Synthesis of Spiropyrrolidines and Spiropyrrolizidines by Azomethine Ylide Cycloaddition of Baylis–Hillman Adducts Derived from *N*-Methyl Maleimide

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Abstract: The stereoselective synthesis of a series of novel spiropyrrolidines and spiropyrrolizidines has been accomplished through an intermolecular 1,3-dipolar cycloaddition of an azomethine ylides with dipolarophiles derived from the Baylis–Hillman reaction of isatins with *N*-methyl maleimide.

Key words: Baylis–Hillman reaction, azomethine ylide cycloaddition, spiropyrrolidines, spiropyrrolizidines

The Baylis–Hillman reaction, one of the most atom-economical and important carbon–carbon bond-forming reactions,[1,2] has made great progress recently in the areas of shortening reaction time, extending the scope of the substrates, asymmetric catalysis, and mechanistic studies.[3–5] Isatin and a number of its derivatives posses a reactive keto-carbonyl group that readily undergoes condensation reactions under mild conditions.[6] It was therefore speculated that isatin would be a suitable electrophilic component for the Baylis–Hillman reaction.[7] The 1,3-dipolar cycloaddition reaction is one of the efficient methods for the construction of heterocyclic units in a highly regioselective and stereoselective manner.[8] In particular, the chemistry of azomethine ylides has gained significance in recent years as it serves as an expedient route for the construction of nitrogen containing five-membered heterocycles, which constitute the central skeleton of numerous natural products.[9,10]

The 1,3-dipole (azomethine ylide) generated by the decarboxylative condensation of isatin and secondary amino acid reacts with dipolarophiles to afford novel spiropyrrolidine or spiropyrrolizidine ring systems.[11] The pyrrolidine moiety is one of the significant core structures among the most extensively studied natural and unnatural heterocyclic compounds with remarkable medicinal activities.[12] In particular, pyrrolidine and its fused derivatives, such as pyrrolizidines and indolizidines, have played a unique role in the design and synthesis of novel biologically active compounds. The spiropyrrolidine framework is an integral part of many natural products such as horsfiline,[13a] elacomine,[13b] alstonisine,[13c] spirotryprostatin A[13d] (Figure 1). In addition spiropyrrolidines have been shown to posses anticancer, antimicrobial, antibiotic, and antineoplastic properties.[14–16]

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In continuation of our research in the area of 1,3-dipolar cycloadditions[17] and Baylis–Hillman chemistry,[18] we herein report a simple and convenient route for the regio- and stereoselective synthesis of spiropyrrolidine and spiropyrrolizidine frameworks using the Baylis–Hillman adducts derived from maleimides and isatins with sarcosine/proline-based dipoles generated via in situ imine formation, decarboxylation, and intermolecular [3+2] cycloaddition.

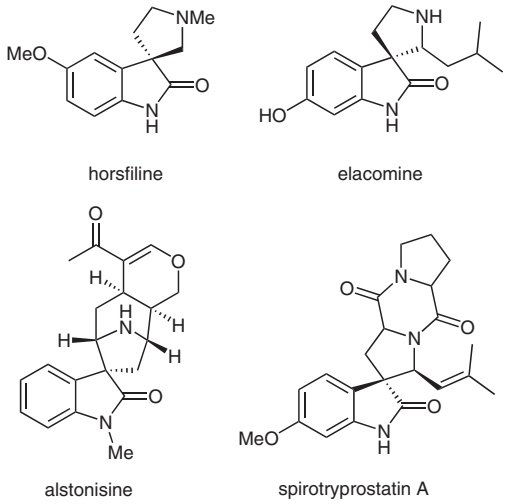
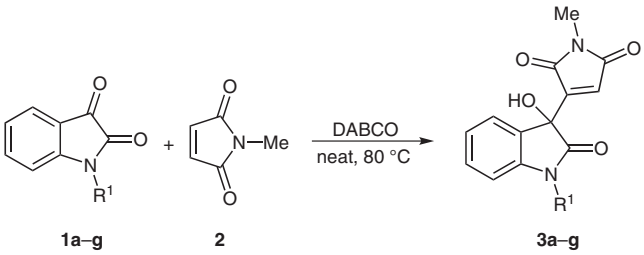


Figure 1

Thus, we synthesized Baylis–Hillman adducts **3a** by the reaction of isatin **1a** with *N*-methyl maleimide **2** in the presence of 30 mol% DABCO at 80 °C under neat conditions (Scheme 1). The reaction yielded Baylis–Hillman adducts **3a** in 79%. Further we have performed the reaction in the presence of solvents like MeOH, THF, and DMSO. The yield was very low. Even when the catalytic amount of DABCO was increased up to 50 mol%, there was no change in the yield.

The structure of the Baylis–Hillaman adduct **3a** was confirmed through NMR and mass spectral analysis.[19] In the ^{1}H NMR spectrum of **3a**, the NMe groups in pyrrolidine and oxindole rings appeared as two singlets at δ = 2.88 and 3.25 ppm, respectively. The proton singlet at δ = 6.77 ppm was assigned to olefinic proton. The OH proton appeared as a broad singlet at δ = 4.73 ppm. In ^{13}C NMR, peaks at δ = 168.9, 169.5, and 174.5 ppm were assigned to amide carbonyl carbons. The mass spectrum revealed the molecular ion peak $[M + H]^+$ at *m/z* = 273.

Under the above conditions the reactions of various substituted isatins **1b–g** with *N*-methyl maleimide **2** were examined and the corresponding Baylis–Hillman adducts **3b–g** were obtained in moderate to good yields (Scheme 1). The results are summarized in Table 1 (entry 1–7). The structure of compound **3f** was further confirmed by single crystal X-ray analysis.[20]



Scheme 1 Synthesis of Baylis–Hillman adducts **3a–g**

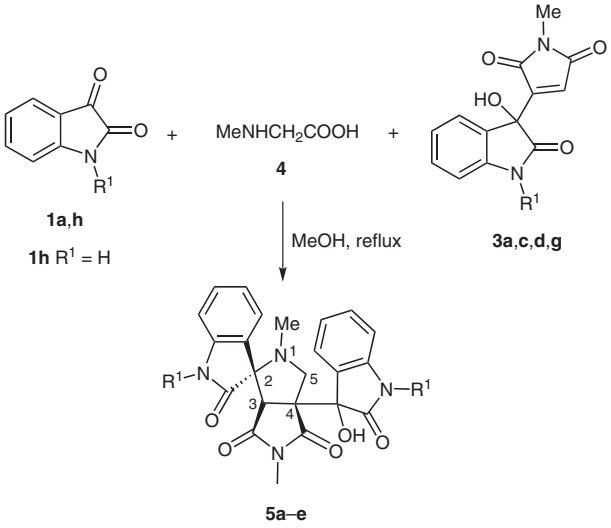
Table 1 Synthesis of Baylis–Hillman Adducts **3a–g**

Entry	Isatin (R^1)		Product	Time (h)	Yield (%)[a]
1	Me	**1a**	**3a**	1.5	79
2	propargyl	**1b**	**3b**	3.0	71
3	Et	**1c**	**3c**	1.5	78
4	All	**1d**	**3d**	2.5	70
5	ethyl metheonate	**1e**	**3e**	4.0	62
6	Bu	**1f**	**3f**	2.0	75
7	Bn	**1g**	**3g**	2.0	72

[a] Isolated yield after column chromatography.

By using the above Baylis–Hillman adducts **3a–g**, we have synthesized spiropyrrolidines and spiropyrrolidizines by azomethine ylide cycloaddition. We first selected Baylis–Hillman adduct **3a** as the starting material for [3+2] cycloaddition with dipoles generated from sarcosine (**4**) and isatin **1a** in methanol for two hours at reflux temperature, which successfully provided the desired spiropyrrolidine **5a** in very good yield (81%, Scheme 2) The compound **5a** was characterized by NMR spectroscopy, mass spectrometry, and elemental analysis.[21]

In the ^{1}H NMR spectrum of compound **5a**, four singlets at δ = 1.99, 2.65, 3.21, and 3.24 ppm were assigned to NMe protons of the two pyrrolidine and two oxindole rings, respectively. The singlet at δ = 3.92 ppm was attributed to C3–H and two doublets at δ = 3.62 (*J* = 11.5 Hz) and 4.32 (*J* = 11.5 Hz) were assigned to protons at C5 carbon. In ^{13}C NMR spectrum, the peak at δ = 74.3 ppm corresponds to the spiro carbon and the amide carbonyl carbons resonated at δ = 174.0, 175.4, 177.1, and 177.6 ppm. The mass spectrum revealed the molecular ion peak $[M + H]^+$ at *m/z* = 461.



Scheme 2 Synthesis of spiropyrrolidines **5a–e**

Encouraged by this result, the reaction of Baylis–Hillman adducts **3a**,**c**,**d**,**g**, isatin **1a**,**h**, and sarcosine **4** in methanol at reflux temperature was carried out to synthesize spiropyrrolidine **5b–e** in 72–81% yields. The results are summarized in Table 2. The structures were further confirmed and stereochemistry was assigned by single crystal X-ray studies of compound **5c**.[22]

Table 2 Synthesis of Spiropyrrolidines **5a–e**

Entry	Dipolarophile **3**	Isatin **1**	Product **5**	Time (h)	Yield (%)[a]
1	**3a**	**1a**	**5a**	2.0	81
2	**3a**	**1h**	**5b**	3.0	76
3	**3d**	**1a**	**5c**	2.5	80
4	**3g**	**1h**	**5d**	3.0	72
5	**3c**	**1h**	**5e**	2.5	78

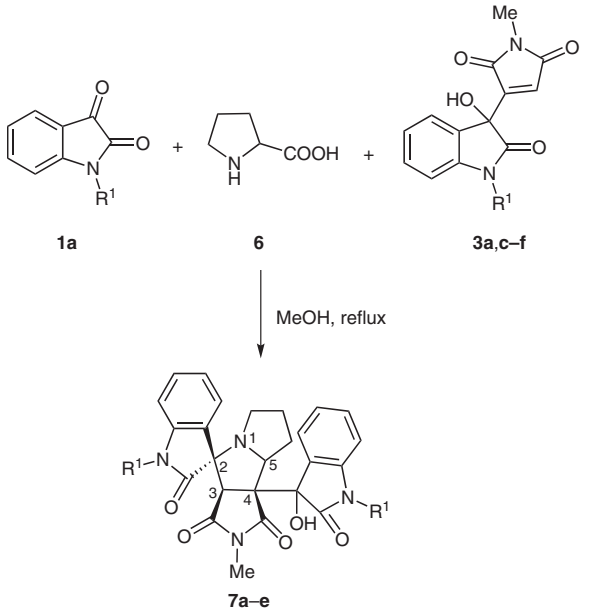
[a] Isolated yield after column chromatography.

To probe further the generality of the reaction, we subjected the Baylis–Hillman adducts **3a**,**c–f** with the dipole generated from isatin and proline in methanol at reflux temperature to synthesize spiropyrrolizidines **7a–e** in 70–86% (Scheme 3). The results are summarized in Table 3.

Table 3 Synthesis of Spiropyrrolizidines **7a–e**

Entry	Dipolarophile **3**	Isatin **1**	Product **7**	Time (h)	Yield (%)[a]
1	**3a**	**1a**	**7a**	1.0	86
2	**3c**	**1a**	**7b**	2.5	75
3	**3d**	**1a**	**7c**	2.5	70
4	**3e**	**1a**	**7d**	1.5	74
5	**3f**	**1a**	**7e**	2.0	81

[a] Isolated yield after column chromatography.



Scheme 3 Synthesis of spiropyrrolizidines **7a–e**

The structure of the spiropyrrolizidine derivatives **7a–e** were confirmed by spectral analyses.[23] The ^{1}H NMR spectrum of compound **7b**, two singlets at δ = 2.70 and 3.21 ppm were assigned to MMe protons of pyrrolidine and oxindole ring, respectively. The singlet at δ = 4.15 ppm corresponds to C3–H and triplet at δ = 4.76 (*J* = 6.9 Hz) ppm was assigned to C5–H. In the ^{13}C NMR spectrum, peak at δ = 75.3 ppm corresponds to the spiro carbon and the amide carbonyl carbons resonated at δ = 174.3, 175.0, and 177.2 ppm. The mass spectrum revealed the molecular ion peak $[M + H]^+$ at *m/z* = 501.

In summary, we have successfully developed a simple and novel protocol for the synthesis of Baylis–Hillman adducts from isatins and *N*-methyl maleimide under neat conditions. Further we have used Baylis–Hillman adducts as a dipolarophiles to synthesize novel spiropyrrolidines and spiropyrrolizidines in good yields.

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(19) **Experimental Procedure for the Synthesis of Baylis–Hillman Adducts 3a–g**

A mixture of isatin **1a**–**g** (1.62 mmol), *N*-methyl maleimide (**2**, 1.35 mmol), and DABCO (30 mol%) was stirred at 80 °C under neat conditions. Completion of the reaction was evidenced by TLC analysis. The residue was dissolved in EtOAc (20 mL) and H_2O washed (2 × 20 mL). The EtOAc layer was dried over anhyd Na_2SO_4, and the solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography with EtOAc–PE (2:8) as an eluent to obtain Baylis–Hillman adducts **3a**–**g**.

Baylis–Hillman Adduct 3a

Colorless solid; mp 148–150 °C. IR: 3368, 3115, 1722, 1610, 1488, 1380, 1162 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.88 (s, 3 H), 3.25 (s, 3 H), 4.73 (br s, 1 H), 6.77 (s, 1 H), 6.91 (d, 1 H, *J* = 7.7 Hz), 7.09 (t, 1 H, *J* = 7.7 Hz), 7.28 (d, 1 H, *J* = 6.9 Hz), 7.38 (t, 1 H, *J* = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8, 26.8, 74.6, 109.4, 123.8, 124.8, 127.5, 128.8, 131.2, 143.9, 147.4, 168.9, 169.5, 174.5. MS: *m/z* = 273 $[M + H]^+$. Anal. Calcd for $C_{14}H_{12}N_2O_4$ (272.08): C, 61.76; H, 4.44; N, 10.29. Found: C, 61.84; H, 4.47; N, 10.16.

(20) Crystallographic data of compound **3f** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication No. CCDC-787472. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].

(21) **Experimental Procedure for the Synthesis of Spiropyrrolidines 5a–e**

A mixture of isatin **1** (1 mmol), sarcosine (**4**, 1.5 mmol), and Baylis–Hillman adducts **3** (1 mmol) was refluxed in MeOH (10 mL). Completion of the reaction was evidenced by TLC analysis. The solvent was removed under vacuo, and the crude product was subjected to column chromatography using EtOAc–PE (2:8) as an eluent to afford pure spiropyrrolidines **5a**–**e**.

3a′-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)-1,2′,5′-trimethyl-3′,3a′-dihydro-2′*H*-spiro{indoline-3,1′-pyrrolo[3,4-*c*]pyrrole}-2,4′,6′(5′*H*,6a′*H*)-trione (5a)

Colorless solid; mp 258–260 °C. IR: 3361, 2963, 1699, 1612, 1471, 1373, 1124 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.65 (s, 3 H), 3.21 (s, 3 H), 3.24 (s, 3 H), 3.62 (d, 1 H, *J* = 11.5 Hz), 3.92 (s, 1 H), 4.32 (d, 1 H, *J* = 11.5 Hz), 5.81 (br s, 1 H), 6.77 (d, 1 H, *J* = 7.7 Hz), 6.82 (d, 1 H, *J* = 7.7 Hz), 6.89–6.93 (m, 2 H), 7.08–7.10 (m, 2 H), 7.26 (t, 1 H, *J* = 6.9 Hz), 7.38 (t, 1 H, *J* = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1, 26.2, 26.4, 34.6, 53.2, 55.0, 63.4, 72.3, 74.3, 108.8, 108.9, 121.8, 123.3, 123.4, 123.9, 126.4, 126.9, 130.4, 130.7, 143.9, 144.1, 174.0, 175.4, 177.1, 177.6. MS: *m/z* = 461 $[M + H]^+$. Anal. Calcd for $C_{25}H_{24}N_4O_5$ (460.17): C, 65.21; H, 5.25; N, 12.17. Found: C, 65.29; H, 5.23; N, 12.24.

(22) Crystallographic data of compound **5c** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication No. CCDC-787473. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].

(23) **Experimental Procedure for the Synthesis of Spiropyrrolizidines 7a–e**

A mixture of isatin **1** (1 mmol), L-proline (**6**, 1.5 mmol), and Baylis–Hillman adducts **3** (1 mmol) was refluxed in MeOH (10 mL). Completion of the reaction was evidenced by TLC analysis. The solvent was removed under vacuo, and the crude product was subjected to column chromatography using EtOAc–PE (2:8) as an eluent to afford pure spiropyrrolizidines **7a**–**e**.

8b′-(1-Ethyl-3-hydroxy-2-oxoindolin-3-yl)-1,2′-dimethyl-6′,7′,8′,8a′-tetrahydro-1′*H*-spiro{indoline-3,4′-pyrrolo[3,4-*a*]pyrrolizine}-1′,2,3′(2′*H*,3a′*H*,8b′*H*)-trione (7b)

Brown solid; mp 230–232 °C. IR: 3342, 2935, 1705, 1610, 1468, 1371, 1089 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, 3 H, *J* = 6.9 Hz), 1.72–1.79 (m, 1 H), 1.87–1.91 (m, 3 H), 2.14–2.18 (m, 1 H), 2.31–2.36 (m, 1 H), 2.70 (s, 3 H), 3.21 (s, 3 H), 3.63–3.69 (m, 1 H), 3.80–3.86 (m, 1 H), 4.16 (s, 1 H), 4.76 (t, 1 H, *J* = 6.9 Hz), 5.66 (br s, 1 H), 6.78 (d, 1 H, *J* = 7.7 Hz), 6.86 (t, 2 H, *J* = 8.4 Hz), 6.93 (t, 1 H, *J* = 7.7 Hz), 7.06 (t, 1 H, *J* = 6.9 Hz), 7.17 (d, 1 H, *J* = 6.9 Hz), 7.26 (t, 1 H, *J* = 7.7 Hz), 7.35 (t, 1 H, *J* = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 24.6, 24.9, 25.8, 26.3, 35.0, 42.3, 58.5, 62.2, 65.0, 66.9, 75.0, 108.7, 108.8, 122.5, 122.9, 124.2, 124.3, 126.4, 127.6, 130.2, 130.5, 143.4, 143.7, 174.3, 175.0, 177.2. MS: *m/z* = 501 $[M + H]^+$. Anal. Calcd for $C_{28}H_{28}N_4O_5$ (500.21): C, 67.19; H, 5.64; N, 11.19. Found: C, 67.42; H, 5.66; N, 11.40.