Ligand-free CuSO₄-Catalyzed C-N Coupling Reaction of Aryl Halides with Alkylamines or *N*-heterocycles in Aqueous Solution System†

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C-N coupling can be achieved successfully under 80 °C in aqueous *n*Bu₄NOH using CuSO₄ as a catalyst. The study of substrate applicability demonstrated that the C-N coupling reaction of aryl iodides and bromides with alkylamines or *N*-heterocycles could be completed smoothly in this catalytic system.

Key Words: C-N coupling, Transition metal catalysis, Tetrabutylammonium hydroxide.

INTRODUCTION

Transition metal-catalyzed C-N cross-coupling reaction (Buchwald-Hartwig Reaction) is an important research direction in modern organic synthesis field¹. Copper catalyst was reported to be a cheaper and more environmentally friendly catalyst than palladium². As various new ligands^{3,4} were discovered, C-N coupling can be performed under moderate conditions in Cu/ligand catalytic system. However, the ligands often became inactivated during the repetitive use of these catalyst systems. Therefore, catalytic systems without ligands are of special interest. Cu(I)-catalyzed C-N cross-coupling reaction was reported using organic anion bases, such as quaternary ammonium hydroxide, which can contribute to form a homogeneous catalytic system⁵. In present work, we report that C-N coupling reaction of aryl iodides and bromides with alkyl amines or *N*-heterocycles could be completed smoothly under 80 °C in aqueous *n*Bu₄NOH using cheap CuSO₄ as catalyst. (Scheme-I)

Scheme-I

EXPERIMENTAL

CuSO₄ (8.0 mg, 0.05 mmol, solid state), aryl iodide or bromide (1.0 mmol in solid state or 0.5 mmol in liquid state) and corresponding amine (1.5 mmol in solid state or 0.75 mmol in liquid state) were added into a Schlenk reaction tube with

stirrers. The sealed reaction tube was aerated Ar atmosphere after vacuumization for three times. Following that, *n*Bu₄NOH (40 % aq, 1.0 mL) was injected into the reaction tube. All the reagents were stirred for reaction for 24 h under 80 °C. The reactive mixture was diluted with ethyl acetate and then further isolated by the basic Al₂O₃ (200-300 mesh) column chromatography. The products were obtained after the elimination of solvent and drying under vacuum for 0.5 h. Characterization of products was performed using Mattson Alpha-Centauri FT-IR, Bruker Avance 300 nuclear magnetic resonance and Finnigan LCQ high-resolution mass spectrometer.

RESULTS AND DISCUSSION

Substrate adaptability to the C-N coupling of aryl iodides:

Adaptability of this reaction system to the substrate has been deduced through different aryl iodides reacting with alkylamines, arylamines and *N*-heterocycles. As shown in Table-1, either of iodobenzenes substituted by an electron-withdrawing group or electron-donating group can couple with alkylamines successfully with relatively high productivity (3a-3f). However, *ortho*-substituted iodobenzene can only yield a rather low productivity (3i). Although the low reactivity of 2-iodine pyridine, the target products can be achieved with a high productivity (80 %) (3 h). It can be deduced that the steric effect of substitutional groups attached to iodobenzenes has more remarkable influence on coupling reactivity than the electronic effect of them. In addition, the couplings of aryl iodides with different *N*-heterocycles showed the different reactivity under this system. The coupling of 4-chloro-

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iodobenzene with morpholine can achieve relatively high productivity (3 g), while the reactions between iodobenzene and pyrazol, imidazole or triazole are in relatively lower yields (**3j-3l**). Furthermore, aryl iodides cannot react with arylamines in this catalytic system.

TABLE-1
SUBSTRATE ADAPTABILITY TO THE C-N
COUPLING OF ARYL IODIDES^{a,b}

$\text{R}_1\text{-C}_6\text{H}_4\text{-I} \quad \text{1} \quad + \quad \text{HNR}_2\text{R}_3 \quad \text{2} \xrightarrow[\text{24h, Ar, 80}^\circ\text{C}]{\text{CuSO}_4 \text{ (5 mol\%)}, \text{nBu}_4\text{NOH (40\% aq.) (1.0 mL)}} \text{R}_1\text{-C}_6\text{H}_4\text{-NR}_2\text{R}_3 \quad \text{3}$

3a (95%)	3b (84%)	3c (76%)

3d (74%)	3e (77%)	3f (74%)

3g (86%)	3h (80%)	3i (34%)

3j (61%)	3k (60%)	3l (58%)

^aReaction conditions: aryl iodide (1 mmol), alkyl amine or N-heterocyclic (1.5 mmol), *n*Bu₄NOH (40 % aq.) (1 mL) and CuSO₄ (0.05 mmol) are at 80 °C under Ar atmosphere for 24 h. ^bYields are given for isolated products

Substrate adaptability to the C-N coupling of aryl bromides: Under the same catalytic system, further study on the C-N coupling of aryl bromides with alkylamines, arylamines and *N*-heterocycles has been carried out (Table-2). Either of bromobenzenes substituted by an electron-withdrawing group or electron-donating group can react with alkylamines with medium yields (**5a-5l**). However, aryl bromides cannot react with arylamines or *N*-heterocycles for C-N coupling, which showed aryl bromides possessing the generally lower reactivity than aryl iodides.

Structural characterization of some products

Benzyl-(4-chloro-phenyl)-amine (3b): Yellow solid. m.p.: 48.3-49.2 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm): 7.32-7.22 (m, 5H), 7.10-7.05 (m, 2H), 6.52-6.48 (m, 2H), 4.24 (s, 2H), 3.89 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ (ppm): 146.5, 138.8, 129.0, 128.6, 127.4, 127.3, 122.1, 114.1, 48.3. IR (neat): (λ_{max}/cm⁻¹): 3671, 3418, 2922, 2851, 1898, 1603, 1508, 1430, 1324, 1271, 1092, 1014, 814, 750, 692. EI-MS: *m/z* = 217 (M⁺).

Benzyl-pyridin-2-yl-amine (3h): White solid. m.p.: 96.4-97.3 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm): 8.06 (d, 1H), 7.37-7.21 (m, 6H), 6.56 (m, 1H), 6.34 (d, 1H), 5.16 (s, 1H), 4.48 (d, 2H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm): 158.8, 148.1, 139.3, 137.4, 128.6, 127.4, 127.1, 112.9, 106.7, 46.2. IR (neat): (λ_{max}/cm⁻¹): 3225, 3024, 2868, 1600, 1528, 1442, 1334, 1152, 1079. EI-MS: *m/z* = 183 (M⁺).

TABLE-2
SUBSTRATE ADAPTABILITY TO THE C-N
COUPLING OF ARYL BROMIDE^{a,b}

$\text{R}_1\text{-C}_6\text{H}_4\text{-Br} \quad \text{4} \quad + \quad \text{HNR}_2\text{R}_3 \quad \text{2} \xrightarrow[\text{Ar, 80}^\circ\text{C, 24h}]{\text{CuSO}_4 \text{ (5 mol\%)}, \text{nBu}_4\text{NOH (40\% aq.) (1 mL)}} \text{R}_1\text{-C}_6\text{H}_4\text{-NR}_2\text{R}_3 \quad \text{5}$

5a (76%)	5b (84%)	5c (67%)

5d (88%)	5e (71%)	5f (71%)

5g (70%)	5h (72%)	5i (65%)

^aReaction conditions: aryl bromide (1 mmol), alkyl amine or N-heterocyclic (1.5 mmol), *n*Bu₄NOH (40 % aq.) (1 mL) and CuSO₄ (0.05 mmol) are at 80 °C under Ar atmosphere for 24 h. ^bYields are given for isolated products

N-Phenyl-benzylamine (5a): White solid. m.p.: 37.1-37.9 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm): 7.31-7.37 (m, 4H), 7.28 (m, 1H), 7.16 (dt, *J* = 12.4, 1.6 Hz, 2H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 4.31 (s, 2H), 4.01 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm): 148.2, 139.5, 129.3, 128.8, 127.6, 127.3, 117.8, 113.0, 48.5. IR (neat): (λ_{max}/cm⁻¹): 3419, 3026, 2924, 2853, 1949, 1602, 1505, 1324, 11267, 989, 749. EI-MS: *m/z* = 182 (M⁺).

Conclusion

Ligand-free C-N cross-coupling reaction has been realized successfully using economic and environmentally-friendly CuSO₄ catalyst in aqueous *n*Bu₄NOH. Either aryl iodide or aryl bromide can react with alkylamine well. More importantly, C-N coupling can also be achieved between aryl iodide and low-active pyrazol, imidazole or triazole. This reaction system showed the advantages of moderate reaction condition, simple experimental operation and relative low amount of CuSO₄ catalyst which can be decreased to 5 mol %, which must have large industrial application value.

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