Copper-Mediated Sequential C–N and N–N Bond Formation: Facile Synthesis of Symmetrical 1,2,4-Triazoles

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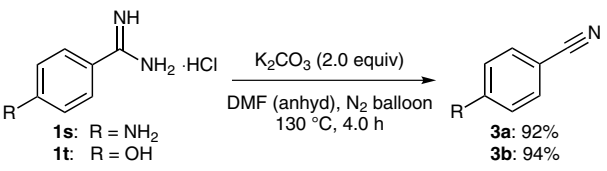
Abstract: Via a one-pot process, catalyzed by $Cu(OAc)_2$, a series of 3,5-disubstituted 4*H*-1,2,4-triazoles was conveniently and efficiently synthesized by using low-toxicity, stable, readily available, inexpensive amidine hydrochloride.

Key words: 1,2,4-triazoles, copper, amidine hydrochloride, N–N bond coupling, de-amine reaction

1,2,4-Triazole-containing compounds are widely used in pesticides,[1] plant growth regulators,[2] medicines[3] (such as some well-known triazole fungicides), dyes,[4] metal complexes,[5] industrial additives, and functional materials.[6] They are also important intermediates in organic synthesis. As an important part of the triazole family, 3,5-disubstituted 4*H*-1,2,4-triazoles (DHTs) have attracted much attention over the past decades. A number of reports have discussed the certain efficient method for the DHTs synthesis. Among them, two of the most extensively used methods for the preparation of DHTs involved the intra- and intermolecular cyclization of acyclic nitrogen-containing amidine and/or hydrazine derivatives[7] and the rearrangement reaction of the five- and six-membered cyclic nitrogen-containing compounds[8] under acid-catalyzed (Brønsted acid or Lewis acid)[9] and/or alkali-catalyzed conditions (pyridine, hydrazine hydrate, sodium hydroxide, potassium carbonate, etc.).[3,10] However, the cases of the transition-metal-catalyzed DHTs synthesis were relatively rare.[5,7a] Here are several worthy of mentioning examples of Cu-catalyzed reactions: Chen et al. prepared two interesting Cu^{I}-DHT coordination polymers by an unprecedented copper-mediated cycloaddition of nitriles and ammonia at 160 °C in three days, in which the Cu^{II} not only acted as a catalyst but also as a coordination center of the metal complexes.[5] Another Cu^{I}-catalyzed oxidative synthesis of DHT derivatives was reported by Nagasawa's group in 2009. Via a procedure of initial amidine C–N formation followed by intramolecular oxidative N–N bond formation, they achieved the catalytic cycle by using molecular oxygen as the oxidant.[7a] In 2005, Chen et al. disclosed that one-pot solvothermal treatments of organonitriles, ammonia and Cu^{II} salts yielded Cu^{I} and DHTs. The mechanism was confirmed by several crystals of isolated copper complex intermediate.[11] Very recently, just when we prepared this manuscript, Fu et al. also reported a similar strategy of dimerization of amidines for the synthesis of the DHT via sequential intermolecular coupling and intramolecular aerobic oxidative dehydrogenation.[12] In this paper, we describe our recent effort to the symmetrical 1,2,4-triazole derivatives during which an anaerobic cascade reaction of deamination and N–N bond coupling by using amidine hydrochloride in the presence of copper took place.

Relying on the features of multiple oxidation states, copper catalysts are widely used in redox reactions, non-redox reactions, single electron transfer processes and synergistic catalysis[13] to construct the carbon–carbon bond, carbon–heteroatom bond and heteroatom–heteroatom bond formation.[14] Combined with our recent research for the direct synthesis of heterocyclic compounds from acyclic acetoacetamides precursors,[15] we used benzimidamide **1a** as the model for the dimerization. The screening of the reaction conditions (Table 1) showed that 3,5-diphenyl-4*H*-1,2,4-triazole **2a** can be finally obtained in 86% yield by treating **1a** (1.0 mmol) with $Cu(OAc)_2$ (0.2 mmol), K_2CO_3 (2.0 mmol), 1,10-phenanthroline (Phen, 0.1 mmol) in anhydrous DMF (2.0 mL) under an inert atmosphere at 130 °C for 24 hours (entry 3). It resulted in a slightly lower yield of **2a** when the reactions were performed at lower temperature at 110 °C (**1a** was recovered in 14% yield) or when the amount of the $Cu(OAc)_2$ was increased or decreased (entries 1, 2 and 4). The lack of any catalytic components, ligand, copper salt or alkali, also dramatically affected the yield of **2a** (entries 5–7). Direct use of commercially available DMF as the solvent, under the conditions of nitrogen protection or open-air, led to a competitive yield in comparison to the optimal conditions (entry 3 vs. entries 8 and 9). Additionally, we considered that the reaction mixture contains chloride ions, so $CuCl_2$ was also tested for this dimerization; as a result, a slightly lower yield (83%) was obtained (entry 10). We then performed the reaction in the presence of CuI, which also gave a slightly lower yield of **2a** (entry 11).[16]



Scheme 1 4-Amino-/hydroxybenzimidamide intramolecular elimination of ammonia

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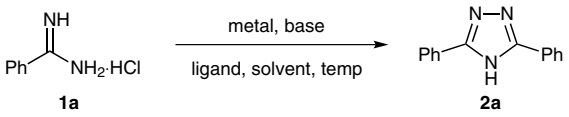
Table 1 Survey of Reaction Conditions[a]



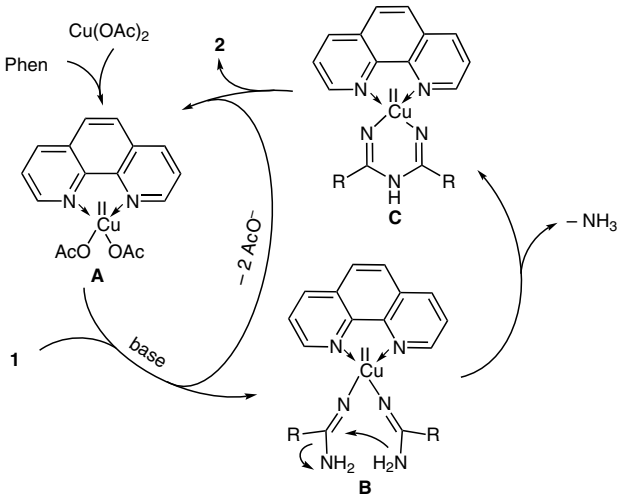
1a 2a

Entry	Catalyst (equiv)	Base	Ligand	Time (h)	Yield (%)[b]
1	$Cu(OAc)_2$ (0.1)	K_2CO_3	Phen	24	72
2	$Cu(OAc)_2$ (0.2)	K_2CO_3	Phen	24	75[c]
3	**$Cu(OAc)_2$ (0.2)**	**K_2CO_3**	**Phen**	**24**	**86**
4	$Cu(OAc)_2$ (0.3)	K_2CO_3	Phen	24	72
5	–	K_2CO_3	Phen	24	0[d]
6	$Cu(OAc)_2$ (0.2)	–	Phen	24	46
7	$Cu(OAc)_2$ (0.2)	K_2CO_3	–	32	72
8	$Cu(OAc)_2$ (0.2)	K_2CO_3	Phen	24	78[e]
9	$Cu(OAc)_2$ (0.2)	K_2CO_3	Phen	24	74[f]
10	$CuCl_2$ (0.2)	K_2CO_3	Phen	24	83
11	CuI (0.2)	K_2CO_3	Phen	24	82

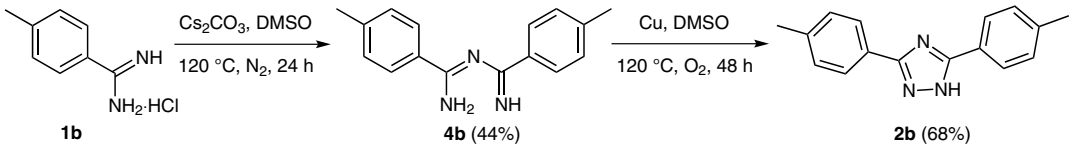
[a] Unless otherwise indicated, all reactions were carried out with **1a** (1.0 mmol), base (2.0 equiv), ligand (0.1 equiv) and DMF (2.0 mL) at 130 °C under dry nitrogen.
[b] Isolated yield.
[c] Reaction was carried out at 110 °C and 14% **1a** was recovered.
[d] Compound **1a** (95%) was recovered.
[e] Reaction was performed in commercially available DMF in N_2.
[f] Reaction was carried out in the open air, and commercially available DMF was used directly as the solvent.

The optimal conditions for this dimerization were finally identified as $Cu(OAc)_2$ (0.2 mmol), K_2CO_3 (2.0 mmol), Phen (0.1 mmol) in anhydrous DMF (2.0 mL) in N_2 atmosphere at 130 °C (Table 1, entry 3). Consequently, we tested the universality of this dimerization of acetoacetamides under the optimal conditions by using aryl-substituted amidine hydrochloride (Table 2). Notably, a variety of substrates **1a**–**n** could be easily converted into the corresponding DHTs **2a**–**n** in moderate to good yields (41–90%). Various electron-donating groups (EDG) substituent (Me, OMe, OEt; compounds **2b**–**f**) and electron-withdrawing groups (EWG) substituent (F, Cl, Br, CF_3 NO_2; compounds **2g**–**n**) on the aryl group were completely tolerated in the current transformation, including unsubstituted benzene ring (compound **2a**). However, the position of the substituents on the aryl group (*para*, *meta* and *ortho* position) affected the yields of **2** dramatically, and *para*- and *meta*-substituted substrates gave relatively higher yields (compounds **2b**–**2d** and **2g**–**2i**). Additionally, as an extension of this dimerization approach, some prepared compounds, such as **2l**, could be used in further functionalization reactions of the Ullmann reaction, Castro–Stephens coupling, Kumada coupling, Heck reaction etc. and **2m** could be widely used in nitrogen-containing compounds synthesis, especially after Béchamp reduction.[17] Surprisingly, the reaction was almost completely shut down when aliphatic acetimidamide hydrochloride **1o** was employed for the screening, even using stronger base (such as Cs_2CO_3) or higher temperature (such as 145 °C or reflux). We deduced that the most likely reason may be due to the low reactivity of **1o**. So, we added the benzamidine to the reaction mixture in batches under the standard conditions. As a result, we got a cross-coupling product 3-methyl-5-phenyl-4*H*-1,2,4-triazole (**2p**) in the yield of 68% after 48 hours. Surprisingly, it failed to provide the desired cross-coupling products **2q** and **2r** when cyclopropylcarbamidine hydrochloride (**1q**) and 2,2,2-trimethylacetamidine hydrochloride (**1r**) were used. These results exhibited the limitation of this method and also it indicated that the current optimal conditions were too mild to fit the aliphatic amidine derivatives to self-dimerize.

Inspired by compound **2m**, we intended to introduce the amino or hydroxyl group directly to DHTs. Unexpectedly, under the optimal conditions, the reaction only provided benzonitrile derivatives **3a** (80%) and **3b** (86%) undergoing an intramolecular elimination of ammonia process rather than an intermolecular dimerization to DHTs **2** when 4-aminobenzimidamide (**1s**) and 4-hydroxybenzimidamide (**1t**) were used as the models (Table 1, entry 3). And the yields of them could be further improved to 92%



Scheme 3 A plausible mechanism



1b 4b (44%) 2b (68%)

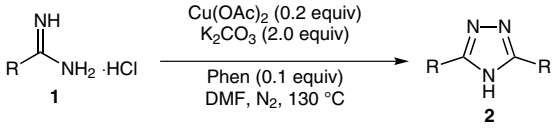
Scheme 2 The work of Fu et al.

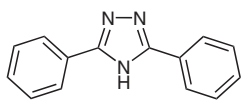
and 94% in the presence of K_2CO_3, respectively,[16] as shown in Scheme 1. It is well known that benzonitriles could be constructed via an intramolecular elimination of ammonia of aryl amidines,[18] but so far it is very rare to achieve such transformation in the presence of the unprotected amino or hydroxyl group.[19]

Fu et al. demonstrated that the intermediate *N*-[amino(*p*-tolyl)methylene]-4-methylbenzimidamide (**4b**) could be obtained in a yield of 44% by treatment of 4-methylbenzamidine hydrochloride (**1b**) with Cs_2CO_3 in DMSO under N_2, then the target product **2b** was provided in 68% yield when **4b** was treated in the presence of Cu powder under O_2 (Scheme 2).[12] But for our strategy, any intermediates, as direct evidence for the mechanism of the self-condensation, were not isolated in the control experiments of quenching the reaction in two hours (Table 1, entry 3) or performing the reaction at slightly lower temperature (Table 1, entry 4). We deduced the proposed mechanism according to the conditions screened in Table 1 together with some previous literature results. In a simplified, generally accepted mechanistic model (Scheme 3), amidine **1** initially reacts with copper(II) complexes[7a,20] **A** to generate the chain copper–ammonia 1:2 complexes transition state **B** under alkaline conditions. Then, **B** affords a six-membered metallacycle species **C** via an intramolecular ammonia elimination.[11,21] Subsequently, the product DHTs **2** is generated in a manner of direct N–N bond formation,[22] and simultaneously, the copper complexes depart into the next coming catalytic cycle.

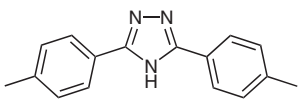
In summary, we have developed a convenient method for the synthesis of symmetrical 1,2,4-triazole via dimerization of amidine hydrochloride in the presence of $Cu(OAc)_2$.[23] Although the mechanism of this reaction cannot explain why the aliphatic-substituted amidine hy-

Table 2 Self-Assembly of Amidine Hydrochloride **1**[a,b]

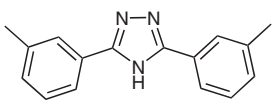




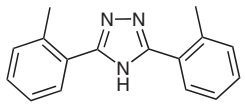
2a, 24 h, 86%



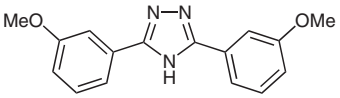
2b, 24 h, 90%



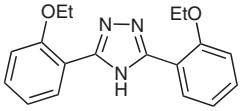
2c, 48 h, 77%



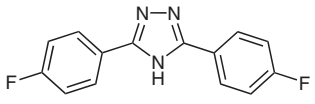
2d, 36 h, 53% [c)]



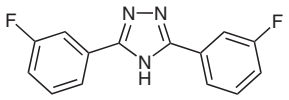
2e, 24 h, 67%



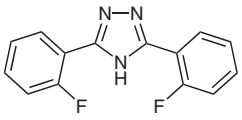
2f, 24 h, 41% [c]



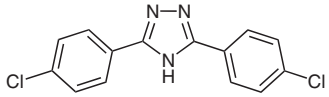
2g, 24 h, 83%



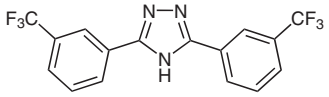
2h, 24 h, 82%



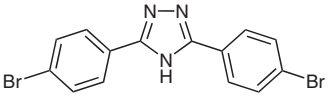
2i, 24 h, 52%[c]



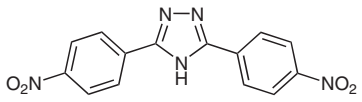
2j, 24 h, 80%



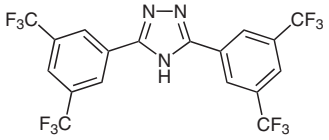
2k, 24 h, 78%



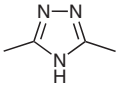
2l, 24 h, 72%



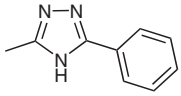
2m, 24 h, 85%



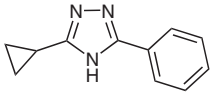
2n, 24 h, 75%



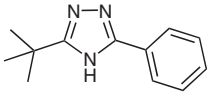
2o, 48 h, trace



2p, 48 h, 68%



2q, 48 h, 0%



2r, 48 h, 0%

[a] All reactions were carried out with amidine hydrochloride **1** (1.0 mmol), $Cu(OAc)_2$ (0.2 mmol), K_2CO_3 (2.0 mmol), Phen (0.1 mmol) in DMF (2.0 mL) in N_2 atmosphere at 130 °C, unless otherwise indicated.
[b] Isolated yield.
[c] Some unidentified mixture was obtained simultaneously.

drochloride **1** did not work well, as an optional method for the symmetrical 1,2,4-triazole synthesis, the process avoided using the carcinogenic hydrazine[24] and volatile reactants such as ammonia used in the traditional methods.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(23) **General Procedure for the Synthesis of Compounds 2a–o**: To a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) were added amidine hydrochloride 1 (1.0 mmol), $Cu(OAc)_2$ (0.2 equiv), K_2CO_3 (2.0 equiv), 1,10-phenanthroline (0.1 equiv) and anhyd DMF (2.0 mL). Then the mixture was well stirred at 130 °C under an inert atmosphere. After cooling off, the mixture was filtered through a pad of celite eluting with CH_2Cl_2 (3 × 6 mL). The volatiles were removed under reduced pressure and the residue was purified by a short flash silica gel column chromatography to give compound **2**. **2a**: white solid; eluent: petroleum ether–EtOAc (3:1). Yield: 86%; mp 191–192 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.05 (d, *J* = 6.4 Hz, 4 H), 7.41–7.49 (m, 6 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 160.53, 131.02, 130.17, 129.89, 127.56. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}N_3$: 222.1026; found: 222.1026.
General Procedure for the Synthesis of Compounds 2p: To a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) were added acetimidamide hydrochloride **1p** (94.5 mg, 1.0 mmol), benzimidamide hydrochloride **1a** (0.5 equiv), $Cu(OAc)_2$ (37 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol), 1,10-phenanthroline (20 mg, 0.1 mmol) and anhyd DMF (2.0 mL). Then the mixture was well stirred at 130 °C under an inert atmosphere. The other two batches of benzimidamide hydrochloride **1a** (0.5 equiv for each) were added to the mixture every 8.0 h. After 48 h (total reaction time), the reaction mixture was cooled, filtered through a pad of celite eluting with CH_2Cl_2 (3 × 6 mL). The volatiles were removed under reduced pressure and the residue was purified by short flash silica gel column chromatography to give compound **2p** as a white solid; eluent: petroleum ether–EtOAc (2:1). Yield: 68%; mp 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 6.0 Hz, 2 H), 7.44 (d, *J* = 6.0 Hz, 3 H), 2.53 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.04, 155.71, 130.08, 129.73, 128.89, 126.44, 12.81. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_9N_3$: 160.0869; found: 160.0874.
General Procedure for the Synthesis of Compounds 3a,b: To a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) were added amidine hydrochloride **1s** or **1t** (1.0 mmol), $Cu(OAc)_2$ (0.2 equiv), K_2CO_3 (2.0 equiv), 1,10-phenanthroline (0.1 equiv) and anhyd DMF

(2.0 mL). Then the mixture was well stirred at 130 °C under an inert atmosphere. After cooling off, the mixture was filtered through a pad of celite eluting with CH_2Cl_2 (3 × 6 mL). The volatiles were removed under reduced pressure and the residue was purified by a short flash silica gel column chromatography to give compound **3a** or **3b**. **3a**: yellow solid; yield: 80%; mp 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.8 Hz, 2 H), 6.62 (d, *J* = 8.4 Hz, 2 H), 4.28 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.80, 133.67, 120.41, 114.33, 99.30. **3b**: white solid; yield: 86%; mp 110–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.57, 134.47, 119.42, 116.63, 102.80.

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