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# Aromatization and chemoselective alkylation of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid and its derivatives

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ABSTRACT

Unprecedented aromatization was observed during N-alkylation reactions of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester, giving rise to 9-alkyl-1-methyl-β-carboline-3-carboxylic acid methyl esters. Inverse addition of base during a similar reaction resulted in a chemoselective alkylation to form novel 3-butyl-1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester as the major product in good yield.



## 1. Introduction

β-Carboline, constituted by fusion of indole and pyridine ring systems with different degrees of aromaticity, is present in various natural products and synthetic compounds.[1,2] Beside various other biological activities, these classes of compounds are also known to possess *anti*-HIV activity.[3] In the course of work directed towards the development of potential *anti*-HIV agents,[4,5] need arose for the preparation of 9-alkyl-1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl esters (**5**) and fully aromatic 9-alkyl-1-methyl-β-carboline-3-carboxylic acid methyl esters (**6**).[6] Synthesis of **5** was attempted by alkylation of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester (**3**). These attempts resulted in the formation of **6** instead of **5**, hence, completing two steps (i.e., oxidation and alkylation) in one-pot.

The aromatization of **3** without decarboxylation during above-mentioned alkylation was surprising, as the aromatization of this class of compounds is generally carried out by various oxidizing agents. Some reports are available where aromatization is observed in the absence of oxidizing agent but not without decarboxylation.[7,8] A method for the aromatization of 3,4-dihydro-β-carboline-3-carboxylic acid in aqueous alkaline conditions exists,[9] but no analogous methods are available for its 1-methyl homologues. Previous reports indicate that 1-methyl homologues do not undergo aromatization in aqueous alkaline conditions.[10] Further, 1-methyl homologues are known to exhibit imine–enamine tautomerism involving C-1 methyl group, but participation of acidic proton at C-3 or base-promoted aromatization is known to be absent in 1 N aqueous sodium hydroxide.[11]

With this background, we decided to study the aromatization of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid and its derivatives. These reactions were successful in anhydrous alkaline conditions, however, the aromatization was not observed in oxygen-free conditions. The aromatization resulted from carbanion formation at C-3 and not due to involvement of indole ring nitrogen. Formation of a carbanion was confirmed by hydrogen–deuterium exchange study of the C-3 proton. Moreover, the carbanion formed was alkylated at C-3 in chemoselective manner for the first time.

## 2. Results and discussion

The synthetic strategy followed is shown in Scheme 1. *N*-acetyl tryptophan (**1**) was obtained by Schotten–Baumann method from the commercially available *dl*-tryptophan. Compound **1** was converted into 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid (**2**)[11] which was then treated with thionyl chloride in methanol to form methyl ester **3**.[12] *N*-(1-methyl-3,4-dihydro-β-carboline-3-carbonyl)morpholine (**4**) was synthesized by treating **2** with methanesulfonyl chloride in the presence of triethyl amine to form reactive mesyl ester derivative, which was reacted in situ with morpholine in dichloromethane.

Scheme 2 shows the results of alkylation of **3**. This reaction did not give the desired 9-alkyl-1-methyl-3,4-dihydro-β-carboline-3-

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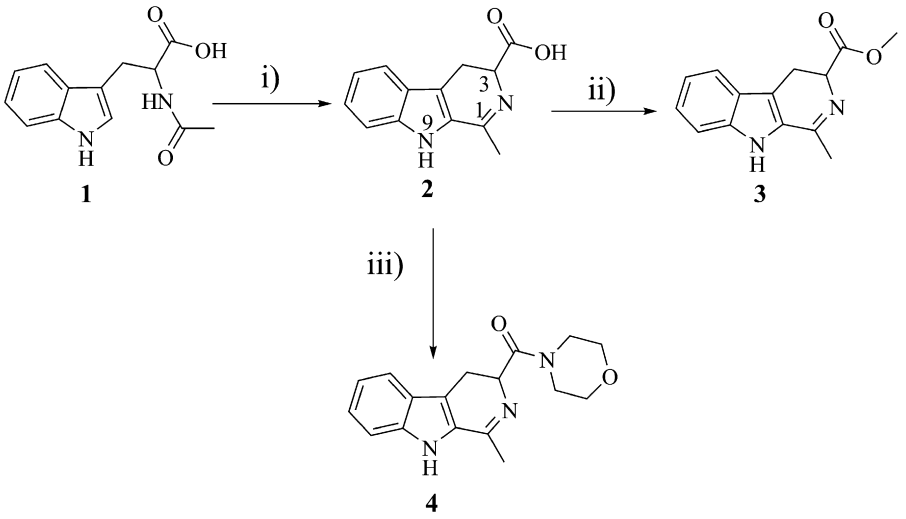
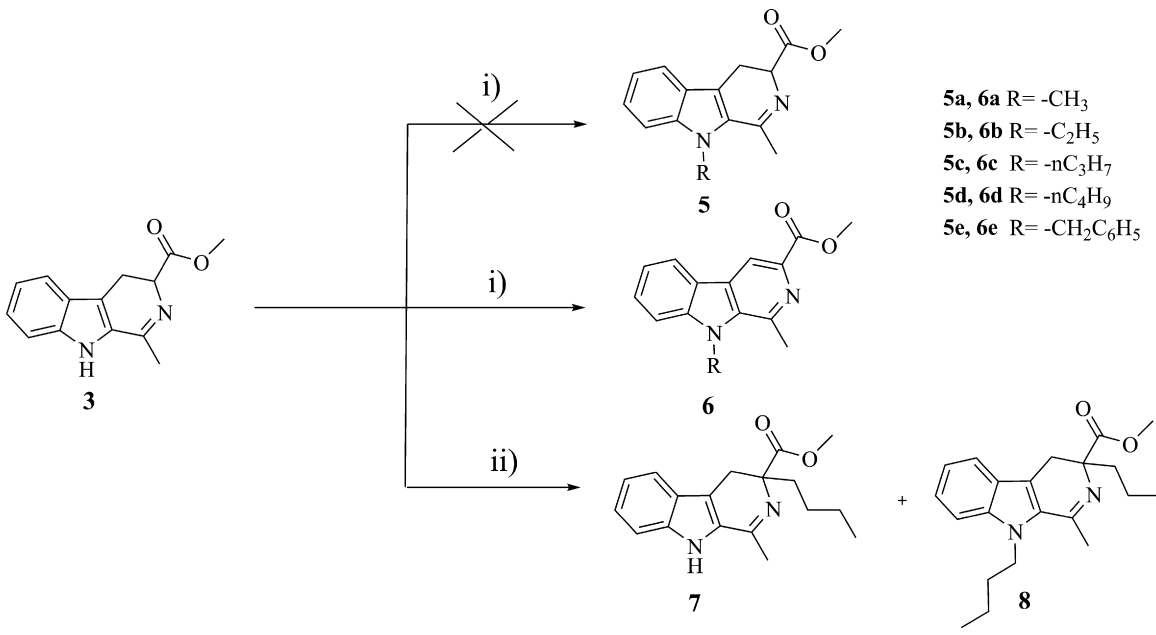
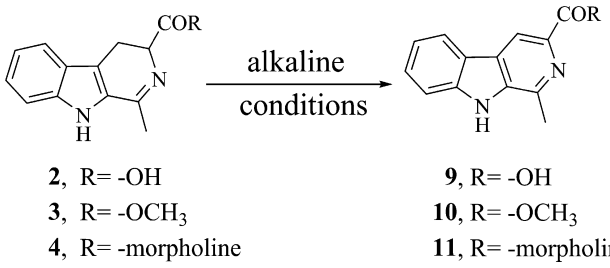



**Scheme 1.** Synthesis of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid and derivatives. Reagents and conditions: (i) dicyclohexylcarbodiimide (DCC), $CH_2Cl_2$, 3 h, 20 °C then add $CF_3COOH$, 1 h, 50 °C, 85%; (ii) $SOCl_2$, MeOH, 30 °C, 6 h, 96%; and (iii) $MeSO_2Cl$, $Et_3N$, $CH_2Cl_2$, 2 h then morpholine, 20 °C, 6 h, 68%.




**Scheme 2.** N-alkylation of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester. Reagents and conditions: (i) NaH, anhydrous DMF, 0 °C, 30 min then RX (X = Br or I), 28 °C, 60 min, (**6a** 85%; **6b** 78%; **6c** 80%; **6d** 75%; **6e** 85%); and (ii) inverse addition: *n*-BuI, anhydrous DMF, degassing by freeze-pump–thaw then NaH, 28 °C, oxygen-free argon atmosphere, 30 min (**7** 76.8%; **8** 12.8%).

carboxylic acid methyl ester derivatives (**5a–e**). Instead, it underwent aromatization to yield 9-alkyl-1-methyl-β-carboline-3-carboxylic acid methyl ester derivatives (**6a–e**). A similar experiment, repeated without alkyl halide, led to complete aromatization of **3** to form 1-methyl-β-carboline-3-carboxylic acid methyl ester (**10**) (Scheme 3). To investigate the nature of oxidizing agent, the same reaction was performed in oxygen-free argon atmosphere. Oxygen-free condition was insured by completely degassing the reaction mixture by four repetitive freeze-pump–thaw cycles. The absence of aromatization during these conditions indicated the involvement of oxygen. Further, compounds **2**, **3** and **4** were treated with different bases in anhydrous and aqueous conditions in order to study their aromatization. It is apparent from examination of the data given in Table 1, that anhydrous condition is essential for aromatization of 1-methyl homologue. It is important to note that the re-protonation at C-3 carbanion will be less in hydrogen acceptor




**Scheme 3.** Aromatization of **2**, **3** and **4** to form **9**, **10** and **11,** respectively (see Table 1 for details).

solvents. This might be the reason for faster reaction rate of aromatization in strong hydrogen acceptor solvent (such as DMF, Table 1, entry 5) as compared to methanol (Table 1, entry 4) or water.[13] Here,

**Table 1**
Aromatization of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid and its derivatives in various alkaline conditions

| Entry | Reaction conditions | Reactant | Time (h) | % Isolated yield[a,b] | % Yield[c] (using water as solvent) |
|---|---|---|---|---|---|
| 1 | NaH, anhydrous DMF, 28 °C | **2** | 4 | 62 | — |
| | | **3** | 0.5 | 80 | — |
| | | **4** | 0.5 | 78 | — |
| 2 | $K_2CO_3$, anhydrous DMF, 50 °C | **2** | 20 | 60 | No reaction |
| | | **3** | 8 | 74 | — |
| | | **4** | 6 | 77 | No reaction |
| 3 | NaOH, anhydrous DMF, 50 °C | **2** | 20 | 62 | No reaction |
| | | **3** | 3.5 | 69 | — |
| | | **4** | 4 | 71 | No reaction |
| 4 | NaOMe, anhydrous MeOH, 65 °C | **2** | 18 | 69 | — |
| | | **3** | 3 | 76 | — |
| | | **4** | 3 | 80 | — |
| 5 | NaOMe, anhydrous DMF, 50 °C | **2** | 8 | 59 | — |
| | | **3** | 0.5 | 65 | — |
| | | **4** | 1 | 70 | — |

[a] Dihydro derivatives completely disappeared (monitored by TLC).
[b] Identity was confirmed by $^1$H NMR, MS and $^{13}$C NMR.
[c] Starting material was recovered.

we hypothesized that aromatization under investigation might involve abstraction of acidic proton at C-3 by base in anhydrous medium. The resulting carbanion can undergo oxidative pathway in a manner similar to that reported for 3,4-dihydro-β-carboline-3-carboxylic acid.[9]

To substantiate our hypothesis, we performed hydrogen–deuterium exchange experiment under conditions similar to that used for aromatization. The experiment was performed on **2** in deuterated sodium methoxide ($NaOCD_3$)/deuterated methanol ($CD_3OD$) mixture and the $^1$H NMR spectra were recorded. Deuterated sodium methoxide ($NaOCD_3$) was prepared by addition of sodium to the deuterated methanol in nitrogen atmosphere. Figure 1 shows the upfield part of the $^1$H NMR spectra of **2**. Here, the peak at $\delta$ 3.41 corresponds to the acidic proton at C-3. Figure 2 shows $^1$H NMR spectra recorded after heating the mixture at 65 °C for 2 h. The decrease in intensity after 2 h indicated the formation of carbanion at C-3.

Formation of the carbanion was further confirmed by quenching it with alkylating agent. This was performed by changing the order of addition of base during alkylation reaction in oxygen-free argon atmosphere. This resulted in alkylation of **3** at C-3 before oxidation. In fact, we were able to isolate 3-butyl-1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester (**7**) as the major product in 76.7% isolated yield, along with 3,9-dibutyl-1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester (**8**) in 12.8% isolated yield.[14] The method is suitable for the synthesis of new C-3 alkylated derivatives in preparative scales. Chemoselectivity in this reaction can be explained by hard and soft acid-base concept (HSAB).[15] The soft electrophile, *n*-butyl iodide, can be attacked by either of the two nucleophiles, N9 anion or C-3 carbanion. Here, the attack was preferred by a soft nucleophile, that is, C-3 carbanion over N9 anion. The chemoselective alkylation presents the evidence for formation of carbanion at C-3. To the best of our knowledge, no method is reported in the literature to prepare C-3 substituted derivatives of 3,4-dihydro-β-carboline class of compounds.

In conclusion, we report a method for aromatization of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid and derivatives accompanied by alkylation in one-pot with excellent yields. Upon inverse addition, alkylation is preferred at C-3, and thus, a new

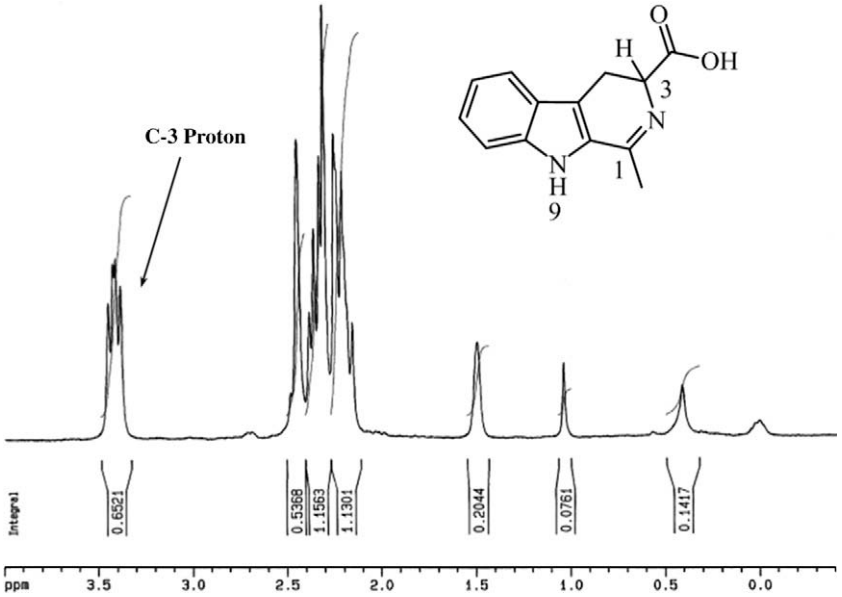



**Figure 1.** Aliphatic region of the $^1$H NMR (300 MHz, $NaOCD_3/CD_3OD$, $Me_4Si$) of **2**.

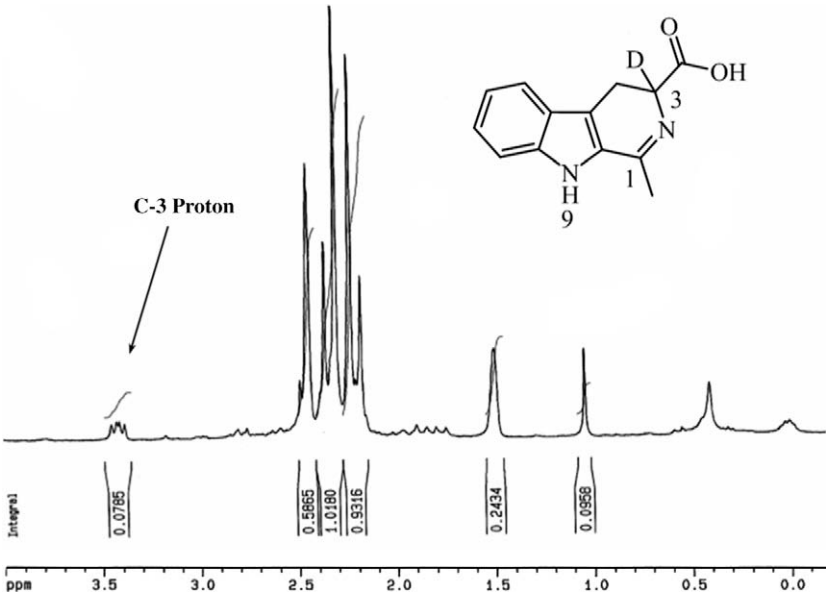



**Figure 2.** Aliphatic region of the $^1$H NMR (300 MHz, $NaOCD_3/CD_3OD$, $Me_4Si$) of **2** showing hydrogen–deuterium exchange of C-3 proton after heating at 65 °C for 2 h.

direct synthesis of 3-substituted derivatives is presented. These methods can find applications in synthetic strategies to obtain biologically important β-carboline-3-carboxylic acid derivatives.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.075.

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14. *General procedure for alkylation of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester* (**3**) (inverse addition): Compound **3** (242 mg, 1.0 mmol), *n*-butyl iodide (0.34 ml, 3 mmol) and anhydrous DMF (10 ml) were mixed together in a 50 ml Schlenk flask. The mixture was degassed by four freeze-pump–thaw cycles to remove oxygen. This was followed by addition of sodium hydride (60%) (48 mg, 1.2 mmol) under argon atmosphere. The mixture was stirred at 28 °C for 30 min. The resulting mixture was poured into cold water, and extracted with ethyl acetate. The organic phase was washed with water and brine, then dried over anhydrous sodium sulfate and evaporated. The oil obtained was purified on Silica Gel 60 (15–40 μm) by dry column vacuum chromatography (DCVC) by using hexane–ethyl acetate as mobile phase in gradient manner to obtain compounds **7** (228.8 mg, 76.7%) and **8** (45.3 mg, 12.8%) as racemic mixture. *3-Butyl-1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester* (**7**): IR (KBr, $cm^{-1}$):3435, 2954, 2854, 1732, 1649, 1553, 1435, 1377, 1322, 1219 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 8.73 (br s, 1H); 7.60 (d, 1H, $J$ = 7.9 Hz); 7.38 (d, 1H, $J$ = 8.2 Hz); 7.26 (m, 1H); 7.14 (m, 1H); 3.69 (s, 3H, $-CO_2CH_3$); 3.44 (d, 1H, $J$ = 16.8 Hz, H-4a); 3.03 (d, 1H, $J$ = 16.8 Hz, H-4b); 2.40 (s, 3H, 1-$CH_3$); 1.93 (m, 2H); 1.26 (m, 4H); 0.87 (t, 3H,, $J$ = 6.9 Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$, ppm): $\delta$ 176.21, 158.07, 137.64, 128.99, 126.21, 125.32, 121.00, 120.66, 115.47, 112.70, 67.78, 53.04, 39.12, 27.54, 27.33, 23.56, 22.60, 14.51; MS APCI: *m/z* 299 $(M+1)^+$, Anal Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.26; H, 7.52; N, 9.35. *3,9-Dibutyl-1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid methyl ester* (**8**): IR (KBr, $cm^{-1}$): 2955, 2871, 1736, 1533, 1457, 1350, 1204; $^1$H NMR (300 MHz, $CDCl_3$, ppm): $\delta$ 7.59 (d, 1H, $J$ = 7.9 Hz); 7.30 (m, 2H); 7.13 (m, 1H); 4.31 (t, 2H, $J$ = 7.2 Hz); 3.63 (s, 3H, $-CO_2CH_3$); 3.38 (d, 1H, $J$ = 16.6 Hz, H-4a); 2.91 (d, 1H, $J$ = 16.6 Hz, H-4b); 2.57 (s, 3H, 1-$CH_3$); 1.91 (m, 2H); 1.68 (m, 2H); 1.23 (m, 6H); 0.89 (m, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$, ppm): $\delta$ 176.09, 158.42, 139.19, 131.22, 125.45, 124.96, 120.77, 120.60, 117.24, 111.01, 67.38, 52.80, 45.30, 38.86, 33.53, 28.03, 27.38, 25.76, 23.60, 20.62, 14.53, 14.32; MS APCI: *m/z* 355 $(M+1)^+$, Anal Calcd. for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.32; H, 8.58; N, 7.88.
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