

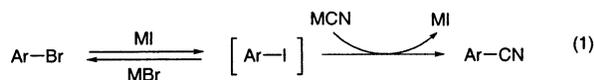
## Copper-Catalyzed Domino Halide Exchange-Cyanation of Aryl Bromides

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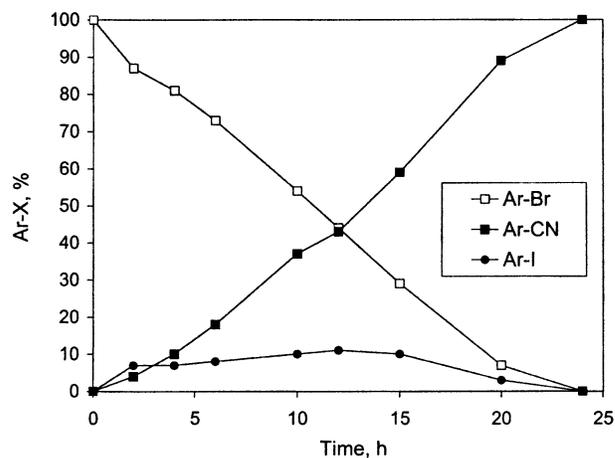
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Reaction of copper(I) cyanide with aryl halides, also known as the Rosenmund–von Braun reaction,<sup>1</sup> is an important method for the preparation of aromatic nitriles.<sup>2</sup> Unfortunately, several problems limit the generality of this classic method; for example, the cyanation of aryl bromides requires extreme reaction conditions (150–280 °C) which may not be compatible with sensitive substrates. This is a serious limitation because aryl bromides are more available and less expensive than the corresponding aryl iodides. In addition, the stoichiometric amount of copper(I) cyanide which is utilized in the reaction may complicate the separation of the nitrile products from the copper halide salts produced in the reaction.<sup>3</sup> When used on the industrial scale, the stoichiometric amounts of the copper salts also present a significant waste disposal problem. More recently, palladium-<sup>4</sup> and nickel-catalyzed<sup>5</sup> aryl cyanation methods have been developed as milder alternatives to the classic Rosenmund–von Braun reaction. Although many successful applications of the palladium-catalyzed aryl cyanation reaction have been documented, the method suffers from poor reliability. A notable improvement was presented in the report by Anderson and co-workers at Lilly who found that the addition of CuI (10 mol %) to the reaction greatly improved the efficiency of this transformation.<sup>6</sup> Still, their procedure necessitated the use of relatively high quantities of the expensive Pd(Ph<sub>3</sub>P)<sub>4</sub> (5 mol %). Presumably, this is required to compensate for catalyst deactivation during the cyanation reaction.<sup>7</sup>



Recently, we reported that 1,2-diamine ligands accelerate copper-catalyzed reactions of aryl halides with such diverse nucleophiles as amides, nitrogen heterocycles, and iodide ion.<sup>8</sup> Our initial attempts at using the cyanide ion as the nucleophile in analogous procedures indicated that diamine ligand **1** was very beneficial for the copper-catalyzed cyanation of aryl iodides. Thus, the cyanation of 5-iodo-*m*-xylene proceeded to >99% conversion after 24 h at 90 °C, comparable results being obtained with either CuI, CuBr, or CuCN as precatalysts (10 mol %).<sup>9</sup> Surprisingly, the cyanation of aryl bromides was much more sensitive to the nature of the copper precatalyst; for example, CuI performed dramatically better than either CuBr or CuCN.<sup>10</sup> This result can be rationalized assuming in situ copper-catalyzed conversion of the aryl bromide into the more reactive aryl iodide followed by the cyanation of the resulting aryl iodide (eq 1). In accord with this hypothesis, addition of 20 mol % KI to the reaction mixture improved the efficiency of the cyanation reaction. Consequently, 10 mol % CuI, 20 mol % KI, 1.0 equiv of the inexpensive diamine ligand **1**, and 1.2 equiv



**Figure 1.** Copper-catalyzed cyanation of 5-bromo-*m*-xylene. Performed with 10 mol % CuI, 1.0 equiv of ligand **1**, 20 mol % KI, 1.2 equiv of NaCN, and toluene as solvent at 110 °C.

of NaCN in toluene at 110 °C was identified as a highly efficient system for the conversion of aryl bromides into aromatic nitriles via concurrent halogen exchange.<sup>11</sup>

The success of the halide exchange-cyanation reaction largely relies on matching the relative rates of the two steps in the domino reaction sequence (eq 1). This is achieved by proper choice of the iodide salt, the cyanide salt, and the solvent, thus ensuring optimal concentrations of the iodide and cyanide salts in the solution. Using the combination of KI, NaCN, and toluene, we find that about 5–10% of the aryl iodide (according to GC analysis) is present throughout the reaction, the concentration of aryl iodide decreasing only toward the end of the cyanation reaction (Figure 1). This result indicates that the rate of halide exchange is comparable to or exceeds the rate of the cyanation of the resulting aryl iodide. If polar solvents, such as DMF or sulfolane, that dissolve sodium cyanide relatively well, are used instead of toluene, very low conversion (<5%) of the aryl bromide is observed. Apparently, high concentration of the dissolved cyanide in the reaction mixture strongly inhibits both the halide exchange and the aryl cyanation reaction. A similar effect has been noted before in both palladium- and copper-catalyzed aryl cyanation reactions.<sup>12</sup>

The copper-catalyzed halide exchange-cyanation reaction tolerates a wide range of functional groups including strongly electron-donating substituents (Table 1, entries 2 and 7), potentially C–H acidic groups (entry 6), as well as free N–H and O–H groups (entries 5, 8, and 9). Although the cyanation reaction is slower with *ortho*-substituted aryl bromides, high yields of the aromatic nitriles can still be obtained at a slightly higher reaction temperature (130 °C; entries 4, 7, and 9). As shown in Table 2, various heteroaryl

**Table 1.** Copper-Catalyzed Cyanation of Aryl Bromides

$$\text{Ar-Br} \xrightarrow[\text{1.2 equiv NaCN}]{\substack{10 \text{ mol\% CuI, 20 mol\% KI} \\ 1.0 \text{ equiv ligand } \mathbf{1}}} \text{Ar-CN}$$
  
 Toluene, 110–130 °C, 24 h

Entry	Ar-Br	Ar-CN	Temp., °C	Yield, % <sup>a</sup>
1			110	90
2			110	91
3			130	90
4			130	98
5			110	80 <sup>b</sup>
6			130	70
7			130	85
8			110	90
9			130	70

<sup>a</sup> Isolated yields (average of two runs); >95% purity as determined by GC and <sup>1</sup>H NMR; all reactions proceeded to >99% conversion of aryl bromide except for entry 7 (98% conversion). <sup>b</sup> Performed for 20 h.

bromides are also excellent substrates for the cyanation reaction. Even heterocyclic substrates containing N–H groups are well tolerated and do not suffer N-arylation (Table 2, entries 1 and 4), presumably because of the high affinity of the cyanide nucleophile toward the copper(I) catalyst.

In summary, we have developed a copper-catalyzed domino halogen exchange-cyanation procedure for aryl bromides. The new method represents a significant improvement over the traditional Rosenmund–von Braun reaction: the reaction conditions are much milder, and the use of stoichiometric amounts of copper(I) cyanide and polar solvents is avoided; therefore, the isolation and purification of the nitrile products is greatly simplified. In addition, the new method exhibits excellent functional group compatibility comparable to that of the analogous Pd-catalyzed cyanation methodology. We are currently exploring other possibilities for combining concurrent copper-catalyzed transformations into domino processes.

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**Supporting Information Available:** Experimental procedures and characterization data for all products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

**Table 2.** Copper-Catalyzed Cyanation of Heteroaryl Bromides

$$\text{Het-Br} \xrightarrow[\text{1.2 equiv NaCN}]{\substack{10 \text{ mol\% CuI, 20 mol\% KI} \\ 1.0 \text{ equiv ligand } \mathbf{1}}} \text{Het-CN}$$
  
 Toluene, 110 °C, 24 h

Entry	Het-Br	Het-CN	Yield, % <sup>a</sup>
1			95
2			74
3			78
4			87 <sup>b</sup>
5			90
6			80

<sup>a</sup> Isolated yields (average of two runs); >95% purity as determined by GC and <sup>1</sup>H NMR; all reactions proceeded to >99% conversion of aryl bromide. <sup>b</sup> Performed for 20 h.

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- (9) Conversion of 5-iodo-*m*-xylene into 3,5-dimethylbenzonitrile (in the absence of added KI) was performed using 10 mol % Cu pre-catalyst, 1.0 equiv of ligand **1**, and 1.2 equiv of NaCN in toluene for 24 h at 90 °C. All three pre-catalysts (CuI, CuBr, CuCN) afforded 96–98% yield (GC) and 99.7–99.9% conversion of aryl iodide.
- (10) Conversion of 5-bromo-*m*-xylene into 3,5-dimethylbenzonitrile using 10 mol % Cu pre-catalyst, 1.0 equiv of ligand **1**, and 1.2 equiv of NaCN in toluene for 24 h at 110 °C provided the following yields of the nitrile product: CuI, 82%; CuBr, 2%; CuCN, 1%.
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