# *Synthesis of Diels-Alder Adducts from Vinyl Heterocycles having Potential Biological Activity*

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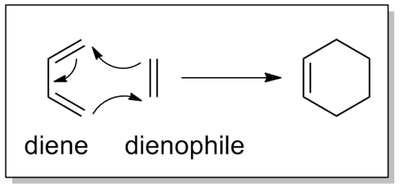
## Introduction

The Diels-Alder reaction is a common ring-forming reaction in organic synthesis. The general reaction involves a conjugated diene and a dienophile as shown below:




Previous research in the Noland Group has focused on Diels-Alder adducts synthesized from derivatives of indole having possible anti-cancer activity. My current work expands upon previous research in the Noland Group, producing Diels-Alder adducts from vinyl heterocycles as starting materials. Two dienes, derived from pyrrole and benzothiophene, will be allowed to react with a series of maleimides to produce several novel Diels-Alder adducts. One adduct has been prepared and is being isolated and fully characterized. All of the prepared adducts will be offered to the NIH for anti-cancer screening.

## Goals

- Synthesis of heterocyclic compounds with potential anti-cancer activity
- Expand upon the range of heterocyclic reaction methods in the Noland Group
- Develop links between structure and biological activity based on past and present research in the Noland Group

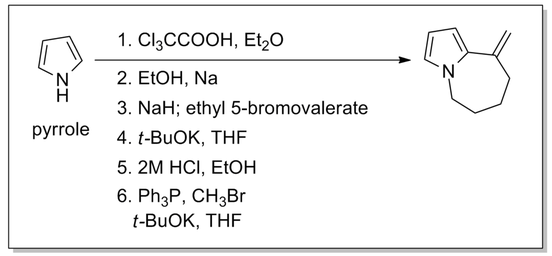
## References

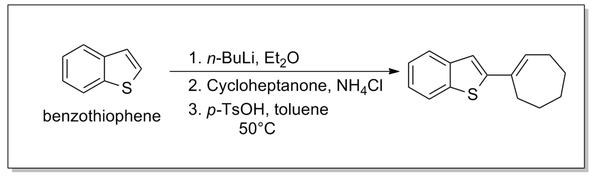
Noland, Wayland E., Lanzatella, Nicholas P., and Sizova, Elena P. "In Situ Vinylpyrrole Synthesis. Diels-Alder Reactions with Maleimides to Give Tetrahydroindoles." Journal of Heterocyclic Chemistry. Volume 46, Issue 3 (May 2009) : 503 – 534.

Wallace, David M., Leung, Sam H., Senge, Mathias O., and Smith, Kevin M. "Rational Tettraarylporphyrin Syntheses: Tetraarylporphyrins from the MacDonald Route." J. Org. Chem. Vol. 25, Issue 16 (April 1994): 7245 – 7257.

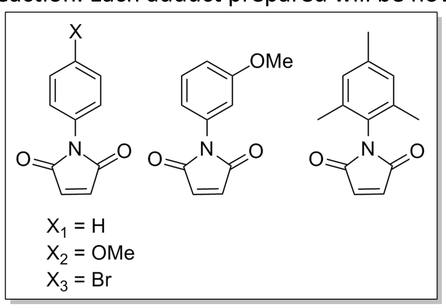
## Methodology

The reaction schemes used to prepare the dienes, using pyrrole and benzothiophene as starting materials, are shown below:




Each diene will be treated with the series of maleimides shown below in the Diels-Alder reaction. Each adduct prepared will be novel.




General conditions for the Diels-Alder reactions:

- Dissolve diene in a minimal amount of toluene
- Add the maleimide and heat to 100°C
- Monitor reaction with TLC
- Upon completion of the reaction, the solvent is removed and the solid is washed and recrystallized, if necessary

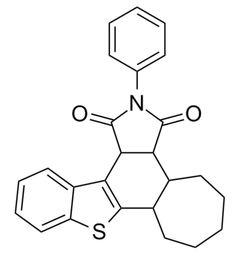
Each isolated adduct will be fully characterized by:

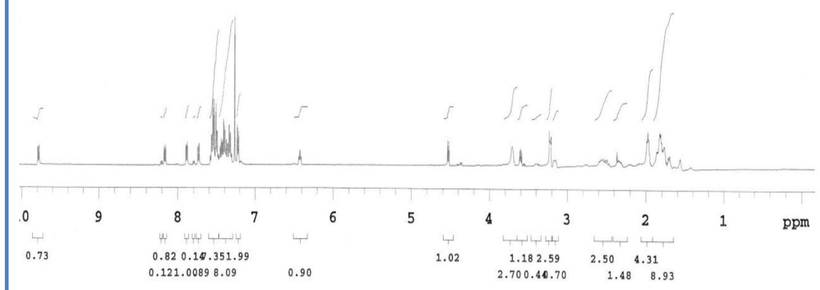
- Spectroscopic methods including various NMR spectral techniques, IR and Mass Spectrometry
- Elemental Analyses

## Acknowledgements

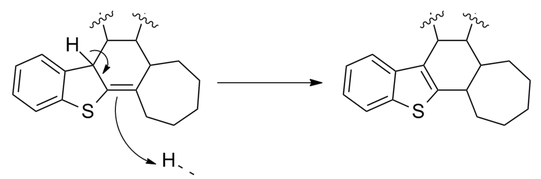
- UROP
- The Noland Group

The proposed structure of the first prepared adduct is shown below, along with the crude $^1H$ NMR spectrum. The adduct is currently being purified before complete characterization:






An interesting feature that has been observed is the tendency to rearomatize via a 1,3-hydride shift.



Initial Diels-Alder adduct — Isolated Diels-Alder Adduct

The adduct that has been prepared, and previous adducts synthesized in the Noland Group have shown this tendency.

## Future Research

Future research will involve the preparation of additional adducts using the additional maleimides available. Once each adduct has been characterized, a sample will be offered to the NIH to test for anti-cancer activity. This research, combined with other iterations of Diels-Alder projects in the Noland Group should provide a comprehensive library of Diels-Alder adducts using pyrrole and benzothiophene starting materials, all possessing potential for biological activity.