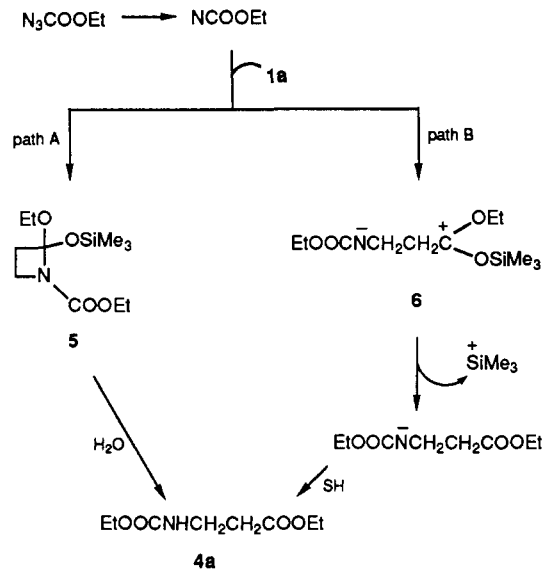
Scheme I



3 H), 1.31 (t, 3 H), 2.56 (d, 1 H), 2.67 (d, 1 H), 3.74 (s, 3 H), 3.63–4.14 (m, 1 H), 4.28 (q, 2 H), 6.26 (br s, 1 H); ^{13}C NMR δ 14.23, 14.43, 34.30, 38.50, 51.47, 60.34; low-resolution MS m/e 189 (M^+), 174, 158, 130, 116; high-resolution MS calcd for $C_8H_{15}NO_4$ 189.1000, found 189.1008.

Methyl 2,2-dimethyl-3-[(ethoxycarbonyl)amino]-propionate (4c): a colorless oil; IR (neat) 3360, 1725, 1680 cm^{-1}; ^{1}H NMR δ 1.28 (s, 6 H), 1.30 (t, 3 H), 3.48 (d, 2 H), 3.78 (s, 3 H), 4.24 (q, 2 H), 5.80 (br s, 1 H); ^{13}C NMR δ 13.88, 14.54, 36.33, 54.70, 60.34; low-resolution MS m/e 203 (M^+), 188, 172, 144, 102; high-resolution MS calcd for $C_9H_{17}NO_4$ 203.1157, found 203.1154.

Methyl 2-phenyl-3-[(ethoxycarbonyl)amino]propionate (4d): a colorless oil; IR (neat) 3365, 3025, 1740, 1685, 770, 700 cm^{-1}; ^{1}H NMR δ 1.32 (t, 3 H), 3.76 (s, 3 H), 3.48–4.00 (m, 3 H), 4.25 (q, 2 H), 6.18 (br s, 1 H), 7.39 (s, 5 H); ^{13}C NMR δ 14.61, 35.31, 36.62, 56.22, 60.41, 126.50, 127.78, 129.56; low-resolution MS m/e 251 (M^+), 236, 220, 192, 102; high-resolution MS calcd for $C_{13}H_{17}NO_4$ 251.1157, found 251.1152.

4-[(Ethoxycarbonyl)amino]tetrahydro-2*H*-pyran-2-one (4e): a colorless oil; IR (neat) 3365, 1735, 1680 cm^{-1}; ^{1}H NMR δ 1.38 (t, 3 H), 1.86–2.26 (m, 2 H), 2.68 (t, 2 H), 3.70–4.21 (m, 1 H), 4.21 (t, 2 H), 4.25 (q, 2 H), 6.23 (br s, 1 H); ^{13}C NMR δ 14.54, 24.58, 35.28, 46.15, 60.41, 61.95; low-resolution MS m/e 187 (M^+), 157, 143, 115; high-resolution MS calcd for $C_8H_{13}NO_4$ 187.0844, found 187.0843.

Ethyl 3-[(ethoxycarbonyl)amino]-4-(trimethylsiloxy)-pentanoate (4f): a colorless oil; IR (neat) 3460, 1760, 1685 cm^{-1}; ^{1}H NMR δ 0.18 (s, 9 H), 1.26 (d, 3 H), 1.30 (t, 3 H), 1.34 (t, 3 H), 2.58 (d, 1 H), 2.66 (d, 1 H), 3.58–4.15 (m, 2 H), 4.18 (q, 2 H), 4.30 (q, 2 H), 5.95 (br s, 1 H); ^{13}C NMR δ 0.72, 14.09, 14.72, 17.23, 34.72, 36.57, 60.11, 60.68, 63.28; low-resolution MS m/e 305 (M^+), 290, 276, 260, 232, 218, 117, 73; high-resolution MS calcd for $C_{13}C_{27}NO_5Si$ 305.1657, foun 305.1660.

Ethyl 2-methyl-2-[[(ethoxycarbonyl)amino]methyl]-3-(trimethylsiloxy)butanoate (4g): a colorless oil; IR (neat) 3460, 1760, 1680 cm^{-1}; ^{1}H NMR δ 0.18 (s, 9 H), 1.24 (d, 3 H), 1.30 (t, 3 H), 1.32 (t, 3 H), 1.36 (s, 3 H), 3.55 (s, 2 H), 3.78 (q, 1 H), 4.19 (q, 2 H), 4.24 (q, 2 H), 6.00 (br s, 1 H); ^{13}C NMR δ 0.74, 14.20, 14.55, 14.92, 17.10, 36.31, 60.12, 60.30, 63.30; low-resolution MS m/e 319 (M^+), 304, 290, 274, 246, 117, 102, 73; high-resolution MS calcd for $C_{14}H_{29}NO_5Si$ 319.1813, found 319.1810.

Ethyl 2-Methyl-3-[(ethoxycarbonyl)amino]butanoate (4h). This product was obtained as a colorless oil and shown to be a 1:1 mixture of diastereomers by GC–MS and ^{13}C NMR: IR (neat) 3350, 1730, 1680 cm^{-1}; ^{1}H NMR δ 1.09–1.52 (m, 12 H), 2.53–3.10 (m, 1 H), 3.40–4.15 (m, 1 H), 4.19 (q, 2 H), 4.25 (q, 2 H), 5.85 (br s, 1 H); ^{13}C NMR δ 10.92, 13.71, 14.03, 14.18, 14.53, 16.71, 36.28, 37.19, 38.43, 39.52, 60.06, 60.38; low-resolution MS m/e 217 (M^+), 188, 172, 144, 116; high-resolution MS calcd for $C_{10}H_{19}NO_4$ 217.1313, found 217.1310.

Regioselective Addition Reactions of Organometallic Reagents with 3-Benzylidene Heterocyclic Imines Leading to the Synthesis of Pyrrolizidines

Duy H. Hua,*,† Didier Bensoussan, and Ana A. Bravo

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

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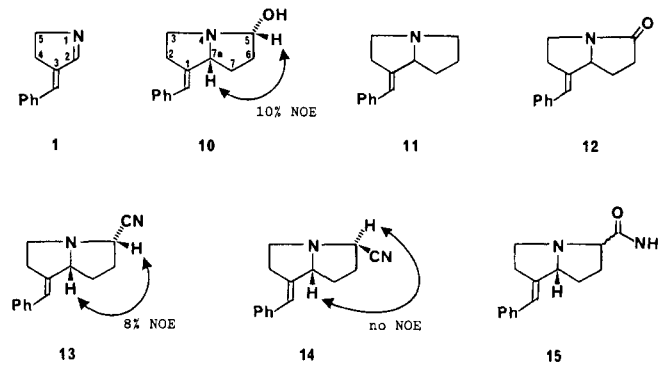
The pyrrolizidine alkaloids, an important class of natural product, have been the subject of many synthetic, pharmacological, and biological studies.[1] During our studies of the construction of functionalized pyrrolizidines, we have investigated addition reactions of organometallic reagents with 3-benzylidene heterocyclic imines, which are ambident electrophiles. Herein we report the regioselective addition of organomagnesium and organolithium reagents with 3-benzylidene-1-pyrroline (**1**)[2] and the subsequent cyclization to pyrrolizidines.

Some addition reactions of imines[3] and α,β-unsaturated aldimines[4] have been reported. We now find that the ambident electrophile **1** undergoes exclusively 1,2-addition with organomagnesium and organolithium reagents. The results are summarized in Table I. The general procedure for these reactions consists of treating enimine **1** with 1.2 equiv of the organomagnesium reagent in THF at −30 °C for 30 min and 25 °C for 1 to 3 h, or with 1.2 equiv of the organolithium reagent in THF at −78 °C for 1 h. The organomagnesium reagents chelate with the nitrogen of **1** at −30 °C to 0 °C and precipitate as brown solids. At 25 °C, these complexes then react to form the 1,2-adduct, which is indicated by the dissolution of the solids. No 1,4-adducts were detected in any case. Thus the reaction path is suggested to consist of the chelation of metal of the reagents with the nitrogen of the imine followed by the nucleophilic attack of the R group at the carbon of the C=N bond.[3b]



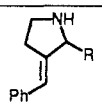
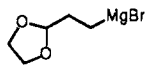
Adduct amine **9** underwent stereoselective ring closure with 1 N HCl[5] in ethanol at 25 °C for 24 h, forming pyrrolizidinol **10** (a single diastereomer) in 90% yield. The stereochemistry was established by ^{1}H NMR spectroscopy (nuclear Overhauser enhancement difference). Irradiation of the 5-H showed 10% enhancement of the 7a-H. The amine intramolecularly attacks the aldehyde from the pro-*R* face. Reduction of **10** with lithium aluminum hydride in THF at 25 °C gave pyrrolizidine **11** in 89% yield. Alternatively, oxidation of **10** with pyridinium chlorochromate (PCC)[6] in CH_2Cl_2 provided lactam **12**[4f] in 86% yield.

Cyclization of **9** was also successfully carried out in 1 N HCl–KCN–CH_2Cl_2 as previously suggested;[1d] at 25 °C for

† Fellow of the Alfred P. Sloan Foundation, 1989–1991.

0022-3263/89/1954-5399$01.50/0

Table I. Reactions of 3-Benzylidene-1-pyrroline (1) with Organometallic Reagents

reagent, RM	
n-BuLi	2 (92)
t-$BuMe_2SiOCH_2CH_2CH_2Li$	3 (59)
EtMgBr	4 (75)
i-PrMgCl	5 (81)
CH_2=$CHCH_2MgBr$	6 (91)
PhMgBr	7 (79)
CH_2=$CHCH_2CH_2MgBr$	8 (45)
	9 (70)

2 days we obtained **13** in 64% yield and **14** in 17% yield. NOE studies established their relative stereochemistry. Irradiation of the 5-H of **13** showed 8% enhancement of the 7a-H, while irradiation of the 5-H of **14** showed no enhancement of the 7a-H. Hydrolysis of **13** with potassium–Al_2O_3–ether–H_2O[7] provided amides **15** (90% yield; based on unrecovered starting cyanides, 40% starting cyanides were recovered) as a mixture of two isomers.

In summary, regioselective additions of organomagnesium and organolithium reagents with 3-benzylidene-1-pyrroline (**1**) provide 2-substituted 3-benzylidenepyrrolidine in good to excellent yields. The subsequent hydrolytic ring closure, e.g., of δ-cyclic acetal amine **9**, leads to various functionalized pyrrolizidines.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were obtained in deuteriochloroform on a Bruker WM-400 (400 MHz in ^1H and 100 MHz in ^{13}C) spectrometer and are reported in ppm (δ units) downfield of internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1330 spectrophotometer and are reported in wavenumbers (cm^{-1}). Mass spectra were determined on a Finnigan 4000 automated gas chromatograph/EI-CI mass spectrometer. High resolution mass spectra were recorded on a Kratos high resolution mass spectrometer. Microanalyses were carried out by the MicAnal Organic Microanalysis, Tucson, AZ. Davisil silica gel, grade 643 (200–425 mesh) was used for the flash chromatographic separation. Enimine **1** was obtained according to the reported procedure.[2] Two isomers (trans and cis) were obtained in the ratio of 95:5. The stereochemistry of the major isomer, **1**, was proven by ^1H NMR spectroscopy using NOE technique. Irradiation of the ortho Hs of the phenyl ring showed 10% enhancement of the 4-Hs and no enhancement of the 2-H.

***trans*-3-Benzylidene-1-pyrroline (1)**: mp 72–73 °C; ^1H NMR δ 7.86 (t, *J* = 2 Hz, 1 H, N=CH), 7.46 (d, 7 Hz, 2 H, ortho Hs), 7.41 (t, *J* = 7 Hz, 2 H, meta Hs), 7.30 (d, *J* = 7 Hz, 1 H, para H), 6.82 (t, *J* = 2.5 Hz, 1 H, =CH), 4.21 (m, 2 H, CH_2N), 2.83 (m, 2 H, CH_2).

***cis*-3-Benzylidene-1-pyrroline**: ^1H NMR δ 8.29 (t, *J* = 2 Hz, 1 H, N=CH), 7.4–7.3 (m, 5 H, Ar H), 6.71 (s, 1 H, =CH), 4.0 (m, 2 H, CH_2N), 2.68 (m, 2 H, CH_2).

The following experiment serves as the general procedure for the reactions of imine **1** with organometallic reagents to form 3-benzylidenepyrrolidines. The organometallic reagents were either prepared in situ or used directly.

3-Benzylidene-2-[3,3-(ethylenedioxy)propyl]pyrrolidine (9). To a warm (35 °C) mixture of 0.16 g (6.6 mmol) of magnesium turnings in 2 mL of THF under argon was added 1.086 g (6 mmol) of 2-(2-bromoethyl)-1,3-dioxolane[8] in 8 mL of THF over a period of 20 min. The mixture was stirred for an additional 1 h at 30 °C and then cooled to 25 °C. This Grignard reagent solution was added to a cold (−30 °C) solution of 0.785 g (5 mmol) of imine **1** via cannula under argon. The brown mixture was stirred at −30 °C for 15 min and then at 25 °C for 2 h. The resulting dark green solution was poured into 50 mL of H_2O containing 5 mL of NH_4OH and extracted with CH_2Cl_2 three times (50 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 0.907 g (70% yield) of **9**: mp 75–76 °C; IR (neat) 3340, 1600; ^1H NMR δ 7.33–7.18 (m, 5 H, Ar), 6.31 (d, *J* = 2.3 Hz, 1 H, =CH), 4.93 (t, *J* = 4.3 Hz, 1 H, CHO), 3.99–3.96 (m, 2 H, CH_2O), 3.87–3.84 (m, 2 H, CH_2O), 3.69 (d, *J* = 7.5 Hz, 1 H, CHN), 3.21–3.19 (m, 1 H, CHN), 2.97 (dt, *J* = 7.5 Hz, 6 Hz, 1 H, CHN), 2.73–2.7 (m, 2 H, CH_2C=), 2.02 (br s, 1 H, NH), 1.93–1.88 (m, 2 H, CH_2), 1.81–1.78 (m, 1 H, CH_2), 1.62–1.59 (m, 1 H, CH_2); ^{13}C NMR δ 146.51 (s, =C), 138.27 (s, Ar), 128.25 (d, 2 C, Ar), 128.13 (d, 2 C, Ar), 126.2 (d, Ar), 120.71 (d, =CH), 104.54 (d, CHO), 64.95 (d, CHN), 64.87 (t, CH_2O), 63.17 (t, CH_2O), 46.08 (t), 32.1 (t), 30.77 (t), 29.53 (t); MS, *m/e* EI 259 (M^+), 198, 158; CI 260 (M + 1); HRMS calcd for $C_{16}H_{21}NO_2$ 259.1569, found 259.1586. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.01; H, 8.33; N, 5.67.

3-Benzylidene-2-butylpyrrolidine (2): ^1H NMR δ 7.38–7.15 (m, 5 H, Ar), 6.33 (d, *J* = 2 Hz, 1 H, =CH), 3.8 (br s, 1 H, CHN), 3.35–3.3 (m, 1 H, CH_2N), 3.06 (dt, *J* = 7.5, 6 Hz, 1 H, CH_2N), 2.83–2.75 (m, 2 H, CH_2), 1.87–1.76 (m, 1 H, CH_2), 1.7–1.6 (m, 1 H, CH_2), 1.58–1.3 (m, 4 H, CH_2), 0.9 (t, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 147.12 (s, C=), 138.27 (s, Ar), 128.16 (d, 2 C, Ar), 127.98 (d, 2 C, Ar), 126 (d, Ar), 120.06 (d, =CH), 63.48 (d, CN), 46.06 (t, CN), 35.16 (t), 32.21 (t), 28.76 (t), 22.8 (t), 13.99 (q). MS, *m/e* EI 215 (M^+), 158. Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83. Found: C, 83.41; H, 9.97.

3-Benzylidene-2-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]pyrrolidine (3): ^1H NMR δ 7.45–7.1 (m, 5 H, Ar), 6.3 (d, *J* = 2 Hz, 1 H, =CH), 3.68 (m, 3 H, CH_2O, CHN), 3.24–3.19 (m, 1 H, CH_2N), 2.95 (dt, *J* = 7.5, 6 Hz, 1 H, CH_2N), 2.7–2.6 (m, 2 H, CH_2), 2.05 (br s, 1 H, NH), 1.8 (m, 1 H, CH_2), 1.8–1.6 (m, 2 H, CH_2), 1.48 (m, 1 H, CH_2), 0.91 (m, 9 H, *t*-Bu), 0.06 (s, 3 H, Me), 0.03 (s, 3 H, Me); ^{13}C NMR δ 144.56 (s, =C), 137.7 (s, Ar), 128.19 (d, 2 C, Ar), 128.05 (d, 2 C, Ar), 126.35 (d, Ar), 121.34 (d, =CH), 63.1 (t, CO), 62.82 (d, CHN), 45.54 (t, CH_2N), 31.21 (t), 31.06 (t), 29.42 (t), 25.86 (q, *t*-Bu), 18.21 (s, *t*-Bu), −5.39 (q, Me); MS, *m/e* EI 331 (M^+), 316, 274, 158; CI 332 (M + 1). Anal. Calcd for $C_{20}H_{33}NOSi$: C, 72.45; H, 10.03. Found: C, 72.28; H, 10.11.

3-Benzylidene-2-ethylpyrrolidine (4): ^1H NMR δ 7.3–7.15 (m, 5 H, Ar), 6.29 (d, *J* = 2 Hz, 1 H, =CH), 3.57 (br s, 1 H, CHN), 3.2–3.15 (m, 1 H, CH_2N), 2.9 (dt, *J* = 7.5, 6 Hz, 1 H, CH_2N), 2.72–2.59 (m, 2 H, CH_2), 2.27 (br s, 1 H, NH), 1.83–1.72 (m, 1 H, CH_2), 1.55–1.46 (m, 1 H, CH_2), 1.07 (t, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 146.8 (s, =CH), 138.0 (s, Ar), 128.5 (d, 2 C, Ar), 128.2 (d,

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2 C, Ar), 126.8 (d, Ar), 120.9 (d, =CH), 65.3 (d, CHN), 46.4 (CH_2N), 32.5 (t), 28.3 (t), 11.4 (q); MS, *m/e* EI 187 (M^+), 158; CI 159 (M + 1). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.10; H, 9.33.

3-Benzylidene-2-isopropylpyrrolidine (5): ^1H NMR δ 7.3–7.12 (m, 5 H, Ar), 6.3 (d, *J* = 2 Hz, 1 H, =CH), 3.58 (s, 1 H, CHN), 3.2 (m, 1 H, CH_2N), 2.9 (dt, *J* = 7.5, 6 Hz, 1 H, CH_2N), 2.76 (m, 1 H, CH_2), 2.63 (m, 1 H, CH_2), 2.04 (m, 1 H, CH), 1.05 (d, *J* = 7 Hz, 3 H, Me), 0.9 (d, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 146.07 (s, =C), 138.33 (s, Ar), 128.19 (d, 2 C, Ar), 128.13 (d, 2 C, Ar), 126.08 (d, Ar), 120.85 (d, =CH), 68.85 (d, CHN), 46.43 (t, CH_2N), 32.56 (t), 32.05 (d), 20.34 (q), 16.56 (q); MS, *m/e* EI 201 (M^+), 186, 158; CI 202 (M + 1). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.37; H, 9.33.

3-Benzylidene-2-(2-propenyl)pyrrolidine (6): ^1H NMR δ 7.35–7.18 (m, 5 H, Ar), 6.33 (d, *J* = 2 Hz, 1 H, =CH), 5.9 (m, 1 H, =CH), 5.15 (d, *J* = 17 Hz, 1 H, $=CH_2$), 5.11 (d, *J* = 10.5 Hz, 1 H, $=CH_2$), 3.73 (br s, 1 H, CHN), 3.2 (m, 1 H, CH_2N), 2.94 (dt, *J* = 7.5 Hz, 6 Hz, 1 H, CH_2N), 2.74–2.67 (m, 2 H), 2.52 (m, 1 H), 2.38 (m, 1 H), 2.2 (br s, 1 H, NH); ^{13}C NMR δ 145.87 (s, =C), 138.04 (s, Ar), 135.27 (d, =CH), 128.19 (d, 2 C, Ar), 127.99 (d, 2 C, Ar), 126.16 (d, Ar), 120.56 (d, =CH), 117.35 (t, $=CH_2$), 62.52 (d, CHN), 45.85 (t, CH_2N), 39.44 (t), 32.21 (t); MS, *m/e* EI 199 (M^+); CI 200 (M + 1). Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.18; H, 8.77; N, 6.91.

3-Benzylidene-2-phenylpyrrolidine (7): ^1H NMR δ 7.38–7.14 (m, 5 H, Ar), 6.02 (d, *J* = 2 Hz, 1 H, =CH), 4.68 (s, 1 H, CHN), 3.35 (m, 1 H), 3.05 (dt, *J* = 7.5, 7 Hz, 1 H), 2.87 (m, 2 H), 2.4 (br s, 1 H, NH); ^{13}C NMR δ 146 (s, =C), 139 (s, Ar), 138 (s, Ar), 129 (d, 2 C, Ar), 128.5 (d, 2 C, Ar), 128.18 (d, 2 C, Ar), 128.13 (d, 2 C, Ar), 127.7 (d, Ar), 127 (d, Ar), 123.8 (d, =CH), 69.0 (d, CHN), 47.2 (t, CH_2N), 27.5 (t); MS, *m/e* EI 235 (M^+); CI 236 (M + 1). Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28. Found: C, 86.89; H, 7.39.

3-Benzylidene-2-(3-butenyl)pyrrolidine (8): ^1H NMR δ 7.38–7.2 (m, 5 H, Ar), 6.32 (d, *J* = 2 Hz, 1 H, =CH), 5.9 (m, 1 H, =CH), 5.11 (d, *J* = 17 Hz, 1 H, $=CH_2$), 5.02 (d, *J* = 10 Hz, 1 H, $=CH_2$), 3.73 (m, 1 H, CHN), 3.27 (m, 1 H, CH_2N), 3.01 (dt, *J* = 7.5, 7 Hz, 1 H, CH_2N), 2.76 (m, 2 H, CH_2), 2.26 (m, 2 H), 1.88 (m, 1 H), 1.63 (m, 1 H); ^{13}C NMR δ 145.38 (s, =C), 138.19 (d, =CH), 137.9 (s, Ar), 128.27 (d, 2 C, Ar), 128.1 (d, 2 C, Ar), 126.34 (d, Ar), 121.06 (d, =CH), 114.96 (t, $=CH_2$), 62.7 (d, CHN), 45.65 (t, CN), 34.27 (t), 31.53 (t), 30.66 (t); MS, *m/e* EI 213 (M^+); CI 214 (M + 1). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98. Found: C, 84.21; H, 8.79.

(5α,7aβ)-1-Benzylidene-5-hydroxyhexahydro-1*H*-pyrrolizine (10). A solution of 0.284 g (1.1 mmol) of amine **9** in 6 mL of ethanol and 6 mL of 1 N HCl was stirred at 25 °C for 1 day. The reaction mixture was made basic with 8 mL of 1 N NaOH and extracted with ether three times. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 0.213 g (90% yield) of **10**: IR (neat) 3400 (br s); ^1H NMR δ 7.34–7.17 (m, 5 H, Ar), 6.29 (d, *J* = 2 Hz, 1 H, =CH), 4.28 (dd, *J* = 6 Hz, 3 Hz, 1 H, OCHN), 4.17 (br s, 1 H, CHN), 3.36 (dq, *J* = 9, 7 Hz, 1 H, CH_2N), 3.25 (dt, *J* = 11, 7 Hz, 1 H, CH_2N), 3.08 (m, 1 H), 2.73–2.63 (m, 2 H), 2.32 (m, 1 H), 1.94–1.77 (m, 2 H); ^{13}C NMR δ 147.03 (s, =C), 138.07 (s, Ar), 128.22 (d, 2 C, Ar), 128.08 (d, 2 C, Ar), 126.19 (d, Ar), 120.48 (d, =CH), 99.1 (d, CO), 69.26 (d, CN), 61.89 (t, CN), 32.36 (t), 31.61 (t), 31.32 (t); MS, *m/e* EI 215 (M^+), 197, 171, 120; CI 216 (M + 1), 214 (M − 1); HRMS calcd for $C_{14}H_{17}NO$ 215.1311, found 215.1266. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found: C, 78.01; H, 8.19.

1-Benzylidenehexahydro-1*H*-pyrrolizine (11). To a solution of 0.215 g (1 mmol) of amine **10** in 6 mL of THF at 25 °C under argon was added 76 mg (2 mmol) of lithium aluminum hydride. After the mixture was stirred at 25 °C for 1 h, 6 mL of NH_4OH, 4 mL of H_2O, and 0.5 mL of 1 N NaOH were added, and the mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using ether and 5% NH_4OH in MeOH as eluent to give 0.177 g (89% yield) of **11**: ^1H NMR δ 7.34–7.16 (m, 5 H, Ar), 6.28 (d, *J* = 2 Hz, 1 H, =CH), 4.03 (t, *J* = 5 Hz, 1 H, CHN), 3.12 (m, 1 H, CH_2N), 3.8 (m, 1 H, CH_2N), 2.82 (m, 2 H), 2.71 (m, 1 H), 2.62 (dt, *J* = 10, 7 Hz, 1 H), 2.2 (m, 1 H), 1.9–1.7 (m, 3 H); ^{13}C NMR δ 147.7 (s, =C), 138.05 (s, Ar), 128.16 (d, 2 C, Ar), 127.99 (d, 2 C, Ar), 126.08 (d, Ar), 120.98 (d, =CH), 69.72 (d, CN), 53.78 (t, CN), 52.89 (t, CN), 32.5 (t), 30.2 (t), 25.46 (t); MS, *m/e* EI 199 (M^+), 171, 122; CI 200 (M + 1). Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60. Found: C, 84.13; H, 8.84.

1-Benzylidenehexahydro-1*H*-5-pyrrolizinone (12). To a mixture of 0.215 g (1 mmol) of alcohol **10** and 0.4 g of 3-Å molecular sieves in 10 mL of CH_2Cl_2 at 25 °C under argon was added 0.431 g (2 mmol) of pyridinium chlorochromate. After the mixture was stirred at 25 °C for 6 h, 30 mL of H_2O and 10 mL of 1 N NaOH were added, and the mixture was extracted with ethyl acetate three times. The combined extracts were washed with H_2O and then with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 0.183 g (86% yield) of lactam **12**: IR (neat) 1660 (C=O); ^1H NMR δ 7.37–7.22 (m, 5 H, Ar), 6.35 (d, *J* = 2.3 Hz, 1 H, =CH), 4.57 (t, *J* = 5 Hz, 1 H, CHN), 4.06 (m, 1 H, CH_2N), 3.1 (m, 1 H, CH_2N), 2.93 (m, 2 H), 2.74 (m, 1 H), 2.55 (m, 1 H), 2.44 (dd, *J* = 11, 9 Hz, 1 H), 2.0 (m, 1 H); ^{13}C NMR δ 175.46 (s, C=O), 142.88 (s, =C), 137.02 (s, Ar), 128.46 (d, 2 C, Ar), 128.23 (d, 2 C, Ar), 126.96 (d, Ar), 122.19 (d, =CH), 64.87 (d, CN), 41.62 (t, CN), 33.86 (t), 31.69 (t), 27.91 (t); MS, *m/e* EI 213 (M^+); CI 214 (M + 1). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.62; H, 7.23.

(5α,7aβ)-1-Benzylidene-5-cyanohexahydro-1*H*-pyrrolizine (13) and (5α,7aα)-1-Benzylidene-5-cyanohexahydro-1*H*-pyrrolizine (14). To a solution of 0.303 g (1.17 mmol) of **9** in 8 mL of CH_2Cl_2 were added 0.479 g (7.4 mmol) of potassium cyanide and 8 mL of 1 N HCl. The mixture was stirred at 25 °C for 2 days, diluted with 9 mL of 1 N NaOH and 10 mL of brine, and extracted with ether three times. The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 0.167 g (64% yield) of **13** (more polar) and 45 mg (17% yield) of **14** (less polar).

For **13**: mp 60–61 °C; IR (neat) 2250 (C≡N); ^1H NMR δ 7.35–7.2 (m, 5 H, Ar), 6.31 (d, *J* = 2.2 Hz, 1 H, =CH), 4.15 (t, *J* = 7.5 Hz, 1 H, 7a-H), 4.05 (t, *J* = 5 Hz, 1 H, 5-H), 3.27 (m, 1 H), 3.15 (m, 2 H), 2.75 (m, 1 H), 2.37 (m, 1 H), 2.25 (m, 2 H), 1.95 (m, 1 H); ^{13}C NMR δ 146.12 (s, =C), 137.7 (s, Ar), 128.3 (d, 2 C, Ar), 128.25 (d, 2 C, Ar), 126.52 (d, Ar), 121.66 (d, =CH), 119.6 (s, C≡N), 69.19 (d, C-7a), 53.69 (d, C-5), 49.91 (t, C-3), 32.1 (t), 31.67 (t), 30.54 (t); MS, *m/e* EI 224 (M^+); CI 225 (M + 1). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.17; H, 7.33; N, 12.57.

For **14**: mp 100–101 °C; IR (neat) 2248 (C≡N); ^1H NMR δ 7.35–7.19 (m, 5 H, Ar), 6.29 (d, *J* = 1.9 Hz, 1 H, =CH), 4.19 (t, *J* = 5 Hz, 1 H, 7a-H), 3.55 (t, *J* = 7.3 Hz, 1 H, 5-H), 3.22 (dt, *J* = 11 Hz, 7 Hz, 1 H, 3-H), 2.95 (m, 1 H, 3-H), 2.78 (m, 2 H), 2.38 (m, 1 H), 2.28 (m, 1 H), 2.0 (m, 1 H), 1.81 (m, 1 H); ^{13}C NMR δ 145.2 (s, =C), 137.49 (s, Ar), 128.33 (d, 2 C, Ar), 128.13 (d, 2 C, Ar), 126.63 (d, Ar), 121.95 (d, =CH), 120.67 (s, CN), 69.54 (d, C-7a), 54.57 (d, C-5), 52.58 (t, C-3), 31.66 (t), 31.55 (t), 29.89 (t); MS, *m/e* EI 224 (M^+); CI 225 (M + 1). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19. Found: C, 80.18; H, 7.37.

3-Benzylidene-5-carbamoylhexahydro-1*H*-pyrrolizine (15). To a slurry of 15 g of dispersed potassium on alumina (prepared according to the reported procedure[7]) in 30 mL of ether under argon was added a solution of 0.55 g (2.46 mmol) of **13** in 5 mL of ether. The reaction mixture was stirred at 25 °C for 1 h, then 30 mL of H_2O was added and the mixture was stirred for an additional 1 h. The mixture was diluted with ethyl acetate, filtered, and washed with ethyl acetate several times. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to give 0.22 g (40% recovery) of cyanides **13** and **14** (ratio of 1:1) and 0.321 g (90% yield; based on unrecovered cyanide) of **15** as a mixture of two isomers: mp 139–140 °C; IR (neat) 3400, 1690 (C=O); ^1H NMR δ 7.53 (br s, 1 H, NH), 7.35–7.17 (m, 5 H, Ar), 6.3 (d, *J* = 2.2 Hz, 1 H, =CH), 5.9 (br s, 1 H, NH), 4.14 (t, *J* = 6 Hz, 1 H, 7a-H), 3.32 (t, *J* = 7.5 Hz, 1 H, 5-H), 3.2 (m, 1 H), 2.9 (m, 1 H), 2.75 (m, 2 H), 2.3–2.19 (m, 2 H), 2.0 (m, 1 H), 1.8 (m, 1 H); ^{13}C NMR (major isomer) δ 177.86 (s, C=O), 146.35 (s, =C), 137.83 (s, Ar), 128.31 (d, 2 C, Ar), 128.15 (d, 2 C, Ar), 126.44 (d, Ar), 121.13 (d, =CH), 70.44 (d), 69.31 (d), 53.68 (t, C-3), 32.76 (t), 31.28 (t), 30.50 (t); ^{13}C NMR (minor isomer) δ 177.85, 143.39, 139.0, 128.89, 128.40, 126.29, 120.93, 73.84, 71.88, 61.84, 34.97, 31.48, 30.69; MS, *m/e* EI 242 (M^+); CI 243 (M + 1). Anal. Calcd for $C_{15}H_{18}N_2O$:

C, 74.35; H, 7.49. Found: C, 74.19; H, 7.68.

Acknowledgment. We gratefully acknowledge financial support from the National Institute of General Medical Sciences (Grant GM36336) and the National Science Foundation (Grant CHE-8800654). This project is in part funded by Wesley Foundation, Wichita, KS (Grant 8802041). We are indebted to Mr. Ken Walsh, Coal Research Center, Southern Illinois University of Carbondale, for obtaining mass spectra.

Registry No. 1, 122949-09-1; *cis*-1, 111532-83-3; 2, 122949-10-4; 3, 122949-11-5; 4, 122949-12-6; 5, 122949-13-7; 6, 122949-14-8; 7, 122949-15-9; 8, 122949-16-0; 9, 122949-17-1; 10, 122949-18-2; 11, 122949-19-3; 12, 122949-20-6; 13, 122949-21-7; 14, 122949-22-8; 15 (isomer 1), 122967-58-2; 15 (isomer 2), 122949-23-9; CH_2=C-H$(CH_2)_2$MgBr, 7103-09-5; [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide, 122949-24-0.

On the Mechanism of the Oxidation of Tosylhydrazines by *N*-Iodosuccinimide

Ding-yah Yang, Oksoo Han, and Hung-wen Liu*

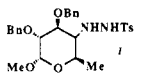
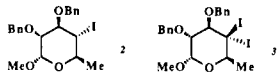
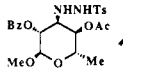
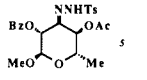
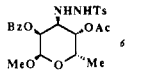
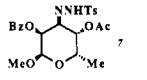
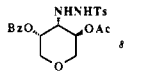
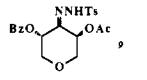
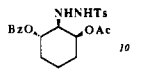
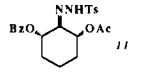
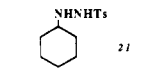
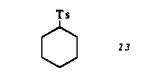
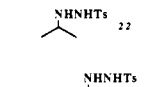
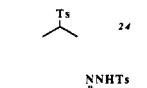
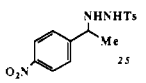
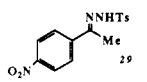
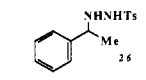
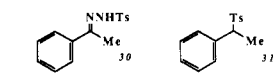
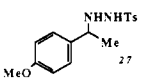
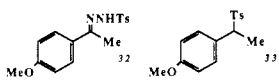
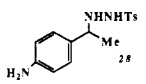
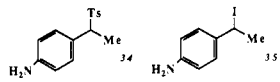
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received March 21, 1989

As part of our continuing efforts to study the mechanism of deoxy sugar biosynthesis at the enzymatic level,[1] it has been necessary for us to develop a general strategy for the synthesis of stereospecifically labeled deoxy sugars.[2] Reviewing the literature, we have found that hydrazines can be oxidized to the corresponding halides with defined stereochemistry by a variety of haloreagents, such as iodine, bromine, *N*-iodosuccinimide, *N*-bromosuccinimide, iodine monochloride, etc.[3] Since sugar hydrazines are readily available from the corresponding hydrazones by reduction with boron reducing agents[4] or from precursors bearing suitable leaving groups by direct nucleophilic displacement with hydrazine, a sequence involving halogen oxidation of the sugar hydrazine followed by hydride reduction of the nascent halide seems to be a compelling approach.[5] Although the key step, halogen oxidation, of this proposed sequence is an intriguing reaction, little is known about its mechanism. It has been suggested that the reaction course may involve a tautomerization step interconverting a diimide intermediate to the corresponding hydrazone.[3a,6] However, the putative hydrazone species has never been isolated, and thus, the mechanistic details of this reaction are still uncertain. In an attempt to clarify the mechanistic ambiguity of this oxidation and to test the feasibility of the proposed sequence for the preparation of stereospecifically labeled deoxy sugar molecules, we have carried out the halogen oxidation on a series of sugar tosylhydrazines. To our surprise, the major product formed in most of these experiments was not the desired halide but rather the corresponding tosylhydrazone or tolyl sulfone derivative,[7] depending on the structure of the parent pyranoside. These unexpected results have prompted us to examine tosylhydrazines of other classes to gain further insight into this oxidation. Reported in this paper are the results of these experiments and their mechanistic implications.

The tosylhydrazines used in this study were all derived from their tosylhydrazone precursors by reduction with $NaBH_3CN$ in acidic THF–MeOH solution at 0 °C.[4,8] Initial experiments with a variety of halogen oxidizing agents showed that iodine/triphenylphosphine/imidazole in toluene at 70 °C was ineffective and iodine/*N*-methylmorpholine in chloroform at low temperature was sluggish. The most effective oxidant was found to be

Table I. Oxidation of Tosylhydrazines by *N*-Iodosuccinimide/*N*-Morpholine/$CHCl_3$

reactant	product	yield
		62% (2:3 = 2:3)
		91%
		95%
		96%
		92%
		93%
		50%
		95%
		90% (30:31 = 4:1)
		81% (32:33 = 3:2)
		56% (34:35 = 4:1)

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(5) It is well-known that alkylhydrazines can be oxidized directly to the corresponding alkanes by ferricyanide, iodate, or periodate in alkaline solution (Whistler, R. L.; Shasha, B. *J. Org. Chem.* **1964**, *29*, 880. Cram, D. J.; Bradshaw, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1108. Reference 3a.) However, the stereochemical course of this direct conversion, in most cases, was not defined.

(6) Cram, D. J.; Bradshaw, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1108.

(7) One should keep in mind that the hydrazines used in all of the previous studies were plain aliphatic and/or aromatic hydrazines. Thus, formation of a toluenesulfinate product was not possible in these reported cases.

(8) Miller, V. P.; Yang, D.-y.; Weigel, T. M.; Han, O.; Liu, H. W. *J. Org. Chem.* **1989**, *54*, 4175.

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