

**A Versatile One-Pot Synthesis of 1,3-Substituted Guanidines
from Carbamoyl-isothiocyanates.**

SUPPORTING INFORMATION

Brian R. Linton[¶], Andrew J. Carr[†], Brendan P. Orner[†], and Andrew D. Hamilton^{*†}

[¶]Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260

[†]Sterling Chemistry Laboratory, Box 208107,
Yale University, New Haven, CT 06511

General Methods

^1H NMR and ^{13}C NMR were recorded on either a Bruker AM-300 or AM-500. NMR chemical shifts are reported in ppm downfield from internal TMS. High resolution mass spectra were determined either at the Department of Chemistry, University of Pittsburgh, using a Varian MAT CH-5 or VG 7070 mass spectrometer, or determined at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, using a Varian 70-VSE. Elemental analysis was carried out by Atlantic Microlabs, Inc., Norcross, GA.

Dichloromethane was obtained from Fisher and distilled from calcium hydride. Silica gel 60 silica (particle size 0.063-0.200 mm, 70-230 mesh ASTM) (EM Science) was used for flash chromatography. Analytical thin layer chromatography (TLC) was conducted using PolyGram 0.25 mm silica gel precoated plates with fluorescent indicator UV₂₄₅. All other reagents were obtained from Aldrich Chemical Company and used without further purification.

General Procedure for the Preparation of Carbamoyl Isothiocyanates (1).

A saturated solution of potassium thiocyanate (40 g) in boiling ethanol (300 mL) was poured into 1.5 L of ethyl ether forming a fine, white powder. The solid was collected by filtration and washed with 300 mL of ethyl ether, before being dried in vacuo over P_2O_5 . Finely powdered potassium thiocyanate was isolated (33 g, 82%).

Alkyl chloroformate (20 mmol) was slowly added to a well-stirred suspension of freshly powdered potassium thiocyanate (10 g, 110 mmol) in 250 mL of 20% toluene/acetonitrile. After stirring for two days no chloroformate was detectable by TLC (silica, 20% dichloromethane/hexanes). The reaction mixture was filtered through celite, and the solid was washed twice with toluene (50 mL). Solvent was removed in vacuo with mild heating, before isolating the carbamoyl isothiocyanate by distillation, or silica chromatography.

General Procedure for the Preparation of Carbamoyl Thioureas (2).

A solution of carbamoyl isothiocyanate **1** (1.0 mmol) in 50 mL dichloromethane was cooled to 0°C before adding alkyl amine **A-G** (1.0 mmol). The ice bath was removed and the solution was stirred for four hours under nitrogen. The solution was washed with 1% HCl, water, brine and dried with Na₂SO₄. Solvent was removed under reduced pressure yielding a white solid. As an alternative to extractive workup, the reaction mixture can be poured into 50 mL pentane. The white solid that forms was collected by filtration and dried in vacuo.

N-Ethoxycarbonyl-N'-benzyl-thiourea (2A). ¹H NMR (300 MHz, DMSO-d₆) δ 10.60 (br, 1H), 10.23 (br, 1H), 7.29 (m, 5H), 4.80 (d, J=5.1Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 1.20 (t, J=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.2, 152.7, 136.1, 128.4, 127.4, 62.2, 48.8, 13.8; HRMS (EI) *m/e* calcd for C₁₁H₁₄N₂O₂S: 238.0776, found 238.0784; Anal. Calcd for C₁₁H₁₄N₂O₂S: C, 55.44; H, 5.92; N, 11.76; found: C, 55.47; H, 5.95; N, 11.75.

N-Ethoxycarbonyl-N'-(t-butyl)-thiourea (2B). ¹H NMR (500 MHz, CDCl₃) δ 9.74 (br, 1H), 7.85 (br, 1H), 4.20 (q, J=7.0 Hz, 2H), 1.55 (s, 9H), 1.30 (t, J=7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 177.2, 152.8, 62.5, 54.5, 28.0, 14.2; HRMS (EI) *m/e* calcd for C₈H₁₆N₂O₂S: 204.0932, found 204.0934; Anal. Calcd for C₈H₁₆N₂O₂S: C, 47.04; H, 7.89; N, 13.71; found: C, 47.26; H, 7.97; N, 13.84.

N-Ethoxycarbonyl-N'-morpholino-thiourea (2C). ¹H NMR (500 MHz, CDCl₃) δ 7.52 (s, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.78 (br, 8H), 1.27 (t, J=7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 150.4, 66.2, 62.6, 52.1, 14.2; HRMS (EI) *m/e* calcd for C₈H₁₄N₂O₃S: 218.0725, found 218.0724; Anal. Calcd for C₈H₁₄N₂O₃S: C,

44.02; H, 6.46; N, 12.83; found: C, 43.73; H, 6.35; N, 12.74.

N-Ethoxycarbonyl-N',N'-diisopropyl-thiourea (2D). ^1H NMR (500 MHz, CDCl_3) δ 6.95 (br, 1H), 4.39 (br, 2H), 4.16 (q, $J=7.0$ Hz, 2H), 1.39 (m, 12H), 1.26 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 178.4, 151.7, 62.0, 52.2, 20.0, 14.2; HRMS (EI) m/e calcd for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: 232.1245, found 232.1251; Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 51.70; H, 8.68; N, 12.06; found: C, 51.66; H, 8.71; N, 12.21.

N-Ethoxycarbonyl-N'-(4-methylphenyl)-thiourea (2E). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.45 (s, 1H), 11.18 (s, 1H), 7.40 (d, $J=8.4$ Hz, 2H), 7.16 (d, $J=8.4$ Hz, 2H), 4.18 (q, $J=7.5$ Hz, 2H), 2.28 (s, 3H), 1.23 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 176.8, 151.9, 133.8, 127.3, 122.7, 60.3, 18.9, 12.4; HRMS (EI) m/e calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: 238.0776, found 238.0782; Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 55.44; H, 5.92; N, 11.76; found: C, 55.45; H, 5.93; N, 11.77.

N-Ethoxycarbonyl-N'-(2-methoxyphenyl)-thiourea (2F). ^1H NMR (500 MHz, CDCl_3) δ 8.64 (d, $J=8.0$ Hz, 1H), 8.48 (br, 1H), 7.18 (m, 1H), 6.99 (m, 1H), 6.92 (d, $J=8.2$ Hz, 1H), 4.26 (q, $J=7.1$ Hz, 2H), 3.89 (s, 3H), 1.32 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.4, 152.6, 150.8, 127.1, 126.6, 123.3, 120.2, 110.6, 62.8, 56.0, 14.2; HRMS (EI) m/e calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: 254.0725, found 254.0722; Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 51.95; H, 5.55; N, 11.02; found: C, 52.04; H, 5.54; N, 11.02.

N-Ethoxycarbonyl-N'-(4-nitrophenyl)-thiourea (2G). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.84 (s, 1H), 11.46 (s, 1H), 8.24 (d, $J=9.0$ Hz, 2H), 7.99 (d, $J=9.0$ Hz, 2H), 4.22 (q, $J=7.0$ Hz, 2H), 1.26 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 176.7, 151.3, 142.2, 142.0, 122.1, 121.9, 60.2, 12.1; HRMS (EI) m/e calcd for

$C_{10}H_{11}N_3O_4S$: 269.0470, found 269.0465; Anal. Calcd for $C_{10}H_{11}N_3O_4S$: C, 44.61; H, 4.12; N, 15.60; found: C, 44.56; H, 4.11; N, 15.68.

General Procedure for the Preparation of Carbamoyl Guanidines (3).

Carbamoyl thiourea **2** (1.0 mmol), alkyl amine **A-G** (1.5 mmol), and diisopropylethylamine (1.0 mmol) were added to 10 mL anhydrous dichloromethane and cooled to 0°C. EDCI (1.5-2.0 mmol) was added and the solution was stirred under nitrogen. After one hour the ice bath was removed and the solution was stirred for an additional 10 hours at room temperature. In cases where TLC indicated unreacted starting material, addition of more amine and EDCI resulted in increased yields. The reaction mixture was washed with 1% HCl, water, brine and dried with Na_2SO_4 . The residue that remained after removal of solvent under reduced pressure was purified by silica chromatography.

N-Ethoxycarbonyl-N',N''-dibenzyl guanidine (3AA). 1H NMR (300 MHz, DMSO- d_6) δ 7.28 (m, 10H), 4.48 (d, $J=5.6$ Hz, 4H), 3.90 (q, $J=7.1$ Hz, 2H), 1.10 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 160.0, 128.6, 127.5, 127.0, 60.5, 44.9, 14.5; HRMS (EI) m/e calcd for $C_{18}H_{21}N_3O_2$: 311.1633, found 311.1634; Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49; found: C, 69.27; H, 6.85; N, 13.48.

N-Ethoxycarbonyl-N'-benzyl-N''-(t-butyl) guanidine (3AB). 1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.49 (br, 2H), 4.13 (q, $J=7.0$ Hz, 2H), 1.34 (s, 9H), 1.24 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 159.4, 128.8, 127.6, 127.1, 60.6, 51.2, 45.3, 24.6, 14.6; HRMS (EI) m/e calcd for $C_{15}H_{23}N_3O_2$: 277.1790, found 277.1790; Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15; found: C, 65.06; H, 8.28; N, 15.17.

N-Ethoxycarbonyl-N'-benzyl-N''-(morpholino) guanidine (3AC). ^1H NMR (500 MHz, CDCl_3) δ 8.70 (br, 1H), 7.35 (m, 2H), 7.29 (m, 3H), 4.39 (d, $J=3.9$ Hz, 2H), 4.11 (q, $J=7.1$ Hz, 2H), 3.69 (t, $J=4.8$ Hz, 4H), 3.42 (t, $J=4.8$ Hz, 4H), 1.29 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.1, 163.6, 137.4, 128.8, 127.7, 126.9, 77.3, 77.0, 76.8, 66.4, 60.9, 49.2, 47.7, 14.5; HRMS (EI) m/e calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3$: 291.1661, found 291.1583; Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3$: C, 61.84; H, 7.26; N, 14.42; found: C, 61.77; H, 7.20; N, 14.53.

N-Ethoxycarbonyl-N'-benzyl-N'',N''-(diisopropyl) guanidine (3AD). ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.22 (m, 5H), 5.35 (br, 1H), 4.27 (d, $J=3.8$ Hz, 2H), 4.02 (d, $J=7.1$ Hz, 2H), 3.95 (m, 2H), 1.20-1.16 (m, 15H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.8, 159.6, 137.3, 128.6, 128.1, 127.6, 60.3, 47.8, 47.1, 21.0, 14.6; HRMS (EI) m/e calcd for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_2$: 305.4224, found 305.2096; Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_2$: C, 66.85; H, 8.91; N, 13.76; found: C, 66.77; H, 8.75; N, 13.89.

N-Ethoxycarbonyl-N'-benzyl-N''-(4-methylphenyl) guanidine (3AE). ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.21 (m, 10H), 5.05 (br, 1H), 4.75 (d, $J=5.5$ Hz, 2H), 4.33 (q, $J=7.0$ Hz, 2H), 2.14 (s, 3H), 1.48 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.4, 158.7, 137.4, 137.1, 132.4, 130.4, 129.4, 128.5, 127.4, 125.6, 60.6, 44.4, 20.7, 14.5; HRMS (EI) m/e calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$: 311.1633, found 311.1634; Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$: C, 69.43; H, 6.80; N, 13.49; found: C, 69.15; H, 6.77; N, 13.26.

N-Ethoxycarbonyl-N'-benzyl-N''-(2-methoxyphenyl) guanidine (3AF). ^1H NMR (500 MHz, CDCl_3) δ 7.34-6.91 (m, 9H), 4.62 (d, $J=5.0$ Hz, 2H), 4.20 (q, $J=7.5$ Hz, 2H), 3.80 (s, 3H), 1.63 (br, 1H), 1.34 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125

MHz, CDCl₃) δ 158.6, 132.4, 124.6, 129.6, 129.5, 128.7, 128.6, 128.3, 128.2, 127.5, 127.3, 63.9, 60.8, 55.6, 45.2, 29.6, 14.6; HRMS (EI) *m/e* calcd for C₁₈H₂₁N₃O₃: 327.1582, found 327.1580; Anal. Calcd for C₁₈H₂₁N₃O₃: C, 66.04; H, 6.47; N, 12.84; found: C, 65.77; H, 6.45; N, 12.80.

N-Ethoxycarbonyl-N'-benzyl-N''-(4-nitrophenyl) guanidine (3AG). ¹H NMR (500 MHz, CDCl₃) δ 8.11 (d, J=9 Hz, 2H), 7.33-7.02 (m, 7H), 4.56 (s, 2H), 4.10 (q, J=7.0 Hz, 2H), 1.23 (t, J=7.0 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 143.1, 137.8, 128.8, 127.6, 125.6, 123.0, 62.3, 45.3, 14.2; HRMS (EI) *m/e* calcd for C₁₇H₁₈N₄O₄: 342.1328, found 342.1327; Anal. Calcd for C₁₇H₁₈N₄O₄: C, 59.64; H, 5.30; N, 16.37; found: C, 59.31; H, 5.30; N, 15.97.

N-Ethoxycarbonyl-N',N''-di(t-butyl) guanidine (3BB). ¹H NMR (500 MHz, CDCl₃) δ 4.05 (q, J=7.0 Hz, 2H), 1.35 (s, 18H), 1.23 (t, J=7.0 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 163.8, 158.8, 60.5, 50.9, 24.7, 14.7; HRMS (EI) *m/e* calcd for C₁₂H₂₅N₃O₂: 243.1946, found 243.1952; Anal. Calcd for C₁₂H₂₅N₃O₂: C, 59.23; H, 10.35; N, 17.27; found: C, 59.33; H, 10.40; N, 17.11.

N-Ethoxycarbonyl-N'-(t-butyl)-N''-(morpholino) guanidine (3BC). ¹H NMR (500 MHz, CDCl₃) δ 5.66 (br, 1H), 4.00 (q, J=7.0 Hz, 2H), 3.65 (t, J=4.5 Hz, 4H), 3.31 (t, J=4.5 Hz, 4H), 1.29 (s, 9H), 1.20 (t, J=7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 161.8, 160.8, 66.1, 60.6, 53.6, 47.7, 29.7, 14.6; HRMS (EI) *m/e* calcd for C₁₂H₂₃N₃O₃: 257.1739, found 257.1735; Anal. Calcd for C₁₂H₂₃N₃O₃: C, 56.01; H, 9.01; N, 16.33; found: C, 55.77; H, 9.06; N, 16.35.

N-Ethoxycarbonyl-N'-(t-butyl)-N'',N''-diisopropyl guanidine (3BD). ¹H NMR (500 MHz, CDCl₃) δ 4.75 (br, 1H), 3.98 (q, J=7.5 Hz, 2H), 3.88 (m, 2H), 1.31

(s, 9H), 1.21 (d, $J=7.0$ Hz, 12H), 1.16 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.7, 157.4, 60.0, 52.8, 46.9, 24.6, 21.0, 14.8; HRMS (EI) m/e calcd for $\text{C}_{14}\text{H}_{29}\text{N}_3\text{O}_2$: 272.2259, found 272.2263; Anal. Calcd for $\text{C}_{14}\text{H}_{29}\text{N}_3\text{O}_2$: C, 66.85; H, 8.91; N, 13.76; found: C, 66.77; H, 8.75; N, 13.89.

N-Ethoxycarbonyl-N'-(t-butyl)-N''-(4-methylphenyl) guanidine (3BE). ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, $J=7.5$ Hz, 2H), 7.20 (br, 2H), 4.84 (br, 1H), 4.32 (q, $J=7.0$ Hz, 2H), 2.48 (s, 3H), 1.54 (s, 9H), 1.48 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.1, 158.2, 136.5, 133.7, 130.4, 125.3, 61.1, 51.9, 29.3, 20.8, 14.7; HRMS (EI) m/e calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2$: 277.1790, found 277.1793; Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2$: C, 64.96; H, 8.36; N, 15.15; found: C, 65.06; H, 8.37; N, 15.22.

N-Ethoxycarbonyl-N'-(t-butyl)-N''-(2-methoxyphenyl) guanidine (3BF). ^1H NMR (500 MHz, CDCl_3) δ 7.11-6.90 (m, 6H), 4.16 (q, $J=7.0$ Hz, 2H), 3.84 (s, 3H), 1.42 (s, 9H), 1.29 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.9, 157.5, 126.9, 125.4, 124.4, 121.0, 120.8, 111.6, 60.9, 55.7, 51.4, 29.4, 14.6; HRMS (EI) m/e calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_3$: 293.1739, found 293.1739; Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_3$: C, 61.41; H, 7.90; N, 14.32; found: C, 61.68; H, 7.79; N, 14.21.

N-Ethoxycarbonyl-N'-(t-butyl)-N''-(4-nitrophenyl) guanidine (3BG). ^1H NMR (500 MHz, CDCl_3) δ 7.20 (d, $J=8.0$ Hz, 2H), 7.08 (d, $J=8.0$ Hz, 2H), 4.75 (br, 1H), 4.20 (q, $J=7.0$ Hz, 2H), 2.36 (s, 3H), 1.40 (s, 9H), 1.33 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.1, 158.2, 147.3, 136.4, 133.8, 130.4, 125.3, 61.0, 51.9, 29.4, 20.8; HRMS (EI) m/e calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_4$: 308.1484, found 308.1482; Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_4$: C, 54.64; H, 6.54; N, 18.17; found: C, 54.54; H, 6.71; N, 17.81.

N-Ethoxycarbonyl-N'-(4-methylphenyl)-N''-(morpholino) guanidine

(3CE). ^1H NMR (500 MHz, CDCl_3) δ 10.07 (s, 1H), 7.12 (d, $J=8.0$ Hz, 2H), 6.95 (d, $J=8.5$ Hz, 2H), 4.16 (q, $J=7.0$ Hz, 2H), 3.60 (t, $J=5.0$ Hz, 4H), 3.41 (t, $J=5.0$ Hz, 4H), 2.30 (s, 3H), 1.31 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.7, 160.2, 136.7, 134.1, 129.8, 121.2, 65.9, 60.8, 46.7, 20.5, 14.2; HRMS (EI) m/e calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3$: 291.1582, found 291.1586; Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_3$: C, 61.84; H, 7.26; N, 14.42; found: C, 61.49; H, 7.27; N, 14.22.

N-Ethoxycarbonyl-N'-(2-methoxyphenyl)-N''-(morpholino) guanidine

(3CF). ^1H NMR (500 MHz, CDCl_3) δ 7.07-6.90 (m, 4H), 4.50 (q, $J=7.5$ Hz, 2H), 3.85 (s, 3H), 3.60 (t, $J=4.5$ Hz, 4H), 3.40 (t, $J=4.5$ Hz, 4H), 1.25 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.6, 159.9, 150.2, 128.2, 124.7, 120.6, 120.5, 111.1, 66.2, 61.0, 55.6, 46.9, 14.4; HRMS (EI) m/e calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_4$: 307.1532, found 307.1528; Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_4$: C, 58.62; H, 6.89; N, 13.67; found: C, 58.70; H, 6.89; N, 13.74.

N-Ethoxycarbonyl-N'-(morpholino)-N''-(4-nitrophenyl) guanidine

(3CG). ^1H NMR (500 MHz, CDCl_3) δ 8.21 (d, $J=6.5$ Hz, 2H), 7.10 (br, 2H), 4.15 (q, $J=7.0$ Hz, 2H), 3.70 (br, 4H), 3.49 (br, 4H), 1.30 (br, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.7, 158.3, 145.2, 142.9, 125.5, 119.1, 66.1, 61.7, 47.1, 14.3; HRMS (EI) m/e calcd for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_5$: 322.1277, found 322.1272; Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_5$: C, 52.17; H, 5.63; N, 17.38; found: C, 51.85; H, 5.61; N, 16.98.

N-Ethoxycarbonyl-N',N'-(diisopropyl)-N''-(4-methylphenyl) guanidine

(3DE). ^1H NMR (500 MHz, CDCl_3) δ 7.06 (d, $J=8.0$ Hz, 2H), 6.91 (d, $J=8.0$ Hz, 2H), 4.01 (q, $J=7.0$ Hz, 2H), 3.84 (m, 2H), 2.28 (s, 3H), 1.25 (d, $J=6.5$ Hz, 12H), 1.20 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.7, 160.2, 138.4, 134.0, 128.4,

121.1, 59.6, 47.0, 19.7, 19.4, 13.3; HRMS (EI) *m/e* calcd for C₁₇H₂₇N₃O₂: 305.2103, found 305.2100; Anal. Calcd for C₁₇H₂₇N₃O₂: C, 66.85; H, 8.91; N, 13.76; found: C, 66.96; H, 8.80; N, 13.58.

N-Ethoxycarbonyl-N',N'-(diisopropyl)-N''-(2-methoxyphenyl) guanidine (3DF). ¹H NMR (500 MHz, CDCl₃) δ 7.52-7.24 (m, 4H), 4.44 (br, 2H), 4.35 (q, J=7.0 Hz, 2H), 4.29 (s, 3H), 1.73 (d, J=7.0 Hz, 12H), 1.56 (t, J=7.0 Hz, 3H); HRMS (EI) *m/e* calcd for C₁₇H₂₇N₃O₃: 321.2052, found 321.2050; Anal. Calcd for C₁₇H₂₇N₃O₃: C, 63.53; H, 8.47; N, 13.07; found: C, 63.41; H, 8.33; N, 13.04.

N-Ethoxycarbonyl-N',N'-(diisopropyl)-N''-(4-nitrophenyl) guanidine (3DG). ¹H NMR (500 MHz, CDCl₃) δ 8.24-7.07 (m, 4H), 4.20 (m, 4H), 1.52 (d, J=7.0 Hz, 12H), 1.3 (t, J=7.0 Hz, 3H); HRMS (EI) *m/e* calcd for C₁₆H₂₄N₄O₄: 336.1797, found 336.1803; Anal. Calcd for C₁₆H₂₄N₄O₄: C, 57.13; H, 7.19; N, 16.66; found: C, 57.40; H, 7.08; N, 16.10.

N-Ethoxycarbonyl-N',N''-(di-(4-methylphenyl)) guanidine (3EE). ¹H NMR (500 MHz, CDCl₃) δ 7.23 (d, J=7.5 Hz, 4H), 7.15 (d, J=7.5 Hz, 4H), 4.16 (q, J=7.0 Hz, 2H), 2.34 (s, 6H), 1.32 (t, J=7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.6, 157.0, 153.7, 133.6, 129.9, 124.1, 61.0, 20.8, 14.5; HRMS (EI) *m/e* calcd for C₁₈H₂₁N₃O₂: 311.0633, found 311.1634; Anal. Calcd for C₁₈H₂₁N₃O₂: C, 69.43; H, 6.80; N, 13.49; found: C, 69.48; H, 6.89; N, 13.39.

N-Ethoxycarbonyl-N'-(2-methoxyphenyl)-N''-(4-methylphenyl) guanidine (3EF). ¹H NMR (500 MHz, CDCl₃) δ 8.22 (br, 1H), 7.21-6.80 (m, 8H), 4.23 (q, J=7.0 Hz, 2H), 3.74 (s, 3H), 2.38 (s, 3H), 1.37 (t, J=7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.6, 156.4, 136.2, 133.3, 130.2, 128.1, 126.3, 129.0, 124.2,

122.4, 121.0, 110.2, 61.0, 55.6, 20.8, 14.5; HRMS (EI) *m/e* calcd for C₁₈H₂₁N₃O₃: 327.1582, found 327.1582; Anal. Calcd for C₁₈H₂₁N₃O₃: C, 66.04; H, 6.47; N, 12.84; found: C, 66.22; H, 6.40; N, 12.84.

N-Ethoxycarbonyl-N'-(2-methylphenyl)-N''-(4-nitrophenyl) guanidine (3EG). ¹H NMR (500 MHz, CDCl₃) δ 8.16-6.70 (m, 8H), 4.24 (q, J=7.5 Hz, 2H), 2.35 (s, 3H), 1.31 (br, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.0, 130.2, 125.0, 123.0, 121.8, 118.8, 62.4, 20.8, 14.2; HRMS (EI) *m/e* calcd for C₁₇H₁₈N₄O₄: 342.1328, found 342.1331; Anal. Calcd for C₁₇H₁₈N₄O₄: C, 59.64; H, 5.33; N, 16.37; found: C, 59.58; H, 5.38; N, 16.34.

N-Ethoxycarbonyl-N',N''-(di-(2-methoxyphenyl)) guanidine (3FF). ¹H NMR (500 MHz, CDCl₃) δ 7.12-6.89 (m, 8H), 4.25 (q, J=7.0 Hz, 2H), 3.74 (s, 6H), 1.36 (t, J=7.0 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 164.6, 156.2, 150.9, 126.1, 125.5, 123.6, 121.0, 110.9, 61.0, 55.7, 14.6; HRMS (EI) *m/e* calcd for C₁₈H₂₁N₃O₄: 343.1532, found 343.1529; Anal. Calcd for C₁₈H₂₁N₃O₄: C, 62.96; H, 6.16; N, 12.24; found: C, 62.86; H, 6.16; N, 12.20.

N-Ethoxycarbonyl-N'-(2-methoxyphenyl)-N''-(4-nitrophenyl) guanidine (3FG). ¹H NMR (500 MHz, CDCl₃) δ 8.22 (d, J=9.0 Hz, 2H), 7.16-6.95 (m, 6H), 4.24 (q, J=7.0 Hz, 2H), 3.95 (s, 3H), 1.31 (t, J=7.0 Hz, 3H); HRMS (EI) *m/e* calcd for C₁₇H₁₈N₄O₅: 358.1277, found 358.1278; Anal. Calcd for C₁₇H₁₈N₄O₅: C, 56.98; H, 5.06; N, 15.63; found: C, 56.86; H, 5.17; N, 15.49.

N-Benzyl-N'-benzyloxycarbonyl thiourea (2A, R¹=Bn). Benzyl chloroformate (2.9 mL, 19.5 mmol) was slowly added to 250 mL of a well-stirred suspension of potassium thiocyanate (10 g, 100 mmol) in 20% toluene:acetonitrile. After stirring for two days, the reaction mixture was passed through celite, and the solid washed with 2x50mL portions of toluene. The combined liquids were concentrated under reduced pressure. The resulting yellow oil was isolated by distillation (b.p. 93-98°C) to give 3.0 g (80%) benzyloxycarbonyl isothiocyanate (**1**, R¹=Bn): ¹H NMR (300 MHz, CDCl₃) δ 7.39 (s, 5H), 5.21 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 149.5, 146.9, 133.8, 128.8, 128.6, 128.5, 70.4.

Benzyloxycarbonyl isothiocyanate (**1**, R¹=Bn) (1.0 g, 5.2 mmol) was dissolved in 50 mL dry dichloromethane and cooled to 0°C. Benzylamine (0.58 mL, 5.3 mmol) was added and the solution allowed to warm to room temperature. After stirring for four hours, the solution was washed with 1% HCl (aq.), water, brine and dried with Na₂SO₄. Solvent was removed under reduced pressure to give a white powder (1.5 g, 97%): ¹H NMR (300 MHz, CDCl₃) δ 9.84 (br, 1H), 8.51 (br, 1H), 7.23 (br, 10H), 5.05 (s, 2H), 4.77 (d, J=5.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 179.2, 152.6, 136.2, 134.5, 128.8, 128.7, 128.2, 127.9, 68.1, 49.6; HRMS (EI) *m/e* calcd for C₁₆H₁₆N₂O₂S: 300.0932, found 300.9385; Anal. Calcd for C₁₆H₁₆N₂O₂S: C, 63.98; H, 5.37; N, 9.33; found: C, 63.79; H, 5.31; N, 9.15.

N-Benzylloxycarbonyl-N',N''-dibenzyl guanidine (3AA, R¹=Bn). ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.11 (m, 15H), 5.07 (s, 2H), 4.34 (br, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 164.1, 160.1, 137.4, 128.2, 127.9, 127.5, 127.1, 66.6, 45.0; HRMS (EI) *m/e* calcd for C₂₃H₂₃N₃O₂: 373.1790, found 373.1794; Anal. Calcd for C₂₃H₂₃N₃O₂: C, 73.97; H, 6.21; N, 11.25; found: C, 73.89; H, 6.22; N, 11.23.

N-Benzyl-N''-(2,2,2-trichloro-1,1-dimethylethoxy)carbonyl-thiourea (2A, $R^1 = \text{Cl}_3\text{C}(\text{CH}_3)_2\text{C}$). To a well-stirred suspension of potassium thiocyanate (4.0 g, 41 mmol) in 120 mL of 20% toluene:acetonitrile was added 2,2,2-trichloro-1,1-dimethylethyl chloroformate (2.9 mL, 19.5 mmol). After stirring for two days, the reaction mixture was passed through celite, and the solid washed with 2x50mL portions of toluene. The combined liquids were concentrated under reduced pressure to give (2,2,2-trichloro-1,1-dimethylethoxy)carbonyl isothiocyanate (**1**, $R^1 = \text{Cl}_3\text{C}(\text{CH}_3)_2\text{C}$) as a pale yellow solid (8.3 g, 99%): ^1H NMR (300 MHz, CDCl_3) δ 1.95 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 150.6, 144.8, 104.8, 92.0, 21.1. To a solution of (2,2,2-Trichloro-1,1-dimethylethoxy)carbonyl isothiocyanate (**1**, $R^1 = \text{Cl}_3\text{C}(\text{CH}_3)_2\text{C}$) (0.3 g, 1.1 mmol) in 10 mL dry dichloromethane cooled to 0°C was added benzylamine (0.13 mL, 1.1 mmol). The solution allowed to warm to room temperature while stirring for three hours at which point TLC indicated complete consumption of starting material. The solution was washed with 1% HCl (aq.), water, brine and dried with Na_2SO_4 . Solvent was removed under reduced pressure to give a white powder (0.42 g, 97%): ^1H NMR (300 MHz, CDCl_3) δ 9.81 (br, 1H), 8.83 (s, 1H), 7.36-7.28 (m, 5H), 4.86 (d, $J=5.2$ Hz, 2H), 1.92 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 179.1, 150.4, 136.1, 128.7, 127.9, 127.8, 104.9, 90.6, 49.4, 21.4; HRMS (FAB) m/e calcd for $\text{C}_{13}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_2\text{S}$: 368.9998, found 368.9970; Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_2\text{S}$: C, 42.24; H, 4.09; N, 7.58; found: C, 42.22; H, 4.13; N, 7.53.

N-(2,2,2-Trichloro-1,1-dimethylethoxy)carbonyl-N',N''-dibenzyl guanidine (3AA, $R^1 = \text{Cl}_3\text{C}(\text{CH}_3)_2\text{C}$). ^1H NMR (300 MHz, CDCl_3) δ 7.26-7.14 (M, 10H), 4.40 (br, 4H), 1.91 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.5, 160.3, 136.8, 128.9, 128.7, 127.2, 88.6, 87.2, 45.3, 21.6; HRMS (FAB) m/e

calcd for $C_{20}H_{22}Cl_3N_3O_6$: 442.0855, found 442.0857.

N-Benzyl-N'-phenoxycarbonyl-thiourea (2A, $R^1=Ph$). Phenyl chloroformate (4.0 mL, 32 mmol) was slowly added to a well-stirred suspension of potassium thiocyanate (10 g, 100 mmol) in 20% toluene:acetonitrile. After stirring for two days, the reaction mixture was passed through celite, and the solid washed with 2x50mL portions of toluene. The combined liquids were concentrated under reduced pressure. The resulting yellow oil was isolated by distillation (b.p. 93-98°C) to give 5.2 g (90%) phenoxycarbonyl isothiocyanate (**1**, $R^1=Ph$): 1H NMR (300 MHz, $CDCl_3$) δ 7.30 (br); MS (EI) m/e 179. Phenoxycarbonyl isothiocyanate (**1**, $R^1=Ph$) (2.0 g, 11 mmol) was dissolved in 50 mL dry dichloromethane and cooled to 0°C. Benzylamine (0.58 mL, 5.3 mmol) was added and the solution allowed to warm to room temperature. After stirring for four hours, the solution was poured into 50mL pentane causing immediate formation of a white precipitate. This solid was collected by filtration and washed with pentane. Excess solvent was removed under reduced pressure to give white solid (3.0 g, 95%): 1H NMR (300 MHz, $CDCl_3$) δ 9.83 (br, 1H), 8.77 (br, 1H), 7.36-7.11 (m, 10H), 4.85 (d, $J=5.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 151.3, 149.5, 135.9, 129.7, 128.9, 128.1, 128.0, 126.7, 121.3, 49.8; HRMS (FAB) m/e calcd for $C_{15}H_{14}N_2O_2S$: 287.0542, found 287.0855; Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78; found: C, 62.66; H, 4.89; N, 9.70.

N-Benzyl-N'-fluorenyl-methoxycarbonyl-thiourea (2A, $R^1=Fluorenylmethyl$). To a well-stirred suspension of potassium thiocyanate (1.2 g, 12 mmol) in 50 mL of 20% toluene:acetonitrile was added 9-fluorenylmethyl chloroformate (1.0 mL, 3.9 mmol). After stirring for two days, the reaction mixture was passed through celite, and the solid washed with 2x50mL

portions of toluene. After removal of solvent under reduced pressure the residue was purified by silica gel flash chromatography (hexanes/ethyl acetate=5:1) to give fluorenyl-methoxycarbonyl isothiocyanate (**1**, R¹=Fluorenylmethyl) as a yellow oil (8.3 g, 99%): ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, J=7.4 Hz, 2H), 7.54 (d, J=7.4 Hz, 2H), 7.37-7.28 (m, 4H), 4.36 (d, J=7.0 Hz, 2H), 4.16 (t, J=7.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 151.5, 142.9, 141.2, 127.9, 127.0, 124.1, 120.1, 68.4, 46.2. Fluorenyl-methoxycarbonyl isothiocyanate (**1**, R¹=Fluorenylmethyl) (0.32 g, 1.1 mmol) was dissolved in 70 mL dry dichloromethane and cooled to 0°C. Benzylamine (0.12 mL, 1.1 mmol) was added and the solution allowed to warm to room temperature. After stirring for four hours, the solution was washed with 1% HCl (aq.), water, brine and dried with Na₂SO₄. Solvent was removed under reduced pressure to give a white powder (0.42 g, 97%): ¹H NMR (300 MHz, CDCl₃) δ 9.96 (br, 1H), 9.01 (s, 1H), 7.71 (d, J=7.4 Hz, 2H), 7.53 (d, J=7.4 Hz, 2H), 7.39-7.25 (m, 9H), 4.84 (d, J=5.3 Hz, 2H), 4.37 (d, J=6.9 Hz, 2H), 4.16 (t, J=6.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 179.2, 152.7, 142.9, 141.2, 136.2, 128.8, 128.0, 127.8, 127.7, 127.2, 124.1, 120.1, 68.2, 49.4, 46.4; HRMS (EI) *m/e* calcd for C₂₃H₂₀N₂O₂S: 388.1245, found 388.1253; Anal. Calcd for C₂₃H₂₀N₂O₂S: C, 71.11; H, 5.19; N, 7.21; found: C, 71.03; H, 5.28; N, 7.18.

One-pot synthesis of N-Ethoxycarbonyl-N',N''-dibenzyl guanidine (3AA). A solution of ethoxycarbonyl isothiocyanate **1** (0.20 g, 1.5 mmol) in 50 mL dichloromethane was cooled to 0°C before adding benzylamine **A** (0.16 g, 1.5 mmol). After stirring for one hour under nitrogen, benzylamine (0.18 g, 1.8 mmol), diisopropylethylamine (0.24 g, 0.18 mmol), and EDCI (0.34 g, 0.18 mmol) were added. The solution was stirred an additional four hours while warming to room temperature. The reaction mixture was washed with 1% HCl, water, brine and dried with Na₂SO₄. The

residue that remained after removal of solvent under reduced pressure was purified by silica chromatography to yield a white solid (0.46 g, 98%): ^1H NMR (300 MHz, DMSO- d_6) δ 7.28 (m, 10H), 4.48 (d, $J=5.6$ Hz, 4H), 3.90 (q, $J=7.1$ Hz, 2H), 1.10 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.3, 160.0, 128.6, 127.5, 127.0, 60.5, 44.9, 14.5; HRMS (EI) m/e calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$: 311.1633, found 311.1634; Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$: C, 69.43; H, 6.80; N, 13.49; found: C, 69.27; H, 6.85; N, 13.48.

One-pot synthesis of N-Ethoxycarbonyl-N'-benzyl-N''-(t-butyl)guanidine (3AB). A solution of ethoxycarbonyl isothiocyanate **1** (0.20 g, 1.5 mmol) in 50 mL dichloromethane was cooled to 0°C before adding benzylamine **A** (0.16 g, 1.5 mmol). After stirring for one hour under nitrogen, butylamine (0.13 g, 1.8 mmol), diisopropylethylamine (0.24 g, 0.18 mmol), and EDCI (0.34 g, 0.18 mmol) were added. The solution was stirred an additional four hours while warming to room temperature. The reaction mixture was washed with 1% HCl, water, brine and dried with Na_2SO_4 . The residue that remained after removal of solvent under reduced pressure was purified by silica chromatography to yield a white solid (0.34 g, 80%): ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.27 (m, 5H), 4.49 (br, 2H), 4.13 (q, $J=7.0$ Hz, 2H), 1.34 (s, 9H), 1.24 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.1, 159.4, 128.8, 127.6, 127.1, 60.6, 51.2, 45.3, 24.6, 14.6; HRMS (EI) m/e calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2$: 277.1790, found 277.1790; Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2$: C, 64.96; H, 8.36; N, 15.15; found: C, 65.06; H, 8.28; N, 15.17.

1,3-N,N'-Bis[(benzyloxycarbonylaminothiocarbonyl)aminomethyl]benzene (4). Benzyloxycarbonyl isothiocyanate (2.70 g, 14.0 mmol) and *m*-xylenediamine (0.95 g, 7.0 mmol) were mixed in dichloromethane (50mL) at 0°C. After stirring for 12 hours, addition of pentane (50mL) caused formation of a white precipitate. which was collected by filtration, washed with additional pentane (50mL) and dried under

vacuum for four hours. Column chromatography (silica/ dichloromethane) resulted in 3.55 g (90%) white powder: m.p. 144-145°C; ^1H NMR (300 MHz, DMSO- d_6) δ 9.95 (br, 2H), 8.43 (s, 2H), 7.37-7.28 (m, 14H), 5.16 (s, 4H), 4.86 (d, $J=5.3$ Hz, 4H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 179.4, 154.6, 136.9, 134.4, 129.4, 128.8, 128.7, 128.3, 127.4, 127.3, 68.2, 49.3; MS m/e calc'd for $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_4\text{S}_2$: 523.1457, found 523.1453; Analysis calc'd for $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_4\text{S}_2$: C, 59.75; H, 5.01; N, 10.72; found: C, 59.55; H, 5.04; N, 10.65.

1,3-Bis[N^2 -benzyloxycarbonyl- N^3 -benzyl-guanidinomethyl]benzene (5).
 1,3- N,N' -Bis[(benzyloxycarbonylaminothiocarbonyl)aminomethyl]benzene (0.10 g, 0.2 mmol), benzylamine (61 mg, 0.60 mmol) and diisopropylethylamine (77 mg, 0.60 mmol) were combined in dichloromethane (20mL) under nitrogen atmosphere, and cooled to 0°C. Ethyl-dimethylaminopropyl-carbodiimide (0.60 g, 8.07 mmol) was added and the reaction was allowed to slowly warm to room temperature. After stirring for 10 hours, the solution was washed with 1% HCl, water, brine and dried with Na_2SO_4 . Removal of solvent under reduced pressure resulted in the isolation of 0.12g (88%) of white foam: m.p. 55-56°C; ^1H NMR (300 MHz, CDCl_3) δ 7.25-6.95 (m, 24H), 4.96 (s, 4H), 4.37 (br, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 161.7, 158.4, 136.7, 129.2, 128.8, 128.4, 128.1, 128.0, 127.9, 127.3, 126.3, 126.1, 67.1, 45.4, 45.0; MS m/e calc'd for $\text{C}_{40}\text{H}_{40}\text{N}_6\text{O}_4$: 669.3189, found 669.3181.



