Jul 11th, 1:30 PM - 2:30 PM

Development of a One-Pot Allylation and Claisen Rearrangement of Acetaminophen by Applying Microwave Radiation

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Abstract

The Claisen rearrangement is a widely applicable organic reaction that involves the shift of a sigma bond across the pi-system of an allyl vinyl ether to produce allylated phenols. In this project, we aim to develop a microwave assisted allylation of a phenol, followed by a subsequent Claisen rearrangement in one pot. The goals of this project are three-fold. First, we aim to accelerate these reactions using microwave assisted organic synthesis because to date, microwave technology has been sparsely used in Claisen chemistry. Second, we aim to perform these reactions in a single pot, enhancing the simplicity and elegance of the reaction. Finally, our research group has an interest in allylated phenols given the allyl group can be used to attach the ring to other molecules. Acetaminophen was chosen as a model phenol to test the chemistry. As a result, this also affords the allyl group can be used to attach the ring to other molecules. Acetaminophen holds great synthetic value due to its ability to create polyfunctionalized molecules and 3 atoms are rearranged as seen in the mechanism below

\[
\text{Acetaminophen + K}_2\text{CO}_3 + \text{allyl bromide} \rightarrow \text{allylated acetaminophen} \]

Microwave Chemistry in College Laboratory

- Microwave chemistry can be very advantageous in a college laboratory setting
- Elizabethtown’s department of chemistry recently obtained microwave and monowave reactors, which accelerates organic reactions and syntheses
- This allows an undergraduate student to both learn new synthetic and characterization techniques
- Use of microwaves rather than reflux techniques creates a safer environment for students

Background on Claisen Rearrangement

- [3,3] sigmatropic rearrangement of an allyl phenyl ether
- A [3,3] sigmatropic rearrangement is when the sigma bonds of the 1, 2, and 3 atoms are rearranged as seen in the mechanism below
- Mechanism is a concerted unimolecular reaction with a cyclic transition state
- Holds great synthetic value due to its ability to create polyfunctionalized molecules

Claisen Rearrangement of 4-Allyloxyacetanilide

- Time in the microwave was decreased until minimum amount needed to complete the rearrangement was observed

\[
\text{N,N-dimethylacetamide} \xrightarrow{\text{MW, 250 °C, 1h}} \text{N,N-dimethylacetanilide}
\]

Microwave Chemistry

- Novel technique that allows syntheses to be completed in a much shorter period of time
- Reactions heated in closed vessel
- According to Arrhenius’s equation the higher the temperature the faster the rate at which the reaction is carried out.

\[
k = Ae^{-\frac{E_a}{RT}}
\]

- *In general a 10 degree increase in temperature (T) doubles the rate (k)*

- Interdisciplinary field called microwave-assisted organic synthesis (MOAS)

One-Pot Synthesis of 4-Acetamido-2-allylphenol

- Through base optimization it was concluded that potassium tert-butoxide is the most suitable base for this reaction.
- Further optimization has been completed with respect to the solvent being used.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conditions (°C)</th>
<th>Mass Isolated (mg)</th>
<th>% Allylated</th>
<th>% Rearranged</th>
<th>% SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>15 min @ 200</td>
<td>111</td>
<td>40</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>1 hr @ 180</td>
<td>72</td>
<td>70</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>1-Butanol</td>
<td>15 min @ 200</td>
<td>127</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N,N-Dimethyl aniline</td>
<td>15 min @ 200</td>
<td>137</td>
<td>67</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>2-Butanol</td>
<td>15 min @ 174</td>
<td>174</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>15 min @ 200</td>
<td>123</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethanol</td>
<td>30 min @ 190</td>
<td>92</td>
<td>&gt;99</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Water</td>
<td>15 min @ 200</td>
<td>25</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>15 min @ 200</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N,N-Dimethylaceta mid</td>
<td>15 min @ 200</td>
<td>113</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Each reaction was run in DMF as solvent in an Anton Paar Microwave 400. Reactions were heated AFAP to specified temperature and then cooled to 55 °C.

- From this optimization table the solvents that were selected for further optimization was DMF.
- The inability for the other solvents to afford the desired rearranged product could be due to the polarity of the solvent itself and its ability to allow different side reactions to occur.

Summary of Progress

- Large-scale yield of allylated acetaminophen has been obtained using conventional heating
- Microwave synthesis of both allylated acetaminophen and the subsequent rearranged product has been completed in DMF
- Current optimization of one-pot synthesis is currently being conducted
- Current optimization is focused on the allyl halide and the counter ion of the tert-butoxide base being used.
- To date these studies have afforded valuable data in optimizing the one-pot synthesis

Conclusion and Future Work

- Allylation of acetaminophen and the subsequent rearrangement have been completed under microwave conditions in one-pot, but full conversion to rearranged product has not been observed
- Future work includes optimization to obtain high yields of rearranged product
- Prospect of being integrated into CH 213 laboratory setting
- Incorporate monowave 50 as means of completing this reaction

Acknowledgements

- Elizabethtown Department of Chemistry and Biochemistry
- MacKay Research Group
  - John Talbott
  - Emily Kagarise
  - Aubrey Maryinak
- NSF CHE-1708699 grant funding

Table: Entry Time (minutes) Ratio (SM:P)

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<td>2</td>
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<tr>
<td>3</td>
<td>5</td>
<td>0.91</td>
</tr>
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*General mechanism of Claisen rearrangement of an allyl phenyl ether with cyclic transition state

*Kürti, L.; Czakó, B. Strategic applications of named reactions in organic synthesis 2005.


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*NSF CHE-1708699 grant funding

*Image 30x59 to 3142x2141

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