Supporting information

Beta-scission of the N-O bond in alkyl hydroxamate radicals: A fast radical trap

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Synthesis of the model compound 12

***tert*- Butyl 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxy)-propionate 7.** A solution of *tert*-butyl 2-bromo propionate **6** (5.1 ml, 30.9 mmole), N-hydroxyphthalimide **5** (4.6 g, 28.1 mmole) and Et_3N (5.9 ml, 42.2 mmole) in DMF (80 ml) was stirred at room temperature for 6.5 h. The mixture was filtered and the filtrate was partitioned between CH_2Cl_2 (2 x 90 ml) and H_2O (2 x 100 ml). The organic layer was washed with $NaHCO_3$ (75 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 25:75 EtOAc/hexane) to give the title compound **7** as a white solid (7.3 g, 89%): TLC R_f = 0.30 (silica, 25:75 EtOAc/hexane); ^{1}H NMR(200 MHz, $CDCl_3$) δ 7.84 (m, 2H, aromatic phthalimide), 7.78 (m, 2H, aromatic phthalimide), 4.80 (q, J = 6.8 Hz, 1H, C*H*COO), 1.61 (d, J = 6.8 Hz, 3H, *CH*$_3$CHCOO), 1.47 (s, 9H, -C(C*H*)$_3$).

***tert*-Butyl 2-(2,2-dimethyl-propionylaminooxy)-propionate 9.** Hydrazine monohydrate (950 µl, 19.5 mmole) was added to a stirred solution of **7** (1.4 g, 4.9 mmole) in methanol (15 ml) at room temperature. A white precipitate appeared after 5 min and the suspension was stirred for another 10 min and then concentrated under reduced pressure and the residue was partitioned between Et_2O (2 x 20 ml) and saturated $NaHCO_3$ (20 ml). The organic layer was concentrated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 (5 ml) and aqueous $NaHCO_3$ (410 mg, in 5 ml H_2O). Pivaloyl chloride (661 µl, 5.4 mmole) was added to the above stirred mixture at room temperature. The reaction mixture was quenched with H_2O (10 ml) after stirring for 1.5 h. The organic layer (10 ml) was washed with brine (10 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 25:85 EtOAc/hexane) to give the title compound **9** as a colorless oil (1.1 g, 95%): TLC R_f = 0.37 (silica, 30:70 EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.92 (br s, 1H, -N*H*), 4.44 (q, J = 7.0 Hz, 1H, C*H*COO), 1.49 (s, 9H, -OC(C*H*)$_3$), 1.46 (d, J = 7.0 Hz, 3H, -C*H*$_3$CHCOO), 1.19 (s, 9H, -OCC(C*H*)$_3$).

***tert*-Butyl 2-[(2,2-dimethyl-propionyl)-methyl-aminooxy]-propionate 10.** A solution of **9** (2.5 g, 10.4 mmole) and NaH (624 mg, 15.6 mmole, 60% in minenal oil) in anhydrous THF (30 ml) was stirred at 0°C for 20 min before adding CH_3I (2.6 ml, 41.6 mmole). The mixture was allowed to warm to room temperature and stirred for 2 days. The reaction was quenched with H_2O (1 ml) and EtOH (1 ml) and concentrated under reduced pressure. The residue was partitioned between Et_2O (50 ml) and H_2O (50 ml). The organic layer was washed with brine (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 15:85 EtOAc/hexane) to give the title compound **10** as a pale yellow oil (1.6 g, 60%): TLC R_f = 0.45 (silica, 25:75 EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.34 (q, J = 6.8 Hz, 1H, C*H*COO), 3.30 (s, 3H, -N*CH*$_3$), 1.49 (s, 9H, -OC(C*H*)$_3$), 1.45 (d, J = 6.8 Hz, 3H, -C*H*$_3$CHCOO), 1.26 (s, 9H, -OCC(C*H*)$_3$).

2-[(2,2-dimethyl-propionyl)-methyl-aminooxy]-propionic acid 11. Trifluoroacetic acid (691 µl, 9 mmole) was added to a stirred solution of **10** (58 mg, 0.22 mmole) in CH_2Cl_2 (5 ml) at 0°C. The mixture was stirred at 0°C for 2 h. The mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (10

ml) and saturated $NaHCO_3$ (10 ml). The aqueous layer was acidified with concentrated hydrochloric acid to pH< 2.0 at room temperature and extracted with EtOAc (10 ml). The organic layer was washed with brine (10 ml), dried ($MgSO_4$) and evaporated to give the title compound **11** as a colorless oil (60 mg, 100%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.42 (q, J = 7.0 Hz, 1H, C*H*COO), 3.54 (s, 3H, -N*CH*$_3$), 1.61 (d, J = 7.0 Hz, 3H, -C*H*$_3$CHCOO), 1.31 (s, 9H, -OCC(C*H*)$_3$).

Photolysis of the model compound 12

Tributylphosphine (411 ml, 1.6 mmole) was added under argon to a stirred suspension of **11** (304 mg, 1.5 mmole, 0.04 M) and 2,2'-dithiobispyridine-1,1'-dioxide (415 mg, 1.6 mmole) in dry CH_2Cl_2 (12 ml) in a dry flask wrapped with aluminum foil. After stirring at room temperature for 45 min, *tert*-butyl thiol (1.67 ml, 15.0 mmole, 0.3 M) was added to the reaction mixture. The mixture was irradiated with two 150w tungsten lamps at ice-bath temperature for 1 h. The solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 30:70 acetone/hexane). t-Butyl 2-pyridyl disulfide **15** was separated as a yellow oil (32 mg, 11%): ^{1}H NMR (200 MHz, $CDCl_3$) d 8.44 (m, 1H, -py), 7.80 (m , 1H, -py), 7.63 (m, 1H, -py), 7.06 (m, 1H, -py), 1.35 (s, 9H, -C(*CH*$_3$)$_3$); N,2,2-trimethylpropionamide **19** corresponding to the N-O scission product was separated as a yellow solid (140 mg, 82%): ^{1}H NMR (200 MHz, $CDCl_3$) d 5.65 (br s, 1H, -N*H*), 2.81 (d, 3H, -NHC*H*$_3$), 1.20 (s, 9H, -C(*CH*$_3$)$_3$); MS (EI) m/z 115; MS (CI) m/z [M+H$^+$] 116.

Synthesis of the cyclopropyl based model 20

2-Cyclopropyl-2-oxoacetate 27. A solution of potassium permanganate (10.2 g, 0.06 mole) in H_2O (1000 ml) was added dropwise to a stirred mixture of cyclopropyl methyl ketone **26** (22.9 g, 0.27 mole) in water (100 ml) containing Na_2CO_3 (0.86 g, 0.008 mole) at 50°C. The mixture was stirred at room temperature for 24 h, methanol (500 ml) was added to the mixture which was then filtered and concentrated under reduced pressure to gave the potassium salt of the title compound (30.4 g, 73% yield). This was converted to the free acid by adding concentrated hydrochloric acid to the aqueous potassium salt solution at 0°C until pH=3.0, the free acid was extracted with CH_2Cl_2 (11 x 50 ml), washed with brine (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled using a water aspirator to give the title compound **27** as a colorless oil: b.p. 72-80^{0}C/20 mm; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.25 (br s), 2.80-2.95 (m), 1.50-1.70 (m), 0.8-1.3 (m).

***tert*-Butyl 2-cyclopropyl-2-oxoacetate 28**. A solution of 2 M $(COCl)_2$ in CH_2Cl_2 (9 ml, 18 mmole) and 1 drop of anhydrous DMF was added to a stirred solution of **27** (1.72 g, 15 mmole) in anhydrous CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 2.5 h until evolution of gas ceased. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (5 ml) and was added via cannula to a stirred solution of anhydrous pyridine (2.2 ml, 27 mmole) and t-butanol (1.6 ml, 16 mmole) in anhydrous CH_2Cl_2 (5 ml). The reaction mixture was stirred at room temperature for 20 hr. The resulting mixture was partitioned between CH_2Cl_2 (25 ml) and H_2O (25 ml), the organic phase was washed with brine (25 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (silica, 5:95 EtOAc/hexane) to give the title compound **28** as a yellow oil (1.64 g, 64%): TLC R_f = 0.27 (silica, 10:90 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (m, 1H, -C*H*CO), 1.56 (s, 9H, -C(C*H*)$_3$),1.20 (m, 2H, -C*H*$_2$), 1.11 (m, 2H, -C*H'*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 160.8, 84.0, 28.0, 18.0, 14.0.

***tert*-Butyl 2-cyclopropyl-2-hydroxyacetate 29.** Methanolic hydrogen chloride (2 M) was added dropwise to a stirred solution of **28** (89.4 mg, 0.52 mmole), sodium cyanoborohydride (26.4 mg, 0.42 mmole) and a trace of bromocresol green (pH 3.8-5.4) in methanol (5 ml) to maintain the yellow color. After stirring at room temperature for 15 min, the solution was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (10 ml) and H_2O (10 ml), the organic phase was washed with brine (10 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 15:85 EtOAc/hexane) to give the title compound **29** as a colorless oil (68.1 mg, 75%): TLC R_f = 0.28 (silica, 15:85 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, J = 6.4 Hz, 1H, -C*H*(OH)), 2.73 (br s, 1H, -CH(O*H*)), 1.51(s, 9H, -C(C*H*)$_3$), 1.08 (m, 1H, -C*H*CH(OH)), 0.50 (m, 3H, -C*H'*$_2$C*H$_a$*CH$_b$), 0.41 (m, 3H, -CH'$_2$CH$_a$C*H$_b$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 82.5, 72.4, 28.3, 145.0, 1.7, 1.4.

***tert*-Butyl cyclopropyl-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxy)-acetate 30.** A solution of diethyl azodicarboxylate (453 µl, 2.9 mmole) in anhydrous THF (5 ml) was added via cannula to a stirred solution of **29** (413 mg, 2.4 mmole), N-hydroxyphthalimide (430.4 mg, 2.6 mmole) and triphenylphosphine (755 mg, 2.9 mmole) in anhydrous THF (10 ml) at room temperature. The resulting yellow solution was stirred at room temperature for 23 h. The mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 ml) and H_2O (40 ml). The organic layer was washed with brine (40 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 20:80 EtOAc/hexane) to give the title compound **30** as a colorless oil (541 mg, 71%): TLC R_f = 0.25 (silica, 20:80 EtOAc/hexane); ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.82 (m, 2H, aromatic phthalimide), 7.77 (m, 2H, aromatic phthalimide), 3.97 (d, J = 9.5 Hz, 1H, C*H*COO), 1.49 (m, 1H, *CH*CHCOO), 1.49 (s, 9H, -C(C*H*)$_3$), 0.69 (m, 3H, C*H$_a$*H$_b$C*H'*$_2$), 0.53 (m, 1H, CH$_a$*H$_b$*CH'$_2$); ^{13}C NMR(100 MHz, $CDCl_3$) δ 167.9, 163.4, 135.1, 134.7, 129.0, 124.3, 123.7, 82.7, 68.2, 28.1, 25.8, 12.0, 4.6, 2.4.

***tert*-Butyl cyclopropyl-(2,2-dimethyl-propionylaminooxy)-acetate 32.** $NH_2NH_2.H_2O$ (318 µl, 6.5 mmole) was added to a stirred solution of **30** (520 mg, 1.6 mmole) in methanol (12 ml) at room temperature. The resulting pale yellow solution was stirred at that temperature for 15 min. The mixture was concentrated under reduced pressure and the residue was partitioned between Et_2O (2 x 20 ml) and saturated $NaHCO_3$ (40 ml). The organic layer was concentrated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 (10 ml) and aqueous $NaHCO_3$ (138 mg, in 10 ml H_2O). Pivaloyl chloride (212 µl, 1.7 mmole) was added to the above stirred mixture at room temperature. The reaction mixture was stirred for 3 h before it was quenched with H_2O (40 ml). The organic layer (40 ml) was washed with brine (40 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 20:80 EtOAc/hexane) to give the title compound **32** as a colorless oil (325 mg, 73%): TLC R_f = 0.18 (silica, 15:85 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72(br s, 1H, -N*H*), 3.77 (d, J = 8.8 Hz, 1H, C*H*COO), 1.49 (s, 9H, -OC(C*H*)$_3$), 1.16 (s, 9H, -OCC(C*H*)$_3$), 1.15 (m, 1H, -C*H*CHCOO), 0.67 (m, 3H, C*H$_a$*H$_b$C*H'*$_2$), 0.56 (m, 1H, CH$_a$*H$_b$*CH'$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 170.8, 87.2, 82.4, 38.2, 28.3, 27.4, 12.0, 4.0, 3.0.

***tert*-Butyl cyclopropyl-(2,2-dimethyl-prpionyl)-methyl-aminooxy)-acetate 33.** Methyl iodide (290 µl, 4.7 mmole) was added to a stirred solution of **32** (316 mg, 1.2 mmole) and NaH (40 mg, 1.7 mmole) in anhydrous DMF (12 ml) at room temperature. The reaction was quenched after 2 h with H_2O (3 x 30 ml) and extracted with Et_2O (2 x 30 ml). The organic layer was washed with brine (30 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column

chromatography (silica, 15:85 EtOAc/hexane) to give the title compound **33** as a colorless oil (186 mg, 56%): TLC R_f = 0.26 (silica, 15:85 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, J= 9.2 Hz, 1H, C*H*COO), 3.35 (s, 3H, -N*CH*$_3$), 1.49 (s, 9H, -OC(C*H*)$_3$), 1.26 (s, 9H, -OCC(C*H*)$_3$), 1.21(m, 1H, -C*H*CHCOO), 0.73 (m, 1H, C*H*$_a$H$_b$CH'$_2$), 0.62 (m, 2H, CH$_a$H$_b$C*H*'$_2$), 0.51 (m, 1H, CH$_a$*H*$_b$CH'$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 169.9, 87.3, 82.0, 39.6, 39.3, 28.2, 27.6, 12.4, 5.2, 2.1.

Cyclopropyl-[2,2-dimethyl-propionyl)-methyl-aminooxy]-acetic acid 34. Trifluoroacetic acid (0.99 ml, 12.9 mmole) was added to a stirred solution of **33** (37 mg, 0.13 mmole) in CH_2Cl_2 (5 ml) at 0°C. The mixture was stirred at 0°C for 3 h. The mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (10 ml) and saturated $NaHCO_3$ (10 ml). The aqueous phase was acidified with concentrated hydrochloric acid to pH< 2.0 at room temperature and extracted with EtOAc (2 x 10 ml). The organic layer was washed with brine (10 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound **34** as a colorless oil (28 mg, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br s, 1H, -COO*H*), 3.72 (d, J = 8.8 Hz, 1H, C*H*COOH), 3.51 (s, 3H, -N*CH*$_3$), 1.27 (s, 9H, -OCC(C*H*)$_3$), 0.74 (m, 2H, CH$_a$H$_b$C*H*'$_2$), 0.56 (m, 1H, C*H*$_a$H$_b$CH'$_2$), 0.49 (m, 1H, CH$_a$*H*$_b$CH'$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 172.0, 88.8, 41.1, 38.4, 27.6, 27.2, 112.4, 4.4, 3.4.

Photolysis of the cyclopropyl based model 20

Triphenylphosphine (12.8 mg, 0.05mmole, 1.1 equiv) was added under argon to a stirred suspension of **34** (10.2 mg, 0.04 mmole, 0.03 M) and 2,2'-dithiobispyridine-1,1'-dioxide (12.3 mg, 0.05 mmole) in dry CH_2Cl_2 (1.5 ml) in a dry flask wrapped with aluminum foil. After stirring at room temperature for 3 h, *tert*-butyl thiol (50 ml, 0.44 mmole, 0.3 M) was added to the reaction mixture. The mixture was irradiated with two 150w tungsten lamps at ice-bath temperature for 1 hr 50 min. The solution was concentrated under reduced pressure and dissolved in CH_2Cl_2 (15ml) and saturated Na_2CO_3(10ml), the organic layer was washed with brine (10ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 30:70 acetone/hexane). t-Butyl 2-pyridyl disulfide **15** was separated as a colorless solid (5.6 mg, 63%): ^{1}H NMR (200 MHz, $CDCl_3$) d 8.44 (m, 1H, -py), 7.80 (m , 1H, -py), 7.63 (m, 1H, -py), 7.06 (m, 1H, -py), 1.35 (s, 9H, -C(*CH*$_3$)$_3$); N,2,2-trimethylpropionamide **19** corresponding to the N-O scission product was separated as a colorless oil (6.8 mg, 84%): ^{1}H NMR (200 MHz, $CDCl_3$) d 5.65 (br s, 1H, -N*H*), 2.81 (d, 3H, -NHC*H*$_3$), 1.20 (s, 9H, -C(*CH*$_3$)$_3$); MS (EI) 115. No evidence (^{1}H NMR and GC/MS) for the formation of compound **25** derived from the cyclopropyl ring opening or compound **22** was found.

When the photolysis of **20** was run in CD_2Cl_2, direct ^{1}H NMR and GC/MS analysis of the photolysis mixture confirmed the identity of **23** and demonstrated the absence of **22** and **25**.