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Synthesis of β-carbolines *via* a silver-mediated oxidation of tetrahydro-β-carbolines

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ABSTRACT

The oxidation of tetrahydro-β-carbolines to β-carbolines using silver carbonate was developed as an alternative to current methods. The oxidation is extremely mild and provides the products in modest to good yields after purification. A number of functional groups are tolerated by this methodology, including reduction-sensitive groups which are often cleaved with other methods. Though the mechanism is not fully understood, the reaction proceeds in an open flask, is not sensitive to light or moisture, and provides a viable synthetic route to compounds that are not easily prepared *via* other methodologies.

Introduction

β-Carbolines are reoccurring molecular motifs in natural products such as hyrtiocarboline (**1**), which was isolated from a Papua New Guinea marine sponge *Hyrtios reticulatus*,[1] and eudistomin V (**2**), which was isolated from Australian ascidian *Pseudodistoma aureum* marine sponges.[2] The β-carboline scaffold is also present in modern pharmaceuticals including Tadalafil (Cialis/Adcirca), a phosphodiesterase-5 inhibitor. In addition, the β-carboline core is found in numerous molecules with antiviral[3,4] and anticancer[5] activities, and also displays inhibitory effects against kinases[6] and acetylcholinesterases,[7] among others (Fig. 1).

Given their utility, a variety of methods have been developed to synthesize β-carbolines. Many synthetic routes begin with the Pictet-Spengler reaction with a tryptamine derivative and an aldehyde to form the corresponding tetrahydro-β-carboline intermediate. This initial reaction is most commonly followed by a palladium[8] oxidation reaction to form the final β-carboline product. However, palladium-mediated oxidation has several drawbacks including catalyst cost, the reduction or cleavage of numerous functional groups and exhaustive purification required to remove the toxic metal to acceptable levels for use in biological studies. Alternative carboline oxidation methods such as potassium permanganate,[9] DDQ[10] and chromium reagents[11] have similar limitations and toxicity to palladium, while hypervalent iodine reagents like IBX[12] are usually required in superstoichiometric amounts and/or often require the presence of certain functional groups[13] to achieve successful β-carboline oxidation.

Our group has recently focused on the synthesis of β-carbolines after Harmine, a naturally occurring β-carboline which was found to be a selective inhibitor of the *Plasmodium falciparum* heat shock 90 protein (PfHsp90).[14] In order to better understand this activity and develop a structure-activity relationship (SAR) model, we began to synthesize a library of β-carboline derivatives of harmine, including numerous analogs containing aromatic halogens.

Results and discussion

Initially, our group synthesized several β-carbolines using a Pictet-Spengler reaction under microwave conditions to precipitate the tetrahydro-β-carboline intermediate, followed by oxidation over palladium on carbon in the microwave to give the final product.[15] Though this procedure could be used to rapidly generate compounds in good yields and excellent purity, a number of functional groups did not survive the palladium-mediated oxidation. We began to test a variety of other palladium and related hydrogenation catalysts to see if we could modulate the oxidation reaction versus the cleavage of sensitive moieties. During these tests, an undergraduate researcher accidently utilized silver carbonate instead of a traditional hydrogenation metal. Much to our surprise, TLC indicated the presence of a β-carboline product which was iso-

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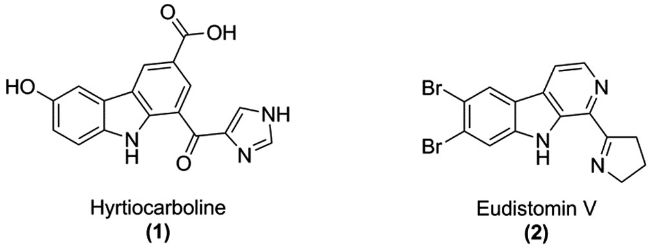


Fig. 1. Structure of hyrtiocarboline (**1**) and eudistomin V (**2**).

lated and confirmed by NMR (Table 1, entry 1). After confirming these surprising results, we scoured the literature and could find no reports of similar silver(I)-mediated carboline oxidations, although silver carbonate has been used with other transition metal systems as an oxidant.[16,17] Given that silver is a fairly mild reagent, we sought to discover if this methodology could be further developed to provide a new route to prepare β-carbolines with reduction-sensitive functional groups.

We first began our methodological studies using 1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline HCl salt (Table 1) and testing various solvents and reagent equivalents.

Using catalytic Ag_2CO_3 gave poor yields, but stoichiometric and superstoichiometric amounts resulted in modest to good yields in DMF, with 2 equivalents giving optimal yields after purification by column chromatography (Table 1, entries 1–5). A variety of other solvents were tested as well, with DMSO and toluene also giving satisfactory results, while protic solvents gave a mixture of by-products (Table 1, entries 6–10). We found that 2 equivalents of Ag_2CO_3 in DMF gave optimal yields, although heating for 16 h at reflux was required. Using DMSO or larger quantities of Ag_2CO_3 gave shorter reaction times but resulted in noticeably lower yields.

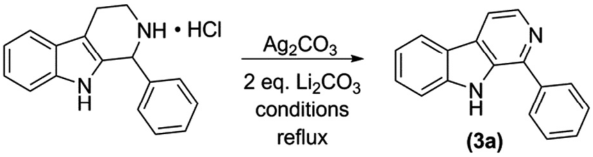
In addition to the methodological studies described in Table 1, we also tested various other conditions to probe the reaction mechanism. Silver(I) oxide, silver(I) nitrate, and silver(I) tetrafluoroborate were also found to provide product (**3a**) when reacted with the hydrochloride salt of 1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline, but with lower observed yields (data not shown). Running the reaction under argon, in the dark, or in a pure oxygen environment had no effect on the observed rate as indicated by TLC. Moreover, the reaction produces small, round metallic solids hypothesized to be Ag(0) based on XRF analysis (data not shown). While the overall mechanism is unclear, these results suggest that neither oxygen nor light participate in this reaction, but that silver alone is reduced during ring oxidation *via* an unknown redox mechanism. This may also explain why two equivalents are required for maximal yields, as two double bonds are formed during the oxidation. While much remains unknown about the mechanism, our studies show that the reaction does not require an inert atmosphere and is not sensitive to light or atmospheric water.

We next decided to investigate whether our optimized conditions would work with a series of oxidation and reduction-sensitive functional groups (Table 2).

We were pleased to find that most functional groups were well tolerated by our methodology, and that the products could be isolated in modest to good yields. Medicinally attractive heteroatom-containing substituents including pyridine (**3i**), thiophene (**3g**) and 1,3-benzodioxyl (**3h**) were also isolated in modest to satisfactory yields. Various reduction-sensitive functional groups were well tolerated by this procedure. Aromatic chlorine (**3b**, **3m**, **3n**), bromine (**3o**) and iodine (**3p**) groups were all successfully oxidized without cleavage of the aromatic-halogen bond as would be seen with many traditional oxidation methods. In addition, β-carbolines bearing either a chloro (**3b**) or methoxy (**3c**) group on the indole were prepared, demonstrating that both electron rich and electron withdrawing groups are tolerated on the indole ring. β-Carbolines containing a variety of alkyl groups were also successfully synthesized using this oxidation, including a cyclopropyl-substituted β-carboline (**3g**). The unsubstituted β-carboline, norharmane (**3d**) was also successfully oxidized using this method, demonstrating that the reaction is not limited by the absence of an electron withdrawing or donating group.

While a number of functional groups were compatible with our procedure, a few key limitations were identified. The oxidation reactions of tetrahydo-β-carbolines with *ortho*-substituted phenyl groups in the R^1 position failed to produce significant yields of the product. The synthesis of β-carbolines bearing an *o*-chlorophenyl, *o*-iodophenyl and *o*-cyanophenyl were attempted, but all three

Table 1
Silver(I) carbonate-mediated oxidation studies.



Entry	Equiv. Ag_2CO_3	Solvent	Time	Isolated yield (%)
1	0.1	DMF	1 d	<5
2	1	DMF	16 h	35
3	1.5	DMF	16 h	35
4	2	DMF	16 h	70
5	4	DMF	3 h	40
6	2	DMSO	5 h	54
7	2	Dioxane	6 h	n.r.
8	2	EtOH	4 h	–[a]
9	2	H_2O	4 h	–[a]
10[b]	2	Toluene	1 d	56

[a] Complex mixture of by-products observed by TLC.
[b] Starting material run as a free base in the absence of Li_2CO_3.