Michael Addition of Amines and Thiols to Dehydroalanine Amides: A Remarkable Rate Acceleration in Water

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Experimental Procedures

General Information: Unless otherwise noted all the reagents were used as purchased. The ^1H NMR spectra were recorded at 300 or 500 MHz and the ^{13}C NMR spectra were recorded at 125.7 MHz. Chemical shifts are reported in ppm relative to internal reference. High-resolution mass was determined using ESI technique. Analytical HPLC was performed using YMC-C₁₈ 4.6 x 50 mm 5 μm Xterra column with 4 min linear gradient from 90:10 to 10:90 Water:CH₃OH containing 0.1% TFA at a flow rate of 4 mL/min with UV detection at 220 nm. Reverse phase MPLC purifications were performed using C₁₈ reverse phase material (YMC Gel ODS-A, S-75 μm) which was packed in a Michel-Miller column. The mobile phase was pumped through the packed Michel-Miller column using an FMI Lab Pump at system pressures generally within the range of 20-80 psi. Typical eluents used for MPLC include mixtures of methanol and water in the presence of trace amount of HCl, or Et₃N.

2-Acetylamino-N-[2-(4-hydroxy-phenyl)-ethyl]-acrylamide (1a): To a stirred solution of 2-acetylamino-acrylic acid (2.582 g, 20.0 mmol), tyramine (2.881 g, 21 mmol), HOBt (0.27 g, 2 mmol) and N,N-diisopropylethylamine (DIEA, 3.5 mL, 20 mmol) in DMF (60 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 7.67 g, 40 mmol) in small portions. The resulting reaction mixture was stirred overnight (16 h), concentrated and purified by flash chromatography on silica gel column using CH₂Cl₂, and 2-5% MeOH/CH₂Cl₂. The fractions containing **1a** were combined and concentrated to afford white solid (2.99 g, 60%). ^1H NMR (500 MHz, DMSO-d₆) δ : 9.17 (1H, s), 9.02 (1H, s), 8.36 (1H, t, J = 5.5 Hz), 6.99 (2H, d, J = 8.2 Hz), 6.67 (2H, d, J = 8.2 Hz), 6.01 (1H, s), 5.31 (1H, s), 3.30-3.26 (2H, m), 2.65 (2H, t, J = 7.5 Hz), 2.00 (3H, s). ^{13}C NMR (125.77 MHz, DMSO-d₆) δ : 168.9, 163.7, 155.4, 135.9, 129.4, 114.9, 101.9, 40.9, 33.9, 23.7. HRMS calcd for C₁₃H₁₅N₂O₃ (M - H): 247.1086; found: 247.1089. Anal. calcd for C₁₃H₁₆N₂O₃: C 62.89, H 6.49, N 11.28; found: C 62.64, H 6.55, N 11.21.

(2-Acetylamino-acryloylamino)-acetic acid (1b): A solution of 2-acetylamino-acrylic acid (3.701g, 28.7 mmol) and glycine *tert*-butyl ester hydrochloride (4.002g, 23.9 mmol) in THF (200 mL) was treated successively with 4-methylmorpholine (11.0 mL, 100 mmol) and isobutyl chloroformate (4.1mL, 31.5 mmol) at room temperature. The reaction was stirred overnight, insoluble salts were removed by filtration, and the filtrate was dried in vacuum. The residue was taken up in ethyl acetate (100 mL) and washed with 1.0 N HCl (100 mL) followed by water (100 mL) and brine (100 mL). The crude product was purified by flash silica gel column chromatography (CH₂Cl₂, then 5% MeOH in CH₂Cl₂) to give the (2-Acetylamino-acryloylamino)-acetic acid *tert*-butyl ester (2.96 g, 51%) as a pale yellow solid. ^1H NMR (300MHz, CDCl₃) δ : 8.01 (1H, br s), 6.63 (1H, br s), 6.49 (1H, s), 5.28 (1H, d, J = 2.8 Hz), 3.98 (2H, d, J = 4.9 Hz), 2.10 (3H, s), 1.48 (9H, s).

A suspension of above *tert*-butyl ester (2.96 g, 12.2 mmol) in CH₂Cl₂ (25 mL) was treated with trifluoroacetic acid (TFA, 25 mL) and stirred for 30 minutes at ambient temperature. The reaction mixture was concentrated by rotary evaporator and triturated with ether to give the crude product (1.99 g, 10.7 mmol, 87.6%) as a yellow solid. The solid residue was triturated with hot methanol (60 °C) to give 1.09 g (48%) of **1b** as a white solid. A second crop was recovered (0.65 g, 28.6%). ^1H NMR (300MHz, DMSO-d₆) δ : 12.60

(1H, br s), 9.03 (1H, s), 8.66 (1H, t, $J = 5.9$ Hz), 6.10 (1H, s), 5.44 (1H, s), 3.81 (2H, d, $J = 5.8$ Hz), 2.01 (3H, s).

2-Acetylamino-N,N-diethyl-acrylamide (1c): To a stirred solution of 2-acetylaminoacrylic acid (1.2912 g, 10 mmol) in THF (100 mL) was added successively 4-methylmorpholine (1.21 mL, 11 mmol), isobutyl chloroformate (1.43 mL, 11 mmol), and diethylamine (1.14 mL, 11 mmol). After stirring for 2.5 h at room temperature, the reaction mixture was filtered and concentrated to give yellow oil. Purification by flash chromatography on silica gel column using 5% MeOH/CHCl₃ provided **1c** as a viscous yellow oil (0.4422 g, 24%). ¹H NMR (500 MHz, CDCl₃) δ : 8.27 (1H, s), 5.64 (1H, s), 4.75 (1H, s), 3.50-3.38 (4H, m), 2.02 (3H, s), 1.16 (6H, t, $J = 7.0$ Hz). HRMS calcd for C₁₁H₂₃N₂O₄ (M + NH₄ + CH₃CN): 243.1821; found: 243.1812.

N-{1-[2-(4-Hydroxy-phenyl)-ethylcarbamoyl]-(E)-propenyl}-benzamide (1d): To a solution of N-benzoyl-L-threonine (1.00g, 4.5 mmol) in dry THF (10 mL) was added methanesulfonyl chloride (0.69 mL, 18.9 mmol) followed by Et₃N (1.87 mL, 13.4 mmol). The mixture was stirred at 40° C for 18 h and cooled, filtered and concentrated. The resulting brown oil was purified by flash chromatography eluting with 10% MeOH/CH₂Cl₂ to give a solid that was re-crystallized from CH₂Cl₂/MeOH/hexane to provide 2-benzoylamino-but-2-enoic acid¹ as white crystals (0.2546 g, 28%, E/Z: 88:12). ¹H NMR (300 MHz DMSO-d₆) δ : 12.50 (1H, s), 9.84 (0.12H, s), 9.52 (0.88 H, s), 7.93 (1.76H, d, $J = 6.9$ Hz), 7.88 (0.24H, d, $J = 7.3$ Hz), 7.60-7.47 (3H, m), 6.68 (1H, q, $J = 6.9$ Hz), 1.94 (0.36H, d, $J = 7.2$ Hz), 1.72 (2.64H, d, $J = 6.9$ Hz).

To a solution of above acid (0.50 g, 2.44 mmol), tyramine (0.32 g, 2.32 mmol) and HOBT (0.31 g, 2.32 mmol) in DMF (20 mL) was added DIEA (0.40 mL, 2.32 mmol) and the resulting mixture was stirred at room temperature for 5 min. To this reaction mixture was EDC (0.44 g, 2.32 mmol) and continued stirring for additional 18 h, and then concentrated. The resulting amber oil was partitioned between 1N HCl, and ethyl acetate. The organic phase was dried (Na₂SO₄), concentrated and purified by flash chromatography eluting with 50%-100% ethyl acetate/hexane to give a residue that was gently warmed in ethyl acetate and hexane to give single isomer as a white solid (0.3875 g, 49%; E-isomer). ¹H NMR (300 MHz DMSO-d₆) δ : 9.45 (1H, s), 9.15 (1H, s), 7.97 (2H, d, $J = 7.3$ Hz), 7.91 (1H, t, $J = 5.9$ Hz), 7.60-7.48 (3H, m), 6.97 (2H, d, $J = 8.4$ Hz), 6.65 (2H, d, $J = 8.4$ Hz), 6.43 (1H, q, $J = 6.9$ Hz), 3.24 (2H, q, $J = 6.9$ Hz), 2.60 (2H, t, $J = 7.5$ Hz), 1.65 (3H, d, $J = 6.9$ Hz). HRMS calcd for C₁₉H₂₁N₂O₃: 325.1552; found: 325.1553.

2-Acetylamino-N-benzyl-acrylamide (1e):² To a stirred solution of 2-acetylaminoacrylic acid (1.2912 g, 10 mmol) in THF (100 mL) was added successively 4-methylmorpholine (1.21 mL, 11 mmol), isobutyl chloroformate (1.43 mL, 11 mmol), and benzylamine (1.2 mL, 11 mmol). After stirring for 3 h at room temperature, the reaction mixture was filtered and concentrated to give yellow residue. Purification by flash chromatography on silica gel column using 2:3 and 1:1 EtOAc/hexanes provided **1e** as a white solid (1.7745 g, 81%). ¹H NMR (500 MHz, CDCl₃) δ : 8.12 (1H, s), 7.35-7.25 (5H, m), 6.60 (1H, s), 6.43 (1H, s), 5.20 (1H, s), 4.50 (2H, d, $J = 5.8$ Hz), 2.09 (3H, s). HRMS calcd for C₁₂H₁₃N₂O₂ (M - H): 217.0977; found: 217.0981.

General Procedure for the Michael Addition to 1e: To a stirred solution of **1e** (0.109 g, 0.5 mmol) in methanol (2 mL) was added water (3 mL) followed by the appropriate nucleophile (5 mmol). After the reaction was complete as judged by LCMS, the reaction mixture was concentrated to afford the product.

2-Acetylamino-N-benzyl-3-methylamino-propionamide (3a):² White solid (0.1245 g, 100% yield). ¹H NMR (500 MHz, CDCl₃) δ: 7.23 (1H, s), 7.33-7.23 (5H, m), 6.79 (1H, d, *J* = 4.9 Hz), 4.48-4.38 (2H, m), 4.33-4.30 (1H, m), 3.16 (1H, dd, *J* = 11.6, 3.4 Hz), 2.51 (1H, dd, *J* = 11.6, 8.2 Hz), 2.40 (3H, s), 2.01 (3H, s). HRMS calcd for C₁₃H₁₈N₃O₂ (M - H): 248.1399; found: 248.1405.

2-Acetylamino-N-benzyl-3-dimethylamino-propionamide (3b):² White solid (0.0564 g, 99% yield). ¹H NMR (500 MHz, CDCl₃) δ: 7.34 (1H, s), 7.34-7.24 (5H, m), 6.60 (1H, br s), 4.53 (1H, dd, *J* = 15, 6.4 Hz), 4.38-4.31 (2H, m), 2.64 (1H, dd, *J* = 12.2, 4.0 Hz), 2.40 (1H, dd, *J* = 12.2, 10.5 Hz), 2.27 (6H, s), 2.00 (3H, s). HRMS calcd for C₁₄H₂₀N₃O₂ (M - H): 264.1712; found: 264.1716.

2-Acetylamino-N-benzyl-3-morpholin-4-yl-propionamide (3c):² White solid (0.1537 g, 100% yield). ¹H NMR (500 MHz, CDCl₃) δ: 8.31 (1H, s), 7.35-7.25 (5H, m), 6.56 (1H, d, *J* = 4.0 Hz), 4.57 (1H, dd, *J* = 14.6, 6.4 Hz), 4.37-4.33 (1H, m), 4.30 (1H, dd, *J* = 14.6, 4.6 Hz), 3.51-3.43 (4H, m), 2.75 (1H, dd, *J* = 12.5, 3.7 Hz), 2.73-2.67 (2H, m), 2.38-2.29 (3H, m), 2.01 (3H, s). HRMS calcd for C₁₆H₂₄N₃O₃ (M + H): 306.1818; found: 306.1819.

2-Acetylamino-N-benzyl-3-methylsulfanyl-propionamide (3d):² The reaction mixture was acidified with aq. HCl (1N, 5 mL), and the resulting white slurry was extracted with CH₂Cl₂ (3 X 25 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to afford **3d** as a white solid (0.128 g, 96%). ¹H NMR (500 MHz, CDCl₃) δ: 7.32-7.24 (5H, m), 7.07 (1H, s), 6.63 (1H, d, *J* = 6.7 Hz), 4.60-4.56 (1H, m), 4.42 (2H, d, *JJ* = 5.5 Hz), 2.86 (1H, dd, *J* = 13.7, 5.5 Hz), 2.77 (1H, dd, *J* = 14.0, 7.6 Hz), 2.11 (3H, s), 1.97 (3H, s). HRMS calcd for C₁₃H₁₉N₂O₂S (M + H): 267.1167; found: 267.1178.

References

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2. Choi, D.; Kohn, H. *Tetrahedron Lett.* **1995**, *36*, 7371-7373.

Figure 1. ^1H NMR spectrum of **1b**

Figure 2. ^1H NMR spectrum of **1c**

Figure 3. ¹H NMR spectrum of **1d**

Figure 4. ^1H NMR spectrum of **1e**

Figure 5. ¹H NMR spectrum of **2g**

Figure 7. ^1H NMR spectrum of **2k**

Figure 8. ^{13}C NMR spectrum of **2k**

Figure 9. ¹H NMR spectrum of **2q**

Figure 10. ¹H NMR spectrum of **2v**

Figure 11. ¹H NMR spectrum of **2w**

Figure 12. ^1H NMR spectrum of **3a**

Figure 13. ¹H NMR spectrum of **3b**

Figure 14. ^1H NMR spectrum of **3c**

Figure 15. ^1H NMR spectrum of **3d**