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Studies of Mild Dehydrogenations in Heterocyclic Systems

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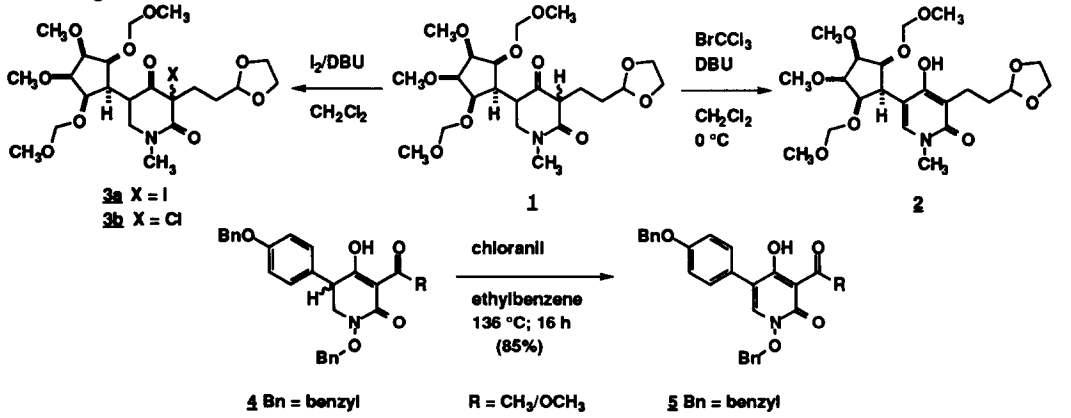
Abstract: *The use of bromotrichloromethane-DBU is described for the selective oxidative conversion of several dihydro-heterocyclic systems to the corresponding heteroaromatics. Oxidative dehydrogenations to afford 4-hydroxy-2-pyridinones are examined under a variety of conditions. Studies of phenylselenenylation and peracid oxidation provide the novel spirocyclic oxirane 10.* Copyright © 1996 Elsevier Science Ltd

The production of heteroaromatics via the dehydrogenation of their dihydro derivatives is of fundamental importance. However, the relative ease of these oxidative transformations varies greatly among the most common heterocyclic systems. The high level of current interest in the synthesis of marine natural products has especially drawn attention to the difficulties for conversion of oxazolines and thiazolines to their parent heterocycles.[1] Promising new methods have been the focus of recent literature.[2] In the course of studies for natural product synthesis,[3] our requirements for dehydrogenation have demanded considerable selectivity as a result of conflicting functional and protecting group interactions. Herein, we report the use of bromotrichloromethane in combination with 1,5-diazabicyclo[5.4.0]undecane (DBU) at 0 °C in methylene chloride as a reagent of choice for mild dehydrogenations.

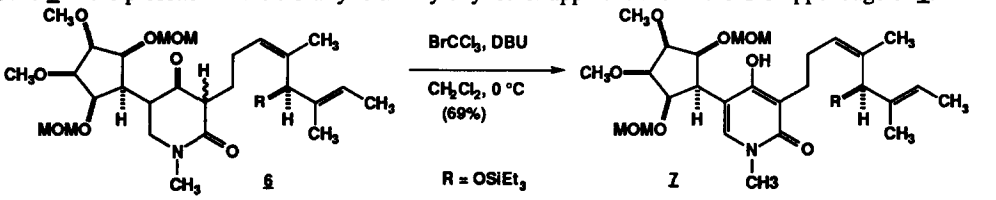
Our studies toward synthesis of funiculosin have examined oxidative processes for the production of the 4-hydroxy-2-pyridinone 2 from its 5,6-dihydro precursor 1. Previous syntheses of tenellin and illicolin H have utilized an efficient chloranil oxidation of 4 to afford pyridinone 5 bearing 3-acyl and 5-aryl substitution.[4] This technique (chloranil or DDQ) produces a plethora of side reactions in the case of our more demanding funiculosin intermediates.



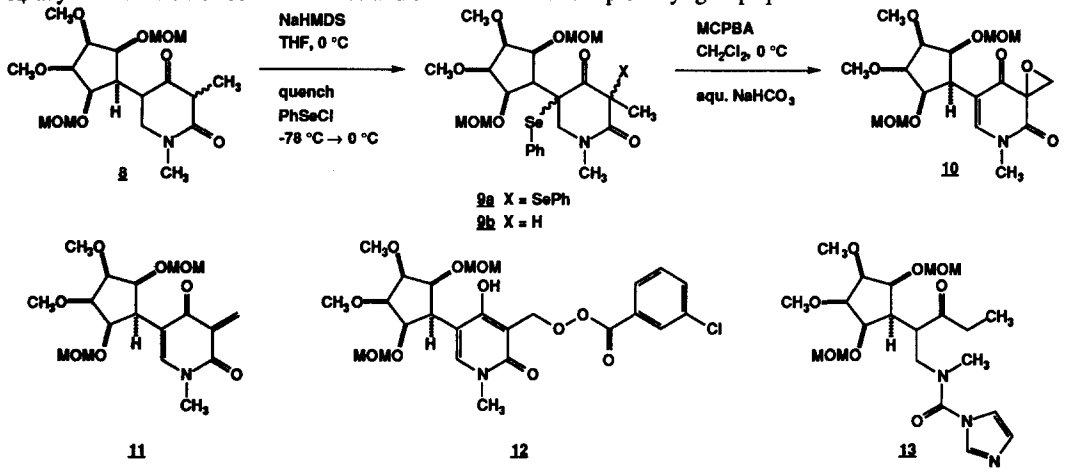
In contrast, the treatment of 1 with $BrCCl_3$ and DBU at 0 °C effects the smooth conversion to the desired 4-hydroxy-2-pyridinone 2 in 78% yield. The use of iodine with DBU (CH_2Cl_2 at 0 °C) gives 2 in modest 50% yields. However, the process of C-iodination to 3a (2:1 ratio of isomers) is a troublesome side reaction, particularly with increasing reaction scale. In fact, mild chlorination with trifluoromethanesulfonyl chloride[5a]

(THF; at -78 °C → 0 °C) consistently produces high yields of the C_3-chloro compounds (3b) within our series of pyridone derivatives.[5b] These halogenated 1,3-dicarbonyl derivatives function as halogenation transfer reagents, whereas no conditions for base-induced HX eliminations have been found. In addition, a variety of classic oxidation reagents fail, including procedures with NBS, activated MnO_2, and Pd metal with air.

Hori and coworkers first reported the use of $BrCCl_3$ and DBU for oxidations of α-ketols to α-diketones, thiols to disulfides, and in particular, the transformation of 3,4-dihydrocoumarin to coumarin.[6] Our efforts toward funiculosin have been advanced by demonstration of the mild and selective oxidation affording pyridone 7 in the presence of the *bis*-allylic triethylsilyl ether apparent within the C-3 appendage of 6.



These studies have been expanded to investigate the synthesis of 2,4-disubstituted oxazoles and thiazoles. Results utilizing the $BrCCl_3$/DBU reagent are summarized in the Table.[7] The survey indicates that common protecting groups, such as allyl and benzyl esters, and sensitive acetals (entries 4,5, and 6) are stable under the reaction conditions. No evidence for initial bromination is observed. However, replacement of the C_4-acyl substitution of our oxazolines and thiazolines with simple alkyl groups provides unreactive materials.

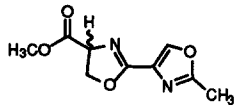
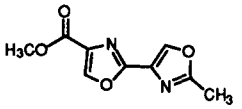
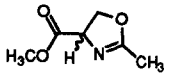
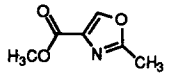
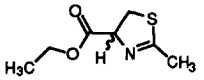
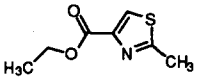
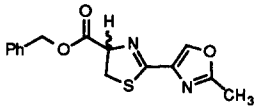
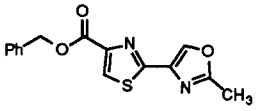
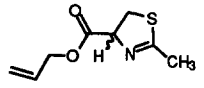
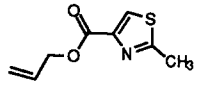
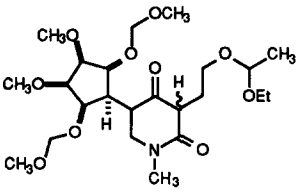
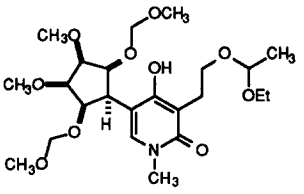
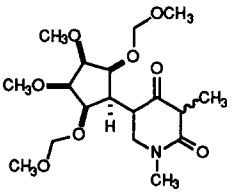
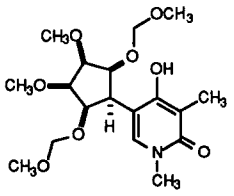


Our direct comparisons with nickel peroxide,[8] NBS/hυ,[9] or phenylselenynylation/elimination[10] techniques have shown that the $BrCCl_3$/DBU reagent offers reproducibly cleaner, higher yielding reactions. A recent report has documented a novel oxidative rearrangement in a series of 2,4-disubstituted oxazolines upon treatment with SeO_2.[11] In our oxidation studies of pyridine-2,4-dione 8, the generation of the dianion leads to *bis*-phenylselenenylation affording diastereomers 9a upon quenching with PhSeCl (3.5 equiv.) at -78 °C. Attempts to selectively produce the C-5 selenides 9b have not been successful. Oxidative eliminations with *meta*-chloroperbenzoic acid, followed by quenching with aqueous $NaHCO_3$, affords the novel spirocyclic oxirane 10 (70-80% yields from 8). The transformation proceeds via facile conjugate addition of peracid to the highly reactive heterocyclic quinone methide 11. Isolation of the unstable perester 12 has allowed us to

separately confirm the base-induced fragmentation to 10. Subsequently, this oxidation process has been combined with the ring closure of the carboxamidimidazolide 13 (NaHDMS, 4 equivs at 0 °C) to directly provide epoxide 10 in 50% overall yield.

Further studies of the scope of $BrCCl_3$/DBU oxidations, and our efforts toward funiculosin synthesis are underway.

Table: Heterocycle Oxidations with $BrCCl_3$/DBU[a]

Entry	Starting Material	Product	Yield[b]
1			87%
2			75%
3			95%
4			92%
5			95%
6			70%
7			68%

[a] Reactions accomplished at 0 °C in CH_2Cl_2 (0.2M) using 1.05 equiv. $BrCCl_3$ and 1.05-2 equivs. DBU

[b] Isolated yields are reported for purified products, which are fully characterized by proton and carbon NMR, infrared, and high-resolution mass spectrometry.

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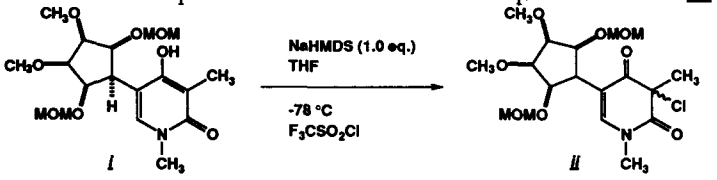
5. a) Hakimelahi, G.H.; Just, G.; *Tetrahedron Lett.* **1979**, 3643. b) The 4-hydroxy-2-pyridinones, such as *i*, also react with trifluoromethanesulfonyl chloride to quantitatively yield *ii*. However, these chlorides did not eliminate to provide access to the intermediate quinone methides 11.



i *ii*

c) Treatment of ester enolates of oxazolines (entries 1 and 2; generated with LiHMDS; THF; -78 °C) with trifluoromethanesulfonyl chloride (3 equivs at -78 °C → 0 °C; 1 hr) directly produces the corresponding oxazoles (52%) in comparable yields to phenylselenenylation/elimination.
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7. The following representative procedure is described: A solution of oxazoline (Table: entry 1) (4.42 g, 21.0 mmol) in CH_2Cl_2 (210 mL) was cooled to 0 °C, and distilled DBU (3.52 g, 23.1 mmol, 3.45 mL) was added. Bromotrichloromethane (4.58 g, 23.1 mmol, 2.3 mL) was then introduced dropwise via syringe over 10 min. After stirring at 0 °C for 6 h, the reaction was complete. Upon washing with saturated aqueous NH_4Cl (2 x 100 mL), the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel; EtOAc) providing the *bis*-oxazole (3.8 g, 87%) as a white solid (m.p. 154-155 °C).
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