STUDIES ON THE SITE-SELECTIVE *N*-ACYLIMINIUM ION CYCLIZATION : SYNTHESIS OF (±)-GLOCHIDINE AND (±)-GLOCHIDICINE

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Abstract --- Studies on the *N*-acyliminium ion cyclization of hydroxylactams bearing both carbon and nitrogen nucleophile in the same molecule are described. The site selection in the cyclization of hydroxylactam could be controlled by the absence or presence of acid catalyst to afford (±)-glochidine and (±)-glochidicine.

N-Acyliminium ions are useful intermediate in organic synthesis.[1] The reaction of such nitrogen-stabilized cation with various nucleophiles has been used as the key C-C bond forming step in the synthesis of alkaloids, such as isoquinoline and indole alkaloids. Although synthetic and mechanistic aspects on the C-C bond formation in *N*-acyliminium ion cyclization have been quite well established,[1,2] examples of the C-N bond formation in the cyclizations are scarce except the report by Johns *et al.*[3] Furthermore, studies on the control of the capture of *N*-acyliminium ions with carbon or nitrogen nucleophiles have received unexpectedly little attention.

Our interest in the control of C-C or C-N bond formation in *N*-acyliminium ion cyclizations prompted us to study the *N*-acyliminium ion cyclization of imidazolo-hydroxylactam (2) bearing both carbon and nitrogen nucleophile in the same molecule.

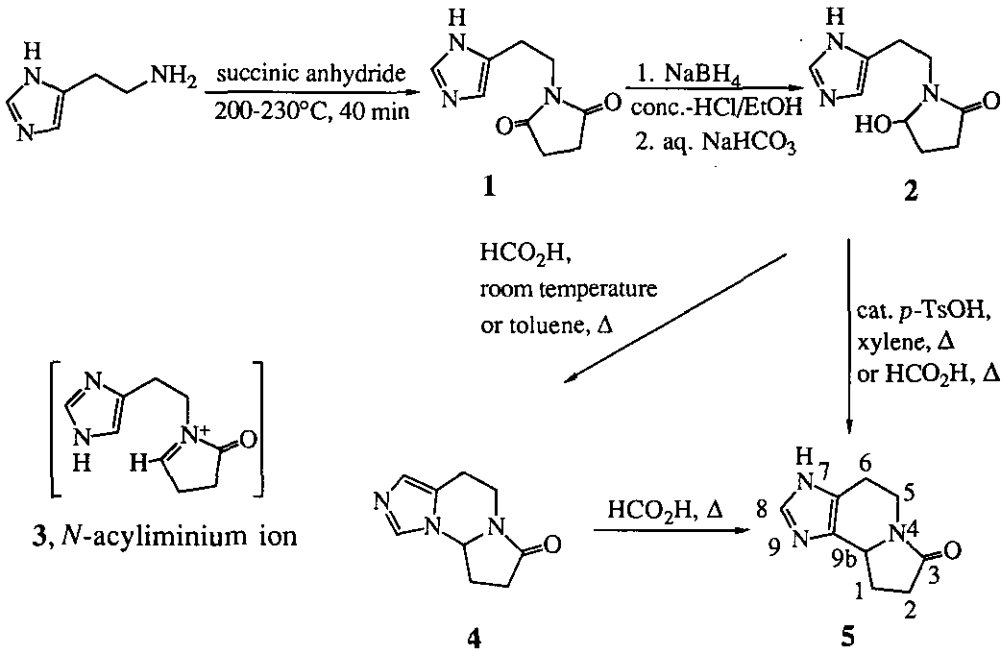
Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday

as a only product. It appears that the C-N bond formation is a kinetically favored process in

Hydroxylactam (2), a good precursor for the generation of *N*-acyliminium ion (3), was prepared as follows. (Scheme 1)

Pyrolytic reaction of histamine dihydrochloride with succinic anhydride gave histamine succinimide (1) in 86 % yield. Reduction of **1** with sodium borohydride[4] at -5~5 °C in ethanolic HCl and subsequent quenching with aqueous sodium bicarbonate solution produced a hydroxylactam (2) in 71 % yield.

Scheme 1



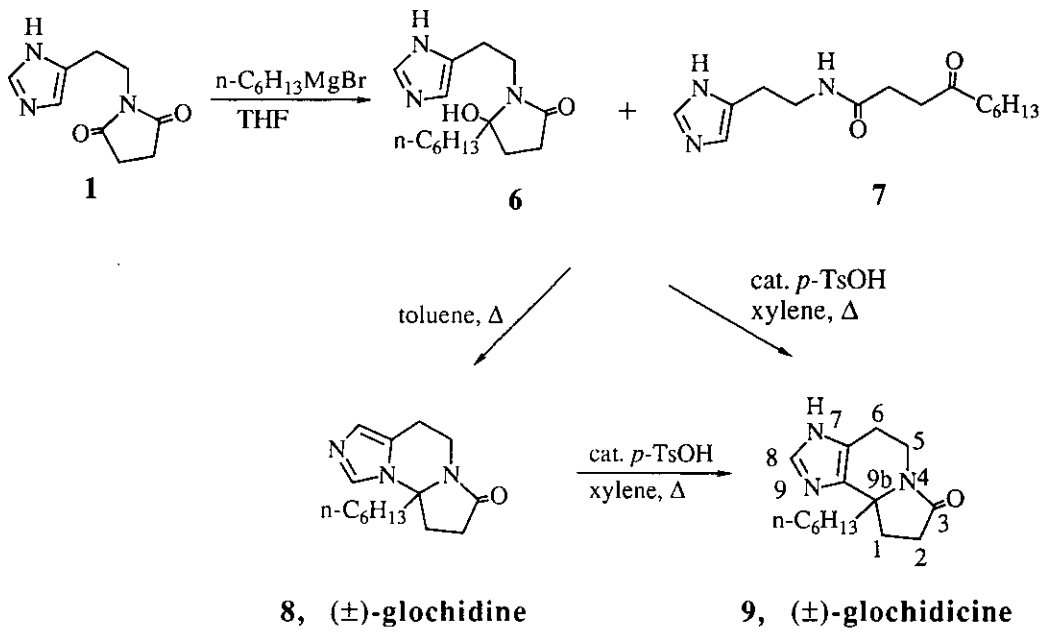
With the hydroxylactam (2) in hand, the *N*-acyliminium ion cyclization was studied. When the reaction was carried out in formic acid, an interesting result came out. It was found that one can achieve the complete selectivity for the C-C and C-N bond formations in the cyclization reaction by simply varing the reaction temperature. At the room temperature (48 h), **4** was obtained in 78 % yield as a sole product. This C-N bond forming cyclization reaction proceeded faster at 50 °C (5 h) to provide **4** in 72 % yield. On the other hand, under refluxing condition (24 h), C-C bond-formed product (5) was produced in 75 % yield as a only product. It appears that the C-N bond formation is a kinetically favored process in

the cyclization of *N*-acyliminium ion (3) and irreversible up to 50 °C. However, at the elevated temperature, the equilibrium takes place and the bond formation of thermodynamically more stable **5** is favored. It has been proven by the fact that **4** is completely converted into **5** at the reflux temperature in formic acid. Interestingly, hydroxylactam (2) showed nearly identical retention time and fragmentation pattern with those of **4** in the GC-mass analysis, suggesting the simple heating effects the C-N bond forming cyclization. Upon heating at the reflux temperature in toluene for 4 h, **2** indeed cyclized to give **4** in 56 % yield. When **2** was subjected to a catalytic amount of *p*-toluenesulfonic acid (TsOH) in refluxing xylene (16 h), the more stable cyclized product (5) was obtained in 92 % yield. Thus, one can control the cyclization pathway of **2** simply with or without the use of acid catalyst while heating.

Based on the promising results, our attention now focused upon the synthesis of (±)-glochidine (8) and (±)-glochidicine (9) using selective *N*-acyliminium ion cylization as shown in Scheme 2.

Glochidine and glochidicine are interrelated imidazole alkaloids, which were isolated from

Scheme 2



1 **6** **7**

8, (±)-glochidine **9, (±)-glochidicine**

the leaves of a New Guinea *Glochidone* species.[3] Their structures were confirmed by the spectroscopic and chemical studies.[3] Our synthesis started with the imide (1). The Grignard reaction of **1** with n-hexylmagnesium bromide afforded a mixture of hydroxylactam (6) and acyclic keto-amide (7). Hydroxylactam (6) could not be separated cleanly due to the fast conversion of **6** to the ring-opened product (7). Since the cyclization of both **6** and **7** gives the same product, the above mixture of **6** and **7** was used for the cyclization reaction without further purification.. This crude mixture was cyclized in refluxing toluene to afford (±)-glochidine (8) in 71 % yield. The other alkaloid (9) was not detected. Cyclization of the same crude mixture of **6** and **7** with a catalytic amount of TsOH in refluxing xylene yielded (±)-glochidicine (9) as a sole product.

In summary, the control of C-C and C-N bond formation in *N*-acyliminium ion cyclizations would provide a promising access to several heterocyclic systems.

EXPERIMENTAL

Histamine dihydrochloride and succinic anhydride were purchased from Aldrich Chemical Co. All other reagents and solvents were obtained commercially and used without purification. Tlc plates and silica gel (230-400 mesh) were used Kieselgel 60 F_{254} and Kieselgel 60. The ^{1}H-nmr spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. Infrared (ir) spectra were obtained on a Bruker IFS120HR FT-IR spectrophotometer using potasium bromide pellet. Melting points (mp) were determined on a Thomas-Hoover capillary melting appratus and uncorrected. Elemental analysis was performed by a Perkin-Elmer 240 DS analyzer. Analytical GC-ms work was performed with a Hewlett-Packard 5988A GC-Mass using a capillary column of SE-54 (17 m x 0.2 mm i.d.); oven temperature was programmed from 120 °C to 280 °C at 20 °C/min; observed retention times of **2, 4** and **5** were at 5.73, 5.75 and 6.59 min, respectively.

***N*-[2-(Imidazol-4-yl)ethyl]succinimide (1)** A mixture of histamine dihydrochloride (10 g, 54 mmol) and succinic anhydride (6 g, 60 mmol) was heated at 200 ~ 230 °C in an oil bath for 40 min and cooled to room temperature. The mixture was diluted with ethanol (200 ml) and neutralized by the addition of saturated aqueous $NaHCO_3$ solution (50 ml). The mixture was filtered, concentrated, and recrystallized from i-propanol to give **1** as a white solid (9 g, 86 %). mp 165-168 °C. *Anal.* Calcd for $C_9H_{11}N_3O_2$: C, 55.94; H, 5.75; N, 21.75.

Found: C, 55.92; H, 5.75; N, 21.73. Ir (KBr) cm^{-1}: 3440 (NH), 1694 (C=O). ^{1}H-nmr (D_2O) δ (ppm): 2.71 (4H, s, CO*CH*$_2$*CH*$_2$CO), 2.86 (2H, t, J=6.7 Hz, *CH*$_2$CH$_2$N), 3.70 (2H, t, J=6.7 Hz, CH$_2$*CH*$_2$N), 6.98(1H, s, imidazole, NH*CH*=C), 7.92 (1H, s, imidazole, N=*CH*NH).

1-[2-(Imidazol-4-yl)ethyl]-2-hydroxy-5-pyrrolidone (2) To a stirred solution of **1** (1 g, 5.18 mmol) in ethanol (50 ml) at -5 °C was added sodium borohydride (1.89 g, 49.96 mmol). Ethanolic hydrochloride solution (20 ml, conc.-HCl/ethanol=1:5) was added dropwise for 30 min. After 30 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (100 ml) and the resulting solid was removed by filtration. The filtrate was concentrated at reduced pressure and the residue was purified by flash column chromatography (MeCN/H_2O = 7:1) to give hydroxylactam (2) as a white solid (0.72 g, 71 %). mp 166-167 °C. *Anal.* Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.36; H, 6.73; N, 21.53. EI-ms (70 eV) *m/z* (rel. int.): 177 (M^+-H_2O, 100), 122 (14), 97 (45), 96 (42), 95 (63), 94 (96), 81 (27), 68 (54), 41 (27). Ir (KBr) cm^{-1}: 3117, 2998, 2938, 1661 (C=O). ^{1}H-nmr (D_2O) δ (ppm): 1.80-1.91 (1H, m, HOCCH$_2$*CH*$_2$CHOH), 2.24-2.39 (2H, m, CH$_2$*CH*$_2$CHOH, CH$_2$*CH*$_2$C=O), 2.48-2.63 (1H, m, CH$_2$*CH*$_2$C=O), 2.81-2.94 (2H, m, *CH*$_2$CH$_2$N), 3.36-3.45 (1H, m, CH$_2$*CH*$_2$N), 3.63-3.73 (1H, m, CH$_2$*CH*$_2$N), 5.78 (1H, dd, *J*=5.8 Hz, 1.8 Hz, CH$_2$*CH*OH), 6.91(1H, s, imidazole, NH*CH*=C), 7.67 (1H, s, imidazole, N=*CH*NH). ^{13}C-nmr (D_2O) δ (ppm): 24.29, 26.96, 28.67, 39.90, 83.40, 116.62, 134.35, 135.47, 177.53.

1,2,3,5,6,10a-Hexahydro-3-oxoimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidine (4)

A solution of **2** (466 mg, 2.39 mmol) in formic acid (10 ml) was stirred at room temperature for 48 h. The solvent was evaporated below 50 °C at reduced pressure. The residue was diluted with methylene chloride (30 ml) and washed succesively with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and evaporated to give nearly pure **4** as a white solid (331 mg, 78 %). mp 159-161 °C. *Anal.* Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.80; H, 6.19; N, 23.71. EI-ms (70 eV) *m/z* (rel. int.): 177 (M^+, 100), 122 (10), 97 (30), 96 (29), 95 (43), 94 (73), 81 (26), 68 (42), 41 (66). Ir (KBr) cm^{-1}: 1689 (C=O). ^{1}H-nmr ($CDCl_3$) δ (ppm): 2.25-2.34 (1H, m, C_1-H), 2.54-2.58 (2H, m, C_1-H, C_2-H), 2.72-2.89 (3H, m, C_2-H, C_6-H x 2), 3.02-3.12 (1H, m, C_5-H), 4.29-4.36 (1H, m, C_5-H), 5.66 (1H, dd, *J*=6.9 Hz, 4.4 Hz, C_{10a}-H), 6.81 (1H, s, C_7-H), 7.48 (1H, s, C_9-H). ^{13}C-nmr ($CDCl_3$) δ (ppm): 20.41, 26.05, 29.41, 36.19, 68.83, 125.09, 125.61, 132.21, 172.97.

1,2,3,5,6,9b-Hexahydro-7*H*-3-oxoimidazo[4,5-*c*]pyrrolo[1,2-*a*]pyridine (5) A solution of **2** (190 mg, 0.97 mmol) in formic acid (10 ml) was refluxed for 24 h. The solvent was evaporated at reduced pressure and the residue was diluted with ethanol (5 ml). After being neutralized with saturated aqueous $NaHCO_3$ solution (10 ml), the mixture was concentrated under reduced pressure to dryness to give a white solid, which was purified by flash column chromatography (MeOH/$CHCl_3$ = 7:1) to give **5** as a white solid (130 mg, 75 %). mp 108-110 °C. EI-ms (70 eV) *m/z* (rel. int.): 177 (M^+, 81), 176 (100), 149 (19), 121 (18), 120 (45), 119 (33), 107 (12), 54 (9), 41 (12). *Anal.* Calcd for $C_9H_{11}N_3O \cdot 1/2H_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.41; H, 6.37; N, 22.25. Ir (KBr) cm^{-1}: 3360, 1660. ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.88-1.94 (1H, m, C_1-H), 2.40-2.47 (1H, m, C_1-H), 2.52-2.68 (3H, m, C_2-H x 2, C_6-H), 2.76-2.87 (1H, m, C_6-H), 2.96-3.06 (1H, m, C_5-H), 4.47 (1H, dd, *J*=13.2 Hz, 5.6 Hz, C_5-H), 5.66 (1H, dd, *J*=8.2 Hz, 5.5 Hz, C_{9b}-H), 7.58 (1H, s, C_8-H). ^{13}C-nmr ($CDCl_3$) δ (ppm): 21.84, 25.35, 31.72, 36.95, 55.34, 123.16, 134.55, 134.86, 174.13.

Preparation of 5 from 4 A solution of **4** (331 mg, 1.87 mmol) in formic acid (15 ml) was refluxed for 24 h. Work-up as above afforded 317 mg (96 %) of **5.**

1-[2-(Imidazol-4-yl)ethyl]-2-hydroxy-2-(n-hexyl)pyrrolidin-5-one (6) A solution of n-hexylmagnesium bromide (prepared from 94 mg of Mg and 705 mg of n-bromohexane in 7 ml of THF) was added dropwise to a suspension of histamine succinimide (1) (0.3 g, 1.55 mmol) in THF (10 ml) at -78 °C. The reaction mixture was warmed up to room temperature for 30 min and stirred for 25 h at the same temperature. The solution was then poured into 5 % aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$ (10 ml x 5). The combined $CHCl_3$ solution was dried ($MgSO_4$), concentrated, and flash column chromatographed (MeOH/$CHCl_3$ = 1:7) to give 0.27 g (ca. 63 %) of **6** containing small amount of N^{α}-*4'*-oxodecanoylhistamine (7).[3a] EI-ms (70 eV) *m/z* (rel. int.): 261 (M^+-H_2O, 20), 204 (18), 180 (68), 168 (100), 124 (40), 95 (93), 94 (30). *Anal.* Calcd for $C_{15}H_{25}N_3O_2$: C, 64.49; H, 9.02; N, 15.04. Found: C, 64.22; H, 9.29; N, 15.04. Ir (KBr) cm^{-1}: 3205, 2931, 2859, 1667. ^{1}H-nmr ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J*=6.7 Hz), 1.21-1.56 (10H, m), 2.38-2.48 (3H, m), 2.67-2.81 (3H, m), 3.43-3.49 (2H, m), 6.81 (1H, s, C_7-H), 7.58 (1H, s, C_9-H), 7.70 (1H, bs).

1,2,3,5,6,10a-Hexahydro-10a-n-hexyl-3-oxoimidazo[1,5-*c*]pyrrolo[1,2-*a*]-pyrimidine (Glochidine, 8) A solution of **6** (125 mg, 0.45 mmol) in toluene (10 ml) was refluxed for 3h. The solution was concentrated and purified by flash column

chromatography (MeOH/$CHCl_3$ = 1:30) to give **8** as a white solid (84 mg, 71 %). mp 63-67 °C (lit.,[3a] 65-67 °C). EI-ms (70 eV) *m/z* (rel. int.): 261 (M^+, 21), 180 (60), 176 (51), 168 (82), 124 (39), 95 (100), 94 (45). Ir (KBr) cm^{-1}: 2920, 2855, 1688. ^{1}H-nmr ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J*=6.7 Hz),1.27 (8H, m), 1.97 (2H, m), 2.43-2.66 (4H, m, C_1-H, C_2-H), 2.85-2.90 (2H, m, C_6-H), 3.07-3.14 (1H, m, C_5-H), 4.29-4.36 (1H, m, C_5-H), 6.77 (1H, s, C_7-H), 7.61 (1H, s, C_9-H). ^{13}C-nmr ($CDCl_3$) δ (ppm): 13.94, 20.12, 22.46, 23.70, 28.90, 29.86, 31.49, 33.48, 41.54, 78.50, 124.81, 132.30, 173.46.

1,2,3,5,6,9b-Hexahydro-9b-n-hexyl-7*H*-3-oxoimidazo[4,5-*c*]pyrrolo[1,2-*a*]-pyridine (Glochidicine, 9) A solution of **6** (180 mg, 0.64 mmol) and catalytic amount of *p*-TsOH·H_2O in xylene (10 ml) was refluxed for 16 h. The solution was concentrated and purified by flash column chromatography (MeOH/$CHCl_3$ = 1:30) to give **9** as a white solid (132 mg, 79 %). mp 102-104 °C (lit.,[3a] 102-103 °C). EI-ms (70 eV) *m/z* (rel. int.): 261 (M^+, 1), 260 (2), 177 (10), 176 (100), 148 (5). Ir (KBr) cm^{-1} : 3727, 2922, 2553, 1661. ^{1}H-nmr ($CDCl_3$) δ (ppm): 0.84 (3H, t, *J*=6.7 Hz), 1.24 (8H, m), 1.72-1.94 (2H, m), 2.05-2.17 (1H, m, C_1-H), 2.25-2.44 (2H, m, C_1-H, C_2-H), 2.54-2.66 (2H, m, C_2-H, C_6-H), 2.73-2.84 (1H, m, C_6-H), 3.04-3.12 (1H, m, C_5-H), 4.36-4.42 (1H, m, C_5-H), 7.48 (1H, s, C_8-H). ^{13}C-nmr ($CDCl_3$) δ (ppm): 14.06, 21.93, 22.60, 24.08, 29.60, 29.81, 31.33, 31.73, 34.70, 39.61, 63.64, 134.15, 134.25, 153.12, 174.45.

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