

Iodine-Catalyzed Guanylation of Amines with *N,N'*-Di-Boc-thiourea

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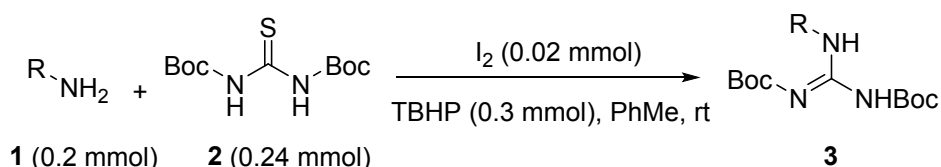
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General Information:

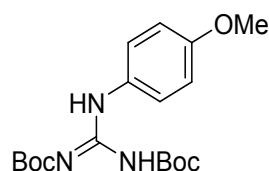
Unless otherwise noted, all reagents were used without further purification. Flash column chromatographies were performed on Qingdao silica gel (200–300 mesh). ^1H , ^{13}C spectra were measured on a NMR instrument (500 MHz for ^1H NMR; 126 MHz for ^{13}C NMR). Chemical shifts of ^1H NMR spectra were recorded relative to internal standard (TMS δ 0.00). Chemical shifts of ^{13}C NMR spectra were recorded relative to solvent resonance (CDCl_3 : δ 77.0).

General procedure for the synthesis of guanidines



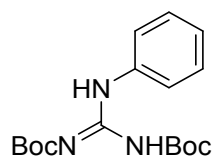
To a solution of *N,N'*-di-Boc-thiourea **2** (66 mg, 0.24 mmol) in PhMe (2 mL) at rt was added amine (0.2 mmol), I_2 (5 mg, 0.02 mmol) 70% aq. TBHP (39 mg, 0.3 mmol) sequentially. The reaction was monitored by TLC using ninhydrin to visualize the amines. The solution was stirred at rt for 0.5–12 h. Upon consumption of the amine, 50 mL DCM was added, the organic phase was washed with H_2O (10 mL) and dried with Na_2SO_4 . After concentration of the organic phase under reduced pressure, the residue was purified by column chromatography on silica gel using EtOAc/PE = 1:9 to give the desired product.

N,N'-Bis(*tert*-butoxycarbonyl)-*N''*-(4-methoxyphenyl)guanidine(**3a**)¹



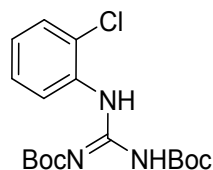
White solid; mp :182–183 °C; 82% yield; ^1H NMR (500 MHz, CDCl_3) δ 11.64 (brs, 0.9 H), 10.17 (brs, 0.9H), 7.48 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 1.53 (s, 9H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.61, 156.75, 153.57, 153.31, 129.78, 123.78, 114.01, 83.47, 79.36, 55.41, 28.17, 28.04.

N,N'-Bis(*tert*-butoxycarbonyl)-*N''*-phenylguanidine (**3b**)²



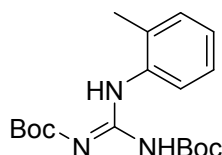
White solid; mp : 135–136 °C; 85% yield; ¹H NMR (500 MHz, Chloroform-*d*) δ 11.64 (brs, 0.9 H), 10.32 (brs, 0.9 H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 1.53 (s, 9H), 1.51 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.53, 153.47, 153.29, 136.79, 128.82, 124.67, 122.11, 83.64, 79.57, 28.14, 28.08.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(2-chlorophenyl)guanidine(3c)³**



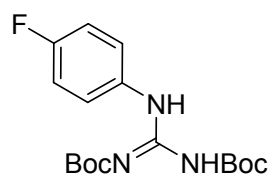
White solid; mp : 134–135 °C; 98% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.63 (brs, 0.9 H), 10.69 (s, 1H), 8.42 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31–7.26 (m, 1H), 7.04 (td, *J* = 7.7, 1.6 Hz, 1H), 1.54 (s, 9H), 1.51 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.39, 153.54, 152.95, 134.16, 129.09, 127.31, 125.09, 125.05, 124.57, 83.77, 79.82, 28.12.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(2-methylphenyl)guanidine(3d)**



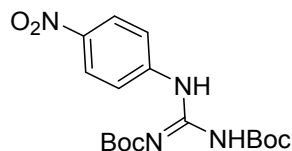
White solid; mp : 136.5–137 °C; 85% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.68 (brs, 0.9H), 10.14 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.18 – 7.14 (m, 1H), 7.11 – 7.02 (m, 1H), 2.30 (s, 3H), 1.54 (s, 9H), 1.48 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.68, 153.95, 153.42, 135.19, 130.27, 130.26, 126.51, 125.23, 124.52, 83.54, 79.51, 28.14, 18.11. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₂₈N₃O₄: 350.2074, found: 350.2070.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(4-fluorophenyl)guanidine(3e)⁴**



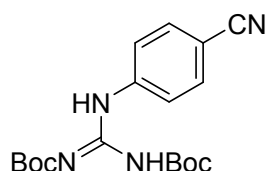
White solid; mp : 125–126 °C; 98% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.63 (brs, 0.9H), 10.28 (s, 1H), 7.66–7.43 (m, 2H), 7.08–6.92 (m, 2H), 1.54 (s, 9H), 1.50 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.48, 159.75 (d, *J* = 244.6 Hz), 153.61, 153.35, 132.82, 123.95 (d, *J* = 8.0 Hz), 115.48 (d, *J* = 22.7 Hz), 83.77, 79.66, 28.13.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(4-nitrophenyl)guanidine(3f)⁴**



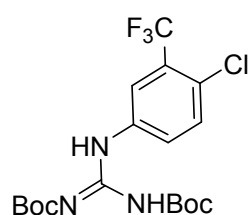
White solid; mp : 187–188 °C; 99% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.60 (brs, 0.9H), 10.76 (brs, 0.9H), 8.21 (d, *J* = 9.1 Hz, 2H), 7.85 (d, *J* = 9.1 Hz, 2H), 1.55 (s, 9H), 1.54 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 177.65, 162.97, 153.07, 143.64, 142.92, 124.77, 121.23, 84.52, 80.38, 28.05, 27.95.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(4-cyanophenyl)guanidine(3g)**



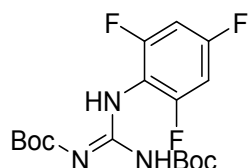
White solid; mp : >260 °C; 97% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.61 (brs, 1H), 10.64 (brs, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 1.55 (s, 9H), 1.52 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 162.93, 153.14, 153.05, 141.00, 132.93, 121.62, 118.76, 107.20, 84.30, 80.16, 28.01, 27.94. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₂₅N₄O₄: 361.1870, found: 361.1875.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(4-chloro-3-(trifluoromethyl)phenyl)guanidine(3h)⁴**



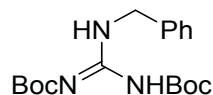
White solid; mp : 130–132 °C; 97% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.59 (brs, 1H), 10.49 (brs, 1H), 8.12–7.73 (m, 2H), 7.45 (d, *J* = 9.4 Hz, 1H), 1.54 (s, 9H), 1.51 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.09, 153.34, 153.29, 135.81, 131.82, 128.58 (q, *J* = 31.5 Hz) 127.30, 126.18, 124.41 (q, *J* = 273.3 Hz), 120.92 (q, *J* = 5.6 Hz), 84.30, 80.08, 28.09, 28.03.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(2,4,6-trifluorophenyl)guanidine(3i)**



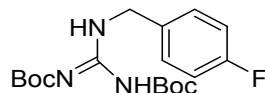
White solid; mp : 154–155 °C; 99% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.65 (brs, 0.9H), 9.53 (brs, 0.9H), 7.09–6.62 (m, 2H), 1.54 (s, 9H), 1.43 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.31, 162.10 (t, *J* = 14.7 Hz), 160.12 (t, *J* = 14.6 Hz), 159.45 (dd, *J* = 15.3, 6.8 Hz), 157.44 (dd, *J* = 15.2, 6.7 Hz), 155.11, 153.24, 110.22 (td, *J* = 16.6, 5.4 Hz), 100.57 (td, *J* = 26.1, 3.0 Hz), 83.92, 79.75, 28.04. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₇H₂₃F₃N₃O₄: 390.1635, found: 390.1637.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-benzylguanidine(3j)²**



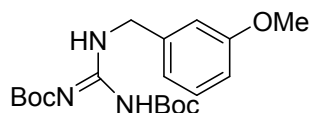
White solid; mp : 126–127 °C; 89% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.54 (brs, 0.9H), 8.58 (brs, 0.9H), 7.47–7.06 (m, 5H), 4.63 (d, *J* = 5.2 Hz, 2H), 1.52 (s, 9H), 1.48 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.62, 156.11, 153.19, 137.26, 128.74, 127.80, 127.60, 83.15, 79.38, 45.05, 28.32, 28.07.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(4-fluorobenzyl)guanidine(3k)**



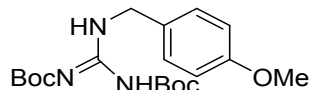
White solid; mp : 106–107 °C; 90% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.53 (s, 1H), 8.56 (s, 1H), 7.33–7.23 (m, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 4.59 (d, *J* = 5.2 Hz, 2H), 1.52 (s, 9H), 1.48 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.58, 163.25, 161.30, 154.64 (d, *J* = 358.8 Hz), 133.11 (d, *J* = 3.2 Hz), 129.54 (d, *J* = 8.2 Hz), 115.59 (d, *J* = 21.4 Hz), 83.26, 79.43, 44.25, 28.31, 28.06. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₈H₂₇FN₃O₄: 368.4289, found: 368.4291.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(3-methoxybenzyl)guanidine(3l)**



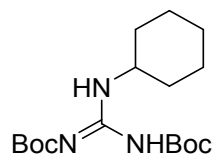
White solid; mp : 85–86 °C; 85% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.54 (brs, 1H), 8.58 (brs, 1H), 7.51–7.07 (m, 1H), 6.94–6.85 (m, 2H), 6.85–6.77 (m, 1H), 4.60 (d, *J* = 5.2 Hz, 2H), 3.80 (s, 3H), 1.52 (s, 9H), 1.48 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.55, 159.81, 156.06, 153.13, 138.81, 129.72, 120.02, 113.47, 113.06, 83.12, 79.31, 55.17, 44.95, 28.28, 28.02. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₉H₃₀N₃O₅: 380.4645, found: 380.4641.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(4-methoxybenzyl)guanidine(3m)⁵**



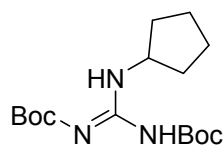
White solid; 80% yield; mp : 103–104 °C; ¹H NMR (500 MHz, CDCl₃) δ 11.53 (s, 1H), 8.49 (s, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 4.55 (d, *J* = 5.0 Hz, 2H), 3.79 (s, 3H), 1.52 (s, 9H), 1.47 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 163.57, 159.10, 155.87, 153.10, 129.26, 129.17, 114.10, 83.02, 79.25, 55.21, 44.52, 28.27, 28.00. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₉H₃₀N₃O₅: 380.2180, found: 380.2194.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-cyclohexylguanidine(3n)⁶**



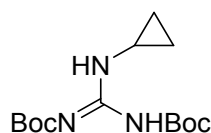
White solid; mp : 133–135 °C; 61% yield; ¹H NMR (500 MHz, Chloroform-*d*) δ 11.54 (s, 1H), 8.31 (s, 1H), 4.33–3.86 (m, 1H), 2.18–1.89 (m, 2H), 1.50 (s, 9H), 1.49 (s, 9H), 1.74–1.18 (m, 8H); ¹³C NMR (126 MHz, CDCl₃) δ 163.86, 155.23, 153.29, 82.75, 78.90, 48.51, 32.73, 28.31, 28.07, 27.98, 25.50, 24.36.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-cyclopentylguanidine(3o)⁷**



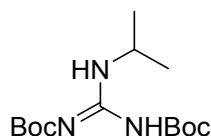
White solid; mp : 143–144 °C; 56% yield; ¹H NMR (500 MHz, Chloroform-*d*) δ 11.51 (brs, 0.9H), 8.35 (d, *J* = 7.9 Hz, 1H), 4.94–4.04 (m, 1H), 2.22–1.97 (m, 2H), 1.77–1.66 (m, 2H), 1.62–1.55 (m, 1H), 1.50 (s, 9H), 1.49 (s, 9H), 1.48–1.41 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 163.77, 155.61, 153.36, 82.88, 79.07, 52.04, 33.16, 28.38, 28.11, 28.03, 23.62.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-cyclopropylguanidine(3p)**



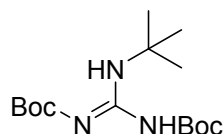
White solid; mp : 124–125 °C; 45% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.51 (s, 1H), 8.30 (s, 1H), 3.27–2.85 (m, 1H), 1.52 (s, 9H), 1.48 (s, 9H), 0.87–0.73 (m, 2H), 0.62–0.51 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 163.63, 157.24, 153.20, 83.02, 79.31, 28.27, 28.01, 23.72, 6.83. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₄H₂₆N₃O₄: 300.3785, found: 300.3781.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-isopropylguanidine(3q)⁷**



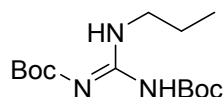
White solid; mp : 100–101 °C; 59% yield; ¹H NMR (500 MHz, CDCl₃) δ 11.51 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 4.62–4.09 (m, 1H), 1.50 (s, 9H), 1.49 (s, 9H), 1.19 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 163.83, 155.23, 153.29, 82.83, 78.99, 42.34, 28.35, 28.08, 22.74.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-*tert*-butylguanidine(3r)⁶**



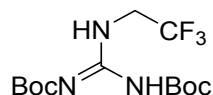
White solid; mp : 140–141 °C; 47% yield; ^1H NMR (500 MHz, CDCl_3) δ 11.42 (s, 1H), 8.25 (s, 1H), 1.48 (s, 9H), 1.48 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.46, 154.43, 153.43, 82.55, 78.38, 52.04, 28.93, 28.38, 28.11.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-propylguanidine(3s)⁴**



White solid; mp: 64–65 °C; 54% yield; ^1H NMR (500 MHz, CDCl_3) δ 11.51 (brs, 0.9H), 8.32 (brs, 0.9H), 3.43 – 3.34 (m, 2H), 1.65 – 1.55 (m, 2H), 1.51 (s, 9H), 1.50 (s, 9H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.67, 156.16, 153.35, 82.96, 79.17, 42.61, 28.33, 28.08, 22.26, 11.36.

***N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-(2,2,2-trifluoroethyl)guanidine(3t)³**



White solid; mp : 126–127 °C; 40% yield; ^1H NMR (500 MHz, Chloroform-*d*) δ 11.50 (brs, 1H), 8.71 (t, J = 5.9 Hz, 1H), 4.39–3.90 (m, 2H), 1.51 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) 163.15, 156.56, 153.03, 123.91 (q, J = 278.3 Hz) 83.88, 79.86, 41.87 (q, J = 34.6 Hz) 28.18, 28.00. HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{23}\text{F}_3\text{N}_3\text{O}_4$: 342.3387, found: 342.3386.

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NMR spectra

