Stanna-Brook Rearrangement of Carboxylic Acid Derivatives. Synthetic Utility and Mechanistic Studies

M. Rita Paleo, M. Isabel Calaza, Paula Graña and F. Javier Sardina*

Departamento de Química Orgánica. Facultad de Química. Universidad de Santiago de Compostela.

15782 Santiago de Compostela. SPAIN.

Supplementary material

Methods and Materials. All reactions requiring anhydrous conditions were conducted in oven-dried glassware under Ar atmosphere. Solvents were distilled immediately before use: THF and Et₂O from Na/benzophenone; benzene and diisopropylamine from CaH₂; MeOH from Mg(OCH₃)₂. Final reaction mixtures were dried over anhydrous Na₂SO₄ before filtration and evaporation of solvents under reduced pressure. Column chromatography was performed using 230-400 mesh silica gel. Melting points were measured using a Büchi apparatus and open-ended capillary tubes. IR were taken in CH₂Cl₂, and NMR spectra in CDCl₃ at room temperature unless otherwise stated. Chemical shifts are reported in ppm (δ) downfield from internal TMS and coupling constants are given in hertz. X-ray crystallography was carried out by the RIAIDT facility, Universidad de Santiago de Compostela. *N*-Phenylfluoren-9-yl-alanine derived oxazolidinone (**1a**) and *N*-phenylfluoren-9-yl-leucine derived oxazolidinone were prepared as described in the literature.¹

General Procedure for the Preparation of *N*-Boc-oxazolidines (1). A solution of *N*-Boc-protected amino acid (5 mmol), paraformaldehyde (195 mg, 6.5 mmol) and *p*-toluensulfonic acid (43 mg, 0.25 mmol) in benzene (50 mL) was heated at reflux with the aid of a Dean-Stark trap, and heating was continued until no starting material was detected by tlc (1-3 h). The reaction mixture was cooled to room temperature, washed with 5% KHCO₃ (2 x 30 mL) and brine (30 mL), dried and concentrated. The crude product was purified by column chromatography or by crystallization from suitable solvents.²

(4*S*)-*N*-tert-Butyloxycarbonyl-4-methyl-1,3-oxazolidin-5-one (1b**).** Crystallization from CH₂Cl₂-hexane gave 825 mg (82% yield) of the product as white needles: mp: 66-67 °C (CH₂Cl₂-hexane); IR 1800, 1708 cm⁻¹; ¹H NMR (330K) δ 5.38 (d, *J* = 4.4, 1H), 5.20 (d, *J* = 4.4, 1H), 4.20 (q, *J* = 6.9, 1H), 1.51 (d, *J* = 6.9, 3H), 1.50 (s, 9H); ¹³C NMR δ 173.1, 151.7, 81.5, 77.2, 50.3, 28.0, 16.4. Anal. Calcd for C₉H₁₅NO₄: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.59; H, 7.58; N, 6.98. [α]_D²⁰ = +103.9° (c 1.4, CH₂Cl₂).

(4*S*)-*N*-tert-Butyloxycarbonyl-4-isopropyl-1,3-oxazolidin-5-one (1c**).** Crystallization from CH₂Cl₂-hexane yielded the product as a white solid (814 mg, 71% yield): mp: 52-54°C (CH₂Cl₂-hexane); IR 1804, 1711 cm⁻¹; ¹H NMR (330K) δ 5.53 (d, *J* = 4.7, 1H), 5.09 (dd, *J* = 4.7, 0.8, 1H), 4.13 (d, *J* = 4.0, 1H), 2.34 (m, 1H), 1.50 (s, 9H), 1.08 (d, *J* = 7.0, 3H), 1.04 (d, *J* = 7.0, 3H); ¹³C NMR δ 171.8, 152.5, 81.6, 78.3, 59.9, 31.1,

27.9, 17.9, 17.5. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.84; H, 8.67; N, 6.13. $[\alpha]_D^{20} = +106.9^\circ$ (c 1.1, CH_2Cl_2).

(4S)-4-Benzyl-N-tert-butyloxycarbonyl-1,3-oxazolidin-5-one (1d). Crystallization from Et_2O -hexane yielded the product as a white solid (68% yield): mp: 79-80°C (Et_2O -hexane); IR 1802, 1710 cm^{-1} ; 1H NMR ($CDCl_3$, 330K) δ 7.26 (m, 3H), 7.16 (m, 2H), 5.20 (bs, 1H), 4.45 (m, 1H), 4.28 (bs, 1H), 3.35 (bd, $J = 13.8$, 1H), 3.13 (dd, $J = 13.8$, 3.1, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 330K) δ 172.1, 151.8, 135.1, 129.7, 128.7, 127.4, 81.9, 78.0, 56.4, 35.9, 28.3. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.79; H, 6.90; N, 5.03. $[\alpha]_D^{20} = +181.4^\circ$ (c 1.1, CH_2Cl_2).

(4S)-N-tert-Butyloxycarbonyl-4-(2-methylthioethyl)-1,3-oxazolidin-5-one (1e). Purification by column chromatography ($EtOAc$:hexane, 1:4) afforded 914 mg of the product as a colorless oil (70% yield): IR 1799, 1709 cm^{-1} ; 1H NMR δ 5.45 (bs, 1H), 5.17 (dd, $J = 4.6$, 0.9, 1H), 4.29 (t, $J = 5.2$, 1H), 2.65-2.44 (m, 2H), 2.30-2.07 (m, 2H), 2.04 (s, 3H), 1.46 (s, 9H); ^{13}C NMR δ 172.4, 151.9, 81.7, 77.6, 53.3, 28.7, 27.9, 14.6. Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.55; H, 7.33; N, 5.36. Found: C, 50.94; H, 7.57; N, 5.35. $[\alpha]_D^{20} = +136.4^\circ$ (c 1.7, CH_2Cl_2).

General Procedure for the Preparation of α -Amino Acids-derived Dimers 2. Method A: A 0 °C solution of diisopropylamine (220 μL , 1.6 mmol) in THF (5 mL) was treated with $nBuLi$ (1.53 mmol) and stirred for 15 min. Tributyltin hydride (360 μL , 1.35 mmol) was added and stirred for an additional 15 min. The solution of Bu_3SnLi thus prepared was cooled to -78 °C and treated with a THF solution (5 mL) of the oxazolidinone **1** (0.9 mmol). The reaction mixture was stirred at -78 °C for 3 h, quenched by addition of pH 7.0 phosphate buffer solution (2 mL) and then partitioned between pH 7.0 phosphate buffer solution and $EtOAc$. The aqueous layer was extracted with $EtOAc$ (10 mL), and the combined organic phase was washed with brine (15 mL), dried, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2 , $EtOAc$:hexane 1:3). **Method B:** A 0 °C solution of bis(tributyltin) (300 μL , 0.6 mmol) in THF (2 mL) was treated with $nBuLi$ (0.6 mmol) and stirred for 15 min, cooled to -78 °C, and treated via cannula with a solution of oxazolidinone **1** (0.4 mmol) in THF (4 mL). The resulting solution was stirred for 3.5 h, then quenched by addition of pH 7.0 buffer solution (2 mL), and partitioned between pH 7.0 phosphate buffer solution and $EtOAc$. The aqueous layer was extracted with $EtOAc$ (10 mL), and the combined organic phase was washed with brine (15 mL), dried, filtered and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2 , $EtOAc$:hexane 1:3).

(4S,4'S,5S,5'S) 4,4'-Dimethyl-3,3'-bis-(9-phenyl-9H-fluoren-9-yl)-5,5'-bi-1,3-oxazolidine-5,5'-diol (2a). Following method A, **1a** was reacted with Bu_3SnLi at -53 °C for 6 h. After the work-up, the crude product was crystallized from $EtOAc$:hexane, and the mother liquor was concentrated and purified by column chromatography (SiO_2 , $EtOAc$: hexane 1:8) to obtain **2a** in 54% combined yield (167 mg): mp: 163-164 °C ($EtOAc$ -hexane); 1H NMR δ 7.72 (d, $J = 7.6$, 2H), 7.56-7.04 (m, 24H), 4.90 (d, $J = 7.3$, 2H), 4.82 (d, $J = 7.3$, 2H), 2.27 (q, $J = 6.8$, 2H), 2.05 (s, 2H), 0.32 (d, $J = 6.7$, 6H); ^{13}C NMR δ 148.0, 147.3, 144.7, 142.5, 139.0, 129.4, 128.4, 128.3, 127.8, 127.3, 127.2, 127.0, 126.6, 125.5, 120.2, 119.4, 104.3, 81.0, 76.9, 56.6, 16.4.

Anal. Calcd for $C_{46}H_{40}N_2O_4$: C, 80.68; H, 5.89; N, 4.09. Found: C, 80.61; H, 6.03; N, 4.07. $[\alpha]_D^{20} = -482.2^\circ$ (c 1.0, CH_2Cl_2).

Di-*tert*-butyl (4*S*,4'*S*,5*S*,5'*S*) 5,5'-dihydroxy-4,4'-dimethyl-5,5'-bi-1,3-oxazolidine-3,3'-dicarboxylate (2b). Following method A, **2b** was obtained in 63% yield (115 mg) as a white foam: IR 1706 cm^{-1} ; 1H NMR (325 K) δ 5.20 (d, $J = 4.7$, 2H), 4.81 (d, $J = 4.7$, 2H), 4.06 (q, $J = 6.6$, 2H), 3.42 (bs, 2H), 1.47 (s, 18H), 1.31 (d, $J = 6.6$, 6H); ^{13}C NMR (325 K) δ 153.0, 105.2, 80.8, 76.4, 54.9, 28.4, 14.3. Anal. Calcd for $C_{18}H_{32}N_2O_8$: C, 53.45; H, 7.97; N, 6.93. Found: C, 53.39; H, 8.34; N, 6.56. $[\alpha]_D^{20} = +104^\circ$ (c 1.0, CH_2Cl_2).

***tert*-Butyl (4*S*) 5-hydroxy-4-methyl-1,3-oxazolidine-3-carboxylate (3b).** Oil isolated as a mixture of diastereomers in a (1:6.5) ratio: IR 1698, 1679 cm^{-1} ; Major diastereomer 1H NMR (330 K) δ 5.23 (d, $J = 3.4$, 1H), 5.09 (d, $J = 3.4$, 1H), 4.94 (d, $J = 3.5$, 1H), 3.87 (q, $J = 6.6$, 1H), 2.92 (bs, 1H), 1.47 (s, 9H), 1.22 (d, $J = 6.5$, 3H); ^{13}C NMR (325 K) δ 152.6, 102.1, 80.3, 77.8, 58.3, 28.5, 17.0. Minor diastereomer: 1H NMR (330 K) δ 5.50 (t, $J = 4.6$, 1H), 5.02 (d, $J = 4.2$, 1H), 4.87 (d, $J = 4.3$, 1H), 3.91 (m, 1H), 2.93 (bs, 1H), 1.47 (s, 9H), 1.27 (d, $J = 6.5$, 3H); ^{13}C NMR (325 K) δ 152.6, 98.0, 80.4, 76.3, 55.2, 28.4, 13.0. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.57; H, 8.56; N, 6.70.

Di-*tert*-butyl (4*S*,4'*S*,5*S*,5'*S*) 5,5'-dihydroxy-4,4'-diisopropyl-5,5'-bi-1,3-oxazolidine-3,3'-dicarboxylate (2c). Following method B, **2c** was obtained in 82% yield (76 mg): mp: 129-131 $^\circ C$ (Et₂O-hexane); IR 1707 cm^{-1} ; 1H NMR ($CDCl_3 + D_2O$, 333 K) δ 5.38 (d, $J = 5.5$, 2H), 4.65 (d, $J = 5.5$, 2H), 4.03 (d, $J = 4.9$, 2H), 2.21 (m, 2H), 1.47 (s, 18H), 1.13 (d, $J = 6.7$, 6H), 1.03 (d, $J = 6.7$, 6H); ^{13}C NMR (330 K) δ 155.0, 106.2, 81.0, 77.8, 64.2, 28.4, 28.2, 22.2, 18.7. Anal. Calcd for $C_{22}H_{40}N_2O_8$: C, 57.37; H, 8.75; N, 6.08. Found: C, 57.11; H, 8.89; N, 5.99. $[\alpha]_D^{20} = +84.8^\circ$ (c 1.0, CH_2Cl_2).

***tert*-Butyl (4*S*) 5-hydroxy-4-isopropyl-1,3-oxazolidine-3-carboxylate (3c).** Following method B, **3c** was isolated in 6% yield (5.5 mg): 1H NMR ($CDCl_3 + D_2O$, 330 K) δ 5.36 (d, $J = 2.8$, 1H), 5.16 (d, $J = 3.5$, 1H), 4.84 (d, $J = 3.5$, 1H), 3.67 (d, $J = 6.3$, 1H), 3.20 (bs, 1H), 1.92 (m, 1H), 1.46 (s, 9H), 0.95 (d, $J = 6.9$, 3H), 0.91 (d, $J = 6.8$, 3H); ^{13}C NMR (330 K) δ 153.6, 98.4, 80.4, 78.7, 68.1, 29.6, 28.4, 18.7, 18.1.

Di-*tert*-butyl (4*S*,4'*S*,5*S*,5'*S*) 5,5'-dihydroxy-4,4'-dibenzyl-5,5'-bi-1,3-oxazolidine-3,3'-dicarboxylate (2d). Following method A or B, 200 mg of **1d** (0.72 mmol) gave a mixture of diastereoisomers in 65% yield (130 mg). The asymmetric dimer was precipitated from CH_2Cl_2 -hexane: mp 112-115 $^\circ C$; IR 1672, 1706 cm^{-1} ; 1H NMR δ 7.20-7.04 (m, 10H), 5.35 (bt, $J = 10.4$, 1H), 5.12 (m, 1H), 4.84 (dd, $J = 10.7$, 20.4, 2H), 4.58 (m, 1H), 4.21 (m, 1H), 3.29-3.13 (m, 4H), 1.88 (bs, 2H), 1.30-1.06 (m, 18H); ^{13}C NMR δ 155.0, 154.5, 154.4, 154.0, 138.7, 138.6, 138.2, 138.1, 129.7, 129.3, 129.2, 128.9, 128.8, 128.4, 128.3, 128.2, 126.5, 126.4, 126.3, 126.2, 104.9, 94.7, 94.1, 93.8, 81.4, 81.0, 80.9, 80.6, 80.3, 79.8, 64.9, 64.6, 63.4, 63.2, 62.0, 61.8, 59.4, 59.3, 33.8, 33.4, 33.2, 28.1, 27.8. Anal. Calcd for $C_{30}H_{40}N_2O_8$: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.73; H, 7.09; N, 5.04. $[\alpha]_D^{20} = +11.2^\circ$ (c 1.0, CH_2Cl_2). When the mixture was warmed at 50 $^\circ C$ in $CDCl_3$, the symmetric dimer was obtained as the only product and recrystallized from Et₂O-hexane: mp 128-130 $^\circ C$; IR 1675, 1680, 1692 cm^{-1} ; 1H NMR (330 K) δ 7.29-7.17 (m, 10H), 5.33 (bd, $J = 5.5$, 2H), 4.70 (d, $J = 5.5$, 2H), 4.40 (dd, $J = 5.5$, 8.5, 2H), 3.09 (s, 2H), 2.96 (m, 4H), 1.27 (s, 18H); ^{13}C NMR δ 153.8, 138.7, 129.8, 128.4, 126.5, 105.2,

80.9, 76.7, 61.6, 35.1, 28.0. Anal. Calcd for C₃₀H₄₀N₂O₈: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.94; H, 7.32; N, 5.02. $[\alpha]_D^{20} = +67.4^\circ$ (c 1.0, CH₂Cl₂).

Di-tert-butyl (4S, 4'S, 5S, 5'S) 5,5'-dihydroxy-4,4'-bis-2-(2-methylsulfanyl-ethyl)-5,5'-bi-1,3-oxazolidine-3,3'-dicarboxylate (2e). Following method B, **2e** was obtained in 63% yield (67 mg) as a white foam: IR 1707 cm⁻¹; ¹H NMR (320 K) δ 5.33 (d, *J* = 5.6, 2H), 4.65 (d, *J* = 5.6, 2H), 4.25 (dd, *J* = 5.0, 8.3, 2H), 3.48 (bs, 2H), 2.61 (t, *J* = 7.2, 4H), 2.10 (s, 6H), 2.07 (m, 2H), 1.92 (m, 2H), 1.45 (s, 18H); ¹³C NMR (320 K) δ 154.2, 105.3, 81.4, 76.8, 58.7, 31.3, 28.9, 28.3, 15.4. Anal. Calcd for C₂₂H₄₀N₂O₈S₂: C, 50.36; H, 7.68; N, 5.34. Found: C, 50.36; H, 7.68; N, 5.27.

Benzil (5). A 0 °C solution of diisopropylamine (147 μ L, 1.05 mmol) in THF (4 mL) was treated with *n*BuLi (1.0 mmol) and stirred for 15 min. Tributyltin hydride (255 μ L, 0.96 mmol) was added and stirred for an additional 15 min. The solution of Bu₃SnLi thus prepared was cooled to -40 °C and treated with methyl benzoate (100 μ L, 0.8 mmol). The reaction mixture was stirred at -40 °C for 4 h, quenched by addition of pH 7.0 phosphate buffer solution (2 mL) and then partitioned between pH 7.0 phosphate buffer solution and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (10 mL), and the combined organic phase was washed with brine (15 mL), dried, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO₂, EtOAc:hexane 1:15) to give 46 mg (55% yield) of **5**, identical to a commercial sample (mp, spectral properties).

Phenanthrenequinone (7). A 0 °C solution of bis(trimethyltin) (380 μ L, 1.85 mmol) in THF (5 mL) was treated with *n*BuLi (1.8 mmol) and stirred for 15 min, cooled to -78 °C, and treated via cannula with a solution of diester **6** (100 mg, 0.37 mmol) in THF (3 mL). The resulting solution was stirred for 5 h, then quenched by addition of pH 7.0 buffer solution (2 mL), and partitioned between pH 7.0 phosphate buffer solution and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (10 mL), and the combined organic phase was washed with brine (15 mL), dried, filtered and concentrated under reduced pressure. The product was purified by column chromatography (SiO₂, EtOAc:hexane 1:6) to give 76 mg of **7** (99% yield). The product was compared with a commercial sample showing identical physical and spectroscopic properties.

Preparation of acylsilanes from *N*-phenylfluoren-9-yl-oxazolidinones and PhMe₂SiLi: General Procedure. A -78 °C solution of **1a**¹ or *N*-phenylfluoren-9-yl-leucine-derived oxazolidinone¹ (0.3 mmol) in THF (6 mL) was treated with PhMe₂SiLi³ (200 mol%) and stirred for 3 h. Then a solution of succinic anhydride (33 mg, 0.33 mmol) in THF (0.5 mL) was added at -78 °C and after 10 min, AcOH (0.2 mL) was added and stirred for 1 h at rt. The reaction mixture was partitioned between EtOAc (15 mL) and satd NaHCO₃ (10 mL), the organic phase was separated and washed with satd NaHCO₃ (10 mL), H₂O (10 mL), and brine (10 mL), dried, filtered and concentrated. Purification by column chromatography (SiO₂, hexane: Et₂O 5:1 + 0.5% Et₃N) afforded the product as a white foam.

(2S)-1-(Dimethyl-phenyl-silanyl)-2-(9-phenyl-9H-fluoren-9-yl-amino)-propan-1-one (17). White foam (93 mg, 69% yield): IR 1640 cm⁻¹; ¹H NMR δ 7.73-7.66 (m, 2H), 7.41-7.15 (m, 15H), 7.06 (d, *J* = 7.5, 1H), 3.81 (bs, 1H), 3.01 (q, *J* = 7.3, 1H), 0.71 (d, *J* = 7.3, 3H), 0.22 (s, 3H), 0.08 (s, 3H); ¹³C NMR δ 246.2, 150.0, 149.9, 144.7, 141.0, 139.7, 134.1, 133.7, 129.6, 128.1, 128.06, 128.0, 127.9, 127.8, 127.6, 126.9, 126.1,

126.0, 125.2, 119.6, 119.5, 73.0, 61.2, 19.0, -4.65, -4.70. Anal. Calcd for C₃₀H₂₉NOSi: C, 80.49; H, 6.53; N, 3.13. Found: C, 80.68; H, 6.76; N, 3.11. $[\alpha]_D^{20} = -115^\circ$ (c 1.3, CH₂Cl₂).

(2S)-4-Methyl-1-(dimethyl-phenyl-silanyl)-2-(9-phenyl-9H-fluoren-9-yl-amino)-pentan-1-one (18).

White foam (104 mg, 71%); IR 1640 cm⁻¹; ¹H NMR δ 7.78-7.68 (m, 2H), 7.41-7.13 (m, 15H), 7.01 (d, $J = 7.5$, 1H), 3.65 (bs, 1H), 2.99 (dd, $J = 9.5, 2.6$, 1H), 1.83 (m, 1H), 0.73 (d, $J = 6.7$, 3H), 0.69 (m, 2H), 0.20 (s, 3H), 0.01 (s, 3H), -0.08 (d, $J = 6.7$, 3H); ¹³C NMR δ 246.4, 150.0, 149.9, 145.5, 141.4, 140.0, 134.5, 134.2, 129.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.5, 127.2, 126.2, 126.1, 119.7, 119.6, 73.1, 63.6, 40.5, 24.1, 24.0, 20.0, -4.7, -4.9. Anal. Calcd for C₃₃H₃₅NOSi: C, 80.93; H, 7.20; N, 2.86. Found: C, 80.80; H, 7.47; N, 2.74. $[\alpha]_D^{20} = -118^\circ$ (c 1.2, CH₂Cl₂).

References

- (1) Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, 62, 6862.
- (2) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Chuhan, J.; Schofield, C. J. *Tetrahedron Lett.* **1995**, 36, 7761.
- (3) Fleming, I.; Newton, T. W.; Roessler, F. J. *Chem. Soc., Perkin Trans I* **1981**, 2527.