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Room-Temperature Aromatization of Tetrahydro-β-carbolines by 2-Iodoxybenzoic Acid: Utility in a Total Synthesis of Eudistomin U

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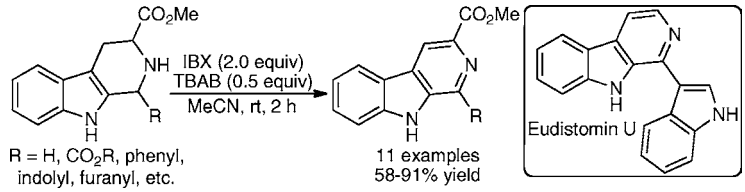
ABSTRACT



2-Iodoxybenzoic acid is a convenient reagent for the dehydrogenation of tetrahydro-β-carbolines to their aromatic forms under mild conditions. The utility of the method was demonstrated in a total synthesis of the marine indole alkaloid eudistomin U.

The aromatic β-carboline moiety is found in numerous natural products and synthetic congeners.[1] Compounds bearing this ring system display a diverse range of biological properties including antimalarial,[2] antitumor,[3] and anti-HIV activities.[4] Others show potent binding affinities toward benzodiazepine receptors in the central nervous system, thereby acting as diazepam antagonists.[5] In light of these pharmacological properties, mild synthetic methods for the construction of the β-carboline unit are desirable. One strategy for its preparation centers on the formal dehydrogenation of a suitable tetrahydro-β-carboline precursor. Transformations of this type have been previously conducted by heating the substrate with palladium on carbon[6] or sulfur[7] in refluxing cumene or xylenes over extended periods of time. Other oxidizing agents such SeO_2[8] and MnO_2[9] also require

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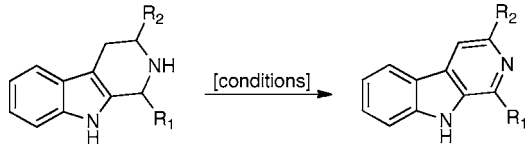
high temperatures and must often be used in excess. Organic-based reagents capable of effecting the dehydrogenation are limited to quinone-derived reagents such as chloranil[10] and DDQ,[11] and yields are often unsatisfactory. Trichloroisocyanuric acid (TCCA) has recently been identified as an additional oxidant.[12]

We were prompted to seek a mild set of conditions for the aromatization of tetrahydro-β-carbolines during our studies in alkaloid synthesis. Aiming to improve upon existing methodologies, we desired a process that would employ an inexpensive oxidant and proceed smoothly at ambient temperature. In this Letter, we describe a new method to achieve this transformation and demonstrate its utility in a total synthesis of the marine indole alkaloid eudistomin U.

Drawn to examples by Nicolaou and co-workers of iodine(V)-mediated syntheses of pyridines from *N*-heterocyclic precursors,[13] our attention turned to hypervalent iodine reagents such as the Dess−Martin periodinane and 2-iodoxybenzoic acid (IBX).[14] A survey of conditions revealed that each could effect the dehydrogenation, though a large excess of the former reagent was required to achieve comparable yields (Table 1, entries 1 and 2). Placement of

Table 1. Optimization Studies on the IBX-Mediated Aromatization of Tetrahydro-β-carbolines



entry	R_1/R_2	reaction conditions[a]	yield (%)[b]
1	Ph/H	DMP (5.5 equiv), CH_2Cl_2, rt, 13 h	70
2	Ph/H	IBX (2.5 equiv), DMSO, rt, 24 h	60
3	Ph/H	IBX (2.5 equiv), DMSO, 45 °C, 9 h	50
4	Ph/CO_2Me	IBX (2.0 equiv), DMSO, rt, 2.5 h	55
5	Ph/CO_2Me	IBX (2.0 equiv), TBAB (0.5 equiv), MeCN, rt, 2 h	77
6	H/CO_2Me	IBX (2.0 equiv), TBAB (0.5 equiv), MeCN, rt, 2 h	89
7	Ph/H	IBX (2.0 equiv), TBAB (0.5 equiv), MeCN, rt, 2 h	53[c]
8	H/H	IBX (2.0 equiv), TBAB (0.5 equiv), MeCN, rt, 2 h	<5[d]

[a] DMP = Dess−Martin periodinane, IBX = 2-iodoxybenzoic acid, TBAB = tetrabutylammonium bromide. [b] Yield determined by ^{1}H NMR analysis of crude reaction mixture. [c] Product accompanied by 47% of 3,4-dihydro-β-carboline intermediate. [d] Product accompanied by 30% of 3,4-dihydro-β-carboline.

an ester group at C(3) led to shorter reaction times (cf. Table 1, entries 3 and 4). In each case, however, amounts (~30%) of partially oxidized 3,4-dihydro-β-carboline intermediates were observed by ^{1}H HMR analysis of the crude reaction mixtures. Gratifyingly, addition of tetrabutylammonium bromide (TBAB)[15] with acetonitrile as the solvent led to enhanced conversions (Table 1, entries 5 and 6). Under these conditions, the desired products could be obtained in good yields within 2 h. Overall, the presence of the ester function at C(3) was important for good conversions; substrates without this group either did not oxidize completely (entry 7) or were mostly inert (entry 8) toward the reaction conditions.

Following the optimized procedure, the generality of the method was explored. A number of tetrahydro-β-carbolines, obtained by Pictet−Spengler condensation of tryptophan methyl ester with the appropriate aldehyde, were examined (Table 2). Yields were generally good and appeared to be dependent on the electronic characteristics of the substituent at C(1); substrates bearing electron-donating groups (Table 2, entries 2 and 3) afforded higher yields than those with electron-withdrawing groups (Table 2, entries 4 and 5). Overall, the conditions proved to be tolerant of aromatic functional groups and did not require protection of the indole nitrogen. We note that these mild conditions offer some advantages over those previously described for the dehydrogenation of a few of these substrates, particularly in regard to reaction time and temperatures. For example, aromatization of **1b** to β-carboline **2b** (Table 2, entry 2) was previously reported to occur in 73% yield after exposure to sulfur in refluxing xylenes for 48 h,[16] while a 77% yield was obtained using selenium dioxide in refluxing dioxane.[17] Similarly, β-carboline **2a** (Table 2, entry 1) has been previously obtained from **1a** in 75% yield upon treatment with sulfur in xylenes for 6 h[17] and in 80% yield employing Pd/C in xylenes after 43 h.[7a]

We next turned our attention to substrates bearing aliphatic or heteroaromatic substituents at C(1), as these systems

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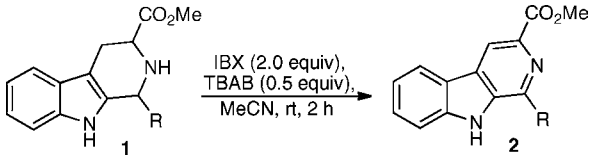
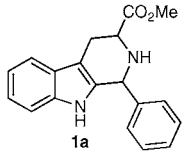
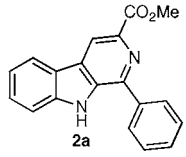
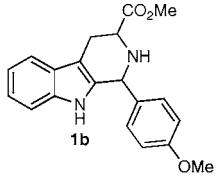
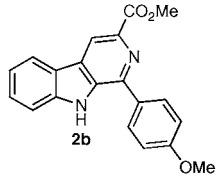
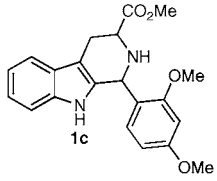
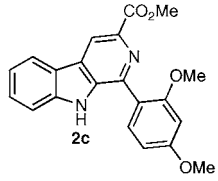
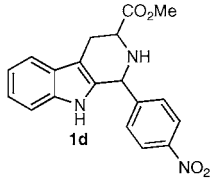
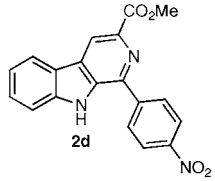
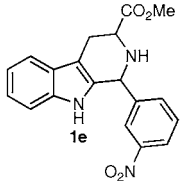
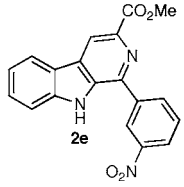
Table 2. IBX-Mediated Oxidation of Tetrahydro-β-carbolines[a]

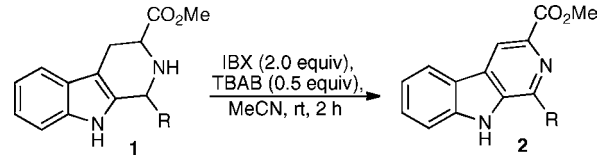


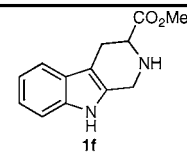
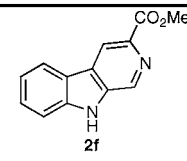
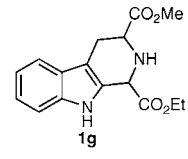
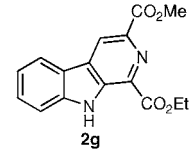
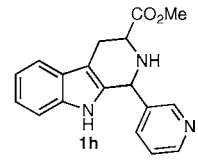
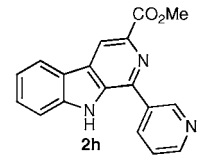
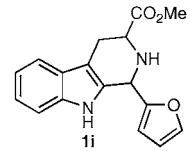
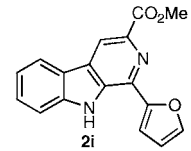
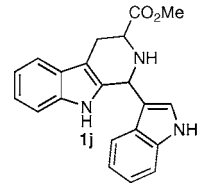
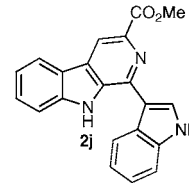
entry	substrate	product	yield (%)[b]
1			77%
2			86%
3			82%
4			58%
5			61%

[a] Reaction conditions: substrate (0.5 mmol), IBX (1.0 mmol), TBAB (0.25 mmol), MeCN (5 mL), rt, 2 h. [b] Isolated, purified yields after flash column chromatography.

would serve to further extend the scope of the methodology and allow access to a variety of interesting β-carboline scaffolds. Oxidation of **1f** proceeded in good yield, as did **1g** having two ester moieties (Table 3, entries 1 and 2). Oxidation of **1h**, a known ligand for the benzodiazepine receptor bearing a 3-pyridinyl moiety,[7a] provided β-carboline **2h** in 91% yield (Table 3, entry 3) and represents an improvement over the 77% yield reportedly obtained using selenium dioxide (9.4 equiv) in refluxing acetic acid.[8b] Aromatization of **1i**, a structural analogue of the anti-HIV agent flazin,[4a,18] was equally facile (Table 3, entry 4). When

Table 3. Mild Aromatization of Tetrahydro-β-carboline Systems[a]



entry	substrate	product	yield (%)[b]
1			89%
2			80%
3			91%
4			80%
5			71%

[a] Reaction conditions: substrate (0.5 mmol), IBX (1.0 mmol), TBAB (0.25 mmol), MeCN (5 mL), rt, 2 h. [b] Isolated, purified yields after flash column chromatography.

bis-indole **1j** was subjected to the reaction conditions, β-carboline **2j** was obtained in 71% yield (Table 3, entry 5).

The facility by which bis-indole **1j** underwent dehydrogenation, together with the structural similarity of β-carboline **2j** to the naturally occurring indole alkaloid eudistomin U, prompted us to undertake a total synthesis of the natural product. Isolated from the marine ascidian *Lissoclinum fragile*, eudistomin U was found to display DNA-binding activity as well as strong antimicrobial properties.[19] Application of the IBX-mediated oxidation would provide a direct entry to its unique framework.[20] Pictet−Spengler condensation of *N*-acetyl indole-3-carboxaldehyde[21] (**3**, Scheme 1) and tryptophan methyl ester

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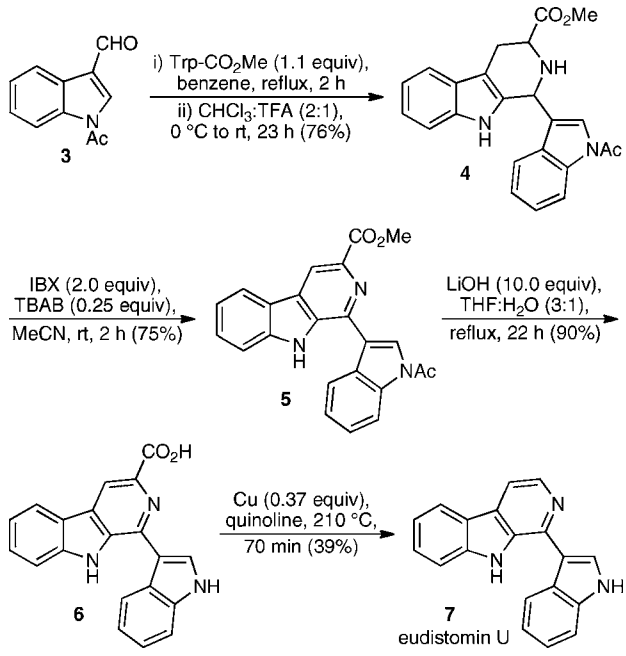
Scheme 1. Application of the IBX-Mediated Aromatization in the Total Synthesis of Eudistomin U



provided tetrahydro-β-carboline **4** as diastereomers (76% yield).[22] Dehydrogenation of **4** under the optimized conditions proceeded smoothly, affording β-carboline **5** in 75% yield. Saponification of the ester moiety was accompanied by loss of the *N*-acetyl group to provide carboxylic acid **6**. Cu/quinoline-mediated decarboxylation of **6** furnished eudistomin U (**7**) whose spectroscopic data was identical to that of natural material.[19]

In summary, we have developed a convenient protocol for the synthesis of aromatic β-carbolines via IBX-mediated dehydrogenation of tetrahydro-β-carboline precursors. The method provides a milder alternative to traditional metal-based reagents and should prove useful in instances when forcing conditions must be avoided. The procedure is especially suited for projected SAR studies and should enable ready access to a diverse array of β-carboline scaffolds for biological evaluation. Finally, the utility of the process was highlighted in a four-step total synthesis of the indole alkaloid eudistomin U. Progress is underway in applying the methodology toward the total synthesis of additional biologically active alkaloid natural products.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For previous syntheses, see: (a) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G.; Adams, L.; Alo, B. *Tetrahedron Lett.* **1995**, *36*, 7085–7088. (b) Molina, P.; Fresneda, P. M.; García-Zafra, S. *Tetrahedron Lett.* **1995**, *36*, 3581–3582.

(21) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915–13928.

(22) The formyl group of indole-3-carboxaldehyde is known to be weakly electrophilic as the compound tends to behave as a vinylogous amide. Use of its *N*-acetyl congener suppressed this behavior and facilitated the Pictet−Spengler reaction.