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An efficient one-pot decarboxylative aromatization of tetrahydro-β-carbolines by using *N*-chlorosuccinimide: Total synthesis of norharmane, harmane and eudistomins

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A facile method for the synthesis of a variety of β-carbolines and their natural products such as norharmane (**2a**), harmane (**2b**), eudistomins I, N, T, and U (**6**, **7**, **9** and **10**) respectively has been successfully developed via decorboxylative aromatization tool by employing *N*-chlorosuccinimide (NCS) as a mild and efficient reagent. Gratifyingly, this reagent system proceeds in a one-pot manner and converted all the tetrahydro-β-carboline acids into their corresponding decorboxylative aromatic products with good to excellent yields. Additionally, this system works well in case of tetrahydro-β-carboline esters to produce their aromatic partners in high yields.

Introduction

It is well-known that β-carboline alkaloids having a tricyclic planar ring system are found in various synthetic/natural indole alkaloids.[1] This class of compounds (norharmane, harmane and harmine) are originally isolated from *Peganum harmala* and a group of β-carbolines,[2] termed as eudistomins (eudistomine I, N, T and U) are isolated from *ascidians*.[3,4] Most of these alkaloids exhibit antibacterial,[5] antimalarial,[6] antitumor,[7] anti-HIV[8] activities, and also shows binding affinity towards 5-hydroxy serotonin receptors,[9] monoamine oxidase[10] and benzodiazepine receptors[11] in the central nervous system. In light of these medicinal properties, there is a need for the development of mild and efficient methods towards the synthesis of β-carboline and their natural products. In recent years, we have been involved in the total syntheses of several natural/unnatural β-carboline alkaloids such as arborescidine alkaloids, quinolactacin B, PDE5 inhibitor, etc.[12] Moreover, the β-carboline ring system has also been used as versatile synthetic intermediates in the development of pharmaceutically useful motifs.[13]

The decarboxylative aromatization is one of the most attractive transformations in the organic synthesis.[14] However, decarboxylative aromatization of tetrahydro β-carbolines that involves C–H bond formation has received considerably less attention. A common method for the decarboxylative aromatization employs transition-metal oxidants at higher temperatures.[15,16] In the past, this transformation was achieved by using $K_2Cr_2O_7$[16] in acetic acid under heating for prolonged reaction times in presence of persulfate employing catalytic silver ($Ag^+/S_2O_8^-$).[17] Generally, Pictet–Spengler reaction followed by decarboxylative aromatization is the most widely studied method to access β-carbolines.[18] On the other hand, aromatization of the tetrahydro-β-carboline carboxylate is reported to be carried out by using mild oxidants like MnO_2,[19] SeO_2,[20] palladium on carbon[21] and sulfur[22] with excess usage of the oxidants as well as prolonged reaction time. Other organic oxidants like DDQ[23] and chloranil[24] were also used for aromatization but the yields are not satisfactory. However, most of these methods require expensive reagents and drastic reaction conditions that lack environmental safety. Hence, the development of inexpensive, operationally simple and environmentally safe protocols that could be carried out under milder reaction conditions are valuable.

Next, *N*-halosuccinimides (NXS, X = Cl, Br and I) are considered as haloginating and mild oxidizing agents that can be used as a source of halogen in radical reactions for various electrophilic additions[25,26] as well as for mild oxidations.[27] Earlier, Roy and co-workers have reported the decarboxylative halogenation of α,β-unsaturated carboxylic acids by using NXS.[28] Later, Kuang and co-workers have reported the stereoselective decarboxylative bromination of α,β-unsaturated carboxylic acids by using NBS and lithium acetate under microwave conditions.[29] However, *N*-chlorosuccinimide (NCS) is a versatile and cost effective reagent for the mild oxidation as well as halogenation, having lesser toxicity than other oxidants.[30] Moreover, the by-product succinimide is highly soluble in water (1 g/3 mL at 25 °C),[31] easy to remove from reaction mixture during the work-up and also in large-scale reactions the succinimide from aqueous phase can be converted into the starting reagent *N*-chlorosuccinimide by treating with the sodium hypochlorite to make the method sustainable.[32] Recently, trichloroisocyanuric acid (TCCA) is also being used for aromatization of tetrhydro-β-carboline esters,[33] but the draw-back of this reagent is solubility of its by-product cyanuric acid (0.27 g/100 ml at 25 °C) in water. Based on these observations, we were prompted to look for a straightforward, operationally simple and high yielding protocol for the synthesis of β-carbolines using *N*-chlorosuccinimide. Therefore, we herein report a new one-pot decarboxylative aromatization tandem aromatization strategy for

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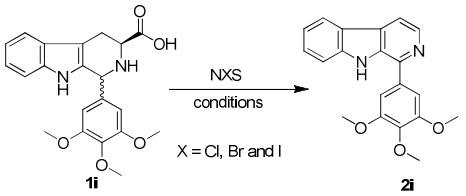
the synthesis of several β-carbolines and their alkaloids such as norharmane (**2a**), harmane (**2b**), eudistomin I (**6**), eudistomin N (**7**), eudistomin T (**9**) and eudistomin U (**10**) in excellent yields. In addition, this method was also successfully applied for the aromatization of tetrahydro-β-carboline ester into their corresponding β-carboline esters in high yields.

Results and Discussion

In this study, we have initially tested the feasibility of the reaction of **1i** with *N*-halosuccinimides (NXS, X = Cl, Br and I, 1.5 equiv.) in the presence of TEA (2 equiv.) and THF as a solvent at ambient temperature for 12 h. It was observed that the product **2i** obtained in moderate yields 60%, 53% and 48% (entry 1, 2, 3, Table 1) with different reagents. Later, when we enhanced the stoichiometric ratio of NXS (2.1 equiv.) and TEA (2.5 equiv.), the desired products were obtained in good yields 85%, 78% and 70% (entry 4, 5, 6, Table 1) respectively. Gratifyingly, the startingmaterials were completely consumed and even the reaction time was also decreased to 30 min. However, increase in the stoichiometric ratio of NXS (3 equiv.) reagent had no effect on yields and even the chlorinated product was not observed in this reaction process. Based on these model experiments, 2.1 equiv. of NCS was found to be slightly superior in comparison to NBS or NIS, and as well cost effective. The effect of solvent on the reaction was also studied by using various solvents such as THF, CH_3CN, 1,4-dioxane, DMF, DMSO, CH_2Cl_2 and it was observed that the product was obtained in 30 min with higher yields in the case of DMF as solvent (Table 1).

Table 1 Optimization of the reaction conditions for the synthesis of β-carbolines.[a]

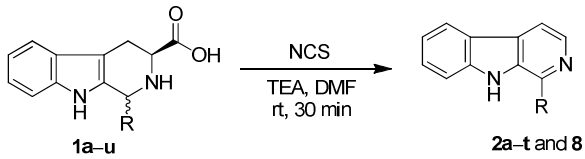


Entry	NXS	equiv.	time (h)	solvent	yield (%)[b]
1	NCS	1.5	12	THF	60[c]
2	NBS	1.5	12	THF	53[c]
3	NIS	1.5	12	THF	48[c]
4	NCS	2.1	1	THF	85
5	NBS	2.1	1	THF	78
6	NIS	2.1	1	THF	70
7	NCS	3.0	1	THF	85
8	NCS	2.1	1	acetonitrile	65
9	NCS	2.1	1	1,4-dioxane	71
10	NCS	2.1	0.5	DMF	92
11	NCS	2.1	1	DMSO	88
12	NCS	2.1	1	DCM	68

[a]Tetrahydro-β-carboline acid (**1i**, 1 equiv.), NXS and TEA. [b]Isolated yield. [c]Starting material was recovered.

After establishing optimal conditions, we studied the reactivity of various tetrahydro-β-carboline acids differing at position-1 and the results are shown in Table 2. The substrates tetrahydro-β-carboline acids successfully synthesized by Pictet-Spengler reaction of L-tryptophan and substituted benzaldehydes. Typically, the substituents on tetrahydro-β-carboline acids slightly affected the yields, wherein good yields are observed in case of aromatic and heteroaromatic rings at position-1 compared to aliphatic substitutions (entry 1, 2, 3 and 4, Table 2). From Table 2, it is observed that the nature of substituents at position-1 considerably influence the yields of the products. For example, substrates with electron-rich groups afforded noticeably high yields compared to electron-poor groups (entry 14 and 15, Table 2). Interestingly, the tetrahydro-β-carboline acids with fused ring systems like napthyl and phenanthryl groups also provided excellent yields (entry 17 and 18, Table 2), howevermoderate yields are observed in case of subsrtates with phenoxy substitutions at position-1 (entry 10 and 11, Table 2). Moreover, the natural β-carboline alkaloids norharmane (**2a**) and harmane (**2b**) are synthesized successfully by using this protocol with appreciable yields (entries 1 and 2, Table 2).

Table 2 One-pot decorboxylative aromatization for the synthesis of β-carbolines **2a–t** and **8** by using NCS[a].



Entry	R	product	yield (%)[b]
1	H	norharmane (**2a**)	80
2	Me	harmane(**2b**)	82
3	n-propyl	**2c**	78
4	4-methoxybenzyl	**2d**	90
5	Phenyl	**2e**	85
6	*p*-tolyl	**2f**	88
7	*p*-methoxy phenyl	**2g**	93
8	3,4,5-trimethoxy phenyl	**2h**	92
9	4-hydroxy-3-methoxy phenyl	**2i**	83
10	3-hydroxyphenyl	**2j**	78
11	4-chlorophenyl	**2k**	80
12	4-fluorophenyl	**2l**	83
13	4-cyanophenyl	**2m**	81
14	4-nitrophenyl	**2n**	79
15	Piperonyl	**2o**	91
16	Napthyl	**2p**	94
17	9-phenanthryl	**2q**	95
18	3-pyridyl	**2r**	91
19	4-fluoro-3-methoxyphenyl	**2s**	88
20	4-trifluorotolyl	**2t**	85
21	*N*-boc-2-phenethylamino	**8**	80

[a]**1** (1 mmol) in DMF, NCS (2.1 equiv.) and TEA (2.5 equiv.) stirred for 30 min at rt. [b] Isolated yield.

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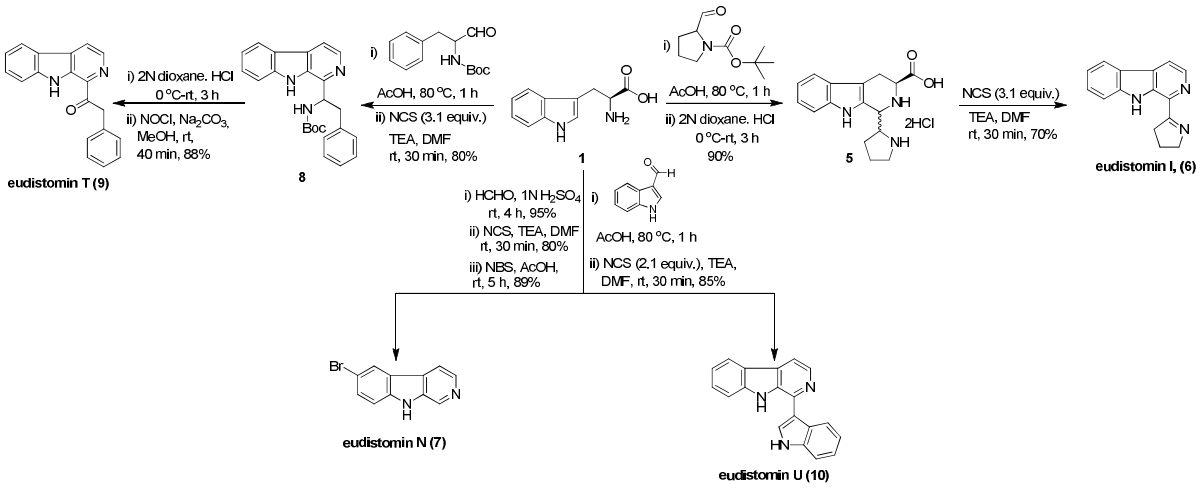

Scheme 1 Total synthesis of eudistomin I (**6**), eudistomin N (**7**), eudistomin T (**9**) and eudistomin U (**10**) by using NCS.

Inspired by the above results, we were prompted to apply this method for the synthesis of marine β-carboline alkaloids like eudistomins I, N, T and U. Eudistomin I, N and T were isolated from Caribbean tunicate *Eudistoma Olivaceum* and shows strong antiviral and antimicrobial activities.[3b,34] In 1987, the total synthesis of eudistomin I was reported,[3b,35] while Rinehart and co-workers in order to characterize the alkaloid isolated eudistomin N, described the synthesis of this bromo-β-carbolines.[3b,36] Moreover, edustomin N was found to be the most potent antiviral agent even compared to harmine.[37] Whereas, eudistomin T was isolated in 1987 by Kinzer and Cardellina II,[38] another marine β-carboline alkaloid eudistomin U was isolated from the marine ascidian *lissoclinum fragile* and was reported to posses antimicrobial as well as anticancer activities with strong DNA binding potential.[4] Both these eudistomins T and U succumbed to their total synthesis six times.[39,40] Overall, from the literature it was observed that the syntheses of such β-carbolines rarely involve decarboxylative aromatization and often utilized either metal catalysts, drastic conditions or prolonged reaction times and with lower yields to construct the core skeleton. In sight of these aspects, we were driven to synthesize these natural β-carbolines from the commercially available starting materials which could be a efficient route with higher yields than the previously reported syntheses.

Initially, we started the total synthesis of eudistomin I from Pictet-Spengler reaction of L-tryptophan (**1**) and *N*-boc prolinal to provide the corresponding *N*-boc pyrrolidinyl tetrahydro-β-carboline acid, which was then directly used for further deprotection of boc group using 2N HCl in 1,4-dioxane to afford the hydrochloride salt **5**. Salt **5** was produced the eudistomin I (**6**) under optimized reaction conditions by using NCS in 70% yield. Interestingly, it was observed that decarboxylation, aromatization and imine formation were successfully achieved in a one-pot manner (Scheme 1).

Next, the synthesis of eudistomin N (**7**) was achieved by the Pictet-Spengler reaction of L-tryptophan (**1**) and formaldehyde followed by decarboxylative aromatization under optimized reaction conditions with NCS to afford norharmane (**2a**). The bromination of **2a** with NBS in acetic acid afforded the eudistomin N (**7**) and it is important to note that the overall yield is considerably higher (91%, Scheme 1).

Subsequently, the total synthesis of eudistomin T (**9**) was also carried out with the acid catalyzed Pictet-Spengler condensation of L-tryptophan with *N*-Boc phenylalaninal and further reaction with NCS provided compound **8**. This compound (**8**) was taken for deprotection of Boc group with 2N HCl in 1,4-dioxane to afford the corresponding amine, which was subsequently treated directly with sodium hypochlorite to produce eudistomin T (**9**, 88%, Scheme 1).

Finally, we also carried out the total synthesis of eudistomin U (**10**) with commercially available L-tryptophan. The Pictet-Spengler reaction of L-tryptophan and indole-3-carbaldehyde followed by reaction with NCS under optimized conditions produced eudistomin U (**10**) in good yield (85%, Scheme 1).

Additionally, to find out the scope of this protocol on the tetrahydro-β-carboline esters, we have reacted various substituted

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Table 3 Synthesis of β-carbolines esters (**4a–h**) by aromatization using NCS[a]

Entry	R	product	yield (%)[b]
1	2-phenethyl	**4a**	81
2	3,4,5-trimethoxy phenyl	**4b**	94
3	1-napthyl	**4c**	95
4	4-chlorophenyl	**4d**	92
5	9-phenanthryl	**4e**	96
6	4-fluoro-3-methoxy phenyl	**4f**	94
7	4-trifluorotolyl	**4g**	91
8	1-*N*-boc-2-phenethyl	**4h**	88

[a]**3** (1 mmol) in DMF, NCS (2.1 equiv.) and TEA (2.5 equiv.) stirred for 30 min at rt. [b]Isolated yield.

tetrahydro-β-carboline esters with NCS. The substrates β-carboline esters were synthesized in two steps from commercially available L-tryptophan methyl ester hydrochloride. Interestingly, all these substartes successfully yielded their corresponding aromatic partners (**4a–h**) in excellent yields (Table 3) with out lossing ester group.

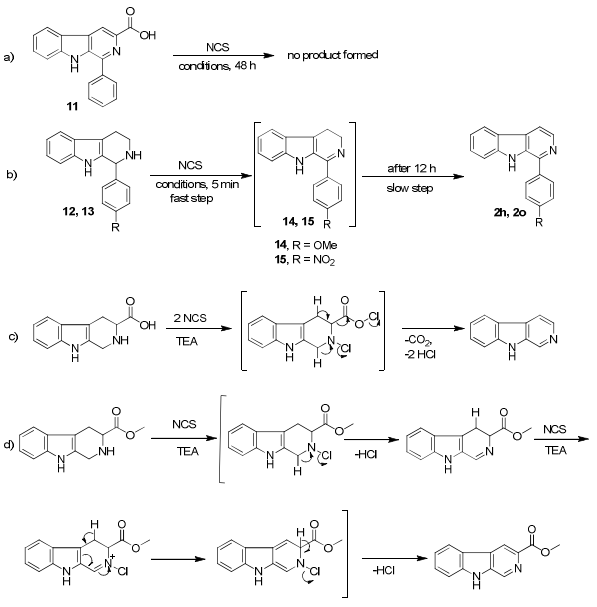

Fig. 1 a) Reaction of NCS with aromatized β-carboline acid (**11**), b) Reaction of NCS with tetrahydro-β-carbolines (**12** and **13**), c) Possible reaction mechanism for the decarboxylative aromatization of tetrahydro-β-carboline acid, d) Plausible reaction mechanism for the aromatization of tetrahydro-β-carboline ester.

Further, to understand the mechanism a test reaction was performed on β-carboline acid (**11**, Figure 1) under optimal conditions. It was observed that even after 48 h, the starting material was remained; it proves the sequence of decarboxylation followed by aromatization. Next, a reaction of tetrahydro-β-carbolines (**12** and **13**) under optimal reaction conditionsprovided partially dehydrogenated products (**14** and **15**) after 5 min, however fully aromatized β-carbolines (**2g** and **2n**, Figure 1) were observed after 12 h. In addition, we saw that the tetrahydro-β-carboline esters (**3a–h**) underwent aromatization only in 30 min. From all these results/findings, It was observed that the ester/acid functionality accelerates the reaction and the mechanism was proposed (Figure 1).

Conclusions

In conclusion, we have developed an operationally simple, mild and efficient protocol for the one-pot decarboxylative aromatization of tetrahydro-β-carboline-3-carboxylic acids to the β-carbolines. This protocol employs a cost effective oxidant *N*-chlorosuccinimide that provides higher yields. This method could utilize an alternative to the traditional heating methods employing harsh metal-based reagents. Moreover, the efficacy of this reagent system was established for the total synthesis of biologically active some of the β-carbolines norharmane, harmane and marine β-carboline alkaloids eudistomin I, N, T and U (**2a**, **2b**, **6**, **7**, **9** and **10**) respectively. Additionally, aromatization of tetrahydro-β-carboline esters to the corresponding β-carboline esters are also achieved successfully in excellent yields.

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An efficient one-pot decarboxylative aromatization of tetrahydro-β-carbolines by using *N*-chlorosuccinimide: Total synthesis of norharmane, harmane and eudistomins

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A mild one-pot synthesis of β-carbolines and their natural products from their tetrahydro-β-carboline acids has been developed via decorboxylative aromatization using *N*-chlorosuccinimide (NCS).