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# One-pot synthesis of bis(indolyl)methane derivatives using zwitterionic-type molten salt-catalyzed (IBS) as an efficient catalyst under solvent-free conditions

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## ABSTRACT

A clean and efficient method for the synthesis of bis(indolyl)methane derivatives with antimony zwitterionic-type molten salt-catalyzed (IBS) as the catalyst under solvent-free conditions is described. This method provides several advantages, such as simple work-up procedure, neutral conditions using a cheap, non-toxic, environment friendly solvent, and high yields.



## KEYWORDS

Bis(indolyl)methane derivatives;
Zwitterionic-type molten salt-catalyzed (IBS);
Solvent-free conditions.

## INTRODUCTION

Multi-component reactions (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks, and show high atom-economy, high selectivity and procedural simplicity due to the formation of carbon- carbon and carbon-heteroatom bonds in one-pot[1]. As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from the two-component reactions in several aspects[2] and permitted rapid access to combinatorial libraries of organic molecules for efficient lead structure identification and optimization in drug discovery[3]. In addition, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and green chemistry[4].

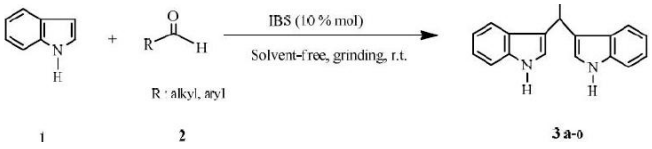
Bis(indolyl)methanes are a biologically valuable group of organic compounds. A large number of these compounds have been isolated from earthly and marine natural sources such as sponges[5]. They are also identified to promote useful estrogen metabolism and are found in cruciferous plants[6]. Bis(indolyl)methanes have many applications in material sciences, agrochemicals and pharmaceuticals[7]. Hence, in the recent years, there is substantial interest in the synthesis of these compounds[8,9]. Many methods are reported to synthesize bis(indolyl)methanes. The reaction of 1H-indole with aldehydes or ketones produces azafulvenium salts which react further with a second 1H-indole molecule to form bis(indol-3-yl)methanes[10]. Nowadays, synthesis of this category of molecules under mild conditions have been reported, with promoters such as $AlPW_{12}O_{40}$[11], $Dy(OTf)_3$/ionic liquid[12], $In(OTf)_3$/ionic liquid[13], MW/Lewis acids ($BiCl_3$, $FeCl_3$, $InCl_3$, $CoCl_2$, $ZnCl_2$)[14], silica sulfuric acid (SSA)[15], acidic ionic liquid[16], trichloro-1,3,5-triazine[17], $H_3PW_{12}O_{40}$[18], and ceric ammonium nitrate (CAN)[19]. However, most of the existing methods involve toxic metal ions and solvents, have high costs and use corrosive reagents. A mild and efficient catalyst for the synthesis of bis(indolyl)methanes is very desirable.

## EXPERIMENTAL

Chemicals were obtained from Merck and Fluka chemical companies. The IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained in $CDCl_3$ using a 400 MHz JEOL FT NMR spectrometer. All melting points were determined on an Electro Thermal 9100 melting point apparatus

## GENERAL PROCEDURE SYNTHESIS OF DIPYRROMETHANES

A mixture of indol (2.0 mmol), aldehyde or ketone (1.0 mmol) and 4-(1-imidazolium) butane sulfonate (41 mg, 10 mol %) were added to a mortar and the mixture was pulverized with a pestle. A spontaneous reaction took place [< 1 min, TABLE 2, monitored by TLC (4:1, hexane/ acetone)]. After completion of the reaction, $CH_2Cl_2$ (10 mL) was added, and insoluble reagents were removed by filtration. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by column chromatography using silica gel with petroleum ether/chloroform as the eluent. Pure products were obtained as solids.

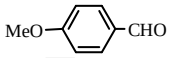
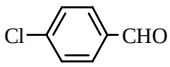
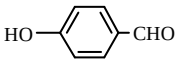
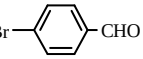
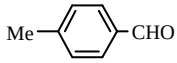
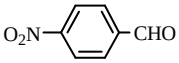



**Scheme 1**

## RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods and the development of green chemical procedures for the transformations in organic synthesis using[20-27], we wish, herein, to report on the use of IBS as a more robust and efficient catalyst in the

**TABLE 1 : Synthesis of bis(indolyl)methanes by the reaction of indole with aldehydes and ketones under a solvent-free condition**

| Entry | Substrate | Product [a] | Time (min) | Yields (%)[b] | M.p., °C (Lit.)[c] |
|---|---|---|---|---|---|
| 1 |  | 3a | 2 | 97 | 126-128 (125-127) |
| 2 |  | 3b | 4.5 | 93 | 126-128 (191-193) |
| 3 |  | 3c | 4 | 92 | 129-131 (131-133) |
| 4 |  | 3d | 3 | 95 | 104-106 (104-105) |
| 5 |  | 3e | 2 | 96 | 74-76 (73-75) |
| 6 |  | 3f | 2 | 97 | 81-82 (81-83) |
| 7 |  | 3g | 7 | 92 | 122-124 (123-125) |
| 8 |  | 3h | 2 | 93 | 110-112 (112-113) |
| 9 |  | 3i | 4 | 92 | 93-95 (94-96) |
| 10 |  | 3j | 5 | 94 | 223-225 (221-223) |
| 11 |  | 3k | 4 | 96 | 144-146 (142-144) |
| 12 |  | 3l | 3 | 85 | 149-150 (150-151) |
| 13 |  | 3m | 5 | 84 | 322-324 (>300) |

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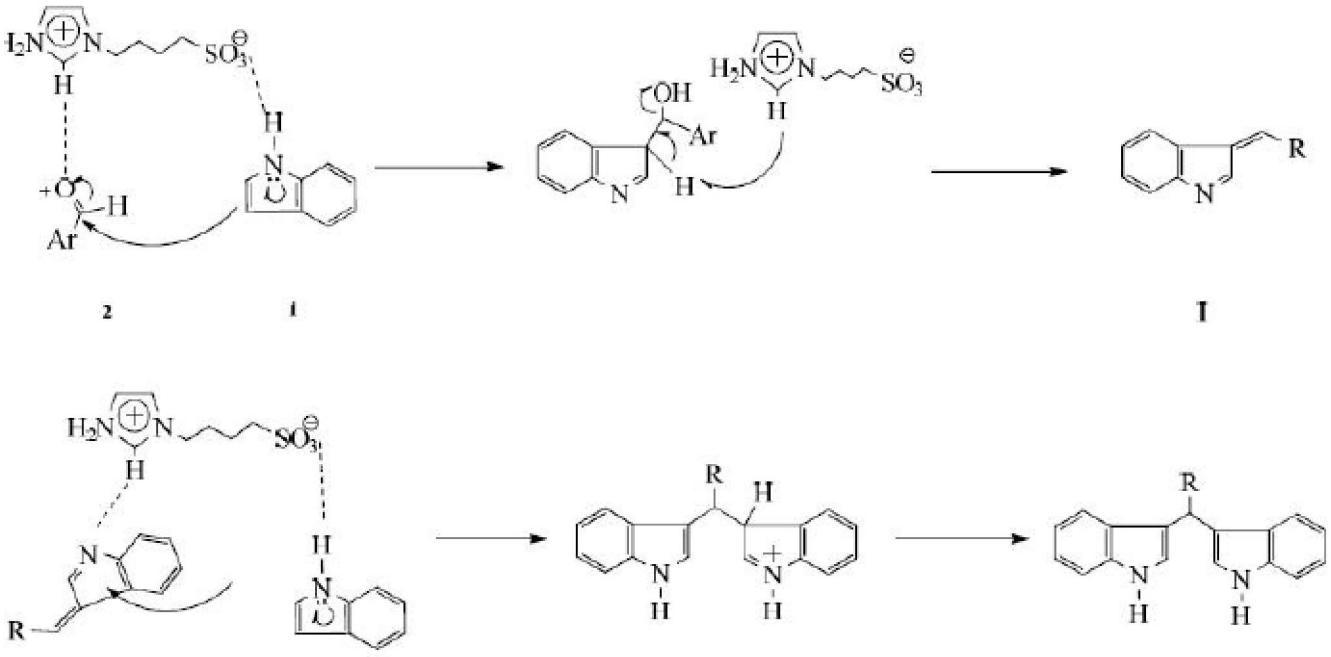

**Scheme 2**

one-pot synthesis of bis(indolyl)methanes (3a-o) from condensation of various aldehydes (2) with indole (1) under a solvent-free condition (Scheme 1 and TABLE 1).

Thus, the aldehydes act as *Michael* acceptors and the indole as the nucleophiles resulting in a *Michael* adduct which, under the influence of IBS, forms an intermediate I which undergoes nuclophilic reactions with indole to afford bis(indolyl)methane derivatives. The advantages or the characteristic aspects of the method described herein, in comparison with those already reported are the following: The yields of products are better than the previously reported yields. In addition, the catalyst IBS is inexpensive and not moisture sensitive and only sub-molar amounts of IBS are required. Longer reaction times are required when smaller amounts of IBS are employed. It is important to note that no bis(indolyl)methane derivatives were formed when the reactions were carried out in the absence of IBS.

## CONCLUSION

The present methodology shows that zwitterionic-type molten salt (IBS) is an efficient catalyst in the one pot synthesis of bis(indolyl)methane derivatives under solvent-free in room temperature. The main advantages of the presented protocol are mild, clean and environmentally benign reaction conditions, as well as the high yields. Furthermore, this method is also expected to find application in organic synthesis due to the low cost of the reagent. It is believed that this method will be a useful addition to modern synthetic methodologies.

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