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8-ENDO-SELECTIVE ARYL RADICAL CYCLIZATION LEADING TO 3-BENZAZOCINES †

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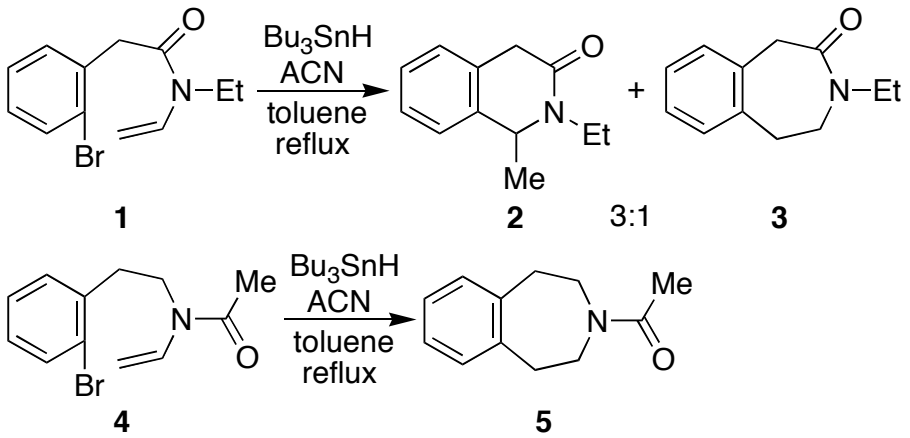
Abstract – Bu_3SnH-mediated radical cyclization of *N*-acyl-3-(2-bromophenyl)-*N*-ethenypropylamines (**14**) occurred in an *endo*-selective manner to give the 3-benzazocine derivatives (**15**) in good yields.

INTRODUCTION

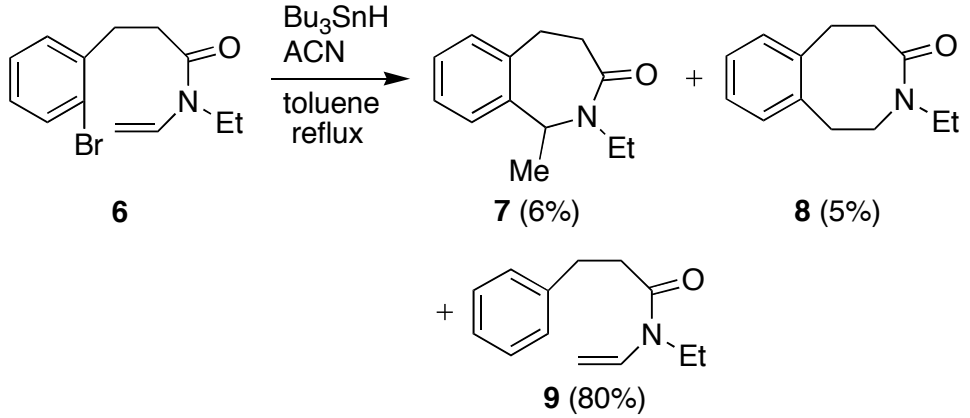
In a previous paper, we reported that Bu_3SnH-mediated radical cyclization of enamide (**1**) gave an isoquinoline derivative (**2**) as the major product along with a 3-benzazepine derivative (**3**) in a ratio of 3:1, and the cyclization of enamide (**4**) gave exclusively a 3-benzazepine derivative (**5**) (Scheme 1).[1] These results strongly indicated that positional change in the carbonyl group of enamide played an important role in deciding the course of radical cyclization. When the carbonyl group of starting enamide could be



Scheme 1. Radical cyclization of compounds (**1**) and (**4**).

† This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

incorporated into the newly formed ring, *exo* radical cyclization predominated (e.g., **1**→**2**), whereas when the carbonyl group was not incorporated into the newly formed ring, *endo* cyclization might result (e.g., **4**→**5**). We soon found, however, that *exo*-selectivity of the radical cyclization was lost even when the carbonyl group is incorporated into the newly formed ring. The radical cyclization of enamide (**6**) gave a 7-*exo* cyclization product (**7**) and an 8-*endo* cyclization product (**8**) in almost equal amounts (Scheme 2), although total yields of the cyclization products were low: the major product was a so-called reduction product (**9**).[2]



Scheme 2. Radical cyclization of compound (**6**).

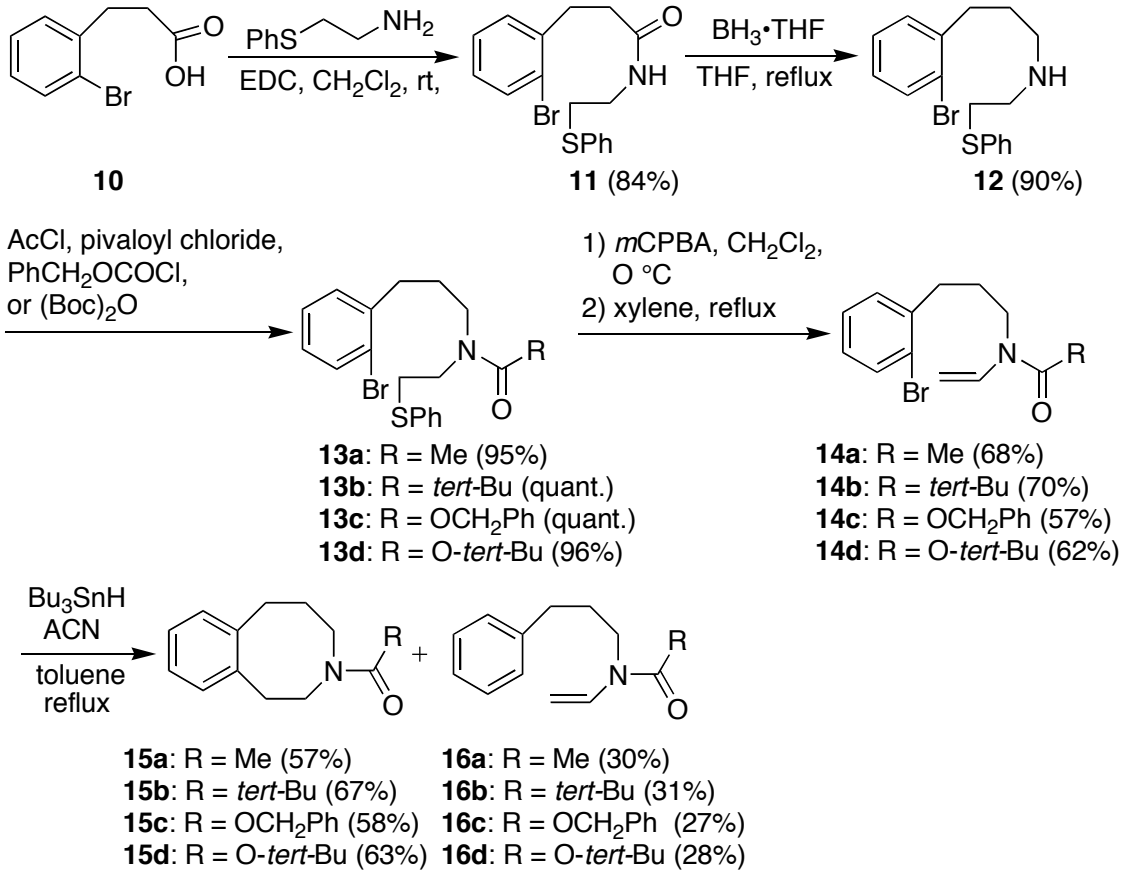
We then turned our attention to enamides (**14**), whose radical cyclizations were expected to occur in an 8-*endo*-selective manner, since their carbonyl groups were not incorporated into the newly formed ring. We describe herein a synthesis of 3-benzazocine derivatives (**15**) by radical cyclization of enamides (**14**).[3]

RESULTS AND DISCUSSION

Scheme 3 shows the synthetic route to the requisite enamides (**14**). Amine (**12**) was obtained by condensation of carboxylic acid (**10**) with 2-(phenylthio)ethylamine followed by reduction of the carbonyl group of the resulting amide (**11**) with BH_3. Acylation of amine (**12**) with acetyl chloride, pivaloyl chloride, carbobenzoxy chloride or $(Boc)_2O$ gave amides (**13a-d**), whose oxidation followed by thermal elimination of the phenylsulfinyl group gave enamides (**14a**-**d**) in 68%, 70%, 57% and 62% yields based on amides (**13a-d**), respectively.

When enamide (**14a**) was treated with a mixture of Bu_3SnH and azobis(cyclohexanecarbonitile) (ACN) (by using the slow addition technique) in boiling toluene, 3-acetyl-3-benzazocine derivative (**15a**) was obtained in 57% yield along with the reduction product (**16a**) (30% yield) (Scheme 3). No 7-*exo* cyclization product was obtained. Similarly, enamides (**14b-d**) gave 3-benzazocine derivatives (**15b**), (**15c**) and (**15d**) in 67%, 58% and 63% yields, respectively. It should be noted that the radical

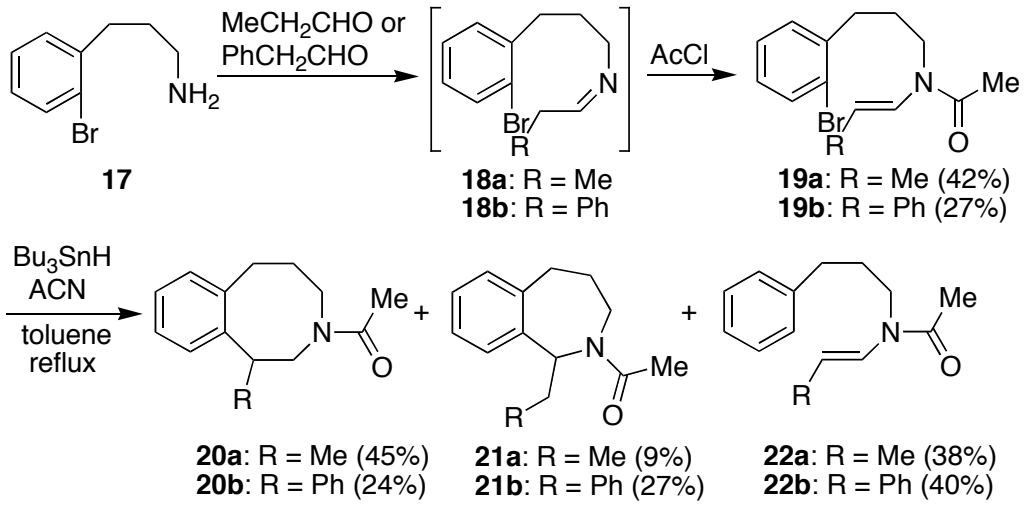
cyclization of enamides (**14a-d**) exclusively took place in an *endo*-manner to give 3-benzazocines (**15a-d**) in good yields.



Scheme 3. Preparation and radical cyclization of compounds (**14a**), (**14b**), (**14c**) and (**14d**).

We next examined the cyclization of enamides (**19a**) and (**19b**) having the methyl or phenyl group at the terminus of the alkenic bond, respectively. Compounds (**19a**) and (**19b**) were prepared by condensation of amine (**17**) and propionaldehyde or phenylacetaldehyde followed by acetylation of the resulting imines (**18a**) and (**18b**) with acetyl chloride, respectively (Scheme 4).

Treatment of compound (**19a**) with Bu_3SnH-ACN in boiling toluene gave 1-methyl-3-benzazocine derivative (**20a**) and 1-ethyl-2-benzazepine derivative (**21a**) in 45% and 9% yields, respectively, along with reduction product (**22a**) in 38% yield (Scheme 4). 7-*Exo* cyclization product (**21a**) may arise from a stable intermediate of a methyl-substituted radical. As expected, treatment of phenyl-substituted compound (**19b**) increased the yield of 7-*exo* cyclization product (**21b**), due to the more stable phenyl-substituted radical intermediate. The ratio of the 8-*endo* cyclization product (**20b**) and the 7-*exo* cyclization product (**21b**) was ca. 1:1.



Scheme 4. Preparation and radical cyclization of compounds (**19a**) and (**19b**).

CONCLUSION

We revealed that Bu_3SnH-mediated radical cyclization of *N*-acyl-3-(2-bromophenyl)-*N*-ethenylpropylamines occurred exclusively in an *endo*-manner to give 3-benzazocine derivatives in good yields. A similar cyclization of a compound having the methyl or phenyl substituent at the terminus of the alkenic bond, however, occurred partially in an *exo* manner to give 2-benzazepine derivatives.

EXPERIMENTAL

General Melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were measured on a JEOL EX 500 (500 MHz) or a JEOL JNM-EX 270 (270 MHz) spectrometer. Chemical shifts (δ) quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX-102A mass spectrometer. Column chromatography was carried out on silica gel 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm) under pressure.

3-(2-Bromophenyl)-*N*-(2-phenylthioethyl)propanamide (11) To a solution of 3-(2-bromophenyl)propionic acid (2.24 g, 9.78 mmol) in CH_2Cl_2 (50 mL) were added 2-(phenylthio)ethylamine[4] (1.50 g, 9.80 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (2.25 g, 11.7 mmol) at rt, and the mixture was stirred for 2 h. The mixture was diluted with water and the organic layer was separated. The organic phase was washed successively with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **11** (3.00 g, 84%) as colorless crystals, mp 84.5-86.0 ˚C (hexane): IR ($CHCl_3$) υ 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 2.45 (2H, t, J = 7.4 Hz), 3.00 (2H, t, J = 6.3 Hz), 3.06 (2H, t, J = 7.4 Hz), 3.43 (2H, q, J = 6.3 Hz), 5.76 (1H, br), 7.03-7.37 (8H, m), 7.52 (1H, d, J = 8.4 Hz);

^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 31.9, 33.2, 36.1, 38.5, 124.1, 126.3, 127.5, 127.9, 129.0, 129.4, 130.5, 132.7, 134.9, 139.8, 171.8. Anal. Calcd for $C_{17}H_{18}BrNOS$: C, 56.05; H, 4.98; N, 3.84. Found: C, 55.76; H, 5.04; N, 3.76.

3-(2-Bromophenyl)-*N*-(2-phenylthioethyl)propylamine (12) To a solution of **11** (2.80 g, 7.69 mmol) in THF (20 mL) was added a 1 M solution of BH_3·THF (35 mL, 34.3 mmol) at rt, and the mixture was heated at reflux for 1.5 h. MeOH was added to the reaction mixture, and the mixture was stirred at rt for 30 min. After evaporation of the solvent, 1*N* HCl was added to the residue, and the mixture was heated at reflux for 1 h. The mixture was basified by adding 1*N* NaOH, and the mixture was extracted with $CHCl_3$. The organic phase was washed successively with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **12** (2.41 g, 90%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.52 (1H, s), 1.79 (2H, quint, J = 7.4 Hz), 2.67 (2H, t, J = 7.4 Hz), 2.76 (2H, t, J = 7.4 Hz), 2.86 (2H, t, J = 6.6 Hz), 3.08 (2H, t, J = 6.6 Hz), 7.01-7.38 (8H, m), 7.51 (1H, d, J = 7.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 30.1, 33.7, 34.1, 48.2, 48.7, 124.3, 126.0, 127.3, 127.4, 128.8, 129.4, 130.2, 132.7, 135.8, 141.2. Anal. Calcd for $C_{17}H_{20}BrNS$: C, 58.28; H, 5.75; N, 4.00. Found: C, 58.27; H, 5.87; N, 4.12.

***N*-[3-(2-Bromophenyl)propyl]-*N*-(2-phenylthioethyl)acetamide (13a) General procedure** To a solution of **12** (1.3 g, 3.71 mmol) in CH_2Cl_2 (40 mL) was added acetyl chloride (437 mg, 5.57 mmol) and Et_3N (676 mg, 6.68 mmol) at 0 ˚C, and the mixture was stirred at the same temperature for 30 min. The mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed successively with a saturated aqueous solution of $NaHCO_3$ and brine. After drying ($MgSO_4$), the mixture was concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 2:1) to give **13a** (1.38 g, 95%) as a colorless oil, whose ^{1}H NMR showed it to be a mixture of two rotamers: IR ($CHCl_3$) υ 1630 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.75-1.90 (2H, m), 1.98 and 2.00 (total 3H, both s), 2.66-2.73 (2H, m), 2.99-3.16 (2H, m), 3.28-3.55 (4H, m), 7.04-7.56 (9H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 13.4, 13.9, 19.2, 21,6, 22.8, 24.7, 28.3, 35.5, 40.2, 126.9, 127.1, 127. 2, 127.6, 128.4, 138.5, 172.0. Anal. Calcd for $C_{19}H_{22}BrNOS$: C, 58.16; H, 5.65; N, 3.57. Found: C, 58.05; H, 5.83; N, 3.78.

***N*-[3-(2-Bromophenyl)propyl]-*N*-(2-phenylthioethyl)trimethylacetamide (13b)** Yield = quant.; colorless oil: IR ($CHCl_3$) υ 1615 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.17 (9H, s), 1.78-1.89 (2H, m), 2.69 (2H, t, J = 7.6 Hz), 3.08 (2H, t-like, J = 7.9 Hz), 3.42 (2H, t-like, J = 7.6 Hz), 3.50 (2H, t-like, J = 7.9 Hz), 7.04-7.41 (8H, m), 7.53 (1H, dd, J = 6.6, 1.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 26.5, 28.3, 28.8 (br), 33.4, 38.9, 47.8, 48.1 (br), 124.3, 127.5, 127.9, 129.0, 130.3, 132.9, 177.4; HRMS calcd for $C_{22}H_{28}{}^{79}BrNOS$: 433.1075, found: 433.1081.

***N*-Benzyloxycarbonyl-*N*-[3-(2-bromophenyl)propyl]-2-phenylthioethylamine (13c)** Yield = quant.; colorless oil: IR ($CHCl_3$) υ 1695 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.83 (2H, br), 2.62-2.73 (2H, m), 3.00-3.16 (2H, m), 3.30-3.51 (2H, m), 5.13 (2H, s), 7.01-7.34 (13H, m), 7.51 (1H, d, J = 7.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 28.9, 31.1, 33.4, 46.9, 47.8, 67.2, 124.3, 126.1, 127.4, 127.7, 127.8, 128.0, 128.5, 129.0, 130.1, 130.2, 132.8, 136.5, 140.6, 140.8; HRMS calcd for $C_{25}H_{26}{}^{79}BrNO_2S$: 483.0868, found: 483.0866.

***N*-[3-(2-Bromophenyl)propyl]-*N*-*tert*-butoxycarbonyl-2-phenylthioethylamine (13d)** Yield = 96%; colorless oil: IR ($CHCl_3$) υ 1685 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.43 (9H, s), 1.74-1.86 (2H, m), 2.68 (2H, t, J = 7.9 Hz), 3.06 (2H, br), 3.27 (2H, br), 3.39 (2H, br), 7.05-7.37 (8H, m), 7.51 (1H, d, J = 7.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 28.4, 31.5, 31.7, 33.5, 47.3, 79.7, 124.3, 126.0, 126.2, 127.4, 127.6, 129.0, 129.2, 130.2, 132.8, 140.9, 170.9; HRMS calcd for $C_{22}H_{28}{}^{79}BrNO_2S$: 449.1024, found: 449.1012.

***N*-[3-(2-Bromophenyl)propyl]-*N*-ethenylacetamide (14a) General procedure** To a solution of **13a** (1.38 g, 3.52 mmol) in CH_2Cl_2 (90 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (*m*CPBA, 65% purity) (934 mg, 3.52 mmol) in CH_2Cl_2 (90 mL) at 0° C over 1.5 h. To the mixture was added 10% aqueous solution of $Na_2S_2O_3$, and the mixture was stirred at the same temperature for 10 min. The organic layer was separated, and washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. A mixture of the residue containing *N*-[3-(2-bromophenyl)propyl]-*N*-(2-phenylsulfinylethyl)acetamide in xylene (170 mL) was heated at reflux for 16 h in the presence of $NaHCO_3$ (1.09 g, 13.0 mmol). The reaction mixture was filtered, and the filtrate was concentrated. The reside was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **14 a** (671 mg, 68%) as a colorless oil: IR ($CHCl_3$) υ 1625, 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.82-1.89 (2H, m), 2.21 (3H, s), 2.76 (2H, t-like, J = 7.9 Hz), 3.70 (2H, t-like, J = 7.7 Hz) 4.32 (1H, d, J = 9.2 Hz), 4.39 (1H, d, J = 15.5 Hz), 6.74 (1H, dd, J = 15.5, 9.2 Hz), 7.02-7.35 (3H, m), 7.52 (1H, d, J = 7.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 22.0, 26.5, 33.5, 41.1, 93.6, 124.4, 127.4, 127.7, 130.2, 132.8, 133.1, 140.7, 169.2: HRMS calcd for $C_{13}H_{16}{}^{79}BrNO$: 281.0415, found: 281.0408.

***N*-[3-(2-Bromophenyl)propyl]-*N*-ethenyltrimethylacetamide (14b)** Yield = 70%; colorless oil: IR ($CHCl_3$) υ 1615, 1655 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.32 (9H, s), 1.83-1.93 (2H, m), 2.75 (2H, t-like, J = 8.1 Hz), 3.70 (2H, t-like, J = 7.7 Hz) 4.26 (1H, d, J = 9.4 Hz), 4.35 (1H, d, J = 15.5 Hz), 7.01-7.08 (1H, m), 7.11 (1H, dd, J = 15.5, 9.4 Hz), 7.22-7.24 (2H, m), 7.52 (1H, d, J = 7.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 26.7, 28.5, 33.6, 39.5, 43.2, 92.2, 124.3, 127.4, 127.6, 130.2, 132.7, 134.0, 140.9, 176.5; HRMS calcd for $C_{16}H_{22}{}^{79}BrNO$: 323.0885, found: 323.0886.

***N*-Benzyloxycarbonyl-*N*-[3-(2-bromophenyl)propyl]ethenylamine (14c)** Yield = 57%; colorless oil: IR ($CHCl_3$) υ 1630, 1705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.90 (2H, br), 2.74 (2H, br), 3.62 (2H, br), 4.20-4.35 (2H, m), 5.20 (2H, s), 7.03-7.06 (2H, m), 7.15-7.21 (2H, m), 7.30-7.36 (4H, m), 7.51 (1H, d, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 26.7, 27.2, 33.4, 42.9, 67.8, 91.8, 124.4, 127.4, 127.7, 128.0, 128.2, 128.5, 130.1, 132.2, 132.8, 136.0; HRMS calcd for $C_{19}H_{20}{}^{79}BrNO_2$: 373.0677, found: 373.0665.

***N*-*tert*-Butoxycarbonyl-*N*-[3-(2-bromophenyl)propyl]ethenylamine (14d)** Yield = 62%; colorless oil: IR ($CHCl_3$) υ 1630, 1700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.48 (9H, s), 1.81 (2H, quint, J = 7.1 Hz), 2.75 (2H, t-like, J = 8.1 Hz), 3.60 (2H, br), 4.15-4.25 (2H, m), 7.02-7.09 (1H, m), 7.20-7.26 (2H, m), 7.52 (1H, d, J = 8.1 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 27.1 (br), 28.2, 33.5, 42.7 (br), 81.0, 90.5, 124.4, 127.4, 127.7, 130.1, 132.8, 140.9; HRMS calcd for $C_{16}H_{22}{}^{79}BrNO_2$: 340.0912, found: 340.0910.

3-Acetyl-1,2,3,4,5,6-hexahydro-3-benzazocine (15a) and *N*-ethenyl-*N*-(3-phenylpropyl)acetamide (16a) General procedure for radical reaction of *N*-acyl-3-(2-bromophenyl)propyl-*N*-ethenylamines (14) To a boiling solution of **14a** (200 mg, 0.709 mmol) in toluene (70 mL) was added dropwise a solution of Bu_3SnH (309 mg, 1.06 mmol) and ACN (34.6 mg, 0.142 mmol) in toluene (30 mL) over 4 h, and the mixture was further heated at reflux for 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 3:1). The first eluate gave **16a** (43.0 mg, 30%) as a colorless oil, whose ^1H NMR spectrum showed it to be a mixture of rotamers: IR ($CHCl_3$) υ 1620, 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, for one rotamer) δ (ppm): 1.81-1.95 (2H, m), 2.18 (3H, s), 2.64 (2H, t, J = 7.6 Hz), 3.64 (2H, t, J = 7.6 Hz), 4.27 (1 H, d, J = 8.2 Hz), 4.35 (1H, d, J = 15.3 Hz), 6.70 (1 H, dd, J = 15.3, 8.2 Hz), 7.14-7.34 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 22.0, 27.8, 33.2, 41.1, 65.3, 93.5, 124.0, 125.9, 126.9, 127.7, 128.28, 128.83, 128.5, 129.2, 133.1, 141.4, 169.2; HRMS calcd for $C_{13}H_{17}NO$: 203.1310, found: 203.1315. The second eluate gave **15a** (81.9 mg, 57%) as colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of isomers: IR ($CHCl_3$) υ 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, for one isomer) δ (ppm): 1.85-2.05 (2H, m), 1.94 and 2.10 (total 3H, s and s), 2.66-2.75 (2H, m), 2.85-2.93 (2H, m), 3.12-3.23 (2H, m), 3.49-3.51 and 3.68 (total 2H, m and br), 7.13-7.27 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 21.0, 21.9, 28.6, 29.1, 30.7, 31.3, 34.6, 34.7, 46.8, 47.5, 49.8, 52.7, 126.4, 126.8, 127.0, 127.2, 129.1, 129.2, 129.6, 129.7, 137.9, 139.3, 139.8, 140.9, 170.0, 170.8; HRMS calcd for $C_{13}H_{17}NO$: 203.1310, found: 203.1312.

1,2,3,4,5,6-Hexahydro-3-trimethylacetyl-3-benzazocine (15b) and *N*-ethenyl-*N*-(3-phenylpropyl)-trimethylacetamide (16b) **15b**: yield = 67%; colorless oil: IR ($CHCl_3$) υ 1615 cm^{-1}; ^1H NMR (270

MHz, $CDCl_3$) δ (ppm): 1.24 (9H, s), 1.92 (2H, br), 2.69 (2H, t, J = 6.3 Hz), 2.94 (2H, br), 3.13 (2H, br), 3.71 (2H, br), 7.10-7.20 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 28.6, 29.5, 30.5, 35.7, 39.0, 48.4, 52.0, 126.3, 127.2, 129.3, 129.5, 138.3, 141.0, 177.1; HRMS calcd for $C_{16}H_{23}NO$: 245.1780, found: 245.1781. **16b**: yield = 32%; colorless oil: IR ($CHCl_3$) υ 1615 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.31 (9H, s), 1.82-1.93 (2H, m), 2.63 (2H, t-like, J = 7.8 Hz), 3.64 (2H, t-like, J = 7.8 Hz) 4.23 (1H, d, J = 9.3 Hz), 4.27 (1H, d, J = 15.4 Hz), 7.09 (1H, dd, J = 15.4, 9.3 Hz), 7.18-7.31 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 28.0, 28.5, 33.3, 39.5, 43.3, 92.1, 125.9, 128.29, 128.31, 134.0, 141.5, 176.4; HRMS calcd for $C_{16}H_{23}NO$: 245.1780, found: 245.1770.

3-Benzyloxycarbonyl-1,2,3,4,5,6-hexahydro-3-benzazocine (15c) and *N*-benzyloxycarbonyl-*N*-ethenyl-3-phenylpropylamine (16c) **15c**: yield = 58%; colorless oil; ^{1}H and ^{13}C NMR spectrum showed compound **15c** to be a mixture of isomers: IR ($CHCl_3$) υ 1680 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, for one isomer) δ (ppm): 1.82-2.02 (2H, m), 2,69 (2H, dd, J = 13.5, 5.9 Hz), 2.82-2.86 (2H, m), 3.02-3.12 (2H, m), 3.58 (2H, br), 5.08 and 5.14 (total 2H, s and s), 7.06-7.34 (9H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 29.2, 29.5, 30.1, 30.6, 35.07, 35.09, 46.2, 47.4, 50.9, 51.3, 66.7, 66.9, 126.4, 126.6, 126.95, 127.0, 127.6, 127.7, 127.78, 127.83, 128.40, 128.43, 129.2, 129.4, 129.5, 129.7, 136.9, 137.0, 139.0, 139.5, 140.1, 140.5, 155.3, 156.2; HRMS calcd for $C_{16}H_{23}NO$: 245.1780, found: 245.1781. **16c**: yield = 32%; colorless oil: IR ($CHCl_3$) υ 1630, 1705 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.80-1.95 (2H, m), 2.62 (2H, br), 3.57 (2H, br), 4.22 (2H, br d), 5.19 (2H, s), 7.15-7.35 (11H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 23.0, 24.7, 28.0, 30.9, 33.1, 42.8, 67.8, 91.7, 125.9, 127.9, 128.0, 128.19, 128.24, 128.3, 128.5, 132.7, 136.0; HRMS calcd for $C_{16}H_{23}NO$: 245.1780, found: 245.1770.

3-*tert*-Butoxycarbonyl-1,2,3,4,5,6-tetrahydro-3-benzazocine (15d) and *N*-*tert*-Butoxycarbonyl-*N*-ethenyl-3-phenylpropylamine (16d) **15d**: yield = 63%; colorless oil; ^{1}H NMR spectrum showed compound **15d** to be a mixture of isomer: IR ($CHCl_3$) υ 1680 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.35 and 1.44 (total 9H, both s), 1.8-1.98 (2H, m), 2.67-2.71 (2H, m), 2.80-2.87 (2H, m), 2.95 and 3.06 (total 2H, br and t, J = 5.8 Hz), 3.46-3.52 (2H, m), 7.10-7.18 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 28.3, 28.5, 29.3, 29.6, 30.5, 30.7, 34.8, 35.2, 46.4, 47.1, 50.5, 50.9, 79.0, 79.2, 126.3, 126.5, 126.80, 126.83, 129.1, 129.39, 129.47, 129.7, 139.0, 139.7, 140.2, 141.0, 154.7, 155.5. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.52; H, 9.09; N, 5.50. **16d**: yield = 28%; colorless oil: IR ($CHCl_3$) υ 1625, 1700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.47 (9H, s), 1.83-1.94 (2H, m), 2.63 (2H, t like, J = 7.9 Hz), 3.50 (2H, br), 4.16 (2H, br d), 7.05 (1H, br), 7.17-7.30 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 28.2, 28.3, 33.2, 42.5 (br), 81.0, 90.4, 125.9, 128.26, 128.34, 132.7, 132.8, 141.4; HRMS calcd for $C_{16}H_{23}NO$: 261.1729, found: 261.1727.

***N*-3-(2-Bromophenyl)propyl-*N*-(1-propenyl)acetamide (19a)** A mixture of 3-(2-bromophenyl)-propylamime (300 mg, 1.40 mmol) and propionaldehyde (81.3 mg, 1.40 mmol) in THF (12 mL) was stirred at 0 °C for 3 h in the presence of MS 4Å (powder, 300 mg). Acetyl chloride (132 mg, 1.68 mmol) and Et_3N (313 mg, 2.10 mmol) were added to the reaction mixture containing imine (**18a**) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into water and the organic layer was separated. The organic phase was washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, After drying ($MgSO_4$), the mixture was concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **19a** (173.1 mg, 42%) as a colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of two rotamers: IR ($CHCl_3$) υ 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, for one isomer) δ (ppm): 1.72 (3H, d, J = 6.6 Hz), 1.80-2.00 (2H, m), 2.17 (3H, s), 2.74 (2H, t, J = 8.1 Hz), 3.67 (2H, t, J = 7.7 Hz), 5.00 (1H, dq, J = 13.8, 6.8 Hz), 6.43 (1H, d, J = 13.8 Hz), 7.02-7.27 (4H, m), 7.52 (1H, d, J = 7.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 15.6, 22.2, 26.8, 33.5. 42.3, 107.8, 124.4, 127.4, 127.6, 128.2, 130.2, 132.7, 140.9, 168.8; HRMS calcd for $C_{14}H_{18}{}^{79}BrNO$: 295.0572, found: 295.0565.

***N*-3-(2-Bromophenyl)propyl-*N*-(2-phenylethenyl)acetamide (19b)** According to the procedure similar to that described for the preparation of **19a**, 3-(2-bromophenyl)propylamime (300 mg, 1.40 mol) and phenylacetaldehyde (168 mg, 1.40 mol) was condensed and the resulting imine (**18b**) was treated with acetyl chloride (132 mg, 1.68 mmol) and Et_3N (313 mg, 2.10 mmol) to give **19b** (133.5 mg, 27%) as a colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of rotamers: IR ($CHCl_3$) υ 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, for one rotamer) δ (ppm): 1.85-2.10 (2H, m), 2.31 (3H, s), 2.78-2.86 (2H, m), 3.66-3.84 (2H, m), 5.85 (1H, d, J = 14.5 Hz), 7.04-7.56 (10H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 22.2, 26.7, 32.3, 32.7, 33.5, 41.9, 62.1, 110.6, 111.2, 124.4, 125.3, 125.6, 126.4, 126.5, 127.4, 126.6, 127.8, 128.2, 128.6, 128.7, 128.8, 130.36, 130.38, 132.77, 132.84, 136.5, 140.6, 141.1, 144.8, 169.2; HRMS calcd for $C_{19}H_{20}{}^{79}BrNO$: 357.0728, found: 357.0727.

3-Acetyl-1,2,3,4,5,6-hexahydro-1-methyl-3-benzazocine (20a), 2-acetyl-1-ethyl-1,3,4,5-tetrahydro-2(2*H*)-benzazepine (21a) and *N*-(3-phenylpropyl)-*N*-(1-propenyl)acetamide (22a) According to the general procedure described above for the radical reaction of **14a**, compound (**19a**) (150 mg, 0.506 mmol) was treated with Bu_3SnH (221 mg, 0.76 mmol) and ACN (24.7 mg, 0.101 mmol), After usual work-up, the residue was chromatographed on silica gel (hexane/AcOEt, 3:1). The first eluate gave **22a** (42.6 mg, 38%) as a colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of two rotamers: IR ($CHCl_3$) υ 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, for one rotamer) δ (ppm): 1.69 (3H, d, J = 6.7 Hz), 1.82-1.89 (2H, m), 2.16 (3H, s), 2.61-2.67 (2H, m), 3.62 (2H, t, J = 7.9 Hz), 4,86-4.96 (1H, m), 6.41 (1H, d, J = 13.4 Hz), 7.1-7.4 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 15.5, 22.2, 28.2, 33.2, 42.5,

107.7, 125.8, 128.2, 128.3, 128.5, 141.6, 168.8; HRMS calcd for $C_{14}H_{19}NO$: 217.1467, found: 217.1465. The second eluate gave **21a** (10.0 mg, 9%) as a colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of two isomers: IR ($CHCl_3$) υ 1625 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.90 (3H × 1/2, t, J = 7.3 Hz), 0.95 (3H × 1/2, t, J = 7.3 Hz), 1.71-1.78 (2H × 1/2, m), 1.87-1.98 (2H × 1/2, m), 2.10 (3H × 1/2, s), 2.13 (3H × 1/2, s), 2.81-2.85 (2H × 1/2, m), 3.03 (1/2 H, br t), 3.10-3.16 (2H × 1/2, m), 3.55 (1/2H, br-t), 3.83 (1/2H, br d), 4.55 (1/2H, dd, J = 9.2, 6.7 Hz), 4.73 (1/2H, br d), 5.52 (1/2H, br), 7.06-7.30 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 11.1, 11.3, 22.4, 25.0, 27.6, 29.2, 35.1, 35.4, 66.2, 126.2, 126.3, 126.9, 127.3, 129.0, 130.5, 131.5, 139.5, 140.3, 140.7, 141.1, 170.1, 170.8; HRMS calcd for $C_{14}H_{19}NO$: 217.1467, found: 217.1469. The third eluate gave **20a** (49.0 mg, 45%) as a colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of two isomers: IR ($CHCl_3$) υ 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.41 (3H, d, J = 6.8 Hz), 1.66 (3H × 3/4, s), 1.89-2.17 (2H, m), 2.00 (3H × 1/4, s), 2.65-2.99 (2H, m), 3.01-3.13 (2H, m), 3.23-3.46 (2H, m), 3.66 (3/4H, dt, J = 9.2. 4.5 Hz), 3.88 (1/4H, dd, J = 12.8, 3.0 Hz), 7.10-7.30 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 16.8, 17.7, 21.0, 21.8, 28.5, 30.0, 31.6, 32.1, 34.4, 47.6, 47.9, 55.5, 59.3, 123.9, 124.8, 126.4, 126.5, 126.8, 128.9, 129.7, 139.7, 141.1, 141.6, 142.8, 169.9, 170.5; HRMS calcd for $C_{14}H_{19}NO$: 217.1467, found: 217.1467.

3-Acetyl-1,2,3,4,5,6-hexahydro-1-phenyl-3-benzazocine (20b), 2-acetyl-1-benzyl-1,3,4,5-tetrahydro-2(2*H*)-benzazepine (21b) and *N*-(2-phenylethenyl)-*N*-(3-phenylpropyl)acetamide (22b) According to the general procedure described above for the radical reaction of **14a**, compound (**19b**) (110 mg, 0.307 mmol) was treated with Bu_3SnH (134 mg, 0.461 mmol) and ACN (15.0 mg, 0.0612 mmol), After usual work-up, the residue was chromatographed on silica gel (hexane/AcOEt, 4:1). The first eluate gave **22b** (34.6 mg, 40%) as a colorless oil, whose ^1H and ^{13}C NMR spectrum showed it to be a mixture of two rotamers: IR ($CHCl_3$) υ 1635, 1670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, for one rotamer) δ (ppm): 1.85-2.0 (2H, m), 2.28 (3H, s), 2.65-2.75 (2H, m), 3.76 (2H, t, J = 7.3 Hz), 5.74 (1H, d, J = 14.0 Hz), 7.13-7.36 (11H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ (ppm): 22.1, 22.2, 27.9, 28.7, 32.0, 32.9, 33.1, 62.1, 110.6, 111.0, 125.3, 125.6, 125.8, 126.0, 126.3, 126.4, 126.5, 126.9, 127.6, 128.38, 128.45, 128.54, 128.6, 128.7, 136.5, 136.8, 140.5, 141.3, 169.0, 169.2; HRMS calcd for $C_{19}H_{21}NO$: 279.1623, found: 279.1622. The second eluate gave **21b** (22.9 mg, 27%) as a colorless oil: IR ($CHCl_3$) υ 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.66-2.00 (3H, m), 1.91 and 1.97 (total 3H, s), 2.82-2.86 (1H, m), 3.14-3.19 (2H, m), 3.33 (1/2H, dd, J = 14.0, 8.5 Hz), 3.47-3.64 (1H, m), 4.61 (1/2H, br d), 4.94 (1/2H, t, J = 7.3 Hz), 5.97 (1/2H, br), 6.84-7.21 (9H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 22.2, 22.3, 27.6, 29.1, 35.2, 35.4, 37.1, 38.5, 41.0, 65.8, 126.1, 126.3, 126.7, 127.1, 127.5, 128.3, 128.57, 128.66, 128.71, 129.1, 130.5, 131.5, 137.7, 139.6, 139.8, 140.3, 170.0, 170.5; HRMS calcd for $C_{19}H_{21}NO$: 279.1623, found: 279.1629. The third eluate gave **20b** (20.6 mg, 24%) as a colorless oil, whose ^1H and ^{13}C NMR

spectrum showed it to be a mixture of two rotamers: IR ($CHCl_3$) υ 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.72 (3H × 2/3, s), 2.01 (3H × 1/3, s), 2.04-2.20 (2H, m), 2.80-2.85 (1H, m), 3.03 (1H, t, J = 14 Hz), 3.17 (2/3H, br), 3.30 (1/3H, br), 3.43 (1/3H, br), 3.71 (2/3H, br), 3.79-3.87 [(1 + 2/3)H, m], 4.08 (1/3H, m), 4.51-4.54 (1/3H, m), 4.66 (2/3H, dd, J = 10.3, 4.8 Hz), 6.79-7.49 (9H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 21.1, 21.9, 28.5, 30.9, 31.7, 32.4, 45.4, 47.7, 48.3, 52.2, 55.8, 126.4, 126.5, 126.7, 126.8, 126.93, 126.97, 127.03, 128.2, 128.4, 128.5, 128.6, 128.9, 129.6, 139.7, 141.0, 141.2, 141.4, 142.1, 142.2, 170.2, 170.7; HRMS calcd for $C_{19}H_{21}NO$: 279.1623, found: 279.1627.

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