



Research Article

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**Microwave-promoted Zirconium (IV) Chloride as an efficient, environmentally benign and recyclable homogeneous catalytic system to synthesis of bis(indolyl)methanes, in PEG as a solvent**

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**ABSTRACT**

*A simple, environmentally benign and highly efficient synthesis of Bis(indolyl)methane by using Microwave-promoted Zirconium (IV) Chloride as a catalyst in PEG as a reaction solvent. Zirconium (IV) Chloride is an attractive catalyst for the electrophilic addition reaction of indole with aldehyde to afford the corresponding bis(indolyl)methane. The procedure is simple, rapid and high yielding. The catalyst exhibited a remarkable reactivity and is reusable in PEG-400 as a solvent. The  $ZrCl_4$  in PEG-400 can be reused up to 4 times without significant loss in yields and selectivity.*

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**INTRODUCTION**

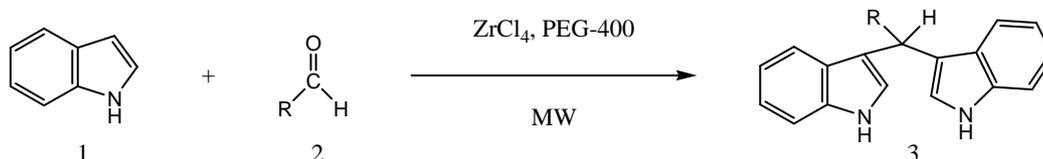
The acid catalyzed reaction of electron rich heterocycles such as indole or pyrrole with 4-dimethyl aminobenzaldehyde is known as Ehrlich test [1,2] and the same reaction of indole with other aldehydes gives corresponding bis(indolyl)alkanes, which is the useful class of biologically active organic compounds[3,4]. The synthesis of bis(indolyl)alkane has attracted interest because of their occurrence in various natural products possessing biological activities and usefulness for drug design [5]. A large number of these compounds have been isolated from earthly and marine sponges and from cruciferous plants [6,7]. Bis(indolyl)methanes have many applications in material sciences, agrochemicals and pharmaceuticals [3-5]. Especially, bis(indolyl)methane is identified to promote estrogen metabolism which is expected to have an application in the prevention of breast cancer in both women and men [8,9]. Due to such biological importance, in the recent years the synthesis of bis(indolyl)methane and its derivatives received considerable attention.

For the synthesis of bis(indolyl)alkane by an acid catalyzed electrophilic substitution reaction of indoles with carbonyl compounds, A variety of protic as well as Lewis acids are known to promote this reaction. However, many Lewis acids are prove to undergo decomposition in the presence of nitrogen containing reactants and this necessitates the use of excess and sometimes stoichiometric amount of Lewis acid catalyst. A variety of catalysts such as  $PPh_3 \cdot HClO_4$ [10],  $InCl_3$  [11],  $Ln(OTf)_3$  [12], cyanuric chloride [13], Iodine[14],  $ZrCl_4$  in acetonitrile [15] and 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquids [16] have been reported to catalyzed this reaction. However, many of these reagents are expensive, need longer reaction time and are not environmental friendly which warrants the development of a new, practical, economic and environmental friendly protocol for the synthesis of bis(indolyl)methanes.

Many chemists have made a great deal of effort to design environmental benign and clean synthetic procedures to replace the classical synthetic methods. Microwave heating is an eco-friendly approach and a valuable tool for synthetic chemists because it is possible to increase the reaction rate and product yields as well as exploits a variety of factors such as milder and more efficient conditions, shorter reaction times, energy conservation, formation of purer products and waste minimization. There is an enormous growth of interest in this promising technique for promoting reactions. [17-22]

On the other hand, the development of green and clean synthetic methods, those involving solvent-free or the use of alternative solvents, such as water, ionic liquids and polyethylene glycol (PEG), has increased in recent years. [23-27] solvents play a critical role in mixing the ingredients to allow molecular interaction. Despite several advantages, the solvent-free methods are restricted to systems where at least one of the reagents is liquid at room temperature, whereas the use of ionic liquids, especially imidazolium systems with PF<sub>6</sub><sup>-</sup> and BF<sub>4</sub><sup>-</sup> anions, have some drawbacks, such as the high cost and liberation of hazardous HF during recycling and ionic liquids safety is still debated and the reactions in water do not give good yields because of the hydrophobic nature of the organic reactants. Thus, the use of PEG and other alternative non-volatile solvents has been shown as an attractive way to cleaner organic synthesis. Recently, polyethylene glycol is found to be an interesting recyclable and eco-friendly solvent system in synthetic chemistry for various organic transformations with unique properties such as thermal stability, commercial availability and immiscibility with a number of organic solvents. In general, PEG is an inexpensive, non-toxic and completely non-halogenated. Green synthetic routes are the main concern of the present century and current synthetic efforts are directed to achieve this goal. Certainly, there is increasing pressure on chemist to replace toxic catalyst and volatile solvents, Currently, PEG is finding extensive use in organic synthesis as it is a well-known green solvent and more suited to microwave irradiation. Also, the use of PEG under MW irradiation is reported in several organic reactions claiming green protocols.[28-31]

In conventional bis(indolyl)methane synthesis reaction highly toxic Lewis acid catalysts have been used and during aqueous reaction workup leave toxic gases which are released in to the environment. Due to the low cost and easy handling of zirconium chloride and the green nature of recyclable PEG encouraged us to combine them together and used their utility for the synthesis of bis(indolyl)methane.



Scheme 1. Synthesis of Bis(indolyl)methane

In continuation of our work on the development of useful synthetic methodologies for the carbon-carbon bond formation [32-34] and biologically active compound synthesis [35-38] reactions we have developed an environmentally benign and highly efficient synthesis of bis(indolyl)methane by using Zirconium (IV) Chloride as a catalyst in PEG as a reaction solvent under microwave irradiation (Scheme-1). However, to the best of our knowledge, no such recyclable Zirconium (IV) Chloride in PEG as a homogeneous catalytic system has been explored for the bis(indolyl)methane synthesis.

## EXPERIMENTAL SECTION

All chemicals and reagents required for the reactions were procured from Sigma-Aldrich and Loba chemicals with purity >98% and used without further purification. The products were characterized using <sup>1</sup>H NMR, <sup>13</sup>C NMR spectrometer with TMS as the internal standard. Column chromatography was performed on silica gel, Merck grade 60-120 mesh size. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F254). The compounds are already well known in the literature.

### Typical procedure

#### General procedure.

A mixture of indole (2 mmol), aryl aldehyde (1 mmol) and ZrCl<sub>4</sub> (5 mol%) in 3mL PEG-400 was taken in a round bottom flask fitted with a guard tube was subjected to domestic microwave (Kenstar, Microwave output 800W ±10%; microwave frequency 2450MHz) irradiation for a 4 min. On completion of reaction (checked by TLC) chloroform (10 mL) was added and the reaction mixture was separated through separating funnel. The catalyst was washed with chloroform (2x10 mL). Removal of solvent from combined filtrate gave the residue, which was purified through a column of silica gel to afford pure bis(indolyl)alkane. The PEG and catalyst was recovered and recycled without affecting the yields of the products. The spectral data of some of the bis(indolyl)methane is summarized below.

#### Spectroscopic data

**3,3'-Bis(indolyl)-4-methylphenylmethane** (Table 2, Entry 2). mp 96 °C; (Lit (94-96 °C [15])); PMR (300 MHz, CDCl<sub>3</sub>): δ = 2.31(s,3H), 5.84(s,1H), 6.64(s, 2H), 6.85-7.40(m, 12H), 7.94(br s, 2H); CMR (75 MHz, CDCl<sub>3</sub>): δ = 136.7, 128.9, 127.1, 123.5, 121.9, 119.9, 119.2, 110., 55.9, 39.8.

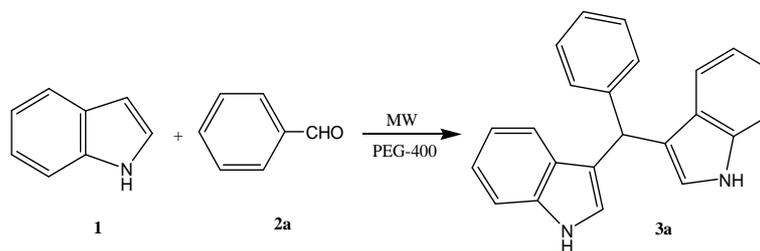
**3,3'-Bis(indolyl)-4-chlorophenylmethane** (Table 2, Entry 4). mp 78 °C; (Lit. (76-77 °C [15]); PMR (300 MHz, CDCl<sub>3</sub>): δ= 5.88 (s, 1H), 6.63 (br s, 2H), 7.00-7.70(m, 12H), 7.92(br s, 2H); CMR ( 75 MHz, CDCl<sub>3</sub>): δ= 136.7, 130.1, 128.1, 126.8, 123.5, 122, 119.8, 119.4, 119.3, 111, 39.8.

**Bis-(4-Nitrophenylmethylene)-Bis-(1h-indole)** (Table 2, Entry 7): mp 218°C (Lit. (221-223 °C [15]); PMR (300 MHz, CDCl<sub>3</sub>): 5.92 (s, 1H), 6.63 (d, 2H), 6.94 (t, 2H), 7.10-7.31 (m, 6H), 7.43 (d, 2H), 7.96 (br s, 2H), 8.16 (d, 2H); CMR (75 MHz, CDCl<sub>3</sub>): 40.3, 111.3, 118.1, 119.4, 119.6, 122.5, 123.6, 126.5, 129.7, 136.7, 151.8.

## RESULTS AND DISCUSSION

At the onset of the research, we made a conscious effort to develop a catalytic system that would address the limitations of the previously reported Lewis acid-catalyzed bis(indolyl)methane synthesis reaction. During the preliminary studies indole (1) was reacted with benzaldehyde (2a) used as the model system in PEG under microwave irradiation. A series of experiments were performed to optimize various reaction parameters, such as the catalyst, catalyst loading and time (Tables 1). Initially we screened various Lewis acid catalysts such as FeCl<sub>3</sub>.6H<sub>2</sub>O, SnCl<sub>4</sub>, AlCl<sub>3</sub>, ZrCl<sub>4</sub> and ZnCl<sub>2</sub> (Table 1, entries 1–5). Among the catalysts examined, ZrCl<sub>4</sub> was found to be the best, providing excellent yields of the desired product **3a**. We further studied catalyst loadings ranging from 3 to 10 mol%; increasing the catalyst concentration from 3 to 5 mol% increased the yield of **3a** to 91%, a further increase to 10 mol% did not improve the yield further (Table 1, entries 4, 6 and 7). On the other hand, the yields of these reactions did not exceed more than 48% under thermal conditions (100 °C) even after long reactions times. The reaction was not successful in the absence of catalyst or MW irradiation. (Table 1, entries 8 and 9). In these reactions no corrosive substances were used and no waste formation was observed. The experimental procedure for these reactions was remarkably simple and required no toxic organic solvent or inert atmosphere. We found that the transformations could be accomplished by exposing a mixture of indole (2 mmol), benzaldehyde (1 mmol), and ZrCl<sub>4</sub> (5 mmol) in 3mL PEG-400 to MW irradiation (170 W, 100–120 °C) for 3.0–5.0 min. The reaction time was optimized at 4 min. (Table 1, entries 4, 10 and 11).

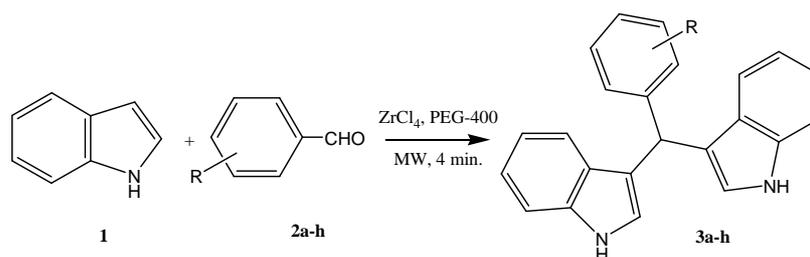
Table 1. Optimization of reaction parameters<sup>a</sup>



Entry	Catalyst	Mol % of catalyst	Time (min.)	Yield (%) <sup>b</sup>
1	FeCl <sub>3</sub> .6H <sub>2</sub> O	5	4	67
2	SnCl <sub>4</sub>	5	4	59
3	AlCl <sub>3</sub>	5	4	76
4	ZrCl <sub>4</sub>	5	4	91
5	ZnCl <sub>2</sub>	5	4	73
6	ZrCl <sub>4</sub>	3	4	72
7	ZrCl <sub>4</sub>	10	4	94
8 <sup>c</sup>	ZrCl <sub>4</sub>	5	600	48
9 <sup>d</sup>	--	--	4	34
10	ZrCl <sub>4</sub>	5	3	68
11	ZrCl <sub>4</sub>	5	5	92

<sup>a</sup>Reaction conditions: Indole (2 mmol), Benzaldehyde (1 mmol), PEG-400 (3 mL), Microwave Irradiation. <sup>b</sup>Isolated yield, <sup>c</sup>By thermal method, <sup>d</sup>Without catalyst.

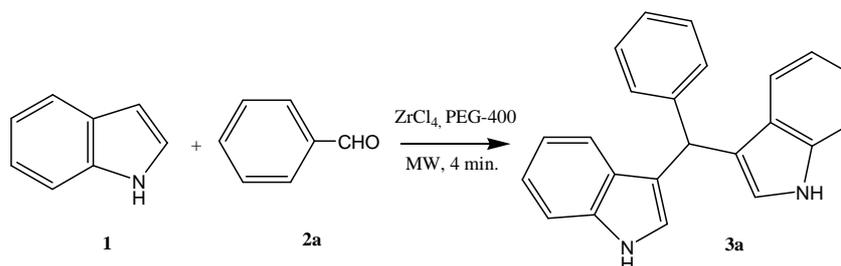
Having optimized reaction conditions in hand, we explored the substrate scope of the ZrCl<sub>4</sub> in PEG-400 catalyzed various aryl aldehydes containing different functional groups were investigated (Scheme 2). Products containing electron-donating **3b** and **3c**, as well as electron withdrawing groups **3d–h** were obtained. Gratifyingly a variety of common functional group, such as alkyl, ether, halo, nitro, amino and cyano were tolerated regardless of the *meta*- or *para*-position, however *ortho* substituted aryl aldehyde gave lower yields of **3e**, possibly due to steric hindrance.

Table 2. Substrate study for bis(indolyl)methane synthesis reaction<sup>a</sup>

Entry	Aldehyde	R-	Product	Yield (%) <sup>b</sup>	MP (°C)Obs. (Lit)
1	2a	-H	3a	91	126 (124-126) <sup>[11]</sup>
2	2b	-4-CH <sub>3</sub>	3b	88	96 (94-96) <sup>[11]</sup>
3	2c	-4-OCH <sub>3</sub>	3c	84	188(190-192) <sup>[11]</sup>
4	2d	-4-Cl	3d	90	78 (76-77) <sup>[11]</sup>
5	2e	-2-NO <sub>2</sub>	3e	68	224 (220-222) <sup>[39]</sup>
6	2f	-3-NO <sub>2</sub>	3f	90	220 (220-222) <sup>[39]</sup>
7	2g	-4-NO <sub>2</sub>	3g	92	218 (221-223) <sup>[11]</sup>
8	2h	-4-CN	3h	87	208 (212-214) <sup>[39]</sup>

<sup>a</sup>Reaction conditions: Indole (2 mmol), arylaldehyde (1 mmol), ZrCl<sub>4</sub>(5mol%), (PEG-400 (3 mL), Microwave Irradiation (4 min). <sup>b</sup>Isolated yield

Additionally, a reuse study of the ZrCl<sub>4</sub> in PEG-400 system was carried out for the reaction of **1a** with **2a** to obtain **3a**. After irradiation for 4 min, the reaction mixture was extracted with a mixture of hexane/ethyl acetate 95/5 (3x 3.0 mL). The upper organic phase was removed, the solvent evaporated and the product **3a** was isolated. The remaining inferior phase containing a mixture of ZrCl<sub>4</sub>/PEG-400 was dried under vacuum and directly reused for further reactions, simple by adding more reagents **1a** and **2a**. **3a** was obtained in 88%, 76% and 68% yields after successive cycles showing a good level of efficiency. (Table 3).

Table 3. Recycle study of the catalytic system<sup>a</sup>

Entry	Run	Yield (%) <sup>b</sup>
1	1 <sup>st</sup>	91
2	2 <sup>nd</sup>	88
3	3 <sup>rd</sup>	76
4	4 <sup>th</sup>	68

<sup>a</sup>Reaction conditions: Indole (2 mmol), benzaldehyde (1 mmol), ZrCl<sub>4</sub>(5mol%), (PEG-400 (3 mL), Microwave Irradiation (4 min). <sup>b</sup>Isolated yield

## CONCLUSION

In conclusion we have developed an efficient ZrCl<sub>4</sub> mediated, green method for the synthesis of bis(indolyl)methane by using PEG-400 as the solvent medium under microwave irradiation. The mild reaction conditions, operational simplicity, and volatile-solvent free conversion, application of a nontoxic and recyclable catalytic system, high yields and rapid formation of the products are the notable advantages of this method. These remarkable characteristics made this new protocol economically and eco-friendly attractive, inexpensive and offering the possibility of perform the reaction in the absence of toxic organic solvents.

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## REFERENCES

- [1] L Morgan; R Schunior. *J. Org. Chem.* **1962**, 27, 3696.
- [2] D Dolphin. *J. Heterocycl. Chem.* **1970**, 7, 275.

- [3] RJ Sundberg. *Academic Press: New York*, 1970.
- [4] S Hibino; T Choshi. *Nat. Prod. Rep.* **2001**, 18, 66-87.
- [5] GR Humphrey; JT Kuethe. *Chem. Rev.* **2006**, 106, 2875-2911.
- [6] G Bifulco; I Bruno; R Riccio; J Lavayre; G Bourdy. *J. Nat. Prod.* **1995**, 58, 1254-1260. [7] R Bell; S Carmeli; NJ Sar. *J. Nat. Prod.* **1994**, 57, 1587.
- [8] AM Zelig. *Journal Medicinal Food*, **1998**, 1, 67-82.
- [9] YC Chang; J Riby; GHF Chang; B Peng; G Firestone; FL Bjeldanes. *Biochemical Pharmacology*, **1999**, 58, 825-834.
- [10] R Nagarajan; PT Perumal. *Synth. Commun.* **2002**, 32, 105.
- [11] G Babu; N Sridhar; PT Perumal. *Synth. Commun.* **2000**, 30, 1609.
- [12] D Chen; L Yu; PG Wang. *Tet. Lett.* **1996**, 37, 4467.
- [13] GVM Sharma; JJ Reddy; PS Lakshmi; PR Krishna. *Tet. Lett.* **2004**, 45, 7729.
- [14] SJ Ji; SY Wang; Y Zhang; TP Loh. *Tetrahedron* **2004**, 60, 2051-2055.
- [15] RR Nagawade; DB Shinde. *Bull. Korean Chem. Soc.* **2005**, 26 (12), 1962-1964.
- [16] JS Yadav; BVS Reddy; S Sunitha. *Adv. Synth. Catal.* **2003**, 345, 349.
- [17] A Loupy. *Microwaves in Organic Synthesis; Wiley-VCH, Weinheim*, **2002**.
- [18] CO Kappe. *Angew. Chem., Int. Ed.*, **2004**, 43, 6250-6284.
- [19] CO Kappe; A Stadler. *Microwaves in Organic and Medicinal Chemistry, Wiley-VCH, Weinheim*; **2005**.
- [20] JP Tierney; P Lidstrom. *Microwave-Assisted Organic Synthesis, Blackwell, Oxford*, **2005**.
- [21] CO Kappe; D Dallinger; SS Murphree. *Practical Microwave Synthesis for Organic Chemists-Strategies, Instruments, and Protocols, Wiley-VCH, Weinheim*, **2008**.
- [22] CO Kappe. *Chem. Soc. Rev.*, **2008**, 37, 1127-1139.14.
- [23] TJ Dickerson; NN Reed; KD Janda. *Chem. Rev.* **2002**, 102, 3325.
- [24] S Chandrasekhar; SS Narasimhulu; NR Sultana; NR Reddy. *Chem. Commun.* **2003**, 1716.
- [25] B Das; P Balasubramanyam; GC Reddy; N Salvanna. *Helv. Chim. Acta*, **2011**, 94.
- [26] J Chen; SK Spear; JG Huddleston; RD Rogers. *Green Chem.* **2005**, 7, 64.
- [27] R Kumar; P Chaudary; S Nimesh; R Chandra. *Green Chem.* **2006**, 8, 356.
- [28] SD Kumar, JS Sandhu. *Indian J. chem.*, **2012**, 51 (B), 1743-1748.
- [29] DJ Heldebrant; PG Jessop. *J. Amer. Chem. Soc.* **2003**, 125, 5600.
- [30] SL Jain; S Singhal; B Sain. *Green Chem.* **2007**, 9, 740.
- [31] VN Vasudevan; SV Rajendra. *Green Chem.* **2001**, 3, 146.
- [32] BJ Khairnar; BM Bhanage. *Synthesis*, **2014**, 46, 1236-1242.
- [33] BJ Khairnar; S dey; VK Jain; BM Bhanage. *Tet. Lett.* **2014**, 55(3), 716-719.
- [34] BJ Khairnar; BM Bhanage. *Synfacts*, **2014**, 10, 0771.
- [35] BJ Khairnar; PS Girase; BR Chaudhari. *J. Chem. Pharm. Res.* **2015**, 7(2), 561-564.
- [36] BJ Khairnar; PS Girase; BR Chaudhari. *Orient. J. Chem.*, **2013**, 29(1), 285-289.
- [37] BJ Khairnar; RS Salunke; PB Patil; SA Patil; RJ Kapade; PS Girase; BR Chaudhari. *E-J. Chem.* **2012**, 9(1), 318-322.
- [38] BJ Khairnar; BR Chaudhari. *J. Chem. Pharm. Res.* **2015**, 7(4), 253-256.
- [39] KRM Naidu; SI Khalivulla; PCR Kumar; O Lasekan. *Org. Commun.* **2012**, 5(3), 150-159.