An In-Depth Report on *“Design and Application of New Pericyclic Strategies”* by Dr. Chris Newton

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Introduction

Dr. Chris Newton is an assistant professor at the Department of Chrmistry at UGA. He received a CAREER award from the National Science Foundation for his research. In 2009, he received his BSc (Chemistry) from Victoria University of Wellington, New Zealand. In 2014 he was awarded a PhD with Michael Sherburn at the Australian National University and then completed a postdoc from 2015 to 2018 with Nicolai Cramer, EPFL, in Switzerland. From 2018–2021 he was a DECRA Fellow, University of Adelaide, Australia.

He has centered his research on cycloaddition pericyclic reactions and natural product synthesis, at UGA. His cycloaddition research on heterodienes and dienophiles, with strategies for their use and synthesis requirements.

Cycloadditions are a class of pericyclic reactions characterized as two-component reactions that proceed through a concerted mechanism to form cyclic products. Pericyclic reactions form a class of concerted reaction types, with cycloadditions being just one of them. In a cycloaddition reaction, terminal π bonds are consumed to form new σ bonds, creating a new ring structure that acts with a single transition state [1].

Summary of research goals

Dr. Newton and his group have researched pericyclic reactions, primarily the Diels-Alder (DA) reaction, with an emphasis on heterodienes and heterodienophiles. The dienophiles considered by his group are shown in Figure 1. Furans and (isobenzo) furans are the primary dienes, although other heterodienes and thiofurans, such as bisketene equivalents and ketenimines, as well as non-heterocompounds, such as benzene and cyclopentadienes, are of interest in the synthesis of biologically active products.

Dienophiles

C=O C=N Nitriles
C=P C=S N=N
N=S C=Si N=O
Acetylides, O=O (Singlet)

Figure 1 Potential Dienophiles

His research continues and expands on research conducted in selected areas within this overarching arena. Examples of previous research include activated triester imines (C=N) with dienes[2], electron poor nitriles with isobenzofurans[3], C=O dienophiles with 5,6-bis (trimethylsilyl) isobenzofuran[4], C=Si dienophiles with (isobenzo)furans[5], C=P dienophiles DA with (isobenzo) furans[6], N=N dienophiles in azo DA reactions[7], C=S dienophiles, in the form of thioacetones in DA reactions with isobenzofurans[8]. Nitroso (N=O) dienophiles with butadiene[9], N=S (thionitroso and sulfur diamides) with butadiene[10], and O=O (singlet oxygen) with furans[11].

The goal of Dr. Newton's research has been to explore hetero DA reactions, with an eye to both developing further techniques and knowledge into synthetic strategies and targeting compounds that are difficult or impractical to synthesize via other known methods.

Discussion of research

Bisketene Equivalents

One branch of synthetic research has used hetero-Diels-Alder (DA) reactions, using a silyloxy furan as a bisketene equivalent, for the efficient synthesis of p-hydroquinones p-HQ.

Previous approaches to substituted derivatives of p-HQ required a large number of synthetic steps to functionalize the molecule from a simple p-HQ or a lower oxidation state aromatic, using protecting groups and selective redox state adjustments, which could be difficult[12, 13].

A synthetic pathway using bisketenes appears promising, except for the instability and tendency of ketenes to undergo [2 + 2] cycloadditions with alkenes. The use of a vicinal bisketene equivalent was considered to bypass previous synthetic problems. A systematic stability study investigated several possible solutions to this problem. Their focus was narrowed to 2,5-bis(tert-butyldimethylsilyloxy) furan as the vicinal bisketene equivalent and a way to circumvent the original motifs' instabilities. It is a robust candidate that outperforms other derivatives in terms of ease of synthesis, DA reactivity, and stability[14].

The conversion of the substituted bisketene equivalent to hydroquinone was achieved by adding N-methylmaleimide (NMM) as the dienophile. Monofunctionalized derivatives, as shown in Figure 2, were well tolerated. Although the rate of MeOH aromatization dropped significantly for sterically demanding silylated intermediates, such as indole or biaryl, the addition of an acid promoted the reaction. Figure 2 shows the scope of the dienes[15]. Figure 3 shows the scope of the dieneophiles used.

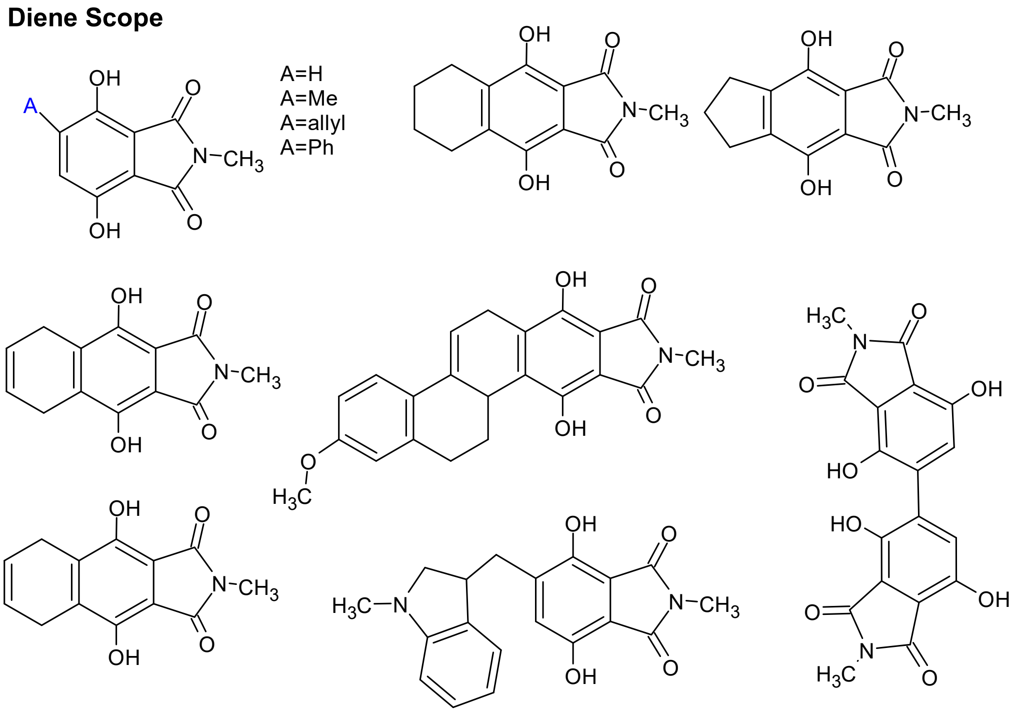

Figure 2 Scope of Dienes considered

This research explored the reaction with acetylenic dienophiles, leading to the formation of p-benzoquinones, which had been hampered in other synthetic motifs by competition from p-HQ formation. Using benzynes, they produced p-iminoquinones from 2,5-bis(tert-butyldimethylsilyloxy) pyrroles.

This branch of research elucidated a large number of p-HQs formed by a new synthetic motif, allowing for the production of a large class of p-HQ compounds under mild conditions, with stable intermediates, and good yields. Some of the compounds they synthesized included a number of potential pharmaceutical compounds, such as indanostatin.

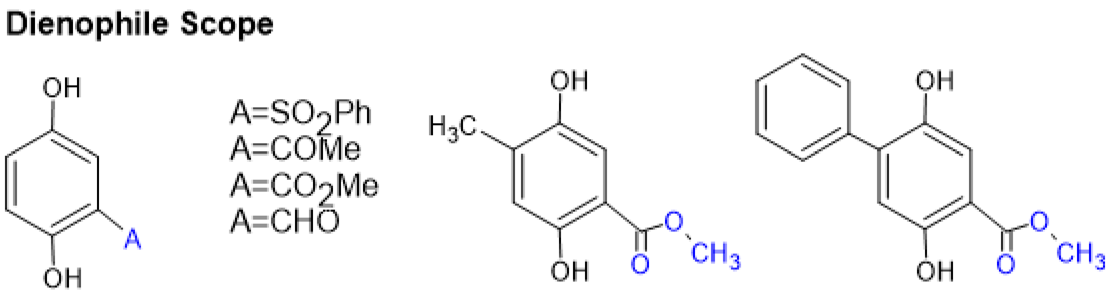

Figure 3 Scope of dienophiles used

Reactions with a Benzyne Dienophile

Cyclic acetylenic intermediates as dienophiles, such as benzyne, allow the introduction of a new substituted ring structure. This research relied on preparing and using 2,5-bis(tert-butyldimethylsilyloxy) furan, referenced earlier and 2-iodophenyl trifluoromethanesulfonate to synthesize 2-methylnapthalene-1,4-dione, via n-butyllithium. The syntheses are shown in Figure 4.

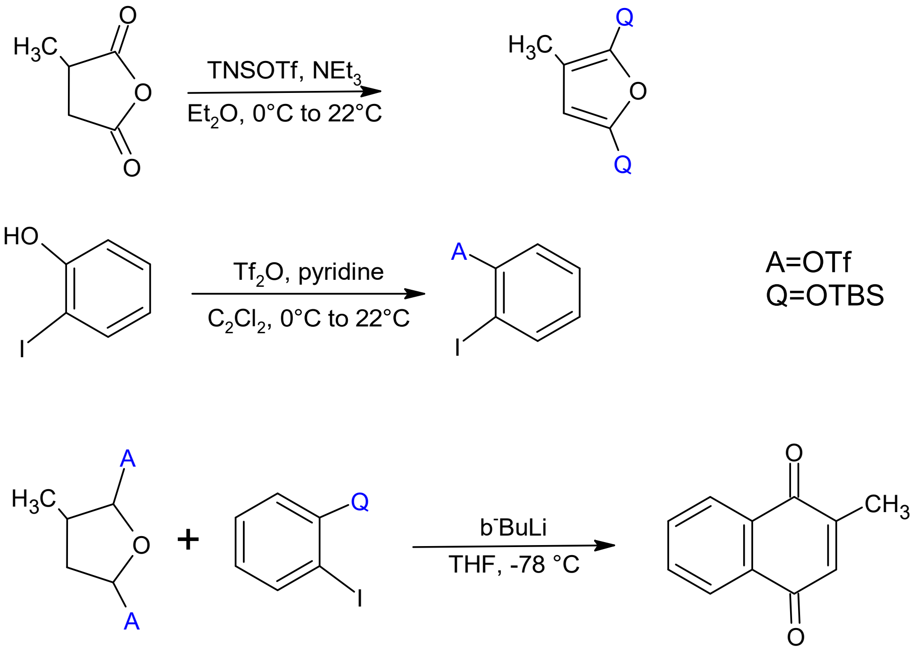

Figure 4

The ring formation strategies for p-hydroquinone and p-benzoquinone synthesis include the Wulff–Dötz reaction, Hauser–Kraus annulation, Moore–Liebeskind rearrangement, oxidative Bergman cyclization, and variants of the Diels–Alder reaction, utilizing oxygenated furans as dienes.

This work led to a protocol for synthesizing highly substituted aromatics, including p-hydroquinones and p-iminoquinones[16].

Unpublished Research

Research that is currently unpublished covers a wider group of dienes and dienophiles. An interesting branch of research includes the use of dienophiles, such as ketenes and ketenimines, with dienes, such as furans and thiofurans. Use of ketene equivalents with furans to form substituted 3-methylidene-2-oxabicyclo[2.2.1]hept-5-enes.

They further explored triazenyl furans, which opened a significant area of potential synthons for heterocycloadditions, specifically hetero-Diels-Alder reactions, resulting in stepwise economic synthetic pathways to pharmaceutical and biological compounds.

The area of interest was the consideration of convergent evolution as a guide for drug discovery by examining convergent biological pathways and using that information to design a synthetic motif to obtain analogs of biologically significant molecules, specifically drugs that may be of use in cancer research.

Conclusions

Dr. Newton’s research widens the use of novel synthetic pathways via heterocycloadditions, primarily the Diels-Alder reaction. The use of (isobenzo)furans and thiofurans as dienes and heterodienophiles and/or acetylenic dienophiles allows bypassing the inherent thermodynamic instability of furan Diels-Alder formed cycloadducts, preventing reversion to reactants via reverse Diels-Alder reaction or conversion to unwanted side-products.

Specific areas have included aza-Diels-Alder cycloadditions via n-aryl ketenimines as strongly reactive aza-dienophiles, often reacting using substituted furans as the dienes, using 2,5-bis(t-butyldimethylsilyloxy) furan being a more commonly used synthon.

He and his group are developing a library of heterocyclic cycloadditions reactions. While there has been research into specific areas of heterocyclic Diels-Alder and other cycloadditions, Dr. Newton and his group are working on compiling a more complete set of reactions and conditions, forming an overarching strategy for new, general pericyclic syntheses with step economy and good yield.

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