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Copper-Catalyzed Cyanation of Heterocycle Carbon−Hydrogen Bonds

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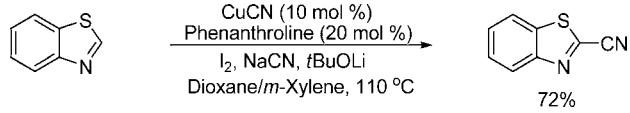
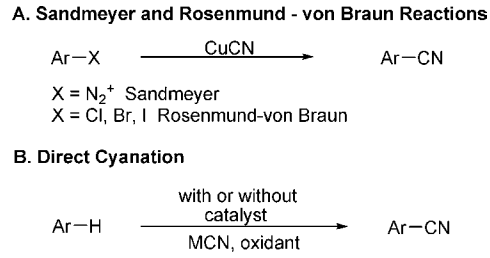
ABSTRACT



A method for regioselective cyanation of heterocycles has been developed. A number of aromatic heterocycles as well as azulene can be cyanated in reasonable to good yields by using a copper cyanide catalyst and an iodine oxidant.

The nitrile functional group is found in many pharmaceuticals and agrochemicals.[1,2] Sandmeyer and Rosenmund−von Braun reactions are classic methods for the synthesis of aromatic nitriles (Scheme 1A).[3] However, both procedures employ a stoichiometric copper(I) cyanide reagent and prefunctionalized starting materials. Cyanation of aryl halides by employing catalytic copper or palladium is also well-known.[4] In contrast, direct cyanation through C−H bond functionalization is more attractive due to the use of readily available reactants.[5] Direct cyanation can be achieved by employing an appropriate oxidant in combination with a cyanide source (Scheme 1B).[6] Methods for direct cyanation of pyridines,[6b] thiophenes,[6c,e] substituted indoles,[6c,e,h] pyrroles,[6c,e] and 2-phenylpyridines[6d,f,g] have been reported in the literature. However, direct transition-metal-catalyzed

Scheme 1. Cyanation Methods



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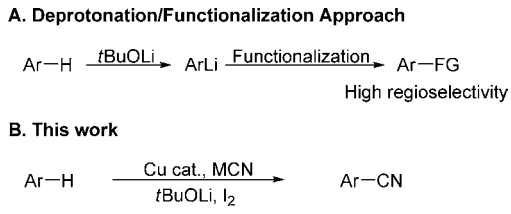
cyanation of acidic heterocycles such as azoles, imidazoles, and triazoles has not been described yet.[6k,l] We report here a method for regioselective, direct cyanation of aromatic heterocycles as well as azulene by employing copper catalysis and an iodine oxidant.

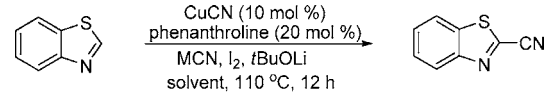
Several key issues need to be addressed for achieving a general cyanation procedure. First, high regioselectivity is required for the procedure to be synthetically relevant. High regioselectivity observed in direct arylation[7] and halogenation reactions[8] (Scheme 2A) is imparted by the initial deprotonation step. This protocol rules out the use of positive cyanide sources due to their incompatibility with strong bases. Consequently, simple cyanide salts such as NaCN or KCN must be employed. Second, choice of base is important. As described earlier,[7,8] *t*BuOLi allows for functionalization of a wide range of substrates possessing DMSO pK_a's below 35−37. Third, the oxidant has to be compatible with all other reagents. It should not react with the organolithium intermediate producing byproducts that can not be converted to the desired cyanation product. Oxygen reactivity with some arylmetals complicates the catalytic system by requiring the use of zinc or magnesium amide bases.[9] Iodine is compatible with copper catalysts, and aryl iodides formed in the reaction of ArLi with I_2 can be converted to aryl cyanides.[4,8] Consequently, we decided to employ iodine as the oxidant in conjunction with *t*BuOLi base and a copper catalyst (Scheme 2B).

Scheme 2. Method Development



Benzothiazole was chosen as a model substrate, and copper(I) cyanide/phenanthroline catalyst was used to screen for suitable reaction conditions. DMF solvent was chosen as a starting point for optimization because it has been successfully used in base-mediated iodination.[8] Several cyanating reagents such as NaCN, KCN, $Zn(CN)_2$, and $K_3[Fe(CN)_6]$ were screened. However, none of these reactions afforded any cyanation product. Solvent screening revealed that 1,4-dioxane yields 42% conversion to the desired product if NaCN is employed as the cyanating reagent (Table 1). The reaction mixture was monitored to gain insight into the reaction pathway. The results indicate that the cyanation is a stepwise reaction. Benzothiazole is iodinated to afford 2-iodobenzothiazole followed by copper-catalyzed cyanation yielding the desired product **2**. Consequently, reaction conditions should be optimized with respect to both iodination and cyanation. Among tested cyanide sources, sodium cyanide provides the highest reactivity due to its solubility in dioxane. However, it has been well-established that high concentration of cyanide will deactivate copper catalyst due to strong complexation.[4] Careful tuning of the solvent polarity led to significant improvement of conversion to the product (Table 1).

Table 1. Optimization of Cyanation Conditions

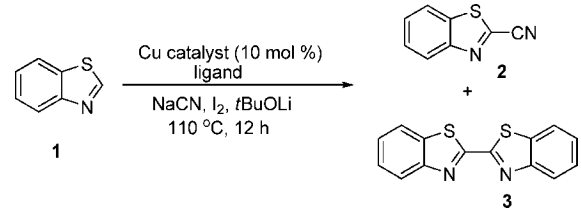


1 **2**

entry	solvent	MCN	**2**[a]
1	DMF	NaCN, KCN, $Zn(CN)_2$, or $K_3[Fe(CN)_6]$	0%
2	dioxane	NaCN	42%
3	dioxane	KCN, $Zn(CN)_2$ $K_3[Fe(CN)_6]$	<2%
4	xylene	NaCN	0%
5	dioxane/xylene (9/1)	NaCN	54%
6	dioxane/xylene (4/1)	NaCN	72%
7	**dioxane/xylene (7/3)**	**NaCN**	**90%**
8	dioxane/xylene (3/2)	NaCN	78%
9	dioxane/xylene (1/1)	NaCN	59%

[a] Conversion by GC reported.

Table 2. Optimization of Copper Catalyst



1

entry	catalyst/ligand	**2**[a]	**3**[a]
1	CuCN/no ligand	<2%	<2%
2	CuCN/phenanthroline (1/1)	60%	16%
3	**CuCN/phenanthroline (1/2)**	**90%**	**<2%**
4	CuCN/bipyridine (1/2)	88%	<3%
5	CuCl/phenanthroline (1/2)	87%	<2%
6	CuI/phenanthroline (1/2)	90%	<2%

[a] Conversion by GC reported. Dioxane/*m*-xylene solvent (7/3).

Ligand optimization is shown in Table 2. The cyanation did not proceed in the absence of phenanthroline. In addition, a considerable amount of benzothiazole dimer byproduct was observed if less than 20 mol % of phenanthroline was used.

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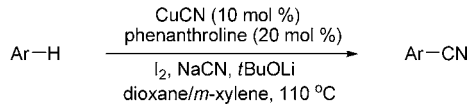
Table 3. Cyanation Scope[a]



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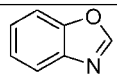
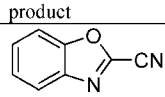
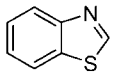
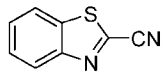
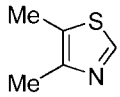
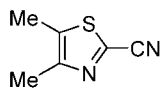
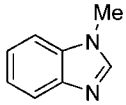
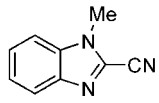
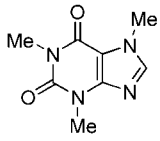
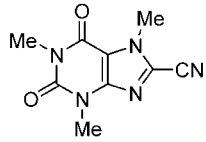
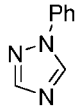
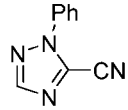
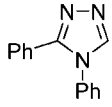
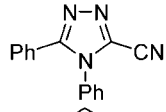
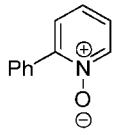
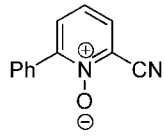
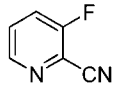
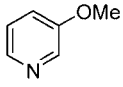
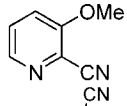
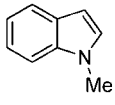
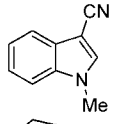
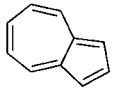
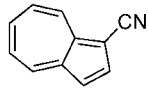
1			63%
2			72%
3			72%
4			51%
5			66%
6			71%
7			55%
8			71%
9[b]			53%
10			45%
11[c]			90%
12[c]			36%

[a] Substrate (1 equiv), *t*BuOLi (2−2.13 equiv), iodine (1.35−1.5 equiv), NaCN (1.3 equiv), CuCN (0.1 equiv), and phenanthroline (0.2 equiv). Yields are isolated yields. [b] Cyanide as the limiting reagent. [c] Substrate (1.5−2 equiv), pyridine (0.76 equiv), Na_3PO_4 (2 equiv), iodine (1−1.35 equiv), and dioxane solvent. Copper(I) catalyst (0.2 equiv), phenanthroline (0.3 equiv), and sodium cyanide (1−1.3 equiv) were added after the iodination step. See Supporting Information for details.

The bipyridine ligand was shown to be almost as efficient as phenanthroline (entry 4). Copper(I) chloride and copper(I) iodide can also be employed as catalysts. The optimized conditions involve CuCN catalyst, phenanthroline ligand, sodium cyanide, iodine oxidant, and mixed dioxane/*m*-xylene solvent. These conditions were applied to cyanation of a variety of heterocycles (Table 3).

Heterocycles such as benzoxazole, benzothiazole, benzimidazole, caffeine, and triazoles are cyanated in reasonable to good yields (entries 1−7). Electron-deficient 2-phenylpyridine oxide is also cyanated in good yield (entry 8). Pyridine derivatives with electron-withdrawing (fluorine) or electron-donating (methoxy) substituents are reactive under the general conditions affording products in acceptable yields (entries 9 and 10). In both cases, the cyano group was introduced at the 2-position. Similar selectivity has been reported by Katritzky in the direct cyanation of pyridines by the addition/elimination approach.[6b]

Indoles constitute an important motif of aromatic compounds encountered in many natural products and pharmaceuticals. Hence, selective functionalization of indoles has attracted much attention in recent years.[10] Wang and coworkers have recently developed a method for palladium-catalyzed cyanation of 1- and 2-substituted indoles by employing 3 equiv of $Cu(OAc)_2$ reoxidant.[6h]

Minor modifications of our general conditions enabled regioselective cyanation of *N*-methylindole and azulene. The following changes in procedure were required for achieving high yield of the product. First, pyridine additive prevents the solidification of the reaction mixture. Second, sodium phosphate base was found to be more efficient than *t*BuOLi in the iodination step. Third, copper catalyst was added to the reaction mixture after the iodination step was complete.

Consequently, the combination of iodine and sodium phosphate in dioxane provided effective iodination conditions that are compatible with the subsequent copper-catalyzed cyanation. Copper catalyst was added after the iodination step in entries 11 and 12 to prevent the oxidation of copper(I) catalyst.[7d] This procedure selectively afforded 3-cyano-1-methylindole in excellent yield (entry 11). Azulene was cyanated in moderate yield (36%) due to low reactivity of iodoazulene intermediate in the cyanation step.

In conclusion, we have developed a method for copper-catalyzed cyanation of aromatic heterocycles and azulene. The use of mild iodine oxidant allows for regioselective sequential iodination/cyanation of heterocycles with acidic C−H bonds, methylindole, and azulene.

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Supporting Information Available: Experimental details, data, and spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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