Section-I

Introduction to Bioactive Molecules and Hypervalent Iodine Reagent.

1.1 INTRODUCTION:

1.1.1 Bioactive molecules.

1.1.2 Hypervalentiodine Reagent.

1.1.3 Nomenclature for Hypervalent Iodine Compounds.

1.1.4 General reactivity of hypervalent iodine.

1.2 LITERATURE SURVEY: TRIVALENT IODINE CHEMISTRY

1.2.1 Preperation of Trivalent Iodine Reagents.

1.3 APPLICATION:

1.3.1 Applications of DIB.

1.3.2 Applications of BTI.

1.4 DVELOPED PREVIOUS METHODS IN OUR LAB:

1.5 CONCLUSION:

1.6 REFERENCES:
1.1 INTRODUCTION:

1.1.1 Bioactive molecules.

Since the beginning of human civilization, medicinal plants have been used by mankind for its therapeutic value. According to the World Health Organization (WHO) in 2008, more than 80% of the world's population relied on traditional medicine for their primary healthcare needs. Medicinal plants produce bioactive compounds used mainly for medicinal purposes. These compounds either act on different systems of animals including man, and/or act through interfering in the metabolism of microbes infecting them. The microbes may be pathogenic or symbiotic. In either way the bioactive compounds from medicinal plants play a determining role in regulating host-microbe interaction in favour of the host. So, their extraction, isolation, purification, characterization and synthesis of these bioactive ingredients from crude extracts by various analytical methods become very important.

Bioactive molecules are those chemical compounds which produced by living organism or synthesized in laboratory, that exert a biological effect on other organisms. The effect may be adverse or beneficial; e.g. - In the case of Thalidomide (R isomer) shows teratogenicity where as S isomer is sedative in nature (Figure 1). This shows the therapeutic activity for diseases belongs to animals and humankind.

The drug discovery industries always regarded natural products as valuable sources for bioactive molecules.
So, natural medicinal products have been used for millennia for the treatment of multiple ailments. Although many have been superseded by conventional pharmaceutical approaches, there is currently resurgence in interest in the use of natural products by the general public, which forms the basis of a world-wide, multi-million dollar major commercial industry. In addition, the pharmaceutical industry continues to examine their potential as sources of novel medicinal compounds to identify novel growth factor, immunomodulatory and potential anti-microbial activity.

**a) Drug discovery: Importance of Natural Products**

For many decades, synthetic chemicals as drugs have been effective in the treatment of most diseases. The pharmaceutical industry has synthesized over 3 million new chemicals in their effort to produce new drugs. Despite their success in developing drugs to treat or cure many diseases, the treatment of certain diseases such as cancer, AIDS, heart disease and diabetes has not been a complete cure due to the complexity of these diseases.

Over the centuries, people have been living in close association with the environment and relying on its flora and fauna as a source of foods and medicines. As a result, many societies have their own rich plant pharmacopeias. In developing countries, due
to economic factors, nearly 80% of the population still depends on the use of plant extracts as a source of medicines.

Natural products also play an important role in the health care system in developed countries. The isolation of the analgesic morphine from the opium poppy, Papaver somniferum, in 1816 led to the development of many highly effective pain relievers.\(^1\) The discovery of penicillin from the filamentous fungus *Penicillium notatum* by Alexander Fleming in 1929 had a great impact on the investigation of nature as a source of new bioactive agents.\(^2\) Natural products can also be used as starting materials for semisynthetic drugs. The main examples are plant steroids, which led to the manufacture of oral contraceptives and other steroidal hormones. Today, almost every pharmacological class of drugs contains a natural product or natural product analogs.

The investigation of higher plants has led the discovery of many new drugs. So far only a small portion of higher plants has been investigated. Consequently, they still remain a big reservoir of useful chemical compounds not only as drugs, but also as templates for synthetic analogues.

**b) Drug Discovery: Recent Developments**

In the past 6 years, five new drugs derived from natural products, namely, apomorphine hydrochloride, galanthamine hydrobromide, nitisinone, tiotropium bromide, and varenicline, has been approved by the US FDA. The following is a brief description of each drug and their therapeutic use. Galantamine (I, Razadyne, Reminyl, Nivalin) was first marketed in 2001 in the USA for the symptomatic treatment of patients with early-onset Alzheimer’s disease.\(^3\) Galantamine (also known as galanthamine) is an alkaloid that was initially isolated from the snowdrop (Galanthus woronowii Losinsk.) in the early 1950s, and has since been found in other plants in the family Amaryllidaceae.\(^4\) Galantamine slows the process of neurological degeneration by inhibiting acetylcholinesterase as well as binding to and modulating the nicotinic acetylcholine receptor.\(^4,5\) Due to the limited availability of the plants of origin of this compound, galantamine is now produced by total synthesis. Nitisinone
(2, Orfadin) was approved by the FDA in 2002 for the treatment of hereditary tyrosinemia type 1 (HT-1). HT-1 is a rare pediatric disease caused by a deficiency of fumaryl acetoacetate hydrolase (FAH), an enzyme essential in the tyrosine catabolism pathway. FAH deficiency leads to the accumulation of toxic substances in the body, resulting in liver and kidney damage. Nitisinone is a derivative of leptospermone (3, a new class of herbicide from the bottlebrush plant [Callistemon citrinus (Curtis) Skeels]. Both nitisinone and leptospermone inhibit 4-hydroxyphenyl pyruvate dioxygenase (HPPD), the enzyme involved in plastoquinone and tocopherol biosynthesis in plants. In humans, inhibition of HPPD prevents tyrosine catabolism, leading to the accumulation of tyrosine metabolites, 4-hydroxyphenyl pyruvic acid and 4-hydroxyphenyl lactic acid, which can be excreted through the urine.

Apomorphine (4, Apokyn) was approved by the FDA in 2004 as an injectable drug for the symptomatic treatment for Parkinson’s disease patients during episodes of “hypomobility” (e.g., persons unable to move or to perform daily activities). Apomorphine is a synthetic derivative of morphine (5), but unlike morphine, apomorphine does not have opioid analgesic properties, and instead is a short-acting dopamine D₁ and D₂ receptor agonist.
Tiotropium bromide (6, Spiriva), an atropine analog, was approved by the FDA in 2005 for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.\textsuperscript{11}

Varenicline (7, Chantix), based on the plant quinolizidine alkaloid, cytosine (8) has been approved by the FDA since 2006 as an aid to smoking cessation.\textsuperscript{12-14} Cytisine (8), an alkaloid isolated from Cytisus laburnum L., has been used to treat tobacco dependence in Eastern Europe (Bulgaria, Germany, Poland, and Russia) for the last 40 years.\textsuperscript{15} Cigarette smoking has been linked to several diseases including cardiovascular disease, COPD, many cancers (particularly lung, mouth, and esophageal), and pregnancy-related complications. Varenicline (7) is a partial agonist with a high affinity for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor, and is a full agonist at $\alpha_7$ neuronal nicotinic receptors.\textsuperscript{14}

Hence, bioactive compounds and its derivatives have captured the imagination of organic chemists for more than a century. Early works in this area mainly focused on the extraction, isolation, and preparation. However, since the isolation of alkaloids as
the active principles from medicinal plants (*i.e.* antibiotics, anti-inflammatory, antihypertensive and antitumor agents), these nucleus has been taken in consideration for pharmacological importance. Therefore, it is not surprising that up to how many methods have already been developed for the synthesis of this kind of heterocyclic systems. However, due to the unavailability of efficient process using classical methods and the need for efficient ways to synthesize more elaborate structures possessing biological activity, the development of novel and convenient methods for the preparation of bioactive compounds still remains an active research area.

1.1.2 **Hypervalent Iodine Reagent:**

Iodine is a member of 17th group element and it is the largest, most polarisable and most electropositive member of the group. Iodine has atomic number 53 and atomic weight 126.9. It commonly exists in monovalent compounds with an oxidation state of -1. It also forms stable polycoordinate, multivalent compounds. It also exhibits I^0, I^{+3}, I^{+5}, I^{+7} oxidation states.

Electronic configuration of Iodine: 1s^2, 2s^2, 2p^6, 3s^2, 3p^6, 3d^{10}, 4s^2, 4p^6, 4d^{10}, 5s^2, 5p^5

**a) Hypervalency**

The elements of group 15-18 show higher oxidation states than normal valency in some molecules. This ability of an atom in a molecular entity to expand its valence shell beyond the limits of the Lewis octet rule is called as “hypervalency.” A description of hypervalency implies a transfer of the electrons from the central (hypervalent) atom to the nonbonding molecular orbitals which it forms with (more electronegative) ligands. Starting from early 1990s, the chemistry of polyvalent iodine compounds experienced has explosive development. This surging interest in iodine compounds is mainly due to the very useful oxidizing properties of polyvalent organic iodine reagents, combined with their benign environmental character and commercial availability. Iodine (I), iodine (III) and iodine (V) derivatives are now routinely used in organic synthesis as reagents for various selective oxidative transformations of complex organic molecules. Several areas of hypervalent organoiodine chemistry have recently attracted especially active interest and research activity. These areas, in
particular, include the synthetic applications of Diacetoxyiodobenzene (DIB) and similar oxidizing reagents based on the iodine (III) derivatives, the development and synthetic use of polymer-supported and recyclable polyvalent iodine reagents, the catalytic applications of organoiodine compounds, and structural studies of complexes and supramolecular assemblies of polyvalent iodine compound.

First polyvalent organic iodine complex, i.e. (dichloroiodo)benzene or PhICl$_2$, was prepared was by German chemist C. Willgerodt in 1886. Its oxidizing properties were known since 1893. $^{17,18,19}$

![Chemical reaction diagram](image)

**b) Factors leading to resurgence of interest**

1. Chemical properties and reactivity is similar to the heavy metal reagents such as Hg(III), Tl(III), Pb(IV) but with less toxicity & environmental issues.

2. Mild reaction conditions and easy handling of hypervalent iodine compounds.

3. Commercial availability.

4. High chemoselective oxidizing properties.

5. Stereoselective and regioselective oxidations.

6. Reduced form of hypervalent iodine reagent can be easily recovered and reused after reoxidation.

**1.1.3 Nomenclature of Hypervalent Iodine Compounds:**

The term hypervalent was established in 1969 for molecules with elements of groups 15-18 bearing more electrons than an octet in their valence shell.

IUPAC rules designate $\lambda$ as non-standard bonding; thus, H$_3$I is $\lambda^3$-iodane and H$_5$I is $\lambda^5$-iodane. Most common structure is aryl-$\lambda^3$-iodane ArIL$_2$ $(L =$ heteroatom ligand) and aryl-$\lambda^5$-iodane ArIL$_4$. 
The Martin-Arduengo nomenclature system has traditionally been used to describe such compounds: \([N-C-L]\) where

- \(N\) is number of valence electrons on the hypervalent iodine
- \(C\) is identity of central atom and
- \(L\) is number of ligands on the central atom.

**Scheme 1.1**: Martin-Arduengo designation for polyvalent iodine

The first two species 8-I-2 and 10-I-3 are called Iodanes and are conventionally considered as derivatives of trivalent iodine. The last two 10-I-4 and 12-I-5 periodinane represents the most common structural types of pentavalent iodine. Till date there are many hypervalent iodine reagents are established some of them are shown in **Table 1.1**

**Table 1.1**: Most frequently used hypervalent iodine reagents
a) **Physical aspects of Hypervalent iodine reagents**

Most hypervalent iodine reagents are solid (amorphous or crystalline) and are stable to atmospheric oxygen and moisture. Certain iodonium compounds are less stable and should be generated in situ. A mild explosion will occur if PhI(OMe)$_2$, PhIO, PhIO$_2$, IBX, and o-iodylbenzoic acid heated at high temperature and in the absence of solvent.
In the solid state, Iodosylbenzene and (tosyliminoiodo) benzene are polymeric structures terminated by water:HO(PhIO)\textsubscript{n}H. Monomeric species are generated in reactive solvents. Secondary I-O bonds are also observed and result in macrocyclic structures.

1.1.4 General Reactivity of Hypervalent Iodine:

Hypervalent iodine chemistry is based on the strongly electrophilic nature of the iodine making it susceptible to nucleophilic attack, in combination with the leaving group ability of phenyliodo nio group (–IPhX). The favorable reduction of the hypervalent iodide to normal valency by reductive elimination of iodobenzene is the key to its reactivity. Reactivity of hypervalent iodine is based on the number of carbon and heteroatom ligands.

Majority of reactions performs oxidation of various functional groups. The heteroatoms occupying the apical sites of the pseudotrigonal bipyramid are essential one is used in ligand exchange and the other in reductive elimination.

a) Advantages

In the past decade, the organic chemistry of hypervalent iodine compounds has experienced an immense development. This growing interest in iodine compounds is due to,

- Mild reaction conditions
- Highly chemoselective oxidizing properties
- Commercial availability
- Benign environmental character and non toxic nature
- Efficiency of the methods
- Stereoselective oxidations
1.2 LITERATURE SURVEY: TRIVALENT IODINE CHEMISTRY$^{21, 22}$

In the recent years, there has been considerable attention on hypervalent iodine compounds mainly trivalent in organic synthesis. A lot of contributors have reviewed a wide range of applications of these powerful and selective oxidising agents.

It has been observed that trivalent iodine compounds synthetic properties are often similar to those of lead and thallium derivatives, somehow with better yields and improved toxicity, which make them more compatible in a pharmaceutical production environment.

1.2.1 Preparation of Trivalent Reagents

a) Iodylbenzene and other noncyclic reagents

The noncyclic iodyl (also known as iodoxy) compounds, RIO$_2$, in general have found only very limited practical application due to their low stability. While the aryl derivatives, ArIO$_2$, can form relatively stable compounds, iodylalkanes are extremely unstable and can exist only at very low temperatures. Recently Skulski and coworkers developed a new procedure for the preparation of various iodylarenes from the corresponding iodoarenes using sodium periodate as the oxidant (Scheme 1.2).

![Scheme 1.2](image)

**Scheme 1.2**: Synthesis of iodylarenes from iodoarenes

Despite their low solubility and explosive character, iodylarenes have found some practical application as oxidizing reagents. Among various ArIO$_2$, iodylbenzene PhIO$_2$ is the most popular reagent. Some of applications are shown below.
• Conversion of substituted 1-naphthols into corresponding 1, 2 and 1, 4 naphthoquinones.

• Allylic oxidation.

• In the stereoselective synthesis of (-)-tetrodotoxin.

• Dehydrogenation protocol in the regioselective synthesis of ring A of polymethylated steroids.

• Synthesis of tricyclo [5.4.0.0] undeca-3,5,9-triene.

• Oxidation-dehydrogenation of 3α-hydroxy-5β-bile acid formyl esters to give oxodienes.

• Oxidation of trans-dehydroepiandrosterone acetate afforded epoxide.

• Sulfides are oxidized to sulfoxides with moderate to good enantioselectivity.

• Carbonylation reaction.

b) Trivalent iodine (III) reagent:

First trivalent organic iodine complex, (dichloroiodo)benzene or PhICl₂, was prepared was by German chemist C. Willgerodt in 1886. Its oxidizing properties were known since 1893.¹⁷-¹⁹

![Scheme 1.3 Synthesis of (dichloroiodo) benzene](image)

Several paths are described for the synthesis of DIB. Iodobenzene may be used as a starting material, and then oxidised by peracetic acid in acetic acid²³ with a conversion yield of 85 %, as follows. The reaction with peracetic acid is exothermic, and can be considered dangerous if not carefully controlled. This method may be used for toluenic and xylenic derivatives.
A. Mc. Killpo et al prepared DIB by using Sodium perborate\textsuperscript{24} in acetic acid (Scheme 1.4).

Another route, known as the safest process for the synthesis of DIB, was investigated by Alcock,\textsuperscript{25} starting from dichloro-iodobenzene in presence of silver salts (Scheme 1.5).

Karele\textsuperscript{26} performed an analogous synthesis in two steps from iodobenzene, using thionyl chloride to yield dichloro-iodobenzene, then aqueous acetic acid in pyridin to convert it to DIB. Other syntheses of DIB are described but their application field seems limited in an industrial environment, due to production costs and feasibility.
Since the structure of trivalent iodine compounds enables a ligand exchange on iodine, it has been possible to use DIB as a precursor in the synthesis of numerous derivatives. The reaction of DIB with trifluoroacetic acid provides an efficient synthesis of BTI. In the same way, two promising derivatives (hydroxy-tosyl-iodobenzene) and (hydroxymesyl-iodobenzene) were synthesized, by following Koser’s method.

c) Temperature effect:

When trivalent iodine compounds are heated above 160°C, generally they become relatively unstable.
1.3 APPLICATION:

1.3.1 Applications of DIB:

1. The Oxidation of enolizable ketones to α-hydroxy-dimethyl-acetals as shown in (Scheme 1.6) α-hydroxy-dimethyl-acetals are building-blocks in the synthesis of "O"-containing heterocycles, when intramolecular participation by a suitably placed hydroxyl group occurs. Several potentially oxidisable groups are unaffected in this reaction, since the mechanism is selective.

```
R' -C=O -R
\  \ / \  \\
\  \ /  \\
\   /    \\
\ /     \\
\ /      \\
\ /  MeOH, KOH  \\
\ /      \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \\
\ /       \
```
4. The primary alcohols are readily oxidized to methyl esters upon treatment with polystyrene supported DIB in the presence of KBr in the acidic aqueous methanol solution (Scheme 1.9). Aldehydes can also be converted to methyl esters by a similar procedure using DIB and NaBr.

5. DIB was recently used for the efficient $\alpha$-hydroxylation or $\alpha$-methoxylation of esters (Scheme 1.10).

6. An efficient procedure for the oxidation of alcohols with DIB in the presence of catalytic amounts of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), originally developed by Piancatelli, Margarita, and co-workers, has been frequently used in recent years. An optimized protocol, published in *Organic Synthesis* for the oxidation of nerol to nepal, consists of the treatment of the alcohol solution in buffered (pH7)
aqueous acetonitrile with DIB and TEMPO (0.1 equiv) at 0°C for 20 min.  (Scheme 1.11)²⁹

![Scheme 1.11: Selective oxidation of -OH](image)

7. Based on the ability of the DIB-TEMPO system to selectively oxidize primary alcohols to the corresponding aldehydes in the presence of secondary alcohols, Forsyth and co-workers have developed selective oxidative conversion of a variety of highly functionalized primary and secondary 1,5-diols into the corresponding δ-lactones. Monitoring of this reaction showed the initial formation of the intermediate lactol species, which then undergoes further oxidation to the lactone. A similar DIB-TEMPO-promoted γ-lactonization has recently been utilized in the asymmetric total synthesis of the antitumor (+)-eremantholide A.³⁰,³¹

![Scheme 1.12: Selective oxidation](image)

8. Synthesis of steroidal spiro-oxetan-3-ones: in this reaction, the use of DIB favours the intramolecular nucleophilic action of C₁₇-α-hydroxyl-group on the intermolecular attack by methoxide. (Scheme 1.13).
9. [Bis(trifluoroacetoxy)iodo]benzene reacts with alkenes in the absence of any additive or catalyst, affording bis(trifluoroacetates), which can be converted into the corresponding diols or carbonyl compounds by hydrolysis. For example, cyclohexene reacts with BTI in dichloromethane under reflux conditions to give cis-1,2-bis(trifluoroacetate) in almost quantitative yield.

10. Oxidation of phenolic derivatives
Phenolic derivatives are oxidised in mild conditions in quinones. DIB is a soft alternative to the use of toxic substances such as lead or thallium derivatives. This reaction is widely used for oxidative coupling. Key-step in the synthesis of epiprettazettine. Another interesting application is the conversion of reticuline to salutaridine and related products with DIB in trifluoroacetic acid.33,34

11. Oxidation of amines
It has been reported that BTI has the ability to oxidise aromatic amines to azo compounds in variable yield. Intramolecular azo group formation is a useful reaction for the formation of dibenzo [c,f] diazepine.\(^{35}\)

**Scheme 1.17:** Preparation of dibenzodiazepine

12. In the presence of BTI, \(\alpha\)-methylthioamides undergo a Pummerer-type rearrangement leading to the formation of nitrogen-containing heterocycles.\(^{36}\)

**Scheme 1.17:** Synthesis of substituted N-methyl,2-pyrrolidinone

13. More generally, T. Kitamura and Y. Fujiwara have presented the applications of DIB and BTI in the chemical pathway of various heterocycles and natural products, such as alkaloids, spirocyclodienones, and spirocyclic isoxazolines. Oxidation can result in an aryl-aryl coupling, an oxidative cyclisation (cyclisation of phenolic oximes is reported), with interesting asymmetric properties in some cases.
Other applications of DIB

- Oxidation of alcohols to carbonyl compounds in presence of different functional groups such as thioethers, amines, alkenes, alkynes. Conversion of alcohols to carboxylic acids
- C₃-hydroxylation of α, β-unsaturated-ketones, such as chromones, flavones, and α-naphtoflavones
- Oxidation of 1,2-diols to 1,2-diketones derivative without cleaving C-C bond
- Conversion of 1,4-diols to γ-lactols
- Cyclization of aryl-substituted unsaturated amine to heterocycles
- Cyclization of amides to γ-lactams and variety of annulated heterocycles
- Oxidation of benzylic position
- Thiols to disulfides
- Oximes and tosyl hydrazones to corresponding carbonyl compounds
- Synthesis of bis(trifluoroacetoxy)iodobenzene (BTI)
- The hydrolysis of thioacetals/thioketals to the corresponding carbonyl compounds
- Oximes to various aldehydes and ketones
- α-Hydroxylation of α-alkynyl carbonyl compounds
• Oxidation of various epoxides and aziridines, to the $\alpha$-hydroxyketones and $\alpha$-aminoketones

• Generation of imines from secondary amines

1.3.2 Applications of BTI

The mild reaction conditions (room temperature, absence of acidic or basic additives), high chemoselectivity, and preparative convenience have made this reagent especially suitable for the oxidation of substrates containing sensitive functional groups (e.g. unsaturated moieties, amino groups, silyl ethers, phosphine oxides, sulfides, selenides).

Unique oxidizing properties and convenience use of advance BTI to be widely employed in the synthesis of biologically important natural products. Recently BTI was used in the key oxidation steps in the syntheses of epiprettazzettine, another interesting application is the conversion of reticuline to salutaridine and related products with DIB in trifluoroacetic acid.

Other applications of BTI

• Oxidation of alcohols to carbonyl compounds in presence of variety of functional groups

• Oxidative iodo-decarboxylation of $\alpha,\beta$-unsaturated carboxylic acids

• Oxidation of glycols with the cleavage of C-C bond

• Construction of heterocycles from substituted amides

• Oxidation of 1,3-dicarbonyl compounds to triones

• Deoximation of aldoximes and ketoximes

• Conversion of $N$-acyl hydroxylamines to acyl nitroso compounds

• Selective deprotection of cyclic 1,3-dithiane to carbonyl compounds

• One-step oxidation of secondary amides to imides
• Direct oxidation of benzylic and related primary amines to the corresponding nitriles
• Synthesis of 2-substituted benzothiazoles via intramolecular cyclization of thioformanilides
• Oxidation of phenols to quinones
• Addition on alkenes and ketones
• Iodination of phenol and phenol ethers
• Oxidation of 4-substituted anilides to \( p \)-quinones and 2-substituted anilides to \( o \)-azaquinones

So with our interest in this iodine (\( \lambda^3 \)) species has grown further to the discovery that its chemistry can be modulated by complexation with a variety of ligands, thus leading to dramatic changes in its reactivity profile. The ligand attached to DIB not only allows moderation of the reagent’s reactivity, but also differentiation between reaction pathways when a number of alternatives are available (Scheme 1.12).

When TEAB was added to BTI a yellow color solution is formed due to complexation (Scheme 1.13). This BTI/TEAB system exerts strong impact on the reactivity of BTI.

1.4 PREVIOUSLY DEVELOPED METHODS IN OUR LAB:
Investigations from our own laboratories have revealed a series of new paradigms for iodine as well as hypervalent iodine mediated reactions under mild conditions, these are presented here.
1. A simple and mild method in water for direct conversion of epoxides to corresponding aldehydes has been developed using sodium paraperiodate (Na$_3$H$_2$IO$_6$). High yields of corresponding aldehydes were obtained.$^{36a}$

![Scheme 1.14: Oxidative cleavage of styrene epoxide to benzaldehyde.](image)

2. A novel method has been developed for the direct conversion of aldehydes to the corresponding nitriles using [bis (trifluoroacetoxy)iodo]benzene in combination with aqueous ammonia at room temperature. The method is mild and gave good to excellent yields of nitriles in the case of both aliphatic and aromatic substrates.$^{37b}$

![Scheme 1.15: Preparation of nitrile from aldehyde.](image)

3. Direct conversion of alkenes to corresponding aldehydes has been developed using sodium paraperiodate (Na$_3$H$_2$IO$_6$) in water. The reagent was found to give excellent yields of corresponding aldehydes.$^{37c}$
CHAPTER-1

SECTION-I

Development and Application of New Methodologies for Synthesis of Bioactive Molecules

4. Diphosphorus tetra iodide reagent system used for regioselective cleavage of epoxides to alcohols.\textsuperscript{37d}

5. Oxidative conversion of aldehyde to corresponding nitrile using aq. NaICl\textsubscript{2} with ammonia.\textsuperscript{37e}

6. Oxidative conversion of alcohol to aldehyde using NaICl\textsubscript{2} at room temperature.\textsuperscript{37f}

7. Conversion of benzoic acid into benzonitrile using diphosphorus tetraiodide and ammonium carbonate in anhydrous carbon disulfide at room temperature.\textsuperscript{37g}
8. A simple and mild system using 4, 4-bis-(dichloroiodo)-biphenyl in combination with TEABr at room temperature has been developed for selective debenzylation of sugars. Acetates, benzoate, and sensitive glycosidic linkages are unaffected. Oxidative dimerization of thioamides to 3,5-disubstituted-1,2,4-thiadiazole.\textsuperscript{37h}

9. Decarboxylative bromination of $\alpha,\beta$-unsaturated carboxylic acids has been developed using diphosphorus tetraiodide in combination with tetraethylammonium bromide (TEAB) at room temperature. High yields of the corresponding bromoalkenes were obtained.\textsuperscript{37i}

10. Decarboxylative bromination of $\alpha,\beta$-unsaturated carboxylic acids has been developed using diphosphorus tetraiodide in combination with tetraethylammonium bromide (TEAB) at room temperature. High yields of the corresponding bromoalkenes were obtained.\textsuperscript{37j}
Scheme 1.23: Bromo-decarboxylation of cinnamic acid using DMP and TEAB.

11. tert-Butyl hypochlorite and tert-butyl hypobromide react with aldoximes and convert them into hydroximinoyl chloride and bromide, respectively; however, under the same reaction conditions, tert-butyl hypoiodite deoximates aldoximes and ketoximes to give corresponding aldehydes and ketones in high yield (94%) in a short reaction time (20 min).

Scheme 1.24: Transformation of oximes to the corresponding carbonyl compounds using tert-butyl hypoiodite.

We have developed some other methodologies and process chemistry around hypervalent iodine chemistry and will be discussed.

Till date the chemistry of polyvalent iodine has been covered in four books\textsuperscript{7a-d} and several comprehensive review papers.\textsuperscript{8-18} Numerous reviews on specific classes of polyvalent iodine compounds and their synthetic applications have been also published.
1.5 CONCLUSION:

The preceding survey of the recent developments in the chemistry of polyvalent iodine compounds reflects an active current interest in this highly versatile class of valuable reagents. From the practical point of view, important are the simplest, traditional reagents, such as (diacetoxyiodo)benzene and Iodosylbenzene, which have been increasingly employed in organic synthesis. This growing interest in iodine (III) compounds is mainly due to their very useful oxidizing properties, combined with their benign environmental character and commercial availability.

Telvekar et al. also demonstrated that DIB can be used for oxidation of alcohols to carbonyl compounds and it is tolerable to various functional groups such as thioethers, amines, alkenes, alkynes.

Unique oxidizing properties and convenience use of advance BTI to be widely employed in the synthesis of biologically important natural products. Recently BTI was used in the key oxidation steps in the syntheses of epiprettazettine. The mild reaction conditions high regioselectivity, chemoselectivity, and preparative convenience have made this reagent especially suitable for the oxidation of substrates containing sensitive functional groups.
1.6 REFERENCES:

17. Publications of A. Varvoglis; Reviews in *Synthesis*, Sept.1984, 709
19. Sharefkin, J. G.; Saltzmann, H.; *Organic synthesis*, 660
   (a) Telvekar, V. N.; Patel, D. J.; Mishra, S. J.; *Synthetic Communications*, **2009**, 39, 311
   c) Telvekar, V. N.; Mishra, S. J.; Patel, D. J.; *Synthetic Communications*, **2009**, 39, 2146
   d) Telvekar, V. N.; Rane, R. A.; *Synthetic Communications*, **2010**, 40, 2108
   f) Telvekar, V. N.; Jadhav, N. C.; *Synthetic Communications*, **2008**, 38, 3107
   (g) Telvekar, V. N.; Rane, R. A.; *Tetrahedron Letters*, **2007**, 48, 6051
   (h) Telvekar, V. N.; *Synthetic Communication*, **2007**, 37, 2647
   (j) Telvekar, V. N.; Arote, N. D.; Herlekar, O. P.; *Synlett*, **2006**, 16, 2495
   (k) Telvekar, V. N.; *Synthetic Communication*, **2005**, 35, 2827
SECTION-II

Process Development for Synthesis of Indole & Indole-3-acetic Acid.

1.2 INTRODUCTION:

1.2.1 Indole chemistry:

1.3 LITERATURE SURVEY:

1.4 OBJECTIVE OF THE WORK:

1.5 DESIGN AND DEVELOPMENT:

1.6 EXPERIMENTAL:

1.7 RESULT AND DISCUSSION:

1.8 SUMMERY AND CONCLUSION:

1.9 REFERENCES:

1.10 SPECTRA:
1.2 INTRODUCTION:

Indole (4) is the commonly used name for the benzopyrrole ring system,\textsuperscript{1,2} consisting of a benzene ring fused to the 2,3-position of a pyrrole ring. Indoles and indole chemistry have been well documented from the mid 19\textsuperscript{th} century, mainly because of the importance of indigo dye. Initial isolation of indole was from the natural indigo dye \textsuperscript{1} by treating with oleum, and this was how indole was named; indigo oleum. The first synthesis of indole was reported by Nobel Prize Winner Alfred Von Baeyer in 1866.\textsuperscript{1} This was achieved by converting indigo dye to isatin \textsuperscript{2} by oxidation and then reduction to oxindole \textsuperscript{3}. Baeyer then reduced oxindole by heating with zinc dust to form indole \textsuperscript{4} (Scheme 1.1).

The indole ring system is found in many natural products, pharmaceutical agents and polymer. The interest and development in indole chemistry started in mid-nineteenth century, with intensive studies of indigo (1), a violet-blue dye from India, originally derived from Indigofera species. Useful investigations of indole chemistry started when indigo was successfully oxidized to isatin (2), which was then reduced to oxindole (3).\textsuperscript{3} later in 1866. A. Baeyer prepared the parent substance, indole, by zinc dust reduction\textsuperscript{4} of oxindole (3), and shortly thereafter he proposed the presently accepted formula in 1869.\textsuperscript{5}

Today the synthesis of indole is usually performed from non-heterocyclic precursors by cyclisation reactions of suitably substituted benzenes. Perhaps the most widely used route is the Fischer indole synthesis,\textsuperscript{6} which also can be used on a large scale, e.g., for production of the stabilizer 2-phenlindole in manufacture of PVC.\textsuperscript{7,8}

\begin{itemize}
  \item \textbf{a) Importance of Indole molecules in today’s life:}
\end{itemize}
Indole and its alkaloids in biological systems have a varied and significant role. Indole have various degrees of structural complexity such as plant auxin\textsuperscript{9} anti-inflammatory, analgesic, anticancer activity, antipyretic, antibiotics, antihypertensive\textsuperscript{10} and essential amino acid\textsuperscript{11} e.g., tryptophan. Hence due to the variety of applications, indoles has attracted the attention of researchers in preparative chemistry. Below (Figure 1) is the schematic presentation for the importance of indole moiety in the synthesis of various API molecules belonging to wide range of therapeutic category from antiprotozoal to anti-HIV.\textsuperscript{12} The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives.\textsuperscript{13} The 2-aryl indole moiety is present in diverse biologically active molecules\textsuperscript{14} displaying antiestrogen\textsuperscript{14b,d} 5-HT\textsubscript{2A} antagonist,\textsuperscript{14f} anti-inflammatory\textsuperscript{14a,c} and cytotoxic properties.\textsuperscript{14e}

**Figure 1**: Structure and therapeutic category of Indole derivatives
b) Indole as a Natural Products:

Derivatives of indole were of interest mainly as dyestuffs until the late 19th and early 20th century when the study of indoles was directed towards natural products. Although indole and indigo are both natural products it was not until the isolation of the amino acid tryptophan 5 in 1901 by the hydrolysis of casein, which the importance of these compounds started to be fully understood. As one the essential amino acids, tryptophan 5 plays a number of important roles in the body, one of which is in the synthesis of the neurotransmitter, serotonin 6(Figure 2). Serotonin (5-HT) is a vital component for the normal function of the central nervous system and is involved in the maintenance of mood, muscle contraction and many other bodily functions. This has made the regulation of serotonin of specific interest in drug development, mainly looking at the interaction of molecules binding to specific reuptake receptors aiming to increase or decrease the quantity of serotonin in the synaptic cleft, for example in the treatment of depression.

Many different natural products contain the basic indole structure. One group is the indolo [2,1-α]isoquinolines such as cryptaustoline, which have been found in the bark of Cryptocarya bowiei. The synthesis of indolo [2,1-α]isoquinolines has been achieved by radical cyclisation of 2-bromobenzyl-3,4-dihydroisoquinolines 7 using AIBN and Bu3SnH, however this gave a mixture of the desired product 8 and aporphine 9. This was overcome be replacing radical cyclisation with base cyclisation to give exclusively 10 (Scheme 1.2).
A recent development in the treatment of inflammatory pain is the antagonism of EP1 receptors. This is an area that has been investigated by Hall and a series of effective antagonistic compounds have been developed. An example of such a compound is shown, and it was thought that an internal hydrogen bond could be involved, which could be mimicked by the indole scaffold in (Figure 3).

The most successful candidate was for $R_1 = t$-Bu, $R_2 = Cl$. 
Another interesting example of an indole-based natural product is Eustifoline-D, 13, which has been isolated from the root bark of *Murraya euchrestifolia*. This shrub is found in Taiwan and has been used in folk medicine as an analgesic and local anesthetic for a number of ailments, including eczema, rheumatism, toothache, and as an anticonvulsant (Figure 4).

![Figure 4](image)

It has been shown that cruciferous vegetables contain a substance called glucobrassicin which, during metabolism, forms indole-3-carbinol 14 and 3,3'-diindolylmethane 15. These compounds have been found to cause cell apoptosis in breast cancer and are thought to have some potential as a preventive and/or cure for prostate cancer (Figure 5).

![Figure 5](image)

Carbazole derivatives have been reported to have interesting biological effects, including antibiotic 16, cytotoxic agent 17, antiviral compound 18, antitumour compound 19 and anti-HIV compound 20. (Figure 6)
1.2.1 Indole chemistry:

The first synthesis of indole was reported by Nobel Prize winner Alfred Von Baeuer in 1866.\textsuperscript{27} The studies in indole chemistry were intensified, when it was discovered that many biologically important alkaloids as well as pharmaceutical agent contain indole scaffold. For instance, the essential amino acid tryptophan (25) in living organisms, the neurotransmitter serotonin (26) and the plant growth hormone indole 3-acetic acid (G) are very important indole derivatives. (Figure 7)
a) **Typical reactivity of indole:**

Perhaps one of the most characteristic reactions of indoles is electrophilic substitution at C-3 in the five–membered ring, which is facilitated by electron-release from the heteroatom. This preference can be rationalized by consideration of the Wheland intermediate **27 (Figure 8)**, in which the enamine system in the five-membered ring does not disturb the aromaticity of the benzene ring. The positive charge in the ring intermediate is, of course delocalized and the aromaticity of the six-membered ring can therefore be retained. In contrast, any attack at C-2 cannot derive assistance from the nitrogen without disrupting the aromaticity of the benzene ring. However, electrophilic substitution can also be occurring at C-2, if for instance the C-3 is occupied by a substituents.²⁸

![Figure 8](image-url)
1.3 **LITERATURE SURVEY:**

On the basis of literature survey, there are so many routes for synthesis of indole and indole-3-acetic acid but most of these routes use expensive catalyst and have more number of steps. While studying reported methods, we have categorized the literature methods into following groups.

1) **Sigmatropic rearrangement**
2) **Nucleophilic cyclisation**
3) **Electrophilic cyclisation**
4) **Nitrene cyclisation**
5) **Reductive cyclisation**
6) **Oxidative cyclisation**
7) **Radical cyclisation**
8) **Using Transition Metal Catalyst**
9) **Base induced cyclisation**

**a) Thermal synthesis of Indole:**

The cyclisation of \( o \)-alkynylanilines has been carried out in many ways, mostly involving some sort of catalyst but an interesting early example is by heating alone.\(^{29}\)

It was known that heating of aniline in the presence of ethyne gave indole via radical intermediates, but it was not known if the radical formed on ethyne attacked at the nitrogen (path b) or the \( o \)-position of the benzene ring (path a). By synthesizing \( o \)-ethynylaniline and heating at 500-700\(^{0}\)C to give indole 28 it was shown that the reaction did indeed proceed by path a (Figure 9).
b) Name Reactions – Synthesis of Indole:

So many different name reactions have been reported for the synthesis of indole by researcher.

I. Sigmatropic rearrangements:

1) Fischer indole synthesis:

The Fischer indole synthesis was used extensively during the past five years to access a wide range of indoles and derivatives.

A one-pot synthesis of indoles from phenylhydrazine hydrochloride and ketones in acetic acid using microwave irradiation. The use of montmorillonite clay and ZnCl₂ under microwave conditions affords 2-(2-pyridyl) indoles at much lower temperatures and with solvent-free acid (Scheme 1.3).²⁰

2) Gassman indole synthesis:
The beautiful Gassman indole-oxindole synthesis,\textsuperscript{31a} which features a [2,3]-
sigmatropic rearrangement (Scheme 1.4), has been used to prepare efficiently 6,7-
dihydroxyoxindole, a subunit of the alkaloids paraherquamide A and marcfortine A.\textsuperscript{31b}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{NH}};
  \node (b) at (1,0) {$R_1$};
  \node (c) at (2,0) {1. t BuOCl};
  \node (d) at (3,0) {\text{SO}};
  \node (e) at (4,0) {R_2};
  \node (f) at (5,0) {2. Raney-Ni};
  \node (g) at (6,0) {R_1};
  \node (h) at (3,1) {\text{Et}_3\text{N}};
  \node (i) at (3,2) {R_2};

  \draw[-stealth] (a) -- (b);
  \draw[-stealth] (b) -- (c);
  \draw[-stealth] (c) -- (d);
  \draw[-stealth] (d) -- (e);
  \draw[-stealth] (e) -- (f);
  \draw[-stealth] (f) -- (g);
  \draw[-stealth] (h) -- (i);
\end{tikzpicture}
\end{center}

Scheme 1.4

The mechanism of Gassman indole synthesis is as shown below.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{NH}};
  \node (b) at (1,0) {$R_1$};
  \node (c) at (2,0) {1. t BuOCl};
  \node (d) at (3,0) {\text{N-Cl}};
  \node (e) at (4,0) {R_2};
  \node (f) at (5,0) {2. [2,3 Sigmatropic rearrangement]};
  \node (g) at (6,0) {\text{Et}_3\text{N}};
  \node (h) at (7,0) {R_1};
  \node (i) at (8,0) {O};
  \node (j) at (9,0) {R_2};
  \node (k) at (10,0) {3. \text{H}_2\text{O}};

  \draw[-stealth] (a) -- (b);
  \draw[-stealth] (b) -- (c);
  \draw[-stealth] (c) -- (d);
  \draw[-stealth] (d) -- (e);
  \draw[-stealth] (e) -- (f);
  \draw[-stealth] (f) -- (g);
  \draw[-stealth] (g) -- (h);
  \draw[-stealth] (h) -- (i);
  \draw[-stealth] (i) -- (j);
  \draw[-stealth] (j) -- (k);
\end{tikzpicture}
\end{center}

Scheme 1.5

3) Bartoli indole synthesis:
The fascinating Bartoli protocol,\textsuperscript{32} which features a [3,3]-sigmatropic rearrangement
analogous to the Fischer indolization step, has been used to prepare 7-bromo-4-
ethylindole in a synthesis of (\(\pm\))-cis-trikentrin A, and 7-bromoindole (Scheme 1.5) in a
synthesis of hippadine.
The mechanism of Bartoli indole synthesis is as shown below.

II. Nucleophilic cyclization:

1) Madelung indole synthesis:

Although the classical Madelung synthesis is rarely employed nowadays, the excellent Houlihan modification, which utilizes BuLi or LDA as bases under milder conditions than the original Madelung harsh conditions, has been extended in several ways. For example, benzylphosphonium salts such as 29 undergo facile cyclization to indoles under thermal conditions (Scheme 1.6). The phosphonium salt can be generated in situ from the corresponding benzyl methyl ether 30. The reaction is especially valuable for the synthesis of 2-perfluoroalkylindoles, although the yields are quite variable. The base catalyzed version of this reaction has been adapted to solid phase synthesis.
2) Smith indole synthesis:

The Smith indole synthesis,\(^{34}\) which involves dilithiation of N-trimethylsilyl-o-toluidine and subsequent reaction with a non-enolizable ester to afford the 2-substituted indole, has been used to synthesize 2-trifluoromethylindole in 47% yield by quenching the above mentioned dianion with ethyl trifluoroacetate.

3) Nenitzescu indole synthesis:

The past five years have seen a resurrection of the Nenitzescu indole synthesis and this classic sequence was used to construct methyl 5-hydroxy-2-methoxymethylindole-3-carboxylate, the key intermediate in a synthesis of the antitumor indolequinone EO 9. This reaction has also been used to prepare a series of N-aryl-5-hydroxyindoles, and it was utilized in the synthesis of a key indole (Scheme 1.7) used to prepare potent and selective s-PLA2 inhibitors.\(^{35}\)
III. Electrophilic cyclization:

The numerous electrophilic cyclization routes to indoles have been available to synthetic organic chemists for 100 years or more. Nevertheless, new examples and applications of this indole ring-forming strategy continue to appear in the literature.

1) Bischler indole synthesis:

Moody and Swann have described a modification of the Bischler synthesis wherein the intermediate \( \alpha \)-(N-arylamino)-ketones are prepared by a Rh-catalyzed insertion reaction. Acid-catalyzed cyclization completes the synthesis (Scheme 1.8).

\[
\begin{align*}
\text{R}^3 & = \text{Me, Et, Ph} \\
\text{R}^2 & = \text{Me, Et} \\
\text{R}^3 & = \text{H, 7-Br, 7-OMe, 5-Cl, 5-NO_2} \\
& \quad \text{5-OMe, 5,7-diOMe}
\end{align*}
\]

IV. Nitrene cyclization:

1) Cadogan–Sundberg indole synthesis:

This powerful indole ring formation method involves the deoxygenation of \( o \)-nitrostyrenes or \( o \)-nitrostilbenes with triethyl phosphite and cyclization of the resulting nitrene to form an indole (Scheme 1.9). The authors propose the formation of carbonyl selenide (COSe) which is the deoxygenation agent. Both 2- and 3-
methylindole can be synthesized in good yields (70%, 69%) from the corresponding 
\( o\)-nitrostyrenes, and indole is obtained in 55% yield.\(^{37}\)

![Scheme 1.9](image)

\[ \text{Scheme 1.9} \]

2) Sundberg indole synthesis:

Which involves the thermolysis of \( o\)-azidostyrenes and cyclization of the resulting 
nitrene to form indoles, to prepare 2-(2-azidoethyl) indole (\textbf{Scheme 1.10}).\(^{38}\) The lack 
of reactivity of the aliphatic azido group is noteworthy.

![Scheme 1.10](image)

\[ \text{Scheme 1.10} \]

3) Hemetsberger indole synthesis: (\textit{Our approach})

The Hemetsberger indole synthesis is related to the Sundberg indole synthesis except 
that the azido group is on the side chain (i.e., \( \alpha\)-azidocinnamate) rather than on the 
benzene ring. The latter study includes a new preparation of the precursor \( \alpha\)- 
azidocinnamates by azide ring opening of epoxides. The Hemetsberger protocol has 
been used to synthesize the ABC rings of nodulisporic acid, the thieno-[3,2-g]indole 
and thieno[3,2-e]indole ring systems, and a precursor CC-1065 and related antitumor 
alkaloids (\textbf{Scheme 1.11}).\(^{39}\)
V. Reductive cyclization:

Like the Fischer indole synthesis, and the Madelung cyclization and its modifications, and the numerous variations of electrophilic cyclization to indoles, reductive cyclization of nitro aromatics is a powerful means of forming indoles, and several new developments have been described in recent years.

1) \(\alpha, \beta\)-Dinitrostyrene reductive cyclization:

Corey and co-workers have been used the Borchardt modification (Fe–HOAc–silica gel–tol–reflux) of the reductive cyclization of \(\alpha, \beta\)-dinitrostyrenes to prepare 6,7-dimethoxyindole in a total synthesis of aspidophytine. The very labile 5,6-dihydroxyindole can be synthesized using the Zn-controlled conditions shown in (Scheme 1.12).\(^{40}\)

2) Reissert indole synthesis:

The classic Reissert indole synthesis, involving the reductive cyclization of \(o\)-nitrophenylpyruvic acid to indole-2-carboxylic acid, was used by Shin and co-workers to prepare a series of 2-ethoxycarbonyl-4-alkoxy methylindoles in a synthesis of fragment E of nosiheptide, and by Sato en route to a series of tricyclic indole derivatives (Scheme 1.13).\(^{41}\)
3) Leimgruber–Batcho indole synthesis:
The Leimgruber–Batcho indole synthesis involves the conversion of an \( \text{o-nitrotoluene} \) to a \( \text{\( \beta \)-dialkylamino-\( \text{o} \)-nitrostyrene} \) with \( \text{dimethylformamide acetal} \), followed by reductive cyclization to an indole (Scheme 1.14).

![Scheme 1.13](image)

![Scheme 1.14](image)
VI. Oxidative cyclization:

1) Watanabe indole synthesis:

The Watanabe indole synthesis is the metal-catalyzed indole synthesis from anilines and glycols, or ethanolamines, and the related intramolecular cyclization of o-aminophenethyl alcohols to indoles. Watanabe, Shim, and co-workers have now extended this reaction to the synthesis of N-alkyindoles in yields up to 78% (N-methylindole) from the reaction of N-alkylanilines with triethanolamine and the catalyst RuCl$_2$-(PPh$_3$)$_3$. The intramolecular version of this reaction occurs with an aluminium orthophosphate–Pd system and also with tetrakis(triphenylphosphine) palladium (Scheme 1.15).\textsuperscript{42}
VII. Radical cyclization:
Radical cyclization routes to indoles and indolines are very popular amongst synthetic chemists, and several new such methodologies have been invented in recent years for the construction of indoles.

1) Tin-mediated cyclisation:
Boger has been one of the pioneers in the development of tin-mediated radical cyclization, notably in the area of CC-1065. An example is depicted in (Scheme 1.16).

2) Murphy indole-indoline synthesis:
Murphy and co-workers have engineered an elegant new radical cyclization methodology involving “radical-polar crossover chemistry”, which uses tetrathiafulvalene (TTF) or sodium iodide to mediate the 5-exo-trig cyclization to indolines or indoles. A simple indole example is shown in Scheme 1.17.
VIII. Using Transition Metal Catalyst:

Many metals have been used to catalyse the cyclisation of $o$-alkynylanilines, including palladium, copper, zinc, indium, iridium, gold, mercury and molybdenum.

a) Palladium Catalysis:

Palladium catalysis is perhaps the most widely used method for both cross-coupling to form $o$-alkynylanilines and cyclisation to form indoles. An early example was in 1985 where $o$-phenylethynylacetanilides 21 were treated with palladium chloride in acetonitrile heated to reflux (Scheme 1.18).  

![Scheme 1.18](image)

b) Copper Catalysis:

This technique has been used in the synthesis of natural products. One such example is Hippadine (Scheme 1.19) which is a lycorine alkaloid isolated from Amaryllidaceae, and is known to have adverse effects on fertility in male rats.  

![Scheme 1.19](image)
c) Zinc Catalysis:
Zinc has been used successfully to catalyse the cyclisation of o-alkynylanilines such as 32. This was achieved by using a strong base, butyl lithium to deprotonate the amine followed by treatment with zinc chloride to give 2-substituted 3-zincioindole, which can then either be treated with NH₄Cl to give 2-substitutided indole 33 or with electrophiles to give 2,3-substituted indoles 34 (Scheme 1.20).

\[ \text{R}_1 \text{NH} \rightarrow \text{BuLi} \rightarrow \text{ZnCl}_2, \text{toluene, Heat, 1 h} \rightarrow \text{NH}_4\text{Cl} \rightarrow 2\text{-substituted 3-zincioindole} \rightarrow \text{CuCN, 2 LiCl, toluene, -78° C, THF} \rightarrow 2,3\text{-substituted indoles} \]

\[ \text{R}_1 = \text{Ph, } ^{1}\text{Bu, } ^{2}\text{Bu, H} \]

\[ \text{NH}_4\text{Cl} \rightarrow 2\text{-substituted indole} 33 \]

\[ \text{Cu(CN). ZnCl} \rightarrow \text{R}_2\text{COCl (MeSiCl)} \rightarrow 2,3\text{-substituted indoles} 34 \]

\[ \text{R}_1 = \text{Ph} \]
\[ \text{R}_2 = \text{Ph, 2-furyl, Me, } ^{1}\text{Bu} \]

\[ 48-99\% \]
\[ 65-97\% \]

Scheme 1.20

\[ \text{d) Indium Catalysis:} \]
Other Lewis acids have been used in the synthesis of indoles, in particular those based on indium. Recently indium tribromide has proven successful, and interestingly depending on the substituent on the alkyne terminal, either an indole or a quinoline is formed. The formation of the indole product 35 occurs when the alkyne terminal in 36 has either alkyl or aryl groups attached, via an intramolecular cyclisation (Scheme 1.21). This synthesis is very versatile, as substituents on C-4 and C-5 of the aniline do not have any significant detrimental effect on the outcome of the reaction, which tolerates halide, nitro, cyano and methyl substituents. Also substituents on the nitrogen do not appear to influence the reaction: anilines give excellent yields and N-benzyl, acetyl and alkoxycarbonyl derivatives all give between 70–78% yield, although the strongly
electron withdrawing groups did require significantly longer reaction times (20 h compared to 1–2 h).

![Scheme 1.21](image)

**Scheme 1.21**

e) Iridium Catalysis:

Iridium catalysis has been shown to be useful as the reactions can be carried out without exclusion of air and water in almost quantitative yields; however as terminal alkynes rearrange to form vinylidene, the synthesis is limited to internal alkynes (Scheme 1.22).

![Scheme 1.22](image)

**Scheme 1.22**

After an extensive mechanistic study involving Ir-D instead of Ir-H and monitoring by NMR it was proposed that the alkyne binds to the Ir(III) centre, activating it towards nucleophilic attack, followed by direct protonolysis of the resulting Ir-C bond.

f) Gold Catalysis:

Gold has been successfully shown to facilitate the cyclisation of o-alkynylaniline in ethanol or aqueous ethanol at room temperature. One-pot cyclisation/conjugate addition synthesis has also been used in the formation of vinyl indoles. These are of synthetic importance as they are precursors of poly(N-vinylindoles), which can be
used as semiconductors and photosensitive materials. This was achieved by reacting $\sigma$-alkynylaniline $38$ with terminal alkynes $39$ in the presence of $\text{AuCl}_3/\text{AgOTf}$ (5 mol%/15 mol %) at room temperature with no solvent (Scheme 1.23).

\begin{center}
\textbf{Scheme 1.23}
\end{center}

**g) Mercury Catalysis:**
An interesting example of cyclisation was by mercury triflate. $51$ Mercury triflate was developed in 1983 as a catalyst for alkene cyclisation. Different reaction conditions for the cyclisation of $\sigma$-alkynylaniline were examined and it was shown that tosyl was the optimal protecting group for the nitrogen. Although toluene appeared to give more satisfactory results with high yields and low catalyst loading, dichloromethane was chosen as the optimal solvent, probably due to lower reflux temperatures and a possibility of solubility issues with toluene.

\begin{center}
\textbf{Scheme 1.24}
\end{center}

Cyclisation to form different 2-substituted indoles $41$ usually occurred within an hour (e.g. for $R^1=p$-methoxybenzyl, hydroxybutyl, butyl) however the compound with $R^1=4$-OTBS-butyl took 15 h and for $R^1=p$-nitrobenzyl and t-butyl it took 24-40 h (Scheme 1.24).

**h) Molybdenum Catalysis:**
Molybenum has been shown to be an active catalyst for the cyclisation of $\sigma$-ethynylanilines. This was achieved by using 0.1 equivalents of metal catalyst with triethylamine as a base to give reasonable to good yields of 42 (Scheme 1.25).

![Scheme 1.25](image1.png)

**Base-Induced Cyclisation:**

Bases have been used successfully in the cyclisation of $\sigma$-ethynylanilines, and in an early example it was shown that this reaction relies on protection of the amine as in 43 (Scheme 1.26). However the removal of the protecting group occurs during work-up which also removes the trimethylsilyl group when $R_1 =$ TMS.52

![Scheme 1.26](image2.png)

Cyclizations also occur under very mild conditions using tetrabutylammonium fluoride (TBAF). Under optimized conditions different substituents are tolerated at $R_1$. 

---

*Development and Application of New Methodologies for Synthesis of Bioactive Molecules*  54
and $R_2$, and depending on the nature of the substituents either indole 44 or $N$-substituted indole 45 is formed (Scheme 1.27).

\[
\begin{align*}
\text{R}_1 &= \text{Ac, Boc, Ms} \\
\text{R}_2 &= \text{Ph, TMS, H, Hex, Bu}
\end{align*}
\]

**Scheme 1.27**

c) **Synthesis of Indole-3-acetic acid:**

**Hemetsberger-Knittel Indole Synthesis:**

The Hemetsberger-Knittel Indole synthesis is a chemical reaction that thermally decomposes a 3-aryl-2-azido-propionic ester into an indole-2-carboxylic acid (Scheme 1.28).\(^{53}\)

\[
\begin{align*}
\text{O} &+ \text{N}_3 \xrightarrow{\text{NaOEt}} \text{O} \xrightarrow{\Delta T} \text{O}
\end{align*}
\]

**Scheme 1.28**

Yields are typically above 70%. However, this is not a popular reaction, due to lack of stability and difficulty in synthesizing the starting material.

More recently Richard A. et al\(^{54}\) reported the synthesis of indole-3-acetic acid. For the first synthetic strategy \((D1)\) the Hemetsberger reaction was employed (Scheme 1.29), and this was initiated with the preparation of the vinyl azide which, upon heating in refluxing xylene, generated the highly electrophilic singlet nitrene species. Thus, the insertion reaction in a less hindered position proceeded at very high.
Why need of new route for the synthesis of Indole?

On the basis of following reason there is need of new route for the synthesis of indole from cinnamic acid.

1. Considering all the aspects of synthetic strategy of indole, it was found that many processes required expensive metal catalyst.

2. Use of starting materials is also expensive, and not easily available.

3. Accordingly there remains a need for simple, cost effective and industrially
feasible process for Indole.

4. Keeping in mind all the above issues, we developed a simple method for the synthesis of Indole and indole-3-acetic acid from cinnamic acid.

1.4 OBJECTIVE OF THE WORK:
Because of the potent biological activity exhibited by various indole derivatives, the methods of construction of this heterocyclic system have been object of considerable attention. The best known and classic among them are the Fischer, Bischler, Madelung, Reissert, Nenitzescu and Gassman procedures. Other interesting methods are based on nucleophilic and free radical addition, intramolecular amidoalkylations, intramolecular cyclisation of ortho aminostyrenes or via organometallic intermediates. However, notwithstanding the availability of a wide variety of approaches, modifications of previous methodologies and new synthesis continue to appear in the literature, in order to improve the efficiency of the reaction and to start from easily available materials.
In this connection we developed a completely new approach to the synthesis of indoles.
Our first aim was to synthesize vinyl azide from cinnamic acid and then azide was cyclized to indole and it can be successfully transfer to indole-3-acetic acid. The literature methods have inherent problem of more number of steps, use of costly, explosive raw material and critical reaction conditions. To overcome these limitations, there is a need for the development of alternative methods.
1.5 DESIGN AND DEVELOPMENT:
Though there are many methods reported for synthesis of indole & indole-3-acetic acid but most of the methods are having limitations as mentioned in above. Therefore still there is broad scope for development of new method for the indole synthesis, so to overcome above mentioned drawbacks. Efforts has been done to develop a new method for direct synthesis of indole from cinnamic acid via vinyl azide which can overcome some of the limitations of existing methods in terms of safety, reaction time, yield, availability of starting materials and cost of reagents.
In the literature it has been found that for direct synthesis of indole scaffold, many methods are reported which uses metals as catalyst. While using such metals required harsh reaction condition.
In the literature it was also found that for the synthesis of indole-3-acetic acid required six steps and hence takes more time with fewer yields.
Hypervalent iodine reagents are very well known for its oxidizing properties. We have tried to extend these oxidizing properties of hypervalent iodine reagents for the oxidative decarboxylation of \(\alpha,\beta\)-unsaturated carboxylic acid and expected that it could be oxidized by hypervalent iodine reagents and can able to give vinyl azide.
Based on this aspect the model reaction was carried out by using cinnamic acid, TEAB and sodium azide with combination of hypervalent iodine (III) reagent such as [bis(trifluoroacetoxy)iodo]benzene (BTI). Reaction was monitored by TLC.
Reaction went to completion after 30 min. After completion of reaction and work up, products containing a mixture of compounds were isolated. These compounds were separated by column chromatography & characterization were carried out by using IR and NMR techniques and their structure were elucidated as (E)-(2-azidovinyl) benzene. The isolated yield was 80% as shown in Scheme 1.30 step I.
After successful experiment of vinyl azide from \(\alpha,\beta\)-unsaturated carboxylic acid with hypervalent iodine (III) reagent with combination of TEAB and sodium azide. We were moved to cyclisation of these azide derivatives to indole using xylene as a solvent under 3 h reflux condition as shown in scheme 1.30 step II with 96% unit yield of indole.
So for our preliminary study, we had successfully developed a simple method for synthesis of vinyl azide. Further synthesis of indole by employing Hemetsberger Knittel approach using cheap and readily available raw materials. In proposed intensified process all the reaction conditions are feasible and mild from industrial point of view. In this route less number of steps will be required and all the reagents commercially available and conditions are easy to handle. The key step in this process is the preparation of vinyl azide. A new route for synthesis of indole and indole-3-acetic acid is shown in the scheme 1.30 step III.

![Scheme 1.30: synthesis of indole-3-acetic acid 4a-4c](image)

**Figure 10**
1.6 EXPERIMENTAL SECTION:

General procedure for synthesis of Indole and IIA from \(\alpha,\beta\)-unsaturated acid

1) Step 1: Synthesis of (2E)-3-phenylacryloyl azide (2a):

To a stirred solution of [bis(trifluoroacet oxy)iodo]benzene (1.28 g, 4.05mmol, 1.2 equiv) in anhyd CH\(_2\)Cl\(_2\) (15 mL) was added TEAB (0.88 g, 4.05mmol, 1.2 equiv) in one portion. The resultant reaction mixture was stirred for 5 min followed by addition of \(\alpha,\beta\)-unsaturated carboxylic acid (0.5 g, 3.37mmol, 1.0 equiv). After completion of addition, sodium azide (0.26 g, 4.05mmol, 1.2 equiv) was added and the mixture was stirred at room temperature until the starting material was completely consumed (TLC). The reaction mixture was diluted with CH\(_2\)Cl\(_2\) and washed successively with 10% sodium bisulfate solution (2x20 mL), 10% sodium bicarbonate (2x15 mL), and water (2x20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product. Pure product was obtained after silica gel column chromatography (10% EtOAc–hexane). (Yield 0.385g, 80 %); IR (cm\(^{-1}\)) 2109 (N\(_3\)), 3062 (CH), 1598, 763 (KBr); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.98 (1H, d), 5.74 (1H, d), 7.18-7.34 (5H, m)

Step 2: Synthesis of indole (3a):

A vinyl azide 3a, 0.725 g, (5 mmol) and xylene (20 mL) was refluxed for 3 h, when the evolution of N\(_2\) had ceased. The xylene was removed under reduced pressure distillation, and the resulting solid was purified by column chromatography, using a mixture of dichloromethane and ethyl acetate (20:5) for elution and providing the pure product (0.48 g, 96 %) was isolated; m. p. 59\(^\circ\)C; IR (cm\(^{-1}\)) (KBr); 3162, 3072, 1625, 755; \(^1\)H NMR (60 MHz, CDCl\(_3\)) \(\delta\) 6.54-7.95 (6H, m)

Step 3: Synthesis of indole-3-acetic acid (4a):

To a two naked RBF fixed with reflux condenser in oil bath was charged with 0.14 g. (2.56 moles, 1.2 equiv.) of 85% potassium hydroxide and 0.25 g. (2.13 moles, 1 equiv.) of indole(3a) and then 0.24 g. (3.20 moles, 1.5 equiv.) of 70% aqueous glycolic acid is added slowly. The solution was stirred at room temperature. The RBF was closed and stirred at 250\(^\circ\)C for about 24 hours. After TLC analysis the reaction
mixture was cooled to room temperature (below 50°C), a 50 ml. of water was added, and further mixture was stirred for 30 min. at 100°C to dissolve the potassium indole-3-acetate salt. The progress of the reaction was monitored by TLC. Then aqueous solution was cooled to 25°C and RBF was rinsed out well with water. The solution is extracted with 2x20 ml. of pet ether. The aqueous phase is acidified at 20–30°C with 12N hydrochloric acid and then is cooled to 10°C. The indole-3-acetic acid that precipitates is collected on a Buchner funnel, washed with copious amounts of cold water, and dried in air.; (0.35g, 94%); mp 163–165°C; IR (cm⁻¹) 3382, 2998, 1687, 782. (KBr); ¹H NMR (60 MHz, CDCl₃) δ 3.81(2H, s), 7.24-7.61(5H, m), 10.54(1H)

2) Step 1: Synthesis of (E)-1-(2-azidovinyl)-4-bromobenzene (2b):
[Bis(trifluoroacetoxy)iodo]benzene (0.33 g, 1.06mmol, 1.2 equiv) in anhyd CH₂Cl₂ (15 mL) was added TEAB (0.22 g, 1.06mmol, 1.2 equiv). After 5 min stirred followed by addition of α,β-unsaturated carboxylic acid (0.2 g, 8.84mmol, 1.0 equiv) and sodium azide (0.1 g, 1.06mmol, 1.2 equiv) was added and the mixture was stirred at room temperature until the starting material was completely consumed (TLC) in a 35 min. Detailed experimental as well as workup procedure is same as explained in general procedure. (0.160g, 82 %); IR (cm⁻¹) (KBr) 2111, 1633; ¹H NMR (60 MHz, CDCl₃) δ 5.63 (d, 1H), 6.37 (d, 1H), 7.28 (m, 2H), 7.52 (m, 2H)

Step 2: Synthesis of indole (3b):
4-Bromo-vinylazide (2b) (1.1 g, 5.0mmol) in anhyd CH₂Cl₂ (15 mL) was refluxed in a xylene (20 mL) for 4 h until the starting material was completely consumed in a 2 h (TLC). Detailed experimental as well as workup procedure was same as explained in general procedure.(0.932g, 97%); m. p. 94-96°C; IR (cm⁻¹) (KBr) 3170, 3075, 1630, 755;¹H NMR (60 MHz, CDCl₃) δ 6.45 (d, 1H), 7.10-8.26 (m, 4H), 7.28 (m, 2H), 7.52 (m, 2H)

Step 3: Synthesis of 6-bromo-indole-3-acetic acid (4b):
Potassium hydroxide (85%) 0.10 g (1.53 moles, 1.2 equiv.), 0.25 g. (1.27 moles, 1 equiv.) of indole(3b) and 70 % aq. glycolic acid 0.14 g. (1.91 moles, 1.5 equiv.) was reacted slowly. The solution was stirred at 250°C for about 24 hours. Detailed experimental as well as workup procedure is same as explained in general procedure.
(0.304g, 95%); m.p. 175°C; IR (cm⁻¹) (KBr); 3385, 3000, 1690, 786; ¹H NMR (60 MHz, CDCl₃) δ 3.85(s, 2H), 7.14-7.85(m, 4H), 11.05(s, 1H)

3) Step 1: Synthesis of (E)-1-(2-azidovinyl)-4-methoxybenzene (2c)

[Bis(trifluoroacetoxy)iodo]benzene (1.0 g, 3.37 mmol, 1.2 equiv) in anhyd CH₂Cl₂ (15 mL) was added TEAB (0.70 g, 3.37 mmol, 1.2 equiv). After 5 min stirred followed by addition of α,β-unsaturated carboxylic acid (0.5 g, 2.80 mmol, 1.0 equiv). Then sodium azide (0.20 g, 3.37 mmol, 1.2 equiv) was added and the mixture was stirred at room temperature until the starting material was completely consumed (TLC) in a 35 min. Detailed experimental as well as workup procedure is same as explained in general procedure. (0.418 g, 85 %); IR (cm⁻¹) (KBr) 2850, 2110, 1632, 1606, 1512, 1399, 1304, 1035, 865; ¹H NMR (60 MHz, CDCl₃) δ 3.81(s, 3H), 5.63 (d, 1H), 6.25 (d, 1H), 6.86 (d, 2H), 7.54 (d, 2H)

Step 2: Synthesis of 4-methoxyindole (3c):

4-methoxy-azide (2c) (0.875 g, 5.0 mmol) was refluxed in a xylene (20 mL) for 4 h until the starting material was completely consumed in a 9h (TLC). Detailed experimental as well as workup procedure is same as explained in general procedure. (0.707 g, 80%); m.p. 94°C; IR (cm⁻¹) (KBr); 3450, 2820, 1620, 1270 755; ¹H NMR (60 MHz, CDCl₃) δ 3.83 (s, 1H), 6.70-8.30 (m, 5H)

Step 3: Synthesis of 6-methoxyindole-3-acetic acid (4c):

Potassium hydroxide (85%) 0.11 g (2.04 moles, 1.2 equiv.), 0.25 g. (1.70 moles, 1 equiv.) of indole(3c) and 70 % aq. glycolic acid 0.19 g. (2.55 moles, 1.5 equiv.) was reacted slowly. The solution was stirred at 250° for about 24 hours. Detailed experimental as well as workup procedure is same as explained in general procedure. (0.235 g, 69%); m.p. 162°C; IR (cm⁻¹) (KBr); 3450, 2820, 1610, 1425; ¹H NMR (60 MHz, CDCl₃) δ 3.58 (s, 2H), 3.85 (s, 3H), 6.90-7.85 (m, 4H), 11.05 (s, 1H)

1.7 RESULTS AND DISCUSSION:

We developed a simple and robust route for indole; we have chosen cinnamic acid, as a commercial available starting material.
A synthesis of indol-3-acetic acid was carried out in following reaction sequence

Step-I Synthesis of (2E)-3-phenylacryloyl azide

Step-II Synthesis of Indole

Step-III Synthesis of Indole-3-acetic acid

After completion of the every step of reaction we performed simple workup and next step was carried out.

**Step-I**

It was observed that 1.2 equivalent of BTI with respect to $\alpha,\beta$-unsaturated carboxylic acid along with 1.2 equivalent of TEAB and 1.2 sodium azide was more efficient to achieve better yield as shown in scheme 1.31.

**Scheme 1.31:** Cinnamic acid converted into vinyl azide using [bis(trifluoroacetoxy)iodo]benzene, sodium azide and TEAB.

**Table 1:** optimized reaction condition

<table>
<thead>
<tr>
<th>Mole ratio</th>
<th>BTI:TEAB:NaN$_3$:Acid (1.2:1.2:1.2:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>CH$_2$Cl$_2$</td>
</tr>
<tr>
<td>Time</td>
<td>30 min.</td>
</tr>
<tr>
<td>Yield</td>
<td>80%</td>
</tr>
</tbody>
</table>

In IR analysis, azide peak appeared at 2100 cm$^{-1}$ and absence of -C=O stretching of acid (1750 cm$^{-1}$) indicates the formation of azide was done completely.

**Step II:** (Scheme 1.32).

A mixture of (2E)-3-phenylacryloyl azide (3a) (2.0 g, 8.1 mmol) and xylene (75 mL) was refluxed for 3 h, when the evolution of N$_2$ had ceased. The xylene was removed under reduced pressure distillation, and the resulting solid was purified by column
chromatography, using a mixture of dichloromethane and ethyl acetate (20:5) for elution and the pure product was isolated. Compound was characterized by physical and spectral properties and optimized conditions for the step are given in table 2.

![Scheme 1.32]

Table 2: Optimized reaction condition

<table>
<thead>
<tr>
<th>Mole ratio</th>
<th>Azide compound 1mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>Xylene</td>
</tr>
<tr>
<td>Time</td>
<td>3 h</td>
</tr>
<tr>
<td>Yield</td>
<td>96%</td>
</tr>
</tbody>
</table>

**Step III: (Scheme 1.33)**

After the successful completion of step II, indole (4a) was treated with glycolic acid in solution of 85% potassium hydroxide at 250°C for 24 h. The electrophilic substitution at C3-position of indole was taken place, giving desired product as indole-3-acetic acid in a good yield, after workup procedure product was isolated. Compound was characterized by physical and spectral properties which exactly matched with authentic data and optimized conditions for the step are given in table 3.

![Scheme 1.33]

Table 3: Optimized reaction condition

<table>
<thead>
<tr>
<th>Mole ratio</th>
<th>Indole:glycolic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>Water</td>
</tr>
<tr>
<td>Time</td>
<td>24 h</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Yield</td>
<td>95%</td>
</tr>
<tr>
<td>Overall yield of IIA</td>
<td>71%</td>
</tr>
</tbody>
</table>

It was observed that, in all steps unit yield of the every product was found to be good. For step I its 80%, then for step II its 96% and for step III its 95%, and hence the overall process yield of this product was 71%.

1.8 SUMMARY & CONCLUSION:

Here in this chapter, we described influence of hypervalent iodine (III) reagent in preparation of azide from α,β-unsaturated acid and ultimately, for synthesis of Indole and then for the synthesis of indole-3-acetic acid. This route comprises cheaper raw material with three reaction steps. The important attributes of the course was no critical reaction condition required and all the reagents are commercially available and reaction condition are easy to handle. On the basis reducing the number of steps and using cost efficient route, we have attained the process improvement for indole and indole-3-acetic acid.

In conclusion, a reaction which employs cheap reactants and mild conditions is now available to synthesize 7-substituted indoles. Since in our opinion this approach to the construction of the indole nucleus is open to very interesting developments.
1.9 REFERENCES:


15. Hopkienns, F. G.; Cole, S. W.; J. Physiol., 1901, 27, 418


27. Elderfield, L.; Heterocyclic compounds. 1954, 3, 5


44. Murphy, J. A.; Scott, K. A.; Sinclair, R. S.; Lewis, N.; *Tetrahedron Lett.*, **1997**, 38, 7295
47. Yin, Y.; Ma, W.; Chai, Z.; Zhao, G.; *J. Org. Chem.*, **2007**, 72, 5731


1.10 SPECTRA: 2a IR
2a NMR
3a NMR
4a IR
4a NMR
2c IR