2020

Electrolytic oxidative coupling of alcohols with aldehydes to form esters

Katherine L. Verboom
Georgia Southern University

Electrolytic oxidative coupling of alcohols with aldehydes to form esters

An Honors Thesis submitted in partial fulfillment of the requirements for Honors in Chemistry.

By
Katherine Verboom

Under the mentorship of Dr. Abid Shaikh

ABSTRACT

There are copious amounts of naturally occurring and synthetic esters known that have a wide range of applications in industry to produce fine chemicals. Traditional methods of ester synthesis involve a reaction between a carboxylic acid and an alcohol in the presence of a Bronsted acid catalyst. The primary objective of this research project was to carry out the ester synthesis using the electrochemical coupling of aldehydes with alcohols instead of with a Bronsted acid catalyst because the electrochemical coupling would be an all-around better alternative of ester synthesis than the traditional method of using the catalyst. Electrochemistry has long been known as an environmentally friendly synthetic tool and has recently attracted significant attention in organic synthesis. A model reaction with 4-methoxybenzaldehyde with methanol was carried out to optimize the reaction parameters for a high product yield and a short reaction time. After having the optimized conditions in hand, a wide range of commercially available aldehydes and alcohols were tested to see how generally this method could be applied. This method of production allowed a variety of esters to be synthesized in a short time with a high product yield. All the products obtained were fully analyzed using NMR spectroscopy.

Thesis Mentor: _____

Dr. Abid Shaikh

Honors Director: _____

Dr. Steven Engel

April 2020
Department of Chemistry

Acknowledgments

First, I would also like to thank my research advisor, Dr. Abid Shaikh, for allowing me to join his research team and conduct research alongside him with other highly capable scientists. I would also like to extend my appreciation to my research partner, Dylan Smeyne, for helping me tremendously throughout this project. In addition, the encouragement from Georgia Southern University's Department of Chemistry and the University's Honors Program made my undergraduate research experience above par while providing me with an abundant amount of opportunities to flourish as an aspiring chemist. Additionally, I greatly appreciate the financial support provided by Georgia Southern University and the College Office of Undergraduate Research (COUR). Finally, I would like to thank my family and friends for offering me the encouragement to successfully pursue my goals.

Introduction

Esters represent one of the most valuable classes of compounds that have widespread applications in pharmacological synthesis, food, perfumes, flavors, and fine chemical synthesis. Considering the widespread prevalence of ester groupings in a variety of biologically important molecules, many synthetic protocols have been reported over the year and are still in the forefront of organic synthesis. Traditionally, the Fischer esterification method has been employed in the synthesis of esters starting from carboxylic acids and alcohols under acid-catalyzed conditions. Many chemical reactions involved the use of esters as starting materials, which led to the development of a large number of coupling reagents that could be applied to diverse pool of carboxylic acids and alcohols.

As an alternative, the oxidative coupling of aldehydes with alcohols to form esters has also been reported using Ru-based catalysts. Due to the limited number of methods known and in search of a catalyst-free approach for the quick access of esters, we envisioned the development of an electrochemical synthesis for the direct coupling of aldehydes and alcohols. Electrochemistry has a long history, but it has not yet been adopted into the chemical industry as a mainstream method of ester formation. The benefits of using electrochemical methods are innumerous; however, one of the well-known benefits include being a green and sustainable. A recent example of electrochemical synthesis of esters involves the use *N*-heterocyclic carbine (NHC) catalyst to generate Breslow intermediate from of an aldehyde (Figure 1), which, on further electrochemical oxidation and coupling with an alcohol, yields a corresponding ester. The formation of the Breslow intermediate substantially lowers the oxidation potential and the reaction occurs at a very low voltage of 0.1 V.

Herein, we developed an electrochemical approach utilizing commercially available aldehydes and alcohols. This method produced the expected esters under electrical current without requiring any type of catalyst. Since the process does not involve a catalyst, the reaction must be carried out with a higher voltage.

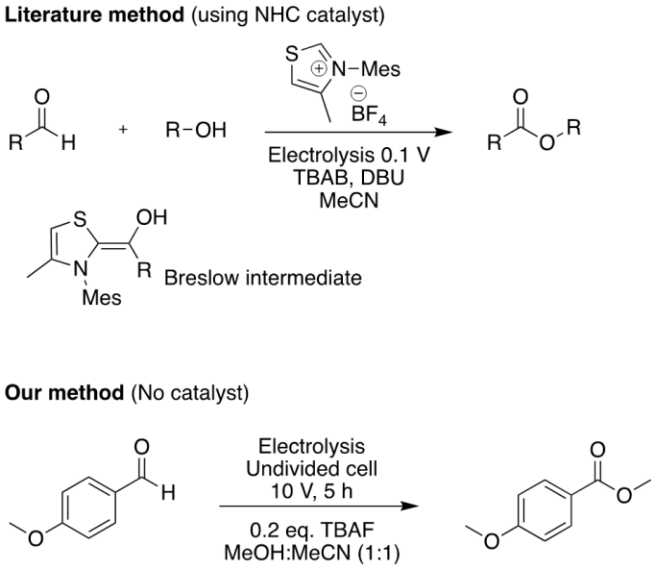


Figure 1. Reaction conditions for previously known reactions and the new proposed method.

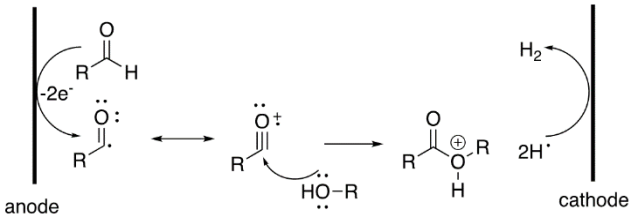
Results and discussion

The goal of this project was to find a more environmentally friendly way of electrochemically converting an alcohol and aldehyde into an ester. A model reaction was run using 4-methoxybenzaldehyde and methanol in order to see if our method was sufficient. This model reaction used 2mmol (250mg) of 4-methoxybenzaldehyde along with a 10 mL mixture of CH3CN and CH3OH (1:1). The mixture was placed in a glass cell along with a magnetic stir bar. 5 mol percent of tetrabutylammonium fluoride (TBAF) was then added to the cell with the reaction mixture. This was then stirred while 10 V passed through the cell with the polarities being reversed on a 5 second interval for 5 hours. Upon analysis using thin layer chromatography (TLC), it was discovered that a new product was formed. Excess solvents were then evaporated

under reduced pressure, and the resulting crude mixture was dissolved in dichloromethane and purified on silica gel to obtain the expected compounds in analytical purity. The product analysis and characterization were carried out using ^{1}H, ^{13}C NMR.

Upon discorvery that the desired product was made, the reaction was further investigated in order to obtain optimal reaction conditions. No further product was yielded after 5 hours and 10V was determined to lead to sufficient product conversion. The generalizability of the method was then investigated by testing other alcohols and aldehydes. Whenever a different alcohol was tested, 4-methoxybenzaldehyde consistently stayed with the aldehyde of which the alcohol was coupled. Likewise, whenever a different aldehyde was being tested, methanol was the alcohol that was used.

Proposed Mechanism:



Conclusion

In summary, we have developed a novel way to synthesize esters from aldehydes and alcohols under electrolytic conditions. The methodology utilized gave good yields using various alcohols and aldehydes coupled with acetonitrile and TBAF under 10V for 5 hours. This methodology is a much more environmentally friendly way of synthesizing esters compared to the normal acid catalyst.

References

1. K. Subramanian; S. L. Yedage; B. M. Bhanage; *J. Org. Chem.* **2017**, 82, 19, 10025-10032.
2. K. L. Yearty; J. T. Sharp; E .K. Meehan; D. R. Wallace; D. M. Jackson; R.W. Morrison; *J. Chem. Educ.* **2017**, 94, 7, 932-935.
3. G. C. Hale; *J. Am. Chem. Soc.* **1925**, 47, 11, 2754-2763.
4. O. Bortolini; C. Chiappe; M. Fogagnolo; A. Massi; C. S. Pomelli; *Org. Chem.* **2017**, 82, 1, 302-312
5. W. Liu; L. Dang; Z. Xu; H. Yu; s. Jin; G. W. Huber; A*CS Catal.* **2018**, 8, 6, 5533-5541.
6. D. J. Chadderdon; L. Xin; J. Qi; Y. Qiu; P. Krishna; K. L. More; W. Li; *Green Chem* **2014**, 16, 3778−3786.

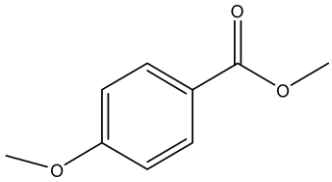
Appendix: Experimental Procedure and Product Characterization

Experimental procedure

The aldehyde (20 drops) was transferred into a specialized glass vial for the ElectraSyn 2.0 in addition to the alcohol (20m drops), acetonitrile (2mL), a very small amount of TBAF, and a stir bar to form the reaction vessel. The graphite electrodes were inserted into the reaction vessel, and the reaction was allowed to occur for a total of 5 hours with a current of 10 volts being applied. After these 5 hours, the excess solvents were evaporated and the crude mixture was run through a column that utilized silica gel. A ten percent mixture of ethyl acetate in hexane was used to separate the desired product. The product analysis and characterization using nuclear magnetic resonance (NMR) was carried out on all the products. This data is summarized below.

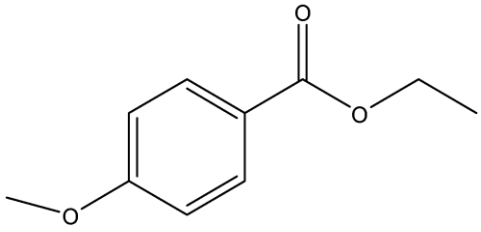
Product Characterization

Mb-1-42



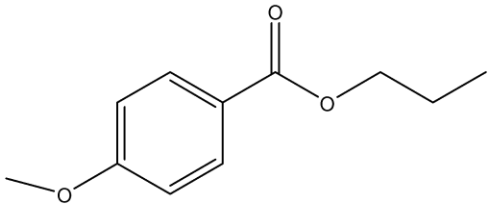
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.97 (d, *J* = 9.06 Hz, 2H), 6.90 (d, *J*=9.06 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 163.29, 131.48, 128.08, 122.58, 113.56, 55.41, 51.85

Mb-1-ethanol reaction



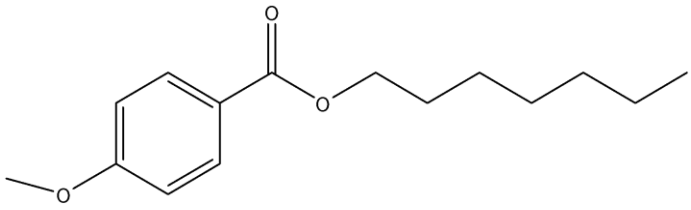
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.98 (d, J=9.12 H, 2H), 6.89 (d, *J*=9.12 Hz, 2H), 4.33 (quart, *J*=7.08, 2H), 3.84 (s, 3H), 1.36 (t, *J*=7.08 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.40, 163.30, 131.40, 122.93, 113.51, 60.57, 55.37, 14.30

Mb-1-58



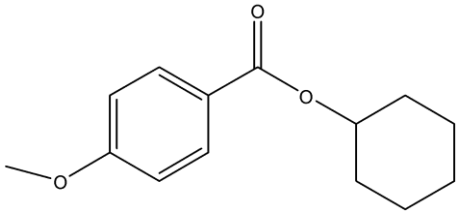
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.98 (d, *J*=8.98 Hz, 2H), 6.90 (d, *J*=8.98 Hz, 2H), 4.23 (t, *J*=6.84, 2H), 3.84 (s, 3H), 1.76 (sextet, *J*=7.30 Hz, 2H), 1.00 (t, *J*=7.30 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.28, 163.23, 131.53, 123.02, 113.39, 66.21, 55.40, 22.16, 10.51

Mb-1-59



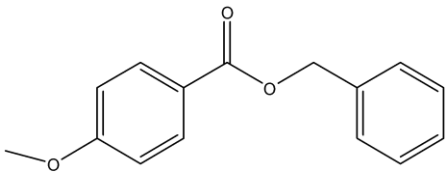
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 4.13 (d, *J*=8.36 Hz, 1H), 3.4 (s, 1H), 3.05 (d, *J*=9.72, 1H), 0.42 (t, *J*=6.61 Hz, 1H), 1.00; ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.21, 131.34, 123.11, 113.16, 64.77, 31.70, 28.96, 28.69, 25.97, 22.53, 14.01

Mb-1-60



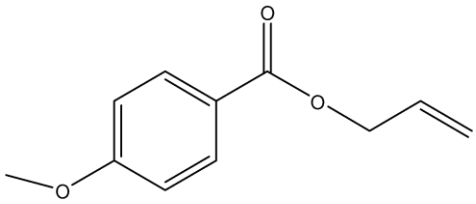
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.98 (d, *J*=9.30 Hz, 2H), 6.89 (d, *J*=9.30 Hz, 2H), 3.84 (s, 3H), 1.28 (m, 12H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 165.73, 163.14, 131.52, 123.51, 113.49, 55.42, 55.31, 31.68, 25.54, 23.72

Mb-1-62



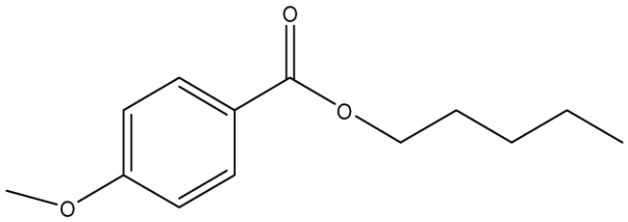
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 8.01 (d, *J*=9.19 Hz, 1H), 7.36 (m, 3H), 6.90 (d, *J*=9.19, 1H), 5.32 (s, 1H), 3.85 (s, 2H), 1.53 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 131.77, 122.49, 113.73, 66.29

Mb-1-64



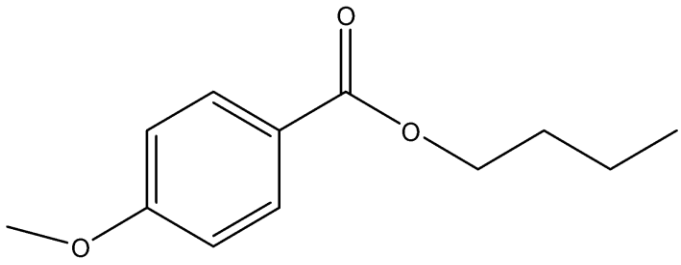
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.98 (d, *J*=8.98 Hz, 2H), 6.90 (d, *J*=8.98 Hz, 2H), 6.01 (m, 1H), 5.38 (d, *J*=17.16 Hz, 1H), 5.25 (d, *J*=10.66 Hz, 1H), 4.78 (d, *J*=5.58 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.00, 163.43, 132.51, 131.80, 122.60, 118.00, 113.58, 65.33, 55.45

Mb-1-68



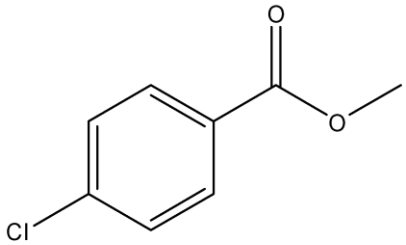
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.98 (d, *J*=8.83 Hz, 2H), 6.89 (d, *J*=8.83 Hz, 2H), 4.26 (t, *J*=7.13, 2H), 3.84 (s, 3H), 1.33-1.58 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.46, 163.20, 131.51, 122.98, 113.54, 64.75, 60.25, 55.38, 31.60, 25.25, 22.64, 14.08

Mb-1-63



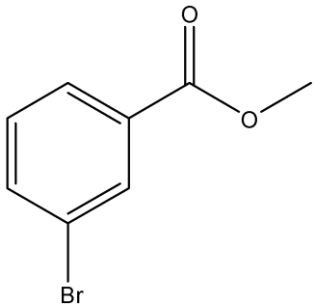
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 8.00 (d, *J*=9.19 Hz, 2H), 6.90 (d, *J*=8.27 Hz, 2H), 6.00 (m, 2H), 5.38 (d, *J*=17.65 Hz, 1H), 5.26 (d, *J*=10.70 Hz, 1H), 4.78 (d, *J*=6.69 Hz, 2H), 4.10 (quart, *J*=6.69 Hz, 1H), 3.84 (s, 3H), more? ; ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.34, 163.16, 131.45, 127.76, 122.92, 113.56, 66.36, 63.18, 55.35, 37.32, 25.29, 22.48

Mb-1-82



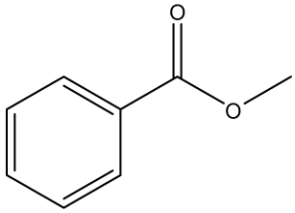
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.95 (d, *J*=8.96 Hz, 2H), 7.39 (d, *J*=8.96 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.19, 139.38, 130.92, 128.65, 128.54, 52.24

Mb-1-83



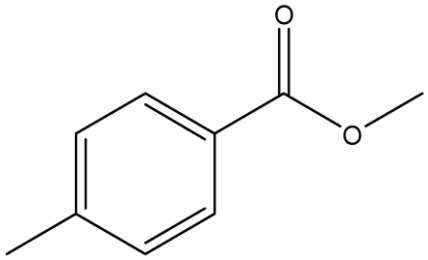
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 8.13 (s, 1H), 7.92 (d, *J*=7.86 Hz, 1H), 7.64 (d, *J*=7.86, 1H), 7.27 (t, *J*=7.86 HzHzH, 1H), 3.89 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 165.61, 135.74, 132.52, 131.94, 129.88, 128.09, 122.39, 52.33

Mb-1-80



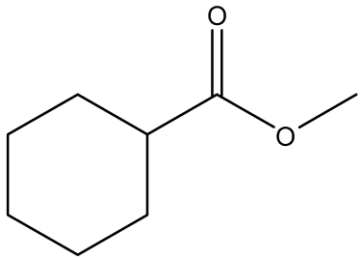
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 8.02 (d, *J*=7.59 Hz, 2H), 7.53 (t, *J*=7.59 Hz, 1H), 7.42 (t, *J*=7.59, 2H), 3.90 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 167.09, 132.84, 130.08, 129.49, 128.32, 52.04

Mb-1-81



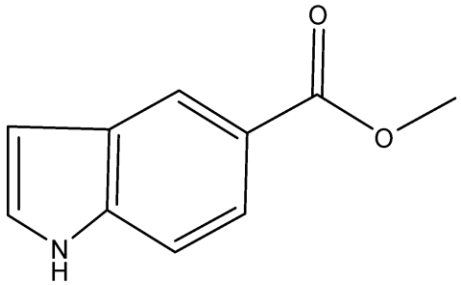
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 7.91 (d, *J*=8.33 Hz, 2H), 7.22 (t, *J*=8.33 Hz, 2H), 3.88 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 167.13, 143.56, 129.58, 128.06, 127.42, 51.93, 21.63

Mb-1-88



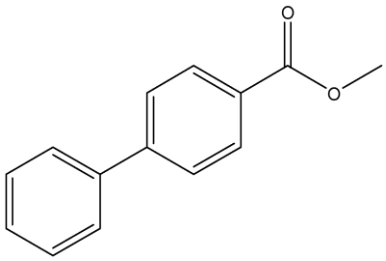
^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 3.63 (s, 3H), 2.27 (quintet, *J*=4.07 Hz, 1H), 1.18-1.92 (m, 12H)HzH; ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 176.57, 51.43, 43.06, 28.97, 25.70, 25.40

Mb-1-89



^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 8.40 (s, 1H), 7.89 (d, *J*=8.79 Hz, 1H), 7.39 (d, *J*=8.79 Hz, 1H), 7.26 (t, *J*=2.82 HzHzH, 1H), 6.63 (septet, 1H), 3.92 (s, 3H), 1.62 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 168.21, 138.38, 127.40, 125.41, 123.72, 123.32, 121.94, 110.66, 103.99, 51.83

MB-1-85



^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm) 8.10 (d, *J*=9.03 2H), 7.65(d, *J*=8.58 2H), 7.61(d, *J*=7.33 2H), 7.45 (t, *J*=7.00 2H), 7.38(t,J= 7.33 1H), 3.93 (s, 3H);^{13}C NMR (63 MHz, $CDCl_3$), δ (ppm) 166.97, 145.58, 139.95, 130.06, 128.87, 128.85, 128.10, 127.23, 126.98, 52.09