Synthesis, Semiempirical, Stereoselectivity and Pharmacological Activity of a New Class of Spiro Pyrrolidine and Isoquinoline Derivatives

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Z. Naturforsch. **61b,** 213 – 220 (2006); received April 22, 2005

1,3-Dipolar cycloaddition of azomethine ylides derived from acenaphthylene-1,2-dione and 5-methyl-benzo[b]-thiophene-2,3-dione with L-proline, thiazolidine-4-carboxylic acid and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid with various electron deficient dipolarophiles leads to the formation of novel spiroheterocycles having two or more chiral centers. Semiempirical studies have been performed to understand the stereochemical course of the reaction. The synthesized cycloadducts have been screened for antimicrobial and toxicological activity.

Key words: Spiro Pyrrolidine, Isoquinoline Derivatives

Introduction

1,3-Dipolar cycloaddition have been concisely summarized in the review article of Houk [1]. They have emerged as powerful tools for the stereoselective construction of complex spiroheterocycles in a single step [2]. Interest in the synthesis of pyrrolidine derivatives *via* azomethine ylides has increased dramatically because these systems have widely been encountered in a number of molecules of interest [3, 4]. Prompted by the growing importance of azomethine cycloadditions for the assembly of biologically relevant spiropyrrolidine heterocycles [5, 6] and in continuation to our recent studies [7 – 9], we report herein the stereoselective synthesis of acenaphthylidene substituted pyrrolidine and isoquinoline derivatives by reaction of acenaphthylene-1,2-dione and 5-methyl-benzo[b]-thiophene-2,3-dione (known as 5-methylthioisatin) with thiazolidine-4-carboxylic acid, L-proline and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in the presence of various ethylenic and acetylenic dipolarophiles. These cycloadditions are virtually free from side reactions and good to excellent yields of cycloadducts have been obtained.

Results and Discussion

The reaction of acenaphthylene-1,2-dione (**1**) with (R)-(-)-thiazolidine-4-carboxylic acid (**2a**) in equimolar ratio in refluxing acetonitrile for 22 h generated, *in situ*, azomethine ylide (**3**) (Scheme 1) which in the presence of dipolarophiles *viz*. ethyl phenyl propiolate, phenyl acetylene and methyl acrylate lead to the stereoselective formation of cycloadducts (**4**), (**5**) and (**6**) in 76%, 72% and 75% yields respectively.

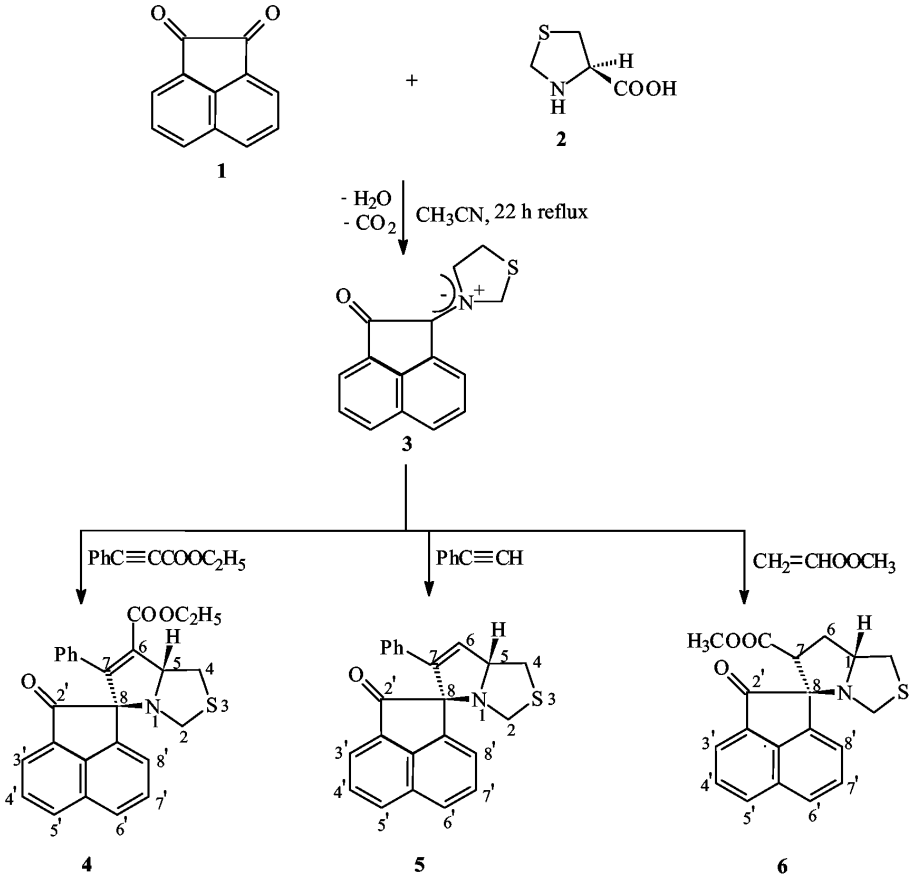
Similarly, reaction of acenaphthylene-1,2-dione (**1**) with 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**7**) in the presence of dipolarophiles such as phenyl acetylene, diphenyl acetylene, phenyl propyne, ethyl phenyl propiolate and methyl acrylate afforded cycloadducts (**9**) and (**10**) in 75% – 85% yields (Scheme 2).

The same methodology was applied to synthesize cycloadducts (**15** – **16**) from 5-methylthioisatin **(11)** and thiazolidine-4-carboxylic acid (**2**) or L-proline (**12**) (Scheme 3).

The results are in good harmony with the observation of Grigg [10, 11] as well as with theoretical calculations. The mechanism for the formation of cycloadducts involves the formation of nonisolable intermediate azomethine ylides (**3**), (**8**) and (**13**, **14**) which subsequently undergo 1,3-dipolar cycloaddition reactions with various dipolarophiles to afford the corresponding spiro cycloadducts. The conclusive evidence for the formation of cycloadducts has been obtained by resolving the X-ray structure of (5*R*,7*R*,8*S*)-Spiro-{7-methoxycarbonyl-1-aza-3-thia-bicylo[3,3,0]-octan-2,1'-acenaphthylene}-2'-one (**6**) [12].

Semiempirical Calculations

In order to understand the stereochemical course of the cycloaddition detailed semiempirical MO studies



Scheme 1.

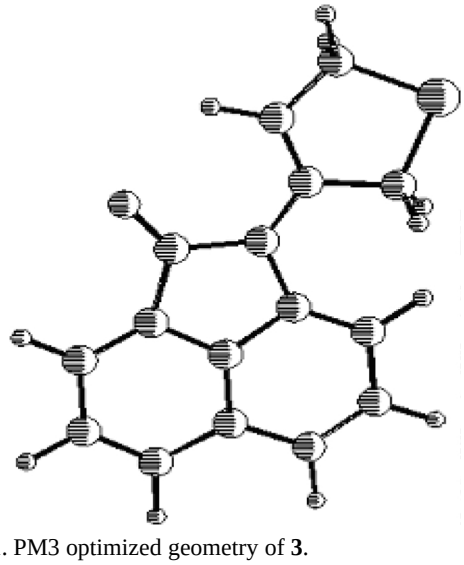
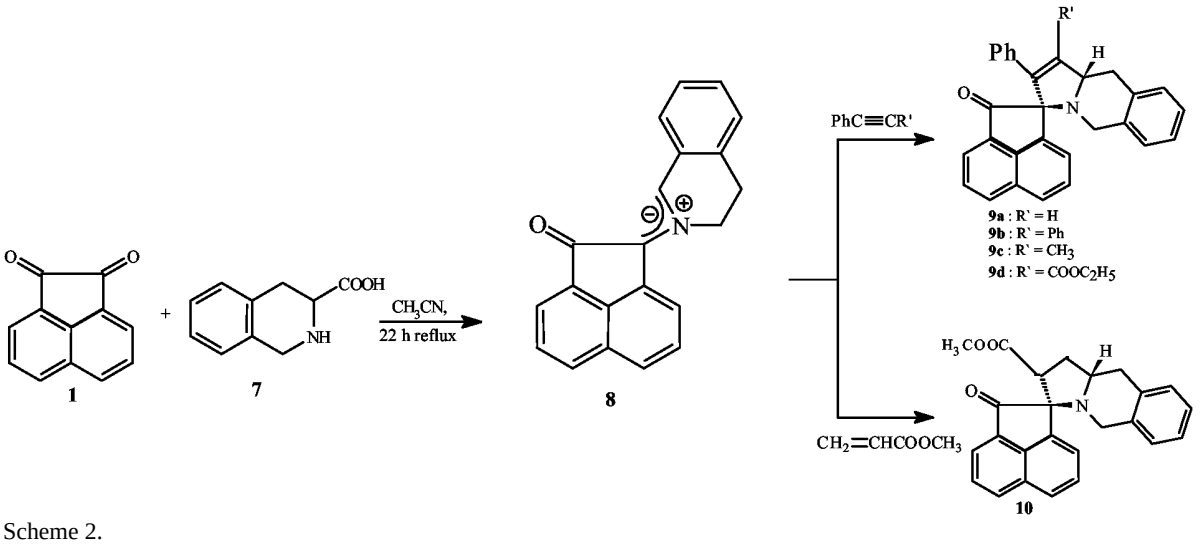


Fig. 1. PM3 optimized geometry of **3**.

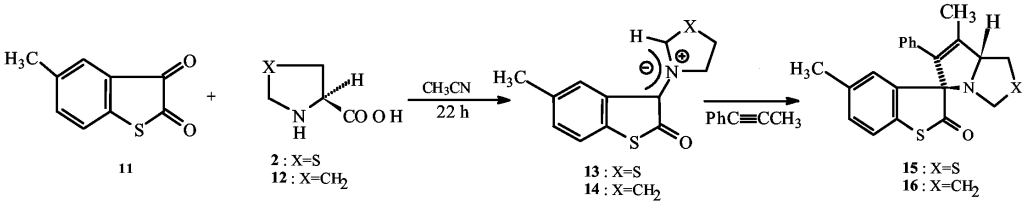
were conducted employing the MOPAC 6 program using AM1 and PM3 hamiltonians [13, 14]. Geometry optimization of azomethine ylide **3** indicated that it has an almost planar structure (Fig. 1).

Instead of having an envelope shape, the thiaproline ring is planar and lies in the same plane as that of acenaphthylene ring. It exists in two isomeric forms, one in which C=O group of acenaphthylene ring and C-H of the dipole are *syn* **3a** and other in which these two groups are *anti* **3b**. Ethyl phenyl propiolate may approach either of the azomethine ylide (Fig. 2) with the formation of products having two chiral centres. Therefore, a total of eight isomers **4a** – **h** would be possible (Fig. 3).

Attack of ethyl phenyl propiolate on *anti* azomethine ylide **3b** may result in the inward movement of thiaproline ring towards the acenaphthene nucleus (Fig. 3) and transition state could not be located even in a single case **4e** – **h**. It may be due to the steric hindrance between the acenaphthene ring and thiaproline ring making the system unstable. The only possibility is the attack on *syn*-amy **3a** leaving only four stereoisomers **4a** – **d**. Out of these four stereoisomers, **4c** and **4d**



Scheme 2.



Scheme 3.

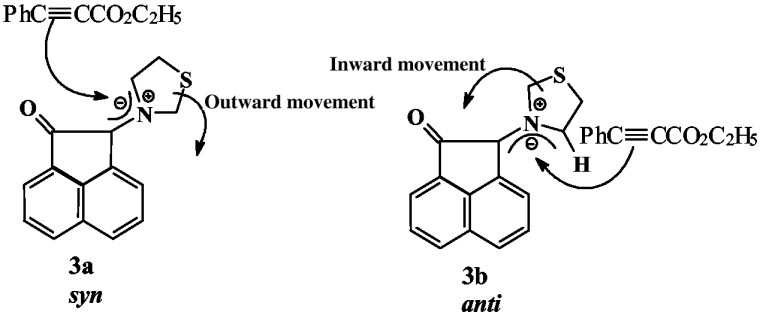


Fig. 2. Attack of ethyl phenyl propiolate on **3**.

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. Thus only two isomers **4a**, **b** have concerted mechanism. From Table 1 we may conclude that $HOMO_{dipole}$ - $LUMO_{dipolarophile}$ energy gap is lower than $LUMO_{dipole}$ - $HOMO_{dipolarophile}$ and therefore the dominant FMO approach is $HOMO_{dipole}$ - $LUMO_{dipolarophile}$.

Both HOMO and LUMO of the dipole show uneven distribution of electronic density along the C-N-C dipole. In the HOMO case, the orbital coefficient is larger at C1 (0.23) than at C2 (−0.47). Similarly, in the LUMO of ethyl phenyl propiolate the orbital coefficient on the carbon atom bearing phenyl group is larger (0.34) than that C-atom bearing $–COOC_2H_5$ group (−0.35) (Fig. 4).

Thus, there is a better orbital overlap between C1 of azomethine ylide **3a** and C-atom bearing phenyl group (Fig. 5).

Of these two isomers, **4a** would be obtained in diastereomeric excess due to the *endo* approach of the phenyl group. The energy profile diagram for this cycloaddition reaction is shown in Fig. 6. The stereochemistry of the other cycloadducts has been assigned similarly.

	ΔH_f (Kcal/mol)	HOMO (eV)	LUMO (eV)	Energy gap (eV) H-L	L-H
Dipole azomethine ylide (**3**)	57.65	−8.04	−0.89	–	–
Dipolarophile ethyl phenyl propiolate	−10.88	−9.71	−0.66	7.07	9.10
Phenyl acetylene	74.65	9.39	−0.07	7.66	8.78
Methyl acrylate	−65.98	−11.06	−0.06	7.67	10.45
Dipole azomethine ylide (**8**)	91.50	−7.42	−0.45	–	–
Dipolarophile ethyl phenyl propiolate	−10.88	−9.71	−0.66	8.08	9.25
Phenyl propyne	64.88	9.08	0.03	7.45	9.53
Diphenyl acetylene	97.81	−8.75	−0.73	6.69	8.29
Phenyl acetylene	74.65	9.39	−0.07	7.49	9.84
Dipole azomethine ylide (**13**)	44.29	−7.95	−0.97	–	–
Phenyl propyne	64.88	9.08	0.03	7.91	8.11
Dipole azomethine ylide (**14**)	28.31	−7.72	−0.67	–	–
Phenyl propyne	64.88	9.08	0.03	7.69	8.31

Table 1. ΔH_f, HOMO and LUMO energies and H-L and L-H energy gaps.

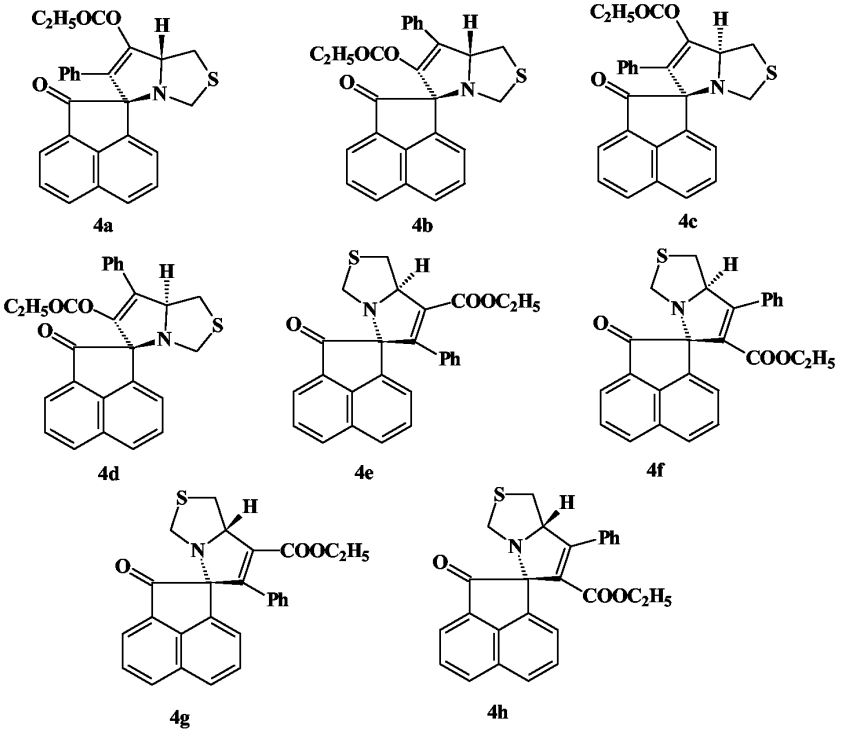


Fig. 3. Eight possible stereo and regioisomers of the cycloadduct **4**.

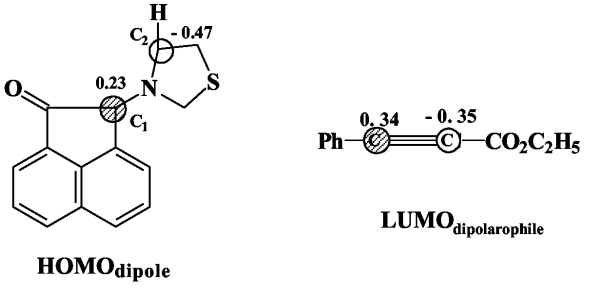


Fig. 4. Atomic orbital coefficients of $HOMO_{dipole}$ and $LUMO_{dipolarophile}$.

Antimicrobial Activity

The cycloadducts **4**, **5**, **6**, **9a**, **9b**, **9c**, **9d** and **10** were tested for their antifungal activity against the fungi *Macrophamina phaseolina* and *Fusarium oxysporium* and antibacterial activity against *E-coli*, *S. aureus* and *Lactobacillus*.

a. Antifungal activity

The radial growth method was used to evaluate the activity against the test fungi. For this purpose potato-dextrose-agar-agar (PDA) medium was prepared. The

Table 2. Antifungal activity of the cycloadducts.

Compound No.	Average radial growth (mm)			
	Macrophamina phaeseolina		*Fusarium oxysporium*	
	500 ppm	1000 ppm	500 ppm	1000 ppm
4	53.3	25.0	28.3	20.0
5	16.0	9.85	20.0	15.6
6	31.6	35.0	36.6	20.0
9a	18.3	10.0	20.0	16.6
9b	23.3	25.0	28.3	13.3
9c	15.0	11.6	20.0	16.6
9d	20.0	20.2	33.3	11.6
10	28.3	23.3	28.3	11.6

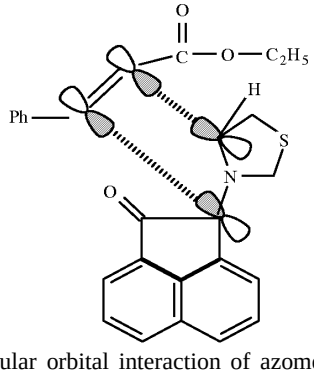


Fig 5. Molecular orbital interaction of azomethine ylide 3 and ethyl phenyl propiolate.

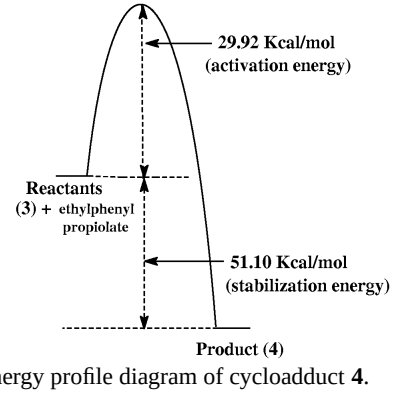


Fig 6. Energy profile diagram of cycloadduct **4**.

compounds to be tested were dissolved in acetone and mixed with the medium in different concentrations (500 ppm and 1000 ppm) and poured into the petridishes uniformly at room temperature. The spores of the selected fungi were then placed on the medium with the help of innoculation needle. These petridishes were then placed in an incubator at 27 °C. Plates without chemicals served as check (control). Check was maintained without adding any chemicals in PDA. The growth of the fungus was ascertained by measuring the fungal colony diameter *i.e.* the horizontal and vertical linear growth of the testing fungus and control. The results of the assay's are summarized in Table 2.

From these data it is clear that the compound **9c** showed pronounced activity in reducing the linear growth of the fungus *Macrophamina phaeseolina* at 500 ppm and 1000 ppm, respectively and was found at par with **9a** and **5** as compared to the control. Similarly, compound **10** was found significantly superior in reducing the linear growth of the test fungus *Fusarium oxysporium* at 1000 ppm and was found at par with the compounds **4**, **9a**, **9b** and **9c**.

Table 3 Antibacterial activity of the cycloadducts.

Compound No.	Inhibition zone of test compound (Activity Index in mm)		
	E. coli	*S. aureus*	*Lactobacillus*
4	10.5	12.6	–
5	4.1	–	–
6	10.9	9.4	–
9a	–	9.2	4.5
9b	–	–	5.6
9c	12.5	–	10.5
9d	10.0	12.5	–
10	8.9	9.5	10.5

b. Antibacterial activity

For the bactericidal assay, the disc diffusion method [15, 16] was adopted. The test organism was preceded over sterilized culture medium plates and the zone of inhibition was measured around the sterilized dried discs of No. 1 filter paper (5 mm in diameter) which was saturated with the solutions of the test compound and reference compound (Streptomycin). Such treated discs were air dried at room temperature to remove any residual solvent which might interfere with the determination of activity. Before incubation, the plates were placed at low temperature for one hour to allow maximum diffusion of the compound from the test discs into the agar plates. Later these plates were incubated at 37 °C for 20 – 24 h after which the zone of inhibition was determined and compared with the respective standard reference zones to calculate the activity index,

$$\text{Activity Index} = \frac{\text{Inhibition zone of test compound (in mm)}}{\text{Inhibition zone of reference drug (in mm)}}.$$

The results are summarized in Table 3 and it can be concluded that compound **9c** and **6** showed high antibacterial activity against *E-coli* whereas compound **4** and **9d** show significant activity against *S. aureus*. Compound **10** showed pronounced activity against *Lactobacillus*.

Toxicological Activity

A preliminary toxicological study was carried out to evaluate the toxicity of the test compounds. Acute toxicity of compounds **15** and **16** was determined on healthy male Albino rats divided equally into four groups (each group containing 4 rats) named A, B, C and D dosed with 0, 50, 100 and 200 mg/kg of test compounds **15** and **16**. The desired concentration for dose preparation was obtained by using peanut oil as vehicle for dilution. The compound was administered orally with a disposable syringe and a 16-G rat feeding needle. The animals were observed daily for gross behavioral and physical change. Pharmacological symptoms such as mild decrease in spontaneous motor activity, sedation and decrease in sensitivity towards touch and heat was observed in the rats which are indicative of the mild analgesic and antidepressant activity of the compound. Toxic symptoms such as nasal bleeding was seen in the rats belonging to D group dosed with test compound **15**. All animals were found to be absolutely normal and active on the 17th day. The summary of the gross animal behavior and physiology is tabulated in Table 4.

Experimental Section

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 (cm^{-1}). The ^{1}H NMR spectra and ^{13}C NMR spectra have been recorded on a Bruker 300 MHz and 75.47 MHz model respectively in $CDCl_3$/DMSO-d_6 using tetramethylsilane as an internal standard. The chemical shifts are given in δ ppm values. Mass spectra were recorded on Autospectrometer EI+ Magnet at Indian Institute of Chemical Technology, Hyderabad. Elemental analyses were performed on a Perkin Elmer Series C, H, N, S Analyzer 2400. Acetonitrile was dried by refluxing with anhydrous calcium chloride for 5 – 6 h and then distilling it. Acenapthylene-1,2-dione and (R)-(-)-thiazolidine-4-carboxylic acid were purchased from Fluka and used as supplied. Column chromatography was performed on silica gel 60 (Merck).

General procedure

The reaction of acenaphthylene-1,2-dione (**1**) with thiazolidine-4-carboxylic acid (**2**) in refluxing acetonitrile for 22 h in the presence of ethyl phenyl propiolate, phenyl acetylene and methyl acrylate afforded following cycloadducts (**4** – **6**):

(5S,8R)-Spiro-7-phenyl-6-ethoxrcarbonyl-1-aza-3-thia-bicyclo-[3.3.0.]-oct-6-ene-8,1'-acenaphthylene-2'-one (**4**): M. p. 170 °C. – IR (KBr): $\tilde{\nu} = 3090$ (C-H_{aro}), 2960 (C-H_{ali}), 1715 (>C=O),690 (C-S) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, CH_3), 3.18 (d, 2H, 4-H), 3.97 (q, 2H, –OCH_2), 4.23 (brs, 2H, 2-H), 4.37 (t, 1H, 5-H), 6.69 – 7.85 (m, 11H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 202.36$ (>C=O), 177.01 (O-C=O), 142.62 – 122.53 (ArC), 115.6, 11.9 (C-7 and C-6), 78.38 (spiro C-8), 69.11 (C-5), 59.75 (C-2), 54.83 (OCH_2), 52.35 (C-4), 20.31 (CH_3). – MS (EI): $m/z = 427$ (M^+). – $C_{26}H_{21}NO_3S$ (427): calcd. C 77.07, H 4.92, N 3.28; found C 77.01, H 4.83, N 3.15.

(5S,8R)-Spiro-7-phenyl-1-aza-3-thia-bicyclo-[3.3.0.]-oct-6-ene-8,1'-acenaphthylene-2'-one (**5**): M. p. 210 °C. – IR (KBr): $\tilde{\nu} = 3010$ (C-H_{aro}), 1720 (>C=O), 1410 (C-N), 690 (C-S) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.26$ (d, 2H, 4-H), 2.89 (d, 1H, 6-H), 3.69 (q, 2H, 5-H), 3.96 (s, 2H, 2-H), 6.93 – 7.62 (m, 11H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 173.47$ (>C=O), 143.12 – 119.08 (ArC), 109.1, 108.7 (C-7 and C-6) 79.13 (spiro C-8), 64.52 (C-2), 58.27 (C-5), 31.01 (C-4). – MS (EI): $m/z = 330$ (M^+). – $C_{23}H_{21}NOS$ (330): calcd. C 77.75, H 4.79, N 3.94; found C 77.27, H 4.56, N 3.81.

(2S,3R,5S)-Spiro-{3-methoxycarbonyl-1-aza-bicyclo-[3.3.0]-octan-2,1'-acenaphthylene}-2'-one (**6**): M. p. 172 °C. – IR (KBr): $\tilde{\nu} = 3010$ (C-H_{aro}), 2950 (C-H_{ali}), 1705 (>C=O), 1425 (C-N), 1120 (C-O), 710 (C-S) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.53$ (dd, 2H, 6-H), 3.06 (d, 2H, 4-H,), 3.22 (t, 1H, 7-H), 3.26 (s, OCH_3), 3.78 (d, 1H, 2β-H), 3.82 (d, 1H, 2α-H), 4.35 (m, 1H, 5-H), 7.60 – 8.15 (m, 6H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 203.41$ (>C=O), 169.54 (O-C=O), 141.62 – 121.01 (ArC), 75.95 (spiro C-8), 67.91 (C-5), 53.23 (C-2), 52.98 (C-4), 50.20 (OCH_3), 37.27 (C-7), 32.71 (C-6). – MS (EI): $m/z = 339$ (M^+), 234 (M^+-C_4H_9OS). – $C_{19}H_{17}NO_3S$ (339): calcd. C 67.26, H 5.01, N 4.13; found C 67.13, H 4.96, N 4.05.

Similarly the reaction of acenaphthylene-1,2-dione **(1)** with 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**7**) in equimolar ratio was carried out in acetonitrile in the presence of phenyl acetylene, diphenyl acetylene, phenyl propyne, ethyl phenyl propiolate and methyl acrylate afforded cycloadducts (**9a** – **d**, **10**):

(6S,9S)-Spiro-{8-phenyl-1-aza-bicyclo[4,3,0]-benzo[c]-non-7-ene-9,1'-acenaphthylene}-2'-one (**9a**): M. p. 170 °C. – IR (KBr): $\tilde{\nu} = 3050$ (C-H_{aro}), 1760 (>C=O), 1320 (C-N) cm^{-1}. – ^{1}H NMR (300 MHz, DMSO): $\delta = 2.07$ (d, 2-H, 5H), 2.50 (s, 2-H, 2H), 2.84 (d, 1-H, 7H), 3.47 (m, 1-H, 6H), 7.08 – 8.27 (m, 15H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 183.99$ (>C=O), 134.34 – 122.47 (ArC), 117.50 (C-8), 111.97 (C-7), 77.43 (spiro C-8), 57.92 (C-6), 26.76, 23.99 (C-2, C-5). – MS (EI): $m/z = 404$

(M^+). – $C_{29}H_{21}NO$ (404): calcd C 87.21, H 5.26, N 3.50; found C 87.00, H 5.24, N 3.48.

(6S,9S)-Spiro-{7,8-diphenyl-1-aza-bicyclo[4,3,0]-benzo [c]-non-7-ene-9,1'-acenaphthylene}-2'-one (**9b**): M. p. 200 °C. – IR (KBr): $\tilde{\nu} = 3220$ C-H_{aro}), 1700 (>C=O), 1420 (C-N), 800 (C-H_{def}) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.05$ (d, 2-H, 5H), 2.47 (s, 2-H, 2H), 3.23 (m, 1-H, 7H), 7.32 – 7.99 (m, 20H, ArH). – MS (EI): $m/z = 476$ (M^+). – $C_{35}H_{26}NO$ (476): calcd C 89.12, H 5.39, N 3.12; found C 88.01, H 5.37, N 3.00.

(6S,9S)-Spiro-{7-methyl-8-phenyl-1-aza-bicyclo[4,3,0]-benzo[c]-non-7-ene-9,1'-acenaphthylene}-2'-one (**9c**): M. p. 220 °C. – IR (KBr): $\tilde{\nu} = 3020$ (C-H_{aro}), 1700 (>C=O), 1400 (C-N) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.13$ (d, 2-H, 5H), 2.50 (s, 2-H, 2H), 3.25 (m, 1-H, 7H), 7.80 – 8.33 (m, 15H, ArH). – MS (EI): $m/z = 409$ (M^+). – $C_{30}H_{19}NO$ (409): calcd. C 87.16, H 5.56, N 3.38; found C 87.12, H 5.51, N 3.32.

(6S,9S)-Spiro-{8-phenyl-7-ethoxycarbonyl-1-aza-bicyclo[4,3,0]-benzo[c]-non-7-ene-9,1'-acenaphthylene}-2'-one (**9d**): M. p. 190 °C. – IR (KBr): $\tilde{\nu} = 3040$ (C-H_{aro}), 2990 (C-H_{ali}) 1710 (>C=O), 1370 (C-N), 790 (C-H_{def}) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (t, 3H, CH_3), 2.35 (d, 2-H, 5H), 2.68 (s, 2-H, 2H), 4.29 (m, 1-H, 6H), 4.31 (q, -OCH_2), 6.99 – 8.65 (m, 15H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 175.63$ (>C=O), 173.79 (O-C=O), 143.12 – 120.19 (ArC), 110.37 (C-7), 108.73 (C-8), 79.13 (spiro C-8), 67.58 (OCH_2), 64.52 (C-6), 58.27 (C-2), 31.43 (C-5), 20.48 (CH_3). – MS (EI): $m/z = 471$ (M^+). – $C_{32}H_{25}NO_3$ (471): calcd. C 81.52, H 5.30, N 2.97; found C 80.11, H 5.28, N 2.96.

(6S,8S,9S)-Spiro-{8-methoxycarbonyl-1-aza-bicyclo-[4,3,0]-benzo[c]-non-7-ene-9,1'-acenaphthylene}-2'-one (**10**): M. p. 224 °C. – IR (KBr): $\tilde{\nu} = 3010$ (C-H_{aro}), 2950 (C-H_{ali}) 1705 (>C=O), 1425 (C-N), 710 (C-O) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.26$ (m, 2-H, 5H), 2.60 (s, 2-H, 2H), 3.89 (m, 1-H, 6H), 3.95 (s, -OCH_3), 6.72 – 7.44 (m, 10H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 180.74$ (>C=O), 173.49 (O-C=O), 143.12 – 123.12 (ArC), 79.29 (spiro C-8), 64.52 (C-6), 58.27 (C-2), 53.32(OCH_3), 38.96 (C-7), 36.09 (C-5), 31.42 (C-2). – MS (EI): $m/z = 351$ (M^+). – $C_{25}H_{21}NO$ (351): calcd. C 78.53, H 5.23, N 3.66; found C 78.52, H 5.22, N 3.64.

On similar grounds a mixture of 5-methylthioisatin (**11**) (0.36 g, 2.0 mmol), (R)-(-)-thiazolidine-4-carboxylic acid (**2**) (0.27 g, 2.0 mmol) and phenyl propyne (0.25 g, 2.0 mmol) was refluxed under nitrogen atmosphere for 22 h in dry acetonitrile After completion of the reaction, as monitored by TLC, unreacted acid was removed by filtration. The filtrate was evaporated in vacuum 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 **15**, **16** was obtained from chloroform/ethylacetate 5 : 1 fraction in 78% yield.

(2R,5S)-Spiro-{4,5-dimethyl-3-phenyl-1-aza-3-thia-bicyclo[3,3,0]-3-octene-2,3'}-5'-methyl-benzo[b]thiophene-2'-one (**15**): M. p. 181 °C. – IR (KBr): $\tilde{\nu} = 3110$ (C-H_{aro}), 1720 (>C=O), 1410 (C-N), 690 (C-S) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.2$ (s,CH_3), 4.1 (s, 3-H, 6H), 2.4 (d, 2-H, 4H), 4.21 (s, 2-H, 2H), 6.58 – 7.38 (m, 8H, ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 183.99$ (>C=O), 134.34 – 122.47 (ArC), 77.43 (spiro C). – MS (EI): $m/z = 356$s (M^+). – $C_{20}H_{22}NOS_2$ (356): calcd. C 67.41, H 6.17, N 3.93; found C 67.33, H 6.11, N 3.93.

(2R,5S)-Spiro-{4-methyl-3-phenyl-1-aza-bicyclo[3,3,0]-3-octene-2,3'}-5'-methyl-benzo[b]thiophene-2'-one (**16**): M. p. 94 °C. – IR (KBr): $\tilde{\nu} = 3100$ (C-H_{aro}), 1725 (>C=O), 690 (C-S) cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.6 – 1.9$ (m, 4H, 6-H+ 7-H), 2.2 (s,CH_3), 2.5 (t, 2-H, 8H), 4.2 (s, 3-H, 4H), 4.6 (t, 1-H, 5H), 6.86 – 7.86 (m, 8H,ArH). – ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): $\delta = 186.90$ (>C=O), 134.34 – 122.47 (ArC), 77.43 (spiro C). – MS (EI): $m/z = 347$ (M^+). – $C_{22}H_{21}NOS$ (347): calcd. C 76.11, H 6.09, N 4.11; found C 76.08, H 6.05, N 4.03.

Acknowledgements

The authors are thankful to UGC, New Delhi for financial assistance. B. Gupta is thankful to UGC, New Delhi for NET-JRF Scholarship. We are also thankful to Durgapura Agricultural Research Station (Jaipur) and Concept Pharmaceuticals (Aurangabad) for helping us to conduct antimicrobial and toxicological study on the cycloadducts.

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