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A simple and efficient 2N2O–Cu(II) complex as a catalyst for N-arylation of imidazoles in water

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Four inexpensive and air- and moisture-stable 2N2O-Cu complexes were synthesized, one of which proved to exhibit good catalytic activity for the N-arylation of imidazoles in water. A variety of aryl iodides and aryl bromides underwent coupling with imidazoles promoted by the catalytic system with moderate to excellent yields. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: N-arylation; copper-catalyzed; N,O ligand; imidazoles; water

Introduction

The synthesis of N-arylimidazole derivatives is of significant importance because their structural motifs are a common occurrence in numerous drugs, natural products and energetic materials.^[1] In the last decade, Cu-catalyzed C-N coupling reaction has proven suitable for the direct N-arylations of imidazole derivatives. To this end, significant efforts have been devoted to the development of transition metal-catalyzed C-N coupling reactions.^[2-4] Several classes of monodentate, bidentate and polydentate chelators have thereby been developed to increase the reaction rates and lower substantially the reaction temperature.^[5-18] However, it is worth noting that these protocols are generally operated using volatile organic solvents with transition metal ions. From the standpoint of green chemistry, the development of environmentally benign reaction media, such as water that is nontoxic, cheap and readily available, in place of organic solvents would be desirable.^[19,20] Hence, as part of our endeavors towards the development of environmentally friendly protocols, efforts were directed towards performing C-X (X = C, N) reactions using water as the sole reaction medium.

Schiff base ligands are recognized as some of the most efficient auxiliaries, and many Schiff base metal complexes are used as excellent catalysts in various organic transformations.^[21] Based on our previous research,^[22] herein we report a soluble 2N2O–Cu complex (1) as catalyst for the N-arylation of imidazoles in water. This catalytic system has several advantages: (1) 2N2O–Cu(II) complex is easy to synthesize; (2) use of water as a green solvent that is used in place of organic solvents, and the N-arylation reactions can be performed without an inert gas atmosphere and with low catalyst loading; and (3) the work-up procedure is simple with excellent yields and broad substrate range.

Experimental

Materials and Instrumentation

All reactions were carried out in air under magnetic stirring conditions unless otherwise noted. ¹H NMR spectral data were recorded with a Bruker DPX-400 spectrometer using tetramethylsilane as internal standard and $CDCI_3$ as solvent. El mass spectra were measured with an LC/Q-TOF MS (Micromass, UK). All reagents were of analytical grade quality and commercially obtained.

Synthesis of Complexes 1-4

A solution of 2 mmol of substituted amine and 2 mmol of sodium 3formyl-4-hydroxybenzenesulfonate in 10 ml of 50% ethanol was stirred at 60 °C for 5 h. Then 1 mmol of $Cu(OAc)_2 \cdot H_2O$ in 10 ml of 50% ethanol was added to that solution, and the mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction solution was diluted with 50 ml of acetone and filtered. The solid product was collected and dried under vacuum to afford the desired complexes 1–4.

Complex 1. Yield 75%. Anal. Calcd for $C_{26}H_{18}CuN_2Na_2O_8S_2$ (%): C, 47.31; H, 2.75; N, 4.24; S, 9.72. Found (%): C, 46.57; H, 2.77; N, 4.20; S, 9.69. MS (negative), m/z: $[(M - Na)]^+$ calculated, 659.0; found, 659.6. IR (KBr, cm⁻¹): 3441 (OH), 1612 (C=N), 1184 (SO₃Na).

Complex 2. Yield 70%. Anal. Calcd for $C_{28}H_{22}CuN_2Na_2O_8S_2$ (%): C, 48.87; H, 3.22; N, 4.07; S, 9.32. Found (%): C, 48.43; H, 3.28; N, 3.98; S, 9.27. MS (negative), m/z: $[(M - Na)]^+$, calculated, 664.0; found, 664.2. IR (KBr, cm⁻¹): 3433 (OH), 1628 (C=N), 1169 (SO₃Na).

Complex 3. Yield 72%. Anal. Calcd for $C_{28}H_{22}CuN_2Na_2O_{10}S_2$ (%): C, 46.70; H, 3.08; N, 3.89; S, 8.91. Found (%): C, 46.80; H, 2.54; N, 3.84; S, 8.79. MS (negative), m/z: $[(M - Na)]^+$, calculated, 690.6; found, 690.2. IR (KBr, cm⁻¹): 3448 (OH), 1616 (C=N), 1184 (SO₃Na).

Complex 4. Yield 75%. Anal. Calcd for $C_{26}H_{14}Cl_4CuN_2Na_2O_8S_2$ (%): C, 39.14; H, 1.77; N, 3.51; S, 8.04. Found (%): C, 39.05; H, 1.81; N, 3.45; S, 8.01. MS (negative), m/z: $[(M - Na)]^+$, calculated: 771.8; found, 772.2. IR (KBr, cm⁻¹): 3430 (OH), 1608 (C=N), 1184 (SO₃Na).

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General Procedure for N-Arylation of Imidazoles and Derivatives

To a 5 ml sealed tube was added complex 1 (0.05 mmol), aryl iodide or bromide (0.5 mmol), imidazole or 1H-benzo[d]imidazole (0.75 mmol), NaOH (1 mmol) and water (1 ml). The mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was guenched with 10 ml of water and extracted with EtOAc $(3 \times 20 \text{ ml})$. The combined EtOAc extracts were dried with anhydrous Na2SO4, filtered and the solvent was removed under reduced pressure. The residue was purified using flash column chromatography on silica gel with PE-EtOAc (from 2:1 to pure EtOAc) as the eluent to afford the desired products. All N-arylimidazoles reported herein are known products and were characterized using melting point, ¹H NMR spectroscopy and GC-MS, the results of which were compared with previously reported literature.

Results and Discussion

Complexes 1-4 could be conveniently synthesized by condensation of the corresponding amines with 5-sulfonatosalicylaldehydes and a sequential addition of copper acetate with good yields (Fig. 1). To evaluate the catalytic efficiency of complexes 1-4, the C-N coupling of 4-iodotoluene with 1H-imidazole was chosen as a model reaction with complexes 1-4 (10 mol%) in the presence of NaOH (4 equiv.) and tetrabutylammonium bromide (TBAB; 10 mol%) at 100 °C for 20 h in water. No desired product is observed in the absence of catalyst (Table 1, entries 1-3). Gratifyingly, complexes 1 and 3 exhibit high catalytic activity for this coupling reaction (Table 1, entries 4 and 6), which both give the desired product in 95% yields, but complexes 2 and 4 show low catalytic activity (Table 1, entries 5 and 7). The results show that the electronic effects and steric hindrance of the ligands have an obvious relation with the catalytic activity, and the electron-rich aryl-substituted N, O bidentate ligands can effectively promote the oxidative addition and reductive elimination of the central copper probably due to the increasing electron density and steric hindrance.

Subsequently, we selected complex 1 as catalyst to further investigate the effects of the other conditions on this reaction. Sodium dodecyl-benzenesulfonate (SDBS) as phase-transfer catalyst fails to show better performance than TBAB (Table 1, entry 8). Decreasing the dosage of NaOH to 2 equiv. still leads to the corresponding product in 95% yield (Table 1, entry 9). Among other bases examined, only KOH is effective for the catalysis, affording 57% yield of the desired product (Table 1, entries 12-15). Furthermore, the dosages of complex 1 and TBAB are also key parameters in the reaction. The results show that decreasing the loading of complex 1 or TBAB reduces the yield of the desired product (Table 1, entry 10). When the dosage of complex 1 is 2%, the yield is the lowest (Table 1, entry 11). Thus, complex 1 (10 mol%), NaOH (2 equiv.) and TBAB (10 mol%) in water at 100 °C are defined as the optimized reaction conditions for additional study.



Figure 1. Structures of complexes 1-4.



^blsolated yields.



^aReaction conditions: arvl halide (0.5 mmol), 1H-imidazole (1.0 mmol), complex 1 (10 mol%), NaOH (1.0 mmol), TBAB (10 mol%), H₂O (1 ml), 100 °C, 20 h.

^bIsolated yields.

The scope of substrates was then investigated using the optimal reaction conditions (Table 2). We first studied the N-arylation of 1Himidazole with various aryl iodides. In general, most aryl iodides react with imidazole smoothly to give the desired products with moderate to excellent yields, such as iodobenzene, 1-ethoxy-4iodobenzene, 1-iodo-4-nitrobenzene, 1-chloro-4-iodobenzene and 4-iodo-1,1'-biphenyl leading to the N-arylated products with 70-99% yields (Table 2, entries 1, 2, 5-7). When 1-(4-iodophenyl) ethanone is used as the coupling partner, the yield drops to 59% (Table 2, entry 4). Also we can see that sterically demanding ortho substituents such as 1-iodo-2-methylbenzene hamper the Narylation reaction (Table 2, entry 3). Although aryl bromides, such as 1-bromo-4-methylbenzene and 1-bromo-4-nitrobenzene, are less reactive than aryl iodides, 40 and 42% yields are still obtained, respectively (Table 2, entries 8 and 9). Interestingly, heteroaryl bromides are also coupled with imidazole to afford the desired product with 85 and 32% yields, respectively (Table 2, entries 10 and 11). To our delight, any iodides react with 1H-benzo[d]imidazole and the corresponding products with moderate to good yields are achieved under the optimized reaction conditions. For example, iodobenzene, 1-iodo-4-methylbenzene and 1-iodo-4-nitrobenzene afford the corresponding products with 61-77% yields (Table 2, entries 12-14). When 4-iodo-1,1'-biphenyl as substrate reacts with 1H-benzo[d]imidazole, the arylated product with 46% yield is obtained (Table 2, entry 15).

Conclusions

We have developed a novel and general catalytic method for N-arylation of 1H-imidazoles promoted by complex 1 in water. The system is efficient for the coupling of imidazoles with ArX (X = I, Br) to give products in moderate to excellent yields. The easy availability of the catalyst, mild reaction conditions, experimental simplicity and broad substrate scope are the features of the catalytic method presented in this paper.

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