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

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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). $^1$H, $^{13}$C spectra were measured on a NMR instrument (500 MHz for $^1$H NMR; 126 MHz for $^{13}$C NMR). Chemical shifts of $^1$H NMR spectra were recorded relative to internal standard (TMS $\delta$ 0.00). Chemical shifts of $^{13}$C NMR spectra were recorded relative to solvent resonance (CDCl$_3$; $\delta$ 77.0).

**General procedure for the synthesis of guanidines**

![Chemical Reaction Diagram]

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$_2$O (10 mL) and dried with Na$_2$SO$_4$. 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)

![Structural Formula]

White solid; mp: 182–183 °C; 82% yield; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.64 (brs, 0.9 H), 10.17 (brs, 0.9 H), 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$_3$) $\delta$ 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)

![Structural Formula]
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)**

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]^+ Caled for C₁₈H₂₈N₃O₄: 350.2074, found: 350.2070.

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

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]^+ Caled for C₁₈H₂₈N₃O₄: 350.2074, found: 350.2070.
White solid; mp : 125–126 °C; 98% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) 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). \(^1\)C NMR (126 MHz, CDCl\(_3\)) δ 163.48, 159.75 (d, \(J = 244.6\) Hz), 153.61, 153.35, 133.82, 123.95 (d, \(J = 8.0\) Hz), 115.48 (d, \(J = 22.7\) Hz), 83.77, 79.66, 28.13.

\(N,N'-\text{Bis(tert-butoxycarbonyl)-}N''-(4\text{-nitrophenyl})\text{guanidine(3f)\(^{4}\)}}$

\[\text{O}_2\text{N} \begin{array}{c} \text{NH} \\ \text{Boc}\text{N} \end{array} \text{NH} \text{Boc} \]

White solid; mp : 187–188 °C; 99% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) 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). \(^1\)C NMR (126 MHz, CDCl\(_3\)) δ 177.65, 162.97, 153.07, 143.64, 142.92, 124.77, 121.23, 84.52, 80.38, 28.05, 27.95. HRMS (ESI-TOF) m/z: [M + H]\(^+\) Calcd for C\(_{18}\)H\(_{25}\)N\(_4\)O\(_4\): 361.1870, found: 361.1875.

\(N,N'-\text{Bis(tert-butoxycarbonyl)-}N''-(4\text{-cyanophenyl})\text{guanidine(3g)\(^{4}\)}}$

\[\text{N} \begin{array}{c} \text{CN} \\ \text{Boc}\text{N} \end{array} \text{NH} \text{Boc} \]

White solid; mp : >260 °C; 97% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) 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). \(^1\)C NMR (126 MHz, CDCl\(_3\)) 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 C\(_{18}\)H\(_{25}\)N\(_4\)O\(_4\): 361.1870, found: 361.1875.

\(N,N'-\text{Bis(tert-butoxycarbonyl)-}N''-(4\text{-chloro-3-(trifluoromethyl})\text{guanidine(3h)\(^{4}\)}}$

\[\text{N} \begin{array}{c} \text{Cl} \\ \text{Boc}\text{N} \end{array} \text{NH} \text{Boc} \]

White solid; mp : 130–132 °C; 97% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) 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). \(^1\)C NMR (126 MHz, CDCl\(_3\)) 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'-\text{Bis(tert-butoxycarbonyl)-}N''-(2,4,6\text{-trifluorophenyl})\text{guanidine(3i)\(^{4}\)}}$
White solid; mp : 154–155 °C; 99% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 11.65\) (brs, 0.9H), 9.53 (brs, 0.9H), 7.09–6.62 (m, 2H), 1.54 (s, 9H), 1.43 (s, 9H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 616.33, 162.10\) (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: \([\text{M} + \text{H}]^+\) Calcd for C\(_{17}\)H\(_{23}\)F\(_3\)N\(_3\)O\(_4\): 390.1635, found: 390.1637.

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

\[
\begin{array}{c}
\text{HN} \\
\text{\hspace{2cm} BocN} \\
\text{\hspace{2cm} Ph} \\
\text{\hspace{2cm} NH\text{Boc}}
\end{array}
\]

White solid; mp : 126–127 °C; 89% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 11.54\) (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). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 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)

\[
\begin{array}{c}
\text{HN} \\
\text{\hspace{2cm} BocN} \\
\text{\hspace{2cm} Ph} \\
\text{\hspace{2cm} NH\text{Boc}} \\
\text{\hspace{2cm} F}
\end{array}
\]

White solid; mp : 106–107 °C; 90% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 11.53\) (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). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 163.58, 163.25, 161.30, 154.64\) (d, \(J = 358.8\) Hz), 133.11 (d, \(J = 3.2\) Hz), 129.54 (d, \(J = 3.2\) Hz), 115.59 (d, \(J = 21.4\) Hz), 83.26, 79.43, 44.25, 28.31, 28.06. HRMS (ESI-TOF) m/z: \([\text{M} + \text{H}]^+\) Calcd for C\(_{18}\)H\(_{27}\)FN\(_3\)O\(_4\): 368.4289, found: 368.4291.

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

\[
\begin{array}{c}
\text{HN} \\
\text{\hspace{2cm} BocN} \\
\text{\hspace{2cm} Ph} \\
\text{\hspace{2cm} NH\text{Boc}} \\
\text{\hspace{2cm} OMe}
\end{array}
\]

White solid; mp : 85–86 °C; 85% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 11.54\) (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). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 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: \([\text{M} + \text{H}]^+\) Calcd for C\(_{19}\)H\(_{30}\)N\(_3\)O\(_5\): 380.4645, found: 380.4641.

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

\[
\begin{array}{c}
\text{HN} \\
\text{\hspace{2cm} BocN} \\
\text{\hspace{2cm} Ph} \\
\text{\hspace{2cm} NH\text{Boc}} \\
\text{\hspace{2cm} OMe}
\end{array}
\]

White solid; 80% yield; mp : 103–104 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 11.53\) (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). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 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: \([\text{M} + \text{H}]^+\) Calcd for C\(_{19}\)H\(_{30}\)N\(_3\)O\(_5\): 380.2180, found: 380.2194.
**N,N'-Bis(tert-butoxycarbonyl)-N''-cyclohexylguanidine(3n)**

White solid; mp: 133–135 °C; 61% yield; \(^1\)H NMR (500 MHz, Chloroform–d) \(\delta\) 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); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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)**

White solid; mp: 143–144 °C; 56% yield; \(^1\)H NMR (500 MHz, Chloroform–d) \(\delta\) 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); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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 C\(_{14}\)H\(_{26}\)N\(_3\)O\(_4\): 300.3785, found: 300.3781.

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

White solid; mp: 100–101 °C; 59% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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)**
White solid; mp: 140–141 °C; 47% yield; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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; $^1$H NMR (500 MHz, Chloroform–d) $\delta$ 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: [M+H]$^+$ Calcd for C$_{13}$H$_{23}$F$_3$N$_3$O$_4$: 342.3387, found: 342.3386.
References

NMR spectra

Chemical Formula: C_{14}H_{12}N_{2}O_{5}
Molecular Weight: 365.43
Chemical Formula: $C_9H_5N_2O_8$
Molecular Weight: 300.40
Chemical Formula: C_{19}H_{22}ClF_{3}N_{2}O_{4}
Molecular Weight: 437.84
Boc-NH-NHBoc
Chemical Formula: C_{14}H_{23}N_{2}O_{4}
Molecular Weight: 341.4520
BocNH
NH

Chemical Formula: C_{14}H_{22}N_{4}O_{6}
Molecular Weight: 357.43
BocNH~NHBOc
Chemical Formula: C_{n}H_{2}N_{2}O_{4}
Molecular Weight: 299.3710
BocNH

Chemical Formula: C_{6}H_{12}N_{2}O_{4}
Molecular Weight: 301.3570