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SYNTHESIS OF FUNCTIONALIZED TETRAHYDRO-*β*-CARBOLINE DERIVATIVES BY MODIFIED PICTET-SPENGLER REACTION

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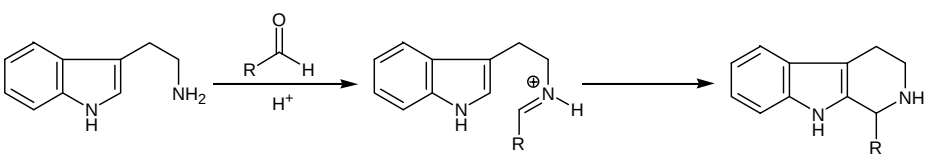
Abstract–Instead of iminium salt in Pictet-Spengler reaction, a series of indole-bearing secondary enamines were synthesized through one-carbon unit transfer reactions of a tetrahydrofolate coenzyme models with tryptamine, and applied to Pictet-Spengler reaction. Reaction of the secondary enamines in acid conditions produced a series of functionalized tetrahydro-*β*-carboline derivatives in good to excellent yields.

INTRODUCTION

The tetrahydro-*β*-carboline ring system is an important structural unit that is commonly encountered in indole alkaloids and synthetic analogues with interesting biological activities.[1,2] The isolation and synthesis of naturally occurring tetrahydro-*β*-carboline derivatives and the synthesis of tetrahydro-*β*-carboline derivatives have received considerable attention in the literature.[3-7] The Pictet-Spengler reaction is one of the most powerful methods for the formation of these ring systems.[8-12] In general, this reaction can be characterized by the formation of an “iminium salt” after an acid-catalyzed reaction of tryptamine and aldehyde (Scheme 1). Then, the “iminium ion” is attacked intramolecularly by electrons of the pyrrole ring to provide C-1 substituted *β*-carboline derivatives. Although Pictet-Spengler reaction has been widely investigated, the substrates were generally restricted to “iminium salt”. Therefore, the approach still has limitations with regards to functionalization of the indole scaffolds, especially in the 1-position, and in most cases, only alkyl groups coming from aldehydes were introduced into 1-position.

Scheme 1

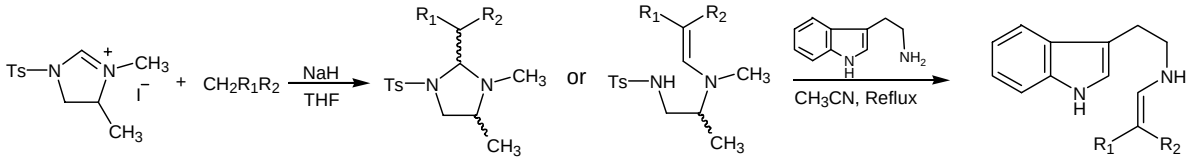


In this paper, we hope to report a modified Pictet-Spengler reaction, that is, an acid-catalyzed cyclization of a series of "indole-bearing secondary enamines" produced by one-carbon unit transfer reactions of a tetrahydrofolate coenzyme models with tryptamine, for the synthesis of functionalized tetrahydro-*β*-carboline derivatives.

RESULTS AND DISCUSSION

In our earlier research, a series of 1-aryl-4,5-dihydroimidazolium iodides and 1-arylsulfonyl-4,5-dihydroimidazolium iodides had been synthesized as the tetrahydrofolate (THF) coenzyme model for the study of one-carbon unit transfer reactions.[13-16] Recently, we synthesized a more activated THF model, 1-tosyl-3,4-dimethylimidazolinium iodide (**1**). It was showed that the model could easily react with a series of aromatic or aliphatic amines to produce a series of *N,N,N′*-trisubstituted 2-methylethylenediamine derivatives.[17] Furthermore, we found that the model could easily react with carbon anions to produce the unsymmetrical trisubstituted imidazolidines (**2**, **3**, **4**),[18] and the ring-opening products, *N,N,N′*-trisubstituted 2-methyl-ethylenediamines (**5**, **6**)[19] (Table 1). Inspired by our published results, we anticipated that the structural property of compound (**2**-**6**) should also assist in substituted one-carbon unit transfer reaction with tryptamine. The observed results were found to be in agreement with our assumption. When compound (**2**-**6**) were treated with tryptamine, the corresponding complete transfer products, a series of secondary enamine (**7**-**11**), were produced in the yields of 58–87% (Table 1), all of which were clearly identified as a single isomer in this case. The reaction was refluxed in acetonitrile and easily followed by TLC. The reaction time was generally from 1 to 24 h and workout was straightforward (see, EXPERIMENTAL).

Table 1 One-carbon unit transfer reactions of addition products (**2**-**6**) with tryptamine.



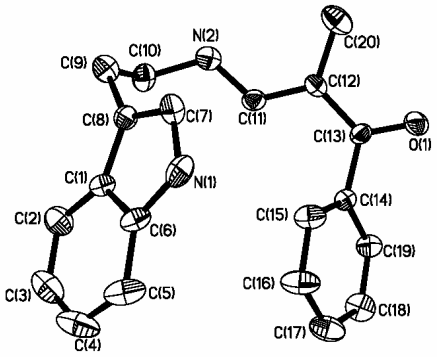
1 **2 - 4** **5, 6** **7 - 11**

Entry	Substrate	R_1	R_2	Product	E/Z	Time (h)	Yield (%)
1	**2**	$-COCH_3$	$-COCH_3$	**7**	--	3	86
2	**3**	$-COOC_2H_5$	$-COCH_3$	**8**	E	1	86
3	**4**	$-COC_6H_5$	$-CH_3$	**9**	E	2	87
4	**5**	–CN	–CN	**10**	--	24	68
5	**6**	–H	$-NO_2$	**11**	Z	18	58

The stereochemistry of compounds (**8**, **9)** was determined to be *E*-type by the X-Ray diffraction (For **8**, see reference 20; For **9**, see Figure 1). However, the stereochemistry of compound (**11)** was deduced to be

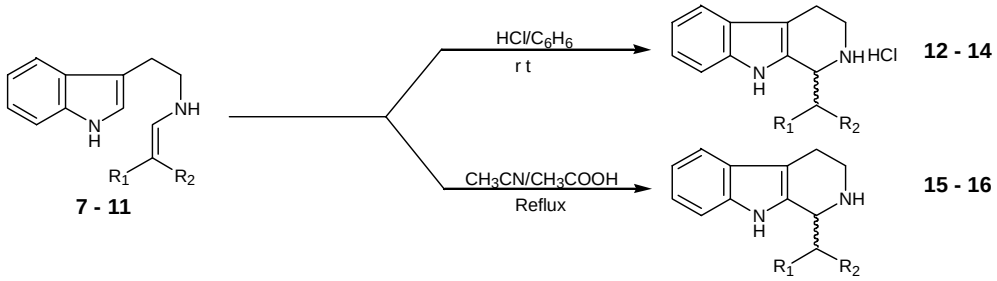
Z-type from the coupling pattern of the adjacent two double bond protons, possibly resulting from the intramolecular hydrogen bond between nitro O atom and the adjacent N-H group.

Figure 1 X-Ray structure of compound (**9**)



Compared to "iminium salt" formed by an acid-catalyzed reaction of tryptamine and aldehyde in Pictet-Spengler condensation, the secondary enamines (**7-11**) were thought by us to be promising substrates for the preparation of tetrahydro-*β*-carboline derivatives. In this case, the construction of the tetrahydro-*β*-carboline skeleton could involve an acid-catalyzed cyclization between indole group and the electrophilic carbon of the secondary enamine unit. The results obtained were in agreement with our assumptions. The indole derivatives (**7-9**) could quickly undergo a cyclization reaction under influence of HCl/C_6H_6 at room temperature, thus leading to the formation of tetrahydro-*β*-carboline derivatives (**12-14**) (Table 2). However, compounds (**10**, **11**) failed to provide any product at the same condition. Interestingly, when compounds (**10**, **11**) were refluxed in CH_3CN/CH_3COOH along with lengthening time, tetrahydro-*β*-carboline derivatives (**15**, **16**) were obtained with good yields (Table 2).

Table 2 Cyclization of indole derivatives for preparation of the tetrahydro-*β*-carboline derivatives (**12-16**).



Entry	R_1	R_2	Product	Time (h)	Yield(%)
1	$-COCH_3$	$-COCH_3$	**12**	0.5	92
2	$-COOC_2H_5$	$-COCH_3$	**13**	0.5	89
3	$-COC_6H_5$	$-CH_3$	**14**	0.5	94[a]
4	–CN	–CN	**15**	24	79
5	–H	$-NO_2$	**16**	15	83

[a] *Anti*-type determined by ^1H NMR analysis.

In conclusion, the present research reported a modified Pictet-Spengler condensation by the application of the indole-bearing secondary enamines chemistry, and provided a new method for the synthesis of a series of functionalized tetrahydro-*β*-carboline derivatives**,** and may enable chemical and biological studies on these derivatives. Ongoing studies are directed at providing mechanistic information, at developing more efficient secondary enamines of the type for the condensation reaction.

EXPERIMENTAL

MS spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^{1}H NMR spectra were recorded at 300MHz with TMS as a spectra standard. Combustion analyses were performed on a Perkin-Elmer 240C or a MOD 1106 instrument. IR spectra were obtained on a Shimadzu IR-1700 spectrophotometer. The TLC was carried out on silica get GF-254 20*20 cm^2 plate. Melting points were uncorrected. All reagents and solvents were purified and dried as required.

General procedure for the preparation of compounds (7-11):

50% Sodium hydride suspended in oil (86.4 mg, 1.8 mmol) was added to a solution of $CH_2R_1R_2$ (1.5 mmol) in 10 mL of dry tetrahydrofuran which was cooled with an ice-water bath. The reaction mixture was stirred for 30 minutes, then the 1-tosyl-3,4-dimethylimidazolinium iodide (**1**) (380 mg, 1 mmol) was added and the mixture was allowed to warm to rt for 2 h. Then the solution was extracted with dichloromethane (3 × 30 mL), the combined organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of dichloromethane in vacuum gave the crude products (**2**-**6**) as diastereomeric mixture. No effort was done to purify the diastereomeric mixture, which was directly applied to the next step.

To the crude products (**2**-**6**) produced from the above process was added 10 mL of acetonitrile followed by tryptamine (160 mg, 1 mmol). The obtained mixture was refluxed and monitored by TLC. Upon completion or after the indicated reaction time, the mixture was filtrated and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc/hexanes, 1:2) to give the desired products (**7**-**11**).

***Compound* (7):** yield 86%, recrystallized from EtOAc as yellow solid, mp 150~152 ^{o}C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.90(s, 3H), 2.45(s, 3H), 3.09(t, *J* = 6.18, 2H), 3.68(m, 2H), 7.03(s, 1H), 7.12-7.23(m, 2H), 7.37(m, 2H), 7.55(d, *J* = 7.8, 1H), 8.20(s, 1H), 11.02 (br, 1H). IR (KBr) cm^{-1}: 3229, 2922, 1644, 1611, 1457, 1436, 1395, 1268, 1130, 1052; MS m/z: 270(M^+). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.34, N, 10.36. Found, C, 70.69; H, 6.67; N, 10.07.

***Compound* (8):** yield 86%, recrystallized from EtOH as white crystals, mp 130^{o}C~132 ^{o}C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.25 (m, 3H), 2.44 (s, 3H), 3.06 (t, *J* = 6.51, 2H), 3.64 (m, 2H), 4.14 (m, 2H), 7.03 (s, 1H), 7.18 (m, 2H), 7.35 (d, *J* = 8.01, 1H), 7.54 (d, *J* = 7.71, 1H), 7.82 (d, *J* = 13.65, 1H), 8.07 (br, 1H),

9.72 (br, 1H). IR (KBr) cm^{-1}: 3354, 3215, 2931, 1676, 1635, 1591, 1485, 1458, 1418, 1365, 1257, 1166, 1061. MS m/z: 300 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found C, 67.72; H, 6.75; N, 9.16.

***Compound (9)**:* yield 87%, recrystallized from DMF as yellow crystals, mp 233°C~235°C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.69 (s, 3H), 2.85 (br, 2H), 3.32 (m, 2H), 6.66 (d, *J* = 13.7, 1H), 6.90-7.50 (m, 10H), 10.89 (br, 1H). IR (KBr) cm^{-1}: 3215, 2850, 1628, 1577, 1506, 1456, 1365, 1224, 1026. MS m/z: 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found C, 78.51; H, 6.62; N, 9.26

Compound (10): yield 68%, recrystallized from EtOH as yellow crystals, mp 234°C~236 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 3.07 (t, *J* = 5.94, 2H), 3.64 (t, *J* = 6.02, 2H), 6.38 (br, 1H), 7.06 (t, *J* = 7.53, 2H), 7.18 (m, 1H), 7.20 (m, 1H), 7.44 (d, *J* = 7.93, 1H), 7.52 (d, *J* = 7.70, 1H), 8.19 (br, 1H). IR (KBr) cm^{-1}: 3319, 3224, 2920, 2219, 2204, 1616, 1558, 1490, 1456, 1180. MS m/z: 236 (M^+). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found C, 71.06; H, 5.10; N, 23.48.

Compound (11): yield 58% as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 3.09 (t, *J* = 6.31, 2H), 3.65 (m, 2H), 6.35 (d, *J* = 5.67, 1H), 6.50 (m, 1H), 7.05 (s, 1H), 7.14-7.28 (m, 2H), 7.40 (d, *J* = 8.01, 1H), 7.56 (d, *J* = 7.76, 1H), 8.31 (br, 1H), 9.23 (br, 1H). IR (KBr) cm^{-1}: 3053, 2922, 2852, 1639, 1550, 1458, 1126. HRMS (EI) *m/z* calcd for $C_{12}H_{13}N_3O_2$ 231.2536 (M^+), found 231.2531.

Procedure for the preparation of compounds (12-16)

For 12-14: The indole derivative (**7-9**) (1 mmol) was dissolved in 10 mL of saturated HCl/benzene solution and stirred for 30 min at 20 °C. After evaporation of the solvent and recrystallization from ethyl alcohol, the desired products were obtained. **For 15, 16:** To a solution of indole derivatives (**10**, **11**) (1 mmol) in 10 mL of acetonitrile was added 1 mL of glacial acetic acid. The reaction mixture was refluxed under nitrogen. Upon completion or after the indicated reaction time, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 4:1) to give the desired products.

***Compound (12)**:* yield 92%, recrystallized from EtOH as white crystals, 200°C (decomp). ^{1}H-NMR (300 MHz, δ ppm, DMSO-d_6): 2.29 (s, 3H), 3.06 (m, 2H), 3.29 (s, 3H), 3.51 (m, 2H), 3.65 (m, 1H), 5.07 (m, 1H), 7.05 (t, *J* = 7.32, 1H), 7.15 (t, *J* = 7.73, 1H), 7.33 (d, *J* = 8.1, 1H), 7.45 (d, *J* = 7.84, 1H), 9.67 (br, 2H). IR (KBr) cm^{-1}: 3232, 3051, 2922, 2736, 1712, 1606, 1494, 1458, 1379, 1207, 1178. MS m/z: 307 (M^+). Anal. Calcd for $C_{16}H_{19}N_2O_2Cl$: C, 62.64; H, 6.24; N, 9.13. Found C, 62.90; H, 6.20; N, 9.47.

***Compound (13)**:* yield 89%, recrystallized from EtOH as yellow crystals, 250°C (decomp). ^{1}H-NMR (300 MHz, δ ppm, DMSO-d_6): 2.93 (m, 2H), 3.13 (m, 1H), 3.43 (m, 1H), 3.56 (m, 1H), 3.75 (s, 3H), 5.05 (m, 1H), 7.04 (t, *J* = 7.47, 1H), 7.14 (t, *J* = 7.23, 1H), 7.37 (d, *J* = 8.01, 1H), 7.46 (d, *J* = 7.68, 1H), 9.53 (br, 2H), 11.08 (s, 1H). IR (KBr) cm^{-1}: 3429, 3254, 3044, 2924, 2706, 1722, 1602, 1454, 1398, 1204, 1181. MS m/z: 309 (M^+). Anal. Calcd for $C_{15}H_{17}N_2O_3Cl$: C, 58.35; H, 5.55; N, 9.07. Found C, 58.69; H, 6.04;

N, 9.44.

Compound (14)*:* yield 94%, recrystallized from EtOH as white crystals, 220°C (decomp). ^{1}H-NMR (300 MHz, δ ppm, DMSO-d_6): 2.09 (d, *J* = 7.20, 3H), 3.04 (m, 2H), 3.28 (m, 2H), 3.61 (d, *J* = 12.54, 1H), 5.03 (m, 1H), 6.83-7.49 (m, 9H). IR (KBr) cm^{-1}: 3418, 3224, 3036, 2937, 1716, 1605, 1554, 1503, 1449, 1382, 1212, 1171. MS m/z: 341 (M^+). Anal. Calcd for $C_{20}H_{21}N_2OCl$: C, 70.48; H, 6.21; N, 8.22. Found C, 70.36; H, 6.20; N, 8.13.

Compound (15)*:* yield 79% as an yellow oil, ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 3.10 (m, 2H), 3.61 (m, 2H), 3.81 (m, 1H), 4.11 (m, 1H), 5.64 (br, 1H), 7.06 (br, 1H), 7.12 (t, *J* = 7.16, 1H), 7.21 (t, *J* = 7.99, 1H), 7.40 (d, *J* = 7.97, 1H), 7.61 (d, *J* = 7.74, 1H). IR (KBr) cm^{-1}: 3413, 3228, 2925, 2264, 2215, 1712, 1604, 1549, 1504, 1445, 1376, 1230. HRMS (EI) *m/z* calcd for $C_{14}H_{12}N_4$ 236.2756 (M^+), found 236.2762.

Compound (16)*:* yield 83% as a brown oil, ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 3.16 (m, 2H), 3.89 (m, 2H), 3.97 (m, 1H), 4.14 (m, 1H), 5.54 (br, 1H), 7.15 (br, 1H), 7.19 (m, 1H), 7.28 (m, 1H), 8.19 (d, *J* = 7.63, 1H), 8.40 (d, *J* = 8.02, 1H). IR (KBr) cm^{-1}: 3258, 3115, 3069, 1607, 1559, 1504, 1425, 1218, 1126. HRMS (EI) *m/z* calcd for $C_{12}H_{13}N_3O_2$ 231.2536 (M^+), found 231.2533.

Crystal data for compound (9)

Empirical formula: $C_{20}H_{20}N_2O$, crystal size: 0.30×0.10×0.10, Monoclinic, a = 11.758(5)Å, b = 9.329(4)Å, c = 15.415(6)Å, α = 90.00°, β = 103.014(7)°, γ = 90.00°, V = 1647.3(12), T = 293(2)K, space group P2(1)/n, Z = 4, d_{calc} = 1.227 g/cm^3, F(000) = 648, 6580 reflections measured, 2895 unique (R_{int}= 0.0332). The final R1 = 0.0761($I > 2\sigma$), 0.1464(all data), wR2 = 0.1311($I > 2\sigma$), 0.1575(all data).

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18. Compounds (**2**-**4**) were obtained as diastereomers. Although isolation and purification of the compounds (**2**-**4**) are possible, these compounds are not substantially purified but are instead converted to compounds (**7**-**9**) by the process shown in Table 1.

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