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Pyridine Core Activation *via* 1,5-Electrocyclization of Vinyl Pyridinium Ylides Generated from Bromo Isomerized Morita−Baylis−Hillman Adduct of Isatin and Pyridine: Synthesis of 3-Spirodihydroindolizine Oxindoles

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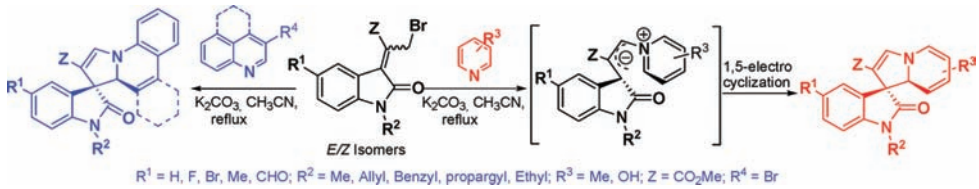
ABSTRACT



An activation of the pyridine nucleus has been achieved via 1,5-electrocyclization of vinyl pyridinium ylides generated from bromo isomerized Morita−Baylis−Hillman adducts of isatin and pyridine under basic conditions. The method has been successfully applied for an efficient synthesis of a number of 3-spirodihydroindolizine-2-oxindoles, which have been found as core structure of secoyohimbane and heteroyohimbane alkaloid natural products.

Oxindoles derivatized at C3 as spirocarbocycles, spiroheterocycles, spirolactones, and spirocyclic ethers are elegant targets in organic synthesis because of their significant biological activities.[1,2] Particularly, 3-spiroindolizine oxindole derivatives have been found as substructures in numerous pharmaceuticals and natural products.[3] Oxindoles of the secoyohimbane (tetracyclic) and heteroyohimbane (pentacyclic) type, isolated from *Mitragyna* and *Aspedosperma*, contain 3-spiroindolizine oxindole moieties as core structural units.[4] Furthermore, some of the spiroindolizine oxindoles

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(1) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(2) Galliford, C. V.; Scheidt, K. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 2. For reviews on spirocycles, see: (a) Krapcho, A. P. *Synthesis* **1974**, 383. (b) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (c) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165, and references therein. (d) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341. (e) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (f) Castaldi, M. P.; Troast, D. M.; Porco, J. A. *Org. Lett.* **2009**, *11*, 3362.

(3) For selected recent examples, see: (a) Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, *11*, 3366. (b) Shintani, R.; Hayashi, S.-Y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754. (c) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (d) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (e) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (f) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135. (g) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (h) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (i) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Tetrahedron* **2004**, *60*, 9503.

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serve as potential synthons for the synthesis of alkaloids, drug intermediates, and clinical pharmaceuticals (Figure 1).[5] A

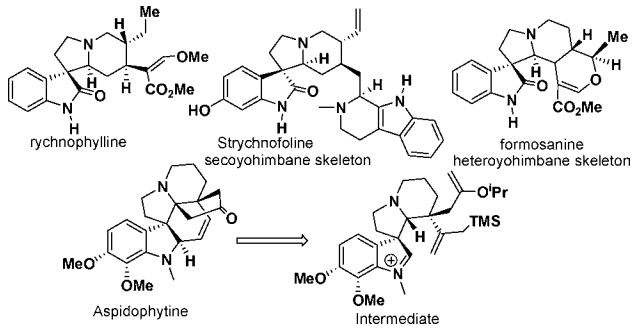


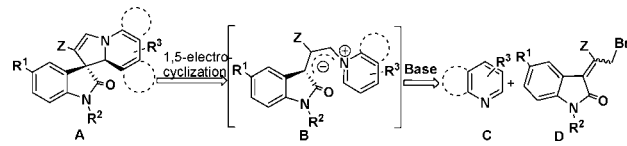
Figure 1. Natural products with 3-spiroindolizine oxindoles as core structures.

number of routes have been developed in pursuit of these structure motifs including magnesium iodide catalyzed ring opening of spirocyclopropane oxindoles with cyclic aldimine[6] to oxidative rearrangements,[7] etc. Given their biological activity and the prevalence of the structural motif they display, a general and efficient strategy toward the core structure of the 3-spiroindolizine-2-oxindole would be attractive.

The synthetic utility of the Morita−Baylis−Hillman (MBH) reaction lies in the dense functionality that is generated, providing handles for further manipulation.[8] Recent years have witnessed an explosive growth in the application of MBH adducts and their derivative in synthetic organic chemistry.[8c] The reactivity pattern of conjugated azomethine ylides, viz., vinyl pyridinium ylide, includes their reactivity not only as 1,3-dipoles but also in sigmatropic rearrangements and electrocyclization reactions.[9] Vinyl pyridinium ylides can be generated by base-induced elimination of HBr from the corresponding pyridinium bromides. Continuing our interest in developing new methods for various spiro oxindoles from MBH adducts,[10] herein we describe a novel route for the synthesis of spirodihydroindolizine oxindoles via a 1,5-electrocyclization of vinyl pyridinium ylide generated from bromo isomerized MBH adduct of isatin and pyridine as a key step.

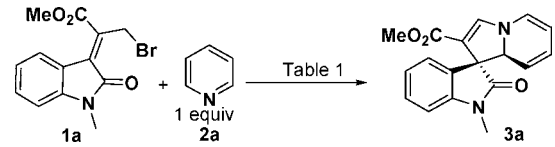
According to a retrosynthetic analysis shown in Scheme 1, the title compounds **A** can be synthesized from the 1,5-electrocyclization of vinyl pyridinium ylide **B** generated from the bromo isomerized MBH adduct of isatin **D** and pyridine derivatives **C**. The bromo isomerized MBH adduct of isatin **D** can be prepared from MBH adducts of isatin via isomerization with HBr.

Scheme 1. Retrosynthetic Analysis



Initially, the 1,5-electrocyclization reaction of *Z*-bromo isomerized MBH adduct **1a** in acetonitrile with pyridine and K_2CO_3 as a base was examined. When the base was added immediately after pyridine addition, the desired spirodihydroindolizine oxindole **3a** was formed only in 15% yield (Scheme 2).

Scheme 2. Optimization of Synthesis of **3a**



The reaction was found to be low-yielding in solvents such as DMF,[11] THF, DME, and acetone, and the formation of reduced alkene product was also observed (Table 1).[9b] Addition of molecular sieves slightly increased the yield of the reaction. Pyridine can also be used as a base for generating the ylide, but the second equivalent of pyridine should be added after

Table 1. Optimization of Reaction Condition

solvent	base	*t* (°C)	time (h)[a]	yield (%)[b]
CH_3CN	K_2CO_3	80	0.5/3	15
CH_3CN	K_2CO_3	80	1/3	30
CH_3CN	**K_2CO_3**	**80**	**2/3**	**86**
CH_3CN	pyridine	80	2/3	79
CH_3CN	Ag_2CO_3	80	2/3	
THF	K_2CO_3	60	2/3	40
acetone	K_2CO_3	56	2/3	
DMF	K_2CO_3	80	2/3	45
DME	K_2CO_3	80	2/3	

[a] Base added after specified time/total reaction time. [b] Isolated yield.

(4) Bindra, J. S. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 84−121.

(5) (a) Dideberg, O.; Lamotte-Brasseur, J.; Dupont, L.; Campsteyn, H.; Vermeire, M.; Angenot, L. *Acta Crystallogr. Sect. B* **1977**, *33*, 1796. (b) Lerchner, A.; Carreira, E. M. *Chem.—Eur. J.* **2006**, *12*, 8208. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(6) Martin, S. F. B.; Benage, L. S.; Geraci, J. E.; Hunter, M.; Mortimore, *J. Am. Chem. Soc.* **1991**, *113*, 6161.

(7) (a) Liu, J.; Brabander, J. *J. Am. Chem. Soc.* **2009**, 12562. (b) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, 10842. (c) Ryan Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2009**, 16404.

(8) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Batra, S.; Singh, V. *Tetrahedron* **2008**, *64*, 4511. (c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (d) Ciganek, E. *Organic Reactions*; Paquette, L., Ed.; Wiley: New York, 1997; Vol. 51, p 201. (e) Nakano, A.; Kawahara, S.; Akamatsu, S.; Morokuma, K.; Nakatani, M.; Iwabuchi, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron* **2006**, *62*, 38. (f) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496. (g) Tang, H.; Zhao, G.; Zhou, Z.; Gao, P.; He, L.; Tang, C. *Eur. J. Org. Chem.* **2008**, 126.

(9) (a) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873. (b) Taylor, E. C. *Chem. Rev* **1979**, *79*, 181. (c) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947. (d) Augstein, W.; Kröhnke, F. *Justus Liebigs Ann. Chem.* **1966**, *697*, 158. (e) Marx, K.; Eberbach, W. *Tetrahedron* **1997**, *53*, 14687. (f) Marx, K.; Eberbach, W. *Chem.—Eur. J.* **2000**, *6*, 2063. (g) Jaung, J. Y.; Jung, Y. S. *Bull. Korean Chem. Soc.* **2003**, *24*, 1565.

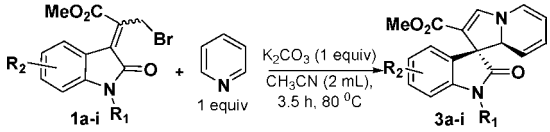
2 h (time required for the generation of pyridinium salt); otherwise the reaction would undergo decomposition.

Among the conditions tested, **3a** was obtained in optimized yield, 86%, when the base (1equiv K_2CO_3) was added 2 h after the addition of pyridine in refluxing acetonitrile. It should be noted that the reaction does not require the isolation of pyridinium salt. The *E*-isomer of **1a** under optimized condition also provided compound **3a** in excellent yield. The results are collected in Table 1.

The structure of **3a** was determined on the basis of detailed spectroscopic analysis (IR, ^{1}H and ^{13}C NMR, and MS). The key five protons of dihydroindolizine ring of spiro oxindole derivative appeared at δ 4.67−6.47 as a doublet of doublets and was further confirmed from analysis of the ^{1}H−^{1}H COSY spectrum. Finally, the mass spectrum showed a molecular ion peak at *m*/*z* 309.64 (M + 1), which supports the assigned structure. Formation of the other inseparable diastereomer was also observed only in a trace quantity as minor peaks seen in the proton NMR spectrum. It is interesting to note that the synthesized compounds have the similar core structural feature of secoyohimbane natural products.

To demonstrate the method as general, a number of bromo isomerized MBH isatin adducts **1a**−**i** were found to be suitable candidates for the synthesis of spirodihydroindolizines oxindoles **3a**−**i** (Scheme 3). The products formed in good to excellent yields of 74−92%, and the results are summarized in Table 2.

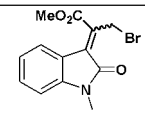
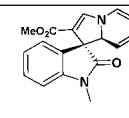
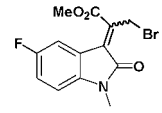
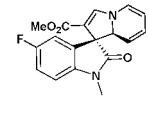
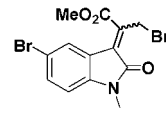
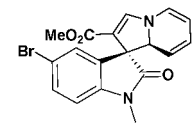
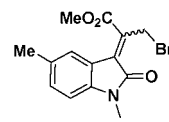
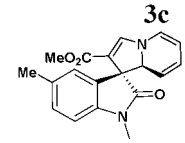
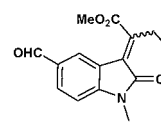
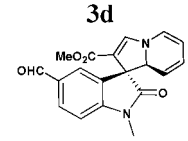
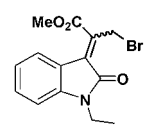
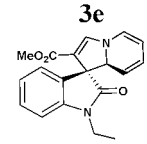
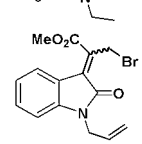
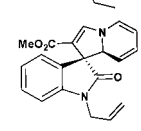
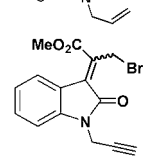
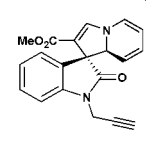
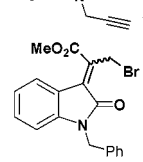
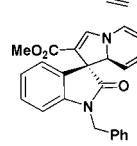
Scheme 3. Synthesis of 3-Spiroindolizine Oxindoles **3a**−**i**



The allyl bromide with a formyl substitution at the fifth position yielded the desired compound in a lower yield (Table 2, entry 5). Several allyl bromides with different *N*-substituents such as propargylic, allylic, and benzylic groups also participated in the reaction affording desired spirocyclic products in good yields (Table 2, entries 7−9). Notably, *N*-benzyl derivatives of isatin show better turnover yield up to 92% (Table 2, entry 9). To our dismay, allyl bromide with a nitrile substituent underwent decomposition under the optimized reaction condition.

The reactions described here may be rationalized by invoking the mechanistic postulate of earlier work.[10b] Formation of the same product from both *E*- and *Z*-isomeric allyl bromides suggests that the reaction proceeds through a common intermediate **G**.

Table 2. Synthesis of Substituted 3-Spirodihydro Indolizine-2-Oxindoles **3a**−**i**[a]

entry	substrate[b]	product	yield(%)[c]
1	 **1a**	 **3a**	86
2	 **1b**	 **3b**	85
3	 **1c**	 **3c**	87
4	 **1d**	 **3d**	85
5	 **1e**	 **3e**	72
6	 **1f**	 **3f**	81
7	 **1g**	 **3g**	78
8	 **1h**	 **3h**	85
9	 **1i**	 **3i**	92

[a] Experimental procedure: **1a**−**i** (0.5 mmol), **2a** (1 equiv), K_2CO_3 (1 equiv), CH_3CN (2 mL). [b] *E*/*Z* mixture was used. [c] Isolated yield.

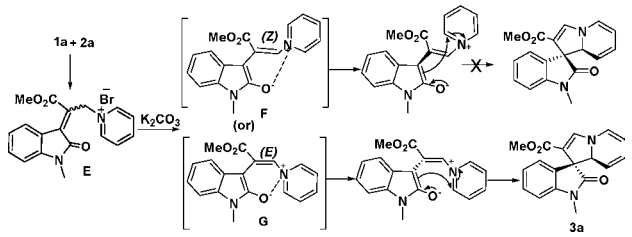
In an initial event, oxindole substituted allyl bromide reacts with pyridine to form pyridinium allylide **E**. Removal of proton from the methylene carbon results the formation of two possible intermediates, i.e., *Z*-ylide **F** and *E*-ylide **G**. The dipole stabilized intermediate **G** undergoes 1,5-electrocyclization, i.e., attack of the carbaion from the front side of the plane to the iminium carbon to yield the spirodihydroindolizine oxindole **3a** as a single diastereomer(Scheme 4). It is interesting to note that the stereochemical outcome of the reaction is important as the final compounds reported herein have core structures similar to those of the natural products (Figure 1).

We then probed the reactions with other substituted pyridines to generalize the scope of the spiroindolazine oxindole forma-

(10) (a) Shanmugam, P.; Viswambharan, B.; Suchithra, M. *Org. Lett.* **2007**, *9*, 4095. (b) Shanmugam, P.; Viswambharan, B. *Synlett* **2008**, 2763. (c) Shanmugam, P.; Viswambharan, B.; Selvakumar, K.; Suchithra, M. *Tetrahedron Lett.* **2008**, *49*, 2611. (d) Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. *Tetrahedron* **2006**, *62*, 4342. (e) Shanmugam, P.; Vaithiyanathan, V. *Tetrahedron* **2008**, *64*, 3322. (f) Selvakumar, K.; Vaithiyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, *46*, 2826.

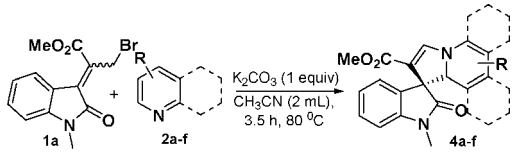
(11) Basavaiah, D.; Devendar, B.; Lenin, D. V.; Satyanarayana, T. *Synlett* **2009**, 411.

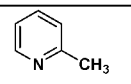
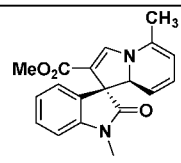
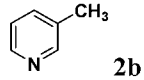
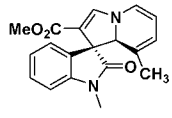
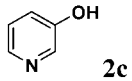
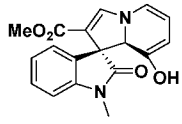
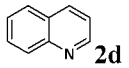
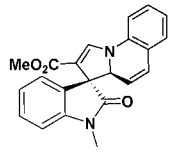
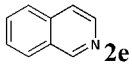
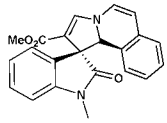
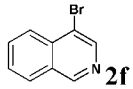
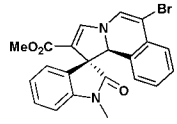
Scheme 4. Plausible Mechanism for the Reaction



tion. We found the substituents on the pyridine ring had a great effect on electrocyclization. The results are shown in Table 3.

Table 3. Synthesis of Substituted Spirodihydroindolizine Oxindoles[a]



entry	substrate	product	yield (%)[b]
1	 **2a**	 **4a**	78
2	 **2b**	 **4b**	71[c]
3	 **2c**	 **4c**	66[c,d]
4	 **2d**	 **4d**	75
5	 **2e**	 **4e**	80
6	 **2f**	 **4f**	85

[a] *E/Z* mixture was used. Reaction condition: **1a** (0.5 mmol), **2b**−**f** (1 equiv), K_2CO_3 (1 equiv), CH_3CN (2 mL). [b] Isolated yield. [c] Two inseparable regioisomeric product. [d] The reaction was conducted at room temperature.

2-Methyl pyridine gave only one regioisomeric product **4a** in 78% yield (Table 3, entry 1), whereas the 3-methyl pyridine gave two inseparable regioisomeric products in the ratio of 1:0.5 and 75% combined yield (Table 3, entry 2). The structure of the major regioisomer was assigned by $^1H-^1H$ COSY spectrum and coupling constant analysis. An electron-withdrawing group such as formyl at the 2-, 3-, and 4-position of the pyridine ring did not fit for the reaction as the substrates failed to furnish the desired products under the optimized reaction condition. The reason may be due to the low nucleophilic nature of the pyridine core. Similarly, the 2- and 4-hydroxyl pyridine also failed to react as a result of keto−enol tautomerism. However, 3-hydroxy pyridine gave the desired product in 66% yield (Table 3, entry 3). Other nitrogen donors such as quinoline, isoquinoline, and 3-bromoisoquinoline were also found to be suitable candidates for 1,5-electrocyclization reaction and gave the desired spirocyclic products. Among all three quinoline derivatives tested, 3-bromoisoquinoline gave better yield than the other two derivatives (Table 3, entry 6). The final structure proof of **4f** was arrived at unequivocally by single crystal X-ray diffraction studies (Figure 2).[12] It is noteworthy to mention here that all three quinoline derivatives selectively gave one diastereoisomer in excellent yield.

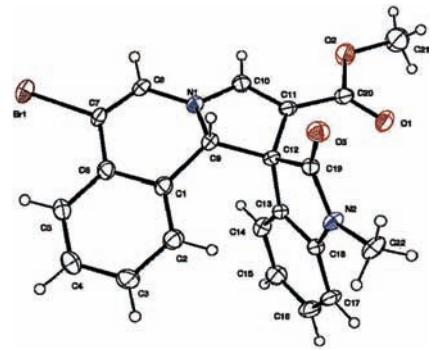


Figure 2. ORTEP diagram of compound **4f.**

In conclusion, we have shown the utility of the bromo isomerized MBH adducts of isatin utilizing pyridinium ylide chemistry and 1,5-electrocyclization for the synthesis of highly functionalized spiroindolizine oxindoles. The synthesized spiroindolizine derivatives are available from simple and facile starting material and can be further manipulated to synthesis natural products such as secoyohimbane and heteroyohimbane.

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Supporting Information Available: Detailed experimental procedure, characterization of the products, mechanism and copies of spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) CCDC 768359 contains the supplementary crystallographic data of compound **4f**.