Synthesis of Four-Membered Ring Heterocycles by the Reaction of 1,3-Dipoles With Carbenes

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A proposal submitted to the Undergraduate Research Program at Shippensburg University

Introduction

The proposed project seeks to develop a synthetic methodology for the formation of a wide variety of four-membered ring heterocycles. Many important organic compounds, such as amoxicillin (Fig. 1) and other pharmaceuticals, contain four-membered rings but there is no known comprehensive method in which a chemist can make any four-membered ring. An efficient pathway for producing four-membered ring heterocycles would be an invaluable tool in the synthesis of a variety of interesting and potentially useful organic compounds.

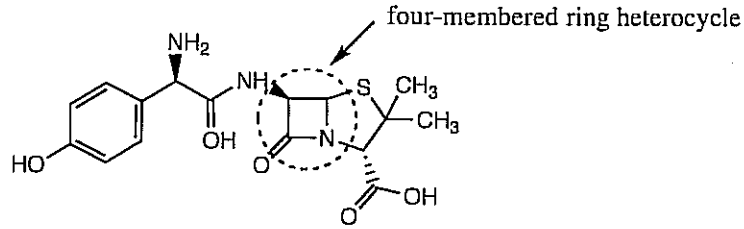
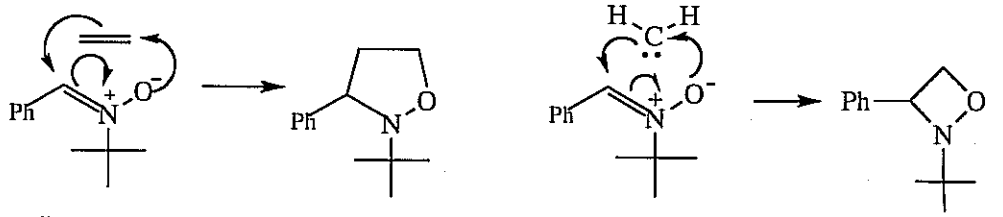


Figure 1. Amoxicillin

Cycloaddition reactions are commonly used to construct rings in organic synthesis. For example, alkenes can combine with 1,3-dipoles to form five-membered rings (Fig. 2)[1]. This project will study the feasibility of a new cycloaddition reaction using carbenes and 1,3-dipoles to form four-membered rings.



alkene + 1,3-dipole = 5-membered ring

carbene + 1,3-dipole = 4-membered ring ???

Figure 2. Cycloaddition Reactions

Proposed Research

The first step of this project will be to synthesize a 1,3-dipole to be used in the cycloaddition reactions. The nitrone shown in Figure 3 was chosen as a suitable 1,3-dipole because it is a stable solid and can be synthesized in one step from the amine using sodium tungstate and hydrogen peroxide[2]

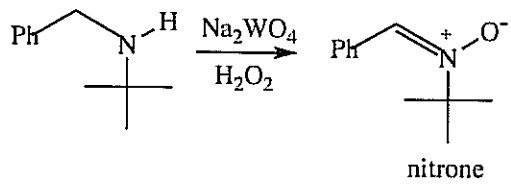


Figure 3: Synthesis of the 1,3-Dipole

Next carbenes of two different reactivities will be synthesized. First we will make a Fischer carbene which is an electrophilic carbene that possesses stabilizing pi-donor groups.[3] The Fischer carbene will be synthesized by using a coordinated metal (molybdenum or tungsten) and combined with a methyl-lithium and a methylating agent (Fig. 4). In contrast, Schrock carbenes are characterized as nucleophilic and carry hydrogen atoms or alkyl groups as substituents on the carbene ligand.[3] The Schrock carbene will be synthesized by combining the Tebbe reagent with pyridine in order to get a carbene intermediate as displayed in Figure 5.[4]

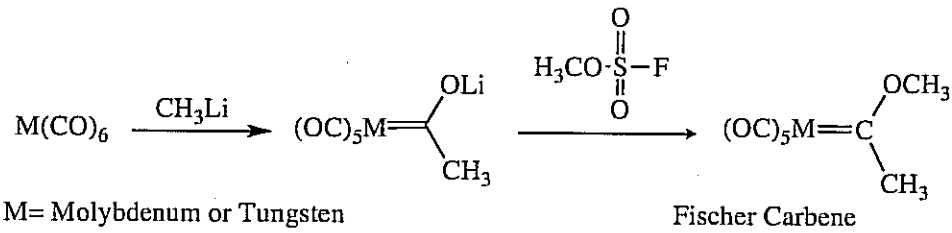


Figure 4: Synthesis of the Fischer Carbene

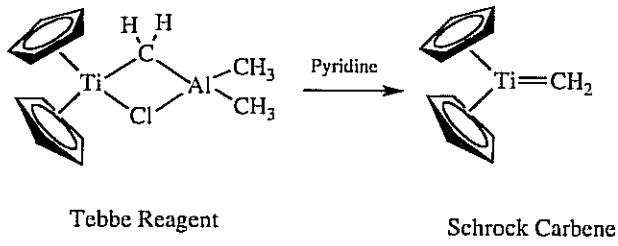


Figure 5: Synthesis of the Schrock Carbene

Finally, the 1,3-dipole and the carbenes will be combined to see if they will form four-membered rings (Fig. 6). The synthesis will be performed under varying temperatures, for varying lengths of time, and in different solvents, so that we will know which conditions are the best in regards to this synthesis. Once the product is formed it will be analyzed using NMR and mass spectroscopy in order to determine the connectivity and cyclic nature of the product. If enough time remains, other carbenes and 1,3-dipoles will be attempted.

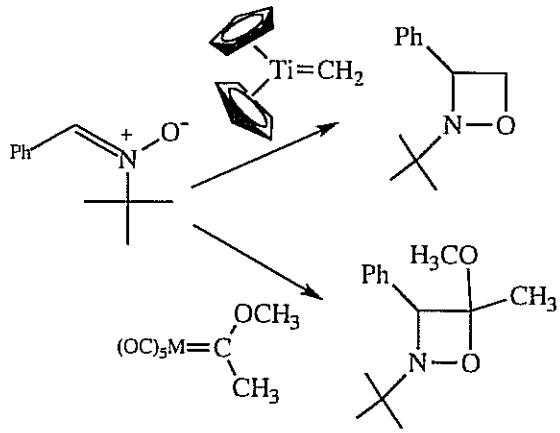


Figure 6: Proposed Synthesis of Two Four-Membered Heterocycles using the 1,3-Dipole and Schrock and Fischer Carbenes

Potential for Education and Role of Student and Faculty Mentor

The opportunity to do this research project and perform organic and inorganic synthesis is very important to me because I plan to study organic and inorganic synthesis in graduate school. The synthetic and instrumental training that Dr. Predecki will provide me with will not only be key to my success as a graduate student in the future, but also be key to success in NMR spectroscopy and synthesis during this research project. Through this project Dr. Predecki and I will work in the lab at least three times a week in order to progress and perform this project in an efficient manner. Additionally Dr. Predecki and I will present this research at the National Meeting of the American Chemical Society in New Orleans, LA in April 2013, which will give me an opportunity to practice my presentation skills at a large research conference attended by thousands of chemists.

References

(1) See March, J. in *Advanced Organic Chemistry,* 4th ed.; Wiley and Sons: New York, 1992.

(2) Murahashi, S-I; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.*, **1990**, *55*, 1736-4.4

(3) Occhipinti, G.; Jensen, V. R., *Organometallics*, **2011**, *30*, 3522-3529.

(4) Hughes, D. L. et. al. *Organometallics,* **1996**, *63*, 2689.

Detailed Budget

Chemicals and Supplies

Tebbe's Reagent 25 mL	$202.50
Methyl Lithium 1.6 molar 100 mL	$64.10
Methylating agent (F3OSO2CH3) 10g	$76.30
Sodium Tungstate 50g	$55.30
Pyridine 100 mL	$100.80
Poster Printing	$40.00
Subtotal for Supplies	$539.00

Student Travel Expenses for the ACS Meeting in New Orleans, LA (Spring 2013)

Airfare	$400.00
Airport Shuttle	$40.00
Lodging (sharing with another student)	$405.00 (3 nights)
Food	$100.00 (4 days)
Registration	$100.00
Subtotal for student travel	$1045.00

Travel for Dr. Predecki to ACS Meeting	$400.00

Total Amount Requested	**$1984.00**

2012-13 UNDERGRADUATE RESEARCH GRANT PROGRAM

[illegible]

Shippensburg University of Pennsylvania: This worksheet is designed to assist you in preparing your proposal budget. Work with your faculty mentor to identify reasonable costs. Enter your information in the "pink" shaded areas. If you prefer, you may create your own worksheet. If you do so, you are expected to use the same budget categories and to use the same layout as provided on this template. Call IPSSP for questions and/or technical assistance: 717-477-1251.

Project Title: Synthesis of Four-Membered Ring Heterocycles by the Reaction of 1,3-Dipoles with Carbenes

Lead Student Name:

Lead Student ID #:

UGR Grant - Proposed Budget

		Prices are from Aldrich			
Supplies	Item	*Chemicals and Acros Organics*	$/unit	#	Price ($)
	Item 1	Tebbe's Reagent (25 mL)	202.50	1	202.50
	Item 2	Methyl Lithium 1.6 M (100 mL)	64.10	1	64.10
	Item 3	Methyl Fluorosulfonate (10 g)	76.30	1	76.30
	Item 4	Sodium Tungstate (50 g)	55.30	1	55.30
	Item 5	Pyridine (100 mL)	100.80	1	100.80
				TOTAL SUPPLIES	499.00

		$
Printing/Posters	Item 1 Poster Printing on Biology Poster Printer	40.00
	TOTAL PRINTING	40.00

		$
Student Travel	ACS Conference Registration	100.00
	Airfare from BWI to New Orleans (Orbitz)	400.00
	Hotel (Lodging for 3 nights; Rooming with ; per diem rate for New Orleans in $135 per night)	405.00
Travel to National Meeting of the American Chemical Society (ACS) in New Orleans, LA April 6 – April 9, 2012	Meals (maximum = $25/day; itemized receipts required)	100.00
	Other Transportation to/from Airport/Hotel in New Orleans	40.00
	TOTAL STUDENT TRAVEL	1,045.00

		$
Other Use for expenses that do not fit categories above.		
	TOTAL OTHER	0.00

		$
Faculty Travel	ACS Conference registration	360.00
	Air fare from BWI to New Orleans (Orbitz)	400.00
NOTE: The maximum faculty award is $400.	Parking (Long term parking BWI $10/day)	40.00
	Hotel (Lodging for 3 nights; Rooming with Dr. Dan Predecki; per diem rate for New Orleans in $135 per night)	405.00
	Meals (maximum = $25/day; itemized receipts required)	100.00
	TOTAL FACULTY TRAVEL	1305.00

TOTAL STUDENT REQUEST	1584.00
TOTAL FACULTY REQUEST ($400 max)	400.00

Consumable supplies are those which will be used-up or spent during your project. (Durable equipment items – including electronics and digital devices – will not be funded unless they are unavailable through the University. Such items must be retained by the University upon project completion.)