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Review Paper

Imidazole and its derivatives and Importance in the Synthesis of Pharmaceuticals: A Review

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Abstract

The term "Imidazole" has gained importance in the modern world with its ability to explore various pharmacological potentials. The importance of the term 'Imidazole" and its derivates are popular since past few years with the synthesis of pharmaceuticals and treatment of various diseases. The imidazole ring occurs in a number of naturally occurring compounds, and very widely distributed in essentials amino acids, L-histidine and its derivatives have powerful pharmacological properties. Purins, present in living systems contain the imidazole ring.

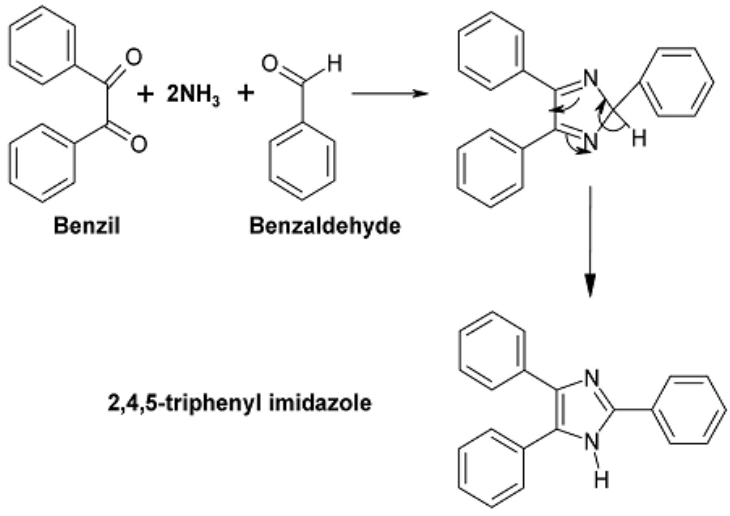
Keywords: Imidazole, antimalarial antibacterial, anticancer, anti-fungal.

Introduction

Imidazole (1, 3-diaza-2,4-cyclopentadiene) is a planner five-member ring system with 3C and 2N atom in 1 and 3 positions. A compound with molecular formula $C_3H_4N_2$. The systemic name for the compound is 1, 3-diazole, one of the annular N bear a H atom and can be regarded as a pyrole type N. It is aromatic, basic in nature: less basic than ammonia and more basic than pyridine. It exhibits tautomerism and 4 and 4 and 5 positions are equivalent. Imidazole is incorporated into many important Biological molecules. The most pervasive is the amino acid "histidine", which has an imidazole side chain. Imidazole has become an important part of many pharmaceuticals synthetic imidazoles are present in many antiprotozal, antifungal, fungicides and antihypertensive medications.

A number of methods for the preparation of simple as well as substituted imidazooles.

Radiszewski Synthesis The condensation of a benzil and benzaldehyde in the presence of ammonia yield 2, 4, 5-triphenylimidazole[1-3].



Scheme-1

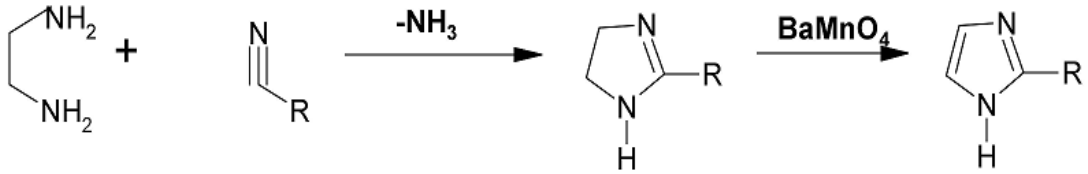
Dehydrogenation of Imidazoline: Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction with $BaMnO_4$ in the presence of sulphur yield 2-substituted imidazoles[4].

From-Halo Ketone: This reaction involves an interaction between an imidine and alpha halo ketones. Similarly, amidine reacts with acyloin or alpha halo ketones to yield imidazoles[4].

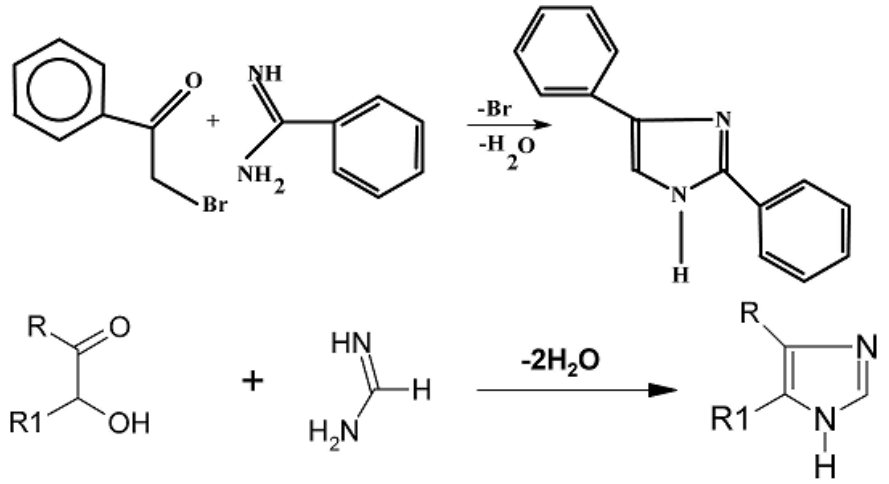
Wallach Synthesis: When N, N′ -dimethyloxamide is treated with phosphorus pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid give N-methyl imidazole[4-8].

Markwald Synthesis: This method involves the action of potassium thiocyanate on α-aminoaldehyde or ketone. The resulting imidazoline thione is desulphurised with Rancy nickel or by oxidation with nitric acid[4-8].

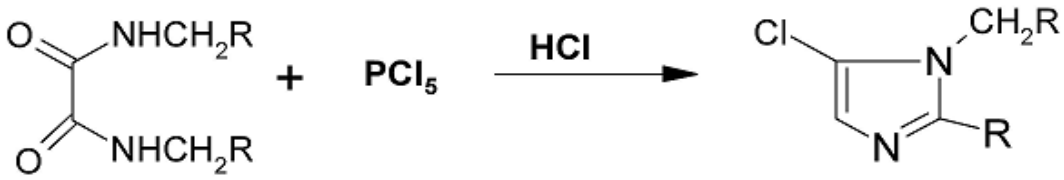
Scheme-7: Imidazole itself can be prepared by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and, then heating the dicarboxylic acid with quinoline in the presence of copper[9].



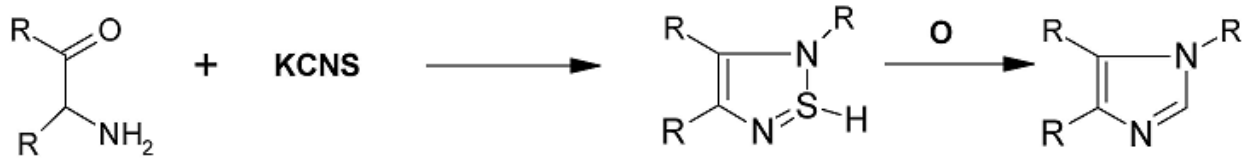
Scheme-2



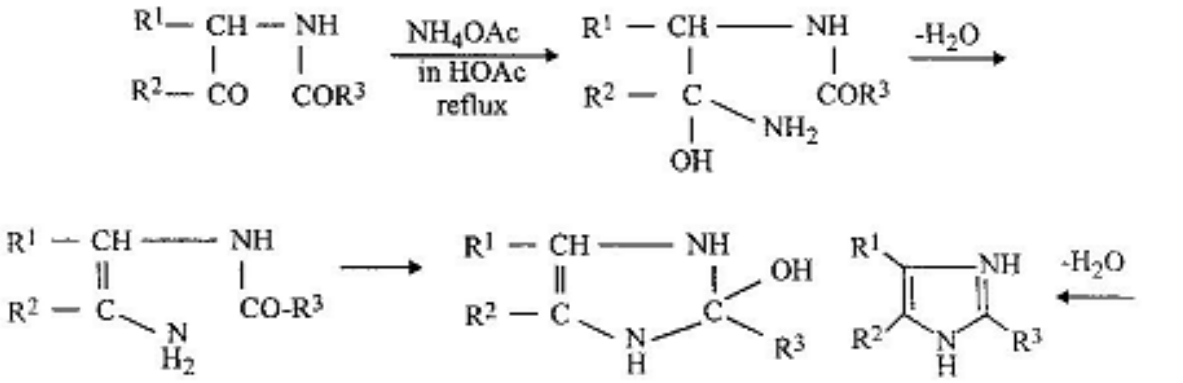
Scheme-3



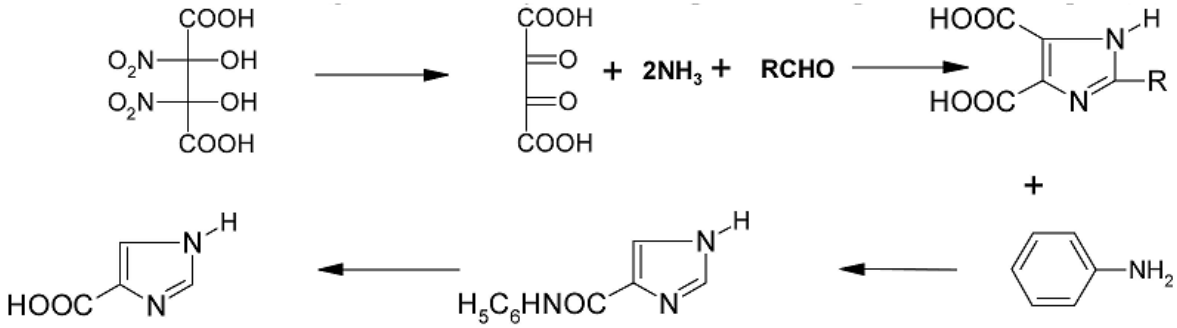
Scheme-4



Scheme-5

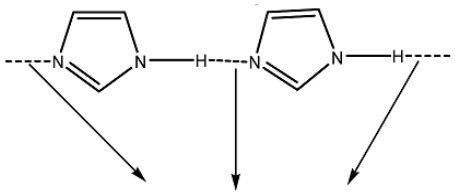


Scheme-6
Cyclisation of α-Acylamino Ketones with Ammonium Acetate[9]



Scheme-7

Physical Properties: Imidazole show amphoteric properties and has pKa of 7.2 more than pyrazole and pyridine. Imidazoles are an aromatic compound possessing a resonance value of 14.2 K cal/ mol, which is almost half the value for pyrazole. The electrophillic substitution occurs frequently in imidazole and nucleophillic substitution happens in the presence of electron withdrawing group in its nucleus. Imidazoles have M. pt. 90° C, it is a weak base and tautomeric substance, since position 4 and 5 are equivalent.



Intermolecular H- bonding

1,2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solvent less microwave-assisted enabled synthesis of 4,5-disubstitued imidazoles.

Literature review for various synthetic Approaches

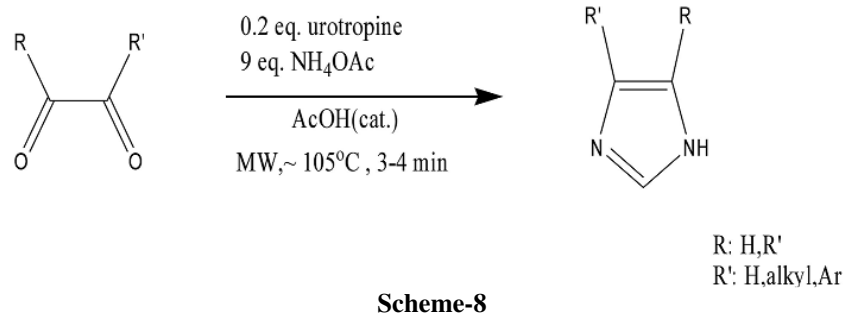
Synthesis of 4,5-Substitued Imidazoles: 1,2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solvent less microwave-assisted enabled synthesis of 4,5-disubstitued imidazoles scheme-8[10].

Synthesis of 2,4(5)-. Diarylimidazoles: A simple and efficient approach for the Synthesis of biologically active 2, 4(5)-diarylimidazoles by parallel synthesis scheme-9[11].

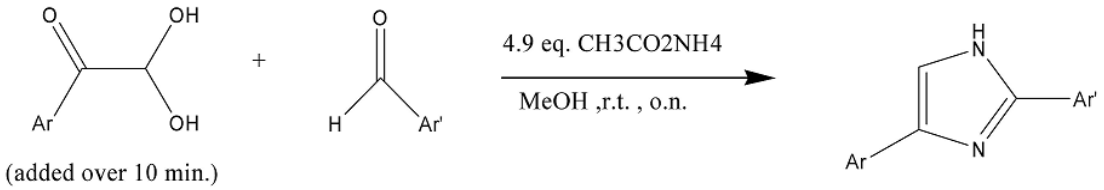
Synthesis of 2, 4, 5-triaryl imidazoles: An improved and rapid one-pot synthesis of 2,4,5-triaryl imidazoles at room temperature. This one-pot methodology offers excellent isolated yields, simple work up procedures and efficient recovery and recycling of the ionic liquid scheme-10[12].

An Efficient Preparation of 2- Imidiazolines: 2- Imidiazolines were easily prepared in good yields from the reaction of aldehyde and ethylenediamine with iodine in the presence of potassium carbonate. The 2- imidiazolines were smoothly oxidized to the corresponding imidiazoles in good yields using (diacetoxyiodo) benzene at room temperature scheme-11[13].

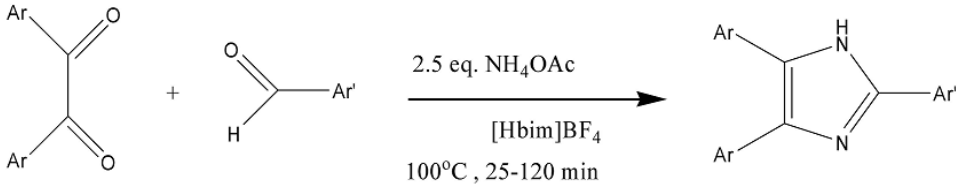
Synthesis of N-aryl derivative of imidazole: A copper-catalyzed N-arylation reaction of imidazole proceeds under very mild conditions in the absence of additional ligand. This protocol tolerates an array of thermally sensitive functional groups, but also achieves high chemo selectivity scheme-12[14].



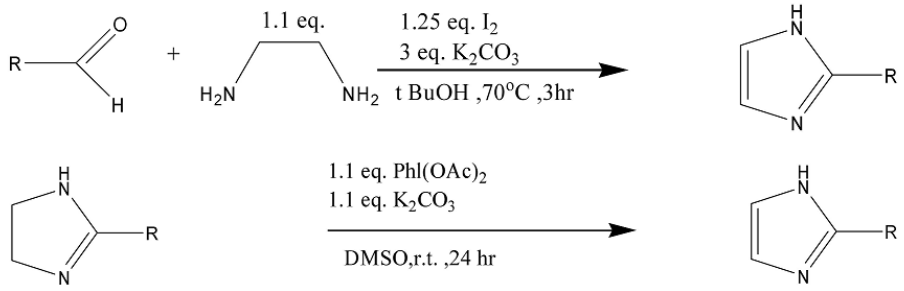
Scheme-8



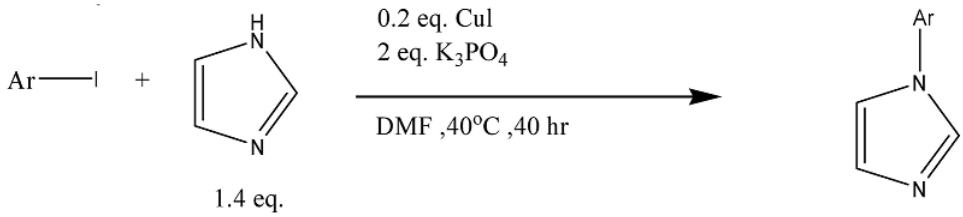
Scheme-9



Scheme-10



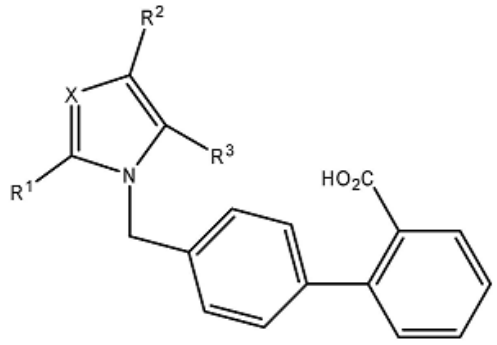
Scheme-11



Scheme-12

Uses of Imidazole in Pharmacological activities: Imidazole derivatives have a wide range of pharmacological activity. Imidazole and its derivative are reported to have, analgesic and anti-inflammatory activity, cardiovascular activity, anti-neoplastic activity, anti- fungal activity, enzyme inhibition activity, antianthelmintic activity, anti-filarial agent, anti- viral activity and anti- ulcer activity. Other than their pharmacological actions they also function as dyestuffs catalysts and polymerizing agents. Simple nitro derivatives of imidazole are effective as antibacterial agents. They also are useful in treating infections caused by protozoans, such as Trichomonus. Imidazole has benefitted several patients through various forms of treatment in diagnosing their diseases. The research on derivatives of imidazole was existing in the past and is continuously developing and varied new potentialities are emerging.

Biological activity of Imidazole: Angiotension II receptor Antagonists: The hydroxymetyl substituent at the 4 position and the carboxy substituent at the 5 position in the imidazole nucleus are favorable for the activity.



X = N, CH ; R^1 =Et, Pr, Bu

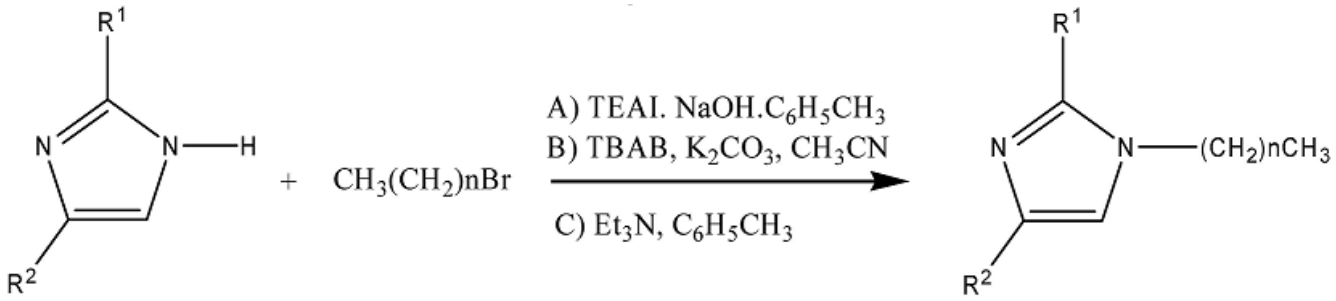
R^2, R^3 = -CH_2OH, CO_2H

N-Alkylated derivatives of imidazole as antibacterial agents: Antibacterial effects of 1-alkylimidazole derivatives increase as the number of carbons in the alkyl chain increase up to nine carbons.

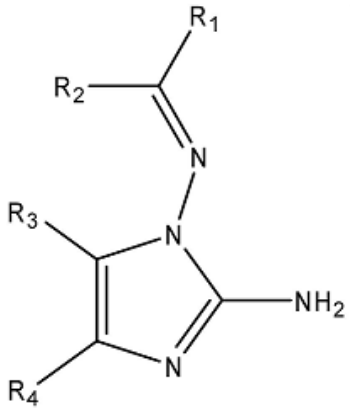
2-Amino-1-arylidenamino imidazoles as orally Active Anticancer agent: 2-Amino-1-arylidenamino imidazoles, a novel class of orally active microtubule-destabilizing anticancer agents.

Conclusion

On the basis of study, imidazole derivatives show various activity against antimicrobial, anti-inflammatory, analgesic, antituberular, anticancer etc. The possible improvements in the activity can be futher achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic compounds. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could expert direct inhibitory effects on membranes, without interference with sterols and sterols esters. Various recent new drugs developments in imidazole derivatives show better effect and toxicity.



Scheme-13
2-Amino-1-arylidenamino imidazoles as orally Active Anticancer agent



R1, R2, R3, R4 = hydrogen, aryl or heterocyclyl

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