A New Entry into β -Lactams via Reaction of Dimethoxycarbene with Isocyanates

**James H. Rigby,* Jean-Christophe Brouet, Patrick J. Burke, Stephanie Rohach,
Shyama Sidique and Mary Jane Heeg**

Department of Chemistry, Wayne State University, Detroit, MI 48202
jhr@chem.wayne.edu

Supporting Information

General. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. All reagents and solvents were of commercial grade and were used as without further purification unless otherwise noted.

Flash chromatography was performed with Whatman silica gel (Purasil 60 A, 230-400 Mesh). Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (EMD, Silica Gel 60F₂₅₄). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Proton nuclear magnetic resonance (¹H NMR) data were acquired on 400 MHz Varian Mercury or 500 MHz Varian Unity-500. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference (CDCl₃: δ 7.24, C₆D₆: δ 7.15). Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Carbon-13 nuclear magnetic resonance (¹³C NMR) data were acquired on 400 MHz Varian Mercury or 500 MHz Varian Unity-500. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl₃: δ 77.00, C₆D₆: δ 128.00). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX-1 FT-IR system, ν_{max} in cm⁻¹. High resonance mass spectrometry (HRMS) data were recorded on a Micromass GCT using a solid state probe. Elemental analyses (Anal.) were performed by Atlantic Microlab, Inc. in Georgia.

Dimethoxycarbene oxadiazoline precursor **1** was prepared as previously described in the literature.¹

3-phenylpropanoic acid

This compound was prepared from the oxidation of the corresponding commercially available alcohol using a general procedure.² This carboxylic acid compound was used to synthesize **3a**.

2-(1,2-dihydronaphthalen-4-yl)acetic acid

This compound was prepared in two steps from α -tetralone using literature procedures.³ This carboxylic acid compound was used to synthesize **5a**.

General procedure for the preparation of acyl azide from the corresponding acids:

Compounds **1a** to **5a** were prepared from the corresponding carboxylic acids as follows: to a solution of the carboxylic acid in anhydrous benzene (0.2 M) was added 1 equiv. of distilled Et₃N. The reaction was then stirred for 30 min. Diphenylphosphorazidate (DPPA, 1 equiv.) was then added dropwise and the resulting reaction mixture was stirred for 40 min. The solvent was removed *in vacuo* and the resulting oil was purified by silica gel chromatography (ratio of 20:1 hexanes/ethyl acetate) to afford the pure acyl azide.

General procedure for the reaction of dimethoxycarbene with isocyanates:

In a flame-dried round bottom flask, acyl azide was dissolved in anhydrous chlorobenzene to a concentration of 0.01 M. 4 equiv. of oxadiazoline **1** were added to the solution. The reaction was then refluxed under argon for 45 min. The solution was allowed to cool down to room temperature and the solvent was removed *in vacuo*. The crude reaction residue was purified using silica gel chromatography (various ratios of hexanes/ethyl acetate, 12:1 up to 6:1, in the presence of 1% Et₃N) to obtain pure products.

1-(2,4-dimethoxyphenyl)-3,3,4,4-Tetramethoxyazetidin-2-one 1b

Acyl azide **1a** (21 mg, 0.093 mmol) and oxadiazoline **1** (45 mg, 0.37 mmol) were refluxed in chlorobenzene (9 mL) to obtain compound **1b** (18 mg, 49%) as a white solid.

Yield 49 % **M.p.** 103-105 °C **I.R** (neat) $\nu_{\max}$ 2925, 2846, 1774, 1607, 1511, 1207 and 1094 cm^{-1} ; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 7.44 (d, J = 8.5 Hz, 1 H), 6.31 (d, J = 2.5 Hz, 1 H), 6.20 (dd, J = 3, 9 Hz, 1 H), 3.52 (s, 6 H), 3.27 (s, 6 H), 3.25 (s, 3 H), 3.24 (s, 3 H); **¹³C NMR** (125 MHz, C₆D₆) δ_{C} 163.9, 161.2, 156.6, 129.3, 128.3, 116.7, 111.3, 109.4, 104.5, 100.0, 55.5, 55.0, 52.3, 51.7; **HRMS** calcd for C₁₅H₂₁NO₇: 327.1318 found: 327.1321

3,3,4,4-Tetramethoxy-1-(1,2-dimethyl-1H-indol-3-yl)azetidin-2-one 2b

Acyl azide **2a** (42 mg, 0.196 mmol) and oxadiazoline **1** (0.12 ml, 0.784 mmol) were refluxed in chlorobenzene (19.6 mL) to obtain compound **2b** (45.5 mg, 68%) as a pale yellow solid.

Yield 68 % **M.p.** 158-160 °C **I.R** (neat) $\nu_{\max}$ 2944, 1774, 1473, 1391, 1273, 1093 and 1030 cm^{-1} ; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 7.98 (m, 1 H), 7.18 (m, 2 H), 6.93 (m, 1 H), 3.55 (s, 6 H), 3.21 (s, 6 H), 2.64 (s, 3 H), 2.08 (s, 3 H); **¹³C NMR** (125 MHz, C₆D₆) δ_{C} 165.6, 135.8, 134.2, 125.0, 121.7, 120.5, 119.1, 111.5, 109.1, 109.0, 107.2, 52.4, 51.5, 28.7, 10.1; **HRMS** Calcd for C₁₇H₂₂N₂O₅: 327.1318 Found: 327.1321

Acyl azide **3a** (56 mg, 0.32 mmol) and oxadiazoline **1** (0.18 ml, 1.28 mmol) were refluxed in chlorobenzene (32 mL) to obtain compound **3b** and **3c** as pale yellow oils.

3,3,4,4-Tetramethoxy-1-phenethylazetidin-2-one 3b

Yield 57 % **I.R** (neat) $\nu_{\max}$ 2945, 1771, 1450, 1400, 1272, 1093 and 1039; **¹H NMR** (500 MHz, C₆D₆) δ_{H} 7.15-6.97 (m, 5H), 3.40 (s, 6H), 3.27-2.24 (m, 2H), 3.13 (s, 6H), 2.99-2.95 (m, 2H); **¹³C NMR** (125 MHz, C₆D₆) δ_{C} 165.4, 139.0, 129.0, 128.7, 128.3, 126.6, 110.4, 109.8, 52.1, 51.6, 42.4, 34.9; **HRMS** calcd for C₁₅H₂₁NO₅: 295.1420 found: 295.1408 **Anal.** calcd for C₁₅H₂₁NO₅: C, 61.00; H, 7.17; N, 4.74; found: C, 61.19; H, 7.11; N, 4.74;

5,5-dimethoxy-1,3-diphenethylimidazolidine-2,4-dione 3c

Yield 3 % **IR** (neat) $\nu_{\max}$ 2916, 1720, 1456, 1259 and 1100 cm^{-1} ; **^1H NMR** (500 MHz, C_6D_6) δ_{H} 7.09-7.08 (m, 5H), 7.03-7.02 (m, 5H), 3.58; 3.46-3.43 (m, 2H), 3.02 (s, 6H), 3.00-2.97 (m, 2H), 2.78 (t, $J = 7$ Hz, 2H); **^{13}C NMR** (125 MHz, C_6D_6) δ_{C} 166.8, 154.7, 139.1, 137.9, 129.3, 129.1, 128.7, 128.7, 128.3, 126.7, 126.6, 103.7, 57.6, 51.7, 51.6, 40.3, 39.1, 35.5, 33.9; **HRMS** calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ [$\text{M}-\text{CH}_3\text{OH}$]: 336.1474 found: 336.1490

Acyl azide **4a** (100 mg, 0.47 mmol) and oxadiazoline **1** (0.30 ml, 1.88 mmol) were refluxed in chlorobenzene (47 mL) to obtain compound **4b** and **4c** as colorless oils.

3,3,4,4-tetramethoxy-1-((1S,2S)-2-phenylcyclopropyl)azetidin-2-one 4b

Yield 65 % **IR** (neat) $\nu_{\max}$ 3010, 2946, 2840, 2360, 1771, 1679, 1407, 1089 and 1035 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ_{H} 7.05-6.97 (m, 3 H), 6.83 (d, $J = 6.84$ Hz, 2 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.21 (s, 3 H), 3.18 (s, 3 H), 2.51-2.44 (m, 2H), 1.77 (p, $J = 4.4$ Hz, 1 H), 0.91 (q, $J = 7.2$ Hz, 1 H); **^{13}C NMR** (100 MHz, CDCl_3) δ_{C} 164.6, 140.1, 128.4, 127.3, 126.2, 126.1, 110.9, 52.2, 52.0, 51.8, 51.7, 32.5, 23.7, 14.7; **HRMS** calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_5$: 307.1420 found: 307.1433

5,5-Dimethoxy-1-((1R,2R)-2-phenylcyclopropyl)-3-((1S,2S)-2-phenylcyclopropyl)imidazolidine-2,4-dione 4c

Yield 14 % **IR** (neat) $\nu_{\max}$ 3024, 2940, 2369, 1724, 1423 and 1101 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ_{H} 7.33-7.19 (m, 10 H), 3.48 (s, 3 H), 3.42 (s, 3 H), 2.76-2.73 (m, 1 H), 2.60-2.48 (m, 3 H), 1.64-1.55 (m, 4 H); **^{13}C NMR** (100 MHz, CDCl_3) δ_{C} 167.1, 155.1, 139.9, 139.2, 128.4, 128.4, 127.0, 126.6, 126.3, 126.0, 52.2, 52.1, 30.5, 30.2, 24.0, 22.9, 22.2, 13.4, 12.6, 12.6; **HRMS** calcd for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4$: 377.1501 found: 377.1512

Acyl azide **5a** (100 mg, 0.53 mmol) and oxadiazoline **1** (0.34 ml, 2.13 mmol) were refluxed in chlorobenzene (53 mL) to obtain compound **5b** as a white solid and **5c** as a colorless oil.

1-((1,2-Dihydronaphthalen-4-yl)methyl)-3,3,4,4-tetramethoxyazetidin-2-one 5b

Yield 55 % **M.p.** 85-86 °C **I.R** (neat) $\nu_{\max}$ 2942, 2839, 1784, 1442, 1270, 1186, 1090 and 1036 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 7.27-7.13 (m, 4 H), 6.06 (t, $J = 4\text{ Hz}$, 1 H), 4.25 (s, 2 H), 3.54 (s, 6 H), 3.41 (s, 6 H), 2.75 (t, $J = 8\text{ Hz}$, 2 H), 2.31 (m, 2 H); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 166.0, 136.2, 132.9, 130.7, 127.6, 127.2, 126.6, 122.2, 110.0, 108.7, 52.4, 52.0, 41.0, 27.8, 22.9; **HRMS** calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5\text{Na}^+$: 356.14684 Found: 356.14589 **Anal.** calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.85; H, 6.95; N, 4.20; found: C, 64.95; H, 6.89; N, 4.18;

1,3-Bis((1,2-dihydronaphthalen-4-yl)methyl)-5,5dimethoxyimidazolidine-2,4-dione 5c

Yield 20 % **I.R** (neat) $\nu_{\max}$ 3070, 2939, 1724, 1444 and 1104 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ_{H} 7.46 (d, $J = 7\text{ Hz}$, 1 H), 6.31 (d, $J = 7.5\text{ Hz}$, 1 H), 7.15- 7.10 (m, 6 H), 6.09 (t, $J = 4.5\text{ Hz}$, 1 H), 6.01 (t, $J = 4.5\text{ Hz}$, 1 H), 4.54 (d, $J = 1\text{ Hz}$, 2 H), 4.37 (d, $J = 1\text{ Hz}$, 2 H), 3.48 (s, 2 H), 3.13 (s, 6 H), 2.75-2.71 (m, 4 H), 2.30-2.27 (m, 4 H); **^{13}C NMR** (125 MHz, CDCl_3) δ_{C} 167.1, 154.9, 136.6, 136.4, 133.2, 132.5, 131.8, 130.2, 129.3, 128.1, 127.6, 127.6, 127.2, 127.0, 126.5, 126.4, 122.8, 122.3, 103.5, 52.0, 51.9, 40.5, 40.3, 28.0, 27.8, 24.1, 23.1, 22.9; **HRMS** calcd for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_4\text{Na}^+$: 467.19413 found: 467.19287

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Unity 500 spectrometer

std menthol

res=0.7Hz

sw probe

April 1 99

lock freq=1.470

new shims

Pulse Sequence: s2pul

1b

12 10 8 6 4 2 0 -2 ppm

Unity 500 spectrometer

Unity 500 spectrometer

ss-II-80-3

Pulse Sequence: s2pul

ss-II-80-2

Unity 500 spectrometer

Pulse Sequence: s2pul

Unity 500 spectrometer

std-menthol-cdcl3-carbon-april11-99

Pulse Sequence: s2pul

proton spectrum

Mercury 400 spectrometer

Pulse Sequence: s2pul

Mercury 400 spectrometer

Carbon spectrum

Pulse Sequence: s2pul

Unity 500 spectrometer

std menthol
res=0.7Hz
sw probe
April 1 99
lock freq=1.470
new shims

Pulse Sequence: s2pul

Unity 500 spectrometer

std menthol
res=0.7Hz
sw probe
April 1 99
lock freq=1.470
new shims
Pulse Sequence: s2pul

Unity 500 spectrometer

std-manthol-cdcl3-carbon-april1-99

Pulse Sequence: s2pul

Unity 500 spectrometer

std menthol
res=0.7Hz
sw probe
April 1 99
lock freq=1.470
new shims

Pulse Sequence: s2pul

Unity 500 spectrometer

std-menthol-cdcl3-carbon-april11-99

Pulse Sequence: s2pul