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# Green approach Synthesis of Bis(indolyl)methanes Under Solvent Free, Catalyst Free Conditions

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***ABSTRACT***
*One-pot, reactions of indole, and aromatic aldehydes under solvent-free, catalyst free conditions leads to the formation of the corresponding bis(indolyl)methanes in moderate to high yields. The key features of these reactions are the simple reaction procedure, no organic solvent or acid catalyst and easy product separation.*

***Key words :*** *Aldehydes, Solvent-free, Bis(indolyl)methanes, Catalyst free.*

## 1. INTRODUCTION

With the advent of green chemistry, chemists are searching for innovative new approaches for the generation, purification, and use of chemical products, which adhere to the 12 principles laid out by Anastas and Warner [1]. For synthetic purposes, innovations to be sought involve the minimization of derivatizations, auxiliary substances, the number of steps, and the maximization of incorporation of starting materials and reagents. Minimizing solvent involves either making solvent completely unnecessary or if one must be used, and then an innocuous solvent is preferable. It is even more desirable, reactions, which take place either neat [2], or in an alternative media such as water [3] or others [4] can impart improved selectivity, enhance reactivity or ameliorate the ease of separation or purification. The concepts of atom economy [5] and step economy [6] provide the guiding principles to design more efficient synthesis.

Indole frameworks have attracted a plethora of research areas due to the large number of applications in material sciences [7], agrochemicals [8], and pharmaceuticals [9].Various indole derivatives, such as 3-substituted indoles, are common components of drugs and are generally found to be of pharmaceutical interest in a variety of therapeutic areas [10]. In addition, 3-substituted indole derivatives are also versatile intermediates in organic synthesis [11], in which bis(indolyl)methanes are important. Bis(indolyl)methanes, which contain two indole or substituted indole units in a molecule, bis(indolyl)alkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin [12] Bis(indolyl)methanes have been obtained by reactions of indoles with various aldehydes or ketones in the presence of either protic [13] or Lewis acids [14]. Most of the previously reported methods suffer from several setbacks such as requirement of a stoichiometric amount of the Lewis acid, expensive and highly toxic catalysts, long reaction times. However these problems were overcome to some extent by recently reported methods, the use of an ionic liquid [15] and the use of $I_2$ [16]. Hence it is desirable to develop an inexpensive, environmentally benign system for synthesis of highly usefull bis(indolyl)methanes under solvent and catalyst free conditions. Herein, we report for the synthesis of various bis(indolyl)methanes and bis(indolyl)alkanes by reaction of indoles with a variety of aldehydes at room temperature (Scheme 1).

## 2. RESULTS AND DISCUSSION

In general many synthetic protocals have been developed for the preparation bis(indolyl)alkanes derivatives, however all these methods suffered from many limitations such as use of expensive reagents, controlled temperatures, drastic reaction conditions, use of costly transition metal catalysts, toxic flammable organic solvents ,longer reaction

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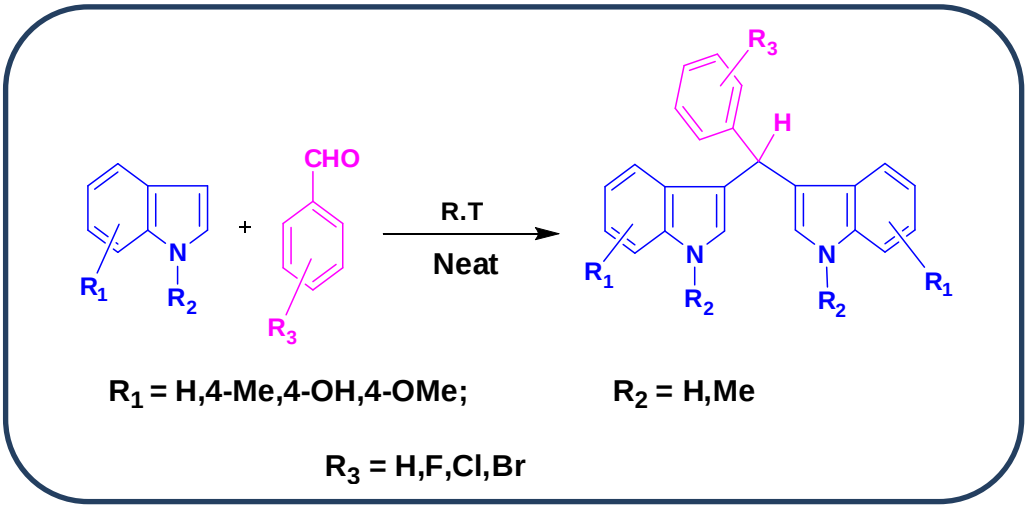
times and complicated work-up procedures, to over come these drawbacks we have developed a convenient and environmentally green methodology for the synthesis of bis(indolyl)alkanes in the absence hazard solvents, we prepare bis(indolyl)alkanes in neat conditions. In general, all the reactions were very clean, and the bis(indolyl)methanes were obtained in high yields (Table 1). The electrophilic substitution reactions of indoles with aldehydes proceeded smoothly at room temperature. The results summarized in Table 1, clearly indicate the scope and generality of the reaction as the reactions of aromatic aldehydes, heterocyclic aldehydes with indoles gave the corresponding bis(indolyl)methanes in excellent yields.

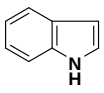
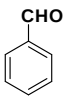
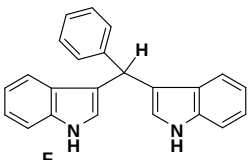
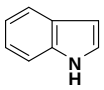
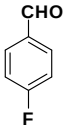
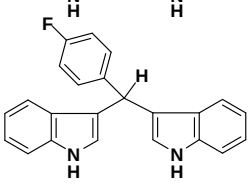
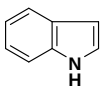
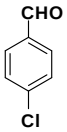
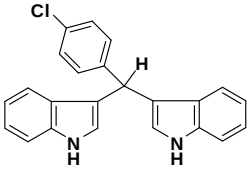
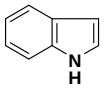
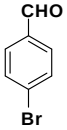
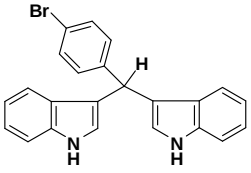
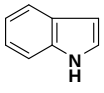
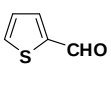
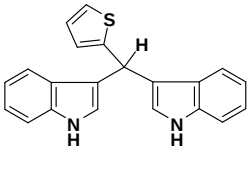
## 3. CONCLUSIONS

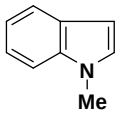
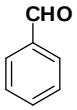
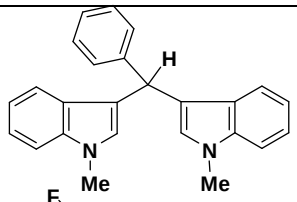
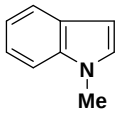
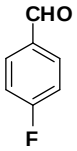
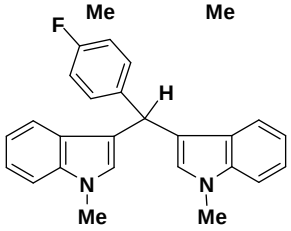
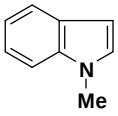
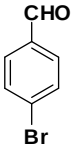
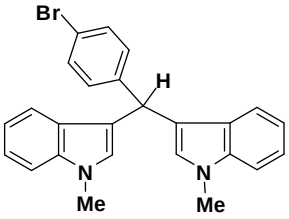
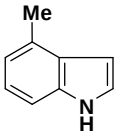
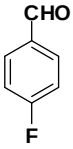
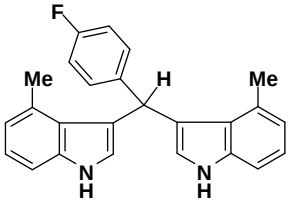
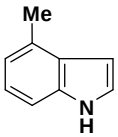
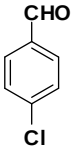
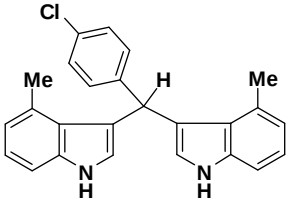
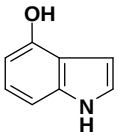
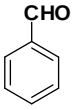
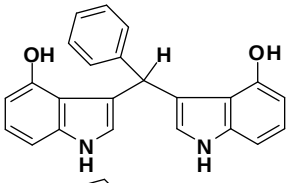
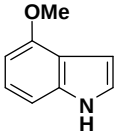
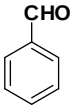
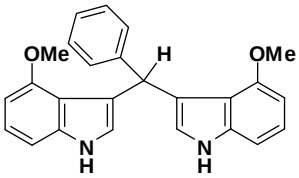
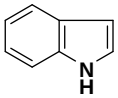
To the best of our knowledge, this is the first report on the synthesis of bis(indolyl)alkanes derivatives in this method.




**Scheme 1.** Synthesis of bis(indolyl)methanes and bis(indolyl)alkanes by reaction of indoles with aldehydes at room temperature.

**Table 1.** The reaction of aromatic aldehyde with indole under solvent-free condition at room temperature

| Entry | Indole | Aldehyde | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  |  |  | 94 |
| 2 |  |  |  | 90 |
| 3 |  |  |  | 86 |
| 4 |  |  |  | 91 |
| 5 |  |  |  | 82 |

| Entry | Indole | Aldehyde | Product | Yield (%) |
|---|---|---|---|---|
| 6 |  |  |  | 80 |
| 7 |  |  |  | 82 |
| 8 |  |  |  | 81 |
| 9 |  |  |  | 79 |
| 10 |  |  |  | 82 |
| 11 |  |  |  | 75 |
| 12 |  |  |  | 83 |
| 13 |  | Ketone | No Reaction | 0 |

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[18]. *General*. All the chemicals were purchased from Sigma Aldrich. Analytical thin layer chromatography (TLC) was carried out using silica gel (*60* $F_{254}$, 0.2 mm layer; *E. Merk*) pre-coated plates. Visualization was accomplished with UV lamp or $I_2$ stain. $^{1}H$ and $^{13}C$ NMR (*Varian 200* or *Bruker 300* spectrometer) $\delta$ in ppm, *J* in Hz. in $CDCl_3$ using TMS as the internal standard. Mass spectra: *VG Autospec*; in *m/z* recorded.

[19]. *General Procedure for the Synthesis of bis(indolyl)methanes*:A mixture of indole (2 mmol) and aromatic aldehyde (1 mmol) was ground thoroughly in a pestle and mortar at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, Water (30 mL) was added to the resulting reaction mixture followed by extraction with EtOAc (4-10 mL). The collected organic phases were dried with $Na_2SO_4$ and the solvent was removed under vacuum to give the corresponding Bis(indolyl)methanes, which did not require any further purification.