

## Accessory Publication

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# The Application of the Schmidt Reaction and Beckmann Rearrangement to the Synthesis of Bicyclic Lactams: Some Mechanistic Considerations.

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### Experimental

15 *General*

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded using a Scimitar Series Varian 800 FT-IR Spectrophotometer with a PIKE Technologies MIRacle ATR fitted with a Varian Resolutions software package (version 4.0).

20 <sup>1</sup>H nuclear magnetic resonance (NMR) spectra were recorded at 300.13 MHz using a Bruker Avance DPX 300 spectrometer equipped with a Silicon Graphics workstation. Chemical shifts ( $\delta$ ) for all <sup>1</sup>H NMR spectra are reported in parts per million (ppm) using tetramethylsilane (TMS) as the internal reference (0.00 ppm) in solvents such as deuterated chloroform (CDCl<sub>3</sub>), *d*<sub>6</sub>-dimethyl sulfoxide (*d*<sub>6</sub>-DMSO), *d*<sub>6</sub>-acetone ((CD<sub>3</sub>)<sub>2</sub>CO), or *d*<sub>4</sub>-methanol (CD<sub>3</sub>OD). Each resonance was  
25 assigned according to the following convention: chemical shift ( $\delta$ ), number of protons, multiplicity, coupling constant(s) (*J* Hz), and proton assignment. Multiplicities are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br, broad; and app, apparent.

<sup>13</sup>C NMR spectra were recorded at 75.5 MHz using a Bruker Avance DPX-300 spectrometer  
30 equipped with a Silicon Graphics workstation. J-Modulated Spin-Echo experiments (JMOD) were routinely used for <sup>13</sup>C NMR spectra for X-nuclei coupled to <sup>1</sup>H in order to determine the number of attached protons. Chemical shifts ( $\delta$ ) for all <sup>13</sup>C NMR spectra are reported in parts per million (ppm), using the central peak of the solvent chemical shift as the reference:<sup>[1]</sup> CDCl<sub>3</sub> (77.2); *d*<sub>6</sub>-

35 DMSO (39.5); (CD<sub>3</sub>)<sub>2</sub>CO (29.9); and CD<sub>3</sub>OD (49.2). Carbon signals are assigned as: C<sub>q</sub>,  
quaternary; CH, methine carbon; CH<sub>2</sub>, methylene carbon; and CH<sub>3</sub>, methyl carbon. Homonuclear  
(<sup>1</sup>H-<sup>1</sup>H) correlation spectroscopy (gradient COSY), NOESY, HSQC, HMQC and HMBC spectra  
were obtained using the standard Bruker pulse sequence for structural assignment of some  
compounds.

40 Electrospray ionisation (ESI) mass spectra were recorded in the positive ion mode, unless otherwise  
stated, using a Micromass Platform II Single Quadrupole Mass Spectrometer in acetonitrile:water  
(1:1) at the specified cone voltage. Electron Impact (EI) mass spectra were recorded using Agilent  
5973N GCMS system fitted with HP-5ms column and at 70 eV cone voltage. The principle ion  
peaks (*m/z*) are reported with their peak intensities (in parentheses), expressed as a percentage of the  
45 base peak (100%). High Resolution Mass Spectrometry (HRMS) analyses were recorded using a  
Bruker Apex-II Fourier Transform Ion Cyclotron Resonance (FTICR) mass spectrometer fitted with  
an electrospray ion source.

Analytical reverse-phase HPLC was performed on a Waters HPLC system fitted with a  
50 Phenomenex® Luna C8 (2) 100Å column (150 × 4.6 mm, 5 μm) using a binary solvent system;  
solvent A: 0.1% TFA/H<sub>2</sub>O; solvent B: 0.1% TFA/CH<sub>3</sub>CN. Isocratic elution was achieved in 60%  
solvent A and 40% solvent B over 20 min at a flow rate of 0.5 mL/min monitored at 260 nm using a  
Waters 996 Photodiode Array detector. Gradient elution was achieved using 100% solvent A to  
100% solvent B over 25 min at a flow rate of 0.5 mL/min monitored at 260 nm. Analytical thin-  
55 layer chromatography (tlc) was carried out on silica gel 60 F<sub>254</sub> pre-coated plates (0.25 mm, Merck)  
and visualised by UV light, iodine or ethanolic 2,4-dinitrophenylhydrazine (2,4-DNP) solution as  
indicated. Flash chromatography was carried out routinely according to the method described by  
Still *et al.*<sup>[2]</sup> using Merck Silica gel 60, 230-400 mesh ASTM.

60 Elemental analyses were carried out by Chemical & MicroAnalytical Services Pty. Ltd. Belmont  
VIC on samples dried overnight over phosphorus pentoxide at room temperature. Elemental  
analyses were carried out on all novel compounds except novel intermediates that were used in the  
subsequent reaction step. Compounds that fell outside the acceptable limits (± 0.4%) for elemental  
analyses were subjected to further analyses using HRMS and HPLC (isocratic and gradient elution).

65 All solvents were redistilled prior to use. Hexane refers to the hydrocarbon fraction boiling at 60-80  
°C and petroleum spirit refers to the hydrocarbon fraction boiling at 40-60 °C. Dry methanol was  
prepared by distilling from calcium hydride and stored over 3Å molecular sieve. Dry ethyl acetate

70 was prepared by washing with aqueous 5% sodium carbonate, saturated sodium chloride, then distilled from calcium sulfate and stored over 4Å molecular sieve. Dry toluene was prepared by drying over calcium chloride, distilled from phosphorus pentoxide and stored over 4Å molecular sieve. Dry acetone was prepared by distilling from calcium sulfate and stored over 4Å molecular sieve. All organic extracts were washed with water, brine, and dried over sodium sulfate prior to evaporation *in vacuo*.

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This section describes the synthesis of 6-chloro-1-tetralone **52**, 7-chloro-1-tetralone **53** and 7-chloro-4-chromanone **55** and their intermediates.

#### *6-Amino-1-tetralone 60*

80 2-Bromo-2-methylpropanamide (2.49 g, 15.0 mmol) was added in one portion to a magnetically stirred solution of 6-hydroxy-1-tetralone **61** (1.62 g, 10.0 mmol) and sodium hydroxide (1.20 g, 30.0 mmol) in *N,N*-dimethylacetamide (50 mL). Stirring was continued overnight at room temperature. Once all of **61** was consumed (by tlc), further sodium hydroxide (3.60 g, 90.0 mmol) was added and stirring was continued for 2 h at 50 °C. Water (100 mL) was then added and stirring was continued for 2 h while heating at reflux. A second portion of water (150 mL) was added and the reaction mixture was cooled in ice-bath. The precipitated crystalline powder was filtered and dried, purified using flash chromatography (50% ethyl acetate in hexane), and recrystallised (dichloromethane/hexane) to afford 6-amino-1-tetralone **60** (890 mg, 55%) as slightly yellow crystals, mp 129-131 °C (lit.<sup>[3]</sup> 129-130 °C).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.89 (1H, d, *J* 8.5, H8), 6.53 (1H, dd, *J* 8.5, 2.5, H7), 6.42 (1H, d, *J* 2.5, H5), 4.11 (2H, br s, NH<sub>2</sub>), 2.83 (2H, t, *J* 6, H2), 2.56 (2H, t, *J* 6.5, H4), 2.07 (2H, app p, *J* 6.5, H3).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 196.8 (CO), 151.3 (C<sub>q</sub>), 147.0 (C<sub>q</sub>), 129.8 (CH), 124.1 (C<sub>q</sub>), 113.2 (CH), 112.5 (CH), 38.9 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>). *m/z* (ESI, 20 V) 162 (100%, (M+H)<sup>+</sup>), 85 (70).

#### 95 *6-Chloro-1-tetralone 52*

A solution of sodium nitrite (173 mg, 2.51 mmol) in water (5 mL) at 0 °C (ice-bath) was added to a magnetically stirred suspension of **60** (360 mg, 2.23 mmol) in aqueous hydrochloric acid (10 mL, 6 M) at 0 °C. This reaction mixture was added dropwise to a solution of copper(I) chloride (267 mg, 2.70 mmol) in concentrated hydrochloric acid (5 mL) at 0 °C. It was allowed to warm up to room temperature and stirred for a further 2 h after which it was neutralised with solid sodium carbonate, extracted with ethyl acetate (3 × 20 mL) and concentrated *in vacuo* to give slightly yellow oil. This material was subjected to flash chromatography (50% chloroform in hexane) and concentration of the appropriate fractions afforded 6-chloro-1-tetralone **52** (180 mg, 45%) as a waxy solid, mp 32-34

105 °C (lit.<sup>[4]</sup> 30-31 °C).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.96 (1H, d, *J* 8, H8), 7.29-7.25 (2H, m, H5, H7), 2.94 (2H, t, *J* 6, H2), 2.65 (2H, t, *J* 6.5, H4), 2.14 (2H, app p, *J* 6.5, H3).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 197.1 (CO), 146.0 (C<sub>q</sub>), 139.7 (C<sub>q</sub>), 131.1 (C<sub>q</sub>), 128.9 (CH), 128.6 (CH), 127.2 (CH), 38.9 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 23.1 (CH<sub>2</sub>). *m/z* (EI, 70 eV) 182 (15%, M<sup>[37Cl]</sup>+) 180 (58, M<sup>[35Cl]</sup>), 165 (14), 152 (100), 124 (37), 115 (19), 89 (39), 63 (15).

110 *4-(4-Chlorophenyl)butanoic acid 65*

Hydrazine hydrate (6.00 mL, 123 mmol) was added dropwise *via* a syringe to a magnetically stirred solution of 3-(4-chlorobenzoyl)propionic acid **64** (10.4 g, 48.9 mmol) and potassium hydroxide (9.00 g, 160 mmol) in triethylene glycol (70 mL). The reaction mixture was stirred at 120-130 °C for 2 h at which time the excess hydrazine and water was distilled off at 200 °C. The reaction mixture was then cooled, diluted with water (100 mL), acidified with aqueous hydrochloric acid (50 mL, 6 M), and the resulting precipitate was filtered and dried *in vacuo* to afford 4-(4-chlorophenyl)butanoic acid **65** (9.52 g, 98%) as a white powder, mp 55-56 °C (lit.<sup>[5]</sup> 54-57 °C).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 10.89 (1H, br s, COOH), 7.26 (2H, d, *J* 8.5, H3', H5'), 7.12 (2H, d, *J* 8.5, H2', H6'), 2.66 (2H, t, *J* 7.5, H4), 2.38 (2H, t, *J* 7.5, H2), 1.95 (2H, app p, *J* 7.5, H3).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 179.9 (COOH), 139.7 (C<sub>q</sub>), 131.9 (C<sub>q</sub>), 129.9 (CH), 128.6 (CH), 34.4 (CH<sub>2</sub>), 33.3 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>). *m/z* (negative ESI, 70 V) 199 (33%, (M<sup>[37Cl]</sup>-H)<sup>-</sup>) 197 (100, (M<sup>[35Cl]</sup>-H)<sup>-</sup>), 127 (25), 125 (68), 59 (36).

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*7-Chloro-1-tetralone 53*

4-(4-Chlorophenyl)butanoic acid **65** (9.25 g, 46.6 mmol) in polyphosphoric acid (70 mL) was stirred for 2 h at 95 °C and then poured into water (500 mL) and further stirred for 2 h at 75 °C. The reaction mixture was then cooled, resulting precipitate filtered, and dried *in vacuo*. This material was subjected to flash chromatography (60% chloroform in hexane) and recrystallisation (dichloromethane/hexane) afforded 7-chloro-1-tetralone **53** (5.36 g, 64%) as slightly yellow plate-like crystals, mp 92-94 °C (lit.<sup>[6]</sup> 94-95 °C).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.96 (1H, d, *J* 2, H8), 7.39 (1H, dd, *J* 8, 2, H6), 7.18 (1H, d, *J* 8, H5), 2.91 (2H, t, *J* 6, H2), 2.63 (2H, t, *J* 6.5, H4), 2.11 (2H, app p, *J* 6.5, H3).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 197.0 (CO), 142.7 (C<sub>q</sub>), 133.8 (C<sub>q</sub>), 133.2 (CH), 132.8 (C<sub>q</sub>), 130.4 (CH), 126.9 (CH), 38.8 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 23.1 (CH<sub>2</sub>). *m/z* (EI, 70 eV) 182 (30%, M<sup>[37Cl]</sup>+) 180 (100, M<sup>[35Cl]</sup>), 165 (28), 152 (98), 124 (78), 115 (31), 89 (51), 63 (19).

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135 *3-(3-Chlorophenoxy)propanoic acid 67*

$\beta$ -Propiolactone (692  $\mu$ L, 11.1 mmol) was added dropwise *via* a syringe to a magnetically stirred solution of 3-chlorophenol **61** (1.29 g, 10.0 mmol) and sodium hydroxide (440 mg, 11.0 mmol) in water (5 mL) at 100 °C. Stirring was continued for 30 min while heating at reflux. The reaction

140 mixture was then cooled, acidified with aqueous hydrochloric acid (6 mL, 2 M), and resulting white precipitate was filtered and dried to afford 3-(3-chlorophenoxy)propanoic acid **67** (669 mg, 33%) as white power, mp 78-80 °C (lit.<sup>[7]</sup> 82-83 °C).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 11.43 (1H, br s, COOH), 7.16 (1H, app t, *J* 8.5, H5'), 6.92 (1H, d, *J* 8.5, H4'), 6.88 (1H, br s, H2'), 6.76 (1H, d, *J* 8.5, H6'), 4.18 (2H, t, *J* 6, H3), 2.79 (2H, t, *J* 6, H2).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 177.3 (COOH), 159.2 (C<sub>q</sub>), 135.0 (C<sub>q</sub>), 130.3 (CH), 121.4 (CH), 115.2 (CH), 113.1 (CH), 63.3 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>). *m/z* (negative ESI, 20 V) 201 (32%, [M<sup>[37]Cl</sup>]-H<sup>-</sup>), 199 (100, [M<sup>[35]Cl</sup>]-H<sup>-</sup>), 129 (25), 127 (70), 91 (78).

#### 7-Chloro-4-chromanone **55**

3-(3-Chlorophenoxy)propanoic acid **67** (650 mg, 3.24 mmol) in polyphosphoric acid (10 mL) was stirred for 2 h at 95 °C and then poured into water (100 mL) and further stirred for 2 h at 75 °C. 150 The reaction mixture was then cooled, resulting precipitate filtered, and dried *in vacuo*. Recrystallisation (dichloromethane/hexane) of this material afforded 7-chloro-4-chromanone **55** (300 mg, 51%) as white crystals, mp 64-65 °C (lit.<sup>[8]</sup> 67-69 °C).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.83 (1H, d, *J* 9, H5), 7.00-6.98 (2H, m, H6, H8), 4.54 (2H, t, *J* 6.5, H2), 2.80 (2H, t, *J* 6.5, H3).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 190.6 (CO), 162.2 (C<sub>q</sub>), 141.8 (C<sub>q</sub>), 128.4 (CH), 122.2 (CH), 119.9 (C<sub>q</sub>), 118.1 (CH), 67.4 (CH<sub>2</sub>), 37.6 (CH<sub>2</sub>). 155 *m/z* (ESI, 70 V) 183 (43%, [M<sup>[35]Cl</sup>]+H<sup>+</sup>), 137 (100), 91 (57).

#### References

- 160 [1] H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.
- [2] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
- [3] D. F. Biggs, A. F. Casy, I. Chu and R. T. Coutts, *J. Med. Chem.* **1976**, *19*, 472.
- 165 [4] C. A. Kerr and I. D. Rae, *Aust. J. Chem.* **1978**, *31*, 341.
- [5] F. E.-F. Ali, P. A. Dandridge, J. G. Gleason, R. D. Krell, C. H. Kruse, P. G. Lavanchy and K. M. Snader, *J. Med. Chem.* **1982**, *25*, 947.
- 170 [6] K. Inoue, S. Ueda, H. Nayeshiro, N. Moritome and H. Inouye, *Phytochemistry* **1984**, *23*, 313.
- [7] T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, W. L. Beears and M. G. Prendergast, *J. Am. Chem. Soc.* **1949**, *71*, 661.
- 175 [8] P. F. Wiley, *J. Am. Chem. Soc.* **1951**, *73*, 4205.