

Supporting Information

Two Useful Photolabile Surfaces for Solid Phase Synthesis

Troy D. Ryba and Patrick G. Harran*

Department of Biochemistry

University of Texas Southwestern Medical Center at Dallas

Dallas, TX 75390-9038

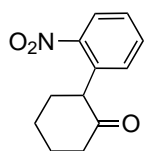
Experimental

General. All operations involving moisture and / or oxygen-sensitive materials were conducted under an atmosphere of dry nitrogen in pre-dried glassware. Unless otherwise noted, materials were obtained from commercially available sources and used without purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and toluene was distilled from sodium, both under a nitrogen atmosphere.

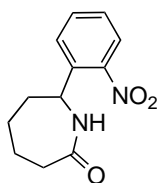
Flash chromatography was performed on E. Merck silica gel 60 (240-400 mesh) according to the protocol of Still, Kahn and Mitra (*J. Org. Chem.* **1978**, *43*, 2923) and thin layer chromatography was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF₂₅₄, 0.25mm). Spots were visualized with long-wave ultraviolet light followed by staining with either potassium permanganate or ceric ammonium molybdate solution.

Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian Inova-400 or Mercury-300 magnetic resonance spectrometer. ^1H NMR chemical shifts are given in parts per million (δ) downfield from tetramethylsilane using the residual solvent signal ($\text{CHCl}_3 = \delta$ 7.27) as an internal standard. ^1H NMR information is tabulated in the following format: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (s) (J) in hertz.

Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrum 1000 using samples prepared as thin films between salt plates. Electrospray-ionization mass spectra (LRMS) were measured at the biopolymers facility, Howard Hughes Medical Institute and Department of Biochemistry, UT Southwestern Medical Center. Combustion analyses were performed by Desert Analytics, Tucson, AZ. Melting points were measured on a Fisher-Johns 12-144 apparatus and are uncorrected.

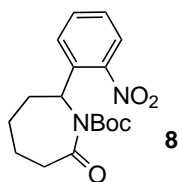


2-(2'-nitrophenyl)cyclohexanone 5: To a stirred solution of 85% nitronium tetrafluoroborate (Aldrich Chem. Co., 1.92 g, 12.3 mmol) in anhydrous CH_3NO_2 (25.5 mL) is added solid 2-phenylcyclohexanone (2.0 g, 11.2 mmol) at 0°C . The resultant indigo solution is stirred at 0°C for 30 min, warmed to rt over 30 min, and quenched with sat. NaHCO_3 . The mixture is partitioned between EtOAc and H_2O , the organic layer washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Flash chromatography on silica gel (10% EtOAc / hexanes) affords pure **5** (1.14 g, 46%) along with a more polar *para* isomer (300 mg, 12%). **5**: R_f = 0.30 (30% EtOAc / hexanes). m.p. $67-69^\circ\text{C}$. IR (film): 856, 1127, 1350, 1524, 1714 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 1.80 (2H, m), 2.05 (2H, m), 2.17 (1H, m), 2.35 (1H, m), 2.51 (2H, m), 4.27 (1H, dd, $J = 5.2, 12.3$), 7.18 (1H, dd, $J = 1.5, 7.8$), 7.39 (1H, td, $J = 1.5, 7.5, 8.7$), 7.57 (1H, td, $J = 1.5, 7.5, 9.0$), 7.95 (1H, dd, $J = 1.5, 8.4$). ^{13}C NMR (75 MHz, CDCl_3): δ 25.7, 27.4, 33.9, 42.3, 53.6, 124.9, 127.9, 130.3, 133.2, 134.1, 149.4, 208.1. Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.52; H, 5.88; N, 6.29.

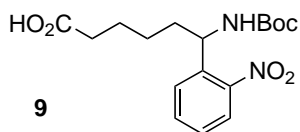


7-(2'-nitrophenyl)caprolactam (7): To a stirred solution of **5** (1.50 g, 6.8 mmol) in toluene (45 mL) at 0°C is added concentrated H_2SO_4 (7.7 mL, 150 mmol). NaN_3 (1.33 g, 20.5 mmol) is added in portions and the resultant biphasic mixture stirred vigorously at 0°C for 30 min. After warming to rt over 20 min, the mixture is diluted with EtOAc, neutralized with sat. NaHCO_3 , washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel

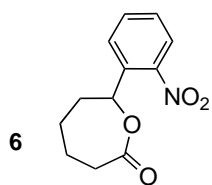
(50% EtOAc / hexanes) affords recovered **5** (150 mg) and **7** (1.59 g, 65% - 73% based on recovered **5**) as a pale yellow solid. **7**: R_f = 0.27 (EtOAc). m.p. = 180-182°C. IR (film): 856, 1349, 1519, 1653 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 1.80 (4H, m), 2.08 (2H, m), 2.58 (2H, dd, J = 3.0, 7.8), 5.04 (1H, dd, 3.6, 9.6), 5.66 (1H, br s), 7.47 (1H, td, J = 1.8, 6.9, 9.9), 7.58 (1H, dd, J = 1.8, 7.8), 7.66 (1H, td, J = 1.2, 7.8, 8.4), 7.87 (1H, dd, 1.5, 8.4). ^{13}C NMR (75 MHz, CDCl_3): δ 20.5, 27.3, 34.5, 35.2, 50.4, 97.6, 122.3, 124.7, 126.5, 131.3, 134.2, 174.9.



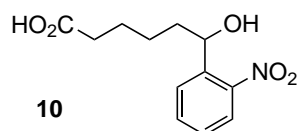
N-tert-butoxycarbonyl-7-(2'-nitrophenyl)caprolactam (8): To a solution of amide **7** (1.28 g, 5.44 mmol) in dry THF (22 mL) is added solid DMAP (997 mg, 8.16 mmol) followed by di-*tert*-butyldicarbonate (3.57 g, 16.3 mmol) via syringe. The result homogenous solution is stirred at rt for 3h, diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Flash chromatography on silica gel (30% EtOAc / hexanes) affords **8** (1.66 g, 91%) as a light yellow solid. **8**: R_f = 0.38 (30% EtOAc / hexanes). m.p. 100-105°C. IR (film): 860, 1347, 1528, 1708, 1730 cm^{-1} . ^1H NMR (300MHz, CDCl_3): δ 1.23 (9H, s), 1.83 (5H, m), 2.22 (1H, m), 2.63 (1H, m), 2.81 (1H, m), 5.60 (1H, dd, J = 3.0, 9.9), 7.38 (1H, td, J = 1.5, 8.1, 8.7), 7.58 (1H, td, J = 1.2, 7.5, 9.0), 7.72 (1H, dd, J = 1.5, 8.1), 7.89 (1H, dd, J = 1.5, 8.4). ^{13}C NMR (75 MHz, CDCl_3): δ 22.2, 25.3, 28.0, 31.7, 38.7, 55.9, 82.7, 124.8, 128.0, 128.1, 133.7, 138.9, 148.1, 152.2, 179.5. Anal. Calcd. For $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 61.11; H, 6.66; N, 8.46.



6-(2'-nitrophenyl)-6-(N-tert-butoxycarbonyl)amino caproic acid (9): Solid LiOH monohydrate (646 mg, 8.62 mmol) is added to a solution of **8** (1.31 g, 3.92 mmol) in 2:1 THF / H_2O (6 mL). The resultant solution is warmed to 45°C and stirred for 4h. After cooling to rt, the mixture is partitioned between Et_2O and H_2O and the organic layer separated. The aqueous layer is neutralized with 10% aqueous HCl and extracted with EtOAc (3 x). The combined extracts are washed with H_2O , brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Recrystallization from hot H_2O affords **9** (1.10 g, 82%) as white needles. **9**: R_f = 0.20 (50% EtOAc / hexanes) m.p.: 129-135°C. Spectroscopic data is more conveniently obtained for a derived (CH_2N_2 , Et_2O) methyl ester: IR (film): 859, 1365, 1526, 1701 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): 1.21 (2H, br s), 1.40 (9H, br s), 1.68 (2H, m), 1.85 (2H, m), 2.33 (2H, t, J = 7.2, 14.4), 3.64 (3H, s), 4.92 (1H, br s, NH), 5.11 (1H, br s), 7.36 (1H, td, J = 1.5, 7.8, 8.7), 7.47 (2H, br d, J = 7.5), 7.56 (1H, td, J = 1.5, 7.8, 8.4), 7.86 (2H, br d, J = 7.8). ^{13}C NMR (75 MHz, CDCl_3): δ 24.7, 26.3, 28.6, 34.0, 36.1, 51.8, 52.1, 77.4, 80.1, 125.2, 128.0, 128.7, 133.4, 148.6, 155.2, 174.0. LRMS (positive electrospray) Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_6$: $[\text{M} + \text{H}]^+$ 367.4. Found: 367.1.



7-(2'-nitrophenyl)caprolactone (6): To a solution of **5** (1.10 g, 5.03 mmol) in anhydrous CH_2Cl_2 (16.7 mL) are added solid Na_2HPO_4 (928 mg, 6.54 mmol) and *m*-CPBA (57-86% reagent, 2.90 g) successively at rt. The resultant white slurry is mixed vigorously for 4h and diluted with CH_2Cl_2 (10 mL). Amine-presenting polystyrene resin (PS-DIEA, 1.35 g, 3.83 mmol/g, Argonaut Technologies) is added and stirring continued until the organic phase clears (~ 30 min). The mixture is filtered and concentrated *in vacuo*. Flash chromatography on silica gel (30% EtOAc / hexanes) affords **6** (1.10 g, 99 %) as a white solid. **6**: R_f = 0.28 (30% EtOAc / hexanes). m.p. 97-99°C. IR (film): 857, 1346, 1525, 1736 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 1.94 (6H, m), 2.79 (2H, dd, J = 2.1, 9.3), 5.96 (1H, d, J = 8.4), 7.46 (1H, td, J = 1.5, 7.8, 9.0), 7.67 (1H, td, J = 1.2, 7.5, 9.0), 7.94 (1H, dd, J = 1.2, 7.8), 8.04 (1H, dd, J = 1.2, 8.4). ^{13}C NMR (75 MHz, CDCl_3): δ 23.1, 28.5, 35.0, 38.2, 77.1, 124.9, 128.1, 128.8, 134.3, 136.9, 146.4, 174.4. LRMS (positive electrospray) Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_4$: $[\text{M} + \text{H}]^+$ 235.2. Found: 235.0.



6-hydroxy-6-(2'-nitrophenyl)caproic acid (10): To a solution of **6** (400 mg, 1.78 mmol) in 1:1 THF / H₂O (2.4 mL) is added solid LiOH monohydrate (147 mg, 1.96 mmol) and the mixture is heated at 40°C for 12h. After cooling to rt, 10 mL water is added and the solution washed with Et₂O (1 x). The aqueous layer is acidified to pH = 5 with 10% aqueous HCl and extracted with EtOAc (3 x). The combined washes are concentrated in *in vacuo* to afford **10** (402 mg, 93%) as a light yellow oil. This material is used without additional purification. **10**: R_f = 0.15 (50% EtOAc / hexanes). IR (film): 856, 1347, 1525, 1706, 3500 (br) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 1.70 (6H, m), 2.37 (2H, dd, J= 2.1, 7.5), 5.26 (1H, dd, J= 3.6, 8.1), 7.41 (1H, td, J= 1.5, 7.5, 9.0) 7.63 (1H, td, J= 1.2, 7.2, 9.0), 7.79 (1H, dd, 1.2, 7.8), 7.89 (1H, dd, 1.2, 8.1). ¹³C NMR (75 MHz, CDCl₃): δ 26.3, 27.6, 35.9, 39.8, 71.1, 126.3, 130.0, 130.1, 135.5, 142.1, 149.7, 181.6.

