Development of a New Green Reaction Synthesis Using Design of Experiment

Sydney Asmus, Taylor Fletcher, and Dr. William R. Carroll*

Department of Chemistry, Tennessee Technological University, Cookeville, TN 38505

Introduction

This research focuses on the optimization of a novel synthesis for both yield and environmental impact. Reducing the impact of chemical reactions on the environment is critical to the advancement of chemistry. This work synthesized a precursor to a potentially pharmaceutically relevant small molecule. An Aldol reaction employed to affix a biologically active terpenoid to a variable group. Design of Experiments is a tool used for optimization as it allows for multiple parameters to be adjusted and analyzed simultaneously. This reaction was optimized to react at a smaller scale in order to be used with nuclear magnetic resonance (NMR) and also align more closely with the principles of Green Chemistry and allow for continuous monitoring. We quantified the compliance with green chemistry tenants using the DOZN score. This work aims to optimize this aldol reaction even further in order to fit all Green Chemistry Principles and even be modified into other molecules that can aid in cancer prevention.

Background

Green Chemistry aims to lessen the negative environmental impacts of chemical processes. This experiment was conducted and designed around the 12 Principles of Green Chemistry, specifically waste prevention, safer solvents and auxiliaries, and real time pollution prevention. This research aims to optimize an aldol reaction to react under green standards in order to lessen the potential environmental impacts of the reaction. In order to rate the “greenness” of the reaction, the DOZN green scoring software will be used.

Overview

For the purpose of this experiment due to the use of the NMR, deuterated solvents are used. In the initial run deuterium oxide, D_2O, is used as the primary solvent unsuccessfully. These experiments focused on optimizing the reaction conditions using a variety of solvents including those that are not readily available as NMR solvents. This was achieved with a coaxial NMR tube containing deuterated chloroform, $CDCl_{3a}$s a reference.

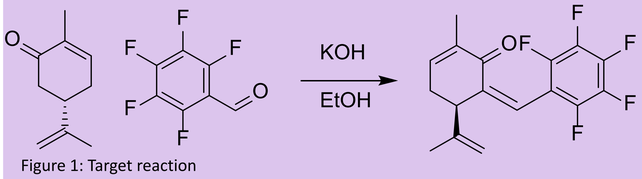

Figure 1: Target reaction

The goal reaction aims to be biologically relevant and aid in cancer prevention. It will allow proteins to form that are able to bond to the enzyme class topoisomerase.

Results

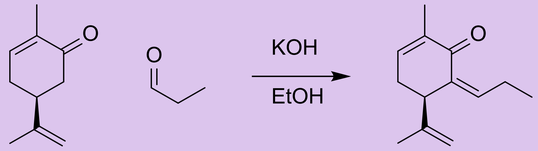

Figure 2: Initial aldol reaction

The initial reaction ran was an aldol condensation reaction. It serves as the basis for developing the reaction that forms topoisomerase bonding proteins.

Figure 3: Initial test of aldol reaction with EtOH

Figure 4: First DMSO reaction in NMR tube

This aldol reaction was optimized to run at a microliter scale; thus, allowing it to be ran using NMR tubes. The use of NMR allows the reaction to be continuously monitored while it is being ran; therefore, allowing the disappearance of reactants and appearance of products to be recorded. NMR requires 500 total microliters of solution which is significantly less than the amount used in this reaction when ran in a round bottom flask or a vial which require 500mL and 50mL, respectively.

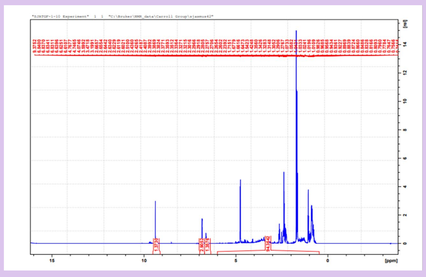

Figure 5.1: Initial DMSO reaction NMR spectra

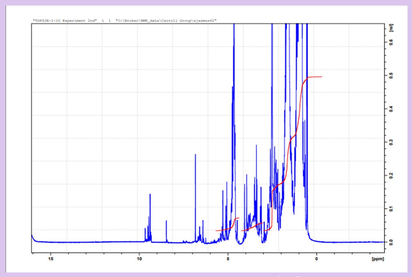

Figure 5.2: DMSO reaction monitored after approx. 96 hours at 60 °C

The implementation of a coaxial tube allows a variety of solvents to be used. It also further optimizes it to require less solution, approximately 400 microliters total.

Figure 6.1: EtOH reaction with d-chloroform coaxial tube

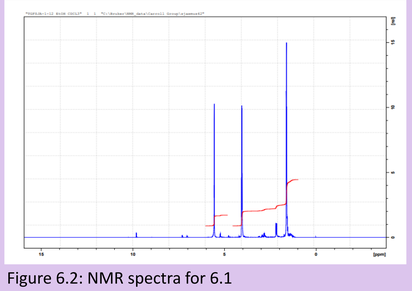

Figure 6.2: NMR spectra for 6.1

Future Work

This research is ongoing with plans to quantify the "greenness" of the reactions with a green scoring software, DOZN, and include the statistical analysis of the optimization of the standard reaction through Design of Experiment (DOE). While conducting this experiment, the use of a coaxial tube was implemented. The continued use of the coaxial tubes will prove to be an important advancement in diversifying potential solvents because the deuterated solvent no longer directly impacts the aldol reaction which allows this reaction to be further optimized for “greenness.” The new product via the final optimized reaction will be identified as well. Topoisomerase enzymes will potentially play an important role in cancer prevention when paired with the final product.

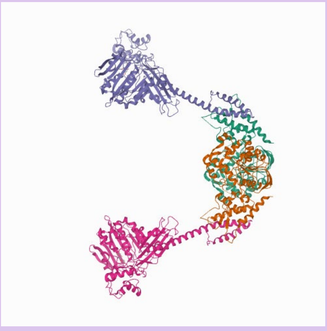

Figure 7: Topoisomerase enzyme 2ZBK

References

(1) The 12 Principles of Green Chemistry. In *Ionizing Radiation and Polymers*; Elsevier, 2013; p 267.

(2) Crouse, D. J. *Laboratory Exercises for Organic Chemistry*; 2020.

(3) Ponnusamy, E.; Whitford, J. DOZN^{TM} – A Quantitative Green Chemistry Evaluator. *J Med - Clin Res & Rev* **2017**, *1* (3), 1–6.

(4) Ardeshir Khazaei, Negin Sarmasti, Jaber Yousefi Seyf and Mahsa Tavasolia. Synthesis of Hexahydroquinoline (HHQ) Derivatives Using ZrOCl2$8H2O as a Potential Green Catalyst and Optimization of Reaction Conditions Using Design of Experiment (DOE)†. *RSC Adv., 2015, 5, 101268* **2015**.

(5) van Tilbeurgh H. Paris-Sud Yeast Structural Genomics (YSG), G. M. C. L. D. D. L. F. F. P. 2ZBK Crystal Structure of an Intact Type II DNA Topoisomerase, 2008.

Acknowledgements

Tennessee Technological University Department of Chemistry