Indole: Synthesis, Properties and Services to Mankind

A Thesis

Submitted for the partial fulfilment of the Degree

of

Master of Science (Chemistry)

by

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Registration No.: 302202014

Under the guidance of

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DECLARATION

I, hereby declare that the dissertation entitled "Indole: Synthesis, Properties and Services to Mankind" being submitted in the partial fulfilment of the requirements for the award of degree of **Master of Science in Chemistry** to the **Department of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** is a record of my own work carried out under the supervision of **Dr. Vikas Tyagi** from Jan-July, 2024. Further, any work of this dissertation has not been submitted to any other university for the award of any other degree or diploma.

Signature of Candidate

Date: 13.06.2024

Place: Sirsa

Full Name of Candidate: Vishesh Bansal

Registration no.: 302202014

CERTIFICATE

This is to certify that the dissertation entitled "Indole: Synthesis, Properties and Services to Mankind" being submitted by **Vishesh Bansal** to the **Department of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** in the partial fulfilment of the requirements for the award of degree of **Master of Science in Chemistry,** is an authentic record of the work carried out by **Vishesh Bansal** under the guidance and supervision of **Dr. Vikas Tyagi**. He has fulfilled the requirements for the submission of this dissertation, which to my knowledge has reached the requisite standard.

The result embodied in the dissertation have not been submitted in part or full to any other University or Institute for the award of any other degree or diploma.

Date: 21-06-24

Place: Patiala

Signature

Dr. Vikas Tyagi
Assistant Professor
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ACKNOWLEDGEMENT

I take this opportunity to express a deep sense of gratitude to my supervisor Dr. Vikas Tyagi (Assistant professor) Department of Chemistry and Biochemistry, TIET, Patiala for providing me with all the facilities in this project and gave me the golden opportunity to do this wonderful project in his lab on the topic “Indole: Synthesis, Properties and Services to Mankind”. This project helped me in knowing a lot of things about how to carry out research work. I came to know about so many new things about Indole and its wide range of precursors and technological advances in the field of indole synthesis, which will certainly help me in my future endeavour.

I would like to thank Ms. Pooja Soam, Research Scholar, who introduced me to the lab activities and made it a very enjoyable experience. A special thanks to her for her constant support throughout the project. I would like to thank all the lab members of the lab of department of Chemistry and Biochemistry for their constant support and making this journey a memorable one.

Date: 13.06.2024 Signature of Candidate

Place: Sirsa Full Name of Candidate: Vishesh Bansal

INDOLE: SYNTHESIS, PROPERTIES AND SERVICES TO MANKIND

ABSTRACT

In the course of the project work entitled “Indole: Synthesis, Properties and Services to Mankind”, the overview of the approaches to synthesis of various indole-based derivatives have been encompassed. There are several fields of science covering the worthy aspects of indole and its derivatives. This report covers approximately a majority of those aspects. It had an emphasis on the synthetic approaches to synthesis of indole and its derivatives. The properties of indole and its applications, and services to mankind as natural product, bio-organic components and medicines are also encapsulated.

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INTRODUCTION

Indole is an aromatic, volatile, crystalline solid with a melting point of 52°C and a persistent odor. It is a fused ring heterocycle of the class of benzo-fused five membered ring heterocycles. This fusion takes place at the 2,3 positions of the pyrrole ring. It is an example of benzo pyrroles. The investigation of indoles is crucial in heterocyclic chemistry. Indole unit occurs in thousands of alkaloids. Most of these alkaloids such as indole-3-acetic acid (**1**), and indole-3-butyric acid (**2**) have important physiological activities. Also, the derivatives of the amino acid tryptophan (**3**) work as plant growth regulators. Tryptamine (**4**) and serotonin (**5**) are hallucinogenic alkaloids that are derived from the amino acid tryptophan.

PROPERTIES OF INDOLE

The properties of indole are divided into the following categories:

ATOMIC PROPERTIES:

Functional Group:	Imine
Central Atom:	Nitrogen
Hybridization:	sp^2

PHYSICAL PROPERTIES OF INDOLE:

Physical properties include the state of the substance at room temperature and various other properties like density, viscosity etc. Indole is a solid at room temperature with a pungent unpleasant odor at higher concentration and a flowery odor at lower concentration.

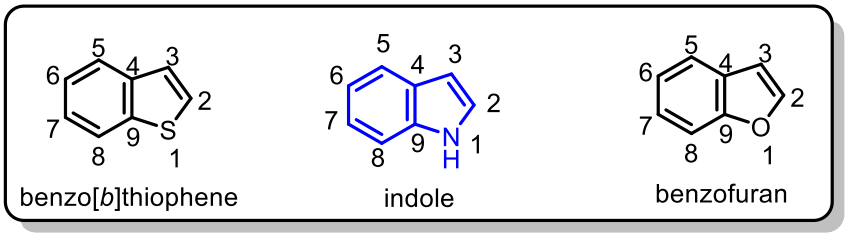
CHEMICAL PROPERTIES OF INDOLE:

Chemical properties include chemically derived values such as reactivity and orientation etc. The various typical values of indole are as under:

Molar Mass:	117.151 $gmol^{-1}$
Density:	1.174 gcm^{-1}
Melting Point:	325-327K
Boiling Point:	526-27K
Acidity pK_a:	16.2 (21.0 in DMSO)
Basicity pK_b:	17.6
Magnetic Susceptibility:	-8.5×10^{-6} cm^3mol^{-1}
Dipole Moment:	2.11 D in Benzene

- Indole acts as a nucleophilic and gives an electrophilic substitution reaction at its pyrrole ring as it is comparatively more nucleophilic.
- The β-position is preferably reactive.

- Indoles having aromaticity in between the benzo thiophene and benzofuran.

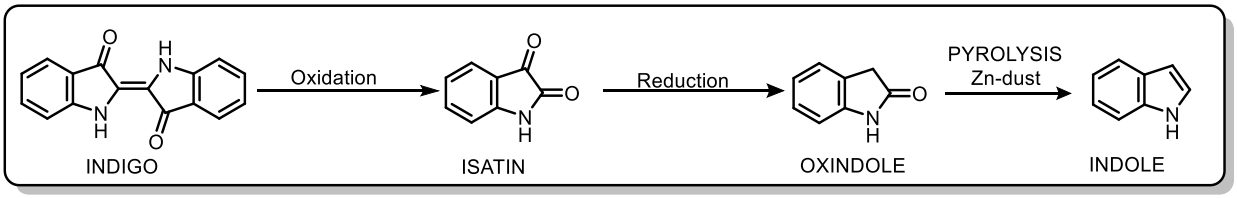


SERVICES TO MANKIND

Indole is an aromatic Nitrogen-containing heterocyclic hydrocarbon having the positions 1 and 3 as the most reactive positions. It has the fourth most abundant biochemical element i.e. Nitrogen in its pyrrole ring. It has the ability to fuse with the infected areas or agents in the mechanism of indole based pharmaceutical products. Indole containing scaffolds are widely used as effective against cancer, diabetes, migraine, tuberculosis, malaria, hypertension and even in bacterial and viral infections. In this way, the indole-based compounds serve the mankind in a variety of ways.

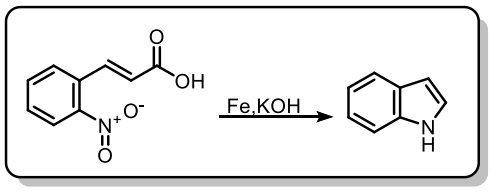
SYNTHESIS

- It's a planer fused aromatic heterocyclic compound found in numerous natural products.
- It was first isolated by Adolf von Bayer in 1866 by pyrolysis of Oxindole (indolin-2-one) with zinc which was obtained by reducing isatin (indoline-2,3-dione) which itself was obtained by oxidation of indigo ((E)-[2,2'-biindolinylidene]-3,3' [1]



Scheme 1: The first indole synthesis by Adolf von Bayer

It was proposed by Adolf von Baeyer and Adolph Emmerling in 1869. It's the alkaline metal catalysed cyclization of o-Nitrocinnamic acid derivative (E)-3-(2-nitrophenyl) acrylic acid to form indole [1].

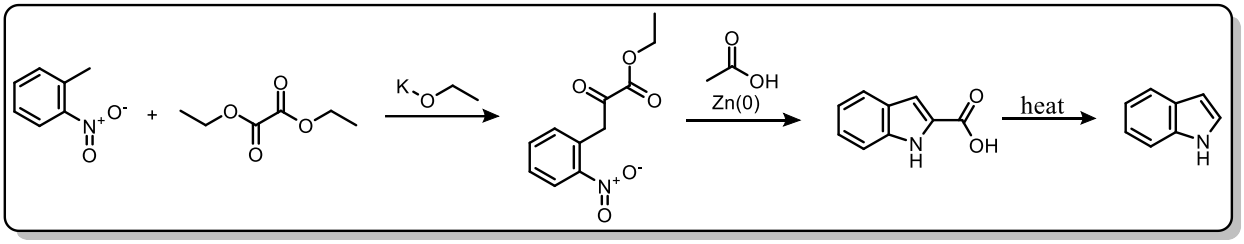


Scheme 2: Baeyer-Emmerling Indole Syntheses

The Reissert Indole Synthesis, which is named after Arnold Reissert, a Prussian chemist was proposed in 1897 [2]. The synthesis involves the condensation of o-nitrotoulene with diethyl

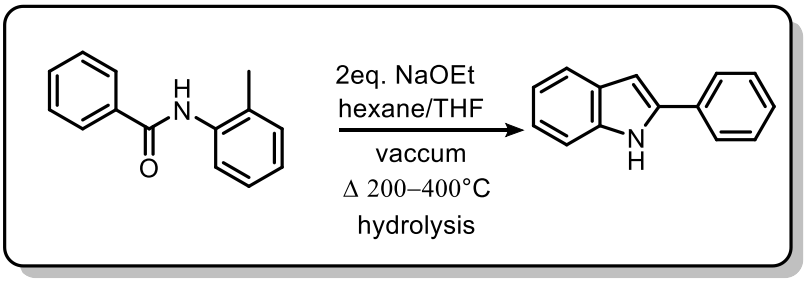
oxalate and o-nitrophenyl pyruvate product is obtained. The catalytic reduction of the nitro group of the product leads to spontaneous cyclization in presence of zinc metal Zn (0) forming indole-2 carboxylic ester, which can be hydrolyzed and decarboxylated.

A modified Reissert Synthesis enables indoles unsubstituted in the five membered ring to be produced directly. This reaction is independent of functionalization of the benzene ring.



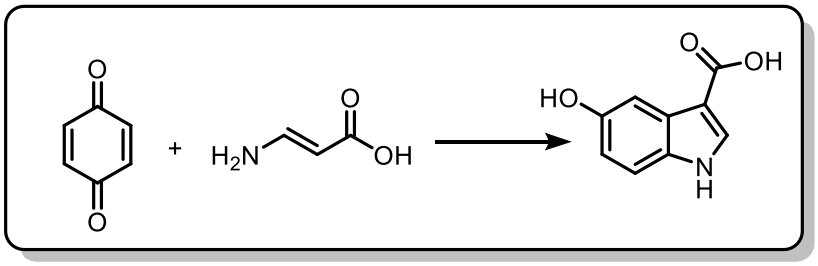
Scheme 3: Reissert Indole Syntheses

It is named after German chemist Walter Madelung who in 1912 found that the o-alkylanilides serve as substrates for the synthesis of α-substituted indoles [2]. It is a type of base catalyzed intramolecular thermal cyclization in the absence of air. The base may include sodium alkoxides or sodamide.



Scheme 4: Madelung Indole Syntheses

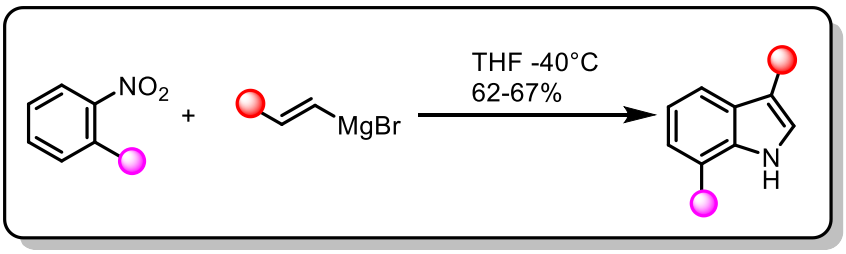
It is named after Costin D Nenitzescu. It was reported in 1929 [2]. The Nenitzescu synthesis provides a direct route for the synthesis of 5-hydroxy indoles. It is especially useful for preparation of 5-hydroxy indole some of which have biological activity. The reaction is a conjugate addition of vinylogous primary or secondary amide to benzoquinone followed by cyclization.



Scheme 5: Nenitzescu Indole Syntheses

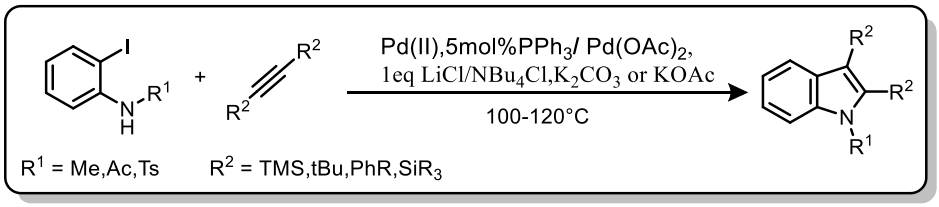
The Nenitzescu reaction occurs under relatively milder conditions. The substrates of the reaction may include mono, di and tri substituted para quinones and β-aminoacrylonitriles, β-aminoacrylamides and β-amino-α,β-unsaturated ketones.

This synthesis was reported by Giuseppe Bartoli in 1989 [2]. He reported that vinyl magnesium bromide and 2-nitrotoluene react at -40°C in THF to form 67% yield of 7-methylindole. The o-substitutions may vary but the m, p-substituted nitrobenzene provide poor or no yield. The methodology of Bartoli synthesis is quite different to that of Fischer synthesis. But mechanistically, the methods are related. Experimentally, a nitrobenzene is used with 3 moles of vinyl magnesium bromide to give 7-substituted indoles.



Scheme 6: Bartoli Indole Syntheses

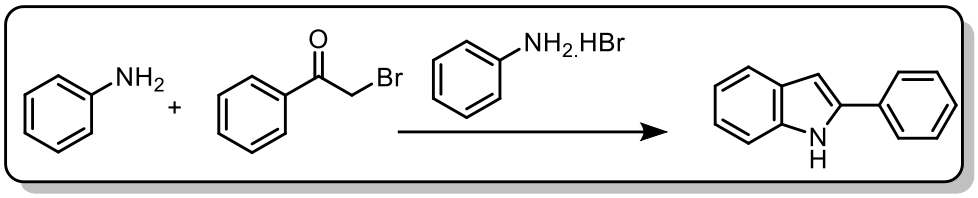
It was reported by Richard C Larock in 1991 [5]. It's also known as Larock heteroannulation. The reaction is best reported with the internal alkynes and α-iodo aniline derivatives in presence of palladium (0) complexes and a weak acid or base salt such as sodium or potassium carbonates or acetates. It is a type of thermal induced metal catalysed cyclisation reaction leading to the production of 1,2,3 substituted indole. On applying these conditions there may be examples of reactions reaching to different indole derivatives. various substituted indoles can be directly synthesized by this reaction.



Scheme 7: Larock Indole Syntheses

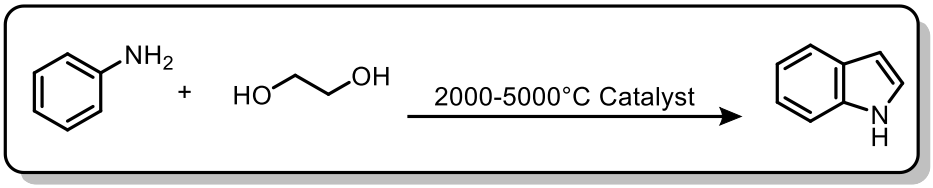
It is named after Augest Bischlar and Richard Mohlau [3]. It's a type of nucleophilic addition followed by cyclization among aniline and α-halo ketones.

Aniline and 2-bromo-1-phenylethan-1-one gets cyclized to give 2-phenyl-1H-indole.



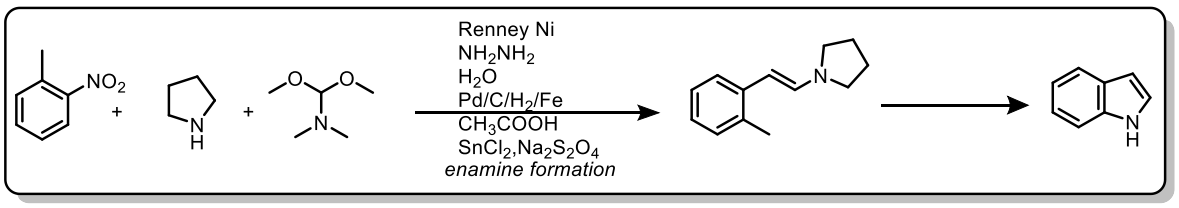
Scheme 8: Bischler-Mohlau Indole Synthesis

Aniline is heated at 2000-5000°C in presence of ethane-1,2-diol and some catalyst.



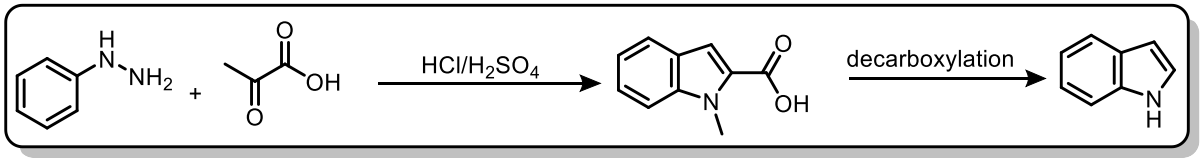
Scheme 9: Vapour Phase Reaction

In 1971, Andrew D Batcho and Willy Leimgruber proposed Batcho-Leimgruber synthesis which involve condensation of o-nitrotoluene derivatives with formaldehyde acetals followed by reduction of the trans-β-dimethylamino-2-nitrostyrene resulting in the formation of indole derivative.



Scheme 10: Batcho- Leimgruber Indole Synthesis

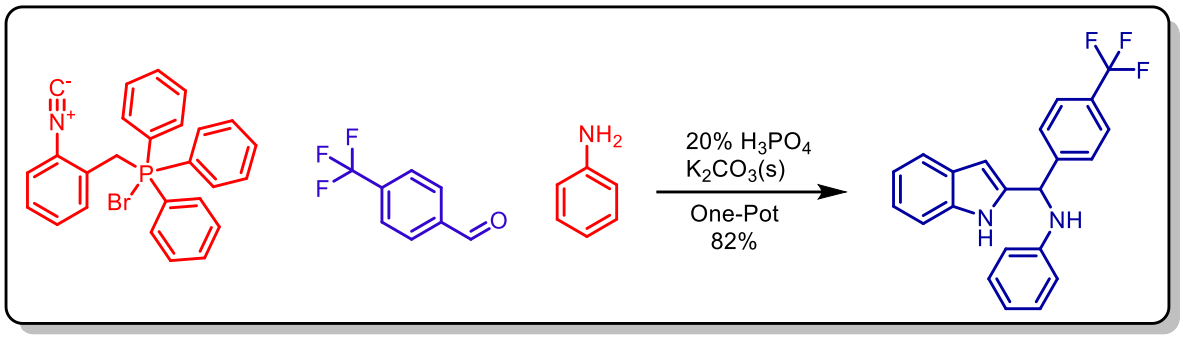
This was done by Fischer and Jordon. It is the most widespread important viable and economic reaction reported by Herman Emil Louis Fischer in 1883. This reaction can be considered as cyclization of an arylhydrazone of an aldehyde or ketone by treatment with acid catalyst or thermal energy to form the indole nucleus. It is often carried out by subjecting an equimolar mixture of arylhydrazone and aldehyde or ketone directly to the indolization condition without isolation of aryldiazonium salt or N-nirtosoarylalkylamine intermediate or by a palladium mediated coupling reaction. These methods are effective when the arylhydrazone or **N-nitrosoarylalkylamine** are unusable or toxic. Various modification of this reaction is discovered recently.



Scheme 11: Fischer Indole Synthesis

LITERATURE SURVEY

Ming-Wu Ding and co-workers in 2017 established a new One-Pot Strategy of Indole synthesis by Ugi-3CR/Wittig Reaction [6]. This was done with an odorless o-Isocyanide substituted Phosphonium salt with aldehyde and amine to produce a 45-82% yield of the Indole. Multicomponent reactions have a high efficiency and atom economy. These are used for synthesis of natural products. Ugi-3CR is an important multicomponent reaction giving diverse heterocycles. Ugi-4CR is also another efficient 4 component reaction using aldehyde, acid, amine and isocyanide: in presence of K_2CO_3(s) and 20% phosphoric acid. Intra-molecular Wittig reaction provide a milder condition pathway for synthesis of various heterocycles.



Scheme 12: Sequential Ugi 3CR Wittig Reaction

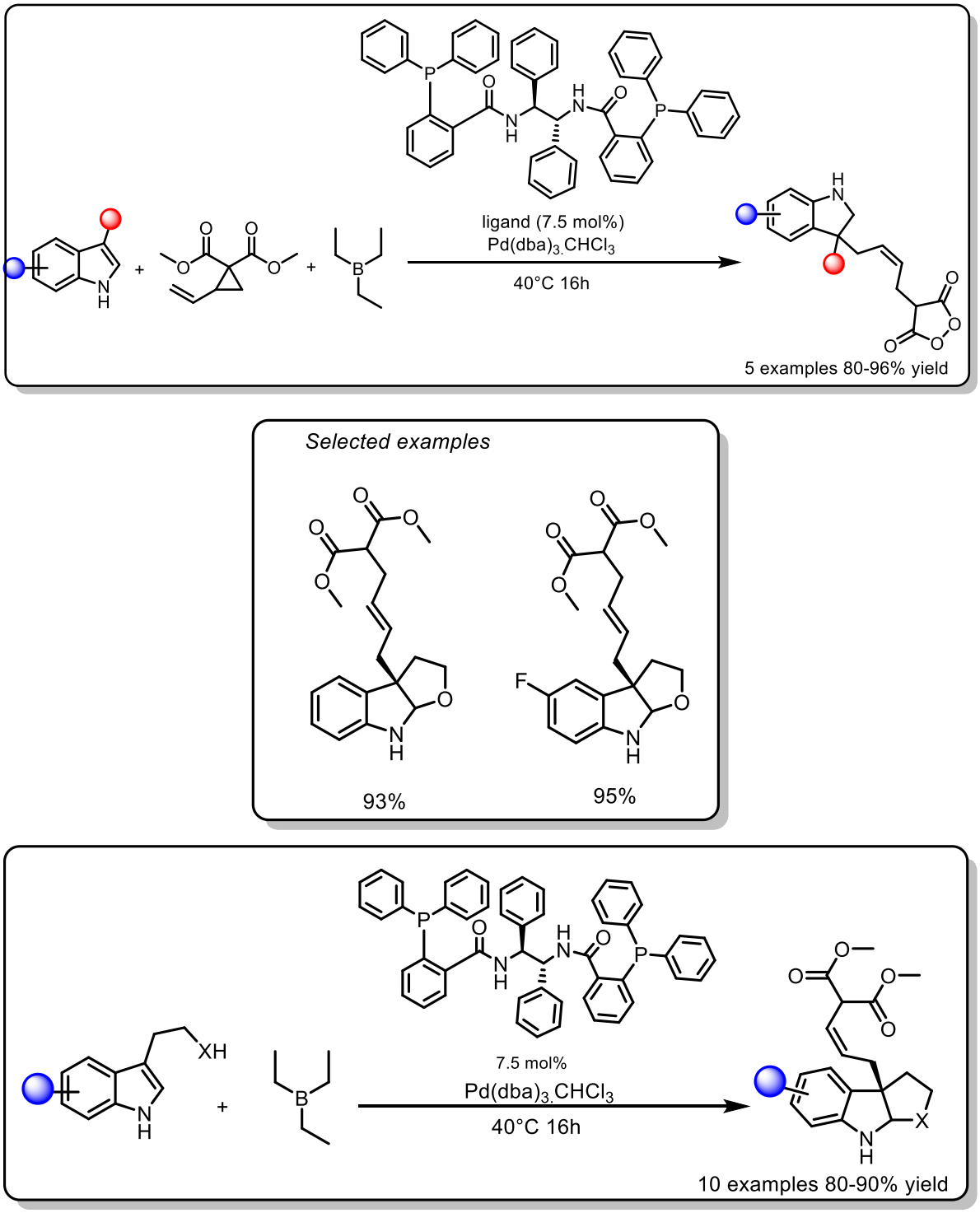
It was also revealed that the attempts of an indole synthesizing 4 component reaction Ugi-4CR failed and the milder, atom economic and efficient Ugi-3CR intramolecular Wittig reaction is adopted as the most important synthetic reaction of indoles.

A class of Nitrogen containing Heterocycles, Pyridazino[4,5-b] indoles are pharmaceutically important compounds having different characteristic properties.

Hence, these become synthetically significant for the research purpose. In past few decades, Pyridazino[4,5-b] indoles have been constructed through various methods. For example, intramolecular cyclization of Pyridazine derived azides from 5-chloropyridazine-3[2H]-one undergoing Suzuki coupling, deprotection, diazotization and azidation reactions in a sequence. The end product is refluxed in xylene to form Pyridazino[4,5-b] indoles. Another pathway of synthesis of Pyridazino[4,5-b] indoles is Vilsmeier Haack reaction followed by condensation of 2-indolecarbohydrazides.

Barry M. Trost in 2018 reported a Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-Substituted 1H-Indoles and Tryptophan Derivatives with Vinylcyclopropanes[7]. Vinylcyclopropanes are known to generate 1,3-dipoles with a palladium catalyst that initially serve as nucleophiles to undergo [3 + 2] cycloadditions with electron-deficient olefins. Indole

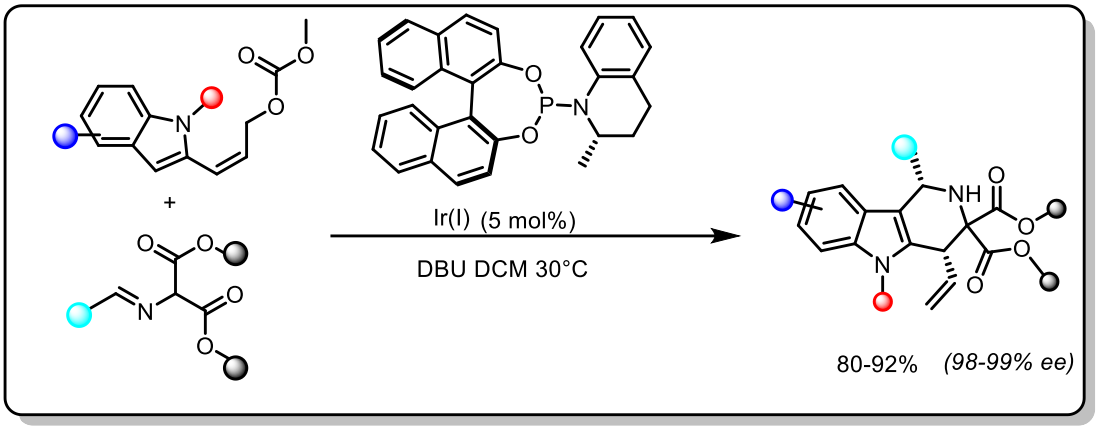
alkaloids display a broad range of anticancer, antibacterial, and antifungal properties such as borreverine is strongly active against Gram- positive bacteria.



Scheme 13: Palladium-Catalyzed Asymmetric Allylic Alkylation

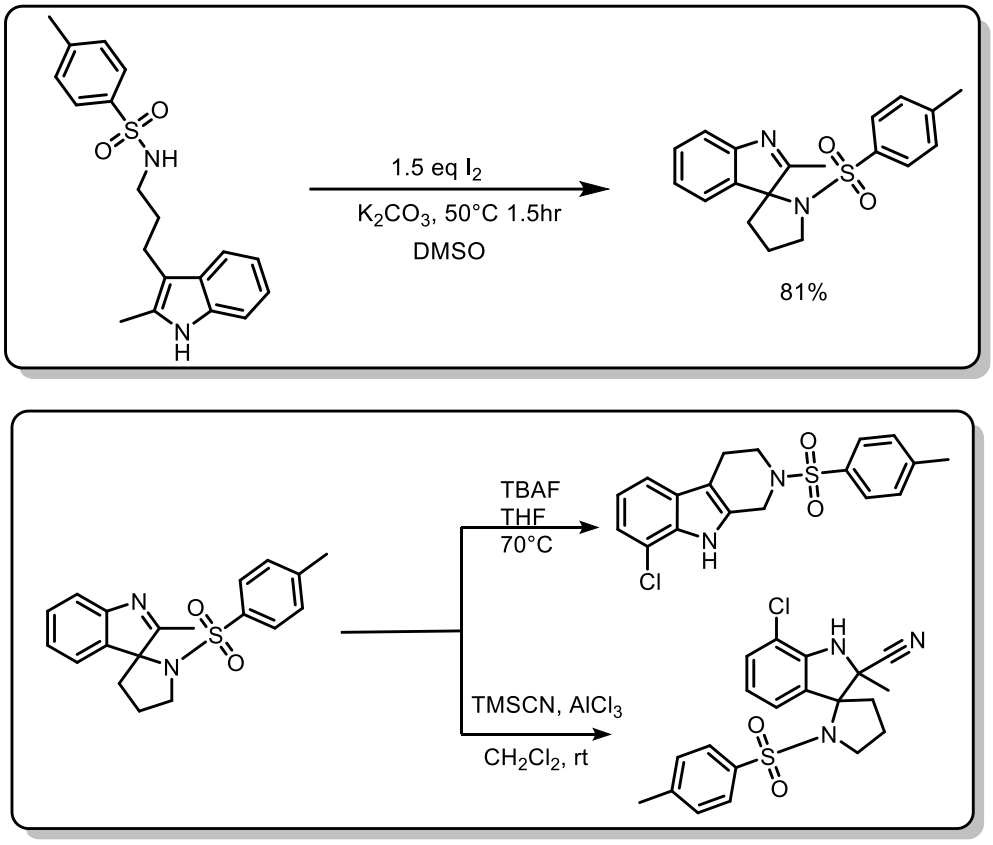
Xiu-Qin Dong in 2021 reported an Ir-catalyzed asymmetric tandem allylation/iso-Pictet−Spengler cyclization of arylidenaminomalonates with indolyl allylic methyl carbonates which provided a direct and practical approach to access synthetically useful and biologically

active tetrahydro-γ-carboline derivatives bearing multiple functional groups and stereo genic centers in good to 44%−96% yields, >20:1 dr, 94% → 99% ee, and excellent stereoselective control [8]. Indolo-b-fused nitrogen heterocyclics such as, chiral tetrahydro-γ-carboline derivatives are prevalent structural motifs in numerous natural products and biologically active molecules, pharmaceutical compounds with a diversity of biological activities.



Scheme 14: Ir-catalyzed asymmetric tandem allylation/iso-Pictet−Spengler cyclization

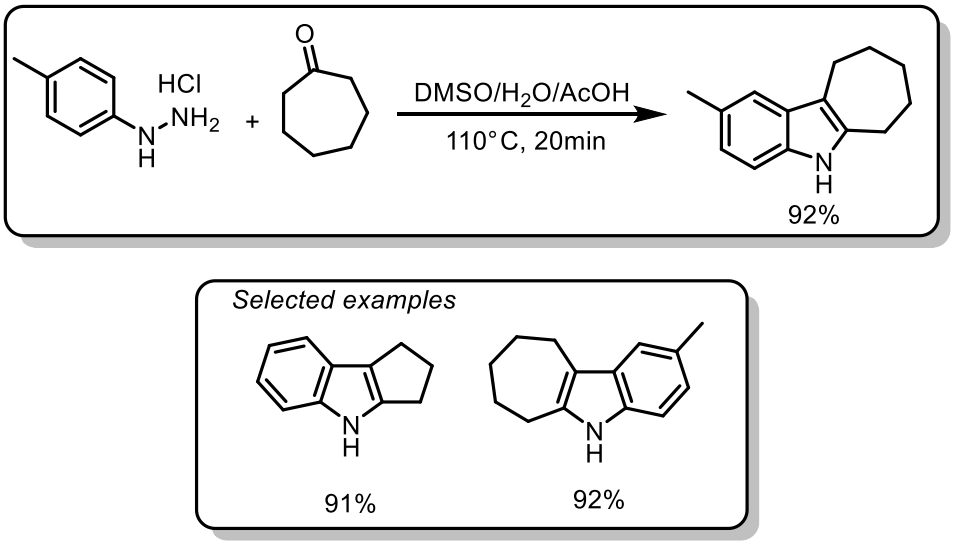
Dong-Liang Mo and others in 2022 reported a transition metal free synthesis of spiroindolenine-3,3'-pyrrolo[2,1-b] quinazolinones through gold(I)-catalyzed dearomative cyclization of N-alkynyl quinazolinone-tethered C2-substituted indoles, with more accessible precoursors and milder conditions [9]. This reaction has a broad substrate scope, good functional group tolerance, and easy gram-scale preparation and transformations. This class of compounds show excellent anti-inflammatory properties. These are also important pharmacophore in the design of new drugs such as rutaecarpine and 8-norrutaecarpine and many natural products. Quinazolinone scaffolds showed various bioactivities, such as anti-platelet aggregation, anti-inflammatory, antibacterial, and anticancer activities. These scaffolds are planar structures. Spiroindolenine scaffolds are also very important spiro-heterocyclic compounds in natural products and in the design of drugs such as spirobacillene B and aristoserratenine, which show bioactivity against cancer cells, microbes, and different types of disease affecting the human body. The obtained spiroindolenine-3,3′-pyrrolo[2,1-b] quinazolinones were tested for their anti-inflammatory activity using RAW264.7 cells by MTT assays.



Scheme 15: Transition metal free synthesis of spiroindolenine-3,3'-pyrrolo[2,1-b] quinazolinones

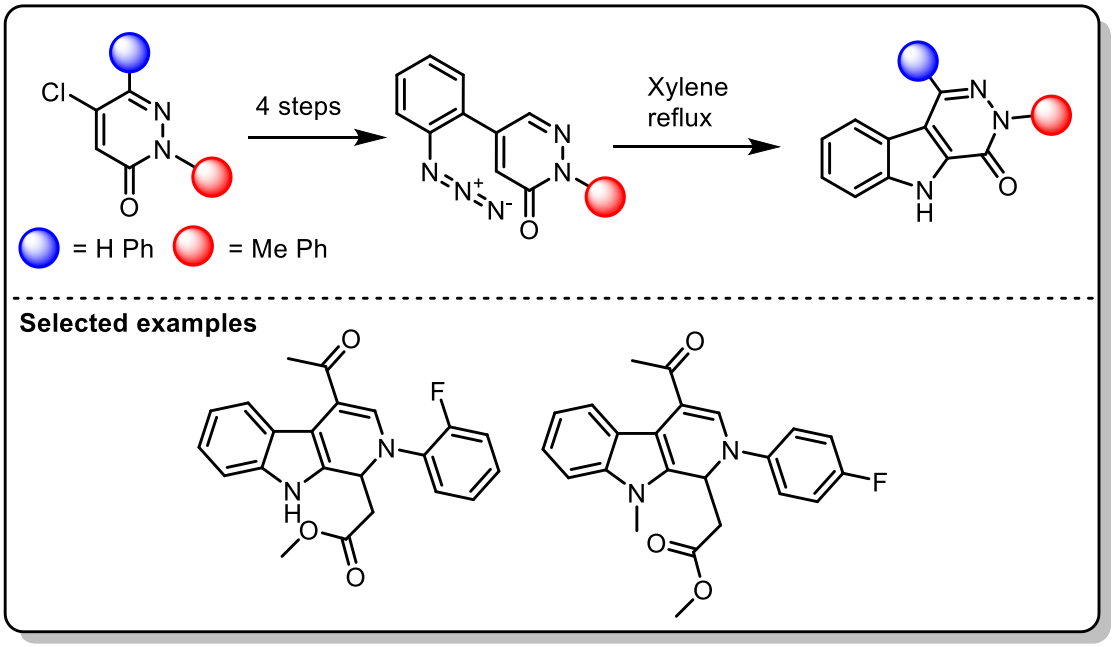
In 2023, Gu's group reported a novel fisher indole approach by using a continuous flow synthetic strategy towards indoles derivative [10]. In this view, they have applied AcOH with DMSO and Water as a solvent. In this approach they have try to overcome various limitations of batch reaction. A library of 18 derivatives have successfully synthesized which provide upto 91% yield.

Indole derivatives are used in many biologically important activities, including anti-cancer, anti-viral such as Continuous flow method has high mixing and high conversion rates. But the phenylhydrazene salts and ammonium salts formed as byproducts have poor solubilities causing hinderance of flow. Most of the indole derivatives and salts etc. can be dissolved in organic solvents or water, making the reaction homogenization difficult. Phenylhydrazene was unstable and gets oxidized easily by air. It is only 95% pure for expensive process, After the solvent optimization these solvents gave homogeneous mixture with the following %conversion and %yield

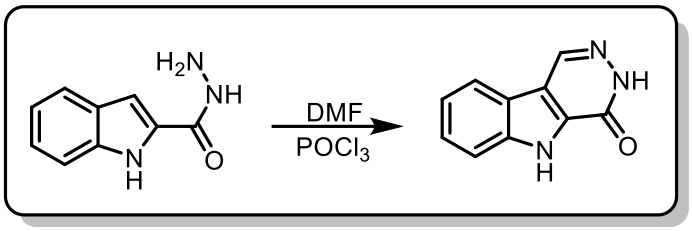


Scheme 16: Continuous Flow Indole Synthesis

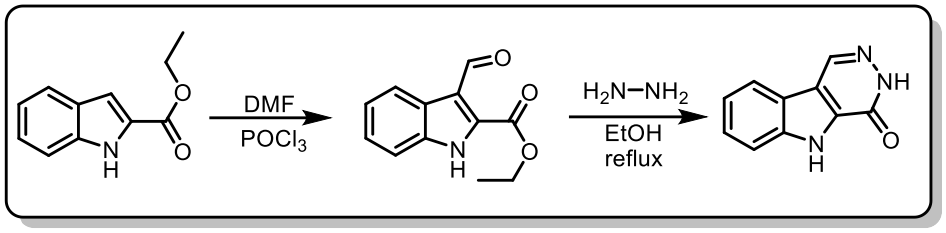
Yang Wang and others in 2024 reported a [3+3] annulation reaction of 2 alkenyl indoles with hydrazonyl chlorides in an alkaline solution forming Pyridazino[4,5-b] indoles [11]. It is an alternative greener option. They used 1a and 2a as the model substrates and when heated at 80°C in the presence of Et_3N the product 3a was obtained at 82% yield. While at lower temperature, the yield obtained was negligible. But when they evaluated the effect with another organic base like Cy_2NMe at 80°C, the yield obtained was up to 91%. But when the research group explored the free N-H 2-alkenylindole, the reaction decomposed and did not give the [3+3] annulation product.



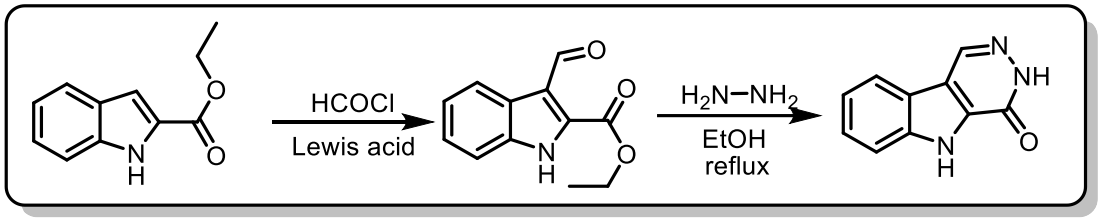
Scheme 17: Five step synthesis: Intramolecular cyclization of 5-chloropyridazin-3[2H]-one



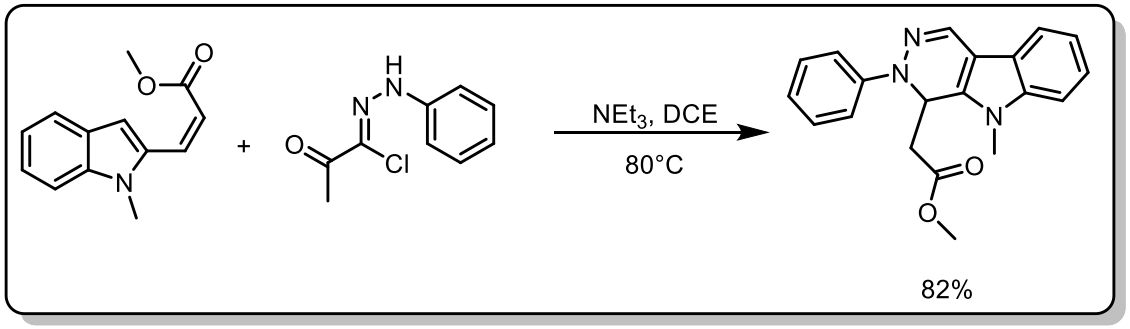
Scheme 18: Cyclization of 2-indolecarbohydrazides Vilsmeier Haack reaction



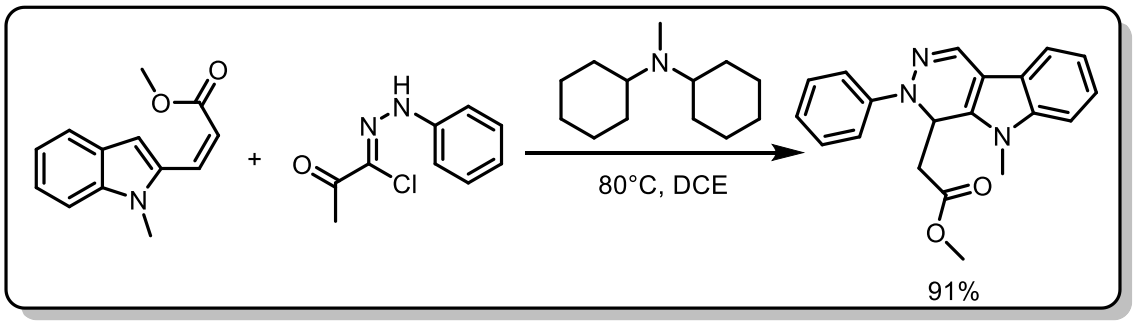
Scheme 19: Vilsmeier Heck reaction followed by hydrazine catalyzed cyclization of indole-2-carboxylates



Scheme 20: Friedel-Craft acylation followed by hydrazine catalyzed cyclization of indole-2-carboxyl

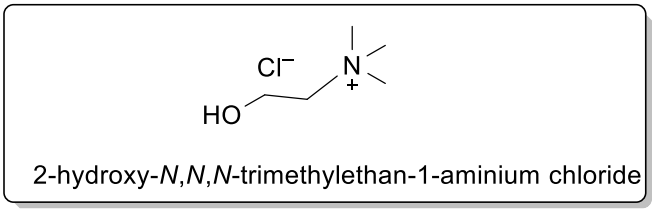


Scheme 21: [3+3] annulation 82% yield

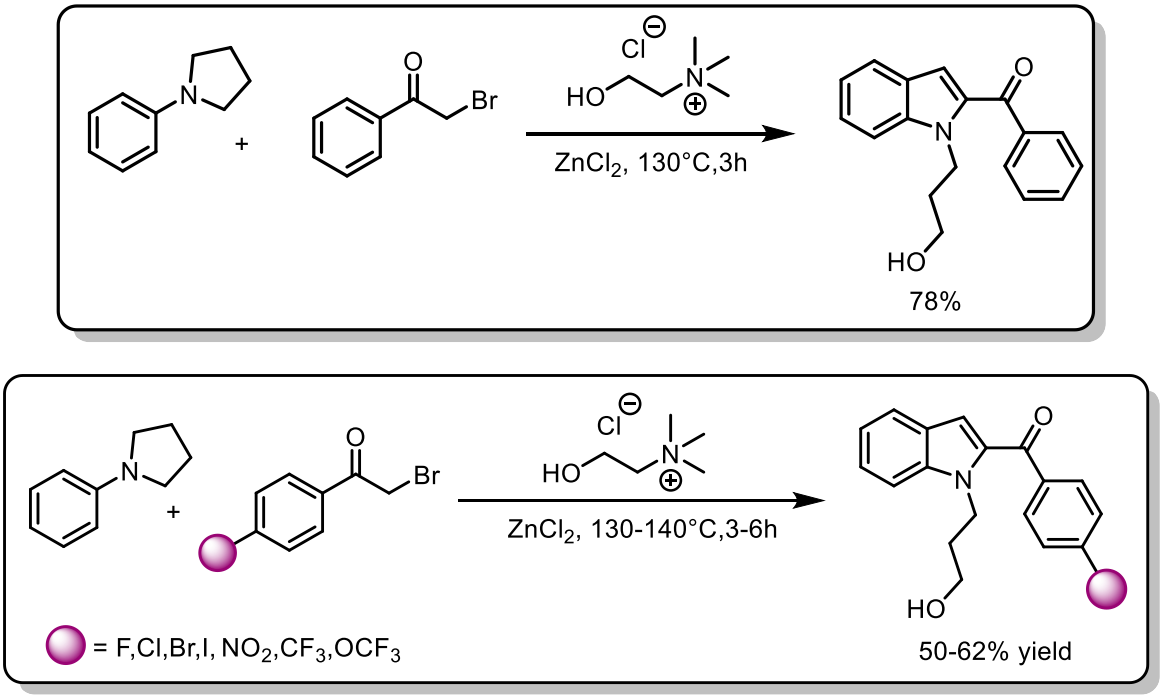


Scheme 22: [3+3] annulation 91% yield

Zongbo Xie and coworkers in 2024 reported a sustainable, environment friendly, catalyst free synthesis of 1,4-hydroxybutyl-2-benzoyl indoles from 2-pyrrolidine benzaldehyde and α-bromoacetophenone in chorine chloride/$ZnCl_2$ eutectic mixture [12]. The solvents with a catalytic effect include polar aprotic solvents such as cyclo pentyl methyl ether, propylene carbonate. Deep eutectic solvents act as a greener alternative with a specific catalytic activity. The following compounds are pharmaceutically capable as inhibitors.



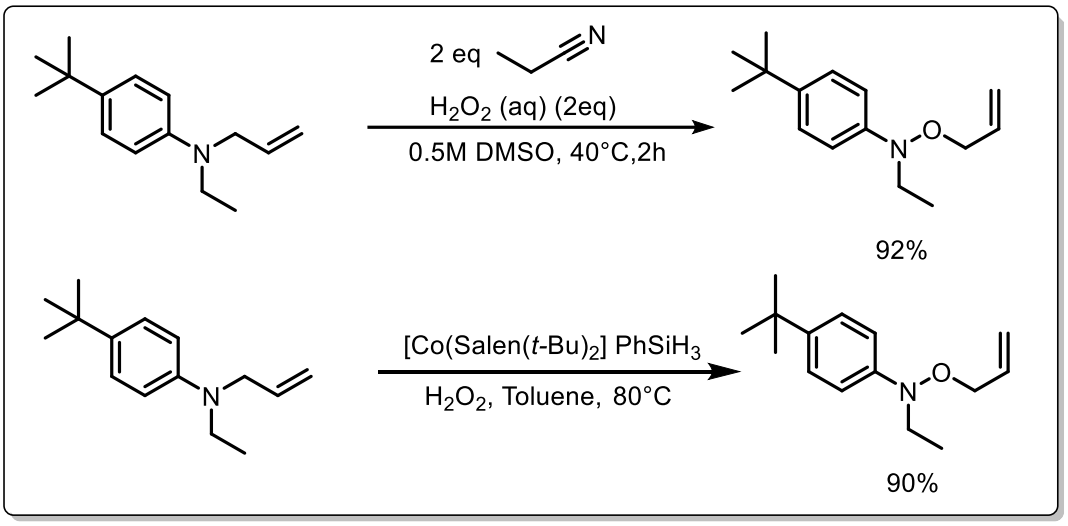
The reaction has a great functional group tolerance and undergo in a precious metal free and additive free conditions. The reaction, when carried out with a 4:1 mixture and heated to 130-140°C for 3 to 6 hours, give a maximum yield of about 78%. The percentage yield depends on the state of the catalytic solvent. In molten state, it gives only 33% yield but in $ChCl/ZnCl_2$ complex it gives 45% yield. He concluded that the substate concentration has no significant role in investigating the yield.



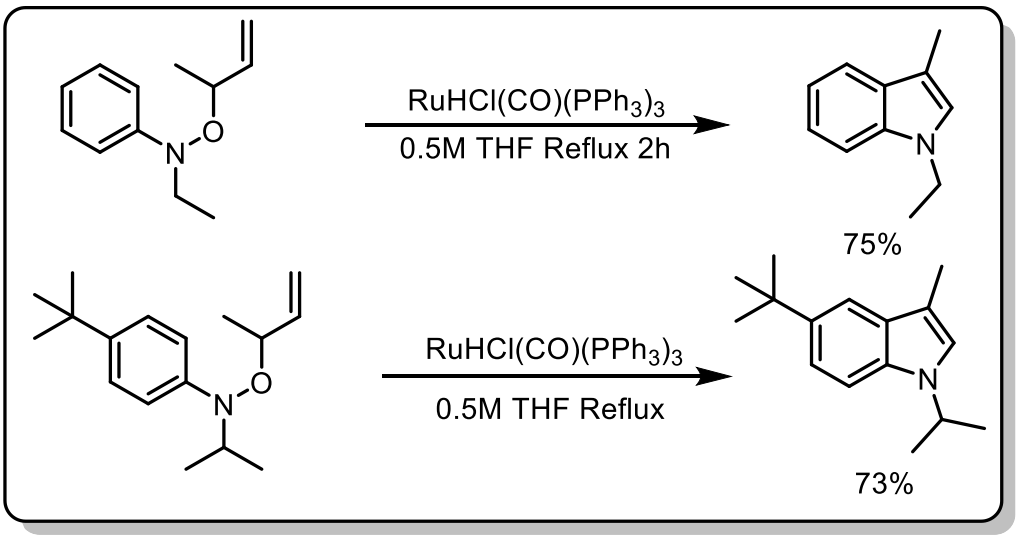
Scheme 23: Synthesis of 1,4-hydroxybutyl-2-benzoyl indoles

Ken-ichi Takao and others in 2023 reported that the Sigma-tropic rearrangement reactions serve an atom economic way of indole synthesis [13]. They observed that the oxidation of N-alkyaniline by environmentally benign hydrogen peroxide followed by a spontaneous [2,3]-

Heidenheimer rearrangement leads to the formation of N-allyloxyaniline. The further treatment of N-allyloxyaniline with a ruthenium catalyst gives N-vinyloxyaniline which finally undergoes [3,3]-sigmatropic rearrangement to give indoles. It is a waste free reaction giving only water as a byproduct. All archive reactions suffer from some shortcomings, which may be qualitative or quantitative or might be related to product isolation or purification. After reaction optimization, it was concluded that H_2O_2 catalyzed N-oxidation gives a wide-ranging percentage yield from appr. 30-91%.



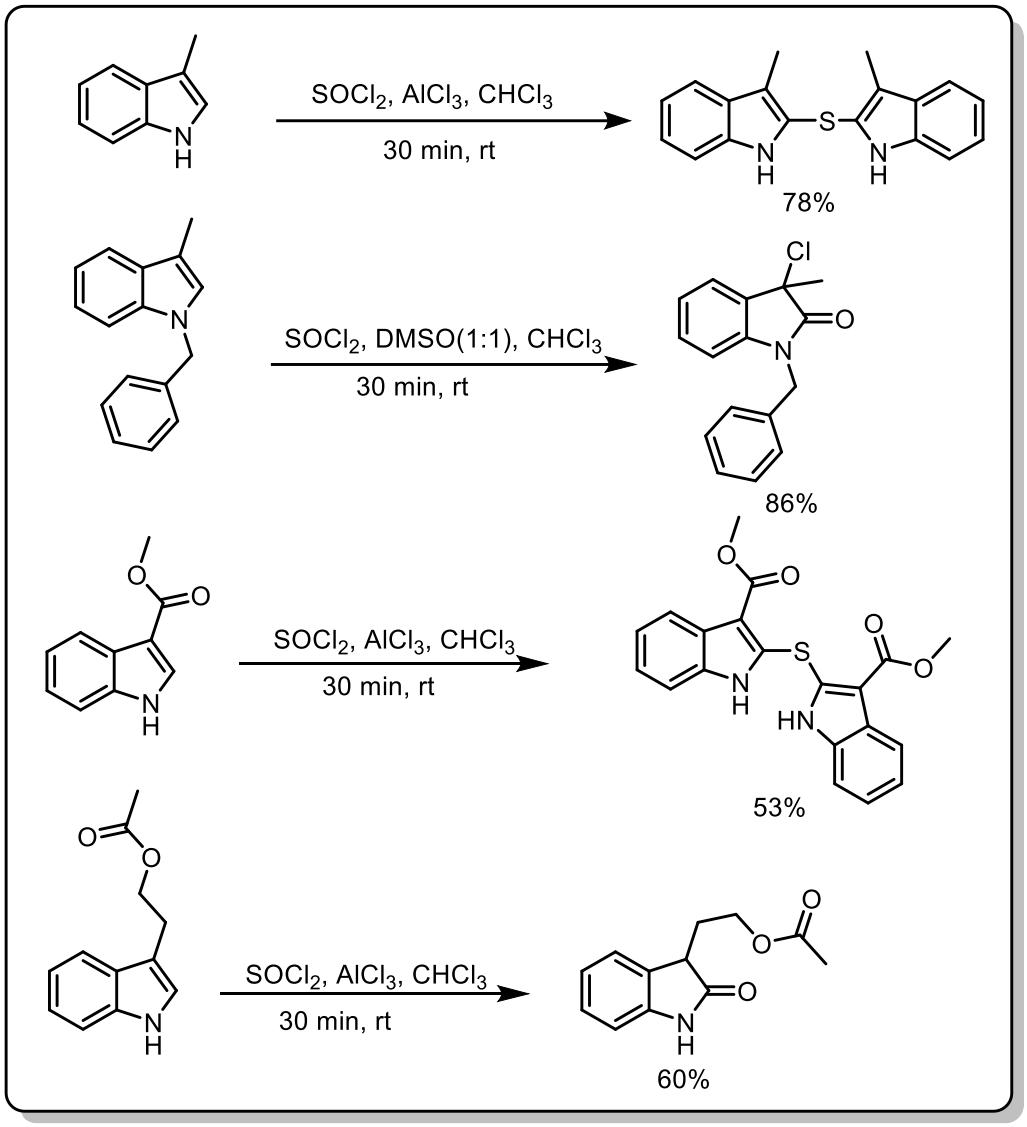
Scheme 24: Synthesis of N-allyoxyaniline by [2,3]-meisenheimer rearrangement



Scheme 25: Cyclization of N-allyoxyaniline by [3,3]-sigmatropic rearrangement

Rohan D. Erande and others in 2024 reported a unified strategy by the tweakening of catalyst-solvent combinations [14]. They achieved a percentage yield of 52-86% by selective functionalization of indoles (to synthesize 2,2'-Thiobisindoles and 3-chloro-3-alkyl substituted oxindoles selectively in a one-pot approach) in $SOCl_2/AlCl_3$ in $CHCl_3$ and $SOCl_2$-DMSO (1:1)

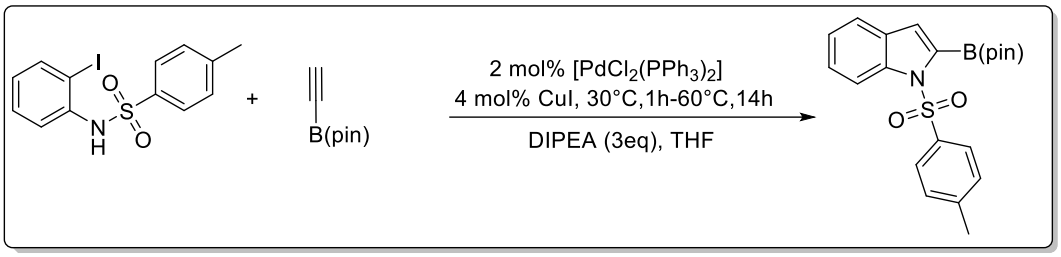
in $CHCl_3$ at 25°C. Indole thioethers and aryl thioethers have antioxidant, antiviral, anticancer properties. Indolin-2-one and 3-haloxindoles have analgesic, antimycobacterial and anti-inflammatory properties. These are also reported as intermediates for the synthesis of various pharmaceuticals. The reaction reported by Supriya Sharma and others is an efficient, transition metal free, milder and broad-spectrum reaction with 53-78% yield.



Scheme 26: Selective functionalization of indoles

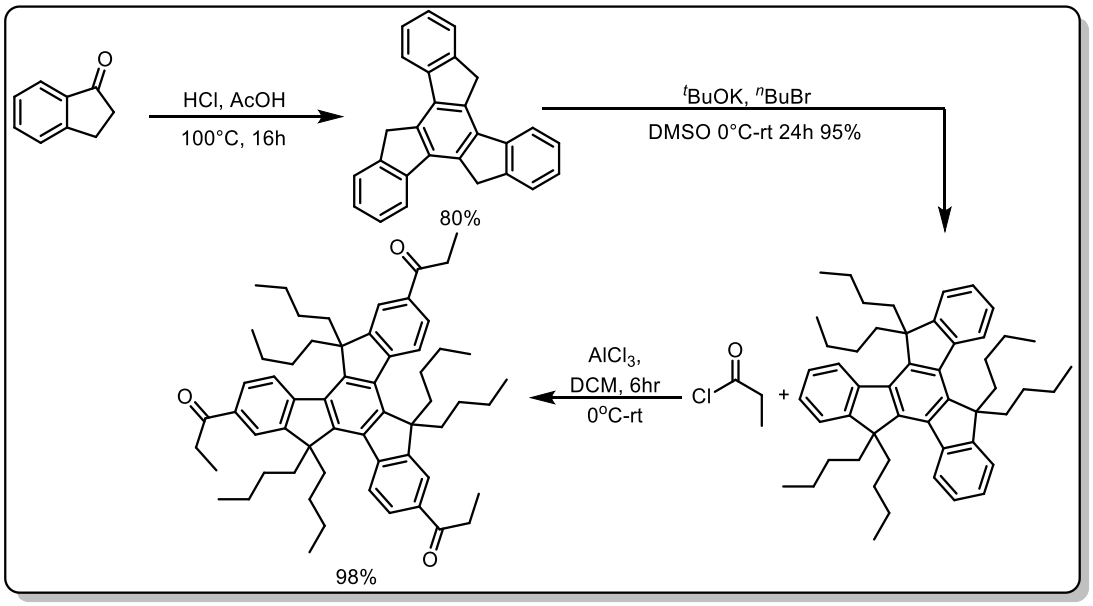
Hiroto Yoshida in 2024 reported the facile preparation of protodeborylation-resistant isoxazolyl-B(den) compounds by cycloaddition of nitrile oxides with ethynyl-B(den) (where den is naphthalene-1,8-diaminato) [15]. The den group present on boron atom in protodeborylation-resistant isoxazolyl-B(den) compounds is vital to the high stability of the products and the perfect regioselectivity due to hydrogen bond-directed orientation in cycloaddition reaction. The decreased Lewis acidity of Boron present in ethynyl-B(den) makes it acceptable for azide-alkyne cycloaddition, Larock indole synthesis and related

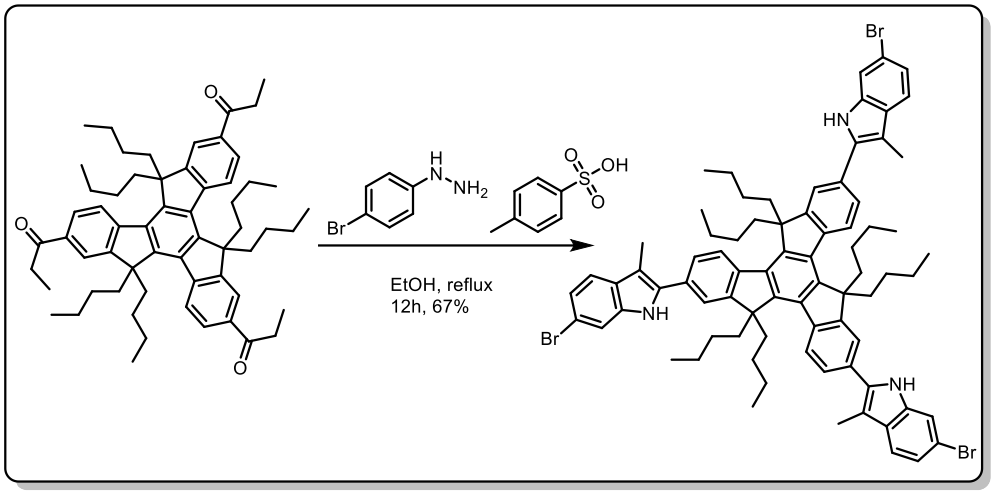
heteroannulations. The Boronated indoles exhibit sufficient protodeborylation resistance and transmetalation-inactive property. The coupling reactions play a vital role in the process of synthesis of organic compounds. In modern day research, the coupling reactions reported in 2000 are predominately and thoroughly studied. The Suzuki-Miyaura coupling of organoboranes and organic electrophiles is the widespread coupling reaction for construction of the carbon framework.



Scheme 27: Larock Indole Synthesis by Suzuki Coupling

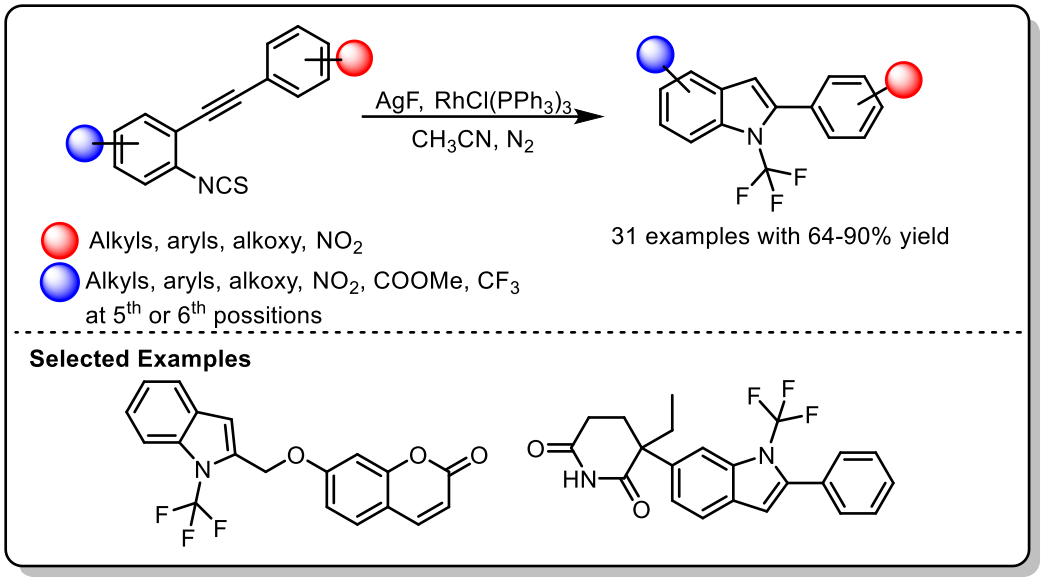
The polyaromatic compounds are a new field of interest due to their ease of synthesis and vast property spectrum. These may help in the synthesis of fullerene fragments, liquid crystals etc. Rashid Ali and others in 2024 reported that the indolotruxenes synthesis give a yield of 52-90% by acid catalyzed co-trimerization, Friedel-craft acylation and Fischer indole synthesis [16]. The research group have studied the photophysical properties of the compounds prepared by them. They applied steady state absorption and fluorescence and time resolved fluorescence spectroscopy for investigation. The assemblage of further indolotruxenes derivative started with the pre-reported derivative through the scheme 24.

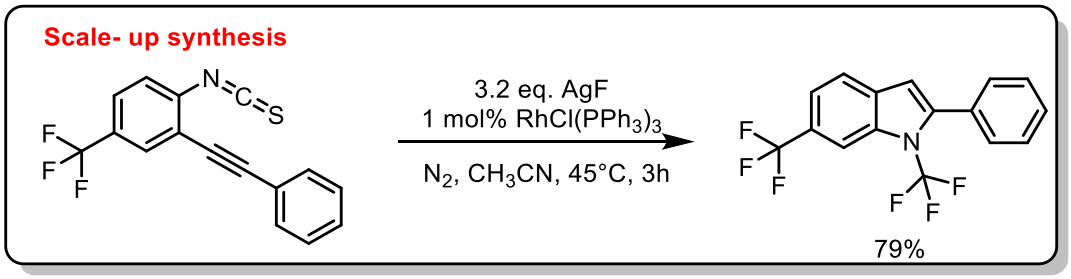




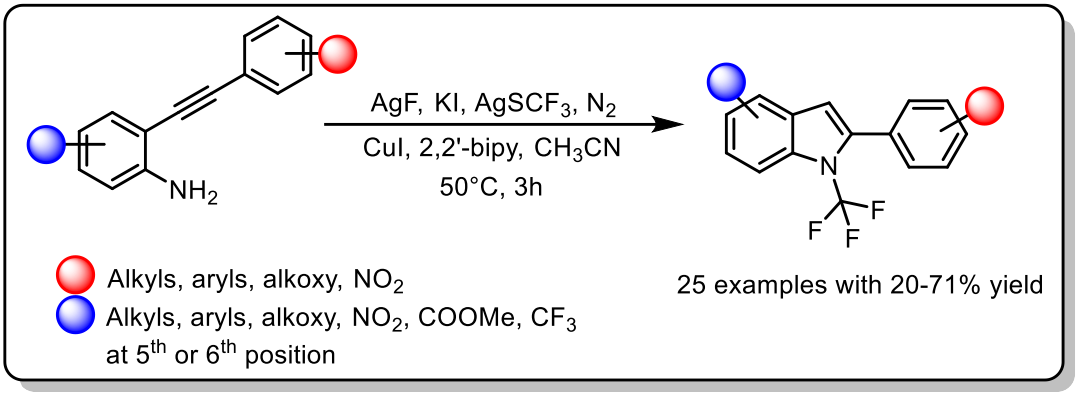
Scheme 28: Synthesis of Indole based Polyaromatics

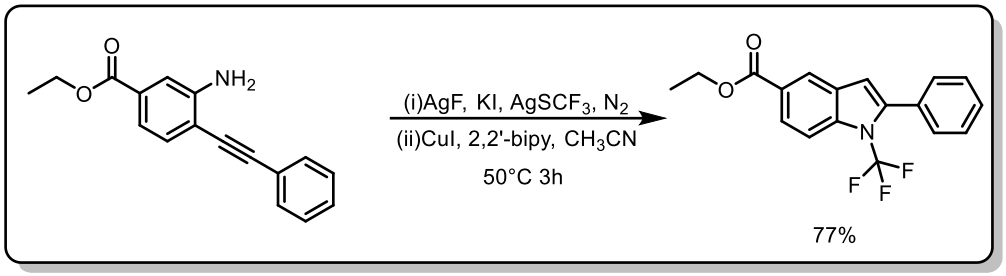
Changge Zheng and group in 2024 reported a Transition-metal-catalyzed straightforward synthesis of N-trifluoromethyl Indoles from 2-alkynylaryl icotheocyanates or 2-alkynylanilines[17]. This N-trifluoromethyl substituted indoles are agrochemically, pharmaceutically important molecules due to their specific physicochemical characteristic such as higher metabolic stability, stronger lipophilicity and greater bioavailability. N-trifluoromethyl substituted indoles have greater lipophilicity and bioavailability than the corresponding N-methyl analogues. N-heteroatoms substituted indole scaffolds are present in natural products which have anti-cancer, anti-diabetic properties.





Scheme 29: General Transition-metal-catalyzed straightforward synthesis of N-trifluoromethyl Indoles





Scheme 30: Transition-metal-catalyzed straightforward synthesis of N-trifluoromethyl Indoles

CONCLUSION

Heterocyclic chemistry is the major discipline of organic chemistry. In heterocyclic chemistry, we study a number of cyclic compounds containing atoms other than carbon (also called hetero atoms like N, O and S) enclosed in the ring. Indole is one of the heterocycles having widespread applications in biology and medicinal chemistry. The indole nucleus occurs as a major part in various alkaloid molecules and pharmaceutically active drugs. Since its inception, indole synthesis has remained one of the major attraction centers for organic chemists. In the above project work a rigorous review of the latest techniques and developments made in the field of indole synthesis has been undertaken. The period of review in this project was confined from 2018 to 2024, with an overview of the historical development since its discovery in 1869 was also included.

The major breakthrough in the indole synthesis was in the year 1883, when Harmann Emil Louis Fischer emerged with his Fischer Indole Synthesis reaction which was a noble prize-winning reaction.

The essence of this review is the study of the different synthetic pathways of indole, which is a benzo-fused pyrrole, and its biologically and pharmaceutically worthy homologues. One line of thought for the various synthetic pathways is through the transition metal catalyzed reactions. These include various metals of the transition series of the periodic table viz. Pd, Rh, Ir, Cu, Ag, Au and Ru. The mechanism of catalysis includes C-H activation.

Various scientists spent their research on the synthetic pathways and methodologies which have been applied in the field of pharmaceutical chemistry during the synthesis of various drugs.

The best choice of 7-substituted indole synthesis is the Bartoli indole synthesis. Various reactions are catalyzed by organometallic compounds such as Grignard reagents. Various syntheses of the anti-cancer drugs involve the vital role of the synthetic reaction of indole combined with other reaction; For example, Fischer indole synthesis combined with Friedel Craft acylation.

The interaction of the catalyst and the solvent have a pivot role in the synthesis approach. Its fine tuning is a vital factor towards the increase of the product yield. The synthesis of indole derivatives through pericyclic reactions opens the doors to newer methods such as [3+2] cycloaddition reactions. Practical approaches also help to increase the yield of the product

along with bypassing the harsh conditions and unstable expensive materials. (For example, Continuous Flow method).

[2,3] Meisenheimer rearrangement provide another way of indole synthesis.

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