A Novel Free-Radical Ring Contraction of a Cyclic Carbamate

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Abstract: During a study on iodocyclocarbamation reactions of 2-styryl-4-piperidones, a novel ring contraction was observed. Iodocyclocarbamation of 2-styryl-4-piperidone **3** gave the bicyclic carbamate **4**. Reduction of **4** under free-radical conditions effected a stereoselective ring contraction to provide oxazolidinone **6**. A three-electron-three-center mechanism is proposed.

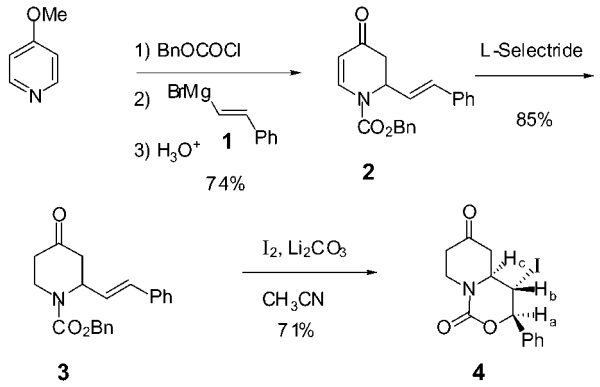
During a study on the iodocyclocarbamation reactions of 1-acyl-2-alkenyl-1,2,3,6-tetrahydropyridines,[1] a related cyclization of 2-styryl-4-piperidones was examined. The Grignard reagent **1**, prepared from *trans*-β-bromostyrene, was added to 4-methoxypyridine and benzyl chloroformate in THF to provide 2,3-dihydro-4-pyridone **2** in 74% yield[2] (Scheme 1). Conjugate reduction with L-Selectride (lithium tri-*sec*-butylborohydride) gave the 4-piperidone **3**,[1,3] which was subjected to the iodocyclocarbamation reaction.[4] Lithium carbonate and iodine were added to **3** in acetonitrile to give the cyclic carbamate **4** in 71% yield. The stereochemistry of **4** was determined by ^{1}H NMR (J_{ab} = 9.6 Hz, J_{bc} = 4.0 Hz).

This highly regio- and stereoselective cyclization can be explained through the mechanism depicted in Scheme 2. Due to A$^{(1,3)}$ strain,[5] the C-2 styryl group of **3** is axial. Iodonium ion formation and subsequent attack by the carbamate carbonyl of the Cbz group leads to the observed product.

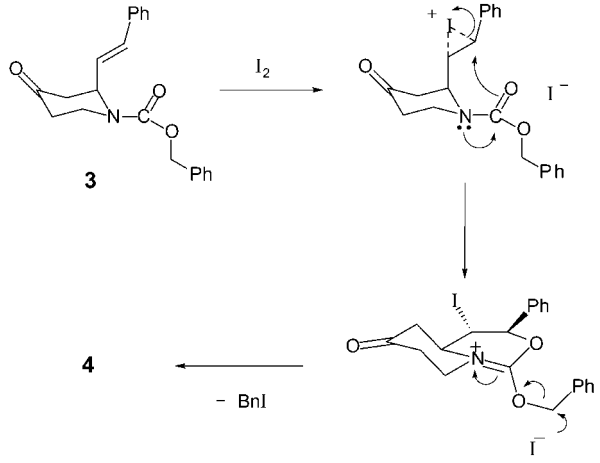
It was hoped that bicyclic carbamate **4** would be a precursor to γ-amino alcohols such as the natural product sedamine (**5**) (Scheme 3). To this end, attempts were made to reductively remove the iodine from **4**. When free-radical conditions were used, either Et_3B/Bu_3SnH or $AIBN/Bu_3SnH$, the ring-contracted product **6** resulted in 70% and 65% yields, respectively. The rearrangement proceeded with complete control of stereochemistry (^{1}H NMR, COSY, and NOESY). Although it has been reported that halolactones can undergo radical ring contractions,[6] this is the first example of a corresponding carbamate rearrangement. The ring contraction of **4** can be rationalized as occurring via a three-electron-three-center mechanism[7] as depicted in Scheme 4.

Although this rearrangement presented itself as an unanticipated event, it has potential value for the stereocontrolled construction of alkaloid building blocks and β-amino alcohols.

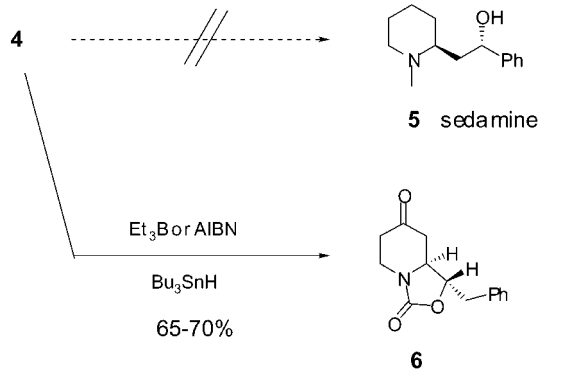
Scheme 1



Scheme 2



Scheme 3



Experimental Section

All reactions described in this section were performed using oven-dried glassware under an argon or dry nitrogen atmos-

(1) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839.
(2) (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. (b) Comins, D. L.; Joseph, S. P.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 793.
(3) (a) Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, 569. (b) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035 and references cited therein.
(4) For related iodocyclocarbamation reactions, see: (a) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654, and references cited therein. (b) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1990**, *55*, 4668.
(5) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841. Johnson, F. *Chem. Rev.* **1968**, *68*, 375. Foley, M. A., Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445 and references cited therein.
(6) Crich, D.; Beckwith, A. L. J.; Filzen, G. F.; Longmore, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 7422.
(7) Lacôte, E.; Renaud, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2259 and references cited therein.

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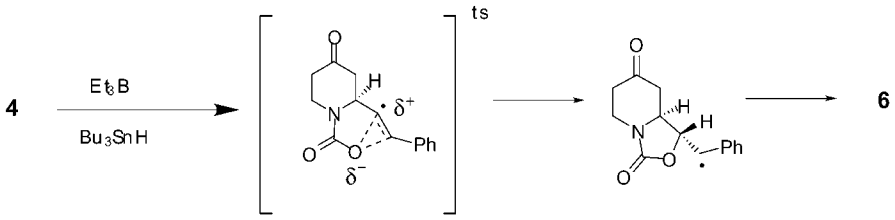
Scheme 4



phere. THF, toluene, and diethyl ether were dried by distillation from sodium/benzophenone. Other reagents and solvents were stored over molecular sieves under argon and used directly. Radial PLC was done using a model 7924T Chromatotron (Harrison Research, Palo Alto, CA) using thin layers of silica gel−gypsum. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

1-(Benzyloxycarbonyl)-2-(2′-*trans*-phenylethenyl)-2,3-dihydro-4-pyridone (2). Magnesium turnings (0.75 g, 41.26 mmol) were mechanically stirred at rt overnight under argon, and then 8 mL of anhydrous THF was added to the flask. Neat *trans*-*β*-bromo-1-styrene (1.51 mL, 8.25 mmol) was added dropwise at rt. The mixture was stirred for 2 h at rt.

To a solution of 4-methoxypyridine (0.75 g, 6.88 mmol) in 100 mL of anhydrous THF at −23 °C was added dropwise benzyl chloroformate (1.03 mL, 7.22 mmol). The reaction mixture was stirred at −23 °C for 1.5 h. The previously prepared Grignard reagent was transferred dropwise via a double-tipped stainless steel needle to the flask containing the *N*-acylpyridinium salt, and the mixture was stirred at −23 °C for 2 h. Saturated aqueous oxalic acid (30 mL) was added. The reaction mixture was warmed to rt and stirred for 2 h. The aqueous layer was extracted with diethyl ether. The combined ether extracts were washed with saturated aqueous Na_2CO_3 and brine and were dried over anhydrous K_2CO_3. Filtration through Celite and concentration in vacuo gave the crude product. Purification by radial PLC (silica gel, 5−20% EtOAc/hexanes) yielded 1.70 g (74%) of **2** as a white solid: mp 107−8 °C; IR (KBr) 2964, 2895, 1726, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, 1 H, J = 8.2 Hz), 7.39−7.27 (m, 10 H), 6.50 (d, 1 H, J = 15.5 Hz), 6.21 (dd, 1 H, J = 6.7 and 18.0 Hz), 5.41−5.24 (m, 4 H), 2.97 (dd, 1 H, J = 6.9 and 16.6 Hz), 2.63 (d, 1 H, J = 16.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 152.7, 141.8, 135.9, 135.1, 133.3, 128.9, 128.8, 128.7, 128.4, 126.8, 123.8, 107.7, 69.4, 55.1, 40.7. Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found; C, 75.73; H, 5.78; N, 4.18.

1-(Benzyloxycarbonyl)-2-(2′-*trans*-phenylethenyl)-4-piperidone (3). L-Selectride (1.50 mL, 1.50 mmol, 1 M in THF) was added dropwise to a −78 °C solution of dihydropyridone **2** (0.50 g, 1.50 mmol) in 10 mL of anhydrous THF. The resulting mixture was stirred at −78 °C for 1 h and then poured into 10 mL of saturated aqueous Na_2CO_3 at 0 °C. The mixture was allowed to warm to rt, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product. Purification by radial PLC (silica gel, 5−30% EtOAc/hexanes) gave 430 mg (85%) of piperidone **3** as a clear oil: IR (neat) 2966, 2919, 1689, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.21 (m, 10 H), 6.48 (d,1 H, J = 15.5 Hz), 6.12 (dd, 1 H, J = 6.7 and 18.0 Hz), 5.40 (b s, 1 H), 5.21 (s, 2 H), 4.29 (m, 1 H), 3.43 (m, 1 H), 2.83−2.30 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 155.5, 136.5, 136.2, 133.0, 128.8, 128.6, 128.4, 128.3, 127.3, 126.8, 68.0, 53.5, 44.4, 40.7, 39.6. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found; C, 75.21; H, 6.37; N, 4.17.

(4*R,5*S**,6*S**)-1-Aza-5-iodo-3-oxa-4-phenylbicyclo[4.4.0]decane-2,8-dione (4).** To a flask covered with aluminum foil, a solution of piperidone **3** (0.61 g, 1.81 mmol) in 17 mL of anhydrous acetonitrile at rt was added along with Li_2CO_3 (0.67 g, 9.05 mmol) and anhydrous iodine (0.97 g, 3.80 mmol). The reaction mixture was stirred overnight at rt. Saturated aqueous Na_2CO_3 (10 mL) was added and the solution was allowed to warm to rt. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with 10% $NaHSO_3$ and brine and were dried over anhydrous K_2CO_3. The solution was filtered through Celite and concentrated in vacuo to give the crude product. Purification by radial PLC (silica gel, 5−50% EtOAc/hexanes) and recrystallization from $CHCl_3$/hexane gave 473 mg (71%) of compound **4** as a yellow solid: mp 177−8 °C; IR (KBr) 2848, 1754, 1707, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5 H), 5.14 (d, 1 H, J = 9.6 Hz), 4.75 (dd, 1 H, J = 4.0 and 9.6 Hz), 4.24 (ddd, 1 H, J = 1.6, 7.2 and 13.6 Hz), 4.05 (dt, 1 H, J = 4.0 and 11.6 Hz), 3.20 (td, 1 H, J = 4.4 and 13.2 Hz), 2.85 (dd, 1 H, J = 4.0 and 14.0 Hz), 2.59−2.42 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 155.2, 138.4, 129.3, 129.2, 128.3, 82.1, 59.9, 47.2, 40.5, 39.8, 32.6; HRMS calcd for $[C_{14}H_{14}INO_3 + H]$ 372.0097 $[(M + H)^+]$, found 372.0092.

6-Aza-8-oxa-9-benzylbicyclo[4.3.0]nonane-3,7-dione (6). To a stirred cloudy solution of compound **4** (0.075 g, 0.202 mmol) in 5 mL of toluene at rt were added tributyltin hydride (0.12 mL, 0.446 mmol) and Et_3B (0.02 mL, 0.02 mmol, 1.0 M in hexane). The reaction mixture was stirred for 30 min and then diluted with EtOAc (7 mL). Saturated aqueous KF (1 mL) and anhydrous KF (0.5 g) were added, and the mixture was stirred for 30 min at rt. The mixture was filtered, and the filtrate was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by radial PLC (silica gel, 5−30% EtOAc/hexanes) to give 34.6 mg (70%) of **6** as a white solid: mp 139−40 °C; IR (KBr) 2923, 1755, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (m, 5 H), 4.41 (ddd, 1 H, J = 5.2, 7.6 and 11.2 Hz), 4.19 (ddd, 1 H, J = 1.6, 7.6 and 13.4 Hz), 3.68 (dt, 1 H, J = 4.8 and 11.2 Hz), 3.21 (dd, 1 H, J = 5.6 and 13.8 Hz), 3.12 (td, 1 H, J = 4.4 and 11.6 Hz), 2.91 (dd, 1 H, J = 7.6 and 13.8 Hz), 2.58−2.46 (m, 1 H), 2.40−2.36 (m, 1 H), 2.30 (dd, 1 H, J = 11.6 and 14.0 Hz), 2.19 (ddd, 1 H, J = 1.6, 4.4 and 14.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 159.0, 134.3, 129.2, 128.9, 127.5, 80.3, 58.4, 45.9, 40.1, 39.7; HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052 (M^+), found 245.1061.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for **4** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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