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Synthesis of Pyrrolidine or Piperidine Ring-fused Azepino[5,4,3-*cd*]indole Derivatives

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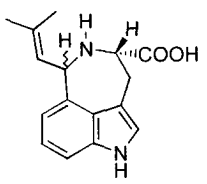
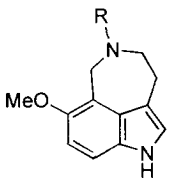
Abstracts: The synthesis of pyrrolidine or piperidine ring-fused 2-phenyl-azepino[5,4,3-*cd*]indole derivatives (**2**) has been accomplished through the *N*-acyliminium ion cyclization of hydroxy- or alkoxylactams (**5**) derived from cyclic anhydrides or chiral hydroxy acids.

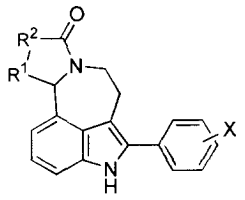
Azepino[5,4,3-*cd*]indole is an interesting heterocycle and forms the skeleton of clavicipitic acid, a derailment product of normal ergot metabolism.[1] Recently, considerable efforts have been devoted to the synthesis of azepino[5,4,3-*cd*]indole derivatives due to their unusual structures and potential biological activities.[2-6] Subsequently, several azepino[5,4,3-*cd*]indole derivatives have been prepared and some of them have been found to possess α_2-adrenoceptor, 5-HT_{1A}, or dopamine D_2 receptor affinity.[3,4] However, there is no report on the synthesis of pyrrolidine or piperidine ring-fused azepino[5,4,3-*cd*]indoles.



Clavicipitic acid



1



2

The usual synthesis of azepino[5,4,3-*cd*]indole derivatives have been achieved by a prior functionalization at the 4-position of indole nucleus followed by the ring closure to form azepine ring.[2] Although the direct cyclizations at the 4-position of indole nucleus through iminium ion intermediate have been published, these methods use only a limited example of iminium or acyliminium ion precursors, which were usually derived from formaldehyde or formaldehyde congener and tryptamines.[5-6] Furthermore, tryptamine rings without electron donating group or with electron withdrawing group were unreactive toward cyclization with formaldehyde under normal or drastic conditions.[5] At this point, we thought that *N*-acyliminium ion cyclization strategy would be more useful in the synthesis of azepino[5,4,3-*cd*]indole derivatives, since *N*-acyliminium ion intermediate can be

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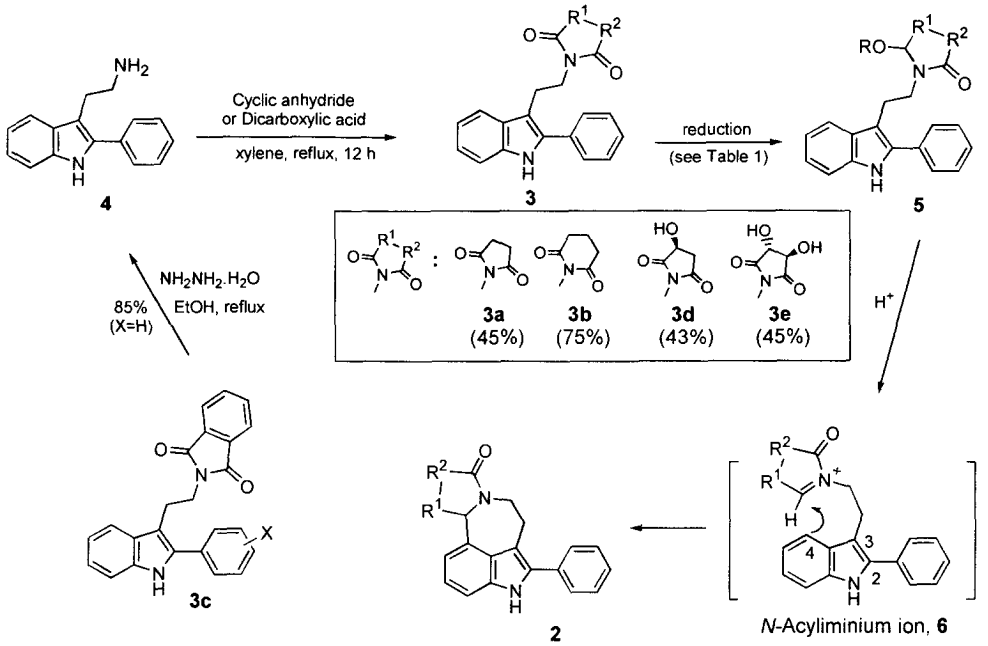
reacted with a broad range of nucleophiles due to the higher reactivity than that of iminium ion intermediate.[7]

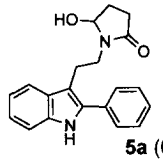
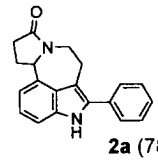
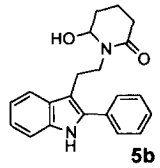
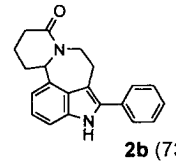
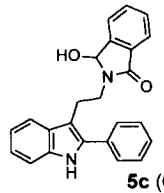
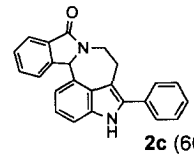
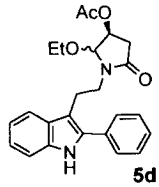
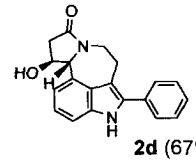
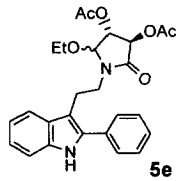
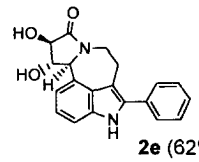
In continuation with our efforts on the synthesis of pharmacologically active compounds,[8-9] we have developed a synthetic method on the synthesis of new type of azepino[5,4,3-*cd*]indole system through several *N*-acyliminium ion intermediate. In this communication, we wish to report the synthesis of pyrrolidine or piperidine ring-fused 2-phenylazepino[5,4,3-*cd*]indole derivatives (**2**) through the *N*-acyliminium ion intermediate (**6**) derived from hydroxy- or alkoxylactams as illustrated in Scheme 1. This synthesis would be very useful to obtain diverse molecules for the study of structure-activity relationships since several series of 2-aryl substituted indol-3-yl-ethylamines,[10] 2-aryl substituted benzothiophen-3-yl-ethylamines and 2-aryl substituted benzofuran-3-yl-ethylamines[11] could be used as starting compounds.



Scheme 1

The phthalimide group in **3c** (X=H)[10] was removed by treatment of hydrazine hydrate in refluxing ethanol to provide **4** in 85% yield. (2-Phenylindol-3-yl)ethylamine (**4**) was condensed with succinic anhydride or glutaric anhydride in refluxing xylene to afford cyclic imides **3a** and **3b** in 45% and 75% yields, respectively. For the synthesis of optically pure pyrrolidino-azepino-indole derivatives, compound **4** was condensed with L-malic acid or L-tartaric acid in refluxing xylene to provide **3d** ($[\alpha]_D^{22}$ = -29.8, *c* 0.85, MeOH) and **3e** ($[\alpha]_D^{22}$ = +33.6, *c* 0.75, MeOH) in 43% and 45% yields, respectively. We first tried reduction of succinimide **3a** with $NaBH_4$ in MeOH or in EtOH in the presence of *conc*-H_2SO_4 system[8] but the reduction was not completed unexpectedly while most of starting material was recovered. However,

Table 1. Reduction of Cyclic Imides (**3a** ~ **3e**) and Cyclization Reaction of Lactams (**5a** ~ **5e**)

Starting Compd	Condition A	Product (**5**) (Yield)	Condition B	Product (**2**) (Yield)
3a	DIBAH, -78 - 0°C	 **5a** (69%)	HCO_2H, reflux	 **2a** (78%)
3b	DIBAH, -78 - 0°C	 **5b** (60%)	HCO_2H, reflux	 **2b** (73%)
3c	DIBAH, -78 - 0°C	 **5c** (62%)	HCO_2H, reflux	 **2c** (60%)
3d	1. $NaBH_4$, 1M H_2SO_4 EtOH, 0°C - rt 2. Ac_2O, NEt_3 CH_2Cl_2, rt	 **5d** (60%)	1. HCO_2H, reflux 2. AcCl, EtOH, rt	 **2d** (67%)
3e	1. $NaBH_4$, 1M H_2SO_4 EtOH, 0°C - rt 2. Ac_2O, NEt_3 CH_2Cl_2, rt	 **5e** (73%)	1. HCO_2H, reflux 2. AcCl, EtOH, rt	 **2e** (62%)

the reduction of **3a** with 2 equivalents of DIBAH proceeded smoothly to furnish hydroxylactam **5a** in 69% yield (Table 1). The reduction of glutarimide **3b** and phthalimide **3c** at the same condition also afforded hydroxylactams **5b** and **5c** in 60% and 62% yields, respectively. On the other hand, the reduction of (3*S*)-3-hydroxysuccinimide **3d** with DIBAH gave the reduced products as nearly 1:1 mixture of regioisomers even at low temperature (–78 °C). Fortunately, the $NaBH_4$ reduction (*conc*-H_2SO_4/EtOH) produced regioselectively the 5-ethoxy-4-hydroxylactam in good yield.[8a] Thus, the reduction of **3d** and **3e** in this condition followed by protection of the hydroxyl groups of the reduced products as acetates provided **5d** and **5e** in 60% and 73% yields for two steps, respectively.

Finally, hydroxylactams (**5a**, **5b**, **5c**) and chiral ethoxylactams (**5d**, **5e**) were subjected to the *N*-acyliminium ion cyclization condition to form azepino[5,4,3-*cd*]indole ring. The cyclization reactions in refluxing formic acid proceeded cleanly in all cases to provide pyrrolidino- and piperidino-azepino[5,4,3-*cd*]indole derivatives in good yields (60 ~ 78%). The cyclization products **2d** ($[\alpha]_D^{22}$ = +70.9, *c* 0.75,

MeOH) and **2e** ($[\alpha]_D^{22}$ = -56.8, *c* 0.50, MeOH) were also obtained in diastereomerically pure forms in accordance with our previous results by treatment of chiral ethoxylactams (**5d**, **5e**) with formic acid followed by deprotection of acetyl group (AcCl/EtOH).[8] The structures of cyclization products were readily confirmed by the comparison of ^{1}H NMR spectra of **5a** and **2a**.[12,13] The signal of H-4 (indole numbering) at 7.65 ppm (d, *J*= 7.71 Hz) in hydroxylactam **5a** was disappeared and the coupling pattern of the signal of H-5 at 7.11 ppm (t, *J*=7.35 Hz) was changed from *triplet* to *doublet* (6.95 ppm, d, *J*=7.41 Hz) without changing coupling pattern of 2-phenyl substituent in the ^{1}H NMR spectrum of the cyclized product **2a**. These spectral data show that the cyclization proceeded through the capture of *N*-acyliminium ion intermediate by the 4-position of indole nucleus resulting in the formation of azepino[5,4,3-*cd*]indole ring.

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11. Chu, L.; Fisher, M. H.; Goulet, M. T. Wyvratt, M. J. *Tetrahedron Lett.* **1997**, *38*, 3871.
12. Data for **5a** : mp 134 ~ 135 °C; IR (KBr) 3288, 2934, 1668, 1458 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 8.35(1H, s), 7.65(1H, d, *J*=7.7 Hz), 7.59(1H, d, *J*=13.6 Hz), 7.41(2H, t, *J*=7.7 Hz), 7.26-7.36(2H, m), 7.19(1H, t, *J*=7.9 Hz), 7.11(1H, t, *J*=7.4 Hz), 4.83(1H, d, *J*=4.4 Hz), 3.69(1H, m), 3.43-3.51(2H, m), 3.25(1H, m), 3.11(1H, m), 2.33(1H, m), 2.10(2H, m), 1.65(1H, m); ^{13}C NMR(75 MHz, $CDCl_3$) δ 174.9, 135.9, 135.1, 132.9, 127.9(2), 126.7(2), 123.8, 122.5, 119.9, 118.9(2), 111.1, 110.1, 83.91, 40.00, 29.20, 28.25, 23.18; MS (*m/z*; rel. intensity, %) 302(M^+-H_2O, 16), 219(56), 206(100), 191(2), 178(15), 151(1), 102(2), 89(1), 77(4).
13. Data for **2a** : mp 234 ~ 235 °C; IR (KBr) 3268, 3056, 2924, 2362, 1662 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64(1H, s), 7.54(2H, d, *J*=7.6 Hz), 7.46(2H, t, *J*=7.5 Hz), 7.26-7.40(2H, m), 7.20(1H, t, *J*=7.7 Hz), 6.95(1H, d, *J*=7.4 Hz), 5.24(1H. t, *J*=7.4 Hz), 4.37(1H, dt, *J*=12.9, 3.2 Hz), 3.38(1H, td, *J*=12.4, 3.0 Hz), 3.21(1H, t, *J*=12.9 Hz), 3.05(1H, *br* d, *J*=15.6 Hz), 2.77(1H, m), 2.50(2H, t, *J*=7.9 Hz), 2.24(1H, m); ^{13}C NMR(75 MHz, $CDCl_3$) δ 174.9, 136.8, 136.2, 134.2, 132.8, 128.8(2), 127.9(2), 127.7, 125.4, 122.2, 116.8, 111.5, 109.5, 63.80, 43.13, 30.60, 28.32, 28.20; MS (*m/z*; rel. intensity, %) 302(M^+, 94), 301(100), 286(17), 272(4), 258(6), 245(21), 242(20), 229(26), 216(15), 203(8), 188(4), 175(2), 164(3), 151(11), 139(4), 126(9), 114(12), 101(4), 87(3), 54(4); HRMS (EI) Calcd for $C_{20}H_{18}N_2O$: (M^+) *m/z* 302.1419. Found: 302.1419.