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

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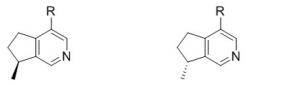
Abstract

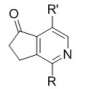
The scope and limitations of a novel methodology to prepare molecules with the cyclopenta[c]pyridine carbon framework was examined. Six substrates were prepared with differing substitution at specific positions along the eight-carbon scaffold and their ability to form cyclopenta[c]pyridine derivatives was examined. Substrates were evaluated using two novel reactions conditions, a two-step cycloaddition-pyridine formation to form the cyclopenta[c]pyridine structure, and a one-step tandem method. Early results suggest substrate substitution patterns dramatically influence the operation of the reaction manifold.

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 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 there are few general methodologies to prepare such molecules.[2,3,4] 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	*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

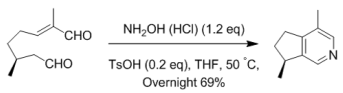
- The purpose of this study is to develop a methodology for the cycloaddition-pyridine formation and to evaluate the scope and limitations of this novel reaction using a variety of suitably substituted substrates.

Retrosynthetic Analysis

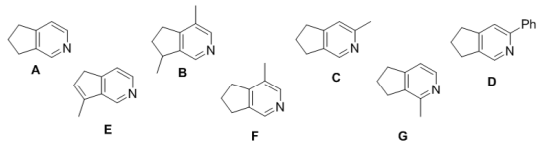
•We aim to prepare compounds with substitution at every position and to examine their performance in the tandem enamine/enal cycloaddition-pyridine formation

Optimized Reaction Conditions

• Model Reaction:

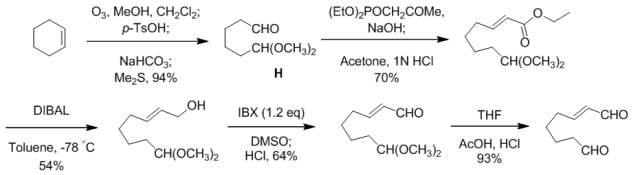


Synthetic Targets

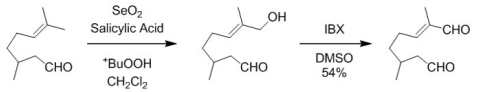


Preparation of Substrates

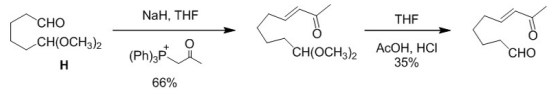
• Substrate for Target **A**:



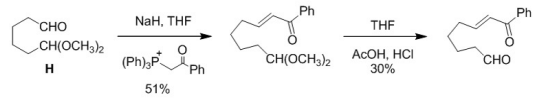
• Substrate for Target **B**:



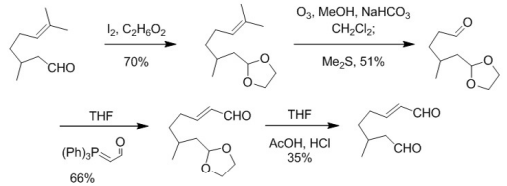
• Substrate for Target **C**:



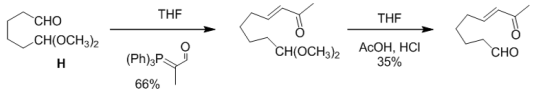
• Substrate for Target **D**:



• Substrate for Target **E**:

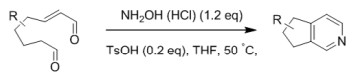


• Substrate for Target **F**:



Performance in the Enamine/Enal Cycloaddition-Pyridine Formation

• Tandem Method:



• Sequential Method:

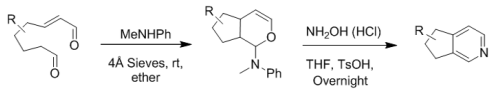
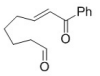


Table 1. Conversion of dicarbonyl substrates into cyclopenta[c]pyridine derivatives

Substrate	Time (h)	Product	Tandem Yield	Sequential Yie
	16		5%	33%
	16		69%	49%
	16		31%	26%
	16		43%	ND
	16		49%	ND
	48		59%	ND

Conclusions

- The tandem enamine/enal cycloaddition-pyridine formation provides a novel route to the cyclopenta[c]pyridine framework.
- The substitution pattern on the dicarbonyl substrate dramatically influences the operation of the reaction manifold. Future substrates will be evaluated with the aim of defining the scope and limitations of this novel reaction.
- The reaction mechanism will be examined using computational techniques to understand differences in substrate performance.

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
(4) Prelog V, Metzler O (1946) Helv Chim Acta 29: 1170