m/z calculated for $C_{21}H_{23}NO_5S$ $(M)^+$: 401.1296,found: 401.1308.

(*E*)-ethyl 3-(3-(4-fluorophenyl)-2-methyl-5-(phenylsulfonyl)isoxazolidin-4-yl)acrylate (21b).

Pale yellow solid (276 mg, 65%);mp110–111 °C;**^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.75 (d, *J*=7.5 Hz, 2H), **7**.58 (t,*J*=7.5 Hz,1H), 7.44 (t, *J*=7.5 Hz, 2H), 7.10 (m, 2H), 6.86 (m, 3H), 5.96 (d, *J*=15.5 Hz, 1H), 5.17 (t, *J*=5.5 Hz, 1H), 4.20 (q, *J*=7.0 Hz, 2H), 3.95 (b, 1H), 3.86 (dd,*J*=4.5, 5.0 Hz, 1H), 2.59 (s, 3H), 1.29 (t, *J*=7.0 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ*165.9, 163.8, 161.8, 144.7, 137.7, 134.5, 131.3, 129.8, 129.8, 129.6, 128.5, 122.7, 115.9, 115.7, 79.7, 76.1, 73.5, 60.8, 42.5, 14.3 ppm.**HRMS(EI)** m/z calculated for $C_{21}H_{22}FNO_5S$ $(M)^+$: 419.1202, found: 419.1201.

General procedure for isoxazolidines 23a-b:

A mixture of (2*E*, 4*E*)-ethyl 5-(phenylsulfonyl) penta-2,4-dienoate **1**(1 mmol), Oxime **22a-b** (1 mmol), NCS (1.1 mmol) and $KHCO_3$ (1.5 mmol)was stirred in dichloromethane(10 mL) at rt for 16 h. The progress of the reaction wasmonitored by TLC. After completion of reaction, water wasadded and the reaction mixture was extracted with DCM(3 X 15 mL). The combined organic layer was dried over $Na_2SO_4$and**e**vaporated under reduced pressure**.** Purification of the residue on a silica gel (230-400 mesh)columnchromatography using 40-50% of ethyl acetate in petroleum ether as eluent furnished analytically pure ((*E*)-ethyl 3-(3-phenyl-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)acrylate **23a** and (*E*)-ethyl 3-(3-(4-fluorophenyl)-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)acrylate **23b.**

(*E*)-ethyl 3-(3-phenyl-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)acrylate (23a).

Colorless solid(234 mg, 60%); mp144.5–145 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.91 (d, *J*=2.40 Hz, 2H), 7.71 (m, 3H), 7.59 (m, 2H), 7.44 (m, 3H), 7.00 (dd, *J*=14.8, 4.0 Hz, 1H), 6.79 (d, *J*=14.8 Hz, 1H), 5.63 (t, *J*=4.4 Hz, 1H), 4.36 (d,*J*=6.0 Hz, 1H),

4.21 (q, *J*=6.9Hz, 2H), 1.20 (t, *J*=6.9 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.7, 153.9, 140.2, 139.4, 133.8, 133.0, 130.8, 129.4, 128.7, 127.9, 127.5, 127.2, 82.1, 62.6, 58.6, 13.8 ppm.**HRMS(EI)** m/z calculated for $C_{20}H_{19}NO_5S$ $(M)^+$: 385.0983, found: 385.0982.

(*E*)-ethyl 3-(3-(4-fluorophenyl)-5-(phenylsulfonyl)-4,5-dihydroisoxazol-4-yl)acrylate (23b).

Colorless solid (257 mg, 63%); mp133–134 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.69 (m, 3H), 7.57 (m, 2H), 7.12 (m, 2H), 6.97 (dd, *J*=14.7, 4.2 Hz, 1H), 6.77 (d, *J*=14.7 Hz, 1H), 5.63 (t, *J*=4.5 Hz, 1H), 4.35 (d, *J*=5.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J*=7.2 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 165.7, 162.4, 152.8, 140.0, 139.4, 133.8, 133.0, 129.4, 129.3, 127.8, 123.8, 123.8, 116.1, 115.8, 82.1, 62.6, 58.5, 13.8 ppm. **HRMS(EI)** m/z calculated for $C_{20}H_{18}FNO_5S$ $(M)^+$: 403.0889, found: 403.0888.

General procedure for the synthesis of *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl) alkylamines (24a-c).

(Chloromethyl)trimethylsilylamine (5 mmol)was added to a solution of benzylamine orcyclopentylamine ortert-butylamine (10 mmol) in acetonitrile (150 mL) and the reaction mixture was refluxed for 16 h.The progress of the reaction wasmonitored by TLC. After completion of reaction, acetonitrile was removed under reduced pressure, water was added and the reaction mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure to furnished analytically pure product *N*-((trimethylsilyl)methyl)(phenyl)methanamineor*N*-((trimethylsilyl)methyl) cyclopentanamineor*N*-((trimethylsilyl)methyl)(phenyl) methanamine , which was used as such for the next step without any purification.To a stirred solution of methanol (12 mmol) and 37% aqueous formaldehyde (12 mmol) at 0 °C was added 2-methyl-*N*-((trimethylsilyl)methyl)propan-2-amine or*N*-((trimethylsilyl)methyl)cyclopentanamine or*N*-((trimethylsilyl)methyl)(phenyl)methanamine (10 mmol) drop wise over a period of 10 min. The resulting mixture was stirred for 2 h, anhydrous K_2CO_3 (2.5 mmol) was added toa mixture and stirred at 0 °C for 30 mins. After completion of the reaction was monitored by TLC,water was added and the reaction mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure to furnished crude product. The pure compound was isolated by fractional distillation to get *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)tert-butylamine or *N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl)cyclopentanamineor*N*-(methoxymethyl)-*N*-((trimethylsilyl) methyl)benzylamine (**24a-c**). All the compounds are liquid.

***N*-(methoxymethyl)-*N*-((trimethyl silyl)methyl)tert-butylamine (24a).**

Colorless oil (87%),**^{1}H NMR** (300 MHz, $CDCl_3$)δ 4.15 (s, 2H), 3.16 (s, 3H), 1.97 (s, 2H), 1.05 (s, 9H), 0.04 (s, 9H) ppm.

***N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl) cyclopentanamine (24b)**.

Pale yellow oil (78%),**^{1}H NMR** (300 MHz, $CDCl_3$)δ 4.10 (s, 2H), 3.21 (s, 3H), 3.15 (m, 1H), 2.22 (s, 2H), 1.32 – 1.83 (m, 8H), 0.04 (s, 9H) ppm.

***N*-(methoxymethyl)-*N*-((trimethylsilyl)methyl) benzylamine (24c).**

Pale yellow oil (90%),**^{1}H NMR** (300 MHz, $CDCl_3$)δ 7.14 – 7.06 (m, 5H), 4.44 (s, 2H), 3.62 (s, 3H), 3.24 (s, 2H), 1.69 (s, 2H), 0.04 (s, 9H) ppm.

General procedure for the synthesis of 3, 3'- bis pyrrolidine (25a-f)

TFA (0.1 mmol) was added to a solution of diene**1a**or **1b** (1 mmol) and **24a**or **24b** or **24c** (3 mmol) in DCM (5 mL). The reaction mixture was stirred at 80 °C in microwave for 30 min. The progress of the reaction wasmonitored by TLC. After completion of reaction,water (30 ml) was added to the mixture and then extracted with DCM (2x30 mL), combined organic layer was washed with 10% $NaHCO_3$ (30 mL), water (30 mL) and saturated brine (30 mL), organic layer was dried over

Na_2SO_4 andevaporated under reduced pressure. Purification of the residue on a silica gel (230-400 mesh)columnchromatography using 30-60% of ethyl acetate in petroleum ether as eluent furnishedanalytically pure inseparable mixture of diastereomers **25a-f** (6:4).

Ethyl-1-tert-butyl-4-(1-tert-butyl-4-(phenylsulfonyl)pyrrolidin-3-yl)pyrrolidine-3-carboxylate (25a and 25a').

Colourless syrup (350 mg, 75%); **^{1}H NMR** (400 MHz,$CDCl_3$) δ7.91 (m, 2H), 7.65-7.53 (m, 3H), 4.14 (q, *J*=7.1 Hz, 2H), 3.82 (m, 1H), 2.42-2.92 (m, 11H), 1.25 (t, *J*=7.1 Hz, 3H), 1.05 (s, 9H), δ 0.93 (s, 9H) ppm.**^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 174.8, 138.6, 138.5, 133.4, 133.4, 128.9,128.8, 128.7, 66.0, 65.9, 60.6, 60.5, 55.2, 53.7, 52.0, 51.9, 51.7, 50.3, 50.2, 50.0,49.7, 49.5, 49.3, 47.3, 47.1, 46.2, 45.9, 44.2, 44.0, 43.7, 42.6, 42.3, 28.2, 26.9, 25.9, 15.4 ppm. **HRMS(EI)** m/z calculated for $C_{25}H_{40}N_2O_4S$ $(M)^+$: 464.2708, found: 464.2705.

Ethyl-1-cyclopentyl-4-(1-cyclopentyl-4-(phenylsulfonyl)pyrrolidin-3-yl)pyrrolidine-3-carboxylate (25band 25b').

Colourless syrup (376 mg, 76%),**^{1}H NMR** (300 MHz, $CDCl_3$)δ 7.93 (m, 2H), 7.64-7.53 (m, 3H), 4.14 (q, 2H), δ 3.76 (m, 1H), 2.32-2.94 (m, 13H), 1.49-1.66 (m, 14H), 1.23 (m, 5H) ppm. **^{13}CNMR** (75 MHz, $CDCl_3$) δ 174.5, 138.4, 133.6, 129.1, 128.8, 66.4, 66.2, 65.8, 60.8, 57.5, 56.9, 56.7, 54.1, 46.0, 44.4, 42.5, 31.7, 31.7, 24.0, 24.0, 23.8, 14.2 ppm**.HRMS(EI)** m/z calculated for $C_{27}H_{40}N_2O_4S$ $(M)^+$: 488.2708, found:488.2708.

Ethyl-1-benzyl-4-(1-benzyl-4-(phenylsulfonyl)pyrrolidin-3-yl)pyrrolidine-3-carboxylate (25c and 25c').

Colourless syrup (361 mg, 67%); **^{1}H NMR** (300 MHz, $CDCl_3$)δ7.89 (m, 2H),δ 7.83 (m, 1H), δ 7.53 (m, 2H) 7.30-7.14 (m, 10H), 4.11 (q, 2H), 3.89 (m, 1H), 3.47 (m, 4H, -$\underline{CH_2}$Ph), 3.04 (m, 1H), 2.84-2.52 (m, 10H), 1.249(t, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.8, 174.5, 138.9, 138.7, 138.6, 138.5, 138.4, 133.7, 133.6, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 128.3, 127.6, 127.1, 66.3, 66.1, 60.8, 60.8, 60.8, 59.7, 59.7, 59.4, 59.4, 59.2, 58.5, 58.3, 58.0, 57.7, 57.0, 54.9, 54.7, 46.5, 46.0, 45.0, 44.5, 43.5, 42.9, 14.2 ppm.**HRMS(EI)** m/z calculated for $C_{31}H_{36}N_2O_4S$ $(M)^+$: 532.2395, found: 532.2394.

Ethyl-4-(4-(4-methoxyphenylsulfonyl)-1-tert-butylpyrrolidin-3-yl)-1-tert-butyl pyrrolidine-3-carboxylate (25d and 25d').

Colourless syrup (360 mg, 72%); **^{1}H NMR** (400 MHz, $CDCl_3$)δ 7.79 (d, 2H), 6.98 (d, 2H), 4.12 (q, 2H), 3.85 (s, 3H, -OCH_3), 3.72 (m, 1H), 2.44-2.92 (m, 11H), 1.25 (t, 3H), 1.03 (s, 9H), 0.92 (s, 9H) ppm.**^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.7, 163.5, 130.9, 130.8, 129.9, 129.7, 114.1, 66.0, 60.6, 55.5, 51.7, 50.1, 49.5, 47.4, 47.2, 45.9, 44.30, 44.0, 42.3, 25.5, 13.2 ppm.**HRMS(EI)** m/z calculated for $C_{26}H_{42}N_2O_5S$ $(M)^+$: 494.2814, found: 494.2814.

Ethyl-4-(4-(4-methoxyphenylsulfonyl)-1-cyclopentylpyrrolidin-3-yl)-1-cyclopentyl pyrrolidine-3-carboxylate (25e and 25e').

Colourless syrup (367 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$)δ 7.77 (d, 2H), 6.96 (d, 2H), 4.11 (q, 2H), 3.87 (s, 3H, -OCH_3), 3.74 (m, 1H), 2.49-3.09 (m, 13H), 1.46-1.77 (m, 14H), 1.23 (m, 5H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ174.6, 163.6, 131.0, 130.8, 114.2, 65.9, 65.8, 60.8, 57.5, 55.6, 54.3, 46.1, 44.4, 31.6, 31.5, 24.0, 23.9, 14.1 ppm. **HRMS(EI)** m/z calculated for $C_{28}H_{42}N_2O_5S$ $(M)^+$: 518.2814, found: 518.2812.

Ethyl-4-(4-(4-methoxyphenylsulfonyl)-1-benzylpyrrolidin-3-yl)-1-benzylpyrrolidine-3-carboxylate (25f and 25f').

Colourless syrup (353 mg, 62%);**^{1}H NMR** (400 MHz, $CDCl_3$)δ 7.77 (dd, 2H), 7.05-7.30 (m, 12H), 4.11 (q, 2H), 3.85 (s, 3H), 3.80 (m, 1H), 3.29-3.56 (m, 4H), 2.53-3.04 (m, 11H), 1.17 (t, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.5, 165.5, 139.4, 138.8, 132.0, 130.0, 129.96, 129.3, 129.2, 128.1, 128.0, 115.6, 67.7, 67.3, 61.9, 60.5, 60.0, 58.5, 57.2, 56.3, 55.4, 47.1, 45.6, 44.5, 43.9 14.4 ppm. **HRMS(EI)** m/z calculated for $C_{32}H_{38}N_2O_5S$ $(M)^+$: 562.2501, found: 562.2500.

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ASSOCIATED CONTENT

*** Supporting Information**

Copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds, COESY, HMBC and NOESY spectra for **21b&23a**. X-ray structures and data of compounds **4a & 9a** (CIF). Additional details on computations, including total energies and Cartesian Coordinates for computed structures and TS structures. The Supporting Information is available free of charge on the ACS Publications website at DOI:

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