5-*ENDO-TRIG* RADICAL CYCLIZATION OF 2-CHLORO- AND 2,2-BIS(PHENYLTHIO)-*N*-METHYL-*N*-(6-PHENYLCYCLOHEX-1-EN-1-YL)ACETAMIDES†

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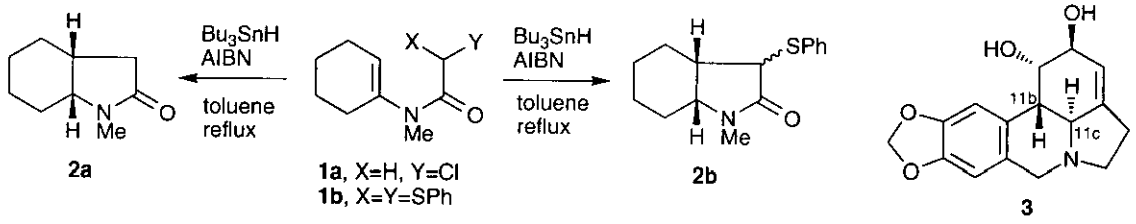
Abstract – Treatment of 2-chloro-*N*-methyl-*N*-(6-phenylcyclohex-1-en-1-yl)-acetamide (**4a**) with Bu_3SnH in the presence of AIBN gave a 2.5:1 mixture of *cis*- and *trans*-fused *N*-methyl-7-phenyloctahydroindol-2-ones (**5a** and **5b**) (13% combined yield), *N*-methyl-*N*-(2-phenylcyclohex-1-en-1-yl)acetamide (**6**) (19%), *N*-methyl-*N*-(6-phenylcyclohex-1-en-1-yl)acetamide (**7**) (13%), and *N*-(cyclohex-1-en-1-yl)-*N*-methyl-2-phenylacetamide (**8**) (4%). Similar treatment of the 2,2-bis(phenylthio)acetamide (**4b**) gave a 1:1 mixture of **5a** and **5b** (61% combined yield) along with **6** (24%) and **7** (trace). Possible mechanisms for the formation of the products (**6**)-(**8**) are also discussed.

Previously we demonstrated that the 2-chloro- (**1a**) and 2,2-bis(phenylthio)acetamides (**1b**), upon treatment with tributyltin hydride (Bu_3SnH) in the presence of azobis(isobutyronitrile) (AIBN), underwent a so-called disfavored '5-*endo-trig*' radical cyclization to give the *cis*-fused octahydroindol-2-ones (**2a**) and (**2b**), respectively.[1] We have now planned to examine the radical cyclization of *N*-(6-arylcyclohex-1-en-1-yl) derivatives (*e.g.*, **4**) in the hope that this reaction might provide a new route to 7-aryl-substituted octahydroindol-2-ones (*e.g.*, **5**), which would serve as potential precursors for the synthesis of lycorine (**3**) and its related compounds.[2] Here we describe results obtained with the readily accessible *N*-(6-phenylcyclohex-1-en-1-yl) derivatives (**4a,b**).



2a **1a**, X=H, Y=Cl; **1b**, X=Y=SPh **2b** **3**

†This paper is dedicated to Professor Koji Nakanishi, Columbia University, on the occasion of his 75th birthday.

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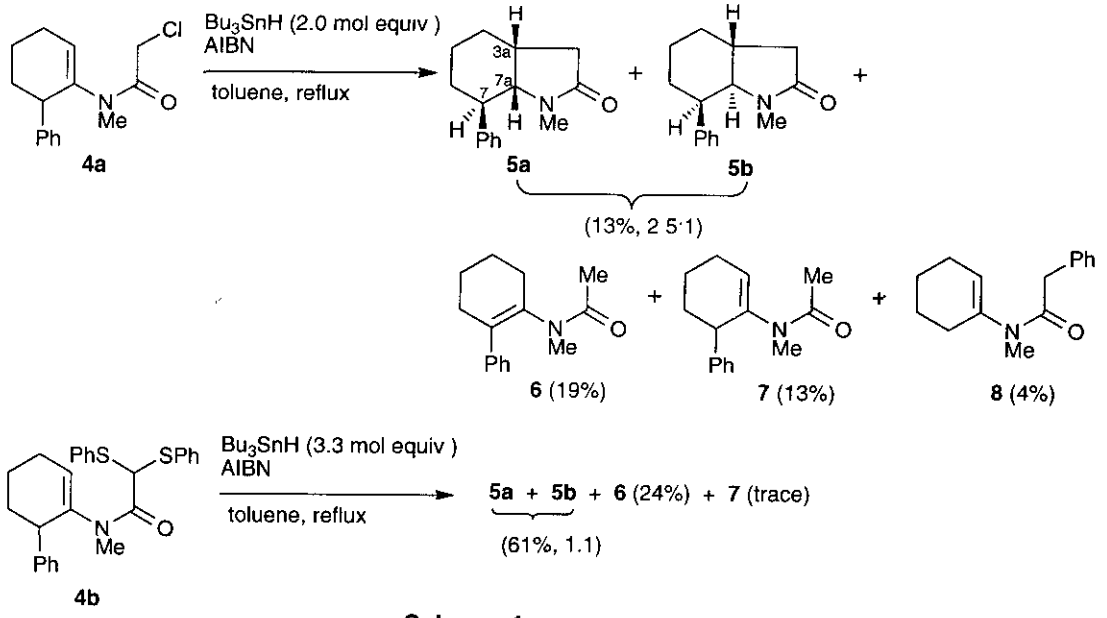
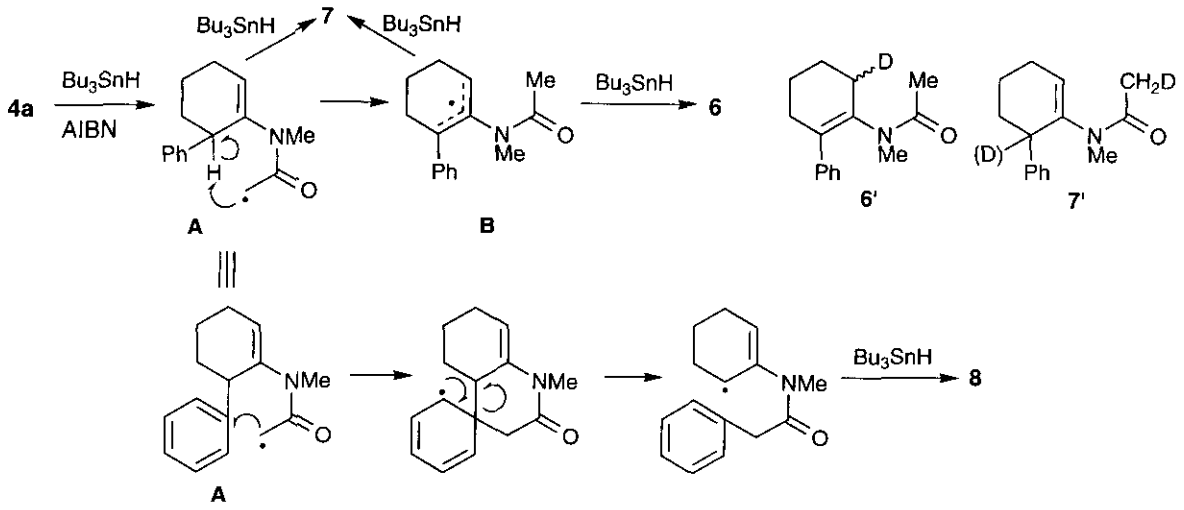
Treatment of **4a** with 2.0 mol equiv. of Bu3SnH in the presence of AIBN in boiling toluene gave the acetamides (**6**) (19%) and (**7**) (13%), the phenylacetamide (**8**) (4%), and the *cis*- and *trans*-fused octahydroindol-2-ones (**5a** and **5b**) as a 2.5:1 mixture (13% combined yield), from which crystalline **5a** was obtained as a pure compound. On the other hand, the 2,2-bis(phenylthio)acetamide (**4b**), when treated with 3.3 mol equiv. of Bu3SnH, gave **6** (24%), **7** (trace), and a 1:1 mixture of **5a** and **5b** (61% combined yield), from which **5b** was obtained as a pure compound. The stereochemistry of **5a** was determined by an X-ray analysis (Figure 1), and that of **5b** was defined by the coupling pattern of the 7a-proton in the ^{1}H-NMR spectrum which occurred at δ 3.40 as a doublet of doublets with $J_{3a,7a}$ = 10.2 and $J_{7,7a}$ = 4.6 Hz (confirmed by decoupling experiments) [the same proton of **5a** appeared at δ 3.59 (dd, $J_{3a,7a}$ = 6.8 and $J_{7,7a}$ = 10.0 Hz)]. These coupling constants are in good aagreement with the reported values for the related compounds.[3] The structures of **6-8** were assigned on the basis of the spectroscopic evidence (see Experimental Section).



Scheme 1

A mechanistic rationalization for the formation of **6** would involve a 1,5-hydrogen atom transfer[4] from the 6-position to the initially formed carbamoylmethyl radical, followed by reduction of the resulting allylic radical (**B**) with Bu3SnH. Compound (**7**) may be formed both by the direct reduction of radical (**A**) and by reduction of radical (**B**). The formation of **8** appears to be the result of an attack of the carbamoylmethyl radical on the phenyl ring followed by ring opening.[5] A support for this mechanistic scheme was derived from the following deuterium experiments. Thus, treatment of **4a** with Bu3SnD gave the corresponding deuterated products (**6'**) and (**7'**). The ^{2}H-NMR spectrum of **6'** showed the incorporation of a deuterium atom at the 6-position and that of **7'** indicated that the *N*-acetyl methyl group and the 6-position are deuterated in a ratio of *ca.* 2:1 (see Experimental).



Scheme 2

The increase of the formation of the cyclized product (**5**) from **4b** may be attributed to the presence of the additional phenylthio group which stabilizes the initially formed carbamoylmethyl radical and provides enough lifetime to take the C-N rotamer required for the cyclization. On the other hand, the radical derived from **4a** is more reactive so that the reaction seems to reflect the C-N rotamer populations.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded with a JASCO IR A-100 spectrophotometer. ^{1}H- (60 or 300 MHz) or ^{2}H- (46 MHz) NMR spectra were measured on a JEOL JNM-PMX 60 or a Varian XL-300 spectrometer, using tetramethylsilane as an internal standard. 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.

2-Chloro-*N*-methyl-*N*-(6-phenylcyclohex-1-en-1-yl)acetamide (4a). A solution of anhydrous methylamine (5 mL, 44.3 mmol) and 2-phenylcyclohexanone (1.52 g, 8.7 mmol) in toluene (10 mL) was heated at 100 °C in a sealed tube for 2 h. After removal of any excess methylamine and solvent, the residue was dissolved in dichloromethane (20 mL). Chloroacetyl chloride (1.47 g, 13.0 mmol) was added to the solution at 0 °C and the mixture was stirred at the same temperature for 10 min. Saturated aqueous $NaHCO_3$ solution (20 mL) was added to it and the whole was stirred for further 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane-ethyl acetate (8:1)]. The first fraction gave **4a** (0.61 g, 27%); mp 95-95.5 °C (from hexane-ethyl acetate); IR ν_{max} (CCl_4) cm^{-1}: 1660; ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.45-2.5 (6H, m), 2.75 (3H, s, NMe), 3.35-3.8 (1H, m, 6-H), 3.85 and 4.12 (1H each, ABq, J = 13 Hz, $COCH_2Cl$), 5.75-6.06 (1H, m, 2-H), 7.20 (5H, s, Ar H). *Anal.* Calcd for $C_{15}H_{18}NOCl$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.27; H, 7.03; N, 5.35. The second fraction gave 2-chloro-*N*-methyl-*N*-(2-phenylcyclohex-1-en-1-yl)acetamide (0.33 g, 14%) as an oil. IR ν_{max} (CCl_4) cm^{-1}: 1650; ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.6-2.7 (8H, m), 2.97 (3H, s,

NMe), 3.68 and 4.04 (1H each, ABq, J = 13 Hz, $COCH_2Cl$), 6.95-7.5 (5H, m, Ar H). *Anal.* Calcd for $C_{15}H_{18}NOCl$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.13; H, 6.84; N, 5.20.

Radical Cyclization of 4a. General Procedure. A solution of Bu_3SnH (829 mg, 2.85 mmol) and AIBN (31 mg, 0.19 mmol) in toluene (60 mL) was added dropwise to a solution of **4a** (500 mg, 1.90 mmol) in boiling toluene (30 mL) over 2.5 h, and the mixture was refluxed for 8 h. Subsequently, a solution of Bu_3SnH (276 mg, 0.95 mmol) and AIBN (16 mg, 0.1 mmol) in toluene (20 mL) was added to it and then heated for 1 h. After removal of the solvent, ether (30 mL) and an 8% aqueous solution of KF (30 ml) were added and the whole was vigorously stirred for 1 h. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 5:1). The first fraction gave *N*-methyl-*N*-(2-phenylcyclohex-1-en-1-yl)acetamide (**6**) (81 mg, 19%) as an oil. IR ν_{max} (CCl_4) cm^{-1}: 1650; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.70-2.55 (8H, m), 1.88 (3H, s, COMe), 2.87 (3H, s, NMe), 7.09-7.34 (5H, m, ArH). *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.43; H, 8.55; N, 5.92. The second fraction gave *N*-methyl-*N*-(6-phenylcyclohex-1-en-1-yl)acetamide (**7**) (57 mg, 13%) as an oil. IR ν_{max} (CCl_4) cm^{-1}: 1645; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.5-2.5 (6H, m), 2.01 (3H, s, COMe), 2.72 (3 H, s, NMe), 3.45-3.57 (1H, m, 6-H), 5.80-5.84 (1H, m, 2-H), 7.13-7.33 (5H, m, ArH). Exact Ms m/z: Calcd for $C_{15}H_{19}NO$: 229.1466. Found: 229.1479. The third fraction gave *N*-(cyclohex-1-en-1-yl)-*N*-methyl-2-phenylacetamide (**8**) (18 mg, 4%) as an oil. IR ν_{max} (CCl_4) cm^{-1}: 1650; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55-1.73 (4H, m), 1.93-2.02 (2H, m), 2.05-2.13 (2H, m), 2.99 (3H, s, NMe), 3.66 (2H, s, $COCH_2Ph$), 5.54-5.58 (1H, m, 2-H), 7.18-7.32 (5H, m, ArH). *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.47; H, 8.27; N, 5.81. The fourth fraction gave a 2.5:1 mixture of *cis*- and *trans*-fused *N*-methyl-7-phenyloctahydroindol-2-ones (**5a** and **5b**) (55 mg, 13%), from which **5a** was obtained as a pure compound by recrystallization from hexane-ethyl acetate, mp 126-127 °C; IR ν_{max} (CCl_4) cm^{-1}: 1680; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33-1.91 (6H, m), 2.22 (1H, dd, J = 15.9, 8.2 Hz, one of 3-H_2), 2.28 (3H, s, NMe), 2.48 (1H, dd, J = 15.9, 12.6 Hz, one of 3-H_2), 2.48-2.58 (1H, m, 3a-H), 2.61-2.73 (1H, m, 7-H), 3.59 (1H, dd, J = 10.0, 6.8 Hz, 7a-H), 7.21-7.35 (5H, m, ArH). *Irradiation of the multiplet centered at δ 2.67 (7-H) converted the signal at δ 3.59 (7a-H) into a doublet with J = 6.8 Hz.* *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.42; H, 8.42; N, 6.06.

***N*-Methyl-*N*-(6-phenylcyclohex-1-en-1-yl)-2,2-bis(phenylthio)acetamide (4b).** Following a procedure similar to that described for the preparation of **4a**, **4b** (1.23 g, 25%) was obtained from 2-phenylcyclohexanone (1.98 g, 11.4 mmol), methylamine (5 mL), and bis(phenylthio)acetyl chloride (3.68 g, 12.5 mmol); mp 110-110.5 °C (from hexane-ethyl acetate); IR ν_{max} (CCl_4) cm^{-1}: 1650; ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.4-2.8 (6H, m), 2.56 (3H, s, NMe), 2.9-3.3 (1H, m, 6-H), 5.15 [1H, br s, $COCH(SPh)_2$], 5.3-5.55 (1H, m, 2-H), 6.9-7.6 (15H, s, Ar H). *Anal.* Calcd for $C_{27}H_{27}NOS_2$: C, 72.77; H, 6.11; N, 3.14. Found: C, 72.62; H, 6.17; N, 3.19.

Radical Cyclization of 4b. Following the general procedure, **4b** (360 mg, 0.81 mmol) was treated three times with Bu_3SnH (259 mg, 0.89 mmol) and AIBN (13 mg, 0.08 mmol). The crude reaction mixture was chromatographed on silica gel (hexane-AcOEt, 8:1). The first fraction gave **6** (43 mg, 24%), the second fraction gave **7** (trace), and the third fraction gave a 1:1 mixture of **5a** and **5b** (112 mg, 61%),

from which **5b** was obtained as a pure compound by recrystallization from hexane, mp 115.5-116 °C; IR ν_{max} (CCl_4) cm^{-1}: 1690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25-2.10 (6H, m), 2.28-2.50 (3H, m), 2.80 (3H, s, NMe), 3.40 (1H, dd, J = 10.2, 4.6 Hz, 7a-H), 3.45-3.51 (1H, m, 7-H), 7.18-7.43 (5H, m, ArH). Irradiation of the multiplet centered at δ 2.40 (3a-H) converted the signal at δ 3.40 (7a-H) into a doublet with J = 4.6 Hz. *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.81; H, 8.45; N, 6.40.

Radical Cyclization of 4a with Bu_3SnD. Following the general procedure, **4a** (400 mg, 1.5 mmol) was treated once with Bu_3SnD (864 mg, 2.25 mmol) and AIBN (49 mg, 0.3 mmol) in toluene and the crude material was chromatographed on silica gel to give **6'** (75 mg, 22%) and **7'** (49 mg, 14%) in addition to a mixture of the deuterated **5a** and **5b** (97 mg, 28%). The ^{2}H-NMR spectrum (in $CHCl_3$) of **6'** showed two singlets at δ 2.08 and 2.38 due to the axial and equatorial deuteriums at the 6-position, and that of **7'** revealed a singlet due to the *N*-monodeuterated acetyl group at δ 2.01 and two singlets due to the 6-deuterium at δ 3.30 and 3.51 in a ratio of 6:2:1.

X-Ray Analysis of 5a. Crystal Data: $C_{15}H_{19}NO$, orthorhombic, space group *Pbca*; a = 15.667(2), b = 18.668(2), c = 8.740(1) Å, V = 2556.3(4) $Å^3$, Dx = 1.19 g/cm^3, $\mu(CuK\alpha)$ = 5.8 cm^{-1}, and Z = 8. Data Collection: A crystal was mounted on a Rigaku AFC7R 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 120.1°. Of 2205 independent reflections collected, 1089 reflections with $I > 3\sigma(I)$ were used for the structure determination and refinement. Data were corrected for Lorenz and polarization effects. Structure Determination and Refinement: The structure was solved by the direct method using the TEXSAN program.[6] The atomic coordinates were refined by the block-diagonal least-squares method, using anisotropic temperature factors for all the non-hydrogen-atoms and isotopic ones for hydrogen atoms. The final R-value was 0.04. The atomic scattering factors were taken from ref. 7.

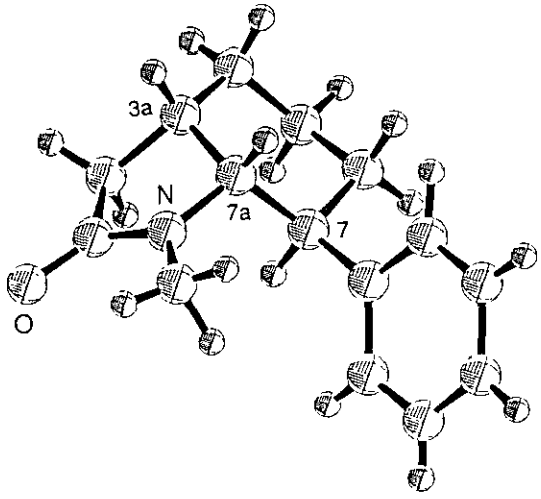


Figure 1. ORTEP Drawing of **5a.**

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