Synthesis of Piperidines Using the aza-Prins Cyclization of n-Aryl Vinylogous Sulfonamides

Dillon P. Cao

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Biography

Dillon P. Cao

Born and raised in Biloxi, MS

2020: B.S in Chemistry (biochemistry emphasis) *University of Southern Mississippi*; Hattiesburg, MS

Donahue Research Group

Research: Investigation of acid-catalyzed cyclizations of n-sulfonyliminium ions to synthesize piperidine derivatives

2020-Current: Finishing first year at *Louisiana State University's* PhD. Program specializing in organic synthesis

Rivas Research Group

Research: Implementing organic methodology and chemical biology to understand mode of action in biological systems with the goal of identifying novel therapeutic compounds.

Matthew Donahue, PhD.

Fatima Rivas, PhD.

Background

Methylphenidate

Trade Name: *Concerta*,
Ritalin

Stimulant medication used to
treat ADHD and narcolepsy

Acid-Promoted Prins Cyclizations of Enol Ethers to Form Tetrahydropyrans

David J. Hart and Chad E. Bennett, *Org. Lett.* 2003, 5 (9), 1499-1502

Acid-Promoted aza-Prins Cyclizations of Vinologous N-Sulfonyl Carbamates to Form Piperidines

Scope of Study

The N-Sulfonyliminium ion provides a powerful electrophile in which electrons can be accepted to encourage cyclization yielding a piperidine.

Hypothesis: The ambiphilic nature of N-Vinylgous sulfonamides will be sufficiently basic to be activated by organic acids to generate an N-sulfonyliminium ion which will then trigger the intramolecular cyclization. The resulting **C₄** carbocation can undergo stereoselective nucleophilic attack to yield the respective **piperidine** derivatives.

Retrosynthetic Analysis

SCAR
\$1.45/gram

SCAR = Sulfinamide Chiral
Auxiliary Reagent

Ts-Protected Amine
p-Toluenesulfonyl chloride
<\$1.00/gram

3-5
steps
----->

Model Substrate

Model Substrate

Michael Addition Base Screen

Base	Solvent	% Conversion	Base	Solvent	% Conversion
CH ₂ Cl ₂	0%	KOH	CH ₂ Cl ₂	0%
NaOD	D ₂ O	0%	KH ₂ PO ₄	D ₂ O	0%
CH ₂ Cl ₂	0%	Cs ₂ CO ₃	DCM	72%
K ₂ CO ₃	D ₂ O	0%		DCM	0%

Key NMR Intermediates

Isomerization to *E*-Isomer

aza-Prins Acid Screen (Current)

Cyclized Piperidine Derivative Library

formic acid (3.77)

methanesulfonic acid (-2.6)

trifluoroacetic acid (-0.26)

Bistriflamide (<-2.66)

aza-Prins-Ritter

aza-Prins-Ritter Derivative Library

GJR-7-001

96%

GJR-7-014

63%

GJR-7-016

60%

GJR-7-038

61%

Acknowledgements

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- **Donahue Research Group**

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