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Study of aza-cyclization of α,β-unsaturated carbonyl moieties and synthetic application to hexahydroapoerysopine

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ABSTRACT

Aza-cyclization of α,β-unsaturated carbonyl moieties with free amine has been studied. An azepine alkaloid, hexahydroapoerysopine, has been synthesized from an enone-ester in a concise manner through the aza-cyclization followed by reductions.

Polycyclic hetero-compounds containing nitrogen are frequently encountered in natural alkaloid compounds, and the structurally related products containing synthetic drugs have shown numerous physiological activities.[1] Especially, the azepine compounds arranged with other rings around have been attracted by many synthetic chemists because of skeletal challenges as well as biological applications.[2,3] Most of the approaches toward the azepine compounds have been focused on the efficient formation of the central seven-membered ring (Fig. 1). As an extension of our interests on the synthesis of the azepine natural products,[4] we want to explore an aza-cyclization reaction by free amine. The free amine addition to the carbonyl or olefin of α,β-unsaturated carbonyl derivatives for the formation of azepine ring has been rarely applied in natural alkaloid synthesis.[5]

Preliminarily, we tested the selectivity of cyclization pathways on compound **3**, condensation to intermediate **5**, or addition to **4**. Compound **3** would be obtained by the deprotection of *N*-Boc protected precursor of **3**. The precursor could be readily prepared by the known Suzuki coupling reaction pathway.[6,7] Upon refluxing the precursor with CF_3CO_2H in toluene followed by addition of K_2CO_3 and concentration, an unstable intermediate was obtained, and the crude product was reduced readily with $NaCNBH_3$ to enamine compound **6** in quantitative yield in three steps. We assumed that the product would be formed from intermediate **5** via pathway b. However, the product **6** might be also formed from intermediate **4** via pathway a through reduction of ketone to alcohol followed by elimination (Scheme 1).

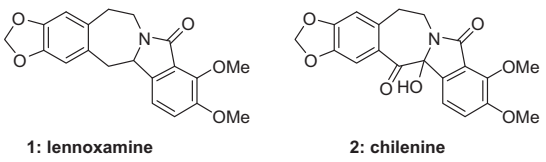
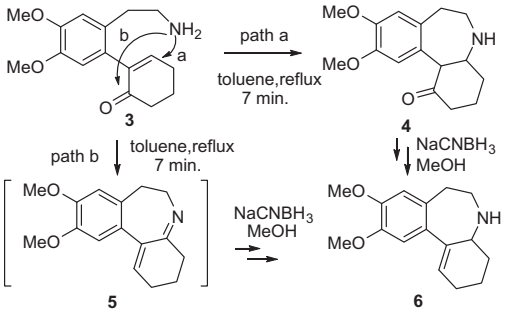


Figure 1.



Scheme 1.

In order to confirm the reaction route, we tried to synthesize a known azepine compound,[5] hexahydroapoerysopine **11** using enone-ester **9** which could induce a sequential cyclization. The compound **9** was synthesized from **7**[6,8] by the Suzuki coupling reaction with vinyl iodide **8** in 78% yield. The iodide compound **8** was prepared from the corresponding enone by iodination

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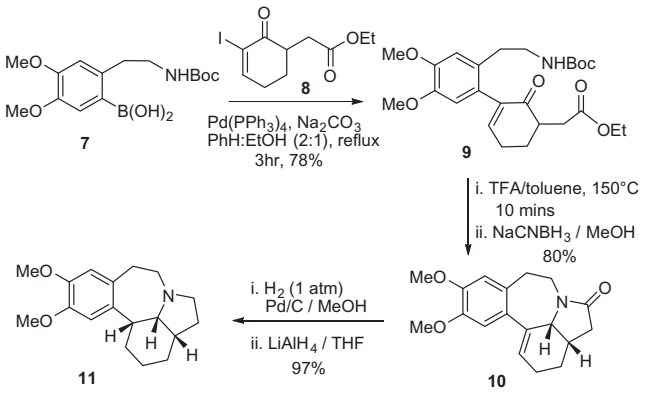

Scheme 2.

followed by elimination.[9] Application of the same conditions to **9** provided **10** in 80% yield, which showed that the initial cyclization should be carried out by amine–carbonyl condensation. Hydrogenation followed by hydride reduction of **10** provided the known **11** in 97% yield (Scheme 2).[10]

Additionally we want to examine the amine cyclization with conjugate ester and imide moieties. First, we prepared a few substrates to figure out the addition reaction aspects on the α,β-unsaturated carbonyl compounds. The substrates **14** could be readily prepared through Suzuki coupling between **7** and vinyl bromide **13** in moderate yields. Although the yields were not satisfactory, we just wanted to find the results of the next reaction instead of optimizing the reaction with vinyl iodide derivatives of **13**. Upon treatment of **14a** or **14b** with CF_3COOH in CH_2Cl_2 at rt followed by concentration and basification with K_2CO_3 in CH_2Cl_2, Michael addition has been found to proceed at rt to afford seven-membered azepine ring products **15a**[12] or **15b** as a single isomer in 99% or 70% yield respectively (Table 1: entries 1 and 2). However, for imide derivatives, **14c** or **14d**, six-membered ring compounds **15c** or **15c′** containing a quaternary center were formed favorably via 6-*exo* addition mode over the seven-membered ring compound **15d** or **15d′** in 2:1 ratio (entries 3 and 4) in 98% combined yields.[13] As expected, ester or imide moieties allowed only Michael type addition reactions differently from α,β-unsaturated carbonyl compounds.

In summary, we could synthesize a tricyclic azepine compound, hexahydroapoerysopine **11** via an aza-cyclization reaction through free amine–carbonyl condensation of α,β-unsaturated ketone followed by sequential reduction. The cyclization of conjugate esters and imides has been investigated under the same condition. In the case of α,β-unsaturated esters, Michael type addition was exclusive to afford the seven-membered ring, however, α,β-unsaturated imides have afforded six-membered ring compounds dominantly via *exo*-type Michael addition. Further synthetic application is under study.

Acknowledgment

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References and notes

1. (a) Cordell, G. A. In *The Alkaloids: Chemistry and Pharmacology*; Academic Press: San Diego, 1998; Vol. 50, (b) Weinstock, J.; Hieble, J. P.; Wilson, J. W. *Drugs Future* **1985**, *10*, 645–651; (c) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414–2421.
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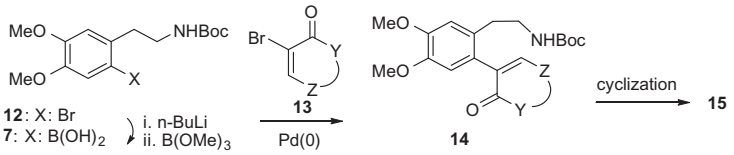
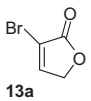
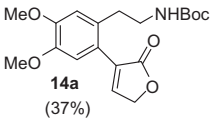
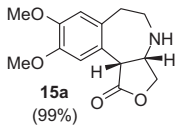
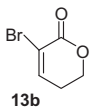
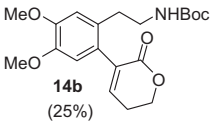
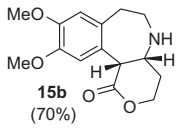
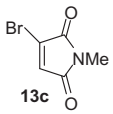
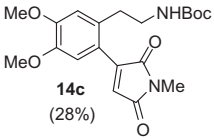
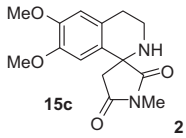
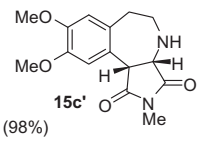
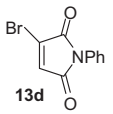
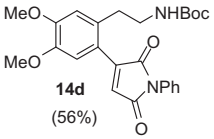
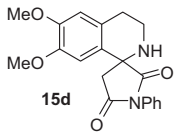
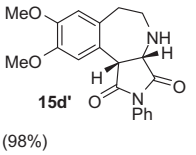
Table 1
Study of cyclization **14**[11]



Entry13	13	14	15
1	 **13a**	 **14a** (37%)	 **15a** (99%)
2	 **13b**	 **14b** (25%)	 **15b** (70%)
3	 **13c**	 **14c** (28%)	 **15c**  **15c′** **2 : 1** (98%)
4	 **13d**	 **14d** (56%)	 **15d**  **15d′** **2 : 1** (98%)

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9. Dubé, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295–2298.
10. Spectral data of **11** were identical to those of the known.[5]
11. *Reaction conditions for **14***: A mixture of **7** and **4** in dioxane:H_2O (3:1) containing $Pd(PPh_3)_4$ (4%) and Na_2CO_3 (2 equiv.) was heated at 150 °C in a sealed tube for 7 min. **15**: a solution of **14** in TFA: CH_2Cl_2 (1:1) was stirred at rt for 30 min. Concentration and treatment with excess K_2CO_3 in CH_2Cl_2 at rt were followed by routine work-up and purification.
12. *Compound **15a** has been characterized more cleanly after acylation of amine, Ac-**15a***: ^{1}H NMR (400 MHz, $CDCl_3$) 1.95 (s, 3H), 2.80–3.08 (m, 4H), 3.59 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.46 (dd, 1H, *J* = 10.9, 2.1 Hz), 4.67 (dd, 1H, *J* = 10.9, 7.6 Hz), 5.95 (dd, 1H, *J* = 9.2, 7.6 Hz), 6.66 (s, 1H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.94, 31.62, 41.25, 48.79, 50.29, 55.92, 56.07, 69.95, 113.54, 115.42, 123.86, 127.75, 148.05, 149.03, 171.12, 176.36, EIMS 306.34 (M^+).
13. The ratio has been detected by ^{1}H NMR, because pure separation of the two isomers was hard. Compound **15d** has also been characterized more cleanly after acylation of amine, Ac-**15d**: ^{1}H NMR (400 MHz, $CDCl_3$) 2.28 (s, 3H), 2.83 (ddd, 1H, *J* = 12.0, 4.0, 4.0 Hz), 3.15 (ddd, 1H, *J* = 12.0, 8.0, 4.0 Hz), 3.18 (d, 1H, *J* = 17.9 Hz), 3.40 (d, 1H, *J* = 17.9 Hz), 3.52 (ddd, 1H, *J* = 12.0, 8.0, 4.0 Hz), 3.82 (s, 3H), 3.89 (s, 3H), 4.03 (ddd, 1H, *J* = 12.0, 4.0, 4.0 Hz), 6.62 (s, 1H), 6.71 (s, 1H); 7.34–7.50 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) 23.02, 30.10, 44.26, 45.25, 56.33, 56.47, 63.57, 107.10, 112.03, 126.53, 126.99, 128.37, 129.06, 129.62, 132.80, 149.21, 149.43, 170.94, 174.54, 176.03.