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Oxone mediated effective aromatization of tetrahydro-β-carbolines: A facile synthesis to β-carboline-3-esters/amides and marinacarboline A and C

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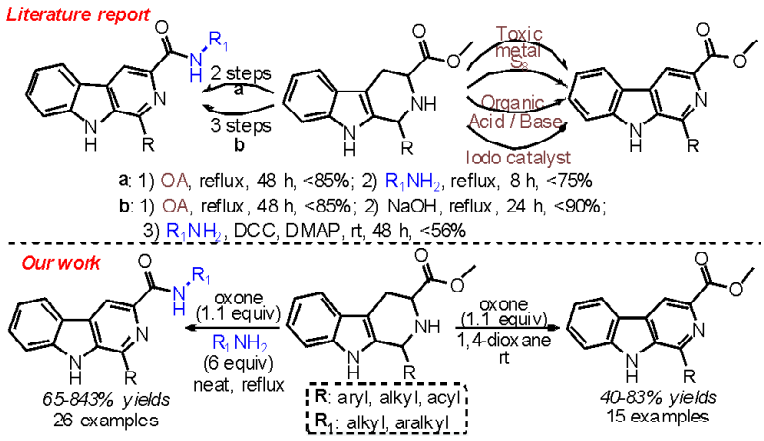
The utility of oxone has been extended to an efficient aromatizing agent and successfully applied to the aromatization of tetrahydro-β-carbolines under mild conditions, to produce aromatized β-carboline esters and amides. It is expediently applicable to all kinds of C-1 subsisted (aryl, alkyl, and acyl) tetrahydro-β-carboline esters. It also gives a direct and productive one-pot conversion of tetrahydro-β-carbolines ester to aromatized β-carboline amide. Further, the application of this method finds an easier route to the synthesis of marinacarbolines A and C.

Keywords: Oxone, aromatization, Picket-Spengler reaction, β-carbolines, tetrahydro-β-carbolines, marinacarbolines.

Introduction

The aromatic β-carboline moiety is found in numerous natural products[1]. Several studies on β-carbolines revealed that appropriate substitution at 1, 3, 6 and 9 affords potency to its skeleton and evidently they exhibit potent medicinal properties[2], therefore, plethora of synthetic methods have been developed to the generation of such scaffold for decades. The most general and efficient method used for the synthesis of β-carbolinesis through Pictet-Spengler reaction between tryptophan methyl ester and appropriate aldehydes followed by the aromatization of tetrahydro-β-carboline ester (THBC ester) generated in the reaction. For the aromatization reaction of THBC ester, different reagents have been utilized which include, (a) toxic metal oxidizing agents such as SeO_2[3], MnO_2[4], $K_2Cr_2O_7$[5], $KMnO_4$[6], $Ag/(NH_4)S_2O_8$[7], Pd[8] and Cu[9], but these metal oxidants can easily oxidizes the C-1 active methylene group to carbonyl[3]. In addition, although S_8[10], DMSO[11] and organic acids (chloranil[12], and trichloroisocyanuricacid[13]) are effective in the dehydrogenation reaction but the yields are often very low. Other oxidizing agents, such as, organic bases (DDQ[14], DBU/O_2[15]) requires functionalized tetrahydro-β-carbolines and iodine based catalysts (NBS[16], I_2[17], IBX[18], $Ph(IOAc)_2$[19], $NaIO_4$[20]) requires additives. Further, the aromatized β-carboline amides (BC amides) are synthesized from THBC ester generally precedes through either two or three step protocol. Along with the above said aromatization, it also associates with amidation/de-esterification followed by amidation (Scheme 1). However, the strategies adopted in at the present time underwent considerable changes in the concern of synthesis of molecules and materials, and these approaches attempt to make use of reagents that are mild, efficient, nontoxic, selective and cost effective. In this context, we developed an oxone mediated aromatization reaction of tetrahydro-β-carboline to aromatized β-carboline wherein generates β-carboline-3-esters (BC esters)/amides (BC amides). Later, this reaction also conveniently utilized in the synthesis of marinacarbolines A and C. The oxidant oxone, potassium peroxymonosulfate, is a stable white crystalline compound, non toxic, water soluble, easy to handle, and economical. Oxone has been used efficiently in numerous transformations, in most of the reactions peroxymonosulfate $(HSO^-_5)_2$ anion has been switched as an active oxidant.

In the survey of the synthesis of various β-carboline de-

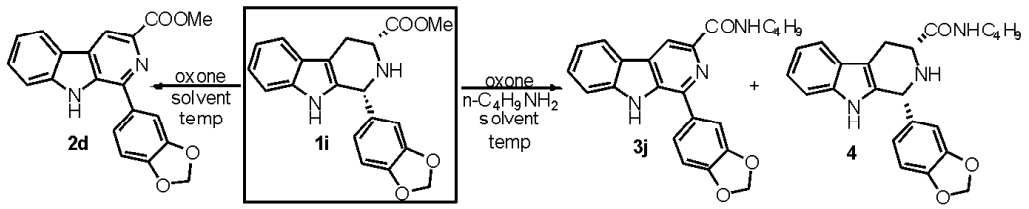


Scheme 1. Reported synthetic approach for the synthesis of BC ester and BC amide.

rivatives, we got an oxidized/aromatized product β-carboline-3-ester **2d** with low yield (10%) in a reaction wherein THBC ester **1i** underwent self oxidation in H_2O at room temperature (entry 1; Table 1). The same reaction could not produced **2d** while it was conducted in the presence of argon atmosphere (entry 2); in addition increasing yield was observed with oxygen atmosphere (O_2 balloon; entry 3). These results provoked us to study the reaction further to improve the yields of the product **2d**. Although, better yield of the product **2d** was observed with bromine based oxidant NBS (1 equiv) and hypervalent iodine oxidant IBX (1 equiv), but it could not be appreciable (entry 4, 5). Later, when the reaction was tested with potassium salts of sulphur acids, the yield of the reaction increased significantly. Amongst, $K_2S_2O_8$ (1 equiv) was produced 34% yield of **2d**, while $KHSO_5$ (1 equiv) gave 43% yield at the same reaction conditions (entry 5, 6). Based on the above hints, we further investigated the reaction by performing it at various reaction conditions under the influence of $KHSO_5$. As an initial exertion, we screened the reaction with different solvents, in those DMSO, DMF and DCM would account very low yields of product **2d** (entry 8, 9 and 10). However, *o*-xylene was produced good yield of product (entry 11), 1,4-dioxane could be the choice of the solvent for the reaction (entry 12). After performed the reaction at various temperatures, time intervals and amounts of oxidant (entry 12–15), we could get the best results for **2d**, when the THBC ester treated with 1.1 equiv of $KHSO_5$ at room temperature for 2 h (82%, entry 13). With these results, we further investigated application with THBC ester for amidation reaction in the same pot along with aromatization. Initially, we conducted a reaction of THBC ester **1i** with 1.1 equiv of oxone and 1.5 equiv of *n*-butylamine in 1,4-dioxane, it was produced 10% of BC amide **3j** along with 45% of **2d** and a small amount of **4** (entry 16). Later it was found that, the reaction produced better yield (81%, entry 17) in solvent free conditions, while in the presence of 6 equiv of *n*-butylamine. After testing the reaction with oxygen atmosphere (entry 18) and at higher temperature (entry 19), no significant betterment in yield was observed. The practical production of BC amide **3j** was observed when THBC ester reacts with 1.1 equiv of $KHSO_5$ and 6 equiv of *n*-butylamine at 80°C in solvent free condition (entry 17).

With the optimized procedure in hand, we established the substrate scope for both aromatized β-carboline-3-esters and β-carboline-3-amides. The expediency of the reaction was verified with respect to various substituted THBC ester including electron withdrawing and electron donating groups was described in Scheme 2. As observed, the room temperature $KHSO_5$ mediated aromatization/oxidation of THBC ester, however showed a bit differences in the yields of the products **2a**-**2o**, but is worked well with all THBC ester compounds being tested. Generally the phenyl group of THBC ester, if contains electron withdrawing groups generated low yielded products (**2b**, **2c**, **2d**, **2e**, and **2f**) than compare to unsubstituted phenyl THBC ester (**2a**, 67%). Furthermore, THBC esters of phenyl groups with electron donating group substitutions (**2g**-**2m**) afforded more yields than unsubstituted one. In addition, piperonal (**2i**, 83%) and dimethyl substituted piperonal (**2m**, 76%) containing THBC esters also produced good yields. Along with these results, both

Table 1. Optimization of reaction conditions[a]



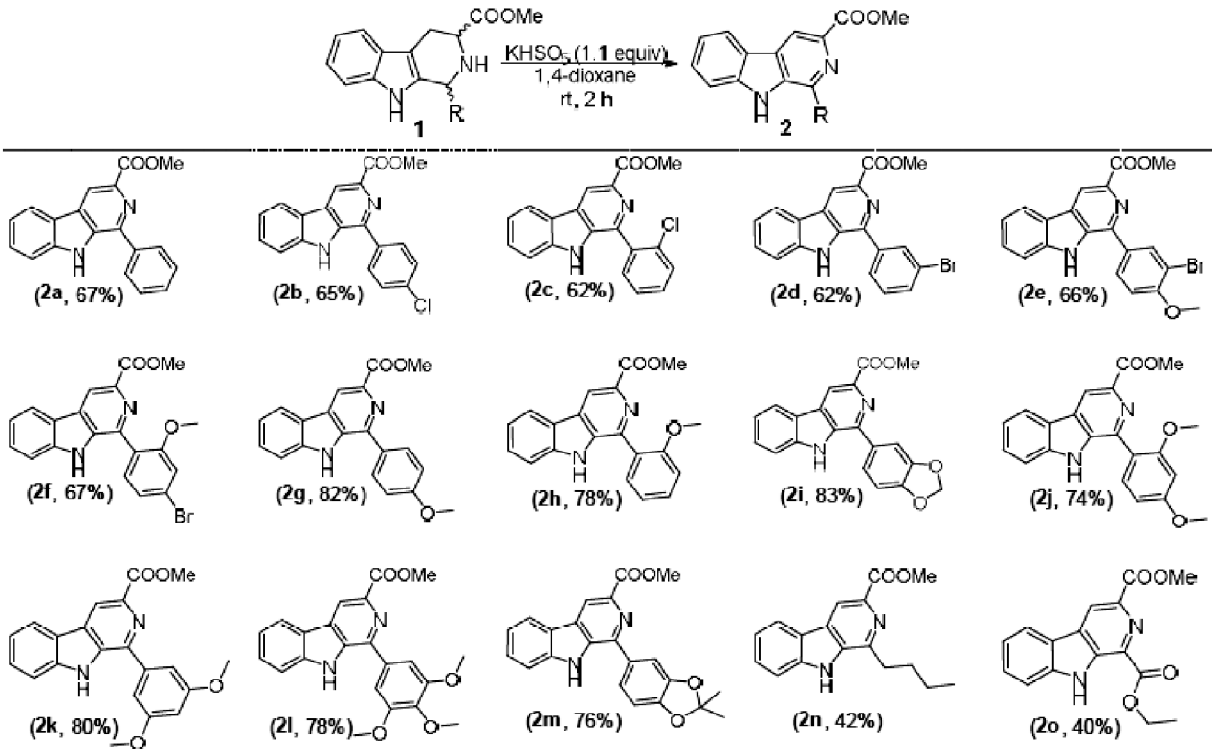
Entry	Oxidant	n-$C_4H_9NH_2$	Solvent	Conditions		Yield (%)		
	(equiv)	(equiv)		t_a (°C)	t_b (h)	**2d**	**3j**	**4**
1	Air	–	H_2O	rt	24	10	–	–
2	Argon	–	H_2O	rt	24	–	–	–
3	O_2 balloon	–	H_2O	rt	24	22	–	–
4	NBS (1)	–	H_2O	rt	24	30	–	–
5	IBX (1)	–	H_2O	rt	24	26	–	–
6	$K_2S_2O_8$ (1)	–	H_2O	rt	24	34	–	–
7	$KHSO_5$ (1)	–	H_2O	rt	24	43	–	–
8	$KHSO_5$ (1)	–	DMSO	rt	24	10	–	–
9	$KHSO_5$ (1)	–	DMF	rt	24	<10	–	–
10	$KHSO_5$ (1)	–	DCM	rt	24	26	–	–
11	$KHSO_5$ (1)	–	*o*-Xylene	rt	24	50	–	–
12	$KHSO_5$ (1)	–	1,4-Dioxane	rt	24	80	–	–
13	$KHSO_5$ (1.1)	–	1,4-Dioxane	rt	2	82	–	–
14	$KHSO_5$ (1.3)	–	1,4-Dioxane	rt	2	82	–	–
15	$KHSO_5$ (1.1)	–	1,4-Dioxane	70	2	80	–	–
16	$KHSO_5$ (1.1)	1.5	1,4-Dioxane	80	24	45	10	< 5
17	$KHSO_5$ (1.1)	6	–	80	9	–	81	< 5
18	$KHSO_5$ (1.1) and O_2	6	–	80	9	–	81	< 5
19	$KHSO_5$ (1.1)	6	–	90	9	–	81	–

[a]Reaction conditions: For **2d**: THBC ester **1i** (1 equiv), 1.1 equiv of oxone in 2 mL of 1,4-dioxane at rt for 2 h; For **3j**: THBC ester **1i** (1 equiv), 1.1 equiv of oxone, and 6 equiv n-$C_4H_9NH_2$ reflux for 9 h at 80°C.

alkyl substituted THBC ester and THBC diesters tolerated well to the reaction conditions and produced **2n**, **2o** respectively with low yields.

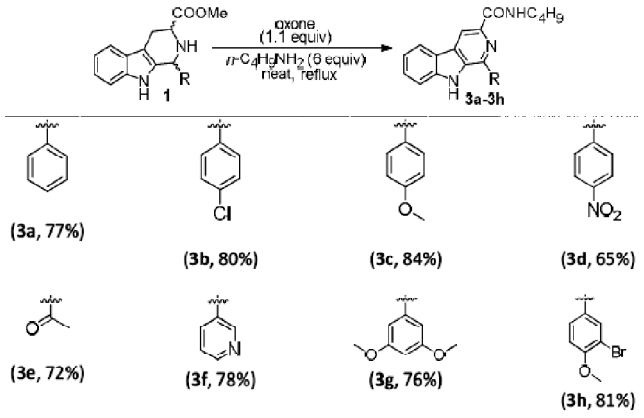
Later, the scope of the reaction was extended to establish the viability in the synthesis of BC amides. To achieve this, two different set of experiments were carried out to test the generality of the method developed. In one set of experiments, a series of different THBC esters **1** were reacted with *n*-butyl amine (Scheme 3) to generate different BC amides (entries **3a**-**3h**). As observed, all the reactions proceeded smoothly to corresponding products. Electron-rich THBC esters gave higher yields of BC amides (entries **3b**, **3c**, **3g** and **3h**) than electron-deficient THBC esters (entries **3d**, **3e**). 1-Acyl and pyridinyl substituted THBC esters were tested and they produced corresponding BC amide **3e**, and **3f** respectively in appreciable yield.

In another set of experiments a series of different reactions performed between **1i** and different amines under optimized conditions were examined (Scheme 4). Yields were generally good for all primary aliphatic and secondary amines being tested (entries **3i**-**3p**). Aliphatic amines such as straight (entries **3i**, **3j** and **3k**), branched (entry **3l**) and substituted (entries **3n**, **3o**) relatively afforded higher yields than those with alicyclic and secondary amines (entries **3m**, **3p**). Reaction with secondary amines comparatively required higher reaction times (entry **3p**). Anilines (entry A_1, A_2, A_3 and A_4) were failed to produce desired product even if tried for 2–3 days under refluxed conditions.



[a]Reaction conditions: THBC ester **1** (1 equiv), 1.1 equiv of oxone in 2 mL of 1,4-dioxane at rt for 2 h.

Scheme 2. Scope of the aromatization of THBC ester.



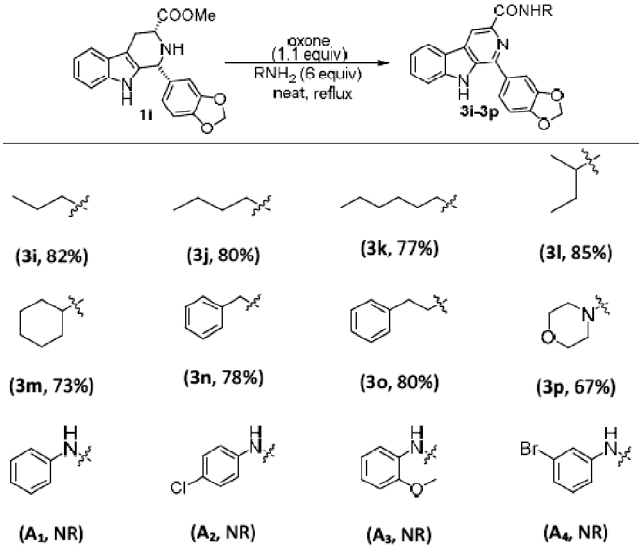
[a]Reaction conditions: THBC ester **1** (1 equiv), 1.1 equiv oxone, 6 equiv n-$C_4H_9NH_2$ refluxed for 9–15 h at 80°C.

Scheme 3. Scope of THBC ester reaction with n-butyl amine[a].

According to the above experimental results it is quite clear that this method is applicable with aliphatic primary amines and secondary amines. In addition, a small library of different BC amides (entries **3q**-**3x**) was generated by assembling the building blocks (Table 2).

On the basis of literature the expected product **5** is not produced in this reaction, instead it gives aromatized BC ester **2**[21]. It initiates with the active anion of oxone, peroxymonosulfate HSO_5^- dissociation into radicals $^{\bullet}OH$, $^{\bullet}OSO_3K$. This radical activates the C-3 hydrogen in THBC ester **1** and results in the formation of a radical intermediate **6**. Later it loses $H^{\bullet}$ radical and forms the intermediate **7.** This further undergoes isomerisation and afterwards produces BC ester **2** through aerobic oxidation (Scheme 5).

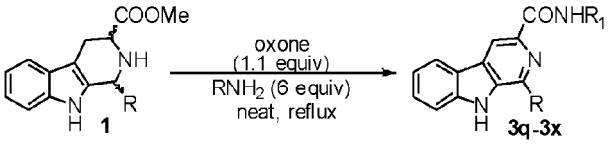
The ease with which BC amides were generated in good yields in short duration of time prompted us to investigate the application of our method towards total synthesis of few marine based indole alkaloids (marinacarbolines A and C)[22]. This synthesis is started with Pictet-Spengler condensation



[a]Reaction conditions: THBC ester **1i** (1 equiv), 1.1 equiv of oxone, and 6 equiv RNH_2 refluxed for 9–15 h at 80°C; NR: no reaction.

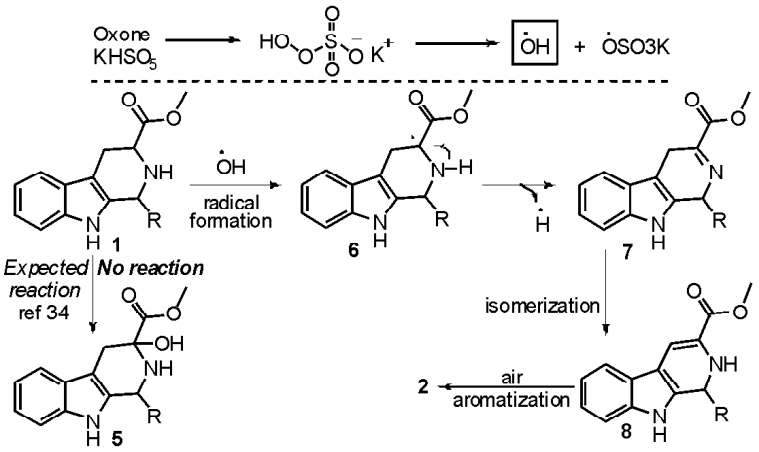
Scheme 4. Scope of the amine used in the reaction[a].

Table 2. Substrate scope of the reaction[a]

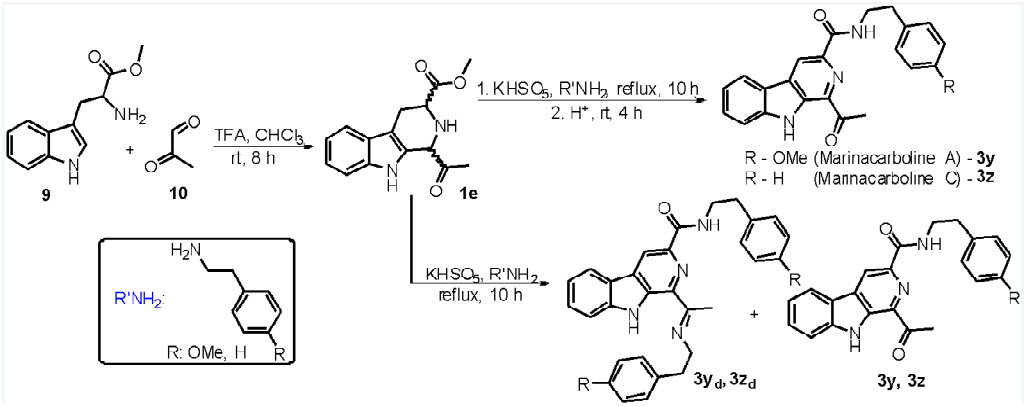


Entry	R	R_1	Yield (%)
3q	$3,5\text{-}(OMe)_2C_6H_3$	$n\text{-}C_3H_7$	77
3r	$4\text{-}OMeC_6H_4$	C_6H_{11}	74
3s	$3,4\text{-}(OMe)_2C_6H_3$	$CH_2C_6H_{11}$	78
3t	$3,5\text{-}(OMe)_2C_6H_3$	$CH_2C_6H_{11}$	80
3u	$4\text{-}OMeC_6H_4$	$CH_2C_6H_{11}$	84
3v	$3,5\text{-}(OMe)_2C_6H_3$	$CH_2CH_2C_6H_5$	75
3w	$3\text{-}C_5H_4N$	Morpholinyl	80
3x	$3,5\text{-}(OMe)_2C_6H_3$	Morpholinyl	74

[a]Reaction conditions: THBC ester **1** (1 equiv), 1.1 equiv of oxone, and 6 equiv aminerefluxed for 9–15 h at 80°C.



Scheme 5. Mechanism for oxone mediated aromatization.



Scheme 6. Synthesis of Marinacarbolines A and C.

of L (or) D-tryptophan methyl ester **9** with pyruvic aldehyde **10** afforded crude THBC ester **1e**, which on further reaction with respective amine in presence of $KHSO_5$ gave us desired product **3y**, **3z** along with disubstituted compound ($\mathbf{3y_d}$, $\mathbf{3z_d}$). To avoid the formation of disubstituted compound the reaction mixture (**1e** and respective amine) after initial reflux for 10 h with $KHSO_5$, was treated with an acid in the same pot at room temperature for 4 h producing desired product **3y**, **3z** in about 40% yield (Scheme 6).

In conclusion, we have demonstrated a practical, time saving and cost efficient oxone mediated aromatization of THBC esters to BC ester. In addition, it also described a competent one-pot neat transformation of THBC ester to BC amide mediated by $KHSO_5$ leads to production of variety of BC esters and amides. The reaction tolerates a wide scope of THBC ester and the methods are simple to conduct. The developed process has been utilized for total synthesis of the indole alkaloid Marinacarboline A and C.

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