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ARTICLE

Cu(OAc)₂·H₂O-Catalyzed Mild Synthesis of Multisubstituted 1,2,4-Triazoles from Amidines with Nitriles via N−N/C−N Coupling

Fei Wang, Qing You, Chaoting Wu, Dewen Min, Tianchao Shi, Yuting Kong, Wu Zhang*

A simple and efficient Cu(OAc)₂·H₂O-catalyzed aerobic oxidation of amidines with nitriles for the synthesis of multisubstituted 1,2,4-triazoles has been achieved. The procedure constructs multisubstituted 1,2,4-triazoles has the advantages of operational simplicity, broad substrate scope, no need for prefunctionalized reagents. A possible mechanism was proposed via cascade N−H functionalization and N−N/C−N bond formations.
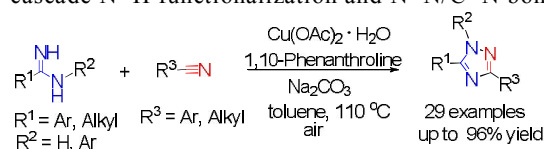
Introduction

1,2,4-triazoles are predominant structural motifs in many functional molecules, natural products, agrochemicals, and pharmaceutical compounds for its potential therapeutic properties such as antibacterial, antifungal and anticancer activities (Figure1).[1] Therefore, much effort has been focused on the synthesis of the 1,2,4-triazoles structure.[2–4] Among them, the most common method was intramolecular and intermolecular condensation reactions of nitrogen-containing compounds.[5] For example, microwave-assisted N-acylation of amide derivatives with hydrazine hydrochlorides[6] and a multistep reaction starting from aldehyde and hydrazine.[7] In addition, great attention has also been paid to developing metal-catalyzed methods[8] such as palladium-catalyzed chemoselective monoarylation of hydrazides.[9]
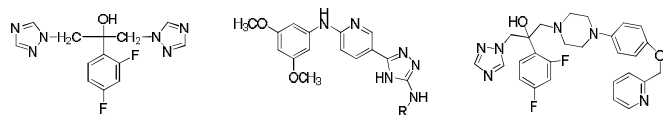

Figure1. Several 1,2,4-triazole derivatives which show biological activities and medicinal value.

Recently, copper-catalyzed C−N bond formations have evolved as major methods for the synthesis of novel heterocyclic compounds with obvious advantages of low cost and environmental friendliness.[10,11] For example, Punniyamurthy has reported copper(II)-catalyzed aerobic oxidative synthesis of 1,3,5-triaryl-1,2,4-triazoles from bisarylhydrazones.[12]

Previous report:

This work:

Scheme 1
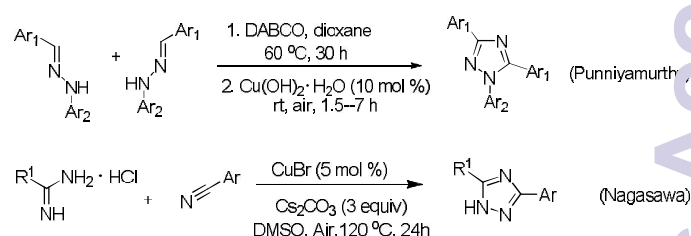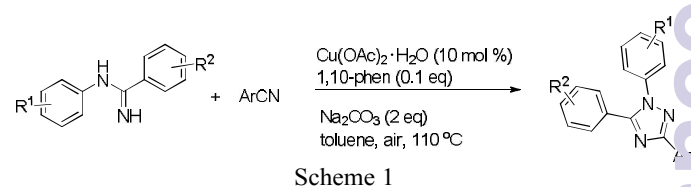
Nagasawa and Ueda reported a copper-catalyzed tandem addition/oxidative cyclization reaction of aryl nitriles with benzamidine hydrochlorides or 2-aminopyridines to give 3,5-disubstituted-1,2,4-triazoles and 1,2,4-triazolopyridine.[13] However, these established methods suffer from some limitations, including operating difficulties, expensive reagents, the formation of undesirable products, restricted substrate scope, and additive or strong base are needed for the transformation.[14] Therefore, developing a green method to synthesize multisubstituted 1,2,4-triazoles at mild conditions without strong base and additive is still meaningful. Inspired by our

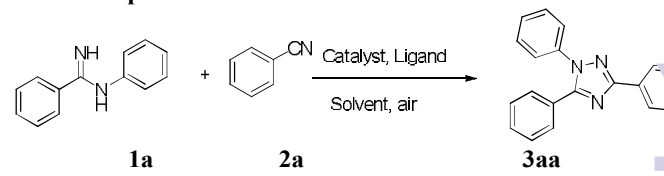previous results on the copper catalyzed formation of C−N, C−C, C−S bonds,[15] especially highly efficient synthesis of quizolines from N-arylated amidines and alcohols.[15e] Herein, we disclose a new cooper-catalyzed synthesis of multisubstituted 1,2,4-triazoles from amidines and nitriles through a N−H functionalization/N−N bond-forming process that uses air as the oxidant in the absence of additives and strong base. From a conceptual standpoint, it should be one of the most straightforward and greener approaches to the preparation of multisubstituted 1,2,4-triazoles.

Results and discussion

It has been reported that the versatility of the reaction depends greatly on the catalyst, ligand, base and solvent used. To optimize the reaction conditions, N-phenylbenzimidamide (**1a**) and benzonitrile (**2a**) were initially chosen as the model substrates in the reaction (Table 1). In the pursuit of our program directed toward the best catalyst, a series of copper sources were screened. The results showed that, the yield of the 1,3,5-triphenyl-1,2,4-triazoles (**3aa**) was considerably high with the Cu(OAc)$_2$·H$_2$O (10 mol %) as the catalyst compared to other copper sources such as Cu(acac)$_2$, Cu(OTf)$_2$, CuO, CuCl$_2$, and CuI (Table 1, entries 1–5). No desired product was observed in the absence of copper salt (entry 6). It was observed that the yield was decreased to 45% in the presence of 5 mol % of catalyst, whereas no significant increment was observed using 20 mol % of catalyst (entries 7 and 8). The experiment results for entries 9-11 in Table 1 also showed DMF, DMSO, and xylene were not as effective as toluene (Table 1, entries 9–11). Further investigation revealed that ligand played an important role and phen (1,10-phenanthroline) proved to be the best ligand (entries 12–13). Decreasing the amount of ligand also resulted in much lower yield (entry 14). The nature of the base has important effect on the reaction and sodium carbonate was found to be the most effective base in the reaction (entries 15–19). It was also observed that much lower yield was obtained if the reaction temperature was lowered (Table 1, entry 20). As a conclusion for the experiments, the optimum results were obtained when amidines (1.0 equiv) and nitriles (1.2-2 equiv) were allowed to react with Cu(OAc)$_2$·H$_2$O (0.1 equiv), phen (0.1 equiv), and Na$_2$CO$_3$ (2.0 equiv) in toluene at 110 °C for 24 h.

With the optimized reaction conditions in hand, we examined the scope of this process, and collect more information to explore the mechanism of the reaction. For that purpose, N-arylamidines with different substituents **1a-1d** and various nitriles **2a-2h** were employed as substrates, and the results are presented in Scheme 2. In general, the presence of an electron-donating or -withdrawing group at the para-position of N-arylamidines was tolerated with good yield. However, nitriles bearing electron-withdrawing groups (4-CF$_3$ or 4-Cl) gave the desired products in higher yields than those with electron-donating groups (4-OMe) on the phenyl ring (Scheme 2, **3aa-**

**Table 1. Optimization of reaction conditions**^{a}

entry	catalyst	ligand	solvent	base	yield (%)^b
1	CuO	phen	toluene	Na$_2$CO$_3$	53
2	CuCl$_2$	phen	toluene	Na$_2$CO$_3$	65
3	Cu(OTf)$_2$	phen	toluene	Na$_2$CO$_3$	70
4	Cu(acac)$_2$	phen	toluene	Na$_2$CO$_3$	73
5	CuI	phen	toluene	Na$_2$CO$_3$	trace
6	-	phen	toluene	Na$_2$CO$_3$	-
7	Cu(OAc)$_2$·H$_2$O	phen	toluene	Na$_2$CO$_3$	45^c
8	Cu(OAc)$_2$·H$_2$O	phen	toluene	Na$_2$CO$_3$	75(76^d)
9	Cu(OAc)$_2$·H$_2$O	phen	DMSO	Na$_2$CO$_3$	22
10	Cu(OAc)$_2$·H$_2$O	phen	DMF	Na$_2$CO$_3$	37
11	Cu(OAc)$_2$·H$_2$O	phen	Xylene	Na$_2$CO$_3$	72
12	Cu(OAc)$_2$·H$_2$O	Ph$_3$P	toluene	Na$_2$CO$_3$	55
13	Cu(OAc)$_2$·H$_2$O	TMEDA^e	toluene	Na$_2$CO$_3$	trace
14	Cu(OAc)$_2$·H$_2$O	phen	toluene	Na$_2$CO$_3$	51^f
15	Cu(OAc)$_2$·H$_2$O	phen	toluene	NaOH	60
16	Cu(OAc)$_2$·H$_2$O	phen	toluene	K$_2$CO$_3$	36
17	Cu(OAc)$_2$·H$_2$O	phen	toluene	t-BuOk	21
18	Cu(OAc)$_2$·H$_2$O	phen	toluene	Et$_3$N	45
19	Cu(OAc)$_2$·H$_2$O	phen	toluene	-	20
20	Cu(OAc)$_2$·H$_2$O	phen	toluene	Na$_2$CO$_3$	42^g

^{a} Reaction conditions: N-phenylbenzimidamide (0.5 mmol), benzonitrile (1 mmol), catalyst (0.1 mmol), ligand (0.1 mmol), base (2 mmol), solvent (2 mL) under reflux in air for 24 h. ^{b} Isolated yield. ^{c} Cu(OAc)$_2$·H$_2$O (5 mol %). ^{d} Cu(OAc)$_2$·H$_2$O (20 mol %). ^{e} N,N,N′,N′-tetramethylethylenediamine. ^{f} 1,10-phenanthroline (5 mol %). ^{g} 90 °C.

3ad). It was worth mentioning that, the influence of steric hindrance was observed in the reaction. For example, nitriles bearing a p-methyl or p-chloro group on the phenyl ring gave the corresponding products in higher yields than those of

nitriles bearing an *o*-methyl or *o*-chloro group (Scheme 2, **3ab, 3ae, 3af, 3ag**). Furthermore, the reaction using a heteroaromatic nitrile also provided triazoles **3ah** in considerable yield. Subsequently, the desired products 3,5-disubstituted-1H-1,2,4-triazoles could be obtained in good yields when benzamidine hydrochloride **4** was used in this reaction (Scheme 3).To our delight, we found that even with the absence of ligand,

**Scheme 2.** Copper-catalyzed synthesis of 1,3,5-trisubstituted-1H-1,2,4-triazoles[a]
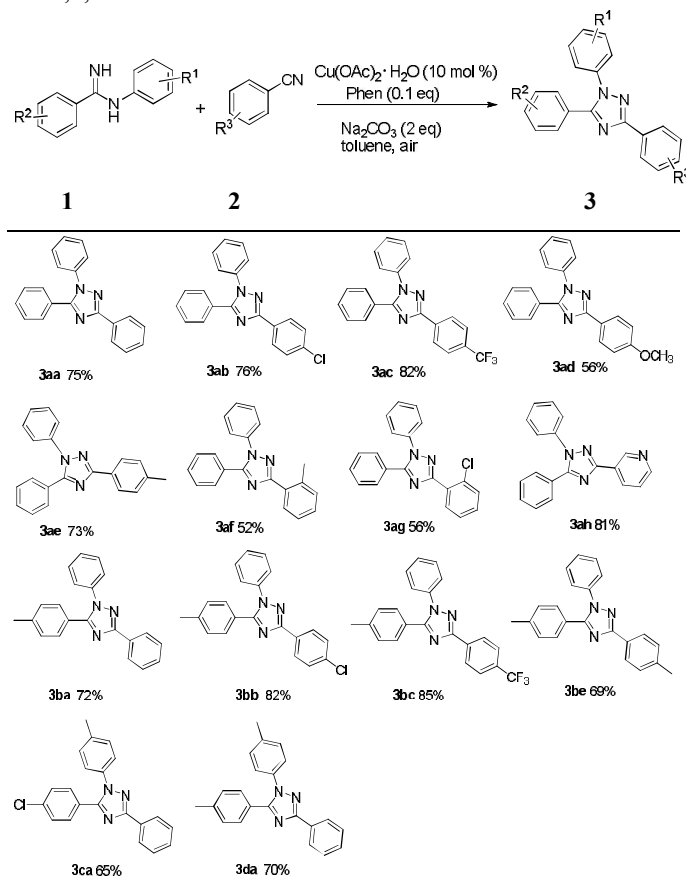
[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), Cu(OAc)$_2$·H$_2$O (10 mol %), 1,10-phenanthroline (10 mol %), toluene (2 mL) 110 °C, 24 h, air.

excellent activity toward the desired product could be achieved with the concentration of Cu(OAc)$_2$·H$_2$O as low as 3 mol %, which made the process even more economically efficient. Similarly, no significant substituent effect was observed, excellent yields were obtained for benzamidine hydrochloride with both electron-donating and electron-withdrawing substituents, while nitriles with electron-withdrawing substituents gave higher yield than those with electron-donating substituents. Furthermore, aliphatic nitrile such as cyclohexyl nitrile was compatible with the cyclization conditions and producing **5ah** in good yields. From ^{1}H NMR and ^{13}C NMR spectra, we found some of products were mixtures when determined in DMSO-d$_6$ (see supporting information), the results are in accordance with Xu's reports.[16] It may be due to the NH-tautomerism. To our delight, the Cu(OAc)$_2$·H$_2$O catalyzed tandem reaction can been applied to gram-scale

synthesis, 85 % yield was obtained when 1.6 g (10 mmol) of benzamidine hydrochloride were used under the optimized conditions.

Scheme 3. Copper-catalyzed synthesis of 3,5-disubstituted-1H-1,2,4-triazoles[a]
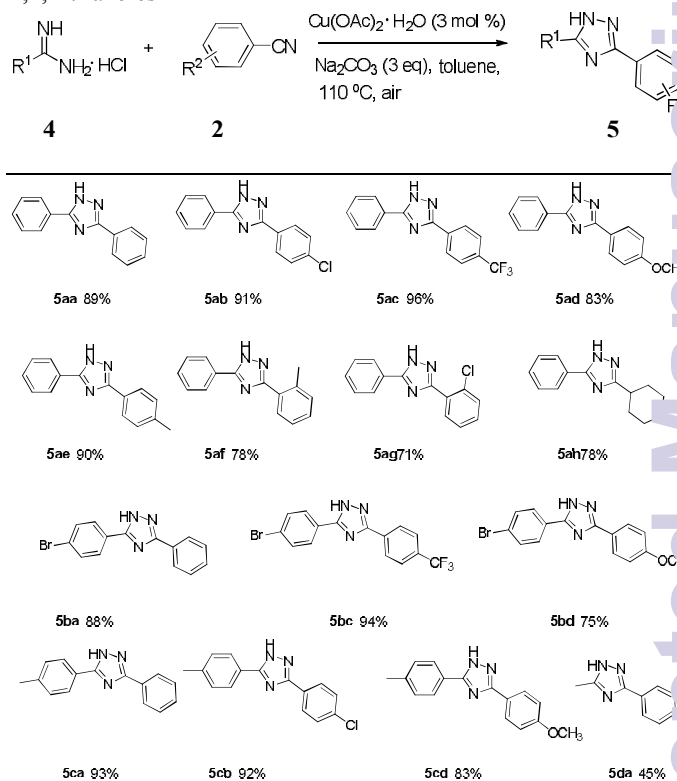

[a] The reactions were carried out using 1 mmol of amidines **4** ,1.2 mmol nitriles **2** and 3 mol % of Cu(OAc)$_2$·H$_2$O with 3 mmol Na$_2$CO$_3$ in toluene at 110 °C in air for 24 h.

Furthermore, some controlled experiments were carried out to gain insight into the reaction mechanism. First, the reaction conditions were applied for the dimerization of benzamidine hydrochloride and symmetrical 1,2,4-triazoles were obtained with moderate yield.[17] Then, a radical inhibitor 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (2 equiv) was added to the reaction, no significant decrease in yield was observed, suggesting that the reaction does not involve radical steps. The yield was dramatically decreased when the reaction under argon atmosphere, which indicates that oxygen is critical to the achievement of the catalytic cycle. Thus, the reaction mechanism of the intermolecular C−N/N−N bond formations of amidines and nitriles to 1,2,4-triazoles derivatives was proposed based on the aforementioned results and literatures,[18] as shown in Scheme 4. At first, the reaction of amidine **1** with Cu(OAc)$_2$ leads to the formation of Cu–N adduct **A** in the presence of base. Then Cu(II) complex **B** was formed by nitrile **2** coordinate to copper. Next intermediate **C** was formed by an intermolecular nucleophilic attack of amidine on nitrile and copper (III) complex **D** was formed via Cu(OAc)$_2$-promoted oxidation of **C**. A subsequent reductive elimination produced the coupling product along with a copper species with lower

oxidation state, which was oxidized to give Cu(II) by oxygen in the air to complete the catalytic cycle.

Scheme 4. Possible mechanism
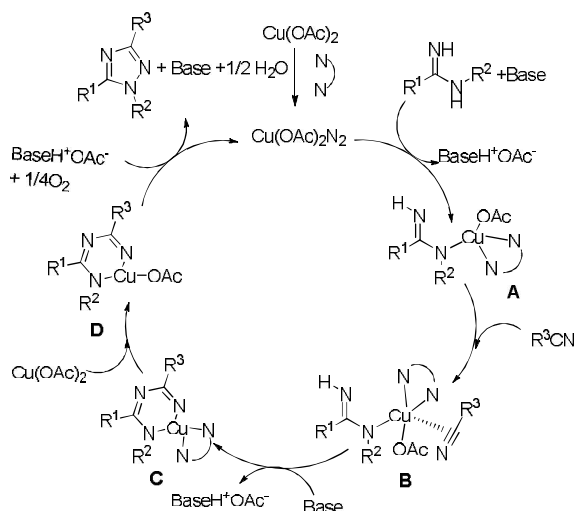
Conclusions

In summary, we have developed an efficient Cu(OAc)$_2$-catalyzed aerobic oxidation of amidines with nitriles for the synthesis of multisubstituted 1,2,4-triazoles involving cascade N−H functionalization/N−N/C−N bond formation steps. We believe that the present conditions provided an attractive alternative to access this important type of heterocycle. Efforts aiming at related copper-catalyzed coupling reactions are under investigation.

Acknowledgements

Experimental

General information

All reactions were carried out in flame-dried reaction vessels. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. The commercially available chemicals were used without further purification. All the N-arylamidines used were synthesized according to reference.[19] All new compounds were fully characterized. Melting points were determined on a melting point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz or a 500 MHz NMR spectrometers using CDCl$_3$ or DMSO-d$_6$ as solvent and TMS as an internal standard. High resolution mass spectral (HRMS) data were obtained with an ionization mode of ESI or APCI on Agilent 6200 LC/MS TOF.

General procedures for 1,3,5-trisubstituted-1H-1,2,4-triazoles

N-arylamidines (1 mmol), nitrile (1.5-2 mmol), Cu(OAc)$_2$·H$_2$O (0.1 mmol), Na$_2$CO$_3$ (2 mmol) and 1,10-phenanthroline (0.1 mmol) were stirred in toluene (2 mL) under reflux in air for 24 h in pre-heated oil bath. After cooling to room temperature, the reaction was extracted with ethyl acetate. The combined organic layer was dried over Na$_2$SO$_4$, filtrated, concentrated and purified by column chromatography on silica gel (300-400 mesh) to give **3aa-3da** with petroleum ether/ethyl acetate as the eluent.

General procedures for 3,5-disubstituted-1H-1,2,4-triazoles.

Benzamidine hydrochloride (1 mmol), nitrile (1.5 mmol), Cu(OAc)$_2$·H$_2$O (0.03 mmol), Na$_2$CO$_3$ (3 mmol) were stirred in toluene (2 mL) under reflux in air for 24 h in pre-heated oil bath. After cooling to room temperature, the reaction was extracted with ethyl acetate. The combined organic layer was dried over Na$_2$SO$_4$, filtrated, concentrated and purified by column chromatography on silica gel (300-400 mesh) to give **5aa-5da** with petroleum ether/ethyl acetate as the eluent.

Notes and references

Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, China. Email: zhangwu@mail.ahnu.edu.cn
Tel: +86-553-3883513; fax: +86-553-3869310

† Electronic Supplementary Information (ESI) available: General experimental procedures, analytic data, images of ^{1}H and ^{13}C NMR of all products and other electronic format. See DOI: 10.1039/b000000x/

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