LOVELY PROFESSIONAL

UNIVERSITY

(December- 2017)

DISSERTATION-II FINAL REPORT

For the Partial Fulfilment of the Degree of Masters of Sciences (Chemistry)

On the project entitled as

"Development of green methodologies for synthesis of bis (indolyl) methane analogues in eco-friendly reaction medium"

TOPIC APPROVAL PERFORMA

School of Chemical Engineering and Physical Sciences

Program: P266-H: M.Sc. (Hons.) Chemistry

COURSE CODE : CHE650 **REGULAR/BACKLOG :** Regular **GROUP NUMBER :** SCRGD0049

Supervisor Name : Dr. Tanay Pramanik **UID :** 16842 **Designation :** Assistant Professor

Qualification : _____ **Research Experience :** _____

SR.NO.	NAME OF STUDENT	REGISTRATION NO	BATCH	SECTION	CONTACT NUMBER
1	Lalit Malkania	11613517	2016	G1603	9882422247

SPECIALIZATION AREA : Organic Chemistry **Supervisor Signature:** _____

PROPOSED TOPIC : Development of green methodologies for synthesis of bis(indolyl)methane analogues in eco-friendly reaction medium

Qualitative Assessment of Proposed Topic by PAC		
Sr.No.	**Parameter**	**Rating (out of 10)**
1	Project Novelty: Potential of the project to create new knowledge	7.00
2	Project Feasibility: Project can be timely carried out in-house with low-cost and available resources in the University by the students.	6.67
3	Project Academic Inputs: Project topic is relevant and makes extensive use of academic inputs in UG program and serves as a culminating effort for core study area of the degree program.	6.67
4	Project Supervision: Project supervisor's is technically competent to guide students, resolve any issues, and impart necessary skills.	6.67
5	Social Applicability: Project work intends to solve a practical problem.	7.00
6	Future Scope: Project has potential to become basis of future research work, publication or patent.	7.33

PAC Committee Members		
PAC Member 1 Name: Dr. Gurpinder Singh	UID: 13608	Recommended (Y/N): Yes
PAC Member 2 Name: Dr. Rekha	UID: 14537	Recommended (Y/N): NA
PAC Member 3 Name: Dr. Ashish Kumar	UID: 16464	Recommended (Y/N): NA
DRD Nominee Name: Dr. Runjhun Tandon	UID: 19532	Recommended (Y/N): Yes

DAA Nominee Name: Dr. Navneet Singh	UID: 19327	Recommended (Y/N): Yes

Final Topic Approved by PAC: **Development of green methodologies for synthesis of bis(indolyl)methane analogues in eco-friendly reaction medium**

Overall Remarks: Approved (with minor changes)

PAC CHAIRPERSON Name: 11800::Dr. Ramesh Chand Thakur **Approval Date:** 28 Oct 2017

CERTIFICATE

This is to certify that Lalit Malkania has completed her dissertation project entitled "**Development of green methodologies for synthesis of Bis (indolyl) methane analogues in eco-friendly reaction medium**" under my guidance and supervision. To the best of my knowledge, the present work is her original investigational study. The dissertation proposal is fit for the submission and the partial fulfillment of the conditions for the award of Master of Science in Chemistry.

Date:

Signature of Supervisor:

NAME OF THE SUPERVISOR:

DR. TANAY PRAMANIK

ASSISTANT PROFESSOR

SUBMITTED BY:

LALIT MALKANIA

REG NO. 11613517

M.Sc. CHEMISTRY (Hons.)

Table of Contents

ACKNOWLEDGEMENT

I acknowledge the Holy Spirit, my greatest help, coach, and strength through this study. Immense appreciation to my supervisor, Dr.Tanay Pramanik for being so gracious and helpful through this work. Sir, I appreciate your humility and modesty.

My acknowledgement also goes to my department and to my H.O.D. Dr. Ramesh Chand Thakur, thanks for providing a wonderful environment and opportunity to do this project. I appreciate your affection of our teachers to clear our doubts at any time of day. Thanks to my tutor, Dr. Tanay Pramanik- thanks for believing in me and for being a part of my world, and for your positive influence on me.

Lastly, much gratitude to my parents, my father Desh Raj whose valuable ideas and encouragement gives me strength and to my mother whose prayers yields great fruits in my life. My thanks and appreciation also goes to my friends who have willingly helped out with their abilities.

INTRODUCTION

GREEN CHEMISTRY

Green chemistry also called as sustainable chemistry. Chemical engineering focused on designing of product in such a way that minimize the use and generation of hazardous substances and environmental chemistry focus on the effect of polluting chemical on nature. Green chemistry focuses on technology approaches to preventing pollution and consumptions of non-renewable resources.

Definition: Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.

PRINCIPLES

In 1998, Paul Anastas and John C Warner published a set of principles to guide the practice of green chemistry.

These are:

- The design of processes to maximize the amount of raw material that ends up in the product
- The use of renewable material feedback's and energy resources
- The use of safe; environmentally benign substances; including solvents, whenever possible
- The design of energy efficient processes
- Avoiding the production of waste, which is viewed as the ideal form of waste material

THE TWELVE PRINCIPLE OF GREEN CHEMISTRY

1. **Prevention**:-It is better to prevent waste then to treat or clean up waste after it has been created.
2. **Atom economy:-** Synthetic method should be designed to maximize the incorporation of all the materials used in the process into the final product.
3. **Less hazardous chemical synthesis:-** Wherever practicable, synthetic method should be designed to use and generate substances that possess a little or no toxicity to human health and the environment.
4. **Designing safer chemicals:-** Chemical should be designed to preserve efficacy of function while reducing toxicity.
5. **Safer solvent and auxiliaries:-** The use of auxiliary substances (solvent separation agents etc.) should be are unnecessary wherever possible and innocuous when used.
6. **Design for energy efficiency**:- Energy requirement for chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic method should be conducted at ambient temperature and pressure.
7. **Use of renewable feedstock**:- A raw material should be renewable rather than depleting wherever technically and economically practicable.
8. **Reduce derivatives**:-Unnecessary derivatization should be minimize or avoided whenever possible.
9. **Catalysis**:- Catalytic reagents are superior to stoichiometric reagents.
10. **Design for degradation**:- Chemical products should be designed so that at the end of their function they breakdown into innocuous degradation products.
11. **Real time analysis for pollution prevention**:- Analytical methodologies need to be further develop to allow for real time, in process monitoring and control prior to the formation of hazardous.
12. **Inherently safer chemistry for accident prevention**:- Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

MULTICOMPONENT REACTIONS

Multicomponent reactions are also known as convergent reactions. In these reactions three or more starting materials reacted together in a single reaction vessel to form a product. The characteristics of these reactions is that all or most of the atoms contribute to the newly formed product. In multicomponent reaction product is assembled according to cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which flow into irreversible step yielding the product. Multicomponent reactions give only one main product and do not give side products. The results depend upon the reaction conditions: solvent, temperature, catalyst, concentration, nature of starting material and functional groups. In these reactions we get only one product that makes multicomponent reactions ideal and eco-friendly reaction system. These types of consideration are important in designing and discovery of novel multicomponent reaction.

BIS (INDOLYL) METHANE

Indoles and their derivatives are the important class of nitrogen containing heterocyclic compounds. The synthesis of bis (indolyl) alkanes has been develop considerable interest in organic synthesis because they are widely occur in the natural products (terrestrial and marine) possessing biological activity (antibacterial, antitumor, anti-fungal) and useful for drug design.

Now days many synthetic chemicals have been prepared by clean procedure, which replace the classical synthetic methods. Microwave irradiation method is one of the new methods, for the synthesis of compounds. Applications of microwave irradiation chemistry explore the efficiency and selectivity of the organic reaction. This method exploits high yield, shorter reaction time, energy conservation, formation of purer products, waste minimization. In this chemical reaction are accelerated because of selective absorption of microwave by polar molecule. A literature survey shows various specific reaction which do not occur under conventional heating but could be possible by microwave irradiation. Moreover Ultrasound irradiation method is also used for the synthesis of the compounds. These two methods are Environment friendly.

Indole and their derivative have several applications in medical chemistry i.e. in medicine due to their biological active properties. Bis (indolyl) alkanes are most active cruciferous substances

that promote the estrogen metabolism and used as antibiotics. The considerable interest in the development of bis (indolyl) alkane in organic synthesis because of their wide occurrance in various natural products particularly from marine sources possessing pharmaceutical activities. They are also known to induce apoptosis in human cancer cell. Among the various indole derivatives, di(1-H-indolyl-3-yl)methane (DIM) and 1,4-bis[di(1H-indol-3-yl)methyl]benzenes shows diverse pharmalogical activities and are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome. These compounds also inhibit/stop the proliferation of both estrogen dependent and independent cultured breast tumor cells. Thus synthesis of bis(indolyl)methane remains important topic in the pharmaceutical sector due to their versatile biological activities. Numbers of methods describing the synthesis of bis (indolyl) methane were reported in the literature employing "Protic acids" and Lewis acids".

The oxidized bis (indolyl) methane contains a conjugated bis (indolyl) methane skeleton which acts as colorimetric sensors and chromogenic sensors. Solvent free reaction provides an efficient technique for various organic reactions which avoids harmful solvents. The acid-catalyzed condensations of indole with carbonyl compounds have provides a useful route for preparation of bis(indolyl)methane. As we know that there is use of mineral acids such as HF, HCl and H_2SO_4 for the synthesis in the chemical processes. Mineral acids are corrosive and hazardous catalyst. So there is great need for green and inexpensive acids instead of mineral acids. Fruit juice is used as green acids in place of mineral acid such as fruit juice of "Citrus limon" contains citric acid which act as an effective acid catalyst by activating the carbonyl group of aldehydes in organic reactions. The most common characteristics that make it green catalyst are easy preparation and handling, separation and workup processes, non-hazardous nature and easier waste disposal. "Montmorillonite clay K10 (MK10)" which is commercially available is an environmentally benign, economically feasible, stable and reusable solid acid catalyst which is used for various organic transformations. This can help in the green chemical synthesis of heterocyclic compounds such as bis (indolyl) methane etc.

Indole and its derivatives are used as antibiotics in the field of pharmaceuticals. It affect the central nervous system and so used as tranquilizer. It's effect in the prevention of cancer due to its ability to modulate certain cancer causing estrogen metabolites. Bis (indolyl) alkane and its derivatives constitute important group of bioactive metabolites of terrestrial.

IMPORTANCE OF BIS (INDOLYL) METHANE

Bis (indolyl) methane also called di (indolyl) methane (DIM), indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties. BIM is a phytonutrient present in most of the vegetables and it serves to regulate the excess estrogen levels. BIM works through creating identical biochemical pathways that serve in the metabolism of the estrogen. BIM exhibit multiple medicinal properties in modern clinical tests, including anti-oxidant, anti-inflammatory and hormone balancing effects.

BIM have some anti-cancer effects, but it has not been studied on human for cancer treatment and also has not been approved by FDA for serving this purpose.

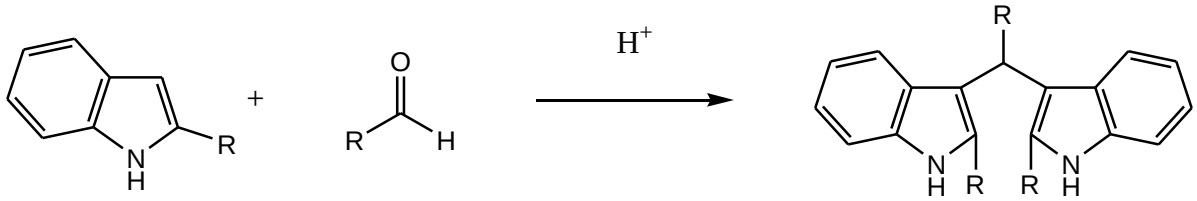
Importance of BIM:

1. **Perimenopause:-** Estrogen dominance is evident in diseases such as perimenopause. BIM is effective in rebuilding equilibrium between estrogen and progesterone before menstruation. No side effects have been reported regarding BIM but it is not advised to lactating women.
2. **Enlarged prostate:-** After the age of 50, estrogen level tends to increase in men while their testosterone level decreases. Because of the increased level of estrogen it gets accumulated in prostate and causes it to become inflamed. BIM regulated the estrogen level.
3. **Estrogen imbalance:-** As the age of males and females increases, the estrogen level also increases in their body and could be metabolized in wrong way. Estrogen that is converted into 16-hydroxy estrogen has been proven to be a causative agent of obesity and various types of cancers. BIM assist to prevent this conversion but it cannot be substituted for cancer treatment or recommended as a cure for certain types of cancer concerned with unbalancing of estrogen.
4. BIM is used for preventing breast, uterine, and colorectal cancer.

Important facts about BIM:

1. **Drug interaction:-** If a person is using any life-saving medicine such as medicine for cardiovascular problems or HIV or birth control pills then they should consult doctor before taking BIM.
2. **Natural sources of BIM:-**Cruciferous vegetables like cabbage, kale, broccoli and cauliflower naturally contain BIM.

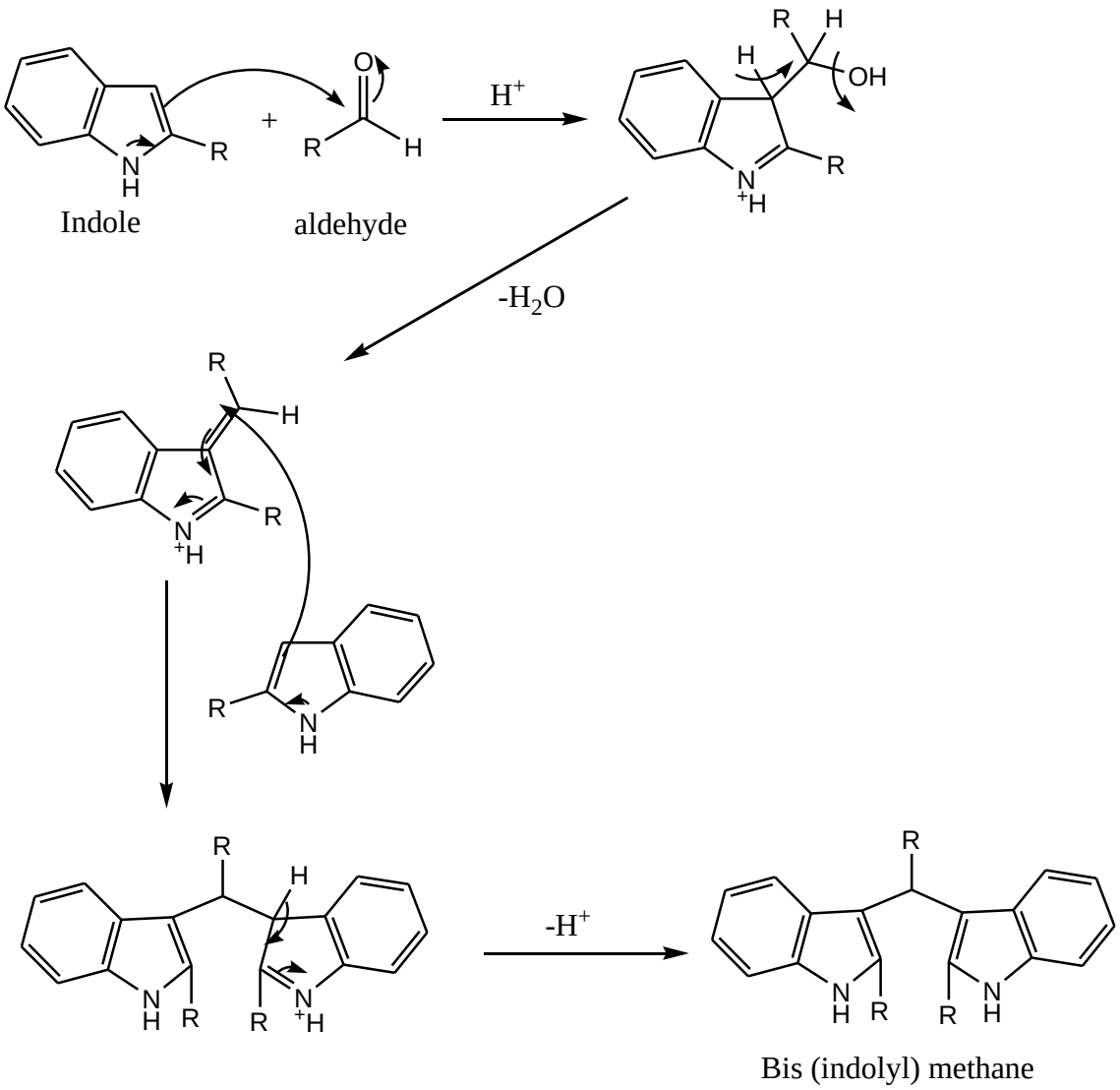
GENERAL REACTION OF SYNTHESIS



Indole Aldehyde Bis (indolyl) methane

The reaction facilitates in acidic medium.

MECHANISM OF THE REACTION



Bis (indolyl) methane

MECHANISM OF MICROWAVE DIELECTRIC HEAT

"Microwaves" are a generic term for electromagnetic waves within the frequency range of 300 MHz to 30 GHz. Electromagnetic waves in this frequency band are used in a variety of applications – microwave ovens in homes, industrial heating, cellular phones, UHF TV broadcasts, ship and airplane navigation, radar for weather observation, and aerospace communications.

Microwave irradiations are widely used to increase the efficiency of the organic reactions because they decrease the reaction time and also increase the reaction sensitivity. Also the reactions which could not occur under conventional heating can be done under this method.

Advantage of microwave heating:

- Unlike other heating methods the dielectric heating can affect higher temperature inside the product than on its surface.
- Due to the heating of the material throughout the whole volume the high uniformity of warming is reached as well as more precise temperature regulation. Overheating of certain parts of the product can be better prevented this way.
- The products can be treated in the suitable packaging since the electromagnetic waves effect does not depend on the thermal conductivity and is not influenced by the external isolating layers.
- Dielectric heating treatment improves the quality of the product resulting in competitive advantage and its higher salability.
- Comparable efficiency of treatment or similar process solution is hardly achievable or even impossible by conventional heating method in many cases.

Microwave irradiated chemical processes are considered highly green methods because this comes under the application of microwave technology for **microwave induced organic reaction enhancement (MORE)** chemistry. MORE chemistry is a non-traditional approach to the experimental set up for the organic reactions. The MORE chemistry techniques make it possible to use simple apparatus and very short reaction times. Depending on the quantity of

reactants, most reactions (on a scale of milligrams to several grams) can be completed in minutes instead of hours.

In comparison to conventional heating, microwave heating transforms the electromagnetic energy into heat. The magnitude of heating depends upon the dielectric properties of the molecule and the absorption of the radiation and heating may be performed selectively. Due to rapid nature of these radiations the whole reaction medium gets heated simultaneously.

PRINCIPLE OF MICROWAVE HEATING

When an electric field is applied to metal, the flow of electrons does not occur when an insulator is placed within that electrical field for an electric conductor having freely moving electrons. However, the phenomenon of polarization, where positive and negative electric charges are displaced from the equilibrium point, resulting in a separation of the charges, does occur. Substances with this kind of nature are called a "**dielectric**." As frequency increases, the component electrons of a dielectric spin, collide, vibrate, rub against each other, and otherwise move violently. Changes in polarity at this time are intense, occurring several ten to several hundred million times per second. This energy becomes "heat", which causes heat to be generated inside the dielectric.

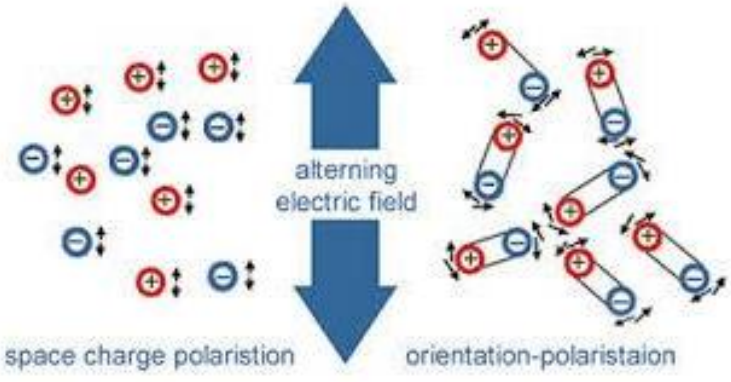
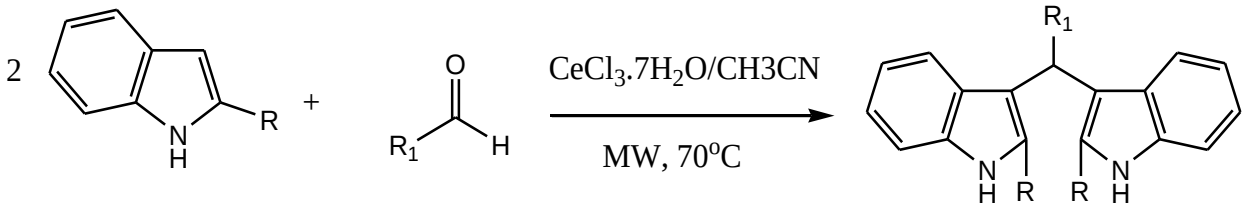


Fig1.3.1 Heating under microwave irradiations

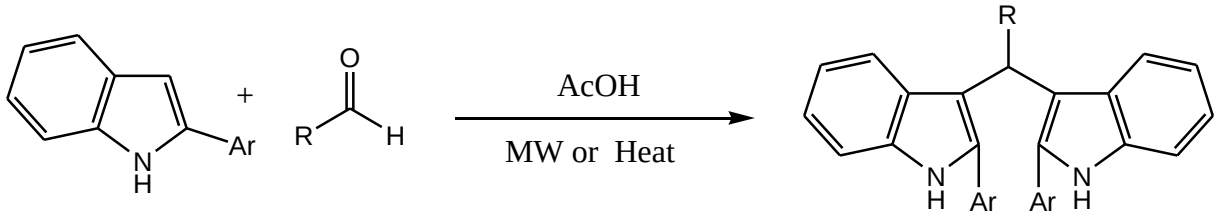
LITERATURE REVIEW

MW assisted synthesis in organic solvent:-

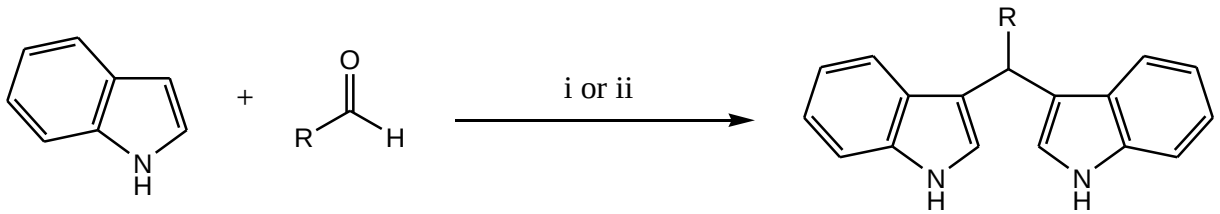
B.Vijayakumar Et al. have reported their work for the synthesis of bis (2-methylindolyl) methane and bis (indolyl) methane under microwave irradiation. They performed their work in the presence of catalytic amount of $CeCl_3.7H_2O$ in CH_3CN. [1]



Magdy Zahran Et al. have reported the reaction of 2-aryl indole with aldehyde in the presence of glacial acetic acid which act as catalyst under microwave irradiation conditions give rise to bis (indolyl) methane and its derivatives. [2]



Aayesha Nasreen has reported the electrophilic substitution reaction of indole with aldehydes by using succinic acid as a green catalyst and water as a green solvent under microwave irradiation. The reaction is chemoselective applicable only to aldehydes. [3]

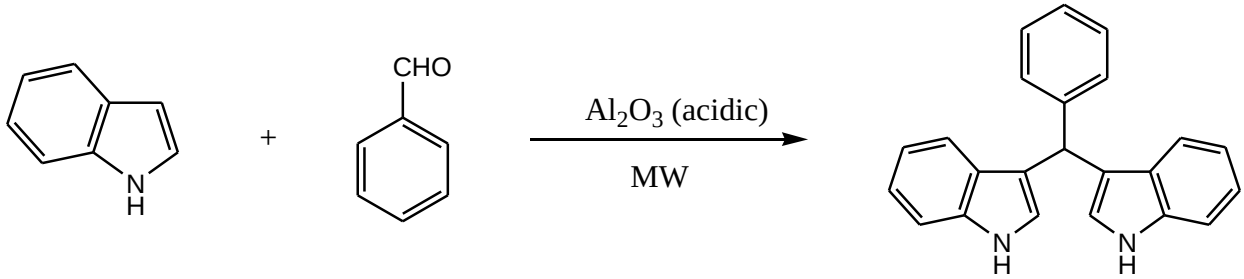


R = alkyl or aryl

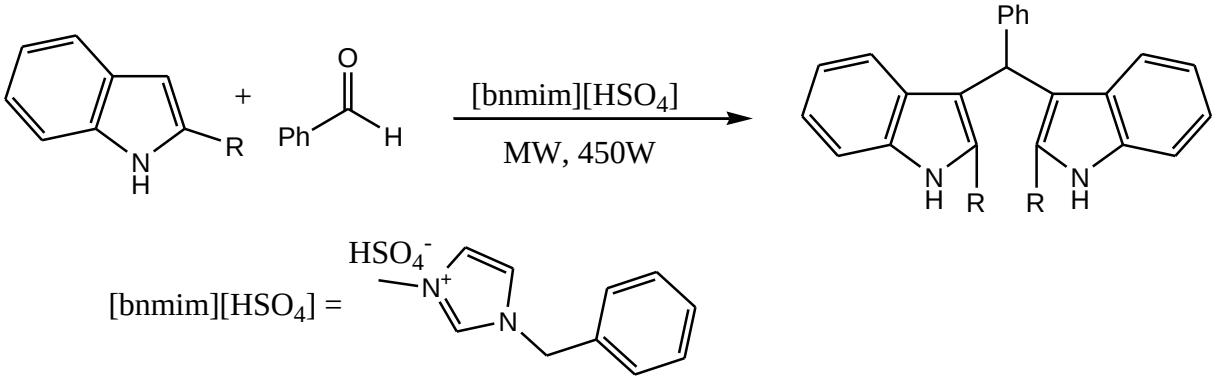
i = succinic acid (10 mol%)/H_2O
ii = microwave irradiation/9-15 min

MW assisted synthesis without any solvent:-

Sandip A.Sadaphal Et al. have reported heterogenous catalyzed reaction between indole and aldehydes give rise to bis(indolyl)methane. Aluminium oxide (acidic) used as a catalyst under microwave irradiation. [4]

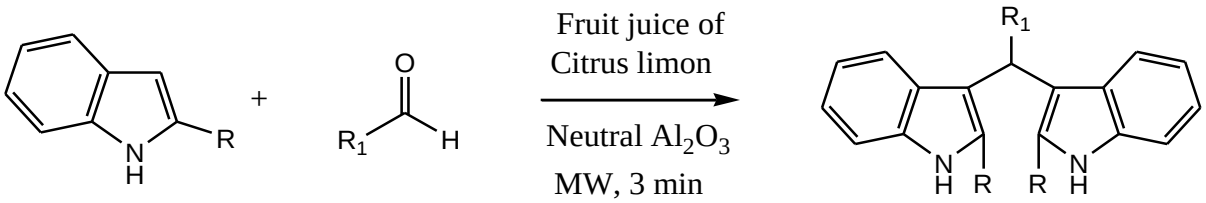


Sandip A.Sadaphal Et al. have reported condensation reaction between Indoles and derivatives with benzaldehydes in microwave irradiation with low reaction time. The reaction is catalyzed by [bnmim][HSO_4] i.e. 1-benzyl-3-methyl imidazonium hydrogen sulfate. [5]



MW assisted Synthesis in fruit juice medium:-

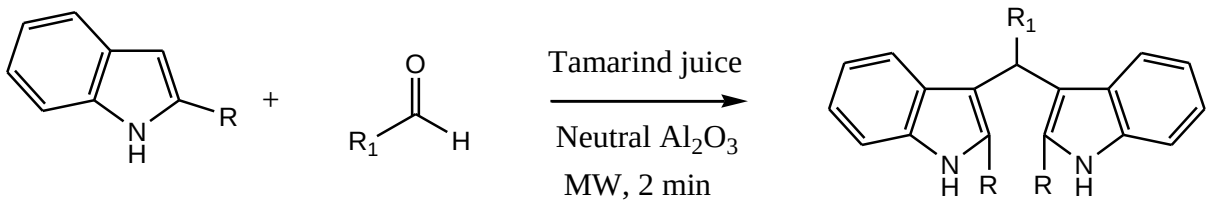
Rammohan Pal reported their work for the synthesis of bis-, tris (indolyl) methane and di bis(indolyl)methane by the reaction of indole with aldehydes in the presence of fruit juice of citrus lemon. The fruit juice act as catalyst. He provides Microwave-assisted efficient and eco-friendly synthesis under solvent free conditions. [6]



R= H, Me

R_1= Aryl, Heteroaryl Alkyl

Rammohan Pal reported their work for the synthesis of bis-, tris (indolyl) methane and tetra indolyl compound where he use aqueous extract of tamarind fruit (Tamarindusindica) as a catalyst. He proceeded by electrophilic substitution reaction of Indoles with aldehydes using microwave irradiation under solvent free conditions. This process is environment friendly. [7]

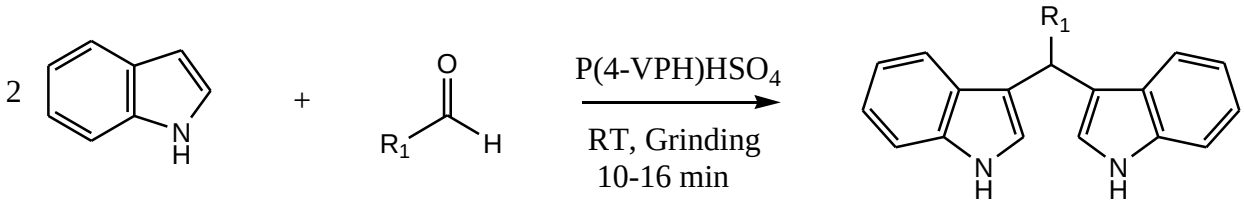


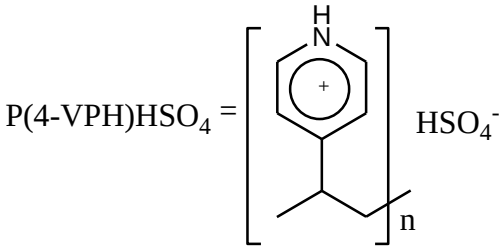
R= H, Me

R_1= Aryl, Heteroaryl Alkyl

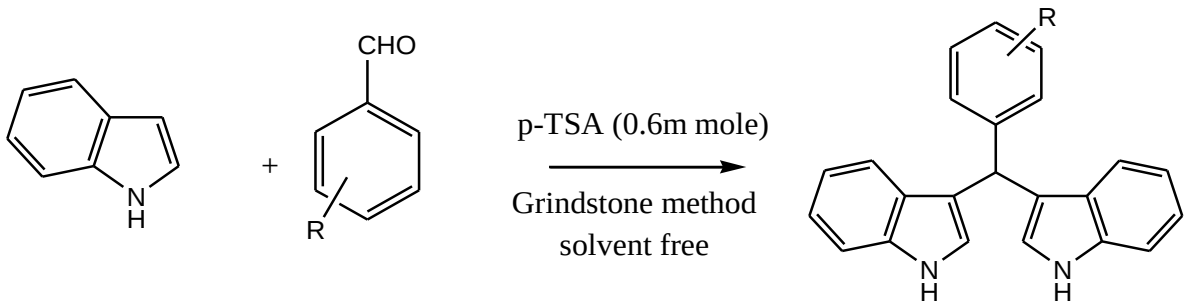
Grindstone assisted synthesis with catalyst:-

Janardhan Banothu Et al. have reported highly efficient and eco-friendly procedure for the synthesis of bis (3-indolyl) methane by the electrophilic substitution reaction of indole with aldehydes. The reaction is catalyzed by poly (4-vinylpyridinium) hydrogen sulfate. [8]

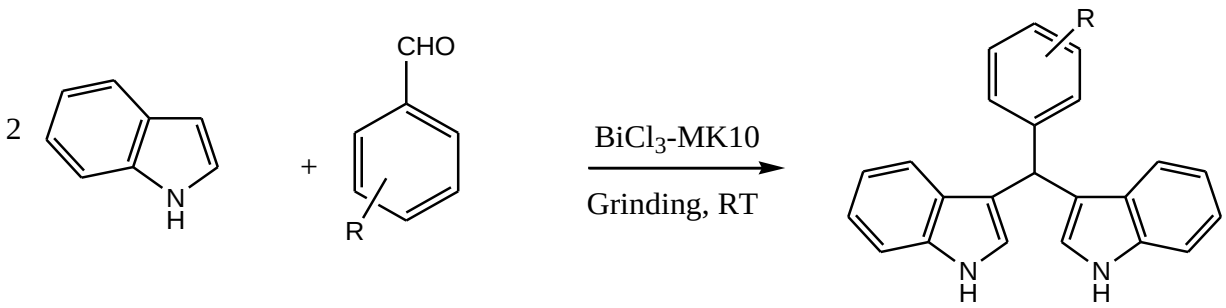




M.A.Pasha Et al. have reported an efficient reaction of indole with various aldehyde and ketones using p-TSA in catalytic amount give bis (indolyl) methane under Grindstone method in the absence of solvent. [9]

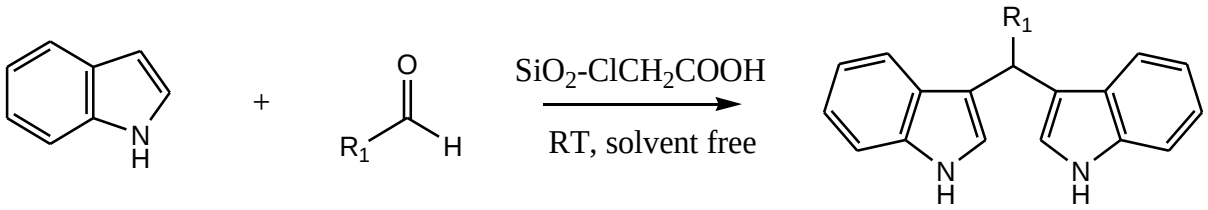


K.Ravi Et al. have reported green process for the synthesis of bis (indolyl) methane derivative under solvent free conditions. They used solid acid catalyst $BiCl_3$-MK10. The catalyst was characterized by SEM. [10]



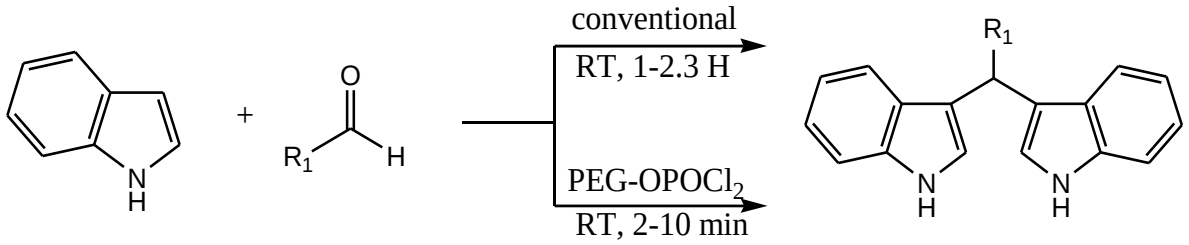
Solvent free synthesis at RT or via Heating:-

DR. Chandam Et al. have reported their work for the preparation of bis (indolyl) methane under solvent free condition. They use silica supported chloro-acetic acid as a catalyst, which is efficient environment friendly heterogeneous and reusable catalyst for the coupling of aldehyde and ketone. [11]

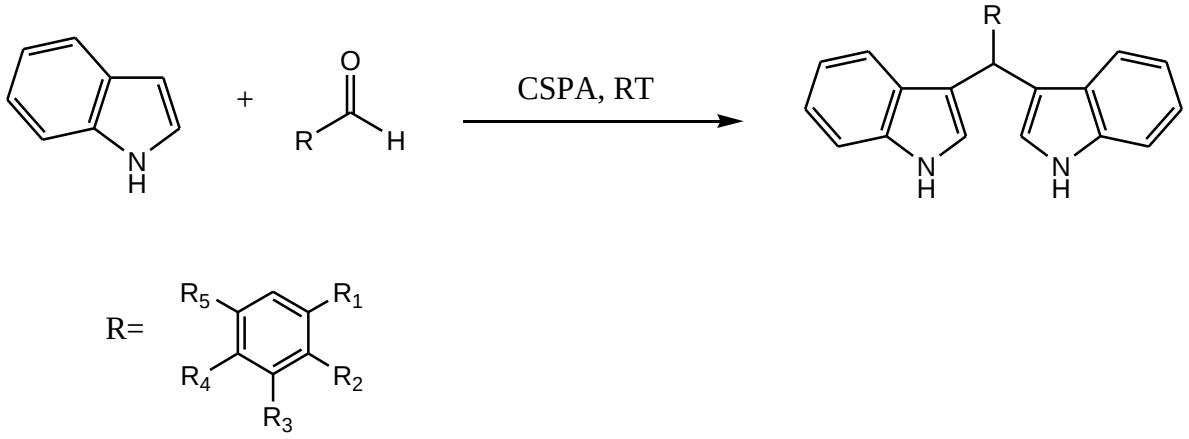


Kalla Reddy Mohan Naidu Et al. have reported the electrophilic substitution reaction of indole with aromatic aldehyde leads to formation of bis (indolyl) methane at very short time and at

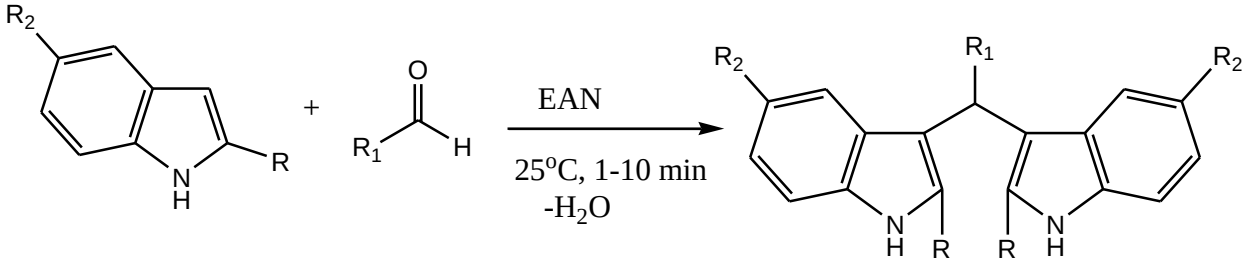
room temperature conditions. They use polymer supported di-chlorophosphate (PEG-$OPOCl_2$) as an efficient catalyst. [12]



S.B.Gaikwad Et al. have reported the electrophilic substitution reaction of indole with various aldehydes and ketones to give corresponding bis (indolyl) methane. They perform the reaction under solvent free conditions and the reaction is catalyzed by Cellulose Supported Perchloric-Acid (CSPA) which is an efficient and reusable solid acid catalyst. [13]

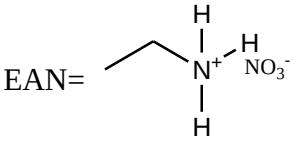


Shafeek A.R.Mulla Et al. have reported their work for an efficient synthesis of bis (indolyl) methane with the help of ethyl ammonium nitrate (EAN). It is a reusable ionic liquid at room temperature. This reaction involves electrophilic substitution reaction of indole with aldehydes. [14]

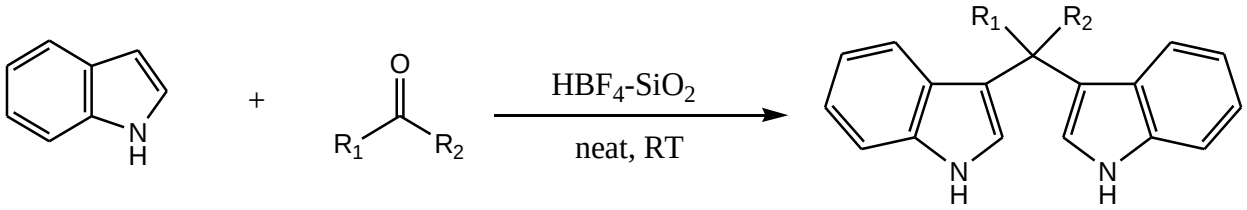


R_2= H, NO_2, OMe

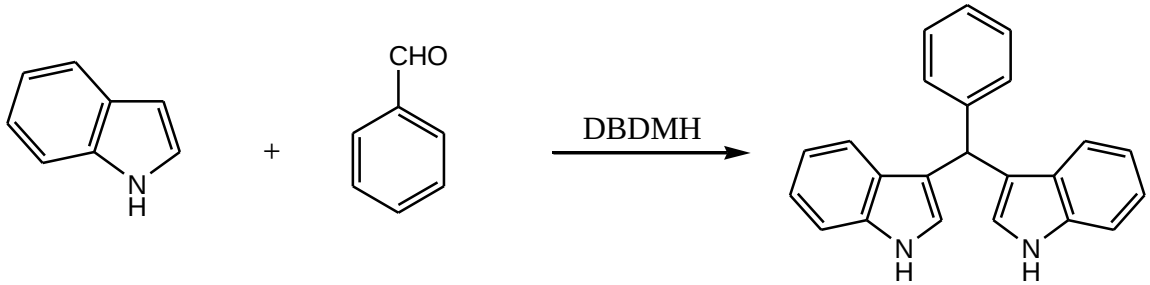
R_1= Aryl, Heteroaryl



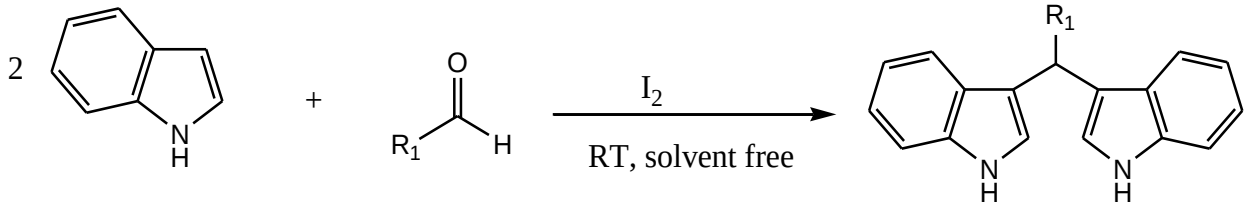
B.P.Bandgar Et al. have reported efficient electrophilic substitution of indole with various aldehyde/ ketones with the help of catalytic amount of HBF_4-SiO_2 under solvent free conditions to give us symmetrical and unsymmetrical bis (indolyl) alkanes respectively. [15]



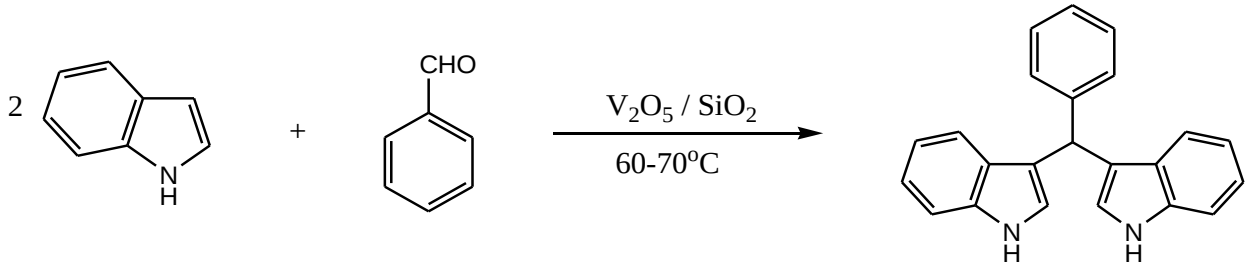
S.F.Hojati Et al. have reported the reaction of indole with carbonyl groups in the presence of catalytic amount of 1,3-dibromo-5,5-dimethylhydantoin(DBDMH) under solvent free conditions and corresponding bis (indolyl) methane are formed. In this method aliphatic aldehyde or ketone are also used. [16]



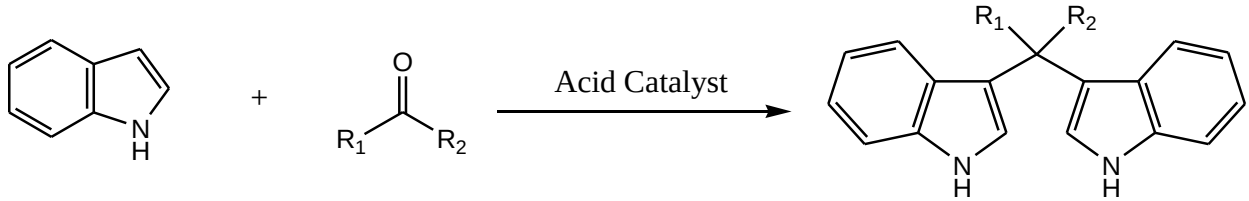
S.J.Ji Et al. have reported the electrophilic substitution reaction of Indoles with various aldehydes gives rise to corresponding bis (indolyl) methane. The reaction is catalyzed by iodine under solvent free conditions. [17]



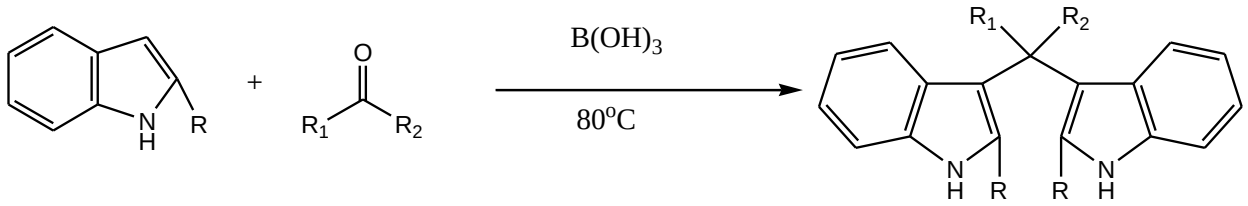
T.K.Khatab Et al. have reported one pot reaction of indole and aromatic aldehyde in the presence of heterogeneous catalyst V_2O_5/SiO_2 for the synthesis of bis (indolyl) methane. [18]



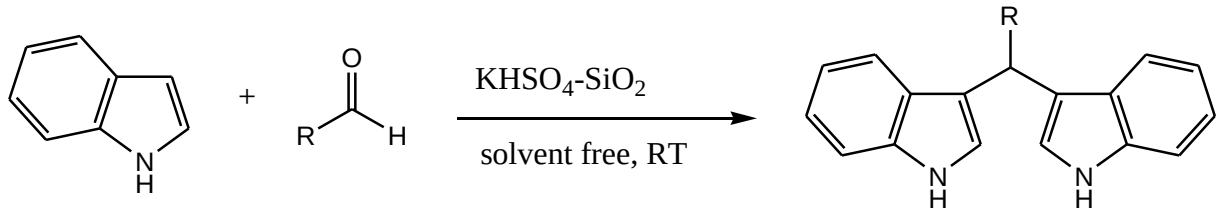
Partha Pratim Kaishap Et al. have reported that bis (indolyl) methane derivative possesses various biological activities including anticancer, antimicrobial, antifungal etc. They performed acid catalyzed reaction between indole and aldehydes or ketones which gives corresponding bis (indolyl) methane. [19]



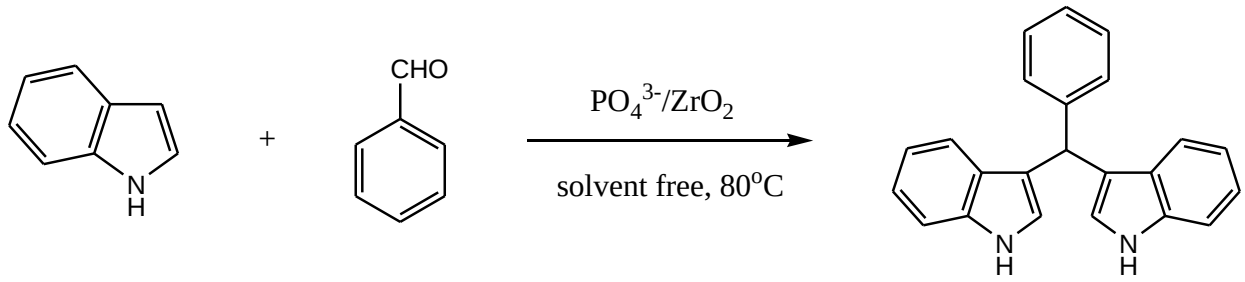
Jhillu S.Yadav Et al. have reported aldehyde and ketone react rapidly with Indoles in the presence of boric acid under solvent free conditions produces bis (indolyl) methane. [20]



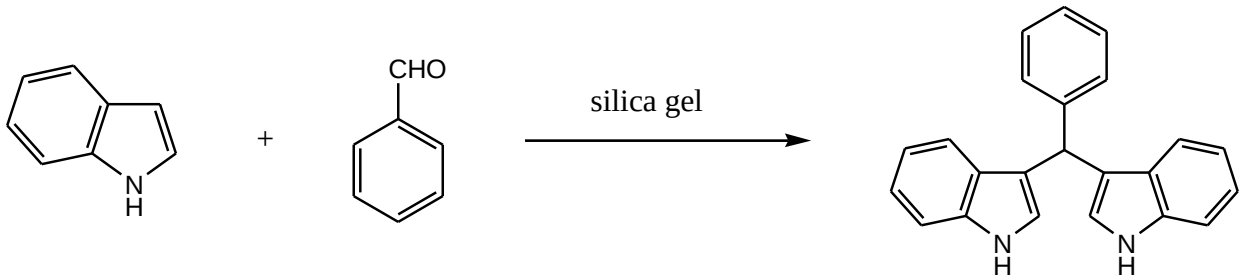
K.Reddi Mohan Naidu Et al. have reported $KHSO_4$-SiO_2 catalyzed highly efficient method for the synthesis of bis (indolyl) methane by the reaction of various aldehydes with indole. This is simple and environment friendly method. [21]



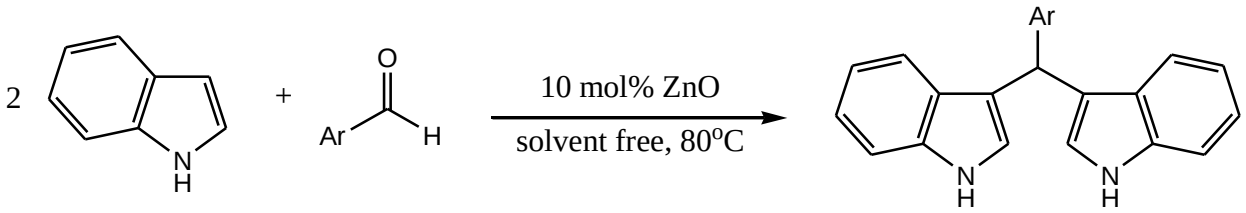
Sharmin V.Nadkarni Et al. have reported the synthesis of bis (indolyl) methane. The reaction is carried out under mild and solvent free conditions and phosphate zirconia which is a solid acid catalyzed the reaction. [22]



Samuel R.Mendes has reported clean and efficient and solvent free method for the synthesis of bis (indolyl) methane with the silica gel. The silica is easily recovered and further use in the reaction without any loss of activity. [23]

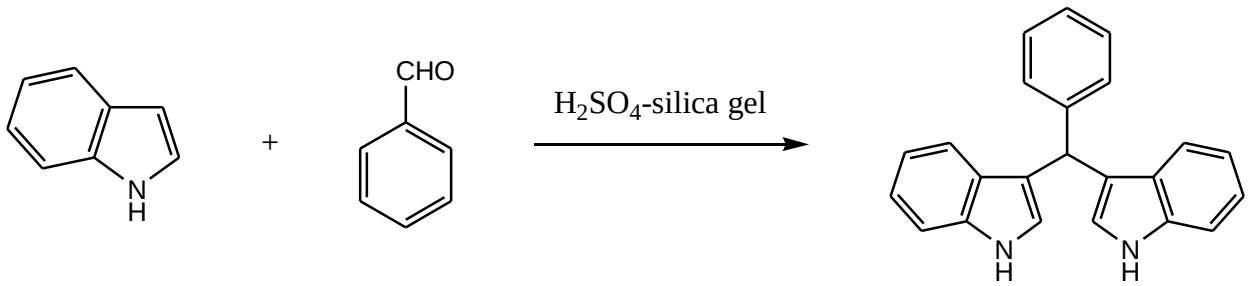


Mona Hosseini-Sarvari has reported an efficient electrophilic substitution reaction of indole with various aldehydes under solvent free condition gives bis (indolyl) methane. The reaction is catalyzed by ZnO, which is very cheap, environment friendly and reusable easily.

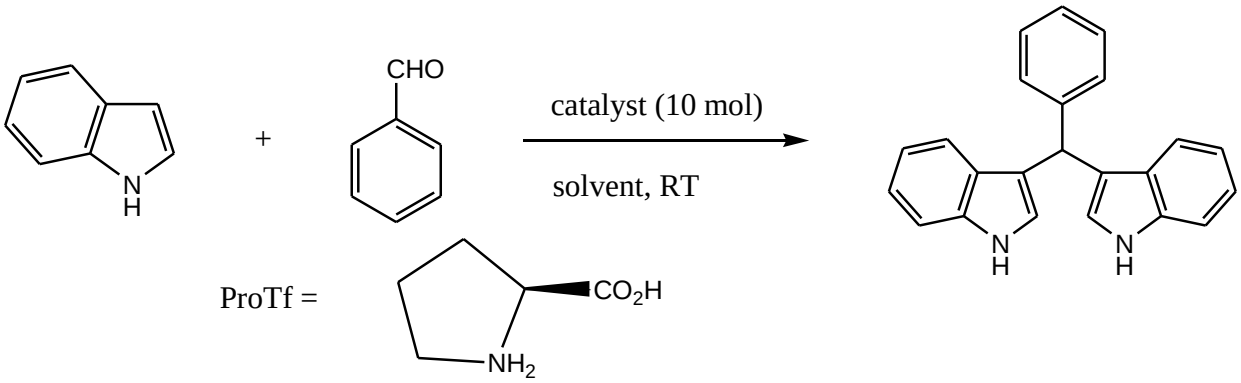


RT synthesis in H_2O or in Organic Solvent:-

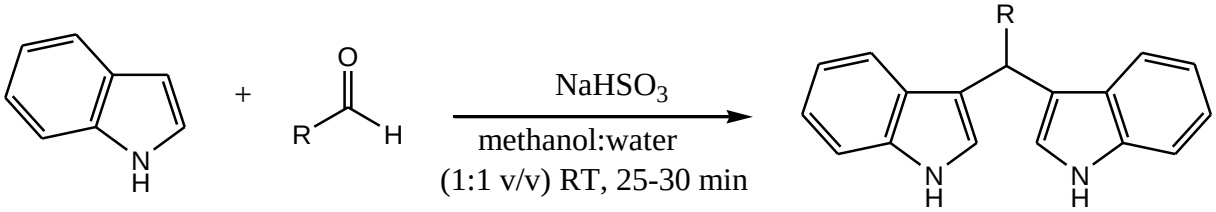
Mohammad Ali Zolfigol Et al. have reported the synthesis of di and tri(bis(indolyl)methane) from di and tri-aldehydes and Indoles in the presence of silica sulfuric acid. Acetonitrile use as a solvent. [24]



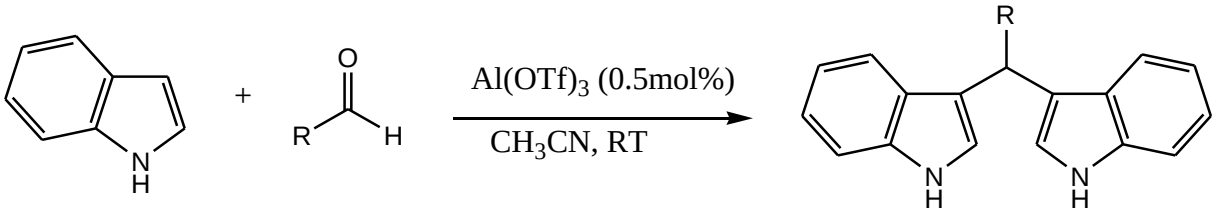
Morteza Shiri has reported condensation reaction of indole and aldehyde or ketones in aqueous media. The reaction is catalyzed by Proliniumtriflate (ProTf) which is prepared by addition of triflic acid. [25]



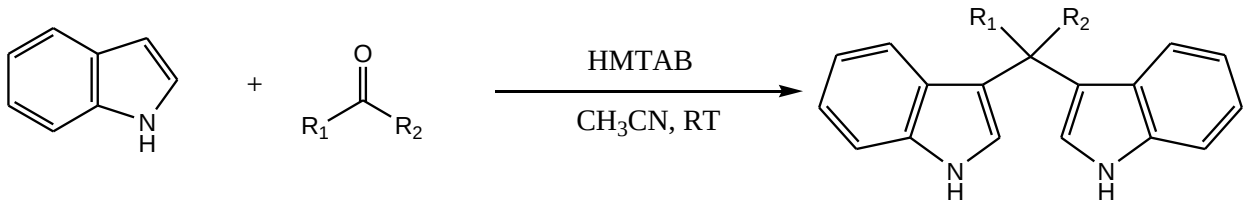
Kuppusamy Sujatha Et al. have reported the synthesis of bis (indolyl) methane by stirring a mixture of indole and aldehyde in methanol: water (1:1 v/v) containing sodium bi-sulfite in catalytic amount at room temperature. [26]



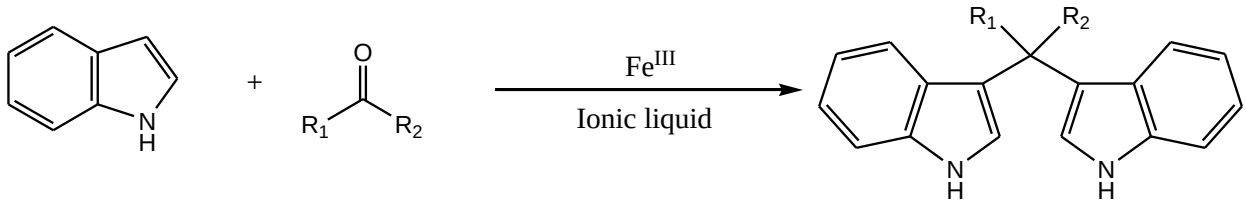
Ahmed Kamal Et al. have reported their work for the synthesis of bis (indolyl) methane by the reaction of indole with aldehydes and the reaction is catalyzed by aluminium triflate (0.5mol%). [27]



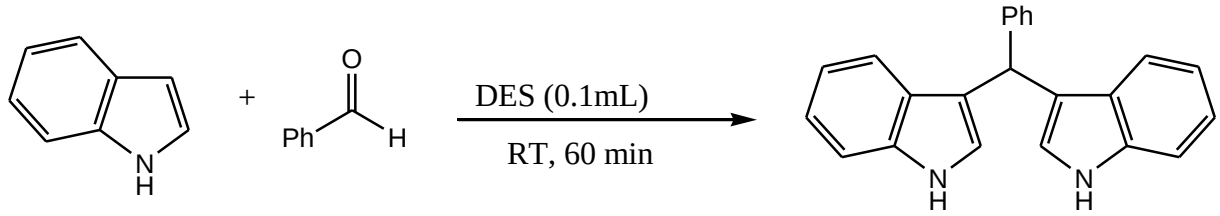
Babasaheb P.Bandgar Et al. have reported the synthesis of bis (indolyl) methane in the presence of hexamethylenetetramine-bromine (HMTAB) in catalytic amount. The aldehydes react with indole via electrophilic substitution reaction in the mild conditions. [28]



Shun-Jun Ji Et al. have reported the electrophilic substitution reaction of indole with various aldehydes gives corresponding bis (indolyl) methane. The reaction is catalyzed by Fe^{III} in ionic liquid. Ionic liquids involve $FeCl3.6H_2O$ which is most efficient catalytic system and simply recycled without loss of activity. [29]

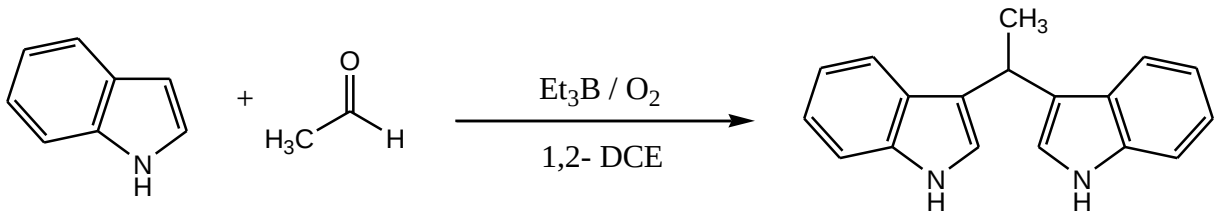


Najmadin Azizi Et al. have reported the convenient and rapid method for the electrophilic substitution reaction of indole and aldehydes by using deep eutectic solvent which is a green and reusable catalyst give corresponding bis (indolyl) methane at room temperature and mild conditions. [30]

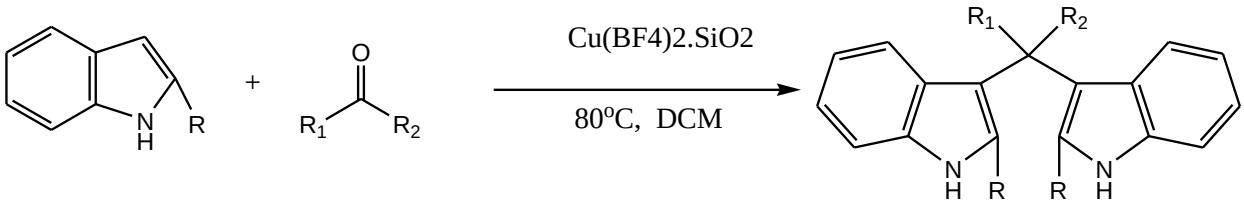


DES = $Ch/SnCl_2$, Ch/Urea, $Ch/ZnCl_2$, $Ch/ZnCl_2/SnCl_2$, Ch/Gly, $Ch/SnCl_2/H_2O$

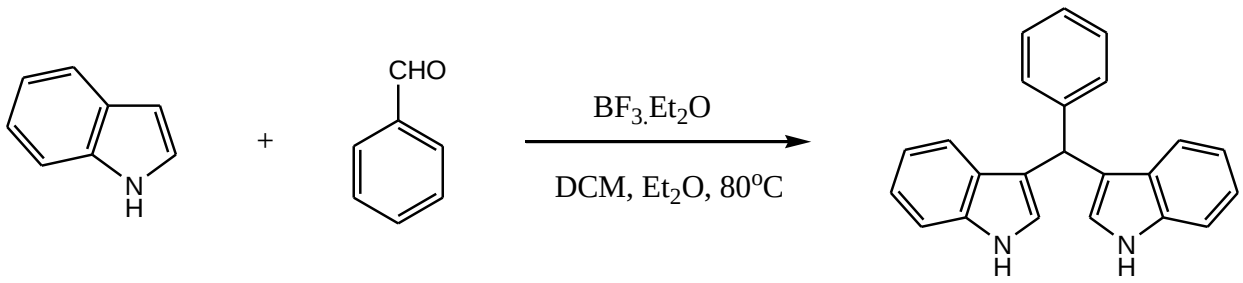
J.Pablo Garcia Merinos Et al. have reported acid catalyzed electrophilic substitution reaction of indole with aldehyde gives corresponding bis(indolyl)methane. They used triethylborane (TEB) as a catalyst. [31]



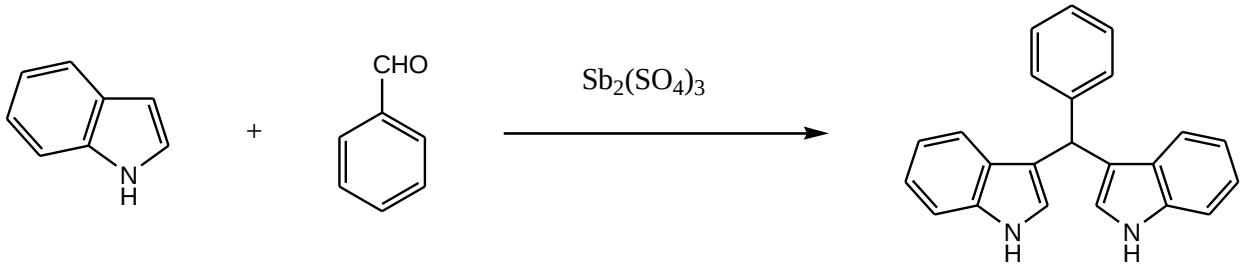
G.A.Meshram Et al. have reported an efficient method for the synthesis of bis (indolyl) methane by the reaction of indole with aldehyde or ketones in the presence of catalytic amount of cupric fluroborate [$Cu(BF_4)_2.SiO_2$]. This catalyst has remarkable selectivity under mild and neutral conditions. [32]



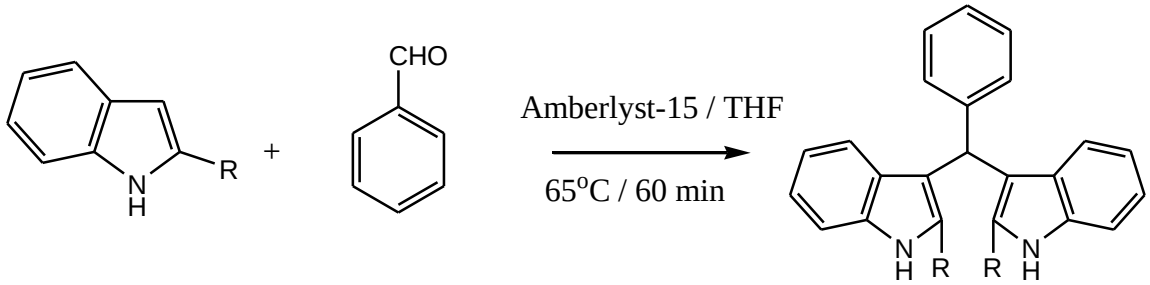
Xia-Fei Xu Et al. have reported the reaction between indole and carbonyl compounds at room temperature. The reaction was catalyzed by $BF_3.Et_2O$ which gives bis (indolyl) methane. [33]



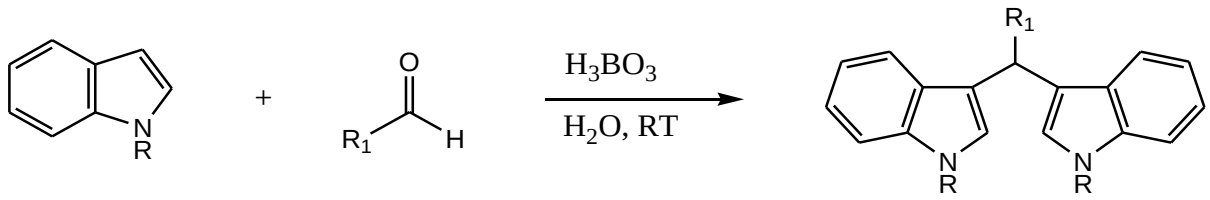
Aswathanarayana Srinivasa has reported the condensation reaction of indole and carbonyl compounds at room temperature. Antimony sulfate used as catalyst which is easily available, recovered in reaction and reuse without much loss of catalytic activity. [34]



Mohammad Almshantaf Et al. have reported their work the organic reaction between Indoles and Benzaldehyde in the presence of organic solvent to produce bis (indolyl) methane. They use heterogeneous catalyst i.e. Amberlyst-15 and THF as a solvent. By this method they produce high yield in comparison to homogeneous catalyzed reaction. [35]



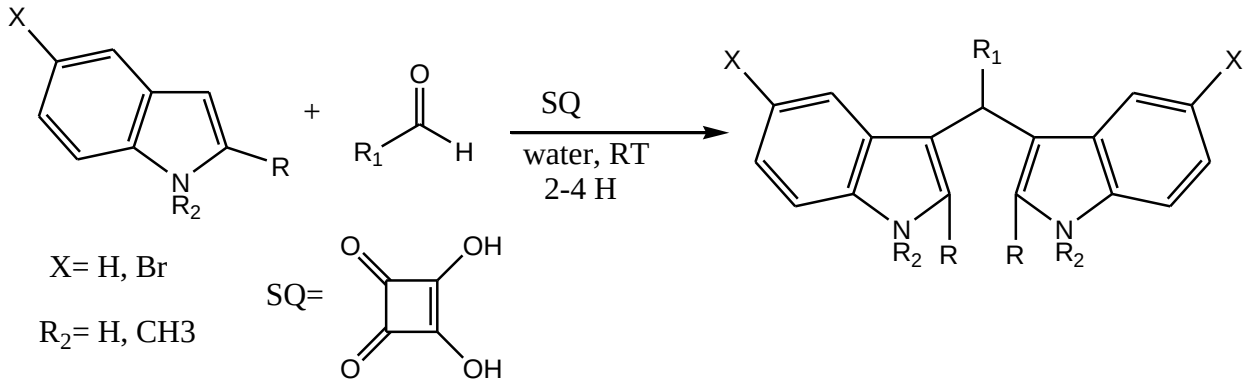
H M Meshram Et al. have reported the efficient reaction between indole and aldehydes by using Boric acid in catalytic amount in aqueous medium to give corresponding bis (indolyl) methane. The aqueous medium provides economic and environmental benefits as compared to other chemicals. [36]



R= H, Me

R_1= 4-methoxyphenyl, 4-methylphenyl, phenyl, 4-nitrophenyl

N.Azizi Et al. have reported electrophilic substitution reaction of indole derivatives, with various aldehydes in water. They used environment friendly squaric acid (SQ) as a catalyst. The advantage of this catalyst is its low sensitivity towards moisture and oxygen, high tolerance of different functional group and due to recyclability makes this catalyst suitable for both laboratory and industrial scale synthesis of bis (indolyl) methane under very mild conditions. [37]

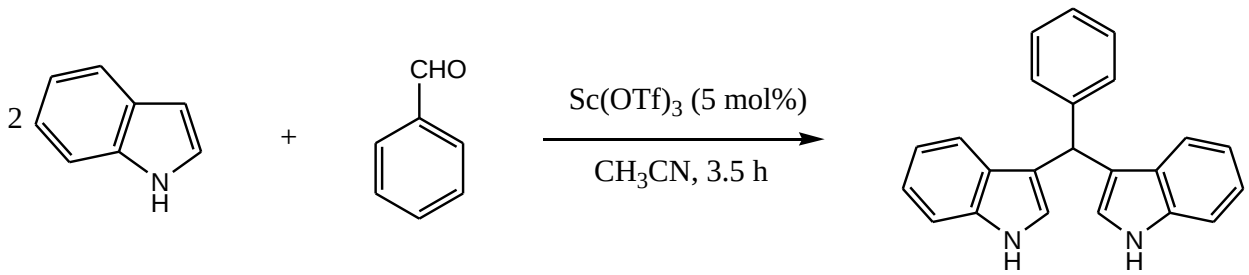


X= H, Br

R_2= H, CH3

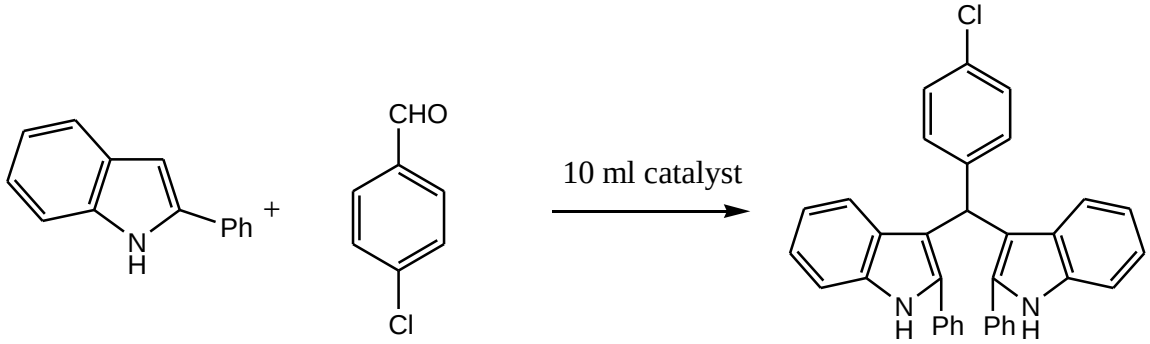
SQ=

Swapna S. Mohapatra Et al. have reported synthetic pathway of bis (indolyl) methane from various indole and structurally divergent aldehydes. The reaction is regioselective at C-3 functionalization of the Indoles and reaction is catalyzed by $Sc(OTf)_3$. [38]

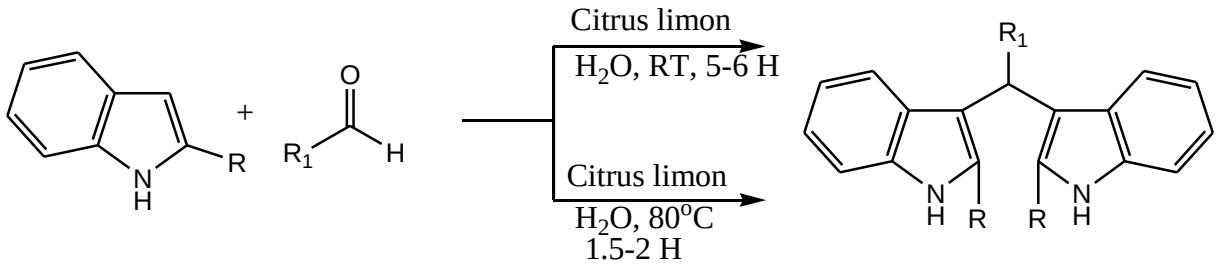


RT synthesis in fruit juice medium:-

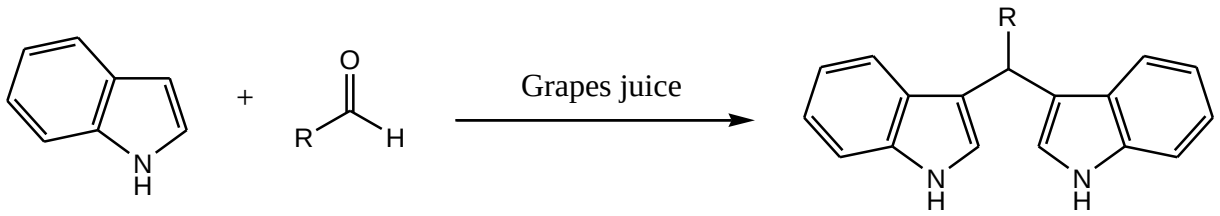
V.B. Suradkar Et al. have reported synthesis of bis-indole from some aromatic aldehydes and 2-phenyl indole. The reaction is catalyzed by natural acid such as Sweet lemon, Citrus limmeta, Tamarind, Butter milk, Pineapple juice. [39]



Rammohan Pal Et al. have reported the synthesis of bis- and tris (3-indolyl) methane in water by the reaction of aldehyde and Indoles at room temperature and 80°C. Citrus limon is act as catalyst in the synthesis. This method lowers the cost of synthesis and eco-friendly. [40]

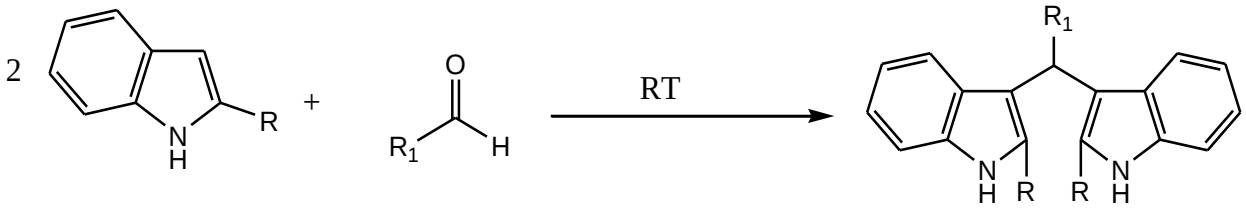


Abrar Sheikh Et al. have reported the synthesis of bis (indolyl) methane by condensation of various aldehydes with indole in aqueous medium. The reaction is catalyzed by grape juice and reaction is totally eco-friendly. [41]



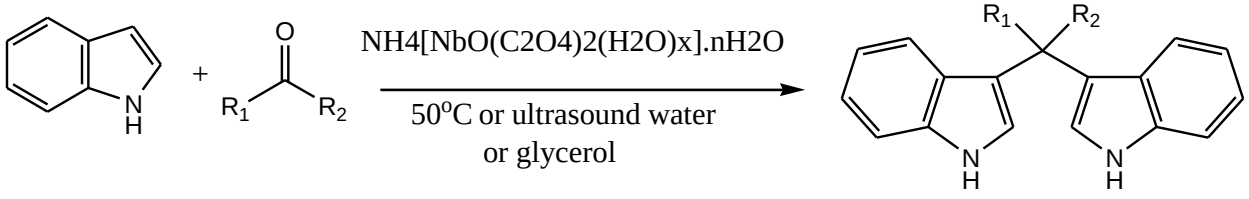
Solvent & Catalyst free synthesis at RT:-

Kashinath L.Dhumaskar Et al. have reported the condensation of indole with aromatic aldehyde give rise to bis (indolyl) methane. They carried out the reaction without using any catalyst and without any use of solvent. [42]

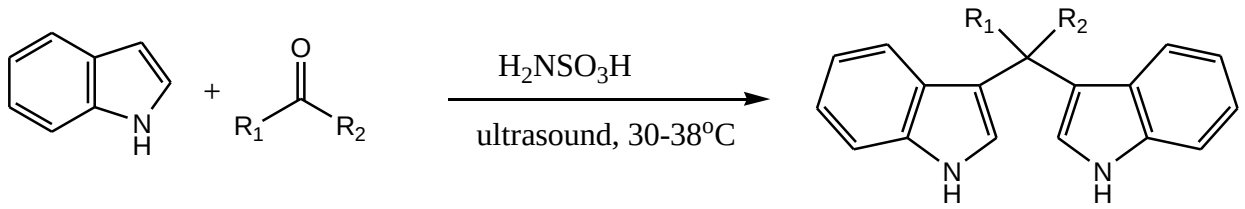


Ultrasound assisted synthesis:-

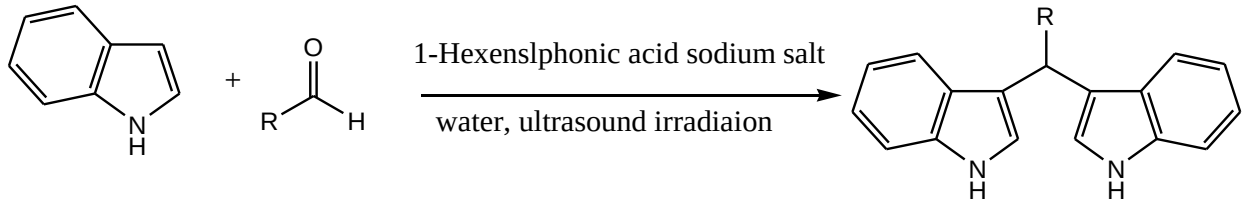
Samuel R.Mendes Et al. have reported synthesis of bis (indolyl) methane using ammonium niobium oxalate (ANO) i.e. $NH_4[NbO(C_2O_4)_2(H_2O)_x].{}_nH_2O$ as a catalyst and water or glycerol as solvent. In this reaction catalyst was easily reused for further reaction without any loss of activity. [43]



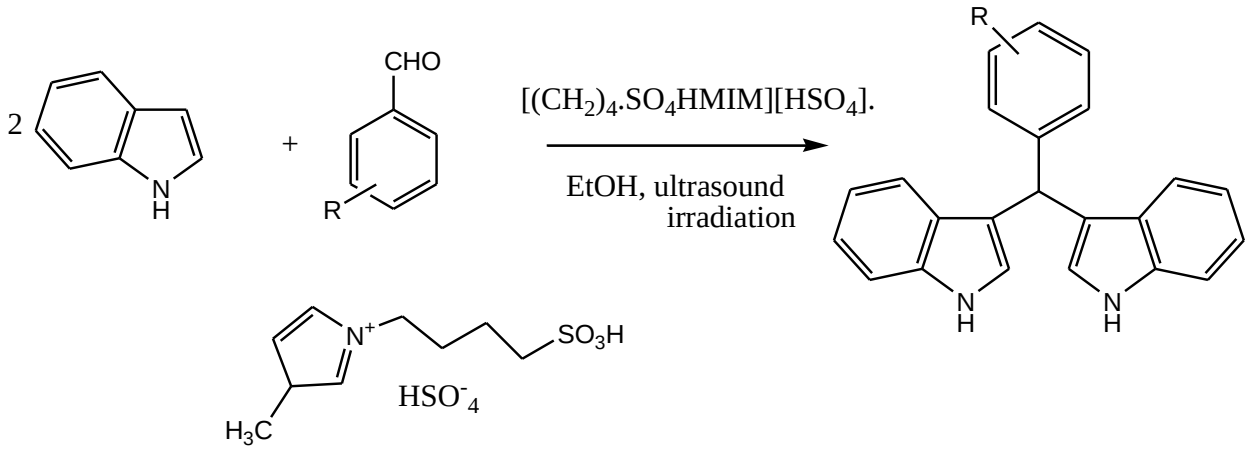
Ji-Tai Li Et al. have reported electrophilic substitution reaction of indole with aromatic aldehydes and ketones catalyzed by aminosulfonic acid at 30-38^{0}C in ethanol give bis (indolyl) methane under ultrasound irradiation. [44]



Ratnadeep S. Joshi Et al. have reported 1-Hexenslphonic acid sodium salt as a catalyst in synthesis of bis (indol-3-yl) methane. The reaction of indole with various aldehydes in water at ambient temperature give desired product under ultrasound irradiation. [45]



Y.Mo Et al. have reported the electrophilic substitution of indole with carbonyl compound give corresponding bis (indolyl) methane under ultrasound irradiation. The reaction is catalyzed by 1-methyl-3-(4-sulfobutyl)-1H-imidazolium bisulfate i.e. $[(CH_2)_4.SO_4HMIM][HSO_4]$. [46]



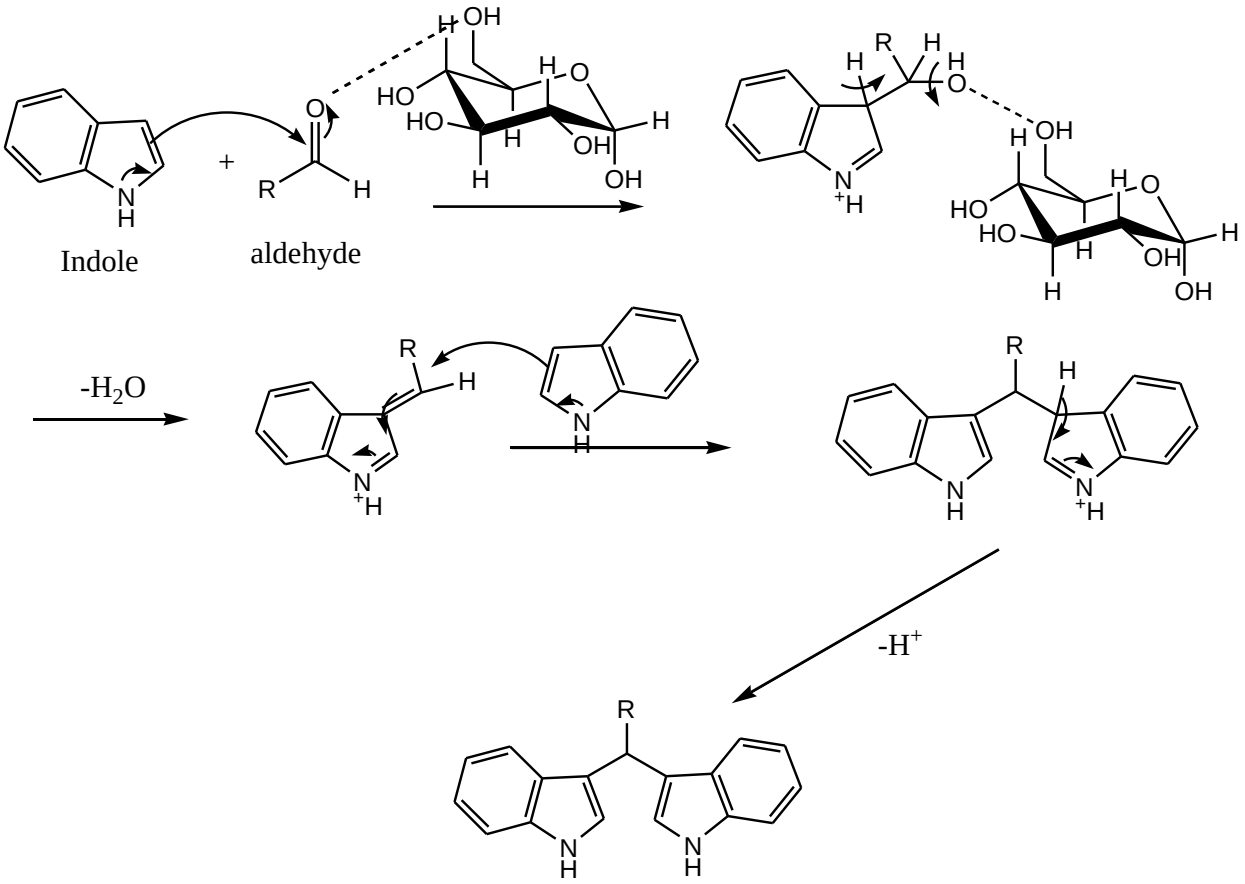
The synthesis of bis (indolyl) methane was PERFORMED by using various organic solvents and with the help of various catalysts. This reaction had taken under consideration of many research groups due to the high applicability in pharmacology. As organic solvents and catalysts are very harmful for the environment, further studies with many catalysts and solvents were used to perform this reaction but all of them are not eco-friendly. As we know mild acidic condition is required for catalyzing the reaction, fruit juice is also reported which is eco-friendly in nature. Reaction is also reported at room temperature but then the reaction time was too much. For increasing the reaction rate microwave irradiation were introduced to the reaction medium. This showed significant reduction in reaction time. A lesser reaction time is required in this approach so it can be considered as a green approach.

RESEARCH GAP

After extensive literature search it was revealed that although toxic acid, fruit juice catalyst synthesis of bis (indolyl) methane in various non eco-friendly organic solvents are reported. To the best of our knowledge, glucose has never been used as a catalyst for synthesis of same compound.

Mechanism of formation of BIM with the help of glucose as:

As we observed that PEG is able to make H-bonding with oxygen of aldehyde and as a result, the electrophilicity of carbonyl carbon will increase due to the formation of this H-bond. We have assumed that same type of H-bonding can also be formed between oxygen of aldehyde and hydroxy group of glucose. Glucose being completely eco-friendly, biodegradable, safe for our health and environment can be used as green solvent. Although glucose has great potentiality to be used as green catalyst but till date it has never been explored as a green catalyst for any multicomponent reaction.



Bis (indolyl) methane

OBJECTIVE

Microwave assisted reaction is considered as green method of synthesis & glucose is considered as a green catalyst. Based on the research gap stated above, we have chosen the following objective for our project-

- Solvent free and catalyst free synthesis of bis (indolyl) methane.
- synthesis of bis (indolyl) methane by doing reaction in aqueous medium without any catalyst
- Use of glucose as green catalyst for synthesis of bis (indolyl) methane.
- Use of aqueous solution of glucose with various concentrations for green synthesis of bis (indolyl) methane.
- Best concentration of glucose solution will be chosen for the same reaction.
- A series of microwave assisted reactions with different aromatic aldehydes will be performed by employing the best concentration of glucose solution.
- A series of ultrasound assisted reactions with different aromatic aldehydes will also be performed by employing the best concentration of glucose solution.

The detection of the suitable compounds will be done using preliminary tests like TLC, melting point. Also, the identification of the compounds will also be confirmed with the help of IR and NMR.

WORKDONE

General scheme for synthesis:

Indole Aldehyde Bis (indolyl) methane

General procedure for synthesis without solvent and catalyst

In a 100 ml borosilicate conical flask I have taken 0.0098 moles of Indole and 0.0049 moles of aldehyde. The reaction mixture was irradiated at 240W under microwave condition for specific time. Stirring and cooling were simultaneously done to the reaction mixture after every 1 minute of the MW irradiation. The progress of reaction was continuously monitored by checking TLC. After the completion of reaction (indicated by TLC) lower down the temperature of reaction mixture, the solid crude product was precipitated and separated out by filtration. The crude was recrystallized from hot ethanol to get pure **Bis (Indolyl) methane** as pinkish white solid powder. The obtained product was characterized by melting point and IR spectroscopy.

General procedure for synthesis in aqueous solution

In a 100 ml borosilicate conical flask I have taken 0.0098 moles of Indole and 0.0049 moles of aldehyde. Then add 10 ml of water. The reaction was mixture irradiated at 240W under microwave condition for specific time. Stirring and cooling were simultaneously done to the reaction mixture after every 1 minute of the MW irradiation. The progress of reaction was continuously monitored by checking TLC. After the completion of reaction (indicated by TLC) lower down the temperature of reaction mixture, the solid crude product was precipitated and separated out by filtration. The crude was recrystallized from hot ethanol to get pure **Bis**

(Indolyl) methane as pinkish white solid powder. The obtained product was characterized by melting point and IR spectroscopy.

General procedure for synthesis in Glucose solution

In a 100 ml borosilicate conical flask I have taken 0.0098 moles of Indole and 0.0049 moles of aldehyde. Then add 10 ml of glucose solution. The reaction mixture was irradiated at 240W under microwave condition for specific time. Stirring and cooling were simultaneously done to the reaction mixture after every 1 minute of the MW irradiation. The progress of reaction was continuously monitored by checking TLC. After the completion of reaction (indicated by TLC) lower down the temperature of reaction mixture, the solid crude product was precipitated and separated out by filtration. The crude was recrystallized from hot ethanol to get pure **Bis (Indolyl) methane** as pinkish white solid powder. This was done for all reactions. The obtained product was characterized by melting point and IR spectroscopy.

Table 1: Microwave assisted reaction in different conditions.

S.No.	Conditions	Reaction time	Yield (%)
1.	No solvent & No catalyst	17 min. (reaction not completed)	
2.	H_2O solvent without any catalyst	10 min.	60
3.	H_2O solvent + 0.5 M glucose	6 min.	74
4.	H_2O solvent + 1 M glucose	5 min.	72
5.	H_2O solvent + 2 M glucose	2 min.	75

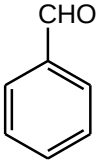
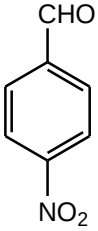
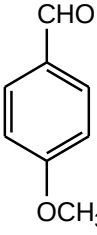
DISCUSSSION ON MICROWAVE ASSISTED REACTIONS:

From the above table it has been cleared that while doing the synthesis of bis (indolyl) methane without using any solvent and without catalyst, the reaction was not completed after 17

minute under microwave irradiation (240 W). Then we performed the reaction in aqueous media. Our reaction completed in 10 minutes under microwave irradiation (240 W**)**. This shows that water provides some influence for the completion of reaction. Further when the reaction was performed in glucose solution, we see that the reaction time decreases this shows that glucose act as catalyst for this reaction. Then we try the different concentration solution of glucose to check the effect of concentration on the reaction rate, and we see that as the concentration of glucose is increased the reaction time is decreased.

By checking the results, the appropriate concentration of glucose (i.e. 2M) was taken for synthesis of bis (indolyl) methane by making the indole to react with a series of aromatic aldehydes.

Table 2: Microwave assisted reaction with different aldehydes:

Entry	Benzaldehyde	Time	Yield	Melting Point	Melting Point (lit.)
1.		2	75	140	140-142
2.		10	80	230	218-220
3.		9	70		

DISCUSSSION ON MICROWAVE ASSISTED REACTIONS:

By using indole and aromatic aldehydes (which contains electron rich and deficient functional groups), a series of Bis (indolyl) methane derivatives were synthesized. Our reactions were done in aqueous glucose medium. It is interesting to note that in the glucose medium the reaction completed in 8-10 minutes. The reaction time for 4-nitrobenzaldehyde is 10 minute while that of simple benzaldehyde is only 2 minutes. This means that the reaction take more time with 4-nitro benzaldehyde. This may be due to the formation of H-bonding between nitro group of benzaldehyde and hydroxyl of glucose. The formation of this H-Bonding between nitro group of benzaldehyde and OH group of glucose has decreased the probability of H-bonding formation between the OH of glucose with the oxygen atom of aldehyde group. Thus the effect of H-bonding is not so severe in case of nitro benzaldehyde.

CHARACTERISATION:

Name: 3-((1H-indol-3-yl)(phenyl)methyl)-1H-indole

Melting Point (observed): 140^0C (observed)

IR Data Analysis:

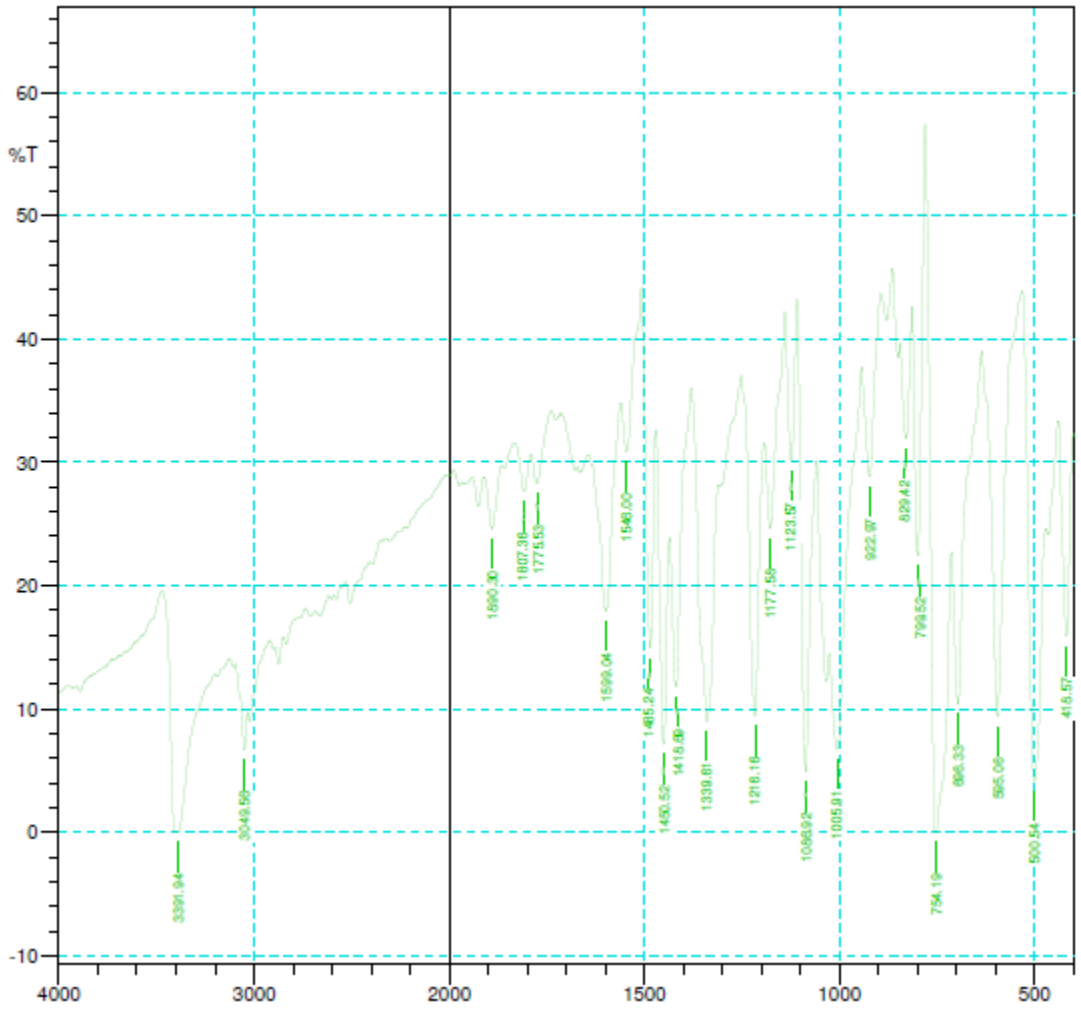
3391.94 cm^{-1} –N-H stretching

3049.56 cm^{-1} – sp^2 stretching

1599.04 cm^{-1} –N-H bending

1450.52 cm^{-1} –C=C aromatic stretching

1086.92 cm^{-1} –C-N stretching


%T
60
50
40
30
20
10
0
-10
4000
3000
2000
1500
1000
500
3391.94
3049.50
1690.30
1807.36
1775.53
1599.04
1540.09
1485.24
1450.52
1416.80
1339.81
1216.16
1177.50
1123.57
1066.92
1005.91
922.97
829.42
799.52
754.19
666.33
595.06
500.54
416.57

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