HETEROCYCLES, Vol. 54, No. 2, pp. 1021-1025, Received, 22nd June, 2000

5-*ENDO-TRIG* RADICAL CYCLIZATION OF *N*-BENZYL-2-HALO-*N*-(6-OXO-1-CYCLOHEXEN-1-YL)-ACETAMIDES†

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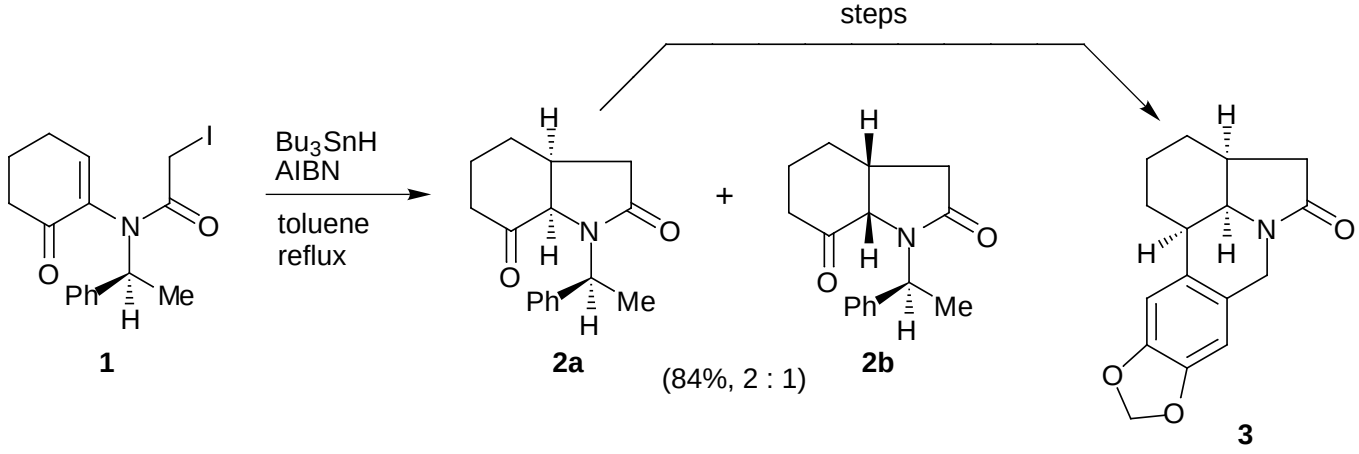
Abstract—*N*-Benzyl-2-halo-*N*-(6-oxo-1-cyclohexen-1-yl)acetamides, upon treatment with Bu_3SnH in the presence of AIBN in boiling toluene, undergo 5-*endo-trig* radical cyclization to give (3a*R**,7a*R**)-*N*-benzyloctahydro-7a-hydroxyindole-2,7-dione in addition to *cis*-*N*-benzyloctahydroindole-2,7-dione.

5-*Endo-trig* radical cyclization of *N*-vinylic α-haloacetamides[1] provides a general access to 5-membered lactams, which has been used for the synthesis of several alkaloids.[2] Recently, we have demonstrated that *N*-(–)-2-iodo-(*S*)-1-phenylethyl-*N*-(6-oxo-1-cyclohexen-1-yl)acetamide (**1**), upon treatment with tributyltin hydride (Bu_3SnH) in the presence of azobisisobutyronitrile (AIBN) in boiling toluene, undergoes 5-*endo-trig* radical cyclization to give an inseparable 2 : 1 diastereomeric mixture of (3a*S*,7a*R*)- and (3a*R*,7a*S*)-octahydroindole-2,7-diones (**2a**) and (**2b**) in 84% combined yield, the former of which was converted into (–)-γ-lycorane (**3**).[3]



In connection with our studies directed towards the total synthesis of lycorine and its related alkaloids,[2b,2c,4] we examined the cyclization of the *N*-benzyl congeners (**6a,b**). In this paper, we report the contrasting behavior of **6a,b**.

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†This paper is dedicated to Professor Shô Itô, Bunri University of Tokushima, on the occasion of his 77th birthday.

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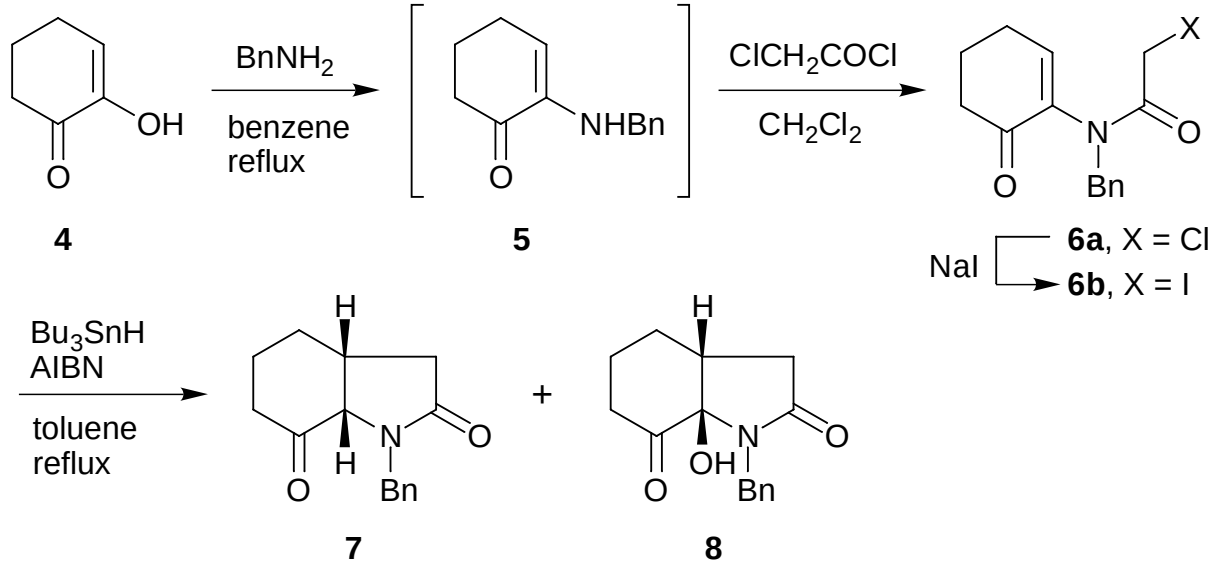
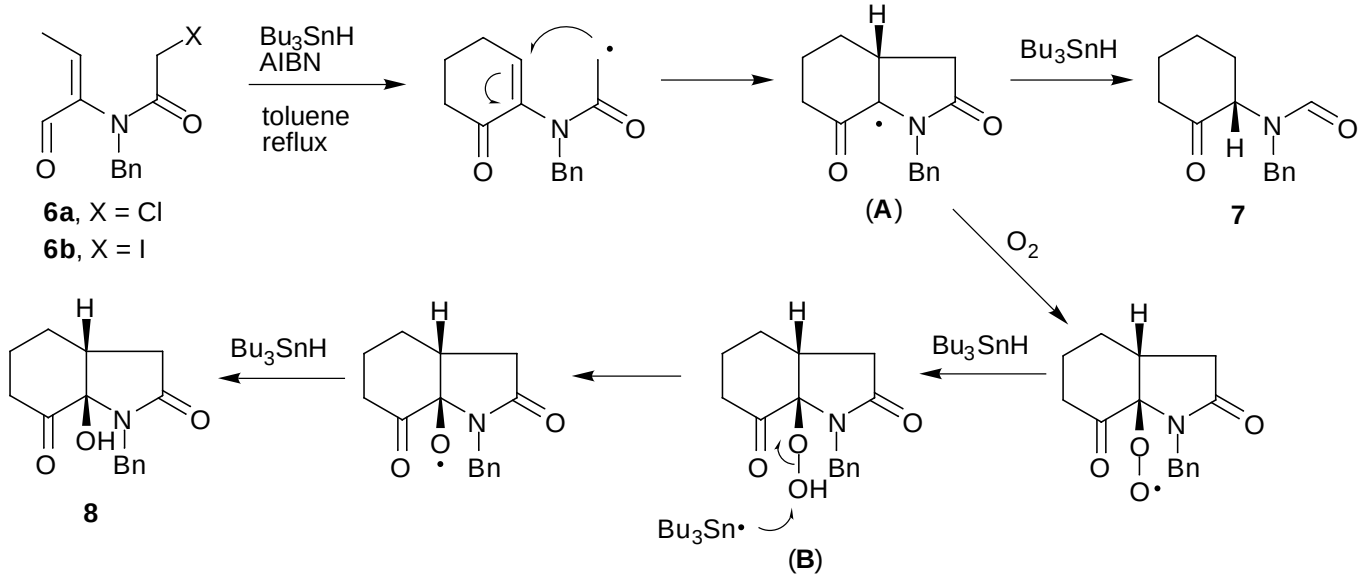
The radical precursors (**6a, b**) were prepared by condensation of cyclohexane-1,2-dione (**4**) with benzylamine followed by treatment of the resulting enamine (**5**) with chloroacetyl chloride to give α-chloroacetamide (**6a**) in 62% yield, which was then treated with sodium iodide to give the α-iodoacetamide (**6b**) in 96% yield.



Scheme 1

Treatment of **6a** with Bu3SnH/AIBN in boiling toluene gave *cis*-*N*-benzyloctahydroindole-2,7-dione (**7**) and (3a*R**,7a*R**)-*N*-benzyloctahydro-7a-hydroxyindole-2,7-dione (**8**) in 43 and 34% yields, respectively. Similar treatment of **6b** gave **7** and **8** in 54 and 27% yields, respectively. The *cis*-stereochemistry of the ring-juncture of compound (**7**) was assigned on the basis of the coupling constant (J = 8.55 Hz) between H-3a and H-7a, which closely resembled those for **2a** (J = 8.3 Hz) and **2b** (J = 7.1 Hz), respectively. The structure of compound (**8**) was determined by an X-Ray analysis (Figure 1), which indicated that the hydroxy group at C-7a and H-3a is *cis*.

The formation of **7** and **8** may be rationalized in terms of the radical intermediate (**A**) stabilized by the captodative effect.[5] Direct Bu3SnH reduction of the radical gives **7**. An attack of the molecular oxygen onto the radical center followed by reduction of the resulting hydroperoxide (**B**) with Bu3SnH would give 8. A similar attack of molecular oxygen on the radical center has been reported.[1e,1i,6] The reason why compound (**1**) gave no hydroxylated compound may be due to steric hindrance by the 1-phenylethyl group on the nitrogen atom, which prevents molecular oxygen from attacking the radical center.



Scheme 2

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded with a JASCO IR A-100 spectrophotometer. ^{1}H- (300 MHz) and ^{13}C-NMR (75 MHz) spectra were measured on a Varian XL-300 spectrometer. δ Values quoted are relative to tetramethylsilane (0 ppm) and $CDCl_3$ (77.02 ppm) for ^{1}H and ^{13}C NMR, respectively, and *J* values are given in Hz. High-resolution MS were obtained with a JEOL JMS-SX 102A spectrometer. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

N-Benzyl-2-chloro-*N*-(6-oxo-1-cyclohexen-1-yl)acetamide (6a)

A solution of cyclohexane-1,2-dione (1.55 g, 13.8 mmol) and benzylamine (1.93 g, 18 mmol) in benzene (50 mL) was refluxed in a flask equipped with a Dean-Stark water separator for 2 h. After removal of the solvent, the residue was dissolved in dichloromethane (30 mL). Chloroacetyl chloride (2.33 mg, 20.8 mmol) was added to the solution at 0 ℃ and the whole was stirred at rt overnight. Sat. aq. $NaHCO_3$ solution (30 ml) was added to it and the mixture was stirred for 10 min. The organic layer was separated, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel [hexane-AcOEt (2:1)] to give **6a** (2.41 g, 62%) as an oil; IR ν_{max} ($CHCl_3$) cm^{-1}: 1690, 1665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.93-2.05 (2 H, m), 2.34-2.54 (4 H, m), 3.89 (2 H, s, $COCH_2Cl$), 4.03 (1 H, d, *J* = 14.6 Hz, one of NCH_2Ph), 5.30 (1 H, d, *J* = 14.6 Hz, one of NCH_2Ph), 6.65 (1 H, t, *J* = 4.1 Hz, C=CH), 7.18-7.33 (5 H, m, ArH). *Anal.* Calcd for $C_{15}H_{16}NO_2Cl$: C, 64.87; H, 5.81; N, 5.04. Found: C, 65.05; H, 5.93; N, 4.88.

N-Benzyl-2-iodo-*N*-(6-oxo-1-cyclohexen-1-yl)acetamide (6b)

To a solution of **6a** (2.01 g, 7.24 mmol) in acetonitrile (20 mL) was added NaI (5.43 g, 36.2 mmol) and the mixture was stirred at rt for 5 h. The insoluble material was filtered off and the solvent was removed. The residue was chromatographed on silica gel [hexane-AcOEt (2:1)] to give **6b** (2.58 g, 96%) as an oil; IR ν_{max} (CCl_4) cm^{-1}: 1690, 1665; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.91-2.09 (2 H, m), 2.25-2.61 (4 H, m), 3.41 and 3.71 (1 H each, ABq, *J* = 9.9 Hz, $COCH_2I$), 3.97 (1 H, d, *J* = 14.6 Hz, one of NCH_2Ph), 5.31 (1 H, d, *J* = 14.6 Hz, one of NCH_2Ph), 6.75 (1 H, t, *J* = 4.2 Hz, C=CH), 7.15-7.35 (5 H, m, ArH). *Anal.* Calcd for $C_{15}H_{16}NO_2I$: C, 48.80; H, 4.37; N, 3.79. Found: C, 48.89; H, 4.55; N, 3.40.

Radical Cyclization of 5a. **General Procedure**. A solution of Bu_3SnH (1.57 g, 5.4 mmol) and AIBN (118 mg, 0.72 mmol) in toluene (100 mL) was added dropwise to a solution of **6a** (1.0 g, 3.6 mmol) in boiling toluene (200 mL) over 4 h, and the mixture was refluxed overnight. After removal of the solvent, ether (20 mL) and an 8% aq. KF solution (20 mL) were added and the whole was vigorously stirred for 30 min. The ethereal layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (2:1)]. The first fraction gave (3a*R**, 7a*R**)-*N*-benzyloctahydro-7a-hydroxyindole-2,7-dione (**8**) (321 mg, 34%), mp 91.0-91.5 ℃ (from hexane-AcOEt); IR ν_{max} (CCl_4) cm^{-1}: 3520, 1715; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.35-1.64 (3 H, m), 1.77-1.93 (2 H, m), 2.08-2.22 (1 H, m), 2.21 (1 H, d, *J* = 17.0 Hz, one of 3-H_2), 2.43-2.52 (1 H, m), 2.94 (1 H, ddd, *J* = 17.0, 7.5, 0.6 Hz), 3.77 (1 H, d, *J* = 15.1 Hz, one of NCH_2Ph), 4.75 (1 H, d, *J* = 15.1 Hz, one of NCH_2Ph), 4.95 (1 H, s, OH), 7.18-7.32 (5 H, m, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 23.4 (CH_2), 30.2 (CH_2), 36.4 (CH_2), 37.3 (CH_2), 42.8 (CH_2), 43.8 (CH), 90.2 (quaternary C), 127.7, 128.6, 129.0, 136.4, 176.2 (NC=O), 208.2 (C=O). HR-MS (FAB) *m/z* calcd for $C_{15}H_{18}NO_3$: 260.1287,

found: 260.1301 (MH^+). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.60; N, 5.40. Found: C, 69.41; H, 6.67; N, 5.37. The second fraction gave *cis-N*-benzyloctahydroindole-2,7-dione (**6**) (374 mg, 43%) as an oil. IR ν_{max} (CCl_4) cm^{-1}: 1720, 1700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.61-2.02 (4 H, m), 2.20 (1 H, ddd, J = 16.4, 10.8, 0.9 Hz), 2.28-2.34 (2 H, m), 2.44 (1 H, dd, J = 8.1, 16.4 Hz), 2.83-2.97 (1 H, m), 3.78 (1 H, d, J = 8.6 Hz, 7a-H), 4.19 (1 H, d, J = 14.9 Hz, one of NCH_2Ph), 5.18 (1 H, d, J = 14.9 Hz, one of NCH_2Ph), 7.19-7.36 (5 H, m, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.3 (CH_2), 26.8 (CH_2), 35.4 (CH_2), 36.9 (CH), 39.7 (CH_2), 46.1 (CH_2), 64.7 (CH), 127.6, 128.3, 128.7, 136.4, 173.9 (NC=O), 209.6 (C=O). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.09; H, 7.17; N, 5.61.

Radical Cyclization of 6b. Following the general procedure, **6b** (1.68 g, 4.55 mmol) was treated with Bu_3SnH (1.98 g, 6.8 mmol) and AIBN (149 mg, 0.91 mmol). The crude reaction mixture was chromatographed on silica gel [hexane-AcOEt (2:1)] to give **8** (315 mg, 27%) and **7** (602 mg, 54%).

X-Ray Analysis of 8. Crystal Data : $C_{15}H_{17}NO_3$, M = 259.30, colorless prismatic, monoclinic, space group $P2_1/a$, a = 11.548(2) Å, b = 8.027(1) Å, c = 13.934(2) Å, β = 94.08(1)°, V = 1288.4(3) $Å^3$, Dx = 1.337 g/cm^3, Z = 4, and $\mu(CuK\alpha)$ = 7.61 cm^{-1}. Data Collection: A crystal was mounted on a Rigaku AFC7/R diffractometer with graphite-monochromated $CuK\alpha$ radiation. The cell dimensions were refined by the least-squares method using 25 reflections. Intensity data were collected using the ω-2θ scan technique to a maximum 2θ value of 120.2 °. Of 1795 independent reflections collected, 1209 reflections with $I>3\sigma(I)$ were used for the structure determination and refinement. Data were corrected for Lorenz and polarization factors. Structure Determination and Refinement: The structure was solved by the direct method using the teXsan program.[7] The atomic coordinates were refined by the block-diagonal least-squares method, using anisotropic temperature factors for all the non-hydrogen-atoms and isotropic ones for hydrogen atoms. The final R (Rw) value was 0.041 (0.066). The atomic scattering factors were taken from ref. 8.

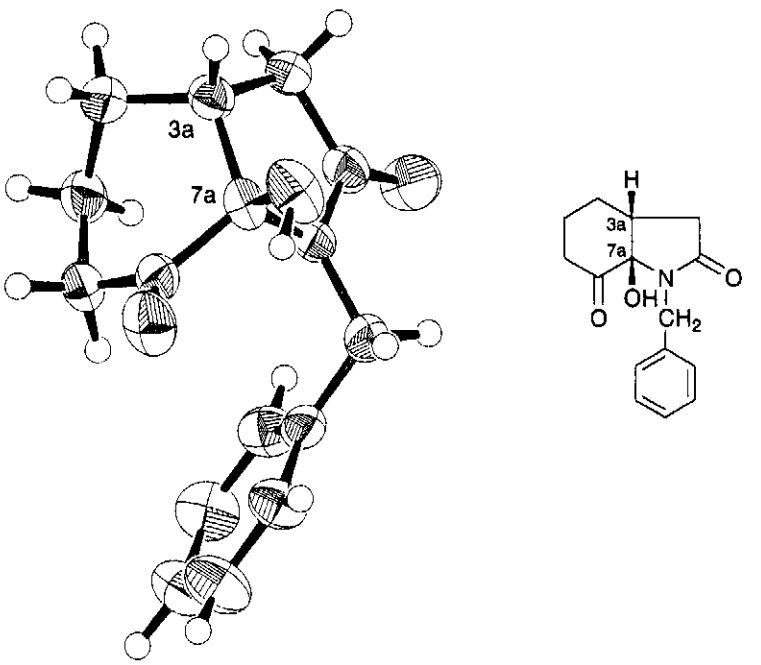


Figure 1. ORTEP Drawing of **8**.

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