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Facile Synthesis of 1,2,4-Triazoles via a Copper-Catalyzed Tandem Addition−Oxidative Cyclization

Satoshi Ueda and Hideko Nagasawa*

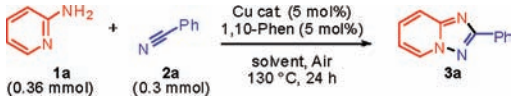
Laboratory of Medicinal and Pharmaceutical Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan

Received June 19, 2009; E-mail: hnagasawa-gifu-pu.ac.jp

The 1,2,4-triazole nucleus is an important structural motif present in a large number of functionalized molecules with a wide variety of uses, including applications in medicinal chemistry, materials science, and organocatalysis. The importance of this heterocyclic moiety has prompted the development of many practical synthetic routes to 1,2,4-triazole derivatives.[1] The majority of these routes rely on intramolecular condensation reactions of *N*-acylamidorazones obtained from hydrazines and carboxylic acid derivatives.[2] Although the existing synthetic methods have provided a wide variety of 1,2,4-triazoles, these typically involve multistep reaction sequences. Recently, Chen and co-workers[3] reported one-pot formation of copper(I) triazolates under stoichiometric solvothermal conditions. Pertinent to the present research, there appears to be no precedent for catalytic synthesis of 1,2,4-triazoles from readily available starting materials. Herein, we report a single-step elaboration of 1,2,4-triazole structure using a conceptually distinct copper-catalyzed oxidative coupling approach.

On the basis of the known ability of transition metals to activate nitriles[4] and the recently developed catalytic oxidative construction of nitrogen heterocycles,[5] we envisioned a direct synthesis of the 1,2,4-triazole nucleus by reaction of 2-aminopyridines and nitriles involving transition-metal-catalyzed N−C bond formation and oxidative N−N coupling. To explore this approach, we selected 2-aminopyridine (**1a**) and benzonitrile (**2a**) for reaction development and screened several transition-metal catalysts in common solvents for their catalytic activity. When **1a** and **2a** were reacted in the presence of 5 mol % CuBr and 1,10-phenanthroline (1,10-Phen)[6] in 1,2-dichlorobenzene (DCB) at 130 °C under an air atmosphere, 2-phenyl-1,2,4-triazolopyridine **3a** was obtained in 39% yield (Table 1, entry 1). The addition of 10 mol % ZnI_2 greatly improved the reaction efficacy, and **3a** was obtained in 81% yield (entry 2).[7] Other zinc salts such as $ZnCl_2$ and $ZnBr_2$ were less effective than ZnI_2 (entries 3 and 4). The reaction also proceeded in other solvents such as toluene and dimethyl sulfoxide (DMSO), albeit in lower yield (entries 5 and 6). Other copper sources, including $CuBr_2$, CuCl, and $Cu(OAc)_2$, could be employed (entries 7−9). In the absence of a copper source, no product formation was observed (entry 10).

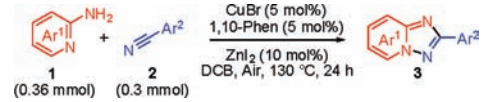
Table 1. Reaction Optimization

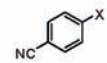
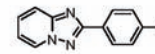
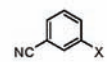
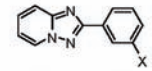
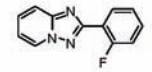
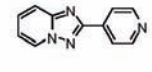
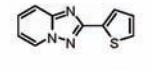
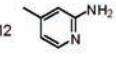
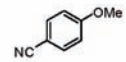
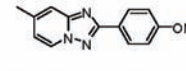
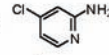
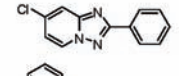
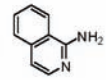
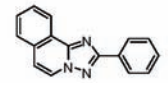


entry	catalyst	solvent	additive (10 mol %)	yield (%)
1	CuBr	DCB	−	39
2	CuBr	DCB	ZnI_2	81 (70)[a]
3	CuBr	DCB	$ZnCl_2$	34
4	CuBr	DCB	$ZnBr_2$	49
5	CuBr	toluene	ZnI_2	71
6	CuBr	DMSO	ZnI_2	35
7	$CuBr_2$	DCB	ZnI_2	73
8	CuCl	DCB	ZnI_2	78
9	$Cu(OAc)_2$	DCB	ZnI_2	76
10	−	DCB	ZnI_2	0

[a] Yield of gram-scale reaction in parentheses.

Table 2. Copper-Catalyzed Synthesis of Triazoloheterocycles



entry	aminopyridine	nitrile	product		yield (%)
1				**3b** (X = F)	80
2				**3c** (X = Cl)	88
3				**3d** (X = Br)	81
4				**3e** (X = Me)	78
5				**3f** (X = OMe)	70
6				**3g** (X = Cl)	82
7				**3h** (X = CF_3)	90
8				**3i** (X = OMe)	71
9				**3j**	70
10				**3k**	73
11				**3l**	69
12				**3m**	71
13				**3n**	60
14				**3o**	87

With the optimum reaction conditions in hand, we next investigated the scope of the oxidative synthesis of triazoloheterocycles (Table 2). Benzonitriles with electron-withdrawing halogen or trifluoromethyl groups gave the corresponding triazolopyridines **3b**−**d**, **3g**, and **3h** in good yield. The reactions with methoxy-substituted benzonitriles were slower than those with electron-deficient benzonitriles and gave triazolopyridines **3f** and **3i** in moderate yields. Heterocyclic substituents such as pyridine and thiophen could be incorporated (**3k** and **3l**). The reaction of a chloro-substituted 2-aminopyridine gave the corresponding product **3n** in moderate yield. The relatively lower yields probably reflect the lower nucleophilicity of the aminopyridines. The reaction

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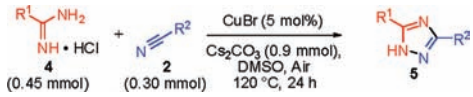
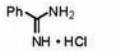
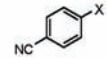
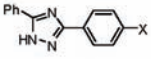
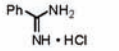
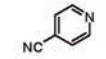
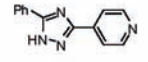
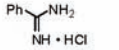
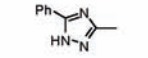
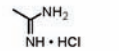
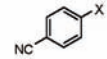
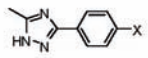
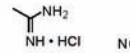
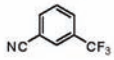
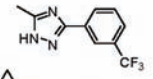
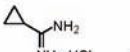
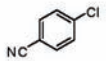
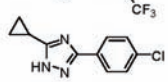
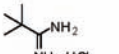
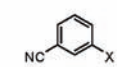
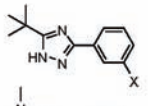
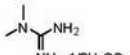
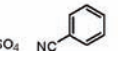
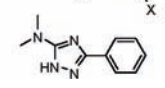
of 1-aminoisoquinoline with benzonitrile gave triazoloisoquinoline **3o**, which is known as a potent nonhormonal antifertility agent,[8] in good yield.

The efficiency of the expeditious copper-catalyzed oxidative coupling process for triazoloheterocycles prompted us to examine the synthesis of 1*H*-1,2,4-triazoles from amidines and nitriles. In contrast to the synthesis of triazolopyridines, the use of ZnI_2 in DCB was not effective in the synthesis of 1,2,4-triazoles. The addition of Cs_2CO_3 resulted in the successful production of the corresponding 1*H*-1,2,4-triazoles from amidines **4** and nitriles **2** (Table 3). The reactions of benzamidine and benzonitriles afforded triazoles **5a**−**c** in good yields (entries 1−3). Acetonitrile could also be employed instead of benzonitriles (entry 4). The reactions of primary, secondary, and tertiary alkyl amidines provided the corresponding 5-alkyl triazoles **5d**−**5k** in moderate to good yield (entries 5−12). Again, electron-deficient benzonitriles provided better yields. 5-Amino-substituted 1,2,4-triazole **5l** was successfully prepared from a guanidine precursor (entry 13).

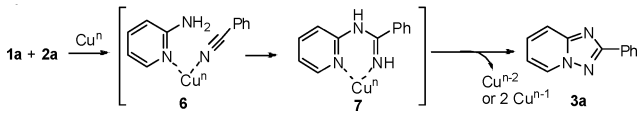
Table 3. Copper-Catalyzed Synthesis of Triazoles



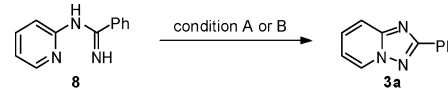
entry	amidine	nitrile	product	yield (%)
1			 **5a** (X = H)	76
2			**5b** (X = CF_3)	82
3			 **5c**	70
4		MeCN	 **5d**	52[a]
5			 **5d** (X = H)	78
6			**5e** (X = Cl)	83
7			**5f** (X = Br)	73
8			 **5g**	85
9			 **5h**	69
10			 **5i** (X = H)	63
11			**5j** (X = Cl)	71
12			**5k** (X = OMe)	55
13			 **5l**	66

[a] MeCN/DMSO (1:3) was used as the solvent.

Scheme 1. Proposed Mechanism for the Copper-Catalyzed Oxidative Synthesis of Triazole Derivatives



In view of the reported intramolecular N−N bond-forming process under oxidative conditions,[9] the present reaction should consist of initial amidine formation[10,11] followed by intramolecular oxidative N−N bond formation in the amidine intermediate (Scheme 1). Thus, copper first promotes nucleophilic attack of 2-aminopyridine **1a** on the nitrile, probably by forming coordinated intermediate **6**, to provide amidine **7**.[12] Subsequent copper-induced oxidative cyclization of the amidine provides triazolopyridine **3a** and reduced copper species.[13] The second step (oxidative N−N bond formation) was confirmed by conversion of amidine **8** to **3a** under the reaction conditions (eq 1):[14]



A: Condition shown in Table 2; 89% yield
B: $Cu(OAc)_2$ (100 mol%), DCB, Ar, 130 °C, 12 h; 79% yield

The cyclization was also achieved effectively by the use of a stoichiometric amount of $Cu(OAc)_2$ under an argon atmosphere.[15] Reoxidation of the reduced copper by molecular oxygen completes the catalytic cycle.

In summary, we have developed an efficient copper-catalyzed oxidative synthesis of 1,2,4-triazole derivatives. The catalytic cycle was achieved by use of molecular oxygen (air at 1 atm) as the oxidant, which produces water as the sole theoretical byproduct. The reaction allows the facile generation of diversity in the construction of 1,2,4-triazoles, which are important privileged structures. Therefore, the reaction described here should be an attractive alternative for the preparation of potentially bioactive compounds.

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

References

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(13) The mechanism for forming the 1,2,4-triazoles (**5**) might resemble that shown in Scheme 1.
(14) The cyclization reaction also proceeded smoothly without ZnI_2, so the relatively soft Lewis acid ZnI_2 is likely to assist the initial amidine formation step.
(15) Copper(I) should be oxidized to copper(II) by the trace amount of water in the solvent and dioxygen for catalyzing the cyclization, but addition of water slightly lowered the reaction efficacy (see the Supporting Information). Consequently, the speciation of copper cannot be specified at present.

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