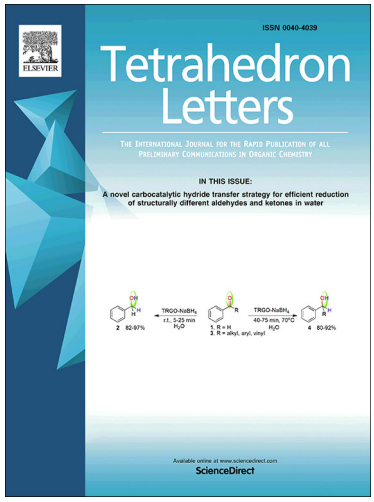

Organic base-promoted efficient dehydrogenative/decarboxylative aromatization of tetrahydro-β-carbolines into β-carbolines under air

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PII: S0040-4039(19)30141-8
DOI: https://doi.org/10.1016/j.tetlet.2019.02.020
Reference: TETL 50614

To appear in: *Tetrahedron Letters*

Received Date: 31 December 2018
Revised Date: 1 February 2019
Accepted Date: 8 February 2019

Please cite this article as: Zhao, Z., Sun, Y., Wang, L., Chen, X., Sun, Y., Lin, L., Tang, Y., Li, F., Chen, D., Organic base-promoted efficient dehydrogenative/decarboxylative aromatization of tetrahydro-β-carbolines into β-carbolines under air, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.02.020

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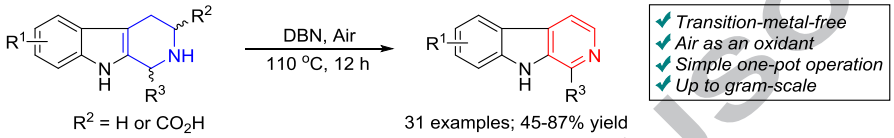

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Organic base-promoted efficient dehydrogenative/decarboxylative aromatization of tetrahydro-β-carbolines into β-carbolines under air

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

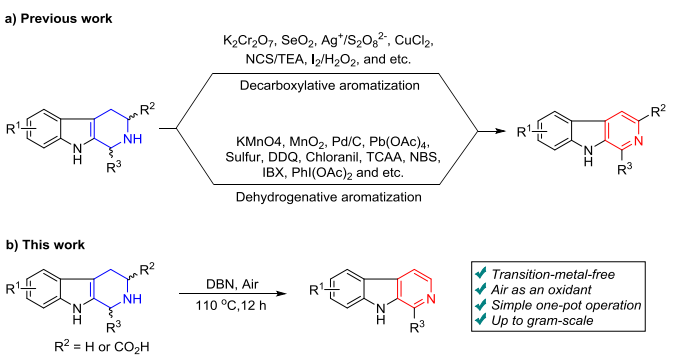
Keywords:
β-Carboline
Dehydrogenation
Decarboxylation
Aromatization

ABSTRACT

Organic base DBN has been identified as an efficient reagent for promoting the dehydrogenative/decarboxylative aromatization of tetrahydro-β-carbolines under air atmosphere, to access the corresponding β-carbolines in moderate to good yields. The utility of this protocol for the gram-scale synthesis of β-carboline alkaloids eudistomin U (**7**) and harmane (**10**) has also been demonstrated.

The β-carboline skeleton is one of the most intriguing indole-based heterocycles, its basic ring system being found in many natural products and pharmaceutical drugs. [1] β-Carboline derivatives have long been known to exhibit excellent antitumor, [2] antiparasitic, [3] antibacterial, [4] and antiviral activities. [5] In addition, some β-carboline derivatives are potential candidates for the treatment of neurodegenerative disorders such as Alzheimer's and Parkinson's disease, due to their inhibition of acetylcholinesterase [6] and human monoamine oxidase. [7]

In view of their important pharmacological properties, a number of synthetic methods have been developed to access these β-carboline derivatives. [8] The classical approach involves the Pictet-Spengler reaction between a tryptamine derivative and an aldehyde to generate the tetrahydro-β-carboline precursor, followed by decarboxylative/dehydrogenative aromatization to yield the corresponding β-carboline (Scheme 1). The traditional decarboxylative aromatization of tetrahydro-β-carboline are carried out at high temperatures with reagents like potassium dichromate ($K_2Cr_2O_7$), [9] selenium dioxide (SeO_2), [10] persulfate with catalytic silver ($Ag^+/S_2O_8^{2-}$) [11] or copper chloride ($CuCl_2$). [12] Recently, transformations of this type have been achieved by employing N-chlorosuccinimide in the presence of trimethylamine (NCS/TEA) [13] or iodine in presence of hydrogen peroxide (I_2/H_2O_2). [14] Another strategy to construct the β-carboline moiety is dehydrogenative aromatization of a suitable tetrahydro-β-carboline unit; these reactions are generally mediated by stoichiometric oxidants, such as potassium permanganate ($KMnO_4$), [15] manganese dioxide (MnO_2), [16] palladium on carbon (Pd/C), [17] lead tetraacetate ($Pb(OAc)_4$), [18] sulfur, [19] 2-iodoxybenzoic acid (IBX), [20] (diacetoxyiodo)benzene ($PhI(OAc)_2$), [21] chloranil [18] or dichlorodicianoquinone (DDQ). [22] Other reagents like trichloroisocyanuric acid (TCCA) [23] and N-bromosuccinimide (NBS) [24] have also been found effective in promoting dehydrogenative aromatization of tetrahydro-β-carboline. Beyond that, few alternative strategies to access aromatic β-carbolines involved elimination of N-tosyltetrahydro-β-carbolines by strong bases, [25] gold (III)-catalyzed cycloisomerization [26] and palladium (II)-catalyzed direct-dehydrogenative annulation. [27] Despite these fruitful efforts for the synthesis of β-carbolines, some of the reported methods suffer from certain drawbacks such as strong oxidants, toxic transition metal reagents, multi-step starting materials, etc.. Therefore, simple and efficient reaction conditions with inexpensive and commercially available reagents for the synthesis of β-carbolines are of considerable challenge.



Scheme 1. Literature reports and the present work for synthesis of β-carbolines from tetrahydro-β-carbolines.

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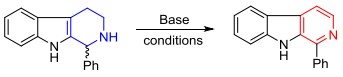
According to the reported methods, [9-11, 14-16, 20-22, 25] the conversion of tetrahydro-β-carbolines into their corresponding β-carbolines was generally accomplished under the basic or oxidizing reaction condition. On the other hand, simple oxygen, especially air, as the terminal oxidant is always the ultimate goal of oxidation reaction, because it is readily available and environmentally friendly. Based on above idea, a new "smart" strategy of basic solvent-promoted aromatization of tetrahydro-β-carbolines under air atmosphere should provide a greener and more practical approach for the preparation of β-carboline derivatives. Hence, we describe an efficient organic base-promoted dehydrogenative/decarboxylative aromatization for the conversion of tetrahydro-β-carbolines into β-carbolines that utilizes air as a terminal oxidant (Scheme 1). In addition, this method has been successfully applied for the gram-scale synthesis of natural β-carboline alkaloids such as eudistomin U (**7**) and harmane (**10**) in moderate yields.

In the beginning of our research, tetrahydro-β-carboline **1a** was chosen as the model substrate (Table 1). Initially, as a test reaction, the effect of various organic bases on **1a** was investigated under air atmosphere from room temperature to reflux temperature. To our surprise, we obtained β-carboline **2a** in 46% yield when **1a** was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) for 12 h at 100 °C under air (Table 1, entry 7). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was another efficient organic base to afford 33% yield of **2a** after refluxing for 12 h (Table 1, entry 6). Other basic solvents such as triethylamine (TEA), N,N-diisopropylethylamine (DIPEA), N,N,N',N'-tetramethylethylenediamine (TMEDA), and N-methylpiperazine (NMPRZ) were also tested, but the reactions in all these solvents were much slower and gave **2a** only in poor yields (Table 1, entries 1-5). It is obvious that DBN and DBU are stronger organic bases with the amidine structure owing to their conjugate acids stabilized by the resonance structure between the two nitrogen atoms. [28] Subsequently, further investigation of temperature revealed that DBN was more effective than DBU, and the reaction temperature is a very important effect factor (Table 1, entries 8-11). When using DBN as the basic solvent under air, increasing the reaction temperature to 110-120 °C led to a significantly improved yield of **2a** (Table 1, entries 9 and 10); whereas decreasing reaction temperature to 90 °C almost failed to yield **2a** with the main intermediate **I** (3,4-dihydro-β-carboline) remaining in the reaction (Table 1, entry 11). In order to investigate the reaction process, high performance liquid chromatography (HPLC) was utilized to monitor the conversion of **1a** to **2a**. As shown in Figure 1, after treating **1a** with DBN for 2 h at 110 °C, two new peaks appeared. These new components were identified as **I** (R_t = 9.6 min) and **2a** (R_t = 10.7 min) by comparison of their retention times (R_t) with corresponding standard compounds. It was observed that along with peak **2a** growing up gradually, the peaks of **1a** and **I** initially declined and then diminished at 12 h. Moreover, the reaction yield was not improved by changing from air to an oxygen balloon, and even if adding stoichiometric peroxides such as hydrogen peroxide (H_2O_2), *t*-butylhydroperoxide (TBHP), and potassium persulfate ($K_2S_2O_8$) (Table 1, entries 12-15). However, the reaction carried out under nitrogen instead of air almost did not afford **2a**, and **I** was founded to be the sole product (Table 1, entry 16). This result indicated that air was essential and powerful enough for the dehydrogenation reaction. Finally, of the reaction conditions screened in Table 1, entry 9 was chosen as the best condition.

Table 1. Optimization of the reaction conditions [a]



Entry	Base/Atm	T (°C)	Additive	Yield (%) [b]
1	TEA/air	90	/	trace
2	DIPEA/air	130	/	7
3	TMEDA/air	125	/	4
4	NMPRZ/air	140	/	6
5	NMM/air	120	/	7
6	DBU/air	100	/	33
7	DBN/air	100	/	46
8	DBU/air	110	/	39
9	DBN/air	110	/	78
10	DBN/air	120	/	77
11	DBN/air	90	/	trace
12	DBN/O_2	110	/	78
13 [c]	DBN/air	110	H_2O_2	75
14 [d]	DBN/air	110	TBHP	74
15 [e]	DBN/air	110	$K_2S_2O_8$	75
16	DBN/N_2	110	/	trace

[a] Unless otherwise noted reaction conditions are as follows: **1a** (1.0 mmol), organic base (5 mL), refluxing under air atmosphere for 12 h.

[b] Isolated yields.

[c] Extra 30% H_2O_2 (1.0 mmol) was added.

[d] Extra 70% aq. TBHP (1.0 mmol) was added.

[e] Extra $K_2S_2O_8$ (1.0 mmol) was added.

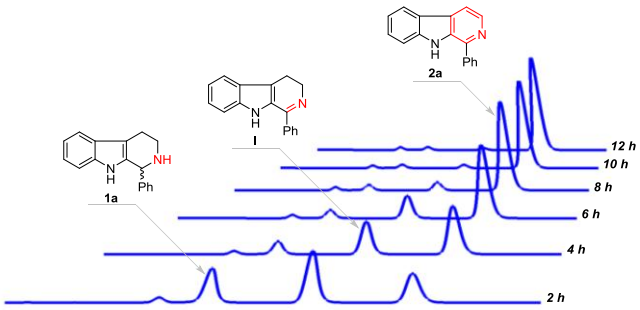
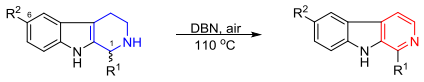


Figure 1. The conversion of **1a** to **2a** in the presence of DBN at indicated time point.

With the optimal reaction conditions in hand, we turned our attention to explore the substrate scope. A wide array of 1-substituted tetrahydro-β-carbolines **1a-1w** were obtained easily *via* the Pictet−Spengler reaction in which tryptamine or 5-methoxytryptamine undergone condensation with various aldehydes followed by ring closure. Then, the dehydrogenative aromatization of these tetrahydro-β-carbolines was conducted under the optimized conditions, and the results were depicted in Table 2. When the 1-position was substituted with aromatic substituents, the nature of groups on the benzene ring considerably influenced the yields of the products. For example, the steric effect of 2-methyl and 2-methoxy on the benzene ring hindered the DBN-mediated dehydrogenation, and the corresponding β-carbolines **2b-2c** were provided in poor yields. It was also apparent that the electronic nature of groups had some effect on the product yields; the strong electron-donating groups (e.g., 2-hydroxyl, 3-methoxy and 4-methoxy) afforded noticeably

higher yields compared to strong electron-withdrawing groups (e.g., 2-fluoro, 3-nitro, 3-chloro and 4-bromine). The corresponding β-carbolines **2d**, **2f** and **2i** could be obtained in > 75% yields, meanwhile, **2e**, **2g**, **2h** and **2j** could be afforded only in 45-66% yields. In addition, substrates with fused-ring and heteroaromatic substituents proceeded smoothly to afford the corresponding products **2k-2n** in good to excellent yields (75-87%), however the aliphatic-substituted substrates were observed to achieve this reaction in moderate yields (**2o**, 47%; **2p**, 67%). Subsequently, 1-substituted 6-methoxy tetrahydro-β-carbolines **1q-1w** were investigated, and the corresponding β-carboline products **2q-2w** were obtained in moderate to good yields (45-79%). It is important that the steric and electronic effects of substituents at 1-position to this conversion was consistent to that of **1a-1p**.

Table 2. DBN-promoted conversion of tetrahydro-β-carbolines into β-carbolines [a]



1 2

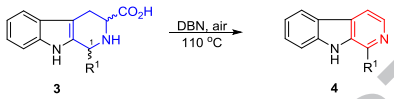
Entry	Substrate	R^1	R^2	Product	Yield (%)[b]
1	**1a**	Phenyl	H	**2a**	78
2	**1b**	2-Methyl phenyl	H	**2b**	35
3	**1c**	2-Methoxy phenyl	H	**2c**	30
4	**1d**	2-Hydroxyl phenyl	H	**2d**	76
5	**1e**	2-Fluoro phenyl	H	**2e**	65
6	**1f**	3-Methoxy phenyl	H	**2f**	79
7	**1g**	3-Nitro phenyl	H	**2g**	66
8	**1h**	3-Chloro phenyl	H	**2h**	50
9	**1i**	4-Methoxy phenyl	H	**2i**	78
10	**1j**	4-Bromine phenyl	H	**2j**	45
11	**1k**	1-Naphthyl	H	**2k**	75
12	**1l**	2-Pyridyl	H	**2l**	81
13	**1m**	2-Thienyl	H	**2m**	79
14	**1n**	2-Furyl	H	**2n**	87
15	**1o**	Isopropyl	H	**2o**	47
16	**1p**	Cyclohexyl	H	**2p**	67
17	**1q**	2-Hydroxyl phenyl	OMe	**2q**	70
18	**1r**	2-Fluoro phenyl	OMe	**2r**	50
19	**1s**	3-Methoxy phenyl	OMe	**2s**	79
20	**1t**	3-Nitro phenyl	OMe	**2t**	45
21	**1u**	1-Naphthyl	OMe	**2u**	73
22	**1v**	2-Pyridyl	OMe	**2v**	65
23	**1w**	Cyclohexyl	OMe	**2w**	60

[a] Reaction conditions: compounds **1a-1w** (1.0 mmol) and DBN (5 mL) at 110 °C under air for 12 h.

[b] Isolated yields.

Next, we turned our attention to explore the scope and generality of decarboxylative aromatization with tetrahydro-β-carboline acids **3a-3f** as reaction substrates under the optimized conditions. As depicted in Table 3, a series of substituents at 1-position were tolerated in the reaction, and the corresponding β-carbolines **4a-4f** were formed in moderate yields (45-60%). Remarkably, the halogen, hydroxyl, nitro and methoxy groups of these desired β-carboline products would be useful handles for further modifications to gain other pharmacologically active molecules.

Table 3. DBN-promoted conversion of tetrahydro-β-carboline acids into β-carbolines [a]



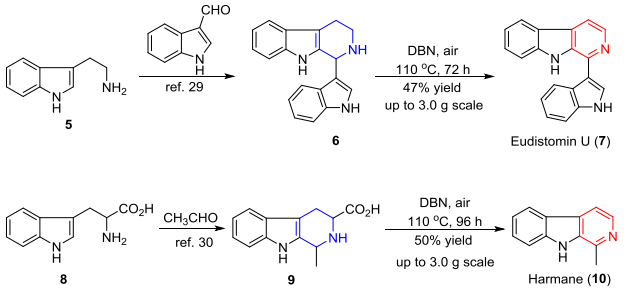
3 4

Entry	Substrate	R^1	Product	Yield (%)[b]
1	**3a**	Phenyl	**4a** (**2a**)	58
2	**3b**	2-Hydroxyl phenyl	**4b** (**2d**)	60
3	**3c**	3-Methoxy phenyl	**4c** (**2f**)	52
4	**3d**	3-Nitro phenyl	**4d** (**2g**)	45
5	**3e**	3-Hydroxyl-4-methoxy phenyl	**4e**	45
6	**3f**	2-Hydroxyl-5-fluoro phenyl	**4f**	51

[a] Reaction conditions: compounds **3a-3f** (1.0 mmol) and DBN (5 mL) at 110 °C under air for 12 h.

[b] Isolated yields.

Furthermore, to apply this method to a wide scope, we attempted the synthesis of natural β-carboline alkaloids like eudistomin U (**7**) and harmane (**10**), which were reported to exhibit anticancer activity due to their DNA-binding ability. [29] Synthesis of eudistomin U (**7**) began with the acid catalyzed Pictet-Spengler condensation of tryptamine (**5**) with indole-3-carboxaldehyde to give the corresponding tetrahydro-β-carboline (**6**). [30] The synthesis of harmane (**10**) started with tryptophan (**8**), which underwent a Pictet-Spengler condensation with acetaldehyde to provide the corresponding tetrahydro-β-carboline acid (**9**). [31] Then, **6** and **9** were subjected to the optimized reaction conditions, and furnished the target alkaloids **7** and **10** in 47% and 50% yield, respectively (Scheme 2). Much to our satisfaction, the DBN-promoted dehydrogenative/decarboxylative aromatization can be reliably run on gram scale.

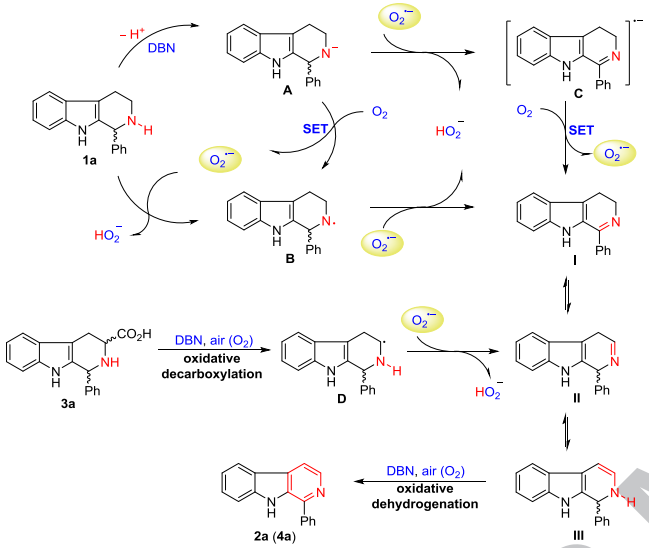


5 6 8 9

Scheme 2. Synthesis of eudistomin U (**7**) and harmane (**10**) *via* DBN-promoted dehydrogenative/decarboxylative aromatization.

On the basis of above results and reported literature, [25b, 32] we proposed a possible reaction mechanism for DBN-promoted dehydrogenative/decarboxylative aromatization process under air, with substrates **1a** and **3a** as an example. As outlined in Scheme 3, DBN acting as a strong organic base abstracts the proton localized on the nitrogen atom in the piperidine ring, to form nitrogen anion **A**. The newly produced **A** is oxidized by air (O_2) to the corresponding nitrogen radical **B** *via* single-electron transfer (SET), meanwhile, delivering a single electron to O_2 can generate oxygen radical anion ($O_2^{\cdot-}$). Then, the highly activated $O_2^{\cdot-}$ rapidly reacts with **1a** to give HO_2^- and nitrogen radical **B**, which is abstracted a hydrogen atom from the benzylic C (sp^3)-H

bond by $O_2^{\cdot-}$, to afford a stable intermediate **I**. On the other hand, hydrogen abstraction of **A** by previously formed $O_2^{\cdot-}$ gives a radical anion **C**, that is readily oxidized by air (O_2) to afford the key intermediate **I**. The structure of **I** was confirmed by ^{1}H NMR and MS (see the supporting information for details). Additionally, oxidative decarboxylation of substrate **3a** could be easily achieved in the DBN/air (O_2) reaction system, and lead to the formation of radical **D**, which would give an unstable intermediate **II** after further oxidation by $O_2^{\cdot-}$. Finally, intermediates **I** and **II** could go through a double-bond isomerization process (from **I**, **II** to **III**), followed by oxidative dehydrogenation again in the DBN/air (O_2) reaction system, to yield the desired product **2a** (**4a**).



Scheme 3. Plausible reaction mechanism.

In conclusion, we have developed a highly efficient protocol for the synthesis of β-carbolines *via* DBN-promoted dehydrogenative/decarboxylative aromatization of tetrahydro-β-carboline precursors under air. The method possessed the advantages of being metal-free, operational simplicity and broad substrate scope, which could serve as a milder alternative to the traditional methods. Additionally, the utility of the process was highlighted in the gram-scale synthesis of β-carboline alkaloids such as eudistomin U (**7**) and harmane (**10**). Further utilizations of this protocol are underway to construct more complex β-carbolines in our laboratory.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant No. 81602957), the Natural Science Foundation of Jiangsu Province, China (Grant No. BK20161035), and the China Postdoctoral Science Foundation (Grant No. 2016M601853).

Supplementary data

Supplementary data associated with this article can be found online at

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Highlights

- An efficient organic base-promoted synthesis of β-carbolines was accomplished.
- This method was successfully applied for the gram-scale synthesis of natural β-carboline alkaloids.
- The method possessed the advantages of being metal-free, operational simplicity and broad substrate scope.