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An easy access to novel steroidal dispiropyrrolidines through 1,3-dipolar cycloaddition of azomethine ylides

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ABSTRACT

A facile one-pot synthesis of novel steroidal dispiropyrrolidines has been accomplished by 1,3-dipolar cycloaddition reaction of various azomethine ylides derived from isatin/acenaphthenequinone/ninhydrin and sarcosine with various estrone derivatives as dipolarophiles, in good yield. The effect of various solvents on the 1,3-dipolar cycloaddition reaction are also studied.

The formation of active steroids by aromatase enzymes has been considered to play an important role in the development of human breast carcinoma.[1,2] It has been documented that increased aromatase activity in the breast cancer tissue is greater compared to the non-malingnant parenchyma.[3–5] The enzyme is the rational target for the development of drugs to treat hormonal-dependent breast cancer.[6–9] In recent years, clinical research on aromatase inhibitors has increased significantly and several oral aromatase inhibitors have been demonstrated to be highly potent and specific inhibitors of estrogen synthesis.[10–12] Our efforts were focused on designing estrogen derivatives that might inhibit or that may possess antiestrogenic activity.

The intermolecular [3+2]-cycloaddition reaction of azomethine ylides with various alkenes and alkynes represents an efficient and convergent method for the construction of pyrrolidine and pyrrolizidine units.[13–15] Functionalised pyrrolidine alkaloids constitute classes of compounds with significant biological activities.[16,17] Spiro compounds represent an important class of naturally occurring substances characterised by highly pronounced biological properties.[18–26] Oxindole derivatives are found to be potent aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol.[27] Spirooxindoles have been reported to behave as poliovirus and rhinovirus 3C-proteinase inhibitors.[28]

In continuation of our studies in the area of cycloaddition reactions[29–36] and with a view to synthesise a rare class of novel dispiroheterocyclic derivatives, we herein report for the first time, the reaction of (*Z*)-16-arylidene estrone derivatives[37] **1a–d** as 2π components in 1,3-dipolar cycloaddition reactions with various azomethine ylides for the facile synthesis of hitherto unknown steroidal pyrrolidines. Thus the dipoles generated from sarcosine **2** and various 1,2-diketones, namely (a) isatin **3**, (b) acenaphthenequinone **6** and (c) ninhydrin **9** were reacted with the steroidal dipolarophiles **1a–d** to afford a series of novel dispirosteroidal pyrrolidines **4a–d**, **7a–d** and **10a–d**. The structures of the cycloadducts were confirmed through spectral and elemental analysis.[38] The reactions were carried out using three different sets of conditions and the results are shown in Table 1.

Table 1
Effect of solvent on the cycloaddition reactions

Entry	R^1	R^2	R^3	Method A		Method B		Method C	
				T (h)	*Y* (%)	*T* (h)	*Y* (%)	*T* (h)	*Y* (%)
4a	H	H	H	8.1	39	5.6	63	6.0	70
4b	H	Cl	H	8.4	43	6.0	62	5.8	68
4c	H	Me	H	8.6	36	6.8	60	7.0	67
4d	OMe	OMe	OMe	8.8	33	7.0	61	7.3	68
7a	H	H	H	8.2	40	5.5	65	5.2	70
7b	H	Cl	H	7.8	36	6.8	64	6.6	72
7c	H	Me	H	8.8	38	5.8	62	6.0	68
7d	OMe	OMe	OMe	8.9	35	5.7	60	5.9	66
10a	H	H	H	8.2	38	6.0	62	5.8	70
10b	H	Cl	H	8.6	35	6.5	61	6.3	69
10c	H	Me	H	8.4	34	6.7	63	6.5	70
10d	OMe	OMe	OMe	8.7	32	6.9	63	6.4	68

T (h): time in hours; *Y* (%): yield in %; Method A: toluene/reflux; Method B: acetonitrile/reflux; Method C: methanol/reflux.

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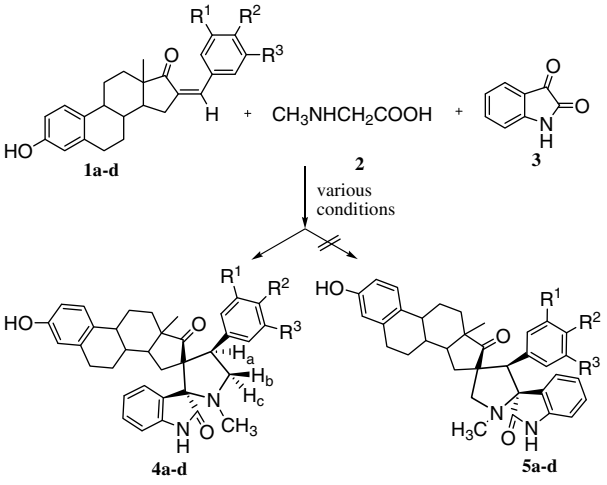
Schemes 1–3 suggest one-pot three component reactions involving sarcosine and isatin/acenaphthenequinone/ninhydrin with various *p*-substituted (*Z*)-16-arylidene estrones for the synthesis of novel dispirosteroidal pyrrolidines **4a–d**, **7a–d** and **10a–d**.

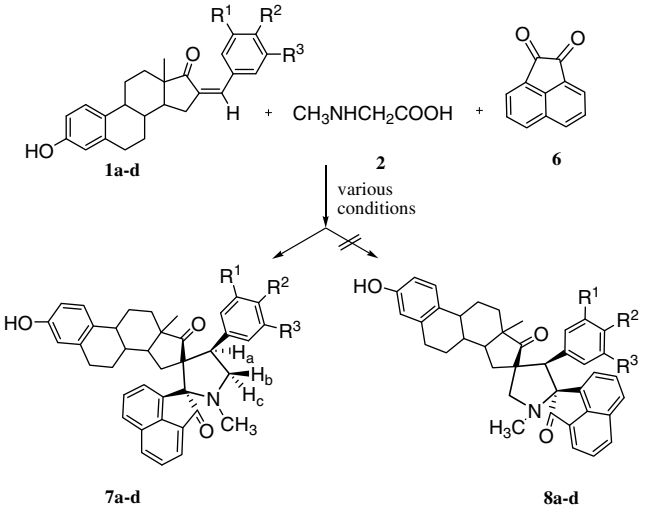
The IR spectrum of the steroidal dispirooxindolopyrrolidine **4a** showed peaks at 1616.9 cm^{-1} and 1702.6 cm^{-1} due to the oxindole and cyclopentanone ring carbonyl groups. The ^1H NMR spectrum of **4a** exhibited singlets at δ 0.50 and δ 2.20 for the C-18 methyl of the estrone and $-NCH_3$ protons of the pyrrolidine moiety. The H_b and H_c protons of the pyrrolidine moiety resonated as two triplets at δ 3.55 (J = 8.0 Hz) and δ 3.96 (J = 9.2 Hz). The benzylic proton H_a occurred as a triplet at δ 4.03 (J = 8.5 Hz), which proved the regiochemistry of the cycloaddition reaction. If the other regioisomer **5a** had been formed, proton H_a would have appeared as a singlet in the ^1H NMR spectrum. On decoupling the $-NCH_2$ proton at δ 3.55, H_b and H_a protons appeared as two doublets at δ 3.98 (J = 8.8 Hz) and δ 4.06 (J = 8.8 Hz). The –NH proton of the oxindole moiety appeared as a singlet at δ 8.01. The ^{13}C NMR spectrum of **4a** showed two peaks at δ 68.18 and δ 78.33 ppm due to the two-spiro carbons. The C-18 methyl carbon of the estrone moiety and the pyrrolidine $-NCH_3$ carbon resonated at δ 14.92 and δ 25.30 ppm. The amide and cyclopentanone carbonyl carbons resonated at δ 178.79 and δ 221.72, respectively. The structure of the product **4a** was further confirmed through mass spectroscopy, which showed a molecular ion peak at 532.6 (M^+) (Scheme 1).

The IR spectrum of the steroidal dispiro-acenaphthenenopyrrolidine **7d** showed peaks at 1705.6 cm^{-1} and 1735 cm^{-1} due to cyclopentanone and acenaphthenenone carbonyl group. The ^1H NMR spectrum of **7d** exhibited singlets at δ 0.56 and δ 2.19 for the C-18 methyl of the estrone and $-NCH_3$ protons of the pyrrolidine moiety. The H_b and H_c protons of the pyrrolidine moiety resonated as two triplets at δ 3.68 (t, 1H, J = 8.0 Hz) and δ 4.01 (t, 1H, J = 8.5 Hz). The benzylic proton H_a occurred as a triplet at δ 4.09 (t, 1H, J = 9.2 Hz). The ^{13}C NMR spectrum of **7d** showed two peaks at δ 69.09 and δ 80.06 ppm due to the two-spiro carbons. The C-18 methyl carbon of the estrone moiety and the pyrrolidine $-NCH_3$ carbon resonated at δ 14.85 and δ 25.05 ppm. The acenaphthenenone and cyclopentanone carbonyl carbons resonated at δ 209.24 and 222.33 ppm. The structure of the product **7d** was further confirmed through mass spectroscopy of **7d**, which showed a molecular ion peak at 657.8 (M^+) (Scheme 2).

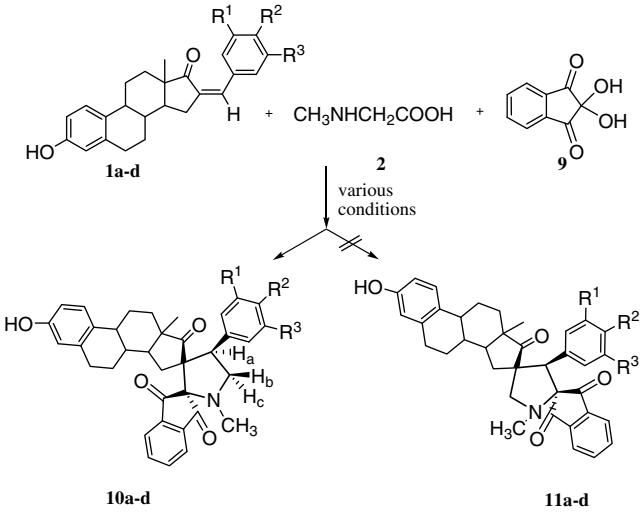
The IR spectrum of steroidal dispiroindanedione-pyrrolidine **10d** showed peaks at 1704.5 $cm^{-1}$and 1732 cm^{-1} due to the cyclopentanone and indanedione carbonyl groups. The ^1H NMR spectrum of **10d** showed singlets at δ 0.16 and δ 2.19 for the C-18



Scheme 1.



Scheme 2.



Scheme 3.

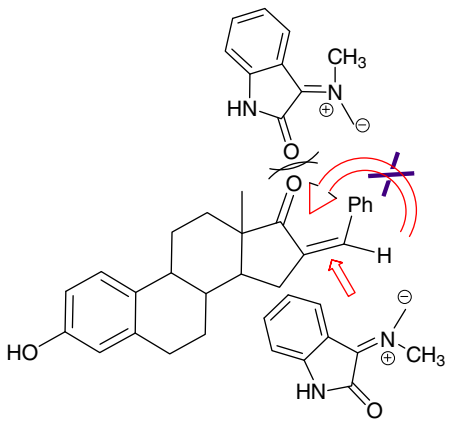


Figure 1. Mode of approach of the azomethine ylide.

methyl of the estrone and $-NCH_3$ protons of the pyrrolidine moiety. The H_b and H_c protons of the pyrrolidine moiety resonated as two triplets at δ 3.67 (t, 1H, J = 9.2 Hz) and δ 3.86 (t, 1H, J = 10.5 Hz). The benzylic proton H_a occurred as a triplet at δ 4.44 (t, 1H, J = 9.5 Hz). The ^{13}C NMR spectrum of **10d** showed two peaks at δ 69.89 and δ 83.16 ppm due to the two-spiro carbons. The C-18 methyl carbon of the estrone moiety and the pyrrolidine $-NCH_3$ carbon resonated at δ 13.02 and δ 25.27 ppm. The indanedione and cyclopentanone carbonyl carbons resonated at δ 199.22, δ 199.96 and δ 218.89 ppm. The structure of the product was further confirmed through mass spectroscopy of **10d**, which showed a molecular ion peak at 635.7 (M^+) (Scheme 3).

The preferred mode of approach of the azomethine ylide is shown in Figure 1. The azomethine ylide approaches the prochiral carbon from the least hindered side of the steroidal dipolarophile, accounting for the high selectivity in the mode of approach in accordance with literature reports.[39–41]

From Table 1, it is evident that the rate of the reaction and the yields of the cycloadducts are good in polar solvents (60–72%).

In conclusion, we have synthesised successfully a series of hitherto unknown steroidal pyrrolidines by 1,3-dipolar cycloaddition reactions. We anticipate that these steroidal dipolarophiles can be further exploited for the synthesis of a variety of complex steroidal heterocycles through cycloaddition reactions. Further work in this direction is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.089.

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38. *Representative procedure for the synthesis of steroidal dispiropyrrolidines derivatives* **4a**. A solution of (*Z*)-16-benzylidene estrone **1** (1 mmol), sarcosine **2** (1 mmol), isatin **3** (1 mmol) in methanol (30 mL) was refluxed for 6 h. The progress of the reaction was evidenced by the TLC analysis. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using petroleum ether/ethylacetate (4:1) as eluent.
Spectral data for **4a**: 1-*N*-Methyl-spiro[2.3′]-oxindole spiro[3.2″]estrone-4-phenyl pyrrolidine. $[\alpha]_D$ +120, (*c* 1, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ 0.48–2.16 (m, 13H), 0.50 (s, 3H, −18 CH_3), 2.20 (s, 3H), 3.55 (t, 1H, J = 8.0 Hz), 3.96 (t, 1H, J = 9.2 Hz), 4.03 (t, 1H, J = 8.5 Hz), 5.35 (br s, 1H), 6.47–7.45 (m, 12H), 8.01(s, –NH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.92, 25.30, 26.73, 29.09, 31.01, 34.92, 36.91, 44.12, 46.84, 47.46, 51.50, 60.47, 68.18, 78.33, 109.18, 112.75, 115.28, 122.89, 126.16, 127.01, 127.45, 128.50, 128.77, 129.52, 130.26, 131.63, 137.75, 139.54, 141.86, 153.49, 178.79, 221.72; IR (KBr): 1616.9, 1702.6 cm^{-1}; EIMS *m*/*z*: 532.6 (M^+); Anal. Calcd for $C_{35}H_{36}N_2O_3$: C, 78.91; H, 6.81; N, 5.25. Found: C, 79.07; H, 6.65; N, 5.25.
Spectral data for **7d**: 1-*N*-Methyl-spiro [2.2′]-acenapthenene-1′-one-spiro [3.2″] estrone-4-(3,4,5-trimethoxyphenyl)-pyrrolidine. $[\alpha]_D$ +182, (*c* 1, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ 0.02–2.43 (m, 13H), 0.56 (s, 3H, −18CH_3), 2.19 (s, 3H), 3.68 (t, 1H, J = 8.0 Hz), 3.87 (s, 6H), 3.90 (s, 3H), 4.01 (t, 1H, J = 8.5 Hz), 4.09 (t, 1H, J = 9.2 Hz), 5.50 (br s, 1H), 6.42–8.08 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.85, 25.05, 26.01, 28.83, 31.14, 31.93, 34.83, 36.33, 43.75, 47.44, 52.18, 56.15, 60.86, 69.09, 80.96, 112.59, 115.14, 120.15, 125.13, 125.87, 127.95, 128.71, 130.29, 131.12, 132.14, 135.54, 137.01, 137.01, 137.58, 143.02, 153.63, 209.24, 222.33; IR (KBr): 1705.6, 1735 cm^{-1}; EIMS *m*/*z*: 657.8 (M^+); Anal. Calcd for $C_{42}H_{43}NO_6$: C, 76.68; H, 6.58; N, 2.12. Found: C, 76.47; H, 6.76; N, 2.34.
Spectral data for **10d**: 1-*N*-Methyl-spiro-[2.2′]- indane-1′,3′-dione-spiro [3.2″] estrone-4-(3,4,5-trimethoxyphenyl)-pyrrolidine. $[\alpha]_D$ +147, (*c* 1, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ 0.71–2.75 (m, 13H), 0.16 (s, 3H, −18CH_3), 2.39 (s, 3H), 3.67 (t, 1H, J = 9.2 Hz), 3.77 (s, 9H), 3.86 (t, 1H, J = 10.5 Hz), 4.44 (t, 1H, J = 9.5 Hz), 6.40–7.95 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.02, 25.27, 26.36, 27.04, 29.09, 31.76, 35.89, 37.24, 44.24, 47.53, 49.40, 51.83, 56.17, 58.17, 60.91, 69.89, 83.16, 107.07, 112.67, 115.31, 122.46, 123.25, 125.90, 131.18, 132.51, 135.69, 136.92, 137.85, 140.81, 141.05, 152.88, 153.73, 199.22, 199.96, 218.89; IR (KBr): 1704.5, 1732 cm^{-1}; EIMS *m*/*z*: 635.7 (M^+); Anal. Calcd for $C_{39}H_{41}NO_7$: C, 73.68; H, 6.49; N, 2.20. Found: C, 73.48; H, 6.34; N, 2.33.
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