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Synthesis of novel spiropyrrolidine/pyrrolizine-oxindole scaffolds through 1,3-dipolar cycloadditions

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ABSTRACT

The one-pot, three-component condensation of sarcosine or proline Schiff bases with several aromatic aldehydes and the Knöevenagel adduct of isatin-malononitrile successfully affords spiropyrrolidine-oxindoles and spiropyrrolizine-oxindoles.

1,3-Dipolar cycloadditions of azomethine ylides with olefinic and acetylenic dipolarophiles represent an important approach for the formation of pyrrolidines and pyrrolizines which are prevalent in a variety of biologically active compounds.[1]

Construction of five-membered pyrrolidines and pyrrolizine rings via simple synthetic methods affords an important class of substances with highly pronounced biological activities.[2] In particular, functionalized pyrrolidines and pyrrolizines with spirooxindole rings are the central skeletons of numerous alkaloids and pharmacologically important compounds.[3]

Some spiropyrrolidines are potential antileukaemic and anticonvulsant agents[4] and possess antiviral and local anaesthetic activities,[5] and this has attracted considerable attention from organic chemists. Recent studies on the synthesis of spiro- or dispiro-heterocycles starting from either sarcosine or proline and different dipolarophiles with oxindole and isatin have been exemplified.[6]

As a part of our own interest in cycloaddition reactions, we report herein the facile synthesis of novel spiropyrrolidine/pyrrolizine-oxindoles via the one-pot, three-component condensation of azomethine ylides (generated in situ from sarcosine or proline and an aromatic aldehyde) with the Knöevenagel adduct 2-oxo-(3*H*)-indole-3-ylidine-malononitrile derived from the reaction of 2-oxo-(3*H*)indole with malononitrile.

The 2-oxo-(3*H*)-indol-3-ylidine-malononitrile Knöevenagel adduct **1** was prepared according to the reported procedure via condensation of isatin and malononitrile.[7] This adduct was subsequently treated with the Schiff bases obtained from condensation of either sarcosine or proline with aromatic aldehydes **2a–d** in refluxing toluene for the appropriate time (see Scheme 1).[8] After removal of the solvent, the residue was subjected to column chromatography. Elution with hexane–ethyl acetate afforded the spiropyrrolidine-oxindoles **3a–d** and **4a–d** and spiropyrrolizine-oxindoles **5a–d** and **6a–d**, respectively. Identification of the products was carried out by spectroscopic methods.[9–12] The yields and reaction times are presented in Tables 1 and 2.

The ^{1}H NMR spectrum of **3a** exhibited a singlet at δ 2.60 for the *N*-CH_3 protons. The *N*-CH_2 protons of the pyrrolidine ring appeared as two doublets at δ 3.92 and δ 3.97. The benzylic proton resonated as a singlet at δ 4.29 and the *N*-H proton was revealed at δ 8.41. The ^{1}H NMR spectrum of **4a** exhibited a singlet at δ 2.47 for the *N*-CH_3 protons whilst the *N*-CH_2 protons of the pyrrolidine ring were apparent as two doublets at δ 3.29 and δ 3.74. The benzylic proton resonated as a singlet at δ 4.86 and the *N*-H proton occurred at δ 8.35. The ^{13}C NMR spectra of **3a** and **4a** showed signals at δ 63.0 and δ 57.5 for the spiro carbons and signals at δ 176.8 and δ 177.4 for the C=O groups. The mass spectra of **3a** and **4a** exhibited molecular ion peaks at *m/z* 328.

Assignment of the molecular structures was carried out using the HMBC spectra of **3a** and **4a**. As seen in Figure 1, long-range couplings are present in **3a** between the C=O group at δ 176.8 and the benzylic CH proton at δ 4.29. On the other hand, the C=O group observed at δ 177.4 in **4a** shows long-range couplings with the *N*-CH_2 protons resonating at δ 3.29. Moreover, long-range couplings between the CN groups appearing at δ 112.8 and δ 114.3 in **3a** with the *N*-CH_2 protons at δ 3.92 and δ 3.97 were observed. Similar couplings between the CN groups at δ 112.0 and δ 112.6 in **4a** with the benzylic CH proton resonating at δ 4.86 were observed.

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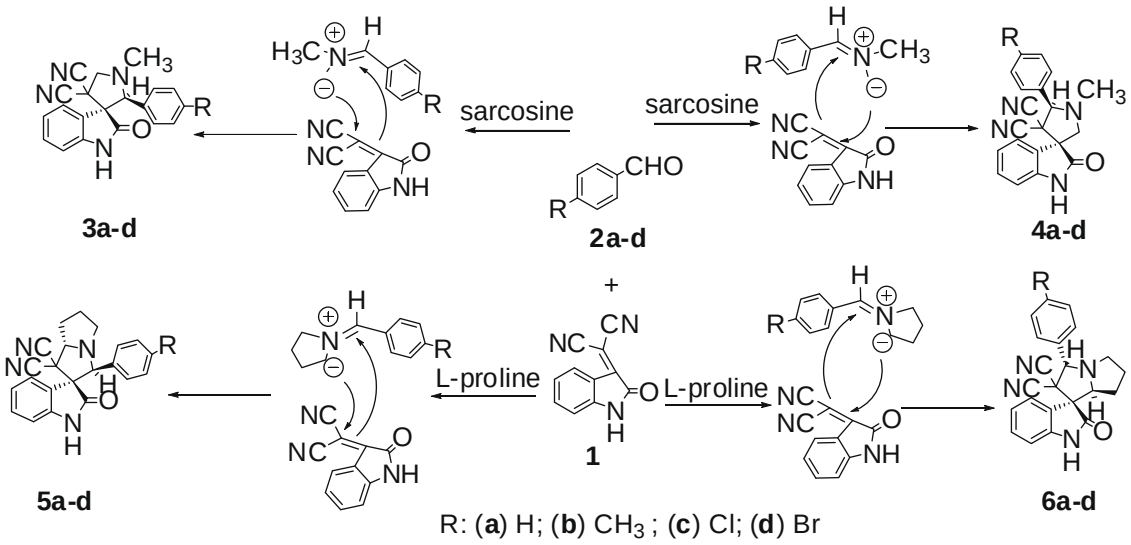


Scheme 1.

Table 1
Cycloaddition results with sarcosine

3/4	R	Total yield (%)	Yield (%)		Time (h)
			3	**4**	
a	H	73	35	38	5
b	CH_3	70	32	38	6
c	Cl	69	33	36	4
d	Br	66	32	34	4

Table 2
Cycloaddition results with proline

5/6	R	Total yield (%)	Yield (%)		Time (h)
			5	**6**	
a	H	60	28	32	11
b	CH_3	56	26	30	11
c	Cl	59	29	30	9
d	Br	59	28	31	9

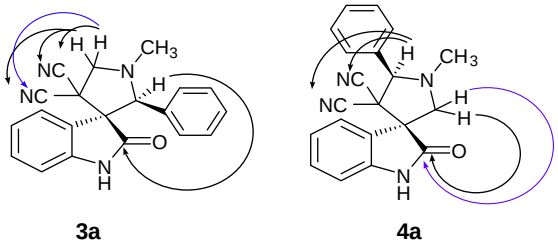
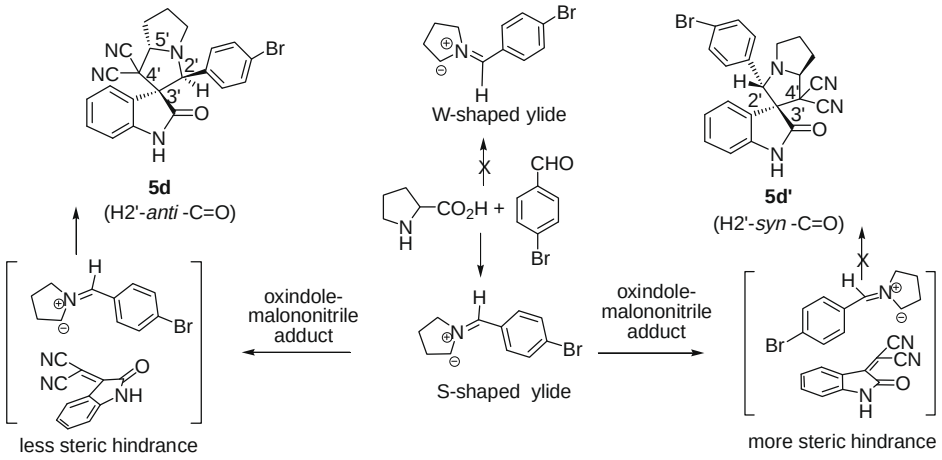


Figure 1. HMBC correlations of **3a** and **4a**.

As shown in Scheme 1, two Michael-type addition pathways can be envisaged for the reaction of azomethine ylides with **1** leading to **3a–d**/**4a–d** and **5a–d**/**6a–d**, respectively. With a few exceptions,[13] a single pyrrolidine or pyrrolizine derivative is usually obtained from the reaction of an azomethine ylide with a dipolarophile due to the availability of only a single Michael acceptor in the chalcone.[14] Therefore, obtaining two spiropyrrolidine-oxindole and spiropyrrolizine-oxindole scaffolds in this work seems to be an exception rather than a rule.

The stereochemistry of H2′ and H5′ in **5d** (see Scheme 2) was shown to be trans by rotating frame Overhauser effect spectroscopy (ROSEY) since these two protons showed no correlations in the relevant spectrum. Determination of the correct molecular structure was carried out by ^{1}H NMR spectroscopy and by comparison of the benzylic C–H chemical shift in **5d** with the H_a chemical shift in the previously reported spirocycle **7d** (Fig. 2).[15] Proton H_a in **7d** is expected to appear at δ 2.50–3.00. As reported, it appears as a doublet at δ 5.23. The 2.23–2.73 ppm deshielding seems likely to be the result of the oxindole C=O group which is located *syn* to H_a. The benzylic H in **5d** is expected to appear at at least δ 3.63 based on Shoolery's rule.[16] Moreover, it is expected to resonate at δ 5.86–6.36 if located *syn* to the oxindole C=O group. The appearance of the benzylic H in **5d** at δ 4.82[11] confirms the *anti* orientation with respect to the oxindole C=O group. In the pyrrolidine-oxindole **3a**, the benzylic H resonates at δ 4.29.[9] The formation of **5d** with the 2′,5′-trans-disubstituted arrangement might be explained easily. The dipolar cycloaddition reaction of an azomethine ylide generated from proline and an aldehyde with a dienophile could lead to a mixture of stereoisomers. From the two possible *W*- and *S*-shaped ylide geometries (Scheme 2), the 2′,5′-cis-disubstituted and the 2′,5′-trans-disubstituted products, respectively, are anticipated to be formed via a suprafacial reaction.[17] Inspection of other reported examples,[17] and product **5d** perhaps shows some general preference for cycloaddition through an S-shaped ylide.[17] Therefore, the formation of compounds **5a–d** and **6a–d** with a trans arrangement between C-2′ and C-5′ is anticipated. Particularly significant is the formation of **5d** and not the diastereomer **5d′** through a transition state with less steric hindrance which establishes the *anti*-relationship between the benzylic H and oxindole C=O groups. The formation of **6d** could also be rationalized accordingly.

In conclusion, spiropyrrolidine-oxindole and spiropyrrolizine-oxindole derivatives, each containing two cyano groups, were successfully prepared and identified. Determination of the spiropyrrolizine-oxindole stereocentre configuration by means of ROSEY is worthy of note. The key role of HMBC spectroscopy in elucidation of molecular structures as carried out herein is of fundamental importance.



Scheme 2.

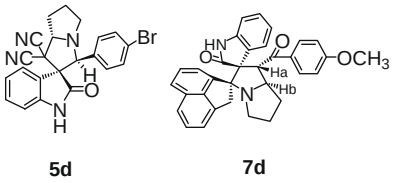


Figure 2.

Acknowledgement

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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.2009.06.033.

References and notes

1. (a) Pearson, W. H.. In *Studies in Natural Product Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1998; Vol. 1, pp 323–358; (b) Bridges, R. J.; Lovering, F. E.; Humphrey, J. M.; Stanley, M. S.; Blakely, T. N.; Cristofaro, M. F.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 115–121.
2. (a) Cordell, G. A. In *The Alkaloids: Chemistry and Biology*; Academic: San Diego, 1998; (b) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651–12666; (c) Xue, J.; Zhang, Y.; Wang, X.-I.; Fun, H. K.; Xu, J. H. *Org. Lett.* **2000**, *2*, 2583–2586; (d) Klumpp, D. A.; Yeung, K. Y.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481–4484.
3. Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639–2641.
4. Abou-Gharbia, M. A.; Doukas, P. H. *Heterocycles* **1979**, *12*, 637–640.
5. Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892–898.
6. Mahalingam, P.; Ragavachary, R. *Tetrahedron* **2006**, *52*, 11274–11281.
7. Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, Sh. M.; El-Bady, Sh. M. *Bioorg. Med. Chem.* **2004**, *12*, 2483–2488.
8. *Representative procedure for the preparation of compounds* **3a**, **4a**: a mixture of sarcosine (89 mg, 1.0 mmol), benzaldehyde (106 mg, 1.0 mmol) and **1** (195 mg, 1.0 mmol) in dry toluene (30 mL) containing molecular sieves (500 mg, 3 Å) was heated at reflux with stirring for 5 h. The solvent was then removed under reduced pressure and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (9:1) as eluent to give the products.
9. *4,4-Dicyano-2-phenyl-N-methyl-spiro-[3,3′]-pyrrolidine-oxindole* (**3a**): cream crystals, mp: 194–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.92 (d, J = 9.3 Hz, 1H), 3.97 (d, J = 9.3 Hz, 1H), 4.29 (s, 1H), 6.79–7.30 (m, 9H), 8.41 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.8, 42.2, 62.5, 63.0, 74.5, 110.5, 112.8, 114.3, 123.2, 123.6, 128.3, 128.5,128.9,130.5,136.3, 140.9, 176.8; IR(KBr): 1710, 2250, 3207 cm^{-1}; MS m/z: 328 (M^+); Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.05; H, 4.95; N, 16.95.
10. *3,3-Dicyano-2-phenyl-N-methyl-spiro-[4,3′]-pyrrolidine-oxindole* (**4a**): white crystals, mp: 234–236 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.29 (d, J = 10.2 Hz, 1H), 3.74 (d, J = 10.2 Hz, 1H), 4.86 (s, 1H), 7.03–7.80 (m, 9H), 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.6, 51.8, 57.5, 61.8, 75.5, 111.0, 112.0, 112.6, 124.2, 125.9, 126.5, 129.0, 129.4, 130.4, 131.2, 133.0, 141.3, 177.4; IR (KBr): 1710, 2252, 3215 cm^{-1}; MS m/z: 328 (M^+); Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 72.78; H, 4.96; N, 17.24.
11. *4′,4′-Dicyano-2′-(p-bromophenyl)-spiro-[3′,3″]-pyrrolizine-oxindole* (**5d**): cream crystals, mp: 209–212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (m, 1H), 2.38 (m, 2H), 2.50 (m, 1H), 2.77 (m, 1H), 3.08 (m, 1H), 4.65 (t, J = 7.0 Hz, 1H), 4.82 (s, 1H), 6.85–7.75 (m, 8H), 8.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 29.4, 47.4, 53.5, 66.6, 72.0, 72.1, 111.0, 111.2, 112.3, 122.6, 123.2, 123.6, 127.4, 129.2, 131.2, 131.8, 134.9, 140.7, 171.6; IR (KBr): 1722, 2252, 3201 cm^{-1}; MS m/z: 432 (M^+); Anal. Calcd for $C_{22}H_{17}N_4OBr$: C, 60.98; H, 3.95; N, 12.93. Found: C, 60.82; H, 4.20; N, 13.02.
12. *3′,3′-Dicyano-2′-(p-bromophenyl)-spiro-[4′,3″]-pyrrolizine-oxindole* (**6d**): cream crystals, mp: 225–227 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (m, 2H), 2.04 (m, 1H), 2.21 (m, 1H), 2.83 (m, 1H), 3.02 (m, 1H), 4.47 (t, J = 7.5 Hz, 1H), 5.49 (s, 1H), 7.01–7.80 (m, 8H), 8.13 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 29.1, 46.8, 54.2, 68.4, 71.6, 74.2, 110.9, 112.6, 113.0, 122.1, 123.0, 123.9, 125.7, 129.1, 131.6, 131.8, 134.8, 141.5, 172.5; IR (KBr): 1716, 2248, 3195 cm^{-1}; MS m/z: 432 (M^+); Anal. Calcd for $C_{22}H_{17}N_4OBr$: C, 60.98; H, 3.95; N, 12.93. Found: C, 61.22; H, 4.11; N, 13.12.
13. Fejes, I.; Nyerges, M.; Szöllõsy, A.; Blaskó, G.; Tkeõ, L. *Tetrahedron* **2001**, *57*, 1129–1137.
14. Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 6809–6813.
15. Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 305–308.
16. Friebolin, H. In *Basic One- and Two-Dimensional NMR Spectroscopy*, 2nd ed.; VCH: Verlagsgesellschaft mbH, Weinheim, 1993; pp 52–53.
17. (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809; (b) Ghandi, M.; Tabatabaei Rezaei, S. J.; Yari, A.; Taheri, A. *Tetrahedron Lett.* **2008**, *49*, 5899–5901.