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Synthesis of Novel Functionalized 3-Spiropyrrolizidine and 3-Spiropyrrolidine Oxindoles from Baylis–Hillman Adducts of Isatin and Heteroaldehydes with Azomethine Ylides via [3+2]-Cycloaddition

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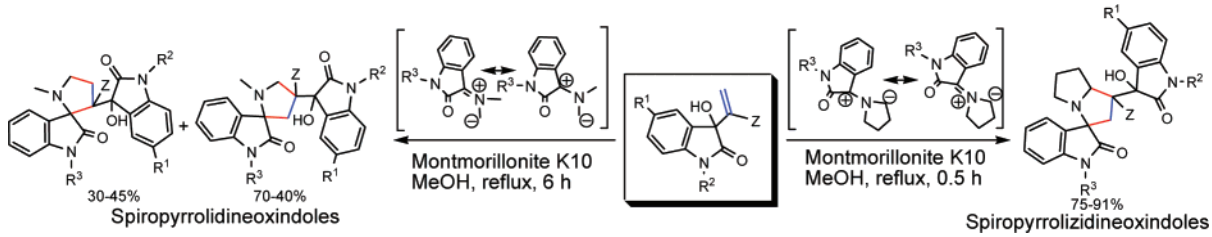
ABSTRACT



A novel regioselective synthesis of a number of functionalized 3-spiropyrrolizidine and 3-spiropyrrolidine oxindoles from Baylis–Hillman adducts of isatin and heteroaldehydes via [3+2] cycloaddition of azomethine ylides in excellent yields has been reported.

Oxindoles derivatized at C3 as spirocarbo- and heterocyclics, spirolactones, and spirocyclic ethers are elegant targets in organic synthesis due to their significant biological activities (Figure 1).[1] These derivatives have been served as potential synthons for the synthesis of alkaloids, drug intermediates, and clinical pharmaceuticals.[1] Hence, a number of synthetic routes have been developed for the expedition of these structural frameworks.[2,3] Azomethine ylides are a class of powerful reagents to utilize in the [1,3]-dipolar cycloaddition reactions which generally afford a range of pharmacologically important heterocyclic compounds.[4] The synthetic versatility of isatin and its derivatives has led to the extensive use of this compound in synthetic organic chemistry.[5] Among various carbon−carbon bond-forming reactions, the Baylis−Hillman reaction is an important reaction giving rise to densely functionalized molecules and is considered to be atom economic.[6] The synthesis of title compounds exploiting Baylis−Hillman adducts of isatin and heteroaldehydes via cycloaddition reaction is unknown. Thus, as part of our research in the area of novel synthetic applications of Baylis−Hillman adducts,[7] particularly with isatin-derived

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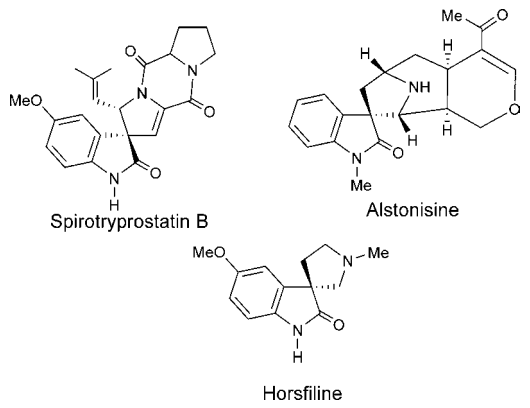
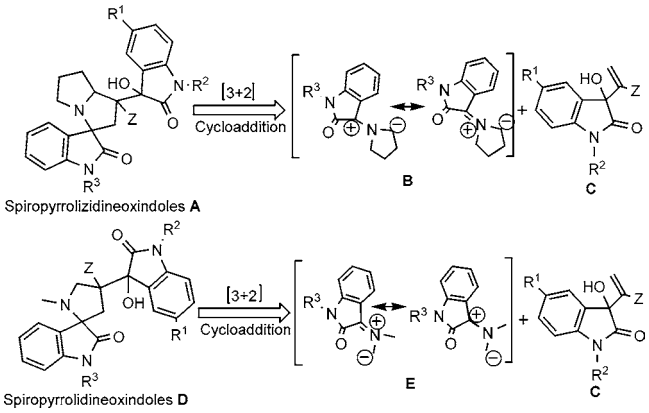


Figure 1. Spirooxindole alkaloid natural products.

Scheme 1. Retrosynthetic Approach for Spiropyrrolizidine and Spiropyrrolidine Oxindole Synthesis



Baylis−Hilman adducts,[8] we explored the [3+2]-cycloaddition reaction of Baylis−Hillman adducts of isatin and heteroaldehydes with azomethine ylides. The reaction afforded novel 3-spiropyrrolizidine and 3-spiropyrrolidine oxindoles. The preliminary results of the study are the content of this letter.

The synthetic strategy for the construction of the title compounds is shown in Scheme 1. Accordingly, the spiropyrrolizidine derivatives of oxindols **A** could be synthesized from the [3+2]-cycloaddition reaction of the Baylis−Hillman adduct of isatin **C** and dipole **B**. Similarly, the spiropyrrolidine derivatives **D** could be synthesized from the dipole **E** and Baylis−Hillman adduct **C**. The dipoles **B** and **E** could be generated in situ from isatin and proline or sarcosine by thermal decarboxylation reaction.

In a prototype experiment, the reaction of the Baylis−Hillman adduct of *N*-methylisatin **1** with in situ generated azomethine ylide **B** (isatin, proline, and eco-friendly montmorillonite K10 clay) in methanol was refluxed for 0.5 h to afford the corresponding spiropyrrolizidine oxindole derivative **8** in 88% yield (Table 1, entry 1). The ^{1}H NMR spectrum of the compound **8** showed a singlet at δ 8.37 and a broad singlet at δ 5.3 due to the hydrogens attached to nitrogen and oxygen at the spiroxindole moiety. Two doublets centered at δ 3.51 and δ 3.26 with a coupling constant J = 14.1 Hz showed the mutually coupled geminal protons at the 2′-carbon of the pyrrolizidine ring.

To check the effect of solvent and catalyst requirements, the reactions in 1,4-dioxane, toluene, and methanol as solvents and with and without montmorillonite K10 clay catalyst were tested. The combination of methanol as a solvent and 100% w/w montmorillonite K10 clay as the catalyst gave better yields and was found as the optimum conditions. Reactions in 1,4-dioxane also provided the same yields as that of methanol, whereas in toluene, poor yields of the products (∼20%) were observed. The adduct of *N*-benzylisatin **2** with dipole **B** under optimized conditions

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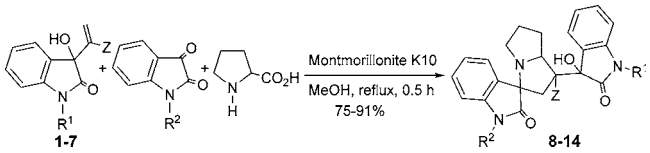
Table 1. Synthesis of Bis[3-spiro-3′-pyrrolizidine]oxindoles from the Baylis−Hillman Adduct of Isatin



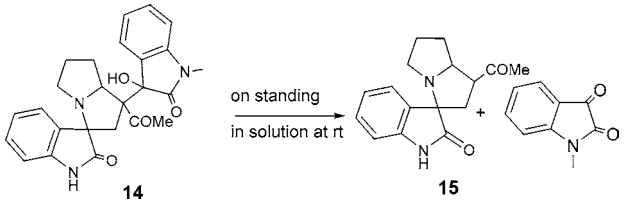
entry	R^1	R^2	Z	yield %
1	methyl	H	CO_2Me	88
2	benzyl	H	CO_2Me	85
3	allyl	H	CO_2Me	90
4	methyl	H	SO_2Ph	75
5	propargyl	H	CO_2Me	89
6	methyl	Me	CN	91[a]
7	methyl	H	COMe	60[b]

[a] Mixture of inseparable regioisomers determined by ^1H NMR. [b] An eliminated product was observed as determined by NMR and mass spectroscopic data.

afforded pyrrolizidine oxindole derivative **9** in 85% yield (Table 1, entry 2). Similarly, other Baylis−Hillman adducts **3**−**7** having different substituents at the heterocyclic nitrogen and at activated alkenes underwent [3+2]-cycloaddition smoothly with dipole **B** and afforded the corresponding spiropyrrolizidine oxindoles **10**−**14** in excellent yields. All the compounds were thoroughly characterized by spectroscopic methods (IR, ^1H, ^{13}C NMR and FAB-mass spectra). The results are summarized in Table 1.

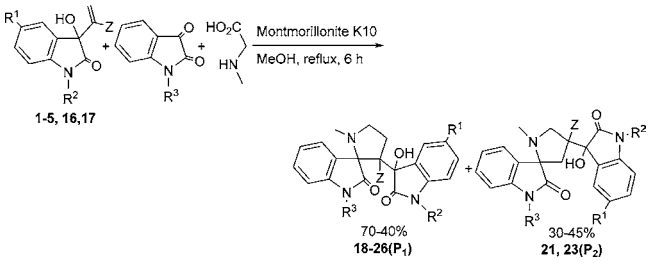
It was noticed that the bis[3-spiro-3′-pyrrolizidine]oxindole **14** is unstable in solution at room temperature and underwent elimination to give spiropyrrolizidine oxindole **15**. However, the compound was found stable when it was stored as crystalline solid. The observation was evidenced from its proton NMR and mass spectral data. The transformation is shown in Scheme 2.

Scheme 2. Elimination of *N*-Methylisatin from **14**



Subsequent to the preliminary study, we extended the study to [3+2]-cycloaddition reaction of Baylis−Hillman adducts **1**−**5**, **16**, and **17** with azomethine ylide **E** derived from sarcosine under optimized reaction conditions to afford spiropyrrolidine oxindole derivatives **18**−**26** in excellent yield. Interestingly, in addition to the major pyrrolidine oxindoles, other regioisomers **21** and **23** were isolated from the reaction of azomethine ylide **E** with *N*-allyl and *N*-propargyl isatin derivatives of Balyis−Hillman adducts (Table 2, entries 3 and 4), respectively. The presence of a

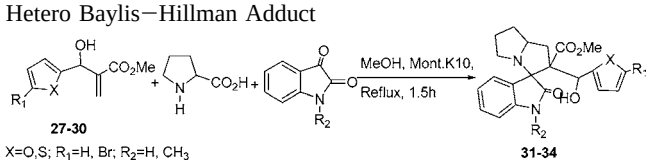
Table 2. Synthesis of Bis[3-spiro-3′-pyrrolidine]oxindoles from the Baylis−Hillman Adduct of Isatin



					yield %	
entry	R^1	R^2	R^3	Z	P_1	P_2
1	H	methyl	Me	CO_2Me	70	–
2	H	benzyl	H	CO_2Me	65	–
3	H	allyl	H	CO_2Me	40	35
4	H	propargyl	H	CO_2Me	40	36
5	H	methyl	Me	CN	65	–
6	Br	H	Me	CO_2Me	70	–
7	NO_2	methyl	H	CO_2Me	60	–

free hydoxyl proton and *N*-H protons in the products was confirmed by D_2O exchange experiments. The results are summarized in Table 2.

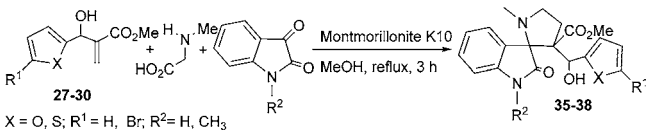
Table 3. Synthesis of 3-Spiropyrrolizidine Oxindoles from the Hetero Baylis−Hillman Adduct



entry	X	R^1	R^2	yield %
1	O	H	H	80
2	O	Br	H	60
3	O	H	CH_3	35
4	S	H	H	25

Having excellent preliminary results, we then turned our attention to examine the reaction of Baylis−Hillman adducts

Table 4. Synthesis of 3-Spiropyrrolidine Oxindoles from the Hetero Baylis−Hillman Adduct

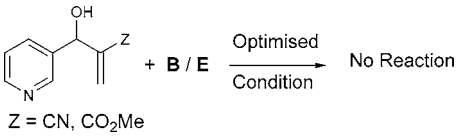


entry	X	R^1	R^2	yield %
1	O	H	H	68
2	O	Br	H	50
3	O	H	CH_3	30
4	S	H	H	22

27−**30** derived from heteroaromatic aldehydes and azomethine ylides **B** and **E**. These reactions under optimized reaction conditions furnished novel spiropyrrolizidine oxindoles **31**−**34** and spiropyrrolidine oxindole derivatives **35**−**38** with 3′-heterocyclic (furan/thiophene) substituents, respectively, in moderate to good yields. The results are collected in Tables 3 and 4.

To our surprise, extension of the methodology to the reaction of the Baylis−Hillman adduct of pyridine-3-aldehyde with azomethine ylides **B** or **E** remined unaffected, and the reaction is shown in Scheme 3.

Scheme 3. Reaction of the Baylis−Hillman Adduct of Pyridine-3-aldehyde and Azomethine Ylides **B** and **E**



In conclusion, we have developed a synthetic route for the construction of functionalized 3-spiropyrrolizidine and 3-spiropyrrolidine oxindoles starting from Baylis−Hillman adducts of isatin and heteroaldehydes with azomethine ylides via [3+2]-cycloaddition. Further studies using these products for total synthesis of indole alkaloids are underway in this laboratory.

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Supporting Information Available: Synthetic procedures and spectroscopic characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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