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Synthesis of Symmetrical and Unsymmetrical *N,N′*-Diaryl Guanidines via Copper/*N*-Methylglycine-Catalyzed Arylation of Guanidine Nitrate

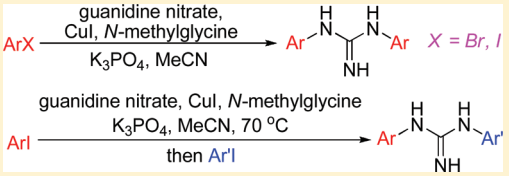
Hui Xing,[†] Ye Zhang,[†] Yisheng Lai,*[,†] Yongwen Jiang,[‡] and Dawei Ma*[,‡]

[†]State Key Laboratory of Natural Medicines, Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, China

[‡]State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: CuI/*N*-methylglycine-catalyzed coupling reaction of guanidine nitrate with both aryl iodides and bromides takes place at 70−100 °C, affording symmetrical *N,N′*-diaryl guanidines with good to excellent yields. Unsymmetrical *N,N′*-diaryl guanidines can be assembled via monoarylation of guanidine nitrate with aryl iodides bearing a strong electron-withdrawing group and subsequent coupling with another aryl iodide.



In the past decade, great attention has been directed to ligand-promoted Ullmann-type coupling reactions.[1] These efforts not only provide mild conditions for coupling of aryl halides and nucleophiles, but also widen the reaction scope by using unusual nucleophiles.[1] In terms of *N*-nucleophiles, sodium azide,[2] ammonia,[3] *N*-acyl hydrazines,[3d,4] *N*-aryl ureas,[5] hydroxyamine derivatives[6] and guanidines[7] have been recently found to be suitable coupling partners. The CuI/*N,N*-diethylsalicylamide-catalyzed N-arylation of guanidine nitrate reported by Antilla and co-workers offers a valuable method for preparing *N,N′*-diaryl guanidines,[7d] which have been found to display some interesting biological activities such as binding with σ-receptors,[8] blocking sodium channels,[9] and antagonizing NMDA receptors.[10] However, in Antilla and co-workers' studies only aryl iodides were examined, and reaction yields in many cases were below 50%.[7d] Additionally, only symmetric *N,N′*-diaryl guanidines could be prepared using this method. Recently, we found that combination of CuI and *N*-methylglycine[11] could catalyze the coupling reaction of guanidine nitrate with both aryl iodides and bromides, providing the corresponding symmetric *N,N′*-diaryl guanidines with good to excellent yields. By tuning the reaction sequence, we could assemble unsymmetric *N,N*-diaryl guanidines from guanidine nitrate and two different aryl iodides. Herein, we wish to disclose our results.

As shown in Table 1, we used reaction of 4-iodoanisole and guanidine nitrate as a model to explore optimized reaction conditions. Since Antilla and co-workers have described that L-proline was not a good ligand for their transformation,[7d] we initially attempted to modify Antilla's conditions by changing ligand from L-proline to *trans*-4-hydroxy-L-proline. Such modification has been found to be effective for N-arylation of ammonia and Boc-protected hydrazine.[3d] We were pleased that CuI/*trans*-4-hydroxy-L-proline-catalyzed reaction worked well in acetonitrile at 80 °C, affording diaryl guanidine **3a** in 84% yield (Table 1, entry 1). Changing the bidentate ligand[1] to *N,N*-dimethylglycine gave a decreased yield (Table 1, entry 2). Similar results were observed in case of picolinic acid, 2-methylquinolin-8-ol, and 2,2′-bipyridine as the ligands (Table 1, entries 4−6). However, the best result was obtained when *N*-methylglycine was employed (Table 1, entry 3). The modification to the bases and solvents indicated that the best combination was K_3PO_4 and acetonitrile (Table 1, entries 7−11). Switching Cu(I) salts from CuI to CuBr, CuCl, and Cu_2O gave inferior results (Table 1, entries 12−14). Further investigations revealed that there was no obvious loss in yield when catalyst loading was reduced to 5 mol % (Table 1, entry 15). At 5 mol % catalyst loading, reaction could complete even at 70 °C (Table 1, entry 16) but gave a decreased yield at 60 °C (Table 1, entry 17). Taken together, we concluded that the optimized conditions were using 5 mol % CuI and 10 mol % *N*-methylglycine as the catalyst, K_3PO_4 as the base, acetonitrile as the solvent, and carrying out the reaction at 70 °C.

The established optimized reaction conditions were then examined by varying aryl halides. As summarized in Table 2, besides electron-rich aryl iodides (Table 2, entries 2−4), electron deficient aryl iodides were found to be applicable (Table 2, entries 5−8). A good yield were observed when relatively bulky 2-methyl iodobenzene was used, thereby giving a facile method for preparing the σ-receptor ligand *N,N′*-di-*o*-toylguanidine (DTG, **3e**).[8] Under the same reaction conditions, poor conversions were seen when aryl bromides were used. However, increasing the reaction temperatures to 90−100 °C and the catalyst loading of CuI to 10 mol % could provide satisfactory results (Table 2, entries 9−20). Although 2-bromopyridine was compatible with these conditions (Table 2, entry 20), no desired coupling products were isolated when other haloheteroarenes like 2-bromofuran, 2-bromothiophene,

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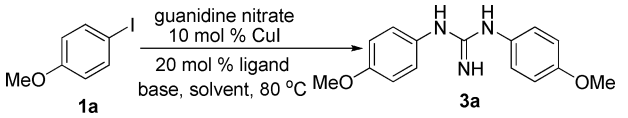
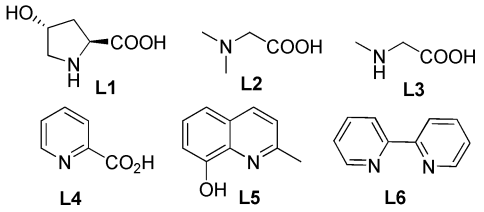
Table 1. CuI-Catalyzed Coupling of Guanidine Nitrate with 4-Iodoanisole under Different Conditions[a]

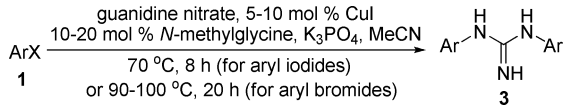




entry	[Cu]	ligand	base	solvent	yield (%)[b]
1	CuI	**L1**	K_3PO_4	MeCN	84
2	CuI	**L2**	K_3PO_4	MeCN	41
3	CuI	**L3**	K_3PO_4	MeCN	90
4	CuI	**L4**	K_3PO_4	MeCN	15
5	CuI	**L5**	K_3PO_4	MeCN	70
6	CuI	**L6**	K_3PO_4	MeCN	72
7	CuI	**L3**	K_2CO_3	MeCN	31
8	CuI	**L3**	Cs_2CO_3	MeCN	40
9	CuI	**L3**	K_3PO_4	toluene	41
10	CuI	**L3**	K_3PO_4	dioxane	58
11	CuI	**L3**	K_3PO_4	DMSO	37
12	CuBr	**L3**	K_3PO_4	MeCN	70
13	CuCl	**L3**	K_3PO_4	MeCN	57
14	Cu_2O	**L3**	K_3PO_4	MeCN	54
15	CuI	**L3**	K_3PO_4	MeCN	90[c]
16	CuI	**L3**	K_3PO_4	MeCN	90[c,d]
17	CuI	**L3**	K_3PO_4	MeCN	78[c,e]

[a]Reaction conditions: 4-iodoanisole (1 mmol), guanidine nitrate (1 mmol), copper salt (0.1 mmol), ligand (0.2 mmol), base (6 mmol), solvent (5 mL), 8 h. [b]Isolated yield. [c]0.05 mmol of CuI and 0.1 mmol of *N*-methylglycine were used. [d]Reaction was performed at 70 °C. [e]Reaction was performed at 60 °C.

Table 2. Assembly of Symmetrical *N,N*-Diaryl Guanidines via CuI/*N*-Methylglycine-Catalyzed Coupling of Aryl Halides and Guanidine Nitrate[a]



entry	X	Ar	product (yield (%)[b])
1	I	C_6H_5	**3b** (90)
2	I	4-$CH_3C_6H_4$	**3c** (85)
3	I	3-$CH_3C_6H_4$	**3d** (88)
4	I	2-$CH_3C_6H_4$	**3e** (81)[c]
5	I	3,4-$(F)_2C_6H_3$	**3f** (92)
6	I	4-$CF_3C_6H_4$	**3g** (72)
7	I	4-ClC_6H_4	**3h** (72)[d]
8	I	4-$MeO_2CC_6H_4$	**3i** (65)[d]
9	Br	4-$MeOC_6H_4$	**3a** (80)
10	Br	C_6H_5	**3b** (81)
11	Br	4-$CH_3C_6H_4$	**3c** (78)
12	Br	3-$CH_3C_6H_4$	**3d** (77)
13	Br	2-$CH_3C_6H_4$	**3e** (71)[c]
14	Br	2-naphthyl	**3j** (74)
15	Br	4-PhC_6H_4	**3k** (61)[e]
16	Br	4-$MeSC_6H_4$	**3l** (67)[e]
17	Br	3-ClC_6H_4	**3m** (82)
18	Br	3-FC_6H_4	**3n** (85)
19	Br	3-AcC_6H_4	**3o** (75)
20	Br	2-pyridinyl	**3p** (72)

[a]Reaction conditions: aryl halide (1 mmol), guanidine nitrate (1 mmol), CuI (0.05 mmol for entries 1–8, or 0.1 mmol for entries 9–20), *N*-methylglycine (0.1 mmol for entries 1–8, or 0.2 mmol for entries 9–20), K_3PO_4 (6 mmol), MeCN (5 mL), 70 °C, 8 h (for aryl iodides) or 90 °C, 20 h. (for aryl bromides). [b]Isolated yield. [c]2 mL of MeCN was used. [d]Reaction was performed with 1 mmol of aryl iodide and 0.5 mmol of guanidine nitrate. [e]Reaction was performed at 100 °C for 32 h.

5-bromoindole, and 6-bromoindole were used. More studies are needed to solve this problem.

When 4-chlorophenyl iodide and methyl 4-iodobenzoate were used, some monoarylation products were isolated. This problem could be solved by decreasing the amount of guanidine nitrate to 0.5 equiv (Table 2, entries 7 and 8). It is easy to understand because after the first arylation, the electron-withdrawing groups in aromatic ring should make the resultant *N*-aryl guanidines less reactive. In this case excess guanidine nitrate could compete with *N*-aryl guanidines to make the coupling stop at the monoarylation stage. When more electron-deficient 4-nitroiodobenzene was employed under our standard conditions, *N*-(4-nitrophenyl)guanidine was found to be a major product, while diarylation product was isolated in a very low yield.

The poor ability of electron-deficient aryl halides for forming diarylation products inplied that we could develop a method to obtain unsymmetrical *N,N′*-diaryl guanidines via a sequential-controlled one-pot coupling reaction. The idea was to carry out the coupling of guanidine nitrate with aryl iodides bearing a strong withdrawing group first, and then add another aryl iodide for second coupling reaction. Accordingly, we conducted a coupling reaction of 4-nitroiodobenzene with guanidine nitrate at 70 °C. After 10 h, 4-iodoanisole was added for further coupling. As we desired, unsymmetrical *N,N′*-diaryl guanidine **4a** was isolated in 69% yield after heating for 8 h (Table 3, entry 1). Using 3-methyliodobenzene for second coupling reaction gave a similar result (Table 3, entry 2). When sterically hindered 2-iodoanisole was employed, the desired product **4c** was isolated in only 49% yield (Table 3, entry 3), presumably because in second coupling step both coupling partners are less reactive. Importantly, two electron-deficient aryl iodides could be utilized for second coupling (Table 3, entries 4 and 5), which would allow assembly of unsymmetrical *N,N′*-diaryl guanidines in a more diverse manner. Next, we attempted to use 3-nitroiodobenzene as a coupling starter and found that our sequential-controlled reaction procedure was still reliable, although slightly low yields were obtained (Table 3, entries 6–8). The similar results were observed when 1-(4-iodophenyl)ethanone (Table 3, entry 9) and methyl 4-iodobenzoate (Table 3, entry 10) were employed as the coupling starters. Noteworthy is that in these reactions, the corresponding symmetrical *N,N′*-diaryl guanidines were still isolated as the minor products. Although more condition studies are required to minimize the side reactions, our method is still comparable with those reported[9,10,12] previously because of its convenient operation and use of commercially available starting materials and inexpensive reagents.

The detailed mechanism for this transformation is still unclear. However, we proposed a possible catalytic cycle as outlined in Scheme 1. It is known that *N*-methylglycine and

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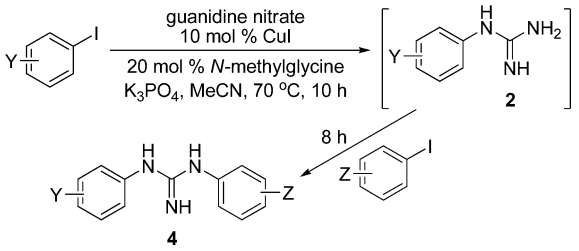
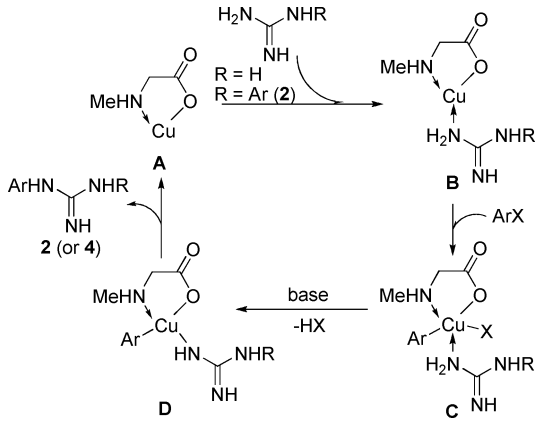
Table 3. One-Pot Synthesis of Unsymmetrical *N,N′*-Diarylguanidines[a]



entry	Y	Z	product (yield (%)[b])
1	4-NO_2	4-OMe	**4a** (69)
2	4-NO_2	3-Me	**4b** (70)
3	4-NO_2	2-OMe	**4c** (49)[c]
4	4-NO_2	4-Cl	**4d** (62)
5	4-NO_2	4-CO_2Me	**4e** (64)
6	3-NO_2	4-OMe	**4f** (55)
7	3-NO_2	3-Me	**4g** (59)
8	3-NO_2	3-CF_3	**4h** (50)
9	4-Ac	4-OMe	**4i** (61)
10	4-CO_2Me	4-OMe	**4j** (57)

[a]Reaction conditions: aryl iodide (1 mmol), guanidine nitrate (1 mmol), CuI (0.1 mmol), *N*-methylglycine (0.2 mmol), K_3PO_4 (6 mmol), MeCN (5 mL), 70 °C, 10 h, and then another aryl iodide (1 mmol), 8 h. [b]Isolated yield. [c]Second coupling was performed at 90 °C for 12 h.

Scheme 1



CuI could form the chelate **A**, which might coordinate with guanidine (or *N*-arylguanidine **2**) to give the complex **B**. Oxidative addition of **B** to aryl halide could deliver the Cu(III) complex **C**, which was reacted with base to afford the complex **D**. Reductive elimination of **D** would produce **2** (or **4**) and regenerate the Cu(I) complex **A**.

In a conclusion, we have revealed that *N*-methylglycine is an effective ligand for promoting CuI-catalyzed direct arylation of guanidine. A number of functionalized aryl iodides and aryl bromides could be employed as the coupling partners, affording the corresponding symmetrical *N,N′*-diaryl guanidines with great diversity. When aryl iodides bearing a strong electron-withdrawing group were used, the reaction could be stopped at the monoarylation stage, and the resultant coupling products could couple with another aryl iodide in situ to afford unsymmetrical *N,N′*-diaryl guanidines. Thus, our method provides a valuable and alternative approach for preparing *N,N′*-diaryl guanidines.

EXPERIMENTAL SECTION

General Procedure for Synthesis of Symmetrical *N,N′*-Diarylguanidines. A Schlenk tube was charged with aryl halides (1.0 mmol), guanidine nitrate (1.0 mmol), *N*-methylglycine (8.9 mg, 0.1 mmol (for aryl iodides) or 17.8 mg, 0.2 mmol (for aryl bromides)), recrystallized CuI (9.5 mg, 0.05 mmol (for aryl iodides) or 19.0 mg, 0.1 mmol (for aryl bromides)), and K_3PO_4 (1.27 g, 6 mmol). The tube was evacuated and backfilled with argon before MeCN (5 mL) was added. The reaction mixture was stirred at the indicated temperatures until the corresponding aryl halide was completely consumed as monitored by TLC. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over Na_2SO_4. Removal of solvent in vacuo followed by purification with column chromatography on silica gel (50:1−20:1 methylene chloride/methanol as eluent) provided the desired product.

1,3-Bis(4-methoxyphenyl)guanidine (3a). 122 mg (90% yield), white solid: mp 154−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, J = 8.7 Hz, 4H), 6.83 (d, J = 8.4 Hz, 4H), 5.16 (br s, 2H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (2C), 151.1, 136.7 (2C), 124.7 (4C), 114.6 (4C), 55.4 (2C); ESI-MS m/z 272.4 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{15}H_{18}N_3O_2$ (M + H)$^+$ 272.1393, found 272.1391.

1,3-Diphenylguanidine (3b). 95 mg (90% yield), white solid: mp 147−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.26 (m, 4H), 7.13- 7.04 (m, 6H), 4.74 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 143.6 (2C), 129.3 (4C), 123.2 (2C), 122.9 (4C); ESI-MS m/z 212.0 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{13}H_{14}N_3$ (M + H)$^+$ 212.1182, found 212.1186.

1,3-Di-*p*-tolylguanidine (3c). 102 mg (85% yield), white solid: mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.1 Hz, 4H), 7.00 (d, J = 8.4 Hz, 4H), 4.80 (br, s, 3H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 140.4 (2C), 133.1 (2C), 130.0 (4C), 123.3 (4C), 20.8 (2C); ESI-MS m/z 240.1 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{15}H_{17}N_3$ (M + H)$^+$ 240.1495, found 240.1492.

1,3-Di-*m*-tolylguanidine (3d). 105 mg (88% yield), white solid: mp 99−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, J = 7.2 Hz, 2H), 6.93−6.86 (m, 6H), 4.82 (br s, 3H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 143.6 (2C), 139.2 (2C), 129.2 (2C), 124.1 (2C), 123.8 (2C), 119.9 (2C), 21.4 (2C); ESI-MS m/z 240.1 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{15}H_{17}N_3$ (M + H)$^+$ 240.1495, found 240.1492.

1,3-Di-*o*-tolylguanidine (3e). 97 mg (81% yield), white solid: mp 177−178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16−6.99 (m, 8H), 5.78 (br s, 3H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 140.3 (2C), 132.9 (2C), 130.9 (2C), 126.9 (2C), 124.93 (2C), 124.85 (2C), 17.9 (2C); ESI-MS m/z 240.1 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{15}H_{17}N_3$ (M + H)$^+$ 240.1495, found 240.1500.

1,3-Bis(3,4-difluorophenyl)guanidine (3f). 130 mg (92% yield), white solid: mp 1554−156 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.21−7.08 (m, 4H), 6.89−6.85 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.3 (dd, 2C, J = 243.5, 13.8 Hz), 152.4, 147.0 (dd, 2C, J = 239.1, 13.1 Hz), 142.8 (d, 2C, J = 6.6 Hz), 118.5 (dd, 2C, J = 5.1, 2.9 Hz), 117.9 (d, 2C, J = 16.8 Hz), 111.6 (d, 2C, J = 18.9 Hz); ESI-MS m/z 284.2 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{13}H_{10}F_4N_3$ (M + H)$^+$ 284.0805, found 284.0802.

1,3-Bis(4-(trifluoromethyl)phenyl)guanidine (3g). 125 mg (72% yield), white solid: mp 107−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 4 H), 7.22 (d, J = 8.4 Hz, 4 H), 6.54 (br s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 140.4 (2C), 128.1 (q, 2C, J = 32.1 Hz), 126.9 (q, 4C, J = 3.6 Hz), 123.7 (q, 2C, J = 270.5 Hz), 123.3 (4C); ESI-MS m/z 348.0 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{15}H_{12}F_6N_3$ (M + H)$^+$ 348.0929, found 348.0920.

1,3-Bis(4-chlorophenyl)guanidine (3h). 101 mg (72% yield), white solid: mp 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.7 Hz, 4H), 7.17 (d, J = 8.4 Hz, 4H), 6.64 (br s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.9, 135.4 (2C), 130.2 (2C), 129.5 (4C), 125.8 (4C); ESI-MS m/z 279.9 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{13}H_{11}Cl_2N_3$ (M + H)$^+$ 280.0393, found 280.0387.

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Dimethyl 4,4′-((Iminomethylene)bis(azanediyl))dibenzoate (3i). 106 mg (65% yield), white solid: mp 166−168 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 8.4 Hz, 4H), 7.42 (d, J = 8.8 Hz, 4H), 3.90 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.6 (2C), 154.5, 143.4 (2C), 131.9 (4C), 128.1 (2C), 123.7 (4C), 52.5 (2C); ESI-MS m/z 328.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{17}H_{18}N_3O_4$ $(M + H)^+$ 328.1292, found 328.1296.

1,3-Di(naphthalen-2-yl)guanidine (3j). 115 mg (74% yield), white solid: mp 125−127 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.99 (d, J = 8.7 Hz, 2H), 7.92−7.89 (m, 6H), 7.55−7.48 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.4, 135.0 (2C), 133.7 (2C), 133.5 (2C), 130.9 (2C), 128.7 (2C), 128.6 (2C), 127.9 (2C), 127.4 (2C), 124.2 (2C), 124.1 (2C); ESI-MS m/z 312.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{21}H_{18}N_3$ $(M + H)^+$ 312.1495, found 312.1506.

1,3-Di([1,1′-biphenyl]-4-yl)guanidine (3k). 111 mg (61% yield), white solid: mp 218−220 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.75 (d, J = 8.7 Hz, 4H), 7.65 (d, J = 7.5 Hz, 4H), 7.48−7.43 (m, 8H), 7.39−7.34 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.2, 141.4 (2C), 141.0 (2C), 135.6 (2C), 129.8 (4C), 129.3 (4C), 128.6 (2C), 127.7 (4C), 126.3 (4C); ESI-MS m/z 364.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{25}H_{22}N_3$ $(M + H)^+$ 364.1808, found 364.1806.

1,3-Bis(4-(methylthio)phenyl)guanidine (3l). 102 mg (67% yield), colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 4H), 7.15 (d, J = 8.7 Hz, 4H), 2.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 136.1 (2C), 135.4 (2C), 128.2 (4C), 124.5 (4C), 16.4 (2C); ESI-MS m/z 304.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{15}H_{18}N_3S_2$ $(M + H)^+$ 304.0937, found 304.0940.

1,3-Bis(3-chlorophenyl)guanidine (3m). 115 mg (82% yield), white solid: mp 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 2H), 7.13 (t, J = 1.8 Hz, 4H), 7.05−6.96 (m, 4H), 4.55 (br s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.1, 146.9 (2C), 135.3 (2C), 131.0 (2C), 123.1 (2C), 122.6 (2C), 120.9 (2C); ESI-MS m/z 280.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{13}H_{12}Cl_2N_3$ $(M + H)^+$ 280.0403, found 280.0402.

1,3-Bis(3-fuorophenyl)guanidine (3n). 105 mg (85% yield), white solid: mp 119−121 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.35−7.28 (m, 2H), 7.09−6.99 (m, 4H), 6.80 (td, J = 8.4, 2.1 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.8 (d, 2C, J = 242.1 Hz), 153.1, 145.1 (d, 2C, J = 10.2 Hz), 131.4 (d, 2C, J = 9.5 Hz), 119.07 (d, 2C, J = 2.2 Hz), 111.07 (d, 2C, J = 21.9 Hz), 110.5 (d, 2C, J = 24.1 Hz); ESI-MS m/z 248.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{13}H_{12}F_2N_3$ $(M + H)^+$ 248.0994, found 248.0983.

1,3-Bis(3-acetylphenyl)guanidine (3o). 110 mg (75% yield), white solid: mp 147−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.47−7.36 (m, 4H), 4.51 (br s, 3H), 2.55 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 200.4 (2C), 152.4, 145.9 (2C), 139.0 (2C), 130.2 (2C), 127.8 (2C), 123.4 (2C), 122.5 (2C), 26.6 (2C); ESI-MS m/z 296.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{17}H_{18}N_3O_2$ $(M + H)^+$ 296.1393, found 296.1393.

1,3-Di(pyridin-2-yl)guanidine (3p). 77 mg (72% yield), white solid: mp 144−146 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (dd, J = 5.2, 1.2 Hz, 2H), 7.92 (td, J = 8.0, 2.0 Hz, 2H), 7.27−7.24 (m, 2H), 7.22 (d, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.3, 153.1 (2C), 147.6 (2C), 140.8 (2C), 121.2 (2C), 115.1 (2C); ESI-MS m/z 214.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{11}H_{12}N_5$ $(M + H)^+$ 214.1087, found 214.1089.

General Procedure for Synthesis of Unsymmetrical *N,N′*-Diarylguanidines. A Schlenk tube was charged with aryl iodide (1.0 mmol), guanidine nitrate (1.0 mmol), *N*-methylglycine (17.8 mg, 0.2 mmol), recrystallized CuI (19.0 mg, 0.1 mmol), and K_3PO_4 (1.27 g, 6 mmol). The tube was evacuated and backfilled with argon before MeCN (5 mL) was added. The reaction mixture was stirred at 70 °C for 10 h before another aryl iodide (1 mmol) was added. After the resultant mixture was heated at 70 °C for 8−12 h, it was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over Na_2SO_4. Removal of solvent in vacuo followed by purification with column chromatography on silica gel (50:1−20:1 methylene chloride/methanol as eluent) provided the corresponding product.

1-(4-Methoxyphenyl)-3-(4-nitrophenyl)guanidine (4a). 197 mg (69% yield), yellow solid: mp 181−183 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.13 (d, J = 9.3 Hz, 2H), 7.26 (d, J = 9.3 Hz, 2H), 7.14 (d, J = 9. 0 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.6, 155.6, 153.3, 142.5, 135.8, 125.8 (2C), 125.0 (2C), 122.4 (2C), 115.3 (2C), 55.7; ESI-MS m/z 287.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{14}H_{15}N_4O_3$ $(M + H)^+$ 287.1139, found 287.1140.

1-(4-Nitrophenyl)-3-(*m*-tolyl)guanidine (4b). 189 mg (70% yield), yellow solid: mp 182−184 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.13 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 7.16 (t, J = 7.8 Hz, 1H), 7.04−6.99 (m, 2H), 6.85 (d, J = 7.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.1, 152.3, 143.6, 142.5, 139.8, 129.7 (2C), 125.8 (2C), 124.7, 123.3, 122.2, 119.8, 21.3; ESI-MS m/z 271.1 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{14}H_{15}N_4O_2$ $(M + H)^+$ 271.1189, found 271.1190.

1-(2-Methoxyphenyl)-3-(4-nitrophenyl)guanidine (4c). 140 mg (49% yield), yellow solid: mp 153−155 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.22 (d, J = 8.7 Hz, 2H), 7.45−7.38 (m, 3H), 7.22 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.97 (t, J = 8.0 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.4, 154.6, 146.6, 145.4, 129.3, 127.3, 126.0 (2C), 125.8, 123.9 (2C), 122.0, 113.1, 56.2; ESI-MS m/z 287.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{14}H_{15}N_4O_3$ $(M + H)^+$ 287.1139, found 287.1147.

1-(4-Chlorophenyl)-3-(4-nitrophenyl)guanidine (4d). 180 mg (62% yield), yellow solid: mp 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 3.89 (br s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.6, 142.7, 130.4, 129.8, 129.8 (2C), 128.4, 125.8 (2C), 123.9 (2C), 121.7 (2C); ESI-MS m/z 291.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{13}H_{12}ClN_4O_2$ $(M + H)^+$ 291.0643, found 291.0645.

Methyl 4-(3-(4-Nitrophenyl)guanidino)benzoate (4e). 201 mg (64% yield), yellow solid: mp 220−222 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.20 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.2 Hz, 4H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.0, 148.7, 142.3, 131.2 (2C), 126.0, 125.6 (2C), 123.9, 121.5 (2C), 120.7 (2C), 115.8, 51.8.; ESI-MS m/z 315.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{15}H_{15}N_4O_4$ $(M + H)^+$ 315.1089, found 315.1093.

1-(4-Methoxyphenyl)-3-(3-nitrophenyl)guanidine (4f). 151 mg (55% yield), yellow solid: mp 105−107 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.19 (s, 1H), 8.14 (d, J = 5.7 Hz, 1H), 7.73−7.65 (m, 2H), 7.29 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.7, 155.6, 150.2, 141.9, 131.5, 131.1, 130.6, 127.3 (2C), 120.7, 119.7, 115.8 (2C), 55.8; ESI-MS m/z 287.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{14}H_{15}N_4O_3$ $(M + H)^+$ 287.1139, found 287.1140.

1-(3-Nitrophenyl)-3-(*m*-tolyl)guanidine (4g). 159 mg (59% yield), yellow solid: mp 163−165 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (t, J = 1.8 Hz, 1H), 8.05 (dt, J = 7.6, 2.0 Hz, 1H), 7.67−7.60 (m, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.13−7.07 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 152.7, 150.2, 149.6, 143.4, 139.8, 130.6, 129.7, 129.4, 124.6, 123.4, 119.8, 117.6, 117.0, 21.3; ESI-MS m/z 271.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{14}H_{15}N_4O_2$ $(M + H)^+$ 271.1190, found 271.1193.

1-(3-Nitrophenyl)-3-(3-(trifluoromethyl)phenyl)guanidine (4h). 162 mg (50% yield), yellow solid: mp 90−92 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (t, J = 2.0 Hz, 1H), 8.09−7.83 (m, 1H), 7.59 (s, 1H), 7.56−7.46 (m, 4H), 7.29 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.6, 150.2, 142.0, 140.8, 132.7 (q, 1C, J = 32.1 Hz), 131.4, 131.3, 130.5, 127.9, 125.1 (q, 1C, J = 269.8 Hz), 122.7 (q, 1C, J = 3.6 Hz), 121.1 (q, 1C, J = 3.7 Hz), 120.5, 119.1; ESI-MS m/z 325.0 $(M + H)^+$; FT-HRMS (ESI) calcd for $C_{14}H_{12}F_3N_4O_2$ $(M + H)^+$ 325.0907, found 325.0904.

1-(4-Acetylphenyl)-3-(4-methoxyphenyl)guanidine (4i). 172 mg (61% yield), white solid: mp 153−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 9.0 Hz, 2H), 7.12 (dd, J = 8.7, 1.5 Hz, 4H), 6.87 (d, J = 9.0 Hz, 2H), 4.45 (br s, 3H), 3.79 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 199.5, 157.3, 152.8, 152.7, 136.9, 131.4, 130.9 (2C), 124.9 (2C), 121.9 (2C), 115.3 (2C), 55.7, 26.1; ESI-MS

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m/*z* 284.1 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{16}H_{18}N_3O_2$ (M + H)$^+$ 284.1394, found 284.1400.

Methyl 4-(3-(4-Methoxyphenyl)guanidino)benzoate (4j). 170 mg (57% yield), white solid: mp 192−194 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.09 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.91 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.5, 160.6, 156.3, 141.3, 132.1 (2C), 129.2, 128.2, 128.1 (2C), 124.6 (2C), 116.1 (2C), 55.8, 52.6; ESI-MS *m*/*z* 300.1 (M + H)$^+$; FT-HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3$ (M + H)$^+$ 300.1343, found 300.1352.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Madw@mail.sioc.ac.cn; lcpu333@yahoo.com.cn.

Notes

The authors declare no competing financial interest.

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