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SHORT COMMUNICATION

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Practical Synthesis of Polysubstituted Haloimidazoles from 1,1-Dibromoalkenes and Amidines

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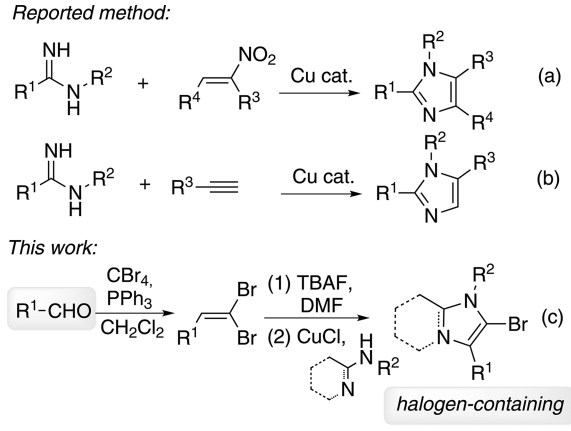
Keywords: Synthetic methods / Regioselectivity / Chemoselectivity / Copper / Nitrogen heterocycles / Alkenes

The copper-catalyzed cycloamination reaction of 1,1-dibromoalkenes with amidines affords a diverse set of polysubstituted haloimidazole derivatives. By using this strategy, high regio- and chemoselectivity has been achieved, using 4,7-diphenyl-1,10-phenanthroline as ligand without the addition of expensive catalysts to provide moderate to good yields.

Introduction

The development of general and efficient methodologies for the synthesis of complex molecular skeletons is a central focus of modern organic chemistry. Polysubstituted imidazole derivatives are the core structures of numerous natural products and pharmaceuticals that possess antimicrobial, anti-inflammatory, antimuscarinic, or antitubercular activities.[1] In particular, haloimidazole derivatives are versatile building blocks because the halogen atom provides an opportunity for further functionalization through transition-metal-catalyzed reactions to form a variety of carbon–carbon and carbon–heteroatom bonds.[2] Consequently, the development of efficient methods for rapid construction of halogenated and aryl-substituted imidazoles has stimulated considerable interest. Among the various types of reactions, functionalized haloimidazoles can be prepared through activation of *N*-acylated α-aminonitrile followed by cyclization, chlorination, and tautomerization reaction.[3] Chen and co-workers reported a simple route for the synthesis of multisubstituted imidazole derivatives through copper-catalyzed cycloaddition reaction from amidines and nitroolefins (Scheme 1, a).[4] Recently, Neuville and co-workers reported the first example of a copper-catalyzed synthesis of 1,2,4-trisubstituted imidazoles by using amidines and terminal alkynes (Scheme 1, b). Although a variety of terminal alkynes can participate in the reaction, internal alkynes are unsuitable.[5]

Although a number of methods are available for the synthesis of this important scaffold,[6] straightforward and regiodefined routes that can be used to construct haloimidazole derivatives from basic chemical materials, such as amidine and alkene derivatives, remain valuable. 1,1-Dibromoalkenes are attractive starting materials in palladium-catalyzed transformations because they are highly reactive and readily available from inexpensive aldehydes.[7] However, reports on the direct cycloamination of 1,1-dibromoalkenes with amidines to construct haloimidazoles are rare, most likely because of the low activity the C=C–H bond of 1,1-dibromoalkenes.[8] It was shown that dehydrobromination of 1,1-dibromoalkenes can provide an efficient method for preparing bromoalkynes as highly reactive cycloaddition substrates. Bases that have been employed for the synthesis of bromoalkynes from 1,1-dibromoalkenes are tetrabutylammonium fluoride (TBAF)[9] and *t*BuOK etc.[10]



Scheme 1. Copper-catalyzed synthesis of imidazoles from amidines.

We have been involved in the development of palladium-catalyzed annulation of bromoacrylamides with isocyanides, including sequences involving a direct nucleophilic addition step.[11] Subsequent to this work, we became interested in developing an annulation reaction synthesis of halogenated imidazoles from 1,1-dibromoalkenes and amidines (Scheme 1, c).

In the development of such as sequence, several challenges must be met: 1) Although the nucleophilic addition reaction of 1,1-dibromoalkenes (bromoalkynes) has been

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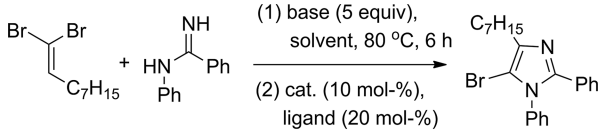
extended to numerous functionalities, it has not yet been applied to unprotected amidines as a nucleophile.[12] 2) Under the palladium or copper-catalyzed system, the reactions usually suffer from inevitable homocoupling of 1,1-dibromoalkenes (bromoalkynes).[7a,13] Herein, we reported the realization of this cycloamination reaction for the synthesis of 1,2,3,5-tetrasubstituted imidazoles from easily available 1,1-dibromoalkenes and amidines by using a sequence involving dehydrobromination and annulation reaction.

Results and Discussion

To identify an effective catalytic system for the cycloamination of 1,1-dibromoalkenes, we developed conditions for the cycloamination of 1,1-dibromoalkenes as shown in Table 1. In optimization trials, copper salt was found to be an efficient catalyst for this kind of transformation. When *N*-phenylbenzamidine reacted with 1,1-dibromonon-1-ene in the absence of copper catalyst, no desired product was observed by GC-MS analysis (Table 1, entry 1). The choice of catalyst is crucial for the success of the cycloamination reaction. $Cu(OAc)_2$ or CuI could provide the desired product whereas palladium salts such as $Pd(PPh_3)_4$ and $PdCl_2$ were totally ineffective (Table 1, entries 2–5). To our delight, the desired halogenated imidazole was obtained in 76% yield when 10 mol-% CuCl was employed (Table 1, entry 4). Essential for the success of the reaction is the use of TBAF·$3H_2O$, which is compatible with 1,1-dibromoalkene

Table 1. Optimization of cycloamination reaction conditions.[a,b]



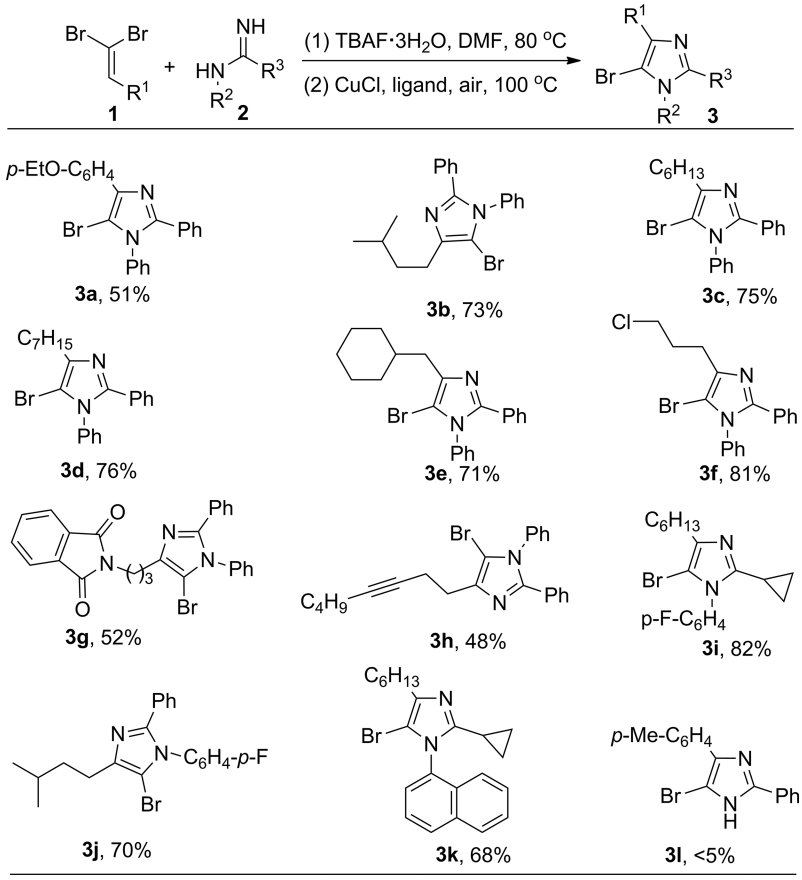
1 **2** **3**

Entry	Catalyst	Base	Solvent	Ligand	Yield [%][b]
1	–	TBAF·$3H_2O$	DMF	**L1**	< 5
2	$Cu(OAc)_2$	TBAF·$3H_2O$	DMF	**L1**	55
3	CuI	TBAF·$3H_2O$	DMF	**L1**	61
4	CuCl	TBAF·$3H_2O$	DMF	**L1**	78(76)
5	$Pd(PPh_3)_4$	TBAF·$3H_2O$	DMF	**L1**	< 5
6	$PdCl_2$	TBAF·$3H_2O$	DMF	**L1**	< 5
7	CuCl	–	DMF	**L1**	–
8	CuCl	*t*BuOK	DMF	**L1**	48
9	CuCl	KOH	DMF	**L1**	< 5
10	CuCl	$CsCO_3$	DMF	**L1**	< 5
11	CuCl	TBAF·$3H_2O$	DMSO	**L1**	52
12	CuCl	TBAF·$3H_2O$	dioxane	**L1**	48
13	CuCl	TBAF·$3H_2O$	DMF	**L2**	36
14	CuCl	TBAF·$3H_2O$	DMF	**L3**	31
15[c]	CuCl	TBAF·$3H_2O$	DMF	**L1**	25
16[d]	CuCl	TBAF·$3H_2O$	DMF	**L1**	62

[a] Reaction conditions: (1) 1,1-dibromonon-1-ene (0.8 mmol), base (5 mmol), solvent (3 mL), 80 °C, 6 h, then (2) catalyst (10 mol-%), *N*-phenylbenzamidine (0.5 mmol), ligand (20 mol-%), 100 °C, 12 h. [b] Isolated yield based on **2**. [c] Under the protection of N_2. [d] Under O_2 atmosphere (1 atm). **L1** = 4,7-diphenyl-1,10-phenanthroline, **L2** = 1,10-phen, **L3** = 2,2′-bipyridine.

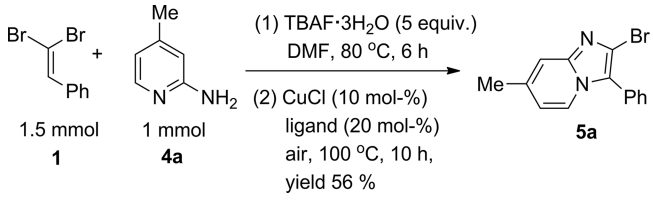
and can also function as an effective turnover reagent (Table 1, entries 4 and 7). Similarly, lower yield of cycloamination product was obtained when other bases such as *t*BuOK, KOH, and $CsCO_3$ were used instead of TBAF·$3H_2O$ (Table 1, entries 8–10). Compared with *N*,*N*-dimethylformamide (DMF), the yields of 5-bromo-4-heptyl-1,2-diphenyl-1*H*-imidazole (**3**) were much lower when dimethyl sulfoxide (DMSO) and 1,4-dioxane were used as the solvents (Table 1, entries 11–12). The observed yields and regioselectivity of the cycloamination process were strongly dependent on the nature of the bidentate nitrogen ligand. The efficiency of the reaction was markedly lower when 4,7-diphenyl-1,10-phenanthroline was replaced with 1,10-phenanthroline and 2,2′-bipyridine (Table 1, entries 13–14). Under the protection of N_2, the desired product **3** was obtained in 25% yield (Table 1, entry 15). However, using copper salts as the promoter and conducting the reaction under oxidative conditions in an O_2 atmosphere (1 atm), afforded a significant amount of alkyne homocoupling product and the imidazole product was obtained only 62% yield (Table 1, entry 16).[14] Finally, the best results were obtained when 1,1-dibromonon-1-ene **1** (0.8 mmol) and TBAF·$3H_2O$ (5.0 mmol) in DMF (3 mL) were stirred for 6 hours at 80 °C. Subsequently, CuCl (10 mol-%), *N*-phenylbenzamidine **2** (0.5 mmol) and 4,7-diphenyl-1,10-phenanthroline (20 mol-%) were added and the mixture was stirred for 12 h at 100 °C under air (Table 1, entry 4).

With the optimized conditions in hand, we next examined the substrate scope for the synthesis of polysubstituted imidazoles (Scheme 2). By varying R^1 substituent of 1,1-dibromoalkenes, it was shown that a range of aryl and alkyl 1,1-dibromoalkenes could be installed. The reaction proceeded smoothly and tolerates a range of aryl- and alkyl-1,1-dibromoalkenes to generally afford tetrasubstituted imidazoles in moderate to good yields. Notably, bromo-substituted imidazole could be prepared, which render them suitable substrates for further functionalization through a range of transition-metal-catalyzed cross-coupling methods. Notably, 2-(5,5-dibromopent-4-enyl)isoindoline-1,3-dione also added to *N*-phenylbenzamidine to afford 2-[3-(5-bromo-1,2-diphenyl-1*H*-imidazol-4-yl)propyl]isoindoline-1,3-dione (**3g**) in moderate yield. When 1,1-dibromodec-1-en-5-yne was examined for compatibility in this cycloamination reaction, it is worth noting that the internal C–C triple bond was tolerated under the present catalysis (**3h**; Scheme 2). We then tested the catalyst system on the reactions of various amidines and found that aryl- and alkyl-amidines underwent the cycloamination reaction across 1,1-dibromoalkenes (**3i**–**l**; Scheme 2). Moreover, these conditions also provide access to imidazoles bearing fluoro substituents, which are often highly appealing to synthetic and medicinal chemists because of the unique biological properties imparted by the fluorine atom (**3j**; Scheme 2).[15] Notably, *N*-naphthyl-substituted amidine also reacted with 1,1-dibromooct-1-ene to afford functionalized halogenated imidazoles in moderate yields (**3k**; Scheme 2). Unfortunately, the reaction with benzamidine hydrochloride only afforded a complex mixture, and imidazoles gave a very low



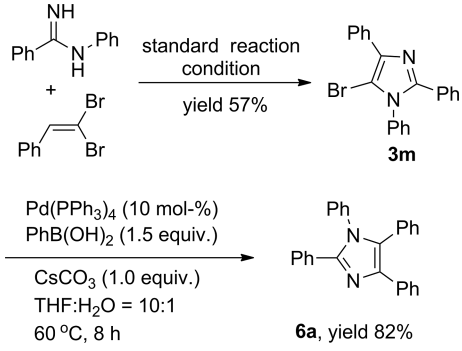
Scheme 2. Synthesis and isolated yield of imidazoles from 1,1-dibromoalkenes and amidines. All reactions were performed with 1,1-dibromoalkenes (0.8 mmol), TBAF·3H$_2$O (5 mmol), amidine (0.5 mmol), CuCl (10 mol-%), 4,7-diphenyl-1,10-phenanthroline (20 mol-%), DMF (3 mL), 100 °C, 10–12 h.

yield (**3l**; Scheme 2). However, interestingly, pyridin-2-amine derivatives could also be used in the cycloamination of 1,1-dibromoalkenes, giving the product in 56% yield (**5a**; Scheme 3).[16]



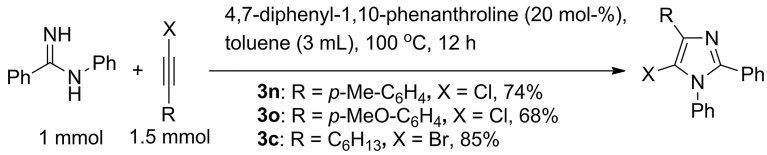
Scheme 3. Synthesis of imidazo[1,2-*a*]pyridines from 1,1-dibromoalkenes and pyridin-2-amines.

These haloimidazoles can be converted directly into 1,2,3,5-tetrasubstituted imidazoles through transition-metal-catalyzed coupling reactions. During the course of these studies, we discovered that the Pd-catalyzed coupling of 5-bromo-1,2,4-triphenyl-1*H*-imidazole with phenylboronic acid gave 1,2,4,5-tetraphenyl-1*H*-imidazole (**6a**) in 82% yield, which is potentially useful for materials science (Scheme 4).



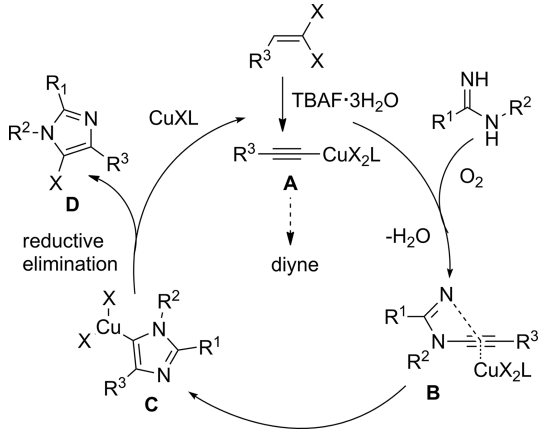
Scheme 4. Synthesis of tetraphenylimidazole from 1,1-dibromo-1-alkene and amidines.

To obtain further insight into the mechanism of the present catalytic process, the direct cycloamination of cholo-alkynes was performed, as shown in Scheme 5. Gratifyingly, chloroalkynes gave exclusively the imidazole products in moderate yields. Interestingly, when bromooct-1-yne was used as starting material, the reaction afforded the corresponding bromo-substituted imidazoles **3c** in 85% yield. Notably, the efficiency of the reaction was markedly higher when 1,1-dibromoalkene was replaced with bromoalkynes.



Scheme 5. CuCl-catalyzed cycloamination reaction of haloalkynes with amidines.

Although detailed experimental evidence is still pending, a plausible mechanism for this reaction is outlined in Scheme 6.[16,17] It is suggested that the reaction is initiated by dehydrobromination of 1,1-dibromoalkenes to produce haloalkynes under TBAF·3H_2O. The alkynyl copper(III) intermediate **A** is then formed by oxidative addition of the Cu^I salt to haloalkyne. Then the alkynyl copper(III) intermediate **A** reacts with an amidine to deliver ynamide intermediate **B** with the aid of O_2.[18] Intermediate **B** would then undergo an intramolecular 5-*endo*-*dig*-cyclization onto the activated C≡C triple bond to produce imidazolylcopper(III) intermediate **C** with the aid of copper salts,[5] which is favored because of the steric bulk of the R^3 substituent. Reductive elimination of intermediate **C** would afford cycloamination product **D** with concurrent formation of Cu^I.



Scheme 6. Tentative mechanism for cycloamination reaction.

Conclusions

We have developed a mild and general method for the efficient synthesis of pharmacologically important diversely functionalized tetrasubstituted imidazoles from amidines and 1,1-dibromoalkenes. The ready accessibility of starting materials and the low cost of the catalytic system makes this process a valuable alternative for the construction of these interesting multisubstituted haloheterocycles. The mechanism and synthetic applications of this reaction are under investigation.

Experimental Section

Reaction of 1,1-Dibromoalkenes and Amidines. Typical Procedure for 3d: A mixture of 1,1-dibromonon-1-ene (0.8 mmol) and TBAF·3H_2O (5 mmol) in DMF (3 mL) was stirred for 6 h at 80 °C. CuCl (10 mol-%), *N*-phenylbenzamidine (0.5 mmol), and 4,7-diphenyl-1,10-phenanthroline (20 mol-%) were then added and the mixture was stirred for 12 h at 100 °C under air. The progress of the reaction was monitored by TLC, and GC–MS analysis was used to determine when the starting materials were completely consumed. When the reaction was complete, the reaction mixture was cooled to room temperature, the solution was filtered though a small amount of silica gel, and the residue was purified by silica gel preparative TLC (*n*-hexane/EtOAc, 10:1), which furnished **3d** as a pale-yellow oil.

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