Review Article

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VARIOUS APPROACHES FOR SYNTHESIS OF IMIDAZOLE DERIVATIVES

Bharti Ashish*, Pandeya S.N.
Department of pharmacy, Saroj Institute of Technology & Management, Sultanpur road, Lucknow, U.P., India

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ABSTARCT
Imidazole, a five-membered heterocycle having three carbon atoms, two nitrogen atoms, and two double bonds, having efficient antimalarial, anti-inflammatory, antibacterial activity against *Escherichia coil*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, anti-cancer, mutagenic activity against *Salmonella typhimurium*, antifungal, antimicrobial, insecticidal, anti-allergic activity etc. The presence of heterocyclic structures exerts various physiologic effects on the body. In the present study we have reviewed several newer approches of synthesizing the substituted imidazole derivatives via catalytic reaction & by the application of various suitable reagents
KEYWORDS: (Imidazole, Synthesis of 4, 5-Substituted Imidazoles, Copper-Catalyzed Cross-Cycloaddition, Angiotensin II receptor antagonists & other biological activities.)

***Author for Correspondence**
M. Pharm student, Email: ashish_bharti22@yahoo.co.in

INTRODUCTION

The heterocycles can be conveniently defined as cyclic organic compounds in which one or more of the ring carbon atoms have been replaced by another element such as N, O, or S. They may be either simple aromatic rings or non-aromatic rings. Some examples are pyridine (C5H5N), pyrimidine (C4H4N2) and dioxane (C4H8O2). More than half of the compounds produced by nature have heterocyclic rings incorporated in their structure.

Heterocycles are found in fossil fuels. Heterocycles containing sulfur and/or nitrogen atoms are useful as components of functional materials since heteroatom's in their rings are helpful to stabilize ions or ion radical species, and extended π-conjugation decreases columbic repulsion. In addition intermolecular interactions caused by heteroatom contacts can be expected to form novel molecular assemblies.

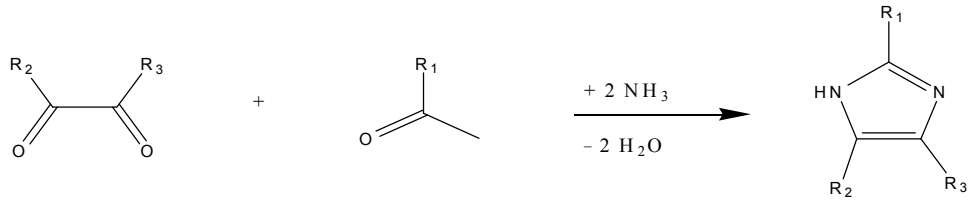
Heterocyclic nitrogen's play in turn an important role in coordination chemistry. Ring-fused heterocycles which contain more than one nitrogen atom are key structures in a large variety of biochemical processes. For example, purines, pteridines and flavines as well as their metal complexes play an important role in many enzymatic reactions. These quinoxaline-type ligands can act as either neutral or anionic chelators and, in addition, could possibly act as bridging ligands.

This leads one to expect that these ligands will exhibit various coordination modes in metal complexes and it is even possible that they can function as controlling ligands in catalytic reaction.

Imidazole is an organic compound with the formula $C_3H_4N_2$. This aromatic heterocyclic is classified as an alkaloid. Imidazole refers to the parent compound whereas imidazoles are a class of heterocycles with similar ring structure but varying substituent's.

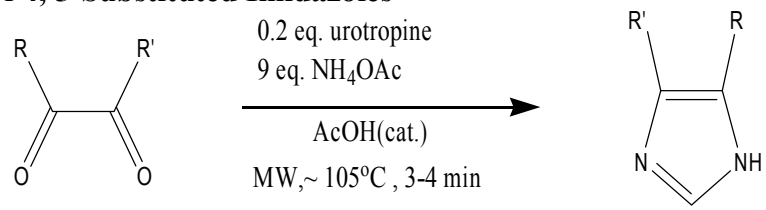
This ring system is present in important biological building blocks such as histidine, and the related hormone histamine. Imidazole can serve as a base and as a weak acid. Many drugs contain an imidazole ring, such as antifungal drugs and nitroimidazole

Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s. His synthesis, as shown below, used glyoxal and formaldehyde in ammonia to form imidazole. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles[1]



LITERATURE REVIEW FOR VARIOUS SYNTHETIC APPROACHES

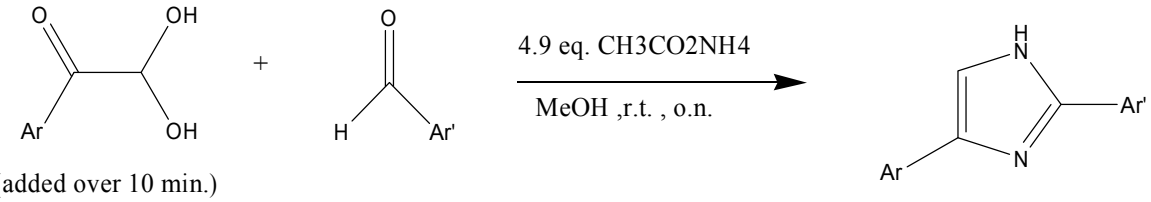
Scheme 1- Synthesis of 4, 5-Substituted Imidazoles



R: H,R'
R': H,alkyl,Ar

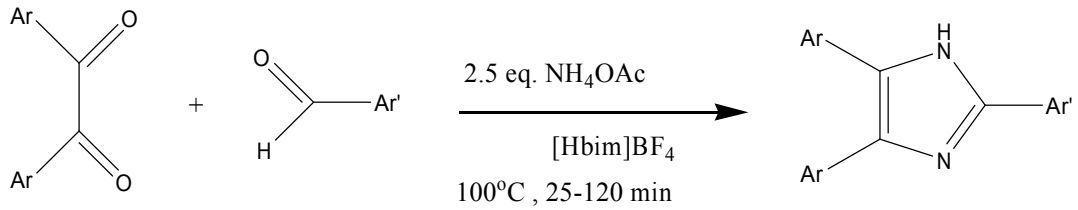
Starting from 1, 2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solvent less microwave-assisted enabled synthesis of 4, 5-disubstituted imidazoles.[2]

Scheme 2-Synthesis of 2, 4(5)-Diarylimidazoles



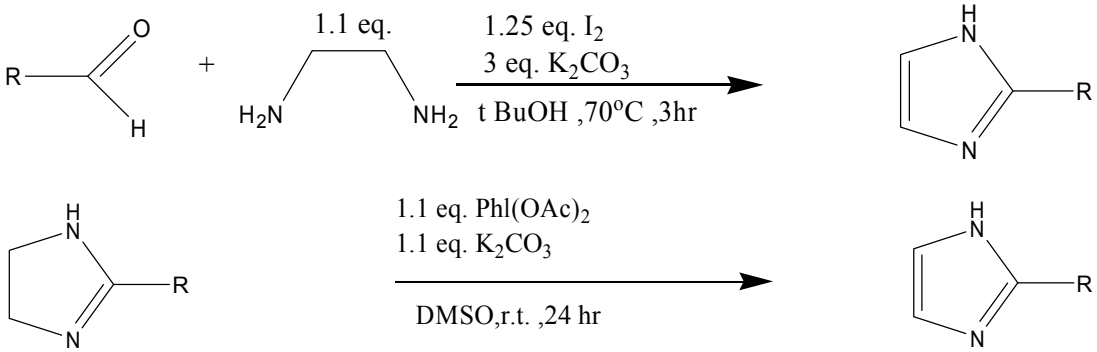
A simple and efficient approach for the synthesis of biologically active 2, 4(5)-diarylimidazoles by parallel synthesis.[3]

Scheme 3- synthesis of 2, 4, 5-triaryl imidazoles



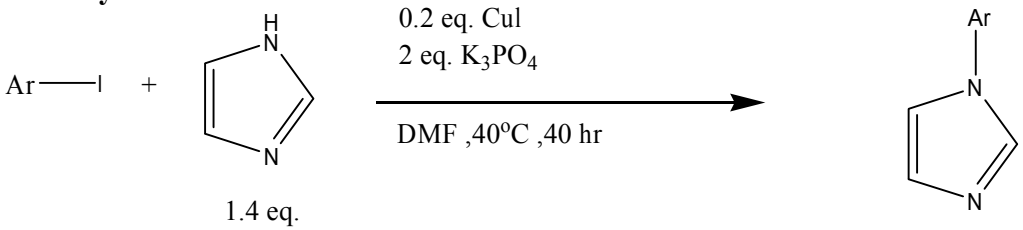
An improved and rapid one-pot synthesis of 2, 4, 5-triaryl imidazoles at room temperature. This one-pot methodology offers excellent isolated yields, simple work up procedures and efficient recovery and recycling of the ionic liquid.[4]

Scheme 4-An Efficient Preparation of 2-Imidazolines



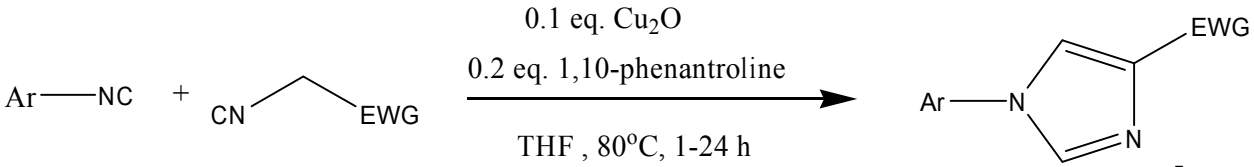
2-Imidazolines were easily prepared in good yields from the reaction of aldehydes and ethylenediamine with iodine in the presence of potassium carbonate. The 2-imidazolines were smoothly oxidized to the corresponding imidazoles in good yields using (diacetoxyiodo) benzene at room temperature.[5]

Scheme 5- Synthesis of N-Aryl derivative of imidazole



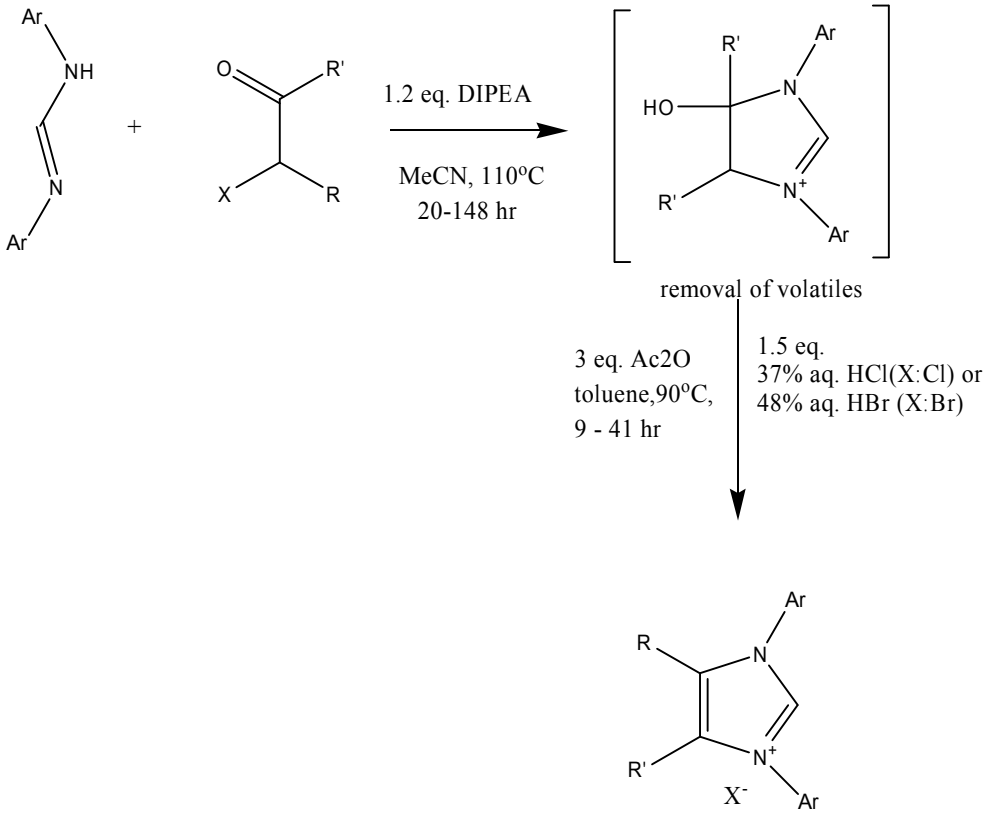
A copper-catalyzed N-arylation reaction of imidazole proceeds under very mild conditions in the absence of additional ligand. This protocol tolerates an array of thermally sensitive functional groups, but also achieves high chemo selectivity.[6]

Scheme 6- Synthesis of Imidazoles through the Copper-Catalyzed Cross-Cycloaddition between Two Different Isocyanides



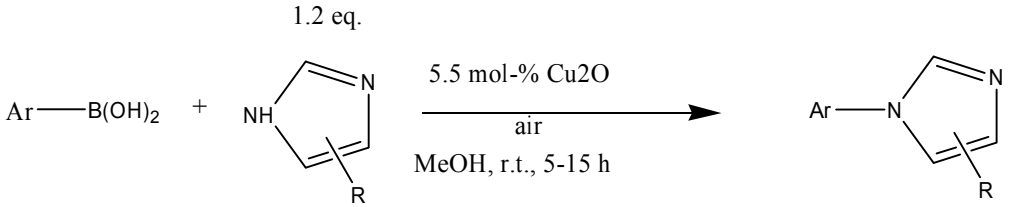
The copper-catalyzed reaction between two different isocyanides produces imidazoles in good yields.[7]

Scheme 7- Synthesis of Highly Substituted Imidazolium Salts.



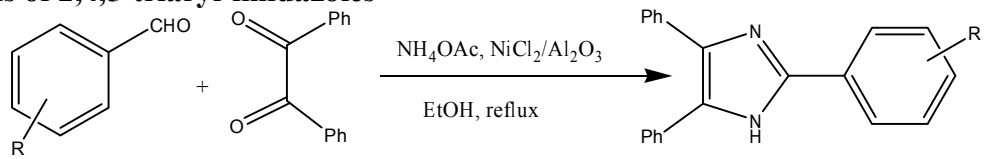
A versatile and modular one-pot method allows the preparation of differently substituted symmetrical and unsymmetrical imidazolium salts from readily available formamidines and α-halo ketones. For many substitution patterns of the imidazolium salt products, this efficient strategy compares favorably with well-known processes in terms of yield, ease of synthesis, and robustness.[8]

Scheme 8- Copper (I) Oxide Catalyzed N-Arylation of Azoles and Amines with Arylboronic Acid at Room Temperature under Base-Free Conditions



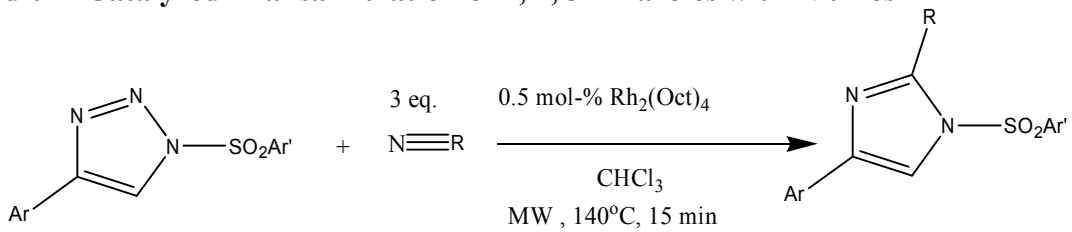
Efficient N-Arylation of azoles and amines with arylboronic acids with heterogeneous copper (I) oxide in methanol at room temperature under base-free conditions.[9]

Scheme 9- Synthesis of 2,4,5-triaryl-imidazoles



Synthesis of 2,4,5-triaryl-imidazoles from benzyl, aldehydes and NH_4OAc, as ammonia source, in the presence of catalytic amount of $NiCl_2 \cdot 6H_2O$ supported onto acidic alumina in very good yields under heterogeneous system.[10]

Scheme 10- Rhodium-Catalyzed Transannulation of 1, 2, 3-Triazoles with Nitriles

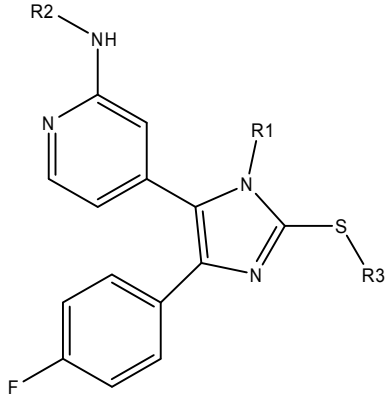


A rhodium (II)-catalyzed reaction of stable and readily available 1-sulfonyl triazoles with nitriles gives the corresponding imidazoles in good to excellent yields via rhodium iminocarbenoids intermediates.[11]

BIOLOGICAL ACTIVITY OF IMIDAZOLE

Inhibitors of Cytokine Release

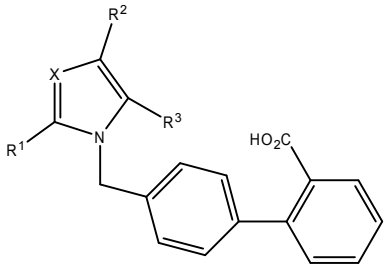
1, 2, 4, 5-tetrasubstituted imidazole derivatives with high anti-inflammatory activity.[12]



9b: R1 = -(CH_2)2-O-CH_3; R2 = CO-CH_3; R3 = -CH_3

9d: R1 = -(CH_2)3-O-CH_3; R2 = CO-CH_3; R3 = -CH_3

Angiotensin II receptor antagonists



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

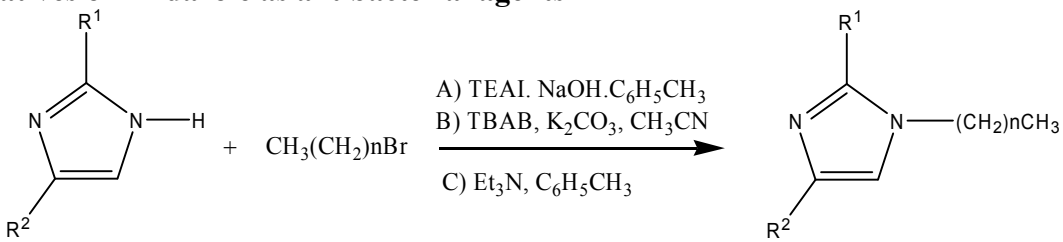
R^2, R^3 = -CH_2OH, CO_2H

The hydroxymethyl substituent at the 4 position and the carboxy substituent at the 5 position in the imidazole nucleus are favorable for the activity.[13]

Oxygen Enhances the Antimalarial Activity of the Imidazoles

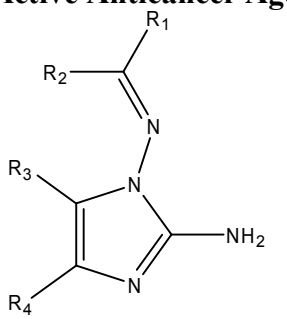
The enhanced antimalarial activity of imidazole in an atmosphere with 17–18% oxygen (the candle jar) vs. 3% or 0.3% oxygen. Based on both morphology and radiometric testing, smaller amounts of the imidazoles required to inhibit parasite growth by 50% in the candle jar vs. 3% or 0.3% oxygen. [14]

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. Also substitution of 2-methyl and 2-methyl-4-nitro groups on the imidazole ring increase the antibacterial activity against Escherichia coil, Staphylococcus aureus and Pseudomonas aeruginosa.[15]

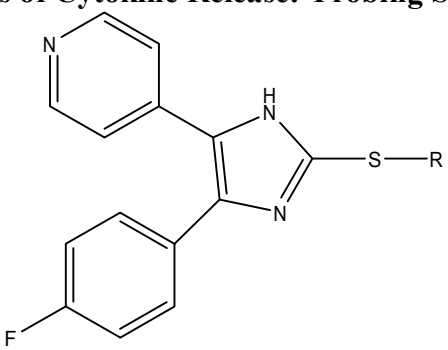
2-Amino-1-arylidenamino Imidazoles as Orally Active Anticancer Agent

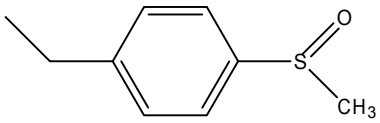


R1, R2, R3, R4 = hydrogen, aryl or heterocyclyl

2-Amino-1-arylidenaminoimidazoles, a novel class of orally active microtubule-destabilizing anticancer agents. Two compounds showed in vivo anticancer activities in both po and intravenously (IV) administered routes and prolonged the life spans of murine leukemic P388 cells-inoculated mice.[16]

Imidazole Inhibitors of Cytokine Release: Probing Substituent's in the 2 Position



R = 

IC_{50} 4.0 (p38), 0.38 (IL-1 beta)

R = -CH_3 IC_{50} 0.63 (p38), 0.04 (IL-1 beta)

Novel 2, 4, 5-trisubstituted imidazole derivatives as potential anticytokine agents.[17]

CONCLUSION

A thorough literature survey revealed that various substitution at 2, 4 & 5 position of imidazole derivative results in the potent anticancer, antibacterial & cytokine release inhibitors. Also there is evidence that hydroxymethyl substituent at the 4 position and the carboxy substituent at the 5 position in the imidazole nucleus are favorable for its Angiotensin II receptor antagonist activity.

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