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Iodine-catalyzed chemoselective dehydrogenation and aromatization of Tetrahydro-*β*-carbolines: a short synthesis of Kumujian-C, Eudistomin-U, Norharmane, Harmane Harmalan and Isoeudistomine-M

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ABSTRACT

Temperature controlled chemoselective dehydrogenation and aromatization of tetrahydro-*β*-carbolines, using molecular I_2 and H_2O_2, in DMSO solvent affords a practical access to a series of corresponding 3, 4-dihydro-*β*-carbolines and *β*-carbolines respectively. This method has been successfully employed in the short synthesis of Kumujian-C, Eudistomin-U, Norharmane Harmane Harmalan and Isoeudistomin-M.

1. Introduction.

Aromatic *β*-carboline alkaloid scaffolds are observed in diverse natural sources[1] and show a broad range of biological activities such as neuroprotection,[2] antiviral,[3] antitumor,[4] anti-HIV,[5] antimalarial,[6] antiplasmodial,[7] anti-leishmanial,[8] anti-allergic[9] etc. Diverse *β*-carbolines derivatives exhibit tyrosine-phosphorylation regulated kinase (DYRK) activity[10] acetylcholinesterase inhibition.[11]The *β*-carboline moiety is a very important synthetic intermediate for a variety of pharmaceutically important natural products and drug molecules (fig. 1). The Significant biological properties of *β*-carboline makes it synthetically important unit.
Enormous efforts have been devoted for inventing efficient and cost-effective catalysts for the dehydro-aromatization of heterocyclic compounds under mild conditions.[12]Several methods have been developed to synthesize *β*-carbolines. Pictet–Spengler reaction is one of the methods used to obtain tetrahydro-*β*-carbolines, which upon dehydrogenation offers *β*-carbolines. The reagents such as $K_2Cr_2O_7$,[13] $KMnO_4$,[14] copper salts,[15] Palladium on carbon,[16,35g] sulphur,[17] SeO_2,[18] MnO_2,[19] NCS,[20] DDQ[21]and NBS [22] have been used for the oxidative aromatization and dehydrogenation. Whereas K. C. Nicolaou *etal.*,*l*[23] have reported IBX-mediated oxidative dehydrogenation of a secondary amine, Shannon S. Stahl *et al.*,[23c] reported oxidation of secondary amines and nitrogen heterocycles using 1,10-phenanthroline-5,6-dione/ZnI_2, recently Subhabrata Sen *et al.*,[24] have used the combination of IBX-$CeCl_3$ for the partial dehydrogenation of tetrahydro-*β*-carbolines to 3,4-dihydro-*β*-carbolines.

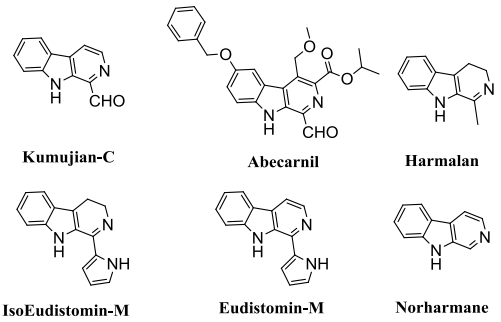


Fig. 1. Carboline alkaloids and drugs.

Recently Water *et al.*, have reported Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX) mediated oxidative aromatization, partial dehydrogenation of tetrahydro-*β*-carbolines at room temperature.[25a] Kamal *et al.*, have reported $PhI(OAc)_2$ (diacetoxyiodobenzene) mediated oxidative decarboxylation of tetrahydro-*β*-carbolines to the corresponding *β*-carbolines[25b].
However, most of the reported methods for the aromatization of tetrahydro-*β*-carbolines generally involve the following drawbacks. Pd mediated reactions need a higher temp. (up to 150 °C), long reaction hours, low yields, along with the possibility of C-N bond cleavage.[26] Selenium mediated reactions need huge

quantity of SeO_2 (10 equiv) offering very less yield (65 %).[27] Sulphur mediated reactions need 2 days to deliver aromatized product in low yields.[28] DDQ and chloranil were found useful in some cases but yields obtained were not satisfactory always.[21] While hypervalent iodine reagent IBX is usually required in super stoichiometric amounts and/or often requires ester functionality for successful *β*-carboline formation.

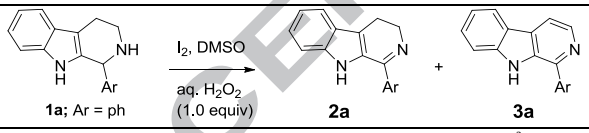
We have been always interested in iodine mediated, significant organo-synthetic transformations. Some of the recent molecular I_2 mediated methods especially oxidative dehydrogenation reactions reported by our research group are, I_2/DMSO mediated facile dehydrogenation of dihydropyridazin-3(2*H*)one,[29] oxidative cyclizations of 2′-hydroxy and 2'- allyloxy chalcones directly to the corresponding flavones and iodoflavones[30] instead of flavanones. Regioselective oxidative dehydrogenation in anilinodihydrochalcones.[30]Aaromatization and halogenation of 3,3a,4,5-tetrahydro-3-aryl-2-phenyl-2*H*-benzo[g]indazoles.[31] Aromatization and in-*situ* iodination of tetrahydrocarbazoles.[32]

In pursuance of our efforts to develop new synthetic methods for the compounds of medicinal importance, we attempted the synthesis of 3,4-dihydro-*β*-carboline, and aromatic-*β*-carbolines using molecular iodine under easy reaction conditions. Additionally, this method has been employed for the synthesis of bioactive alkaloids such as Kumujian-C, Eudistomin-U Isoeudistomin-U, Norharmane, Harmane, Harmalan, and Isoeudistomin-M.

1. Result and Discussion

Accordingly, when tetrahydro-*β*-carboline **1a** was stirred with 10 mol% molecular iodine at r.t. in DMSO, we got 3,4-dihydro-*β*-carboline **2a** with 50% yield (entry 1, Table1). Increasing amount of molecular iodine to 25 mol% could not improve the yield significantly (55%) (Entry2, Table1). It is reported in the literature that peroxide promotes the dehydrogenation reaction.[33] Therefore, we employed TBHP and H_2O_2 (100 mol% each) along with 10 mol% I_2 in separate reactions, resulting in 60% yield of the selectively oxidized product **2a** (3, 4-dihydro-*β*-carboline) (Entry 3, Table1). Increasing the I_2 to 25 mol% could not lead to better yield.

Table 1. Optimization of oxidative dehydrogenation and aromatization reaction

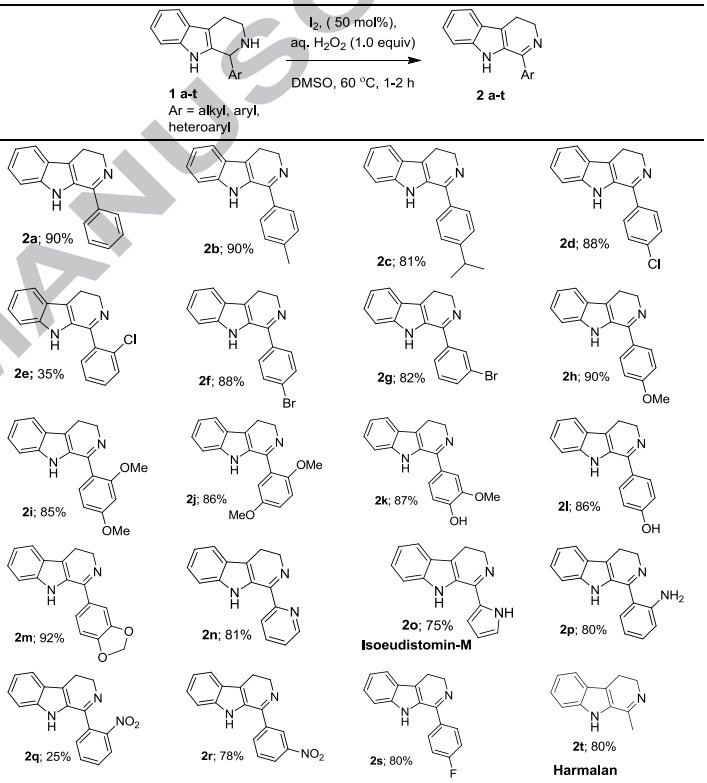


Entry	I_2 (mol%)	Oxidant (100 mol%)	Temp (°C)	Time (h)	Yield[a] % (**2a**)	Yield[b] % (**3a**)
1	10	-	RT	4	50	-
2	25	-	RT	4	55	-
3	10	H_2O_2	RT	3	60	-
4	25	H_2O_2	RT	3	60	-
5	10	H_2O_2	60	4	65	-
6	25	H_2O_2	60	4	72	-
7	50	H_2O_2	60	2	90	-
8	100	H_2O_2	60	2	90	-
9	10	TBHP	RT	4	54	-
10	25	TBHP	RT	4	56	-
11	25	H_2O_2	80	2	87	Trace
12	25	H_2O_2	100	10	-	88
13	50	H_2O_2	100	8	-	89
14	75	H_2O_2	100	8	-	90
15	100	H_2O_2	100	8	-	90

[a,b].Clear TLC observed in long rage wavelength.

Therefore we thought to increase the temperature, accordingly, when the reaction was carried out at 60 °C a slight increase in yield of the 2a (65%) was observed. Use of 25 mol% of I_2, resulted in 72% yield at 60 °C. To our delight, we got 90 % yield of 2a with 50 mol% I_2 in just 2 hours. However no further improvement was observed in terms of the yield with 100 mol% of I_2. Changing the peroxide from H_2O_2 to *tert*- butylhydperoxide (TBHP) with 10 and 25 mol% of I_2 at room temperature could lead to 54 and 56% of 2a. Therefore we decided to continue with H_2O_2. Further, to check the effect of enhanced temperature. The reaction was carried out at 80 °C with 25 mol% I_2 surprisingly, resulted in 87% of 2a and a trace quantity of aromatized product *β*-carboline 3a.However at 20 °C increases in temperature offered exclusively the *β*-carboline 3a in 88% yield over 10 hours. Increasing the iodine quantity to 50, 75 and 100 mol% could lead to 89-90% yield at the most (entry 13, 14, and 15, table 1). Therefore we preferred to continue with 25 mol% of I_2. Notably, an increase in the reaction temperature minimizes the use of molecular iodine and offers the aromatized product (Entry 12, Table 1). Here the controlled dehydrogenation and the aromatization of tetrahydro-*β*-carboline is temperature dependent.

Table 2. Chemoselective dehydrogenation of tetrahydro-*β*-carboline



[a] Yields: 35% 3,4-dihydro-*β*-carboline; 50% *β*-carboline

[b] Yields: 25% 3,4-dihydro-*β*-carboline; 55% *β*-carboline

Having the selective oxidation and aromatization condition in hand, we planned to explore the selective oxidation condition first. Accordingly, a range of tetrahydro-*β*-carbolines was subjected under the selective oxidation condition (entry 7, Table 1), substrates bearing electron-donating substituents offered excellent yields (up to 92%) (Entry 2m, Table 2). In case of *ortho*-amino substitution, dihydro-*β*-carboline was obtained in 80% yield (entry 2p, table 2). However, in case of electron-withdrawing substituents like *ortho*-NO_2 and *ortho-chloro* the obtained yields of the dihydro-*β*-carbolines were 25% and 35% respectively, along with 55% and 50% corresponding *β*-carbolines. Slight low yields were observed in case of heterocyclic aryl rings (entry 2n, and 2o, Table 2).

A range of tetrahydro-*β*-carbolines was next examined to probe the substrate scope of I_2-H_2O_2 mediated aromatization process. Tetrahydro-*β*-carbolines with the substitutions such as Me, OMe and halogens on the phenyl ring offered *β*-carbolines in very good yields (table 3). Interestingly, tetrahydro-*β*-carbolines bearing an *o*-chlorophenyl, *o*-nitrophenyl got converted into the corresponding *β*-carboline in quite better yields, (Entry 3e and 3q, Table 3) contrary to the chemoselective dehydrogenation of the same substrates (Entry 2e and 2q, Table 2)

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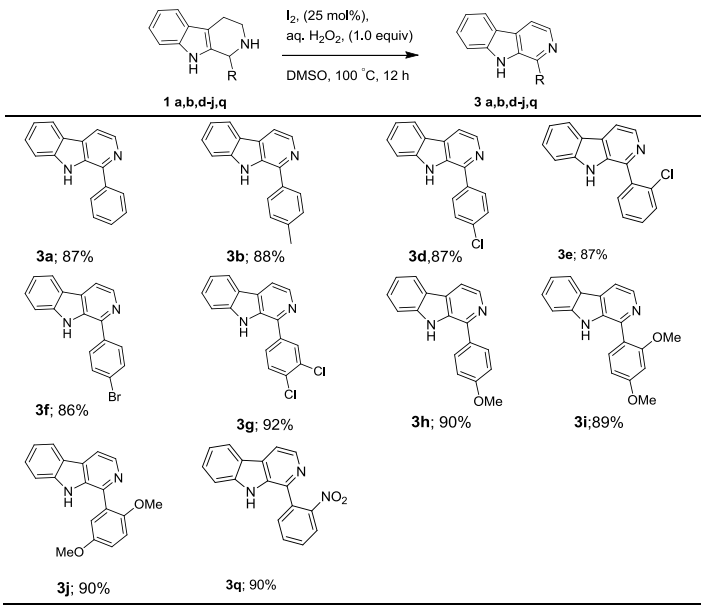
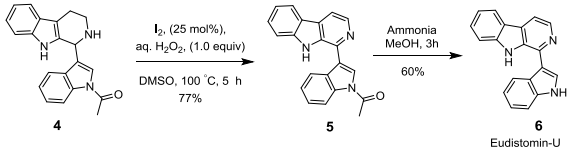
Table 3. Synthesis of *β*-carbolines.

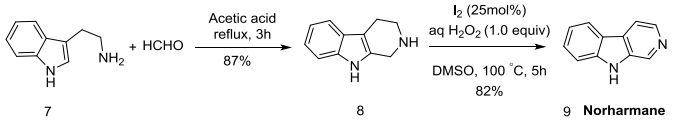


The various tetrahydro-*β*-carbolines underwent the oxidative dehydrogenation prompted us to investigate the applicability of this method toward the synthesis of some important marine alkaloids such as Kumujian-C, Eudistomin-U, Norharmane, Harmane. Kumujian-C isolated from root wood of *Picrasma quassioides*[34a]. Eudistomin-U was isolated from the marine ascidian *lissoclinum fragile* and was reported to possess anticancer activities with strong DNA binding potential, antimicrobial activity as well as exhibit antiviral activities against herpes simplex virus-1 and polio vaccine type-1 virus.[34b] There are seven reports available for the synthesis of Eudistomin-U[22,25,35].Eudistomin-U was first reported by Molina et al.,using an iminophosphorane intermediate.[35a] Queguiner *et al*.,prepared the natural product via sequential metalations[35b]. While Yamaguchi & Itami reported a novel oxidative C–H/C–H coupling in their total synthesis.[35c] Witulski Bernhard and Co-worker used a novel Ru or Rh-catalyzed [2+2+2] cyclization to generate the natural product[35d]. More recently Stephen Water and co-worker reported aromatization of Pictet-Spengler intermediate to generate eudistomin-U[25].Later Kamal and co-worker used NCS & $PhI(OAc)_2$ reagent for the total synthesis of alkaloid[22,25]. However, most of these syntheses need expensive metal catalysts,[35] critical reaction conditions prolonged reaction hours, multistep reaction sequence, resulting in low overall yield. We describe an efficient, three-step synthesis of Eudistomin-U. Synthesis of Eudistomin-U commenced with Pictet-Spengler reaction of tryptamine and N-acetyl-Indole-3-carbaldehyde to obtain the tetrahydro-*β*-carboline core **4**. Followed by oxidation of the obtained core **4** using I_2-DMSO under optimized conditions produced aromatized intermediates **5** (77% yields) subsequence deprotection gives eudistomin-U (60% yields, Scheme1).



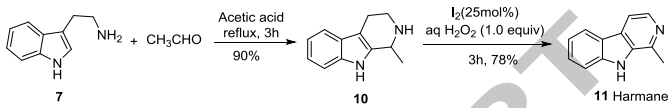
Scheme 1. Synthesis of eudistomin-U.

Synthesis of Norharman[22,25b] **9** has been carried out by Pictet Spengler cyclization reaction of tryptamine & formaldehyde (37-41% W/V) to obtain 1,2,3,4-tetrahydro-*β*-carboline 87% **8.** The oxidation of tetrahydro-*β*-carboline **8** under the optimized reaction condition gives **9** in (82% yield Scheme2).



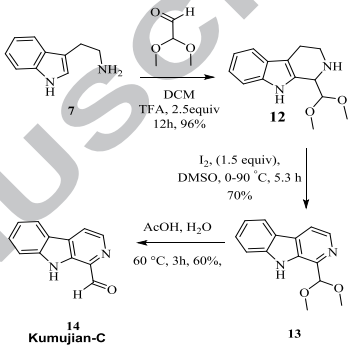
Scheme 2. **Synthesis of norharmane.**

Subsequently, Pictet-Spengler condensation of tryptamine & acetaldehyde provides 1-methyl-1,2,3,4-tetrahydro-*β*-carboline **10** 90% yield. Dehydrogenation of **10** under the optimized conditions proceeded smoothly, affording Harmane[22,25b]**11** in (78% yield Scheme3).



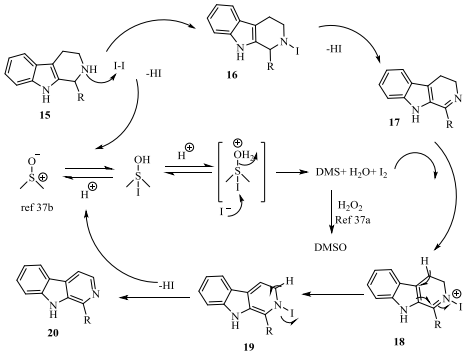
Scheme 3. Synthesis of harmane.

Finally, we also carried out the total synthesis of Kumujian-C **14,** which consists of formyl group at the C-1 position of ring C. We planned to apply aromatization reaction for the synthesis of Kumujian-C.



Scheme 4: Synthesis of Kumujian-C

Accordingly, the required tetrahydro-*β*-carboline **12** was achieved from the tryptamine **7** and dimethoxy glyoxal. The I_2 mediated aromatization of ring C under the optimized reaction condition (Entry 12, Table 1) offered intermediate **13** which upon stirring in AcOH at 60 °C delivered Kumujian-C[36] **14** in 40% overall yield.



Scheme 5: a Plausible mechanism for the I_2/DMSO/H_2O_2 mediated aromatization of tetrahydro-*β*-carbolines.

N-iodination of tetrahydro-*β*-carboline **15** takes place in the first step to give intermediate **16**. The dehydroiodination of N-iodotetrahydrocarboline results in the imine intermediate **17**. This imine intermediate gives ammonium intermediate **18** on further N-iodination. Subsequent deprotonation and dehydro-iodination offer the *β*-carboline. The generated HI further reacts with DMSO to regenerate the molecular iodine, along with dimethyl sulfide (DMS).[37b] The regeneration of molecular I_2 helps to continue the cycle. The formed dimethylsulfide is oxidized to DMSO in presence of H_2O_2 to speed up the reaction time.[37a]

Conclusion

In summary, we have developed a simple, efficient and metal free iodine mediated method, for the chemoselective dehydrogenation and aromatization of tetrahydro-*β*-carbolines to 3,4-dihydro-*β*-carbolines and *β*-carbolines. This protocol has been utilized for the synthesis of a library 3,4-dihydro-*β*-carboline derivatives as well as bioactive alkaloids Kumujian-C **14**, Eudistomin-U **5**, Isoeudistomin-M **2o,** Norharmane **8,** Harmane **10** and Harmalan **2t** analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at……

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Tetrahedron Letters

Highlights

- ✓ 30 Examples.
- ✓ I_2 catalysed chemoselective dehydrogenation of tetrahydro-*β*-carboline to 3,4-dihydro-*β*-carboline.
- ✓ I_2 catalysed a new synthesis of synthesis Kumujian-C, Eudistomin-U, Harmalan and Isoeudistomine-M.
- ✓ Products synthesized in good to excellent yields.

Graphical Abstract

Iodine-catalyzed chemoselective dehydrogenation and aromatization of Tetrahydro-*β*-carbolines: A short synthesis of Kumujian-C, Eudistomin-U, Norharmane, Harmane, Harmalan and Isoeudistomin-M

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