CONVENIENT SYNTHESIS OF MONOBENZYLATED HYDRAZIDES VIA AQUEOUS ZINC-MEDIATED ADDITION REACTIONS

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Supplementary Material

Compound characterization data for <i>5a-5h</i> , <i>5j</i> , <i>5k</i> , <i>5m</i>	S2-S7
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N'-[(*tert*-butoxy)carbonyl]-*N*-[(4-methylphenyl)methyl](*tert*-butoxy)carbohydrazide (**5b**). According to Method A, from 0.185 g (1 mmol) of 1-(bromomethyl)-4-methylbenzene was obtained 0.296 g (88% yield) of **5b** as a white solid: mp 92.0-92.8 °C; ¹H NMR (CDCl₃, 60 °C) δ 7.14 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.32 (br s, 1H), 4.56 (br s, 2H), 2.31 (s, 3H), 1.47 (s, 9H), 1.42 (s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 155.3, 155.0, 137.0, 134.2, 129.1, 128.5(br), 81.2, 80.9, 53.3, 28.3, 28.2, 21.0. Anal. Calcd for C₁₈H₂₈N₂O₄: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.34; H, 8.59; N, 8.31.

N'-[(*tert*-butoxy)carbonyl]-*N*-[(3,5-dimethylphenyl)methyl](*tert*-butoxy)carbohydrazide (**5c**). According to Method A, from 0.199 g (1 mmol) of 1-(bromomethyl)-3,5-dimethylbenzene was obtained 0.258 g (74% yield) of **5c** as a white solid: mp 108.5-109.4 °C; ¹H NMR (CDCl₃, 60 °C) δ 6.89 (s, 1H), 6.87 (s, 2H), 6.18 (br s, 1H), 4.54 (s, 2H), 2.28 (s, 6H), 1.49 (s, 9H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 155.5, 155.1, 138.1, 137.2, 129.2, 126.3, 81.4, 81.1, 53.6(br), 28.4, 28.3, 21.3. Anal. Calcd for C₁₉H₃₀N₂O₄: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.41; H, 8.87; N, 7.95.

N'-[(*tert*-butoxy)carbonyl]-*N*-[(3-chlorophenyl)methyl](*tert*-butoxy)carbohydrazide (**5d**). According to Method A, from 0.206 g (1 mmol) of 1-(bromomethyl)-3-chlorobenzene was obtained 0.305 g (86% yield) of **5d** as a white solid: ¹H NMR (CDCl₃, 60 °C) δ 7.28 (s, 1H), 7.23-7.22 (m, 2H), 7.18-7.15 (m, 1H), 6.40 (br s, 1H), 4.58 (s, 2H), 1.47 (s, 9H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 155.3, 155.1, 139.5, 134.4, 129.8, 128.6, 127.7, 126.7, 81.7, 81.3, 53.4(br), 28.3, 28.2. Anal. Calcd for C₁₇H₂₅ClN₂O₄: C, 57.22; H, 7.06; N, 7.85. Found: C, 57.40; H, 7.26; N, 7.78.

***N*'-[(2-bromophenyl)methyl]-*N*'-[(*tert*-butoxy)carbonyl](*tert*-butoxy)carbohydrazide (5e).** According to Method A, from 0.250 g (1 mmol) of 1-bromo-2-(bromomethyl)benzene was obtained 0.335 g (86% yield) of **5e** as a white solid: 97.2-98.1 °C; ¹H NMR (CDCl₃, 60 °C) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.40 (br s, 1H), 4.76 (s, 2H), 1.47 (s, 9H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 155.3, 155.0, 136.4, 132.9, 130.5(br), 129.0, 127.4, 124.0(br), 81.5, 81.2, 53.8(br), 28.3(both *tert*-butyl groups). Anal. Calcd for C₁₇H₂₅BrN₂O₄: C, 50.88; H, 6.28; N, 6.98. Found: C, 50.78; H, 6.39; N, 6.87.

***N*'-[(*tert*-butoxy)carbonyl]-*N*'-[(2-iodophenyl)methyl](*tert*-butoxy)carbohydrazide (5f).**¹ According to Method A, from 0.297 g (1 mmol) of 1-iodo-2-(bromomethyl)benzene was obtained 0.351 g (79% yield) of **5f** as a white solid: mp 122.5-124.5 °C; ¹H NMR (CDCl₃, 60 °C) δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.32-7.26 (m, 2H), 6.93 (dt, *J* = 7.9, 2.5 Hz, 1H), 6.40 (br s, 1H), 4.71 (s, 2H), 1.47 (s, 9H), 1.44 (s, 9H). ¹³C NMR (CDCl₃, 60 °C) δ 155.3, 155.0, 139.6, 139.4, 129.8, 129.1, 128.3, 99.0, 81.5, 81.1, 58.2(br), 28.3(2C).

***N*'-[(*tert*-butoxy)carbonyl]-*N*'-[(3-methoxyphenyl)methyl](*tert*-butoxy)-carbohydrazide (5g).** According to Method A, from 0.201 g (1 mmol) of 1-(bromomethyl)-3-methoxybenzene was obtained 0.350 g (99% yield) of **5g** as a colorless viscous oil: ¹H NMR (CDCl₃, 60 °C) δ 7.21 (t, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H), 6.83 (s, 1H), 6.79 (d, *J* = 8 Hz, 1H), 6.30 (br s, 1H), 4.58 (s, 2H), 3.77 (s, 3H), 1.48 (s, 9H), 1.43 (s, 9H). ¹³C NMR (CDCl₃, 60 °C) δ 160.0, 155.4, 155.1, 138.9, 129.5, 120.8(br), 114.2, 113.2, 81.4, 81.1, 55.2, 53.7(br), 28.3, 28.2. HRMS (TOF EI) *m/z* [M]⁺ Calcd for C₁₈H₂₈N₂O₅Na: 375.1890; Found 375.1892.

methyl 3-([(tert-butoxy)carbonyl]([(tert-butoxy)carbonyl]amino)amino)methyl)-benzoate (5h).² According to Method B, from 0.386

g (2 mmol) of methyl 3-(bromomethyl)benzoate was obtained 0.253 g (74% yield) of **5h** as a white solid: mp 73.0-74.1 °C (lit.² 74-75 °C); ¹H NMR (CDCl₃, 60 °C) δ 7.95 (s, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 6.25 (br s, 1H), 4.66 (s, 2H), 3.90 (s, 3H), 1.49 (s, 9H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 167.0, 155.4, 155.2, 137.9, 133.1, 130.8, 129.6, 128.9, 128.7, 81.8, 81.4, 53.8(br), 52.1, 28.4, 28.3. Anal. Calcd for C₁₉H₂₈N₂O₆: C, 59.98; H, 7.42; N, 7.36. Found: C, 60.00; H, 7.63; N, 7.32.

***N'*-[*(tert*-butoxy)carbonyl]-*N*-(naphthalen-1-ylmethyl)(*tert*-butoxy)carbohydrazide (**5j**)**. According to Method A, from 0.221 g (1 mmol) of (2-naphthyl)bromomethane was obtained 0.300 g (81% yield) of **5j** as a pale yellow solid: mp 97.2-98.5 °C; ¹H NMR (CDCl₃, 60 °C) δ 7.76-7.74 (m, 3H), 7.68 (s, 1H), 7.41-7.38 (m, 3H), 6.41 (br s, 1H), 4.76 (br s, 2H), 1.48 (s, 9H), 1.40 (br s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 155.4, 155.1, 134.7, 133.5, 133.0, 128.2, 127.8, 127.6, 127.3(br), 126.5(br), 126.1, 125.8, 81.4, 81.0, 54.0, 53.9(br), 28.3, 28.2. Anal. Calcd for C₂₁H₂₈N₂O₄: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.82; H, 7.72; N, 7.51.

***N'*-[*(tert*-butoxy)carbonyl]-*N*-(1-phenylethyl)(*tert*-butoxy)carbohydrazide (**5k**)**.³ According to Method A, from 0.185 g (1 mmol) of (1-bromoethyl)benzene was obtained 0.257 g (77% yield) of **5k** as a white solid: mp 86.5-88.0 °C (lit.³ 87-88 °C); ¹H NMR (CDCl₃, 60 °C) δ 7.30-7.20 (m, 5H), 6.01 (br s, 1H), 5.41 (br m, 1H [this signal is a quartet, *J* = 7 Hz, at 60 MHz]), 1.52 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 9H), 1.43 (br s, 9H); ¹³C NMR (CDCl₃, 60 °C) δ 155.8, 154.8, 141.5, 128.4, 127.4(2C), 81.2, 80.9, 55.9(br), 28.3, 28.2(br), 17.0.

***N'*-[*(tert*-butoxy)carbonyl]-*N*-(pyridin-3-ylmethyl)(*tert*-butoxy)-carbohydrazide (**5m**)**. To 0.195 g (3 mmol) of Zn and 1.5 g K₂HPO₄ was added 1.5 mL H₂O and the contents stirred until the salt dissolved completely. A solution of 0.46 g (2 mmol) of **4** in 2 mL of THF was

added followed immediately by 0.253 g (1 mmol) of 3-(bromomethyl)pyridine•HBr. The contents were stirred to sufficiently mix the heterogenous mixture without splashing the contents unnecessarily. After stirring for 18 hours, the organic layer was removed. Fresh THF (2 mL) was added to the gelatinous white aqueous layer, the layers thoroughly mixed and the organic layer removed. This was repeated two additional times. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Chromatography (SiO₂ using 1:1 hexanes: ethyl acetate) afforded 91.4 mg (28% yield) of **5m** as a white solid: mp 133.4-134.2 °C; ¹H NMR (CDCl₃, 60 °C) δ 8.51 (d, *J* = 4.8 Hz, 1H), 7.63 (dd, *J* = 8.3, 6.8 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.15 (dd, *J* = 6.8, 4.8 Hz, 1H), 6.81 (br s, 1H), 4.76 (s, 2H), 1.49 (s, 18H); ¹³C NMR (CDCl₃, 60 °C) δ 157.6, 155.7, 155.1, 149.3, 136.5, 122.2, 122.0(br), 81.5, 81.0, 55.6(br), 28.3, 28.2. Anal. Calcd for C₁₆H₂₅N₃O₄: C, 59.42; H, 7.79; N, 12.99. Found: C, 59.30; H, 7.91; N, 12.78.

***N*-benzyl-*N'*-(ethoxycarbonyl)ethoxycarbohydrazide (6).**⁴ To 0.195 g (3 mmol) of Zn metal in 1 mL sat. aq. NH₄Cl solution was added 0.348 g (2 mmol) of diethyl azodicarboxylate. Stirring was begun and a solution of 0.171 g (1 mmol) benzyl bromide in 2 mL of THF was added via syringe. The reaction vessel was capped and the mixture allowed to stir until the yellow color of the azodicarboxylate was discharged (10 min). The reaction mixture was filtered through a plug of glass wool into a centrifuge tube. The organic layer was removed. The aqueous layer was washed 2 × 2 mL of THF. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Column chromatography on SiO₂ using a 1:1 mixture of hexanes: ethyl acetate as eluent afforded 0.180 g (68% yield) of **6** as a colorless viscous liquid: ¹H NMR (CDCl₃, 60 °C) δ 7.31-7.23 (m, 5H), 6.76 (br s, 1H), 4.65 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (CDCl₃, 60 °C) δ 156.3, 155.9, 136.6, 128.5(2C), 127.6, 62.5, 61.8, 53.8, 14.4, 14.3.

***N*-(1-phenylethyl)-*N'*-[(propan-2-yloxy)carbonyl](propan-2-yloxy)carbohydrazide (7).**⁵ To 0.195 g (3 mmol) of Zn metal in 1 mL sat. aq. NH₄Cl solution was added 0.404 g (2 mmol) of diisopropyl azodicarboxylate. Stirring was begun and a solution of 0.171 g (1 mmol) benzyl bromide in 2 mL of THF was added via syringe. The reaction vessel was capped and the mixture allowed to stir until the yellow color of the azodicarboxylate was discharged (30 min). The reaction mixture was filtered through a plug of glass wool into a centrifuge tube. The organic layer was removed. The aqueous layer was washed 2 × 2 mL of THF. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. Column chromatography on SiO₂ using a 4:1 mixture of hexanes: ethyl acetate as eluent afforded 0.286 g (97% yield) of **7** as a white solid: mp 90.0-90.5 °C; ¹H NMR (CDCl₃, 60 °C) δ 7.31-7.22 (m, 5H), 6.58 (br s, 1H), 4.96 (heptet, *J* = 6.0 Hz, 1H), 4.92 (heptet, *J* = 6 Hz, 1H), 4.64 (s, 2H), 1.24 (d, *J* = 6 Hz, 6H), 1.19 (d, *J* = 6 Hz, 6H); ¹³C NMR (CDCl₃, 60 °C) δ 155.9, 155.6, 136.8, 128.5(2C), 127.6, 70.2, 69.6, 53.8(br), 22.0, 21.8.

***N*-benzyl-*N'*-[(benzyloxy)carbonyl](benzyloxy)carbohydrazide (8).**⁶ To 0.195 g (3 mmol) of Zn metal in 1 mL sat. aq. NH₄Cl solution was added 0.596 g (2 mmol) of dibenzyl azodicarboxylate. Stirring was begun and a solution of 0.171 g (1 mmol) of benzyl bromide in 2 mL of THF was added via syringe. The reaction vessel was capped and the mixture allowed to stir until the yellow color of the azodicarboxylate was discharged (15 min). The reaction mixture was filtered through a plug of glass wool into a centrifuge tube. The organic layer was removed. The aqueous layer was washed 2 × 2 mL of THF. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Column chromatography on SiO₂ using a 3:1 mixture of hexanes: ethyl acetate as eluent afforded 0.278 g (71% yield) of **8** as a white solid: mp 79.5-80.5 °C (lit.⁶ 80-81 °C); ¹H NMR (CDCl₃, 60 °C) δ 7.26-7.21 (m, 15H), 6.78 (br s, 1H), 5.13 (s, 2H), 5.05 (s, 2H), 4.66 (s, 2H); ¹³C NMR (CDCl₃, 15 MHz) δ 156.1, 155.7, 136.1, 135.8, 135.6, 128.5, 128.2, 128.1, 128.0, 127.8, 68.2, 67.5,

53.8 [the 15 MHz spectral data is provided since the 100 MHz spectrum, even at 60 °C was still complex].

N'-[(*tert*-butoxy)carbonyl]-*N'*-(prop-2-en-1-yl)(*tert*-butoxy)carbohydrazide (**9**).⁷ To 0.195 g (3 mmol) of Zn metal in 1 mL sat. aq. NH₄Cl solution was added 0.23 g (1 mmol) of **4**. Stirring was begun and a solution of 0.24 g (2 mmol) allyl bromide in 2 mL of THF was added via syringe. The reaction vessel was capped and the mixture allowed to stir until the yellow color of the azodicarboxylate was discharged (15 min). The reaction mixture was filtered through a plug of glass wool into a centrifuge tube. The organic layer was removed. The aqueous layer was washed 2 × 2 mL of THF. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Column chromatography on SiO₂ using a 4:1 mixture of hexanes: ethyl acetate as eluent afforded 0.139 g (52% yield) of **9** as a white solid: mp 72.3-73.0 °C (lit.^{7a} 74-74.4 °C); ¹H NMR (CDCl₃, 60 °C) δ 6.45 (br s, 1H), 5.85 (ddt, *J* = 17.0, 10.4, 6.2 Hz, 1H), 5.17 (dm, *J* = 17.0 Hz, 1H), 5.14 (dm, *J* = 10.4 Hz, 1H), 4.04 (d, *J* = 6.2 Hz, 2H), 1.47 (s, 9H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 15 MHz) δ 155.2, 155.2, 133.3, 117.4, 81.2, 81.1, 52.9(br), 28.3(2C).

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^1H NMR Spectrum of Compound 5a (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5a (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5b (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5b (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5c (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5c (CDCl_3 , 60 $^\circ\text{C}$)

^1H NMR Spectrum of Compound 5d (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 5d (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5e (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5e (CDCl_3 , 60 $^\circ\text{C}$)

^1H NMR Spectrum of Compound 5f (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 5f (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5g (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5g (CDCl_3 , $60\text{ }^\circ\text{C}$)

^1H NMR Spectrum of Compound 5h (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5h (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5j (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 5j (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5k (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 5k (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 5m (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 5m (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 6 (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 6 (CDCl_3 , 60 $^\circ\text{C}$)

^1H NMR Spectrum of Compound 7 (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 7 (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 8 (CDCl_3 , 60 °C)

^{13}C NMR Spectrum of Compound 8 (CDCl_3 , 60 °C)

^1H NMR Spectrum of Compound 9 (CDCl_3 , 60 $^\circ\text{C}$)

^{13}C NMR Spectrum of Compound 9 (CDCl_3 , 60 $^\circ\text{C}$)