Synthesis of Butenolides

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Introduction

Fungal infections are common throughout the world. These infections are a result of invading fungi in the body in which the immune system cannot handle the injury.[1] The fungal infections or mycoses can also cause a wide range of diseases to humans that further lead to disseminated infections which involve the brain, heart, lungs, liver, spleen, and kidneys.[2]

The spectrum of mycoses is a result of the infection site, route of pathogen, virulence, and epidemiology of the fungus.[2] The infection of the site is typically based on the type, degree, and the host response to the mycoses. Infections can be further classified to the level of infection such as superficial, cutaneous, subcutaneous, or deep infection.

The route of infection in which the mycoses can take maybe exogenous or endogenous.[2] Exogenous will include examples such as airborne, or absorption. An endogenous infection will involve the colonization of the fungus or reviving an old colony. [2,3] The overall effectiveness of the fungi infection is mainly due to primary or opportunistic infections. For instance, if a healthy human were to get infected that would be due to a primary pathogen. In contrast, if a human who had a compromised immune system and got infected, this would be an example of an opportunistic pathogen. [2]

The fungi *Candida albicans* causes a very common opportunistic fungal infection referred to as Candidiasis.[3] Current treatments for this infection involve the use of antibiotics, cytotoxic therapy, corticosteroids, and vascular catheters. A differential diagnosis and associated treatment are difficult. Although there has been a recent development for new techniques for identifying and treating candidiasis. [3] Looking into new techniques lead researchers to the use of metabolites.

Metabolites are referred to as any substance that may be involved in a metabolic pathway. These are small biomolecules that are secreted from nature, or they can be synthetically made. They can be either primary or secondary metabolites, whereas the primary are directly involved with survival aspects for the organism, and the secondary metabolites are not. Moreover, the survivability of an organism is dependent upon the growth, development, and reproduction. Having metabolites for an extended period may lead to long term damage towards the organism's ability to survive.[3,4]

Bombardolides are part of the Coprophilous fungus, *Bombardioidea anartia.*[6] This fungus interferes with other competitive fungi by producing secondary metabolites that which indirectly inhibit growth. Knowing that secondary metabolites have these agnostic effects, researchers are trying to figure out how to utilize them as antifungal agents. There are two main solutions to obtain butenolides. These methods would make use of isolation or synthetic routes. Isolation techniques would involve separation from the butenolide from the matrix. Synthetic routes would make use of the chemicals and intentionally construct the desired butenolide.

The Tunicate *Lissoclinum patella* appears to have the bombardolide lissoclinolide. As well as, the actinomycete *Micropolyspora venezuelensis* releases tetrenolin. Both compounds are metabolites of similar structure to the bombardolides.[4] They are unsaturated butenolides that are not from the animal kingdom.[8] These include ligustilide from the *Ligusticum* and *Angelica* of the plant kingdom. *Penicillium* of the fungi kingdom does secrete carolic acid metabolite. The unsaturated

butenolides are similar to the γ-Lactones, but it is found that these compounds are inseparable mixtures of the entgegen and zusammen forms.[8]

In the mid-twentieth century, a metal complex, ruthenium (III) chloride (RuCl3) was found to catalyze an organic reaction which constitutes alkenes.[9] This type of organic reaction is referred as olefin metathesis. Incidentally, it is a method which redistributes double bonds, or olefins. On these bonds have desired substituents which are required to form the target molecule.

The initial complex of the ruthenium complex, $RuCl_2(PPh_3)$, was made in 1995. This referred as the first-generation Grubbs catalyst, named after the chemist Robert H. Grubbs, who had developed the synthetic pathway for this catalyst. There was a small drawback to this catalyst in which the reactivity was not as high compared to Molybdenum (Mo) catalysts. Thus, Grubbs continued to improve upon the first-generation catalyst for higher reactivity.[9] This led to the Grubbs second-generation catalyst which had better properties than the former catalyst (Figure 1).

Researcher Amir H. Hoveyda, worked with Grubbs to further improve the ruthenium catalyst. Thereafter, these researchers synthesized the Hoveyda-Grubbs catalyst which have been highly used for any olefin metathesis (Figure 1). With the renditions that were done on the Grubbs and Hoveyda-Grubbs catalyst, these catalysts were chosen to due to stability it had towards functional groups, air and moisture stability, and the wide range of solvent compatibility.

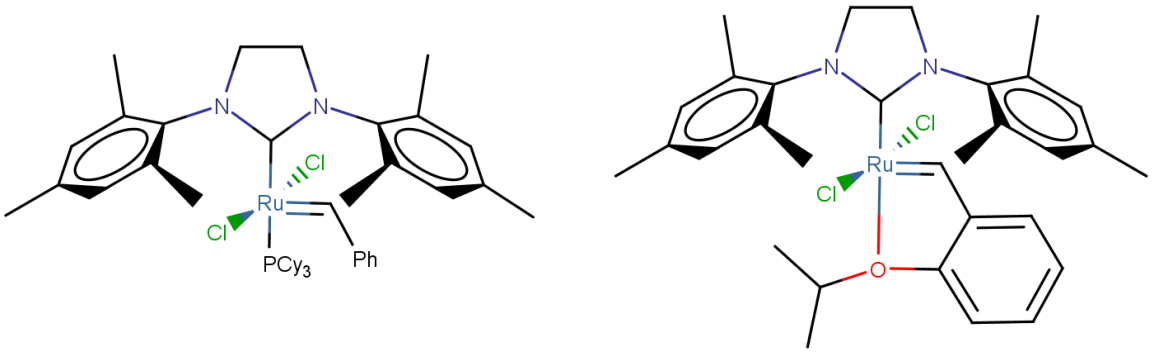

Figure 1. Ruthenium metal catalysts used for Ring Closing Metathesis (RCM). Grubbs generation II (Left) and Hoveyda-Grubbs generation II (Right).

This experiment involves the synthetic route in building a butenolide and involves the cyclization of 1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate using Grubbs' second-generation catalyst (Figure 2). Using this catalyst will allow for higher yield products and perform the RCM without strict conditions.

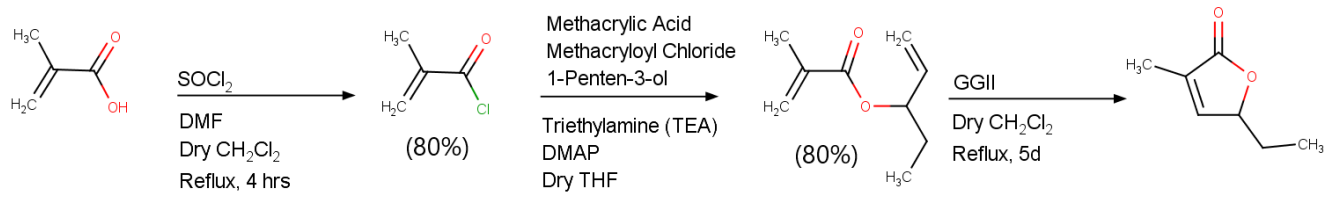

Figure 2. Reaction scheme of synthesizing an acyl chloride, ester, and butenolide.

Mechanism for RCM

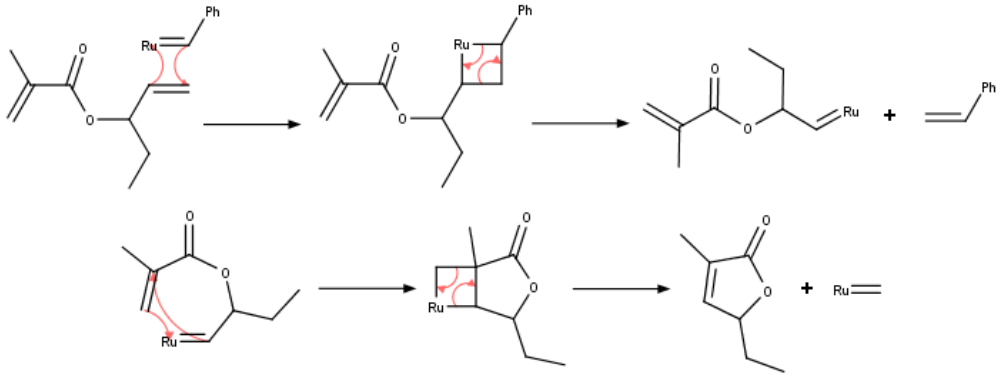

Figure 3. Ring closing metathesis of Grubbs' catalyst.

Experimental

Preparation of Methacryloyl chloride[13]

Placed 1 eq. methacrylic acid, 4 eq. thionyl chloride, 5 drops DMF, and dry DCM to reflux for 4 hrs. After the reflux, separation via distillation was done to retrieve the acyl chloride product.

Preparation of 1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate[14]

This procedure was performed under room conditions. There was 32 mmol of methacrylic acid, 32 mmol of acyl chloride, 32 mmol of 1-penten-3-ol, 64 mmol of TEA, 23 mmol of DMAP, and 30.0 mL of dry THF were mixed for 3 hrs. 30.0 mL of 10% HCl was used to quench the reaction. The organic solvent was then evaporated via nitrogen gas, and then extracted 3x using dry DCM. The organic layer was once again evaporated with nitrogen gas.

Results

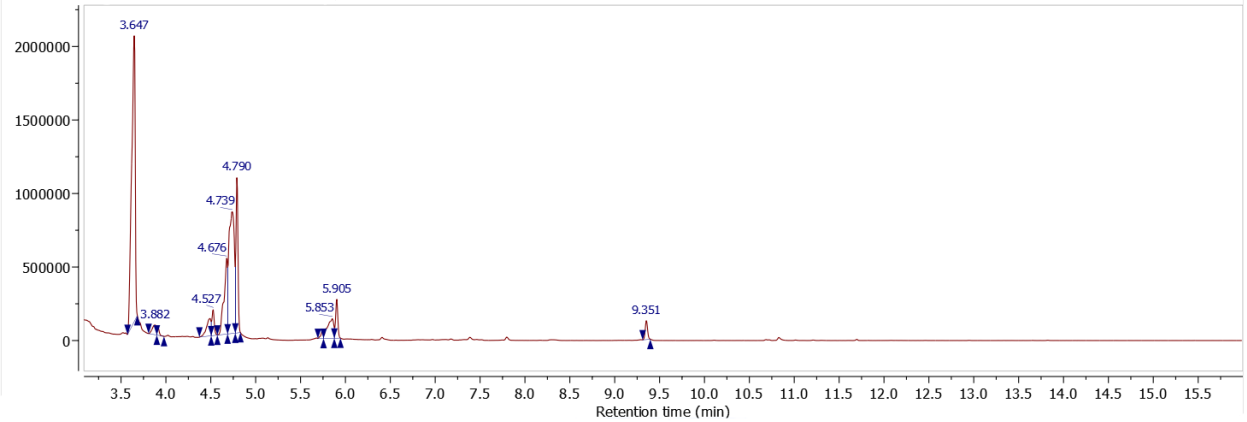

Figure 4. Total Ion Chromatogram (TIC) of Methacryloyl chloride.

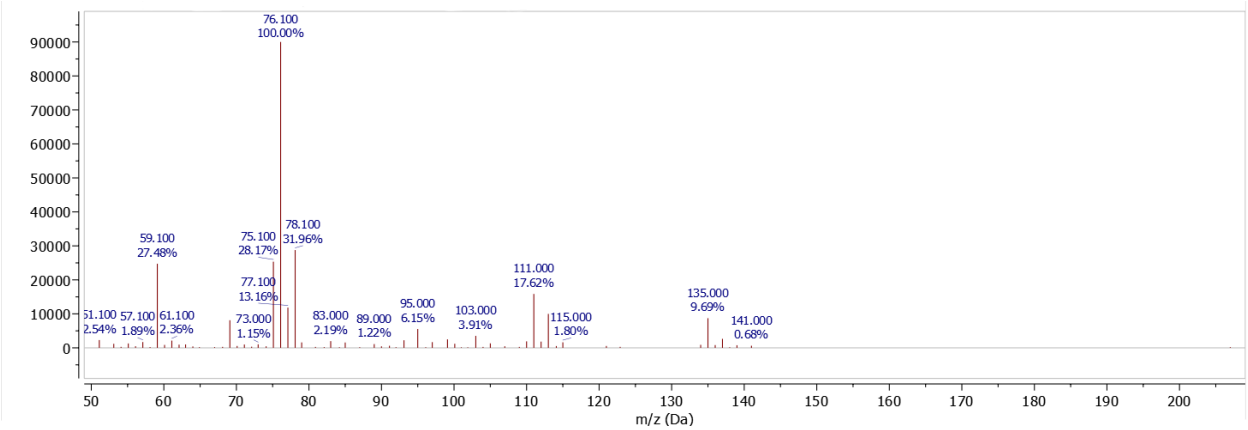

Figure 5. Mass spectrum of Methacryloyl chloride at 5.905 min.

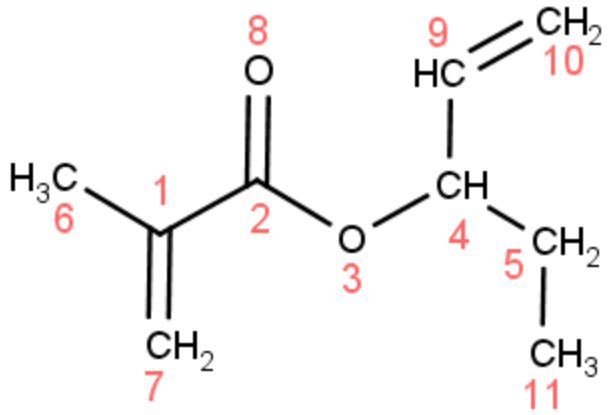

Figure 6. Atomic arrangement of 1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate for peak assignment.

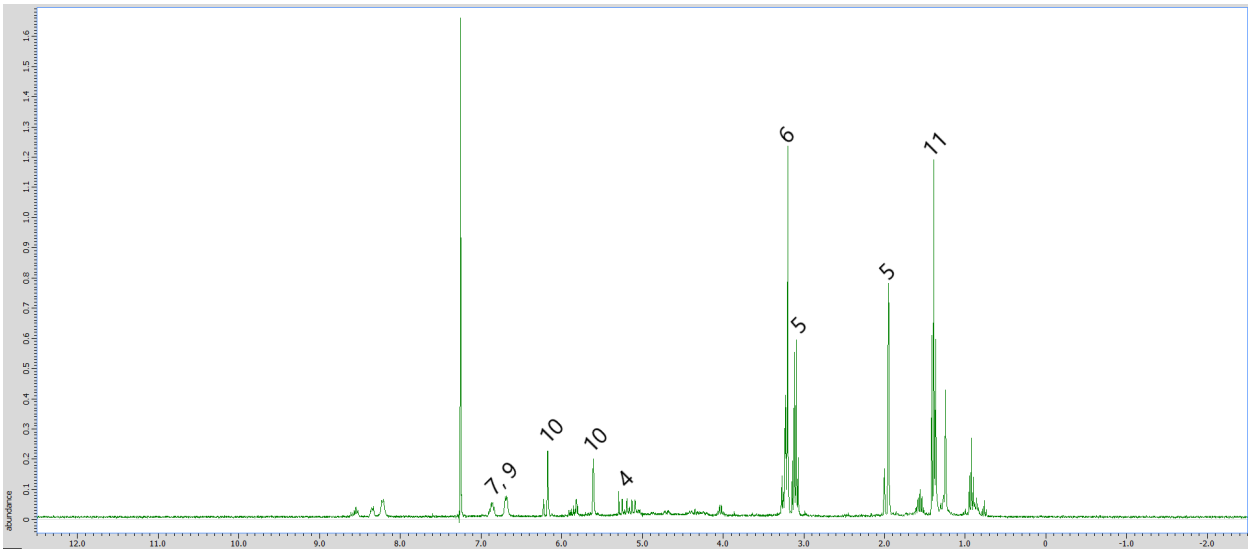

Figure 7. Labeled experimental ^{1}H NMR of 1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate.

Discussion

Methacryloyl Chloride

In Figure 5, at 5.905 min, CIMS *m/z* 104 (M^+, rel int 0.307), 105 (1.46), 103 (3.91), 100 (13.3), 69 (9.01).

The M^+ peak is indicative of the molecular weight of methacryloyl chloride, $C_4H_5{}^{35}ClO^+$ (m/z 104). However, this complex is being fragmented in the mass spectrum, the C-H bonds can be fragmented and will lead to a complex such as $C_3H_5{}^{35}ClO^+$ (m/z 103). The calculated isotopic abundance of Cl consists of, ^{35}Cl (75%) and ^{37}Cl (25%). Therefore, an observed 3:1 ratio for a

compound with a single chlorine atom is expected to be seen. In this analyte, the isotopic distribution is seen for ions $C_3H_5{}^{35}ClO^+$ (m/z 103) and $C_3H_5{}^{37}ClO^+$ (m/z 105). The C-Cl bond may also be easily fragmented, and thus leading to an ion such as $C_4H_5O^+$ (m/z 69). This product was believed to be at 80% conversion due to impurities that were in the reactant, thionyl chloride. From looking at Figure 5, there is evidence that the acyl chloride product has been made.

1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.867 – 6.683 (m, 3H), 6.229 (ddd, 1H), 6.174 (ddd, 1H), 5.294 – 5.031 (dtt, 1H), 3.200 (d, 1H), 3.144 - 3.170 (dqd, 1H), 1.951 (dqd, 1H), 1.389 (t, 3H).

Due to an incomplete conversion of the methacryloyl chloride, there were expected to be impurities in the ^{1}H NMR which lead to peak shifts. Referring to Figure 7, it has shown that the ester product has been made, but there are impurities in this product that will need to be further extracted.

Conclusion

This protocol has shown that the acyl chloride and ester product can be made from simple reactants. Furthermore, the characterization via mass spectroscopy and ^{1}H NMR, provides evidence that the co-products are made. With this procedure, it moves a step closer in creating the target product, a Butenolide. However, there will need to be refinement to the protocol for improved yield and purity for both the acyl chloride and ester products.

Future Work

1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate

Additional characterization, e.g., GC-MS, will need to be carried out such that further evidence may show that the desired target ester was synthesized. More specifically, the compound that has a retention time at 9.357 min and a peak at 139.000 m/z will need to be identified.

Ring Closing Metathesis (RCM)

In future work the extension of the current synthesized product would be ideal for RCM.

Experimental for RCM

0.05 eq. of Grubbs (II) will be added to the 1-Ethyl-2-propen-1-yl 2-methyl-2-propenoate with 1 eq. of 0.05 M DCM. The mixture will be refluxed for 5 days. Purification of this compound will be conducted through a column chromatography by silica gel with 3:1 of pentane to ethyl acetate to yield the γ-Lactone. (13)

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How can I perform a reaction of conversion of benzoic acid to benzoyl chloride using thionyl chloride, and monitor the progress of this reaction?

https://www.researchgate.net/post/How_can_I_perform_a_reaction_of_conversion_of_benzoic_acid_to_benzoyl_chloride_using_thionyl_chloride_and_monitor_the_progress_of_this_reaction.

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