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# Copper-catalyzed coupling of aryl halides and nitrite salts: a mild Ullmann-type synthesis of aromatic nitro compounds

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**Abstract**—Nitration of aromatic halides proceeded smoothly in the presence of catalytic amounts of Cu bronze and *N*,*N*′-dimethylethylenediamine. Sodium nitrite-18-crown-6, or tetra-*n*-butylammonium nitrite ($n$-$Bu_4NNO_2$) turned out to be efficient nitrating agents. The aromatic nitro compounds were synthesized under essentially neutral conditions.

Aromatic nitro compounds are important starting materials for the manufacture of various industrial products such as pharmaceuticals, dyes and plastics. These compounds are mainly produced by the nitration of the aromatic compounds in the presence of an excess of nitric acid or a mixture of nitric acid and sulfuric acid.[1] This classic method is widely used in the industry as well as in the laboratory. Though some new promising methods have been recently reported,[2–4] the development of a new, safe and efficient method for the synthesis of aromatic nitro compounds is still highly desirable.

The recent development of the copper[5,6] and palladium-catalyzed[5g,h,7,8] C(aryl)–nitrogen bond formation reactions of haloarenes prompted us to examine the possibility of the synthesis of aromatic nitro compounds from aryl halides and nitrites.[9] In this letter, we report a new copper-catalyzed coupling of aryl halides and nitrite salts.

The results of the optimization of the catalysts, ligands and nitrite salts for the reaction of 4-iodoanisole (**1a**) are summarized in Table 1. Though the nitration reaction did not proceed by the addition of potassium nitrite ($KNO_2$) to a mixture of **1**, transition metals ($Ni(cod)_2$–$PPh_3$, $Pd(PPh_3)_4$, CuI) and DMF, this reaction proceeded when a stoichiometric amount of 18-crown-6 and a catalytic amount of Cu catalyst were added. For example, 4-nitroanisole (**2a**) was isolated in 36% yield when CuI was used as the catalyst (entry 1). The catalytic activity of the Cu complex increased by the addition of *N*,*N*′-dimethylethylenediamine (**3**)[5a–c,k,10] as a ligand and the yield of **2a** increased to 62% (entry 2). The progress of the reaction was very slow when a catalytic amount (10 mol %) of 18-crown-6 or a stoichiometric amount of $NaNO_2$–15-crown-5 was used (entries 3–4). The choice of the ligand was important for the efficient progress of the reaction, and the yield of **2a** did not improve when a monodentate amine ligand such as $Et_3N$ or *i*-$Pr_2NH$, or a bidentate phosphine ligand (DPPE) was used. While *N*,*N*′-diethylethylenediamine (**4**) turned out to be a good ligand for this reaction (entry 5), other amine ligands such as **5–10** (Fig. 1) gave poor results. We also screened suitable Cu catalysts for the reaction. While $CuOTf{\cdot}1/2\ C_6H_6$ was less reactive (entry 6), Cu bronze turned out to be a highly active catalyst (entry 7). The screening of the nitrites revealed that $n$-$Bu_4NNO_2$, a soluble and commercially available nitrite, was an excellent reagent, and the reaction proceeded in the absence of 18-crown-6 (entry 8). The yield of **2a** was not significantly affected even when the reaction was carried out in the presence of a smaller amount (5 mol %) of the catalyst, and the reaction was complete in 3 h when compound **3** was selected as the ligand and a small excess (1.2 equiv) of $n$-$Bu_4NNO_2$ was used (entry 11).[11] It is also noteworthy that this reaction proceeded smoothly when other solvents such as toluene (entry 10), 1,4-dioxane (74% yield of **2a**) and acetonitrile (82% yield of **2a**) were used.

The optimized reaction condition was used to examine the scope of this new nitration reaction, and the results

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*Keywords*: Nitration; Copper catalyst; Aryl iodide; Nitroarenes; Nitrites.

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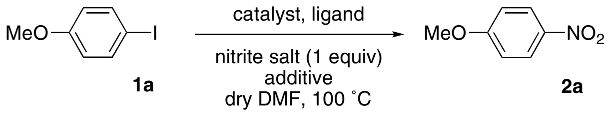
**Table 1.** Effect of catalyst, ligand and nitrite salts on the reaction of **1**[a]



| Entry | Catalyst (mol %) | Ligand (mol %) | Nitrite salt | Additive (mol %) | Time (h) | Yield of **2a** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | CuI (15) | — | $KNO_2$ | 18-Crown-6 (100) | 24 | 36 |
| 2 | CuI (15) | **3** (30) | $KNO_2$ | 18-Crown-6 (100) | 24 | 62 |
| 3 | CuI (15) | **3** (30) | $KNO_2$ | 18-Crown-6 (10) | 48 | Trace |
| 4 | CuI (15) | **3** (30) | $NaNO_2$ | 15-Crown-5 (100) | 24 | Trace |
| 5 | CuI (15) | **4** (30) | $KNO_2$ | 18-Crown-6 (100) | 24 | 71 |
| 6[c,d] | CuOTf·1/2 $C_6H_6$ (10) | **3** (20) | $KNO_2$ | 18-Crown-6 (100) | 49.5 | 63 |
| 7[d] | Cu bronze (10) | **3** (20) | $KNO_2$ | 18-Crown-6 (100) | 22 | 78 |
| 8[d] | Cu bronze (10) | **3** (20) | $n$-$Bu_4NNO_2$ | — | 22 | 81 |
| 9[d] | Cu bronze (5) | **4** (10) | $n$-$Bu_4NNO_2$ | — | 24 | 66 |
| 10[d,e,f] | Cu bronze (5) | **3** (10) | $n$-$Bu_4NNO_2$ | — | 24 | 73 |
| 11[d,e] | Cu bronze (5) | **3** (10) | $n$-$Bu_4NNO_2$ | — | 3 | 81 |

[a] Reaction conditions: To a mixture of catalyst, ligand (30 mol %) and additive in dry DMF (1 mL) was added 4-iodoanisole and the mixture was stirred at 100 °C under Ar.

[b] Isolated yields.

[c] DMSO was used as the solvent.

[d] A smaller amount (0.3 mL) of the solvent was used.

[e] A small excess (1.2 equiv) of the nitrite was used.

[f] Toluene was used as the solvent.

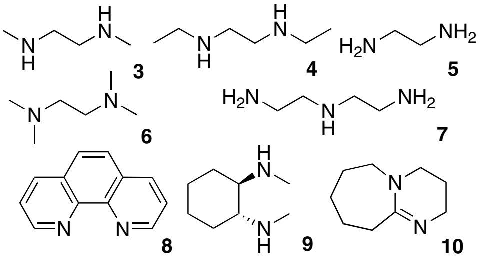
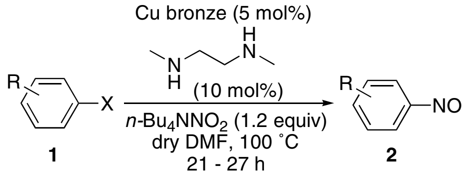


**Figure 1.** Ligands examined for the nitration of **1a**.

**Table 2.** Cu-catalyzed nitration of haloarenes[a]



| Entry | R | X | Yield of **2** (%)[a] |
|---|---|---|---|
| 1 | 4-MeO (**1a**) | I | 81[b] |
| 2 | H (**1b**) | I | 65 |
| 3 | 4-$t$-Bu (**1c**) | I | 91 |
| 4 | 4-BnO (**1d**) | I | 71 |
| 5 | 3-Me (**1e**) | I | 69 |
| 6 | 3-MeO (**1f**) | I | 65 |
| 7 | 4-$CH_3CONH$ (**1g**) | I | 57 |
| 8 | 4-$H_2N$ (**1h**) | I | 45 |
| 9 | 4-Me (**1i**) | I | 25 |
| 10 | 3-$O_2N$ (**1j**) | I | 28 |
| 11 | **1j** | I | 23[b] |
| 12 | 4-MeO (**1k**) | Br | 53[c] |
| 13 | **1k** | Br | 34[b] |

[a] Isolated yields.

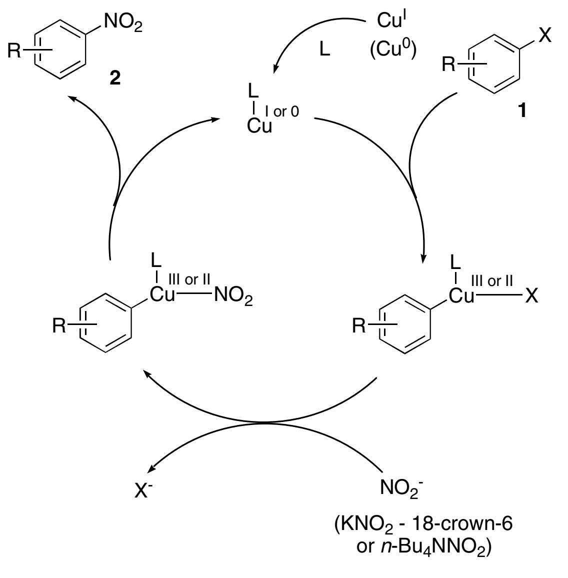
[b] The reaction time was 3 h.

[c] Larger amounts of Cu bronze (10 mol %) and amine ligand (20 mol %) were used.

were summarized in Table 2. Nitrobenzene (**2b**) and 4-*tert*-butyl-1-nitrobenzene (**2c**) were isolated in 65% and 91% yields from the corresponding iodides, respectively (entries 2–3). Some electron-rich aryl iodides such as **1d**–**g** were also good substrates for this reaction, and the corresponding nitroarenes were isolated in good yields (entries 4–7). However, the reactions of 4-iodoaniline (**1h**) and 4-iodotoluene (**1i**) gave poor results (entries 8–9). Furthermore, the yield of **2j**, which was obtained by the nitration of 3-nitroiodobenzene (**1j**), was disappointing (entry 10). The reactivity of 4-bromoanisole (**1l**) was much lower compared to **1a**, and the product was isolated in 53% yield in the presence of larger amounts of Cu bronze (10 mol %) and the amine ligand (20 mol %) (entry 12). The lower reactivity of **1j** and **1k** compared to **1a** was confirmed by carrying out the reactions at shorter periods (entries 1, 11 and 13).

Though we have not carried out any mechanistic study, it is reasonable to postulate a mechanism[12] similar to other Ullmann-type reactions. The insertion of a Cu(I) species[13] to the carbon–halogen bond should initially take place, followed by the halogen–nitrite exchange reaction and reductive elimination of the Cu species. The soluble ammonium salt should supply the nitrite ion efficiently (Scheme 1).

In summary, we developed a new method for the synthesis of aromatic nitro compounds. This new reaction proceeds under essentially neutral condition and provides an attractive alternative to the conventional methods (electrophilic substitution), which are generally carried out under drastic conditions.



**Scheme 1.**

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11. Representative procedure: Cu bronze was purchased from Aldrich (Cu powder, 1–5 μm, cat. No. 292583), and used as received. A tube with screw-cap was charged with **1a** (234 mg, 1.0 mmol), Cu bronze (3.2 mg, 0.05 mmol), tetra-*n*-butylammonium nitrite (346.2 mg, 1.2 mmol), anhydrous DMF (0.3 mL) and *N*,*N*′-dimethylethylenediamine (10.6 μL, 0.10 mmol) under Ar. The mixture was stirred at 100 °C for 3 h. The reaction mixture was directly purified by silica gel column chromatography (hexane/AcOEt = 30:1) to give **2a** as a pale yellow oil (124 mg, 0.81 mmol, 81%).
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13. The Cu(I) species could be generated from Cu bronze and haloarenes. See, Ref. 12d. Alternatively, the Cu(0) species might act as the catalyst for this reaction.