

Synthesis of Spirocyclohexadienyl-2-Oxindoles by 6 π -Electrocyclization of Trienes Derived from Wittig Reaction of Morita-Baylis-Hillman Carbonates and α,β -Unsaturated Aldehydes

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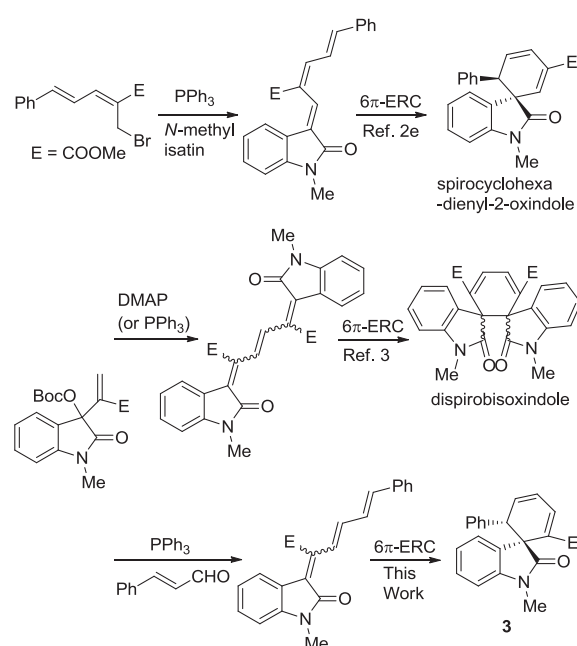
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 α,β -Unsaturated aldehydes, Wittig reaction

Spirooxindoles exist in a huge number of natural substances and pharmaceutically interesting compounds.¹ Thus, tremendous efforts have been devoted to efficient protocols to access these important motifs over the past years.^{1–5} Recently, we reported the synthesis of spirocyclohexadienyl-2-oxindoles by 6 π -electrocyclic ring closure (6 π -ERC) of the trienes, derived from Morita-Baylis-Hillman (MBH) adducts of cinnamaldehyde and isatin (Scheme 1).^{2c} Very recently, we also reported the synthesis of dispirobisoxindole from MBH carbonates of *N*-methylisatin (Scheme 1).³ During the course of our study, we decided to examine the synthesis of structurally related spirocyclohexadienyl-2-oxindoles^{4,5} with different substitution pattern by 6 π -ERC of the trienes, derived from MBH carbonates of *N*-methylsatin and cinnamaldehyde, as shown in Scheme 1.

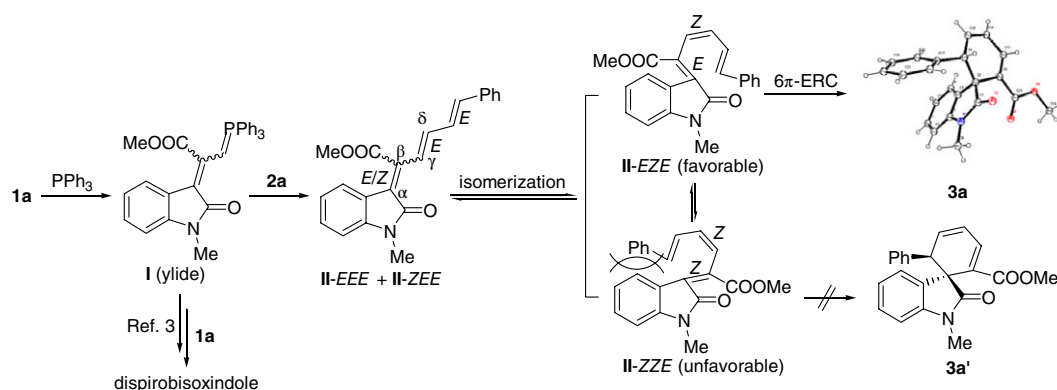
At the outset of our experiment, the reaction of MBH carbonate **1a** and *trans*-cinnamaldehyde (**2a**, 1.1 equiv) in 1,2-dichlorobenzene (ODCB) was examined at 150°C in the presence of PPh₃ (1.0 equiv).³ To our delight, spirocyclohexa-2,4-dienyl-2-oxindole **3a** was obtained in good yield (69%) in short time (2 h). The formation of the other diastereomer (**3a'**, *vide infra*, Scheme 2) was not observed. The structure of **3a** was unequivocally confirmed by its crystal structure (*vide infra*, Scheme 2).⁶ However, two diastereomeric dispirobisoxindoles (see, Scheme 1) have been formed as side products in appreciable yield (23%), as in our previous paper.³ When we carried out the reaction in refluxing *p*-xylene (5 h), the yield of **3a** increased to 74%, and the yield of dispirobisoxindoles decreased (18%). The yield of **3a** increased slightly (77%) when we carried out the reaction in refluxing toluene; however, a long reaction time (24 h) was required. When we used an excess amount of **2a** (2.0 equiv) in refluxing xylene (5 h), the yield of **3a** increased up to 85%. In the reaction mixture, the formation of only a trace amount (<5%) of dispirobisoxindole was observed.⁷

Encouraged by the results we synthesized various spirooxindoles **3b–3l**, and the results are summarized in Table 1. Various spirooxindoles **3b–3e** were synthesized in

good to moderate yields (67–89%) by the reactions of substituted isatin derivatives **1b–1e** with **2a**. The reaction of **1a** and *trans*-3-(2-furyl)acrolein (**2b**) afforded **3f** in moderate yield (60%). The reaction of crotonaldehyde (**2c**) gave **3g** in good yield (78%). In the reaction, we used an excess amount of **2c** (3.0 equiv) because the boiling point of **2c** (104°C) was lower than the reaction temperature (138°C). The reactions of **1a** with α -methyl-*trans*-cinnamaldehyde (**2d**) and α -bromocinnamaldehyde (**2e**) afforded **3h** and **3i** in good yields (68% and 84%, respectively). However, the reactions with α -substituted aliphatic aldehydes, *trans*-2-methyl-2-butenal (**2f**) and 1-cyclohexene-1-carboxaldehyde (**2g**), produced the corresponding spirooxindoles **3j** (23%) and **3k** (33%) in low yields with 3.0 equiv. of **2f** or **2g**. The result might be due to sluggish reactivity in the Wittig reaction of α -branched α,β -enals **2f** and **2g**.⁸ In addition, base-catalyzed self-condensation of crotonaldehyde derivatives



Scheme 1. Synthesis of spirocyclohexadienyl-2-oxindoles.

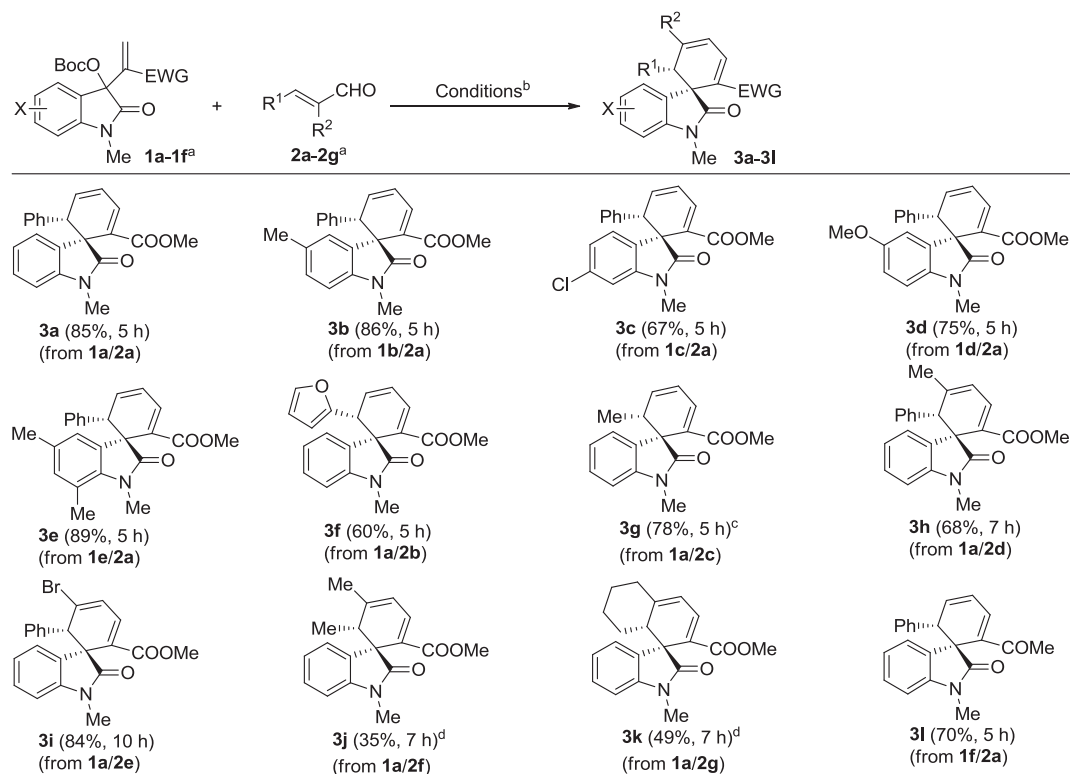


Scheme 2. Proposed mechanism.

would be another plausible reason for the low yield.⁹ In these regards, the yields of **3j** (35%) and **3k** (49%) were improved by using an excess amount (5.0 equiv) of **2f** or **2g**. The reaction of acetyl derivative **1f** and **2a** gave **3l** in moderate yield (70%).

The reaction mechanism could be proposed, as shown in Scheme 2. The reaction of **1a** and PPh₃ generated the

corresponding phosphorous ylide **I**.^{3,10} A following Wittig reaction of **I** and **2a** afforded the corresponding triene **II** as a *E/Z* mixture at the α,β -position.¹¹ A following thermal double bond isomerization^{3,12} at the γ,δ -position would afford **II-EZE** and **II-ZZE**. As noted above, only one diastereomeric spirooxindole **3a** was obtained. The result stated that **II-ZZE** triene did not undergo the following 6 π -ERC

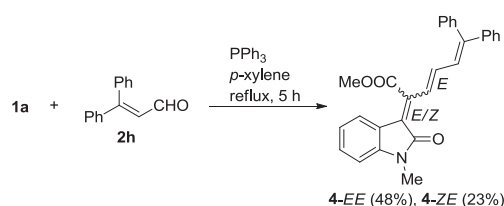
Table 1. Synthesis of spirooxindole **3**.

^a Substrates: **1a**: X = H, EWG = COOMe; **1b**: X = 5-Me, EWG = COOMe; **1c**: X = 6-Cl, EWG = COOMe; **1d**: X = 5-OMe, EWG = COOMe; **1e**: X = 5,7-Me₂, EWG = COOMe; **1f**: X = H, EWG = COMe; **2a**: R¹ = Ph, R² = H; **2b**: R¹ = 2-furyl, R² = H; **2c**: R¹ = Me, R² = H; **2d**: R¹ = Ph, R² = Me; **2e**: R¹ = Ph, R² = Br; **2f**: R¹ = Me, R² = Me; **2g**: R¹-R² = -(CH₂)₄-.

^b Conditions: **1** (0.5 mmol), **2** (2.0 equiv), PPh₃ (1.0 equiv), *p*-xylene, reflux, given time in parenthesis.

^c **2c** (3.0 equiv).

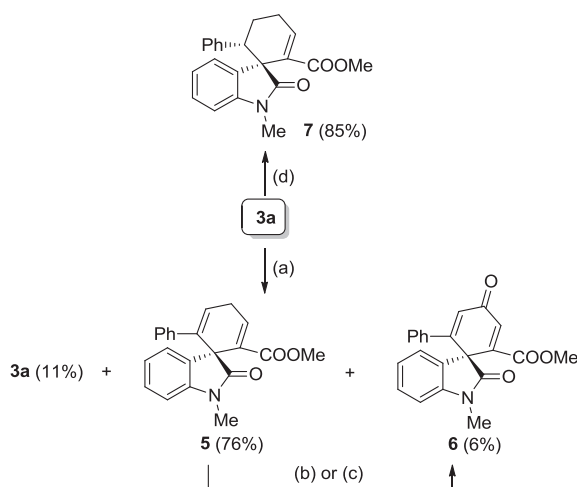
^d **2f** (5.0 equiv) and **2g** (5.0 equiv).

Scheme 3. The reaction of **1a** and **2h**.

presumably due to severe steric hindrance around the terminal phenyl moiety.^{2e}

The reaction of **1a** and β -phenylcinnamaldehyde (**2h**) produced the corresponding triene **4** in moderate yield (71%), as shown in Scheme 3. The triene **4** was not converted to the corresponding spirooxindole even under refluxing phenyl ether solution (5 h) presumably due to steric effects in the 6π -electrocyclization.^{2e}

In order to show the synthetic applicability of **3a**, we examined a double bond isomerization, as shown in Scheme 4. To our delight, the isomerization of **3a** in 1,2-dichloroethane (DCE) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.1 equiv) at room temperature for 12 h afforded spirocyclohexa-2,5-dienyl-2-oxindole **5** in good yield (76%). In the above isomerization of **3a** to **5**, a small amount of **3a** (11%) was remained even after a long time. Actually, the reverse isomerization of **5** into **3a** in the presence of DBU (0.1 equiv) in DCE at room temperature for 12 h produced **3a** in low yield (10%) along with recovered **5** (83%). The result stated that **3a** and **5** are in equilibrium in the presence of DBU. In the reaction, the formation of spirocyclohexa-2,5-dienone **6** was observed in a trace amount (6%). This compound **6** could be synthesized in good yield (77%) from **5** according to the reported allylic oxidation method employing pyridinium dichromate



Scheme 4. Chemical transformations of **3a**. (a) DBU (0.1 equiv), DCE, rt., 12 h; (b) PDC (3.0 equiv), *t*BuOOH (3.0 equiv), benzene, Celite, rt., 24 h, 77%; (c) DBU (3.0 equiv), DCE, O₂ balloon, rt., 1 h, 46%; (d) Pd/C (10%, w/w), H₂ balloon, MeOH/EtOAc (2:1), rt., 2 h.

(PDC) and *t*BuOOH.¹⁴ The conversion was also conducted in a reasonable yield (46%) by aerobic oxidation in the presence of DBU under O₂ balloon atmosphere.¹⁵ A typical catalytic hydrogenation of **3a** in the presence of Pd/C afforded **7** in good yield (85%) in short time (2 h).^{2e,13f}

In summary, various spirocyclohexadienyl-2-oxindoles have been synthesized in good yields by thermal 6π -electrocyclization of trienes, derived by the Wittig reaction of MBH carbonates of *N*-methylisatin and α,β -unsaturated aldehydes.

Experimental

Typical Procedure for the Synthesis of **3a:** A solution of **1a** (174 mg, 0.5 mmol), **2a** (132 mg, 1.0 mmol), and PPh₃ (131 mg, 0.5 mmol) in *p*-xylene (1.5 mL) was heated to reflux for 5 h under N₂ balloon atmosphere. Removal of the volatiles and column chromatographic purification process (*n*-hexane/EtOAc, 3:1) afforded **3a** (147 mg, 85%) as a white solid. Other compounds were synthesized similarly, and all spectroscopic data including **3a** are summarized in Supporting Information.

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Supporting Information. Additional supporting information is available in the online version of this article.

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6. CCDC 1550540 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
7. During the evaluation process, one of the reviewers suggested the possibility of reducing the formation of dispirobisoxindole side product by using an excess amount of PPh_3 . Thus, we carried out the reaction of **1a** (0.5 mmol) and **2a** (2.0 equiv) in refluxing *p*-xylene (5 h) in the presence of PPh_3 (2.0 equiv); however, the yield of **3a** (84%) was not increased and the formation of dispirobisoxindole was still observed, albeit in a trace amount (<5%). A small amount of dispirobisoxindole might be formed via an aerobic oxidation of ylide **I**, Wittig reaction with **2a**, and subsequent 6π -ERC as noted in our previous paper.³
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11. Actually, when we carried out the reaction of **1a** and **2a** in refluxing benzene in the presence of PPh_3 , **II-EEE** (40%), **II-ZEE** (23%) and **3a** (24%) were isolated after a long reaction time (30 h). The result stated that isomerization of **II-EEE/II-ZEE** to **II-EZE** and/or its 6π -ERC required higher temperature in order to obtain **3a** in a reasonable yield. In addition, both **II-EEE** and **II-ZEE** could be converted to **3a** in high yields (93% and 92%, respectively) in refluxing *p*-xylene in short time (2 h).
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