A facile entry into a novel class of dispiroheterocycles through 1,3-dipolar cycloaddition

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Dedicated to Professor S. Swaminathan, Emeritus Professor, Department of Organic Chemistry, University of Madras on his 80th birthday

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Abstract

The cycloaddition reaction of non-stabilized azomethine ylides, generated through decarboxylation and deprotonation, with (***E***)-2-arylidene-1-tetralones as dipolarophile has been investigated. A high degree of regioselectivity has been observed in the synthesis of a new class of functionalised dispiroheterocyclic compounds bearing a tetralone, acenapthenequinone and oxindole framework.

Keywords: Tetralone, azomethine ylide, dispiroheterocycles

Introduction

Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[1-3] The most developed avenue for the synthesis of these compounds depends on the cycloaddition to an exocyclic bond.[4-6]

Although highly substituted spiropyrrolidines are known, there seems to be no report on the synthesis of dispiro substituted pyrrolidine heterocycles. 1,3-Dipolar cycloaddition provides a way for the synthesis of many dispiroheterocycles through the cycloaddition reaction of non-stabilised azomethine ylides with the olefinic dipolarophiles. Highly substituted pyrrolidines have attracted much interest as they contribute the central structural element of many alkaloids and pharmacological active compounds.[7,8]

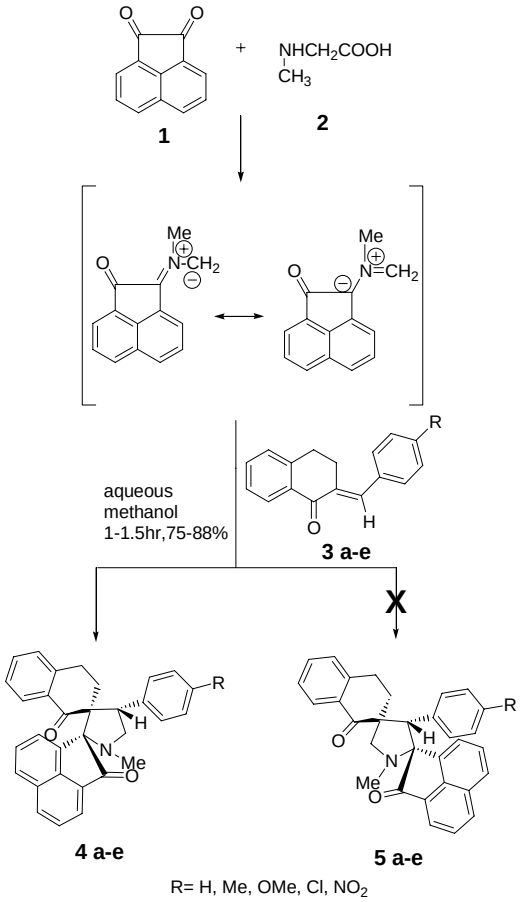
As a part of our study[9,10] on the synthesis of novel dispiropyrrolidinyl derivatives we have examined the 1,3-dipolar cycloaddition reaction of *E*-2-arylidene-1-tetralones with the azomethine ylide generated through a decarboxylation and deprotonation method.

Results and Discussion

Decarboxylative method

The 1,3–dipolar cycloaddition reactions of *E*-2-arylidene-1-tetralones with non-stabilized azomethine ylides, generated by decarboxylative condensation of the bifunctional ketone, acenaphthenequinone, with secondary amino acids, gave a series of novel dispiropyrrolidinyl derivatives in good yield.

E-2-arylidene-1-tetralones are conformationally restricted *s-cis* enones which readily cycloadd to the non-stabilized ylides generated *in situ* by the decarboxylative condensation of acenapthenequinone **1** and sarcosine **2**to afford dispiropyrrolidinyl derivatives, 1′,2′,3′,4′-tetrahydronaphthalen-1′-one-spiro[3′.3]*N*-methyl-(4-aryl)-pyrrolidine-2-spiro-2″-acenaphthen-1″-ones **4a-e** in a highly regioselective manner (Scheme 1).



Scheme 1

The dispiroheterocyclic ring structures of products **4a-e** were confirmed by IR, $^{1}H/^{13}C$ NMR and mass spectral studies. The IR spectrum of **4a** showed two peaks corresponding to tetralone and acenapthenequinone ring carbonyls at 1670.9 and 1714.2 cm^{-1}, respectively. The NMR

spectrum of the cycloadduct **4a** exhibited a doublet of doublets at δ 5.17 due to the C-4 benzylic proton of the pyrrolidine ring. The regiochemical outcome of the Azomethine ylide cycloaddition with conformationally restricted *s-cis* enone, 2-arylidene-1-tetralones **3a-e** is probably attributed to the involvement of the *anti*-ylide[11] in the transistion state where the *exo*-orientation of the dipolarophile to W-periphery of the ylide prevents the formation of *syn*-ylide which is not observed due to the unfavorable steric repulsions between the carbonyl oxygen of the acenaphthequinone ring and tetralone-1-one ring systems. Further, the regiochemistry of the cycloadduct **4a** was established by the coupling pattern in its ^{1}H NMR spectrum. Also, the ^{13}C NMR showed two signals at δ 69.9 ppm and δ 71.2 ppm due to the spiro carbon atoms and peaks at δ 192.7 ppm, δ 199.6 ppm due to the tetralone and acenaphthequinone ring carbonyls, respectively. Identical results were observed for the other derivatives irrespective of the nature of the substituents present in the arylidene moiety of the tetralone as indicated in Table 1.

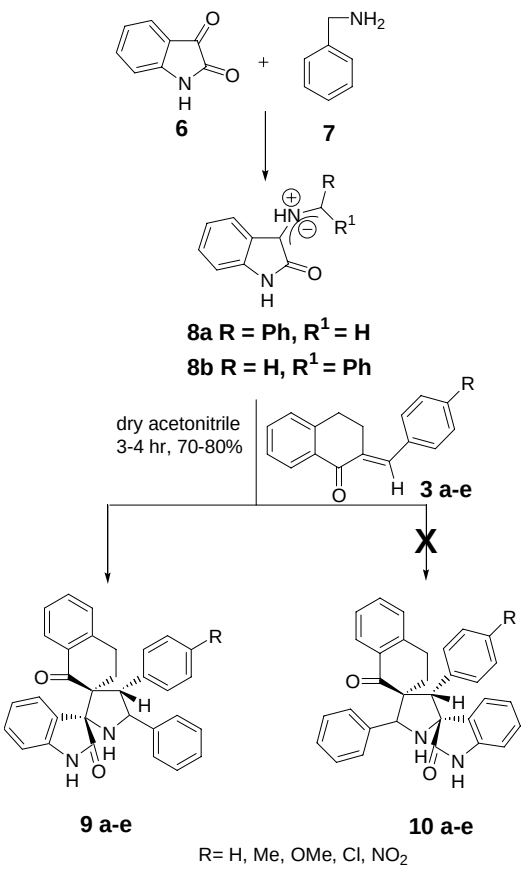
Table 1. Synthesis of 1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro[3′.3]*N*-methyl-(4-aryl)-pyrrolidine-2-spiro-2″-acenaphthen-1″-ones **4a-e**

Compound	R	Reaction time (h)	Yield (%)
4a	H	1.5	82
4b	Me	1.0	72
4c	OMe	1.3	76
4d	Cl	1.5	88
4e	NO_2	1.2	75

Deprotonation method

In this method the non-stabilized azomethine ylide generated by treating benzylamine **7** with isatin **6**, is reacted with 2-arylidene-1-tetralones to afford a series of dispiropyrrolidinyl oxindoles in acetonitrile at ambient temperature. Condensation of benzylamine with isatin could give rise to two configurationally distinct azomethine ylides, **8a** and **8b** the transition state leading to the azomethine ylide **8a** is favoured over **8b** due to the developing steric interaction between the carbonyl moiety and the phenyl group.[12] Thus, **8a** preferentially interacts with dipolarophile. The azomethine ylide **8a** so generated readily reacts with 2-arylidene-1-tetralones to give a series of novel dispirooxindole derivatives in a regioselective manner. The above reaction gave single dispiropyrrolidinyl oxindole heterocycles in all cases, as evidenced by TLC and spectral analyses.

The reaction of the ylide with *E*-2-arylidene-1-tetralones afforded a series of novel dispiroheterocycles, 1′,2′,3′,4′-tetrahydronaphthalene-1′-one-spiro-[2′.3]-(4-aryl)-pyrrolidine-spiro-[2.2″]-oxindole **9a-e** with high regioselectivity in good yield (Scheme 2).



Scheme 2

The structures of the products **9a-e** were confirmed by IR, $^{1}H/^{13}C$ NMR and mass spectral studies. The IR spectrum of **9a** shows a peak at 1686.3 cm^{-1} for the tetralone carbonyl which is 10 cm^{-1} greater than benzylidene tetralone, which indicates the loss of conjugation. The peak at 1718.5 cm^{-1} confirms the presence of the oxindole moiety. The ^{1}H NMR spectrum of **9a** shows a multiplet in the region δ 2.44-2.76 for the tetralone ring methylene protons. The N-CH proton of the pyrrolidine moiety resonates as a doublet at δ 4.91 (J = 9.7 Hz) while the NH proton of the pyrrolidine ring appears as a singlet at δ 8.3. The benzylic proton H_a exhibits a peak at δ 5.63 as a doublet (J = 9.7 Hz). The ^{13}C NMR shows signals at δ 192.5 and 178.2 for tetralone and oxindole ring carbonyls, respectively, which confirms the structure of the products. Identical results were observed for the other derivatives irrespective of the nature of the substituents present in the arylidene moiety of the tetralone-1-one, as indicated in Table 2.

In summary, we have studied the reactivity of *s-cis* restricted tetralones with two different azomethine ylides generated through decarboxylative and deprotonation methods. These studies showed that, in most cases, the azomethine cycloadditions are highly regioselective, giving good yields of novel dispiroheterocycles. These methods provide easy access to various dispiroheterocyclic frameworks, which frequently occur in alkaloids.

Table 2. Synthesis of 1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro-[2′.3]-(4-aryl)-pyrrolidine-spiro-[2.2′′]-oxindoles **9a-e**

Compound	R	Reaction time (h)	Yield (%)
9a	H	3.5	76
9b	Me	3.2	72
9c	OMe	4.0	70
9d	Cl	3.9	80
9e	NO_2	3.0	74

Experimental Section

General Procedures. All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on JEOL 400 MHz and 100 MHz, respectively. Elemental analyses were carried out on a Perkin Elmer 250B. MS spectra were recorded on a JEOL HF 303DX spectrometer.

The starting *(E)*-2-arylidene-1-tetralones **(3a-e)** were prepared according to a literature procedure[12,13].

General procedure for the synthesis of dispiroheterocycles 4a-e and 8a-e

Decarboxylative method

A solution of *(E)* 2-arylidene-1-tetralone **3a-e** (1 mmol), acenapthenequinone **1** (1 mmol) and sarcosine **2** (1 mmol) in 20 mL of aqueous methanol was refluxed until the disappearance of starting material as evidenced by TLC. The solvent is removed under reduced pressure and the crude product is purified by column chromatography using petroleum ether:ethyl acetate (9:1) as eluent.

Deprotonation method

A solution of *(E)* 2-arylidene-1-tetralone (1 mmol), isatin (1 mmol) and benzylamine (2 mmol) in 20 mL of dry acetonitrile was refluxed until the disappearance of the starting material as monitored by TLC. The solvent was then evaporated under reduced pressure and the residue was separated by column chromatography with petroleum ether-ethyl acetate (8:2) as eluent.

1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro[2′.3]-(4-phenyl)-*N*-methylpyrrolidine-spiro[2.2′′]-acenaphthen-1′′-one (4a). mp: 180°C; IR (KBr): 1670.9, 1714.2 cm^{-1}; ^{1}H NMR: δ 1.24-1.9 (m, 4H), 2.15 (s, 3H), 3.61 (dd, *J* = 8.6, 7.4 Hz, 1H), 4.23 (dd, *J* = 11.2, 8.6 Hz, 1H), 5.17 (dd, *J* = 11.2, 7.4 Hz, 1H), 6.6-8.1 (m, 15H); ^{13}C NMR: δ 25.9, 28.7, 31.2, 35.6, 69.9, 71.2, 74.7, 119.7, 121.6, 122.3, 122.7, 123.9, 124.0, 124.3, 125.1, 125.6, 127.5, 129.0, 130.3, 133.8, 134.5, 135.2, 135.8, 136.1, 137.2, 138.0, 139.1, 142.4, 143.9, 144.1, 192.7, 199.60; MS m/z:

442.9 (M^+); Anal. Calcd for $C_{31}H_{25}NO_2$ C, 83.97; H, 5.64; N, 3.16. Found: C, 84.19; H, 5.8; N, 2.85.

1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro[2′.3]-(4-*p*-methylphenyl)-*N*-methyl pyrrolidine-spiro[2.2″]-acenaphthen-1″-one (4b). mp: 176°C; IR (KBr): 1670.0, 1720.0 cm^{-1}; ^1H NMR: δ 1.3-2.0 (m, 4H), 2.2 (s, 3H), 3.7 (dd, *J* = 8.9, 7.3 Hz, 1H), 4.32 (dd, *J* = 11.0, 8.9 Hz, 1H), 5.0 (dd, *J* = 11.0, 7.3 Hz, 1H), 6.6-7.9 (m, 14H); ^{13}C NMR: δ 25.3, 29.0, 32.3, 34.9, 68.1, 70.2, 73.4, 120.4, 121.1, 123.3, 124.0, 124.8, 125.6, 126.1, 127.5, 127.8, 128.2, 128.4, 128.9, 129.0, 129.3, 130.0, 132.3, 132.7, 133.2, 135.9, 136.0, 137.4, 138.0, 198.2, 204.9; MS m/z: 457.2 (M^+); Anal. Calcd for $C_{32}H_{27}NO_2$: C, 84.03; H, 5.9; N, 3.06. Found: C, 83.84; H, 6.11; N, 2.86.

1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro[2′.3]-(4-*p*-methoxyphenyl)-*N*-methyl pyrrolidine-spiro[2.2″]-acenaphthen-1″-one (4c). mp: 198°C; IR (KBr): 1668.0, 1715.6 cm^{-1}; ^1H NMR: δ 1.1-2.1 (m, 4H), 2.14 (s, 3H), 3.46 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.7 (s, 3H), 4.3 (dd, *J* = 10.8, 9.0 Hz, 1H), 5.3 (dd, *J* = 10.8, 7.2 Hz, 1H), 6.8-7.6 (m, 14H); ^{13}C: δ 26.5, 30.3, 33.4, 35.1, 54.9, 64.9, 72.1, 74.6, 117.3, 119.1, 120.9, 121.2, 121.8, 122.0, 122.1, 122.6, 123.7, 124.4, 125.0, 126.1, 126.4, 127.8, 128.2, 129.6, 132.7, 133.1, 133.4, 142.3, 142.7, 143.0, 143.6, 144.9, 145.0, 197.3, 199.0; MS m/z: 472.9 (M^+); Anal. Calcd for $C_{32}H_{27}NO_3$: C, 81.18; H, 5.71; N, 2.96. Found: C, 81.39; H, 5.51 N, 3.04.

1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro[2′.3]-(4-*p*-chlorophenyl)-*N*-methyl pyrrolidine-spiro[2.2″]-acenaphthen-1″-one (4d). mp: 173°C; IR (KBr): 1673.8, 1710.4 cm^{-1}; ^1H NMR: δ 1.3-2.2 (m, 4H), 2.17 (s, 3H), 3.56 (dd, *J* = 9.0, 7.4 Hz, 1H), 4.23 (dd, *J* = 11.3, 9.0 Hz, 1H), 5.2 (dd, *J* = 11.3, 7.4 Hz, 1H), 6.7-7.8 (m, 14H); ^{13}C NMR: δ 25.7, 28.1, 32.6, 35.9, 68.2, 72.2, 75.9, 120.3, 121.0, 121.6, 122.4, 122.7, 123.7, 124.0, 124.3, 124.6, 124.8, 125.1, 125.6, 126.0, 126.9, 127.1, 127.8, 127.9, 130.1, 132.6, 133.5, 137.2, 145.6, 193.7, 203.1; MS m/z: 478 (M^+); Anal. Calcd for $C_{31}H_{24}NO_2Cl$: C, 77.9; H, 5.02; N, 2.9. Found: C, 78.2; H, 4.82; N, 2.75.

1′,2′,3′,4′-Tetrahydronaphthalen-1′-one-spiro[2′.3]-(4-*p*-nitrophenyl)-*N*-methyl pyrrolidine-spiro[2.2″]-acenaphthen-1″-one (4e). mp: 176°C; IR (KBr): 1670.0, 1714.4 cm^{-1}; ^1H NMR: δ 1.2-2.0 (m, 4H), 2.3 (s, 3H), 3.78 (dd, *J* = 8.6, 7.3 Hz, 1H), 4.4 (dd, *J* = 11.4, 8.6 Hz, 1H), 5.34 (dd, *J* = 11.4, 7.3 Hz, 1H), 6.7-8.0 (m, 14H); ^{13}C NMR: δ 26.3, 27.8, 33.0, 36.1, 70.2, 71.3, 71.6, 121.3, 122.6, 122.8, 124.0, 124.3, 124.6, 124.7, 125.1, 125.3, 125.4, 125.7, 126.1, 126.2, 126.7, 129.0, 131.1, 131.9, 132.0, 132.8, 133.5, 142.1, 143.7, 194.4, 200.9; MS m/z: 488 (M^+); Anal. Calcd for $C_{31}H_{24}N_2O_4$: C, 76.2; H, 4.92; N, 5.74. Found: C, 76.4; H, 4.70; N, 5.94.

1′,2′,3′,4′-Tetrahydronaphthalene-1′-one-spiro-[2′.3]-(4-phenyl)-pyrrolidine-spiro-[2.2″]-oxindole (9a). mp: 170°C; IR (KBr): 1686.8, 1718.5 cm^{-1}; ^1H NMR: δ 2.44-2.76 (m, 4H), 4.91 (d, *J* = 9.7 Hz, 1H), 5.63 (d, *J* = 9.7 Hz, 1H), 6.71-8.0 (m, 18H), 8.49 (s, 1H); ^{13}C NMR: δ 25.6, 29.3, 39.1, 49.3, 62.3, 70.3, 115.01, 115.08, 116.2, 118.9, 119.1, 120.3, 120.7, 124.3, 124.8, 125.1, 125.9, 127.3, 128.5, 130.2, 132.2, 132.4, 133.2, 140.2, 172.6, 200.5; MS m/z: 470.3 (M^+); Anal. Calcd for $C_{32}H_{26}N_2O_2$: C, 81.7; H, 5.53; N, 5.96. Found: C, 81.90; H, 5.73; N, 5.76.

1′,2′,3′,4′-Tetrahydronaphthalene-1′-one-spiro-[2′.3]-(4-*p*-methylphenyl)-pyrrolidine-spiro-[2.2′′]-oxindole (9b). mp: 170°C; IR (KBr): 1689.8, 1712.5 cm^{-1}; ^{1}H NMR: δ 2.2-2.6 (m, 7H), 4.82 (d, *J* = 10 Hz, 1H), 5.54 (d, *J* = 10 Hz, 1H), 6.81-7.90 (m, 17H), 8.4 (s, 1H); ^{13}C NMR: δ 25.9, 27.1, 34.3, 40.2, 50.3, 68.5, 73.9,116.2, 116.8, 117.3, 119.2, 119.9, 120.2, 120.4, 121.3, 122.2, 122.9, 123.2, 125.1, 125.6, 125.8, 132.2, 132.8, 134.6, 139.2, 177.3, 201.3; MS m/z: 484.3 (M^+); Anal. Calcd for $C_{33}H_{28}N_2O_2$: C, 81.82; H, 5.78; N, 5.78. Found: C, 81.64; H, 5.99; N, 5.95.

1′,2′,3′,4′-Tetrahydronaphthalene-1′-one-spiro-[2′.3]-(4-*p*-methoxyphenyl)-pyrrolidine-spiro-[2.2′′]-oxindole (9c). mp: 158°C; IR (KBr): 1683.8, 1714.5 cm^{-1}; ^{1}H NMR: δ 2.3-2.5 (m, 4H), 3.57 (s, 3H), 5.0 (d, *J* = 9.7 Hz, 1H), 5.7(d, J=9.7Hz, 1H), 6.6-7.8 (m, 17H), 8.3 (s, 1H); ^{13}C NMR: δ 24.6, 29.3, 40.5, 42.7, 51.9, 69.9, 74.3, 117.2, 121.1, 124.2, 124.3, 127.3, 127.5, 128.3, 128.9, 130.2, 132.2, 132.5, 133.7, 135.6, 138.4, 138.6, 139.7, 139.8, 140.7, 176.2, 201.2; MS m/z: 500 (M^+); Anal. Calcd for $C_{33}H_{28}N_2O_3$: C, 79.2; H, 5.6; N, 5.6. Found: C, 79.42; H, 5.26; N, 5.8.

1′,2′,3′,4′-Tetrahydronaphthalene-1′-one-spiro-[2′.3]-(4-*p*-chlorophenyl)-pyrrolidine-spiro-[2.2′′]-oxindole (9d). mp: 155°C; IR (KBr): 1685.8, 1716.5 cm^{-1}; ^{1}H NMR: δ 2.32-2.65 (m, 4H), 4.72 (d, *J* = 9.8 Hz, 1H), 5.41 (d, *J* = 9.8 Hz, 1H), 6.57-7.5 (m, 17H), 7.9 (s, 1H); ^{13}C NMR: δ 26.5, 30.3, 35.1, 54.9, 72.1, 74.6, 119.1, 121.2, 122.0, 122.6, 123.7, 125.0, 126.1, 126.3, 127.8, 128.1, 128.3, 129.7, 132.7, 133.4, 134.3, 134.7, 137.2, 141.1, 174.2, 203.6; MS m/z: 505 (M^+); Anal. Calcd for $C_{32}H_{25}N_2O_2Cl$: C, 76.12; H, 4.95; N, 5.55. Found: C, 76.31; H, 4.77; N, 5.3.

1′,2′,3′,4′-Tetrahydronaphthalene-1′-one-spiro-[2′.3]-(4-*p*-nitrophenyl)-pyrrolidine-spiro-[2.2′′]-oxindole (9e). mp: 168°C; IR (KBr): 1683.4, 1717.2 cm^{-1}; ^{1}H NMR: δ 2.1-2.4 (m, 4H), 4.76 (d, *J* = 9.4 Hz, 1H), 5.73 (d, *J* = 9.4 Hz, 1H), 6.7-7.8 (m, 17H), 8.1 (s, 1H); ^{13}C NMR: δ 26.8, 29.0, 37.9, 55.2, 59.2, 72.5, 120.3, 121.0, 122.4, 122.7, 123.7, 124.0, 124.6, 124.8, 125.7, 125.8, 127.1, 127.3, 132.2, 133.1, 133.7, 135.6, 135.8, 139.1, 139.9, 176.2, 202.3; MS m/z: 515.3 (M^+); Anal. Calcd for $C_{32}H_{25}N_3O_4$: C, 74.56; H, 4.85; N, 8.15. Found: C, 74.72; H, 4.65; N, 8.36.

Acknowledgements

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