

Rapid Construction of Bioindole Frameworks Using DABCO Under Aqueous Reaction Media

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Abstract : An efficient and rapid synthesis of diversely functionalized bioindole framework is described by the reaction of oxindoles with isatins using DABCO under aqueous medium. The generality of the reaction to afford the desired bioindole framework is well demonstrated by screening different structurally varied oxindole nucleophiles as well as isatin electrophiles. The scope of reaction was further strengthened by demonstrating its scale-up potential. Mild reaction condition, shorter reaction time, high isolated yield of the product with good diastereoselectivity, column chromatography-free purification, wide scope of substrate and environmentally benign medium are attractive features of the present protocol.

Keywords - Isatin; Oxindole; DABCO; Bioindole

I. INTRODUCTION

3,3'-Bioindoles is the important structural framework in the class of alkaloids which have been used as a precursor for synthesis of complex nitrogen containing heterocyclic molecules.¹ To be specific, they have been employed successfully to synthesize a number of cyclotryptamine alkaloids² like (+)-chimonanthine,³ meso-calycanthine⁴ and (-)-idiospermuline⁵ (**Figure 1**). 3,3'-Bioindoles have also been utilized to access other polycyclic framework such as hexahydrodiazachrysenes.⁶ Furthermore the dienolates of 3,3'-bioindoles can be effectively used for construction of contiguous quaternary carbon stereocenters by using double Steglich rearrangements.⁷ 3,3'-Bioindoles framework is synthesized by various methods, however the first step towards the synthesis of this framework involves the direct addition of oxindole based nucleophile to the isatin electrophile. Two main approaches were employed for the synthesis of 3,3'-bioindoles framework which includes direct condensation of isatin with oxindoles and dimerization of two isatin molecules. Literature shows that the synthesis molecular scaffold containing the 3,3'-Bioindoles framework can be accomplished by the condensation of isatin with oxindole under different reaction conditions.⁸⁻¹⁰ Similarly synthesis of 3,3'-Bioindoles framework is also accomplished by dimerization of two isatin molecules under different reaction conditions.¹¹⁻¹² Lakshmi *et al* also developed diastereoselective three component reaction of isatin, diazo-isatin and benzyl alcohol to afford 3,3'-bioindoles framework using Rh₂(OAc)₄ DCM under inert atmosphere.¹³ Catalyst-free method for the synthesis of 3,3'-bioindoles framework is also reported by the reaction of isatin with different oxindoles.¹⁴ However, this particular method takes 24 h reaction time for completion to afford the desired bioindole framework.

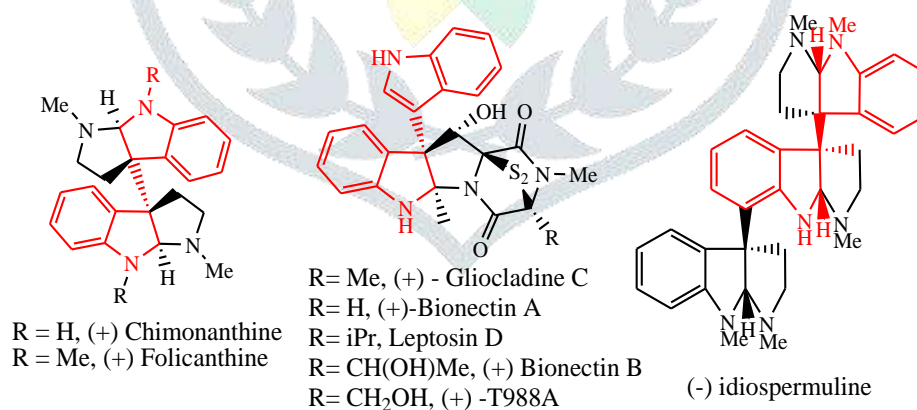


Figure 1: Examples of natural products & pharmaceutically important compounds containing bioindole frameworks

Although different methods are available for the synthesis of substituted 3,3'-Bioindoles framework, all of them require either catalyst or additive. Furthermore, these methods afford less yields of the desired product and require longer reaction times. So to overcome all these associated problems, we were thinking to employ 1,4-Diazabicyclo[2.2.2]octane (DABCO) as a catalyst for the reaction of isatin with different oxindoles to afford desired 3,3'-Bioindoles framework under good yield and shorter reaction time. DABCO is a green solid base which has been utilized in various organic transformations.¹⁵ Surprisingly, the DABCO have not explored in the reaction of oxindole with isatin to 3,3'-Bioindoles framework. In this context, we envisioned the aldol reaction between isatin and oxindole to afford 3,3'-Bioindoles framework using DABCO. In continuation of our work on synthesis of oxindole framework,¹⁶ we wish to report, DABCO catalyzed rapid synthesis of bioindoles framework by the reaction of isatin and oxindole under aqueous medium at room temperature.

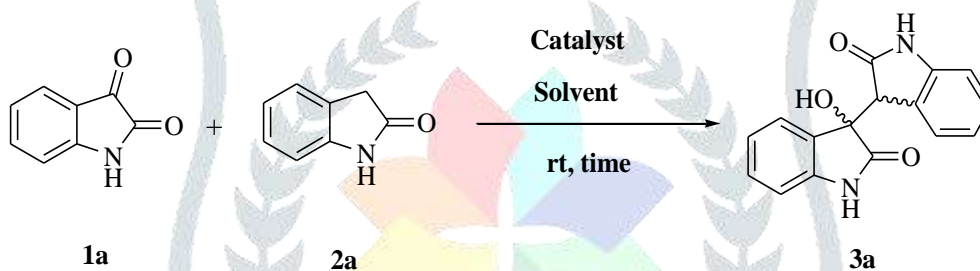
II. GENERAL METHOD:

General procedure for the synthesis of bioindole frameworks:

To the stirred mixture of oxindole **2(a-c)** (1mmol) & DABCO (5mol %) in 5 ml water, isatin **1(a-h)** (1.0 mmol) was added at room temperature and resulting reaction mixture was stirred for the stipulated time (5-10 min). The progress of the reaction was monitored by TLC as well as by the visualization of the change in color of the reaction mixture from red (at the beginning of the reaction) to white (at the end of the reaction). The obtained thick white precipitate was filtered and washed with water. Then it was dried to afford the desired product **3(a-j)** in very good yield and diastereoselectivity. The spectral data obtained for the compounds **3(a-j)** was in good accordance with the reported data.

III. RESULTS AND DISCUSSION

We begin our work by testing the reaction of isatin with oxindole in the presence of water in the absence catalyst (**Scheme 1**). Reaction goes to completion after 24 hr to give the desired product in quantitative yield with very good diastereoselectivity (entry 1, **Table 1**). Reaction worked well under catalyst-free condition in water, however longer reaction time was a major concern. Hence, to reduce the reaction time, we were thing to employ suitable base catalyst for this reaction. Keeping in mind the acidity of oxindole C-3 proton, a mild base might be sufficient to catalyze this reaction. DABCO have been employed as an efficient and mild catalyst in various reactions. In the context, we also attempted the reaction of oxindole with isatin in the presence of water with 20 mol % of DABCO catalyst. The reaction of oxindole **2a** with isatin **1a** in the presence of 20 mol% DABCO in water was completed within 5 min to afford the desired bioindoles product **3a** with 96% yield with 89:11 diastereomeric ratio (entry 2, **Table 1**). We have also done the catalyst loading study for this reaction, in which 5 mol % was found sufficient to catalyze this reaction (entry 3-5, **Table 1**). Furthermore, the role of different solvents on the efficiency of this reaction was also studied, where water was emerged as a best choice (entry 6-9, **Table 1**). In polar organic solvents the reaction isolated yield of the desired product was less due to use of extraction & column chromatographic purification. However, when the reaction was carried out in the water, the desired product can be obtained with sufficiently pure form just by filtration and does not require any solvent extraction and column chromatography purification.



Scheme 1 Reaction of isatin with oxindole under different reaction conditions

Table 1 Optimization of reaction condition^a

Entry	Catalyst	Solvent	Time	Yield (%)	dr ^b
1	-	Water (5ml)	24 h	99	96/04
2	DABCO (20 mol%)	Water (5ml)	5 min	96	89/11
3	DABCO (10 mol%)	Water (5ml)	5 min	96	91/09
4	DABCO (5 mol%)	Water (5ml)	5 min	99	96/04
5	DABCO (2 mol%)	Water (5ml)	30 min	98	96/04
6	DABCO (5mol%)	DMSO (5ml)	5 min	81	91/09
7	DABCO (5mol%)	DMF (5ml)	5 min	83	92/08
8	DABCO (5mol%)	THF (5ml)	5 min	87	93/07
9	DABCO (5mol%)	Ethanol (5ml)	5 min	85	90/10
10	DABCO (5mol%)	Distilled water (5ml)	5 min	99	96/04
11	DABCO (5mol%)	HPLC H ₂ O (5ml)	5 min	99	96/04
12	DABCO (5mol%)	Water (2 ml)	5 min	97	95/05
13	DABCO (5mol%)	Without solvent	12 hr	-	-

^aReaction conditions: isatin **1a** (1 mmol), oxindole **2a** (1 mmol) in the presence of catalysts and solvent. ^bBy ¹H NMR analysis.

It is also important to mention that, the progress of the reaction can be judged by visualizing the change in the colour of the reaction mixture from red to off-white colour (**Figure 2**). As a part of the study, we also performed the reaction in distilled as well as HPLC grade water, however similar results were obtained as obtained with water (entry 10-11 **Table 1**). The reaction can even perform in less quantity of water to get the desired product, however the dilution of the reaction mixture is required for the filtration process (entry 12 **Table 1**). The reaction in the absence of solvent does not show the formation of any product up to 12

hr. With these results, we selected the stirring of isatin **1a** (1 mmol) with oxindole **2a** (1 mmol) in the presence of 5 mol% DABCO in 5 mL water at rt as the optimized reaction condition to afford the desired bioxindoles product **3a** (entry 4, **Table 1**).

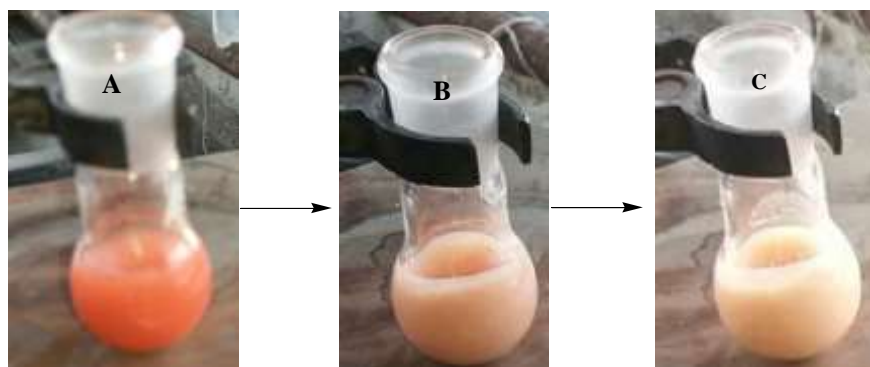
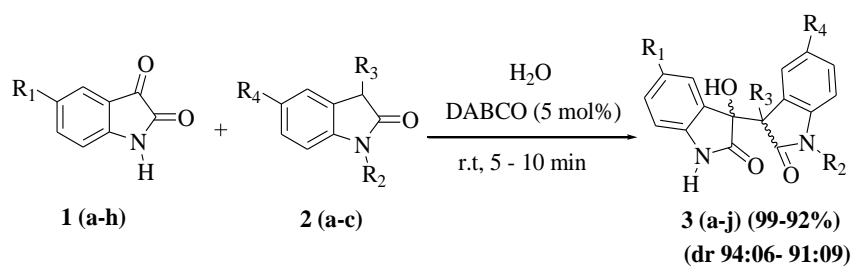
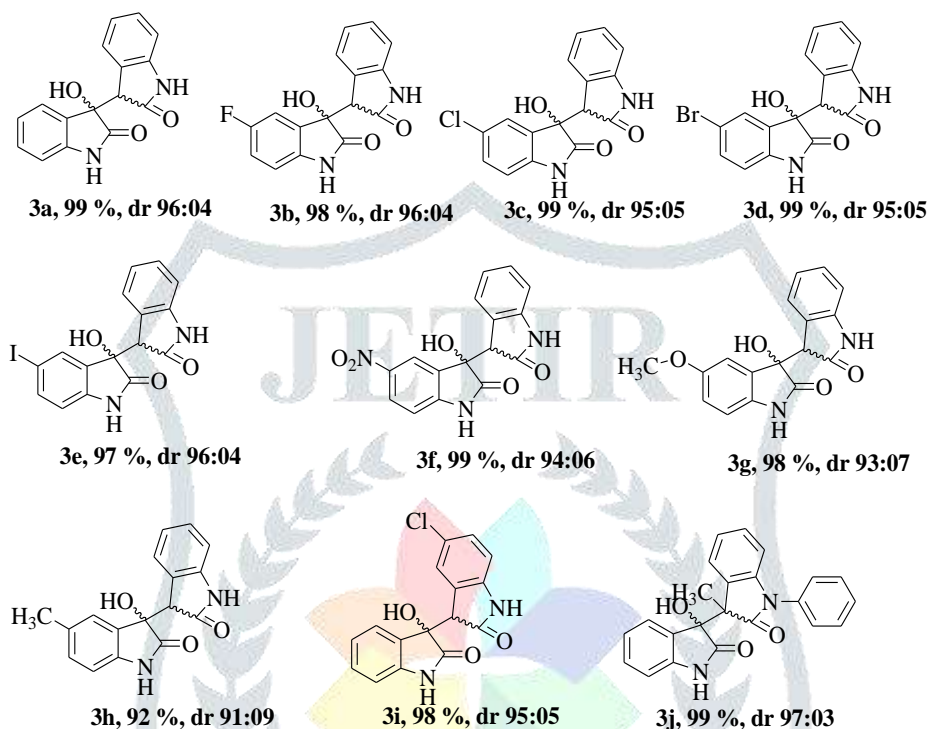


Figure 2: Photographs of progress of the reaction of isatin (**1a**, 1 mmol) with oxindole (**2a**, 1 mmol) in the presence of DABCO (5 mol%) in 5 mL of water at rt. **A:** At the beginning of reaction, **B:** after 3 min, **C:** After 5 min.

The optimized reaction condition was also applied to other different isatin as well as oxindole derivatives. We observe that, the reaction was general in which various oxindoles (1 mmol) and substituted isatins (1mmol) reacted smoothly in the presence of 5 mol% DABCO in 5 mL water to afford desired products (**Scheme 2**). Halogen substituted isatin derivatives like 5-floro isatin, 5-chloro isatin, 5-bromo isatin, 5-iodo isatin were reacted smoothly with oxindole to give the corresponding bioxndole product. Other isatin derivatives such as 5-nitro isatin, 5-methoxy isatin and 5-methyl isatin also reacted smoothly with oxindole to afford the desired products. 5-chloro oxindole was also screened in this reaction and found equally efficient. The generality of the method was further established by using 3-methyl-1-phenyl-oxindole in this reaction. It is worthy to mention that 3-methyl-1-phenyl-oxindole having methyl substituent at C-3 position were also reacted very smoothly in the same fashion with isatins and afforded desired bioxndole products in very high yield and diastereoselectivity. In general, the electronic effect of substituents was examined in this reaction. It was observed that, the developed protocol was successful with isatin bearing electron withdrawing as well as an electron donating substituent.

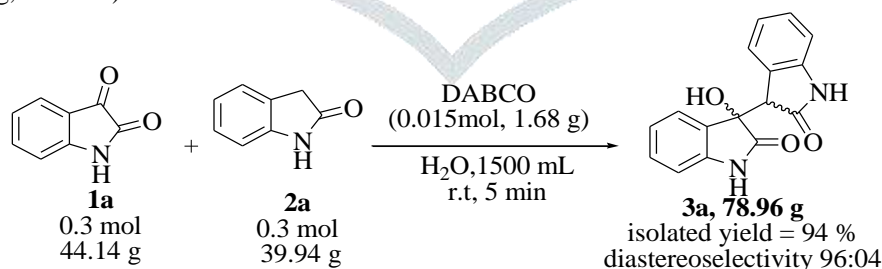


$R_1 = \text{H, F, Cl, Br, I, NO}_2, \text{Me, OMe}; R_2 = \text{H, Me}; R_3 = \text{H, Ph}; R_4 = \text{H, Cl}$



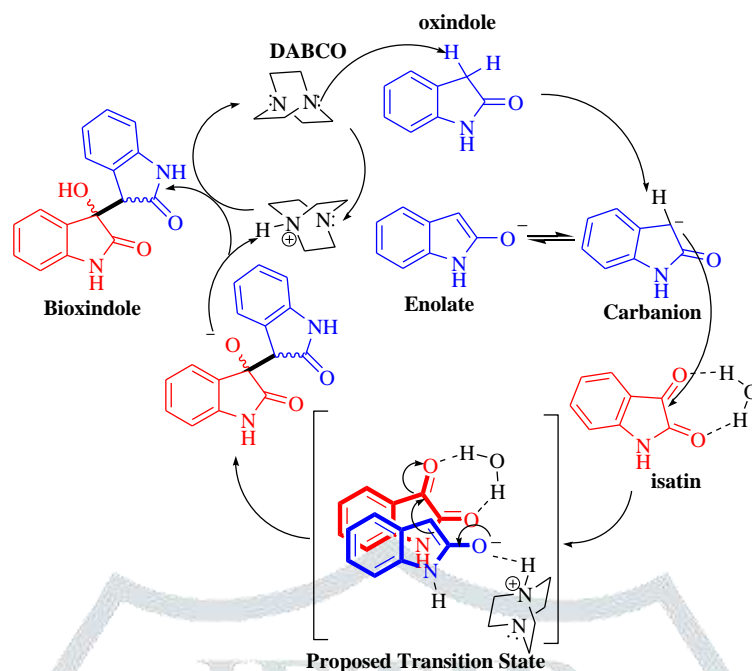
Scheme 2: Synthesis of bioindole frameworks using DABCO under aqueous medium

Further, we have tested the optimized reaction condition at a larger scale to demonstrate the scale-up potential of this reaction. In this context, we added the isatin **1a** (0.3 mol, 44.14 g) to the stirred mixture of oxindole **2a** (0.3 mol, 39.94 g) & DABCO (0.015mol, 1.68 g) in 1500 mL tap water at rt (**Scheme 3**). Reaction progressed the same way in which change in color was observed from red to white. The obtained thick white precipitate was filtered, washed and dried to afford the desired product **3a** with 94% yield (78.96 g, dr 96:04)



Scheme 3: Gram-scale synthesis of **3a**

The possible mechanism for the formation of bioindole framework is shown below in **scheme 4**. Catalyst DABCO abstract one of the C-3 acidic proton of oxindole to form oxindole carbanion which was stabilized enolate formation¹⁹. The oxindole carbanion attacks on the keto group of isatin to form desired product. The proposed transition state for the formation of the desired diastereoselective products is shown below. Finally protonation from protonated catalyst afford desired bioindole framework.



Scheme 4: Plausible mechanism for the formation of desired product.

IV. CONCLUSION

In summary, we have demonstrated DABCO catalyzed rapid synthesis of bioindole frameworks under aqueous medium. The developed method is a general route for the efficient synthesis of bioindole with very high isolated yields under environmentally benign reaction conditions. Furthermore, the products were obtained in sufficiently pure form simply by filtration. In addition to its simplicity, this method has a wide scope of substrates which tolerated a variety of functionalized isatins as well as oxindole derivatives. Furthermore, the method is also applicable for large scale synthesis. The developed method provides easy access to important precursor substituted 3,3'-bisoxindole framework which can be useful in the synthesis of different natural products as well as preparation of a library of pharmaceutically important compounds. The studies on an asymmetric version of this reaction employing chiral cinchona alkaloids derived organocatalysts is currently ongoing in our laboratory and results will be published elsewhere in due course.

V. Acknowledgments

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