Copper-Catalyzed Synthesis of 1,2,4-Triazoles via Sequential Coupling and Aerobic Oxidative Dehydrogenation of Amidines

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Abstract: A convenient, efficient, and practical copper-catalyzed one-pot method for the synthesis of 1,2,4-triazoles has been developed via reactions of amidines. The procedure underwent sequential base-promoted intermolecular coupling (nucleophilic substitution) between two amidines and intramolecular aerobic oxidative dehydrogenation, and the inexpensive, convenient, and efficient method for the synthesis of 1,2,4-triazoles will attract much attention in academic and industrial research.

Key words: copper, aerobic oxidative, dehydrogenation, amidines, 1,2,4-triazoles

Nitrogen heterocycles occur widely in various natural products and biologically active molecules.[1] The 1,2,4-triazole derivatives are widely used in medicinal chemistry, materials science, and organocatalysis, and their synthesis has attracted much attention.[2] The common methods are from intramolecular cyclizations of *N*-acylamidorazones that are prepared via couplings of hydrazines and carboxylic acid derivatives,[3] but they often provide 1,2,4-triazoles in low yields. Therefore, it is highly desired to develop a simple and practical approach to 1,2,4-triazole derivatives. Recently, transition-metal-catalyzed aerobic oxidative formation of bonds is a focal field,[4] and some nitrogen heterocycles, such as benzimidazoles,[5] carbazoles,[6] indazoles,[7] *N*-methoxylactams,[8] and indolines,[9] have been prepared via the aerobic oxidative strategy, in which expensive palladium-, rhodium-, and ruthenium-based catalysts are often necessary. During the past few years, there have been excellent progress in copper-catalyzed cross-couplings with inexpensive and low toxic copper-catalysts, and wide application with good functional tolerance has been explored.[10,11] Recently, several efficient copper-catalyzed aerobic oxidative methods for the synthesis of nitrogen heterocycles have been developed by us[12] and other groups.[13] Nagasawa and coworkers have developed an efficient copper-catalyzed synthesis of 1,2,4-triazole derivatives via coupling of amidines with nitriles.[14] Herein, we report a novel, convenient, and efficient copper-catalyzed one-pot synthesis of 1,2,4-triazoles via sequential coupling and aerobic oxidative dehydrogenation of amidines.

Reaction of benzamidine hydrochloride (**1a**) with cyclopropanecarboxamidine hydrochloride (**1i**) was used as the model to optimize reaction conditions including the catalysts, bases, solvents, temperature, and reaction time. As shown in Table 1, the copper-catalyzed one-pot synthesis of 3-cyclopropyl-5-phenyl-1*H*-1,2,4-triazole (**2i**) underwent sequential two-step procedures: intermolecular coupling (nucleophilic substitution) between two amidines and intramolecular aerobic oxidative dehydrogenation. The first-step coupling was performed at 120 °C for 24 hours under N_2 atmosphere, and the second step, the intramolecular formation of the N–N bond, was carried out at 120 °C for 24 hours under O_2. In order to prevent homogeneous coupling of benzamidine hydrochloride (**1a**; we found that aromatic amidines easily self-coupled), **1a** was added (3 × 0.25 mmol) every eight hours. Seven copper catalysts (0.1 equiv) were screened by using two equivalents of Cs_2CO_3 as the base (relative to amount of **1i**), and DMSO as the solvent (Table 1, entries 1–7), and Cu powder exhibited the highest activity (Table 1, entry 7). Only trace amount of target product was observed in the absence of copper catalyst (Table 1, entry 8). Other bases were determined (Table 1, entries 9–12), and they were inferior to Cs_2CO_3 (compare entries 7, 9–12, Table 1). Affect of solvents was also investigated (compare entries 7, 13–15, Table 1), and DMSO provided the highest efficiency. We attempted different temperature (Table 1, entries 16 and 17), and 120 °C was suitable (Table 1, compare entries 7, 16, and 17). The second step, the aerobic oxidative dehydrogenation, was elongated to 48 hours, and a higher yield was afforded (Table 1, entry 18). When the one-pot, two-step reaction was performed under N_2 (Table 1, entry 19) or air (Table 1, entry 20), lower yields were provided. We changed amount of **1a** (Table 1, entries 21 and 22), and the results showed that four equivalents of **1a** (**1a** was added by ratio of 2:1:1) gave **2i** in 72% yield (Table 1, entry 22).

With the optimum reaction conditions in hand, the scope of the copper-catalyzed one-pot synthesis of 1,2,4-triazoles was investigated. As shown in Table 2, the examined substrates provided moderate to good yields. Aromatic amidines self-coupled to give homogeneous

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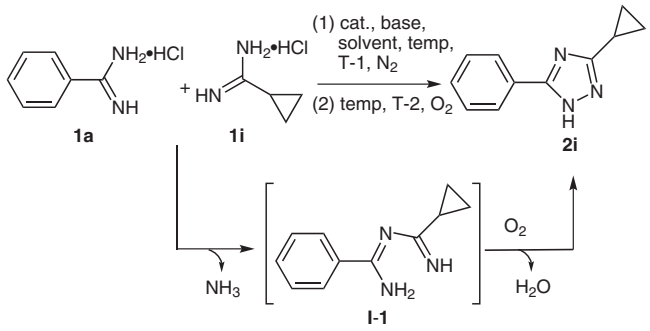
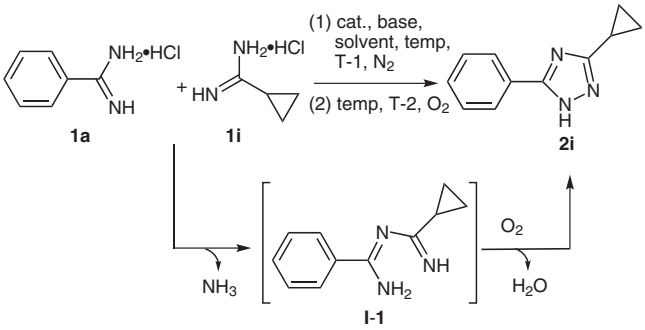
products (Table 2, entries 1–5). Heterogeneous reactions of aromatic amidines with aliphatic amidines were also performed well (Table 2, entries 6–19), but aromatic amidines were required to add to the system (3×) by the ratio (2:1:1) every eight hours in order to prevent self-reaction of the aromatic amidines. In the copper-catalyzed reaction, no ligand or additive was needed. The reactions could tolerate some functional groups including C–Cl bond (Table 2, entries 3, 14–16), nitro (Table 2, entry 4), and N-heterocycle (Table 2, entries 5, 17–19) in the substrates.

Table 1 Copper-Catalyzed One-Pot Synthesis of 3-Cyclopropyl-5-phenyl-1*H*-1,2,4-triazole (**2i**) via Reaction of Benzamidine Hydrochloride (**1a**) with Cyclopropanecarboxamidine Hydrochloride (**1i**): Optimization of Conditions[a]



Entry	Catalyst	Base	Solvent	Temp (°C)	T-1 (h)/ T-2 (h)	Yield (%)[b]
1	CuI	Cs_2CO_3	DMSO	120	24/24	31
2	CuBr	Cs_2CO_3	DMSO	120	24/24	38
3	CuCl	Cs_2CO_3	DMSO	120	24/24	38
4	Cu_2O	Cs_2CO_3	DMSO	120	24/24	33
5	CuO	Cs_2CO_3	DMSO	120	24/24	27
6	$Cu(OAc)_2$	Cs_2CO_3	DMSO	120	24/24	21
7	Cu	Cs_2CO_3	DMSO	120	24/24	44
8	–	Cs_2CO_3	DMSO	120	24/24	trace
9	Cu	NaOAc	DMSO	120	24/24	17
10	Cu	K_2CO_3	DMSO	120	24/24	35
11	Cu	K_3PO_4	DMSO	120	24/24	34
12	Cu	KO*t*-Bu	DMSO	120	24/24	28
13	Cu	Cs_2CO_3	dioxane	120	24/24	5
14	Cu	Cs_2CO_3	*o*-xylene	120	24/24	34
15	Cu	Cs_2CO_3	DMF	120	24/24	42
16	Cu	Cs_2CO_3	DMSO	90	24/24	trace
17	Cu	Cs_2CO_3	DMSO	140	24/24	38
18	Cu	Cs_2CO_3	DMSO	120	24/48	52
19	Cu	Cs_2CO_3	DMSO	120	72	28[c]
20	Cu	Cs_2CO_3	DMSO	120	72	41[d]

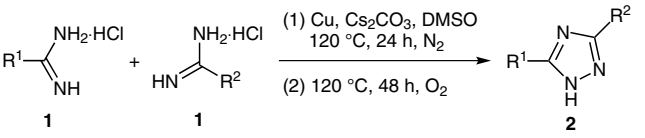
Table 1 Copper-Catalyzed One-Pot Synthesis of 3-Cyclopropyl-5-phenyl-1*H*-1,2,4-triazole (**2i**) via Reaction of Benzamidine Hydrochloride (**1a**) with Cyclopropanecarboxamidine Hydrochloride (**1i**): Optimization of Conditions[a] (continued)



Entry	Catalyst	Base	Solvent	Temp (°C)	T-1 (h)/ T-2 (h)	Yield (%)[b]
21	Cu	Cs_2CO_3	DMSO	120	24/48	64[e]
22	Cu	Cs_2CO_3	DMSO	120	24/48	72[f]

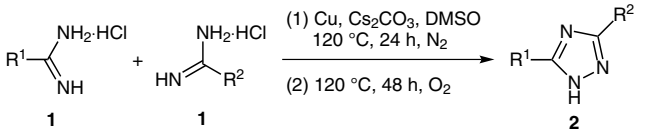
[a] Reaction conditions: benzamidine hydrochloride (**1a**, 3 × 0.25 mmol) was added (3×) every 8 h, cyclopropanecarboxamidine hydrochloride (**1i**, 0.5 mmol), catalyst (0.1 mmol), base (2 mmol), solvent (1.5 mL), under nitrogen atmosphere for the first step, under oxygen balloon (1 bar) for the second step.
[b] Isolated yield.
[c] Under O_2 for the two steps.
[d] Under air for the two steps.
[e] Conditions: **1a** (3 × 0.5 mmol) and Cs_2CO_3 (2.5 mmol) were added (3×) every 8 h.
[f] Conditions: **1a** (1 mmol+2 × 0.5 mmol) and Cs_2CO_3 (3.0 mmol) were added (3×) every 8 h.

Table 2 Copper-Catalyzed One-Pot Synthesis of 1,2,4-Triazoles via Sequential Coupling and Aerobic Oxidative Dehydrogenation of Amidines[a]



Entry	**1**	R^1	**1**	R^2	**2**	Yield (%)[b]
1	**1a**	Ph	**1a**	Ph	**2a**	62
2	**1b**	4-MeC_6H_4	**1b**	4-MeC_6H_4	**2b**	61
3	**1c**	4-ClC_6H_4	**1c**	4-ClC_6H_4	**2c**	60
4	**1d**	3-$O_2NC_6H_4$	**1d**	3-$O_2NC_6H_4$	**2d**	64
5	**1e**	4-pyridyl	**1e**	4-pyridyl	**2e**	53
6	**1a**	Ph	**1f**	Me	**2f**	80
7	**1a**	Ph	**1g**	Et	**2g**	45[c]
8	**1a**	Ph	**1h**	*n*-Pr	**2h**	40[c]
9	**1a**	Ph	**1i**	*c*-Pr	**2i**	72
10	**1a**	Ph	**1j**	*t*-Bu	**2j**	49

Table 2 Copper-Catalyzed One-Pot Synthesis of 1,2,4-Triazoles via Sequential Coupling and Aerobic Oxidative Dehydrogenation of Amidines[a] (continued)



1 **1** **2**

Entry	**1**	R^1	**1**	R^2	**2**	Yield (%)[b]
11	**1b**	4-MeC_6H_4	**1f**	Me	**2k**	85
12	**1b**	4-MeC_6H_4	**1g**	Et	**2l**	42[c]
13	**1b**	4-MeC_6H_4	**1i**	*c*-Pr	**2m**	91
14	**1c**	4-ClC_6H_4	**1f**	Me	**2n**	75
15	**1c**	4-ClC_6H_4	**1i**	*c*-Pr	**2o**	78
16	**1c**	4-ClC_6H_4	**1j**	*t*-Bu	**2p**	51
17	**1e**	4-pyridyl	**1f**	Me	**2q**	70
18	**1e**	4-pyridyl	**1i**	*c*-Pr	**2r**	84
19	**1e**	4-pyridyl	**1j**	*t*-Bu	**2s**	86

[a] Reaction conditions: amidine-1 + amidine-2 (1.0 mmol) for entries 1–5, amidine-1 (2.0 mmol) for entries 6–19 [added (3×: 1 mmol + 2× 0.5 mmol) every 8 h], amidine-2 (0.5 mmol) for entries 6–19, Cu powder (0.1 mmol), Cs_2CO_3 (1.5 mmol for entries 1–5; 3.0 mol for entries 6–19), DMSO (1.5 mL), reaction temperature (120 °C), reaction time (24 h for the first step; 48 h for the second step), under nitrogen atmosphere for the first step, under oxygen balloon (1 bar) for the second step.
[b] Isolated yield.
[c] Conditions: 0.5 mL *t*-BuOH were added.

We explored the reaction mechanism for the synthesis of 1,2,4-triazoles. As shown in Scheme 1, treatment of 4-methylbenzamidine hydrochloride (**1b**) was first carried out in the presence of Cs_2CO_3 in DMSO under N_2 (no addition of Cu powder), and *N*-[amino(*m*-tolyl)methylene]-4-methylbenzamidine (**I-2**) was obtained in 44% yield (**I-2** was purified by recrystallization which led to the loss of some product because of its high polarity, Scheme 1, i). The synthesized *N*-[amino(*m*-tolyl)methylene]-4-methylbenzamidine was treated in the presence of Cu powder under O_2, and the target product **2b** was provided in 68% yield (Scheme 1, ii). Therefore, a possible mechanism for the synthesis of 1,2,4-triazoles is proposed in Scheme 2. Amidine hydrochlorides transformed into free amidines in the presence of base (Cs_2CO_3), and intermolecular nucleophilic attack of amino in one amidine to carbon in another one leads to intermediate **I**. Treatment of **I** with copper in the presence of O_2 provides Cu(III) complex **II** (the similar metal complexes have been reported in the previous literature[15]), and reductive elimination of **II** affords the target product (**2**)[14] leaving Cu(I) complex **III**. Further, reaction of **III** with **I** regenerates **II**, and the target product **2**[16] continuously is provided in the catalytic cycle.

In summary, we have developed a convenient, efficient, and practical copper-catalyzed one-pot method for the synthesis of 1,2,4-triazoles. The protocol uses readily available substituted amidines as the starting materials, inexpensive Cu powder as the catalyst, and economical and environment friendly oxygen as the oxidant, and the corresponding 1,2,4-triazoles were obtained in moderate to good yields. The procedure underwent sequential base-promoted intermolecular coupling (nucleophilic substitution) between two amidines and intramolecular aerobic oxidative dehydrogenation, and the inexpensive, convenient, and efficient method for the synthesis of 1,2,4-triazoles will attract much attention in academic and industrial researches because of the wide application of these compounds in various fields.

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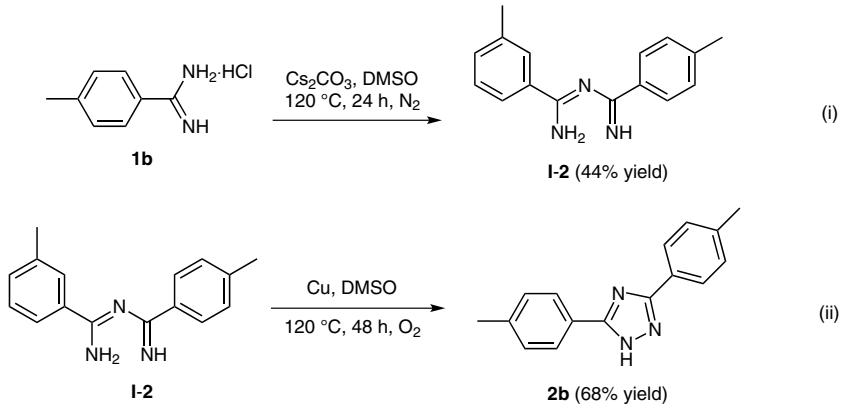
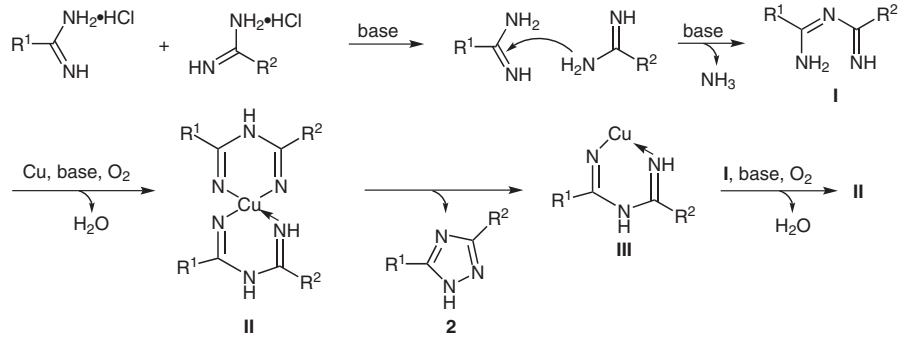


Scheme 1 (i) Treatment of 4-methylbenzamidine hydrochloride (**1b**) in the presence of Cs_2CO_3 in DMSO under N_2 leading to *N*-[amino(3-tolyl)methylene]-4-methylbenzamidine (**I-2**); (ii) copper-catalyzed aerobic oxidation of **I-2** leading to **2b** in the presence of Cu powder under O_2



Scheme 2 Possible mechanism for synthesis of 1,2,4-triazoles

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(16) **General Procedure for the Synthesis of Compounds 2a–s**

A 10 mL Schlenk tube was charged with a magnetic stirrer and DMSO (1.5 mL). For entries 1–5 in Table 2, aromatic amidine (1 mmol), Cu powder (0.1 mmol, 6.4 mg), and Cs_2CO_3 (2 mmol, 489 mg) were added to the tube. The mixture was stirred at 120 °C for 24 h under nitrogen atmosphere, and then the nitrogen atmosphere was changed into oxygen atmosphere (other conditions were kept). The following aerobic oxidative intramolecular formation of N–N bond was carried out at 120 °C for 48 h. The resulting mixture was cooled to r.t. and filtered, and the solid was washed with EtOAc (3 × 3 mL). The combined filtrate was concentrated by a rotary evaporator, and the residue was purified by column chromatography on silica gel using PE–EtOAc as eluent to give the desired target product. For entries 6–19 in Table 2, aromatic amidine (1.0 mmol),

aliphatic amidine (0.5 mmol), Cu powder (0.1 mmol, 6.4 mg), and Cs_2CO_3 (3.0 mmol, 978 mg) were added to the tube. The mixture was stirred at 120 °C under nitrogen atmosphere, and additional aromatic amidine (2 × 0.5 mmol) was added to the resulting solution after 8 h and 16 h, respectively. The reaction was performed for a total 24 h under nitrogen atmosphere, and then the nitrogen atmosphere was changed into oxygen atmosphere (other conditions were kept). The following aerobic oxidative intramolecular formation of N–N bond was carried out at 120 °C for 48 h. The workup procedure was similar to that of entries 1–5 in Table 2. Data for three representative examples are given here.

3-Methyl-5-phenyl-4*H*-1,2,4-triazole (2f)[14]

Eluent: PE–EtOAc (1:1); yield 64 mg (80%); white solid; mp 163–165 °C (lit.[14] mp 163–165 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 13.75 (s, 1 H), 7.95 (d, 2 H, J = 7.56 Hz), 7.44–7.33 (m, 3 H), 2.35 (s, 3 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.8, 154.3, 131.7, 129.3, 129.1, 126.2, 126.1, 12.5. ESI-MS: m/z = 160.3 $[M + H]^+$; m/z = 182.2 $[M + Na]^+$.

3-(4-Chlorophenyl)-5-cyclopropyl-4*H*-1,2,4-triazole (2o)[14]

Eluent: PE–EtOAc (6:1); yield 85 mg (78%); white solid; mp 203–205 °C (lit.[14] mp 202–203 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 13.71 (s, 1 H), 7.91 (d, 2 H, J = 8.9 Hz), 7.57–7.40 (m, 2 H), 2.09–1.96 (m, 1 H), 1.06–0.80 (m, 4 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.2, 160.1, 133.7, 131.0, 129.2, 127.9, 8.6, 7.5. ESI-MS: m/z = 220.2 $[M + H]^+$; m/z = 242.0 $[M + Na]^+$.

4-(5-Methyl-4*H*-1,2,4-triazol-3-yl)pyridine (2q)[17]

Eluent: PE–EtOAc (4:1); yield 56 mg (70%); white solid; mp 104–106 °C (lit.[17] mp 207–209 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 13.94 (s, 1 H), 8.81–8.55 (m, 2 H), 7.91 (d, 2 H, J = 3.4 Hz), 2.44 (s, 3 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 159.4, 154.8, 150.8, 139.1, 120.5, 12.2. ESI-MS: m/z = 161.2 $[M + H]^+$; m/z = 183.1 $[M + Na]^+$.

(17) Lipinski, C. A.; Lamattina, J. L.; Oates, P. J. *J. Med. Chem.* **1986**, *29*, 2154.