



Acynitrilium ion-arene spiroannulations : studies toward the synthesis of the Lycopodium alkaloid serratine
by Gregory Randall Luedtke

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:

The use of C-acynitrilium ions as cyclization initiators in azacycle synthesis has been expanded by the development of spiroannulations terminated by phenolic silyl ethers.

This method was utilized in the synthesis of the A and D rings contained within the tetracyclic Lycopodium alkaloid serratine. Utilizing the functionality contained within this spirocycle, the B ring of serratine was also secured in a Michael addition ring annulation.

Functionalization of the imine contained within this three-ring component, which was hoped to be utilized in the closure of the final ring within the serratine skeleton, was not successful.

ACYLNITRILIUM ION - ARENE SPIROANNULATIONS: STUDIES TOWARD
THE SYNTHESIS OF THE *LYCOPODIUM* ALKALOID
SERRATINE

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of the requirements for the degree

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APPROVAL

of a thesis submitted by

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This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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Dedicated to the memory of my father, Randall Harvey Luedtke, and my grandfathers, Harvey August Luedtke and Marvin Draeger Hayes. They were all with me at the beginning of my college schooling, I only wish they could have been here with me at the end.

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ABSTRACT

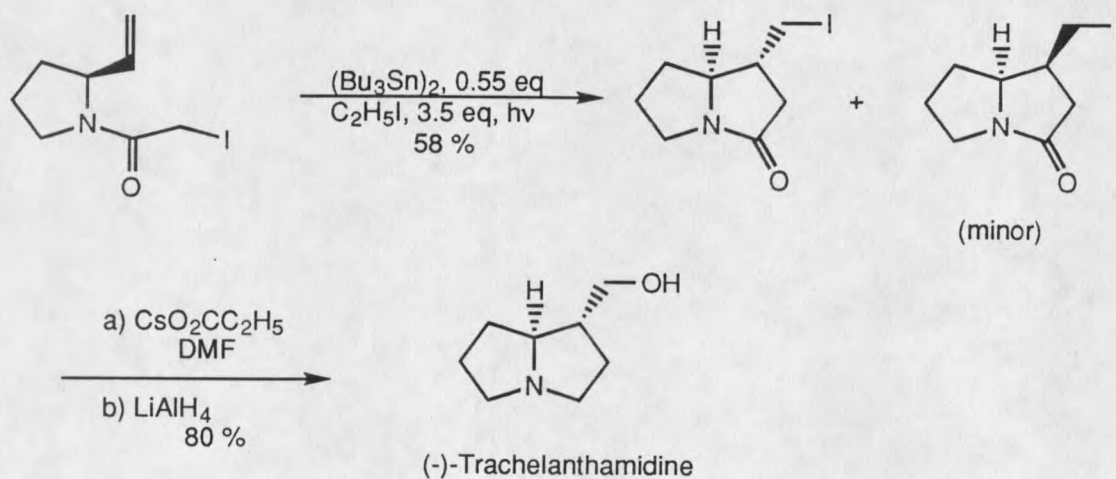
The use of *C*-acylnitrilium ions as cyclization initiators in azacycle synthesis has been expanded by the development of spiroannulations terminated by phenolic silyl ethers.

This method was utilized in the synthesis of the A and D rings contained within the tetracyclic *Lycopodium* alkaloid serratine. Utilizing the functionality contained within this spirocycle, the B ring of serratine was also secured in a Michael addition ring annulation.

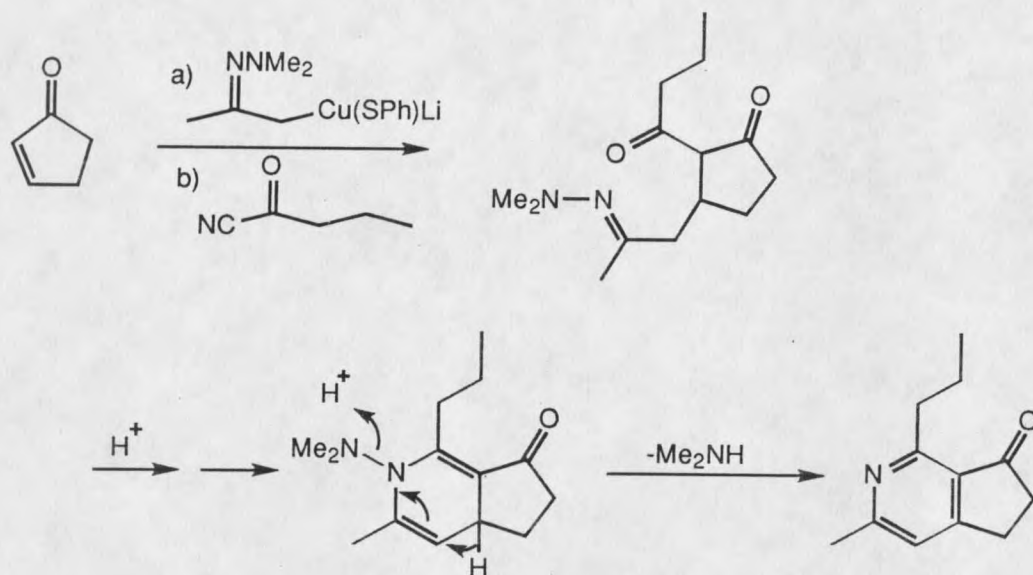
Functionalization of the imine contained within this three-ring component, which was hoped to be utilized in the closure of the final ring within the serratine skeleton, was not successful.

INTRODUCTION

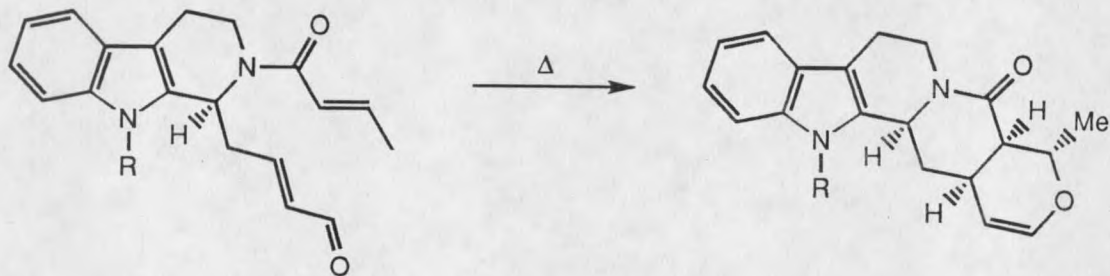
The interest in alkaloids as major synthetic targets has increased in recent years due to a heightened desire to study their biological properties. However, relatively few general methods have been developed for the assembly of nitrogen containing heterocycles. Representative methodologies include: free radical cyclizations, as illustrated by the key step leading to the synthesis of (-)-trachelanthamidine by Jolly and Livinghouse¹ (Eq. 1); anion initiated cyclizations, as utilized by Kelly and Liu² in their development of a new pyridine synthesis (Scheme 1); and cycloaddition reactions, as exemplified by Martin in the synthesis of 2-oxindole alkaloids (Eq. 2).³



Eq. 1



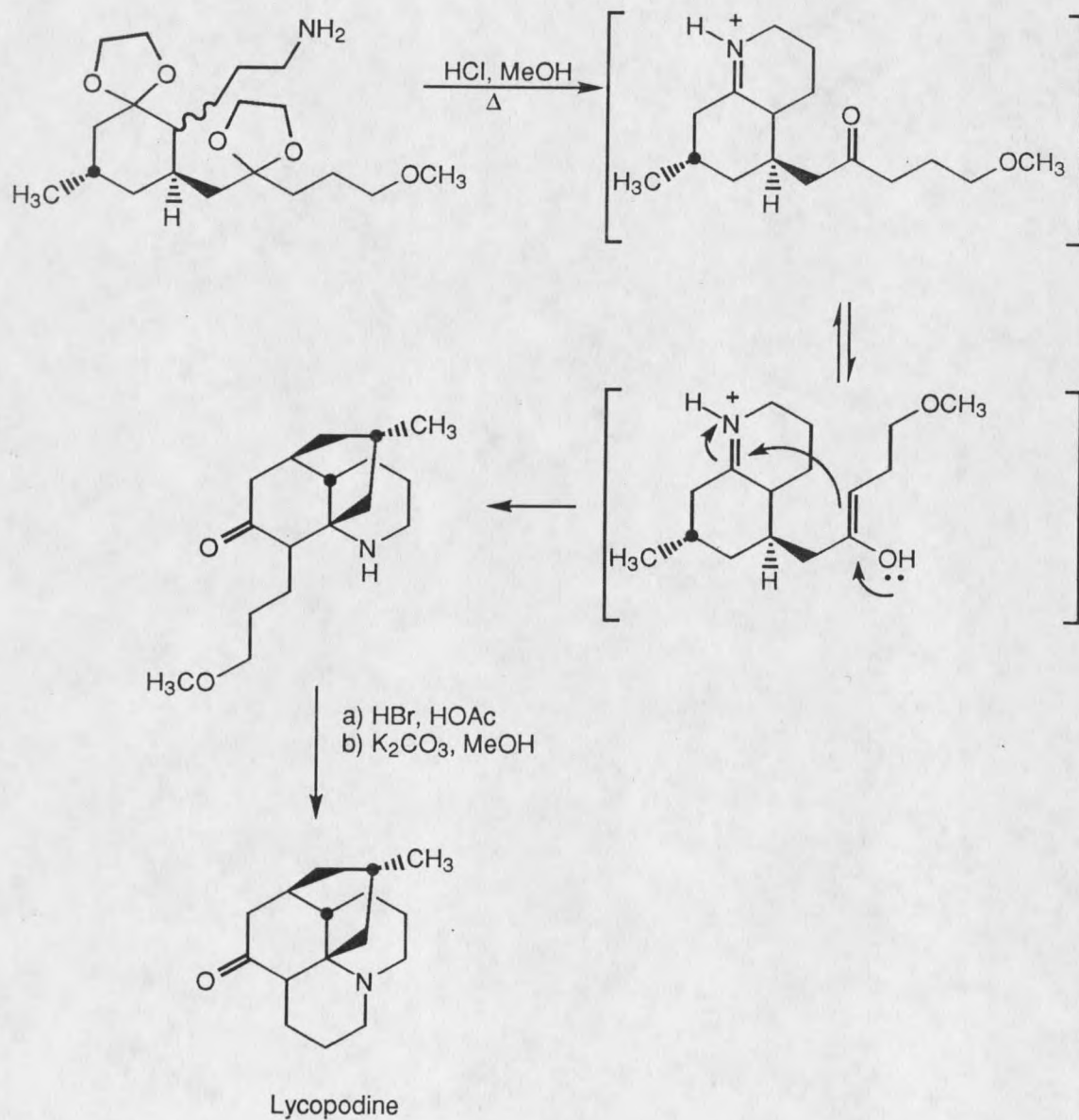
Scheme 1



Eq. 2

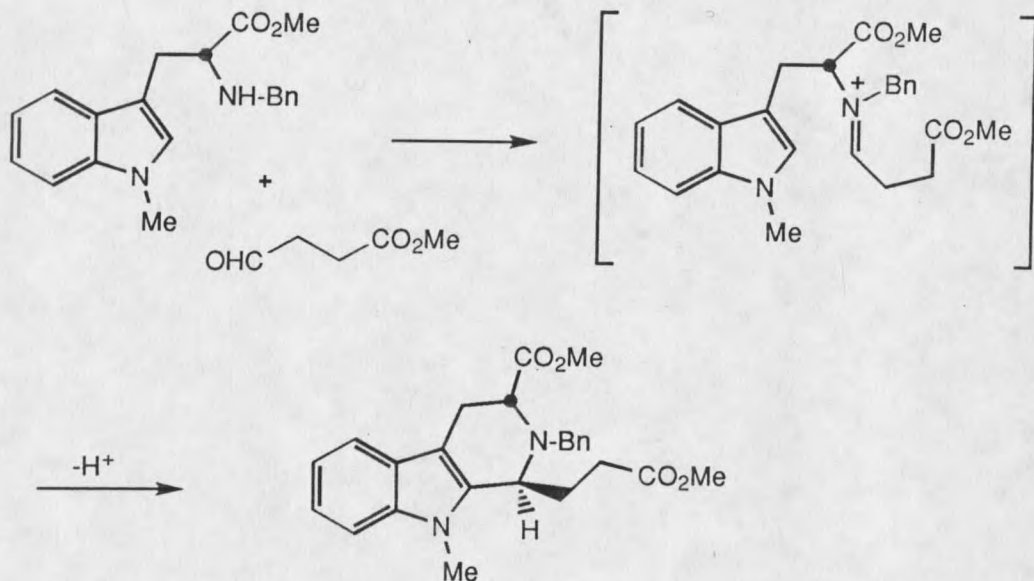
Perhaps the most widely used methods for the synthesis of alkaloids utilize nitrogen stabilized cations as reaction initiators. Some of the earliest methods in this class of reaction involved the use of iminium ions as reactive intermediates. These methods include the Mannich reaction, used by

Heathcock⁴ in the synthesis of Lycopodine (Scheme 2), and the Pictet-Spengler reaction, of which the stereochemical aspects were recently examined by Cook⁵ (Eq. 3).



Scheme 2

4

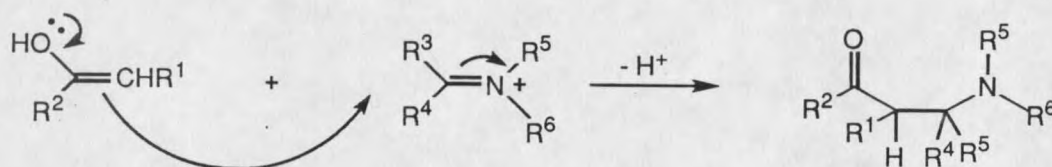


Eq. 3

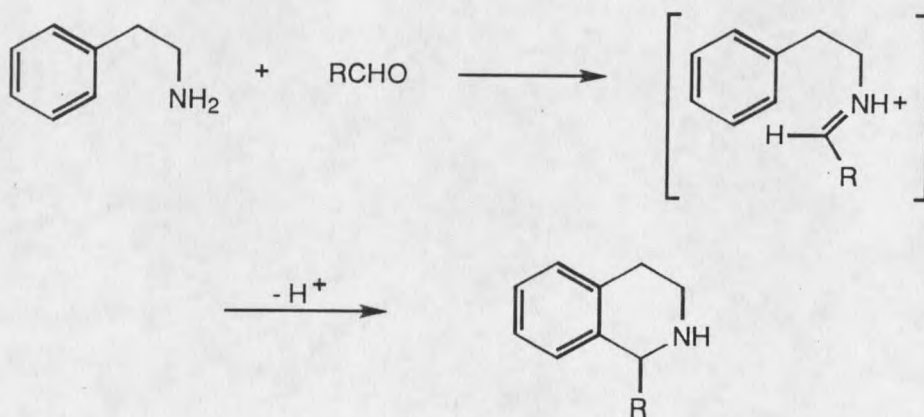
Many developments have occurred in recent years that have extended the use of nitrogen stabilized cations to the synthesis of natural products. However, even with the variety of procedures available, further methods which will facilitate the synthesis of complex heterocycles are needed. The work described herein is an effort toward that end.

BACKGROUND

Nitrogen stabilized cations are very frequently used in the synthesis of azacycles. One commonly used method involves the use of an iminium ion as a reactive intermediate. The most well known reactions of this type include the Mannich reaction, in which an enolizable carbonyl moiety serves as the reaction terminator, and the Pictet-Spengler reaction, in which an aromatic ring acts as the nucleophilic component (Scheme 3 and Eq. 4)



Scheme 3



Eq. 4

