Novel Regio- and Stereoselective Synthesis of Functionalized 3-Spiropyrrolidines and 3-Spiropyrrolizidines Using the Baylis–Hillman Adducts Derived from Nitroolefins

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Received 2 October 2008

Abstract: A facile regio- and stereoselective synthesis of functionalized 3-spiropyrrolidines and 3-spiropyrrolizidines using the Baylis–Hillman adducts derived from nitroolefins via intermolecular [3+2] cycloaddition reaction is reported.

Key words: Baylis–Hillman reaction, intermolecular [3+2] cycloaddition, azomethine ylides, 1,3-dipolar cycloaddition, spiro compounds

The Baylis–Hillman reaction is an important carbon–carbon bond-forming reaction which is atom economical and simple providing densely functionalized molecules.[1–5] Due to the multifunctionality of Baylis–Hillman adducts they represent valuable starting materials for a variety of novel classes of organic compounds.

The spiropyrrolidine framework is an integral part of many natural products such as horsfiline (**1**),[6] elacomine (**2**),[7] alstonisine (**3**),[8] and spirotryprostatin A (**4**)[9] (Figure 1). In addition spiropyrrolidines have been shown to posses anticancer, antimicrobial, antibiotic, and antineoplastic properties.[10–12]

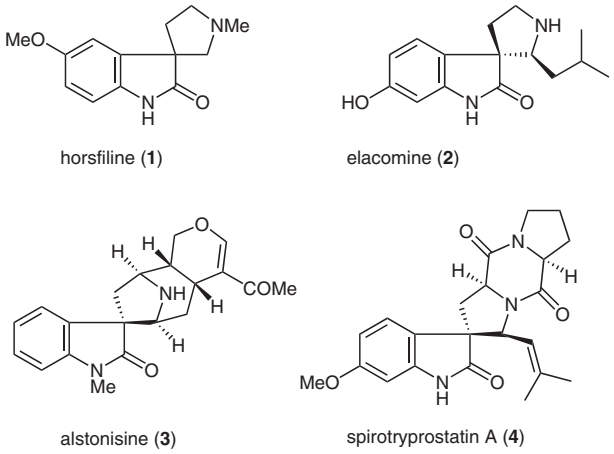


Figure 1

The synthesis of nitrogen- and oxygen-containing heterocycles continues to be an important and challenging area in the field of organic chemistry.[13–16] The 1,3-dipolar cycloaddition reaction is one of the most important and useful methods for the preparation of five-membered heterocycles. The reaction of azomethine ylides with alkenes provides the pyrrolidine moiety which is present in numerous natural products and biologically active molecules.[17,18a] Utilizing azomethine ylide based [3+2] cycloaddition reaction, a variety of spiropyrrolidines have been reported in the literature.[18a–18e]

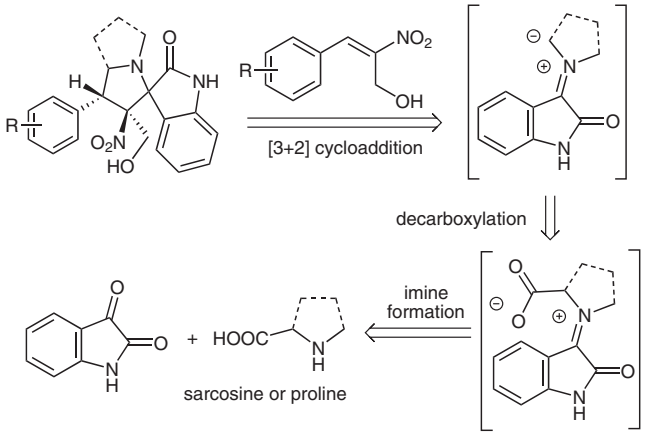
In the Baylis–Hillman reaction electron-deficient olefins are utilized although nitroolefins have only been used as the activated olefinic component in a couple of reports.[19] Recently a novel type of Baylis–Hillman adduct **5** derived from β-substituted nitroolefins has been reported.[19b] but so far no further transformations have been studied.

We envisaged that this novel class of β-substituted Baylis–Hillman adduct **5** derived from β-aryl nitroolefins would be a useful starting material for the construction of spiropyrrolidine compounds via azomethine ylide based [3+2] cycloaddition. It is well documented in the literature that Baylis–Hillman adducts have been utilized for the synthesis of various heterocycles[1,3,20] but the synthesis of heterocyclic spiro compounds using Baylis–Hillman adducts derived from nitroolefins was not known to date.

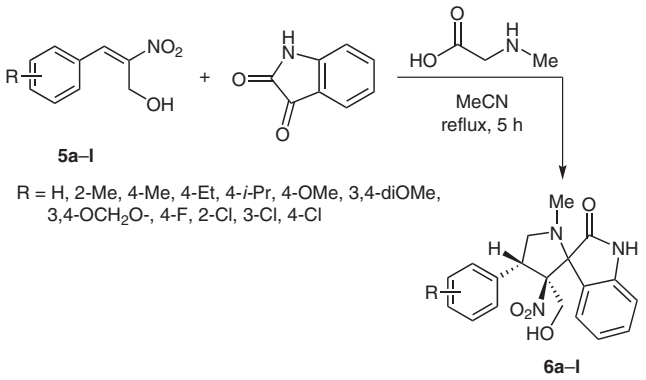
In continuation of our interest in the field of Baylis–Hillman chemistry,[21–24] we herein report a simple and convenient route for the regio- and stereoselective synthesis of 3-spiropyrrolidine and 3-spiropyrrolizidine frameworks using the Baylis–Hillman adducts derived from nitroolefins with sarcosine/proline-based dipoles generated via in situ imine formation, decarboxylation, and intermolecular [3+2] cycloaddition as shown below in the retrosynthetic strategy (Scheme 1).

We first selected (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**5a**), a Baylis–Hillman adduct derived from nitrostyrene, as a starting material for [3+2] cycloaddition reaction with dipoles generated from sarcosine with isatin. Best results were obtained when **5a** was treated with isatin and sarcosine without any catalyst in acetonitrile as solvent for 5 hours at reflux temperature, which successfully provided the desired 3-spiropyrrolidine compound **6a** in very good yield (82%) after usual workup followed by column chromatography. The compound **6a** was characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis (Scheme 2).

SYNLETT 2009, No. 6, pp 1014–1018
Advanced online publication: 16.03.2009
DOI: 10.1055/s-0028-1088206; Art ID: D34808ST



Scheme 1



Scheme 2

Encouraged by this result, we prepared a variety of (*E*)-2-nitro-3-arylprop-2-en-1-ols **5b–l** as starting materials for the preparation of 3-spiropyrrolidine compounds. As before treatment of these with isatin and sarcosine in acetonitrile for five hours at reflux temperature successfully led to the desired 3-spiropyrrolidine compounds **6b–l** in 60–80% yields (Scheme 2). The results are summarized in Table 1.

Worthy of note was the high regio- and stereoselectivity obtained in the each case, which was clearly evidenced by ^{1}H NMR data and X-ray crystal analysis.[25] The ^{1}H NMR spectrum of compound **6a** showed a singlet for NCH_3 proton at δ = 2.18 ppm and triplet for benzylic proton at δ = 4.97 ppm. The NCH_2 protons of pyrrolidine ring appeared as two triplets at δ = 3.53 and 4.04 ppm. The O-attached CH_2 protons appeared as multiplet in the region of δ = 3.75–3.94. The NH proton of oxindole ring appeared at δ = 7.74 ppm. The aromatic protons appeared in the region of δ = 6.82–7.57 ppm.

Had the other regioisomer been formed, the benzylic proton should have been appeared as singlet which we did not observe in any of the cases **6a–l**. Comparison of the ^{1}H NMR spectra of the crude and recrystallized products showed them to be identical which confirming the stereoselectivity of the reaction. Furthermore the structure **6a** was confirmed by X-ray crystallographic analysis.

Table 1 Synthesis of 3-Spiropyrrolidine Compounds from the Baylis–Hillman Adducts[a]

Allyl alcohol	R	Product[b]	Yield (%)[c]
5a	H	**6a**[d]	82
5b	2-Me	**6b**	75
5c	4-Me	**6c**	76
5d	4-Et	**6d**	77
5e	4-*i*-Pr	**6e**	60
5f	4-OMe	**6f**	61
5g	3,4-di-OMe	**6g**	62
5h	3,4-OCH_2O	**6h**	60
5i	4-F	**6i**	64
5j	2-CI	**6j**	80
5k	3-CI	**6k**	64
5l	4-CI	**6l**	70

[a] All reactions were carried out using Baylis–Hillman alcohol **5a–l** (2 mmol) with sarcosine (2 mmol) and isatin (2 mmol) in MeCN (8 mL) under reflux conditions for 5 h.
[b] All products gave satisfactory IR, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), mass spectrometry, and elemental analyses.
[c] Yields of the pure products **6a–l** obtained after column chromatography (SiO_2, 20% EtOAc in hexanes).
[d] Structure was further confirmed by single-crystal X-ray analysis.

The X-ray crystal-structure analysis of compound **6a** showed that the relative stereochemistry (Figure 2) of the phenyl group and CH_2OH group in the vicinal positions is *cis*. Similarly the NO_2 group and benzylic proton are also in a *cis* orientation.

To probe further the generality of the reaction, we subjected adducts **5a–d,j,l** with the dipole generated from isatin and proline. Best results were obtained when **5a–d,j,l** were treated with isatin and proline without catalyst in acetonitrile as solvent for two hours at reflux temperature,

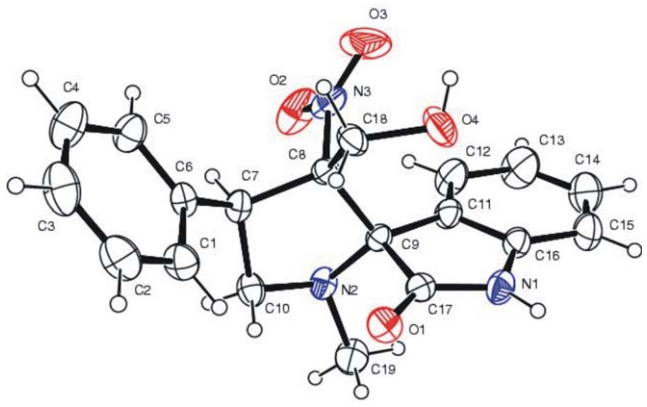


Figure 2 ORTEP diagram of **6a**

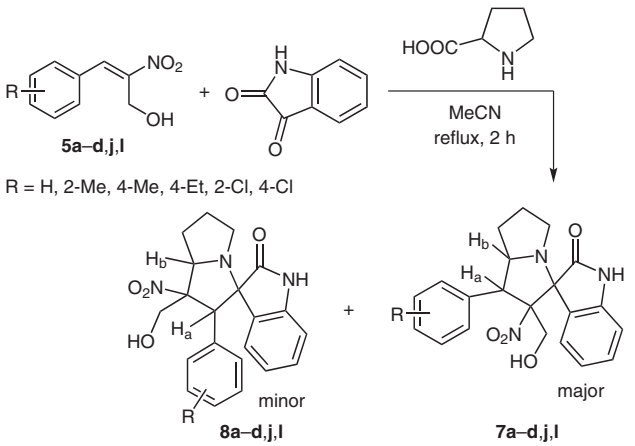
Table 2 Synthesis of 3-Spiropyrrolizidine Compounds from the Baylis–Hillman Adducts[a]

Allyl alcohol	R	Product[b]	Yield (%)[c]	Product[b]	Yield (%)[c]	Yield of **7** + **8** (%)
5a	H	**7a**	52	**8a**	33	85
5b	2-Me	**7b**	65	**8b**	25	90
5c	4-Me	**7c**	59	**8c**	35	94
5d	4-Et	**7d**[d]	52	**8d**	37	89
5j	2-CI	**7j**	60	**8j**	20	80
5l	4-CI	**7l**	62	**8l**	31	93

[a] All reactions were carried out using Baylis–Hillman alcohol **5a–d,j,l** (2 mmol) with proline (2 mmol) and isatin (2 mmol) in MeCN (8 mL) under reflux conditions for 2 h.
[b] All products gave satisfactory IR, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), mass spectrometry, and elemental analyses.
[c] Yields of the pure products **7a–d,j,l** and **8a–d,j,l** obtained after column chromatography (SiO_2, **7a–d,j,l**: 30% EtOAc in hexanes; **8a–d,j,l**: 40% EtOAc in hexanes).
[d] Structure was further confirmed by single-crystal X-ray analysis.

successfully provided the desired 3-spiropyrrolizidine compounds **7a–d,j,l** in good yields (52–65%) along with other regioisomers **8a–d,j,l** in 20–37% yields (Scheme 3). The compounds **7a–d,j,l** and **8a–d,j,l** were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analyses (Scheme 3). The results are summarized in Table 2.

The NMR data and X-ray crystal-structure analysis[25] showed that the proline- and isatin-based [3+2] cycloaddition reaction with the BH adducts yielded regioisomeric compounds that were successfully separated by column chromatography.



Scheme 3

The ^{1}H NMR spectrum of compound **7a** showed a doublet for H_a proton at δ = 4.29 ppm and the H_b proton appeared as multiplet in the region of δ = 4.47–4.56 ppm. The pyrrolidine ring protons appeared as multiplets in the region of δ = 1.50–2.76 ppm. The hydroxymethylene protons appeared as a multiplet in the region of δ = 4.39–4.44 ppm and a doublet of doublet at δ = 4.98 ppm.

The ^{1}H NMR spectrum of compound **8a** showed a singlet for the H_a proton (benzylic proton) at δ = 5.29 ppm and the

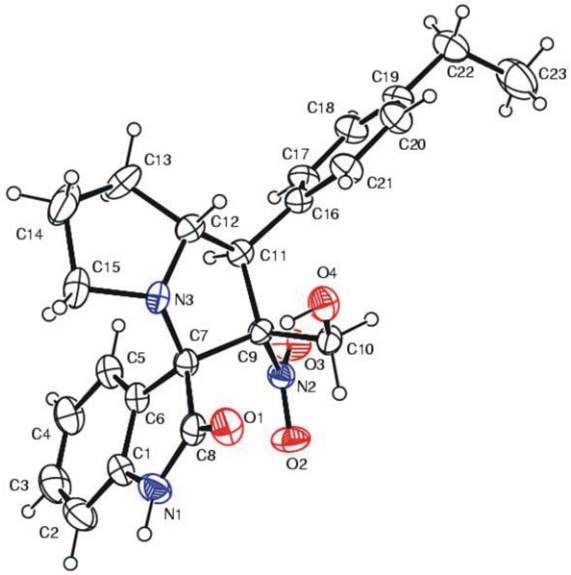
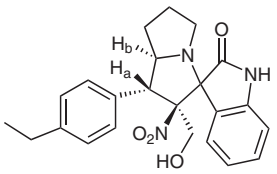


Figure 3 ORTEP diagram of **7d**

H_b proton appeared as a triplet at δ = 4.77 ppm. The pyrrolidine ring protons appeared as multiplets in the region of δ = 1.37–3.30 ppm. Hydroxymethylene protons appeared as two doublet of doublets at δ = 4.15 and 4.49 ppm.

The X-ray crystal structure of the compound **7d** showed that the relative stereochemistry (Figure 3) of the aryl and CH_2OH groups to be *cis*. Similarly the NO_2 group and benzylic proton are also in a *cis* orientation. The benzylic proton (H_a) and pyrrolidizine proton (H_b) at the ring junction are in a *trans* orientation as shown in Figure 4.

In conclusion, we have successfully developed a simple and novel protocol for the facile synthesis of functionalized 3-spiropyrrolidine with high regio- and stereoselectivity. We have also demonstrated that this method is useful for making novel 3-spiropyrrolizidine frameworks using Baylis–Hillman adducts derived from nitroolefins.



7d

Figure 4

Typical Experimental Procedure of 6a

A mixture of (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**5a**, 2 mmol, 0.36 g), isatin (2 mmol, 0.29 g), and sarcosine (2 mmol, 0.18 g) in MeCN (8 mL) was refluxed for 5 h. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated, and the resulting crude mass was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over anhyd Na_2SO_4. The organic layer was concentrated and the residue purified by column chromatography on SiO_2 (Acme 100–200 mesh), using EtOAc–hexanes (2:8) to afford **6a** as a colorless solid in 82% (0.58g) yield.

Typical Experimental Procedure of 7a and 8a

A mixture of (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**5a**, 2 mmol, 0.36 g), isatin (2 mmol, 0.29 g), and L-proline (2 mmol, 0.23 g) in MeCN (8 mL) was refluxed for 2 h. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated, and the resulting crude mass was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer obtained was washed with brine (3 × 10 mL) and dried over anhyd Na_2SO_4. The organic layers were concentrated and purified by column chromatography on SiO_2 (Acme 100–200 mesh), using EtOAc–hexanes (3:7) to provide **7a** as a colorless solid in 52% (0.11 g) yield and **8a** as a colorless solid (Acme 100–200 mesh), using EtOAc–hexanes (4:6) in 33% (0.07 g) yield.

Spectroscopic Data for Selected Compounds

Compound 6a

Mp 160–162 °C. IR (KBr): 3484, 3227, 1717, 1544, 1337 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 2.89 (dd, 1 H, *J* = 2.7, 9.0 Hz), 3.53 (t, 1 H, *J* = 9.0 Hz), 3.78 (dd, 1 H, *J* = 3.0, 10.5 Hz), 3.90–4.07 (m, 2 H), 4.97 (t, 1 H, *J* = 9.0 Hz), 6.82–7.57 (m, 9 H), 7.74 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.77, 49.40, 56.78, 64.17, 77.23, 105.05, 110.15, 123.38, 124.46, 125.20, 128.18, 128.78, 129.99, 130.48, 134.75, 141.55, 176.06. MS: *m/z* = 354 [M^+ + 1]. Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.56; H, 5.39; N, 11.94.

Compound 7a

Mp 148–150 °C. IR (KBr): 3463, 3197, 1709, 1540, 1336 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.62 (m, 1 H), 1.87–2.10 (m, 3 H), 2.48–2.56 (m, 1 H), 2.69–2.76 (m, 1 H), 3.87 (t, 1 H, *J* = 12.0 Hz), 4.27 (d, 1 H, *J* = 10.2 Hz), 4.39–4.56 (m, 2 H), 4.95 (dd, 1 H, *J* = 3.6, 8.1 Hz), 6.87–7.81 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.88, 32.74, 47.89, 56.59, 64.51, 69.88, 78.03, 105.54, 111.22, 122.96, 124.98, 125.52, 127.99, 128.56, 130.70, 130.88, 134.19, 140.86, 179.78. MS: *m/z* = 380 [M^+ + 1]. Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.41; H, 5.46; N, 11.14.

Compound 8a

Mp 170–172 °C. IR (KBr): 3467, 3185, 1709, 1535, 1345 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.50 (m, 1 H), 1.80–2.05 (m, 2 H), 2.71–2.31 (m, 2 H), 2.67 (td, 1 H, *J* = 2.4, 5.4 Hz), 3.26 (q, 1 H, *J* = 8.4 Hz), 4.15 (dd, 1 H, *J* = 4.5, 8.7 Hz), 4.49 (t, 1 H, *J* = 10.5 Hz), 4.78 (t, 1 H, *J* = 5.4 Hz), 5.29 (s, 1 H), 6.72–7.52 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.04, 27.69, 48.50, 59.23, 65.28, 69.60, 73.67, 104.73, 110.22, 122.73, 125.31, 126.25, 128.33, 128.96, 129.43, 130.01, 131.79, 141.40, 178.87. MS: *m/z* = 380 [M^+ + 1]. Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.42; H, 5.49; N, 11.16.

Acknowledgment

We thank DST (New Delhi) for the financial support under fast track scheme for the young scientists. We thank DST-FIST for the funding program at the Department of Organic Chemistry, University of Madras, Chennai.

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(25) The X-ray crystal structure data of **6a** and **7d** have been deposited at the Cambrigde Crystallographic Data Centre and allocated the deposition numbers CCDC 676397 (**6a**), and CCDC 676668 (**7d**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.