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Synthesis Characterization of Imidazole Derivatives and Benzoin Moiety

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Abstract:

Medicinal chemistry or pharmaceutical chemistry is a discipline at the intersection of chemistry it involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also include the study of existing drugs their biological properties and their quantitative structure-activity relationship (QSAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products.

In other words Medicinal chemistry is defined as a discipline which concerned with determination of the influence of chemical structure on biological activity. In medicinal chemistry one can synthesize new compound with the several modification in the main structure and then can identify their biological activity.

INTRODUCTION

Reaction with oxidizing and reducing agents

Imidazole itself is stable to auto oxidation and to the action of chromic acid but is attacked by epotassium permanganate. However, imidazole generally opens its ring to form oxamide with H_2O_2 . Reaction of imidazole with oxygen in the presence of sensitizer (single oxygen) gives an imidazoline derivative. Imidazolium dichromate, which is a mild oxidizing agent, has been employed for the oxidation of allylic and benzylic alcohol to the corresponding carbonyl compound.

CHEMISTRY OF IMIDAZOLE

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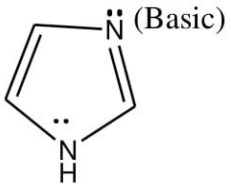
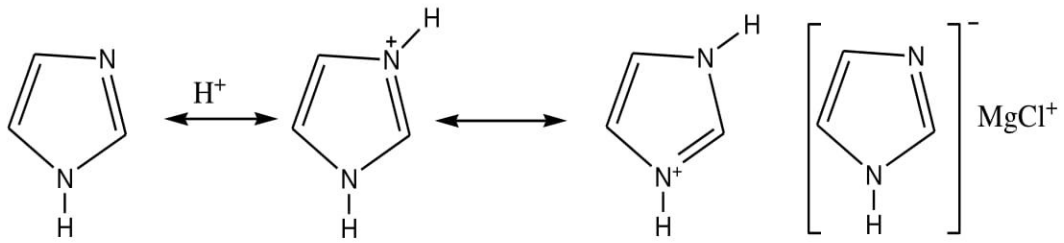


(Acidic)

(3)

Imidazoles have properties which are similar to both pyrrole as an acid and pyridine as a base (3). The electrophilic reagent would attack on the unshared electron pair on N-3 position, but not that on the 'pyrrole' nitrogen since it is the part of the aromatic sextet. While the imidazole ring is rather susceptible to electrophilic attack on an annular carbon, it is much less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituent's elsewhere in the ring. In the absence of such activation the position most probable site to nucleophilic attack is C-2. The fused benzene ring in benzimidazole provides sufficient electron withdrawl to allow a variety of nucleophilic substitution reaction at C-2. The overall reactivity of imidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance. These predict electrophilic attack in imidazole at N-3 or any ring carbon atom, nucleophilic attack at C-2 or C-1 and also the amphoteric nature of the molecule. In benzimidazole the nucleophilic attack is predicted at C-2. The reactivity of benzimidazole ion at the C-2 position with nucleophiles is enhanced compared with the neutral molecule.

Reaction with acids



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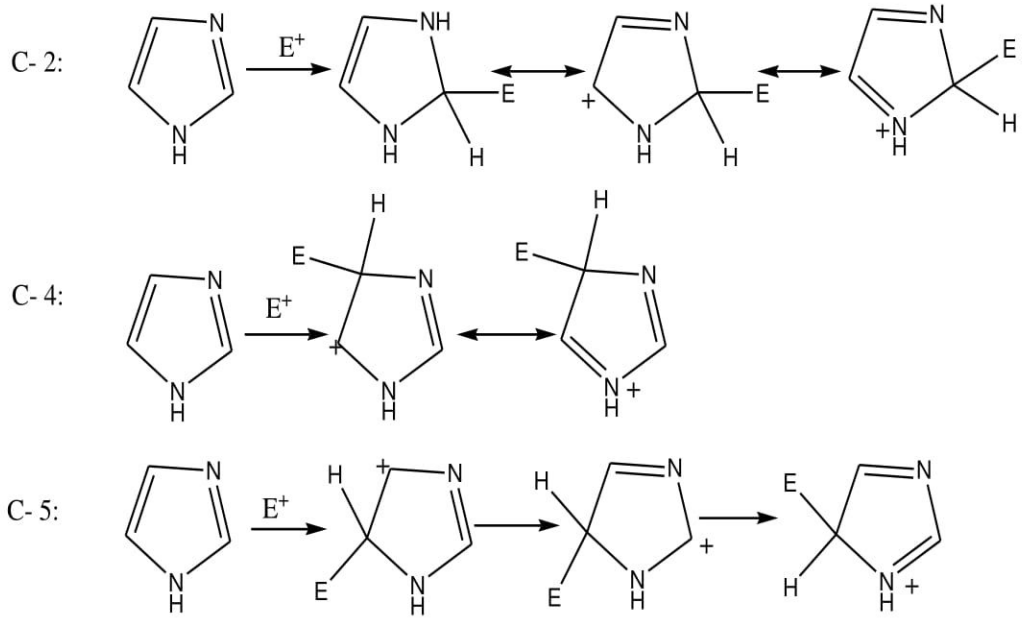
Usually imidazole gives crystalline salt after reacting with acids. It also possesses weakly acidic properties which is pseudo acidic property and thus forms salts of the following type with Grignard reagent or more metals. Imidazole forms silver salt with ammonical silver nitrate, which is sparingly soluble in water (4).

Electrophilic substitution

Imidazole possesses increased reactivity towards electrophilic attack. It is more susceptible to electrophilic attack than pyrrazole and thiazole and more so than from furan and thiophene also. From the following resonance structure of the intermediate ion; it is evident that the attack takes place at the 4th and 5th position in imidazole ring. It may be noticed that the attack at C-2 involves a canonical form which is highly unfavoured at positive N at position-3 (5).

Halogenation of imidazole is very complex and varies considerably depending on the substrate, reagent and reaction condition (Suzuki, *et al,* 1986; Suzuki, *et al,* 1992; El-Feky, *et al*, 1995; Isikdag, *et al,* 1999).



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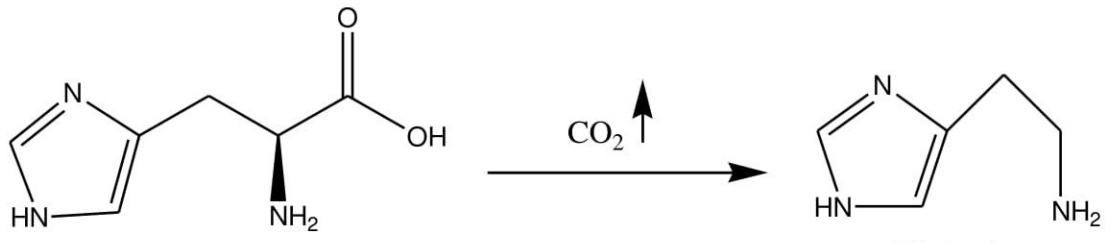
AMPHOTERISM

Imidazole is amphoteric. So, it can work as both an acid and as a base. As an acid, the pKa value of imidazole is 14.5, which makes it less acidic than carboxylic acids, phenols, and amides, but slightly more acidic than alcohols. The acidic proton is located on N-1 position. As a base, the pKa value of the conjugate acid is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is N-3. Protonation gives the imidazolium cation, which is symmetrical (Baroniya, et al, 2010).

Biological importance and application of imidazole



Histidine (8)

Histamine (9)

Imidazole is incorporated into many important biological molecules. The most important is the amino acid histidine (8), which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital role in the structure and binding functions of hemoglobin. Histidine can be decarboxylated to histamine (9), which is also a common biological compound. It is a component of the toxin that causes urticaria, i.e. allergic (Baroniya, 2010). The relationship between histidine and histamine are shown above:

One of the applications of imidazole is in the purification of His-tagged proteins in immobilized metal affinity chromatography (IMAC). Imidazole is used to elute tagged proteins bound to Ni ions attached to the surface of beads in the chromatography column. An excess of imidazole is

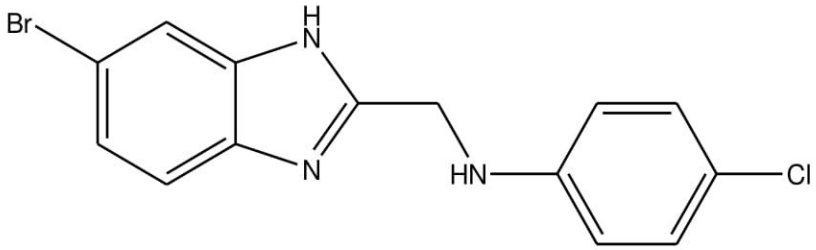
passed through the column, which displaces the His-tag from nickel co-ordination, freeing the His-tagged proteins.

Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans that stimulate the central nervous system. It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA activities.

A number of substituted imidazoles, including cotrimoxazole, are selective inhibitors of nitric oxide synthase, which makes them interesting drug targets in inflammation, neurodegenerative diseases and tumors of the nervous system (Castano, *et al*, 2008; Bogle, *et al,* 1994) Other biological activities of the imidazole pharmacophore relate to the down regulation of intracellular Ca^{++} and K^{+} fluxes, and interference with translation initiation (Khalid, *et al,* 2005).

Anti-Inflammatory Activity

Kavitha, *et al* 2010 has synthesized a series of 2-methylaminibenzimidazole derivatives and newly synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound shows analgesic activity and compared with standard nimesulide drug.



N-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-chloroaniline

Yashoda *et al*, 2009 synthesized a series of 1-substituted 2, 4, 5 triphenyl imidazoles by the reaction equimolar mixture of 2, 4, 5 triphenyl imidazole with chloro compound in the presence of anhydrous potassium carbonate. Anti-inflammatory activity was screened by carageenan induced rat paw oedema method. Antimicrobial activity was screened by disc-plate method. All the compounds showed mild to moderate activities.

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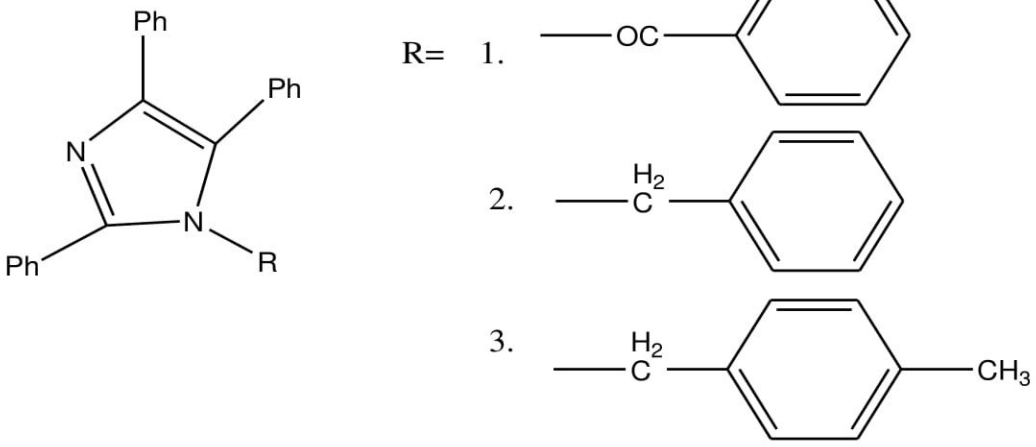
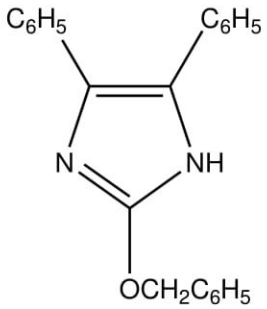


Puratchikody *et al*, 2007 studies on 2-substituted-4, 5-diphenyl-1H-imidazoles and checked the anti-inflammatory activity based on Carrageenan-induced paw edema method. This compound shows maximum activity and indomethacin used as reference drug.



2-(benzyloxy)-4,5-diphenyl-1*H*-imidazole

SYNTHETIC WORK

Material and methods

The melting points of the synthesized derivatives were estimated by the capillaries method and are uncorrected. Spectral analysis of newly synthesized compounds was done. IR Spectra (KBr), ^{1}H NMR ($CDCl_3$) and the mass spectra (dry helium) of synthesized compounds were recorded from CDRI, Lucknow.

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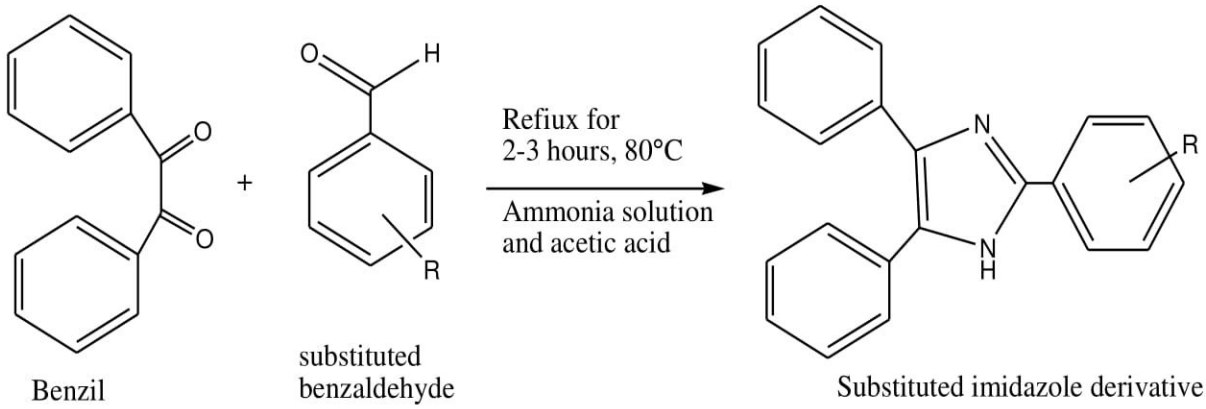
General Procedure

Step 1

Accurately weighed quantity of benzil (2.65 gm), ammonia solution (5 ml) and substituted benzaldehdye (1.5 ml) were taken and dissolved in 50 ml glacial acetic acid in a 100 ml RBF. The reaction mixture was heated to reflux for 5 hrs on heating mantle with occasionally shaking. After completion of reaction 300 ml cold water was added to reaction mixture which resulted in precipitation of product. The mixture was kept in fridge overnight. The product immediately filtered and neutralized with 5% ammonium solution. The compound was recrystallized and purified from absolute ethanol to yield colourless or pale yellow crystalline compound.



Benzil

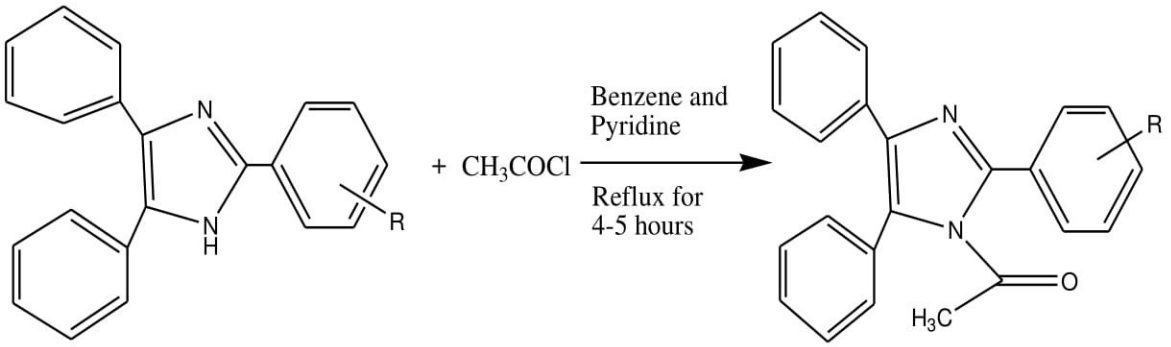
substituted
benzaldehyde

Substituted imidazole derivative

Step 2

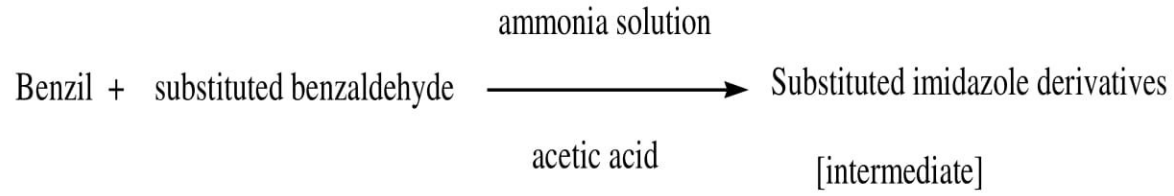
Substituted imidazole derivatives (0.5 gm) and freshly prepared acid chloride solution (2.5 ml) were taken in RBF with benzene (30 ml) as a solvent and pyridine (0.5 ml) as a catalyst for 4-5 hours. Completion of reaction was checked by the single spot on TLC. Cool the reaction mixture on room temperature and then pour it into the ice water. Shake the mixture well in crushed ice and kept it in cold temperature for overnight. The compounds

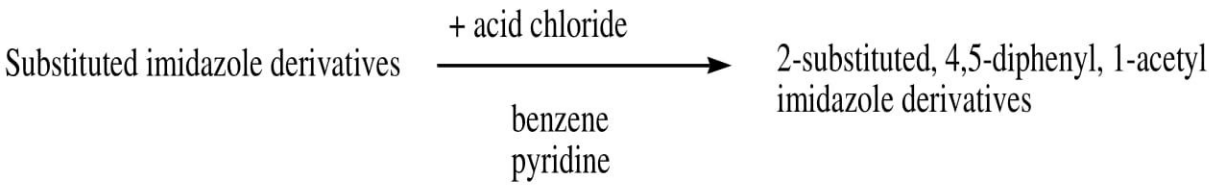
were isolated and collected by the filtration. Product was recrystallized by ethanol. A coloureless product was obtained.



2-(substituted phenyl),4,5- diphenyl, 1-acetyl imidazole derivative

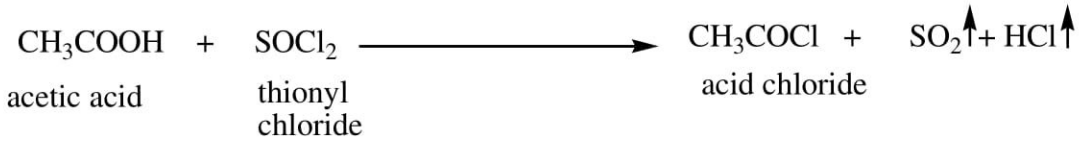
Scheme:





Synthesis of acid chloride:

Excess amount of thionyl chloride (4 ml) was taken in the RBF with acetic acid (2.5 ml) at 80°C on heating mantle and refluxed it for 2-3 hrs. Reaction was carried in the fuming chamber due to its corrosive nature. Precautions were taken during the reaction because thionyl chloride is a hazardous chemical. Excess thionyl chloride was removed by distillation. And the completion of reaction was estimated by the TLC.



Pharmacological Screening

Antimicrobial Activity

Throughout history, there has been a continual battle between humans and the multitude of microorganisms that cause infection and disease. Bubonic plague, tuberculosis, malaria and human immunodeficiency virus/acquired immunodeficiency syndrome pandemic have affected substantial portions of the human population causing significant morbidity and mortality. In the beginning around the middle of the 20th century, major advances in antibacterial drug and other means of infections helped to turn the tide in favor of human. Almost as soon as antibacterial drugs were deployed, bacteria responded by manifesting various forms of resistance. As antimicrobial usage increased, so did the level and complexity of the resistance mechanisms exhibited by bacterial pathogens (Tenover, 2006). The introduction of antibiotics for the chemotherapy of bacterial infections has been the one of the most important medical achievements of the past 50 years. However, the emergence of bacterial resistance to antibiotics undermines the therapeutic utility of existing agents, creating a requirement for the search of new antibacterial drugs. Plants remain the most common source of antimicrobial agents. Many of the existing synthetic drugs cause various side effects. Hence, drug development from plant based compounds could be useful in meeting this demand for newer drugs with minimal side effects. Antibacterial active principles isolated from higher plants appear to be one of the most important alternative approaches to contain antibiotic resistance and the management of diseases. Large scale evaluation of local flora exploited in traditional medicine for various biological activities is a

necessary first step in the isolation and characterization of active principle and further leading to drug development (Satish *et al.*, 2008).

Fungi are significant destroyers of foodstuffs and grains during storage which render them unfit for human consumption by retarding their nutritive value. More than 300 fungal metabolites are reported to be toxic to human and animals. The main toxic effects are carcinogenicity, genotoxicity, terratogenicity, nephrotoxicity, hepatotoxicity, reproductive disorders and immunosuppressant. Plant metabolites appear to be one of the better alternatives as they are known to have minimal environmental impact and danger to consumers in contrast to the synthetic pesticides (Satish *et al.*, 2007).

CHEMISTRY

Synthesized derivatives (IMD 1- IMD 10)

New imidazole derivatives were synthesized on the basis of **Radiszewski Synthesis.** In this research we synthesized imidazole derivatives by refluxing benzil with various substitutes of benzaldehyde. According to the literature reviews substitutes of benzaldehyde gives more active agents. Benzil was accurately weighed as required and dissolved in the little amount of solvent acetic acid and then substitute of benzaldehyde was dissolved in acetic acid with few percent of ammonia solution. The reaction was refluxed for 4-5 hours using heating mantle. Product was collected after pouring the reaction mixture into the ice water and then recrystallized and purified by ethanol.

2-substituted phenyl, 4, 5 diphenyl 1-*H* imidazole derivatives were synthesized in first step which further reacted with acid chloride. It was refluxed for 3-4 hours in the presence of pyridine as a catalyst and with benzene as a solvent. After cooling the reaction mixture at room temperature it was poured into the crushed ice and shaked and then it was kept in fridge overnight. After a day it was collected after filteration and recrystallized by

ethanol. The scheme was established by melting point, TLC, NMR, IR, Mass spectra. Then compounds were screened for antibacterial and antifungal activity.

CONCLUSION

Newly synthesized imidazole (1, 3-diaza-2, 4-cyclopentadiene) derivatives were found good antifungal and antibacterial agents. Some of them are promising and need to be further investigated to get better agents. Imidazole is a better nucleus which may be used further for good and improved antimicrobial activity in future. Structures of imidazole derivatives were confirmed by IR, ^{1}H NMR and Mass spectroscopy studies. The results of antimicrobial screening showed that all compounds possess activity against all organisms used. The compounds show good antibacterial activity against gram negative and gram positive bacteria, respectively. Nitro-imidazoles show activity against only anaerobes bacterias such as *Escherichia coli* and *Staphhylococcus aureus*. Other remaining compounds show moderate activity with reference compound Ampicillin and Fluconazole. Compounds which have halo-substitution show good antifungal activity. As we consider all results obtained from antibacterial and antifungal tests together we can say that all imidazole derivatives tested are active against bacteria and fungi.

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