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ALUM CATALYZED GREEN SYNTHESIS OF BIS-INDOLYLMETHANES IN POLYETHYLENE GLYCOL AND WATER USING MICROWAVE IRRADIATION

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Abstract:
A sustainable approach to synthesize bis-indolylmethanes by employing alum as a catalyst, with polyethylene glycol (PEG) and water serving as environmentally friendly solvents. Microwave irradiation (MWI) significantly accelerates the reaction, leading to improved yields and shorter reaction times. The method not only reduces environmental impact but also proves cost-effective, demonstrating its potential for practical applications in sustainable synthesis.
Keywords: Alum, indole, carbonyl compounds, bis(indolyl)methanes, water, Microwave irradiation

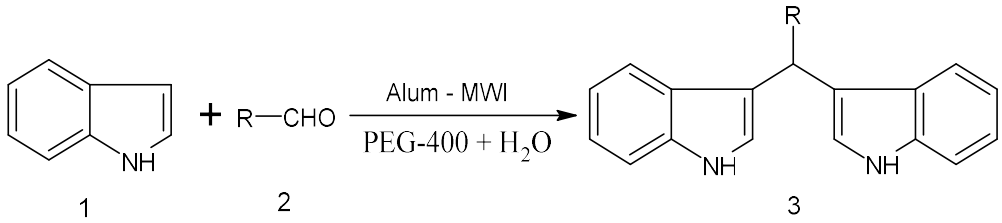
Introduction

Indole stands out as a privileged molecule in organic chemistry, with numerous derivatives established as pharmaceuticals.[1] Over the past decade, several bis(indolyl)methanes have been discovered in natural sources and some members exhibit promising biological activity. Specifically, bis(indolyl)methanes are recognized for their ability to enhance estrogen metabolism in humans, suggesting their potential as a preferred treatment for breast cancer. [2-3] Given these compelling biological activities and diverse applications, there is a current focus on developing protocols for the synthesis of bis(indolyl)methanes.

Various catalysts, including Brønsted acids (e.g., HCl, H_2SO_4)[4] and Lewis acids like $AlCl_3$, $BF_3.Et_2O$[5], and others[6-8], have been employed to achieve facile and efficient production of this group of indoles. Traditional Lewis acid catalysts, however, face challenges related to moisture sensitivity, making them prone to decomposition or deactivation in the presence of water. Some cases necessitate more than stoichiometric amounts of Lewis acids because these acids are trapped by nitrogen-containing reactants. To address these issues and ensure efficient synthesis, recent efforts have introduced alternative catalysts such as $NaHSO_4$-SiO_2, I_2, NBS, montmorillonite K-10, ionic liquids, and rare earth triflates to this reaction[9-12]. Despite the variety of reported procedures, several drawbacks persist, including low yield, prolonged reaction times, excessive reagent/catalyst usage, and the formation of hazardous by-products during aqueous work-up. Additionally, the majority of these methods involve expensive rare chemicals or require special preparation. These challenges underscore the need for further development of an environmentally benign and economical alternative for the synthesis of bis-

indolylmethanes.

In recent years, there has been a growing emphasis on adopting environmentally benign procedures and reagents for key reactions in organic chemistry. Notably, alum, recognized for its relatively non-toxic and cost-effective nature, has emerged as a versatile catalyst in various significant organic reactions. This includes its application in reactions such as Biginelli, Pechmann reaction[13-14], as well as in the synthesis of isoquinolonic acids, 2,3-dihydroquinazolin-4(1H)-ones, 1,3,4-oxadiazoles, for the synthesis of 1,5-benzodiazepines[15-20]. Building upon our prior investigations into indole chemistry[21] this paper presents alum as a mild, efficient, economical, and environmentally friendly catalyst for the synthesis of bis-(indolyl)methanes in Polyethylene Glycol and Water as green media Using Microwave Irradiation (**Scheme I**).



Scheme I: Synthesis of bis-(indolyl)methanes in Polyethylene Glycol and Water as green media Using Microwave Irradiation.

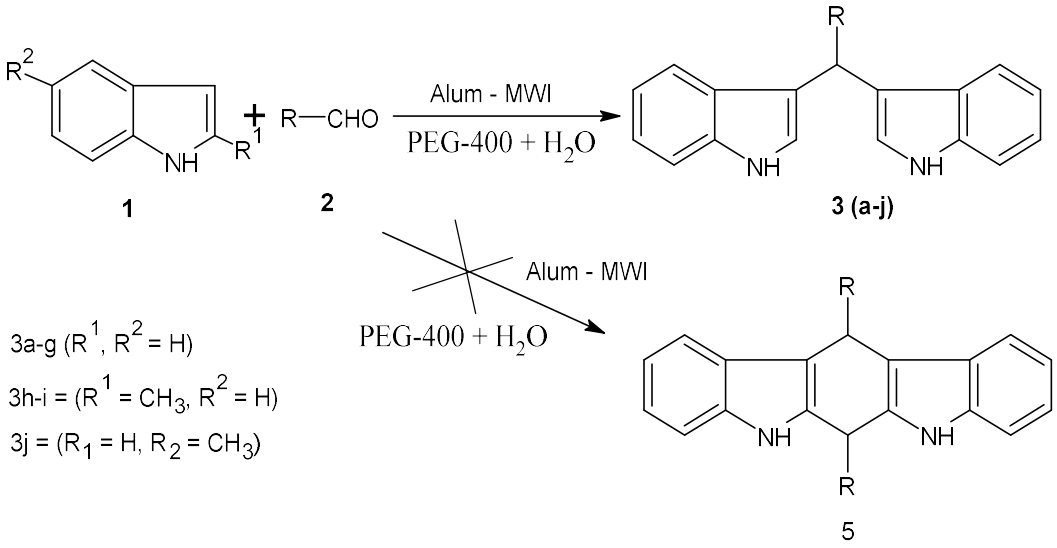
Result and Discussion:

Initially a mixture of benzaldehyde (1 mmole) and indole (2 mmole) in 3 mL of water and 3 ml PEG-400 was irradiate under MWI upto 18 min, yielding 3,3'-bis(1H-indolyl)phenylmethane **3a** in very poor yield. Then alum catalyst is used to catalyzed this reaction and used a mixture of benzaldehyde (1 mmole), indole (2 mmole), and alum (0.1 mmole) in 3 mL of water and 3 ml PEG-400 was irradiate under MWI for 12-14 min yielding 3,3'-bis(1H-indolyl)phenylmethane **3a** in a 68% yield. Further, optimizing the catalyst quantity and modifying reaction conditions involved the use of varying amounts of alum catalyst in similar reaction setups with identical reactants (Table I). The results demonstrated that 0.50 mmol of alum successfully catalyzed the condensation of benzaldehyde and indole, resulting in a shorter reaction time and yield is 95%. However, increasing the alum catalyst quantity and extending the reaction duration did not yield any significant improvements in either reaction time or overall yield (Table I).

Table I - Effect of catalyst for the synthesis of bisindolyl(phenyl)methanes.

S.N.	Amount of catalyst (Alum) in mmol	Reaction Time in min	Yields (%)
1	0.10	14.0	68
2	0.20	12.0	75
3	0.30	10.0	86
4	0.40	9.0	90
5	0.50	8.0	95
6	0.60	8.0	95
7	0.80	8.0	95

Moreover, this protocol was effectively employed in the synthesis of bis(indolyl)methanes from a variety of substituted indoles and diverse aldehydes, yielding good to excellent results (84-95%) as illustrated in (Table II). The approach demonstrated its efficacy across different types of substituted aldehydes (Table II) without the formation of any undesirable side products. It is worth mentioning here in present procedure when equimolar quantities of **1** and **2** are used, yields clearly bis(indolyl)methane **3** is obtained; contrary to earlier reports there is no formation of indolo[2,3-b]carbazoles **5** (**Scheme II**). Further obtained bis(indolyl)methanes were characterized by their melting points and spectral analysis data.



Scheme I: Synthesis of bis-(indolyl)methanes in Polyethylene Glycol and Water as green media Using Microwave Irradiation.

Table II - Alum mediated Synthesis of bis-(indolyl)methanes **(3)**.

S.N.	R	Indole	Product	Time	Yield (%)
1	Ph	1H-indole	**3a**	8	95
2	4-MeO-C_6H_4	1H-indole	**3b**	12	90
3	4-Me-C_6H_4	1H-indole	**3c**	10	93
4	4-Cl-C_6H_4	1H-indole	**3d**	8	92
5	3-NO_2-C_6H_4	1H-indole	**3e**	11	90
6	4-NO_2-C_6H_4	1H-indole	**3f**	10	92
7	4-OH-C_6H_4	1H-indole	**3g**	13	84
8	Ph	2-methyl-1H-indole	**3h**	9	92
9	4-Me-C_6H_4	2-methyl-1H-indole	**3i**	9	93
10	Ph	5-methyl-1H-indole	**3j**	10	92

In conclusion, the proposed protocol provides bis(indolyl)methanes in excellent yields, utilizing a mild, efficient, environmentally benign, reusable, and cost-effective catalyst, alum, in water. This stands in contrast to several previously employed catalysts that are expensive,

moisture-sensitive, and environmentally unfriendly, addressing contemporary concerns. Additionally, this method demonstrates a broader scope and is free from the formation of any by-products.

Experimental Section

Melting points were determined in open capillary and compared with those of authentic samples. IR spectra were obtained by using Perkin-Elmer 237B infrared spectrometer in KBr discs. ^{1}H NMR spectra were recorded in Varian Gemini 300 spectrometer (300 MHz) spectrophotometer using tetramethylsilane (TMS) as internal standard. Alum used was of commercial grade and procured from SD Fine Chem Ltd. All other chemicals were purified by distillation or crystallization prior to use.

Typical experimental procedure for the synthesis of 3,3'-bis(indolyl)phenylmethane:

To a medium of PEG-400 (3mL) and water (3mL) indole (2 mmole), benzaldehyde (1 mmole) and alum (0.5 mmole) was added. Then reaction-mixture was irradiated under microwave irradiations for the 8 min. Reaction completion was monitored by TLC (hexane:ethyl acetate, 3:1 v/v), after completion of reaction, reaction-mixture was cooled to RT and solid thus obtained was filtered and washed thoroughly with cold water. Recrystallized with EtOH to afford pure bis(indolyl)phenylmethane, **3a** in 94% yield.

General experimental procedure for the synthesis of bis(indolyl)methanes:

To a mixture of alum (0.5 mmole) was added indole (2 mmole, 2 equiv.), aldehyde (1 mmole, 1 equiv.) and PEG-400 (3mL) and water (3mL) reaction-mixture was irradiated under microwave irradiations for time see table II. Reaction completion was monitored by TLC (hexane:ethyl acetate, 3:1 v/v), after completion of reaction, reaction-mixture was cooled to RT and solid thus obtained was filtered and washed thoroughly with cold water. Recrystallized with EtOH to afford pure bis(indolyl)phenylmethane.

3,3'-(phenylmethylene)di(1H-indole) (3a): IR (KBr): 3480, 3010, 1600, 1531, 1460, 1425, 1214, 1090 cm^{-1}; ^{1}H NMR (CDCl3): δ 5.90 (1H, s), 6.66 (2H, s), 7.10-7.58 (13H, m), 7.93 (2H, br, s, NH); ^{13}C NMR (CDCl3): δ 143.6 136.5, 128.0, 126.8, 123.3, 122.2, 120.2, 119.2, 118.9, 111.0, 39.9; EIMS: m/z 322 (M+)

3,3'-Bis(indolyl)-4-methoxyphenylmethane (3b). IR (KBr): 3484, 3020, 2849, 1615, 1516, 1464, 1411, 1325, 1220, 1097, cm-1; ^{1}H NMR (CDCl3): δ 3.78(3H, s), 5.83(1H, s), 6.66(2H, d), 6.80(2H d), 7.0 0(2H, t, J = 7.20 Hz), 7.24(2H, t, J = 7.20 Hz); 7.28-7.45(6H, m), 7.92(2H, br, NH); ^{13}C NMR ($CDCl_3$): δ 136.8, 135.7, 127.1, 123.1, 122.0, 119.6, 119.3, 119.0, 118.6, 113.3, 111.2, 55.4, 38.5. EIMS: m/z 352 (M+).

3,3'-Bis(indolyl)-4-chlorophenylmethane (3d): IR (KBr): 3480, 3022, 2916, 1611, 1532, 1460, 1424, 1230, 1025 cm^{-1}; ^{1}H NMR (CDCl3): δ 5.88 (1H, s), 6.66 (2H, d, J = 8.20 Hz), 7.10-7.87 (12H, m), 7.91(2H, br, NH); ^{13}CNMR ($CDCl_3$): δ 136.7, 130.2, 128.3, 126.5, 123.7, 122.2, 120.3, 119.5, 119.2, 111.3, 39.8. EIMS: m/z 356 (M+).

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