Manipulation of N, O Nucleophilicity: Efficient Formation of 4-N-Substituted 2,4-Dihydro-3H-1,2,4-Triazolin-3-ones

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Supporting Information

Experimental Data for Compounds

Analytical methods: All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Flash chromatography was carried out with EM science Silica gel 60 (neutral, 230-400 mesh). ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 500 NMR Spectrometer with chemical shifts reported in ppm relative to the residual deuterated solvent. HRMS was recorded on a Micromass QT of Ultima API US mass spectrometer by FAB. LCMS was recorded on Applied Biosystem API-150.

General procedure for the preparation of 1-formyl semicarbazides from corresponding amines (compounds 8, 17-23, and 33): Phosgene (5.0 eq., 15.0 mmol, 20% in toluene) was added dropwise to a vigorously stirring mixture of amine (3.0 mmol) in CH₂Cl₂ (30 mL) and saturated NaHCO₃ solution (30 mL) at 0 °C. The mixture was stirred at 0 °C for 3 hours before it was diluted with CH₂Cl₂ (50 mL) and the aqueous phase was separated. The organic phase was washed with cold NH₄Cl solution, brine, and dried over MgSO₄. Solvent was removed to about 5 mL under reduced pressure at room temperature. The residue was dissolved in CH₃CN (15 mL) and treated with NH₂NHCHO (3.0 eq., 9.0 mmol) at room temperature. The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with HCl (50 mL, 0.5 N). The aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), and dried over

MgSO₄. After filtration and concentration, the crude product was purified using flash column chromatography to give 1-formyl semicarbazide.

General procedure for ring closure of 1-formyl semicarbazides to form triazolinones (compounds 9, 24-30, and 34): TMSBr (10.0 eq., 10.0 mmol) was added to a stirring mixture of 1-formyl semicarbazide (1.0 mmol) and (NH₄)₂SO₄ (0.4 eq., 0.4 mmol) in HMDS (10 mL) at room temperature. The resulting reaction mixture was heated at 140 °C (bath temperature) for 30 hours before it was cooled down to room temperature. The system was diluted with EtOAc (25 mL) and washed with HCl (5 mL, 1.0 N). The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), and dried over MgSO₄. After filtration and concentration, the crude product was purified using flash column chromatography to give desired triazolinone.

1-formyl semicarbazide 8:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **8** (0.46 g, 67 %). ¹H NMR (500 MHz, CD₃OD) δ 8.04 (s, 1 H), 7.44 (d, *J* = 7.0 Hz, 2 H), 7.30 (t, *J* = 7.0 Hz, 2 H), 7.18 (t, *J* = 7.0 Hz, 1 H), 6.73 (br. s, 1 H), 1.65 (s, 6 H). ¹³C NMR (125 MHz, CD₃OD) δ 169.1, 162.1, 148.1, 128.2, 126.3, 124.9, 55.4, 29.4. HRMS (FAB+) calculated for C₁₁H₁₆N₃O₂ (M + H)⁺ 222.1243, found 222.1245.

1-formyl semicarbazide 17:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **17** (0.40 g, 59 %). ¹H NMR (500 MHz, CD₃OD) δ 8.08 (s, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.30 (s, 2 H), 3.78 (s, 3 H). ¹³C NMR (125 MHz, CD₃OD) δ 168.9, 162.3, 159.3, 131.7, 128.5, 113.8, 54.7, 43.1. HRMS (FAB+) calculated for C₁₀H₁₄N₃O₃ (M + H)⁺ 224.1035, found 224.1026.

1-formyl semicarbazide 18:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **18** (0.74 g, 91 %). ^1H NMR (500 MHz, CD_3OD) δ 8.04 (s, 1 H), 7.33-7.07 (m, 10 H), 6.07 (s, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 169.1, 162.3, 142.6, 128.6, 127.6, 127.4, 58.0. HRMS (FAB+) calculated for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 270.1243, found 270.1240.

1-formyl semicarbazide 19:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **19** (0.50 g, 57 %). ^1H NMR (500 MHz, CD_3OD) δ 8.07 (s, 1 H), 7.39-7.26 (m, 5 H), 4.60 (AB quart, J = 22.5, 12 Hz, 2 H), 3.64 (m, 1 H), 3.32 (m, 1 H), 2.12 (m, 1 H), 1.97 (m, 1 H), 1.75 (m, 1 H), 1.67 (m, 1 H), 1.33 (m, 4 H). ^{13}C NMR (125 MHz, CD_3OD) δ 169.0, 162.1, 139.3, 128.3, 127.9, 127.5, 80.5, 71.2, 53.8, 32.0, 30.8, 24.4, 23.9. HRMS (FAB+) calculated for $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 292.1661, found 292.1674.

1-formyl semicarbazide 20:

Flash chromatography (silica gel, EtOAc/MeOH = 5/1) afforded semicarbazide **20** (0.58 g, 89 %). ^1H NMR (500 MHz, CD_3OD) δ 8.05 (s, 1 H), 7.20 (dd, J = 5.5, 3.5 Hz, 2 H), 7.14 (dd, J = 5.5, 3.5 Hz, 2 H), 4.5 (m, 1 H), 3.23 (dd, J = 16.0, 7.5 Hz, 2 H), 2.85 (dd, J = 16.0, 6.5 Hz, 2 H). ^{13}C NMR (125 MHz, CD_3OD) δ 169.0, 162.3, 141.2, 126.7, 124.6, 51.9, 39.7. HRMS (FAB+) calculated for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 220.1086, found 220.1076.

1-formyl semicarbazide 21:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **21** (0.33 g, 50 %). ^1H NMR (500 MHz, CD_3OD) δ 8.09 (s, 1 H), 7.55-7.40 (m, 5 H), 6.07 (s, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 168.7, 162.2, 134.8, 129.1, 129.0, 127.0, 118.2, 45.1. MS (ESI, $\text{M} + \text{H}^+$) 219.1.

1-formyl semicarbazide 22:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **22** (0.54 g, 76 %). ^1H NMR (500 MHz, CD_3OD) δ 8.08 (s, 1 H), 7.29-7.20 (m, 5 H), 3.03 (s, 2 H), 1.29 (s, 6 H). ^{13}C NMR (125 MHz, CD_3OD) δ 169.2, 162.1, 138.5, 130.8, 128.0, 126.2, 53.3, 45.0, 27.0. HRMS (FAB+) calculated for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}^+$) 236.1399, found 236.1393.

1-formyl semicarbazide 23:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **23** (0.55 g, 87 %). ^1H NMR (500 MHz, CDCl_3) δ 9.53 (br. s, 1 H), 8.13 (s, 1 H), 8.09 (br. s, 1 H), 6.29 (br. s, 1 H), 2.49 (s, 1 H), 2.14 (m, 2 H), 1.64 (m, 7 H), 1.30 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 161.6, 86.4, 72.2, 51.6, 37.9, 52.7, 22.7. HRMS (FAB+) calculated for $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}^+$) 210.1243, found 210.1243.

1-acetyl semicarbazide 33:

Flash chromatography (silica gel, EtOAc/MeOH = 10/1) afforded semicarbazide **33** (0.66 g, 73 %). ^1H NMR (500 MHz, CD_3OD) δ 7.38 (d, $J = 7.5$ Hz, 2 H), 7.33 (t, $J = 7.5$ Hz, 2

H), 7.26 (dt, $J = 7.5, 2.5$ Hz, 1 H), 4.60 (AB quart, $J = 20, 12$ Hz, 2 H), 3.64 (m, 1 H), 3.30 (ddd, $J = 9.0, 9.0, 4.5$ Hz, 1 H), 2.10 (m, 1 H), 2.0 (s, 3 H), 1.99 (m, 1 H), 1.75 (m, 6 H). ^{13}C NMR (125 MHz, CD_3OD) δ 172.2, 159.6, 139.4, 128.3, 127.9, 127.5, 80.4, 71.1, 53.8, 31.8, 30.7, 24.4, 23.9, 19.6. MS (ESI, $\text{M} + \text{H}$) $^+$ 306.2.

Triazolinone 9:

Flash chromatography (silica gel, hexane/EtOAc = 1/3) afforded triazolinone **9** (0.132 g, 65 %). ^1H NMR (500 MHz, CDCl_3) δ 10.80 (br. s, 1 H), 7.40 (s, 1 H), 7.42-7.32 (m, 5 H), 2.00 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 144.2, 136.2, 129.2, 128.1, 125.5, 60.3, 28.6. HRMS (FAB $^+$) calculated for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}$ ($\text{M} + \text{H}$) $^+$ 204.1137, found 204.1129.

Triazolinone 24:

Flash chromatography (silica gel, hexane/EtOAc = 1/2) afforded triazolinone **24** (0.184 g, 90 %). ^1H NMR (500 MHz, CD_3OD) δ 7.75 (s, 1 H), 7.28 (d, $J = 9.0$ Hz, 2 H), 6.92 (d, $J = 8.5$ Hz, 2 H), 4.77 (s, 2 H), 3.79 (s, 3 H). ^{13}C NMR (125 MHz, CD_3OD) δ 160.1, 155.8, 138.1, 129.4, 128.4, 114.3, 54.7, 44.9. HRMS (FAB $^+$) calculated for $\text{C}_{10}\text{H}_{12}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 206.0930, found 206.0923.

Triazolinone 25:

Flash chromatography (silica gel, hexane/EtOAc = 1/1) afforded triazolinone **25** (0.203 g, 81 %). ^1H NMR (500 MHz, CD_3OD) δ 7.59 (s, 1 H), 7.40 (m, 6 H), 7.22 (d, $J = 7.0$ Hz, 4 H), 6.47 (s, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 155.4, 138.7, 137.1, 129.1, 128.5, 128.1, 60.2. HRMS (FAB $^+$) calculated for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}$ ($\text{M} + \text{H}$) $^+$ 252.1137, found 252.1139.

Triazolinone 26:

Flash chromatography (silica gel, hexane/EtOAc = 1/2) afforded triazolinone **26** (0.186 g, 68 %). ¹H NMR (500 MHz, CDCl₃) δ 11.04 (br. s, 1 H), 7.32 (t, *J* = 6.5 Hz, 2 H), 7.29 (s, 1 H), 7.26 (t, *J* = 7.5 Hz, 1 H), 7.19 (d, *J* = 6.5 Hz, 2 H), 4.51 (AB quart, *J* = 114.0, 12.0 Hz, 2 H), 3.86 (ddd, *J* = 12.5, 10.0, 4.5 Hz, 1 H), 3.65 (ddd, *J* = 10.0, 10.0, 4.5 Hz, 1 H), 2.34 (m, 1 H), 2.04 (m, 1 H), 1.86 (m, 3 H), 1.39 (m, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 155.9, 138.3, 136.7, 128.9, 128.2, 77.9, 71.0, 58.3, 31.3, 31.0, 25.3, 24.4. HRMS (FAB+) calculated for C₁₅H₂₀N₃O₂ (M + H)⁺ 274.1556, found 274.1552.

Triazolinone 27:

Flash chromatography (silica gel, hexane/EtOAc = 1/2) afforded triazolinone **27** (0.161 g, 80 %). ¹H NMR (500 MHz, CD₃OD) δ 7.58 (s, 1 H), 7.30 (dd, *J* = 5.5, 3.5 Hz, 2 H), 7.23 (dd, *J* = 5.5, 3.5 Hz, 2 H), 4.85 (m, 1 H), 3.43 (dd, *J* = 16.0, 7.0 Hz, 2 H), 3.20 (dd, *J* = 16.0, 5.5 Hz, 2 H). ¹³C NMR (125 MHz, CD₃OD) δ 155.5, 140.2, 136.0, 127.3, 124.7, 53.8, 38.6. HRMS (FAB+) calculated for C₁₁H₁₂N₃O (M + H)⁺ 202.0980, found 202.0975.

Triazolinone 28:

Flash chromatography (silica gel, hexane/EtOAc = 1/2) afforded triazolinone **28** (0.104 g, 60 %). ¹H NMR (500 MHz, CDCl₃) δ 10.59 (br. s, 1 H), 7.56-7.54 (m, 5 H), 7.48 (s, 1 H), 6.31 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 154.0, 134.7, 131.0, 130.3, 127.6, 115.3, 46.9. MS (ESI, M+H-CN)⁺ 174.1.

Triazolinone 29:

Flash chromatography (silica gel, hexane/EtOAc = 1/1) afforded triazolinone **29** (0.161 g, 74 %). ^1H NMR (500 MHz, CD_3OD) δ 7.38 (s, 1 H), 7.23 (m, 3 H), 7.03 (m, 2 H), 3.25 (s, 2 H), 1.58 (s, 3 H). ^{13}C NMR (125 MHz, CD_3OD) δ 155.8, 137.1, 136.7, 130.2, 128.2, 126.8, 58.5, 43.6, 25.6. HRMS (FAB+) calculated for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}$ ($\text{M} + \text{H}$) $^+$ 218.1293, found 218.1282.

Triazolinone 30:

Flash chromatography (silica gel, hexane/EtOAc = 1/1) afforded triazolinone **30** (0.147 g, 77 %). ^1H NMR (500 MHz, CDCl_3) δ 11.0 (br. s, 1 H), 7.85 (s, 1 H), 2.79 (s, 1 H), 2.52 (dt, J = 12.0, 9.5 Hz, 2 H), 2.05 (br. d, J = 12.0 Hz, 2 H), 1.84-1.73 (m, 5 H), 1.34 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 154.9, 136.4, 82.2, 77.1, 58.2, 35.3, 24.9, 23.5. HRMS (FAB+) calculated for $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}$ ($\text{M} + \text{H}$) $^+$ 192.1137, found 192.1134.

Triazolinone 34:

Flash chromatography (silica gel, hexane/EtOAc = 1/2) afforded triazolinone **34** (0.115 g, 40 %). ^1H NMR (500 MHz, CDCl_3) δ 7.32 (t, J = 7.5 Hz, 2 H), 7.26 (t, J = 7.5 Hz, 1 H), 7.16 (d, J = 7.5 Hz, 2 H), 4.47 (AB quart, J = 105.5, 11.5 Hz, 2 H), 4.11 (m, 1 H), 3.59 (m, 1 H), 2.54 (m, 1 H), 2.32 (br. d, J = 12.5 Hz, 1 H), 2.20 (s, 3 H), 1.85 (m, 3 H), 1.44-1.26 (m, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.0, 146.6, 138.8, 128.8, 128.0, 76.8, 71.8, 59.7, 32.1, 28.6, 25.6, 24.5, 12.8. HRMS (FAB+) calculated for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 288.1712, found 288.1714.