

## Novel Methods of Synthesis of Heterocyclic Compounds

Sakshi D. Nataalkar , vashnavi S. Rumade, Aparna C.kanekar, Komal S. Chavan,  
Shravani S. Prbhudesai, ShravaniR.Mhetre, GayatriK.Budraksh  
Corresponding Author: Prof. BangarSampat S., prof. Pawar Rahul A.

College Name : Shree saraswati institute of pharmacy tondavali, kankavali,sindhudurg

Date of Submission: 10-08-2024

Date of Acceptance: 20-08-2024

**ABSTRACT:** Heterocyclic compounds are the class of organic compounds . there are various previous methods are available in many research and review papers but no single research and review paper available for newer methods of synthesis of heterocyclic compounds. Mainly there are two class of heterocyclic compounds 1. Five membered heterocyclic compounds 2. Six membered heterocyclic compounds. Heterocyclic means compounds containing more than one elements.

### I. INTRODUCTION:

**Heterocyclic compound**, any of a major class of organic chemical compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon . The cyclic part of heterocyclic indicates that at least one ring structure is present in such a compound, while the prefix heterorefers to the noncarbon atoms, or heteroatoms, in the ring. In their general structure, heterocyclic compounds resemble cyclic organic compounds that incorporate only carbon atoms in the rings—for example, cyclopropane (with a three-carbon-atom ring) or benzene (with a six-carbon-atom ring)—but the presence of the heteroatoms gives heterocyclic compounds physical and chemical properties that are often quite distinct from those of their all-carbon-ring analogs.

Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds, as are most hallucinogens. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics.

### PYRIDINE

Pyridine is a heterocyclic compound having six membered ring. pyridine most commonly use as a solvent and reaction intermediate in pharmaceutical organic synthesis.

#### 1. Bohlmann-Rahtz Pyridine Synthesis

• **Statement-:** It is a condensation type reaction in which ethynylketones condense with enamines results in formation of an aminodiene intermediate that after heating - induced E/Z isomerization, to produce a cyclodehydration to yield 2,3,6-trisubstituted pyridines.

- **General Reaction-:**
- **Mechanism-:**

#### 2.Chichibabin Pyridine Synthesis

• **Statement-:**  
The condensation reaction of aldehydes ,ketones and alpha beta unsaturated carbonyl compounds called as chichibabin pyridine synthesis.

- **General Reaction-:**
- **Mechanism-:**

#### 3.Hantzsch Dihydropyridine Synthesis

• **Statement-:** preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a  $\beta$ -ketoester in the presence of catalyst ammonia called as hantzschdihydropyridine synthesis reaction.

- **General Reaction-:**
- **Mechanism-:**

The reaction proceeding through a Knoevenagel Condensation product as a key intermediate: an ester enamineA second key intermediate, which is produced by condensation of the second equivalent of the  $\beta$ -ketoester with ammonia:

Further condensation between these two fragments gives the dihydropyridine derivative:

#### 4. Hantzsch Pyridine Synthesis

- **Statement:-**

Condensation of an aldehyde with two equivalents of a  $\beta$ -ketoester followed by dehydrogenation generate dihydropyridine derivatives.

- **General Reaction:-**

- **Mechanism:-**

#### 5. Krohnke Pyridine Synthesis

- **Statement:-**

1,4-Michael addition of  $\alpha$ -pyridinium methyl ketone salts to  $\alpha,\beta$ -unsaturated carbonyl ketones, results in formation of the 1,5-dicarbonyl compounds which is after ring closure, to yield substituted pyridines

- **General Reaction:-**

- **Mechanism:-**

#### Isoquinoline

Isoquinoline is heterocyclic compound comes under the class of fused ring heterocyclic compound. It is also called benzopyridine derivative. It alters the mitochondrial functions and increases apoptosis.

#### 1) Pomeranz-Fritsch Isoquinoline Synthesis

- **Statement:-** Synthesis of isoquinoline from benzyl halides or aromatic aldehydes and aminoacetal.

- **General Reaction:-**

- **Mechanism:-**

#### OXAZOLE

Oxazole is a main nucleus compound of various oxazole derivatives. Oxazole areazole derivatives with oxygen and nitrogen.

#### 1) Cornforth Oxazole Rearrangement –

- ❖ **Statement –**

Thermal rearrangement of 4-carbonyl substituted oxazoles via zwitterionic dicarbonyl nitrile yield followed by ring closure

- ❖ **Reaction -**

- ❖ **Mechanism –**

The mechanism of the Cornforth rearrangement begins by a thermal pericyclic ring opening which

#### INDOLE

furnishes a nitrile intermediate **1**, which then undergoes rearrangement to the oxazole, which is isomeric to the starting compound.

The ylide intermediate has several resonance contributors and the stability of said structures affects the outcome of the reaction, since the intermediate will revert to the starting material if the third resonance structure is most stable. Whether the reaction takes place is dependent on the energy difference between the starting material and the product.<sup>[1][4][5]</sup>

#### 2) Robinson -Gabriel Synthesis -

- ❖ **Statement -**

organic reaction in which a 2-acylamino-ketone reacts intramolecularly followed by a dehydration to give an oxazole

- ❖ **Reaction-**

- ❖ **Mechanism-**

Protonation of the keto moiety (**1**) is followed by cyclization (**2**) and dehydration (**3**), the oxazole ring is less basic than the starting 2-acylamidoketone and so may be readily neutralized (**4**).<sup>[4]</sup> Labeling studies have determined that the amide oxygen is the most Lewis basic and therefore is the one included in the oxazole.<sup>[5]</sup>

#### 3) Van-Leusen Oxazole Synthesis –

- ❖ **Statement – reaction between aldehyde and Tosylmethylisocyanide gives oxazole**

- ❖ **Reaction -**

- ❖ **Reaction Mechanism -**

The reaction is driven by the unique reactivity of TosMIC, which includes acidic protons, sulfonic acid as a leaving group and an isocyanide group that contains an oxidizable carbon atom:

After adding the deprotonated TosMIC to the aldehyde and bond formation between the resulting hydroxy group and the isocyanide group, an oxazoline results as an intermediate:

#### 4) Fischer Oxazole Synthesis –

- ❖ **Statement –**

The condensation of cyanohydrins and aromatic aldehyde in the presence of dry hydrochloric acid gives oxazole

- ❖ **General Reaction –**

- ❖ **Reaction Mechanism -**

Indole is a fused ring heterocyclic organic compound containing six member ring fused with five member ring. It is used to making essential

amino acid Tryptophan and also making indoleacetic acid.

### 1) Baeyer-Emmerling Indole Synthesis-

▪ **Statement-**

Reaction between ortho-nitrocinnamic acid and iron powder in strongly basic solution obtained indole .

▪ **General Reaction-**

▪ **Reaction Mechanism –**

The reaction of iron powder with o-nitrocinnamic acid reduces the nitro group to a nitroso. The nitrogen then condenses with a carbon on the alkene chain with loss of a molecule of water to form a ring. Decarboxylation gives indole.

### 2) Bischler-Mohrlau Indole Synthesis-

▪ **Statement-**

Formation of 2-aryl-indoles from  $\alpha$ -bromoacetophenone and excess aniline called as Bischler Mohrlau indole synthesis reaction.

### Furan

#### 1) Feist-Benary Furan Synthesis.

• **Statement:-** reaction of  $\alpha$ -halogenated ketones or aldehydes and 1,3-dicarbonyl compounds in the presence of base to form furan.

• **General Reaction:-**

**Stage 1. Formation of the enolate**

**Stage 2. Alkylation by attack on the halogenated ketone**

**Stage 3. Enolization and cyclization**

**Stage 4. Dehydration.**

### PYRROLE

Pyrrrole is a five membered heterocyclic compound containing Nitrogen heteroatom. Use to formation of metal complexes' .

#### 1) Van Leusen synthesis:-

• **Statement :-**

The conversion of a ketone into a nitrile with one additional carbon atom in a single pot using tosylmethylisocyanide (TosMIC) as a synthon called as van leusen pyrrole synthesis reaction.

• **General Reaction :-**

• **Reaction Mechanism:-**

#### 2) Borton-zord Pyrrole Synthesis:-

• **Statement :-**

This reaction use to preparation of pyrrole derivatives via the reaction of a nitroalkene with an  $\alpha$ -isocyanide under basic conditions.

▪ **General Reaction-**

▪ **Reaction Mechanism-**

The first two step involve the reaction of the  $\alpha$ -bromoacetophenone with molecules of aniline to form intermediate 4. The charged aniline forms a decent enough leaving group for an electrophilic cyclization to form intermediate 5, which quickly aromatizes and tautomerizes to give the desired indole 7.

### 3) Bartoli Indole Synthesis –

▪ **Statement –**

Formation of 7-substituted indoles from ortho-substituted nitroarenes (or nitrosoarenes) and alkenyl Grignard reagents

▪ **General Reaction –**

▪ **Reaction Mechanism-**

• **General Reaction :-**

• **Reaction Mechanism :-**

#### 3) Polity -Robinson pyrrole Synthesis :-

• **Statement :-**

The Polity-Robinson Pyrrole Synthesis involve The Conversion of azines to 3,4-disubstituted pyrroles using

• **General Reaction :-**

• **Reaction Mechanism :-**

#### 4) Vilsmeier Pyrrole Synthesis :-

• **Statement :-**

The Vilsmeier reaction is an alternative to Friedel-Crafts acylation and avoids the use of strong Lewis acids such as AlCl<sub>3</sub>. This method is particularly useful for formylation because it works well with Me<sub>2</sub>NCHO (DMF) instead of dimethylacetamide to add a formyl (CHO) group rather than a methyl ketone.

• **General Reaction :-**

• **Reaction Mechanism :-**

#### 1) Formation of an iminium cation:-

#### 2) Nucleophilic substitution:-

#### 3) Hydrolysis of an iminium salt :-

#### 5) Clauson - Kaas Pyrrole Synthesis :-

• **Statement :-**

Synthesis of pyrrole the condensation of 2,5-dialkoxytetrahydrofurans with primary amines reaction called as Clauson - Kaas Pyrrole Synthesis

- **General Reaction :-**
- **Reaction Mechanism:-**

### IMIDAZOLE

Imidazole is a five member heterocyclic compound. Various imidazole derivatives synthesis by imidazole. Imidazole derivatives used to treat various infective diseases.

#### ❖ **Staab Carbonylimidazol Synthesis**

##### ❖ **Statement :-**

1,1'-Carbonyldiimidazole (CDI) is an organic compound with the molecular formula  $C_3H_3N_2)_2CO$ . It is a white crystalline solid. It is often used for the coupling of amino acids for peptide synthesis and as a reagent in organic synthesis reaction :

##### ❖ **General Reaction:-**

##### **Reaction Mechanism :-**

- **Radziszewski Imidazole Synthesis :-**

##### **Statement:-**

It is a multi-component reaction used for the synthesis of imidazoles from a 1,2-dicarbonyl, an aldehyde, and ammonia or a primary amine.

- **General Reaction :-**
- **Reaction Mechanism :-**
- **Van Leusen Imidazole Synthesis :-**

##### • **Statement :-**

Van Leusen Imidazole Synthesis allows the preparation of imidazoles from aldimines by reaction with tosylmethylisocyanide (TosMIC). The reaction has later been expanded to a two-step synthesis in which the aldimine is generated in situ: the Van Leusen Three-Component Reaction (vL-3CR)

- **General Reaction :-**
- **Reaction Mechanism :-**

##### • **Bredereck Imidazole Synthesis:-**

##### • **Statement:-**

Method for synthesizing substituted imidazoles by condensing  $\alpha$ -diketone or  $\alpha$ -hydroxyketone with formamide. This reaction is

often used to synthesize unsubstituted imidazole derivatives at the C2 position.

- **General Reaction:-**
- **Reaction Mechanism :-**

### THIOPHENE

#### 1. **Baumann – Fromm Thiophene Synthesis**

- **Statement :-** Formation of thiophene derivatives from styrene and sulfur under heat.

- **General Reaction :-**
- **Reaction Mechanism:-**

#### • **Hinsberg Thiophene Synthesis**

- **Statement:-** Preparation of thiophene carboxylic acids from  $\alpha$ -diketones and dialkylthiodiacetates

- **General Reaction:-**
- **Reaction Mechanism**

#### 2. **Fiesselmann Thiophene Synthesis**

- **Statement :-** Condensation of thioglycolic acid with  $\alpha,\beta$ -acetylenic esters which upon treatment with base yields 3-hydroxy-2-thiophenecarboxylic acid

- **General Reaction:-**
- **Reaction Mechanism:-**

#### 3. **Krollpfeiffer Thiophene Synthesis**

- **Statement :-** Synthesis of benzothiophenes through formation of sulfonium salts

- **General Reaction:-**
- **Reaction Mechanism:-**

### Quinoline

#### 1. **Combes Quinoline Synthesis**

- **Statement :-** It involves the condensation of unsubstituted anilines with  $\beta$ -diketones to form substituted quinolines .

- **General Reaction:-**
- **Reaction Mechanism:-**

#### **Qonrad Limpach Quinoline Synthesis:-**

- **Statement:-** the condensation reaction of aniline with  $\beta$ -ketoesters to form 4-hydroxyquinolines.

- **General Reaction:-**
- **Reaction Mechanism :-**

### 3) Camps Quinoline Synthesis:-

- **Statement** :-a chemical reaction whereby an o-acylaminoacetophenone is transformed into two different hydroxyquinolines called The Camps quinoline synthesis reaction.

- **General Reaction:-**

- **Reaction Mechanism:-**

### 4) Friedlander Quinoline Synthesis:-

- **Statement:-**a chemical reaction by the condensation of 2-aminobenzaldehydes or ketones with aldehyde or ketone compound to form quinoline derivative called The Friedländer synthesis reaction.

- **General Reaction:-**

- **Reaction Mechanism:-**

### 4. Dobner Miller Quinoline synthesis

- **Statement:-** Reaction between aniline with  $\alpha,\beta$ -unsaturated carbonyl compounds to form quinolines.

- **General Reaction:-**

- **Reaction Mechanism:-**

### 5. Niementowski Quinoline Synthesis:-

- **Statement:-** The Niementowski quinoline synthesis is the chemical reaction of anthranilic acids and ketones (or aldehydes) to form  $\gamma$ -hydroxyquinoline derivatives.

- **General Reaction:-**

- **Reaction Mechanism:-**

## II. CONCLUSION:

From the survey of various journals, papers and reference books it is concluded that novel synthetic name reactions of synthesis of heterocyclic compounds are not mentioned. These newer methods are useful for synthesis of various heterocycles.

## REFERENCES:

1. Reaction flash application
2. [www.google.com](http://www.google.com)
3. Wikipedia.