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Facile synthesis of novel dispiroheterocylic derivatives through cycloaddition of azomethine ylides with acenaphthenone-2-ylidine ketones

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ABSTRACT

The regioselective synthesis of a series of novel dispiropyrrolidines and dispiropyrrolizidines has been accomplished through intermolecular 1,3-dipolar cycloaddition of azomethine ylides obtained from 1,2-diones like isatin and acenaphthenequinone with acenaphthenone-2-ylidine ketone dipolarophiles in methanol under reflux conditions.

Highly functionalized pyrrolidines widely occur in natural products and biologically active compounds.[1] Spirooxindole ring system is the central skeleton of numerous alkaloids and pharmacologically important compounds.[1a] Gelsemine, pseudotabersonine, morronside, formosanine, informosanine, and mitraphylline are some of the alkaloids containing spirooxindole ring systems.[2,3] Hence, much attention has been paid to the synthesis of such interesting compounds. Of particular interest are the spiropyrrodinyloxindole ring systems that are found in alkaloids like horsifiline, spirotryptostatine A and B, elacomine etc.[4] The derivatives of spiropyrrolidinyl oxindole have found wide biological applications such as antimicrobial and antitumoral agents as well as inhibitors of human NK-1 receptor.[5]

The 1,3-dipolar cycloaddition of azomethine ylides with olefins or acetylenic dipolarophiles is an important general method for the construction of pyrrolidines and pyrrolizidines.[6–8] The synthesis of spiropyrrolidine, spiropyrrolizidine, and spirothiapyrrolizidine derivatives via 1,3-dipolar cycloaddition reaction of azomethine ylides derived from 1,2-diones like isatin, acenaphthenequinone, and ninhydrin, and secondary amino acids like sarcosine, L-proline, and L-thioproline has been reported.[9] The scope of 1,3-dipolar cycloaddition reaction in the synthesis of spiro compounds has been broadened by the use of different dipolarophiles.[10]

Dipolarophiles derived from isatin and acenaphthenequinone have also been reported.[11] To the best of our knowledge, there has been no report on acenaphthenone-2-ylidine ketones[12] employed as dipolarophiles in cycloaddition of azomethine ylides. In continuation of our research in the area of 1,3-dipolar cycloadditions,[13] herein, we report the synthesis of the dispiro heterocycles containing the spirooxindole and spiroacenaphthenone ring systems through the regioselective cycloaddition reaction of azomethine ylides derived from isatin or acenaphthenequinone and secondary amino acids such as sarcosine and L-proline with the acenaphthenone-2-ylidene ketone.[14]

We first investigated the three-component reaction involving isatin **1a**, sarcosine **2**, and (*E*)-2-(2-(4-methoxyphenyl)-2-oxoethylidene)acenaphthylen-1(2*H*)-one **4a** in methanol under reflux. The reaction afforded highly substituted dispirooxindole **5a** as the only product in 82% yield. When the reaction mixture was analyzed, no signals corresponding to the other isomer **5′a** were observed in both ^{1}H and ^{13}C NMR spectra. We then probed the effect of solvent for any noticeable change in regioselectivity and yield. Various other solvents such as ethanol, toluene, and acetonitrile were used as the reaction medium to optimize the reaction conditions. The reaction in methanol reached completion in 70 min, with an isolated yield of 82% making methanol the suitable solvent. The formation of the product was identified by mass spectrometry which showed a HRMS *m*/*z* value of 489.1818 $(M+H)^{+}$. The regioselective addition and the structure of the product **5a** were confirmed using spectroscopic data.

The ^{1}H NMR spectrum of **5a** displays a singlet at 2.09 ppm attributable to the $-NCH_3$ protons of the pyrrolidine ring. The singlet at 3.45 ppm could be ascribed to the $-OCH_3$ protons of the benzoyl ring. While the two triplets at 3.42 and 4.67 ppm could

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be expected from the $-NCH_2$ protons of the pyrrolidine ring, the triplet at 4.90 ppm must represent the pyrrolidine ring proton attached to benzoyl group. The formation of other regioisomer **5′a** is ruled out as it would have exhibited a singlet in the ^1H NMR spectrum for both the $-NCH_2$ protons of pyrrolidine ring and the pyrrolidine ring proton attached to benzoyl group. Thus, the ^1H NMR spectrum of **5a** clearly demonstrates the regiochemistry of the reaction. A broad singlet appeared at δ 9.94 ppm due to the presence of –NH proton (D_2O exchangeable) of the oxindole ring.

The ^{13}C NMR spectrum of **5a** shows two peaks at 66.4 and 79.4 ppm arising from the two spiro carbons. The pyrrolidine $-NCH_3$ and $-OCH_3$ resonate at 35.1 and 55.7 ppm, respectively. The peaks at 176.4, 196.1, and 203.6 ppm indicate the presence of oxindole, benzoyl, and acenaphthenone carbonyl groups, respectively. The absence of any other peaks in the ^{13}C NMR spectrum is an evidence to prove the absence of the other regioisomer. The regioselectivity observed in the formation of **5a** may be due to the steric factors associated with secondary orbital interactions (SOI) between the dipolarophile **4a** and the ylide derived from isatin **1a** and sarcosine **2** (Fig. 2).[11]

We broadened the scope of this three-component reaction to different isatins **1a–e**, sarcosine **2**, and acenaphthenone2-ylidine ketones **4a–d**. The corresponding dispiropyrrolidines **5a–5h** were obtained in good yields (79–87%) under optimized conditions. The results are summarized in Table 1 (Scheme 1). The regiochemical outcome of the cycloaddition reaction was confirmed by single crystal XRD analysis of the cycloadduct **5f** (Fig. 1).[15]

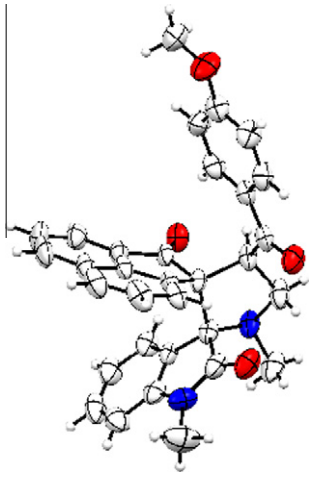


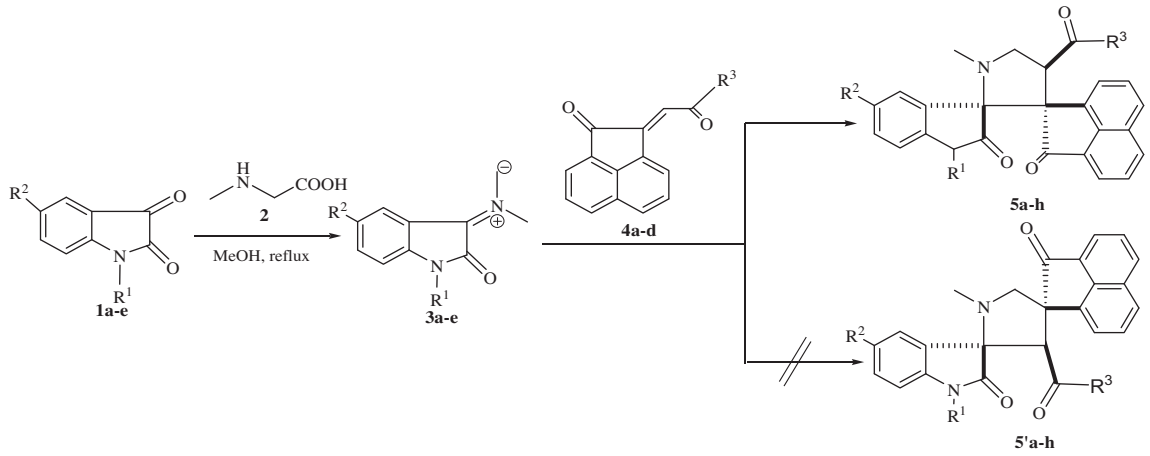
Figure 1. ORTEP diagram of compound **5f**.

A series of dispiropyrrolizidines **7a–7h** were obtained under the comparable reaction conditions (Scheme 2) by substituting

Table 1
Synthesis of dispiropyrrolidine and dispiropyrrolizidine derivatives

Entry	R1	R2	R3	Secondary amino acid	Product	Yield[a] (%)	Time (min)
1	H	H	4-Methoxy phenyl	**2**	**5a**	82	70
2	H	H	4-Bromo phenyl	**2**	**5b**	85	70
3	H	H	4-Phenyl phenyl	**2**	**5c**	80	70
4	H	H	2-Acetonaphthyl	**2**	**5d**	87	65
5	H	Cl	4-Methoxy phenyl	**2**	**5e**	87	70
6	CH_3	H	4-Methoxy phenyl	**2**	**5f**	79	85
7	Allyl	H	4-Methoxy phenyl	**2**	**5g**	82	80
8	Benzyl	H	4-Methoxy phenyl	**2**	**5h**	80	75
9	H	H	4-Methoxy phenyl	**6**	**7a**	83	80
10	H	H	4-Bromo phenyl	**6**	**7b**	84	75
11	H	H	4-Phenyl phenyl	**6**	**7c**	88	70
12	H	H	2-Acetonaphthyl	**6**	**7d**	86	65
13	H	Cl	4-Methoxy phenyl	**6**	**7e**	86	70
14	CH_3	H	4-Methoxy phenyl	**6**	**7f**	89	80
15	Allyl	H	4-Methoxy phenyl	**6**	**7g**	90	80
16	Benzyl	H	4-Methoxy phenyl	**6**	**7h**	87	80

[a] Isolated yield.



Scheme 1. Synthesis of dispiropyrrolidine derivatives.

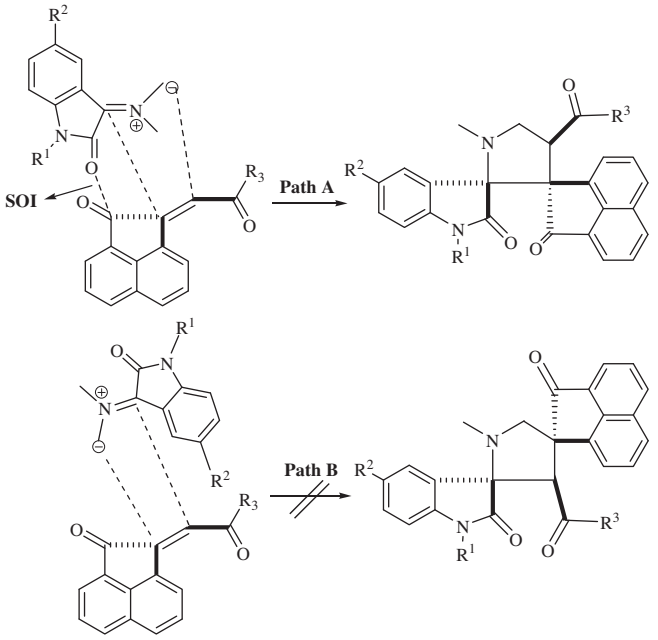


Figure 2. Mode of approach of azomethine ylide **3a**.

sarcosine with another secondary amino acid L-proline **6** in good yields (83–90%) as summarized in Table 1.

The structure of compound **7a** was confirmed by using ^{1}H, and ^{13}C NMR spectra and by mass analysis. While the multiplet at δ 1.89–2.63 in the ^{1}H NMR spectrum suggests the presence of pyrrolidine ring, the multiplet at δ ~4.63–4.67 ppm indicates $-NCH_2$ proton of pyrrolidine ring. The doublet at δ 5.61 (J = 8.6 Hz) points to the presence of pyrrolidine ring proton attached to benzoyl group and singlet at 3.67 ppm stems from $-OCH_3$ attached to benzoyl group. In ^{13}C NMR spectrum of **7a** shows two peaks at δ 73.0 and 78.2 arising from the two spiro carbons. The peaks at δ 178.5, 196.6, and 199.5 denote the presence of oxindole, benzoyl and acenaphthenone carbonyl groups, respectively. The observed mass of the product HRMS m/z 515.1946 $(M+H)^+$ further confirmed the formation of compound **7a**.

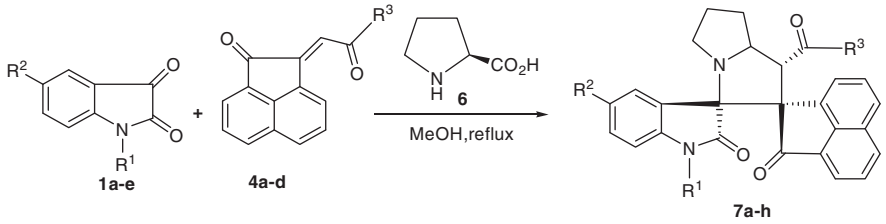
We further extended this three-component 1,3-dipolar cycloaddition reaction to azomethine ylides generated from acenaphthenequinone **8**, sarcosine **2**, and L-proline **6** to prepare the corresponding dispiropyrrolidines **9a–d** and dispiropyrrolizidines **10a–d** in good yields (83–90%) as shown in Scheme 3 and Table 2.[15]

The ^{1}H NMR spectrum of **9a**, displays a triplet at δ 5.11 indicating the presence of pyrrolidine ring proton attached to benzoyl group. The two triplets appearing in the range δ 3.36 and 4.75 arise from the $-NCH_2$ protons of pyrrolidine ring. The signals at δ 67.6 and 82.7 in the ^{13}C NMR spectrum of **9a**, are attributed to the presence of two spiro carbons. While the peak at δ 196.3 is ascribed to

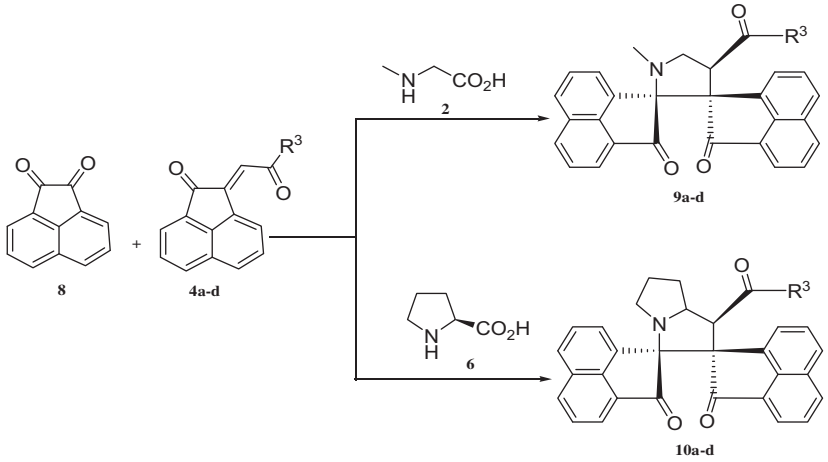
Table 2
Synthesis of dispiropyrrolidines and dispiropyrrolizidines

Entry	R^3	Secondary amino acid	Product	Yield[a] (%)	Time (min)
1	4-Methoxyphenyl	**2**	**9a**	85	90
2	4-Bromophenyl	**2**	**9b**	83	90
3	4-Phenyl phenyl	**2**	**9c**	87	90
4	2-Acetonaphthyl	**2**	**9d**	87	80
5	4-Methoxy phenyl	**6**	**10a**	88	90
6	4-Bromo phenyl	**6**	**10b**	90	90
7	4-Phenyl phenyl	**6**	**10c**	88	90
8	2-Acetonaphthyl	**6**	**10d**	86	80

[a] Isolated yield.



Scheme 2. Synthesis of dispiropyrrolizidines.



Scheme 3. Cycloaddition of dipolarophiles and azomethine yildes derived from acenaphthenequinone.

the benzoyl carbonyl group, peaks at δ 203.1 and 204.3 characterize the carbonyl groups of the two acenaphthenone moieties. The observed mass of the product HRMS m/z 524.1859 (M+1) further confirmed the formation of compound **9a**.

Both the dipole and dipolarophile used in the present study are asymmetrical. The reactions were carried out with the *E*-isomer of electron-deficient dipolarophiles. The conformation of azomethine ylide involved in the formation of **5f** appears to be in *anti*-conformation, as the *syn*-conformer shows a large steric energy according to MM2 and DFT calculations (Supplementary data). The proposed transition state (Fig. 2) appears to favor secondary attractive orbital interactions and facilitate the regioselective 1,3-dipolar cycloaddition.[16] However, the role of electronic and steric effects of the substituents in directing the regioselective addition cannot be ruled out.[16c,17] In conclusion, we have reported for the first time acenaphthenone-2-ylidine ketones as dipolarophiles in the 1,3-dipolar cycloaddition with azomethine. We have also reported the synthesis of novel dispiropyrrolidine derivatives in good yields with very high regioselectivity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.061.

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12. Synthesis of acenaphthenone-2-ylidine ketones (**4a–d**): A mixture of acenaphthenequin-one (1.82 g, 10 mmol), acetophenone derivatives (10 mmol) and powdered KOH (0.5 g) in methanol (25 mL) was refluxed at 60 °C for 1 h and the reaction mixture was allowed to stand overnight at room temperature. The solid formed was separated by filtration and purified by crystallization from methanol/dichloromethane (2:1) mixture.
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14. Typical experimental procedure for **5**, **7**, **9**, **10**: A mixture of isatin **1a–e** or acenaphthenequinone **8** (0.5 mmol), sarcosine **2** or L-proline **6** (0.6 mmol), and acenaphthenone-2-ylidine ketones **4a–d** (0.5 mmol) in methanol was refluxed for an appropriate period of time indicated in the text and cooled to room temperature. The solid formed was separated by filtration, dried and crystallized from ethanol to obtain the pure products in good yield (79–90%).
Compound (**5a**): white solid; mp = 210–212 °C; IR (KBr): 3199, 1709, 1676, 1600, 1509, 1466 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.13 (s, 3H), 3.50 (s, 3H), 3.42 (t, 1H, i = 8 Hz), 4.67 (t, 1H, J = 8.5 Hz), 4.90 (t, 1H, J = 8.5 Hz), 6.30 (d, 1H, J = 7.64 Hz), 6.44 (d, 2H, J = 8.4 Hz), 6.85 (t, 3H, J = 7.64 Hz), 6.93 (t, 1H, J = 7.64 Hz), 7.17–7.19 (m, 3H), 7.37–7.38 (m, 2H), 7.52 (t, 1H, J = 7.64 Hz), 7.62 (t, 1H, J = 4.6 Hz), 7.67 (d, 1H, J = 6.88 Hz), 7.92 (d, 1H, J = 7.64 Hz), 9.96 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 35.1, 50.1, 54.2, 55.7, 66.4, 79.4, 109.5, 113.5, 121.6, 124.5, 125.0, 125.2, 127.5, 128.2, 128.4, 129.7, 129.8, 130.6, 132.1, 132.2, 134.8, 141.3, 143.3, 162.7, 176.4, 196.1, 203.6. HRMS: m/z 489.1818 $(M+H)^+$ [Calcd 489.1814].
Compound (**5f**): white solid mp = 185–187 °C; IR (KBr): 1718, 1667, 1599, 1507, 1466 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.3 (s, 3H), 2.64 (s, 3H), 3.54 (s, 3H), 3.60 (t, J = 9 Hz, 1H), 4.92–4.97 (m, 2H), 6.22 (d, 1H, J = 7.64 Hz), 6.30 (d, 2H, J = 8.41 Hz), 6.89 (t, 1H, J = 7.64 Hz), 6.97 (t, 1H, J = 6.88 Hz), 7.25–7.33 (m, 4H) 7.40–7.45 (m, 3H), 7.69 (d, 1H, J = 6.88 Hz), 7.73 (d, 1H, J = 8.41 Hz). ^{13}C NMR (125 MHz, $CDCl_3$)) δ:.25.1, 35.4, 49.7, 54.7, 55.2, 66.7, 79.7, 107.2, 113.0, 121.4, 122.2, 123.5, 124.5, 124.8, 127.0, 127.3, 127.9, 129.3, 129.7, 130.7, 131.3, 132.1, 134.1, 141.6, 144.3, 162.5, 174.8, 195.7, 204.4. HRMS: m/z 503.1967 $(M+H)^+$ [Calcd 503.1965].
Compound (**7a**): white solid; mp = 180–182 °C; IR (KBr): 3324, 1726, 1692, 1602, 1508, 1466 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 1.89–1.94 (m, 2H), 2.17–2.21 (m, 2H), 2.53–2.63 (m, 2H), 3.67 (s, 3H), 4.63–4.67 (m, 1H), 5.61 (d, 1H, J = 8.6 Hz), 6.14–6.2 (m, 2H), 6.49 (d, 1H, J = 8 Hz), 6.71(d, 2H, J = 8.6 Hz), 6.76 (t, 1H, J = 7.5 Hz), 7.26 (d, 2H, J = 8 Hz) 7.36 (d, 1H, J = 6.88 Hz), 7.41 (t, 1H, J = 8 Hz), 7.79 (t, 1H, J = 8 Hz), 7.90 (d, 1H, J = 8.6 Hz), 8.01 (d, 1H, J = 8 Hz), 8.06 (d, 1H, J=6.85 Hz),10.45 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 30.6, 31.4, 47.3, 54.2, 55.9, 66.7, 73.0, 78.2, 109.7, 113.9, 120.8, 121.4, 125.4, 125.6, 126.1, 128.1, 128.7, 129.6, 130.0, 130.2, 130.4, 132.4, 136.3, 141.3, 142.4, 163.3, 178.5, 196.6, 199.5. HRMS: m/z 515.1946 $(M+H)^+$ [Calcd 515.1971].
Compound (**9a**): yellow solid; mp = 220–222 °C; IR (KBr): 1715, 1677, 1596, 1466, 1425 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.51 (s, 3H), 3.52 (s, 3H), 3.36 (t, 1H, J = 8.45, 9 15 Hz), 4.75 (t, 1H, J = 8.4, 9 15 Hz), 5.11 (t, 1H, J = 8.45, 9.15 Hz), 6.45 (d, 2H, J = 8.4), 7.24–7.78 (m, 13H),7.93 (d, 1H, J = 7.65), ^{13}C NMR (125 MHz, DMSO-d_6) δ: 35.2, 50.6, 54.9, 55.7, 67.9, 82.7, 113.7, 120.4, 121.6, 124.3, 124.8, 125.7, 126.2, 128.1, 128.2, 128.4, 128.8, 129.6, 129.8, 130.1, 130.5, 131.8, 132.0, 132.2, 134.4, 134.5, 140.9, 141.6, 162.8, 196.3, 203.1, 204.3. HRMS: m/z 524.1859 $(M+H)^+$ [Calcd 524.1856].
15. The detailed X-ray crystallographic data (CCDC number for **5f** is 892288) is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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