Highly Stereoselective Synthesis of Isoindole Derivatives Containing an Azetidinone Ring
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Experimental

General information

IR spectra were recorded on a commercial Spectrophotometer (Bruker Tensor 27 FT-IR). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded on a Bruker 400 Ultrashield NMR Magnet (400 MHz for \textsuperscript{1}H NMR and 80MHz for \textsuperscript{13}C NMR) with TMS as the internal standard and \textsuperscript{13}C NMR were reported with complete proton decoupling. Elemental analysis (CHNS) was recorded on a Leco 923 and Melting point were recorded on Electrothermal-9200. Data are reported as follows: chemical shift $\delta_{H}$ and $\delta_{C}$ (ppm), coupling constants $J$ (Hz), integration and multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). Solvents for reaction were distilled prior to use: Toluene, dichloromethane, hexane and ethyl acetate. Triethyl amine (Et$_3$N) was pre-dried over sodium wire. Column chromatography was carried out using Sigma-Aldrich silica gel 40 Angstrom ($\AA$).

General procedure for preparation of imines (7)

Distilled aniline (50 mmol, 4.56 mL) in 8 mL in toluene was added to a solution of distilled benzaldehyde (50 mmol, 5.1 mL) the mixture was heated under reflux for 7 h in the presence of calcium sulfate. The mixture was filtered and then the solvent was evaporated. The crude products were purified by crystallization from hexane to give the product.

Preparation of $\gamma$-(N-isoindolyl) butanoic chloride (9)

To $\gamma$-(N-isoindolyl) butanoic acid I (0.69 g, 3.0 mmol) was added oxalyl chloride (5.0 ml) and dried DMF (5 µL, 0.06 mmol). With heating to reflux $\gamma$-(N-isoindolyl) butanoic acid went into solution and refluxed for 4 h. The excess of oxalyl chloride was distilled and the saccharinyl acetyl chloride was obtained as a black solid

General Procedure for the Synthesis of $\beta$-Lactams 8a
A suspension of 4-(1,3-dioxoisindolin-2-yl)butanoic acid acid 3 (0.41 g, 1.8 mmol), 2-chloro-N-methylpyridinium iodide 5 (0.53 g, 2.1 mmol) and triethylamine 4 (0.18 mL, 1.8 mmol) in anhydrous dichloromethane (25 ml) were refluxed under a nitrogen atmosphere for 10 h. A solution of the N-benzylideneaniline 7 (0.18 g, 1.0 mmol) in anhydrous dichloromethane (10 ml) and triethylamine (0.20 mL, 2.0 mmol) were added and refluxing was continued for an additional 10 h. After cooling, the solution was washed with water, 5% HCl aqueous solution, and then with water. The organic layer was dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude products were purified by column chromatography (silica gel, n-hexane/ethyl acetate, 3:1). *Trans*2-(2-(2-oxo-1,4-diphenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8a) was obtained as the only product.

**Spectra data**

**2-(2-(2-oxo-1,4-diphenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8a)**

White solid 660 mg, yield 86%; mp: 176-177 °C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 1753, 1760 (C=O). Anal. Calcd. for C$_{25}$H$_{20}$N$_2$O$_3$ (396.45): C, 75.74; H, 5.08; N, 7.07. Found: C, 75.35; H, 5.03; N, 6.89. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.01-7.84 (m, 14H, Ar), 4.75 (d, $^3$J$_{H-H}$ = 2.4 Hz, 1H, CH), 3.89 (t, $^3$J$_{H-H}$ =6.9 Hz, 2H, CH$_2$), 3.23 (t of d, $^3$J$_{H-H}$ = 2.4 Hz, $^3$J$_{H-H}$ = 7.84 , 1H, CH), 2.27-2.44 (m, 2H, CH$_2$). $^{13}$C NMR (80 MHz, CDCl$_3$) δ 168.2, 166.4, 137.5, 137.4, 134.0, 132.1, 129.20, 129.0, 128.6, 123.9, 123.3, 116.9, 61.1, 58.2, 36.0, 27.9.

**2-(2-(1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8b)**

White solid 751 mg, Yield 91%; mp: 88-89 °C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 1744, 1750 (C=O). Anal. Calcd. for C$_{26}$H$_{22}$N$_2$O$_4$ (426.48): C, 73.23; H, 5.20; N, 6.57. Found: C, 73.36; H, 5.26; N, 6.59. H NMR (400 MHz, CDCl$_3$) δ 6.75, 7.83 (m, 13H, Ar), 4.70 (d, $^3$J$_{H-H}$ = 2.3 Hz, 1H, CH), 3.87 (t, $^3$J$_{H-H}$ =7.2 Hz, 2H, CH$_2$), 3.73 (s, 3H, OCH$_3$), 3.21 (t of d, $^3$J$_{H-H}$ = 2.3 Hz, $^3$J$_{H-H}$ = 7.5Hz,1H, CH), 2.26-2.42 (m, 2H, CH$_2$). $^{13}$C NMR (80 MHz, CDCl$_3$) δ 168.2, 165.8, 137.5, 137.4, 134.0, 133.9, 132.1, 129.20, 128.6, 123.9, 123.3, 116.9, 61.3, 58.2, 55.4, 36.0, 27.9.

**2-(2-(1-(4-bromophenyl)-2-oxo-4-phenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8c)**

White solid 547 mg, yield 59%; mp: 168-169 °C. IR (KBr) ($\nu_{max}$, cm$^{-1}$): 1752, 1760 (C=O). Anal. Calcd. for C$_{25}$H$_{19}$BrN$_2$O$_3$ (475.35): C, 63.17; H, 4.03; N, 5.89. Found: C, 62.81; H, 4.21; N, 5.91. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.8-7.83 (m, 13H, Ar), 4.72 (d, $^3$J$_{H-H}$ = 2.5 Hz, 1H, CH),
Anal. Calcd. for C
White solid 671 mg, yield 8
2H, CH
3.88 (t, 3J_{H-H} = 7.2 Hz, 2H, CH₂), 3.24 (t of d, 3J_{H-H} = 2.5 Hz, 3J_{H-H} = 7.1 Hz, 1H, CH), 2.23-2.42 (m, 2H, CH₂).
\(^{13}\)C NMR (80 MHz, CDCl₃) δ 168.2, 166.3, 136.9, 136.4, 134.0, 132.1, 132.0, 129.3, 128.8, 125.9, 123.3, 118.5, 116.5, 61.2, 58.5, 35.9, 27.7.

2-(2-(1-(4-chlorophenyl)-2-oxo-4-phenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8d)

White solid 589 mg, yield 71%; mp: 116-117°C. IR (KBr) (ν_{max}, cm\(^{-1}\)): 1753, 1760 (C=O). Anal. Calcd. for C\(_{25}\)H\(_{19}\)ClN\(_2\)O\(_3\) (430.89): C, 69.69; H, 4.44; N, 6.50. Found: C, 69.21; H, 4.25; N, 6.24. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.05-7.83 (m, 13H, Ar), 4.71 (d, 3J\(_{H-H}\) = 2.4 Hz, 1H, CH), 3.89 (t, 3J\(_{H-H}\) = 7.1 Hz, 2H, CH₂), 3.20 (t of d, 3J\(_{H-H}\) = 2.4 Hz, 3J\(_{H-H}\) = 6.2 Hz, 1H, CH), 2.29-2.42 (m, 2H, CH₂). \(^{13}\)C NMR (80 MHz, CDCl₃) δ 168.2, 166.2, 137.3, 135.9, 134.4, 134.0, 132.1, 129.4, 129.1, 127.4, 124.1, 123.3, 116.9, 60.7, 58.2, 35.9, 27.8.

2-(2-(2-oxo-4-phenyl-1-(p-tolyl)azetidin-3-yl)ethyl)isoindoline-1,3-dione (8e)

White solid 693 mg, yield 87%; mp: 169-170°C. IR (KBr) (ν_{max}, cm\(^{-1}\)): 1744, 1750 (C=O). Anal. Calcd. for C\(_{26}\)H\(_{22}\)NO\(_3\) (484.48): C, 76.08; H, 5.40; N, 6.82. Found: C, 76.20; H, 5.45; N, 6.73. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.01, 7.84 (m, 13H, Ar), 4.71 (d, 3J\(_{H-H}\) = 2.4 Hz, 1H, CH), 3.88 (t, 3J\(_{H-H}\) = 7.2 Hz, 2H, CH₂), 3.20 (t of d, 3J\(_{H-H}\) = 2.4 Hz, 3J\(_{H-H}\) = 7.5 Hz, 1H, CH), 2.27-2.42 (m, 2H, CH₂), 2.26 (s, 3H, CH₃). \(^{13}\)C NMR (80 MHz, CDCl₃) δ 168.2, 166.1, 137.5, 135.1, 133.9, 133.4, 132.1, 129.5, 129.1, 128.5, 126.0, 123.3, 116.9, 61.1, 58.2, 36.0, 27.9, 20.9.

2-(2-(2-oxo-1-phenyl-4-(p-tolyl)azetidin-3-yl)ethyl)isoindoline-1,3-dione (8f)

White solid 678 mg, yield 85%; mp: 140-141°C. IR (KBr) (ν_{max}, cm\(^{-1}\)): 1753, 1760 (C=O). Anal. Calcd. for C\(_{26}\)H\(_{22}\)NO\(_3\) (484.48): C, 76.08; H, 5.40; N, 6.82. Found: C, 75.78; H, 5.78; N, 7.13. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.01, 7.83 (m, 13H, Ar), 4.70 (d, 3J\(_{H-H}\) = 2.4 Hz, 1H, CH), 3.87 (t, 3J\(_{H-H}\) = 7.2 Hz, 2H, CH₂), 3.21 (t of d, 3J\(_{H-H}\) = 2.4 Hz, 3J\(_{H-H}\) = 6.7 Hz, 1H, CH), 2.25-2.41 (m, 2H, CH₂), 2.34 (s, 3H, CH₃). \(^{13}\)C NMR (80 MHz, CDCl₃) δ 168.2, 166.5, 138.4, 137.6, 134.3, 133.9, 132.1, 129.8, 129.0, 126.0, 123.8, 123.3, 117.0, 61.1, 58.2, 36.0, 27.9, 21.2.

2-(2-(2-(4-chlorophenyl)-4-oxo-1-phenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8g)

White solid 632 mg, yield 75%; mp: 130-131°C. IR (KBr) (ν_{max}, cm\(^{-1}\)): 1753, 1760 (C=O). Anal. Calcd. for C\(_{25}\)H\(_{19}\)ClN\(_2\)O\(_3\) (430.89): C, 69.69; H, 4.44; N, 6.50. Found: C, 69.23; H, 4.19; N, 6.08. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.02-7.83 (m, 13H, Ar), 4.70 (d, 3J\(_{H-H}\) = 2.4 Hz, 1H, CH), 3.88 (t, 3J\(_{H-H}\) = 7.0 Hz, 2H, CH₂), 3.21 (t of d, 3J\(_{H-H}\) = 2.4 Hz, 3J\(_{H-H}\) = 6.6 Hz, 1H, CH), 2.27-2.44 (m, 2H, CH₂). \(^{13}\)C NMR (80 MHz, CDCl₃) δ 168.2, 166.1, 137.3, 135.9, 134.4, 134.0, 132.1, 129.4, 129.1, 127.4, 124.1, 123.3, 116.9, 60.6, 58.2, 36.0, 27.8.

2-(2-(2-(4-methoxyphenyl)-4-oxo-1-phenylazetidin-3-yl)ethyl)isoindoline-1,3-dione (8h)

White solid 671 mg, yield 81%; mp: 130-131°C. IR (KBr) (ν_{max}, cm\(^{-1}\)): 1753, 1760 (C=O). Anal. Calcd. for C\(_{26}\)H\(_{22}\)NO\(_4\) (426.48): C, 73.23; H, 5.20; N, 6.57. Found: C, 73.43; H, 5.14; N,
6.27. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.81, 7.83 (m, 13H, Ar), 4.68 (d, $^3$J$_{H-H}$ = 2.4 Hz, 1H, CH), 3.89 (t, $^3$J$_{H-H}$ = 7.6 Hz, 2H, CH$_2$), 3.80 (s, 3H, OCH$_3$), 3.21 (t of d, $^3$J$_{H-H}$ = 2.4 Hz, $^3$J$_{H-H}$ = 6.6 Hz, 1H, CH), 2.26-2.42 (m, 2H, CH$_2$). $^{13}$C NMR (80 MHz, CDCl$_3$) $\delta$ 168.2, 166.6, 159.7, 137.6, 133.9, 132.1, 129.2, 129.0, 127.3, 123.8, 123.3, 117.0, 114.5, 61.0, 58.2, 55.3, 36.0, 27.8.

2-(2-(1-(naphthalen-1-yl)-2-oxo-4-(p-tolyl)azetidin-3-yl)ethyl)isoindoline-1,3-dione (8i)

Oil 568 mg, yield 63%; IR (KBr) ($\nu_{\text{max}}$, cm$^{-1}$): 1753, 1760 (C=O). Anal. Calcd. for C$_{30}$H$_{24}$N$_2$O$_3$ (460.54): C, 78.24; H, 5.25; N, 6.08. Found: C, 77.98; H, 5.57; N, 5.61. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.98-8.21 (m, 15H, Ar), 5.01 (d, $^3$J$_{H-H}$ = 2.5 Hz, 1H, CH), 3.93 (t, $^3$J$_{H-H}$ = 7.2 Hz, 2H, CH$_2$), 3.44 (t of d, $^3$J$_{H-H}$ = 2.5 Hz, $^3$J$_{H-H}$ = 6.2 Hz, 1H, CH), 2.36-2.57 (m, 2H, CH$_2$), 2.24 (s, 3H, CH$_3$). $^{13}$C NMR (80 MHz, CDCl$_3$) $\delta$ 168.3, 167.5, 138.4, 134.4, 134.1, 133.9, 132.6, 132.1, 129.6, 128.2, 127.9, 127.0, 126.4, 126.4, 126.4, 125.2, 124.1, 123.3, 119.3, 63.3, 56.8, 36.2, 28.0, 21.1.
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H1 CDCl3 D:\ Administrator 36

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number of scans: 32

freq. of 0 ppm: 400.13000 MHz
processed size: 32768 complex points
LE: 0.300  GF: 0.0000
Hz/cm: 190.990  ppm/cm: 0.47732

Compound 8a
Compound 8a
Compound 8a
Compound 8a
Compound 8a
Compound 8a
Compound 8a
Compound 8b
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Compound 8b
Compound 8b
Compound 8b
Compound 8b
SpinWorks 3: 1
H1 CDC13 D:\\ Administrator 29

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transmitter freq.: 400.132601 MHz
time domain size: 32768 points
width: 841.75 Hz = 21.0360 ppm = 0.266682 Hz/pt
number of scans: 32

Compound 8c
Compound 8c
Compound 8c
Compound 8c
Compound 8d
Compound 8d
Compound 8d
Compound 8d
Compound 8d
Compound 8e
Compound 8e
Compound 8e
Compound 8e
Compound 8e
Compound 8f
Compound 8f
Compound 8f
Compound 8f
Compound 8f
Compound 8g
Compound 8g
Compound 8g
Compound 8g
SpinWorks 3: B8

C13c CDCl3 D:\Administrator 17

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image domain size: 12768 points
width: 252.5253 Hz = 250.9597 ppm = 0.770646 Hz/pt.
number of scans: 1500

freq. of 0 ppm: 100.612759 MHz
processed size: 32768 complex points
LB: 1.000  GF: 0.0000
Hz/cm: 885.580  ppm/cm: 8.8090

Compound 8g
Compound 8g
Compound 8h
Compound 8h
Compound 8h
Compound 8h
Compound 8h
Compound 8h
Compound 8h
Compound 8i
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