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

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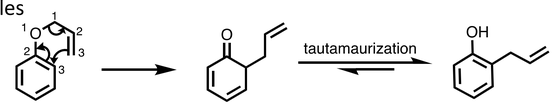
Abstract

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 derivatives which like acetaminophen, could have analgesic properties. Initial studies reveal that the Claisen rearrangement of allylated acetaminophen requires a reaction time of under ten minutes in the microwave compared to hours when performed under reflux. Further optimization of other components of the reaction are ongoing.

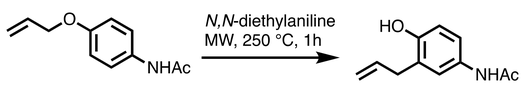
Background on Claisen Rearrangement

- [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



*General mechanism of Claisen rearrangement of an allyl phenyl ether with cyclic transition state

- Thermal reaction; literature reports successful microwave assisted Claisen rearrangement as seen below



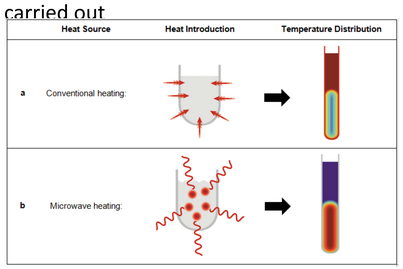
Kürti, L.; Czakó, B. *Strategic applications of named reactions in organic synthesis* ; 2005.
Schmidt, B.; Wolf, F. *J. Org. Chem.* **2017**, *82*, 4386–4395.

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 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)

Obbermayer, D.; Kremsner, J. M.; Stadler, A. *Minutes, Not Hours! A Practical Guide to High-Speed Organic Synthesis in Modern Microwave Reactors* ; Anton Paar, 2016.

Microwave Chemistry in College Laboratory

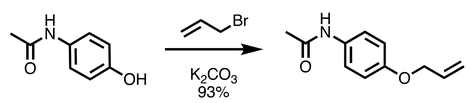
- Microwave chemistry can be very advantageous in a college laboratory setting
- Elizabethtown's department of chemistry recently obtained microwave and monowave reactors, which accelerates organic reactions and syntheses
  - This allows an undergraduate student to both learn new synthetic and characterization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

*Microwave 400, Monowave 50, and reaction vial

Cravotto, G.; Carnaroglio, D. *Microwave chemistry*; De Gruyter, 2017.

Allylation of Acetaminophen

- Acetaminophen is combined with K_2CO_3 and allyl bromide in acetone
- Refluxed for 12 hours at 50 °C
- This reaction was used to successfully obtain allylated acetaminophen in high yields



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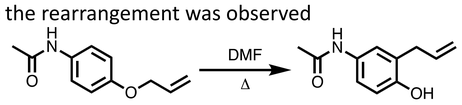
Claisen Rearrangement of 4-Allyloxyacetanilide

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



Entry	Time (minutes)	Ratio (SM:P)
1	30	0:100
2	10	0:100
3	5	9:91

*Each reaction was run in DMF as solvent in an Anton Paar Microwave 400. Reactions were heated AFAP to 250 °C and then cooled to 55 °C.

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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.

Solvent	Conditions (°C)	Mass isolated (mg)	% Alllylated	% Rearranged	% SM
DMF	15 min @ 200	111	40	60	0
Isopropyl Alcohol	1 hr @ 180	72	70	30	0
1-Butanol	15 min @ 200	127	100	0	0
N,N-Dimethyl analine	15 min @ 200	137	67	33	0
2-Butanol	15 min @ 200	174	100	0	0
Acetonitrile	15 min @ 200	123	100	0	0
Ethanol	30 min @ 190	92	>99	<1	0
Water	15 min @ 200	25	100	0	0
1,4-Dioxane	15 min @ 200	100	100	0	0
N,N-Dimethylacetamide	15 min @ 200	113	100	0	0

*Each reaction was run in a 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