Tetrahedron 72 (2016) 8537–8541

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iodine-catalyzed one-pot decarboxylative aromatization of tetrahydro-β-carbolines

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ARTICLE INFO

Article history:
Received 5 July 2016
Received in revised form
24 October 2016
Accepted 31 October 2016
Available online 14 November 2016

Keywords:
β-Carboline
Decarboxylative aromatization
Iodine
Hydrogen peroxide
Tetrahydro-β-carboline

ABSTRACT

A synthetic strategy was developed for the preparation of β-carbolines by one-pot decarboxylation and aromatization of tetrahydro-β-carboline-3-carboxylic acids by employing 10 mol% of iodine in presence of oxidant aqueous H_2O_2. The method was also successfully extended for the aromatization of tetrahydro-β-carboline-3-methyl esters. The utility of the method was demonstrated in the synthesis of β-carboline alkaloids norharmane, harmane and eudistomin N.

1. Introduction

β-Carbolines,[1] are of great importance in the field of pharmaceuticals and are also versatile building blocks for bioactive compounds, natural products and drugs.[2] Compounds bearing aromatic β-carboline skeleton have been found to exhibit a wide variety of biological properties, such as, antitumor,[3] antimalarial,[4] anti-HIV[5] and antibacterial[6] activities. Moreover, certain β-carboline derivatives have also exhibited excellent binding affinities towards benzodiazepine receptors,[7] 5-hydroxyserotonin receptors,[8] and monoamine oxidase[9] in the central nervous system. Compounds bearing a β-carboline moiety are playing an important role as versatile synthetic intermediates in the synthesis of pharmaceutically important molecules.[10]

Their importance has attracted organic chemists to develop new synthetic strategies to construct the β-carboline moiety. Dehydrogenation of a suitable tetrahydro-β-carboline unit is a general method for its synthesis. This transformation involves heating the substrate with palladium on carbon,[11] sulfur,[12] SeO_2,[13] and $K_2Cr_2O_7$[14] with excess usage of the reagents and extended reaction times. DDQ[15] and chloranil[16] were also found useful reagents for aromatization, but the yields are not always satisfactory. IBX-mediated aromatization of tetrahydro-β-carbolines is known to produce β-carbolines at room temperature.[17] We have also developed a $CuCl_2$ catalyzed protodecarboxylation and aromatization of tetrahydro-β-carbolines.[18] Recently, NCS[19] and iodobenzene diacetate[20] were also found to perform the decarboxylative aromatization of tetrahydro-β-carbolines. However, these methods require 2 equivalents of the reagents which are expensive. Hence, the development of easy, economical and conventional methods for the aromatization of tetrahydro-β-carbolines is desirable.

Molecular iodine has been utilized in pharmaceutical and organic syntheses due to its inexpensive, non-toxic, environmental friendly nature and operational simplicity.[21] Usually, I_2 has been extensively used in combination with TBHP in many oxidative transformations to overcome the drawbacks of the metal catalysed reactions.[22] For any iodine catalyzed reactions, the reduced iodide species have to be reoxidised to iodine to maintain the catalytic cycle. This oxidation can be attained with an external oxidant like TBHP. If this process can be accomplished with the help of an environmental friendly and cheap oxidant such as aqueous hydrogen peroxide, the method would be very impressive. Hence, we aspired to report a novel and an efficient protocol for the aromatization of tetrahydro-β-carbolines employing a catalytic

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http://dx.doi.org/10.1016/j.tet.2016.10.069

amount of iodine in presence of hydrogen peroxide.

2. Results and discussion

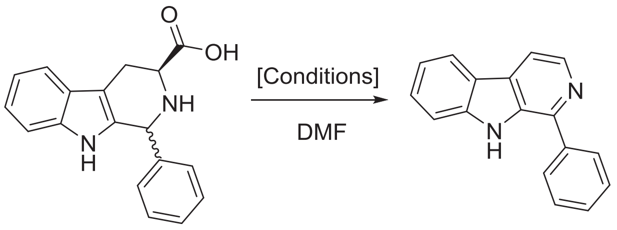
Our initial investigations focused on identifying conditions that would best attain the one-pot decarboxylation and aromatization of 1-phenyl-tetrahydro-β-carboline-3-carboxylic acid **1a** to aromatic β-carboline **2a** (Table 1). When 10 mol% of iodine was used in DMF at room temperature, the yield of the product was only 12% after 24 h (Table 1, entry 1). Increasing the amount of catalyst to 20 mol% and 50 mol% did not affect the yield of the product (entry 2–3, Table 1). Encouragingly, the product **2a** was formed in 64% yield using 10 mol% of I_2 in DMF at 100 °C (Table 1, entry 4). By increasing or decreasing the mol% of I_2, there was not much variation of yield (entry 5–6). Adding 1 mmol of external oxidant, hydrogen peroxide, delivered the product **2a** in 86% yield in 1 h (entry 7, Table 1). Changing the amount of iodine catalyst in the presence of oxidant has no effect on the yield (entry 8–9, Table 1).

Under the optimal conditions, our attention shifted to explore the scope of the aromatic process with a variety of tetrahydro-β-carboline-3-carboxylic acids (Scheme 1). A variety of aliphatic and aromatic substituents at position-1 of tetrahydro-β-carboline acids[23] are well tolerated under the optimized reaction conditions. The substrates containing aromatic substituents delivered better yields compared to those with aliphatic substituents. The electronic nature of the substituents plays an important role on outcome of the reactions. The substrates carrying electron-rich groups (**2b**, **2c**) furnished products in higher yields than those bearing electron deficient groups (**2d**-**2f**). Naturally occurring β-carbolines, norharmane (**2g**) and harmane (**2h**), were also synthesized in good yields.

The same method was also successfully extended to tetrahydro-β-carboline methyl esters. These esters were subjected to aromatization to provide the corresponding products **4a**–**d** in good yield without losing the ester group as shown in Scheme 2. A variety of substituents were found to be well tolerated. β-Carboline esters with electron donating groups provided better yields than the ones with electron withdrawing groups.

Finally, the synthesis of eudistomin N (**5**) was accomplished using the current protocol as shown in Scheme 3. Norharmane (**2g**) was synthesized by one-pot decarboxylative aromatization with I_2

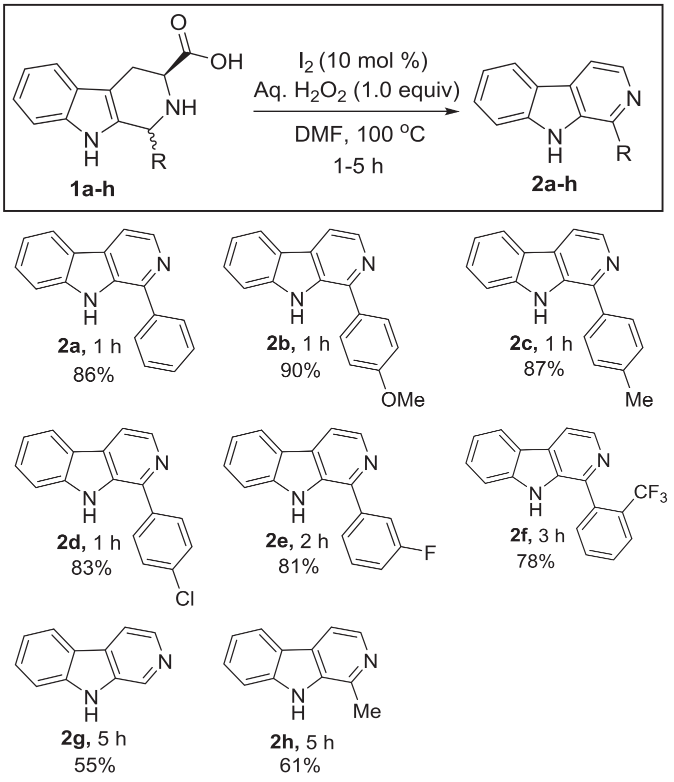
Table 1
Screening of the reaction conditions.



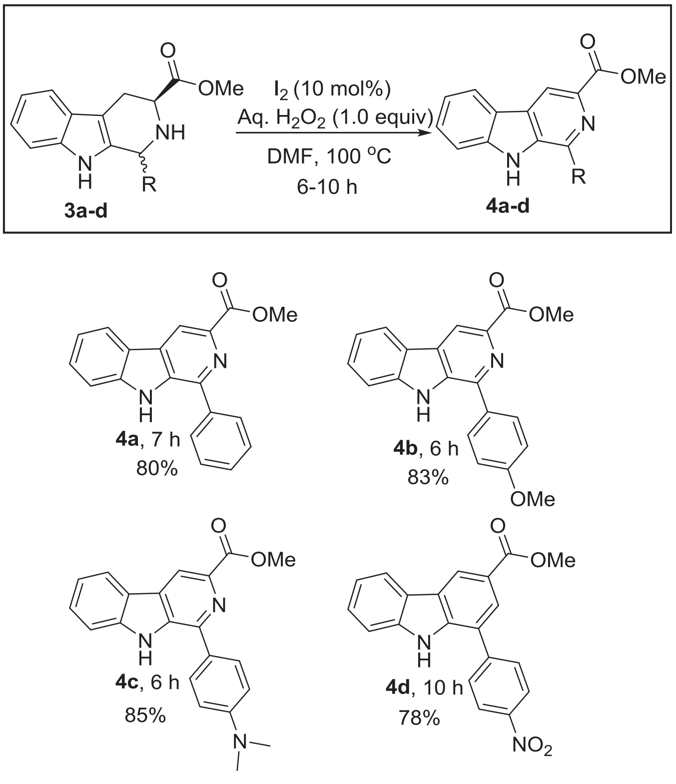
Entry	I_2 (mol %)	Temp (°C)	Time (h)	Yield (%)[a]
1	10	RT	24	12
2	20	RT	24	10
3	50	RT	24	10
4	10	100	3	64
5	20	100	3	60
6	5	100	3	61
7[b]	10	100	1	86
8[b]	5	100	1	77
9[b]	20	100	1	81

[a] Isolated yields.

[b] 1 mmol of aq H_2O_2 was added.



Scheme 1. Synthesis of β-carbolines.



Scheme 2. Aromatization of tetrahydro-β-carboline-3-carboxylic esters.