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Copper-Catalyzed Oxidative Diamination of Terminal Alkynes by Amidines: Synthesis of 1,2,4-Trisubstituted Imidazoles

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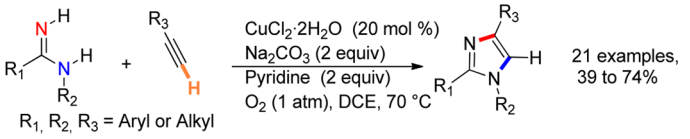
ABSTRACT



An efficient copper-catalyzed synthesis of 1,2,4-trisubstituted imidazoles using amidines and terminal alkynes has been developed. Overall, the oxidative process, which involves Na_2CO_3, pyridine, a catalytic amount of $CuCl_2 \cdot 2H_2O$, and oxygen (1 atm), consisted of a regioselective diamination of alkynes allowing the synthesis of diverse imidazoles in modest to good yields.

Metal promoted transformations involved in carbon–heteroatom bond formation hold a central place in organic chemistry. This field has been especially productive allowing the functionalization of a broad variety of nitrogen nucleophiles through Pd- and Cu-catalyzed reactions.[1] In addition to single event (C–N bond formation), strategies involving multiple bond formation have appeared in the literature including strategies for the synthesis of useful heterocycles.[2] Diamination belongs to this area of research and has been actively pursued.[3] While this strategy has been essentially devoted to the functionalization of alkenes, related reactions involving alkynes are limited.[4]

Amidines are important units found in various drugs or natural products and play an important role as precursors for the synthesis of diverse heterocycles such as benzimidazoles, quinazolines, imidazoles, or pyrimidines.[5] Given the importance of N-arylated amidines, a number of transition-metal-catalyzed *N*-arylative procedures have been described.[6] Among these, Cu-catalyzed oxidative

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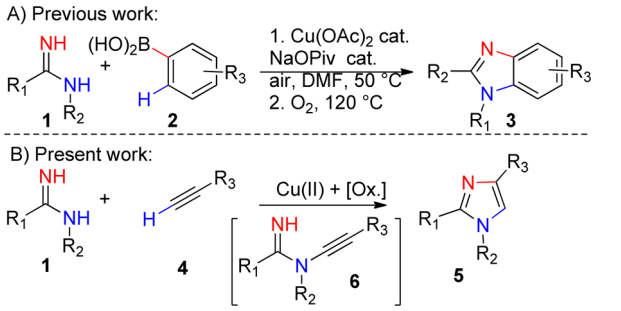
conditions have allowed direct C−H functionalization.[7,8] *N*-Alkyl and *N*-alkenyl amidines were also recently shown to be versatile units giving access to various azaheterocycles under aerobic oxidative conditions, as demonstrated by Chiba in a series of publications.[9]

We have been interested in tandem metal-catalyzed transformation for the synthesis of a heterocyclic structure[10] including strategies involving C−N and C−H bond functionalization.[11] Recently, we became involved in the development of Cu-catalyzed aerobic oxidative transformation to build a C−N bond.[12] In this context, we extended the Chan−Lam−Evans reaction[13] to the selective *N*-arylation of amidines and the direct synthesis of benzimidazoles (Scheme 1A).[14] Given the proximity of imidazoles with such heterocycles and the interest associated to their broad applications,[15] we reasoned that they could be prepared following a similar transformation.[16] Unfortunately, attempts to react amidines with vinylboronic acid derivatives, instead of arylboronic acid, under similar reaction conditions were unsuccessful.

As an alternative to the boronic acid residue, we thought to use a terminal alkyne, reasoning that the imidazole

Scheme 1. Cu-Catalyzed Aerobic Process Involving Amidines



could be formed according to a tandem sequence involving a direct *N*-alkynylation followed by a cyclizative hydroamination (Scheme 1B).[17] Support for the feasibility of the *N*-alkynylation was based on the work of Sthal, describing a Cu-catalyzed aerobic oxidative synthesis of *N*-alkynylheterocycles and *N*-alkynylamides, recently extended to the synthesis of yninines.[18,19] In addition, Fujii and Ohno demonstrated that *N*-arylated amidines could react with 1-triisopropylsilethynyl benziodoxolone under Cu-catalyzed reaction conditions to afford quinazolines and that the reaction could rely on the formation of an *N*-alkylynated species.[20]

Herein, we report conditions that allow trisubstituted imidazoles to be formed from easily available amidines and terminal alkynes. The new Cu-catalyzed process used oxygen as a co-oxidant and consisted of the regioselective addition of two distinct N-atoms across the alkyne.

To explore the reactivity of amidines toward acetylenes, we followed Stahl's work.[19a] In that event, *N*-tolyl benzimidamide (**1a**) and ethynylbenzene **2a** (2 equiv) were reacted in the presence of $CuCl_2 \cdot 2H_2O$ (20 mol %), pyridine (2 equiv), and Na_2CO_2 (2 equiv) under oxygen (1 atm), with gentle heating (70 °C) (Table 1, entries 1 and 2). Interestingly, we found that the reaction furnished imidazole **4a** as the major compound and the oxidized quinazoline **7a** as a minor byproduct.

Based on this result, we undertook an optimization study presented in Table 1.[21] The following observations were made during these trials: Formation of quinazoline **7a** could not be suppressed, but yields remained low whatever the conditions (< 13%). The formation of 1,4-diphenylbuta-1,3-diyne resulting from a Glaser−Hay dimerization

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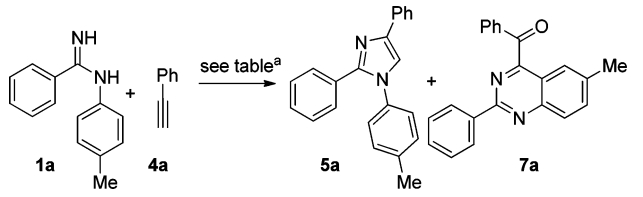
(21) See the Supporting Information for additional data.

Table 1. Survey of Reaction Conditions



entry	additive (equiv)	addition time, temp (°C)	solvent	yield (%)[b]
1	Na_2CO_3 (2)/pyridine (2)	0 h, 70	toluene	14 (5)
2	Na_2CO_3 (2)/pyridine (2)	10 h, 70	toluene	60 (9)
3	Na_2CO_3 (2)/pyridine (2)	10 h, 100	toluene	34 (13)
4[c]	Na_2CO_3 (2)	10 h, 70	toluene	34 (11)
5[c]	pyridine (2)	10 h, 70	toluene	27 (6)
6	–	10 h, rt	toluene	0 (0)
7	–	10 h, 70	toluene	60 (nd)
8	–	10 h, 70	DCE	65 (9)
9	Na_2CO_3 (2)	10 h, 70	dioxane	13 (nd)
10	Na_2CO_3 (2)/pyridine (2)	10 h, 70	DMF	0 (0)
11	–	5 h, 70	THF	0 (0)
12	–	10 h, 70	DMSO	35 (8)
13	–	5 h, 70	toluene	54 (11)
14	Ph_3PO (0.2)	10 h, 70	DCE	68 (nd)
15	Na_2CO_3 (2)/pyridine (2)	10 h, 70	DCE	71 (7)

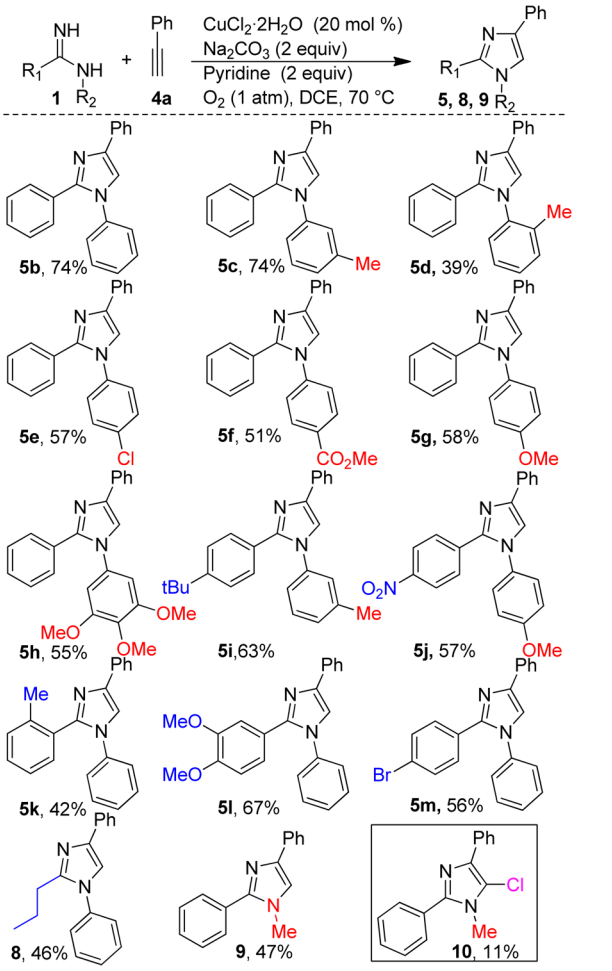
[a] $CuCl_2 \cdot 2H_2O$ (0.2 equiv), amidine (1.0 equiv) (C = 0.2 M), additive, O_2 (1 atm), 24 h; ethynylbenzene (2.0 equiv) (C = 0.2 M) was added dropwise for the indicated time. [b] Isolated yield; yield in parentheses refers to **7a**; nd = not determined but present. [c] Under air.

process of the alkyne[22] could be minimized by applying a 10 h slow addition of the acetylenide to the reaction (Table 1, entries 1, 2, and 12). Solvents greatly influence the reaction, which was best performed in toluene or dichloroethane (DCE) (Table 1, entries 8 to 12). Gentle heating (70 °C) was required to effect the desired transformation, but higher temperatures proved to be deleterious (Table 1, entries 2, 3, and 6). Additive-free conditions furnished good results (Table 1, entry 8) but, as noted later, were not general.[23] Among the additives/ligands that were evaluated [tetramethylethylenediamine (TMEDA), bipyridine (Bipy), triphenylphosphine oxide, tributylphosphine, 1,2-bis(diphenylphosphine)ethane, *N*,*N*-diisopropylethylamine, triethylamine, cesium carbonate, potassium *tert*-butoxide], the combination of sodium carbonate and pyridine provided the best outcome.[21]

With suitable conditions in hand [$CuCl_2 \cdot 2H_2O$ (0.2 equiv), amidine (1.0 equiv) (C = 0.2 M in DCE), pyridine (2 equiv), Na_2CO_3 (2 equiv), O_2 (1 atm), 24 h; dropwise addition of ethynylbenzene (2.0 equiv) (C = 0.2 M in DCE) over 10 h], the scope of this new Cu-catalyzed reaction was examined.

Benzamidine itself was not compatible with the present reaction, leading exclusively to the formation of

Scheme 2. Scope of Cu-Catalyzed Synthesis of Imidazoles: N-Substituted Amidines



1,4-diphenylbuta-1,3-diyne, but the reaction was successfully extended to various N-substituted amidines (Scheme 2). The reaction tolerated functional groups such as alkyl, ether, ester, nitro, chloro, or bromo, and overall, the expected 1,2,4-triarylimidazoles were obtained in modest to good yields ranging between 39% and 74%. The electronic nature of the residue found at either the *C*- or *N*-position of *N*-arylated benzamidines did not substantially impact the reaction outcome, as seen with the synthesis of **5f** and **5g** or **5l** and **5m**. The reaction was however found to be sensitive to steric hindrance, even if imidazoles **5d** and **5k** could be obtained in useful yields. The reaction was not limited to *N*-arylated benzamidines, as *C*- or *N*-alkyl imidazoles **8**[24] and **9** were isolated in reasonable yields. Interestingly, in the case of *N*-methylbenzamide, the chlorinated imidazole **10** was also isolated in 11% yield.[25]

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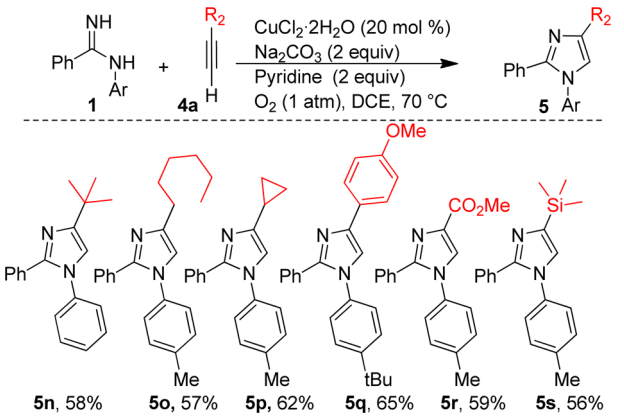
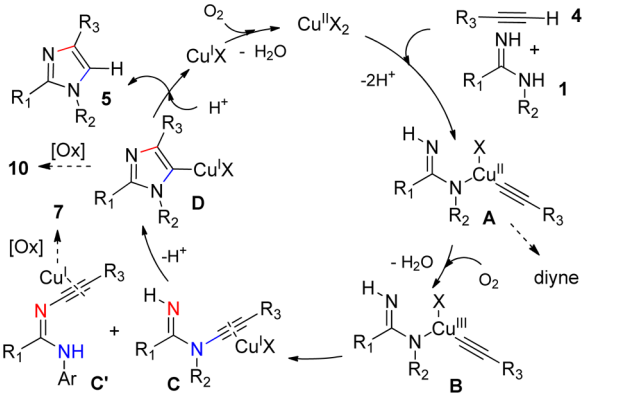
(24) Because of the instability of *N*-phenylbutyrimidamide under the conditions, addition and overall time were 4 and 6 h, respectively.

(25) When *N*-methylbenzamide was reacted with 1.1 equiv of $CuCl_2 \cdot H_2O$ under otherwise identical conditions, **9** and **10** were isolated in 6% and 34% yields, respectively. For a related haloamination process, see: Too, P. C.; Chiba, S. *Chem. Commun.* **2012**, *48*, 7634–7636.

Scheme 3. Scope of the Copper-Catalyzed Synthesis of Imidazoles Using Various Terminal Alkynes



Scheme 4. Possible Mechanism



We finally evaluated the scope of the reaction with respect to the alkyne coupling partner. As illustrated in Scheme 3, the reaction was found to be compatible with various terminal alkynes such as aryl, primary and tertiary alkyl, cyclopropyl, and silyl-substitued alkynes. The electronic nature of the substituent of the alkyne had no significant impact on the reaction, as both 1-ethynyl-4-methoxybenzene and methyl propiolate provided the corresponding imidazoles **5q** and **5r** in comparable yields. The reaction was however restricted to terminal alkynes, as, with diphenylacetylene or ethyl 3-phenylpropiolate, no reaction occurred.

A proposed catalytic cycle for the reaction is shown in Scheme 4. The reaction would be initiated by a Cu-promoted activation of the alkyne and the amidine to deliver complex **A**. Oxidation of complex **A**, followed by reductive elimination, would form the Cu-bounded alkynylacetimidamides **C**.[26] Complex **C** would next undergo an intramolecular 5-*endo*-dig-cyclization onto the activated alkyne thereby forming, after deprotonation, imidazolyl-copper(I) complex **D**. Finally, protonolysis would liberate imidazole **5** and the reoxidation of the Cu(I) complex to the Cu(II) complex would close the catalytic cycle. The mechanism is consistent with the formation of 1,4-diphenyl-buta-1,3-diyne or chlorinated imidazole **10** possibly deriving from complex **A** or **D** through the activation of a second equivalent of alkyne or an oxidative process,[25] respectively. Regioisomeric alkynylacetimidamides **C′** could be involved in the formation of quinazoline **7** following an aerobic carbooxygenation.[27]

In summary, we have developed an efficient and regioselective access to 1,2,4-trisubstitued imidazoles from terminal alkynes and amidines. The process, which used copper as the catalyst and oxygen as the co-oxidant, involves the selective addition of two distinct N-atoms across the triple bond, making the process particularly cheap and atom efficient. Further studies aimed at gaining mechanistic insights, as well as expanding the process to other heterocycles, are being pursued.

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Supporting Information Available. Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) We were not able to identify intermediate **6**. Even if internal alkynes did not react, alternatives mechanisms, such as amino-cupration/C−N bond formation (ref 4c/4e) or [3 + 2] annulation of a nitrene (ref 9b), cannot be excluded.

(27) *N*-(2-Alkynylphenyl)amidine could also be a precursor; see refs 9b and 20.

The authors declare no competing financial interest.