Review On Synthesis Of Benzimidazole From O-phenyldiamine

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Abstract

Benzimidazole derivatives, which were first discovered in 1944, are a diverse group of nitrogen-containing heterocyclic compounds. They have been recognized for their potential as biologically active compounds and have been extensively studied. The benzimidazole nucleus and its derivatives have proven to be valuable therapeutic agents, particularly in the treatment of conditions such as ulcers and parasitic infections. Additionally, these derivatives have demonstrated various pharmacological activities, including antimicrobial, antiviral, anticancer, anti-inflammatory, and analgesic effects.

Key word: *Benzimidazole, O-phenylenediamine, the synthesis of Hydrochloride.*

1.Introduction

Benzimidazole, an organic compound, is categorized as a heterocyclic aromatic compound. It is highly valued as a pharmacophore and is regarded as a privileged structure in medicinal chemistry. Nowadays, it is extensively acknowledged as a favored moiety because of its various pharmacological properties. A prominent benzimidazole compound occurring naturally is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. [1]

Benzimidazole has been employed for numerous years in the examination of structural alterations and their pharmacological impacts. Various analogs of benzimidazole have been created through the introduction of fluorine, propylene, and Tetrahydroquinoline, resulting in substances that demonstrate improved stability, bioavailability, and significant biological efficacy. (2-3). Medicinal chemists would unquestionably view them as privileged 'sub-structures' for drug design due to their strong affinity towards various enzymes and protein receptors.

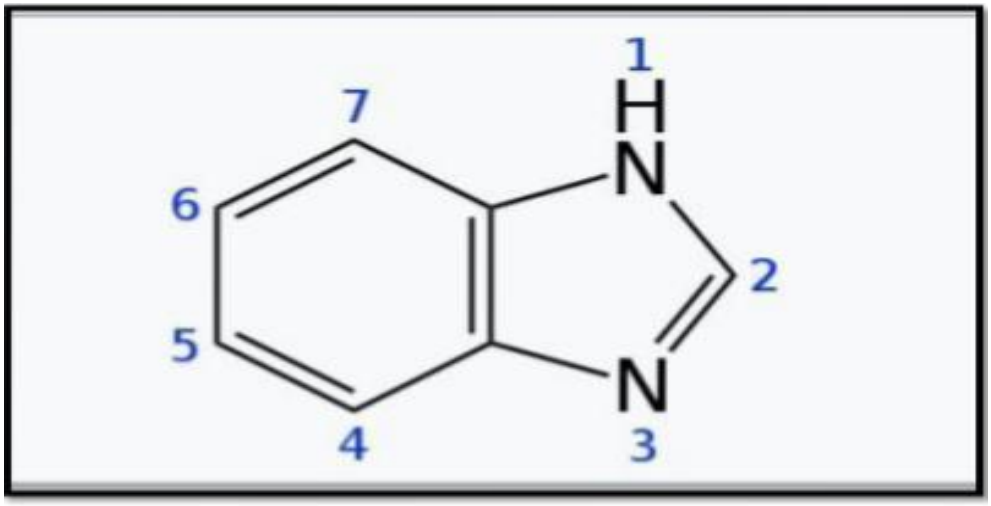
The integration of the nucleus is a crucial synthetic approach in drug discovery research. Benzimidazole and its derivatives have garnered significant interest in recent years for their therapeutic properties. [4]

Benzimidazole derivatives exhibit high efficacy in the field of medicine, showcasing a wide range of beneficial therapeutic properties such as anti-inflammatory, antimicrobial, and diuretic effects. [5] antiviral, Anticancer, Antiprotozoal, Antiulcer, Anti-oxidant can be rewritten as: antiviral, cancer-fighting, protozoa-fighting, ulcer-fighting, and oxidative stress-reducing. [6] Anti-asthmatic, anti-diabetic, cysticidal, analgesic, antihypertensive, anthelmintic, anti-HIV, anti-convulsant, and spasmolytic properties.

Numerous studies have been conducted in the field of biochemical and pharmacological research to confirm the impressive effectiveness of benzimidazoles in combating various strains of microorganisms. Benzimidazole and its derivatives have shown great potential in the treatment of multiple diseases, gaining considerable recognition as important pharmacophores and privileged structures in medicinal chemistry. In order to create more powerful chemotherapeutic agents, several research endeavors have concentrated on the synthesis and evaluation of novel benzimidazole derivatives.

A comprehensive analysis of literature has revealed the importance of substitutions at positions 1, 2, and 5 of the benzimidazole ring in determining their pharmacological effects. This extensive review seeks to present a summary of the different derivatives of benzimidazole and their respective pharmacological activities.

2. Structure with properties of Benzimidazole.



- **Melting point:** 170°c to 171°
- **Molecular formula:** C6H7H2
- **IUPAC Name:** 1H-1,3-Benzimidazole compound.
- **Synonym:** 1H-Benzo[d] imidazole
- **Molecular weight:** 118.g/mole
- **Solubility:** soluble in alcohol, very slightly soluble in water.
- **Boling point:** 360°c
- **Uses :** Antiviral, Anticancer, Antiprotozoal, Antiulcer, Anti-oxidant.

3. Synthesis for Benzimidazole by o-Phenylenediamines

Requirements

- **Chemical:**

1.Formic acid(3 .48ml)

2. O – phenylenediamine(1g)

3. Sodium hydroxide(10%)

4. Charchol(2g)

• Glassware and apparatus:

1.Reflux condenser

2. Beaker

3. Glass rod

4. Spatula

5. Pertidish

6. Round bottom flasks

7. Water bath

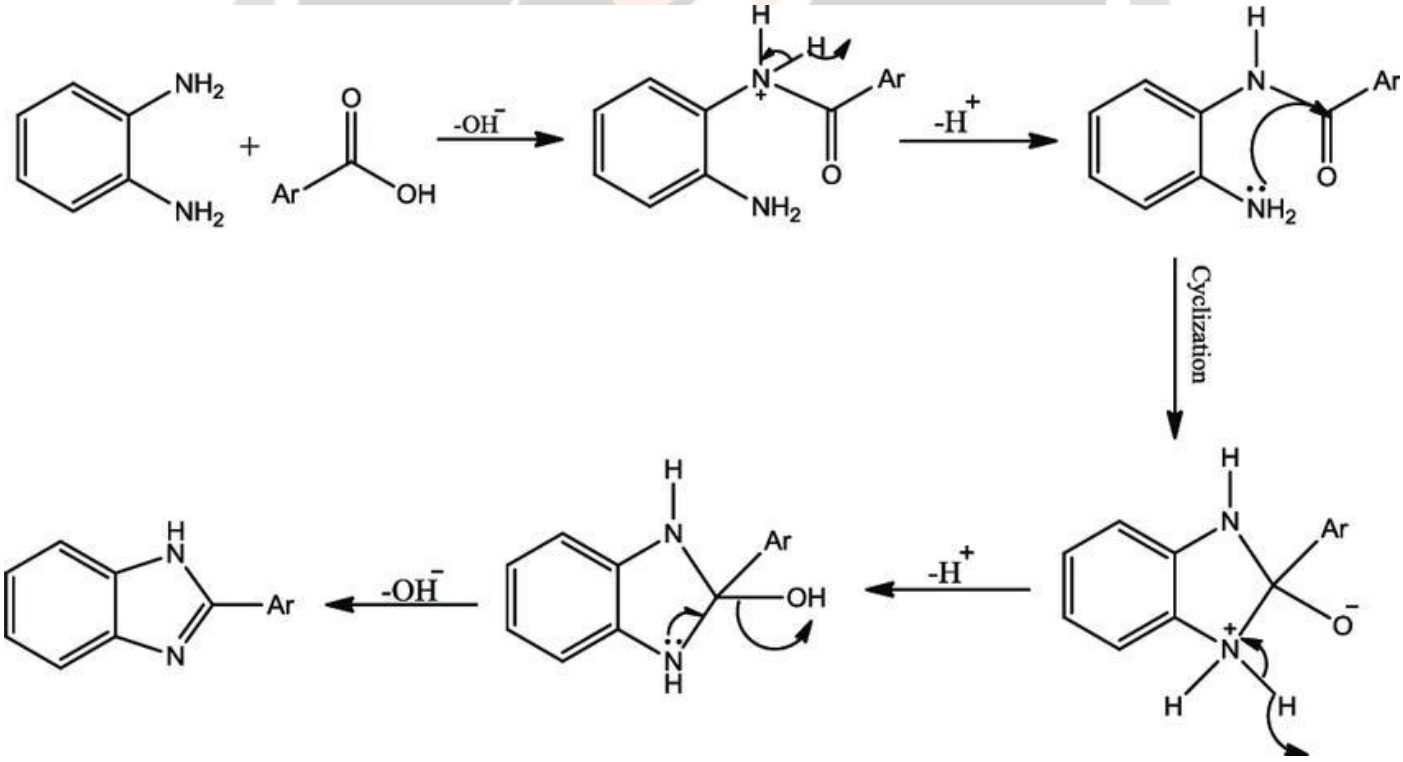
8. Measuring cylinder

9. Filter paper

10. Buchner funnel

Principle: The synthesis of benzimidazole is influenced by the Condensation type of reaction, which occurs when the two carbon-nitrogen bonds in benzimidazole are disconnected, resulting in the formation of o-phenylenediamine and formic acid. Consequently, by simply heating the o-phenylenediamine and formic acid, benzimidazole can be synthesized.

Mechanism Reaction Of Benzimidazole:



Procedure:

• O-phenylenediamine (1g) is reacted with 3.48ml of 90% formic acid in a round bottom flask. A round bottom flask is used to combine 1g of O-phenylenediamine with 3.48ml of 90% formic acid. The reaction between 1g of O-phenylenediamine and 3.48ml of 90% formic acid takes place in a round bottom flask.

• The mixture obtained was then subjected to heating in a water or sand bath for a duration of 2 hours. Following this, the reaction mixture should be allowed to cool to room temperature in the laboratory, after which 10% Sodium hydroxide solution should be added gradually with complete mixing until the mixture is slightly alkaline to red litmus.

• The Crude Benzimidazole was gathered through filtration and washed with chilled water.

• The pristine substance was acquired through the process of recrystallization in boiling water.

Recrystallization Benzimidazole:

• The synthesized product will be dissolved in 50ml of boiling water during the recrystallization process. Then, 2gm of decolorizing carbon will be added, and the mixture will be digested for 15 minutes.

• Quickly pass through a preheated Buchner funnel and flask connected to a pump. Chill the filtered liquid to approximately 10°C.

• Separate the benzimidazole using a filter, rinse with 25ml of chilled water, and then dry at a temperature of 100°C. The result will be pure benzimidazole with a melting point of 171-172°C.

4: Synthesis of benzimidazole:

Hoebrecker was responsible for the synthesis of the initial benzimidazole compound. [7] 2,5-Dimethylbenzimidazole was acquired through the reduction and dehydration process of 2-nitro-4-methylacetanilide.

The majority of benzimidazole syntheses commence with benzene derivatives containing nitrogen-containing groups positioned ortho to each other. In other words, the initial compound contains the designated function by formula. Numerous techniques have been documented for the production of benzimidazoles. The majority of these approaches entail the condensation of ortho-phenylenediamine and its derivatives with carboxylic acids or aldehydes.

Different methods for synthesizing benzimidazole derivatives have been discovered. One such method involves the condensation of o-phenylenediamine with ortho esters, using various Lewis acid catalysts. Some examples of these catalysts include ZrCl4, SnCl4, TiCl4, ZrOCl29H2O, and HFCl4.

Various synthetic methods for benzimidazoles have been categorized based on the initial substance of o-phenylene diamines[8].

4.1. By reaction with carboxylic acids

A review of the literature indicates that o-phenylenediamines readily undergo reactions with the majority of carboxylic acids to produce 2-substituted benzimidazoles, typically yielding very high amounts. This reaction is commonly conducted by heating the reactants together on a steam bath, heating them under reflux or at a higher temperature, or heating them in a sealed tube.[9].

Phillip's method is widely utilized[10] The synthesis of benzimidazoles commonly involves the condensation of o-diaminobenzenes with carboxylic acids or their derivatives. This method is typically carried out by heating the reagents together in the presence of concentrated hydrochloric acid. It is widely used for the preparation of a wide range of benzimidazoles. Hollan et al. have also reported a different reaction using the appropriate imidate ester (trichloroacetimidate) with o-phenylenediamine or its salt. This reaction specifically yields 2-trichloromethyl benzimidazole at room temperature, which serves as an important precursor for 2-carboxylic benzimidazoles [11].

Rithe and colleagues have successfully synthesized a range of 2-substituted benzimidazole derivatives with satisfactory yields through a convenient one-step reaction. This reaction involves the condensation of o-phenylenediamine (0.01 mol) and various aromatic acids (0.1 mol) in the presence of ammonium chloride as a catalyst at a temperature range of 80-90°C. The reaction exhibits a green and economically feasible approach[12].

Saberi has documented the production of 2-benzimidazoles using microwave irradiation and solvent-free conditions. This process is facilitated by alumina, silica gel, and zeolite HY as catalysts. In accordance with Scheme 6, a mixture of o-phenylene-diamine (2 mol) and aromatic, ali-phatic, or heterocyclic carboxylic acids (2 mol) is thoroughly combined with 50 mg of either alumina, silica gel, or zeolite in a mortar. The resulting mixture is then subjected to irradiation in an oven for a duration of 5-9 minutes at a power range of 160-560 W.[13].

4.2-By reaction with aldehydes

Under appropriate circumstances, aldehydes have the potential to undergo a reaction with o-Phenylenediamines, resulting in the formation of 2-substituted benzimidazoles.

The reaction is most effectively carried out under oxidative conditions due to the involvement of oxidation. This oxidation can be achieved by either exposing the reaction to air or, more conveniently, by utilizing other oxidizing agents such as cupric acetate. Weidenhagen was the first to introduce this particular reagent. Weidenhagen's approach involves reacting the diamine and aldehyde in either water or an alcoholic solution in the presence of cupric acetate or a similar cupric salt. The cuprous salt of the benzimidazole then separates, and it can be easily decomposed into the free benzimidazole and cuprous sulfide using hydrogen sulfide. The sulfide can be easily removed through filtration. By employing Weidenhagen's method, excellent yields of 2-substituted benzimidazoles can be obtained.

Various conditions have been reported for the condensation of phenylenediamines with aldehydes. It has been demonstrated that this reaction can be accomplished in the presence of sodium Metabisulphite. [14].

The reaction reported by Suheyla et al. involves the pre-formation of the bisulfite adduct of the aryl aldehyde in order to prepare Benzimidazole. In this process, the aryl aldehyde is added separately to an aqueous solution of sodium metabisulfite, which is dissolved in ethanol [15]; The precipitated adduct resulting from the reaction was filtered and dried. Subsequently, o-phenylenediamine in DMF was introduced to the adduct, and the resulting mixture was heated at 130oC for a number of hours to produce benzimidazole, or by heating in the presence of nitrobenzene. [16]. Mann and colleagues employed a blend of unsubstituted or substituted phenylenediamine and suitable aldehyde in nitrobenzene, heated at 140°C. The resulting mixture was then cooled, filtered, and water added, resulting in the formation of benzamidazole.

The synthesis of benzimidazole derivatives has been reported by Venkateswarlu et al. They utilized lanthanum chloride as a highly effective catalyst for the one-pot synthesis of 2-substituted benzamidazole derivatives. This synthesis involved the reaction of o-phenylenediamine and various aldehydes in the presence of 10 mol% lanthanum chloride in acetonitrile at room temperature. [17].

Lin et al. synthesized benzimidazoles through a Direct one-step method, which involved the use of air as an oxidant. This alternative approach utilized Phenylenediamines and aldehydes as starting materials.[18].

Rushi et al. have reported 2-substituted benzimidazoles have been synthesized in excellent yields in a single pot under Solvent-free conditions from o-phenylenediamine and aldehy- Des in the presence of a catalytic amount of indium triflate [In(OTf)3] at room temperature [19].

A range of benzimidazole derivatives were successfully synthesized with good to high yields through the reaction of o-phenylenediamine and various aromatic aldehydes. This synthesis was carried out at 50°C using sodium hexafluroaluminate, Na3AlF6, as a highly effective catalyst.

4.3. By reaction with esters

The formation of benzimidazoles can also be achieved by reacting o-phenylenediamines with esters. The reaction between esters and o-phenylenediamines was initially studied by Von Niementowski. When equimolecular quantities of 3,4-diaminotoluene dihydrochloride and ethyl formate are heated in a sealed tube at 225°C for 3 hours, 84% of 5(or 6)-methylbenzimidazole hydrochloride is obtained. [13].

The ethyl chloride formed does not further alkylate the product. Under the same conditions, ethyl acetate only produces a low yield of 2,5(or 2,6)-dimethylbenzimidazole, and esters of higher molecular weight acids would likely result in poor yields of benzimidazoles. To obtain a high yield of 2-Methylbenzimidazole, one can let a mixture of o-phenylenediamine and ethyl acetate stand.

4.4 By reaction with amides

Only a small number of amides have been employed in the production of benzimidazoles. Nevertheless, favorable results have been achieved in the majority of instances. The amides utilized in these cases.

When o-phenylenediamine hydrochlorides and benzamide are heated to 240–250°C in equimolecular amounts, a nearly complete yield of 2-phenylbenzimidazole is obtained.

4.5 By reaction with acid chlorides

Benzimidazoles or monoacylated or diacylated o-Phenylenediamines can be obtained by treating o-phenylenediamines with acid chlorides, depending on the experimental conditions. If acetyl chloride is reacted with 3,4-diaminotoluene in a benzene solution without cooling, it results in the formation of 2,5 (or 2,6)-dimethylbenzimidazole. However, when the reaction is carried out with cooling, diacetyl-o-phenylenediamine is produced.

The majority of reactions involving o-phenylenediamines and acid chlorides to produce benzimidazoles have utilized aroyl chlorides. Typically, these reactions are conducted by heating the components together at temperatures ranging from 200 to 220°C, under reflux conditions, or on a steam bath in the presence of pyridine or a similar basic substance. Due to the

acylation potential of benzimidazoles lacking a grouping in the l-position with acid chlorides, most reactions have employed N-substituted o-phenylenediamines, compounds obtained through the reaction of acid .

5.Conclusion:

Benzimidazoles exhibit one of the most valuable biological activities. They find application in numerous therapeutic uses, including as anti-inflammatory, anti-anxiety, and antimicrobial compounds.

This review provides chemists with efficient and cost-effective methods for synthesizing benzimidazole through the condensation reaction between ortho-phenylene diamine and various compounds under different conditions. It serves as a valuable resource for chemists and professionals in this field, enabling them to obtain firsthand information on benzimidazole synthesis. Moreover, it aids in the development of protocols for large-scale production of benzimidazoles, with the potential for continuous improvement and the creation of new, economically viable, and environmentally friendly protocols for the synthesis of important pharmacophores based on benzimidazoles in the future.

6: Reference

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