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Copper-Catalyzed Guanidinylation of Aryl Iodides: The Formation of *N,N′*-Disubstituted Guanidines

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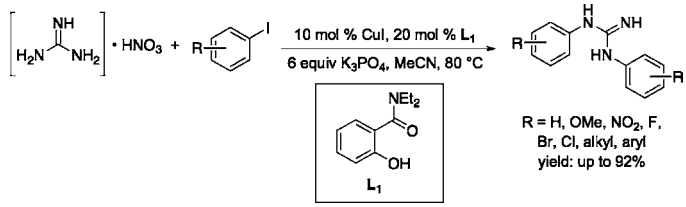
ABSTRACT



A copper-catalyzed cross-coupling reaction of guanidine nitrate with aryl iodides was used for the formation of *N,N′*-disubstituted guanidines to be used as potential therapeutics for strokes. A relatively inexpensive commercially available guanidine salt and a series of aryl iodides together with copper iodide and *N,N*-diethylsalicylamide as an efficient catalyst/ligand system provided a simple diarylation procedure.

Numerous guanidine-containing compounds have important biological activity and are, therefore, of pharmaceutical interest.[1] In a specific example of diaryl guanidine biological activity, Ajmo and collaborators showed that the σ-1/σ-2 ligand *N,N′*-di-*o*-tolyl guanidine (DTG) could be used as a potent neuroprotective agent following a stroke, decreasing the size of the resulting infarct by ~80%.[2] Activation of σ receptors has been found to modulate numerous ionic channels present in cortical neurons that are responsible for neural firing, Ca^{2+} signaling, K^+ regulation, and neurotransmitter release.[3,4] Several of these channels are regulated by σ receptors, such as ASIC1a, and have been associated with neuronal injury following ischemic stroke.[5] The success of the pan-selective σ agonist DTG as a therapeutic agent for the treatment of stroke has prompted attempts to improve the efficacy and/or potency of this compound. Substitutions to the parent compound are thought to increase the membrane permeability, receptor binding affinity, and specificity of the agonist. Synthesis of guanidines

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(1) (a) De Deyn, P. P.; Marescau, B.; Quereshi, I. A.; Mori, A. In *Guanidino Compounds in Biology and Medicine*; John Libbey and Co.: London, 1997; Vol. 2. (b) Rodriguez, F.; Rozas, I.; Kaiser, M.; Brun, R.; Nguyen, B.; Wilson, W. D.; Garcia, R. N.; Dardonville, C. *J. Med. Chem.* **2008**, *51*, 909. (c) Keller, M.; Pop, N.; Beck-Sickingger, A.; Bernhardt, G.; Buschauer, A. *J. Med. Chem.* **2008**, *51*, 8168. (d) Gee, K. R.; Durant, G.; Holmes, D.; Magar, S. S.; Weber, E.; Wong, S. T.; Keana, J. F. W. *Bioconjugate Chem.* **1993**, *4*, 226. (e) Evindar, G; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (f) Powell, D.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913.

(2) Ajmo, C. T., Jr.; Vernon, D. O.; Collier, L.; Pennypacker, K. R.; Cuevas, J. *Curr. Neurovasc. Res.* **2006**, *3*, 89.

(3) (a) Albers, G. W.; Amarenco, P.; Easton, J. D.; Sacco, R. L. Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* **2004**, *126*, 483. (b) Astrup, J.; Syrrion, L.; Branston, N. M.; Lassen, N. A. *Stroke* **1997**, *8*, 51. (c) For pharmacology review, see: Su, T- P.; Maurice, T. *Pharmacol. Ther* **2009**, *124*, 195.

(4) (a) Zhang, H.; Cuevas, J. *J. Neurophysiol.* **2002**, *87*, 2867. (b) Zhang, H.; Cuevas, J. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 1387. (c) Waldmann, R.; Champigny, G.; Bassilana, F.; Heurteaux, C.; Lazdunski, M. *Nature* **1997**, *386*, 173. (d) Katnik, C.; Guerrero, W. R.; Pennypacker, K. R.; Herrera, Y.; Cuevas, J *J. Pharmacol. Exp. Ther.* **2006**, *319* (3), 1355.

(5) (a) Herrera, Y.; Katnik, C.; Rodriguez, J. R.; Hall, A. A.; Willing, A.; Pennypacker, K. Cuevas. *J. J. Pharmacol. Exp. Ther.* **2008**, *327*, 492. (b) Xiong, Z. G.; Zhu, X. M.; Chu, X. P.; Minami, M.; Hey, J. *Cell* **2004**, *118*, 687.

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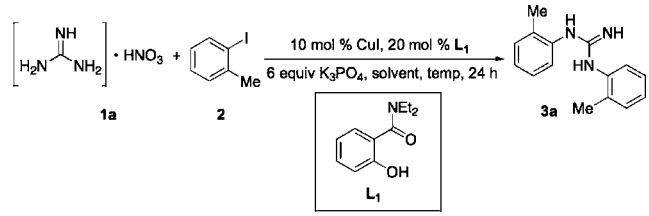
with arene substitution can represent a technical challenge in many instances. Traditional methods have included the addition of cyanogen bromide to aniline[6] or the addition of amines to functionalized thioureas.[7] However, cyanogen bromide is quite hazardous, limiting its attractiveness as a starting material. Methods utilizing substituted thioureas are not direct, requiring the separate preparation of each precursor. Therefore we sought to develop a direct catalytic guanidinylation of aryl halides for access to *N*,*N*′-diaryl guanidines we desired for biological testing.

Copper-mediated Ullmann[8] (C−C, C−N, or C−O bond formation) and Goldberg[9] (C−N bond formation with amides) reactions have been used for decades in a variety of applications, including industrial processes. A limitation of this chemistry is the use of stoichiometric amounts of copper. However, a more important consideration is probably the limits on reactivity. Palladium-catalyzed cross-coupling reactions are widely used alternatives for similar bond-forming reactions. However, despite the great success of these methods, alternative procedures utilizing an inexpensive metal like copper are highly desirable.[10] Recently, catalysts employing copper in conjunction with suitable ligands have played an important role in opening new possibilities for the development of efficient catalytic C−N bond-forming processes.[11] Buchwald and Kwong reported that *N*,*N*-diethylsalicylamide and its analogues were excellent ligands for copper in the cross-coupling of amines with aryl bromides, even in a solvent-free environment.[12]

Since the double arylation of guanidines is not commonly found in the literature, the development of a mild, cost-effective, and straightforward copper-catalyzed method using commercially available guanidine nitrate and aryl halides would be potentially beneficial. Perhaps the closest methodology in the literature for the direct arylation of guanidines was the work of Deng and co-workers that focused on the copper-catalyzed formation of substituted benzimidazoles.[13] Importantly, the creation of structural analogues to DTG could provide for new biological testing, as related to ischemic stroke, of the arylated guanidine analogues.[14]

We initiated our studies by exploring conditions that enabled copper-catalyzed cross-coupling using 1 mmol of each substrate at 0.2 M, 10 mol % of CuI, 6 equiv of base, and 20 mol % of *N*,*N*-diethylsalicylamide as a ligand. It should be noted that the yield was determined with the aryl halide as the limiting reagent, as an excess of guanidine was required for the double arylation. When 2 equiv or more of the aryl halide (correct stoichiometry for double arylation) was used, a mixture of di- and triarylation products, with lower overall yield, was found. After screening various solvents, double amination was found to proceed efficiently in acetonitrile, allowing for a 92% yield (Table 1, entry 13). Other coordinating solvents such as diethyl ether and THF, along with protic solvents such as ethanol, resulted in conditions where low yields were obtained (entries 2, 6, and 7). Toluene, dioxane, and DMF were suitable solvents at higher temperatures, but a diminished yield of the product was found (entries 1, 5, and 8). The optimal temperature for reaction in acetonitrile was determined to be 80 °C, with lower or higher temperatures allowing for decreased yield (entries 10−12, 14). Other copper salts such as CuBr and CuCl (anhydrous) were metal sources capable of catalyzing the reaction, but inferior results compared to that of the CuI salt were found (entries 15 and 16).

Table 1. Optimization of Reaction Conditions for the Copper-Catalyzed Cross-Coupling of Guanidine Nitrate with 2-Iodotoluene



entry[a]	solvent	temp, °C	yield, %[d,e]
1	toluene	110	17
2	ether	25	0
3	DME	80	0
4	DCM	40	0
5	1,4-dioxane	110	24
6	THF	95	0
7	ethanol	80	0
8	DMF	80	10
9	DMSO	80	0
10	MeCN	20	0
11	MeCN	40	7
12	MeCN	60	89
13	MeCN	80	92
14	MeCN	100	88
15[b]	MeCN	80	82
16[c]	MeCN	80	32

[a] The reaction used 1 mmol of guanidine nitrate and 1 mmol of 2-iodotoluene. [b] CuBr was used in place of CuI. [c] Anhydrous CuCl was used. [d] Isoated yields. [e] 0.2 M in substrate.

(6) Weber, E.; Sonder, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784.

(7) (a) Bergfeld, M. et al. *U.S. Patent 4,898,978*, 1990. (b) For a review on guanidine methods, see: Katritzy, A.; Rogovoy, B. V. *Arkivoc* **2005**, *iv*, 49. (c) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300. (d) Powell, D. A.; Batey, R. A. *Chem. Commun.* **2001**, 2362.

(8) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (b) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (c) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (d) Lang, F.; Zewge, D.; Houpis, I.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251.

(9) Goldberg, I. *Ber. Dtsch. Ges.* **1906**, *39*, 1691.

(10) (a) Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430. (b) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397.

(11) (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (b) Antilla, J. C.; Baskin, J. M.; Barder, T.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7723.

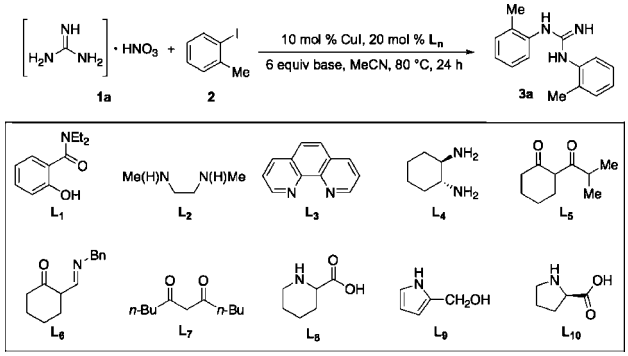
(12) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793.

(13) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742.

(14) Cortes-Salva, M.; Behensky, A.; Ajmo, C.; Pennypacker, K.; Cuevas, J.; Antilla, J. *Design, synthesis and evaluation of guanidine analogs as potential drugs for stroke therapeutics*; Presented at the 237th American Chemical Society National Meeting, March, 2009, Salt Lake City, UT; no. 1216243.

A variety of ligands such as $\mathbf{L_2}-\mathbf{L_{10}}$,[11,13] used in previous studies with copper, were tested against *N*,*N*′-diethylsalicylamide ($\mathbf{L_1}$)[12] (Table 2, entries 1−9). As an example, cyclohexane-1,2-diamine ($\mathbf{L_4}$)[11b,c] was a ligand for copper and promotion of the double guanidinylation, albeit with inferior results (entry 3). To our surprise, our first ligand of choice, *N*,*N*-diethylsalicylamide $\mathbf{L_1}$ (entry 10), was the most suitable, allowing for the highest reactivity (92% yield). Various bases such as K_2CO_3, Cs_2CO_3, and KO*t*-Bu (entries 11−13) were used with no improvement in reactivity. Product formation was not significantly observed when control experiments without ligand or base were performed (not shown). When the reaction concentration was increased from 0.2 to 0.4 M, a decrease in yield was noted (entry 16).

Table 2. Ligand and Base Effects on Reactivity

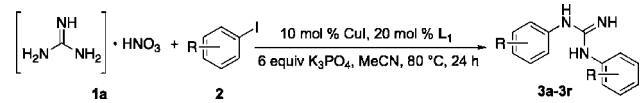


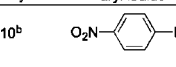
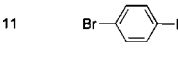
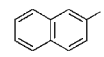
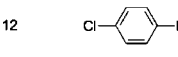
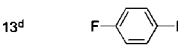
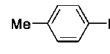
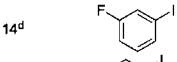
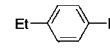
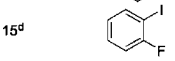
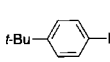
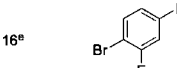
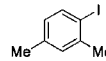
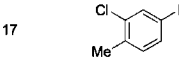
entry[a]	ligand	base	yield, %[b]
1	L_2	K_3PO_4	15
2	L_3	K_3PO_4	0
3	L_4	K_3PO_4	45
4	L_5	K_3PO_4	0
5	L_6	K_3PO_4	10
6	L_7	K_3PO_4	0
7	L_8	K_3PO_4	19
8	L_9	K_3PO_4	8
9	L_{10}	K_3PO_4	15
10	L_1	K_3PO_4	92
11	L_1	K_2CO_3	0
12	L_1	CS_2CO_3	0
13	L_1	KO*t*-Bu	14
14[c]	L_1	K_3PO_4	58
15[d]	L_1	K_3PO_4	64
16[e]	L_1	K_3PO_4	76
17[f]	L_1	K_3PO_4	5

[a] All reactions used 1 mmol of guanidine nitrate and 1 mmol of 2-iodotoluene with a 0.2 M concentration. [b] Isolated yields. [c] Guanidine carbonate was used. [d] Guanidine sulfate was used. [e] The reaction was 0.4 M in substrate. [f] The reaction performed without solvent (neat).

The optimized reaction conditions, 10 mol % CuI, 20 mol % $\mathbf{L_1}$, 6 equiv of K_3PO_4, 1 mmol of guanidine nitrate (**1a**) and 1 mmol of 2-iodotoluene (**2**), MeCN as the solvent at 0.2 M, and 80 °C under an argon atmosphere for 24 h, were used for the double guanidinylation. Table 3 shows the summary of results for the evaluation of various substituted aryl iodides. In order to demonstrate advantages of this catalytic system, we conducted reactions where we could probe the electronics and sterics of the aryl halide.

Table 3. Aryl Iodide Substrate Scope for the Guanidinylation of Guanidine Nitrates



entry	aryl iodide	yield, %[a]	entry	aryl iodide	yield, %[a]
1		92	10[b]		46
2[b]		83	11		19
3		50	12		35
4[b,c]		64	13[d]		62
5[b,c]		49	14[d]		53
6		39	15[d]		33
7		30	16[e]		55
8		80	17		67
9		47	18[d]		75

[a] All reactions were performed with 1 mmol of **1** and 1 mmol of **2** at 0.2 M; isolated yields are shown. [b] 15 mol % of CuI was used. [c] Reaction was performed with 1 mmol of **1** and 0.5 mmol of **2**. [d] 1,4-Dioxane was used as the solvent. [e] Toluene was used as the solvent.

It was shown that 2-iodotoluene and iodobenzene were excellent substrates, with the former providing *N*,*N*′-di-*o*-tolylguanidine (DTG) in a very high yield (Table 3, entry 1 and 2). Substrate scope was extended using 3-iodotoluene and 4-iodotoluene to obtain the *meta* and *para* disubstituted guanidines, giving a moderate yield (entries 4 and 5). The trend of reactivity of the guanidinylation for the methyl-substituted aryl iodides was *ortho* > *meta* > *para*. We further explored substrates with a more electron-donating effect, such as *o*-methoxy, which produced a decrease in yield, giving only 47% (entry 9). Extending aromaticity with 2-napthalene substitution (entry 2) provided a substrate that was converted to product in a 50% yield. This was an indication that the cross-coupling was less efficient because of steric hindrance in comparison to iodobenzene (entry 2). Additionally, heteroaryl iodides, such as 3-iodothiophene are good substrates for the guanidinylation reaction (entry 18). It was observed that halogen-substituted aryl iodides contributed a stronger electron-withdrawing effect that still allowed for reactivity with the cross-coupling reaction (entries 13−17). Halogen substitution in the *para* position showed an increase in yield in accordance with increasing electronegativity (entries 11−13). Disubstituted aryl iodides promoted reactiv-

ity higher than that of those with monosubstitution in the two cases examined (entries 16 and 17).

In conclusion, a copper-catalyzed cross-coupling reaction of guanidines with aryl iodides to form disubstituted guanidines with moderate yields was discovered. By using mild and inexpensive reagents, we have successfully developed an expedient preparation of molecular entities based on a medicinally interesting parent compound, DTG. These analogues may show higher affinity than DTG for the σ receptor and consequently may be superior therapeutic agents for the treatment of ischemic stroke.[14]

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

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