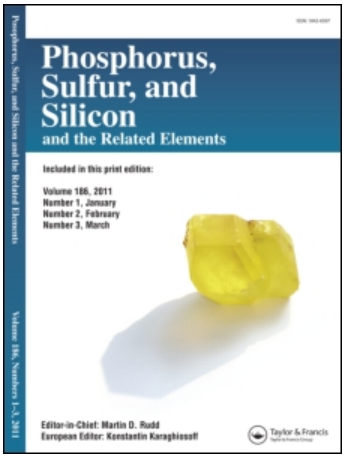

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[3+2]-CYCLOADDITION REACTIONS OF THIOISATIN WITH L-PROLINE AND (R)-(-)-THIAPROLINE

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[3+2]-CYCLOADDITION REACTIONS OF THIOISATIN WITH L-PROLINE AND (R)-(−)-THIAPROLINE

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The [3+2]-cycloaddition reactions of cyclic secondary α-amino acids viz L-proline and (R)-(−)-thiaproline with 5-methylthioisatin via azomethine ylide in the presence of dipolarophiles afford azabicyclooctane derivatives in moderate-to-good yields. The cycloadducts have been characterized by elemental analysis and spectral techniques viz IR, ^{1}H NMR, ^{13}C NMR, MASS. In addition, stereochemical aspects of the cycloaddition have been ascertained by MOPAC-6 calculations using AM1 hamiltonians.

Keywords: 1,3-Dipolar cycloaddition reactions; 5-methylbenzo-[b]thiophene-2,3-dione; L-proline; (R)-(−)-thiazolidine-4-carboxylic acid; semiempirical calculations; spectral characterization

INTRODUCTION

The occurrence of heterocyclic compounds in nature is widespread, and the use of natural and synthetic heterocycles in many commercial spheres such as the industrial, pharmaceuticals, and medicinal fields is enormous.[1,2] 1,3-Dipolar cycloaddition reactions constitute a core reaction resource in heterocyclic chemistry. It has found[3] wide synthetic applications in organic chemistry as they open access to polyfunctionalized five-membered heterocycles, often in highly regio- and stereoselective fashion (Scheme 1).

Earlier we reported 1,3-dipolar cycloaddition reactions of isatin derivatives[4,5] and acenaphthylene-1,2-dione.[6] Prompted by these results we have extended this strategy to another α-dione,

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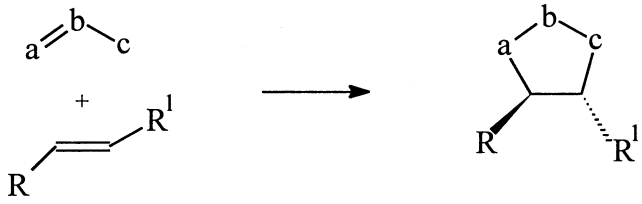


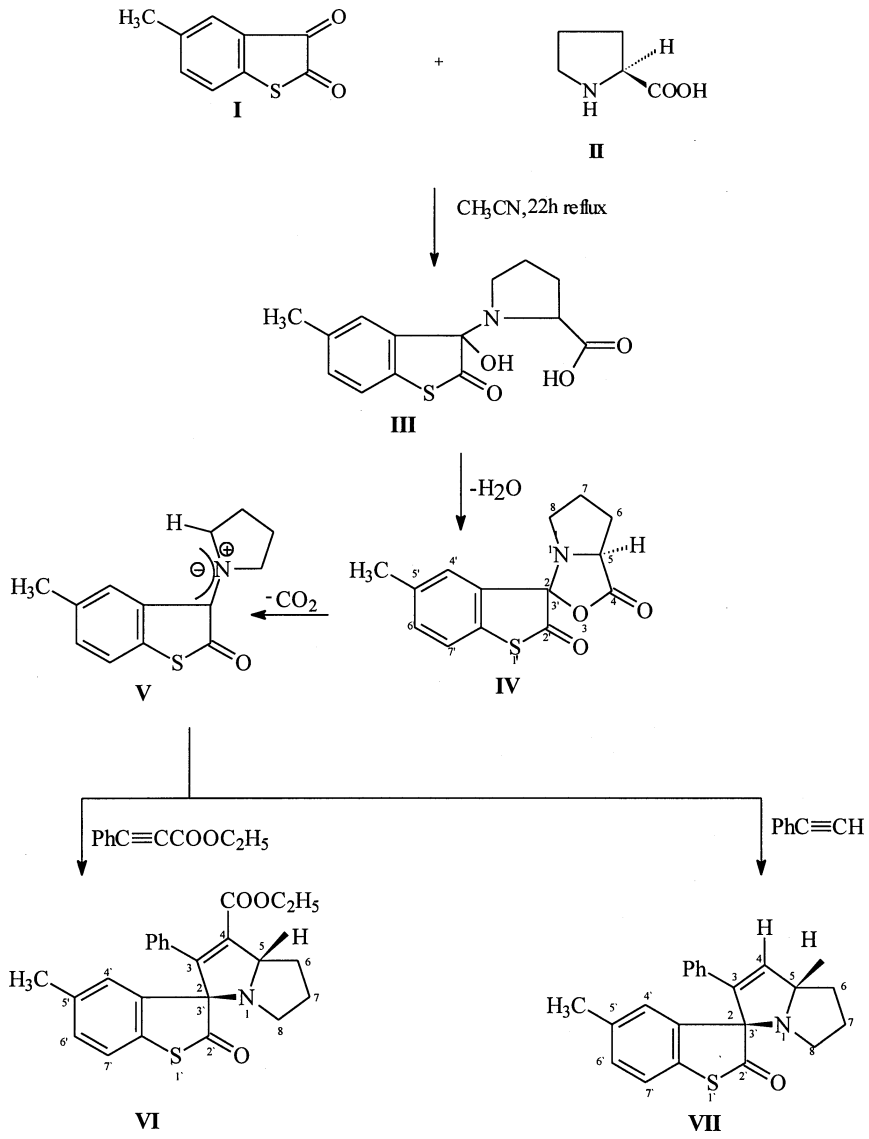
SCHEME 1

i.e., 5-methylbenzo(b]-thiophene-2,3-dione commonly known as 5-methylthioisatin.

Thioisatin is found to be inactive in the treatment of hypoxic cells[7] but is determined to be an inhibitor of poliovirus.[8] The chemistry of thioisatin has been reviewed.[9] However, its 1,3-dipolar cycloaddition reactions have remained unexplored. Thus we report herein 1,3-dipolar cycloaddition reactions of 5-methylthioisatin with L-proline and (R)-(−)-thiazolidine-4-carboxylic acid commonly known as *thiaproline* in the presence of various ethylenic and acetylenic dipolarophiles.

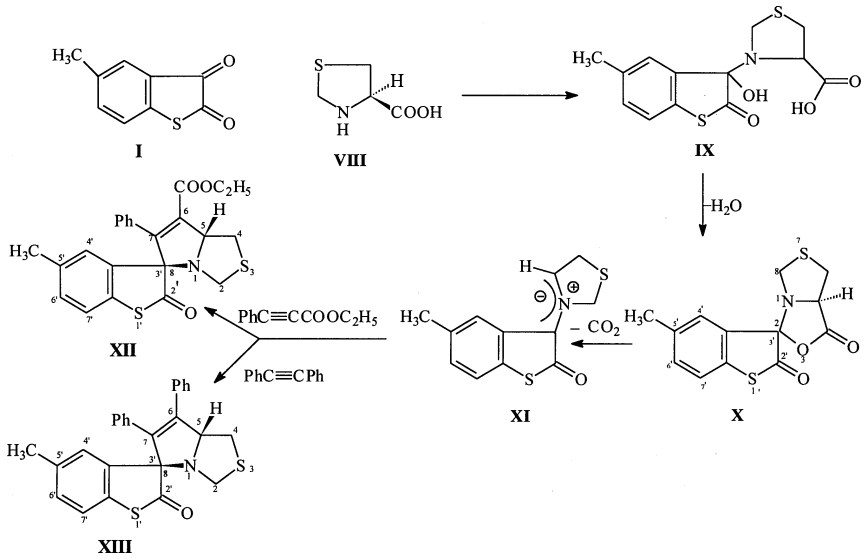
RESULTS AND DISCUSSIONS

The reaction of 5-methylthioisatin **I** with L-proline **II** was carried out in the molar ratio of 1:1 in acetonitrile for 20 h to give oxazolidinone derivative (2S,5S)-spiro-{1-aza-3-oxa-bicyclo[3,3,0]-octane-2,3′}-5′-methylbenzo[b]-thiophene-2′-one **IV** in 69% yield. When the same reaction was carried out with ethyl phenyl propiolate and phenyl acetylene as dipolarophiles, spiro polycyclic compounds (2R,5S)-spiro-{3-ethoxycarbonyl-1-aza-bicyclo[3,3,0]-2-octene-2,3′}-5′-methyl-benzo[b]-thiophene2′-one **VI** and (2R,3S)-spiro-{3-Phenyl-1-aza-bicyclo[3,3,0]-2-octene-2,3′}-5′-methyl-benzo[b]-thiophene-2′-one **VII** were obtained in 78% and 65% yields, respectively (Scheme 2). Analogous reaction with thiazolidine-4-carboxylic acid **VIII** afforded thiazolidinone derivative (2S,5S)-spiro-{1-aza-3-oxa-7-thia-bicyclo[3,3,0]-octane-2,3′}-5′-methyl-benzo[b]-thiophene-2′-one **X** in 63% yield. Such an oxazolidinone derivative has been previously prepared by the reaction of L-proline and pivaldehyde as reported by Seebach et al.[10] However, when the same reaction was carried out with ethyl phenyl propiolate and diphenyl acetylene, it produced (5R,8R)-spiro-{6-ethoxycarbonyl-7-phenyl-1-aza-3-thia-bicyclo[3,3,0]-6-octene}-5′-methyl-benzo[b]-thiophene-2′-one **XII** and (5R,8R)-spiro-{6,7-diphenyl-1-aza-3-thia-bicyclo-[3,3,0]-6-octene}-5′-methyl-benzo[b]-thiophene-2′-one **XIII** in 72% and 70% yields,



SCHEME 2

respectively (Scheme 3). In both cases, the reaction proceeds by the formation of nonisolable intermediate azomethine ylides **V** and **XI**, which subsequently undergo 1,3-dipolar cycloaddition reactions with various dipolarophiles to afford spiro compounds. These results are in good agreement with the theoretical calculations as well as those



SCHEME 3

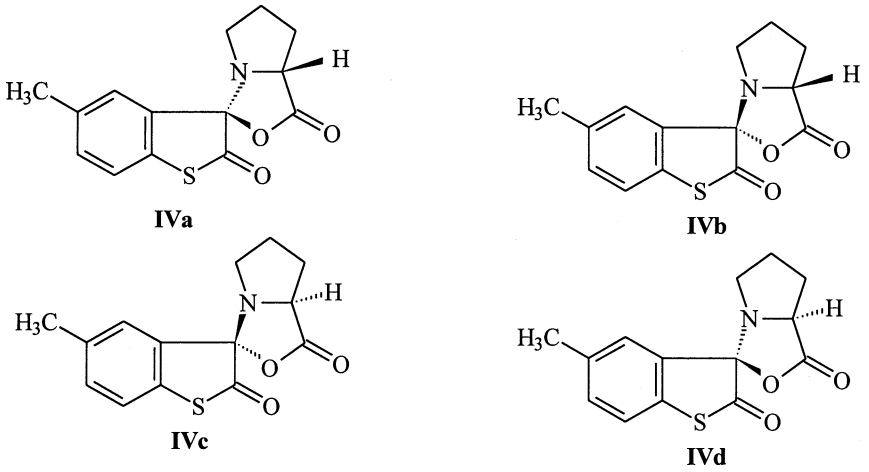
reported by Grigg et al.[11,12] for the reaction of carbonyl compounds with amines.

SEMIEMPIRICAL MOLECULAR ORBITAL CALCULATIONS

Semiempirical calculations have been carried out using MOPAC-6 program on AM1 hamiltonians. Oxazolidinone compound **IV** derived from cyclocondensation of 5-methylthioisatin **I** with L-proline **II** or thiazolidine-4-carboxylic acid **VIII** contains two chiral centers, and therefore a total of four stereoisomers, **IVa–IVd**, are possible (Scheme 4).

We have been able to optimize the geometry of all the four isomers. Since product **IV** is formed upon dehydration of iminium species **III,** the stereochemistry at C-5 should remain unchanged with regard to the L-proline. On this basis, the possibility of stereoisomers **IVa** and **IVb** may be ruled out. Of the remaining isomers, **IVc** has a high ΔH_f value, and thus the expected product is **IVd.**

In the presence of dipolarophiles, the intermediate lactonic species **IV** or **X** may undergo decarboxylation to give azomethine ylides **V** or **XI**, which subsequently undergo 1,3-dipolar cycloaddition reaction to give spiro polycyclic compounds. Optimized geometry of azomethine ylide



SCHEME 4

XI indicates that it has a plannar structure, wherein thiazolidine ring lies in the same plane as that of thioisatin moiety (Figure 1).

The ΔH_f, HOMO and LUMO energies, and HOMO-LUMO and LUMO-HOMO energy gaps of azomethine ylide **V** and **XI** with dipolarophiles are given in Table II. The transition state of the concerted 1,3-dipolar cycloaddition reaction is usually controlled by frontier molecular orbitals of dipolarophiles and dipoles. From Table II we may conclude that the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ energy gap is lower

TABLE I Physical and Analytical Data of Compounds

Compound no.	Physical state	Molecular formula	m.p. (C)	Yield (%)	Elemental analysis calcd. (found)			
					C	H	N	S
IV	Dark brown powder	$C_{14}H_{13}NO_3S$	80	69	61.09 (61.00)	4.72 (4.31)	5.00 (4.82)	11.60 (11.53)
VI	Light yellow powder	$C_{24}H_{23}NO_3S$	95	78	71.11 (71.05)	5.67 (5.55)	3.45 (3.31)	7.90 (7.76)
VII	Light brown powder	$C_{21}H_{19}NO_3S$	101	65	75.67 (75.53)	5.70 (5.62)	4.80 (4.61)	9.60 (9.42)
X	Dusty brown powder	$C_{12}H_{11}NO_3S_2$	100	63	53.93 (53.80)	4.11 (4.05)	5.24 (5.04)	23.97 (23.72)
XII	Pale yellow powder	$C_{23}H_{21}NO_2S_2$	108	72	67.81 (67.61)	5.51 (5.32)	3.43 (3.30)	15.72 (15.52)
XII	Yellow brown powder	$C_{25}H_{21}NOS_2$	90	70	72.28 (72.09)	5.06 (5.01)	3.37 (3.29)	15.42 (15.48)

TABLE II ΔH_f, HOMO and LUMO Energies, and H-L and L-H Energy Gaps

	ΔH_f (kcal/mol)	HOMO (kcal/mol)	LUMO (kcal/mol)	Energy gaps (kcal/mol)	
				H-L	L-H
Dipole					
Amy **V**	28.31	−7.72	−0.67		
Dipoarophiles					
Etph	10.80	−9.71	−0.66	7.06	9.04
Phac	74.65	9.39	−0.07	7.65	8.72
Dipole					
Amy **XI**	44.29	−7.95	−0.97		
Dipoarophiles					
Etph	−10.80	−9.71	−0.66	7.29	8.74
Dpa	97.81	−8.75	−0.44	7.51	7.78

Amy, azomethine ylide; Phac, phenylacetylene; Etph, ethylphenylpropiolate, dpa, diphenylacetylene.

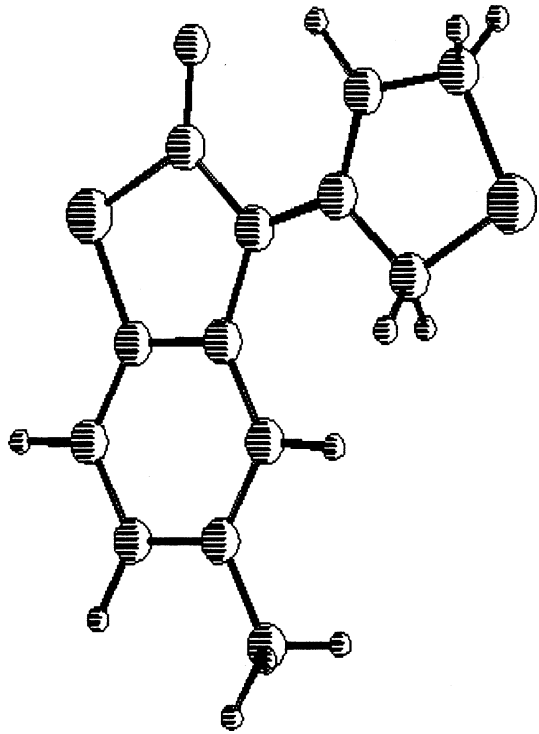
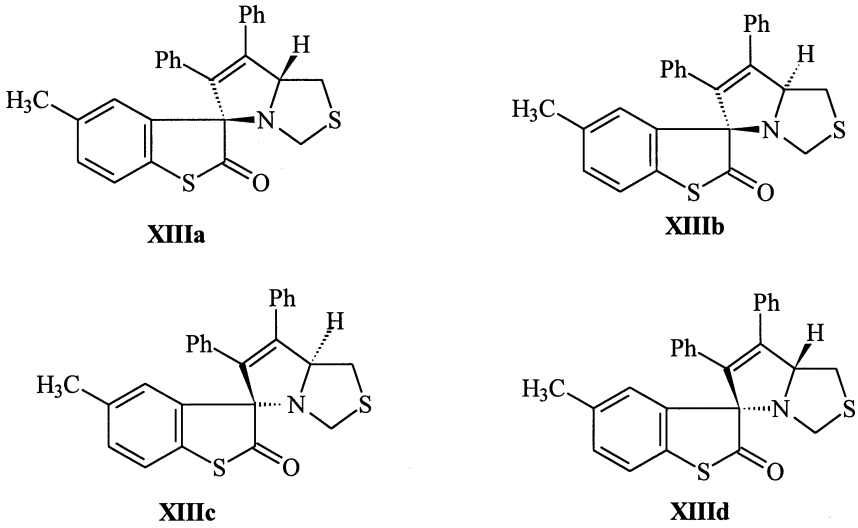


FIGURE 1 Optimized geometry of azomethine ylide **XI**.



SCHEME 5

than the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ gap, and therefore the dominant FMO approach is $HOMO_{dipole}$-$LUMO_{dipolarophile}$.

Attack of diphenyl acetylene on the planar azomethine ylide **XI** from either side results in the formation of products having two chiral centers. Therefore, $2^2 = 4$ isomers, **XIIIa–XIIId**, are possible (Scheme 5). We have optimized the geometry of all the four isomers. Results show that all isomers have the same ΔH_f, indicating that thermodynamically all are nearly equally stable.

Frontside attack of diphenyl acetylene (Figure 2) results in the formation of the products **XIIIc–d**. However, in the case of the frontside attack of diphenyl acetylene the transition state could not be located. This may be attributed to the steric hinderence between the

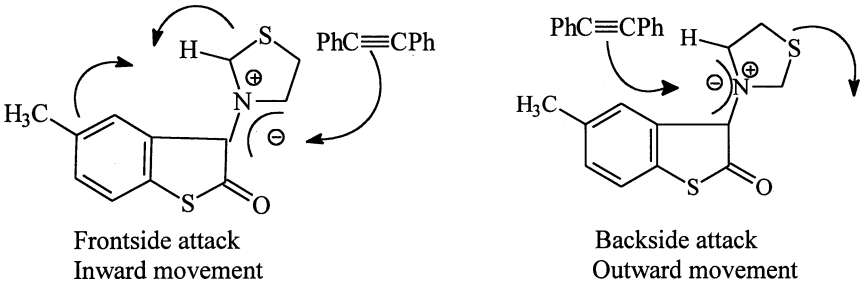


FIGURE 2 Attack of diphenyl acetylene on azomethine ylide **XI**.

TABLE III ΔH_f-R, ΔH_f-Ts, ΔH_f-P, Ea, and Stabilization Energy of Amy **XI** with Dipoarophiles

Product	R	Ts	P	Ea	Stablization energy
Amy **XI** + dpa	−15.21	173.86	102.95	58.65	118.16

5-methylthioisatin ring and the thiazolidine ring, because frontside attack would result in the inward movement of thiazolidine ring towards 5-methylthioisatin ring, making the system unstable and transition state geometry fail to produce. This leaves only the possibility of backside attack for consideration.

Out of remaining two possibilities **XIIIa** and **XIIIb**, in case of **XIIIb** where N and H atoms on the adjacent carbon atom do not lie on the same side, the transition state could not be located because concerted mechanism is not possible in such a situation. This leaves only one structure, **XIIIa**, for consideration. We have optimized the transition state in this case. This can be explained using FMO approach: the favoured path involves the $HOMO_{dipole}$ and $LUMO_{dipolarophile}$. Besides a secondary interaction between the two phenyl rings, the endo approach also favors the formation of product **XIIIa**. The molecular orbital interaction between the azomethine ylide **XI** and diphenyl acetylene can be diagrammatically represented as in Figure 3.

From the above discussion, we can conclude the following:

1. The azomethine ylides **V** and **XI** have almost planar structure.
2. The dominant FMO approach is $HOMO_{dipole}$-$LUMO_{dipolarophile}$, as this energy gap is lower than $LUMO_{dipole}$-$HOMO_{dipolarophile}$ gap (Figure 4).

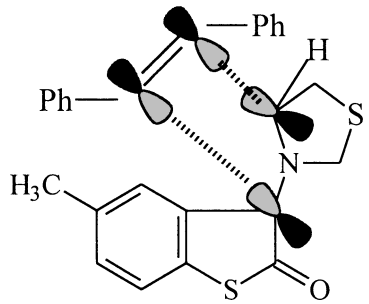


FIGURE 3 Molecular orbital interaction between azomethine ylide **XI** and diphenyl acetylene.

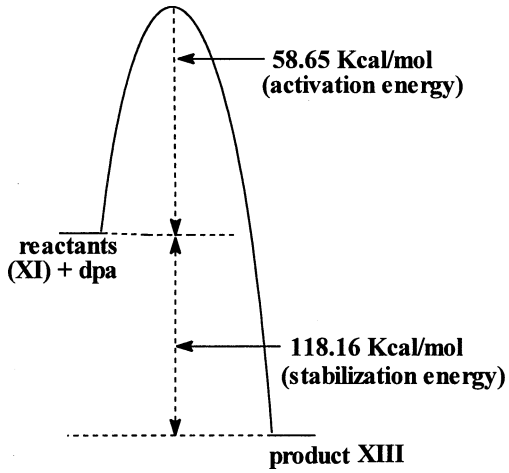


FIGURE 4 Stabilization energy and activation energy of any **XI** with diphenyl acetylene(dpa).

SPECTRAL STUDIES

The structure of all synthesized heterocycles **IV**, **VI**, **VII**, **X**, **XII**, and **XIII** has been ascertained from their spectral data. The IR spectrum of compound **IV** showed characteristic bands at 3040 cm^{-1} due to C—H aromatic vibrations, at 1720 cm^{-1} due to C=O, at 1400 cm^{-1} due to C—N stretching, and at 1190 cm^{-1} due to C—O—C stretching. Its ^{1}H NMR spectrum showed following signals: a singlet at δ 1.2 for CH_3, a multiplet in the range of δ 1.65–1.91 for 7-H (2H), a quartet at δ 2.58 for 6-H (2H), a triplet at δ 4.26 for 8-H (2H), another triplet at δ 4.63 for 5-H (1H) and a multiplet in the range of δ 6.48–8.47 ppm for aromatic protons (3H). Its ^{13}C NMR spectrum showed signals at δ 178.51 for lactonic carbon and at 173.47 for carbonyl carbon, and aromatic carbons appeared in the range δ 143.12–119.63 ppm, spiro carbon appeared at δ 79.13, the bridgehead carbons appeared at δ 58.27, three methylene carbons appeared at δ46.86 (C-8), 39.26 (C-6), 27.03 (C-7), and methyl carbon appeared at δ 23.99 ppm. The spectral details of remaining compounds are compiled in Table IV.

EXPERIMENTAL

All the reactions were carried out under nitrogen atmosphere. The melting points were determined in open glass capillaries and are

TABLE IV Spectral Data of Compounds

Compound no.	IR (cm^{-1})	^{1}H δ (ppm)	^{13}C δ (ppm)
IV	3090 (Caro), 1720 (>C═O), 1400 (C—N), 1190 (C—O)	1.2 (s, CH_3), 1.65–1.91 (m, 7–7, 2H), 2.58 (q, 6-H, 2H), 4.26 (t, 8-H, 2H), 4.63 (t, 5-H, 1H), 6.48–8.47 (m, ArH)	178.51 (>C═O, C-2′), 173.47 (>C═O, lactonic), 143.12–119.63 (ArH), 79.13 (spiro), 58.27 (C-5), 46.86 (C-8), 27.03 (C-6), 23.99 (C-7)
VI	2990 (C-Hali.), 1710 (>C═O), 1470 (C—N), 790 (C-Haro)	1.01 (t, CH_3), 1.2 (s, CH_3) 1.6–2.2 (m, 6H + 7H, 4H), 2.57 (t, 8-H, 2H), 4.04 (q, OCH_2), 4.45 (t, 5-H, 1H), 6.52–7.98 (m, ArH)	178.17 (>C═O), 174.75 (>C═O, ester), 142.47–120.41 (ArC), 114.71 (C-4), 108.91 (C-3), 71.29 (spiro), 59.42 (C-5), 57.92 (OCH_2), 46.54 (C-8), 31.12 (C-6), 26.76 (C-7), 13.16 (CH_3)
VII	1720 (>C═O), 670 (C-S), 800 (C-Haro)	1.2 (s, CH_3), 1.8–1.9 (m, 6H + 7H, 4H), 2.16 (t, 8-H, 2H), 2.74 (d, 4-H, 1H), 4.75 (t, 5-5, 1H), 6.58–7.38 (m, ArH)	
X	1720 (>C═O), 1400 (C—N), 1200 (C—O, 680 (C-S)	1.2 (s, CH_3), 3.01 (m, 6-H, 2H), 3.63 (d, 8-H, 2H), 7.56–8.38 (m, ArH)	188.99 (>C═O), 178.63 (0-C—O), 79.29 (spiro), 52.13 (C-2), 34.93 (C-6)
XII	3090 (C-Haro), 2960 (C-Hali.), 1715 (>C═O), 690 (C-S)	1, 2 (s, CH_3), 3.18 (d, 4-H, 2H), 3.97 (q, $0CH_2$), 3 (s, 2-H, 2H), 4.37 (t, 5-H, 1H), 6.6–.85 (m, ArH)	
XIII	3110 (C-haro), 1720 (>C═O), 1410 (C—N), 690 (C—S)	1.2 (s, CH_3), 2.2 (d, 4-H, 2H), 4.21 (s, 2-H, 2H), 6.93–7.62 (m, ArH)	

uncorrected. The IR spectra were recorded on a Nicolat Magna IR^{TM} spectrometer model in KBr pellets. All the ^{1}H NMR, and ^{13}C NMR spectra were recorded on a Brucker 300 MHz model in $CDCl_3$ using tetramethylenesilane (TMS) as an internal standard. Chemical shifts are given in δ ppm values. Mass spectra were recorded on a JEOL-SX 102 (FAB). Most of the spectra have been recorded at CDRI, Lucknow, India. Elemental analysis were performed on Perkin Elmer series C, H, N, and S analyzer-2400. All the solvents were purified by standard procedures.[13,14] Column chromatography was performed on silica gel 60 mesh (Merck). The semiempirical calculations were performed on MOPAC- 6 program using AM1 hamiltonian.

A Representative Method for the Synthesis of Oxazolidinone IV

A reaction mixture of 5-methylthioisatin (**I**, 0.36 g; 2.0 mmol) and L-proline (**II**, 0.23 g, 2.0 mmol) in the equimolar ratio was refluxed under a nitrogen atmosphere for 20 h in dry acetonitrile. It was then allowed to stand overnight, but no crystallization occurred. Hence it was further concentrated to half of its volume and allowed to crystallize to afford oxazolidinone derivative **IV** as dark brown powder (69%), m.p. 80°C.

A Representative Method for the Synthesis of Cycloadduct VII

A mixture of 5-methylthioisatin (**I**, 0.36 g, 2.0 mmol) and L-proline (**II**, 0.23 g, 2.0 mmol) and phenyl acetylene(**VII**, 0.219 g, 2.0 mmol) in equimolar amount was refluxed under a nitrogen atmosphere for 20 h in dry acetonitrile. After completion of the reaction, as monitored by thin layer chromatography (TLC), unreacted acid was removed by filteration. The filterate was evaporated in vaccum to half of its volume and allowed to crystallize. However, no crystals appeared even after standing for 48 h, and hence the crude product was subjected to column chromatography over silica gel, whereby compound **VII** was obtained as light brown powder from chloroform/ethylacetate (5:1) fraction in 65% yield, m.p. 101°C.

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