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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-diarylacetylene derivatives, in that they acted in an electrophilic manner. Substituents also play a key role in the magnitude of electrophilic or nucleophilic reactivity. For example, nitro groups enhance the electrophilic quality of neutral heteroaromatic 10- π electron systems, such as 4,6-dinitrobenzofurazan (Goumont, Sebban, Marrot, & Terrier, 2004) or 2,1,3-benzoxadiazoles (Sebban et al., 2012) and 6- π electron systems, such as in 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. The versatility of a compound that has this ability is typically seen where it acts as the diene or dienophile in an NED-DA reaction and a dienophile or diene in an IED-DA reaction, respectively, depending on the reaction partner (Goumont, Sebban, Marrot, & Terrier, 2004). An example of this relationship can be observed, in which dienes, such as cyclopentadienones, which are very reactive in an IED fashion, are required to provoke [4+2] cycloadditions with diphenylacetylene (Collins, Yap, & Falles, 2001). Other compounds have a different sort of flexibility as they can be used in the same manner for both NED and IED reactions, and can change because of a reactant that has the opposite demand (Butler & Coyne, 2015).

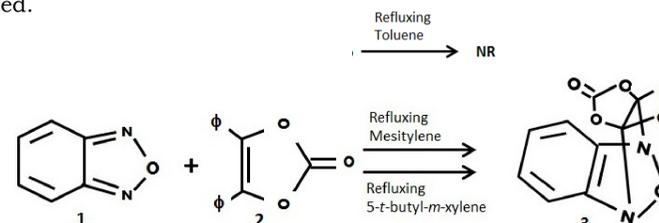
Microwave promotion has proven to be a very useful method in organic synthesis especially in more recent years, and will most likely continue being so. Many reactions can take place under conventional heating, but the use of a microwave instrument often results in shorter reaction times, often allows lower reaction temperatures, and often increases product yields and purity (Dallinger & Kappe, 2007). Moreover, this can largely be done without much change in the designed reaction conditions (Baar, Fakone, & Gordon, 2010). Microwave promotion can accomplish these beneficial feats by improving the efficiency and, therefore, minimizing the energy content, as reported by Dong et al. (2011) when investigating the RDA reaction.

Establishing a reaction temperature which is high enough to get the forward DA reaction to occur, without being high enough to cause RDA to occur to some extent, often proved to be very difficult, as we explored by refluxing reaction mixtures in solvents with varying boiling points. RDA has been investigated by several chemists, including Dong et al. (2011).

Our Progress Report

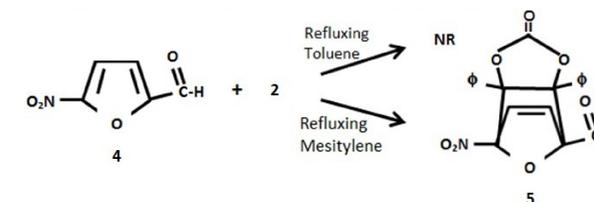
Some examples of the reactions done by ONU Honors Program undergraduate research student, Kristen Richey, are summarized below. MW refers to the use of our Biotage microwave instrument, "Initiator" model. The structures of the products indicated below, are the expected products, based on the evidence 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.

Benzofurazan **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 benzofurazan, to try to 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.

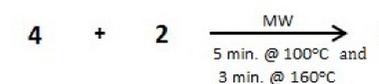


4,5-diphenyl-1,3-dioxol-2-one **2** was reacted with 5-nitro-2-furaldehyde **4**, as the diene. The nitro group (-NO₂) and the formyl group (-CHO) conjugated with the aromatic ring should provide the desired IED electron-deficiency by drawing electron density away from the "diene" by resonance. No reaction was observed in toluene, but in mesitylene, the TLC analysis of the reaction mixture showed a single product and both reactants still

present. The structure depicted for product **5** is that which would be expected from an IED-DA reaction and is based, in part, on the IR peak at 847.76 cm⁻¹ which suggests the presence of a HC=CH group, which is found only in the adduct and not in either of the reactants.



With no complete reactions observed using conventional heat sources, including the above examples plus numerous others not mentioned here, microwave (MW) heating was tried, including several combinations of reactants, with several different sets of MW conditions. As one example, the same two reactants as above, **4** and **2**, were used. The solvent was *o*-dichlorobenzene, and two sets of MW conditions were used, as indicated below, resulting in incomplete reactions, again with compound **5** as an expected product. The other runs gave similar results.



Future Research

Because none of the above reactions were definitive nor produced desired complete 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.

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