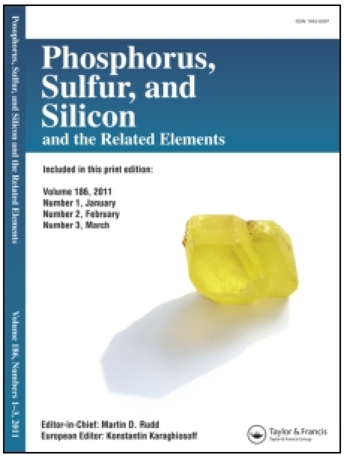

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Stereoselective [3 + 2] Cycloaddition Reactions of Azomethine Ylides Derived from 5-Methylbenzo[B]thiophene-2,3-dione and Piperidine-2-Carboxylic Acid

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Stereoselective [3 + 2] Cycloaddition Reactions of Azomethine Ylides Derived from 5-Methylbenzo[B]thiophene-2,3-dione and Piperidine-2-Carboxylic Acid

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A series of spiropyrrolidines have been synthesized in 68–76% yield by 1,3 dipolar cycloaddition reaction of azomethine ylides generated by a decarboxylative route from 5-methylbenzo[b]thiophene and piperidine-2-carboxylic acid with different acetylenic and ethylenic dipolarophiles. The stereochemical course of the cycloaddition has been investigated by spectral data and AM1 quantum chemical method. The novel spiro compounds have been characterized by elemental analyses and spectroscopic techniques.

Keywords 1,3-Dipolar cycloaddition; 5-methylbenzo[b]thiophene-2,3-dione; piperidine-2-carboxylic acid; dipolarophiles; semiempirical stereoselectivity; spectral characterization

INTRODUCTION

The 1,3-dipolar cycloaddition reaction has been established as "the single most important method for the construction of heterocyclic five membered rings in organic chemistry".[1,2] These reactions have found widespread use as a high yielding and efficient, regio- and sterecontrolled method for the synthesis of different heterocyclic compounds. The 1,3-dipolar cycloaddition reactions of azomethine ylides occupy a unique position in the synthesis of pyrrolidines[3]; an important building block in the synthesis of many natural products and pharmaceuticals.[4] As an extension of our studies on 1,3-dipolar cycloadditions of isatin derivatives and acenaphthylene-1,2-dione,[5] we have

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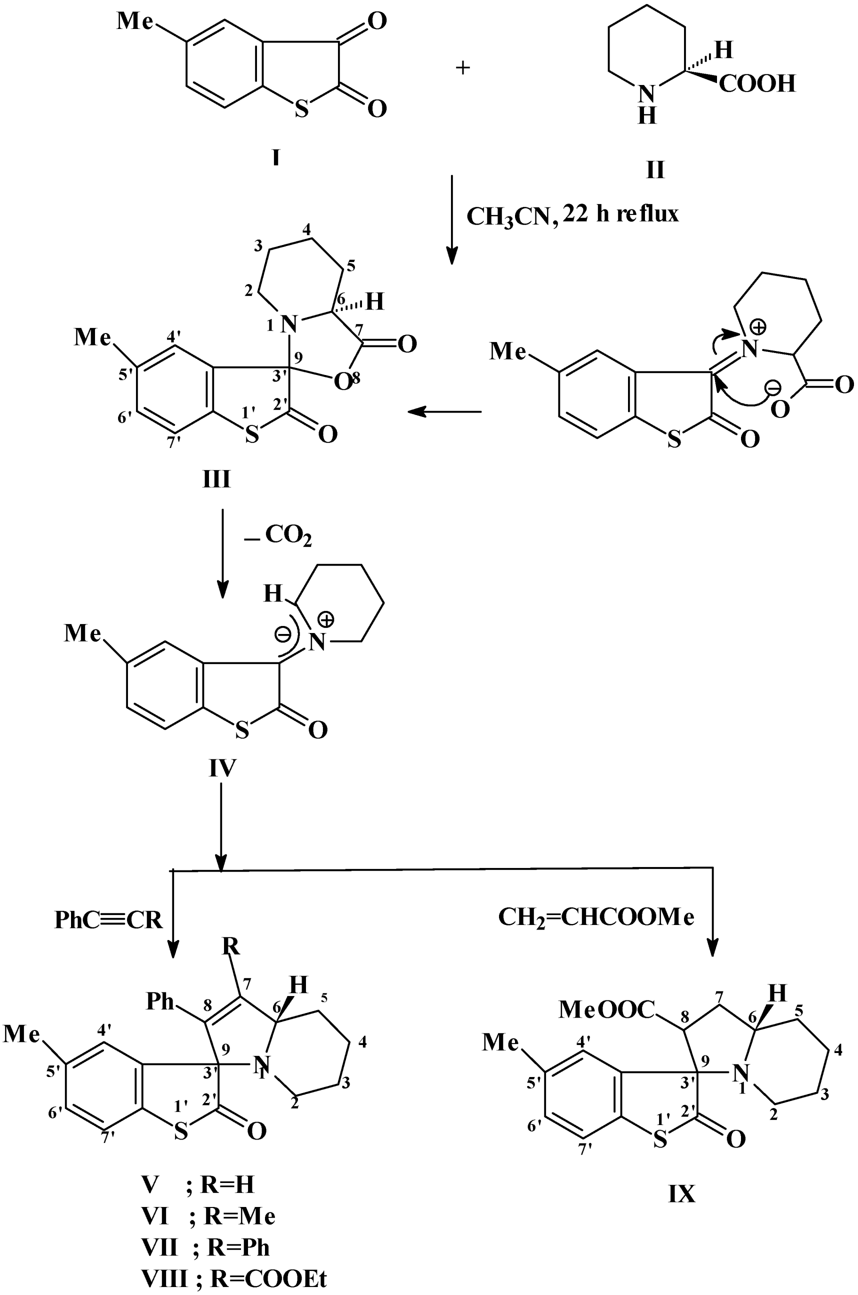
chosen benzo[b]thiophene nucleus with piperidine-2-carboxylic acid for the present investigation because the former has been reported to possess active antiosteoporotic,[6,7] antifungal[8] properties, as well as has been determined to be inhibitor of poliovirus,[9] while the later is well recognized as HIV protease inhibitor,[10] analgesic and diuretic agent.[11] Therefore, a molecule incorporating these two moieties might be expected to be an effective biomolecule.

RESULT AND DISCUSSION

Azomethine ylides can be generated in situ by the decarboxylation of the intermediate iminium species and can be trapped as cycloadducts in the presence of various dipolarophiles.[12] Thus an equimolar mixture of 5-methylbenzo[b]thiophene-2,3-dione (5-methylthioisatin) **I** and piperidine-2-carboxylic acid (pipecolinic acid) **II** was refluxed for 22 h in the absence of any dipolarophile, whereby it afforded oxazolidinone derivative (6S, 9S) spiro-{1-aza-8-oxa-bicyclo[4,3,0]-nonan-9,3′}-5′-methylbenzo[b]thiophene-7,2′-dione **III** in 74% yield. Formation of such an oxazolidinone derivative has been previously reported by Seebach et al.[13] in the case of proline with pivaldehyde. When the same reaction was carried out in the presence of different ethylenic and acetylenic dipolarophiles, viz phenyl acetylene, 1-phenyl-1-propyne. diphenyl acetylene, ethylphenyl propiolate, and methyl acrylate, it afforded (6S, 9R) spiro-{8-phenyl-1-aza-bicyclo [4,3,0]-7-nonen-9,3′}-5′-methylbenzo[b]thiophene-2′-one **V**, (6S, 9R)-spiro-{8-phenyl-7-methyl-1-aza- bicyclo [4,3,0]-7-nonen-9,3′}-5′-methylbenzo[b]thiophene-2′-one **VI**, (6S, 9R) spiro-{7,8-diphenyl-1-aza-bicyclo [4,3,0]-7-nonen-9,3′}-5′-methylbenzo[b] thiophene-2′-one **VII**, and (6S, 9R) spiro-8-phenyl-7-ethoxycarbonyl-1-aza-bicyclo[4,3,0]-7-nonen-9,3′}-5′-methylbenzo[b]thiophene-2′one (**VIII**), and (6S, 8S, 9R) spiro-{8-methoxycarbonyl-1-aza-bicyclo [4,3,0]-nonane-9,3′}-5′-methylbenzo[b]thiophene-2′-one **IX**, respectively, in 68–76% yields. The reaction proceeds via formation of intermediate azomethine ylide **IV** that subsequently undergoes 1,3-dipolar cycloadditions with various dipolarophiles to afford spiro compounds (Scheme 1). The cycloadducts **V** to **IX** are optically active and their specific rotations $[\alpha]_D{}^{20}$ were in the range 47°–63°.

The structure of the products was ascertained from their spectral features. The IR spectrum of oxazolidinone derivative **III** showed absorption bands at 1720 and 1690 cm^{-1} due to lactonic C =O and carbonyl groups whereas absorptions at 1290 and 760 cm^{-1} were associated with C-N and C-S stretching vibrations. Its ^{1}H NMR spectrum showed following signals: δ 2.05 as a singlet for methylene protons (3-H to 5-H),



SCHEME 1 Reaction of 5-methylbenzo[b]thiophene,2.3-dione with piperidine-2-carboxylic acid in absence and presence of different dipolarophiles.

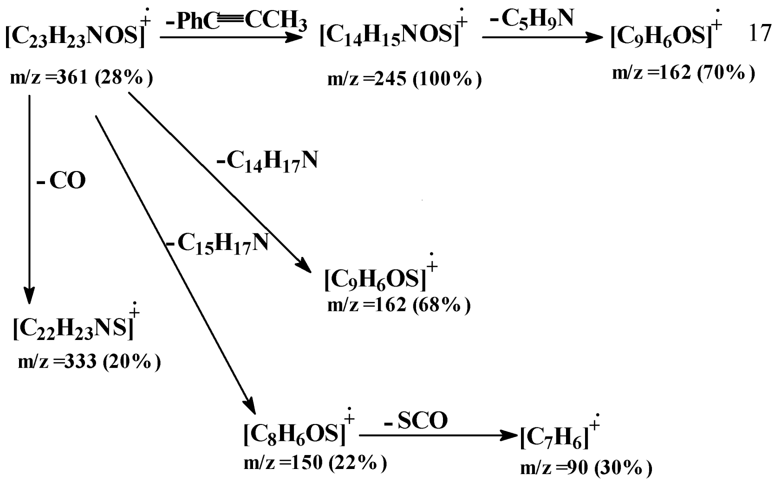
δ 2.29 as a triplet for 2-H, δ 2.5 as a singlet due to methyl protons, δ 4.08 as a triplet for 6-H, aromatic protons were seen as multiplet in the region δ 7.0–7.9 ppm. Its ^{13}C NMR spectrum showed the C-2′ carbonyl carbon signal at δ 180.18 ppm whereas the lactone ring carbon resonated at δ 170.03; the benzenoid carbons appeared in the region δ 135.92–123.68 ppm; the chiral carbons C-9 and C-6 were observed at δ 80.82 and δ 60.12 ppm respectively; methylene carbons (C-3, C-5, C-2 and C-4) appeared at δ 47.58, δ 27.73 δ 25.20 δ 21.40 ppm, respectively, and the methyl carbon appeared at δ 19.22 ppm.

The IR spectrum of the typical 1-phenyl-1-propyne cycloadduct **VI** showed characteristic bands at 1710, 1290, and 790 cm^{-1} for >C =O, C-N and C-S stretching vibrations respectively. Its ^{1}H NMR spectrum showed a singlet at δ 2.0 for methylene protons (3-H to 5-H), a multiplet at δ 2.18 for 6-H, a triplet at δ 2.29 for 2-H, a singlet at δ 2.40 for methyl protons of thioisatin ring, a doublet at δ 2.54 for C-7 CH_3 protons which preferentially supports the formation of **VIa** over **VIb** and a multiplet in the range of δ 6.99–7.85 ppm for aromatic protons. The stereochemical course of the cycloaddition reaction was further supported by the ^{1}H NMR spectrum of phenyl acetylene cycloadduct (**Va/Vb**), in which a quartet appeared at δ 3.3 due to 6-H and a doublet at δ 2.3 for 7-H supporting the structure **Va** (Scheme 3). The ^{13}C NMR spectrum of **VI** showed a signal at δ 181.42 for carbonyl carbon, aromatic carbons appeared in the range δ 134.23–118.63 ppm, the olefenic carbons appeared at δ 112.27 and 110.19, spiro carbon appeared at δ 78.28, C-6 at δ 54.17, C-2 at δ 53.46, C-5 at 34.82, C-4 at δ 29.57 and C-3 at 24.49 ppm and methyl carbons at δ 15.83 ppm. Additional evidence was gathered from its mass spectrum. The molecular ion peak and base peaks were present at m/z 361 and 245 respectively along with other prominent peaks. The mass fragmentation pattern of **VI** has been depicted in Scheme 2. These results are in good harmony with the observation of Grigg et al.,[14] as well as with the theoretical calculations. Physical and spectral data have been tabulated in Table I and Table II respectively.

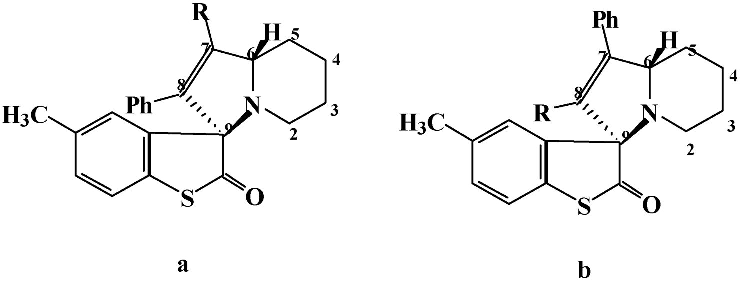
SEMIEMPIRICAL MOLECULAR ORBITAL STUDIES

The stereochemical course of the cycloaddition was ascertained by AM1 quantum chemical calculations on MOPAC 6 program. Oxazolidinone derivative **III** contains two chiral centers and therefore a total of four stereoisomers **IIIa-IIId** could be possible (Scheme 4).

Since **III** is formed by dehydration of the intermediate iminium species, the stereochemistry at C-6 should remain unaltered with respect to the piperidine ring. The configuration at C-6 and C-9 is therefore in analogy with the previously assigned configuration of the [3,3,0]



SCHEME 2 Mass fragmentation pattern of cycloadduct VI.



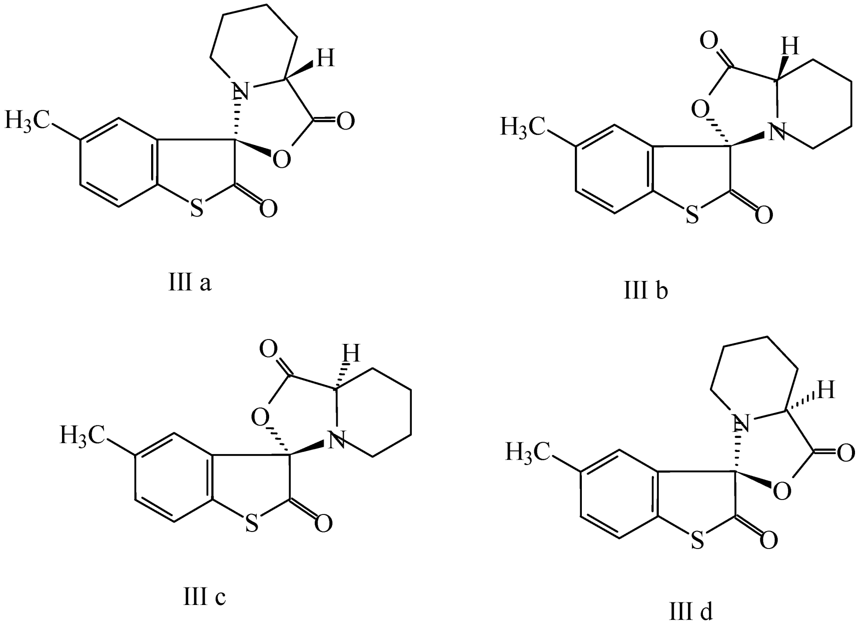
V a ; R= H **V b ; R=H**

VI a ; R= Me **VI b ; R=Me**

SCHEME 3 Stereoisomers of cycloadduct V and VI.

bicyclic N,O-acetal obtained by the condensation of proline and pivaldehyde as reported by Seebach et al.[13]On this basis, the possibility of stereoisomers **IIIa** and **IIIb** may be ruled out. Out of the remaining two isomers, **IIIc** has high ΔH_f ($\Delta H_f = -56.515$ Kcal/mol) as compared to isomer **IIId** ($\Delta H_f = -62.098$ Kcal/mol). Hence, the expected product is **IIId**.

The intermediate lactonic species may undergo decarboxylation to give azomethine ylide **IV** that subsequently undergoes 1,3-dipolar



SCHEME 4 Four possible stereoisomers of oxazolidinone III.

cycloaddition with various dipolarophiles to afford azabicycloadducts. The optimized geometry of azomethine ylide **IV** indicates that it has a planar structure wherein the piperidine ring lies in the same plane as that of thioisatin moiety. It may exist in two isomeric forms one in which >C=O and C—H of the dipole are *syn* to each other **IV**$_{\text{syn}}$ and the other one in which they are *anti* **IV**$_{\text{anti.}}$ (Figure 1).

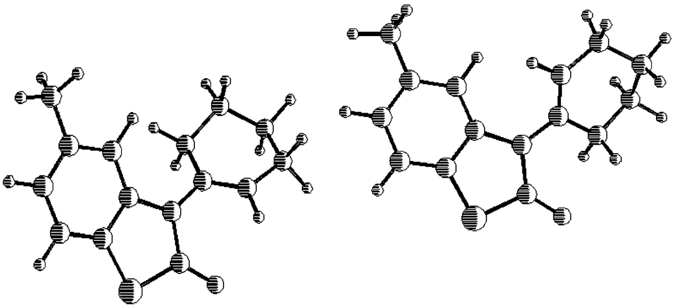
TABLE I Physical and analytical data of cycloadducts

Compd. no.	Physical state	Molecular formula	m.p. °C	Yield	$[\alpha]_D{}^{20}$	Elemental analysis calcd/found C	H	N	S
III	Chocolate brown powder	$C_{15}H_{15}NO_3S$	90	74	—	62.28 (61.12)	5.19 (4.89)	4.84 (4.60)	11.07 (10.94)
V	Bright yellow powder	$C_{22}H_{21}NOS$	188	75	52	76.08 (75.53)	6.05 (5.97)	4.03 (4.01)	9.22 (9.12)
VI	Shiny brown powder	$C_{23}H_{23}NOS$	220	76	50	76.45 (76.11)	6.37 (6.05)	3.87 (3.64)	8.86 (8.14)
VII	Brown powder	$C_{28}H_{25}NOS$	175	68	48	79.43 (78.97)	5.91 (5.87)	3.30 (3.14)	7.56 (7.10)
VIII	Light brown powder	$C_{25}H_{25}NO_3S$	200	74	63	77.51 (76.17)	6.45 (6.29)	3.61 (3.42)	8.26 (8.10)
IX	Reddish brown powder	$C_{18}H_{21}NO_3S$	180	70	47	65.25 (64.95)	6.34 (5.98)	4.22 (4.01)	9.66 (9.53)

TABLE II Spectral data of the cycloadducts

Compd No.	IR (cm^{-1})	^{1}HNMR (δ ppm)	^{13}CNMR (δ ppm
III	2920 (C-Haro), 2855 (C-Hali), 1720 (lactone >C=O), 1690 (C=O), 1290 (C-N), 1230 (C-O), 760 (C-S)	2.05 (s, 3-H+4-H+5-H, 6H), 2.29 (t, 2-H, 2H), 2.50 (s, CH_3, 3H), 4.08 (t, 6-H, 1H), 7.0–7.9 (m, ArH)	180.18 (.C=O), 170.03 (O—C=O), 135.91-123.68 (ArC), 80.82 (Spiro C), 60.12 (C-6), 47.58 (C-3), 27.73 (C-5), 25.20 (C-2), 21.40 (C-4), 19.22 (CH_3)
V	3050 (C-Haro), 2925 (C-Hali), 1715 (>C=O), 1295 (C-N), 780 (C-S)	2.1 (s, 3-H+4-H+5-H, 6H), 2.2 (t, 2-H, 2H), 2.3 (d, 7-H, 1H), 2.4 (s, CH_3, 3H), 3.3 (q, 6-H, 1H), 7.1-7.9 (m, ArH)	182.5 (C=O), 136.5–120.13 (ArC), 114.1–112.2 (C=C), 70.09 (Spiro C-9), 57.52 (C-6), 55.11 (C-2), 36.21 (C-5), 30.30 (C-4), 25.32 (C-3), 16.42 (CH_3)
VI	2930 (C-Haro), 2860 (C-Hali), 1710 (>C=O), 1290 (C-N), 790 (C-S)	2.0 (s, 3-H+4-H+5-H, 6H), 2.15 (t, 2-H, 2H), 2.3 (m, 6-H, 1H), 2.4 (s, CH_3', 3H), 2.5 (d, CH_3, 3H), 6.9–7.8 (m, ArH)	181.42 (C=O), 134.23–118.63 (ArC), 112.21–110.19 (C=C), 78.28 (Spiro C-9), 54.17 (C-6), 53.46 (C-2), 34.82 (C-5), 29.57 (C-4), 24.49 (C-3), 15.83 (CH_3)
VII	3075 (C-Haro), 2930 (C-Hali), 1680 (>C=O), 1280 (C-N), 765 (C-S)	1.4 (s, 3-H+4-H, 4H), 2.0 (q, 5-H, 2H), 2.3 (t, 2-H, 2H), 2.5 (t, 6-H, 1H), 2.54 (s, CH_3, 3H), 6.9–8.0 (m, ArH)	183.1 (C=O), 134.9-119.5 (ArC), 110.7-109.2 (C=C), 75.12 (Spiro C-9), 52.2 (C-6), 50.7 (C-2), 32.9 (C-5), 27.8 (C-4), 22.4 (C-3), 18.1 (CH_3)
VIII	3060 (C-Haro), 2925 (C-Hali), 1675 (O—C=O), 1650 (>C=O), 1290 (C-N), 1225 (C-O), 760 (C-S)	1.2 (s, CH_3), 2.0 (s, 3-H+4-H+ 5-H, 6H), 2.15 (t, 2-H, 2H), 2.27 (t, 6-H, 1H), 2.40 (s, CH_3, 3H), 3.5 (q, OCH_2), 6.8–7.8 (m, ArH)	
IX	3040 (C-Haro), 2915 (C-Hali), 1740 (O—C=O), 1710 (>C=O), 1280 (C-N), 1230 (C-O), 755 (C-S)	2.29 (s, 3-H+4-H+ 5-H, 6H), 2.31 (t, 2-H, 2H), 2.37 (t, 6-H, 1H), 2.40 (s, CH_3, 3H), 3.34 (t, 7-H, 2H), 4.03 (t, 8-H, 1H),4.25 (s, OCH_3,3H), 6.7-7.5 (m, ArH)	

Mass spectrum of **VI** m/z: 361 [$C_{23}H_{23}NOS$]$^{\cdot+}$[$M^{\cdot+}$] (28%), 333 [$M^{\cdot+}$-CO](32%), 245 [$M^{\cdot+}$-C_9H_8](100%), 162 [$M^{\cdot+}$- C_9H_8, C_5H_9N], 150 [$M^{\cdot+}$-$C_{15}H_{17}N$](22%), 90 [$M^{\cdot+}$-$C_{15}H_{17}N$, SCO](30%).

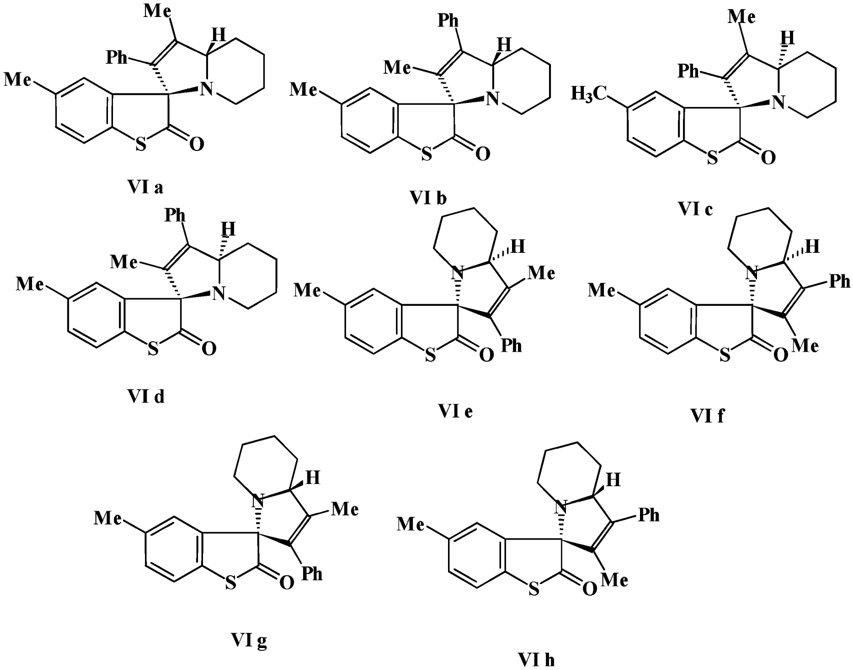


$\mathbf{IV}_{syn}$ $\mathbf{IV}_{anti}$

FIGURE 1 Optimized geometries of azomethine ylide IV.

Attack of dipolarophile, such as 1-phenyl-1-propyne on *syn* or *anti* azomethine ylide may produce a cycloadduct **VI** having two chiral centers and therefore a total of 4 + 4 = 8 stereoisomers could be possible (Figure 2).

Frontside attack of phenyl propyne (Figure 3) on azomethine ylide **IVsyn** results in the formation of products **VIe-h.** However, the



VI a **VI b** **VI c** **VI d** **VI e** **VI f** **VI g** **VI h**

FIGURE 2 Possible stereoisomers of phenyl propyne cycloadduct VI.

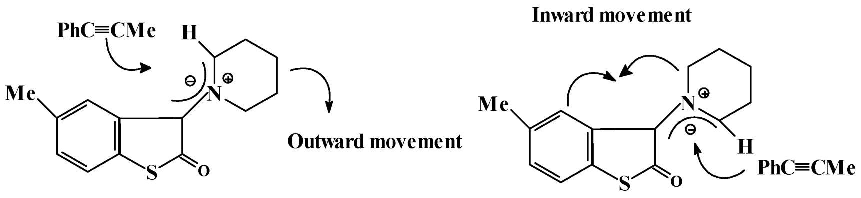


FIGURE 3 Backside attack and frontside attack of phenyl propyne on amy IV.

transition state could not be located even in a single case. This may be attributed to the steric hindrance between the thioisatin ring and the piperidine ring because frontside attack results in the inward movement of the piperidine ring towards the thioisatin ring making the system unstable and hence failing to produce transition state geometry.

This leaves only four isomers **VIa-VId** for consideration. Of these four possibilities, in two cases **VIc** and **VId**, where N and H atoms on the adjacent carbons do not lie on the same side, the transition state could not be located because a concerted mechanism is not possible in such a situation. Out of the remaining two possibilities **VIa** and **VIb**, we could optimize the transition state in the case of **VIa** only. This can be explained using the FMO approach along with the *endo* approach of the phenyl ring. The transition state of the concerted 1,3-dipolar cycloadditions in usually controlled by Frontier Molecular Orbitals (FMO's) of dipolarophiles and dipole (amy). From Figure 4, it may be concluded that $\mathrm{HOMO_{dipole}}$-$\mathrm{LUMO_{dipolarophile}}$ energy gap is lower than

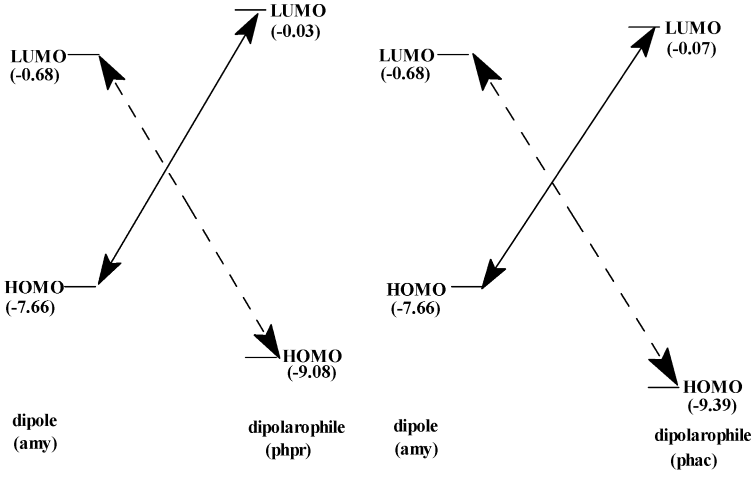


FIGURE 4 Correlation diagram indicating HOMO and LUMO energies of dipole and dipolarophiles and H-L and L-H energy gaps.

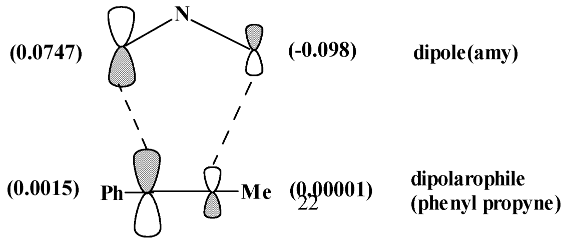


FIGURE 5 Atomic orbital coefficients and overlapping of dipole (amy) and dipolarophile (phenyl propyne).

the $\mathrm{LUMO}_{\mathrm{dipole}}$-$\mathrm{HOMO}_{\mathrm{dipolarophile}}$ gap and therefore the dominant FMO approach is $\mathrm{HOMO}_{\mathrm{dipole}}$-$\mathrm{LUMO}_{\mathrm{dipolarophile}}$.

In the HOMO of amy (dipole), the orbital coefficient is larger at C_1 (0.0747) than at C_2 (−0.098). Similarly in the LUMO of 1-phenyl-1-propyne the atomic orbital coefficient on the C-atom bearing the phenyl group is larger (0.0015) than that of the atom away from it (0.00001) (Figure 5).

An efficient orbital overlap between C of azomethine ylide and the C-atom bearing the phenyl group results in the formation of product **VI a**, ruling out the possibility of **VI b.** The optimized geometry of transition state is shown in Figure 6. Thus cycloadduct **VIa** could be formed in diastereoisomeric excess due to the *endo* approach of the phenyl ring which is in good harmony with experimental results.

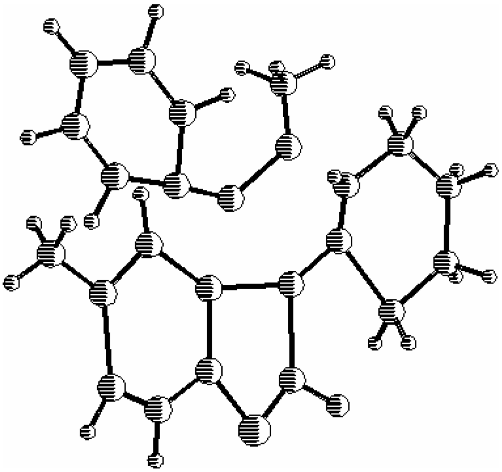


FIGURE 6 AM1 optimized geometry of transition state of cycloadduct VI.

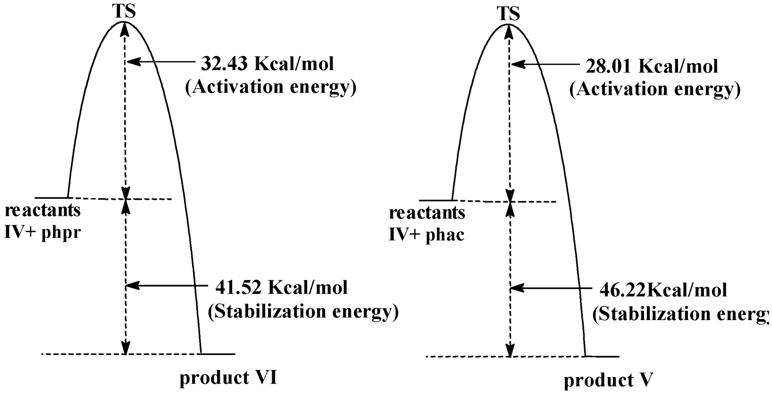


FIGURE 7 Stabilization energy and activation energy of amy (IV) with phenyl propyne and diphenyl acetylene.

The energy profile diagrams for the reactions of amy **IV** with phenyl propyne and phenyl acetylene is depicted in Figure 7. Parallel calculations have been performed on other cycloadducts and the following conclusions may be drawn:

1. Geometry optimization of the amy indicated that it has an almost planar structure.
2. The dominant FMO approach is $\mathrm{HOMO_{dipole}}$-$\mathrm{LUMO_{dipolarophile}}$ as this energy group is lower than the $\mathrm{LUMO_{dipolar}}$-$\mathrm{HOMO_{dipolarophile}}$ group (Figure 4).
3. The *endo approach* is favored and the phenyl group lies towards the thioisatin ring.

EXPERIMENTAL

The uncorrected melting points were taken in open glass capillaries. The IR spectra were recorded on a Nicolet Magna IR Spectrometer Model 550 in KBr pellets and band positions are reported in wave numbers ($\mathrm{cm^{-1}}$). The ^{1}H NMR spectra and ^{13}C NMR spectra have been recorded on a Bruker DRX-300 MHz and 75.47 MHz model respectively in $\mathrm{CDCl_3}$using tetramethylsilane as an internal standard. The chemical shifts are given in δ ppm values. The mass spectra were recorded on a JEOL-SX 102 (FAB). Most of the spectra were recorded at CDRI, Lucknow, India. Elemental analyses were performed on a Perkin Elmer Series C, H, N, S Analyzer 2400. The solvents were purified by standard procedures.[15,16] The optical rotations were measured on a D line of Na lamp at 5893 A° wavelength, at 20°C in 1g concentration.Acetonitrile was dried by refluxing with anhydrous calcium chloride for 5–6 h and then distilling it. Pipecolinic acid were purchased from Merck and Aldrich and used as supplied. Column chromatography was performed on silica gel 60 (Merck).

Computational Details

All calculations have been carried out at MOPAC 6 program using AM1 hamiltonians on PCL-Pentium 4, PC MODEL for windows, version 5.13 Serena software was used as a graphical interface for drawing and visualizing all structures and for preparing input files for MOPAC6. The energy terms has been given in Kcal/mol.

Synthesis of Oxazolidione Derivative III

A reaction mixture of 5-methylthioisatin **I** (0.36 g; 2.0 mmol) and pipecolinic acid **II** (0.260 g; 2.0 mmol) in the equimolar ratio was refluxed under a nitrogen atmosphere for 22 h in dry acetonitrile. It was then allowed to stand overnight, but no crystallization occurred. Hence, it was further concentrated to half its volume and allowed to crystallize whereby it afforded oxazolidinone derivative III as chocolate brown powder (75%), m.p. 90°C.

A Representative Method for the Synthesis of Cycloadduct VI

A mixture of 5-methylthioisatin **I** (0.36 g; 2.0 mmol) pipecolinic acid **II** (0.260 g; 2.0 mmol) and phenyl propyne (0.232 g, 2.0 mmol) in equimolar amount was refluxed under a nitrogen atmosphere for 20 h in dry acetonitrile. The completion of reaction was monitored by TLC. The crude product was column chromatographed over silica gel, whereby chloroform/ethylacetate (3:1) fraction afforded the cycloadduct **VI** as shiny brown solid (0.63 g, 75%), m.p. 220°C.

The cycloadducts **V** to **IX** are optically active and their specific rotations $[\alpha]_D^{20}$ were in the range 47°–63°.

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