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## Graphical Abstract

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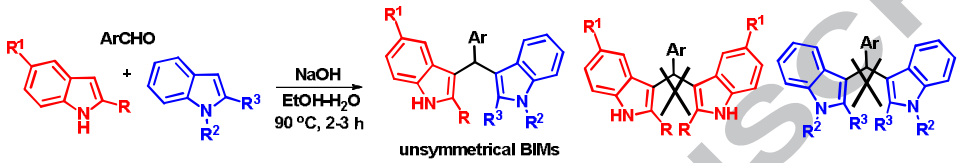

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# Base-promoted three-component cascade approach to unsymmetrical bis(indolyl)methanes

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ABSTRACT

Here we report a base-catalyzed reaction of two different indoles with aldehydes under heating to produce unsymmetrical bis(indolyl)methanes (BIMs), in which one of the indole ring must be N-substituted. Mixture of EtOH-$H_2O$ is used as solvent. The reaction did not give symmetrical BIMs of N-substituted indoles or N-H indoles. However, traces of latter were formed in few cases, especially when electron-rich aldehydes were used. Diversely substituted indoles and aldehydes were used for the reaction. The reaction proceeds *via* 3-indolylalcohol, which we confirmed through isolation. The method also gives good yield on multigram scale reaction.



## Introduction

During the last few decades, multi-component process (MCP), a green technology achieved much interest in synthetic chemistry due to their advantages of atom economy, simplified mode of operation, and energy savings.[1] Moreover, reduced reaction steps, waste, and cost are the additional advantages of the MCPs.[1] There has also been an increasing interest to replace hazardous solvents with environment friendly solvents such as water, ethanol, PEG, etc.[2] The cascade reaction which is also known as domino or tandem reaction is arguably first reported through the synthesis of tropinone.[3] Thereafter, the use of cascade reactions has flourished in the area of total synthesis, which is reflected by the numbers of published review articles.[4]

The importance of indole and their derivatives is well recognized by the synthetic as well as biological chemists.[5] 3,3-Bisindolylmethane (BIM) is one such important indole derivative has attracted lot of chemists and biologists due to its enormous bioactivity. For example, BIM increases the 2-hydroxylation of estrogen metabolites that helps to reduce the risk of breast and prostate cancer.[6] It is also under clinical trials for Cervical Dysplasia, a pre-cancerous condition caused by the Human Papilloma Virus.[7] It worked as HIV-1 integrase inhibitor,[8] and exhibit antibacterial activity.[9] It has been reported that the reaction of indoles with aldehydes or ketones can easily afford BIMs in the presence of a catalyst. The strategy is very simple, straightforward and provides always symmetrical BIMs.[10] But the synthesis of unsymmetrical BIMs is still highly desired in synthetic chemistry. There are only few reports for the synthesis of unsymmetrical BIMs, and all the methods use pre-functionalized indole derivative which reacts with a different indole molecule to form unsymmetrical BIMs.[11] However, they have a number of disadvantages and limitations such as use of two or more synthetic steps, expensive catalysts and highly unstable starting material. In continuation of our work on BIMs,[12] here we disclose an efficient base-catalyzed three-component cascade approach to unsymmetrical BIMs (Scheme 1). We believe this is the first report of three-component one-pot synthesis of unsymmetrical BIMs.

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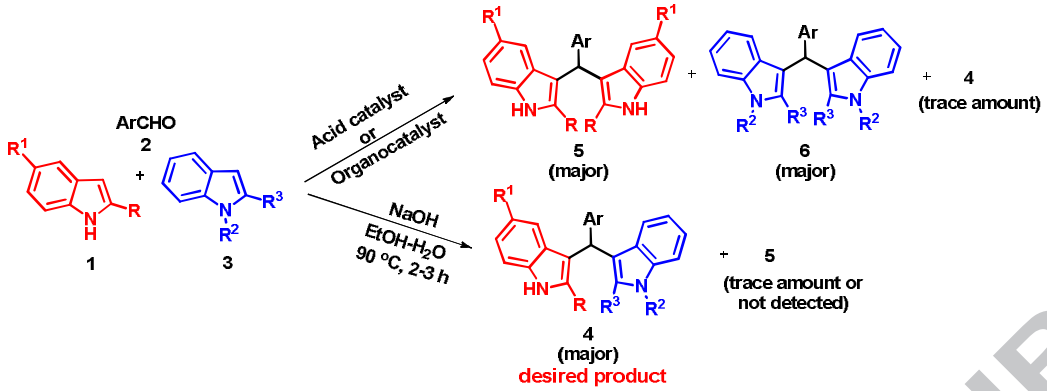
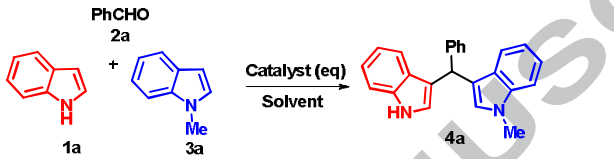
## Results and discussion

We started our study with the reaction of indole (**1a**), benzaldehyde (**2a**) and 1-methylindole (**3a**), which we considered as our model reaction, in the presence of different catalysts and solvents. After a careful screening of variety of catalysts, we established the optimum conditions for the synthesis of **4a**, in which sodium hydroxide (1.0 eq.) was used as catalyst in EtOH-$H_2O$ (1:1) as solvent at 90 ºC furnishing 85 % yield (entry 9, Table 1).[13] A trace of **5a** was also detected in the crude product. Decreasing the loading of base catalyst decreased the product yield, whereas increase of the same did not affect the yield (entries 10-11, Table 1). Using of either pure ethanol or water as solvent afforded lower yield (entries 5 and 7, Table 1). There was also a decrease in the product yield with the increase in the ratio




**Scheme 1**. Synthesis of unsymmetrical BIMs

**Table 1**. Optimization of the reaction condition[a]

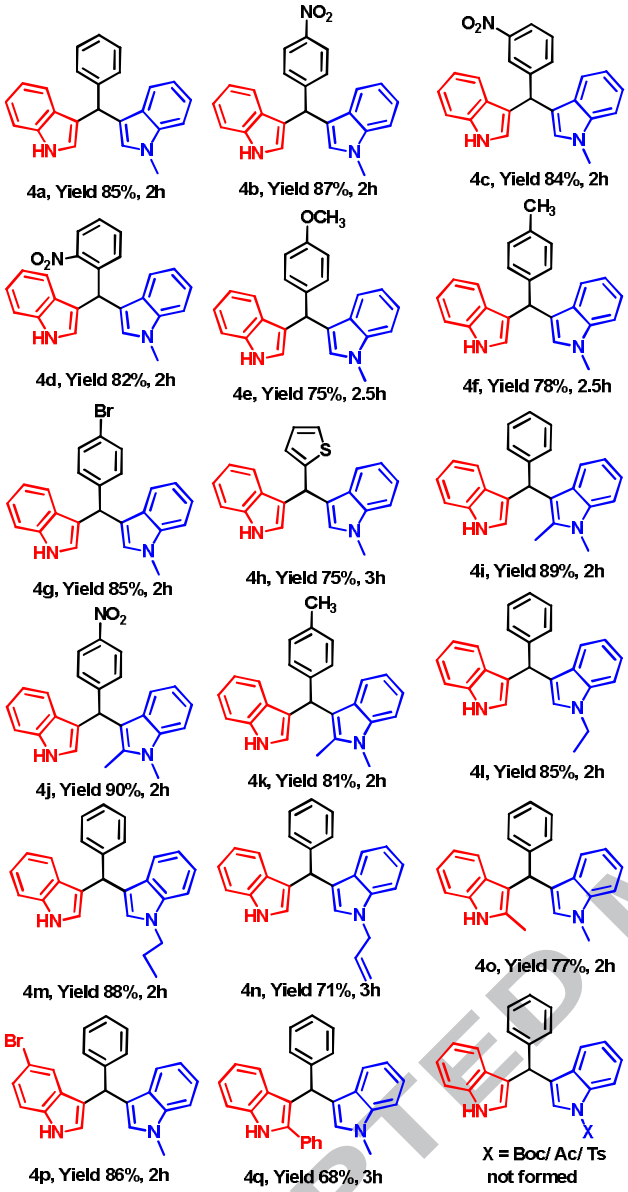



| Entry[c] | Catalyst (eq) | Solvent | Temp. (°C) | Time (h) | Yield 4a (%) |
|---|---|---|---|---|---|
| 1 | *p*-TsOH.$H_2O$ (0.1) | EtOH | reflux | 3 | Trace[b] |
| 2 | LiCl (0.1) | EtOH | reflux | 3 | Trace[b] |
| 3 | $I_2$ (0.1) | EtOH | reflux | 1 | Trace[b] |
| 4 | L-Proline (0.2) | EtOH | reflux | 3 | Trace[b] |
| 5 | NaOH (1.0) | EtOH | reflux | 3 | 58 |
| 6 | NaOH (1.0) | MeOH | reflux | 3 | 40 |
| 7 | NaOH (1.0) | $H_2O$ | reflux | 3 | 20 |
| 8 | NaOH (1.0) | $CH_3CN$ | reflux | 3 | 24 |
| **9** | **NaOH (1.0)** | **EtOH-$H_2O$ (1:1)** | **90** | **2** | **85** |
| 10 | NaOH (0.8) | EtOH-$H_2O$ (1:1) | 90 | 2 | 60 |
| 11 | NaOH (1.3) | EtOH-$H_2O$ (1:1) | 90 | 2 | 85 |
| 12 | NaOH (1.0) | EtOH-$H_2O$ (1:1) | 100 | 2 | 84 |
| 13 | NaOH (1.0) | EtOH-$H_2O$ (1:1) | 80 | 2 | 68 |
| 14 | NaOH (1.0) | EtOH-$H_2O$ (1:1) | RT | 20 | 38 |
| 15 | NaOH (1.0) | EtOH-$H_2O$ (1:2) | 90 | 2 | 42 |
| 16 | KOH (1.0) | EtOH-$H_2O$ (1:1) | 90 | 2 | 83 |
| 17 | $K_2CO_3$ (1.0) | EtOH-$H_2O$ (1:1) | 90 | 4 | 30 |
| 18 | $Et_3N$ (1.0) | EtOH-$H_2O$ (1:1) | 90 | 4 | NR[d] |
| 19 | DMAP (1.0) | EtOH-$H_2O$ (1:1) | 90 | 4 | NR |
| 20 | $Cs_2CO_3$ | EtOH-$H_2O$ (1:1) | 90 | 4 | NR |

[a] Unless otherwise mentioned, all the reactions were performed by using **1a** (1.0 mmol, 117 mg), **2a** (1.0 mmol, 106 mg), **3a** (1.0 mmol, 131 mg). [b] **5a** and **6a** were formed predominantly. [c] Entries 5-17 also produced traces of **5a**. [d] NR: no reaction.

of water in the solvent mixture (entry 15, Table 1). Polar aprotic solvent such as $CH_3CN$ gave poor yield (entry 8, Table 1). At room temperature, the reaction produced only 38 % of yield after 20 h of stirring (entry 14, Table 1). We found KOH is nearly as good as NaOH to catalyze the reaction (entry 16, Table 1).

With the optimized condition in hand, we subsequently investigated the substrate scope for the synthesis of **4** by employing a variety of aldehydes and indoles. To our delight, compound **4** containing a broad range of substituents were formed in moderate to good yield, as summarized in Scheme 2. We also noticed that electron-rich aldehydes gave lower yield of **4** than electron-deficient aldehydes as the former produced minor amount of symmetrical BIM **5** along with **4** (e.g., **4b** *vs.* **4e**, Scheme 2). Functional groups on the phenyl ring such as -$NO_2$, -Br, -Me, -OMe were very much compatible. Heterocyclic aldehydes such as thiophene-2-carboxaldehyde also furnished the desired product in good yield (**4h**, Scheme 2). 2-Phenylindole produced the product with relatively lower yield (**4q**, Scheme 2). Though minor amount of **5** was formed in the few cases, however, we did not observe **6** in the crude product. When N-substituted indoles such as N-Boc/-acyl/-tosylindoles were separately treated with NH-indole and benzaldehyde under optimized condition, we obtained only **5** and no cross reaction




**Scheme 2**. Substrate scope for the synthesis of **4**. Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), NaOH (1.0 eq, 40 mg), EtOH-$H_2O$ (1:1, 2.0 mL) at 90 ºC. Products were purified by column chromatography using silica gel (100-200 mesh) and yields are for the isolated products. In case of **4e**, **4f** and **4k**, little amount of **5e** (12 %), **5f** (9 %) and **5k** (7 %) were also formed.

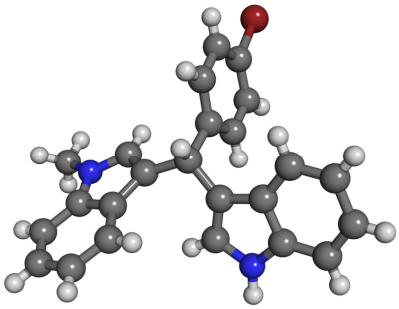
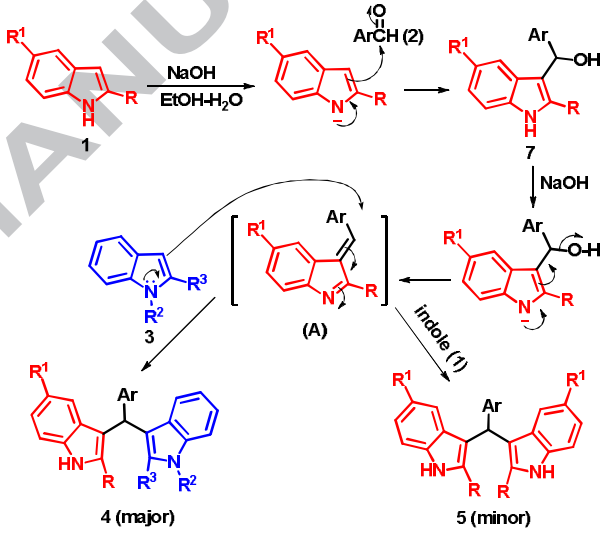


**Figure 1**. Single crystal X-ray structure of **4g**

was observed. We believe that the reason must be due to the poor nucleophilicity of the mentioned N-substituted indoles. Our model reaction gave us 88 % of **4a** when performed on 10 g scale showing that the reaction could be easily scaled up to multigram scale. Products were characterized by NMR and mass spectroscopy as well as single crystal X-ray crystallography (Figure 1).[14]

A tentative mechanism is proposed for the reaction (Scheme 3). First, the base abstracts the N-H proton of indole **1** and the resulting anion attacks the aldehyde to generate the 3-indolylalcohol **7**. NaOH again deprotonates the N-H proton of **7** and finally eliminates the -OH group to generate the alkylideneindolenine intermediates **A**. **A** was then attacked by N-alkylindole **3** to give the desired product **4**. Additionally, **A** reacts with indole **1** to furnish small amount of symmetrical bisindolylmethanes **5** as side product in few cases. To support the mechanism, we isolated the indolylalcohol **7** (by stopping the reaction before completion) and characterized. Since the presence of water in the reaction enhanced the yield of **4**, we believe that the water might help to solubilize the base catalyst into the reaction medium. However, water alone as solvent gave only poor yield due to insolubility of organic substrates into it.




**Scheme 3**. Tentative mechanism proposed for the reaction

In conclusion, we have successfully developed a 3-component cascade approach for the synthesis of unsymmetrical bis(indolyl)methanes. The reaction proceeds through the formation of alkylideneindolenine intermediate. The reaction is free from hazardous metal or Lewis acid catalyst and uses environment-friendly solvent. The reaction could easily be scaled up to multigram scale with good yield. To the best of our knowledge, this is the first report of one-pot multi-component synthesis of unsymmetrical bis(indolyl)methanes. We anticipate that this method would offer efficient and cost effective way to obtain this important class of compounds.

## Acknowledgments

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13. **General procedure for the synthesis of compound 4**: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol) and NaOH (1.0 mmol, 40 mg) were taken in a screw-top V-vial. EtOH-$H_2O$ (1:1, 2.0 mL) as solvent was added to this. Closed the vial and heated at 90 $^oC$ in an oil bath for specified time. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under vacuum and extracted with dichloromethane (DCM). Removed the DCM under vacuum and the crude product was purified by column chromatography (silica gel 100-200 mesh, hexane-ethyl acetate as eluent) to obtain **4** as pure product. For multigram scale reaction, the same procedure has been followed.
14. Crystallographic data for compound **4g** have been deposited with CCDC 1532121 and can be obtained free of charge from the Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk/conts/retrieving.html.

## Highlights

The main highlights of the manuscript are-

- Metal-free cascade approach to unsymmetrical bis(indolyl)methanes.
- Base catalyzed reaction using EtOH-$H_2O$ as solvent.
- The reaction could be easily scaled up.
- First report of their synthesis by multi-component strategy.