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Synthesis of Imidazoles through the Copper-Catalyzed Cross-Cycloaddition between Two Different Isocyanides

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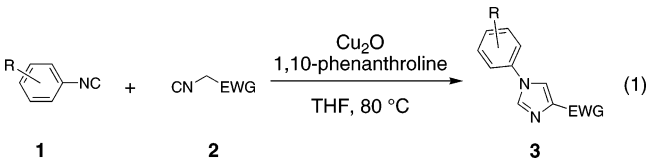
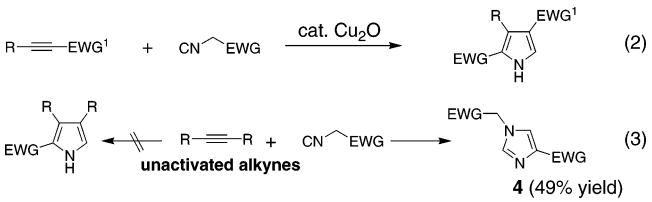
Imidazoles are one of the important classes of heterocyclic compounds because of their wide utilities.[1] They are often seen as a building block in naturally occurring and biologically active compounds. Recently, imidazoles are also used as the materials for ligands and ionic liquid. Due to their characteristic properties, many methodologies have been developed for constructing imidazole rings:[1−3] for example, (1) the reaction of α-diketones and α-haloketones (or their derivatives) with formamide (Bredereck synthesis), (2) base-produced cyclization reaction between *p*-tosylmethyl isocyanide and aldimine or imidoyl chloride. However, many of these reaction conditions require the use of strong base or high temperature or produce acids as byproducts. In view of recent demands for development of environmentally benign processes, a mild, catalytic, and atom economical methodology must be developed. To the best of our knowledge, only few catalytic reactions which produce imidazoles have been reported.[2] Recently, Grigg et al. reported the silver-catalyzed dimerization reaction of isocyanoacetate to produce the corresponding imidazoles[2b] (only two examples); however, the catalytic heterocoupling reaction between two different isocyanides is not discovered.

We herein report that the copper-catalyzed cross-cycloaddition between arylisocyanides **1** and isocyanides **2** produces the 1,4-disubstituted imidazoles **3** in very high yields (eq 1).



During the course of research on the copper-catalyzed pyrrole synthesis between activated alkynes and isocyanides (eq 2),[4,5] the use of *unactivated* alkynes did not produce the desired pyrroles; instead the reaction gave the imidazole **4** (EWG = CO_2Et) in 49% yield (eq 3) as the homo-cycloaddition product[2b] of ethyl isocyanoacetate. It seemed to us that the use of *activated* C-heteroatom triple bonds, such as R−NC or R−CN, might induce the cross-cycloaddition leading to a different type of heterocycles.



We first examined the reaction of 4-methoxy-1-isocyanobenzene **1a** (R = OMe in eq 1) with ethyl isocyanoacetate **2a** (EWG = CO_2Et) under the conditions shown in Table 1. Interestingly, the reaction with copper powder gave 4-ethoxycarbonyl-1-(4-methoxyphenyl)imidazole **3a** in a good yield (entry 1). CuCl or $CuCl_2$ gave only trace amounts of the product or no reaction took place (entries 2 and 4). Fortunately, the reaction with Cu_2O produced the product in a good isolated yield (entry 3). Among the ligands (other amines, phosphines, etc.) tested, the 1,10-phenanthroline/Cu_2O system gave the best result. The reaction with Cu_2O catalyst in the absence of 1,10-phenanthroline gave the product in a lower yield. The role of the ligand is not clear at present. The silver[2b] and rhodium[5b] catalysts were ineffective (entries 5 and 6). As a result of further investigation, the use of 1.4 equiv of **2a** gave an excellent yield (entry 7). This cross-cycloaddition did not proceed in the absence of the copper catalysts (entry 8).

Table 1. Effects of Metal Catalysts in the Reaction of **1a** with **2a**[a]

entry	catalyst	**3a**, yield, %[b]
1	Cu powder	78
2	CuCl	trace
3	Cu_2O[c]	83 (73)
4	$CuCl_2$	0[g]
5	AgOAc[d]	18
6	$RhH(PPh_3)_4$[d,e]	0[g]
7	Cu_2O[c,f]	99 (93)
8	none	0[g]

[a] Unless otherwise noted, the reaction between **1a** (0.3 mmol) and **2a** (0.3 mmol) was conducted in THF (1.2 mL) in the presence of a catalyst (60 μmol, 20 mol %) and 1,10-phenanthroline (60 μmol, 20 mol %) at 80 °C for 3 h. [b] NMR yield using dibromomethane as an internal standard. Isolated yield is shown in parentheses. [c] 10 mol % of the catalyst was used. [d] Without 1,10-phenanthroline. [e] 5 mol % of the catalyst was used. [f] **2a** (0.42 mmol, 1.4 equiv) was used. [g] No reaction.

Table 2. Copper-Catalyzed Imidazole Synthesis Using Various Isocyanobenzenes **1** and **2a**[a]

entry	**1**	R	time, h	**3**	yield, %[b]
1	**1a**	4-OMe	3	**3a**	93
2	**1b**	3-OMe	2	**3b**	98
3	**1c**	2-OMe	2	**3c**	88
4	**1d**	4-COOMe	2	**3d**	98
5	**1e**	4-CN	1.5	**3e**	97
6	**1f**	4-NO_2	1	**3f**	88
7	**1g**	4-Cl	5	**3g**	93
8	**1h**	4-TMS−C≡C	2	**3h**	91
9	**1i**	H	2.5	**3i**	93
10	**1j**	1-naphthyl	4	**3j**	95
11	**1k**	2,6-dimethyl	4	**3k**	92

[a] The reaction between **1** (0.5 mmol) and **2a** (0.7 mmol) was conducted in THF (2.8 mL) in the presence of Cu_2O (70 μmol, 10 mol %) and 1,10-phenanthroline (140 μmol, 20 mol %) at 80 °C for the time indicated in Table 2. [b] Isolated yield.

We carried out the reaction of various arylisocyanides **1** with ethyl isocyanoacetate **2a** under the optimized conditions (Table 2). The *o*- and *m*-methoxy-substituted isocyanobenzenes **1b** and **1c** gave the products **3b** and **3c**, respectively, in good yields (entries

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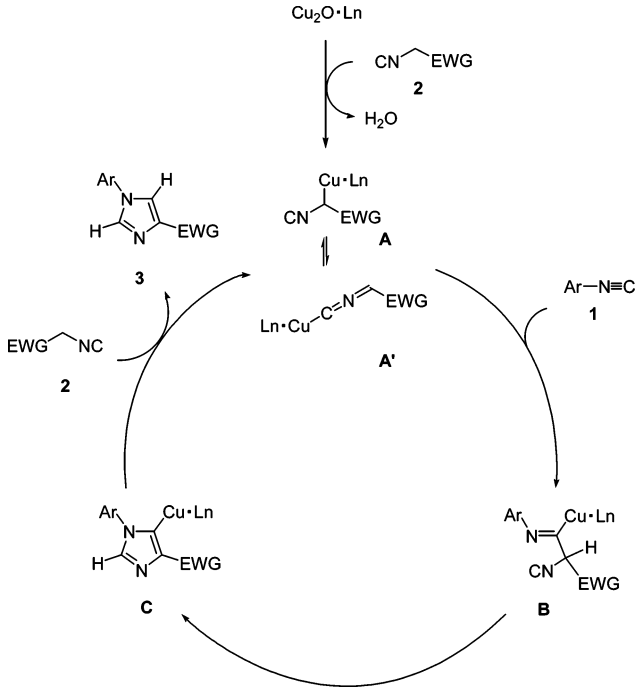
Table 3. Copper-Catalyzed Imidazole Synthesis Using Various Isocyanides **2** and Isocyanobenzene **1d**[a]

entry	2	EWG	time, h	3	yield, %[b]
1	**2b**	CO_2t-Bu	3	**3l**	97
2	**2c**	$P(O)(OEt)_2$	24	**3m**	62
3	**2d**	$CONEt_2$	20	**3n**	71
4	**2e**	Ph	24	**3o**	trace[c]

[a] The reaction between **1d** (0.5 mmol) and **2** (0.7 mmol) was conducted in THF (2.8 mL) in the presence of Cu_2O (70 μmol, 10 mol %) and 1,10-phenanthroline (140 μmol, 20 mol %) at 80 °C for the time indicated in Table 3. [b] Isolated yield. [c] NMR yield; significant amounts of **1d** and **2e** were recovered.

Scheme 1. A Plausible Mechanism for the Copper-Catalyzed Cross-Cycloaddition between Isocyanides **1** and **2**



2 and 3). The reactions of isocyanobenzenes having an ester **1d**, cyano **1e**, and nitro **1f** proceeded smoothly to give the corresponding products **3d**−**f**, respectively, in good to excellent yields (entries 4−6). The reaction tolerated a functional group, such as chloro (**1g**) or alkynyl (**1h**), giving the products **3g** and **3h** in 93 and 91% yields, respectively (entries 7 and 8). Nonsubstituted isocyanobenzene **1i** gave the imidazole **3i** in 93% yield (entry 9). Even sterically hindered isocyanobenzenes **1j** and **1k** underwent the cross-cycloaddition to give the corresponding imidazoles **3j** and **3k** in 95 and 92% yields, respectively (entries 10 and 11). We also tried the reaction between **2a** and aliphatic isocyanides, such as *n*-butyl or cyclohexyl isocyanide. Unfortunately, only 12 and 10% yields of the corresponding imidazoles were obtained; the major products were the homo-cycloadducts of type **4**.

Next we examined the effect of electron-withdrawing groups in the isocyanide **2** (Table 3). Installation of a bulky *tert*-butyl group in the ester moiety, as shown in **2b**, did not affect the reaction progress, and the imidazole **3l** was produced in an excellent yield (entry 1). The isocyanides having phosphonate **2c** and amide **2d** gave the corresponding products **3m** and **3n** in 62 and 71% yields, respectively, although longer reaction times were needed to consume the substrates (entries 2 and 3). Benzylisocyanide **2e**, which could react with an activated alkyne to give the corresponding pyrrole,[4] gave only traces of the desired product (entry 4).

A plausible mechanism for the copper-catalyzed cross-cycloaddition between isocyanides **1** and **2** is depicted in Scheme 1. The reaction starts with activation of a C−H bond of the isocyanides **2** by the influence of Cu_2O catalyst. The α-cuprioisocyanide **A** or its tautomer **A′** is formed by the reaction between **2** and Cu_2O through the extrusion of H_2O.[6,7] Then, the nucleophilic addition of the intermediate **A** and/or **A′** to arylisocyanide **1** takes place to generate the intermediate **B**. Intramolecular attack of the nitrogen atom derived from arylisocyanide **1** to the carbon atom of the CN− group, followed by 1,3-hydrogen shift, would produce the cyclized intermediate **C**; this is a formal [3 + 2] cycloaddition process. The C−Cu bond in the intermediate **C** is protonated by **2** to produce the 1,4-disubstituted imidazole **3** with regeneration of the copper intermediate **A** and/or **A′**.

In conclusion, we have developed a new efficient synthetic procedure for 1,4-disubstituted imidazoles via the cross-cycloaddition between two different isocyanides. Further studies on the mechanistic details are underway in our laboratory.

Supporting Information Available: Experimental procedures and characterization data of relevant compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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