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A Regio and Stereoselective 1, 3-Dipolar Cycloaddition for the synthesis of Novel Spiropyrrolizidines and their Antibacterial Evaluation.

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Abstract
This project was carried out with a aim to synthesize novel heterocycles through 1,3-dipolar cycloaddition of azomethine ylides derived from acenaphthenequinone and L-proline to a series of (E)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones to afford novel monospiropyrrolizidines quantitative yields chemo-,region- and stereoselectively. These compounds are synthesized and were screened for their in vitro antibacterial activity using disc diffusion method. The antibacterial activity is enhanced by the introduction of electron-withdrawing halogens (fluorine and chlorine substituent's) in the aryl rings. The structures of all the products were elucidated with the help of [1]H, [13]C and 2D NMR spectral data.

I. Introduction

Most of the organic synthesis involves the stepwise construction of target skeletons by linear convergent sequences of reactions[1-2]. Recently, there has been much interest in the development of methods that encompass "multicomponent synthesis" reactions involving the combination of three or more components in a single synthetic transformation. Combining several transformations into a one-pot reaction has proved to be an excellent strategy to increase the efficiency of organic synthesis[3]. It has proved to be quite difficult to design useful biologically active compounds, because the active moiety of the compound is often unknown. Therefore different combinational libraries are usually assayed and active molecules are isolated and analyzed. Heterocyclic compounds containing five and six membered rings have occupied a prominent place among various classes of organic compounds for their diverse biological activities[4].

The compound containing the pyrrolidine ring system is found in various natural products as fundamental nuclei and highly substituted pyrrolidines have attracted much interest because they contribute the central structural element of many alkaloids and pharmacologically active compounds[11-13]. Spiro compounds which represent important classes of naturally occurring substances are characterized by their pronounced biological properties[5-10]. Spirooxindole ring systems are found in a number of alkaloids such as (-)-horsfiline, (-)-spirotryprostatin A, (+)-elacomine, Gelesmine, formosanine, isoformosanine, pseudotabersonine and mitraphylline[14] (**Fig.1**) and their derivatives find wide biological applications as antimicrobial[15] and antitumor agents[16]. Some spiropyrrolidines are potential anti-leukemic, anticonsultant agents[17], antiviral[18], and local anaesthetic[19] and antiplatelet[20] activities.

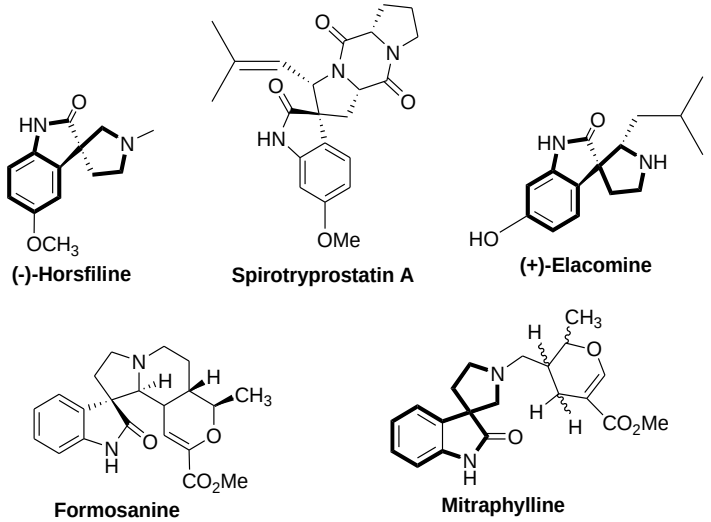
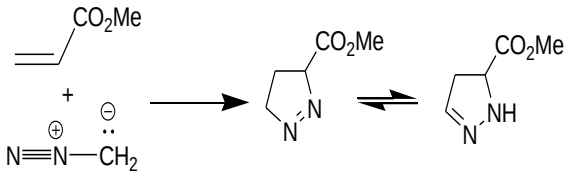


Figure1. Structure of naturally occurring spiro-oxindole alkaloids.

Isatins (1H-indole-2,3-dione) are synthetically versatile substrates, and they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles, quinolines and spiro compounds and as a raw material for drug synthesis. Isatin and its derivatives possess interesting biological activities and widely used as precursors for many natural products[21].

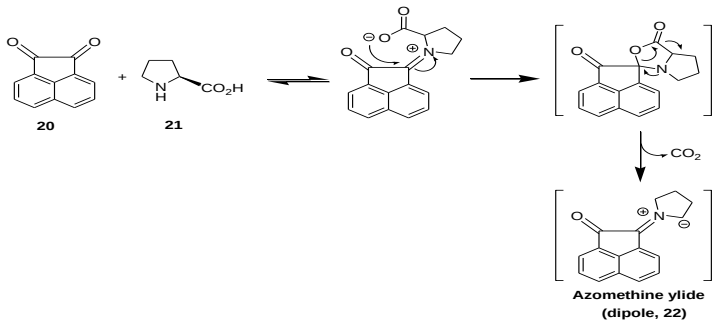
II. Results and Discussions

1,3-Dipolar cycloadditions are fundamental processes in organic chemistry, and have taken a prominent place as a synthetic strategy for the synthesis of complex heterocyclic systems. These cycloadditions are analogous to the concerted [□^{4s} + □^{2s}] Diels-Alder reaction. The 1,3-dipolar components are compounds whose representation requires ionic structures which include charges on atoms bearing, 1,3-relationship. These type of molecules which are called, 1,3-dipoles are isoelectronic with allyl anion. They have four □ electrons and each has at least one charge separated resonance structure with opposite charges in a 1,3 relationship. The other reactant (dipolarophile) in a dipolar cycloaddition has unsaturated bonds like, C=C, C≡C and bonds such as C=O and C≡N. The 1,3-dipolar cycloadditions are useful reactions for the synthesis of five membered heterocyclic rings. 1,3-dipoles, bearing a functional group able to behave as a dipolarophile, are extremely interesting substrates
Mechanistically the transition state for 1,3-dipolar cycloaddition is not very polar and the reaction rate is sensitive to solvent polarity. A 1,3-dipole represents a structural variant of the diene component in the Diels-Alder reaction; in the dipolar compound, four □-electrons are distributed over three atoms instead of the four in a diene. Moreover, the HOMO and LUMO of a 1,3-dipole are similar in a symmetry to that in a diene with respect to the two-fold axis and to the mirror plane which bisects the molecule. A concerted cycloaddition, reaction of an alkene with diazomethane to give a pyrazoline belongs to this class



Ylides

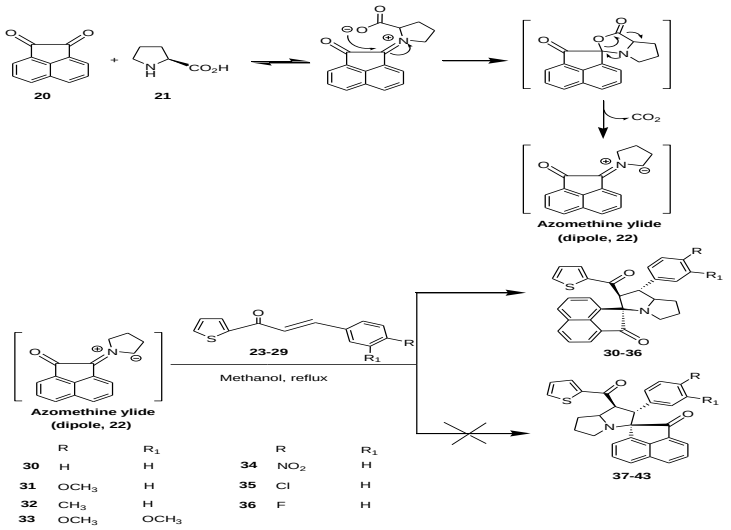
Ylides are defined as compounds in which a positively charged hetero atom is connected to a carbon carrying a negative charge. They are also referred as vicinal ionic (i.e., with positive and negative charges on adjacent atoms) intermediates. The ylides react as strong nucleophiles. Azomethine ylides have been used to synthesize pyrrolidines with various substituents allowing the introduction of several functional groups in a single operation. Azomethine ylides can be generated by a number of methods of which decarboxylation[40] route offers a convenient method for the synthesis of substituted pyrrolidines. In this method a ketone and a secondary amino acid are condensed to generate the reactive intermediate which is then trapped by dipolarophiles. The reaction of azomethine ylides with various dipolarophiles results in highly substituted five membered nitrogen heterocycles. The 1,3-dipole (azomethine ylide **22**) generated by the decarboxylate condensation of acenaphthenequinone **20** and *L*-proline **21**(**Scheme 2**) reacted with dipolarophile containing exocyclic double bond to afford novel spiropyrrolizidine ring systems[40].



Scheme 2. Synthesis of azomethine ylide **22**

In the present study, we describe a facile and rapid one-pot synthesis of thiophenoyl bearing novel monospiro-pyrrolizidines **30-36**, by the cycloaddition reaction of (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones**23-29** with the azomethine ylide derived from acenaphthenequinone **20** and *L*-proline **21** by decarboxylate route (**Scheme 3**).

This reaction afforded a series of novel monospiro-pyrrolizidine **30-36** containing the one acenaphthenequinone **20** ring system by a regio and stereo controlled cycloadddition of the azomethine ylide to the exocyclic bond of (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones**23-29** in all cases.



Scheme 3. Synthesis ofspiropyrrolizidines **30-36**

In order to find out the effect of solvent on the cycloaddition reaction, the reaction was carried out with acenaphthenequinone **20**, *L*-proline **21** and (*E*)-3-(*p*-chlorophenyl)-1-(thiophen-2-yl)-prop-2-en-1-one**28** in six different solvents and the results are given in **Table 3**. The yield of the cycloadduct **35** was lower and a longer reaction time was required in *i*-propanol, *t*-butanol, acetonitrile and dimethylformamide compared to methanol or ethanol. This can be due to the diminished stabilization of the polar transition states and/or intermediates involved in this reaction in *i*-propanol, *t*-butanol, acetonitrile and dimethylformamide. Methanol is the best solvent for this reaction since it gives a maximum yield with lesser reaction time.

Table 3
Synthetic results of 35 under different reactions conditions

Solvent	Time (hr)	Yield of 35 (%)
MeOH	10	94
EtOH	10	85
i-PrOH	15	61
t-BuOH	15	65
CH_3CN	18	58
DMF	10	48

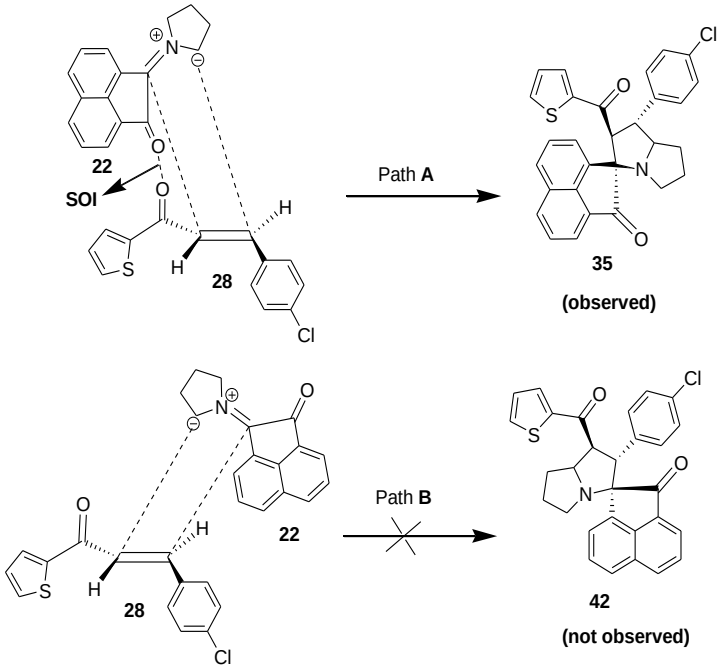
Encouraged by this success, we extended this reaction of acenaphthenequinone **20** with *L*-proline **21** and (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones**23-29** under optimized conditions. The corresponding monospiro-pyrrolizidines **30-36** were synthesized in high yield (88-95 %), and the results are summarized in **Table 4**. It can be seen the **Table 4** that the nature of the substituents in aryl groups on the (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones**23-29** had no significant effect on the final yield of the products.

Table 4
Synthetic results of monospiropyrrolizidines 30-36 via three-component reaction

Entry	R	Products	Isolated yield (%)
1.	H	**30**	90
2.	4-OCH_3	**31**	92
3.	4-CH_3	**32**	96
4.	3,4-$(OCH_3)_2$	**33**	88
5.	4-NO_2	**34**	93
6.	4-Cl	**35**	94
7.	4-F	**36**	95

Scheme 3. Synthesis ofspiropyrrolizidines **30-36**

Although the detailed mechanism of the above reaction is not fully clarified, the formation of regioisomer **35** could be explained as follows: decarboxylative condensation of the acenaphthenequinone **20** with *L*-proline **21** gives the azomethine ylide (dipole **22**) which then undergoes 1,3-dipolar cycloaddition reaction with the (*E*)-3-(*p*-chlorophenyl)-1-(thiophen-2-yl)-prop-2-en-1-one**28** (dipolarophile) regioselectively as shown in **Figure 2 (path A)**. The regio selectivity in the product formation can be explained by considering the secondary orbital interaction (**SOI**)[41-42] of the orbital of the carbonyl group of dipolarophile **28** with those of the ylide **22** as shown in **Figure 2**. Accordingly, the observed regioisomer **35** via **path A** is more favouable because of the secondary orbital interaction which is not possible in **path B**.



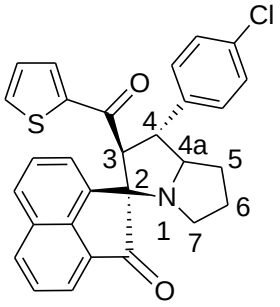
SOI- Secondary orbital interaction

Figure 2. Mode of approach of azomethine ylide **22**

3.1 Analysis of cycloadducts

The IR, ^{1}H, ^{13}C spectra have been recorded for the synthesized compounds. The compound **35** has been considered as the representative compound and to give additional evidence for the structure 2-D NMR spectra (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY and HMBC) were recorded. The complete characterization of the representative compound spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-chlorophenyl)-pyrrolizidine **35** is discussed below.

3.1.1 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4- (*p*-chlorophenyl)-pyrrolizidine35



35

Analysis of IR spectrum

In the IR spectrum of cycloadduct **35**, the absorption bands at 1720 and 1651 cm^{-1} correspond to acenaphthenequinone and thiophenoyl ring carbonyl groups, respectively. The aromatic C-H stretching appeared at 2943 and 2872 cm^{-1}. The spectrum is reproduced in **plate 1.**

Analysis of ^{1}H NMR spectrum

In the ^{1}H NMR spectrum of the cycloadduct **35**, the six methylene protons of the pyrrolizidine ring appear as multiplets in the region of δ 1.79-2.87 ppm. The pyrrolizidine ring proton of H-4 which is attached to the phenyl moiety exhibits a triplet at δ 4.06 ppm (J = 10.6 Hz). The pyrrolizidine ring proton of H-3 which is attached to the thiophenyl moiety appeared as a doublet at δ 4.84 ppm (J = 11.2 Hz), which proved the regiochemistry of the cycloaddition reaction. If the other regioisomer **42** had been formed, the pyrrolizidine ring proton of C-3 which is attached to the thiophenyl moiety would have appeared as a triplet in the ^{1}H NMR spectrum. The -NCH proton of the pyrrolizidine ring exhibit a multiplet in the region δ 4.29-4.35 ppm. The aromatic protons appeared as multiplets in the region of δ 6.63-8.00 ppm. The spectrum is reproduced in **plate 2**.

Analysis of ^{13}C NMR spectrum

In the ^{13}C NMR spectrum of the cycloadduct **35**, a peak at δ 205.86 and 189.81 ppm are corresponding to acenaphthenequinone and thiophenyl carbonyl groups, respectively. The aromatic ring carbons exhibited in the region of δ 122.01-144.29 ppm. The spiropyrrolizidine carbon at C-2 merged with solvent$CDCl_3$ signal due to this reason we have recorded the same sample with DMS0-d_6. For this solvent the spiro carbon resonate at δ 76.40 ppm. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7 appeared at δ 64.98, 53.10, 71.64, 29.74, 26.52 and 48.92 ppm respectively. The spectrum is reproduced in **plate 3**.

Analysis of 2D NMR spectrum

^{1}H-^{1}H COSY spectrum

In order to confirm these assignments, ^{1}H-^{1}H COSY spectrum was recorded for compound **35**, as a representative exampleand the ^{1}H-^{1}H COSY correlation of compound **35** is reproduced in **plate 4**.The doublet at δ 4.84 ppm (J = 11.2 Hz) reveals cross peak with the triplet centered at δ 4.06 ppm (J = 10.6 Hz) and this triplet shows cross peak with the multiplet in the region of δ 4.29- 4.35 ppm. This clearly indicates that this doublet is due to pyrrolizidine ring proton at H-3 which is attached to the thiophenoyl moiety and the triplet is due to pyrrolizidine ring proton at H-4 which is attached to the phenyl moiety.

The multiplet in the region δ 4.29-4.35 ppm which corresponds to pyrrolizidine –NCH proton at H-4aexhibit cross peaks with the two multliplets in the region of δ 1.79-1.84 and 2.04-2.09 ppm respectively and these two multiplets gives cross peak with the another two multiplets in the region of δ 1.86-1.91 and 1.97-2.01 ppm. This clearly shows that the multliplets (δ 1.79-1.84 and 2.04-2.09 ppm) originate from the pyrrolizidine ring protonat H-5 and another two multiplets at δ 1.86-1.91 and 1.97-2.01 ppm are due to two methylene protons of the pyrrolizidine ring at H-6. The remaining multiplets at δ 2.46-2.51 and 2.81-2.87 ppm are due to two methylene protons of the pyrrolizidine ring group at H-7. The ^{1}H-^{1}H one bond correlations are given in **Table 5**.

Table 5
^{1}H-^{1}H COSY spectrum for 35

^{1}H-^{13}C COSY spectrum

Pyrrolizidine ring protons	Chemical shifts (ppm)	Correlation in the COSY spectrum (ppm)
H(3)	4.84 (d, 1H)	4.06 (t, 1H)
H(4)	4.06 (t, 1H)	4.29-4.35 (m, 1H)
H(4a)	4.29-4.35 (m, 1H)	1.79-1.84 (m, 1H) 2.04-2.09 (m, 1H)
H(5)	1.79-1.84 (m, 1H) 2.04-2.09 (m, 1H)	1.86-1.91 (m, 1H) 1.97-2.01 (m, 1H)
H(6)	1.86-1.91 (m, 1H) 1.97-2.01 (m, 1H)	2.46-2.51 (m, 1H) 2.81-2.87(m, 1H)

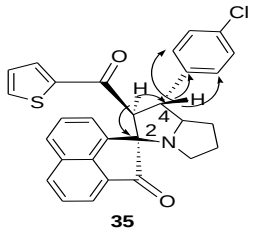
In order to explain these assignments, ^{1}H-^{13}C COSY spectrum of compound **35** was also recorded and is reproduced in **plate 5**. From the ^{1}H-^{13}C COSY spectra the signals of all carbons containing hydrogen could be assigned unambiguously. In the ^{1}H-^{13}C COSY spectrum of **35** (**plate 5**)the signal at δ 64.98 ppm shows correlation with the pyrrolizidine ring proton of H-3 at δ 4.84 ppm (J = 11.2 Hz). This clearly shows that the signal at δ 64.98 ppm is due to C-3 carbon. The signal at δ 53.10 ppm shows cross peak with pyrrolizidine ring proton of H-4 which is attached to the phenyl moiety exhibit a triplet at δ 4.06 ppm (J = 10.6 Hz). This also clearly confirms that this signal is due to the C-4 carbon.

From proton chemical shifts of H-4a and H-5 for **35** the corresponding carbon resonances are obtained from ^{1}H-^{13}C COSY cross peaks. The signals at δ 71.64 and 29.74 ppm are due to C-4a and C-5 carbons respectively in **35**. The other signals at δ 26.52 and 48.92 ppm are obviously due to the C-6 and C-7 carbons. The ^{1}H-^{13}C one bond correlations are given in **Table 6**.

HMBC spectrum

In order to explain these assignments,HMBCspectrum of compound **35** was further also recorded representative exampleand is shown in **Figure 3**.The 1H doublet at δ 4.84 ppm (J = 11.2 Hz) and they show HMBC^{s} (**plate 6**) with C-2 and C-4, at δ 77.00 (merged with $CDCl_3$ signal) and 53.10 ppm respectively. This clearly indicates that this doublet is due to pyrrolizidine ring proton at H-3 which is attached to the thiophenoyl moiety. Similarly the 1H triplet at δ 4.06 ppm (J = 10.6 Hz)

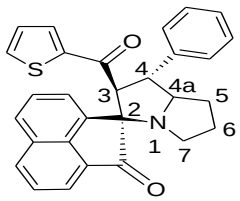
and they show HMBC^{s} (**plate 6**) with δ 71.64 (C-4a), 129.55 (phenyl ring ortho carbon atoms) and 144.29 ppm (ipso carbon atom of the phenyl ring) respectively. This clearly shows that the triplet originates from the pyrrolizidine ring proton at H-4 which is attached to the phenyl moiety.



35

Figure 3. Selected HMBC^{s} of **35**

3.1.2 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4- phenyl-pyrrolizidine30



30

Analysis of IR spectrum

In the IR spectrum of cycloadduct **30**, the absorption bands at 1716 cm^{-1} corresponding to acenaphthenequinone ring carbonyl. The absorption bands at 2949 and 2864 cm^{-1} correspond to aromatic C-H stretching. The absorption bands at 1651 cm^{-1} are due to thiophenoyl carbonyl group. The spectrum is reproduced in **plate 7**.

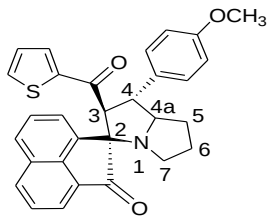
Analysis of ^{1}H NMR spectrum

The ^{1}H NMR spectrum of the cycloadduct **30** exhibited a multiplet in the range of δ 1.83-2.86 ppm for the pyrrolizidine ring methylene protons. The benzylic proton (H-4) resonating at δ 4.09 ppm (J = 10.6 Hz) appeared as a triplet. The NCH proton of the pyrrolizidine ring appeared as a multiplet at δ 4.35-4.39 ppm. The H-3 proton attached with the thiophenyl moiety appeared as a doublet at δ 4.93 ppm (J = 11.2 Hz). The aromatic protons exhibited multiplets in the region of δ 6.63-8.00 ppm. The spectrum is reproduced in **plate 8**.

Analysis of ^{13}C NMR spectrum

In the ^{13}C NMR spectrum of the cycloadduct **30**, a peak at δ 206.10 ppm confirms the presence of an acenaphthenequinone ring carbonyl group. A peak observed at δ 189.91 ppm is for the thiophenoyl ring carbon. The spiro carbon at C-2 merged with solvent $CDCl_3$ signal. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7 appeared at δ 64.91, 53.67, 71.89, 29.30, 26.63 and 48.93 ppm respectively. The aromatic ring carbons appeared in the region of δ 121.91-144.44 ppm. The spectrum is reproduced in **plate 9**.

3.1.3 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-methoxyphenyl)-pyrrolizidine31



31

Analysis of IR spectrum

In the IR spectrum of cycloadduct **31,** the absorption bands at 1720 and 1647 cm^{-1} are corresponding to acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl, respectively. The aromatic C-H stretching frequencies exhibit peaks at 2943 and 2854 cm^{-1}. The spectrum is reproduced in **plate 10**.

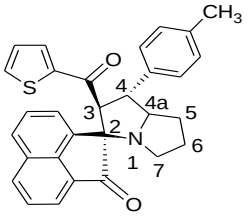
Analysis of ^{1}H NMR spectrum

In the ^{1}H NMR spectrum of the cycloadduct **31,** the pyrrolizidine ring methylene protons exhibited in the region of δ 1.80-2.85 ppm. The aromatic methoxy protons appeared as a singlet at δ 3.80 ppm. The H-4 proton attached to the phenyl moiety exhibited as a triplet at δ 4.04 ppm (J = 10.6 Hz). The N-CH proton of the pyrrolizidine ring exhibited as a multiplet at δ 4.30-4.34 ppm. The H-3 proton attached to the thiophenyl group appeared as a doublet at δ 4.87 ppm (J = 11.2 Hz). The aromatic protons exhibited multiplets in the region of δ 6.64-7.99 ppm. The spectrum is reproduced in **plate 11**.

Analysis of ^{13}C NMR spectrum

In the ^{13}C NMR spectrum of the cycloadduct **31**, peaks at δ 206.14 and 189.99 ppm correspond to acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl, respectively. The aromatic ring carbons exhibit in the region of δ 114.18-158.63 ppm. The spiro carbon at C-2 merged with solvent $CDCl_3$ signal. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7 appeared at δ 65.02, 52.97, 71.77, 29.89, 26.64 and 48.90 ppm respectively. The aromatic methoxy carbon exhibited at δ 55.22 ppm. The spectrum is reproduced in **plate 12**.

3.1.4 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-methylphenyl)-pyrrolizidine32



32

Analysis of IR spectrum

In the IR spectrum of cycloadduct **32,** the absorption bands at 1651 and 1720 cm^{-1} are due to thiophenoyl ring carbonyl and acenaphthenequinone ring carbonyl, respectively. The absorption bands at 2970 and 2870 cm^{-1} are due to aromatic C-H stretching frequencies. The spectrum is reproduced in **plate 13**.

Analysis of ^{1}H NMR spectrum

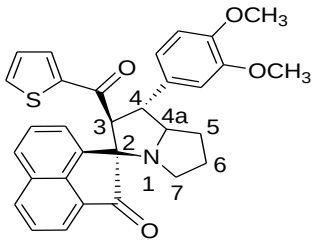
The ^{1}H NMR spectrum of the cycloadduct **32** exhibited a multiplet in the range of δ 1.83-2.85 ppm for the pyrrolizidine ring methylene protons. The benzylic protons (H-4) resonating at δ 4.06 ppm (J = 10.6 Hz) appeared as a triplet. The aromatic methyl protons appeared at δ 2.33 ppm as a singlet. The N-CH proton of the pyrrolizidine ring appeared as a multiplet at δ 4.31-4.36 ppm. The H-3 proton attached with the thiophenoyl group appeared as a doublet at δ 4.91 ppm (J = 11.2 Hz). The aromatic protons appeared as a multiplet at δ 6.63-7.99 ppm. The spectrum is reproduced in **plate 14**.

Analysis of ^{13}C NMR spectrum

In ^{13}C NMR spectrum of cycloadduct **32**, a peak at δ 206.18 ppm confirms the presence of an acenaphthenequinone ring carbonyl group. The carbonyl group attached to the thiophenoyl ring exhibited a peak at δ 189.52 ppm. The aromatic ring carbons exhibited in the region of δ 121.87-144.49 ppm. The spiro carbon at C-2 merged with solvent $CDCl_3$ signal. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7

appeared at δ 64.91, 53.33, 71.87, 29.90, 26.65 and 48.91 ppm respectively. The aromatic methyl carbon exhibited at δ 21.03 ppm. The spectrum is reproduced in **plate 15**.

3.1.5 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4(3, 4-dimethoxyphenyl)-pyrrolizidine33



33

Analysis of IR spectrum

Inthe IR spectrum of cycloadduct **33**, the absorption bands at 1720 and 1651 cm^{-1} are corresponding to acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl, respectively. The aromatic C-H stretching frequencies appeared at 2954 and 2873 cm^{-1}. The spectrum is reproduced in **plate 16**.

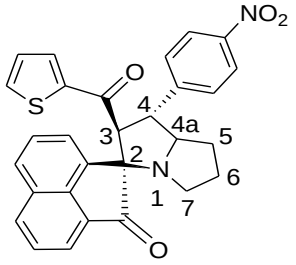
Analysis of ^{1}H NMR spectrum

In the ^{1}H NMR spectrum of the cycloadduct **33**, the pyrrolizidine ring methylene protons exhibited in the region of δ 1.81-2.85 ppm. The aromatic methoxy protons appeared as singlets at δ 3.85 and 3.95 ppm. The H-4 proton attached to the phenyl moiety exhibited as a triplet at δ 4.05 ppm (J = 10.6 Hz). The N-CH proton of the pyrrolizidine ring exhibited as a multiplet at δ 4.32-4.38 ppm. The H-3 proton attached to the thiophenoyl group appeared as a doublet at δ 4.87 ppm (J = 11.2 Hz). The aromatic protons exhibited multiplets in the region of δ 6.65-8.00 ppm. The spectrum is reproduced in **plate 17**.

Analysis of ^{13}C NMR spectrum

In the ^{13}C NMR spectrum of the cycloadduct **33**, peaks at δ 206.12 and 190.02 ppm correspond to acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl, respectively. The aromatic ring carbons exhibited in the region of δ 111.36-149.13 ppm. The spiro carbon at C-2 merged with solvent $CDCl_3$ signal. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7 appearedat δ 65.11, 53.42, 71.69, 30.01, 26.69 and 48.86 ppm respectively. The aromatic methoxy carbons exhibited at δ 55.88 and 55.98 ppm. The spectrum is reproduced in **plate 18**.

3.1.6 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-nitrophenyl)-pyrrolizidine34



34

Analysis of IR spectrum

In the IR spectrum of cycloadduct **34**, the acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl show the absorption bands at 1720 and 1654 cm^{-1}, respectively. The absorption bands at 2958 and 2858 cm^{-1} are due to aromatic C-H stretching frequencies. The spectrum is reproduced in **plate 19**.

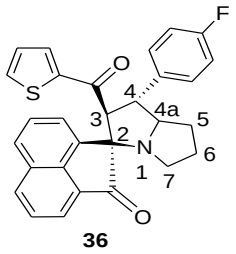
Analysis of ^{1}H NMR spectrum

The ^{1}H NMR spectrum of the cycloadduct **34** exhibited a multiplet in the range of δ 1.71-2.83 ppm for the pyrrolizidine ring methylene protons. The benzylic proton (H-4) resonating at δ 4.11 ppm (J = 10.4 Hz) appeared as a triplet. The N-CH proton of the pyrrolizidine ring appeared as a multiplet at δ 4.26-4.32 ppm. The H-3 proton attached with the thiophenyl group appeared as a doublet at δ 4.77 ppm (J = 10.8 Hz). The aromatic protons appeared as a multiplet at δ 6.53-8.13 ppm. The spectrum is reproduced in **plate 20**.

Analysis of ^{13}C NMR spectrum

The ^{13}C NMR spectrum of cycloadduct **34**, a peak at δ 205.47 ppm confirms the presence of an acenaphthenequinone ring carbonyl group. The carbonyl attached to the thiophene ring exhibited at δ 189.57 ppm. The aromatic ring carbons exhibited in the region of δ 122.21-147.96 ppm. The spiro carbon at C-2 merged with solvent $CDCl_3$ signal. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7 appeared at δ 65.04, 53.53, 71.60, 29.60, 26.40 and 48.97 ppm respectively. The spectrum is reproduced in **plate 21**.

3.1.7 Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-fluorophenyl)-pyrrolizidine36



36

Analysis of IR spectrum

In the IR spectrum of cycloadduct **36**, the acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl show the absorption bands at 1716 and 1647 cm^{-1}, respectively. The aromatic C-H stretching frequencies appeared at 2947 and 2850 cm^{-1}. The spectrum is reproduced in **plate 22**.

Analysis of ^{1}H NMR spectrum

In the ^{1}H NMR spectrum of the cycloadduct **36**, the pyrrolizidine ring methylene protons exhibited in the region of δ 1.79-2.87 ppm. A triplet at δ 4.07 ppm (J = 10.6 Hz) is assigned to the H-4 proton attached to the phenyl moiety. The N-CH proton of the pyrrolizidine ring exhibited as a multiplet at δ 4.29-4.35 ppm. The H-3 proton attached with the thiophenyl appeared as a doublet at δ 4.84 ppm (J = 10.8 Hz). The aromatic protons exhibited multiplets in the region of δ 6.63-8.00 ppm. The spectrum is reproduced in **plate 23**.

Analysis of ^{13}C NMR spectrum

A peak at δ 205.94 and 189.90 ppm are corresponding to acenaphthenequinone ring carbonyl and thiophenoyl ring carbonyl, respectively. The peaks in the region of δ 115.56-161.94 ppm are assigned to the aromatic ring carbons. The spiro carbon at C-2 merged with solvent $CDCl_3$ signal. The pyrrolizidine ring carbons at C-3, C-4, C-4a, C-5, C-6 and C-7 appeared at δ 65.08, 52.95, 71.73, 29.77, 26.54 and 48.91 ppm respectively. The spectrum is reproduced in **plate 24**.

3.2 Antibacterial studies

In order to know the effect of substituents in the phenyl ring on the biological activities the following compounds **30-36** were tested for their antibacterial activities by disc diffusion method and the results are presented in **Table 7**. The bacteria viz., *Escherichia coli*,*Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella paratypi* were used for this study. DMSO was used as a negative control and Ciprofloxacin was used as standard.

The spiro compounds with chlorine and fluorine substituents, **35** and **36** showed good antibacterial activity against *S. aureus, S. paratyphi* and *P. aeruginosa.*

The antibacterial assay showed that compounds **30**, **32** and **34** have the lower activity against most of the bacterial strains studied. The compounds **35** and **36** are moderatly active against *E.Coli.*

When the halogens were replaced by a methoxy group (compound **31)**,there was a decrease in activity against *S. paratyhpi,* whereas replacement with a methyl group (compound **32**) resulted in a decreased activity towards *S. aureus.*

Table 7

Antibacterial activities of compounds 30-36by zone of inhibition method (Diameter of the zone of inhibition in mm)

S.No	Organism	30	31	32	33	34	35	36	Ciprofloxacin
1	*E.coli*	10	14	09	13	10	12	12	15

2	*S.aureus*	13	15	12	10	12	18	19	30
3	*P.aeruginosa*	11	14	12	12	13	15	16	26
4	*S. paratyphi*	10	14	12	11	10	16	16	30

Summary

The thesis work describes the synthesis of novel Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-aryl-pyrrolizidines **30-36** from acenaphthenequinone, *L*-proline and (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones**23-29** using methanol as a solvent. The compounds were synthesized by the 1,3 cycloaddition reaction of (*E*)-3-(*p*-chlorophenyl)-1-(thiophen-2-yl)-prop-2-en-1-one **28** with the azomethine ylide derived from acenaphthenequinone and *L*-proline by a decarboxylate route. The reaction gives good yield in methanol. The IR, ^{1}H-NMR, ^{13}C-NMR spectral data have been recorded for the synthesized compounds. The compound **35** has been considered as the representative compound and to give additional evidence for the structure 2-D NMR spectrum (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY and HMBC) were recorded. The possibility of the formation of the other regiomer was ruled out from the ^{1}H NMR spectral spiliting pattern for the benzylic proton. Identical results were observed for the other derivatives (**30-34** and **36)** irrespective of the nature of the substituents present in the arylidene moiety of the **23-27** and **29**.

The following compounds were synthesized

1. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-phenyl-pyrrolizidine (**30**)
2. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-methoxyphenyl)-pyrrolizidine (**31**)
3. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-methylphenyl)-pyrrolizidine (**32**)
4. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(3,4-dimethoxyphenyl)-pyrrolizidine (**33**)
5. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-nitrophenyl)-pyrrolizidine (**34**)
6. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-chlorophenyl)-pyrrolizidine (**35**)
7. Spiro-[2.2']-acenaphthene-1'-one-3-thiophenoyl-4-(*p*-fluorophenyl)-pyrrolizidine (**36**)

The compounds **30-36** were preliminarily screened for their biological activities against the bacteria viz., *Escherichia coli,Staphylococcus aureus, Pseudomonas aeruginosa* and *Salmonella paratypi*. The antibacterial activities of these compounds were carried out against culture of the above bacteria. The biological behavior revealed that chloro and fluoro substituents on the phenyl ring (**35** and **36**)show better antibacterial activities than the other substituted compounds.

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