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Accessing the Cyclopenta[c]pyridine Structure: Development of an Enamine/Enal Cycloaddition Pyridine Formation Methodology

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Accessing the Cyclopenta[c]pyridine Structure: Development of an Enamine/Enal Cycloaddition Pyridine Formation Methodology

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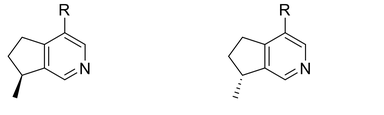
Abstract

The synthesis of 6,7-dihydro-5H-cyclopenta[c]pyridine was completed in six steps culminating in a tandem enamine-enal cycloaddition/pyridine formation. While the tandem reaction gave rise to target pyridine with consistently low yield (5%), an analogous sequential method allowed for the unadorned cyclopenta[c]pyridine structure to be prepared with improved albeit modest yield (31%). To examine if higher yields would be obtained for cyclopenta[c]pyridine structures with lower volatility, (*E*)-2,6-dimethyl-2-octenedial was prepared and converted to actinidine using the tandem protocol with 60% yield. Using (*E*)-2,6-dimethyl-2-octenedial as the model substrate, the reaction conditions for this transformation were optimized. It was found that the optimal reaction temperature is 50 °C and that the presence of an *p*-toluenesulfonic acid (*p*-TsOH) substantially improved the rate of the reaction without sacrificing yield or product purity.

Background

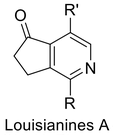
- Semiochemicals are a class a small organic molecules that mediate interactions between animal species. The Hofferberth Lab has endeavored to prepare macroscopic quantities of terpene-derived semiochemicals to study the nature of a unique ant-butterfly mutualism in nature.[1]
- Over the course of this program, we have discovered a novel synthesis of actinidine that allows for macroscopic quantities of the insect semiochemical to be prepared in enantiomerically pure form in two synthetic steps from commercially available citronellal. The key step in this reaction is a tandem enamine/enal cycloaddition-pyridine formation that results in the bicyclic, cyclopenta[c]pyridine framework.
- Many natural products contain the cyclopenta[c]pyridine framework, but few methodologies have detailed the synthesis of such molecules.[2] Improved access to the cyclopenta[c]pyridine core will allow for the preparation both novel compounds and chemicals with known biological activity (See Below).



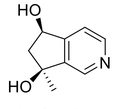
S-(-)

R-(+)

S-(-)	R	R-(+)
(+)-Deoxyrhexifoline	CO_2Me	
(+)-Boschniakinic acid	CO_2H	(-)-Plantagonine
(+)-Boshniakine	CHO	(-)-Indicaine
(+)-Actinidine	CH_3	(-)-Actinidine



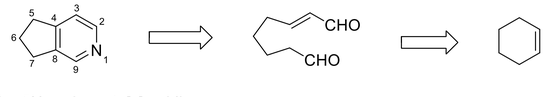
Louisianines A - D
(R = OH, H; R' = allyl, isoallyl)



(-)-Oxerine

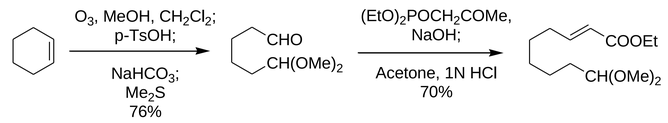
- The purpose of this study is to develop a methodology for the key cycloaddition-pyridine formation and to evaluate the limitations of the reaction beginning with a simplified model substrate, (*E*)-2-octenedial.[3]

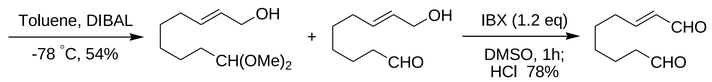
Target and Retrosynthetic Analysis



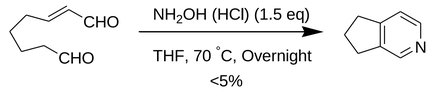
6,7-dihydro-5H-cyclopenta[c]pyridine

Preparation of Model Substrate

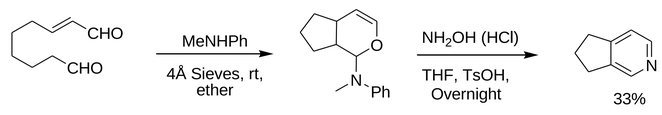




Enamine/Enal Cycloaddition-Pyridine Formation

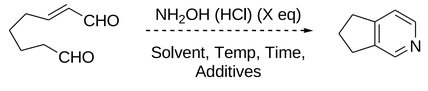


•Alternate Sequential Method:



Optimization of Reaction Conditions

• Model reaction for optimization:



•Equivalents of reactants and additives:

Reactant	Equivalents	Result
NH_2OH	1.3-3	No Change
TsOH	0.2-1.2	Increased Rate
H_2O	0.1	Increased Rate
$NaHCO_3$	1	No Effect

•Solvent:

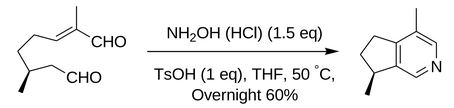
Solvent	Result*
Benzene	No Reaction
Et_2O	No Reaction
EtOH	No Reaction
DMF	Trace
DMSO	Present**
DCM	No Reaction
THF	Present

•Temperature (Rxn in DMSO):

Temperature (˚C)	Time to Completion
RT	>24h
30	>24h
40	Overnight
50	Hours
60	Hours
70	Decomposition <1h

*Pyridine formation as determined by TLC
**Difficult isolation of pyridine constituent

Preparation of Actinidine Using Optimized Conditions

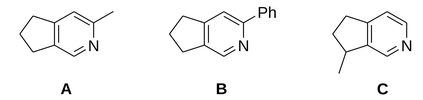


• Due to difficulty in isolating 6,7-dihydro-5H-cyclopenta[c]pyridine, the previously optimized reaction parameters were further optimized using (*E*)-2,6-dimethyl-2-octenedial as the model substrate.

Current and Future Work

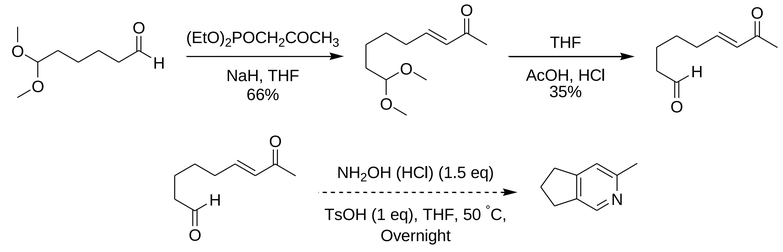
•The next phase of the project will explore how the presence and location of substituents on the substrate affects the reaction.

• Targets:



A B C

• Synthesis of substrate for preparation of A:



Conclusions

- The tandem enamine/enal cycloaddition-pyridine formation represents a novel route to the cyclopenta[c]pyridine framework.
- The unadorned cyclopenta[c]pyridine structure can be prepared under numerous reaction conditions. The consistently low yield is believed to be due to the volatility of the target and consequent difficulty in its isolation.
- Future substrates will be evaluated using the optimized reaction conditions to define the scope and limitations of this novel preparation of the cyclopenta[c]pyridine framework.

Acknowledgements

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References

(1) Fraser, A.M.; T. Tregenza, N.; Wendell, E.; N.E. Pierce. J. Evol. Biol. **2002,** 15, 861

(2) Robert, N.; Hoarau, C.; Marsais, F. *Tetrahedron*, **2007**, 63, 3702

(3) Schreiber, S.L.; Meyers, H.V.; Wiberg, K.B. *J. Am. Chem. Soc.* **1986**, 108, 8274