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Synthetic Emergence in *N*-Arylimidazoles: A Review

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ABSTRACT Immense therapeutic potential of *N*-arylimidazoles prompted various researchers worldwide to develop different synthetic routes to these heterocycles. The present review highlights and summarises various synthetic approaches, conventional as well as greener protocols involved in the synthesis of *N*-arylimidazoles in the past two decades. The reported methods involve two basic approaches toward the synthesis of *N*-arylimidazoles (i) synthesis of imidazole moiety using open chain substrates and (ii) *N*-arylation of imidazoles.

KEYWORDS Azoles, Imidazoles, *N*-Arylimidazoles, Copper catalysts.

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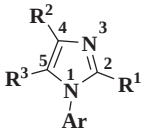
INTRODUCTION

Imidazole belongs to azoles family and has been first synthesized by the reaction of glyoxal with ammonia. Initially, it was named as glyoxalin. It exists in two equivalent tautomeric forms at room temperature and possesses similar properties such as pyrrole and pyridine. It is an integral part of several natural products such as histamine, biotin, alkaloids, and nucleic acids. On fusion with pyrimidine, it forms purine ring which is the most widely occurring nitrogen-containing heterocycle in nature. Imidazole also provides functional group sites that could be modified to yield a variety of bioactive heterocycles.[1-3] Imidazole and its derivatives have occupied unique place in the field of medicinal chemistry due to their diverse biological activities such as antibacterial,[4] antifungal,[5] anti-inflammatory,[6] antimalarial,[7] histamine-H_3 antagonist,[8] farnesyl transferase and geranyl transferase-1inhibitor,[9] antioxidant,[10] antitumor,[11] antiparasitic,[12] and antiprotozoal.[13] Various drugs having substituted imidazole moiety are available in market such as dimetridazole, azathioprine, carnidazole, mezlocillin, metronidazole, and mizoribine.

Among the imidazole derivatives, *N*-arylimidazoles (**1**) have shown immense potential as key structural motifs in medicinally important compounds, such as tyrosine kinase inhibitors,[14,15] γ-secretase modulators,[16] serotonin receptor antagonists,[17] and glycine transporter type-1 inhibitors.[18] These are also known to be an integral part of drugs that show adrenoreceptor α_2-antagonist,[19] histamine H_1 receptor antagonist,[20-22] anxiolytic,[23,24] antifungal properties, etc.[25-28]



(**1**)

***N*-Arylimidazoles**

Merely a single review is there on the bioactive derivatives of *N*-arylimidazoles,[28] and to the best of our knowledge,

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no review is yet reported on the synthesis and properties of *N*-arylimidazoles. Thus, it is worthwhile to prepare an updated detailed review on the same. The present review summarises the developments in the synthesis of *N*-arylimidazoles. The reported methods involve two basic approaches for the synthesis of *N*-arylimidazoles: (i) Constructing imidazole moiety from open chain substrates and (ii) *N*-arylation of imidazoles (with no substituent at position 1) **Chart 1**. Accordingly, the methods are described in two sections **2** and **3** starting from open chain compounds and imidazoles, respectively.

SYNTHESIS OF *N*-ARYLIMIDAZOLES FROM OPEN CHAIN SUBSTRATES

N-Arylimidazoles (**4**) have been synthesised in very high yields by introducing different aryl groups from the corresponding *N*-arylformamides (**3**) and *N*-formylglycine esters (**2**) at room temperature[29] in the presence of proline ligand [**Scheme 1**].

N-Arylimidazoles (**7**) containing electron withdrawing group have been obtained in very good yields when aryl isocyanides (**5**) are treated with isocyanides (**6**) in the presence of 1,10-phenanthroline as a ligand[30] in a copper-catalysed cross-cycloaddition [**Scheme 2**].

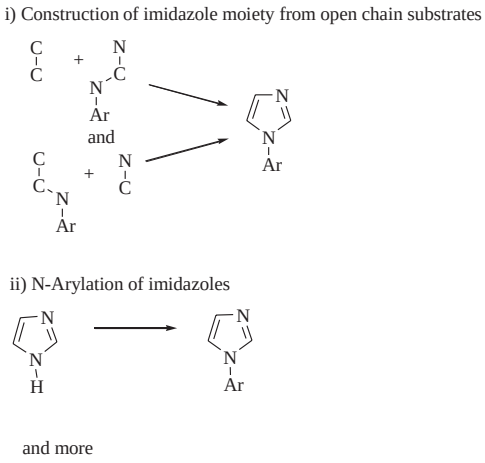


Chart 1: Basic strategies for N-arylimidazoles

Copper halides support a range of sensitive functional groups leading to high yielding synthesis of arylated imidazoles in the absence of specific ligands. The use of protic as well as aprotic solvent has led to successful *N*-arylation.

Pooi *et al*. reported a straightforward and high yielding synthesis of 1,4-diaryl-1*H*- imidazoles (**10, 13**) from aryl isocyanides **(9)** and benzyl isocyanides **(8)** through NHC-Cu catalyzed isocyanide insertion into alcohol, forming *N*-arylformimidate (**12**) intermediate. The intermediate then subsequently promoted to the desired diarylimidazole **(13)** with **8** in the presence of base[31] (KOtBu) [**Scheme 3**].

N-Arylimidazoles (**16**) have been obtained using arylacetic acids (**14**), *N*-arylbenzamidines (**15**), and nitroalkanes in the presence of 2,2′-bipyridyl as a ligand and DMF using copper sulfate as a catalyst[32] **[Scheme 4]**.

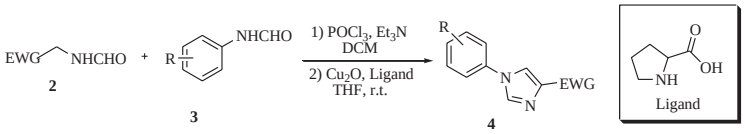
N-Arylimidazole quinoline-2-ones (**21**) were synthesized by condensing hydrazino carbonyl-phenyl vinylacetamide derivative (**17**) with coumarins in acetic acid by two different processes – a two-step process and another one-pot process[33] [**Scheme 5**].

In an another method, anilines (**22**) and ethyl glyoxylate (**23**) were treated in methanol to obtain α-anilino-α-methoxyacetates (**24**) which were cyclized with TosMIC (toluenesulfonylmethyl isocyanide) to give *N*-arylimidazole-5-carboxylates[34] **(25)** [**Scheme 6**].

Imidazole-thiones (**28**) have been synthesized from aminoacetaldehyde diethyl acetal and arylisothiocyanate[35] (**26**) [**Scheme 7**].

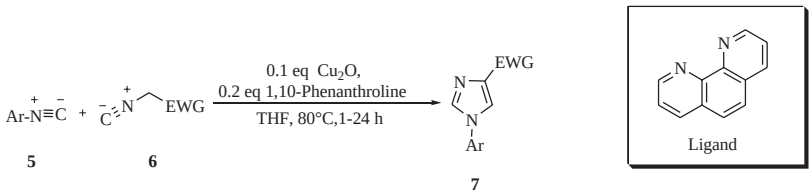
SYNTHESIS THROUGH *N*-ARYLATION OF IMIDAZOLES

Some traditional methods, which have been used for the synthesis of *N*-arylimidazoles, involve S_NAr substitution reaction of imidazoles with activated aryl halides or classical Ullmann-type coupling reaction.[36,37] These methods suffer from serious drawbacks such as the use of stoichiometric amount of copper reagents, high reaction temperature, and long reaction time period. Therefore, further developments focused on the use of catalysts mainly Cu salts. Some *N*- and *O*- containing ligands have also been used to facilitate



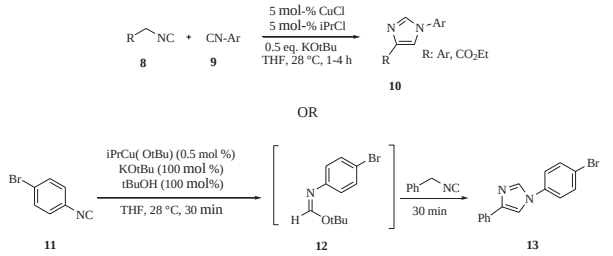
R= H; 4-OMe, 3-OMe, 2-OMe, 4-NO_2, 3-NO_2 , 2-NO_2, 4-Me, 3-Me, 2-Me, 4-Cl, 3-Cl, 2-Cl

Scheme 1: *N*-Arylimidazoles from *N*-arylformamides and *N*-formylglycine esters

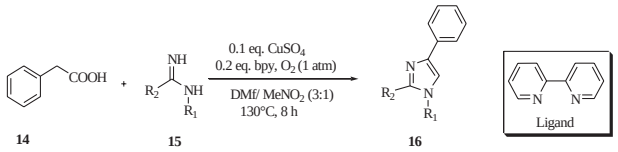


Scheme 2: *N*-Arylimidazoles from aryl isocyanides

the copper catalysed C-N coupling reactions.[38-42] Further, realising the potential of ligands, a series consisting of mono and bidentate ligands have been developed and tested to improve the efficiency of the reactions associated with Ullmann-type C-N bond formation.[43-46] The Lam-Chan reaction (Cu-catalysed cross-coupling between imidazoles and arylboronic acids) has also been found a better alternative

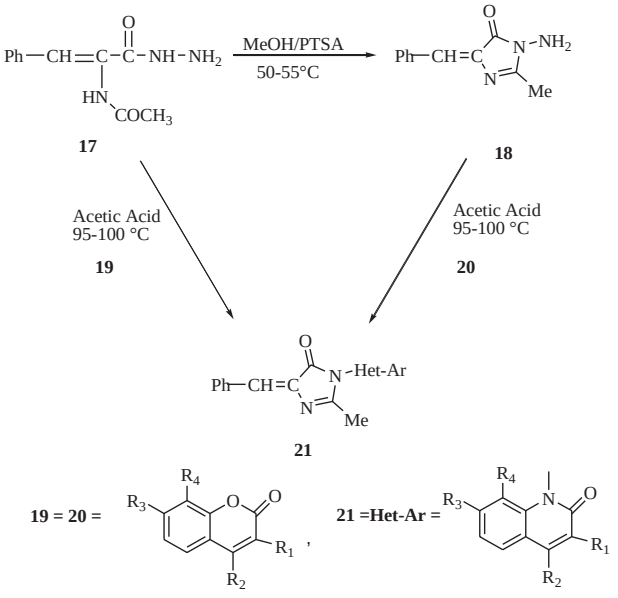


Scheme 3: *N*-arylimidazoles from benzyl isocyanide derivatives



R_1: 2-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4 -ClC_6H_4 4-MeC_6H_4 4-$OMeC_6H_4$
R_2: 3-ClC_6H_4, 4 -ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$

Scheme 4: *N*-Arylimidazoles from *N*-arylbenzamidines



R_1: H, CH_3, Cl, Br; R_2: H, CH_3, Cl, Br,C_6H_5; R_3: H, OH, NH_2, R_4:H,CH_3

Scheme 5: *N*-arylimidazoles from coumarins

because of low-temperature requirement[47-51] but the selection of solvents,[52] bases,[53] additives,[54] and substrate types[55] often needs to be optimized. Therefore, the present section highlights the recent synthetic developments in *N*-arylimidazoles through catalysis. The synthetic methods have been classified and discussed on the basis of the nature of catalysts.

Synthesis of *N*-arylimidazoles using copper and its oxide

The synthesis of *N*-arylimidazoles can be achieved using copper or its oxide as a catalyst with or without ligand.

2-(Hydrazinecarbonyl)pyridine-*N*-oxides, proline, 4,7-dimethoxy-1,10-phenanthroline, 1,10-phenanthroline, and β-ketoimine ligands are used with copper powder or copper oxide to synthesise arylated imidazoles (**31**) in very good yields under ambient conditions for both electron-withdrawing and donating groups. For example, *N*-arylation of imidazoles (**30**) has been carried out with aryl halides (**29**) in water without an inert atmosphere in the presence of tetra-n-butyl ammonium bromide (TBAB) and the ligand 2-(2-hydrazinecarbonyl)pyridine-*N*-oxides[56] [**Scheme 8**].

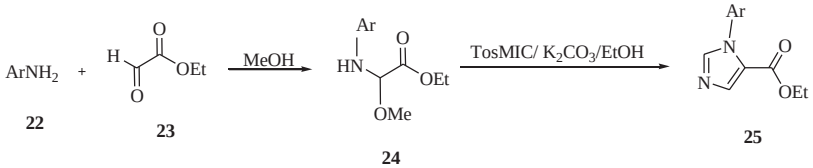
In an another approach, the ligand, 4,7-dimethoxy-1,10-phenanthroline has been found efficient for polyethyleneglycol (PEG) accelerated N-arylation (**34**) of variety of hindered and functionalized imidazoles and benzimidazoles (**32**) with aryl iodides and bromides[57] (**33**) [**Scheme 9**].

Xue *et al*. have reported that β-ketoimine works as an efficient, inexpensive, and facile ligand for the Cu_2O-catalysed *N*-arylation **(37)** of imidazoles (**36**) with the electron rich, neutral, and electron deficient aryl bromides and iodides[58] **(35)** [**Scheme 10**].

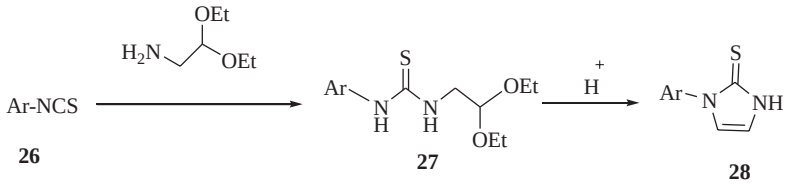
Cu_2O along with 1-(2-methylhydrazine-1-carbonyl) isoquinoline-2-oxide in aqueous medium proves to be a simple and efficient catalytic system for *N*-arylation **(40)** of imidazoles (**39**). Moreover, use of NaOH under above conditions brings about *N*-arylation of imidazole with 4-methoxyiodobenzene[59] **(38)** [**Scheme 11**].

Various solvents such as water, dimethyl formamide (DMF), methanol, and ethanenitrile along with mild bases such as K_2CO_3, LiOH, and Cs_2CO_3 have led ligand free arylation to obtain desired products in considerably good yields.

One-pot synthesis of *N*-arylimidazoles (**43**) from indole, pyrazole, and imidazole **(42)** and aryl halides **(41)** has been carried out in water under air without using arylboronic acids, palladium, and base in the presence of copper based ionic liquid promoter[60] [**Scheme 12**], similarly synthesis of

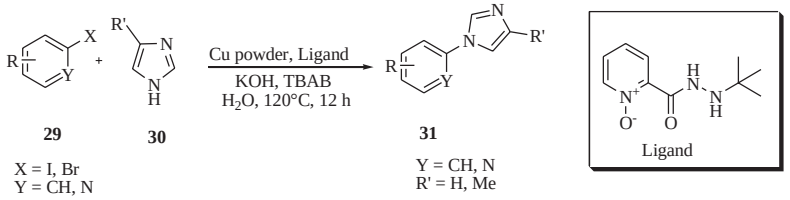


Scheme 6: *N*-Arylimidazoles from ethyl glyoxylate and aniline

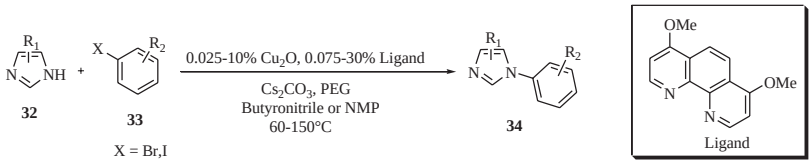


Ar: 2,4,6-$Cl_3C_6H_2$; 2,4,- $C_6H_3(NO_2)(OMe)$; 3,4,5-$(MeO)_3C_6H_2$; 3,5-$(CF_3)_2C_6H_3$

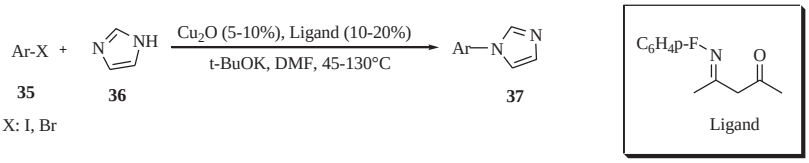
Scheme 7: *N*-Arylimidazole from aminoacetaldehyde diethyl acetal and aryl isothiocyanates



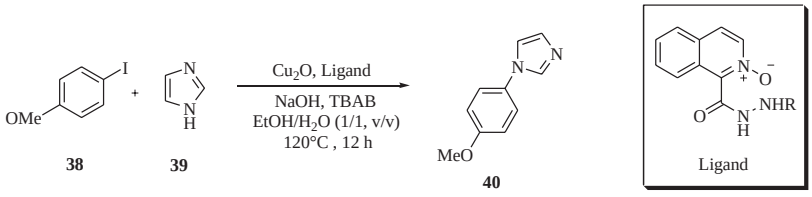
Scheme 8: *N*-Arylation of imidazoles using aryl halides



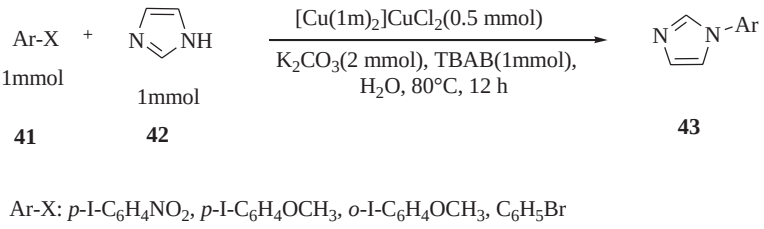
Scheme 9: *N*-Arylation of imidazoles using imidazoles, benzimidazoles, aryl iodides, and bromides



Scheme 10: *N*-Arylation of imidazoles using aryl bromides/iodides



Scheme 11: *N*-Arylation of imidazoles using 4-methoxyiodobenzene



Ar-X: *p*-I-$C_6H_4NO_2$, *p*-I-$C_6H_4OCH_3$, *o*-I-$C_6H_4OCH_3$, C_6H_5Br

Scheme 12: *N*-Arylation of imidazoles using aryl halides in ionic liquid

N-arylimidazoles **(43)** has been carried out with activated copper using LiOH as base from aryl halides **(44)** and imidazoles **(45)**[61] [**Scheme 13**].

Wang *et al*., in an Ullmann type reaction, established a protocol for Cu-catalysed *N*-arylation (**49**) of *N*-containing heterocycles (**48**) with aryl or heteroaryl iodides and bromides (**47**).[62] The procedure has shown a broad range of functional groups acceptance (electron donating as well as withdrawing) on both of the cross-coupling partners results in good to excellent yields [**Scheme 14**].

Various arylboronic acids (**50**) and amines have been converted to the corresponding *N*-arylazoles (**52**) and *N*- arylamines in a reaction efficiently catalysed with heterogeneous copper(I) oxide in methanol at room temperature under base free conditions[63] [**Scheme 15**].

N-Arylimidazoles (**55-57**) can be obtained by treating imidazole (**54**) with 2,4-difluoroiodobenzene (**53**) in the presence of copper catalyst.[64] The presence of both fluoro and iodo substituents has promoted S_NAr reaction at the C-F bond and copper-catalysed Ullmann-type coupling reaction at the C-I bond [**Scheme 16]**.

Imidazoles (**58**) have been successfully arylated (**60**) with a wide range of chloro and fluoroarenes (**59**) using recyclable copper-exchanged fluorapatite catalyst in DMF solvent and K_2CO_3 as a base[65] [**Scheme 17**].

N-Arylated imidazoles (**63**) were synthesised from imidazole (**62**) and arylboronic acids **(61**) in the presence of a catalytic amount of SiO_2-NHC (N-Heterocyclic carbenes)-CuI in methanol at room temperature[66] **[Scheme 18]**.

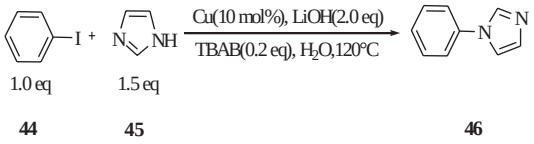
Synthesis of *N*-arylimidazoles using copper halides

1-(5,6,7,8-Tetrahydroquinolin-8-yl)ethanone, 3-(diphenylphosphino)propanoic acid, oxazolidin-2-one, benzotriazole, (1S, 2S)-1,2-dimethylcyclohexane, and 1,10-phenanthroline, (1R, 2R)-cyclohexane-1,2-diamine, N(1),N(2)-dimethylethane-1,2-diamine, and quinolin-8-ol along with a base have been proven as highly efficient ligands affording *N*-arylated imidazoles under mild reaction conditions.

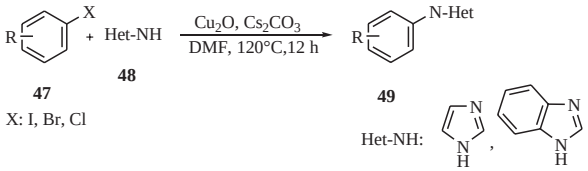
Ligand 1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanone mediated copper catalysed approach for *N*-arylation **(66**) of azoles (**65**) with a variety of substituted aromatic bromides and iodides (**64**) under mild conditions has been employed with great functional group compatibility and excellent selectivity[67] [**Scheme 19**].

N-Arylimidazoles (**69**) have been prepared under mild conditions using copper bromide as a catalyst from various N, O, and S nucleophilic reagents **(68)** with aryl halides **(67)** along through ligand 2-oxocyclohexanecarboxylate[68] **[Scheme 20]**.

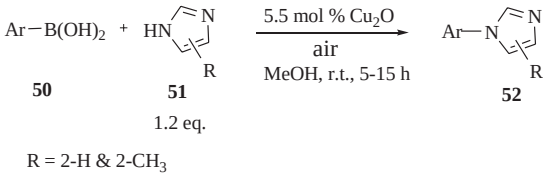
3-(Diphenylphosphino)propanoic acid is reported to be an efficient ligand for the copper-catalysed C–N coupling reactions for *N*-Arylation (**72**) of imidazole (**71**) with variety of substituted aryliodides[69] **(70) [Scheme 21**].



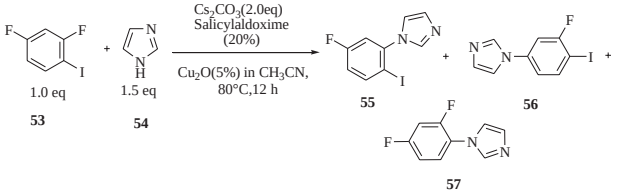
Scheme 13: *N*-Arylation of imidazoles using aryl iodide



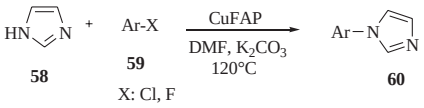
Scheme 14: *N*-Arylation of imidazoles using benzimidazoles and aryl halides



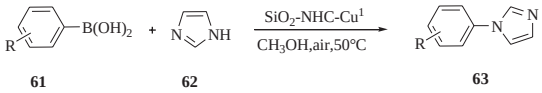
Scheme 15: *N*-Arylation of imidazoles using arylboronic acids and amines



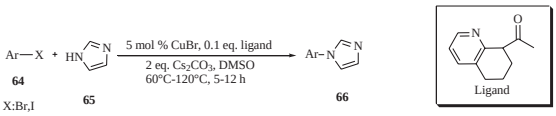
Scheme 16: *N*-Arylation of imidazoles using 2,4-difluoroiodobenzene



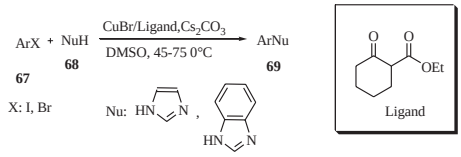
Scheme 17: *N*-Arylation of imidazoles using chloro/ fluoroarenes



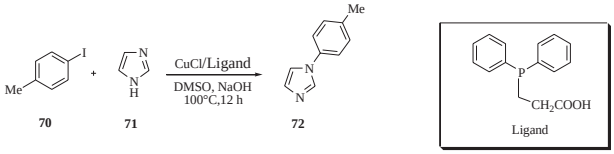
Scheme 18: *N*-Arylation of imidazoles using arylboronic acid



Scheme 19: *N*-Arylation of imidazoles using aromatic bromides/iodides with ligand 1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanone



Scheme 20: *N*-Arylation of imidazoles using aromatic bromides/iodides with ligand 2-oxocyclohexanecarboxylate

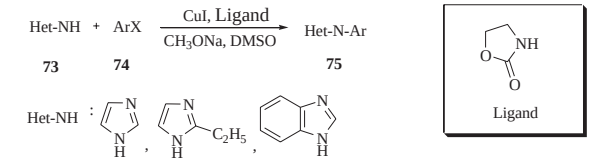


Scheme 21: *N*-Arylation of imidazoles using aryl iodides with ligand 3-(Diphenylphosphino)propanoic acid

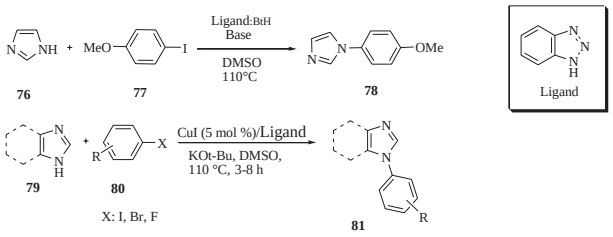
Oxazolidin-2-one acts as a facile ligand for N-arylation of pyrrole, indole, and imidazole **(73)** with aryl halides (74) in the Cu-I catalyzed reactions[70] (**75**) [**Scheme 22**].

Another Cu-catalyzed *N*-arylation (**78**) of imidazoles (**76**) with substituted aryliodide (**77**), a combination of copper iodide and benzotriazole (BtH) has proved to be an efficient and inexpensive catalyst[71] [**Scheme 23**].

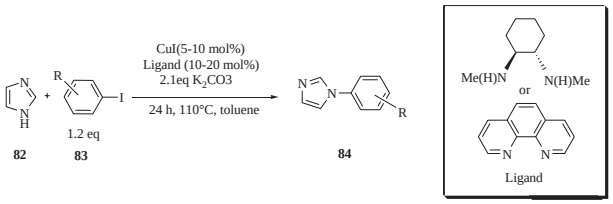
Synthesis of meta-*bis*(1-imidazolyl)benzenes (**84**) has been achieved through copper-catalysed coupling of variety of substituted aryl halides (**83**) and imidazole (**82**) in the presence of racemic trans-1,2-cyclohexanediamine[72] [**Scheme 24**].



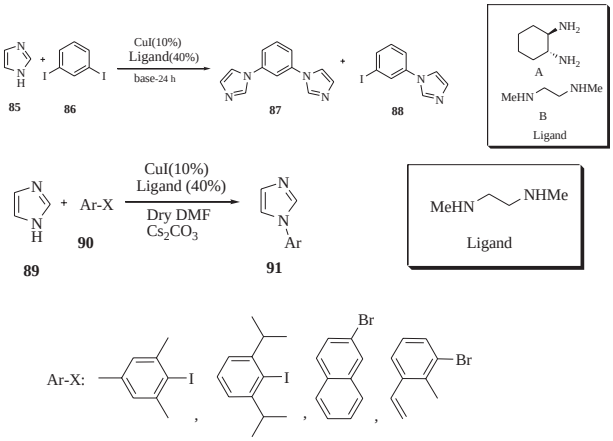
Scheme 22: *N*-Arylation of imidazoles using aryl halides with Ligand oxazolidin-2-one



Scheme 23: *N*-Arylation of imidazoles using *p*-methoxyiodobenzene



Scheme 24: *N*-Arylation of imidazoles using 1,3-diidobenzene



Scheme 25: *N*-Arylation of imidazoles using 1,3-diidobenzene

Alcalde *et al*. have chosen the ligand combination of racemic *trans*-1,2-cyclohexanediamine and *N,N*-dimethylenediamine for coupling of imidazole (**85**) and 1,3-diidobenzene (**86**) for an Ullmann-type condensation that affords bis(imidazole) (**87, 88**), the simple structural motif based on meta-bis(1-imidazoyl) benzenes in excellent yields[73] **[Scheme 25]**. Furthermore, the first ever synthesis of sterically hindered 1-mesitylimidazole has been reported with 50% isolated yields after chromatographic purification.

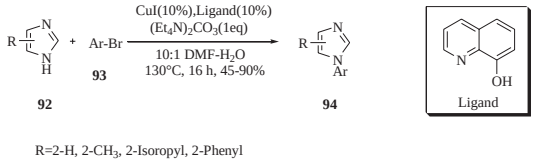
In a heterogeneous system consisting of tetraethylammonium carbonate as a base, supported by 8-hydroxyquinilone as ligand and water as cosolvent, CuI has successfully catalysed *N*-arylation (**94**) of imidazoles (**92**) with aryl bromides[74] (**93**) [**Scheme 26**].

Hexamethylenetetramine when used as a ligand, transformed imidazole (**96**) when treated with aryl chlorides and bromides (**95**) into their corresponding *N*-arylated Imidazole[75] **(97)** [**Scheme 27**].

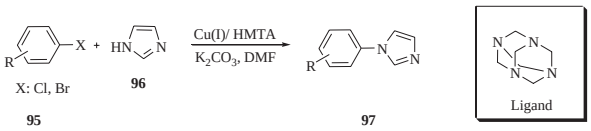
The ratio of imidazole-phenylboronic acid has played a crucial role for coupling of imidazole (**99**) with arylboronic acid **98** in protic solvent[52] in the ratio of more than 1.2:1 in developing *N*-arylimidazole (**100**) [**Scheme 28**].

High chemoselectivity has resulted into *N*-arylation (**103**) of imidazole (**102**) with a variety of aromatic bromides and iodides[76] **(101)** [**Scheme 29**].

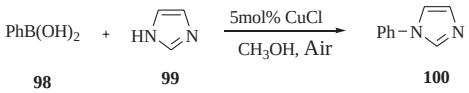
An efficient, facile, mild, and base free *N*-arylation (**106**) of imidazoles (**105**) with arylboronic acids (**104**) using copper-exchanged fluorapatite catalyst have been preceded at room temperature[77] [**Scheme 30**].



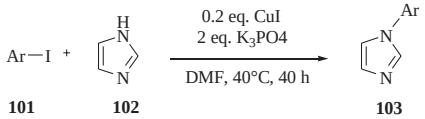
Scheme 26: *N*-Arylation of imidazoles using aryl bromide



Scheme 27: *N*-Arylation of imidazoles using hexamethylenetetramine



Scheme 28: *N*-Arylation through coupling of imidazole with arylboronic acid



Scheme 29: *N*-Arylation of imidazoles using aryl bromides/ iodides

Synthesis of *N*-arylimidazoles using copper acetate

Copper acetate along with ligands 4,4'-dimethyl-2,2'-bipyridine and sparteine in water as solvent have been used to achieve arylation of imidazoles under mild conditions. In one of the greener copper catalyzed and efficient methods, *N*-arylimidazoles (**109**) have been obtained by oxidative coupling of arylboronic acids (**107**) with imidazoles (**108**) in water and base-free conditions using an amphiphilic surfactant[78] [**Scheme 31**].

Mao *et al*. have developed arylated imidazoles (**112**) from aryl iodide (**110**) and imidazole (**111**) with catalyst $Cu(OAc)_2.H_2O$/ (-) sparteine[79] [**Scheme 32**].

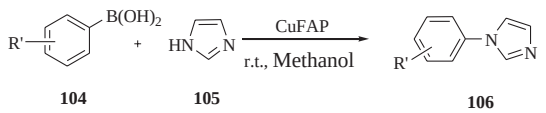
Copper acetate has catalysed *N*-arylation (**115**) of imidazole (**114**) in the absence of ligands as well as through aryl/heteroaryl C-N cross-coupling approach through the arylboronic acid (**113**)/cupric acetates but it requires longer reaction time[47] [**Scheme 33**].

Unsymmetric arylimidazolium and triazolium salts (**118**) can be synthesised from *N*- substituted imidazoles (**116**) and diaryliodonium salts (**117**) using a copper catalyst[80] [**Scheme 34**].

Miscellaneous Synthesis of *N*-arylimidazoles

N-Arylation can also be carried out through cobalt-catalysed coupling of diaryliodonium salts with imidazole, microwave-assisted methods (with/without solvent), use of ionic liquids and nano particles, copper-complex catalysed, and photocatalysed reactions. Most of these methods are environment friendly, highly efficient and inexpensive which furnished in good yields.

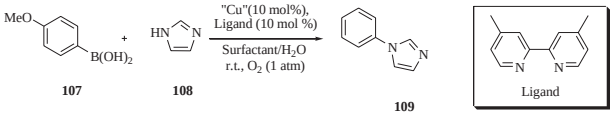
N-Arylation (**121**) of imidazole (**120**) with diaryliodonium salt (**119**) was carried using Cobalt(II) acetate as a catalyst and K_2CO_3 as a base in DMF[81] **[Scheme 35]**.



104 **105** **106**

R': H,CH_3,OCH_3, NO_2, F,Cl,CF_3

Scheme 30: *N*-Arylation of imidazoles using copper-exchanged fluorapatite



107 **108** **109**

Scheme 31: *N*-Arylation of imidazoles using arylboronic acids and amphiphilic surfactant

Solvent-free coupling reaction between imidazole (**122**) and differently substituted aryl bromides (**123**) has been carried out under microwave irradiation using L-amino acids and copper salts as catalysts[82] to get *N* –arylimidazole (**124**) [**Scheme 36**].

Yang *et al*. have reported a ligand-free copper-catalysed Ullmann reaction in tetraethyl orthosilicate and microwave-assisted synthesis of *N*-arylimidazoles[83] (**127**) from 1*H*-imidazoles **(126)** and aryl halides **(125)** [**Scheme 37**].

The use of ionic liquid $[Bmim]_4BF_4$ as a reaction medium has led to the reduction in reaction time with increased yields of *N*-arylimidazoles[84] (**130**) from N-heteroaryls **(129)** and aryl/ heteroaryl halides (**128**) [**Scheme 38**].

Collman *et al*. have synthesized and applied a series of binuclear bis-μ-hydroxo copper(II) complexes to the coupling of imidazoles (**131**) with arylboronic acids (**132**) in dry CH_2Cl_2 at room temperature under oxygen to get *N*-arylation of imidazole (**133**).[50] In a similar approach, the reaction is reported to be selectively performed in an N-methyl-2-pyrrolidone and water(NMP/H_2O) mixture at ambient temperature and atmosphere using [Cu(OH) TMEDA]$_2Cl_2$ dimer as the catalyst without the addition of base[53] [**Scheme 39**].

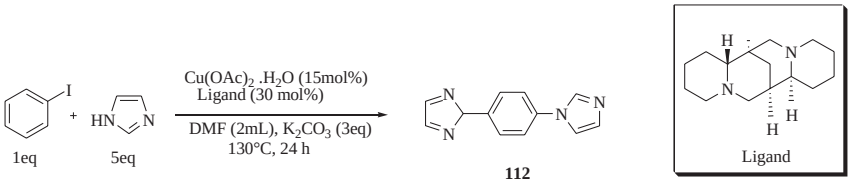
A novel, green photocatalytic route for *N*-Arylation (**139**) of imidazoles (**138**) with arylboronic acids (**137**) involving the C-N cross–coupling reactions has been reported over a Cu/graphene catalyst[85] [**Scheme 40**].

Synthesis of *N*-arylimidazoles (**142**) from aryl halides (**140**) and imidazole (**141**) under mild conditions using copper nanoparticles (CuNPs) has been developed in excellent yields[86] **[Scheme 41**].

Several bases have been tested for the Cu-grafted nanomaterial Cu–MPTA-1 (mesoporous poly-triallylamine) *N*-arylation (**145**) of imidazoles (**143**) with iodobenzene (**144**) in water as a solvent. The best results have been obtained with iodobenzene using KOH in water[87] at 120°C for 12 h [**Scheme 42**].

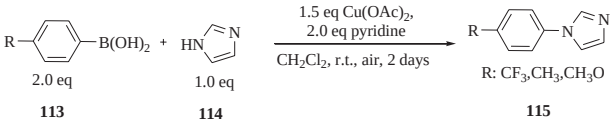
Magnetically recoverable nanocatalyst-copper nanoparticles on nanosized silica-coated maghemite (CuNPs/Mag Silica) have been used for the copper-catalysed *N*-arylation (**148**) of imidazoles (**147**) with aryl bromides and iodides (**146**) under ligand-free conditions[88] [**Scheme 43**].

An environmentally sound process for *N*-arylation (**151**) of imidazoles (**150**) with aryl halides (**149**) using copper oxide/acetylene black (CuO/AB) in toluene and a base has afforded the product with 100% yield[89] [**Scheme 44**].

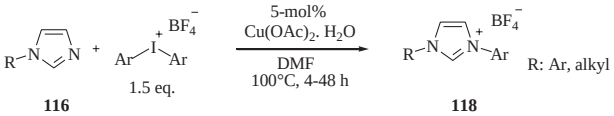


1eq 5eq **110** **111** **112**

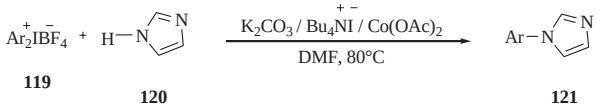
Scheme 32: *N*-Arylation of imidazoles using aryl iodide and catalyst



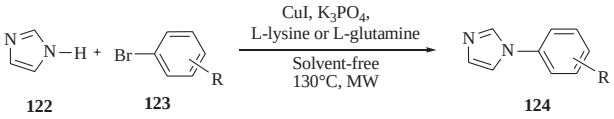
Scheme 33: *N*-Arylation of imidazoles using arylboronic acid/cupric acetate



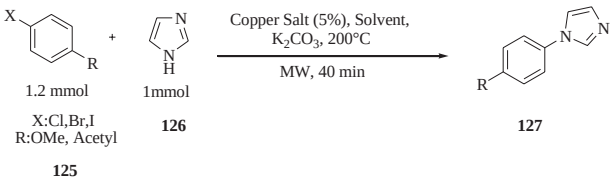
Scheme 34: *N*-Arylation of imidazoles using diaryliodonium salts and copper acetate



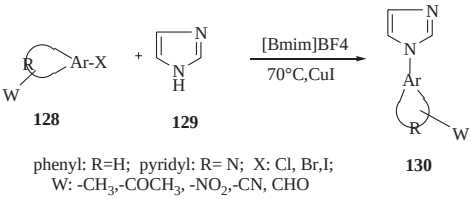
Scheme 35: *N*-Arylation of imidazoles using diaryliodonium salt and cobalt acetate



Scheme 36: *N*-Arylation of imidazoles using aryl bromides under solvent free condition



Scheme 37: *N*-Arylation of imidazoles through Ullmann reaction

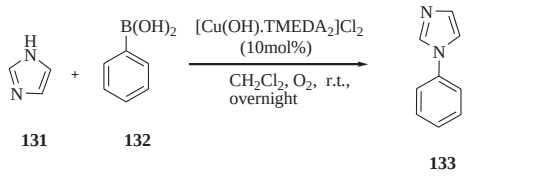


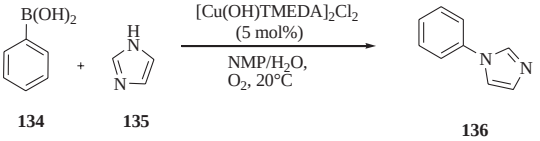
phenyl: R=H; pyridyl: R= N; X: Cl, Br,I;
W: -CH_3,-$COCH_3$, -NO_2,-CN, CHO

Scheme 38: *N*-Arylation of imidazoles using ionic liquid

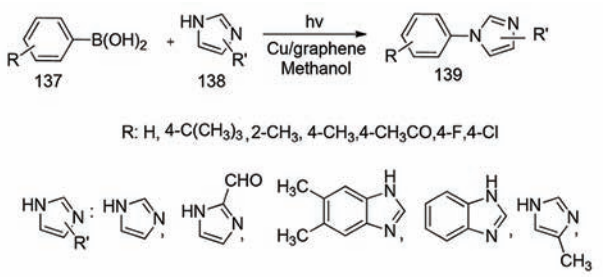
Liu *et al*. have reported the arylation (**154**) of benzimidazole (**153**) with a variety of aryl iodides (**152**), bromides **152** promoted by salen copper (II) complex in moderate to excellent yields under mild conditions[90] [**Scheme 45**].

A novel strategy adopted by Wang *et al*., involving mild reaction conditions involving aryl halides (**155**) and N-heteroarylimidazole (**156**) catalyzed by a sulfonato-Cu

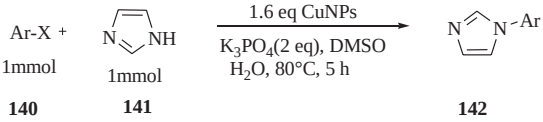




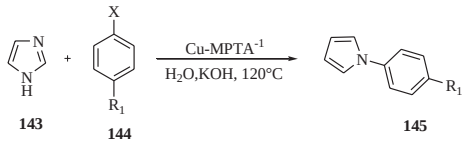
Scheme 39: *N*-Arylation of imidazoles using arylboronic acids



Scheme 40: A greener approach towards *N*-arylation of imidazoles using arylboronic acids



Scheme 41: *N*-Arylation of imidazoles using copper nanoparticles



X:I, Br; R_1:H, Me, OMe,COMe, NO_2

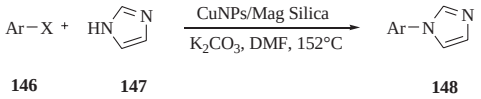
Scheme 42: *N*-Arylation of imidazoles using Cu-grafted nanomaterial

(salen) complex to get N-arylimidazole[91] (**157**) [**Scheme 46**].

Copper-complexes (mononuclear $[CuLCl]ClO_4$ and binuclear $[Cu_2L_2(\mu\text{-}1,1\text{-}N_3)_2](ClO_4)_2$)catalysed *N*-arylation (**160**) of imidazole (**158**) with aryl iodides (**159**) (electron-poor or electron-rich) resulted in a highly efficient, user-friendly, sustainable, and low-cost protocol[92] [**Scheme 47**].

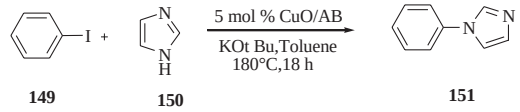
Boron trifluoride derivative of N-arylated imidazole *N*-oxides (**164**) was obtained by condensing aromatic amines (**161**) with formaldehyde (**162**) and butane-2,3-dione monooxime (**163**) in the presence of boron trifluoride etherate in acetic acid or chloroform. These could be easily reduced to their corresponding *N*-arylated imidazoles (**165**) by reducing with iron in acetic acid[93] [**Scheme 48**].

N-Substituted 2,4-diarylimidazoles (**170**) were synthesized under solvent-free conditions in a one-pot reaction using four components: 2-bromoacetophenone (**166**), an aldehyde (**168**), a primary amine (**167**), and ammonium acetate[94] **(169) [Scheme 49]**.



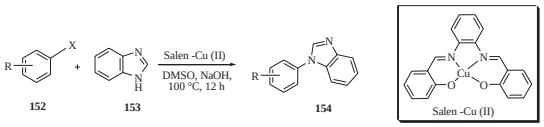
146 **147** **148**

Scheme 43: *N*-Arylation of imidazoles using CuNPs on nanosized Mag Silica



149 **150** **151**

Scheme 44: *N*-Arylation of imidazoles using CuO hollow nanospheres on acetylene black



152 **153** **154**

Scheme 45: *N*-Arylation of imidazoles using salen copper (II) complex

CONCLUSION

Imidazole and its derivative *N*-substituted imidazole attracted various researchers to design and synthesize such compounds due to their growing medicinal value. The present review has covered recently reported important approaches toward the synthesis of *N*-substituted imidazole involving two basic approaches, i.e., constructing imidazole moiety from open-chain substrates and *N*-arylation of imidazoles. Since variously substituted *N*-arylimidazoles are associated with diverse biological activities, this review might stimulate further studies for the development of potential compounds as a replica of therapeutic agents.

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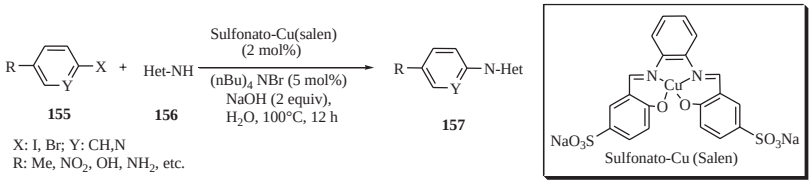
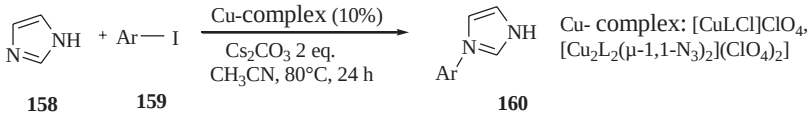


155 **156** **157**

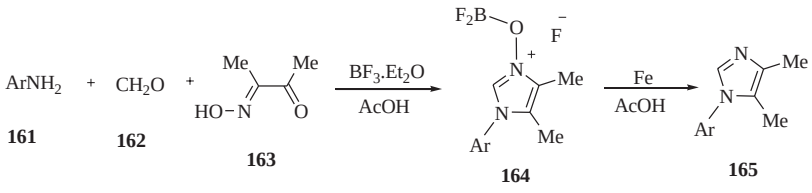
X: I, Br; Y: CH,N
R: Me, NO_2, OH, NH_2, etc.

Scheme 46: *N*-Arylation of imidazoles using sulfonato-Cu salen complex



158 **159** **160**

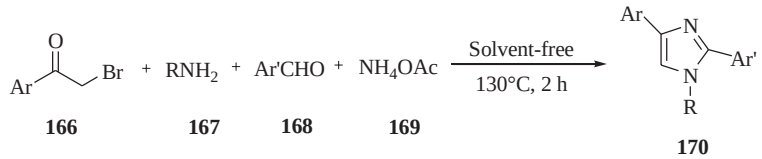
Scheme 47: *N*-Arylation of imidazoles using mononuclear and binuclear Cu-complexes



161 **162** **163** **164** **165**

Ar: Ph; 2,4,6-$Me_3C_6H_2$; 4-$MeOC_6H_4$; 3-FC_6H_4; 2,4,6-$(MeO)_3C_6H_2$; 3-ClC_6H_4;4-$NO_2C_6H_4$,3-Py

Scheme 48: Synthesis of *N*-arylated imidazole using metallic iron



166 **167** **168** **169** **170**

Ar: Ph; 4-BrC_6H_4, R: Ph; Bn; n-Pr, Ar': Ph, 4-$NO_2C_6H_4$; 3-$NO_2C_6H_4$; 4-MeC_6H_4; 4-ClC_6H_4

Scheme 49: Synthesis of *N*-arylated imidazole by multicomponent reaction

CONFLICTS OF INTEREST

The authors declare that they have read policy and guidelines of the journal and there are no conflicts of interest.

REFERENCES

[1] Prakash, O., Rani, N., Goyal, S. Hypervalent iodine in the synthesis of bridgehead Heterocycles: novel and facile syntheses of 3-substituted-5, 6-dihydroimidazo [2, 1-b] thiazoles and 3-phenylthiazolo[3,2-a]benzimidazole from acetophenones using [hydroxy(tosyloxy)iodo] benzene, *J. Chem. Soc. Perkin Trans.*, **1992**, *1*, 707–709.

[2] Lung-Toung, R., Tam, T.F., Zhao, Y., Simpson, C.D., Desilets, W.D., Karimian, K. Synthesis of 3-substituted bicyclic imidazo[1,2-d][1,2,4]thiadiazoles and tricyclic benzo[4,5]imidazo[1,2-d][1,2,4]thiadiazoles, *J. Org. Chem*., **2005**, *70*, 6230–6241.

[3] Aggarwal, R., Kumar, R., Kumar, V. A facile and rapid one-pot synthesis of 1,4-diaryl-2- mercapto imidazoles under solvent-free conditions, *J. Sulfur Chem.*, **2007**, *28*, 617–623.

[4] Rani, N., Sharma, A., Singh, R. Imidazoles as promising scaffolds for antibacterial activity: A review, *Mini Rev. Med. Chem.*, **2013**, *13*, 1812–1835.

[5] Gupta, G.K., Saini, V., Khare R., Kumar, V. 1, 4-diaryl-2-mercaptoimidazoles as a novel class of antimicrobial agents: Design, synthesis and computational studies, *Med. Chem. Res.*, **2014**, *23*, 1–12.

[6] Wright, S.W., Harris, R.R., Collins, R.J., Corbett, R.L., Green, A.M., Wadman, E.A., Batt, D.G. Novel 1-(pyridylphenyl)-1-phenyl-2-imidazolylethanols with topical antiinflammatory activity, *J. Med. Chem.*, **1992**, *35*, 3148–3155.

[7] Jain, R., Vangapandu, S., Jain, M., Kaur, N., Singh, S., Singh, P.P. Antimalarial activities of ring-substituted bioimidazoles, *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1701–1704.

[8] Grabmann, S., Sadek, B., Ligneau, X., Elz, S., Ganellin, C.R., Arrang, J.M., Schwartz, J.C., Stark H., Schunack, W. Progress in the proxifan class: Heterocyclic congeners as novel potent and selective histamine H_3-receptor antagonists, *Eur. J. Pharm. Sci.*, **2002**, *15*, 367–378.

[9] Nguyen, D.N., Stump, C.A., Walsh, E.S., Fernandes, C., Davide, J.P., Ellis-Hutchings, M., Robinson, R.G., Williams, T.M., Lobell, R.B., Huber, H.E., Buser, C.A. Potent inhibitors of farnesyl transferase and geranyl transferase-I, *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1269–1273.

[10] Soujanya, Y., Sastry, G.N. Theoretical elucidation of the antioxidant mechanism of 1,3-dihydro-1-methyl-2H-imidazole-2-selenol (MSeI), *Tetrahedron Lett.*, **2007**, *48*, 2109–2112.

[11] Chen, J., Wang, Z., Lu, Y., Dalton, J.T., Millera, D.D., Li, W. Synthesis and antiproliferative activity of imidazole and imidazoline analogs for melanoma, *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 3183–3187.

[12] Hussain, T., Siddiqui, H.L., Rehman, M.Z., Yasinzai, M.M., Parvez, M. Anti-oxidant, anti-fungal and anti-leishmanial activities of novel 3-[4-(1*H*-imidazol-1-yl) phenyl]prop-2-en-1-ones, *Eur. J. Med. Chem.*, **2009**, *44*, 4654–4660.

[13] Valdez, C.A., Tripp, J.C., Miyamoto, Y., Kalisiak, J., Hruz, P., Andersen, Y.S., Brown, S.E., Kangas, K., Arzu, L.V., Davds, B.J., Gillin, F.D., Upcroft, J.A., Upcroft, P., Fokin, V.V., Smith, D.K., Sharpless, K.B., Eckmann, L. Synthesis and electrochemistry of 2-ethenyl and 2-ethanyl derivatives of 5-nitroimidazole and antimicrobial activity against *Giardia lamblia*, *J. Med. Chem.*, **2009**, *52*, 4038–4053.

[14] Kantarjian, H., Giles, F., Wunderle, L., Bhalla, K., O'Brien, S., Wassmann, B., Tanaka, C., Manley, P., Rae, P., Mietlowski, W., Bochinski, K., Hochhaus, A., Griffin, J.D., Hoelzer, D., Albitar, M., Dugan, M., Cortes, J., Alland, L., Ottmann, O.G. Nilotinib in imatinib resistant CML and Philadelphia chromosome positive ALL, *N. Engl. J. Med.*, **2006**, *354*, 2542–2551.

[15] Weisberg, E., Manley, P., Mestan, J., Cowan-Jacob, S., Ray, A., Griffin, J.D. AMN107 (nilotinib): A novel and selective inhibitor of BCR-ABL, *Br. J. Cancer*, **2006**, *94*, 1765–1769.

[16] Huang, X., Aslanian, R., Zhou, W., Zhu, X., Qin, J., Greenlee, W., Zhu, Z., Zhang, L., Hyde, L., Chu, I., Cohen Williams, M., Palani, A. the discovery of pyridone and pyridazone heterocycles as γ-secretase modulators, *ACS. Med. Chem. Lett.*, **2010**, *1*, 184–187.

[17] Harada, K., Aota, M., Inoue, T., Matsuda, R., Mihara, T., Yamaji, T., Ishibashi, K., Matsuoka, N. Anxiolytic activity of a novel potent serotonin 5-HT2C receptor antagonist FR260010: A comparison with diazepam and buspirone, *Eur. J. Pharmacol.*, **2006**, *553*, 171–184.

[18] Graham, J.P., Langlade, N., Northall, J.M., Roberts, A.J., Whitehead, A. An efficient and scalable synthesis of the spirocyclic glycine transporter inhibitor GSK2137305, *J. Org. Process Res. Dev.*, **2011**, *15*, 44–48.

[19] Mohan, J.C., Shah, S.N., Chinchansurkar, S., Dey, A., Jain, R. Rediscovering chirality role of S-metoprolol in cardiovascular disease management, *J. Assoc. Physicians India*, **2017**, *65*, 74–79.

[20] Toyoda, M., Nakamura, M., Nakada, K., Lida, M., Nakamura, M., Otani, M., Etoh, T., Nakagawa, H., Morohashi, M. Effect of epinastine hydrochloride, a second- generation histamine H1-receptor antagonist, on sensory neurons *in vitro*, *Allergol Int.*, **2005**, *54*, 565–572.

[21] Griffin, A., Hamling, K.R., Knupp, K., Hong, S., Lee, L.P., Baraban, S.C. Clemizole and modulators of serotonin signalling suppress seizures in Dravet syndrome, *Brain*, **2017**, *140*, 669–683.

[22] Shafiee, A., Khoobi, M. *Astemizole*, *Encyclopedia of Toxicology*, Academic Press, Cambridge, Massachusetts, **2014**.

[23] Sawhney, S., Singh, R.K., Chakraberty, S. Use of intrathecal midazolam or fentanyl as an adjunct to spinal anaesthesia with bupivacaine for lower limb surgery: A randomised controlled study, *Med. J. Armed Forces India*, **2019**, *75*,176–183.

[24] Varma, S. Treatment strategies and psychopharmacology: Benzodiazepines and hypnotics, *Medicine*, **2016**, *44*, *764–767*.

[25] Ruiz, J.L.S., Carbo, J.S., Camomany, A.C.C., de Febrer, N.B., Bellowa, L.H., Montances, A.B., Souto, E.B., Naveros, B.C. Clotrimazole multiple W/O/W emulsion as anticandidal agent: Characterization and evaluation on skin and mucosae, *Colloids Surf. B Biointerfaces*, **2019**, *175*, *166–174*.

[26] Amaral, A.C., Saavedra, H.V., Souza, A.C.O., de Melo, M.T., Tedesco, A.C., Morais P.C., Felipe, M.S.S., Bocca, A.L. Miconazole loaded chitosan-based nanoparticles for local treatment of vulvo vaginal candidiasis fungal infections, *Colloids Surf. B Biointerfaces*, **2019**, *174*, 409–415.

[27] Tiwari, N., Sivakumar, A., Mukherjee, A., Chanderasekaran, N. Enhanced antifungal activity of Ketoconazole using rose oil based novel micro emulsion formulation, *J. Drug Deliv. Sci. Tecnol.*, **2018**, *47*, 434–444.

[28] Pastor, M.I., Yus, M. Bioactive N-phenylimidazole derivatives, *Curr. Chem. Biol.*, **2009**, *3*, 385–408.

[29] Bonin, M.A., Giguere, D., Roy, R. N-Arylimidazole synthesis by cross-cycloaddition of isocyanides using a novel catalytic system, *Tetrahedron*, **2007**, *63*, 4912–4917.

[30] Kanazawa, C., Kamijo, S., Yamamoto, Y. Synthesis of imidazoles through the copper catalyzed cross-cycloaddition between two different isocyanides, *J. Am. Chem. Soc.*, **2006**, *128*, 10662–10663.

[31] Pooi, B., Lee, J., Choi, K., Hirao, H., Hong, S.H. Tandem insertion-cyclization reaction of isocyanides in the synthesis of 1,4-Diaryl-1*H*-imidazoles: Presence of N- arylformimidate intermediate, *J. Org. Chem.*, **2014**, *79*, 9231–9545.

[32] Pardeshi, S.D., Sathe, P.A., Vadagaonkar, K.S., Melone, L., Chaskar, A.C. Copper catalyzed simultaneous activation of C-H and N-H bonds: Three-component one-pot cascade synthesis of multisubstituted imidazoles, *Synthesis*, **2017**, *50*, 361–370.

[33] Rao, G.V.P., Rajitha, B., Reddy, Y.T., Reddy, P.N. Synthesis of new aryl imidazole quinolone-2-ones, *Heterocycl. Commun.*, **2004**, *10*, 469–474.

[34] Chen, B.C., Bednarz, M.S., Zhao, R., Sundeen, J.E., Chen, P., Shen, Z., Skoumbourdis, A.P., Barrish, J.C. A new facile method for the synthesis of 1-arylimidazole-5-carboxylates, *Tetrahedron. Lett.*, **2000**, *41*, 5453–5456.

[35] Palmer, J.H., Parkin, G. Synthesis and structural characterization of 1-arylimidazole-2- thiones and N,N'-aryldiethoxyethylthioureas with electronically diverse substituents: A manifold of hydrogen bonding networks, *New J. Chem.*, **2014**, *38*, 4071–4082.

[36] Ley, S.V., Thomas, A.W. Modern synthetic methods for copper-mediated C (aryl) [bond] O, C (aryl) [bond] N, and C (aryl) [bond] S bond formation, *Angew. Chem. Int. Ed.*, **2003**, *42*, 5400–5449.

[37] De Meijere, A., Diederich, F. *Metal-Catalysed Cross-Coupling Reactions*. 2nd ed. Wiley-VCH, Weinheim, **2004**.

[38] Antilla, J.C., Klapers, A., Buchwald, S.L. The copper-catalyzed *N*-arylation of indoles, *J. Am. Chem. Soc.*, **2002**, *124*, 11684–11688.

[39] Yang, K., Qiu, Y., Li, Z., Wang, Z., Jiang, S. Ligands for copper-catalyzed C-N bond forming reactions with 1 Mol% CuBr as catalyst, *J. Org. Chem.*, **2011**, *76*, 3151–3159.

[40] Cristau, H.J., Cellier, P.P., Spindler, J.F., Taillefer, M. Mild conditions for copper catalysed *N*-arylation of pyrazoles, *Eur. J. Org. Chem.*, **2004**, *4*, 695–709.

[41] Monnier, F., Talliefer, M. Catalytic C-C, C-N, and C-O Ullmann-type coupling reactions: Copper makes a difference, *Angew. Chem. Int. Ed.*, **2008**, *47*, 3096–3099.

[42] Strieter, E.R., Bhayana, B., Buchwald, S.L. Mechanistic studies on the copper-catalyzed *N*-arylation of amides, *J. Am. Chem. Soc.*, **2009**, *131*, 78–88.

[43] Kunz, K., Scholz, U., Ganzer, D. Renaissance of ullmann and goldberg reactions progress in copper catalyzed C-N-, C-O- and C-S-coupling, *Synlett*, **2003**, *15*, 2428–2439.

[44] Beletskaya, I.P., Cheprakov, A.V. Copper in cross-coupling reactions: The post-Ullmann chemistry, *Coord. Chem. Rev.*, **2004**, *248*, 2337–2364.

[45] Ma, D., Cai, Q. Copper/amino acid catalyzed cross-couplings of aryl and vinyl halides with nucleophiles, *Acc. Chem. Res.*, **2008**, *41*, 1450–1460.

[46] Monnier, F., Talliefer, M. Catalytic C-C, C-N, and C-O Ullmann- type coupling reactions, *Angew. Chem. Int. Ed.*, **2009**, *48*, 6954–6971.

[47] Lam, P.Y.S., Clark, C.G., Saubem, S., Adams, J., Winters, M.P., Coan, D.M.M., Combs, P. New aryl/heteroaryl C-N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation, *Tetrahedron Lett.*, **1998**, *39*, 2941–2944.

[48] Combs, A.P., Saubem, S., Rafalski, M., Lam, P.Y.S. Solid supported aryl heteroaryl C-N cross-coupling reactions, *Tetrahedron Lett.*, **1999**, *40*, 1623–1626.

[49] Lam, P.Y.S., Vincent, G., Clark, C.G., Deudon, S., Jadhav, P.K. Copper-catalyzed general C-N and C-O bond cross-coupling with arylboronic acid, *Tetrahedron Lett.*, **2001**, *42*, 3415–3418.

[50] Collman, J.P., Zhong, M., Zeng, Li, Costanzo, S. The $[Cu(OH)\cdot TMEDA]_2Cl_2$-catalyzed coupling of arylboronic acids with imidazoles in water, *J. Org. Chem.*, **2001**, *66*, 1528–1531.

[51] Chiang, G.C.H., Olsson, T. Polymer-supported copper complex for C-N and C-O cross coupling reactions with aryl boronic acids, *Org. Lett.*, **2004**, *6*, 3079–3082.

[52] Lan, J.B., Chen, L., Yu, X.Q., You, J.S., Xie, R.G. A simple copper salt catalysed the coupling of imidazole with arylboronic acids in protic solvent, *Chem. Commun.*, **2004**, *2*, 188–189.

[53] Berkel van, S.S., van den Hoogenband, A., Terpstra, J.W., Tromp, M., Leeuwena van, P.W.N., van Strijdoncka, G.P.F. Base-free anaerobic Cu (II) catalysed aryl-nitrogen bond formations, *Tetrahedron Lett.*, **2004**, *45*, 7659–7662.

[54] Evans, D.A., Katz, J.L., West, T.R. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine, *Tetrahedron Lett.*, **1998**, *39*, 2937–2940.

[55] Collman, J.P., Zhong, M. An efficient diamine-copper complex-catalyzed coupling of arylboronic acids with imidazoles, *Org. Lett.*, **2000**, *2*, 1233–1236.

[56] Wu, F.T., Yan, N.N., Liu, P., Xie, J.W., Liu, Y., Dai, B. A general copper powder-catalyzed ullmann-type reaction of 3-halo-4(1*H*)-quinolones with various nitrogen-containing nucleophiles, *Tetrahedron Lett.*, **2014**, *55*, 3249–3251.

[57] Altman, R.A., Koval, E.D., Buchwald, S.L. Copper-catalyzed *N*-arylation of imidazoles and benzimidazoles, *J. Org. Chem.*, **2007**, *72*, 6190–6199.

[58] Xue, F., Cai, C., Sun, H., Shen, Q., Rui, J. β-Ketoimine as an efficient ligand for copper catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides, *Tetrahedron Lett.*, **2008**, *49*, 4386–4389.

[59] Xie, J.W., Yao, Z.B., Wang, X.C., Zhang, J. Cu_2O/1-(2-methylhydrazine-1-carbonyl)- isoquinoline 2-oxide catalyzed C-N cross-coupling reaction in aqueous media, *Tetrahedron*, **2019**, *75*, 3788–3792.

[60] Heidarizadeh, F., Majdi-Nasab, A. A green, homogeneous and reusable surfactant/copper based ionic liquid for the *N*-arylation of indoles, pyrazoles and imidazoles, *Tetrahedron Lett.*, **2015**, *56*, 6360–6363.

[61] Yang, Q., Wang, Y., Lin, D., Zhang, M. N-arylation of heterocycles catalyzed by activated-copper in pure water, *Tetrahedron Lett.*, **2013**, *54*, 1994–1997.

[62] Wang, X., Wang, M., Xie, J. Cu_2O/Cs_2CO_3/DMF: An efficient catalytic system for *N*- arylation of imidazole with aryl halides under ligand-free conditions, *Synth. Commun.*, **2017**, *47*, 1797–1803.

[63] Sreedhar, B., Venkanna, G.T., Kumar, K.B.S., Balasubrahmanyam, V. Copper (I) oxide catalyzed *N*-arylation of azoles and amines with arylboronic acid at room temperature under base-free conditions, *Synthesis*, **2008**, *5*, 795–799.

[64] Jitchati, R., Batsanov, A.S., Bryce, M.R. N-Arylation of nitrogen heterocycles with 2,4- difluoroiodobenzene, *Tetrahedron*, **2009**, *65*, 855–861.

[65] Choudary, B.M., Sridhar, C., Kantam, M.L., Venkanna, G.T., Sreedhar, B. Design and evolution of copper apatite catalysts for *N*-arylation of heterocycles with chloro-and fluoroarenes, *J. Am. Chem. Soc.*, **2005**, *127*, 9948–9949.

[66] Liu, P., Li, P., Wang, L. SiO_2-NHC-Cu^I-catalyzed *N*-arylation of imidazoles with arylboronic acids under base-free reaction conditions, *Syn. Commun.*, **2012**, *42*, 2595–2605.

[67] Chen, H., Wang, D., Wang, X., Huang, W., Ding, Q.C.K. Mild conditions for copper catalyzed *N*-arylation of imidazoles, *Synthesis*, **2010**, *9*, 1505–1511.

[68] Lv, X., Bao, W. A β-Keto ester as a novel, efficient, and versatile ligand for copper (I)- catalyzed C-N, C-O, and C-S coupling reactions, *J. Org. Chem.*, **2007**, *72*, 3863–3867.

[69] Liu, Y.S., Liu, Y., Ma, X.W., Liu, P., Xie, J.W., Dai, B. 3-(Diphenylphosphino) propanoic acid: An efficient ligand for the Cu-catalyzed *N*-arylation of imidazoles and 1*H*-pyrazole with aryl halides, *Chinese Chem. Lett.*, **2014**, *25*, 775–778.

[70] Hengchang, M., Shang, W., Qiansheng, S., Ziqiang, L. Oxazolidin-2-one as efficient ligand for the copper-catalyzed *N*-arylation of pyrrole, imidazole and indole, *Lett. Org. Chem.*, **2010**, *7*, 212–218.

[71] Verma, A.K., Singh, J., Sankar, V.K., Chaudhary, R., Chandra, R. Benzotriazole: An excellent ligand for Cu-catalyzed *N*-arylation of imidazoles with aryl and heteroaryl halides, *Tetrahedron Lett.*, **2007**, *48*, 4207–4210.

[72] Antilla, J.C., Baskin, J.M., Barder, T.E., Buchwald, S.L. Copper-diamine-catalyzed *N*-arylation of pyrroles, pyrazoles, indazoles, imidazoles, and triazoles, *J. Org. Chem.*, **2004**, *69*, 5578–5587.

[73] Alcalde, E., Dinares, I., Rodrıguez, S., de Miguel, C.G. Synthetic approaches to sterically hindered N-arylimidazoles through copper-catalyzed coupling reactions, *Eur. J. Org. Chem.*, **2005**, *2005*, 1637–1643.

[74] Liu, L.B., Frohn, M., Xi, N., Dominguez, C., Hungate, R., Reider, P.J. A soluble base for the copper-catalyzed imidazole *N*-arylations with aryl halides, *J. Org. Chem.*, **2005**, *70*, 10135–10138.

[75] Cao, C., Lu, Z., Cai, Z., Pang, G., Shi, Y. Cheap Cu(I)/hexamethylenetetramine (HMTA) catalytic system for C-N coupling reactions, *Synth. Commun.*, **2011**, *42*, 279–284.

[76] Zhu, L., Li, G., Luo, L., Guo, P., Lan, J., You, J. Highly functional group tolerance in copper-catalyzed N-arylation of nitrogen-containing heterocycles under mild conditions, *J. Org. Chem.*, **2009**, *74*, 2200–2202.

[77] Kantam, M.L., Venkanna, G.T., Sridhar, C., Sreedhar, B., Choudary, B.M. An efficient base-free *N*-arylation of imidazoles and amines with arylboronic acids using copper exchanged fluorapatite, *J. Org. Chem.*, **2006**, *71*, 9522–9524.

[78] Inamoto, K., Nozawa, K., Kadokawa, J., Kondo, Y. Efficient use of a surfactant for copper catalyzed coupling reaction of arylboronic acids with imidazoles in water, *Tetrahedron*, **2012**, *68*, 7794–7798.

[79] Mao, J., Hua, Q., Guo, J., Shi, D. Natural alkaloids for copper-catalyzed *N*-arylation of amines and nitrogen-containing heterocycles, *Catal. Commun.*, **2008**, *10*, 341–346.

[80] Lv, T., Wang, Z., Lan, J., You, J., Gao, G. Copper-catalyzed direct aryl quaternization of N-substituted imidazoles to form imidazolium salts, *J. Org. Chem.*, **2013**, *78*, 5723–5730.

[81] Wang, L., Chen, Z.C. Hypervalent iodine in synthesis 57: An efficient method for the synthesis of N-arylimidazoles by the cobalt-catalysed coupling of diaryliodonium salts with imidazoles, *J. Chem. Res.*, **2000**, *8*, 367–369.

[82] Chow, W.S., Chan, T.H. Microwave-assisted solvent-free N-arylation of imidazole and pyrazole, *Tetrahedron Lett.*, **2009**, *50*, 1286–1289.

[83] Yang, X.D., Liang, L., Zhang, H.B. Ligand-free copper-catalyzed arylation of imidazole and N, N'-carbonyl diimidazole, and microwave-assisted synthesis of N-Aryl-1H-imidazoles, *Helv. Chim. Acta*, **2008**, *91*, 1435–1442.

[84] Meshram, H.M., Reddy, B.C., Ramesh, P., Rao, N.N. An efficient and improved protocol for the *N*-arylation of *N*-heteroaryls using Ionic liquid as a reaction media, *Pharm. Chem.*, **2012**, *4*, 1544–1551.

[85] Cui, Y.L., Guo, X.N., Wang, Y.Y., Guo, Y.X. Visible-light-driven photocatalytic *N*-arylation of imidazole derivatives and arylboronic acids on Cu/graphene catalyst, *Sci. Rep*., **2015**, *5*, 12005.

[86] Pai, G., Chattopadhyay, A.P. *N*-Arylation of nitrogen containing heterocycles with aryl halides using copper nanoparticle catalytic system, *Tetrahedron Lett.*, **2016**, *57*, 3140–3145.

[87] Islam, S., Salam, N., Kundu, S., Roy, A.S., Mondal, P., Roy, S., Bhaumik, A. Cu-grafted mesoporous organic polymer: A new recyclable nanocatalyst for multi-component, *N*- arylation and *S*-arylation reactions, *Catal. Sci. Technol.*, **2013**, *3*, 3303–3316.

[88] Nador, F., Volpe, M.A., Alonso, F., Radivoy, G. Synthesis of *N*-aryl imidazoles catalyzed by copper nanoparticles on nanosized silica-coated maghemite, *Tetrahedron*, **2014**, *70*, 6082–6087.

[89] Kim, A.Y., Lee, H.J., Park, J.C., Kang, H., Yang, H., Song, H., Park, K.H. Highly efficient and reusable copper-catalyzed *N*-arylation of nitrogen-containing heterocycles with aryl halides, *Molecules*, **2009**, *14*, 5169–5178.

[90] Liu, Y., Zhang, Q., Ma, X., Liu, P., Xie, J., Dai B., Liu, Z. Salen-Cu(II) complex catalyzed *N*-arylation of imidazoles under mild conditions, *Int. J. Org. Chem*., **2013**, *3*, 185–189.

[91] Wang, Y., Wu, Z., Wang, L., Li, Z., Zhou, X. A simple and efficient catalytic system for *N*-arylation of imidazoles in water, *Chem. Eur. J.*, **2009**, *15*, 8971–8974.

[92] Milenković, M.R., Papastavrou, A.T., Radanović, D., Pevec, A., Jagličić, Z., Zlatar, M., Gruden, M., Vougioukalakis, G.C., Turel, I., Anđelković, K., Čobeljić, B. Highly-efficient *N*-arylation of imidazole catalyzed by Cu(II) complexes with quaternary ammonium-functionalized 2-acetylpyridine acylhydrazone, *Polyhedron*, **2019**, *165*, 22–30.

[93] Mityanov, V.S., Perevalov, V.P., Tkach, I.I. Synthesis of 2-unsubstituted 1- arylimidazoles, *Chem. Heterocycl. Compd.*, **2013**, *48*, 1793–1800.

[94] Adib, M., Ansari, S., Feizi, S., Damavandi, J., Mirzaei, P. A one-pot, four-component synthesis of N-substituted 2,4-diarylimidazoles, *Synlett*, **2009**, *20*, 3263–3266.

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