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# A New Approach to Isoindolobenzazepines *via* A Ring-Expansion of Isoindoloisoquinoline: Synthesis of Lennoxamine and Chilenine

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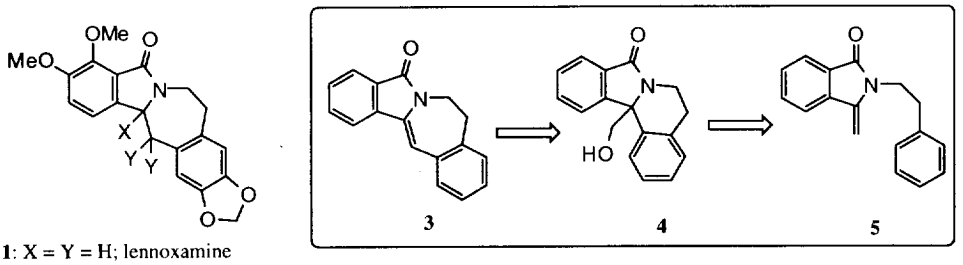
**Abstract**. A convenient short-step synthesis of lennoxamine **1** and chilenine **2** is described. The key steps are the preparation of an acyliminium ion precursor and a novel expansion of the six-membered ring to a seven-membered ring. 

Lennoxamine **1** and chilenine **2**, isolated from the Chilean barberries species, are grouped into isoindolobenzazepine alkaloids.[1] Syntheses of **1** or **2** have been reported by several groups.[2]

In this paper, the synthesis of **1** and **2** is focused on a facile approach to isoindoloisoquinoline **4** using an *N*-acyliminium ion precursor obtained by the oxidation of methylideneisoindolone **5** followed by a ring-expansion reaction of **4** to isoindolobenzazepine skeletons **3** (Fig 1).




**1**: X = Y = H; lennoxamine
**2**: X = OH, Y-Y = O; chilenine

Fig. 1

Various methods for the preparation of alkoxycarbamates and alkoxylactams as precursors of the *N*-acyliminium ion[3] are reported. A partial reduction of the corresponding carbonyl groups of imides, an anodic methoxylation of amides, a Grignard addition to the cyclic imides and a condensation of ketones or aldehydes with amides or amines are most frequently used for this purpose. Recently, an oxidation of the endocyclic enamides, which provides alkoxycarbamates, the alkoxylactams or enamide epoxides, has been reported,[4] while there are only a few reports involving exocyclic enamides.[5] Since the intramolecular cyclization of the alkynylamides to the exocyclic enamides under the basic conditions was previously established by us,[6] the oxidation of these exocyclic enamides was applied to a strategy for the synthesis of **1** and **2** as shown in Scheme 1.

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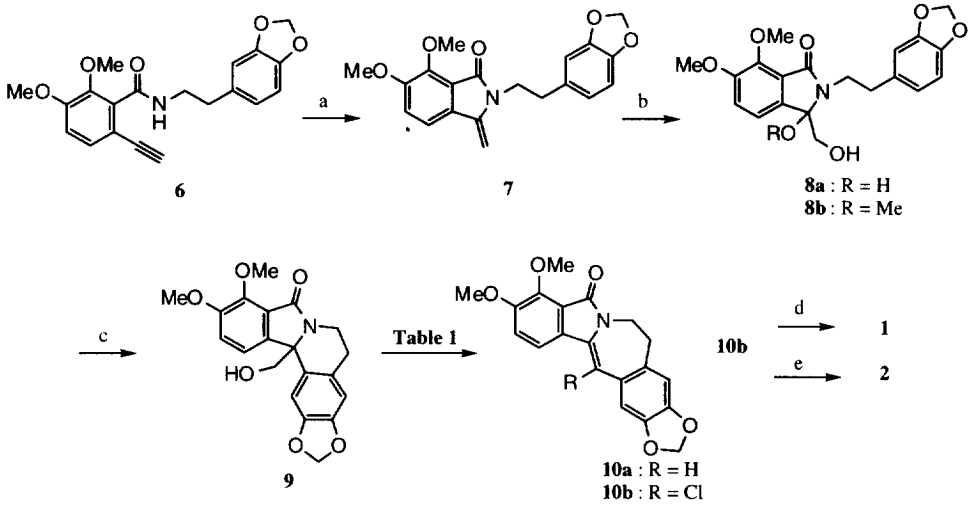
Scheme 1[a]




[a] *Reagents and Conditions* : a) cat. LHMDS, THF, r.t. 93%; b) excess DMD, MeOH / acetone (= 2 : 1), -78°C ~ -30°C, then, 10% $Na_2S_2O_3$; c) 2 eq. $BF_3$·$OEt_2$, $CH_2Cl_2$, -45°C ~ 0°C, 88% (from **7**); d) cat. 5% Pd-C, $H_2$ (1 atm), THF-MeOH (= 1 : 1). 96%; e) excess DMD, acetone, -78°C ~r.t., 42%.

The starting *o*-ethynylbenzamide **6** was easily prepared according to our previously reported procedure.[6a] Although the cyclization of the *o*-ethynylbenzamide derivatives to the methylideneisoindolones under stoichiometric basic conditions (1eq. LHMDS) was previously shown,[6a] treatment of **6** with a catalytic amount of LHMDS (0.1 eq) was found to be equally effective. However, the use of a catalytic amount of n-BuLi resulted in low yield (10%). Oxidation of **7** with *m*CPBA in $CH_2Cl_2$ afforded the unexpected *N*-phenethylphthalimide.[7] Use of dimethyldioxirane (DMD) in acetone afforded not the expected epoxide as reported by Burgess,[4b] but the diol **8a** in quantitative yield, which was, however, unstable and insoluble in organic or aqueous solvents. On carrying out the reaction in the presence of methanol (MeOH / acetone = 2 : 1), the relatively stable methoxylactam **8b** could be obtained.[8] When this crude material **8b** was treated with $BF_3$·$OEt_2$ in $CH_2Cl_2$, cyclization of **8b** *via* an acyliminium ion intermediate[9] proceeded smoothly to give 12b-(hydroxymethyl)isoindoloisoquinoline **9** in excellent yield (88%, from **7**). For the rearrangement of **9** to **10**, a number of acidic conditions were attempted, e.g., HBr-AcOH, conc. $H_2SO_4$, polyphosphoric acid, $CF_3SO_3H$ at room and higher temperature conditions, but these conditions afforded no product having a seven-membered ring system. As Yamauchi *et al.*[10] reported a 1,2-aryl migration of 2-hydroxypropiophenone dimethyl acetals with $SO_2Cl_2$, the ring-expansion reaction of **9** with $SO_2Cl_2$ was then examined and the results are summarized in Table 1. The reaction was due to the additive effect of the basic solvents, namely, addition of $Et_3N$ suppressed the contamination of impurities (Entry 3 to Entry 1) and pyridine facilitated this reaction (Entry 4 to Entries 2 and 3). The best result was obtained using $CHCl_3$ / pyridine (= 4 : 1) containing 5 eq of $Et_3N$, in which **10a** was formed in 75% yield. Catalytic hydrogenation (10%Pd-C, $H_2$, 3 atms, AcOH, 2 days) of **10a** afforded desired lennoxamine **1**,[11] though the yield was not completely satisfactory (38~51%).

**Table 1**. Convertion of **9** into **10**

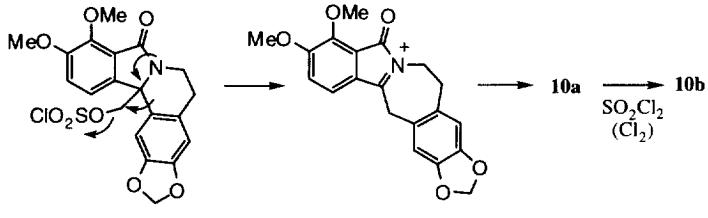
| Entry | $SO_2Cl_2$(eq.) | Conditions[a] | Product (%) | |
|---|---|---|---|---|
| | | | **10a** | **10b** |
| 1 | 1.5 | $CHCl_3$ / Pyridine (1 : 1) | 0 | trace [b] |
| 2 | 1.5 | DMF / $Et_3N$ (1 : 1) | N.R | |
| 3 | 3.0 | $CHCl_3$ / $Et_3N$ (4 : 1) | 45 | 0 [c] |
| 4 | 3.0 | $CHCl_3$ / Pyridine (4 : 1), $Et_3N$ (5 eq) | 75 | 0 [c] |
| 5 | 3.0, then 1.3 | $CHCl_3$ / Pyridine (4 : 1), $Et_3N$ (5 eq) | 0 | 76[d] |

a) To the solution of **9** in mixed solvents was added dropwise $SO_2Cl_2$ at -78°C and then the solution was warmed to r.t. followed by standing overnight at ambient temperature. b) A mixture of uncharacterizable products was formed and no starting material was detected. c) A varied amount of starting material was always recovered. d) After the complete reaction of **9** with $SO_2Cl_2$, further 1.3 eq of $SO_2Cl_2$ and then 2 eq of $Et_3N$ were added dropwise.

And then, after the complete reaction of **9** with $SO_2Cl_2$, further addition of $SO_2Cl_2$ (1.3 eq) and $Et_3N$ (2 eq) to the reaction mixture afforded chlorinated enamide **10b** in 76% yield (Entry 5). Catalytic hydrogenation of **10b** progressed easily to afford lennoxamine **1** in 96% yield.

A plausible mechanism for this ring-expansion reaction is shown in Scheme 2. At the first step, chlorosulfonylation of a hydroxy group with $SO_2Cl_2$ afforded **11**, which underwent the migration of the more electron-rich 2,3-methylenedioxyphenyl group to give **10a** *via* the most stable acyliminium ion **12**. However, the role of pyridine in this reaction is not clearly elucidated.

Scheme 2




**11** **12**

Compound **10a** has already been converted into **2** in a one-pot procedure (DMD and then aq. $NaHCO_3$, 38% yield) by Fang and Danishefsky.[2i] Oxidation of **10b** with DMD also afforded **2**[11] in 42% yield.

In conclusion, the methylideneisoindolone **7** (exocyclic enamide) is oxidized by DMD to the alkoxylactam **8**, an *N*-acyliminium ion precursor, which is useful for the synthesis of isoindoloisoquinoline **9**. Further, a new, facile route to lennoxamine **1** and chilenine **2** *via* the ring-expansion reaction of isoindoloisoquinoline skeleton **9** to isoindolobenzazepine **10** is presented.

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7. The same result has been reported by Back et al.[5a]
8. Typical procedure of **8b**: To a DMD-acetone solution (0.078 M, 30 ml) was added dropwise a solution of **7** (555 mg, 1.57 mmol) in MeOH / acetone (12 ml / 6 ml) at -78°C. The resulting suspension was warmed to -30°C over 0.5 h, whereupon, the system became a clear solution. The reaction mixture was quenched with 10% $Na_2S_2O_3$ at -78°C. The organic solvent was removed *in vacuo*, and the residue was extracted with $CHCl_3$ (× 8) according to a conventional work-up to give **8b** (626 mg, quant.) as a white solid. Recrystallization from AcOEt gave a colorless crystal, mp 155-156°C; $^1$H NMR (300 MHz, $CDCl_3$-one drop of $D_2O$) δ: 7.12 (d, $J$ = 8.2 Hz, 1H), 7.09 (d, $J$ = 8.2 Hz, 1H), 6.78 (m, 3H), 5.93 (s, 2H), 4.12 (s, 3H), 3.91 (s, 3H), 3.84 (d, $J_{AB}$ = 12.0 Hz, 1H), 3.72 (d, $J_{AB}$ = 12.0 Hz, 1H), 3.66 (m, 1H), 3.38 (m, 1H), 3.00 (m, 2H), 2.83 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$)δ: 166.66, 153.96, 147.67, 146.98, 146.08, 134.34, 132.92, 124.54, 121.71, 117.95, 115.93, 109.28, 108.31, 100.82, 92.92, 65.66, 62.38, 56.47, 50.05, 41.41, 34.35; IR(KBr) 3320, 1645, 1465, 1420, 1230, 1080 cm$^{-1}$; MS *m/z* 401 ($M^+$); *Anal.* Calcd for $C_{21}H_{23}O_7N$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.68; H, 5.81; N, 3.51.
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11. The spectral data ($^1$H NMR, IR and mass) of **1** and **2** showed complete agreement with those of authentic samples, respectively, reported in the literature.[2b,1c]