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Ligand-Free Copper-Catalyzed Arylation of Amidines

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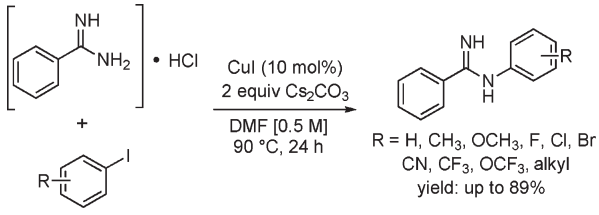
Received November 9, 2010



Copper-catalyzed cross-coupling reactions of amidine salts were utilized to synthesize monoarylated amidines in moderate to high yields with ligand-free conditions. DMF was the superior solvent for the *N*-arylation of benzamidines, while MeCN was used in the formation of *N*-aryl amidines in moderate to high yield.

Amidines are moieties found in current antiviral,[1] anti-inflammatory,[2] and antithrombotic[3] drugs presumably because of their unique structural properties. Amidines are also important precursors used in the formation of quinazolinones,[4] benzimidazoles,[5] and obesity treatment drugs.[6]

After developing a new copper-catalyzed cross-coupling reaction suitable for the preparation of *N*,*N*′-disubstituted guanidines,[7] we believed that aryl amidines could also be prepared by direct arylation methods. Amidines of this type could provide structural mimics of the diaryl guanidines we are currently investigating as calcium channel blockers in ischemic stroke therapy with biological collaborators.[8]

Standard methods for the synthesis of substitued amidines often utilize Pinner reaction protocols.[9] These reactions are generally performed by the addition of amines to nitriles substituted with electron-withdrawing groups.[10] The nitrile activation is usually promoted through the use of relatively costly catalysts,[11] aluminum amides,[12] high temperatures,[13] or stoichiometric amounts of CuCl.[14] Chang presented a three-component synthesis using azides, alkynes, and amines for the formation of *N*-sulfonylamidines using CuI as catalyst.[15] Other amidines were prepared using sulfonyl azides in order to diminish the production of toxic byproducts when CuCl was used as catalyst.[16] It is also possible to arylate amidines to form benzimidazoles with *N*,*N*′-dimethylethylenediamine as a ligand with temperatures ranging from 100 to 165 °C.[17]

Ullmann[18] (C−C, C−N, or C−O bond formation) and Goldberg[19] (C−N amide bond formation) reactions are very

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Published on Web 01/20/2011 DOI: 10.1021/jo102235u

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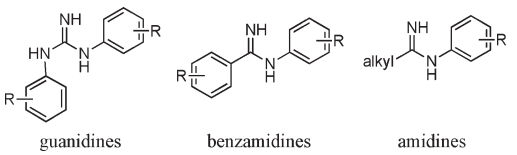
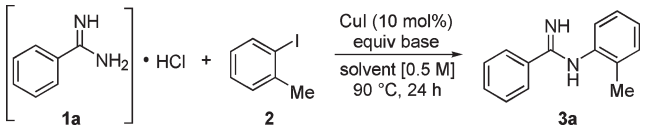


FIGURE 1. Calcium channel blockers.

TABLE 1. Copper-Catalyzed Conditions for the Synthesis of *N*-*o*-Tolyl Benzamidine



entry[a]	solvent	base	equiv base	yield, %
1[b]	toluene	Cs_2CO_3	2	16
2[b]	1,4-dioxane	Cs_2CO_3	2	25
3[c]	DMSO	Cs_2CO_3	2	23
4[c]	MeCN	Cs_2CO_3	2	18
5	DMF	Cs_2CO_3	2	89
6	DMF	Cs_2CO_3	1	29
7	DMF	Cs_2CO_3	1.5	39
8	DMF	Cs_2CO_3	3	56
9	DMF	Cs_2CO_3	4	42
10	DMF	Cs_2CO_3	5	42
11	DMF	K_3PO_4	2	2
12	DMF	K_2CO_3	2	1
13	DMF	KO*t*-Bu	2	5

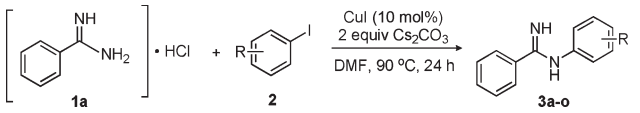
[a]Reaction conditions: 1 mmol of benzamidine salt and 1 mmol of 2-iodotoluene [0.5 M] in solvent indicated. [b]Reaction temperature 110 °C. [c]Reaction temperature 80 °C.

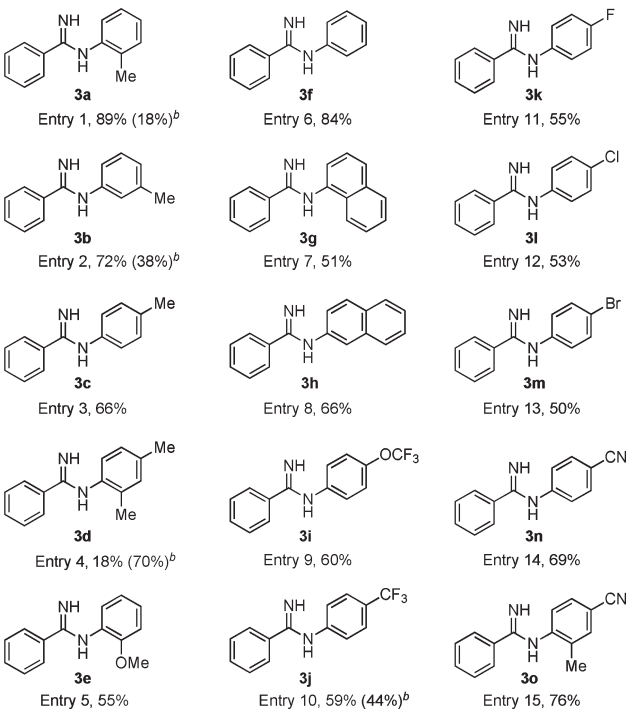
useful and have been widely used in industrial and academic settings. However, in the traditional conditions, stoichiometric amounts of copper were required. More recently, it was shown that copper used in these reactions could be employed with the aid of various ligands for the development of catalytic processes.[20] Ligand free copper catalysis for C−N,[21] C−O,[22] and C−S[23] bond formation reactions embodies another desirable direction for this chemistry.

Our goal was to develop a straightforward amination procedure utilizing substituted aryl halides and commercially available amidine or benzamidine salts for the formation of *N*-arylated amidines and *N*-arylated benzamidines (Figure 1).

During the onset of our exploration of copper-catalyzed conditions for amidine arylation, we found that typical copper ligands for the arylation of amides, amines, or guanidines did not provide for rate acceleration. We then went forward with the ligand-free studies by exploring conditions that enabled the copper-catalyzed reaction using the benzamidine salt (**1a**), aryl iodide **2**, and CuI (Table 1). We began by screening various solvents in the presence of 2 equiv of Cs_2CO_3 as the base. Of the solvents investigated (entries 1−5) the reaction was found to proceed efficiently in DMF, giving 28%, 35%, 59%, and 89% yields in 4, 8, 16, and 24 h, respectively. Additionally we confirmed that 2 equiv of the base was ideal; when the amount of base was decreased (entries 6 and 7) or increased

TABLE 2. Study on the Aryl Iodide Substrate Scope [a]





[a]Reactions conditions: 1 mmol of benzamidine salt and 1 mmol of aryl iodide [0.5 M] in DMF. [b]Yields for the product **3a**, **3b**, **3d**, and **3j** in MeCN at 80 °C are given in parentheses.

(entries 8−10) a dramatic lowering of yield was observed.[24] It is speculated that additional base could cause catalyst inhibition, leading to a lower yield. Evaluation of additional bases such as K_3PO_4, K_2CO_3, and KO*t*-Bu (entries 11−13) provided conditions that gave a much lower yield of the arylation product relative to Cs_2CO_3.

Table 2 presents a summary of results varying the sterics and electronics on the aryl iodide reactants. 2-Iodotoluene was an excellent substrate, providing the *N*-*o*-tolyl benzamidine in a very high yield (entry 1). Substrate scope was extended to include 3-iodotoluene and 4-iodotoluene, obtaining the meta and para monoarylated benzamidine in moderate yield (entries 2 and 3). The reactivity trend for the methyl-substituted aryl iodides was found to be ortho > meta > para (entries 1−3). We explored substrates with a stronger electron-donating effect, such as *o*-methoxy (entry 5), and found a decrease in yield to 55% when compared to *o*-methyl (entry 1). A drastic decrease in reactivity was observed when iodobenzene was used (entry 6). Interestingly, sterically hindered substrates showed good reactivity (entries 7 and 8), demonstrating

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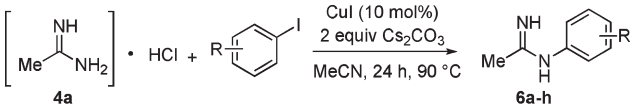
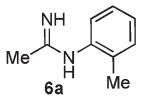
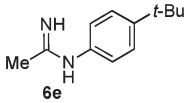
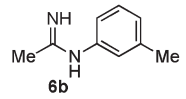
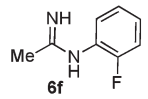
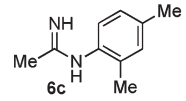
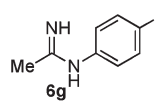
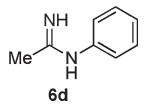
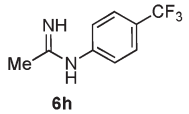
(24) Experiments were performed by exposing product **3a** from 3 to 5 equiv of Cs_2CO_3 with DMF as solvent at 90 °C for 24 h. No signs of decomposition were observed and a full recovery of **3a** was found.

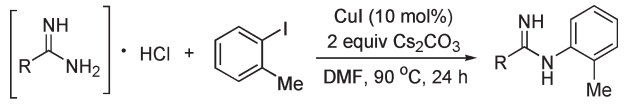
TABLE 3. Expansion of Substrate Scope with Various Aryl Iodides

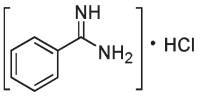
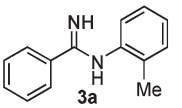
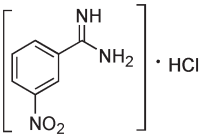
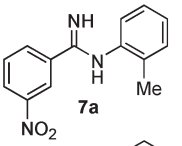
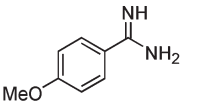
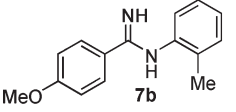
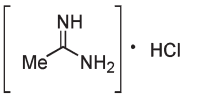
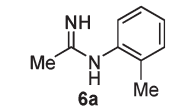
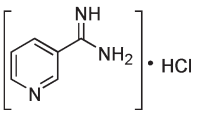
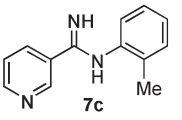


entry	product	yield, %[a]	entry	product	yield, %[a]
1	 **6a**	54 (54)[b]	5	 **6e**	52
2	 **6b**	84	6	 **6f**	47 (29)[b]
3	 **6c**	65	7	 **6g**	69
4	 **6d**	84 (35)[b]	8	 **6h**	62

[a]Reaction conditions: 1 mmol of benzamidine salt and 1 mmol of aryl iodide [0.5 M] in MeCN. [b]Yields in DMF at 90 °C are given in parentheses.

TABLE 4. Expansion of Amidine Salt Substrate Scope



entry[a]	amidine	product	yield, %
1		 **3a**	84
2		 **7a**	68
3		 **7b**	52
4		 **6a**	54
5		 **7c**	37

[a]All reactions used 1 mmol of amidine salt and 1 mmol of aryl halide [0.5M] in DMF.

that the arylation is possible even in cases where steric hindrance is increased. The reaction also was shown to proceed when electron-withdrawing groups were used in the 4-position of the aryl iodides (entries 10−14). Disubstituted aryl iodides were also evaluated in the chemistry and provided for a moderate yield of the arylation product with the benzamidine chloride salt (entries 4 and 15). Moreover, MECN showed lower yields in most of the cases (entries 1, 2, and 10).

Expansion of substrate scope to include acetamidine was also performed with the hydrochloride salt (Table 3). In this case, the optimal solvent was found to be acetonitrile, but all other reaction conditions were identical. DMF was also tested showing lower reactivity (entries 4 and 6). The reaction conditions allowed the arylation to proceed with electron-donating groups present, allowing for a moderate to high yield of the product (entries 2−4). When using iodobenzene, the highest yield (84%) was found for acetamidine arylation (entry 5). The reaction also tolerated disubstituted aryl iodides (entry 3) as well as strong electron-withdrawing groups (entries 6−8).

To demonstrate how the arylation method could be applied to a wide variety of amidine moieties, additional studies were performed (Table 4). Benzamidine salts bearing electron-donating groups (entry 2) or electron-withdrawing groups (entry 3) were well tolerated. It was also observed that isonicotinamidine hydrochloride could also be arylated, albeit with lower chemical yield (entry 5).

In conclusion, we have developed a general method for the synthesis of monosubstituted amidines using a ligand-free copper-catalyzed protocol. By using mild conditions and inexpensive reagents we have successfully developed a procedure to prepare a number of arylated amidines in moderate to good yield that could be used as potential compounds for future evaluation as ischemic stroke therapeutics.

Experimental Section

General Procedure for *N′*-*o*-Tolyl Benzamidine (3a). To a flame-dried screw-cap reaction tube was added benzamidine hydrochloride (1 mmol, 0.1556 g), 2-iodotoluene (1 mmol, 0.2840 g), CuI (0.1 mmol, 0.0190 g), and Cs_2CO_3 (0.6499 g, 2 equiv) under argon. DMF (2 mL) was added with a syringe and the mixture was heated in an oil bath. After the resulting solution was stirred for 24 h, the product was extracted with ethyl acetate and washed with water three times. The organic layer was dried over anhydrous Na_2SO_4 and filtered. Following concentration under reduced pressure, the residue was purified by silica gel chromatography (4:1 = EtOAc:hexanes) providing **3a** (190.1 mg, 89%) as a white solid. Mp 106.3−107.0 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.12 (s, 3H), 6.12 (br, s, 2H), 6.78 (d, 1H, J = 7.55 Hz), 6.94 (t, 1H, J = 7.27 Hz), 7.15−7.24 (m, 2H), 7.50 (d, 3H, J = 11.08 Hz), 8.03 (d, 2H, J = 6.15 Hz). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 152.9, 149.1, 135.8, 130.3, 129.9, 128.7, 127.1, 126.6, 125.9, 121.8, 120.9, 17.6. HRMS (ESI) $C_{14}H_{14}N_2$ calcd for ($[M + H]^+$) 211.1229, found 211.1253

General Procedure for *N′*-*o*-Tolyl Amidine Acetamidine (6a). To a flame-dried screw-cap reaction tube was added amidine hydrochloride (1 mmol, 0.0945 g), 2-iodotoluene (1 mmol, 0.2840 g), CuI (0.1 mmol, 0.0190 g), and Cs_2CO_3 (0.6499 g, 2 equiv). Under argon MeCN (2 mL) was added with a syringe and the mixture was heated at 80 °C in an oil bath for 24 h. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The product was obtained by silica gel chromatography

(hexanes:EtOAc = 1:4), providing **6a** (63.5 mg, 42%) as a light yellow solid. Mp 68.9−69.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 1H), 2.24 (s, 3H), 6.97 (s, 1H), 7.14 (t, 3H, J = 7.94 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5, 126.8, 123.3, 122.3, 18.2. HRMS (ESI) $C_9H_{12}N_2$ calcd for ($[M + Na]^+$) 171.0892, found 171.1027.

Acknowledgment. We thank The James and Ester King Biomedical Research Foundation (Florida Department of Health) and the Biomolecular Identification Targeting Therapeutics Research Grants (University of South Florida) for their financial support.

Supporting Information Available: Experimental procedures, characterization, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.