



Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Grape juice Catalysed Synthesis of Bis (Indolyl) Methanes in Aqueous Medium: A Green Approach

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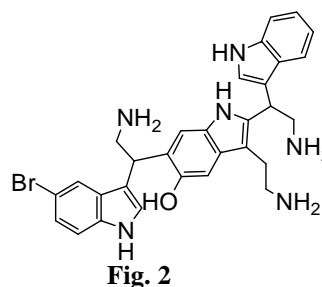
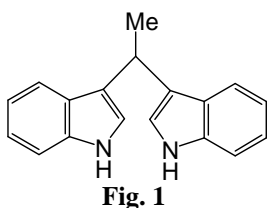
ABSTRACT

Grape juice catalysed synthesis of bis (indolyl) methane derivatives were accomplished via condensation of different aryl aldehydes with indole in aqueous medium on reflux to furnish the product in excellent yield. The grape juice can be extracted very easily and reaction goes to completion with in few hours. The approach is totally non-polluting having several advantages, such as shorter reaction time mild reaction condition and simple workup.

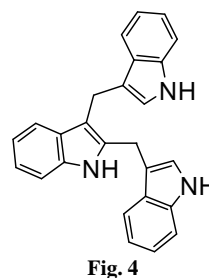
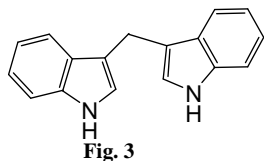
Keywords: Bis (Indolyl) Methanes, Grape Juice, Aqueous medium, Green Chemistry

INTRODUCTION

Pharmacological and industrial thrusts put forwarded the indole scaffolds as the molecules of synthetic interests. Various indole derivatives have been known to be playing vital role in pharmaceuticals[1]. Bis (indolyl) methanes are the heterocyclic compounds with two nitrogen atoms. Bis (indolyl) methanes have been the point of attraction for the chemists since few years amongst the box of indole moieties. A large number of bis (indolyl) methanes and bis (indolyl) ethanes have been isolated from the marine sources. Vibrindole A (**Fig. 1**) is a metabolite of the marine bacterium, *Vibrio parahaemolyticus* and is isolated from the toxic mucous of boxfish *Ostracion cubicus* while (\pm) gelliusinus A and B (**Fig. 2**) (diastereomeric trisindole alkaloids) represents the major components of a deep water Caledonian sponge[2].



Bis (indolyl) methanes are found to be exhibiting biological activities such as antimicrobial, antioxidant [3] properties. Some 3,3'-diindolylmethane derivatives evaluated as cytotoxic agents[4]. In addition to this, vibrindole A exhibits antibacterial activity against *Staphylococcus aureus*, *S. albus* and *B. subtilis* using gentamycin as a standard drug[5] It is known that, 3,3₀-diindolylmethane (**Fig. 3**) and 2-(indol-3-yl-methyl)-3,3₀-diindolylmethane (**Fig. 4**) possess various pharmaceutical potencies and they are also utilized in treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome[6]



The acid catalyzed reaction of electron rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde is known as Ehrlich test [7] for electron rich heterocycles such as pyrroles and indoles. The analogous reaction of indoles with other aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. Further addition of second molecule of indole to azafulvenium salt produces bis (indolyl) methanes. Common route for the synthesis of bis (indolyl) methanes is an electrophilic substitution reaction of indoles with aromatic or aliphatic aldehydes and ketones catalyzed by protic acids or lewis acids. On the other fold, researchers are competing for developing the economic, eco-friendly, easily accessible methodologies for the synthesis of bis (indolyl) methane by using various catalytic systems and reaction conditions [8-15].

Use of aqueous media as a reaction solvent has attracted much attention in synthetic organic chemistry for several reasons. In comparison with organic solvents, water is cheap, safe and reduces the use of harmful organic solvents and leads to the development of environmentally friendly chemical processes. In addition, reactions in aqueous media illustrate unique reactivity and selectivity that are not usually observed in organic media. However, organic solvents are still used instead of water for mainly two reasons. First, most organic substrates are not soluble in water and as a result, water cannot function as a reaction medium. Second, many reactive substrates, reagents and catalysts are sensitive towards water and are decomposed or deactivated in aqueous media. Therefore, efforts to carry out organic reactions in water pose an important challenge in the area of reaction design [16]

In this report we have investigated the synthesis of various bis (indolyl) methanes in aqueous medium catalyzed by grape juice at reflux temperature.

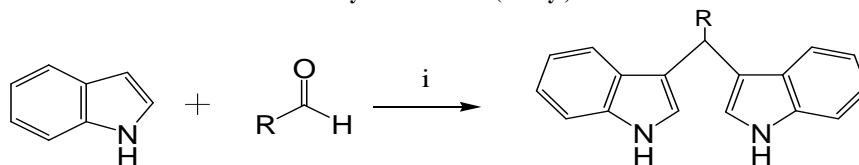
EXPERIMENTAL SECTION

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra and ¹H NMR. IR spectra were recorded on Perkin-Elmer FT-IR-1710 instrument. ¹H NMR was recorded on BrukerMSL-300 MHz and BrukerMSL-200 MHz instrument using TMS as an internal standard.

General procedure for the synthesis of bis (indolyl) methanes

To a mixture of indole (2 mmol) and aromatic aldehyde (1mmol) taken in round bottom flask was added 5 ml of water and 1 ml of grape juice. The reaction mixture was refluxed for 3-4 hrs. The progress of reaction was monitored by TLC. After completion of the reaction, the solid product was extracted with ethyl acetate and the solvent was removed under vacuum. The crude product so obtained was purified by column chromatography (Ethyl acetate: Hexane, 1:9). The structures of the synthesized compounds were confirmed by spectral analysis data.

Scheme: Synthesis of bis -(indolyl)methanes



Entry-1, R =Phenyl, 2, R=p-methoxy phenyl, 3, R=p-chloro phenyl, 4, R=p-nitro phenyl, 5, R=P-tolyl, 6, R=thienyl.

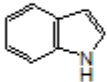

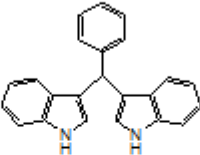
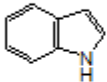
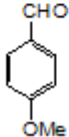
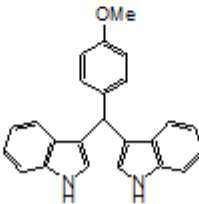
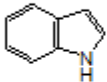
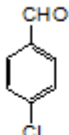
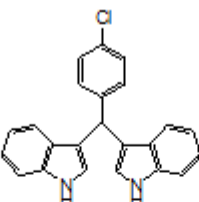
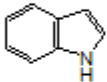
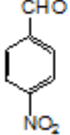
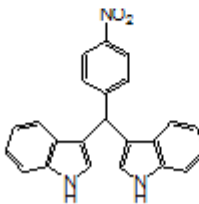
RESULTS AND DISCUSSION

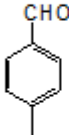
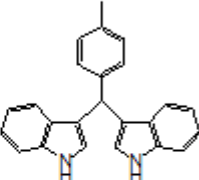
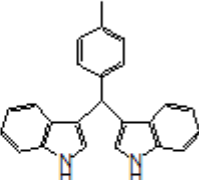
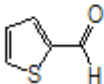
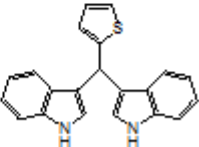
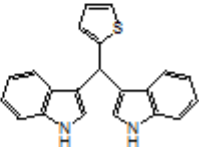
We presented here the green protocol for the synthesis of bis (indolyl) methanes in aqueous medium employing inexpensive, non-toxic and easily available grape juice as a natural acid catalyst. The reaction was carried out at reflux within a short period of time

While carrying out the reactions of indole with carbonyl compounds we come to know that, this electrophilic substitution reaction can be made to occur more efficiently by using water as solvent medium in presence of natural acids obtained from natural resources. The reaction was performed under reflux condition. The consumption of the reactants was observed since 30 min but the complete reaction or disappearance of the reactants was observed after 3hrs as evidenced by thin layer chromatography. We utilized various aryl aldehydes compounds to check the applicability of this methodology and the results are in agreement to declare the presented method as a fruitful approach for the development of environmentally benign and eco-friendly protocols in organic synthesis. The results are summarized in the following **Table**.

The scope of the reaction is justified by the reaction of various substituted aldehydes with indole reflecting the smooth transformation to the corresponding bis (indolyl) methanes. Satisfied with the results and the scope of application, we extended our reaction using heterocyclic aldehydes which provided us fruitful results.

Table 1

Entry	Indole	Aldehydes	bis (indolyl) methanes	Yield (%)	M. P. °C (°C)[Ref.]
1				70	146-147 (148-152)[17]
2				66	186-189 (185-186)[17]
3				74	76-78 (78-80)[18]
4				75	220-223 (218-221)[17]

Entry	Indole	Aldehydes	bis (indolyl) methanes	Yield (%)	M. P. (°C) [Ref.]
5				68	95-98 (95-96)[18]
6				73	150-152 (152-153)[18]

Since all the products have been reported previously in the literature so they were characterized by comparison of M.P, IR and NMR spectra with authentic samples.

CONCLUSION

In continuation of our efforts to develop environmentally green protocols for the synthesis of heterocycles, we have presented a neat methodology for the synthesis of bis (indolyl) methanes by utilizing easily available natural acid catalyst. We introduced water as a solvent medium for the reaction between indole and various substituted aryl aldehydes. Water promoted reactions could be a fertile approach for the development of environmentally benign and eco-friendly protocols in organic synthesis.

Acknowledgement

Authors are thankful to Anjuman Khairul Islam's Trust Mumbai, for financial assistance.

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