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DBU-catalyzed [3 + 2] cycloaddition and Michael addition reactions of 3-benzylidene succinimides with 3-ylidene oxindoles and chalcones†

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A metal-free DBU catalyzed protocol has been developed for the regioselective [3 + 2] cycloaddition reactions of 3-benzylidene succinimides with 3-ylidene oxindoles to furnish spirooxindole derivatives. The 3-benzylidene succinimides underwent Michael addition with chalcones to provide benzylidene succinimide-tethered propanones. All the reactions proceeded under mild conditions and the products were isolated by simple filtration and washing with ethanol in good yields. The current methodology utilizes simple precursors and provides functionally-rich succinimides with two to five contiguous stereocenters in excellent diastereoselectivity and with complete regioselectivity.

Introduction

Succinimide and its derivatives are of great scientific interest in the family of nitrogen containing compounds because of their remarkable pharmacological profiles. These compounds are reported to have various biological activities such as anti-epileptogenic, antinociceptive and antagonistic activities.[1] Numerous efforts have been made by the researchers from time to time to synthesize these moieties. There are many reports in the literature of maleimide being used as a Michael acceptor to furnish products with succinimide as an integral part of the structure.[2] However, there are sporadic reports known in the literature where 3-benzylidene succinimides were used either in cycloaddition reactions or as Michael donors.[3] As a result, there exists a broad scope for the development of user friendly, simple and environmentally benign approaches to synthesize more functionally-rich succinimides from easily accessible succinimide derivatives. The functionalization of an allylic centre has always been an important concern to organic chemists as it greatly contributes to the synthesis of various biologically active molecules.[4] Michael addition is one of the favourable ways to achieve C–C bond formation.[5] Similarly cycloaddition reactions have been considered as a major tool to construct C–C bonds in organic synthesis and therefore have attracted significant attention in recent years.[6]

In addition to this, cyclopentanes are a class of compounds endowed with decisive biological and pharmacological activities, like antiviral, hepatitis B and significant antitumor activities.[7] Moreover, cyclopentane scaffolds can serve as intermediates in natural product synthesis and as lead compounds in the development of new drugs.[8] Owing to their wide spectrum of biological activities, the synthesis of cyclopentane derivatives attracted tremendous attention in the field of organic synthesis and the construction of highly substituted derivatives has been an important concern for organic chemists since decades.[9] When the oxindole moiety is spirocyclized to cyclopentane, it upswings to a special class of biologically important natural alkaloids such as notoamide A, cirinalins A, citrinadin B, and cyclopiamine B and could lead to the synthesis of highly stereocentric and more fertile bioactive compounds (Fig. 1).[10,11] We utilized 3-ylidene oxindoles in the reactions with various electron-rich arenes and 1,4-benzoxazinones for the synthesis of 2,3-difunctionalized benzofuran, lactone bearing indolin-2-one scaffolds and multisubstituted pyrrole polyheterocycles.[12] Recently, Du reported a similar kind of cycloaddition of 3-benzylidene succinimides with enoates, though the reaction took a longer time.[3a] However, to the best of our knowledge, the cycloaddition of 3-benzylidene succinimides with enones is not known in the literature. Later the same group reported the Michael addition of 3-benzilidine succinimides with nitrostyrenes.[3c] In a report published by Tan and co-workers in 2010, benzylidene succinimides were used in Mannich-type allylic addition with imines.[3d] To the best of our knowledge, no reports are available for the reactions of 3-benzylidene succinimides with chalcones. We envisioned that the base catalyzed reactions of 3-benzylidene succinimides with enones such as 3-ylidene oxindoles and

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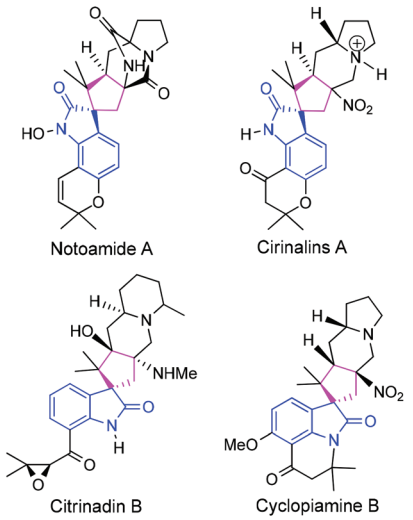
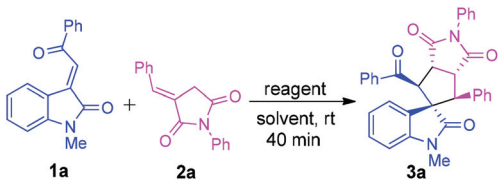


Fig. 1 Biologically important spirooxindoles.

chalcones would provide access to bioactive fragments in a single structure *via* Michael addition and [3 + 2] cycloaddition strategies. Herein, we report rapid protocols for the synthesis of spirooxindoles and benzylidene succinimide-tethered propanones with promising control over regioselectivity as well as diastereoselectivity through DBU-catalyzed mild reactions with no by-product formation.

Table 1 Optimization of conditions for the synthesis of spirooxindole **3a**[a]



Entry	Reagent	Solvent	dr[b]	Yield[c] (%)
1	NEt_3	DCE	—	Nr
2	DIPEA	DCE	—	Nr
3	DABCO	DCE	—	Nr
4	K_2CO_3	DCE	—	Nr
5	DBU	DCE	—	Traces
6	DBU	DCM	—	Traces
7	DBU	Toluene	—	Traces
8	DBU	MeOH	98 : 02	43
9	DBU	EtOH	86 : 14	60
10	DBU	IPA	93 : 07	28
11[d]	DBU	EtOH	90 : 10	75
12[e]	DBU	EtOH	91 : 09	80
13[f]	DBU	EtOH	93 : 07	71

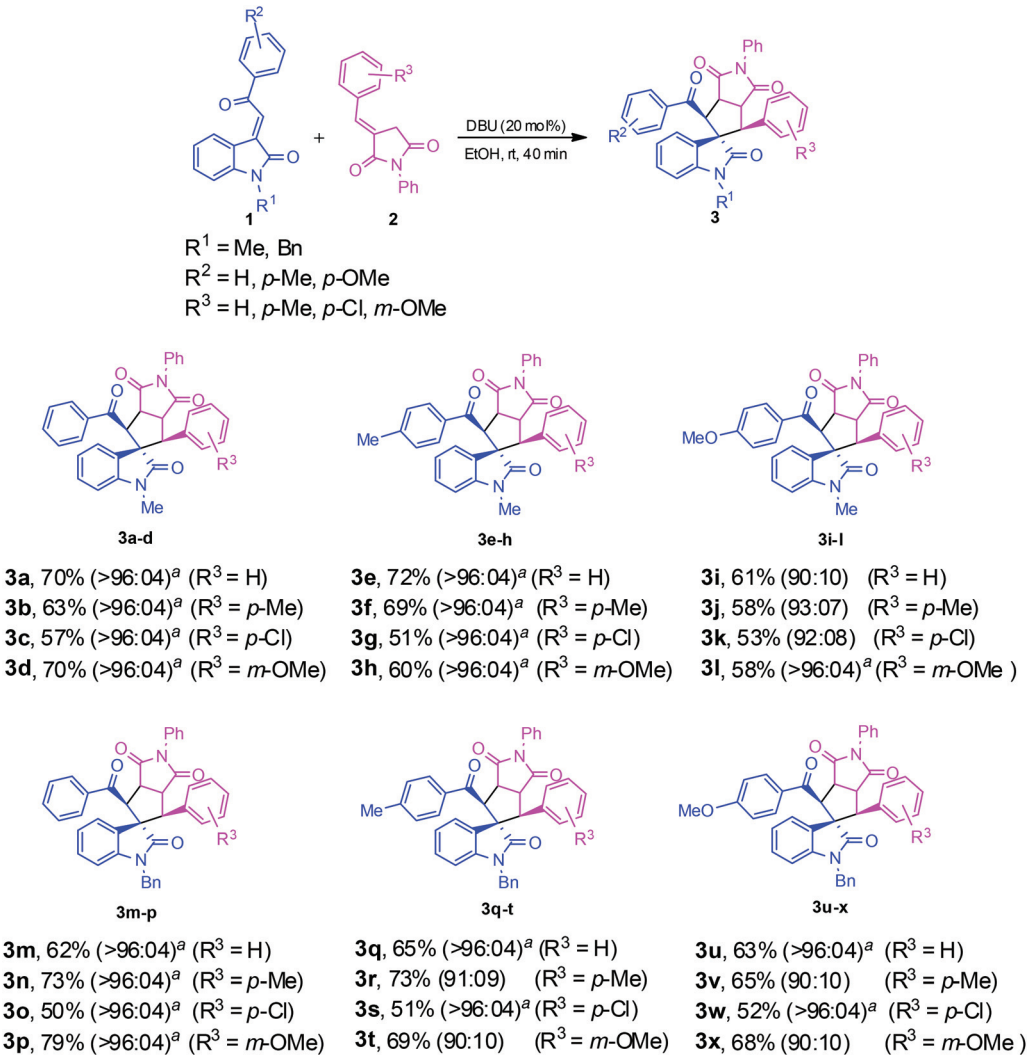
[a] Reaction conditions: Unless otherwise specified, all reactions were carried out using **2a** (0.1 mmol), **1a** (0.1 mmol), and a reagent (0.1 mmol) in 2 mL solvent at room temperature for 40 min. [b] The dr was determined by ^{1}H NMR analysis of the crude product having **3a** and its diastereomer. [c] Isolated yield of **3a** and its diastereomer after column chromatography. Nr: No reaction. [d] 50 mol% of DBU was used. [e] 20 mol% of DBU was used. [f] 10 mol% of DBU was used.

Results and discussion

To establish the optimum reaction conditions, we commenced our research by investigating the reaction of 3-ylidine *N*-methyloxindole **1a** and 3-benzylidene *N*-phenylsuccinimide (**2a**) as model substrates. When the reaction was performed in the presence of triethylamine in DCE at room temperature, no product was observed (Table 1, entry 1). To check the feasibility as per the mutual reactivity of the reactants, bases such as DIPEA, DABCO and K_2CO_3 were examined and it was observed that these bases were unable to drive the reaction (entries 2–4) whereas the reaction involving DBU furnished trace amounts of **3a** (entry 5). The spirooxindole **3a** was obtained *via* [3 + 2] cyclization of 3-ylidine oxindole **1a** with 3-benzylidene succinimide **2a**. After screening of various bases, DBU was found to be a promising base to furnish product **3a**. Subsequently, to assess the solvent effect, the reaction was studied by performing it in different solvents (entries 6–10). EtOH was identified as the optimal solvent furnishing the spirooxindole **3a** in 40 min in 60% yield with 86 : 14 diastereoselectivity (entry 9). Encouraged by this promising result, we further varied the amount of DBU and found that on decreasing the amount of base to 50 mol% the product was obtained in an increased yield of 75% with very good diastereoselectivity (entry 11). When **1a** was treated with **2a** in the presence of 20 mol% of DBU, the reaction afforded spirooxindole **3a** in 80% yield with 91 : 09 diastereoselectivity (entry 12). However, there was no appreciable variation in the yield of the product on further diminishing the base to 10 mol% (entry 13). Thus, 20 mol% DBU in EtOH at room temperature was considered as the optimized reaction condition for the model reaction. Gratifyingly, when the crude reaction mixture was subjected to filtration followed by simple washing with ethanol, a single diastereomer **3a** was isolated in 70% chemical yield.

With the optimized reaction conditions in hand, we proceeded to study the functional group compatibility and scope of the present DBU catalyzed protocol for the synthesis of spirooxindoles **3** using a variety of 3-ylidine oxindoles **1a–c** and 3-benzylidene succinimides **2a–d**. Products **3a–l** were obtained in good yields and excellent diastereoselectivities (Scheme 1). The reactions of 3-benzylidene succinimides **2a–d** bearing electron-withdrawing and electron-donating groups proceeded well.

We tested the applicability of the present methodology for 3-ylidine oxindoles with a bulky protecting group to ascertain its effect on the stereochemical outcome of the reaction. When *N*-benzyl protected oxindoles were used in the reaction, no significant changes in the yield and diastereoselectivity of the products were noticed. The reaction proceeded smoothly to furnish the desired products **3m–x** in 50–80% yield with excellent diastereoselectivity (Scheme 1). In the case of 3-ylidine oxindoles, the ones bearing electron-donating groups participated in the cycloaddition smoothly. When the unsubstituted/parent



Scheme 1 Reaction of 3-benzylidene succinimides **2a–d** with *N*-protected 3-ylidene oxindoles **1a–f**. All reactions were carried out using **2a** (0.1 mmol), **1a** (0.1 mmol), and DBU (0.02 mmol) in 2 mL of EtOH at room temperature for 40 min. The dr was determined by ^{1}H NMR analysis of the isolated product.[a]No minor diastereomer was observed in the ^{1}H NMR spectrum.

3-ylidine *N*-methyl oxindole (**1a**) was treated with various substituted 3-benzylidene succinimides **2a–d**, the cyclized products **3a–d** were obtained in 57–70% yield with diastereoselectivity up to >99%. Similarly, the reaction of 4-methyl and 4-methoxy substituted 3-ylidine *N*-methyloxindoles **1b, c** and 3-benzylidene succinimides afforded the corresponding products **3e–l** in 51–72% yield with excellent diastereoselectivities.

The structures of spirooxindoles were confirmed by detailed spectral analysis obtained from ^{1}H and ^{13}C NMR, and HRMS experiments of the isolated products. For instance, in the ^{1}H NMR of **3a**, the protons H_a and H_d appear as doublets at δ 4.10 and 4.90 ppm, respectively, and the protons H_b and H_c appear as doublet of doublets at δ 4.21 and 5.04 ppm, respectively (Fig. 2). The connectivity of the protons that are coupled with each other and between protons and carbons of spirooxindole **3a** was identified by two-dimensional ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY experiments, respectively (Fig. S6 and S7, ESI†).

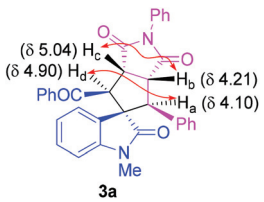


Fig. 2 Selected ^{1}H NMR chemical shifts (ppm) and NOE correlations in **3a**.

The results obtained from NMR studies were further confirmed by the single crystal X-ray analysis of compound **3a** (Fig. 3, also see the ESI†).[13] The crystals were grown by a slow evaporation process from dichloromethane.

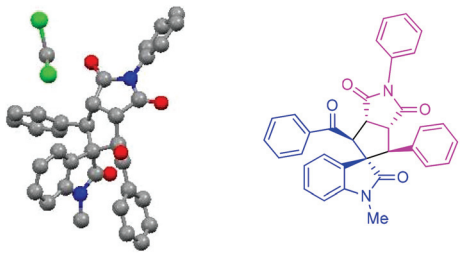


Fig. 3 The ORTEP plot of the crystal structure of **3a** (the trapped dichloromethane is also shown).

To further explore the scope of 3-benzylidene succinimide **2a**, we carried out its reaction with chalcone **4a**, and it was observed that the reaction proceeded through Michael addition to furnish Michael adduct **5a** in 64% yield and excellent diastereoselectivity. To evaluate the substrate scope of the reaction, chalcones **4a–f** were treated with 3-benzylidene succinimides **2a–d**. As shown in Scheme 2, a variety of chalcones bearing electron-rich and electron-deficient groups on both the phenyl rings were amenable for the reaction, and produced **5a–p** in 8 h with yields up to 83%. Notably, the donors **2b–d** bearing 4-chloro, 4-methyl and 3-methoxy groups on the benzylidene moiety could also be well tolerated.

Then we explored the scope of *N*-aryl benzylidene succinamide **2e** with chalcone derivatives **4a** and **4b**. The reaction proceeded smoothly under the optimized reaction conditions to provide the corresponding Michael adducts **5q** and **5r**, each in 67% yields. Interestingly, the cyclization of initial Michael adducts did not take place. Similarly, benzyl protection also worked well towards this protocol and furnished **5s** in 65% yield (Scheme 3).

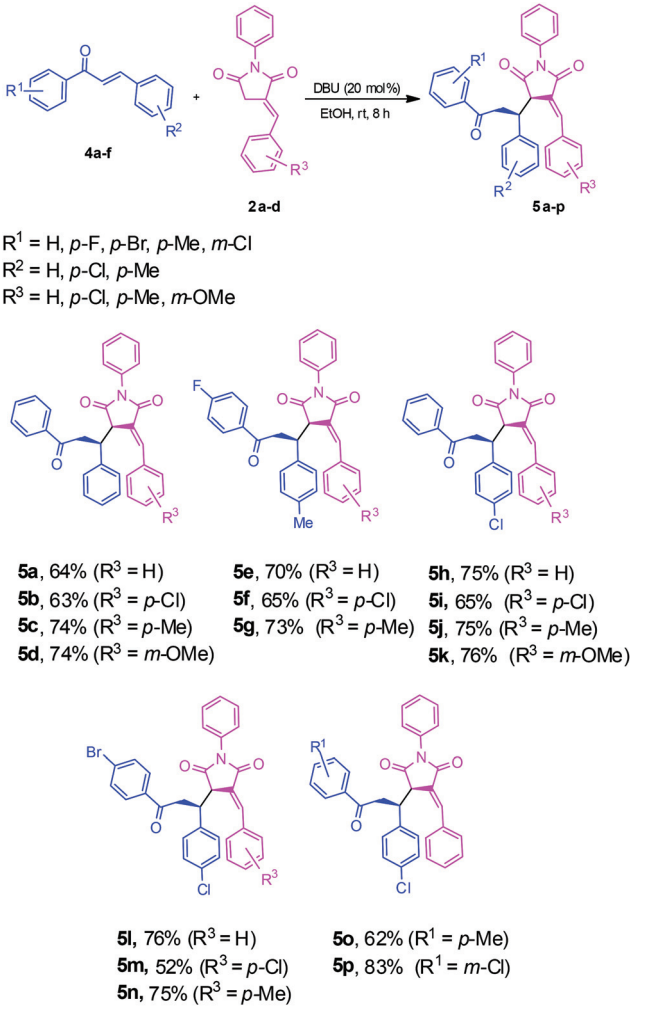
Furthermore, we extended the scope of this protocol to benzoylmethylidene malonate **6a**. To our delight, the reaction of 3-benzylidene succinimide **2a** with **6a** showed good compatibility and produced Michael adduct **7a** in high yield with excellent diastereoselectivity (Scheme 4).

The structures of Michael adducts were confirmed by detailed analysis obtained from ^{1}H and ^{13}C NMR, and HRMS spectral data of the isolated products. For instance, in the ^{1}H NMR of Michael adduct **5b**, protons H_a and H_a' appear at δ 3.27 and 4.68 ppm, respectively, each as doublet of doublets and proton H_b appears at δ 4.14 as doublet of triplets and proton H_c appears at 4.51 ppm as doublet of doublets (Fig. 4).

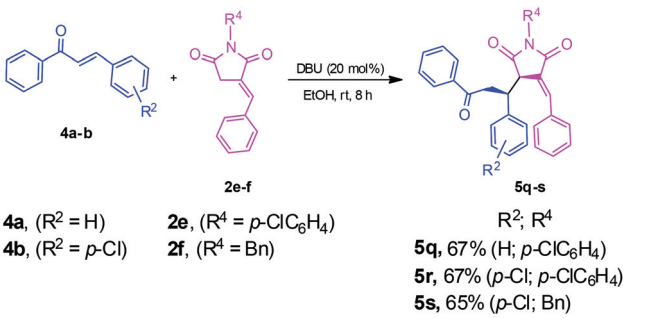
The connectivity of the protons that are coupled with each other and between the protons and carbons of Michael adduct **5b** was identified by two-dimensional ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY experiments, respectively (Fig. S9 and S10, ESI†).

The results obtained from NMR studies were further confirmed by the single crystal X-ray analysis of compound **5h** (Fig. 5, also see the ESI†).[14]

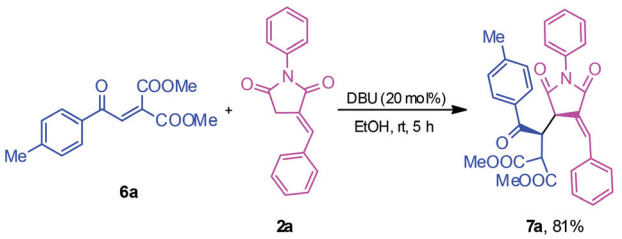
The plausible mechanism for the formation of spirooxindole is depicted in Fig. 6. Firstly, the anion generated from



Scheme 2 Reactions of 3-benzylidene succinimides **2a–d** with chalcones **4a–f**. All reactions were carried out with **2a** (0.1 mmol), **1a** (0.1 mmol), and DBU (0.02 mmol) in 2 mL of EtOH at room temperature for 8 h. No minor diastereomer was observed in the ^{1}H NMR spectra of the isolated products.



Scheme 3 Reactions of 3-benzylidene succinimides **2e,f** with chalcones **4a,b**. All reactions were carried out using **2** (0.1 mmol), **4** (0.1 mmol), and DBU (0.02 mmol) in 2 mL of EtOH at room temperature for 8 h. No minor diastereomer was observed in the ^{1}H NMR spectra of the isolated products.



Scheme 4 Reaction of 3-benzylidene succinimide **2a** with benzoylmethylidene malonate **6a**. The reaction was carried out using **2a** (0.1 mmol), **6a** (0.1 mmol), and DBU (0.02 mmol) in 2 mL of EtOH at room temperature for 5 h. No minor diastereomer was observed in the ^{1}H NMR spectrum of the isolated product.

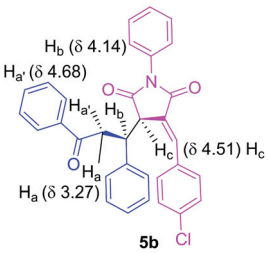


Fig. 4 Selected ^{1}H NMR chemical shifts (ppm) in **5b**.

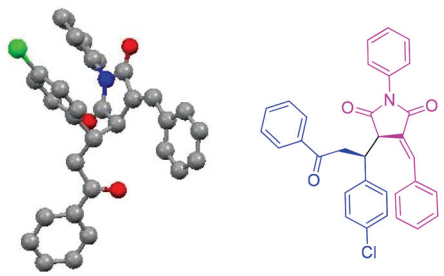


Fig. 5 The ORTEP plot of the crystal structure of **5h**.

3-benzylidene *N*-phenylsuccinimide (**2a**) by the abstraction of a proton with DBU attacks on the β-carbon of the amide functionality in **1a** to produce anion **A**. The electron-donation by the nitrogen atom of oxindole reduces the electron-withdrawing ability of both ketone as well as amide functionalities. Consequently the steric factor would greatly facilitate the attack at a sterically less hindered β-position. The carbanion **A**, being benzylic and α- to carbonyl, is highly stabilized and acts as a soft nucleophile. The aromatic ring of the benzylidene moiety may participate in resonance to the benzyl carbonium ion centre that facilitates 5-exo-trig cyclization at a soft electrophilic centre of **B** leading to tetracyclic system **C**. The hydroxyenamine **C** tautomerises to more stable imide **3a**. In the case of chalcone **4** or benzoylmethylidene malonate **6a**, the ketone enolates and the malonate enolates are more stable than amide enolates derived from 3-vinylidene oxindoles due to the resonance effect and relatively strong electron-withdrawing groups present in the former acceptors. Thus the enolates from **4** and **6a**, being more stable, do not take part in the second Michael addition. The excellent diastereoselectivity realised in the reactions of 3-benzylidene succinimides with the enones studied may be attributed to the presence of steric bulk in the vicinity of reacting sites.

Conclusions

In conclusion, we have successfully demonstrated DBU-catalyzed regioselective reactions of a series of enones *viz*. 3-ylidine oxindole, chalcones and benzoylmethylidene malonate with 3-benzylidene succinimides; the reaction proceeded *via* a [3 + 2] cycloaddition strategy and when treated with 3-ylidine oxindole **1** it followed Michael addition with other enones chalcones **4** and benzoylmethylidene malonate **6a**. The current rapid protocol offers valuable functionalized succinimides with two to five contiguous stereocenters in excellent diastereoselectivities and with complete regioselectivities from easily accessible starting materials. Moreover, this methodology is simple and does not require purification steps such as column chromatography and recrystallization.

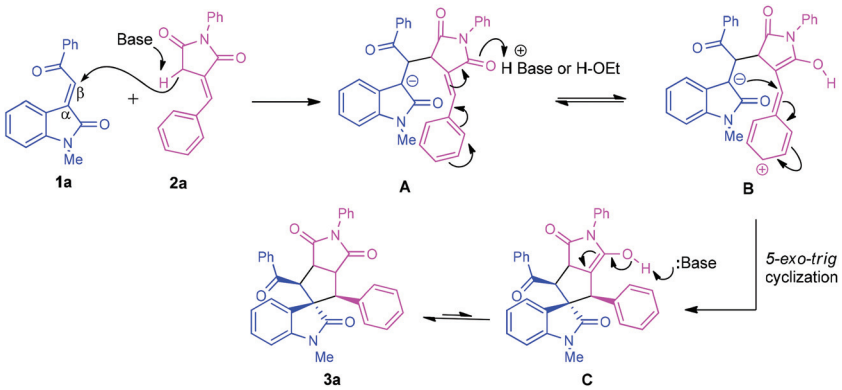


Fig. 6 Plausible reaction mechanism for the formation of spirooxindole.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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