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A facile and regioselective synthesis of Spiro pyrrolidines and pyrrolizines through 1, 3 -dipolar cycloaddition protocol

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ABSTRACT

Intermolecular 1, 3-dipolar cycloaddition reaction of azomethine ylides, generated through decarboxylation route, with various substituted benzylidene acetophenone (Chalcones) as dipolarophiles has been investigated. A new class of functionalized spiroheterocycles with pyrrolidine and pyrrolizine framework has been synthesized with high regioselectivity. The structures were established by spectroscopic techniques as well as single crystal X-ray analysis.

Keywords: spiro pyrrolidines, spiro pyrrolizines, 1, 3-dipolar addition, azomethine ylides.

INTRODUCTION

Intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide with olefins are considered as one of the most useful method for the construction of the pyrrolidine structural unit.^{1,2} This method is widely used in the synthesis of natural products such as alkaloids and pharmaceuticals.³ Spiro-oxindole ring system represents an important class of naturally occurring substances characterised by highly pronounced biological properties.⁴⁻⁶ Oxindole derivatives are found to be potent aldose reductase inhibitors (ARI), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol.⁷

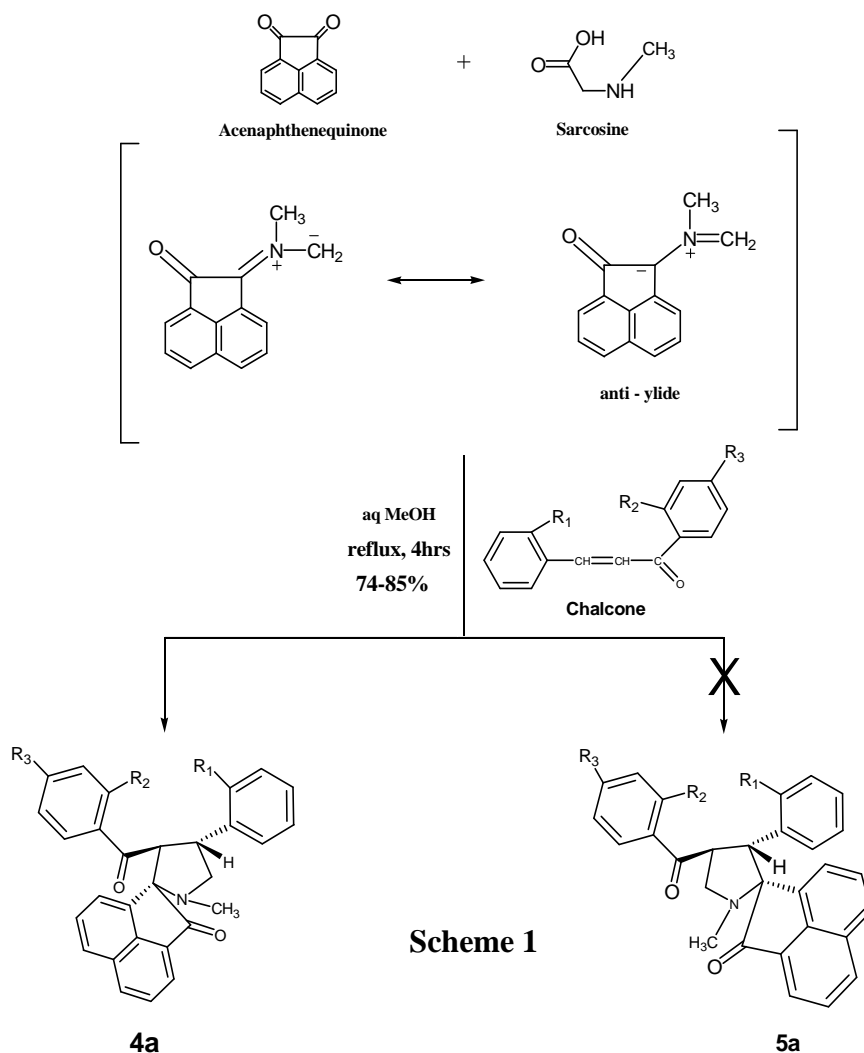
Pyrrolidine and oxindole alkaloids⁸ constitute another class of compounds with significant biological activities which are normally found in rhyncophylline, corynoxine, nitrphylline, vincatine, horsifiline etc.⁹ As a part of our ongoing research¹⁰ program in the area of cycloaddition reaction of azomethine ylides with 3-arylidene-4-chromanones, we herein report the highly regioselective synthesis of spiro pyrrolidines and pyrrolizines through 1,3-dipolar cycloaddition protocol.¹¹ Although highly functionalised and substituted spiro pyrrolidines are known, there seems to be no report on the synthesis of dispiroheterocycles using

acenaphthenequinone, isatin and chalcone moiety. The construction of novel dispiropyrrolidinyl derivatives (**4a-f**) was achieved through the 1,3-dipolar cycloaddition reactions of (E)- 1,3-Diphenyl-2-propen-1-one (**3**) with the azomethine ylides generated from acenaphthenequinone (**1**) and sarcosine (**2**) through decarboxylation method.

MATERIALS AND METHODS

Refluxing a solution of (E) - 1,3-Diphenyl-2-propen-1-one (**3**) in boiling aqueous methanol with acenaphthenequinone (**1**) and sarcosine (**2**) afforded 1-N-methyl-spiro [2.2'] acenapthen-1'-one (4-phenyl pyrrolidin-3-yl) (phenyl) methanone (**4**) (Scheme1, Table 1). The reaction gave a single product in all cases as evidenced by thin layer chromatography (TLC). The reaction afforded a series of novel spiro derivatives (**4a-f**) through regioselective cycloaddition of azomethine ylides with the exocyclic double bond of 1,3-Diphenyl-2-propen-1-one (**3**) in all cases. No trace of the other regioisomer (**5a-f**) was detected. The cycloaddition proceeded smoothly to afford the *syn-endo* cycloadduct. The regio and stereochemical outcome of the cycloaddition was determined by spectrochemical and single crystal X-ray analysis.

RESULTS AND DISCUSSION



Scheme 1

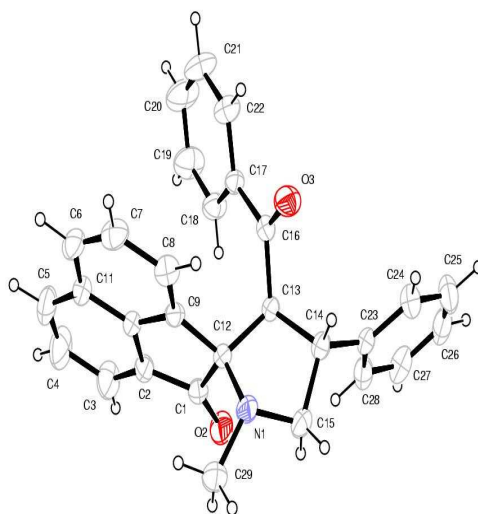
The IR spectra of **4** showed two carbonyl peaks at 1686 cm^{-1} and 1744 cm^{-1} which correspond to the benzyl and acenaphthenequinone carbonyl groups respectively. The ^1H NMR spectrum of the cycloadduct exhibited a singlet at δ 1.98 which corresponds to N - CH_3 protons. A multiplet at δ 4.52 corresponds to benzylic proton. A doublet at δ 4.58 corresponds to benzoyl methyl proton. A doublet at δ 3.54 corresponds to N - CH_2 proton. A multiplet from δ 6.9 – 8.81 corresponds to 16 aromatic protons. Also the ^{13}C NMR showed a signal at δ 76.78 due to the Spiro carbon atom, and peaks at δ 197.96 and δ 208.24 correspond to the benzyl and acenaphthenequinone carbonyl groups. The mass spectrum of the compound shows a peak at m/z 417.02 (M^+) which corresponds to the molecular weight of the compound.

Identical results were obtained with other derivatives and it has been observed that the cycloaddition had taken place regioselectively across the exocyclic double bond of the chalcones irrespective of the nature of the substituent present in the arylidene moiety.

Table 1. 1-N-methyl-spiro [2.2'] acenaphthen- 1'-one (4-phenyl pyrrolidin-3-yl) (phenyl) methanone (**4a-f**) via Scheme 1

Compound	R ₁	R ₂	R ₃
4a	-H	-H	-H
4b	-H	-OH	-H
4c	-H	-OH	-OH
4d	-Cl	-H	-H
4e	-Cl	-OH	-H
4f	-Cl	-OH	-OH

In continuation of our research, we synthesized another series of novel Isatin - spiropyrrolizines (**7a-f**) (Scheme 2, Table 2), which are structurally similar to compounds **4a-f** but differ in the N-methyl group where a pyrrolizine moiety replaces the N-methyl group and isatin moiety replacing the acenaphthene group.



ORTEP diagram of compound 4a¹¹

of (E)-1,3-Diphenyl-2-propen-1-one (**3**) in boiling aqueous methanol with isatin (**1**) and L-proline (**6**) afforded Spiro [2.3'] oxidolino (hexahydro-4-phenyl-4-H-pyrrolizin-3-yl)(phenyl)methanone (**7**). The reaction proceeded via formation of an azomethine ylide which readily undergoes 1,3-dipolar cycloaddition reaction with chalcones to give a single cycloadduct, in a one pot three component process as evidenced by thin layer chromatography (TLC) and spectral studies. The reaction afforded a series of novel spiro derivatives regioselectively in all cases as no trace of the other regioisomer was detected.

The IR spectral analysis of Spiro [2.3'] oxidolino (hexahydro-4-phenyl-4H-pyrrolizin-3-yl)(phenyl)methanone showed two carbonyl peaks at 1684 cm^{-1} and 1736 cm^{-1} which corresponded to the benzoyl and Isatin ring carbonyl groups. The ^1H NMR of the cycloadduct exhibited a triplet at δ 4.17 which corresponded to benzylic proton. A quartet at δ 2.59 corresponds to -NCH proton. A multiplet from δ 1.83 – 1.88 corresponds to the -CH₂ protons of the pyrrolizine ring. A singlet at δ 7.86 corresponds to -CONH proton. A multiplet from δ 6.9 - δ 8.2 corresponds to 14 aromatic protons. ^{13}C NMR spectra of **25** exhibit the presence of Spiro carbon at δ 72.85, benzyl and Isatin ring carbonyls at δ 179.81 and 198.61 δ . The mass spectrum of the compound showed a peak at m/z 408.15 (M^+) which corresponded to the molecular weight of the compound. Identical results were observed for the other derivatives irrespective of the nature of the substituent present in the arylidene ring.

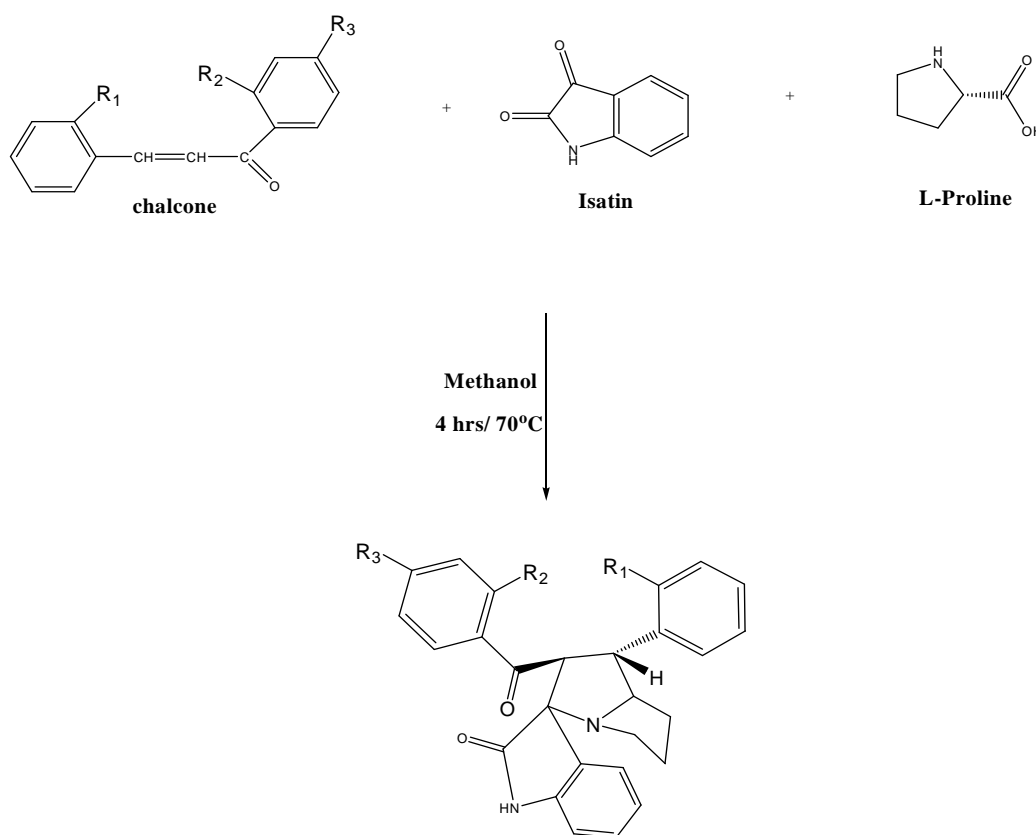
**Scheme 2**

Table 2. Spiro [2.3'] oxidolino (hexahydro-4-phenyl-4 H-pyrrolizin-3-yl) (phenyl) methanone (7a-f) via Scheme 2

Compound	R ₁	R ₂	R ₃
7a	-H	-H	-H
7b	-H	-OH	-H
7c	-H	-OH	-OH
7d	-Cl	-H	-H
7e	-Cl	-OH	-H
7f	-Cl	-OH	-OH

In conclusion, we synthesized a new class of spiro- pyrrolidines and pyrrolizines through cycloaddition of azomethine ylides generated from acenaphthenequinone, isatin, sarcosine and L-proline with chalcones. In both cases, the azomethine ylide was generated through decarboxylative route and the cycloadditions are highly regioselective, giving good yields of novel dispiroheterocycles. The reaction in particular is of interest since it paves the way for the synthesis of a variety of biologically significant spiro-oxindole pyrrolizines and spiroprrolidines derivatives using easily available starting materials.

Spiro-compound 4a: IR (KBr): 1686, 1744 cm⁻¹; ¹H NMR (CDCl₃/400 MHz): δ 1.98 (s, 3H) , 3.54(d,2H,N-CH₂ ,J=4.8 Hz) , 4.52 (m,1H, benzylic) , 4.58(d,1H,J=3.6Hz), 6.9–8.81 (m,16H – aromatic), ¹³CNMR(CDCl₃/400MHz):δ40.57,44.44,76.78,129.27,131.49,197.96,208.24; EIMS m/z : 417.02 (M⁺) .

Spiro-compound 4b: IR (KBr): 1690, 1738 cm⁻¹; ¹H NMR (CDCl₃/400 MHz): δ 2.17 (s, 3H) , 3.40(d,2H,N-CH₂ ,J=4.6Hz) , 4.48(m,1H,benzylic),4.56 (d,1H,J=3.8Hz), 5.12(s,1H,-OH), 6.81–7.69(m,15H–aromatic), ¹³CNMR(CDCl₃/400MHz):δ38.17,57.64, 73.15, 128.56, 131.49, 160.71, 198.61, 207.83 ; EIMS m/z : 433.17 (M⁺).

Spiro-compound 4c: IR (KBr): 1676, 1734 cm⁻¹; ¹H NMR (CDCl₃/400 MHz): δ 2.17 (s, 3H) , 3.44 (d,2H,N-CH₂ ,J=4.8Hz) , 4.46 (m,1H, benzylic) , 4.56 (d,1H,J=3.7Hz), 5.12(s,2H,-OH), 6.21–7.89 (m,14H – aromatic); ¹³C NMR (CDCl₃/400 MHz): δ 38.17,57.64,73.15, 128.56,131.49,162.11 , 164.35,198.61, 207.83; EIMS m/z: 449.16 (M⁺).

Spiro-compound 4d: IR (KBr): 1686, 1744 cm⁻¹; ¹H NMR (CDCl₃/400 MHz): δ 1.98 (s, 3H) , 3.54(d,2H,N-CH₂ ,J=4.75Hz) , 4.52 (m,1H,benzylic), 4.58 (d,1H,J=3.6Hz) ,6.9–8.81 (m,15H–aromatic); ¹³CNMR (CDCl₃/400MHz): δ40.57, 44.44, 76.78, 129.27,131.49,133.54, 197.96,208.24; EIMS m/z : 451.13 (M⁺) .

Spiro-compound 4e: IR (KBr): 1687, 1734 cm⁻¹; ¹H NMR (CDCl₃/400 MHz): δ 2.12 (s, 3H) , 3.42(d,2H,N-CH₂ ,J=4.8Hz) , 4.46 (m,1H, benzylic) , 4.54 (d,1H,J=3.8), 5.16 (s,1H,-OH), 6.88–7.72(m,14H–aromatic), ¹³CNMR(CDCl₃/400MHz):δ38.17,57.64, 73.15, 128.56, 131.49, 133.54, 160.71, 198.61, 207.837 EIMS m/z : 451.13 (M⁺).

Spiro-compound 4f: IR (KBr): 1672, 1738 cm⁻¹; ¹H NMR (CDCl₃/400 MHz): δ 2.18 (s, 3H) , 3.48 (d,2H,N-CH₂ ,J=4.6Hz) , 4.40 (m,1H,benzylic), 4.52 (d,1H,J=3.6Hz), 5.14(s,2H,-OH),

6.28–7.69(m,13H–aromatic), ^{13}C NMR($\text{CDCl}_3/400\text{MHz}$): δ 38.17, 57.64, 73.15, 128.56, 131.49, 133.52, 162.11, 164.35, 198.61, 207.83; EIMS m/z : 483.12 (M^+).

Spiro-compound 7a: IR (KBr): 1686, 1744 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/400$ MHz): 2.06 (s, 3H) , 3.42(d,2H,N- CH_2 , $J=4.5\text{Hz}$) , 4.46 (m,1H, benzylic) , 4.58(d,1H, $J=3.6\text{Hz}$),6.85–7.90 (m,14H – aromatic) ,7.81 (s,1H, CONH), ^{13}C NMR ($\text{CDCl}_3/400$ MHz): δ 27.12,44.44,54.32, 57.83, 73.05, 129.27, 131.49, 189.71,197.54; EIMS m/z : 382.54 (M^+).

Spiro-compound 7b: IR (KBr): 1682, 1728 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/400$ MHz): 2.04 (s, 3H) , 3.46 (d,2H,N- CH_2 , $J=4.8\text{Hz}$) , 4.40 (m,1H, benzylic) , 4.52(d,1H, $J=3.8\text{Hz}$), 5.12 (s,1H,-OH) , 6.80–7.79 (m,13H , aromatic), 7.81 (s,1H, CONH), ^{13}C NMR ($\text{CDCl}_3/400$ MHz): δ 27.24,44.36,54.30, 57.79, 73.05, 129.27, 131.49,160.71, 189.70, 197.52 EIMS m/z : 398.16 (M^+).

Spiro-compound 7c: IR (KBr): 1676, 1730 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/400$ MHz): δ 2.06 (s, 3H) , 3.44(d,2H,N- CH_2 , $J=4.75\text{Hz}$) , 4.42 (m,1H, benzylic) , 4.51(d,1H, $J=3.7\text{Hz}$), 5.12 (s,2H,-OH) , 6.85–7.79 (m,12H , aromatic), 7.81 (s,1H, CONH), ^{13}C NMR ($\text{CDCl}_3/400$ MHz): δ 27.14,44.38,54.20, 57.74, 73.05, 129.27, 131.49,162.11,164.30, 189.72, 197.48; EIMS m/z : 414.16 (M^+).

Spiro-compound 7d: IR (KBr): 1680, 1720 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/400$ MHz): δ 2.04 (s, 3H) , 3.40 (d,2H,N- CH_2 , $J=4.6\text{Hz}$) , 4.42 (m,1H, benzylic) , 4.54(d,1H, $J=3.7\text{Hz}$), 6.85–7.90 (m, 13H – aromatic) ,7.81 (s,1H, CONH), ^{13}C NMR ($\text{CDCl}_3/400$ MHz): δ 27.12,44.44,54.32, 57.83, 73.05, 129.27, 131.49, 133.52, 189.71, 197.54; EIMS m/z : 416.13 (M^+).

Spiro-compound 7e : IR (KBr): 1686, 1724 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/400$ MHz): δ 2.06 (s, 3H) , 3.42(d,2H,N- CH_2 , $J=4.8\text{Hz}$) , 4.42 (m,1H, benzylic) , 4.51(d,1H, $J=3.8\text{Hz}$), 5.10 (s,1H,-OH) , (6.80–7.79 m,12H , aromatic), 7.81 (s,1H, CONH), ^{13}C NMR ($\text{CDCl}_3/400$ MHz): δ 27.14,44.38,54.20, 57.74, 73.05, 129.27, 131.49,133.5,162.11,164.30, 189.72, 197.48; EIMS m/z : 432.12 (M^+).

Spiro-compound 7f : IR (KBr): 1672, 1728 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/400$ MHz): δ 2.04 (s, 3H) , 3.44 (d,2H,N- CH_2) , 4.42 (m,1H, benzylic) , 4.51(d,1H), 5.12 (s,2H,-OH) , (6.85–7.79 m,12H , aromatic), 7.81 (s,1H, CONH), ^{13}C NMR ($\text{CDCl}_3/400$ MHz): δ 27.14, 44.38, 54.20, 57.74, 73.05, 129.27, 131.49,133.5, 162.11,164.30, 189.72, 197.48EIMS m/z : 448.12 (M^+).

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