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A facile synthesis of novel dispiroheterocycles through solvent-free microwave-assisted [3+2] cycloaddition of azomethine ylides

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Abstract—A comparative study of the synthesis of novel dispiro pyrrolo/pyrrolizidino ring systems by the cycloaddition of azomethine ylides generated by a decarboxylative route from sarcosine/proline and isatin with the dipolarophile 9-arylidine-fluorene using four different methodologies is described. A solvent-free microwave-assisted approach gave products with the highest yields in a short time. Additionally, our solvent-free approach allowed the use of 4-*N*,*N*-dimethylaminobenzaldehyde, which failed to yield the desired cycloadducts under conventional approaches.

There has been a gradual change from traditional reaction conditions to more environmentally friendly routes.[1–3] This growth of green chemistry holds significant potential for reduction of the by-products, a reduction in waste production and lowering of energy costs. Microwave heating can now be used in reactions for the synthesis of various heterocyclic compounds.[4–6] The most evident improvements are reduced reaction times and cleaner reactions due to fewer side reactions. The intermolecular [3+2] cycloaddition reactions of azomethine ylides with various alkenes and alkynes represent an efficient and convergent method for the construction of pyrrolidine and pyrrolizidine units.[7] Recently, microwave-assisted reaction of intermolecular [3+2] cycloadditions have been reported.[8]

Functionalised pyrrolidine, pyrrolizidine and oxindole alkaloids constitute classes of compounds with significant biological activity and the spiro oxindole ring system is a structural feature found in a variety of oxindole alkaloids.[9,10] Several oxindole derivatives are known to possess antibacterial, antiprotozoal and anti-inflammatory activities.[11] Spirooxindoles have been reported to behave as aldose reductase, poliovirus and rhinovirus 3C-proteinase inhibitors.[12]

As a part of our endeavour[13–15] to synthesise novel dispiro oxindole derivatives, we have examined 1,3-dipolar cycloaddition reactions of the unusual dipolarophiles 9-arylidene fluorenes, with the dipoles generated from isatin and cyclic and acyclic secondary amino acids, namely, sarcosine and proline.[16] The azomethine ylides so generated were reacted with the dipolarophiles under four different conditions to afford a series of novel dispiro oxindole derivatives **4a**–**f** and **7a**–**f**. The structures of the dispiro oxindole derivatives were confirmed through spectral analysis.[17]

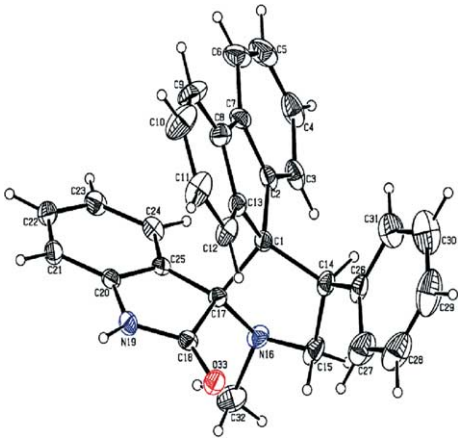

Figure 1. ORTEP diagram of **4a**.

Keywords: Azomethine ylide; Cycloaddition; Dispiro oxindole.
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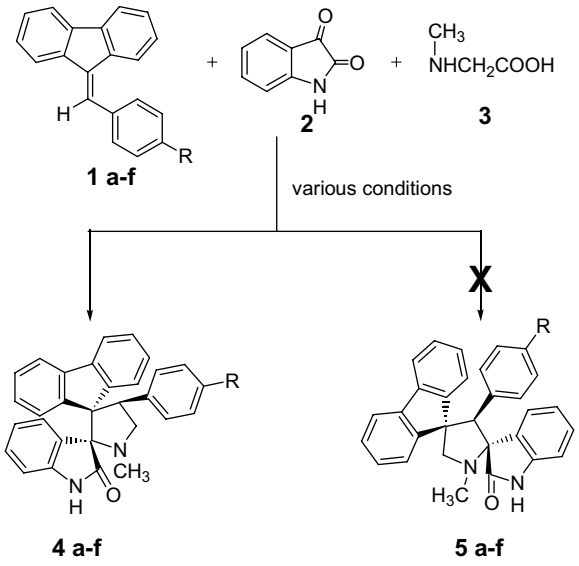
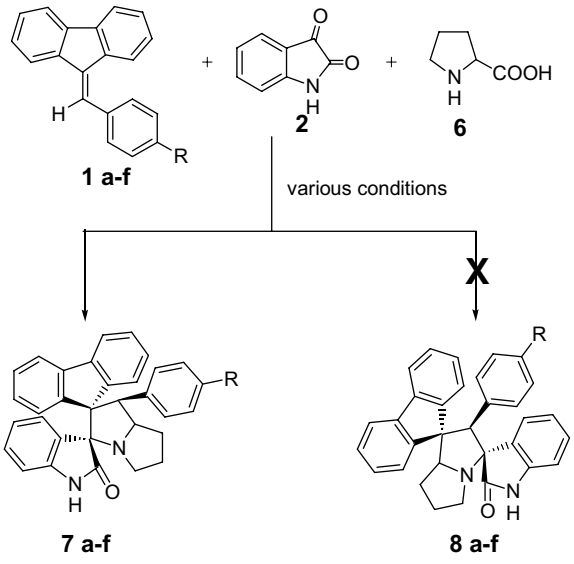


Scheme 1.



Scheme 2.

R: (a) H; (b) Me; (c) OMe; (d) Cl; (e) NO_2; (f) $N(CH_3)_2$

4	Method A		Method B		Method C		Method D	
	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
a	5.0	50	5.0	54	2.5	85	2.0	87
b	7.0	52	4.2	58	3.0	80	4.0	82
c	6.5	58	6.5	56	4.5	78	4.5	79
d	6.0	60	4.5	64	5.0	89	6.0	83
e	5.5	62	5.0	68	2.0	90	2.0	92
f	8.0	3	7.0	14	3.0	86	3.5	90

Method A: Conventional methanol/reflux; Method B: methanol/MW; Method C: K-10 Montmorillonite/MW; Method D: neat/MW.

4	Method A		Method B		Method C		Method D	
	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
a	3.0	65	3.5	68	2.0	87	1.0	90
b	3.5	60	4.0	62	3.5	84	2.5	89
c	2.5	64	4.2	59	4.0	78	3.0	80
d	3.0	70	3.2	72	5.5	83	1.5	94
e	2.0	78	2.7	80	2.0	90	0.5	96
f	4.5	4	5.0	20	6.0	88	3.2	92

Method A: Conventional methanol/reflux; Method B: methanol/MW; Method C: K-10 Montmorillonite/MW; Method D: neat/MW.

The IR spectrum of the pyrrolo-oxindole derivative **4b** showed a peak at 1710 cm^{-1} due to the oxindole carbonyl group. The ^1H NMR spectrum of **4b** demonstrated a singlet at δ 2.39 for the N–CH_3 protons and another singlet at δ 2.11 for the C–CH_3 protons. The N–CH_2 protons of the pyrrolidine moiety resonated as two doublets of doublets at δ 3.76 and 4.40. The benzylic proton exhibited a doublet of doublets at δ 4.65 (J = 9.8, 8.7 Hz). The ^{13}C NMR spectrum of **4b** showed two peaks at δ 68.5 and 78.9 ppm due to the two spiro carbons. The amide carbonyl carbon resonated at δ 177.0 ppm. The structure of the product was further confirmed through mass spectra. The structure of **4a** was finally confirmed by X-ray diffraction studies (Fig. 1).

Similarly, the IR spectrum of pyrrolizidino-oxindole derivative **7b** showed a peak at 1706 cm^{-1} due to the oxindole carbonyl group. The ^1H NMR spectrum of **7b** showed a multiplet in the region 1.82–2.93 for the pyrrolizidine ring protons. The phenyl substituted methyl protons resonated as a sharp singlet at δ 2.03. The benzylic proton resonated as a doublet at δ 4.13 (J = 10.2 Hz). The ^{13}C NMR spectrum of **7b** showed two peaks at δ 69.1 and 74.8 ppm for the two spiro carbons. The amide carbonyl carbon resonated at δ

178.4 ppm. The structure of the product was further confirmed through mass spectra.

Schemes 1 and 2 suggest multicomponent reactions involving isatin, and proline/sarcosine with various *p*-substituted (*E*) arylidene fluorenes for the synthesis of the dispiro oxindole derivatives. The reactions were performed under four different sets of reaction conditions.

Conventional alcohol reflux afforded moderate yields at best, 50–60% and required longer reaction times. The arylidene fluorene with a *p*-$N(CH_3)_2$ substituent did not react under these conditions.

Similar examination of [3+2] cycloadditions using methanol under microwave irradiation gave a slight improvement of yields. However, difficulties were still encountered when using the $-N(CH_3)_2$ derivative.

In our final series of experiments, we examined the equivalent solvent-free reaction, simply by gentle grinding of the three components with and without K-10 Montmorillonite clay irradiation of the mixture under microwave conditions. This afforded the anticipated cycloadducts in excellent yields with high regio and stereoselectivity and also of sufficient purity. The arylidene fluorene with a *p*-$N(CH_3)_2$ substituent also reacted under these conditions to give the corresponding cycloadduct in good yield.

In conclusion, we have shown that it is possible to apply the tenets of green chemistry for the generation of novel dispiro oxindoles via [3+2] cycloaddition of azomethine ylides.

Acknowledgement

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16. Representative procedure for the preparation of dispiro pyrrolidine/pyrrolizidine derivatives.
Method A: A solution of isatin (1 mmol), sarcosine/proline (1 mmol) and 9-arylidene fluorene (1 mmol) was refluxed in methanol. Completion of the reaction was evidenced by TLC analysis. The solvent was removed in vacuo. The crude product was subjected to column chromatography using petroleum ether–ethyl acetate (8:2) as eluent.
Method B: A solution of isatin (1 mmol), sarcosine/proline (1 mmol) and 9-arylidene fluorene (1 mmol) in methanol was irradiated under microwave conditions (600 W). After completion of the reaction, the solvent was evaporated and the crude product was subjected to column chromatography using petroleum ether: ethyl acetate (8:2) as eluent.
Method C: A mixture of isatin (1 mmol), sarcosine/proline (1 mmol) and 9-arylidene fluorene (1 mmol) were ground with K-10 Montmorillonite clay and irradiated under microwave conditions (600 W). After completion of the reaction, the product was extracted with dichloromethane, the organic layer dried over $MgSO_4$, the solvent removed in vacuo and the residue crystallised from methanol.
Method D: A mixture of isatin (1 mmol), sarcosine/proline (1 mmol) and 9-arylidene fluorene (1 mmol) were ground and irradiated under microwave condition. After completion of the reaction, the mixture was allowed to stand at room temperature until it solidified and the product was recrystallised from methanol.
17. Fluorene spiro[9.3′]-1-*N*-methyl (4′-phenyl)-pyrrolidine-spiro[2′.3″]-oxindole **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.78 (dd, $J = 9.9$, 7.4 Hz, 1H), 4.45 (dd, $J = 8.6$, 7.4 Hz, 1H), 4.67 (dd, $J = 9.9$, 8.6 Hz, 1H), 6.46–7.5 (m, 17H); ^{13}C NMR δ 36.1, 51.1, 56.3, 68.2, 79.7, 109.6, 118.8, 119.0, 121.3, 125.3, 125.9, 126.2, 126.3, 126.5, 127.2, 127.3, 127.7, 128.8, 129.1, 137.7, 140.5, 141.2, 141.2, 142.3, 177.4; IR (KBr): 1705 cm^{-1}; Mass *m/z*: 428.3 (M^+); Anal. Calcd for $C_{30}H_{24}N_2O$: C, 84.11; H, 5.64; N, 6.54. Found: C, 84.36; H, 5.75; N, 6.24. Fluorene-spiro[9.2′]-(1′-phenyl)-pyrrolizidine-spiro [3′.3″]-oxindole **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84–2.49 (m, 7H), 4.15 (d, $J = 9.6$ Hz, 1H), 6.3–8.4 (m, 17H); ^{13}C NMR δ 14.7, 30.3, 32.4, 46.5, 57.3, 68.9, 74.8, 110.6, 118.9, 119.0, 120.8, 124.6, 125.8, 126.0, 126.5, 127.1, 127.7, 127.8, 128.3, 128.5, 129.1, 130.3, 135.3, 139.9, 141.1, 142.0, 142.2, 178.3; IR (KBr): 1710 cm^{-1}; Mass *m/z*: 454 (M^+); Anal. Calcd for $C_{32}H_{26}N_2O$: C, 84.58; H, 5.73; N, 6.16. Found: C, 84.43; H, 5.53; N, 6.51.