

Sequential Bicyclization to the Skeleton of Lennoxamine and Chilenine Using Pd Catalyst

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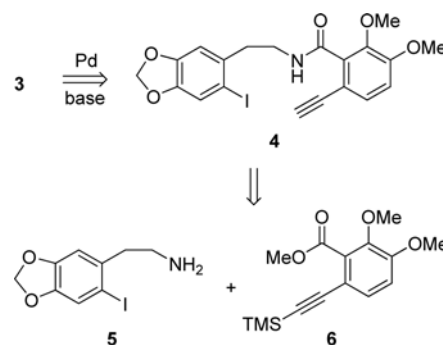
Key Words : Bicyclization, Lennoxamine, Chilenine, Palladium catalyst

Lennoxamine **1** and chilenine **2** which have an isoindolo-benzazepine framework were isolated from *Berberis empertrifolia* Lam¹ and *Berberis darwinii* Hook.² Although these alkaloids have been known to show weak biological activities, their unique tetracyclic ring system has garnered much attention from synthetic chemists. In the numerous synthetic approaches,³ the formation of core 7- and 5-membered rings, actually synthesis of dehydrolennoxamine **3**, has been the key target (Figure 1). In this communication we want to suggest an efficient method to the molecule, achieving the formal synthesis. Conversion of **3** to lennoxamine and chilenine has been already achieved.⁴

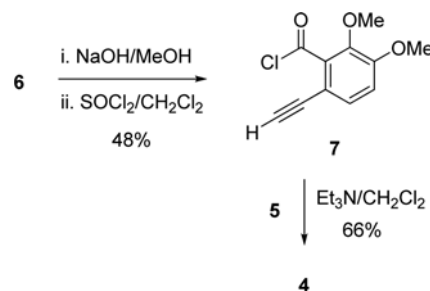
As most of the cyclization methods published until recently have been stepwise approaches, we wished to suggest a sequential bicyclization process from intermediate **4** in one pot. The bicyclization approach has been rare for the synthesis of **3** except radical cascade reaction to lennoxamine **1**.³ⁱ The molecule equipped with iodine on aromatic ring, amide, alkyne functional groups was expected to undergo the desired transformation upon treating with Pd. The precursor **4** would be prepared concisely from the known compounds **5** and **6** (Scheme 1).^{5,6}

Synthesis of **4** was carried out first by preparation of **7**, reaction of **6** with NaOH/MeOH to form a benzoic acid intermediate and the following treatment with SOCl₂/CH₂Cl₂ (48% in two steps). Coupling of **5** and **7** in the presence of TEA in CH₂Cl₂ afforded the requisite precursor **4** in 66% yield (Scheme 2).⁷

Bicyclization of **4** was attempted under the various conditions using palladium catalyst. In the use of K₂CO₃ as a base,



Scheme 1



Scheme 2

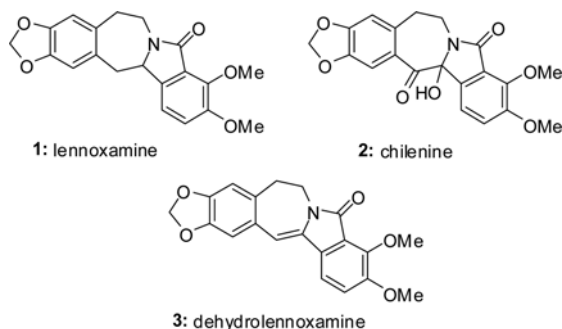
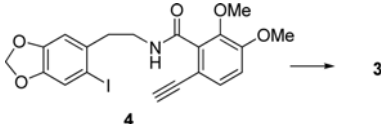


Figure 1

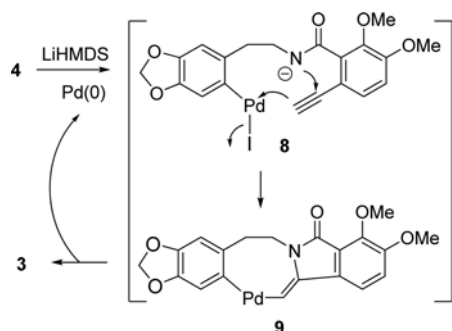
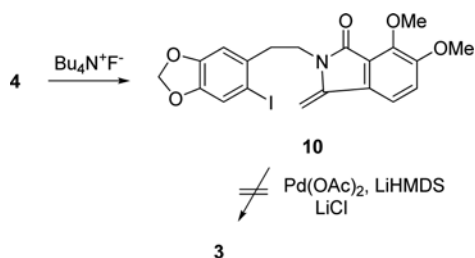
neither Pd(OAc)₂ nor other palladium catalysts such as Pd(PPh₃)₄, Pd(dba)₂, Pd(PPh₃)₂Cl₂ with or without ligands provided the desired compounds at all. Decomposition was detected mainly (entry 1). However, the presence of stronger base LiHMDS was found to make the reaction get started (entry 2), and among several palladium reagents, Pd(OAc)₂ was the most practical and efficient. Though not much, the addition of LiCl increased the yields moderately (entries 3–7). The role of LiCl for the increasing the reaction yields cannot be still clearly explained. The best combination, Pd(OAc)₂/LiHMDS/LiCl/DMF, was selected to afford 55% yield (entry 4).

The mechanism of the transformation is suggested as follow; Oxidative addition and deprotonation to **8**, which should induce the proposed bicyclization to **9**, was then followed by reductive elimination to afford the desired product **3** (Figure 2).

When we applied the same conditions (Table 1, entries 3

Table 1. Conditions for bicyclization of **4**


Entry	Conditions ^a	Yield ^b (%)
1	Pd(OAc) ₂ , K ₂ CO ₃ , LiCl, DMF	0
2	Pd(OAc) ₂ , CsCO ₃ , LiCl, DMF	0
3	Pd(OAc) ₂ , LiHMDS, DMF	26
4	Pd(OAc) ₂ , LiHMDS, LiCl, DMF	55
5	Pd(PPh ₃) ₄ , LiHMDS, LiCl, DMF	15
6	Pd(OAc) ₂ , LiHMDS, LiCl, toluene	30
7	Pd(OAc) ₂ , LiHMDS, LiCl, DMSO	45

^aReaction temperature: 100 °C. ^bIsolated yields**Figure 2****Scheme 3**

to **7**) to the compound **10** prepared by cyclization of **4** under base, none of the conditions provided **3** at all, instead decomposition was detected mostly. Although the intermediate **10** is excluded in this transformation process,^{3d} it is not still certain whether the proposed intermediate **8** would perform

the desired bicyclization in stepwise or concurrent manner (Scheme 3).

In summary, we developed a bicyclization pathway to the skeleton of isoindolobenzazepine alkaloids in one pot from the amide **4**. The proper arrangement of the required functional groups is proposed to allow the sequential cyclization after palladium insertion.

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- Compound **4**: ¹H NMR (400 MHz, CDCl₃) δ 2.92 (s, 1H), 2.99 (t, 2H, *J* = 6.8 Hz), 3.06 (s, 1H), 3.66 (q, 2H, *J* = 6.8 Hz), 3.80 (s, 3H), 3.88 (s, 3H), 5.94 (s, 1H), 6.80 (s, 1H), 7.11 (d, 1H, *J* = 2.0 Hz), 7.24 (s, 1H), 7.86 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 39.73, 39.81, 55.97, 61.21, 77.18, 82.52, 87.91, 101.47, 109.55, 117.94, 118.03, 118.50, 126.52, 126.79, 134.64, 146.99, 147.85, 148.34, 152.08, 164.21. EIMS 479 (M⁺).