4RECENT PROGRESS IN THE SYNTHESIS OF IMIDAZOLE DERIVATIVES *VIA* CYCLIZATION OF ALKYNES AND NITROGEN COMPOUNDS

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Abstract. *Imidazole derivatives are constituent of numerous natural compounds and many biologically active structures. In addition, imidazoles have been also successfully utilized as intermediaries in organic transformations for the synthesis of more elaborated structures. This characteristic makes them important substrates for further transformations. This chapter describes the efforts in the synthesis of imidazole derivatives using the reaction of alkynes with nitrogen-compounds under transition metal-catalyzed and metal-free conditions.*

Contents

1. Introduction

Imidazole derivatives are constituent of numerous natural compounds and many biologically active structures.[1-4] In addition, imidazoles have been also successfully utilized as intermediaries in organic transformations for the synthesis of more elaborated structures.[5] Because of their peculiar chemistry and pharmacological applications, the works covering the synthesis and application of imidazoles have been intensified in recent years.[6] Although many synthetic approaches have been developed to the synthesis of imidazoles, most of the practical syntheses reported to date involves the reaction of α-diketone, aldehyde, and ammonium acetate,[7] the one-pot cyclization of α-hydroxyketones, primary alcohols and ammonium acetate,[8] alkynes oxidation followed by cyclization with aldehydes and ammonium acetate,[9,10] and isocyanide bond [3+2] cycloaddition reactions.[11,12] Despite the extensive use of alkynes as a substrate in the

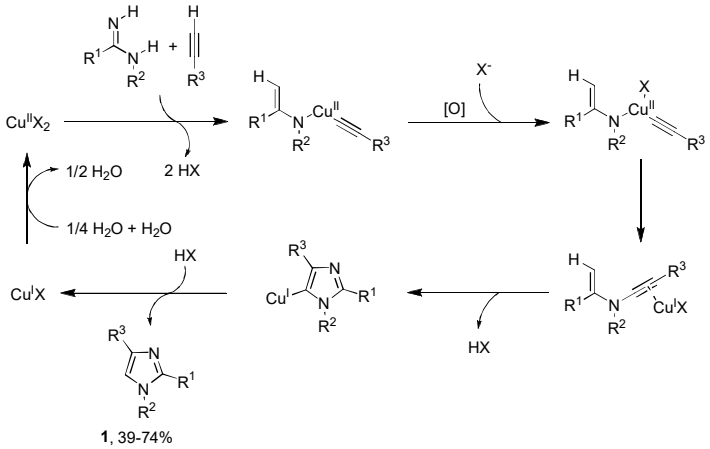
synthesis of imidazoles, the addition and cycloaddition reactions into carbon-carbon triple bond are the most prominent. Numerous approaches have been developed for the synthesis of *N*-heterocycles by using alkynes as substrate.[13-17] The substituted alkynes have electronic polarization in the triple bond, which makes the α- and β-carbons electrophilic and nucleophilic, respectively.[18] As a result, several options are available in the literature reporting the regioselective addition of the electrophiles and nucleophiles onto the carbon-carbon triple bond of the alkynes, leading to functionalized imidazoles.[19,20] The prime aim of this chapter is to summarize the main reactions of interest to the synthetic chemist for the preparation of imidazoles by using alkynes and a nitrogen source as substrates. This chapter will cover the data published mostly in the past decade.

2. Synthesis of imidazoles

2.1. Transition metal-catalyzed synthesis of imidazoles

2.1.1. Copper-catalyzed synthesis of imidazoles

Copper salts have been also shown to promote the cyclization of alkynes and nitrogen compounds in the formation of imidazoles. One methodology explored the catalytic efficiency of copper salts in promoting the preparation of 1,2,4-trisubstituted imidazoles **1** using terminal alkynes and amidines (Scheme 1).[21] The reaction involved a regioselective copper-catalyzed oxidative diamination of terminal alkynes using oxygen as the co-oxidant. The catalytic cycle starts with the formation of a copper(II)-diyne complex by activation of the alkyne and the amidine. Oxidation of the copper(II)-diyne intermediate followed by reductive elimination affords the alkynylacetimidamides, which *via* an intramolecular 5-*endo*-dig cyclization and protonation give the imidazole. Another methodology explored the reactivity of *N*-propargyl amidines with copper(II) catalyst in the presence of molecular oxygen as the oxidant, leading to 4-benzoylimidazoles **2** (Scheme 2).[22] The cyclization reactions were carried out with $Cu(OAc)_2$ (10 mol %) and 1,10-phenanthroline (10 mol%) in the presence of O_2 (1 atm) in DMF at 80 °C.



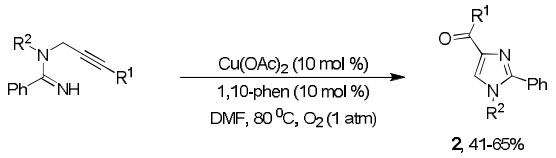
R^1 = *n*-C_3H_7, C_6H_5, 2-Me-C_6H_4, 4-*t*-BuC_6H_4, 3,4-$(MeO)_2$-C_6H_3, 4-Br-C_6H_4; R^2 = Me, C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-MeO-C_6H_4, 3,4,5-$(MeO)_3$-C_6H_2, 4-Cl-C_6H_4, 4-MeO_2C-C_6H_4; R^3 = *c*-C_3H_5, *t*-C_4H_9, *n*-C_6H_{13}, C_6H_5, 4-MeO-C_6H_4, MeO_2C, Me_3Si.

Scheme 1

2.1.2. Gold-catalyzed synthesis of imidazoles

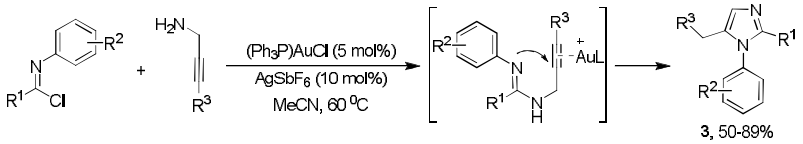
It has been well recognized that gold catalysts can efficiently activate the carbon-carbon triple bonds toward the nitrogen nucleophilic addition to give *N*-heterocycles. This chemistry was utilized in the formation of 2-fluoroalkyl imidazole derivatives **3** starting from propargyl amidines (Scheme 3).[23,24] The reactions were carried out with Ph_3AuCl (5 mol%) as a catalyst, in the presence of $AgSbF_6$ (10 mol%) as a cocatalyst and acetonitrile as a solvent at 60 °C. Under these conditions, a range of substituents on propargyl

amidines were tolerated giving the products in yields ranging from 50 to 89%. The authors observed that the addition of an electrophilic source, such as NIS, in the reaction medium led to imidazole-5-carbaldehydes.



R^1 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4; R^2 = $C_6H_5CH_2$, CH_2=$CHCH_2$.

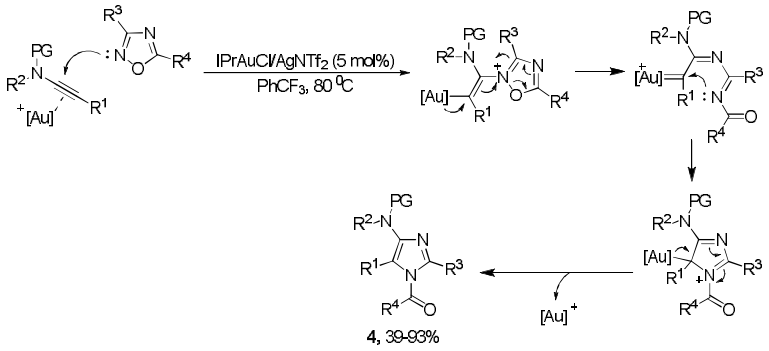
Scheme 2



R^1 = F_3C, BrF_2C, HF_2C, F_3C, $F_3CF_2CEtO_2C$; R^2 = H, 2-Me, 3-Me, 4-Me, 4-MeO, 2-Br, 2-Cl, 4-O_2N, 4-EtO_2C, 3-F_3C, 4-NC; R^3 = H, C_6H_5.

Scheme 3

The gold-catalyzed cyclization of ynamides with saturated 1,2,4-oxadiazoles gave *N*-acyl-substituted 4-aminoimidazoles **4** (Scheme 4).[25] The reaction involved the regioselective intermolecular addition of 1,2,4-oxadiazoles to the activated carbon-carbon triple bond leading to the formation of α-imino gold carbenes, which allowed the intermolecular transfer of *N*-acylimino nitrenes to ynamides, followed by an intramolecular chemoselective [3+2] annulation. A similar protocol was reported in parallel using 4,5-dihydro-1,2,4-oxadiazole, as the nucleophilic nitrene equivalent, which gave NH-, alkyl-, and aryl-substituted 4-aminoimidazoles **5** (Scheme 5).[26]



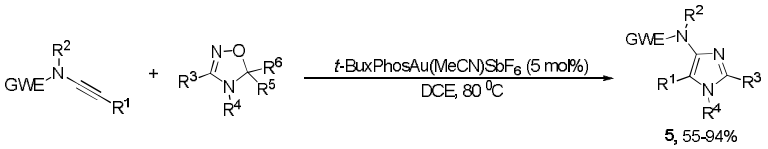
R^1 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Br-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 3-thienyl; R^2 = Me, C_6H_5; R^3 = Et, C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4: R^4 = Bz, Ac, 4-MeO_2C-C_6H_4C(O), 4-F-C_6H_4C(O); PG = Bs, Ms, Ns, Ts.

Scheme 4

2.1.3. Lanthanum-catalyzed synthesis of imidazoles

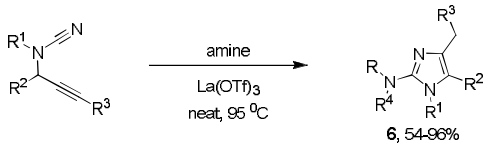
The use of lanthanum-catalyzed cyclization of alkynes and nitrogen compounds has been rarely reported for the preparation of imidazoles. In a particular example, 2-aminoimidazoles **6** were prepared *via* a lanthanum(III)-catalyzed hydroamination of propargyl guaninidines and tertiary amines (Scheme 6).[27] The reaction was best catalyzed with $La(OTf)_3$ in the presence of amine and the complete absence of solvents, at

95 °C. When the amines have a higher molecular weight, the reactions could not be performed under solvent-free conditions. In these cases, the use of 2-propanol as a solvent became a good option.



R^1 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 4-EtO_2C-C_6H_4, 4-O_2N-C_6H_4, 2-naphthyl; R^2 = Me, C_6H_5; R^3 = *n*-C_4H_9, *c*-C_3H_5, *c*-C_6H_{11}, C_6H_5; R^4 = H, *n*-C_4H_9, C_6H_5, 4-Cl-C_6H_4, Bn; R^5 = H, Me; R^6 = H, Et, C_6H_5; EWG = Ms, Ts.

Scheme 5

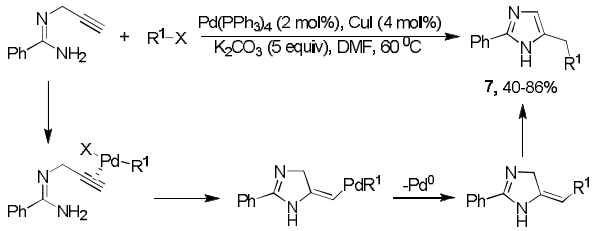


R^1 = Me, allyl, Bn; R^2 = H, *n*-C_4H_9, 4-BnO-$C_6H_4CH_2$; R^3 = *n*-C_5H_{11}, Bn, 4-Me-$C_6H_4CH_2$; amines = morpholine, methyl allyl amine, pyrrolidine, diallylamine, methyl benzyl amine, 4-iperidone ethylene acetal, isoindoline, tetrahydroisoquinoline.

Scheme 6

2.1.4. Palladium-catalyzed synthesis of imidazoles

The reaction of *N*-propargyl-benzamidines with aryl halides catalyzed by palladium and copper salts afforded 4-substituted-2-phenylimidazoles **7** (Scheme 7).[28] This reaction proceeds *via* an intermolecular aminopalladation to give the vinyl-palladium intermediary, followed by a reductive elimination and aromatization to afford the imidazole products (Scheme 7). In another approach, 2-fuoroalkyl-5-benzyl imidazoles **8** were prepared *via* an intermolecular aminopalladation of fluorinated propargyl amidines with aryl iodides (Scheme 8).[29]



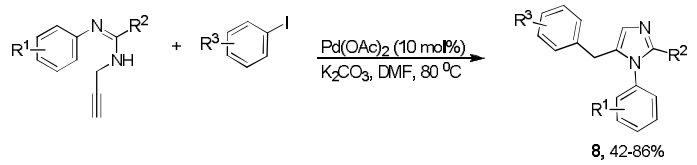
R^1 = C_6H_5, 3-F_3C-C_6H_4, 4-O_2N-C_6H_4, 4-MeC(O)-C_6H_4, 2-O_2N-C_6H_4, 5-pyrimidyl; X = Br, I.

Scheme 7

2.1.5. Rhodium-catalyzed synthesis of imidazoles

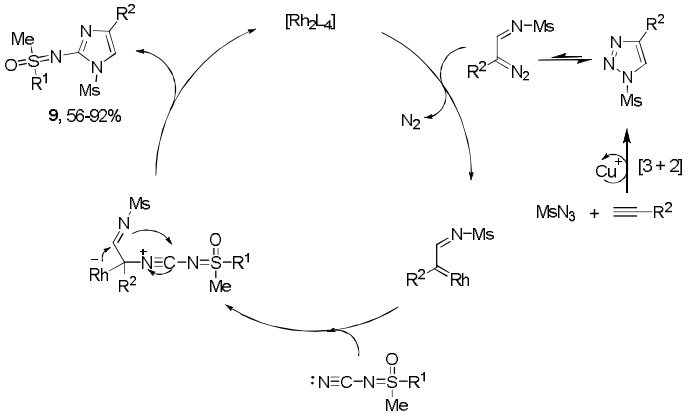
A cooperative catalytic system formed by rhodium and copper salts was used for the preparation of *N*-imidazolyl sulfoximines **9** from *N*-cyano sulfoximines, terminal alkynes, and *N*-mesyl azide in a one-pot procedure (Scheme 9).[30] The reaction took place in good yields using $Rh_2(OPiv)_4$ (2 mol%) and CuTC (10 mol%) in toluene, at room temperature for 1 h and then, stirred at 80 °C for 30 min. The possible role of the

copper catalyst is to promote the formation of α-diazo imine intermediary from alkyne and azide, which reacts with the rhodium catalyst giving the rhodium-carbenoid. The nucleophilic attack of sulfoximine to rhodium-carbenoid and the addition of nitrilium ion afford the corresponding imidazole (Scheme 9).



R^1 = H, 2-MeO, 4-MeO, 4-Cl; R^2 = F_3C, BrF_2C, HF_2C; R^3 = H, 3-Me, 3-MeO, 4-MeO, 4-MeO_2C, 4-EtO_2C, 2-F, 4-F_3C.

Scheme 8



R^1 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F_3C-C_6H_4; R^2 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F_3C-C_6H_4.

Scheme 9

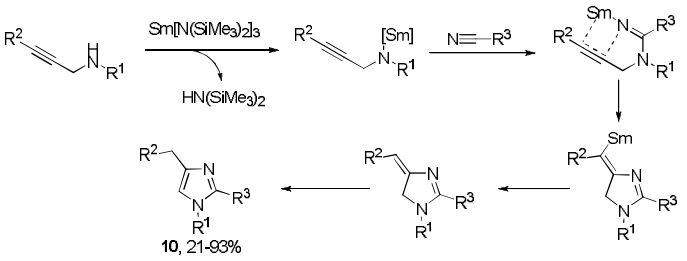
2.1.6. Samarium-catalyzed synthesis of imidazoles

Although lanthanide-catalyzed cyclization reactions play a significant role in the synthesis of heterocycles, the use of samarium-catalyzed cyclization of alkynes with amino compounds has been reported only rarely. In an example, the reaction of propargylamines and nitriles in the presence of $Sm[N(SiMe_3)_2]_3$, in THF, at 60 °C for 24 h gave 1,2,4-trisubstituted imidazoles **10** (Scheme 10).[31] The yields of imidazoles were influenced by the steric effects and the presence of strong coordinating atoms on nitriles, such as MeO, NO_2, and NC. High yields were obtained with both terminal and internal propargyl amines. In the proposed mechanism, the activation of nitrogen-hydrogen bond gives the samarium-amido complex with the release of $HN(SiMe_3)$. The insertion of one nitrile into the samarium-nitrogen bond affords the samarium-amidinate intermediate. The intramolecular addition of nitrogen to alkyne leads to cyclization, with the formation of vinyl-samarium complex, which affords the product after protonation and isomerization (Scheme 10).

2.1.7. Silver-catalyzed synthesis of imidazoles

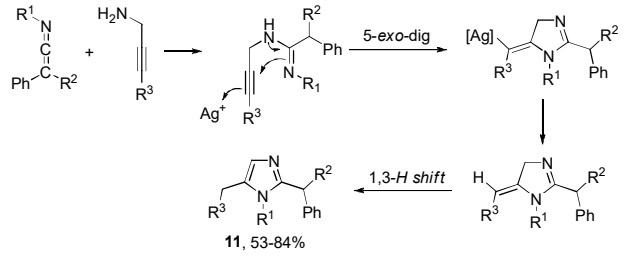
The application of silver salts as catalysts in the cyclization reactions of alkynes and nitrogen compounds was also explored for the synthesis of imidazoles. Propargylamines with ketenimines have been employed as substrates in a cascade reaction catalyzed by AgOTf giving as the product 1,2,5-trisubstituted 1*H*-imidazoles **11** (Scheme 11).[32] The cyclization takes place *via* a nucleophilic addition of the propargylic amine to ketenimine, followed by a silver-catalyzed electrophilic cyclization reaction of the alkyne, and a

tautomerism/isomerism/metal-H exchange cascade (Scheme 11). The authors observed that by using molecular iodine instead of silver catalyst, 5-formyl-1,2-disubstituted imidazoles were obtained.



R^1 = Me, C_6H_5, 4-MeO-C_6H_4, $C_6H_5CH_2$, $C_6H_5CH_2CH_2$; R^2 = H, *t*-C_4H_9, *c*-C_3H_5, C_6H_5, Me_3Si; R^3 = *n*-C_4H_9, C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-F_3C-C_6H_4, 4-O_2N-C_6H_4, 4-pyridyl, 2-thienyl, $C_6H_5CH_2$, 4-*t*-Bu-$C_6H_4CH_2$, 2-Me-$C_6H_4CH_2$, 4-MeO-$C_6H_4CH_2$, 4-F-$C_6H_5CH_2$.

Scheme 10



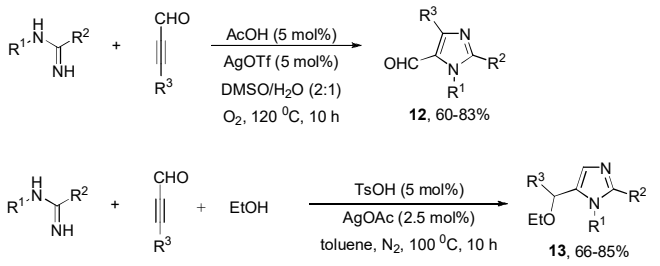
R^1 = C_6H_5, 4-Me-C_6H_4, 2,5-$(Et)_2$-C_6H_4, 4-MeO-C_6H4, 2-Br-C_6H4, 3-Br-C_6H_4, 4-Br-C_6H_4, 3-O_2N-C_6H_4, 4-O_2N-C_6H_4, 4-EtO_2C-C_6H_4, 3-pyridyl; R^2 = Me, C_6H_5; R^3 = H, C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 2-Br-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4.

Scheme 11

Amidines have been also demonstrated to be useful substrates for the silver-catalyzed preparation of imidazoles. The treatment of amidines and enynals with AgOTf (5 mol%) in the presence of a catalytic amount of acetic acid led to 1,2,4-triarylimidazoles **12** (Scheme 12).[33] The reaction conditions tolerated a broad range of aryl substituted groups at the amidine and aldehyde. Similarly, the addition of alcohols or water in the reaction media led to the formation of 5-alkoxyimidazoles **13** (Scheme 12).[34] Mechanistically, these two reactions differ from each other mainly in the first step. In the silver-catalyzed reaction of amidine and aldehyde in the presence of acetic acid, the key intermediate is the product of amidine addition to the alkyne, which gave the product *via* dehydrogenation oxidation (Scheme 13). However, when the reaction is carried out in the presence of alcohols or water, the key intermediate is the condensation product of amidine with an aldehyde, which delivers the product *via* an intramolecular cyclization, followed by the nucleophilic addition of alcohols or water (Scheme 14).

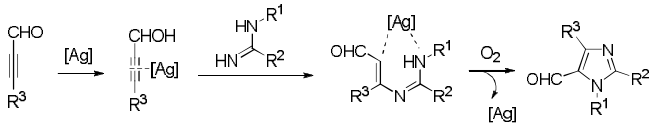
The reactivity of propargylazide derivatives in the silver(I)-catalyzed cyclization reactions was explored for the synthesis of polysubstituted imidazoles **14** (Scheme 15).[35] In this protocol, $AgNO_3$ (10 mol%) and DMAP (10 mol%) catalyzed the sequential reaction utilizing propargylazide, triphenylphosphine, isocyanates, and amines as substrates, giving substituted imidazoles in yields ranging from 59 to 89%. Propargyl azides having electron-rich and electron-poor aromatic ring directly bonded to alkyne, alkyl, and aryl isocyanates as well as primary and secondary amines were well tolerated under the reaction conditions. The imidazoles are formed through the initial reaction of azide with triphenylphosphine giving iminophosphorane, which reacts with phenyl isocyanate affording the carbodiimide. The addition of amine

to carbodiimide produces the guanidine intermediate, which affords the products *via* a 5-*exo*-dig cyclization and isomerization catalyzed by silver and DMAP (Scheme 15).

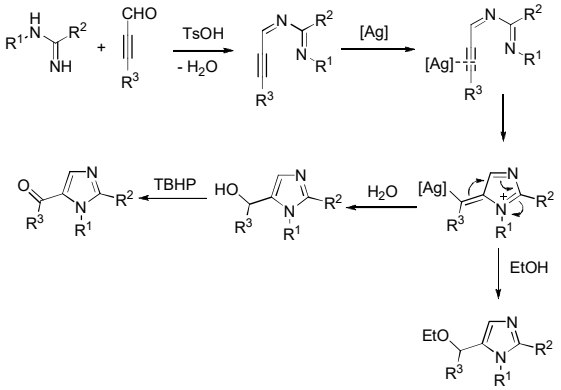


R^1 = C_6H_5, 3-Me-C_6H_4, 4-Me-C_6H_4, 3,4-$(Me)_2$-C_6H_3, 3-NeO-C_6H_4, 4-MeO-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4; R^2 = C_6H_5, 3-Me-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 3-Br-C_6H_4; R^3 = C_6H_5, 3-Me-C_6H_4, 4-Me-C_6H_4, 3,5-$(Me)_2$-C_6H_3, 4-Br-C_6H_4.

Scheme 12



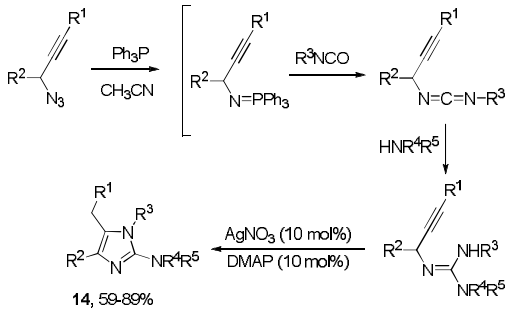
Scheme 13



Scheme 14

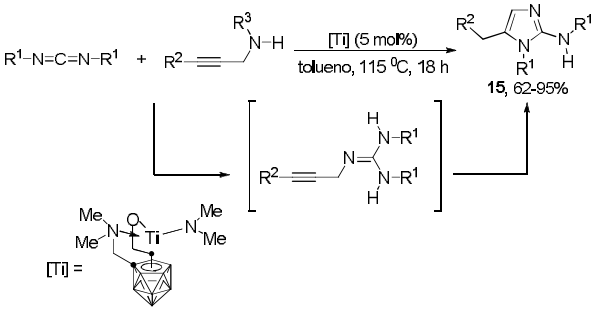
2.1.8. Titanium-catalyzed synthesis of imidazoles

Imidazoles are also accessible *via* the reaction of alkynes with nitrogen sources using the titanium complex as a catalyst. In one example reported, 2-aminoimidazoles **15** were obtained in good yields in the reaction of propargylamines with carbodiimides using titanacarborane monamide as a catalyst (Scheme 16).[36] The reaction conditions were studied and other metal (Ti, Zr, and Hf) complexes were also tested; however, only the titanacarborane complex was efficient to catalyze the cyclization. The reaction mechanism was studied, in which the ^{1}H-NMR analysis confirmed that guanidinoalkyne was the key intermediate for this reaction.



R^1 = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4; R^2 = H, Me; R^3 = *i*-C_3H_7, n-C_4H_9, C_6H_5, 3-Me-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4; R^4 = R^5 = Et, piperidinyl, morpholinyl, $PhCH_2$(Me), *n*-C_3H_7, *n*-C_4H_9, *t*-C_4H_9.

Scheme 15



R^1 = *i*-C_3H_5, *c*-C_6H_{11}, 4-Me-C_6H_4; R^2 = H, C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Br-C_6H_4, 2-F_3C-C_6H_4, 4-F_3C-C_6H_4; R^3 = H, Me,

Scheme 16

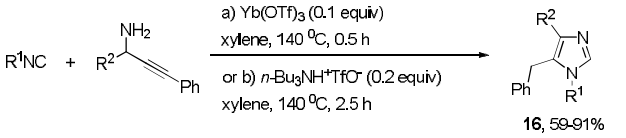
2.1.9. Ytterbium-catalyzed synthesis of imidazoles

Alkynes and nitrogen compounds have been also successfully cyclized by using ytterbium catalysts in the preparation of imidazoles. Thus, imidazoles **16** were prepared selectively *via* a [3+2] heteroannulation of propargylamines with isonitriles (Scheme 17).[37] The reaction gave the products in good yields when $Yb(OTf)_3$ (10 mol%) was used as a catalyst in the presence of xylene as a solvent at 140 °C. The authors observed that increasing the amount of catalyst leads to the selective formation of dihydropyridines, *via* a [4+2] heteroannulation, instead of imidazoles.

2.2. Transition metal-free synthesis of imidazoles

2-Thio- and 2-oxoimidazoles **17** were prepared through an addition-cyclization-isomerization reaction of propargylcyanamides with thiol and alcohol nucleophiles (Table 1, entry 1).[38] *N*-[2-(1-alkynyl)phenyl]carbodiimides and isocyanides in the presence of cesium carbonate led to the formation of indolyl imidazole derivatives **18** *via* an initial [3+2] cycloaddition followed by a protonolysis and isomerization sequence (Table 1, entry 2).[39] Carbodiimides were also applied as substrates to the reactions with propargyl amines promoted by bases, giving 2-iminoimidazoles **19** (Table 1, entry 3).[40] Amidine hydrochlorides and bromoacetylenes have proven to be useful substrates for the synthesis of di- and trisubstituted imidazoles **20** in a metal-free protocol (Table 1, entry 4).[41] Substituted imidazoles **21** have been obtained by oxidative [2+2+1] annulations of alkynes, nitriles, and iminoiodanes promoted by boron trifluoride nitrile complexes (Table 1, entry 5).[42] When subjected to acid conditions, internal alkynes,

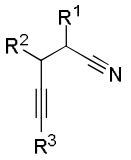
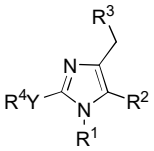
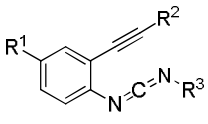
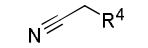
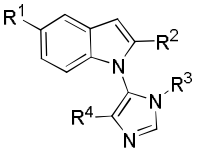
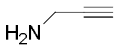
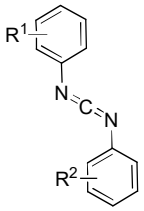
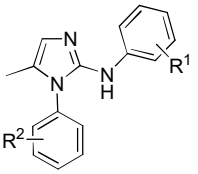
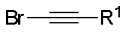
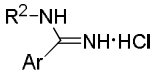
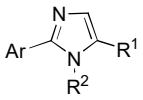
aldehydes, and anilines gave imidazole derivatives **22** via a multicomponent reaction methodology (Table 1, entry 6).[9] Benzyl and aliphatic amines can acted as the nitrogen nucleophiles in the organoiodine(III)-promoted hydroamination-azidation-cyclization sequence of alkynes affording substituted imidazoles **23** (Table 1, entry 7).[43]

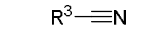
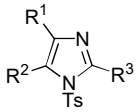
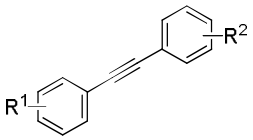
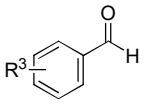
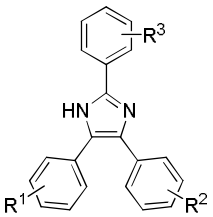
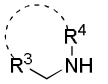
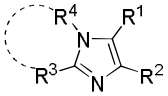


R^1 = *n*-C_4H_9, *t*-C_4H_9, c-C_6H_{11}, $(Ph)_2CH$; R_2 = C_6H_5, 4-Me-C_6H_4, 4-Ph-C_6H_4, 4-Br-C_6H_4, 3,4-$(Cl)_2$-C_6H_3, 4-F-C_6H_4, 3-thienyl, 2-naphthyl.

Scheme 17

Table 1. Transition metal-free synthesis of imidazoles.

entry	alkyne	reagents	imidazoles, yield
1		R^4OH/R^4SH (3 - 10 equiv) *i*-Pr_2NEt (5 - 15 equiv) *i*-PrOH (0.25M) 120 °C, 12-24 h	 Y = S, O **17**, 53-97%
2		 Cs_2CO_3, DMSO 40 °C	 **18**, 47-85%
3		 NaOH, DMSO 80 °C, 2 h	 **19**, 53-80%
4		 K_2CO_3, bipy, toluene H_2O, 120 °C, air	 **20**, 27-88%

5		 PhINTs (1.8 equiv) BF_3·R^3CN (2.4 equiv) r.t., 4 h	 **21**, 23-72%
6		 PivOH (1 equiv) NH_4OAc (4 equiv) DMSO, H_2O, 140 ^{0}C under air	 **22**, 65-90%
7		 $PhI(OCOCF_3)_2$ (2.0 equiv) $TMSN_3$ (4.0 equiv) DCE (0.04 M) -5 ºC, air	 **23**, 30-85%

3. Synthesis of imidazolidine

Imidazolidine derivatives are known to possess antispasmodic, anticancer, anti-inflammatory, and analgesic activities.[44] They have been widely used as intermediaries in organic transformations as chiral ligands, in the synthesis of imidazoles, and organometallic chemistry as auxiliaries. Accordingly, new routes for the preparation of imidazolidine derivatives have constantly appeared in the literature. One of the most convenient methodologies for the preparation of imidazolidines is the cyclization reaction of alkynes and nitrogen compounds.

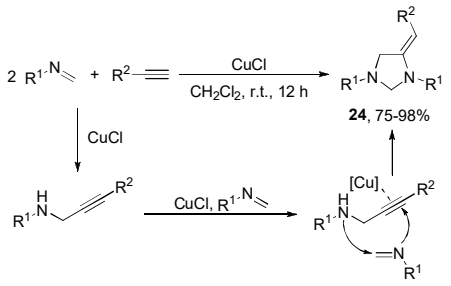
3.1. Transition metal-catalyzed synthesis of imidazolidines

3.1.1. Copper-catalyzed synthesis of imidazolidines

The copper-catalyzed cyclization of alkynes and nitrogen compounds was successfully applied to the synthesis of imidazolidines. Functionalized imidazolidines **24** were prepared through the copper(I)-catalyzed domino three-component coupling and cyclization reaction involving two imine units and terminal alkynes (Scheme 18).[45] The authors studied the optimization of the reaction conditions finding that the use of CuCl (20 mol%), in dichloromethane, at room temperature gave the products in best yields. The reaction mechanism proposed would involve an initial formation of propargylamine *via* the reaction of alkyne with imine. The subsequent cyclization of propargylamine with the second molecule of imine, promoted by copper, affords the product (Scheme 18).

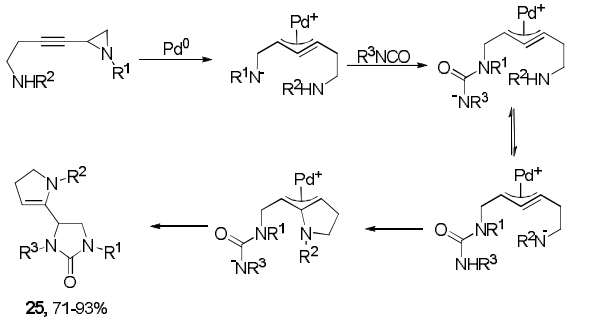
3.1.2. Palladium-catalyzed synthesis of imidazolidines

The cyclization of alkynes with nitrogen compounds using palladium as a catalyst was also developed for the synthesis of imidazolidines. When $Pd(PPh_3)_4$ (5 mol%) in THF at room temperature was applied to a variety of 2-alkynylaziridines and isocyanates, 4-(4,5-dihydropyrrol-2-yl)imidazolidin-2-one derivatives **25** were obtained in good yields (Scheme 19).[46] Based on the results obtained, the authors suggested that the reaction mechanism starts with the formation of allenylpalladium(II) intermediate from the palladium(0)-catalyzed ring-opening of aziridine. One cyclization onto the central carbon atom of allenylpalladium and the second cyclization of the resulting η^3-allylpalladium complex give the products (Scheme 19).



R^1 = *c*-C_6H_{11}, C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 3,5-$(Me)_2$-C_6H_3, 4-MeO-C_6H_4, $C_6H_5CH_2$; R^2 = MeO_2C, EtO_2C.

Scheme 18



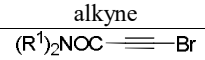
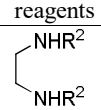
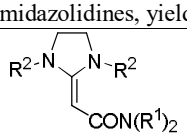
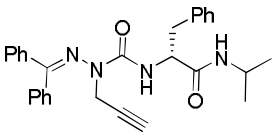
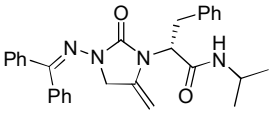
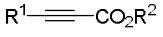
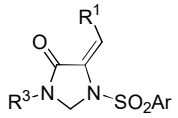
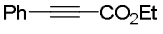
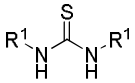
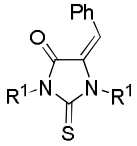
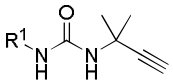
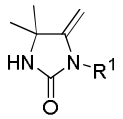
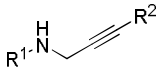
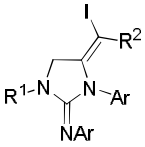
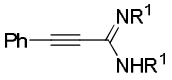
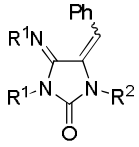
R^1 = Ts, Ms, Mts; R^2 = Ts, Mts; R^3 = C_6H_5, 2-Me-C_6H_4, 4-Me-C_6H_4, 4-i-Pr-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 3-F_3C-C_6H_4, 3-O_2N-C_6H_4.

Scheme 19

3.2. Transition metal-free synthesis of imidazolidines

The transition metal-free intramolecular or intermolecular cyclization of alkynes and nitrogen compounds has been developed for the synthesis of imidazolidines. The intermolecular cyclization of *N*,*N*′-protected ethylenediamine with bromopropilamide promoted by K_3PO_4, under heating, led to the stereoselective preparation of unsymmetrically protected 2-alkylidene-1,3-imidazolidines **26** (Table 2, entry 1).[47] A base-promoted cyclization was also applied to the aza-propargyl glycinamides using sodium hydride to give *N*-amino-imidazolinones **27** (Table 2, entry 2).[48] Four-component one-pot procedure was described for the preparation of imidazolidinones **28** starting from arylsulfonyl isocyanate, alkyl propiolate or dialkyl acetylenedicarboxylate, triphenylphosphine, and thioureas as dinucleophiles (Table 2, entry 3).[49,50] Phosphines were also suitable catalysts for the intramolecular cyclization of arylpropiolates with thioureas leading to imidazolidinethiones **29** (Table 2, entry 4).[51] TBAF was also efficient to promote the cyclization of propargyl urea to imidazolidinones **30** (Table 2, entry 5). The process occurred exclusively *via* a 5-*exo*-dig *N*-cyclization mode without the formation of six-membered *N*-heterocycles.[52] The cyclization of propargyl amines with carbodiimides can be performed in the presence of iodine giving imidazolidin-2-imines **31** *via* an halocyclization reaction (Table 2, entry 6).[53] In addition to bases, acids, and halogen, the alkaline earth can also be used as the catalyst in the cyclization of alkynes with nitrogen compounds. Reactions of propargyl amidines with isocyanates in the presence of a catalytic amount of strontium amide complex provided the functionalized bicylo[3.2.2]nonadienes (4-imino)-imidazolidinones **32** (Table 2, entry 7).[54,55]

Table 2. Transition metal-free synthesis of imidazolidines.

entry	alkyne	reagents	imidazolidines, yield
1		 K_3PO_4 (2 equiv) DMF, 70 - 100 ^{0}C	 **26**, 33-91%
2		NaH (2.5 equiv) MeCN, r.t., 2 h	 **27**, 78%
3		R^3NH_2 + $ArSO_2NCO$ PPh_3, CH_2Cl_2, r.t.	 **28**, 80-90%
4		 Bu_3P (20 mol%)	 **29**, 39-73%
5		TBAF (1.0 equiv) THF, reflux	 **30**, 70-98%
6		ArN=C=NAr + I_2, K_2CO_3 ethyl acetate, r.t., 12 h	 **31**, 62-99%
7		$R^2N=C=O$ $[Sr[N(SiMe_3)_2]_2(THF)_2]$ C_6D_6, r.t.	 **32**, 53-99%

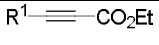
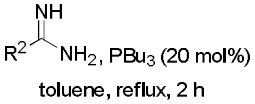
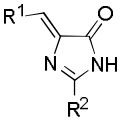
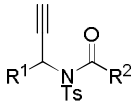
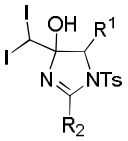
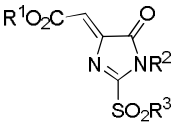
4. Synthesis of imidazolines

Imidazolines are important *N*-heterocyclic compounds in medicinal chemistry because they present significant biological activities.[56-58] They can be prepared by several classical methods, as well as by more recent protocols, which have been developed to increase the reaction efficiency.[59] Here we will describe some selected examples involving the preparation of imidazolines starting from alkynes and nitrogen compounds.

4.1. Transition metal-free synthesis of imidazolines

Transition metal-free protocols have been employed to the synthesis of imidazolines by using the phosphine-catalyzed cyclization of alkynes, halocyclization of alkynes, and multicomponent cyclization. In a representative reaction, phosphine-catalyzed the tandem addition and intramolecular cyclization of amidine on arylpropiolates leading to 4-arylidene-5-imidazolines **33** (Table 3, entry 1).[60] Halogens can also be applied to the cyclization of alkynes to form imidazolines. Terminal propargylamide when treated with NIS in the presence of trimethylsilyl azide led to the formation of diiodomethylated imidazolines **34** (Table 3, entry 2).[61] The four-component reaction between sodium arylsulfinates, trichloroacetonitrile, benzylamines, and acetylenedicarboxylates, in water, at room temperature was developed for the preparation of sulfonyl-imidazoline derivatives **35** (Table 3, entry 3).[62]

Table 3. Transition metal-free synthesis of imidazolines.

entry	alkyne	reagents	imidazolines, yield
1			 **33**, 68-90%
2		NIS (2.4 equiv) $TMSN_3$ (3.6 equiv) H_2O (2. 0 equiv) DCE, 60 ^{0}C	 **34**, 15-80%
3		CI_3CN, R^2-NH_2 R^3-SO_2Na^+ H_2O, r.t., 5 h	 **35**, 41-90%

5. Conclusion

Numerous approaches have been developed for the synthesis of *N*-heterocycles by using alkynes as the substrate. The substituted alkynes have electronic polarization in the triple bond, which makes the α- and β-carbons electrophilic and nucleophilic, respectively. As a result, several options are available in the literature reporting the regioselective addition of electrophiles and nucleophiles onto the carbon-carbon triple bond of the alkynes, leading to functionalized imidazoles. The prime aim of this chapter was to summarize the main reactions of interest to the synthetic chemist for the preparation of imidazoles by using alkynes and a nitrogen source as substrates. Although the methodologies for preparing imidazoles have come a long way, because of their wide practical application, this area is in constant growth and new and modern procedures for the synthesis of these compounds will always appear.

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