Synthesis of 1,5-diisopropyl substituted 6-oxoverdazyls.

Emily C. Paré[a], David J. R. Brook[a,b]*, Aaron Brieger[a], Mick Badik[a] and Marie Schinke[a]

[a] *Department of Chemistry and Biochemistry, University of Detroit Mercy, Detroit MI 48221*
Fax:313 993 1144; Tel: 313 993-2495; E-mail:brookd@udmercy.edu

[b] Current Address: Department of Chemistry, Santa Clara University, Santa Clara, CA 95053

Supplementary Material

2,4-Diisopropyl-6-(6-methylpyridin-2-yl)-1,2,4,5-tetrazinan-3-one (7b)

6-Methylpyridine-2-carboxaldehyde (2 mmol) gave 551mg (99%) of the corresponding tetrazane with m.p. 151-154 ˚C; (calcd for $C_{14}H_{23}N_5O$: C 60.62 H 8.36 N 25.25. found: C60.51 H 8.50 N 24.95); ν_{max}(NaCl plate)/cm^{-1} 3227 (N-H) 2969 (C-H) 1630 (C=O) 1599 1579; δ_H (300 MHz, $CDCl_3$) 1.0 (6H, d, J=6.6) 1.02 (6H, d, J=6.6), 2.47 (3H, s), 4.31 (1H, s) 4.60 (2H, septet, J=6.6), 7.10 (1H, d, J=8), 7.16 (1H, d, J=8), 7.57 (1H, t, J=8); δ_C (75 MHz, $CDCl_3$) 18.5, 19.5, 24.3, 47.8, 71.1, 120.6, 123.9, 137.5, 153.5, 153.7, 158.9; MS (electrospray) 278 (MH^+, 100%)

1,5-Diisopropyl-3-(6-methylpyridin-2-yl)-6-oxoverdazyl (8b)

2,4-Diisopropyl-6-(6-methylpyridin-2-yl)-1,2,4,5-tetrazinan-3-one (200 mg) was refluxed with with 1.5 mol eq. benzoquinone in 5 mL toluene and the resulting solution filtered and evaporated. Chromatography of the residue on silica gel eluting with 9:1 CH_2Cl_2/EtOAc followed by recrystallization from EtOH/H_2O gave the verdazyl as an orange crystalline solid (125 mg, 62%) with m.p. 112-113˚C; UV-vis (MeCN) 410, 450 nm(sh); ν_{max}(NaCl plate)/cm^{-1} 2975, 2927 (C-H), 1683 (C=O); MS (electrospray) 275(MH^+, 100%); HPLC under the conditions for **8a** above eluted the product at 7.8 min (96% pure by integration).

2,4-Diisopropyl-6-quinolin-2-yl-1,2,4,5-tetrazinan-3-one (7c)

Quinolin-2-carboxaldehyde (0.5 mmol) gave 84mg (54%) of the corresponding tetrazane with m.p. 148-150˚C (EtOH/H_2O); (found: C 64.56 H 7.33 N 21.99. calcd for $C_{17}H_{23}N_5O$•1/4 H_2O: C 64.23 H 7.45 N 22.03); ν_{max}(NaCl plate)/cm^{-1} 3232 (N-H), 3060 (C-H), 2970 (C-H), 2932 (C-H), 1619 (C=O) 1598 (C=N); δ_H (300 MHz, $CDCl_3$) 1.12 (6H, d, J=6.6), 1.15 (6H, d, J=6.6), 4.56 (3H, br s), 4.70 (2H, septet, J=6.6), 7.50 (1H, d, J=8.4), 7.56 (1H, t, J=8), 7.74 (1H, t, J=8), 7.84 (1H, d, J=8), 8.06 (1H, t, J=8) 8.21 (1H, d, J=8.4); δ_C (75MHz, $CDCl_3$) 18.6, 19.6, 47.8, 71.5, 121.3, 127.2, 127.9, 129.3, 130.2, 137.5, 147.6.3, 153.9, 154.7; MS (electrospray) 314 (MH^+, 100%)

1,5-Diisopropyl-3-(quinolin-2-yl)-6-oxoverdazyl (8c)

2,4-Diisopropyl-6-quinolin-2-yl-1,2,4,5-tetrazinan-3-one (63 mg) was refluxed with with 1.5 mol eq. benzoquinone in 2 mL toluene and the resulting solution filtered and evaporated. Chromatography of the residue on silica gel eluting with CH_2Cl_2 gave the verdazyl as an orange-brown crystalline solid (36 mg, 58%) with m.p. 113-114˚C; UV-vis (MeCN) 410 nm; ν_{max}(NaCl plate)/cm^{-1} 2926, 2855 (C-H), 1687 (C=O); MS (electrospray) 311(MH^+); HPLC under the conditions for **8a** above eluted the product at 10.4 min (96% pure by integration).

2,4-Diisopropyl-6-imidazol-2-yl-1,2,4,5-tetrazinan-3-one (7d)

Imidazole-2-carboxaldehyde (2.7 mmol) gave 643 mg (96%) of the corresponding tetrazane. Recrystallization from ethanol/water gave white blocky crystals with m.p. 270-273(dec); (found C 51.61, H 7.74, N 32.86. calcd for $C_{11}H_{20}N_6O$•1/4H_2O C 51.44 H 8.05 N 32.72); ν_{max}(NaCl plate)/cm^{-1} 3146 (N-H), 3086, 2920 (C-H)1577 (C=O); δ_H (300 MHz, dmso-d6) 1.00 (12H, d, J=6.6), 4.42 (3H, m), 5.08 (2H, d, J=11.8, exchanges with D_2O) 7.02 (2H, br s); δ_C (75 MHz, dmso-d6) 19.0, 19.9, 47.3, 67.2, 143.1, 154.0, 172.6; MS (electrospray) 253 (MH^+, 100%)

1,5-Diisopropyl-3-(imidazol-2-yl)-6-oxoverdazyl (8d)

Oxidation of 252 mg (1mmol) of 2,4-diisopropyl-6-imidazol-2-yl-1,2,4,5-tetrazinan-3-one with 164 mg (1.5 mmol) benzoquinone in 5 mL toluene gave a sticky red residue. Chromatography on silica gel eluting with 1:9 CH_2Cl_2/EtOAc followed by recrystallization from dichloromethane/heptane gave the verdazyl as a red crystalline solid (142 mg, 56%) with m.p. 192-195˚C (dec); UV-vis (MeCN) 420, 500 nm; ν_{max}(NaCl plate)/cm^{-1} 2925 (C-H), 1683 (C=O); MS (electrospray) 250 (MH^+, 100%); HPLC under the conditions for **8a** above eluted the product at 5.1 min (99% pure by integration).

2,4-Diisopropyl-6-(4-hydroxyphenyl)-1,2,4,5-tetrazinan-3-one (7e)

p-Hydroxybenzaldehyde (0.5 mmol) gave 101mg (73%) of the corresponding tetrazane with m.p. 208˚C (dec); (found C 58.57 H 7.88 N 19.28. calcd for $C_{14}H_{22}N_4O_2$•0.5 H_2O: C 58.52 H 8.07 N 19.50.); ν_{max}(NaCl plate)/cm^{-1} 3233 (N-H), 2979 (C-H) 1606 (C=C) 1588 (C=O); δ_H (300 MHz, dmso-d6) 1.01 (6H, d, J=6.6), 1.04 (6H, d, J=6.6), 4.22 (1H, t,) 4.48 (2H, septet, J=6.6), 4.99 (2H, d, J=10.4, exchanges with D_2O) 6.77 (2H, d, J=6.6), 7.33 (2H, d, J=6.6), 9.54 (1H, br s, exchanges w D_2O); δ_C(75 MHz, dmso-d6) δ 18.9, 20.1, 47.3, 72.0, 115.5, 127.5, 128.4, 154.0, 157.9; MS (electrospray) 279 (MH^+, 100%)

1,5-Diisopropyl-3-(4-hydroxyphenyl)-6-oxoverdazyl (8e)

Oxidation of 55 mg (0.2 mmol) of 6-(4-hydroxyphenyl)-2,4-diisopropyl-1,2,4,5-tetrazinan-3-one with 1.5 mol eq. benzoquinone in 2 mL toluene gave a red solid. Chromatography on silica gel eluting with CH_2Cl_2 followed by recrystallization from dichloromethane/heptane gave the verdazyl as a red crystalline solid (39 mg, 70%) with m.p. 188-190˚C; UV-vis (MeCN) 420, 520, 550(sh); ν_{max}(NaCl plate)/cm^{-1} 3312 (OH) 2924 (C-H), 1654 (C=O); MS (electrospray, negative ion mode) 274(M–H, 100%); HPLC under the conditions for **8a** above eluted the product at 12.8 min (97% pure by integration).

2,4-Diisopropyl-6-(2-Hydroxyphenyl)-1,2,4,5-tetrazinan-3-one (7f)

Salicylaldehyde (0.5 mmol) gave 98mg (71%) of the corresponding tetrazane with m.p. 200-203˚C (dec); (found: C 60.15 H 7.93 N 20.03. calcd for $C_{14}H_{22}N_4O_2$: C 60.41 H 7.97 N 20.13); ν_{max}(NaCl plate)/cm^{-1} 3225 (N-H), 2977 (C-H) 1611 (C=C) 1561 (C=O); δ_H (300 MHz, dmso-d6) 1.00 (6H, d, J=6.6), 1.01 (6H, d, J=6.6), 4.50 (3H, m), 4.99 (2H, d, J=11.28, exchanges with D_2O), 6.81 (td, 1H, J=7.5, 0.8), 6.86 (dd, 1H, J=7.5, 0.8), 7.17 (td 1H, J=7.5, 1.4), 7.37 (dd, J=7.5, 1.4), 9.78 (bs, 1H, exchanges w D_2O); δ_C (75 MHz, dmso-d6) 18.8, 20.0, 47.5, 68.2, 116.1, 119.6, 123.2, 127.6, 129.8, 154.0, 155.3; MS (electrospray) 279 (MH^+, 100%)

1,5-Diisopropyl-3-(2-hydroxyphenyl)-6-oxoverdazyl (8f)

2,4-Diisopropyl-6-(2-hydroxyphenyl)-1,2,4,5-tetrazinan-3-one (30 mg) was refluxed with with 1.5 mol eq. benzoquinone in 5 mL toluene and the resulting solution filtered and evaporated. Chromatography of the residue on silica gel eluting with CH_2Cl_2 gave the verdazyl as a fuschia crystalline solid (22 mg, 73%) with m.p. UV-vis (MeCN) 422, 523, 560 nm. ν_{max}(NaCl plate)/cm^{-1} 3158 (OH) 2978, 2929 (C-H), 1683 (C=O); MS (electrospray, solution in 0.1 N NaOH, negative ion mode) 571 (26%, $M^-{}_2Na^+$), 275(100, M^-); HPLC under the conditions for **8a** above eluted the product at 12.3 min (97% pure by integration).

2,4-Diisopropyl-6-(4'-biphenyl)-1,2,4,5-tetrazinan-3-one (7g)

Biphenyl-4-carboxaldehyde (0.5 mmol) gave 60 mg (36 %) of the corresponding tetrazane. Recrystallization from heptane gave a white solid with m.p. 199-200˚C; (found: C 70.58, H 7.49, N 16.55. calcd for $C_{20}H_{28}N_4O$: C 70.98 H 7.74 N 16.24); ν_{max}(NaCl plate)/cm^{-1} 3228 (N-H), 3054, 3031, 2970, 2933 (C-H), 2920 (C-H) 1701 (C=O), 1599 (C=C); δ_H (300 MHz, $CDCl_3$) δ 1.17 (6H, d, J=6.6), 1.18 (6H, d, J=6.6) 3.77 (2H, d, J=11.5, NH) 4.66 (1H, t, J=11.5), 4.72 (2H, septet, J=6.6) 7.36 (1H, m), 7.46 (2H, m), 7.59 (2H, m), 7.64 (4H, m); δ_C (75 MHz, $CDCl_3$) 18.5, 19.7, 47.9, 71.0, 126.7, 127.2, 127.5, 127.8, 129.0, 134.6, 140.5, 141.9, 154.4; MS (electrospray) 339 (MH^+ 100%)

1,5-Diisopropyl-3-(4'-biphenyl)-6-oxoverdazyl (8g)

Oxidation of 36 mg (0.1mmol) of 2,4-diisopropyl-6-(4'-biphenyl)-1,2,4,5-tetrazinan-3-one with 15 mg (0.15 mmol) benzoquinone in 3 mL refluxing toluene for 1h gave an orange red solution that was evaporated to give a red solid. Chromatography on silica gel eluting with CH_2Cl_2 followed by recrystallization from dichloromethane/heptane gave the verdazyl as a red crystalline solid (23 mg, 64%) with m.p. 175-176˚C; UV-vis (MeCN) 420, 500 nm. ν_{max}(NaCl plate)/cm^{-1} 2974, 2926 (C-H), 1665 (C=O); MS (electrospray) 336 (M^+, 100%); HPLC 150 mm C18 reverse phase column, eluting isocratically for 2 min with 70% acetonitrile/30% 0.1 M aqueous ammonium acetate (pH 6.95) followed by a gradient to 100% acetonitrile over 7.5 min and isocratic elution thereafter. Product elutes at 11.5 min (98% pure).