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A novel MgI_2 mediated unusual dimerization–spirocyclopropanation of bromo isomerised Morita–Baylis–Hillman adduct of isatin: a facile synthesis of 3-spirocyclopropane-2-oxindole derivatives

Kandapalam Arun Prasath Lingam [a], Asit Baran Mandal [b], Ponnusamy Shanmugam [a,*]

[a] Organic Chemistry Division, Central Leather Research Institute, Council of Scientific and Industrial Research (CSIR), Adyar, Chennai 600 020, India
[b] Chemical Laboratory, Central Leather Research Institute, Council of Scientific and Industrial Research (CSIR), Adyar, Chennai 600 020, India

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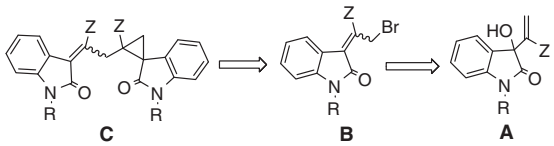
ABSTRACT

A novel magnesium iodide mediated unusual dimerization–spirocyclopropanation of bromo isomerised Morita–Baylis–Hillman adducts of isatin afforded highly functionalized 3-spirocyclopropane-2-oxindole derivatives as regioisomers in good combined yield. It has been observed that the regioselectivity is dependent on the nature of electron withdrawing group at the activated position. A plausible mechanism involving organomagnesium reagent has been proposed.

Construction of highly strained three membered carbocyclic frameworks is a challenging task for synthetic chemists[1] and it has been used as a starting material for the synthesis of number alkaloid natural products.[2] Ring opening of the cyclopropanes in a regio- and stereo-selective manner often provide interesting and stereoselective products thereby gaining importance of both theoretical and synthetic point of view.[3] In view of their importance as synthons, numerous synthetic methods and synthetic manipulation have been developed.[4] Ring-expansion reaction of spiro[cyclopropan-1,3′-oxindoles][5] with a range of imines afforded spiro[pyrrolidin-3,3′-oxindoles] which are known to have iontropic[6] and herbicidal[7] and HIV-1 inhibiting properties.[8] Further, cyclopropanes also provide access to useful synthetic intermediates with reactivity that can be tuned by conjugation, substitution with electron-withdrawing and/or donating groups.[9] Magnesium iodide (MgI_2) as a powerful reagent has been used for the synthesis of Baylis–Hillman adducts,[10] cyclopropane ring opening reaction and a number of synthetic transformations.[11] In situ generation of Grignard reagent by magnesium–halogen exchange reaction has been used for efficient synthetic purposes and is a useful method for carbon–carbon bond formation reaction.[12] The synthetic utility of the Morita–Baylis–Hillman (MBH) reaction lies in the dense functionality that is generated, providing handles for further manipulation.[13] As part of our research interest in the novel synthetic applications of MBH adducts,[14] recently we have reported a simple method for the synthesis of spirocyclopropane-2-oxindoles via reductive cyclization protocol.[14d] Further investigation on the reaction of bromo isomerised MBH adduct of isatin with magnesium iodide resulted in an unusual dimerization followed by spirocyclopropanation, thus providing allylic 3-spirocyclopropane-2-oxindole derivatives as a separable mixture of diastereomers and the details of the work is presented in this manuscript.

According to a retrosynthetic analysis shown in Scheme 1, the dimerized spirocyclopropane oxindole **C** can be synthesised from the bromo isomerised MBH adduct **B** with MgI_2, via Michael type addition of in situ generated organomagnesium reagent to another molecule of bromo isomerised MBH adduct followed by spirocyclization. The MBH adduct **A** and bromo derivative **B** can be prepared as per the literature.[15]

Our initial idea is to generate the organo magnesium reagent[12a] using magnesium iodide with *E*- and *Z*-bromo isomerised MBH



Scheme 1. Retrosynthetic analysis of 3-spirocyclopropane-2-oxindoles.

* Corresponding author. Tel.: +91 471 2515275; fax: +91 471 2491712.
E-mail address: shanmu196@rediffmail.com (P. Shanmugam).

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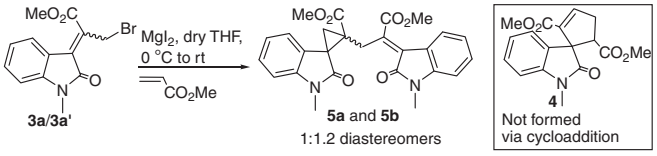
adduct of isatin **3a**/**3a**′ and to trap it with methyl acrylate to synthesise 3-spirocyclopentane-2-oxindole derivative **4** via cycloaddition reaction. However, the reaction did not afford any expected product **4**, instead it furnished the unexpected dimerized 3-spirocyclopropane-2-oxindoles **5a** and **5b** as a mixture of separable diastereomers in good combined yield. The reaction is shown in Scheme 2.

The structure of the new compounds **5a** and **5b** were established by the analysis of spectroscopic data such as FT-IR, ^{1}H, ^{13}C NMR, DEPT 135, FAB-mass and single crystal X-ray data. Thus, the observed coupling constants of methylene protons ($\delta = 2.44$ and 2.07, $J = 5.35$ Hz) and allylic methylene protons ($\delta = 4.51$ and 4.10, $J = 16.05$ Hz) of the spirocyclopropane are sufficient evidence to assign the structure of compound **5a**. Besides, the dimerization of the product was established from the ^{1}H NMR spectrum as it showed two ester methoxy proton at $\delta = 3.94$, $\delta = 3.56$ and two *N*-methyl protons at $\delta = 3.29$, $\delta = 3.21$ and was further supported by FAB mass spectrum. Final proof of the structure and relative configuration has been arrived from single crystal XRD data[16] shown in Figure 1.

Interestingly, when the mixture of *E* and *Z* isomers of bromo isomerised MBH derivatives **3a** and **3a**′ in dry THF with 1 equiv of MgI_2 afforded functionalized 3-spirocylopropyl-2-indolones **5a** and **5b** as a diastereomeric mixture in 32% combined yield in the product ratio of 1:1.2 as evidenced by ^{1}H NMR (Scheme 3). Remarkably, the reactions of individual *E* and *Z* isomers of bromo isomerised MBH derivatives under conditions described above have also afforded functionalized 3-spirocylopropyl-2-indolones **5a** and **5b** almost in the same yield and ratio indicating that both the isomers undergo product formation through a common intermediate. Hence, mixture of isomers was used for the rest of experiments.

In order to optimise the reaction condition, experiments with change in the number of equivalents of MgI_2, use of magnesium turnings and varied reaction time have been carried out (Table 1). Thus, an experiment with magnesium turnings under reflux condition did not provide the desired 3-spiroyclopropane-2-oxindole (Table 1, entry 1). Experiment with Mg-turnings and a



Scheme 2. Synthesis of 3-spirocyclopropane derivatives **5a** and **5b**.

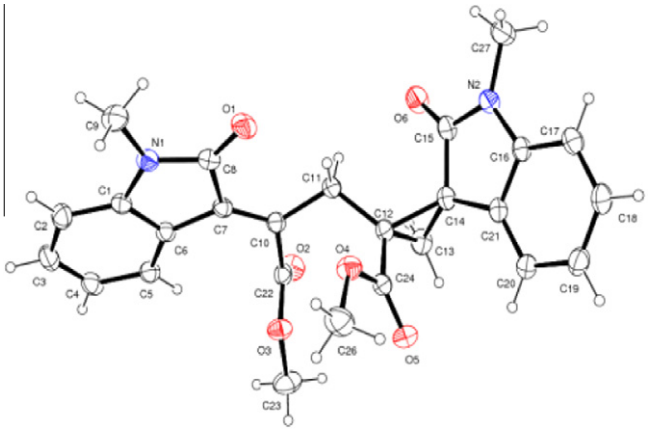
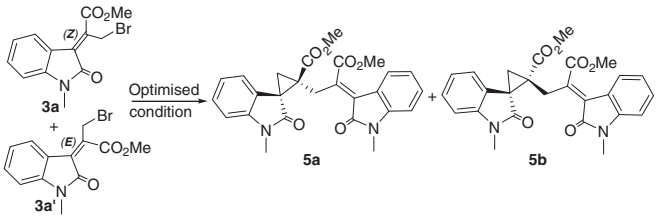


Figure 1. ORTEP diagram of compound **5a**.

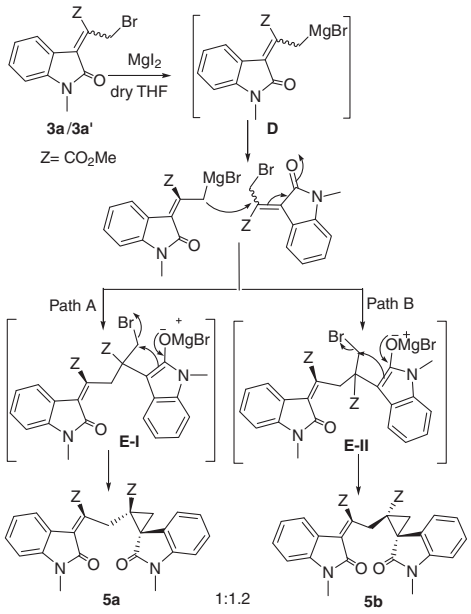


Scheme 3. Synthesis of spirocyclopropane derivatives of oxindole **5a** and **5b** from *E* and *Z* isomers **3a** and **3a**′.

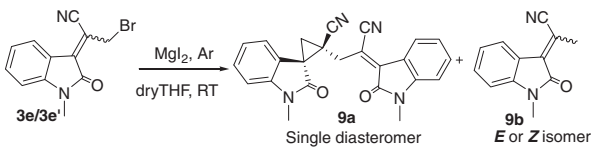
Table 1
Optimization of synthesis of 3-spirocyclopropane-2-oxindole derivatives **5a** and **5b**

Entry	Reagent	Equivalents reagent	Time (h)	Combined yield **5a**/**5b**[a] (%)
1	Mg turnings	2	6	–
2	Mg/cat. I_2	2	2.5	22
3	Mg/cat. I_2	1	3	15
4	MgI_2	0.5	2	10
5	MgI_2	1	3	35
6	**MgI_2**	**1.5**	**2**	**52**
7	MgI_2	0.2	4	Trace
8	MgI_2	2	2	32

[a] Isolated yield after column chromatography.



Scheme 4. Proposed mechanism for the formation of **5a** and **5b**.



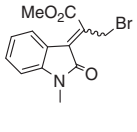
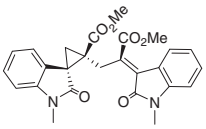
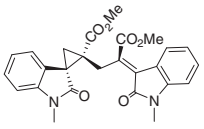
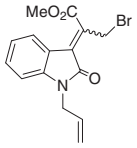
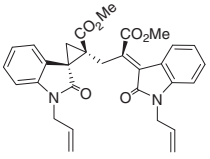
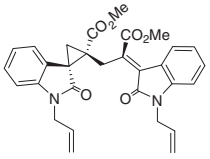
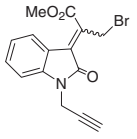
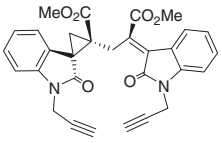
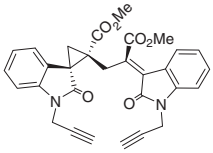
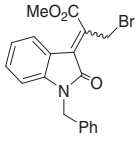
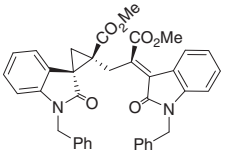
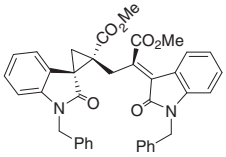
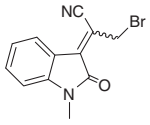
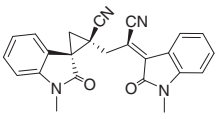
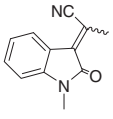
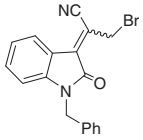
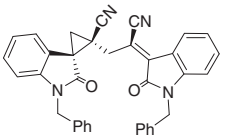
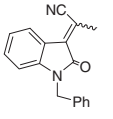
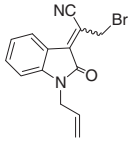
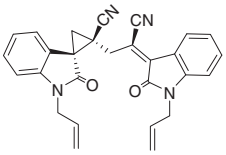
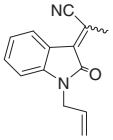
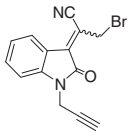
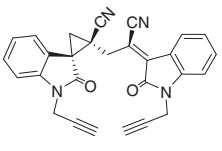
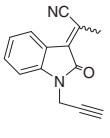
Scheme 5. Synthesis of **9a** and **9b**.

catalytic amount of iodine furnished the expected spirocyclopropane in 30% yield (Table 1, entry 2). When the number of equivalents of MgI_2 gradually increased (up to 1.5 equiv), yield of the product improved and the reaction time considerably reduced. However, excess use of the MgI_2 in the reaction resulted in the decomposition of the products. Thus, an optimum yield (52%)

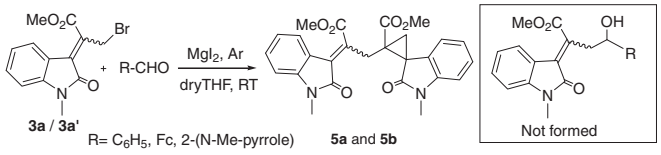
was obtained with 1.5 equiv of MgI_2, dry THF as solvent at room temperature under argon atmosphere.

Based on the product formation, a plausible mechanism has been proposed as outlined in Scheme 4. Accordingly, in situ generated common reactive intermediate alkyl magnesium derivative **D** obtained from reaction of both *E*- and *Z*-bromo isomerised MBH adduct with MgI_2 is believed to undergo a Michael type conjugate addition with another molecule of bromo isomerised MBH derivative to afford intermediates **E-I** and **E-II**. Intermediates **E-I** and **E-II** upon spirocyclization by the elimination of bromide via path A and

Table 2
Synthesis of 3-spirocyclopropane-2-oxindole derivatives **5**(**a**–**b**)–**12**(**a**–**b**)

Entry	Reactant (*E* and *Z*)[a]	Time (h)	Products	Ratio	Combined yield[b]
1	 **3a/3a'**	1.5	 **5a**  **5b**	1:1.2	52
2	 **3b/3b'**	2	 **6a**  **6b**	1:1.3	41
3	 **3c/3c'**	3.5	 **7a**  **7b**	1:1	40
4	 **3d/3d'**	2.5	 **8a**  **8b**	1:1.5	40
5	 **3e/3e'**	2	 **9a**  **9b**	1:0.5	40
6	 **3f/3f'**	3.5	 **10a**  **10b**	1:0.3	29
7	 **3g/3g'**	1.5	 **11a**  **11b**	1:0.4	39
8	 **3h/3h'**	1	 **12a**  **12b**	1:0.5	38

[a] *E* and *Z* mixture used as a starting material.
[b] Isolated yield after column chromatography.



Scheme 6. Attempted allylation reaction of **3a/3a′** with aldehydes.

path B afforded 3-spirocylopropyl-2-indolones **5a** and **5b** as a mixture of diastereomers, respectively.

Interestingly, when the nitrile substituted bromo isomerised MBH adducts **3e/3e′** of isatin was examined under the conditions described for **3a/3a′**, the dimerization–cyclopropanation reaction afforded only one diastereoisomeric product **9a** along with reduced product **9b** (<10%) as shown in Scheme 5. The reduction product **9b** is formed due to high reactivity of cyano bromo isomerized MBH adduct during the magnesium metal insertion. It should be noted that only a single diastereomer has been synthesised using *E* and *Z* mixture of bromo isomerised MBH adduct may be due to a free rotation of the C–C bond in the intermediate.

Encouraged by the preliminary results and in order to demonstrate the scope and limitation of the method described above, a number of isomerised bromo MBH adducts **3a–3h** under optimized conditions were made to undergo dimerization–cyclopropanation to afford the corresponding functionalized 3-cylopropyl-2-indolones in good yield. The results are collected in Table 2. It has generally been observed that the ester substituted bromo derivatives afforded diastereomeric mixture of products whereas the nitrile derivatives afforded single diastereomer along with reduced product. It is noteworthy to mention that this is first report to generate alkyl magnesium derivative from bromo isomerised MBH adduct of isatin using MgI_2 and dimerization–cyclopropanation. The formation moderate yields of the products can be rationalized due to other than the products isolated; the remainder of the materials appears to be complex mixture and is found difficult in isolation by column chromatography.

To understand the reactivity pattern, nature of reactive intermediate and to avoid the dimerization–cyclopropanation, we envisaged to trap the organomagnesium reagent thus formed initially with aldehydes such as benzaldehyde, heteroaldehyde and ferrocenealdehyde to get the corresponding allylated product.[17] However, to our dismay, all the reactions provided only the 3-spirocyclopropane-2-oxindoles as products and not even a trace of allylated product was observed (Scheme 6). The reason for not observing the allylated products with aldehydes can be rationalised as it is believed that the intermediate formed is more reactive towards dimerization–spirocyclopropanation than the Grignard addition to the aldehydes.

In conclusion, we have demonstrated a novel MgI_2 mediated short and efficient synthesis of highly functionalised strained 3-spirocyclopropane-2-oxindole derivatives from *E*- and *Z*-bromo isomerised derivatives of MBH adduct of isatin. A plausible mechanism for the formation of diastereomeric 3-spirocyclopropane-2-oxindole systems has been explained via formation of organomagnesium intermediate. The diastereoisomers were distinguished by comparison and evaluation of ^1H NMR chemical shifts, coupling constants and single crystal X-ray data. The compounds reported herein can be used as synthons for the synthesis of indole alkaloid natural products.

Acknowledgments

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Supplementary data

Supplementary data (general experimental procedure, complied spectroscopic data of new compounds and scanned copies of spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.009.

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16. Crystallographic data for **5a** have been deposited (CCDC 806108) with the Cambridge Crystallographic Data Centre. Copy of the data can be obtained free of charge on application to 12, Union Road, Cambridge CB21EZ, UK (fax: +441223 336 033; e-mail: deposit@ccdc.cam.ac.uk)
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