Progress Toward the Synthesis of Novel Heterocyclic Compounds: Via Diels-Alder Reactions, Including Microwave Promotion

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Introduction

As one of the most well-known types of cycloaddition reactions, the Diels-Alder (DA) reaction has been around for a very long time. Even so, it holds much promise for the future, as a very powerful method for synthesizing novel compounds with several potential uses. Classical, or “normal-electron-demand” (NED) DA reactions involve electron-rich dienes and electron-poor dienophiles. One subject of this research, however, involves just the opposite electronic distribution, called “inverse-electron-demand” (IED) DA reactions. Such reactions have been investigated to a much lesser extent than have the NED-DA reactions, and therefore the IED reactions deserve more attention, so as to further the usefulness of DA reactions in general.

As the second subject of this research, microwave promotion was explored versus conventional heating methods, such as a sand or oil bath, which can be a slower and a less efficient technique for energy transfer because it depends on the thermal conductivity of the oil or sand. On the other hand, microwave irradiation works by internal heating, which can be a much more effective means of heating, provided the solvent being used absorbs the energy effectively (Dallinger & Kappe, 2007).

As the third subject of this research, it appeared that retro-Diels-Alder (RDA) reactions were involved, at least in some of our reactions. RDA is (obviously) undesirable for our project.

Discussion

Because IED-DA reactions are a developing area of organic synthesis, research still needs to be done to define the line between the two classes (NED and IED). Studies have discovered different aspects that contribute to the inverse character of these reactions. The reactivity of some compounds is dependent upon the electronic character of their substituents as is evidenced in studies by several research groups. Oakdale and Boger (2010) found that the aryl groups determined the behavior of 1,2-diarylacetene derivatives, in that they acted in an electrophilic manner. Substituents also play a key role in the magnitude of electron-rich or nulceophilic reactivity. For example, nitro groups enhance the electrophilic quality of neutral heteroaromatic 10-pi electron systems, such as 4,6-dinitrobenzofuran (Goumont, Sebban, Marrot, & Terrier, 2004) or 2,1,3-benzoxadiazoles (Sebban et al., 2012) and 6-pi electron systems, such as benzenoid aromatic compounds (Terrier, Dust, & Buncel, 2011).

Another significant factor in how a compound reacts in a Diels-Alder reaction is the other reactant being used. There are certain dienes or dienophiles that can react in either IED-DA reactions or NED-DA reactions. Moreover, the use of catalysts could facilitate complete reactions.

Future Research

Because none of the above reactions were definitive nor produced desired completion of the reactions, more research is still needed. Further analyses, such as nuclear magnetic resonance spectroscopy, and further procedures such as column chromatography, should be done. Future endeavors regarding IED-DA reactions should include different combinations of reactants. Moreover, the use of catalysts could facilitate complete reactions.

References


Our Progress Report

Some examples of the reactions done by ONU Honors Program undergraduate research student, Kristen Richey, are summarized below. MW refers to the use of our Biotage microwave instrument, “Initiator” model. The structures of the products indicated below, are the expected products, based on the evidence which had been obtained for their structures at the time this poster was written.

However, at that point, none of the product structures had been rigorously proven. But, the latest results will be explained by Dr. Armstrong, to anyone who asks.

Benzoazofuran 1 was reacted with 4,5-diphenyl-1,3-dioxol-2-one 2 in refluxing toluene. No reaction (NR) was detected by TLC analysis, as indicated below. It was decided that a higher-boiling solvent should be used. Accordingly, in the next trial, the same two reactants were used but this time with refluxing mesitylene as the solvent. A TLC analysis indicated a product was formed, but both reactants were still present in the reaction mixture. Another experiment with these conditions was run with a 30% excess of benzoazofuran, to try and get all of the 4,5-diphenyl-1,3-dioxol-2-one to react. However, a TLC analysis of this reaction mixture showed the same results. A longer reflux of this run resulted in multiple products showing up on the TLC. In a final endeavor to push this reaction to completion (with reactants hopefully absent) but with a single product, refluxing 5-tert-butyl-m-xylene was used as the solvent, to see if the higher boiling point would make a difference. But, the TLC revealed two products in the reaction mixture along with some of the two reactants (still present). It was unclear as to if the expected product (3) was formed.

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