Conversion of *N*-Acyl-4-acyloxy-β-lactams into 1,3-Oxazin-6-ones: Two Consecutive Pseudopericyclic Processes

Mateo Alajarín, Angel Vidal, Pilar Sánchez-Andrada, Fulgencio Tovar, and Ginés Ochoa

Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, 30100 Murcia, Spain.

alajarin@fcu.um.es

Supporting Information

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC200 or on a Varian Unity 300 spectrometer. Mass spectra were recorded on a Hewlett-Packard 5993C or on a VG-Autospec spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 instrument.

Materials: 4-Acetoxy-2-azetidinone and 4-benzoyloxy-2-azetidinone are commercially available.

2-Azidobenzoyl chloride,[1] 4-formyloxy-1-(4-methoxyphenyl)-3-methyl-2-azetidinone,[2,3] *cis*-4-formyloxy-3-methyl-2-azetidinone[2,3] and *trans*-4-acetoxy-3-methyl-2-azetidinone[2] were prepared following previously reported prodecures.

Reaction of 2-Azidobenzoyl chloride with 4-Acetoxy-2-azetidinone. To a solution of 4-acetoxy-2-azetidinone (0.39 g, 3 mmol) and 2-azidobenzoyl chloride (1.09 g, 6 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise a solution of Et_3N (1.51 g, 15 mmol) in dry CH_2Cl_2 (15 mL), with ice cooling, and the mixture was stirred overnight. Then the mixture was poured into water (100 mL), the organic layer was separated and the aqueous one extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layer was washed with saturated $NaHCO_3$ aqueous solution (2 x 100 mL), water and brine, dried over $MgSO_4$, and evaporated. The resulting mixture was separated by column chromatography (silica gel, elution with *n*-hexane/ EtOAc 7:3 v/v) yielding 4-acetoxy-1-(2-azidobenzoyl)-2-azetidinone (**2**) and 2-(2-azidophenyl)-6*H*-1,3-oxazin-6-one (**3**).

4-Acetoxy-1-(2-azidobenzoyl)-2-azetidinone **(2):** R_f = 0.5, yield 43%; mp 125-126°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 2130, 2092, 1806, 1763, 1681 cm^{-1}; ^1H NMR

($CDCl_3$) δ 2.17 (s, 3 H), 3.07 (dd, 1 H, *J* = 2.4, 16.8 Hz), 3.49 (dd, 1 H, *J* = 4.8, 16.8 Hz), 6.59 (dd, 1 H, *J* = 2.4, 4.8 Hz), 7.16-7.27 (m, 2 H), 7.49-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.84, 45.24, 73.13, 118.93, 124.71, 125.10 (s), 130.14, 133.15, 138.99 (s), 161.22 (s), 162.76 (s), 169.58 (s); mass spectrum *m/z* (relative intensity) 274 (M^+, 7), 134 (100). Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.67; N, 20.43. Found: C, 52.27; H, 3.55; N, 20.58.

2-(2-Azidophenyl)-6H-1,3-oxazin-6-one **(3):** R_f = 0.6; yield 12%; mp 124-126°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 2127, 1759 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.25 (d, 1 H, *J* = 6.8 Hz), 7.23-7.32 (m, 2 H), 7.56-7.61 (m, 1 H), 7.87 (d, 1 H, *J* = 6.8 Hz), 7.95 (dd, 1 H, *J* = 1.5, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 109.90, 120.04, 121.91 (s), 124.87, 131.83, 133.72, 140.00 (s), 154.25, 158.14 (s), 163.73 (s); mass spectrum *m/z* (relative intensity) 214 (M^+, 48), 186 (100). Anal. Calcd for $C_{10}H_6N_4O_2$: C, 56.08; H, 2.82; N, 26.16. Found: C, 56.25; H, 2.87; N, 26.01.

Conversion of 4-Acetoxy-1-(2-azidobenzoyl)-2-azetidinone (2) into 2-(2-Azidophenyl)-6*H*-1,3-oxazin-6-one (**3**). To a solution of 4-acetoxy-1-(2-azidobenzoyl)-2-azetidinone (**2**) (0.55 g, 2 mmol) in dry CH_2Cl_2 (25 mL) DBU (0.61 g, 4 mmol) was added at once. The mixture was stirred at room temperature for 2 h, then washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography to give 2-(2-azidophenyl)-6*H*-1,3-oxazin-6-one (**3**) (yield: 78%).

General Procedure for the One-Step Preparation of 1,3-Oxazin-6-ones 3 and 5. To a solution of the corresponding 4-acyloxy-2-azetidinone **4** (2 mmol) and the acyl chloride (4 mmol) in dry CH_2Cl_2 (30 mL), with ice cooling, was added dropwise a solution of DBU (1.52 g, 10 mmol) in dry CH_2Cl_2 (15 mL) in about 1 h, and the stirring continued for 2-5 h at room temperature. Then the mixture was poured into saturated $NaHCO_3$ aqueous solution (100 mL), the organic layer was separated and the aqueous one extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layer was washed water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (silica gel, elution with *n*-hexane/ EtOAc).

2-(2-Azidophenyl)-6H-1,3-oxazin-6-one **(3)**: yield 41%. Physical and spectral data as above.

2-Phenyl-6H-1,3-oxazin-6-one **(5a)**: yield 69%; mp 86-87°C (lit.[4] mp 85-87°C).

2-(4-Chlorophenyl)-6H-1,3-oxazin-6-one **(5b)**: yield 58%; mp 111-113°C (lit.[4] mp 112-114°C).

2-(2-Furyl)-6H-1,3-oxazin-6-one **(5c)**: yield 44%; mp 118-119°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 1763, 1603, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.16 (d, 1 H, *J* = 6.8 Hz), 6.64 (dd, 1 H, *J* = 1.6, 3.4 Hz), 7.40 (dd, 1 H, *J* = 0.8, 3.4 Hz), 7.71 (dd, 1 H, *J* = 0.8, 1.6

Hz), 7.80 (d, 1 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 109.12, 112.99, 118.76, 146.88 (s), 147.86, 154.75, 156.92 (s), 157.26 (s); mass spectrum *m/z* (relative intensity) 163 (M^+, 24), 95 (100). Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.58. Found: C, 58.75; H, 2.97; N, 8.35.

2-[(E)-2-Phenylethenyl]-6H-1,3-oxazin-6-one **(5d)**: yield 50%; mp 200-201°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.15 (d, 1 H, *J* = 6.8 Hz), 6.71 (d, 1 H, *J* = 16.1 Hz), 7.40-7.43 (m, 3 H), 7.55-7.60 (m, 2 H), 7.74 (d, 1 H, *J* = 6.8 Hz), 7.86 (d, 1 H, *J* = 16.1 Hz); ^{13}C NMR ($CDCl_3$) δ 109.32, 118.39, 128.37, 129.16, 130.94, 134.30 (s), 144.06, 154.87, 158.34 (s), 164.97 (s); mass spectrum *m/z* (relative intensity) 199 (M^+, 33), 131 (100). Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.08; H, 4.67; N, 7.17.

2-tert-Butyl-6H-1,3-oxazin-6-one **(5e)**: yield 76%; bp 45-50°C (0.40 Torr) [lit.[5] bp 45-50°C (0.40 Torr)].

2-Ethyl-6H-1,3-oxazin-6-one **(5f)**: yield 40%; bp 38-43°C (0.20 Torr) [lit.[5] bp 45-50°C (0.20 Torr)].

2-(4-Bromophenyl)-6H-1,3-oxazin-6-one **(5g)**: yield 53%; mp 134-135°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 1746, 1607, 1543 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.23 (d, 1 H, *J* = 6.7 Hz), 7.64 (d, 2 H, *J* = 8.6 Hz), 7.82 (d, 1 H, *J* = 6.7 Hz), 8.07 (d, 2 H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 109.85, 128.79 (s), 129.99, 132.31, 154.57, 158.01 (s), 164.03 (s), one quaternary carbon was not observed; mass spectrum *m/z* (relative intensity) 253 (M^+ + 2, 76), 251 (M^+, 82), 185 (88), 183 (100). Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.64; H, 2.40; N, 5.55. Found: C, 47.44; H, 2.31; N, 5.67.

Preparation of *cis*-4-Formyloxy-3-methyl-1-[(*E*)-2-phenylethenyloxy]-2-azetidino-ne (*cis*-14) and *trans*-4-Acetoxy-3-methyl-1-[(*E*)-2-phenylethenyloxy]-2-azetidinone (*trans*-15). Compounds *cis*-**14** and *trans*-**15** were prepared by reaction of cinnamoyl chloride with *cis*-4-formyloxy-3-methyl-2-azetidinone and *trans*-4-acetoxy-3-methyl-2-azetidinone, respectively, under the reaction conditions described for the preparation of 4-acetoxy-1-(2-azidobenzoyl)-2-azetidinone (**2**).

cis-4-Formyloxy-3-methyl-1-[(E)-2-phenylethenyloxy]-2-azetidinone **(*cis*-14)**: yield 67%; mp 117-119°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 1792, 1722, 1696, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3 H, *J* = 7.7 Hz), 3.46 (dq, 1 H, *J* = 4.8, 7.7 Hz), 6.46 (d, 1 H, *J* = 4.8 Hz), 7.05 (d, 1 H, *J* = 15.8 Hz), 7.15-7.21 (m, 3 H), 7.37-7.41 (m, 2 H), 7.67 (d, 1 H, *J* = 15.8 Hz), 7.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.88, 49.27, 75.00, 117.65, 128.72, 128.92, 131.08, 133.87 (s), 147.04, 159.37, 162.26 (s), 166.50 (s); mass spectrum *m/z* (relative intensity) 259

(M^+, 10), 131 (100). Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.67; H, 5.17; N, 5.21.

***trans-4-Acetoxy-3-methyl-1-[(E)-2-phenylethenyloxy]-2-azetidinone* (*trans*-15)**: yield 69%; mp 141-142°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 1796, 1752, 1692, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (d, 3 H, *J* = 7.6 Hz), 2.15 (s, 3 H), 3.21 (dq, 1 H, *J* = 1.6, 7.6 Hz), 6.08 (d, 1 H, *J* = 1.6 Hz), 7.29 (d, 1 H, *J* = 15.6 Hz), 7.39-7.42 (m, 3 H), 7.59-7.63 (m, 2 H), 7.89 (d, 1 H, *J* = 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 11.17, 20.78, 53.24, 79.45, 117.97, 128.76, 128.98, 131.09, 134.04 (s), 146.97, 162.50 (s), 166.57 (s), 169.79 (s); mass spectrum *m/z* (relative intensity) 273 (M^+, 6), 131 (100). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.77; H, 5.37; N, 5.21.

Preparation of 5-Methyl-2-[(*E*)-2-phenylethenyl]-6*H*-1,3-oxazin-6-one (16). To a solution of *cis*-**14** or *trans*-**15** (2 mmol) in dry CH_2Cl_2 (25 mL) DBU (0.61 g, 4 mmol) was added at once. The mixture was stirred at room temperature for 5 h, then washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (elution with *n*-hexane/EtOAc 7:3 v/v).

***5-Methyl-2-[(E)-2-phenylethenyl]-6H-1,3-oxazin-6-one* (16):** yield 63% from *cis*-**14**; 76% from *trans*-**15**; mp 158-159°C; colorless prisms (chloroform/*n*-hexane); IR (Nujol) 1730, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 6.67 (d, 1 H, *J* = 16.2 Hz), 7.39-7.41 (m, 3 H), 7.52-7.56 (m, 3 H), 7.77 (d, 1 H, *J* = 16.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.44, 118.41, 119.29 (s), 128.08, 129.03, 130.51, 134.44 (s), 142.38, 150.61, 160.18 (s), 162.46 (s); mass spectrum *m/z* (relative intensity) 213 (M^+, 32), 212 (100). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.41; H, 5.05; N, 6.43.

References

1.- Porter, T. C.; Smalley, R. K.; Teguiche, M.; Purwono, B. *Synthesis* **1997**, 773.

2.- Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.

3.- Alcaide, B.; Aly, M. F.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 8819.

4.- Stájer, G.; Szabó, A. E.; Fülöp, F.; Bernáth, G. *Synthesis* **1984**, 345.

5.- McNab, H.; Withell, K. *Tetrahedron* **1996**, *52*, 3163.