Microwave Assisted Syntheses for the Organic Chemistry Lab

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Abstract

Microwave synthetic methods were devised for three lab reactions: The synthesis of aspirin, phenytoin, and a Claisen condensation. These reactions are all done in either general chemistry or organic chemistry. Under conventional heating methods, the aspirin synthesis requires heating at 55 °C for 30 minutes. The phenytoin synthesis, with conventional heating methods, proceeds at reflux for 1.5 hours. The Claisen condensation, under normal conditions, is heated at 100 °C for 30 minutes. The proposed microwave methods provide shorter reaction times while maintaining similar, if not better, yields. The aspirin and phenytoin syntheses were shortened to 7 minutes, and the Claisen condensation was shortened to 4.5 minutes. The microwave method produced a 46% yield for aspirin, while conventional yield was 47.4%. The phenytoin synthesis conventionally gives a 19.4% yield, but under the microwave method gives a 79% yield. The Claisen condensation conventionally gives a 28.6% yield, while the current microwave method gives a 16.2% yield.

Introduction

In organic chemistry, many syntheses take hours under normal heating conditions. Microwave chemistry allows such reactions to proceed at a fraction of the time, and boosts better yields. A microwave emits oscillating magnetic fields, causing polar molecules to rotate along with the magnetic field. This movement of molecules causes more interactions between molecules.

Microwave reactions have been shown to be much faster1, making these reactions useful. One such use is applying microwave chemistry in the undergraduate organic lab. Using a microwave in the organic chemistry lab can help students learn about optimization, while reducing wasted time in the lab. Students can run multiple reactions in the time it usually takes to run one reaction.

Aspirin can be used as a painkiller, but it is also given to people who are at a higher risk of heart attack. Aspirin lowers the risk of forming blood clots in arteries, decreasing the risk of heart attack. As well as being a blood thinner, aspirin is an analgesic that is used to reduce swelling. The synthesis of aspirin is an organic reaction known as an acetylation. The reaction proceeds when the alcoholic group of salicylic acid attacks one of the carbonyl groups of acetic anhydride.

Phenytoin is an anti-convulsant drug prescribed for epilepsy. The synthesis is accomplished by reacting benzil with excess urea under basic conditions. The final step occurs via a Pinnaco-like rearrangement. Published methods for preparing phenytoin involves refluxing the reaction mixture for 2 hours2. However, there are not many methods for synthesizing this drug in a laboratory-grade microwave. The method developed here is a new, more efficient microwave synthesis.

The Claisen condensation is a reaction between 2 molecules of ethyl phenylacetate facilitated by potassium t-butoxide. In the reaction, the t-butoxide abstracts a hydrogen atom from the α-carbon, forming a carbanion that attacks the carbonyl group of another ethyl phenylacetate. While microwave facilitated Claisen condensations are known, the method has yet to be applied to this specific reaction.

Synthesis of Aspirin

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\text{Synthesis of Aspirin}
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\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{H}_2\text{SO}_4 & \quad \text{MW-7 min} \\
175 \text{ Watts} \\
\rightarrow & \quad \text{HO} \quad \text{HO} \\
\text{46%} & \quad \text{MW-7 min} \\
\end{align*}
\]

Results: Aspirin

Under the conventional conditions, salicylic acid and acetic anhydride are heated at 55 °C for 30 minutes. Aspirin is recrystallized from ethanol, and the final product analyzed by melting point and GC/MS. However, analysis of the GC/MS data showed that recrystallizing with ethanol resulted in a trans-esterification. The microwave procedure involves reacting salicylic acid with acetic anhydride for 7 minutes at 175 watts in the microwave, shortening the reaction time to 7 minutes. To prevent the trans-esterification, water was used to recrystallize the resulting aspirin. Using conventional heating, aspirin was isolated with a yield of 47%, while the shorter microwave method resulted in a comparable 46% yield.

Synthesis of Phenytoin

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\text{Synthesis of Phenytoin}
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\begin{align*}
\text{O} & \quad \text{O} \\
\text{HN} & \quad \text{HN} \\
\text{KOH} & \quad \text{MW-7 min} \\
70 \text{ Watts} \\
\rightarrow & \quad \text{O} \quad \text{O} \\
\text{79%} & \quad \text{MW-7 min} \\
\end{align*}
\]

Results: Phenytoin

The synthesis of phenytoin requires refluxing benzil and urea in ethanol for 1.5 hours using conventional heating. However, ethanol proves to be a poor solvent for microwave synthesis and the insolubility of the reactants in ethanol at room temperature required the use of a different solvent. Dimethyl sulfoxide (DMSO) is known to be a good microwave solvent and dissolved all of the reactants. Furthermore, KOH is a better base than NaOH, thus KOH was used in these reactions. The reaction was subjected to microwave irradiation at 70 watts for 7 minutes. The products were analyzed through NMR spectroscopy and melting point. The microwave procedure shortened the reaction time from 90 to 7 minutes with an increase in yield from 19 to 79%.

Claisen Condensation

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\text{Claisen Condensation}
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\begin{align*}
\text{O} & \quad \text{O} \\
\text{KO t-BU} & \quad \text{MW-4.5 min} \\
300 \text{ Watts} \\
\rightarrow & \quad \text{O} \quad \text{O} \\
\text{16.2%} & \quad \text{MW-4.5 min} \\
\end{align*}
\]

Results: Claisen

The Claisen Condensation, under conventional conditions, is heated at 100 °C for 30 minutes. The Claisen product is neutralized with acid after and the product is extracted with ether and then isolated. In the microwave procedure, the ethyl phenylacetate and potassium t-butoxide are microwaved at 300 watts for 4.5 minutes using a wellof stir bar. The wellon stir bar is necessary because ethyl phenylacetate does not interact with microwaves very well. The product is analyzed with IR spectroscopy and melting point. Currently, the microwave procedure gives a 16.2% yield. Further directions for this procedure involve changing the base to sodium ethoxide.

Conclusion

Microwave irradiation provides great advantages over conventional heating methods. The phenytoin synthesis successfully proves the advantages of microwave irradiation. The microwave method increased the yield of phenytoin by 60% while decreasing the reaction time significantly. The microwave-assisted aspirin synthesis has a comparable yield while decreasing the reaction time. The Claisen condensation has decreased the reaction time, and further work could produce higher yields.

Acknowledgements

I’d like to thank Dr. Carolyn Weinreb for guiding my research and re-teaching organic when I needed it. I’d also like to thank Dr. Derek Wierda for giving me the opportunity to do this research. Additionally I’d like to thank my fellow researchers Briana Goddard and James Cummings for bouncing ideas around when I was stuck.

References