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Facile and Short Synthesis of (±) 1-Hydroxy Indolizidine and (±) Coniceine from Picolinic Acid Ethyl Ester *via* Cross Claisen Condensation

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New short synthesis of (±) 1-hydroxy indolizidine (**4**) and (±) coniceine (**5**) are described starting from picolinic acid ethyl ester (**6**). The key steps are the conversion of the picolinic acid ethyl ester into β-keto ester **7** *via* cross Claisen condensation and hydrogenation of the β-keto ester in to hydroxy bicyclic amide (**8**) using PtO_2/H_2.

Keywords: 1-Hydroxy indolizidine, Coniceine, β-keto ester, Cross Claisen condensation.

INTRODUCTION

Azabicycles such as indolizidines, quinolizidines and pyrrolizidines are very important, because of their presence in numerous biologically active natural products. Among these, synthesis of indolizidine alkaloids and its derivatives received more attention due to their frequent appearance in the naturally occurring bioactive molecules[1-7]. Few indolizidine alkaloids isolated from plants and animals have shown considerable biological activities[8,9]. Particularly hydroxylated indolizidines such as lentiginosine (**1**), swainsonine (**2**) and castanospermine (**3**) (Fig. 1) are potent inhibitors of α and β-glycosidases and also used in cancer chemotherapy[10,11]. 1-Hydroxy indolizidines are considered as key precursors in the biosynthesis of toxic indolizidine alkaloids salframin and swainsonine in fungus *Rhizoctonia leguminicola*[12].

There are many racemic and asymmetric synthesis of 1-hydroxy indolizidine[13-26] and coniceine[27-31] starting from different racemic and enantio-pure starting materials. Although numerous racemic and enantio-selective synthesis are known for these indolizidine alkaloids, the need and development of new short synthetic routes are of interest. The scope of synthesizing these indolizidines starting from pyridines has not been explored extensively. To the best of our knowledge, there are few reports using pyridine derivatives as starting materials[32-34] in the synthesis of indolizidine natural products.

EXPERIMENTAL

Preparation of ethyl 3-oxo-3-(pyridin-2-yl)propanoate (7): To the solution of ethyl acetate (59 mL, 596 mmol) and compound **6** (15 g, 99.3 mmol) in anhydrous THF (150 mL), LiHMDS (298 mL, 1 M sol. in THF, 298 mmol) was added quickly at -50 °C and stirred at the same temperature for 0.5 h. After completion of the reaction (monitored by TLC), reaction mixture was quenched with acetic acid (15 mL) and water (150 mL), basified with saturated solution of sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layer washed with water (150 mL), brine solution (150 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude was purified by column chromatography (hexane/ethyl acetate 20:80) to afford compound **7** (16.5 g, 86 %) as a pale yellow liquid. R_f (20 % ethyl acetate in hexane) 0.4; ^{1}H NMR of compound **7** recorded as keto enol mixtures. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, 1H, *J* = 4.4 Hz), 8.64 (d, 0.16H, *J* = 4.8, Hz), 8.08 (d, 1H, *J* = 7.6 Hz), 7.92 (d, 0.15H, *J* = 8 Hz), 7.93 (t, 1H, *J* = 7.6 Hz), 7.85 (t, 0.17H, *J* = 7.6 Hz), 7.5 (t, 1H *J* = 6 Hz), 7.35 (t, 0.15H, *J* = 5.6 Hz), 4.32 (q, 0.35H, *J* = 6.8 Hz), 4.23 (m, 4H), 1.36 (t, 0.49H, *J* = 6.8 Hz), 1.25 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 168.1, 152.3, 148.9, 136.9, 127.4, 122.0, 89.3, 61.1, 44.7, 14.0. MS ESI): (*m/z*) calcd for $C_{10}H_{11}NO_3$ [M-H]⁻, 192.05; found 192.05.

Preparation of hexahydro-1-hydroxyindolizidin-3-(5H)one (8): Platinum oxide (200 mg) was added to the solution of compound **7** (2 g, 10.3 mmol) in ethanol (20 mL), and heated to 70 °C under 100 Psi hydrogen pressure for 14 h. After completion of the reaction (monitored by TLC), RM was filtered through a pad of celite and washed with ethanol (15 mL). Filtrate was concentrated under reduced pressure to

get compound **8** (1.3 g, 81 %), as light yellow oil, which is mixture of *cis*:*trans* (1:3) isomers. R_f (10 % MeOH/CHCl$_3$) 0.5; ^{1}H NMR (400 MHz, CDCl$_3$) : δ 4.41 (m, 0.26H), 4.16-4.09 (m, 2H), 3.44-3.39 (m, 0.27H), 3.31-3.26 (m, 1H), 2.77-2.63 (m, 2.5H), 2.39-2.36 (m, 1.2H), 2.12 (br, 1H, OH), 2.05-2.02 (m, 1.34H), 1.93-1.84 (m, 1.25H), 1.73-1.69 (m, 1.63H), 1.46-1.42 (m, 1.4H), 1.37-1.27 (m, 1.2H), 1.16-1.09 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.4, 171.3, 70.4, 65.9, 65.6, 61.8, 40.9, 40.2, 40.1, 39.9, 30.3, 24.5, 24.3, 23.9, 23.3, 23.1.MS (ESI):(*m/z*) calcd for C$_8$H$_{13}$NO$_2$ [M + H]$^+$, 156.09; found 156.22.

Preparation of octahydroindolizin-1-ol (4): To the suspension of LiAlH$_4$ (176 mg, 4.9 mmol), in dry THF (10 mL), a solution of compound **6** (380 mg 2.4 mmol) in dry THF (4 mL) was added at 0 °C and stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), RM was quenched slowly by adding 0.2 mL of 10 % aq. NaOH solution and 0.5 mL of water. The resulting solid was filtered through a pad of celite and washed with ethyl acetate (10 mL). Filtrate was dried over Na$_2$SO$_4$ and concentrated. Crude was purified by column chromatography (silica gel, hexane/ethyl acetate 3:7) to get compound **4** (290 mg, 84 %), as a colourless liquid, which is mixture of *cis*:*trans* (1:3) isomers. R_f (10 % MeOH/CHCl$_3$) 0.3; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.11-4.06 (m, 0.27H), 3.95-3.90 (m, 1H), 3.09-3.03 (m, 0.5H), 3.01-2.98 (m, 2H), 2.38-2.32 (m, 1.1H), 2.30-2.17 (m, 1.3H), 2.03-1.97 (m, 3H), 1.83 (m, 2H), 1.55-1.46 (m, 2H) 1.30-1.21 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$), 76.0, 72.8, 70.9, 69.0, 53.4, 53.1, 52.7, 52.4, 33.1, 31.7, 25.0, 24.8, 23.9, 23.7. MS (ESI):(*m/z*) calcd for C$_8$H$_{15}$NO [M + H]$^+$, 142.12; found 142.21.

Preparation of octahydro-3-oxoindolizin-1-yl methane sulfonate (9): To the solution of compound **7** (300 mg, 1.9 mmol) and triethyl amine (0.38 mL 2.7 mmol) in anhydrous dichloromethane (10 mL), methane sulfonylchloride (266 mg, 2.3 mmol) was added at 0 °C and stirred at RT for 16 h. After completion of reaction (monitored by TLC), RM was quenched with cold water (10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layer was washed with water (10 mL) and saturated brine solution (10 mL) and dried over Na$_2$SO$_4$. Evaporation of solvent under reduced pressure gave compound **9** (400 mg, 88 %) as a light brown liquid, which is mixture of *cis*:*trans* (1:3) isomers. R_f (5 % MeOH/CHCl$_3$) 0.7 ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.3 (s, 0.28H), 4.88-4.81(m, 0.83H), 4.21-4.16 (m, 1.1H), 3.68 (s, 0.7H), 3.65-3.59 (m, 1H), 3.07 (s, 3H), 2.96-2.84 (m, 1H), 2.76-2.61 (m, 2.2H), 2.14-2.06 (m, 2H), 1.97-1.92 (m, 1H), 1.74-1.67 (m,1H), 1.51-1.23 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 168.8, 74.4, 63.2, 60.2, 52.5, 40.4, 40.1, 38.5, 38.1, 37.0, 31.4, 29.7, 25.4, 24.1, 23.6, 23.1, 22.9. MS (ESI):(*m/z*) calcd for C$_9$H$_{15}$NO$_4$S [M + H]$^+$, 234.07; found: 234.08.

Preparation of 6,7,8,8a-tetrahydroindolizin-3(5H)-one (10): DBU (0.3 mL, 2.06 mmol) was added to the solution of compound **8** (300 mg, 1.28 mmol) in anhydrous THF (5 mL) and stirred at room temperature for 16 h. After completion of reaction (monitored by TLC), RM was quenched with cold water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water (10 mL), saturated brine solution (5 mL) and dried over Na$_2$SO$_4$ and evaporated

to dryness. Crude was purified by column chromatography (silica gel, hexane/ethyl acetate 2:8) to afford compound **10** (200 mg, 85 %), as a pale yellow liquid. R_f (5 % MeOH/CHCl$_3$) 0.3; ^{1}H NMR (400 MHz, CDCl$_3$) : δ 7.02 (m, 1H), 6.16 (m, 1H), 4.31 (m, 1H), 3.88 (m, 1H), 2.87-2.80 (m, 1H), 2.14-2.08 (m, 1H), 1.98-1.90 (m, 1H), 1.55-1.48 (m, 1H) 1.32-1.27 (m, 2H) 1.08-1.01 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 168.8 146.9, 127.2, 61.3, 39.1, 30,6, 25.2, 23.3. MS (ESI):(*m/z*) calcd for C$_8$H$_{11}$NO [M + H]$^+$, 138.08; found : 138.04

Preparation of hexahydroindolizin-3(5H)-one (11): Pd-C (40 mg) was added to the solution of compound **9** (400 mg 2.9 mmol) in ethanol (10 mL) and stirred at room temperature under 15 psi of hydrogen pressure for 6 h . After completion of reaction (monitored by TLC), the mixture was filtered through a pad of celite and washed with ethanol (10 mL). Filtrate was evaporated to dryness in vacuum to get compound **11** (314 mg, 80 %), as light brown viscous oil. R_f (10 % MeOH/CHCl$_3$) 0.4; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.12 (m, 1H), 3.43 (m, 1H), 2.64 (m, 1H), 2.37-2.33 (m, 2H), 2.33-2.18 (m, 1H), 1.87 (m, 2H), 1.70-1.67 (m, 1H), 1.63-1.59 (m, 1H), 1.58-1.57 (m, 1H), 1.39-1.33 (m, 2H), 1.19-1.10 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.6, 57.2, 40.1, 33.5, 29.6, 25.2, 24.3, 23.5. MS (ESI):(*m/z*) calcd for C$_8$H$_{13}$NO [M + H]$^+$, 140.10; found: 140.13.

Preparation of octahydroindolizine (5): To a solution of compound **11** (100 mg, 0.7 mmol) in THF (5 mL), was cooled to 0 °C and borane-methyl sulfide complex in THF (1.05 mL, 2.0 M sol. in THF, 2.1 mmol) was added drop wise under nitrogen atmosphere. The reaction mixture was allowed to room temperature and stirred for 16 h. The reaction mixture was quenched with cold water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine solution (5 mL) and dried over Na$_2$SO$_4$ evaporated to dryness. Purification of crude by column chromatography (silica gel, methanol/ethyl acetate) affords compound **5** (65 mg, 75 %) as pale yellow liquid. R_f (20 % MeOH/CHCl$_3$) 0.1; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.3-2.55 (m, 5H), 2.05-1.74 (m, 4H), 1.6-1.3 (m, 6H); ^{13}C NMR (400 MHz, CDCl$_3$): δ 65.4, 60.4, 53.4, 27.0, 24.1, 20.97, 19.3, 18.6. MS (ESI):(*m/z*) calcd for C$_8$H$_{15}$N [M + H]$^+$, 125.12; found: 126.01.

RESULTS AND DISCUSSION

In continuation of earlier research work[35,36] in the area of cross Claisen condensation and its use in the synthesis of β-keto esters, here in we wish to report the first synthesis of indolizidine alkaloids (±) 1-hydroxy indolizidine (**4**) and (±) coniceine (**5**) (Fig. 1) starting from commercially available picolinic acid ethyl ester *via* cross Claisen condensation.

As shown in the retrosynthetic analysis (**Scheme-I**), the key intermediate hydroxy bicyclic amide **8** can be prepared from the picolinic acid ester in two steps and the reduction of this hydroxy bicyclic amide using lithium aluminium hydride gave (±) 1-hydroxy indolizidine. (±) Coniceine was obtained in four steps from hydroxy bicyclic amide **8**.

Our method of preparations is outlined in **Scheme-II** and **III**. As depicted in **Scheme-II**, the inexpensive commercially available picolinic acid ethyl ester **6** was converted into the corresponding β-keto ester using LiHMDS and EtOAc at
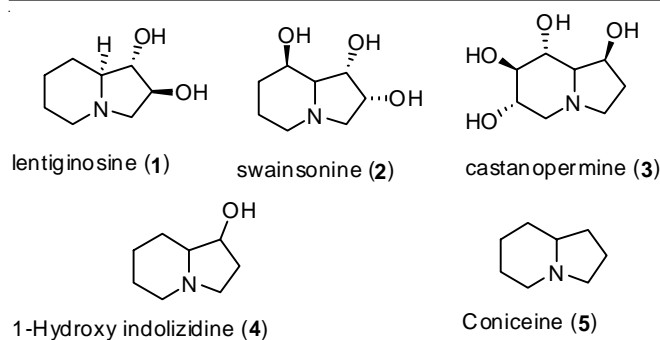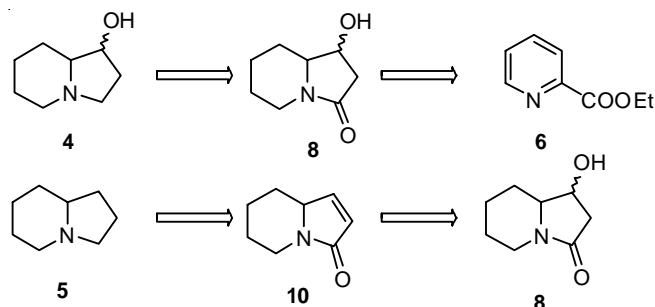
Fig. 1. Structures of indolizidine alkaloids

Scheme-1: Retro synthesis path way for (±) 1-hydroxy indolizidine and (±) coniceine

-50 °C[37]. The β-keto ester **7** was successfully hydrogenated using PtO$_2$/H$_2$ in ethanol at 100 psi to get the key intermediate hydroxy bicyclic amide **8** in 81 % yield. Interestingly we did not observe the complete reduction of keto group in to -CH$_2$ group. Reduction using PtO$_2$/H$_2$ produced the mixture of diastereomers in the ratio of 1:3 (*syn*:*anti*), respectively. Heimgartner *et al.*[34] reported that increased diastereo-selectivity during the pyridine ring reduction can be achieved when there is a 3-alkoxy substitution in the pyridine ring. Reduction of hydroxy bicyclic compound **8** using lithium aluminium hydride in THF afford 1-hydroxy indolizidine (**4**) in 84 % yield[14,15]. ^{1}H NMR of 1-hydroxy indolizidine (**4**) complied with the reported data[26]. More importantly purifications in any of the these steps were not perfomed.

Synthesis of (±) coniceine was outlined in **Scheme-III**. Hydroxy bicyclic amide (**8**) was easily converted into enamide **10** in two steps by following the procedure reported by Lennartz and E. Steckhan[38] Simple hydrogenation of enamide 10 using Pd-C/ethanol at 15 psi produced bicyclic amide **11** in 80 % yield. (±) Coniceine (**5**) was obtained by reducing
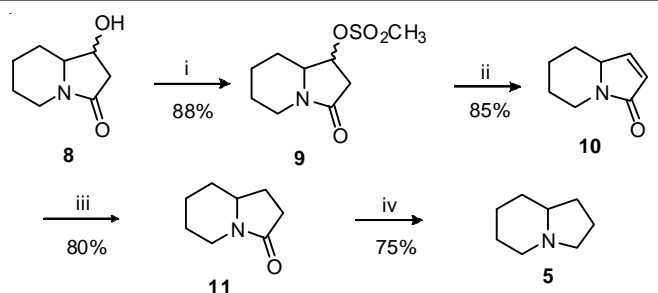
(i) Ms-Cl, Et$_3$N, DCM, 0°C to RT, 6 h (ii) DBU, THF, 0°C, 6 h (iii) Pd-C, H$_2$ (15 Psi), EtOH, 6 h (iv) BH$_3$.SMe$_2$, THF, RT, 15 h

Scheme-III: Synthesis of (±) coniceine

amide **11** using BH$_3$.Me$_2$S in 75 % yield[32]. ^{1}H NMR values of (±) coniceine are complied with the reported values.

Conclusion

In conclusion, an efficient, short and high yielding method is developed to synthesize hydroxy indolizidine and coniceine from the inexpensive, commercially available, picolinic acid ethyl ester.

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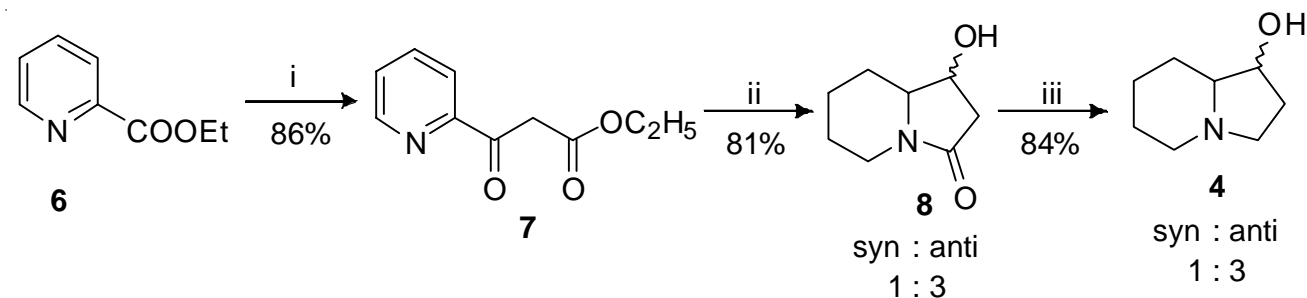
(i) LiHMDS, EtOAc, THF, -40°C, 1 h (ii) PtO$_2$, H$_2$ (100 psi), EtOH, 70°C, 14 h (iii) LAH, THF, 0°C to RT, 1 h

Scheme-II: Synthesis of (±) 1-hydroxy indolizidine

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