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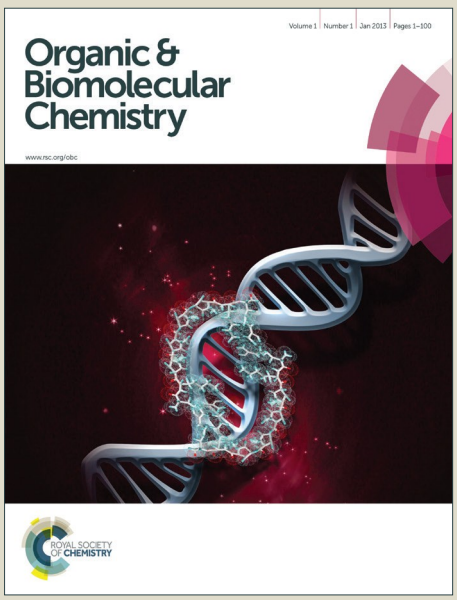

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ARTICLE

Copper-Catalyzed Arylation of Biguanide Derivatives *via* C–N Cross–Coupling Reactions

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An efficient copper-catalyzed cross-coupling reaction of biguanide hydrochloride derivatives with both aryl iodides and bromides under mild conditions has been developed. The reaction occurred in good yields and tolerated aryl halides containing functionalities such as nitriles, sulfonamides, ethers, and halogens. Alkyl and cyclic substituted biguanidines were also well tolerated .

Biguanides are found widely as core structures in a large variety of compounds that exhibit important biological activity.[1] Biguanide derivatives have been shown to exhibit antimicrobial, antiviral, antiplaque, and to influence gastric acid secretion etc. effects.[2] Given example, dimethylbiguanide hydrochloride is the one of the most effective and frequently administered antihyperglycemic type 2 diabetes drugs which is the first-line treatment because of better long-term outcomes compared with those of other therapies such as insulin secretagogues.[3] It belongs to the biguanide family that also includes other compounds with antihyperglycemic properties.[4] Synthesis of biguanide with arene substitution can represent a technical challenge in many instances. Traditional methods have included the reaction cyanoguanidines or dicyanimide with arylamines in the presence of hydrochloric acid.[5] Despite these advantages, several drawbacks remain associated with such reactions, including the use of harsh acids and generating byproducts. Thus, development of new methods for their synthesis is still needed. To the best of our knowledge, there are not reported cases of the arylation of biguanide. Therefore we sought to develop a direct catalytic biguanidinylation of aryl halides for access to aryl biguanide we desired for biological testing.

Utilization of transition metal-catalyzed cross-coupling reactions has been attracting much attention in recent years, and it has become one of the most versatile strategies for the synthesis of natural products, pharmaceuticals, organic functional materials, and so on.[6] Compared with other metals, the use of Cu(I) presents the major advantages of being inexpensive and easy to handle. Copper-catalyzed Ullmann-type C-N coupling has a history of more than one hundred years, and as a cost-effective and versatile C-N coupling, it is still actively used in the field of organic synthesis, including industrial processes.[7-12] Herein, we report a copper-catalyzed synthesis of aryl biguanide derivatives from aryl halides and biguanide.

Our initial investigations of this copper-catalyzed coupling of aryl halides with biguanide focused on 4-iodoanisole (**1a**) with dimethylbiguanide hydrochloride (**2a**) in the presence of CuI, 2,2′ -bipyridine (**L_1**), and K_3PO_4 in THF at 80 ℃ under N_2. We were excited that the desired product **3a** could be detected in 90% yield (Table 1, entry 1). The structure of **3a** was determined with *X*-ray data (Figure S1). A higher or lower reaction temperature did not facilitate the reaction (Table 1, entries 2 – 3). Furthermore, a variety of solvents were examined and THF as the solvent was most beneficial to this reaction (Table 1, entries 1, 4 – 8). The product yield was significantly affected by the nature of the base used: K_2CO_3, 14%; KOH, 30%; Cs_2CO_3, 43%; CsOAc, 0% (Table 1, entries 9 –12). A number of ligands commonly associated with copper catalyzed C–N cross-couplings were used in the presence of 10 mol % of CuI as a catalyst and 6.0 equiv of K_3PO_4 as a base in THF. The results showed that ligand **L_2** gave a litter better activity over ligand-free conditions. When amino acid ligands were used, the desired cross-coupled *N* – aryl biguanide was also obtained in good yield (Table 1, entries 15 – 16). Reducing the amount of CuI or ligand or the base resulted in a slightly lower yield or only a trace amount of the product, respectively. As a result, other copper salts such as CuBr, CuCl, and $CuCl_2$ were also screened (entries 17 – 19), but none of them could match the value of CuI. Notably, no reaction was observed in the absence of the Cu catalyst or base (Table 1, entries 20, 22).

In order to assess the scope of this process, we have examined the addition to several aryl halides and dimethylbiguanide under the optimized conditions indicated in entry 1 of Table 1. The results are summarized in Table 2. We first examined the reactions of aryl iodides bearing various functional groups on the aromatic ring. Aryl iodides containing *p*-EtO or *p*-Ph groups on the benzene ring were tolerated for the reaction, obtaining the corresponding products **3b** and **3c** in 62 and 77% yields, respectively (Table 2, entries 2 – 3). Under the same reaction

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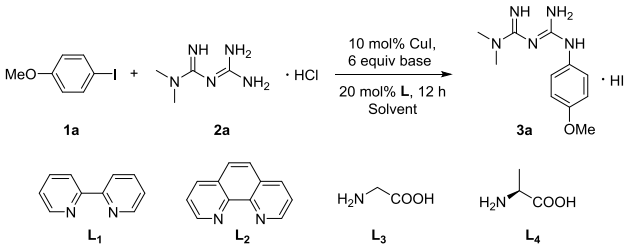
conditions, the biguanidinylation of methylsubstituted aryl iodides took place smoothly to afford the corresponding *N*- aryl biguanides **3d-f** with 34 – 78% yield (Table 2, entries 4 – 6). The trend of reactivity of the biguanidinylation for the methylsubstituted aryl iodides was *para* > *meta* > *ortho*. Aromatic rings of phenyliodides with an electron withdrawing such as F, Cl, Br or CN group gave good isolated yields of the corresponding products (Table 2, entries 8 – 12). Additionally, 1-[(4-Iodophenyl)sulfonyl]-pyrrolidine is good substrate for the biguanidinylation reaction (Table 2, entry 14). Also due to there are several halogen atoms in the reaction, we determine the structure by the single crystal *X*-ray analysis of 3o (figure S1).

Table 1. Catalyst screening in the synthesis of 3a

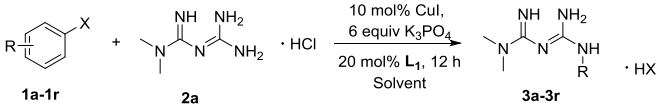


Entry	Ligand	Base	Solvent	Temp. (℃)	Yield (%)[a]
1	**L1**	K_3PO_4	THF	80	90
2	**L1**	K_3PO_4	THF	60	35
3	**L1**	K_3PO_4	THF	100	83
4	**L1**	K_3PO_4	dioxane	80	65.
5	**L1**	K_3PO_4	DMF	80	42
6	**L1**	K_3PO_4	EtOH	80	32
7	**L1**	K_3PO_4	DMSO	80	48
8	**L1**	K_3PO_4	CH_3CN	80	63
9	**L1**	K_2CO_3	CH_3CN	80	14
10	**L1**	KOH	CH_3CN	80	30
11	**L1,**	Cs_2CO_3	CH_3CN	80	43
12	**L1**	CsOAc	CH_3CN	80	0
14	**L2**	K_3PO_4	THF	80	41
15	**L3**	K_3PO_4	THF	80	72
16	**L4**	K_3PO_4	THF	80	83
17[b]	**L1**	K_3PO_4	THF	80	52
18[c]	**L1**	K_3PO_4	THF	80	36
19[d]	**L1**	K_3PO_4	THF	80	16
20[e]	**L1**	K_3PO_4	THF	80	0
21	-	K_3PO_4	THF	80	28
22	**L1**	-	THF	80	0

[a] All reactions were performed with 1 mmol of **1a** and 1 mmol of **2a** in solvent (5 mL); isolated yields are shown. [b] CuBr was used in place of CuI. [c] CuCl was used in place of CuI. [d] $CuCl_2$ was used in place of CuI. [e] CuI was not used.

Further investigations indicated that aryl bromides did not work for the above reaction conditions because only a trace of coupling products was isolated. However, after some attempts we were pleased to notice that when dioxane as solvent and K_2CO_3 as base were used, the coupling reaction of bromobenzene with dimethylbiguanide provided **3o** in 63% yield under the catalysis of 10 mol% CuI and 20 mol% **L1** at 110 °C (Table 2, entry 15). A variety of aryl bromides, including those MeO, Me, F and Cl substituents, showed great ability to react with biguanides under these conditions, providing the corresponding coupling products in 31 – 57% yield (Table 2, entries 16 – 19). The *X*-ray data of **3o** showed that the bromo ion is banding with *N1-H* with hydrogen bond (**Figure 1**).

Table 2. Scope of the synthesis of 3



Entry	Aryl Halide	R	X	Product	Yield (%)[a]
1	1a	4-$MeOC_6H_4$	I	**3a**	90
2	1b	4-$EtOC_6H_4$	I	**3b**	62
3	1c	4-PhC_6H_4	I	**3c**	77
4	1d	4-MeC_6H_4	I	**3d**	87
5	1e	3-MeC_6H_4	I	**3e**	78
6	1f	2-MeC_6H_4	I	**3f**	34
7	1g	Ph	I	**3g**	86
8	1h	4-FC_6H_4	I	**3h**	73
9	1i	4-ClC_6H_4	I	**3i**	82
10	1j	3-ClC_6H_4	I	**3j**	82
11	1k	4-BrC_6H_4	I	**3k**	70
12	1l	4-NCC_6H_4	I	**3l**	94
13	1m	4-$O_2NC_6H_4$	I	**3m**	40
14	1n	4-(1-pyrrolidine) sulfonyl	I	**3n**	88
15[b]	1o	Ph	Br	**3o**	63
16[b]	1p	4-$MeOC_6H_4$	Br	**3p**	57
17[b]	1q	4-$MeOC_6H_4$	Br	**3q**	52
18[b]	1r	4- ClC_6H_4	Br	**3r**	31

[a] All reactions were performed with 1 mmol of **1** and 1 mmol of **2a** in THF (5 mL) at 80 °C; isolated yields are shown. [b] K_2CO_3 was used in place of K_3PO_4, 1,4-dioxane was used in place of THF, at 110 °C.

Finally, this reaction also occurred with aryl halides and cyclic amino substituted biguanide (Table 3). In these cases, morpholine biguanides and piperdine biguanides could be used as the starting materials. They could work well and afforded **3t**, **3u** and **3v** in good yields (Table 3, entries 1 – 3). However, no products were obtained from the reaction of 2-bromopyridine with **2a**.

Experimental section:

General Methods:

Under otherwise noted, materials such as compound **2** were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using silica gel 60 F254 and visualized using UV light. Column chromatography was performed with silica gel (mesh 300~400). ^1H NMR and ^{13}C NMR spectra recorded on a Bruker Avance 500 MHz spectrometer in DMSO-*d6* with Me_4Si as an internal standard. All products are new compounds, data were reported as follows: chemical shift in parts per million (δ), multiplicity (s =

singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet), coupling constant in Hertz (Hz) and integration.

General Procedure for Synthesis of Biguanide hydroiodide:

To a mixture of biguanide hydroiodide (1.0 mmol), aryl iodide (1.0 mmol), 2-(pyridin-2-yl) pyridine (0.2 mmol), and K_3PO_4 (6.0 mmol) in THF (5 mmol), was added CuI (10 mol %). The resulting mixture was than sealed and stirred for 12 h at 80 ℃. After completion, the reaction mixture was filtered and the precipitates were washed with methanol. The mixture was evaporated under vacuum, and the residue was purified by flash chromatography with CH_2Cl_2 and CH_3OH (3:1) as the eluent to give the pure product.

***N*-(4-methoxyphenyl)-dimethylbiguanide hydroiodide (3a)**

Yellow solid; Mp: 203-204 ℃; IR (KBr, cm^{-1}): 3850.68, 3448.42, 2357.29, 1634.31, 1583.19, 1558.78, 1435.81, 1258.91, 1087.14, 771.21; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.46 (s, 2H), 7.24 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.62 (s, 2H), 3.73 (s, 3H), 2.94 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 155.8, 154.3, 131.1, 123.5, 113.9, 55.2, 37.6; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{11}H_{18}N_5O$ 236.1511, found 236.1510. Anal. Calcd for $C_{11}H_{18}IN_5O$: C, 36.38; H, 5.00; N, 19.28. Found: C, 36.33; H, 5.04; N, 19.26.

***N*-(4-ethoxyphenyl)-dimethylbiguanide hydroiodide (3b)**

Yellow solid; Mp 161-162 ℃; IR (KBr, cm^{-1}): 3295.08, 3196.88, 2973.78, 2920.38, 1628.41, 1585.84, 1537.92 , 1511.00, 1413.88, 1238.72, 1043.71, 823.61; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 7.43 (s, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.59 (s, 2H), 3.98 (d, J = 6.5 Hz, 2H), 2.94 (s, 6H), 1.30 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 155.2, 154.3, 131.1, 123.6, 114.5, 63.2, 37.6, 14.7; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{12}H_{20}N_5O$ 250.1668, found 250.1664.

***N*-(1, 1'-biphenyl)-dimethylbiguanide hydroiodide (3c)**

Yellow solid; Mp: 223-224 ℃; IR (KBr, cm^{-1}): 3365.02, 3296.09, 2923.39, 1629.50, 1583.88, 1527.46, 1409.62, 1381.35, 1050.64, 826.32; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.60-7.66 (m, 6H), 7.30-7.48 (m, 5H), 6.69 (s, 2H), 2.98 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.2, 153.2, 139.5, 138.2, 134.8, 128.8, 127.0, 125.8, 125.2, 121.0, 37.6; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{16}H_{20}N_5$ 282.1719, found 282.1722.

***N*-(4-methylphenyl)-dimethylbiguanide hydroiodide (3d)**

Yellow solid; Mp: 195-196 ℃; IR (KBr, cm^{-1}): 3343.42, 3190.06, 2923.06, 2855.17, 1630.82, 1588.19, 1545.25, 1541.90, 1415.37, 1204.94, 1052.22, 810.68; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (s, 1H), 7.51 (s, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 6.61 (s, 2H), 2.95 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.1, 153.8, 135.9, 132.6, 129.2, 121.3, 37.7, 20.4; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{11}H_{18}N_5$ 220.1562, found 220.1570.

***N*-(3-methylphenyl)-dimethylbiguanidehydroiodide (3e)**

Yellow solid; Mp: 203-204 ℃; IR (KBr, cm^{-1}): 3421.56, 3366.23, 2923.92, 1635.22, 1595.50, 1548.05, 1421.21, 1302.22, 1133.87, 777.93; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.54 (s, 2H), 7.14-7.19 (m, 3H), 6.83-6.90 (m, 1H), 6.63 (s, 2H), 2.96 (s, 6H), 2.26 (s, 3H); 13C NMR (125 MHz, DMSO-d_6) δ 160.0, 153.4, 138.5, 137.9, 128.5, 124.0, 121.4, 118.1, 37.6, 21.1;HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{11}H_{18}N_5$ 220.1562, found 220.1568.

***N*-(2-methylphenyl)-dimethylbiguanide hydroiodide (3f)**

Yellow solid; Mp: 177-178 ℃; IR (KBr, cm^{-1}): 3422.89, 3360.99, 1631.56, 1537.20, 1487.97, 1402.70, 1384.20, 1045.63, 891.45; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.40 (s, 2H), 7.07-7.39 (m, 4H), 6.73 (s, 2H), 2.91 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.7, 154.9, 136.1, 132.2, 130.3, 126.1, 125.7, 125.3, 37.5, 17.7; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{11}H_{18}N_5$ 220.1562, found 220.1565.

***N*-phenyl-dimethylbiguanide hydroiodide (3g)**

Yellow solid; M p: 168-169 ℃; IR (KBr, cm^{-1}): 3345.46, 3198.33, 2921.70, 1634.49, 1587.18, 1549.85, 1415.50, 1381.24, 1048.22, 934.46, 756.77; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.57 (s, 2H), 7.39 -7.21 (m, 4H), 7.05 (t, J = 7.3 Hz, 1H), 6.64 (s, 2H), 2.96 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.1, 153.4, 138.6, 128.7, 123.2, 120.8, 37.7; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{10}H_{16}N_5$ 206.1406, found 206.1399.

***N*-(4-fluorophenyl)-dimethylbiguanide hydroiodide (3h)**

Yellow solid; Mp: 168-169 ℃; IR (KBr, cm^{-1}): 3376.72, 3301.46, 2925.41, 1640.13, 1595.19, 1536.78, 1496.55, 1406.29, 1379.67, 1051.30, 842.41; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.54 (s, 2H), 7.34-7.37 (m, 2H), 7.11-7.15 (m, 2H), 6.64 (s, 2H), 2.95 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.2, 158.3 (d, J = 226.9 Hz), 153.6, 134.9 (d, J = 1.8 Hz), 123.2 (d, J = 7.9 Hz), 115.3 (d, J = 22.5 Hz), 37.72; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{10}H_{15}FN_5$ 224.1311, found 224.1306.

***N*-(4-chlorophenyl)-dimethylbiguanide hydroiodide (3i)**

Yellow solid; Mp: 168-169 ℃; IR (KBr, cm^{-1}): 3377.11, 3206.11, 2922.65, 1637.41, 1597.10, 1484.61, 1376.84, 1086.14, 834.77; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.63 (s, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 6.67 (s, 2H), 2.96 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.2, 153.0, 137.7, 128.5, 126.8, 122.2, 37.6; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{10}H_{15}ClN_5$ 240.1016, found 240.1011.

***N*-(3-chloorophenyl)-dimethylbiguanidehydroiodide (3j)**

Yellow solid; Mp: 225-226 ℃; IR (KBr, cm^{-1}): 3345.10, 3197.02, 3125.67, 1634.71, 1599.66, 1582.43, 1539.95, 1416.99, 1376.01, 1049.72, 949.85; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 1H), 7.68 (s, 2H), 7.57 (s, 1H), 7.29-7.34 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.08(d, J = 8.0 Hz, 1H), 6.70 (s, 2H), 2.92 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.3, 152.7, 140.4, 132.9, 130.2, 122.6, 119.9, 118.8, 37.7; H RMS (ESI) m/z $[M-I]^+$ calcd for $C_{10}H_{15}ClN_5$ 240.1016, found 240.1011.

***N*-(4-bromophenyl)-dimethylbiguanide hydroiodide (3k)**

Yellow solid; Mp: 236-237 ℃; IR (KBr, cm^{-1}): 3411.59, 3295.95, 3188.29, 1615.58, 1530.72, 1479.56, 1401.73, 1286.09, 1048.19, 831.22; ^{1}HNMR (500 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.64 (s, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 6.69 (s, 2H), 2.96 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.2, 153.0, 138.2, 131.4, 122.5, 114.8, 37.7; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{10}H_{15}BrN_5$ 284.0511, found 284.0507.

***N*-(4-cyanophenyl)-dimethylbiguanide hydroiodide (3l)**

Yellow solid; Mp: 236-237 ℃; IR (KBr, cm^{-1}): 3379.63, 3297.74, 2926.87, 2218.26, 1637.21, 1572.67, 1523.88, 1408.49, 1377.86, 1112.62, 941.96; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (s, 1H),

7.79 (s, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 6.78 (s, 2H), 2.98 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.4, 152.0, 143.5, 133.0, 119.7, 119.1,104.1, 37.8; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{11}H_{15}N_6$ 231.1358, found 231.1358.

***N*-(4-nitrylphenyl)-dimethylbiguanide hydroiodide (3m)**

Yellow solid; Mp: 219-220 ℃; IR (KBr, cm^{-1}): 3421.64, 3075.92, 1634.00, 1549.05, 1505.03, 1406.95, 1384.27, 1108.01; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.19 (d, *J* = 9.2 Hz, 2H), 7.85 (s, 2H), 7.65 (d, *J* = 9.2 Hz, 2H), 6.84 (s, 2H), 3.00 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.5, 151.8, 145.7, 141.6, 124.8, 119.1, 37.8; HRMS (ESI) m/z $[M-I]^+$ $C_{10}H_{15}N_6O_2$ 251.1256, found 251.1253**.**

***N*-(4-(pyrrolidin-1-ylsulfonyl))-dimethylbiguanide hydroiodide (3n)**

Yellow solid; Mp: 225-226 ℃; IR (KBr, cm^{-1}): 3373.98, 3294.60, 3194.54, 1631.60, 1571.95, 1522.20, 1427.74, 1377.26, 1338.24, 1241.62, 1067.31, 711.90; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.40 (s, 1H), 7.77 (s, 2H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 6.77 (s, 2H), 3.11 (t, *J* = 6.5 Hz, 4H), 2.99 (s, 6H), 1.64 (t, *J* = 6.5 Hz, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.4, 152.3, 143.3, 129.4, 128.4, 119.4, 47.7, 37.7, 24.7; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{14}H_{23}N_6O_2S$ 339.1603, found 339.1603.

***N*-(amino(phenylamino)methylene)piperidine-1-carboximid amide hydroiodide (3s)**

Yellow solid; Mp: 207-208 ℃; IR (KBr, cm^{-1}): 3203.69, 3128.73, 1631.34, 1578.22, 1542.40, 1446.38, 1382.24, 1295.83, 1101.09, 753.52; ^{1}H NMR (500 MHz, MSO-d_6) δ 8.99 (s, 1H), 7.62 (s, 2H), 7.29-7.36 (m, 4H), 7.03-7.07 (m, 1H), 6.69 (s, 2H), 3.43 (t, J = 5.2 Hz , 4H), 1.54-1.60 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.3, 153.9, 138.6, 128.7, 123.3, 120.9, 45.9, 25.0, 23.4; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{13}H_{21}N_5$ 246.1719, found 246.1723.

2-[imino(morpholino)methyl]-1-phenylguanidine hydroiodide (3t)

Yellow solid; Mp: 186-187 ℃; IR (KBr, cm^{-1}): 3406.89, 3303.83, 3196.52, 632.72, 1537.59, 1487.44, 1444.11, 1383.91, 1121.80, 1006.53, 759.57; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.71 (s, 2H), 7.33-7.29 (m, 4H), 7.07 (s, 1H), 6.84 (s, 2H), 3.63 (t, J = 4.7 Hz s, 4H), 3.44 (t, J = 4.7 Hz s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.8, 154.6, 138.2, 128.7, 123.6, 121.2, 65.3, 45.0; HRMS (ESI) m/z $[M-I]^+$ calcd for $C_{12}H_{18}N_5O$ 248.1511, found 248.1509.

General Procedure for Synthesis of biguanide hydrobromides:

To a mixture of biguanide hydrochloride (1.0 mmol), aryl bromide (1.0 mmol), 2-(pyridin-2-yl) pyridine (0.2 mmol), and K_2CO_3 (6.0 mmol) in dioxane (5 mmol), was added CuI (10 mol %). The resulting mixture was then sealed and stirred for 12 h at 110 ℃. After completion, the reaction mixture was filtered and the precipitates were washed with methanol. The mixture was evaporated under vacuum, and the residue was purified by flash chromatography with CH_2Cl_2 and CH_3OH (3:1) as the eluent to give the pure product.

***N*-phenyl-dimethylbiguanide hydrobromide (3o)**

White solid; Mp: 239-240 ℃; IR (KBr, cm^{-1}): 3422.24, 1637.21, 1587.56, 1551.56, 1488.87, 1383.99, 1261.09, 1047.83, 757.24; 1H NMR (500 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.62 (s, 2H), 6.98-7.44 (m, 5H), 6.81 (s, 2H), 2.97 (s, 6H); 13C NMR (125 MHz, DMSO-d_6) δ 160.2, 153.4, 138.9, 128.6, 122.9, 120.4, 37.7; HRMS (ESI) m/z $[M-Br]^+$ calcd for $C_{10}H_{16}N_5$ 206.1406, found 206.1403.

***N*-(4-methoxyphenyl)-dimethylbiguanide hydrobromide (3p)**

White solid; Mp: 205-206 ℃; IR (KBr, cm^{-1}): 3410.23, 3340.57, 3176.18, 1633.76, 1592.42, 1556.73, 1513.30, 1240.26, 1033.23, 831.01; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.52 (s, 2H), 7.27 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 6.83 (s, 1H), 6.74 (s, 1H), 3.71 (s, 3H), 2.95 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 155.5, 154.3, 131.7, 122.7, 113.8, 55.2, 37.6; HRMS (ESI) m/z $[M-Br]^+$ calcd for $C_{11}H_{18}N_5O$ 236.1511, found 236.1515. Anal. Calcd for $C_{11}H_{18}BrN_5O$: C, 41.78; H, 5.74; N, 22.15. Found: C, 41.77; H, 5.78; N, 22.11.

***N*-(4-methylphenyl)-dimethylbiguanide hydrobromide (3q)**

White solid; Mp: 240-241 ℃; IR (KBr, cm^{-1}): 3422.23, 1633.96, 1540.93, 1486.07, 1414.87, 1383.81, 1121.80, 1049.57, 813.90; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.56 (s, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.76 (s, 2H), 2.96 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 160.1, 153.7, 136.2, 132.1, 129.0, 120.8, 37.6, 20.4; HRMS (ESI) m/z $[M-Br]^+$ calcd for $C_{11}H_{18}N_5$ 220.1562, found 220.1559.

***N*-(4-chlorophenyl)-dimethylbiguanide hydrobromide (3r)**

Yellow solid; Mp: 244-245 ℃; IR (KBr, cm-1): 3406.78, 1633.08, 1544.34, 1484.95, 1383.80, 1091.24, 809.72; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.79 (s, 1H), 7.68 (s, 2H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H), 6.87 (s, 2H), 2.97 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.3, 153.1, 138.1, 128.5, 126.4, 121.6, 37.7; HRMS (ESI) m/z $[M-Br]^+$ calcd for $C_{10}H_{15}ClN_5$ 240.1016, found 240.1020.

2-(imino(morpholino)methyl)-1-phenylguanidine hydrobromide (3u)

Yellow solid; Mp: 227-228 ℃; IR (KBr, cm^{-1}): 3423.71, 1631.82, 1536.34, 1489.41, 1445.79, 1115.21, 1006.08, 758.31; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (s, 1H), 7.75 (s, 2H), 7.29-7.36 (m, 4H), 7.06 (t, *J* = 7.1 Hz, 1H), 6.93 (s, 2H), 3.60-3.68 (m, 4H), 3.42-3.50 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.9, 154.6, 138.5, 128.7, 123.4, 120.9, 65.3, 45.1; IR(KBr, cm^{-1}): 3423.71, 1631.82, 1536.34, 1489.41, 1445.79, 1115.21, 1006.08, 758.31. HRMS (ESI) m/z $[M-Br]^+$ calcd for $C_{12}H_{18}N_5O$ 248.1511, found 248.1516.

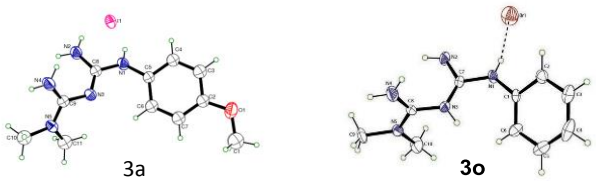
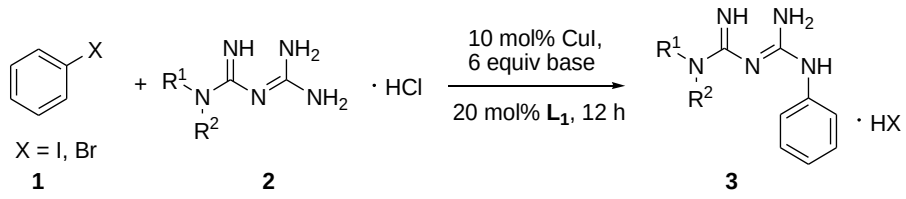


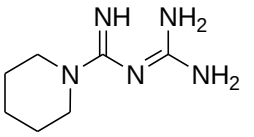
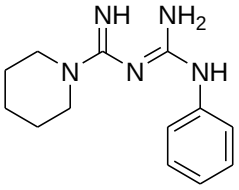
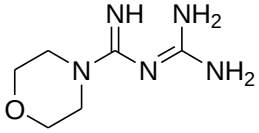
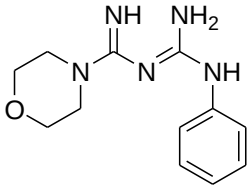
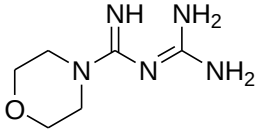
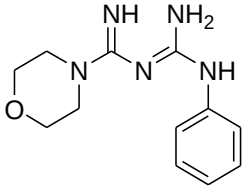
Figure S1. Crystal structure of **3a** (50% ellipsoids) and **3o** (50% ellipsoids). Selected bond lengths of **3a** (Å): C1-O1 1.414 (5); C2-O1 1.372 (4); C2-C3 1.379 (5); C2-C7 1.384 (5); C3-C4 1.377 (5); C4-C5 1.392 (4); C5-C6 1.382 (4); C5-N1 1.418 (4); C6-C7 1.386 (5); C8-N3 1.299 (4); C8-N1 1.353 (4); C8-N2 1.354 (4); C9-N5 1.320 (4); C9-N4 1.328 (4); C9-N3 1.353 (4); C10-N5 1.456 (4); C11-N5 1.461 (4).

Selected bond lengths of **3o** (Å): C1–C6 1.355 (13); C1–C2 1.413 (13); C1–N1 1.412 (11); C2–C3 1.385 (15); C3–C4 1.365 (19); C4–

C5 1.354 (19); C5–C6 1.401 (15); C7–N3 1.271 (12); C7–N2 1.376 (12); C7–N1 1.375 (11); C8–N4 1.318 (13); C8–N5 1.323 (11); C8–N3 1.348 (12), C9–N5 1.461 (11); C10–N5 1.480 (12).

Table 3. Scope of the synthesis of 3



Entry	X	Diguanide **2**	Product **3**	Yield (%)[a]
1	I	 · HCl	 · HI **3s**	76
2	I	 · HCl	 · HI **3t**	66
3[b]	Br	 · HCl	 · HBr **3u**	60

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), CuI (10 mol %), $\mathbf{L_1}$ (20 mol%), K_3PO_4 (6 mmol), THF (5 mL), 80 °C. Isolated yields. [b] K_2CO_3 was used in place of K_3PO_4, 1,4-dioxane was used in place of THF, 110 °C.

Conclusions

In conclusion, we have developed an efficient and mild CuI catalyzed the Ullmann-type C – N coupling reaction of biguanide and aryl halide for the synthesis of *N*–aryl biguanide derivatives. The reaction is applicable to a wide range of substrates with various substituted aryl halides and biguanide derivatives in moderate yields. We anticipate that the arylation of Diguanide is capable of offering a new synthetic approach to biologically and medicinally important aryl iguanids.

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