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Synthesis of Medicinally Relevant Thiazolyl Aryl Ketones Under Mild Conditions

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Abstract

Purpose: The growing amount of clinical resistance observed in current antifungal drugs and in anti-HIV pharmaceuticals is a concern in the medical community. The purpose of this study is to develop a mild synthetic process for biomedically relevant thiazolyl aryl ketones that can be used to develop antifungal and anti-HIV drugs. We hypothesized that the proposed synthetic technique would be more efficient, produce fewer unwanted byproducts, and be more tolerant of functional groups than existing methods.

Methods: Prior to each of the ketone reactions, the necessary salt was synthesized by mixing thiazole and 9-bromofluorene neat in a reaction tube heated to 85 °C. The reaction was monitored for the disappearance of 9-bromofluorene, at which point the heating was stopped and the solid product was triturated to remove impurities and characterized using ^{1}H NMR analysis. For each of the various ketone reactions, the aldehyde and base were added to a reaction tube and heated to 60 °C. Once heated, a solution of the salt (3-fluorenylthiazole) was mixed with the solvent, either methanol or THF, and was added dropwise via syringe. Conversion of the aldehyde to the ketone product was monitored by thin layer chromatography (TLC). The product ketone was purified using column chromatography and analyzed for purity by ^{1}H NMR spectroscopy. This study was the repeated for each of the chosen aldehydes. The preparation of thiazolyl salicyl ketone was further analyzed for solvent effects by the introduction of 5% and 10% water, respectively, using otherwise identical reaction conditions. In these reactions, the ketone was isolated using preparative TLC and gravity filtration to separate the silica gel from the desired product. If the ketone was produced after the addition of water, then the reaction may be able to be conducted without the use of anhydrous methanol solvent. Instead, methanol bought in bulk could be substituted and the cost of production would be substantially reduced.

Results: The 3-fluorenylthiazol salt was produced in 91% yield. The yields for the thiazolyl phenyl ketone, thiazolyl 4-fluorophenyl ketone, and the thiazolyl salicyl ketone were 11%, 50%, and 55% yield respectively. Production of thiazolyl salicyl ketone with the addition of 5% water into the solvent produced the ketone with 11% yield. Production of thiazolyl salicyl ketone with the addition of 10% water into the solvent produced a ketone with 13% yield in trial 1 and 56% yield in trial 2.

*Discussion***:** The study found that the two-step synthesis method was successful in producing the desired ketones. These findings suggest that this reaction mechanism could be further optimized to increase reaction yield in order to produce medicinally relevant ketones under mild conditions. Also, upon the addition of water to the solvent, the thiazolyl salicyl ketone was able to be produced in moderate yields in one trial. In this particular trial, salt and salicylaldehyde were added before the solvent and the base suggesting the order that reagents were added affected the percent yield of the ketone. The success of the trial provides promising results that suggest the synthetic method could be conducted without the use of anhydrous methanol thereby decreasing the cost of synthesis by utilizing water in replacement for methanol. Also, substituting water for methanol would provide a safety advantage if enough methanol is replaced so that the solvent is no longer flammable. Overall, the results provide the conclusion that the synthetic technique could be used to produce thiazolyl aryl ketones under mild conditions.

Introduction

Azoles are five-membered aromatic heterocyclic rings that contain at least one nitrogen atom along with at least one additional non-carbon atom including nitrogen, sulfur, or oxygen (Sheehan et. al., 1999). These common structures are extremely useful and have many industrial and pharmaceutical applications. Heterocyclic compounds have been used in the synthesis of dyes, pesticides, herbicides, and most important for this study, the sub-class of azoles have been used in the production of drugs with various antifungal and anti-human immunodeficiency virus (HIV) properties (Dua et.al., 2011). In 2011, it was estimated that 90% of new drugs contain a heterocyclic system (Dua et.al.). The interest in using these compounds, and azoles specifically, lies in their ability to participate in or hinder biochemical reactions in the body (Dua et. al., 2011). Though the mechanism of action is not specific to azoles, these compounds exert their effects by changing the three-dimensional conformation of proteins altering their effects on the body's tissues or inhibiting their action (Nelson et. al., 2014). This project focuses on the production of thiazolyl ketones in a mild and efficient manner. Due to the medicinal properties of azole containing compounds, an improved synthesis is particularly attractive.

*AntiFungal Properties***:** The mortality rate associated with invasive fungal infections, especially in immunocompromised patients, is a growing concern for the medical community (Badali et. al., 2013). A deficient immune system may allow certain opportunistic fungi to become life threatening in immune impaired patients. These at-risk patients include those suffering from conditions such as HIV, cancer, any undergoing cytotoxic or immunosuppressive therapies, transplant recipients, and those with breaks in skin or mucosal barriers (Pagniez et. al., 2002). The severity of fungal infections in these patients has made it more important to develop new

antifungal agents that are efficiently synthesized while still effective in their inhibitory affect on fungi. Current treatment methods are proving inadequate as fungal resistance to therapies are growing, furthering the need for improved, more numerous antifungal agents (Yilmaz et. al., 2013). In study analyzing FDA approvals of compounds with pharmaceutical targets, the number of approvals per year has decreased 75% from its peak in 1996, and only 11.7% of these current approvals target fungal species (Kinch et. al., 2014). These statistics show that it is vital to produce antifungal compounds that overcome resistance.

Drugs such as fluconazole and clotrimazole, (Figure 1), are common azole containing medications used to target the synthesis of an essential fungal membrane component, ergosterol (Nelson et. al., 2014). They inhibit the cytochrome P_{450} enzyme 14α-demethylase, thereby preventing the conversion of lanosterol to ergosterol (Nelson et. al., 2014). Ergosterol is a vital part of the plasma membrane structure of a fungal cell and contributes to membrane fluidity much like cholesterol does to mammalian membranes. A decrease in the production of ergosterol leads to a decline in membrane integrity, a leak of cytoplasmic components, and ultimately affects the growth and reproduction of the fungal cell (Nelson et. al., 2014). A promising thiazolyl antifungal agent, abafungin, (Figure 1) inhibits the enzyme sterol-C-24-transferase, affecting ergosterol synthesis and membrane integrity. Abafungin also seems to have some direct effects on the plasma membrane, possibly through interaction with specific phospholipids, although the exact mechanism of action still requires further study (Borelli et.al., 2008). Abafungin's multiple modes of action make the drug less susceptible to the development of fungal resistance to its properties.

Each of these compounds have mechanism that capitalize on inhibiting the production of vital fungal membrane proteins thereby causing a decline in membrane integrity in the overall

fungal cell population. This study explores the synthesis of molecular entities that are intermediates in the production of pharmaceuticals compounds with these antifungal benefits.

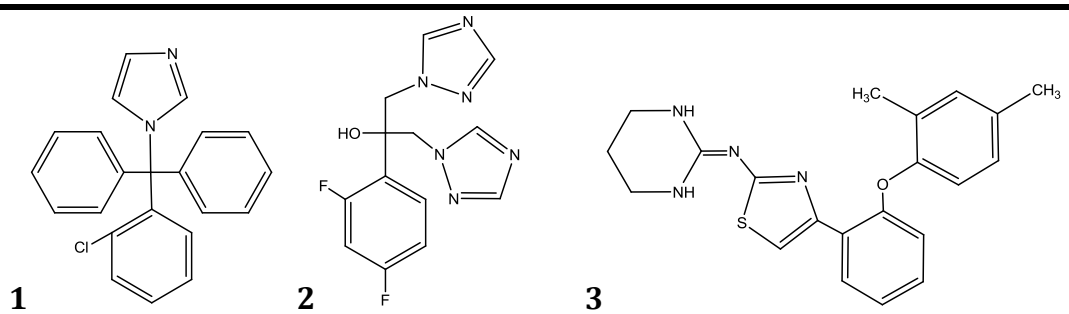


Figure 1. The molecular structures of Clotrimazole, (1) Fluconazole (2), and Abafungin (3).

Uses as a Reverse Transcriptase Inhibitor: Treatment of HIV has dramatically improved in the last twenty years after the implementation of combination therapy, whereby HIV patients take two or more anti-HIV drugs together (Romines et. al., 2006). Nonnucleoside reverse transcriptase inhibitors (NNRTI's) have been important to this line of therapy due to their ability to allosterically bind to aspartate and other catalytic residues of the reverse transcriptase active site, preventing it from converting viral RNA into DNA (Gerwurz et. al., 2004). Therefore, NNRTI's interaction with reverse transcriptase blocks harmful genetic information from being incorporated into the host cell's genome. Though the use of NNRTI's have been demonstrated as efficient in fighting HIV, certain point mutations that affect bases that code for amino acids near the drug binding pocket are associated with the development of clinical resistance to these drugs. In a study of first-time anti-retroviral treatments in patients from 44 U.S. cities, nearly one-third of participants had a decreased therapeutic response to all currently used NNRTI's and 18% had a decreased therapeutic response to at least one NNRTI (Romines et. al., 2006). Due to an increasing amount of resistance, it is important to identify compounds that can be used as NNRTI's and that prove efficacious against resistant HIV strains. A promising potential template for NNRTI's are phenyl heteroaryl ketones similar to those produced in this study. These

compounds and those similar were found to have excellent potency in vitro to mutants that were resistant to other prominent NNRTI's such as nevirapine and efavirenz (Romines et. al., 2006). In 2001, a thiazolyl aryl ketone compound and benzophenone, seen in (Figure 2), was patented due to its inhibitory affect on reverse transcriptase (Andrews et. al., 2001). When used as NNRTI's, the relevance of these compounds could increase the receptivity to treatment in otherwise resistant strains of HIV. Overall, thiazolyl compounds have a variety of medicinal uses, and research on these compounds will prove vital in the progression of treatment for diseases in this area, as well as the previously discussed treatment of fungal infections.

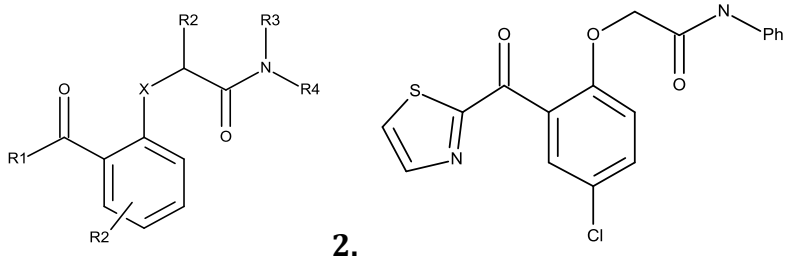
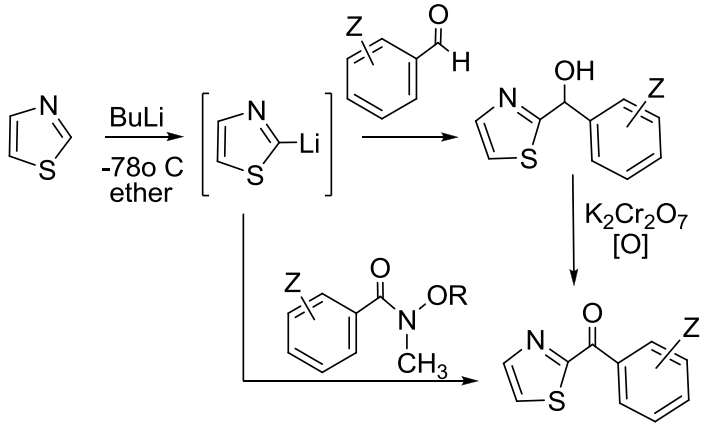


Figure 2. The molecular structures of a patented benzophenone (1) and a thiazolyl compound (2) used as an inhibitor of reverse transcriptase.

Previous Methods of Synthesis: Thiazolyl ketones are traditionally synthesized in harsh conditions as in (Scheme 1) by utilizing a Grignard reagent, an organolithium compound, or a Weinreb Amide, whereas the project I conducted focuses on the synthesis of thiazolyl ketones under less hazardous conditions and a novel mechanism. Under non-mild conditions, this type of reaction can be carried out via a Grignard reagent, an aryl-magnesium halide, or an organolithium compound to form secondary alcohols which can then be deprotonated using an oxidizing agent (Organometallic chemistry," 2013). Potassium dichromate, the oxidation agent used in (Scheme 2), is extremely toxic and a known carcinogen. Producing the ketones without the use of harmful reagents is desirable in order to provide the best laboratory safety during production. Another common issue with this method is the over-addition of the Grignard reagent

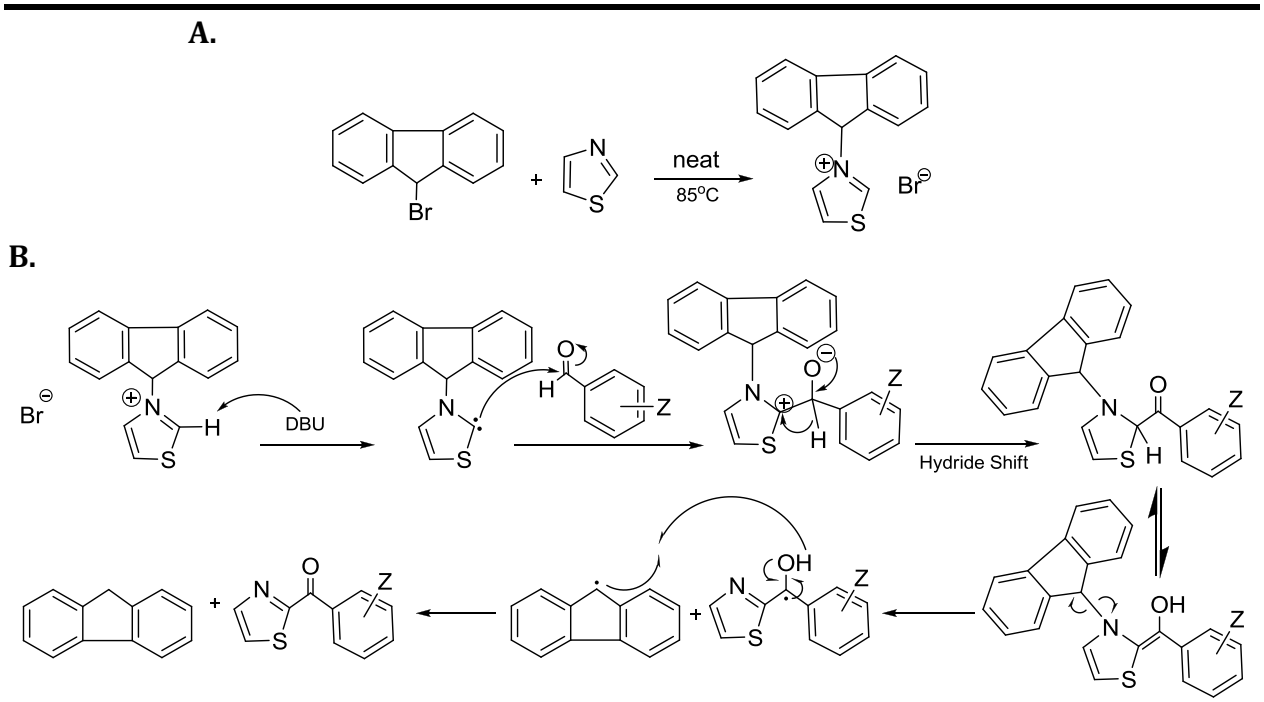
resulting in the formation of tertiary alcohols even with carefully controlled conditions lowering the efficiency of this synthesis method. To combat this, an alternative synthesis route uses a Weinreb Amide along with a Grignard reagent to produce two subsequent nucleophilic reactions to yield the ketone (Scheme 1). Though this method does not have problems with over-addition, reactions with Grignard reagents are very temperamental due to their nature to react violently with water and the requirement that they be conducted at very low temperatures. Also, greater than 2 equivalents of the nucleophilic reagent are needed to produce substantial results (Liu et. al., 2002). Finally, there is risk that the leaving group from the Weinreb Amide could deprotonate a hydrogen-containing substituent group, for example the hydroxyl group in salicylaldehyde, before the nucleophilic between the amide and aldehyde therefore creating an unwanted side product. The purpose of this study is to develop a mild synthetic process of biomedically relevant thiazolyl aryl ketones that would be more efficient, produce fewer unwanted byproducts, and more tolerant of functional groups than existing methods.



Scheme 1. Production of ketones using a Grignard reagent followed by oxidation of the alcohol, and using and an alternative route using a Weinreb Amide with a Grignard reagent.

In this study, thiazolyl ketones were synthesized in two steps by first producing a salt, then by reacting the created salt with various aldehydes. The ketone products were produced using benzylic aldehydes of various levels of nucleophilicity using: benzaldehyde,

salicylaldehyde, 3-pyridinecarboxylaldehyde, 4-fluorobenzaldehyde, and with ortho-tolualdehyde. The mechanism is believed to occur via radical intermediates and can be seen in (Scheme 2).



Scheme 2. (A) Salt Formation (B) Proposed mechanism for the mild synthesis of thiazolyl ketones.

Methods

Salt Formation: In order to create the necessary salt for the process, 9-bromofluorene and thiazole were mixed in order to produce 3-fluorenylthiazole. 9-bromofluorene was chosen due to its ability to produce a stable radical intermediate and is the limiting reagent. Both reactants were mixed together neat in a pressure tube at room temperature. The tube was capped and heated to 85 ^{o}C. The mixture was then monitored for the appearance of a solid by crude NMR to see the disappearance of the limiting reagent. Once appeared, the solid product was triturated with diethyl ether to remove any soluble organic impurities. The remaining product was dried using a vacuum pump for 2 hours. ^{1}H NMR spectroscopy was used to confirm that the salt has been formed.

Ketone Synthesis: For the formation of the final ketone product, one of the various aldehydes identified as reagents in the study and 1,8-diazabicycloundec-7-ene (DBU) were added neat to a reaction tube. The tube was capped and heated to 60 °C. Once heated, a solution of the salt and methanol was added to the aldehyde-containing reaction tube dropwise via syringe. The reaction tube was monitored periodically with thin-layer chromatography (TLC) for the conversion of aldehyde to the ketone product.

Purification of the Ketone-Containing Product: Column chromatography was performed to isolate the ketone beginning with a 1:99 ethyl acetate: hexane solvent and incrementally increasing in polarity as each fraction of reaction product was collected. Each fraction collected from the column will be characterized using TLC analysis in 10:90 ethyl acetate: hexane. Using this evaluation, the product-containing layer was identified and isolated. The product solution

was lastly concentrated using the rotary evaporator then dried using the vacuum pump for at least 24 hours.

Final Ketone Product Analysis: The final dried ketone product was analyzed by using ^{1}H NMR spectroscopy as well as a calculation of percent yield to confirm this method's efficiency. The study will then be repeated for each of the chosen aldehydes.

Further Analysis of the Effects of Polarity in the Solvent on the Formation of Thiazolyl Salicyl Ketone: The same synthesis method as described above with slightly different conditions was conducted to produce the salicylaldehyde containing ketone. In this portion of the study, salicylaldehyde and 1,8-diazabicycloundec (DBU) were added neat to the reaction tube. The solution was capped and heated to 60 °C. Once heated, the solution of the salt, 3-fluorenylthiazole, and methanol solvent solution containing 10% water was added to the reaction tube. The introduction of water into the solvent added a greater amount of polarity to the reaction environment and the effects were evaluated.

Another trial with 10% water was repeated manipulating the reaction conditions in order to evaluate if this would increase the product's percent yield. In this case, the salt and salicylaldehyde were first added to the reaction tube and heated to 60 °C. Then, the solvent, again 10% water and methanol, was added followed by the DBU base. The reaction progression was monitored using TLC analysis in order to determine the formation of the ketone product.

Lastly, the reaction was then repeated using 5% water. The same methods were used to conduct this reaction as in the second 10% reaction. The salt and the salicylaldehyde were first added to the reaction tube and heated to 60 °C. Then, the solvent, again 5% water and methanol, was added followed by the DBU base.

In order to isolate the ketones, each of the reactions ran in 10% water and 5% water was isolated through a preparative TLC. The ketone containing band, yellow in color and usually near the middle of the TLC plate, was collected one along with the silica gel in that band of the plate. The product band was separated from the silica gel using gravity filtration and dichloromethane as the solvent. In each of the water-containing reactions these purification techniques were used. All of the collected products were concentrated using the rotary evaporator and dried on the vacuum pump for 24 hours. The reaction yield was calculated and the products were characterized using ^{1}H NMR spectroscopy.

Results

After subjecting the 9-bromofluorene and thiazole to reaction conditions, the 3-fluorenylthiazole salt (**1**) was produced a white solid obtained in a 91% yield. The ^{1}H NMR signals observed were at 7.33 (singlet, 1H), 7.42 (triplet, 2H), 7.60 (multiplet, 4H), 8.05 (multiplet, 3H), 8.32 (doublet, 1H), and 10.63 (singlet, 1H) ppm. The reaction with benzaldehyde and the previously produced salt resulted in a mixture of products. The desired product was isolated from the filtrate via column chromatography, and a yellow compound confirmed to be the thiazolyl phenyl ketone (**2**) isolated in 11% yield. The ^{1}H NMR signals confirmed the formation of the product and were observed at 7.56 (triplet, 2H), 7.67 (triplet, 1H), 7.75 (doublet, 1H), 8.13 (doublet, 1H), 8.51 (doublet, 2H). The ketone-forming reaction was repeated with 4-fluorophenyl ketone as the chosen aldehyde. The 4-fluorophenyl ketone (**3**) was isolated using column chromotography in 50% yield. The ^{1}H NMR signals confirmed the formation of the product and were observed at 7.04 (multiplet, 1H), 7.25 (multiplet, 2H), 7.40 (multiplet, 2H), 7.74 (multiplet, 1H). Again, a reaction was conducted with salicylaldehyde and the 3-fluorenylthiazole salt to produce the thiazolyl salicyl ketone (**4**), a yellow solid, with 55% yield. The ^{1}H NMR signals confirmed the formation of the product and were observed at 7.05 (multiplet, 2H), 7.53 (triplet, 1H), 7.71 (doublet, 1H), 8.14 (doublet, 1H), 9.19 (doublet, 1H), 12.18 (singlet, 1H). Reactions with the aldehydes 3-pyridinecarboxylaldehyde and with ortho-tolualdehyde were conducted. The reaction resulted in complex compound mixtures that were unable to be isolated from each other during column chromatography and the ^{1}H NMR did not produce clean compound results.

The reaction with salicylaldehyde was further analyzed upon the addition of water to the solvent. The reaction was conducted with the addition of 5% water into methanol and the

thiazolyl salicyl ketone (**5**) was isolated via preparative TLC with 11% yield. The ^{1}H NMR signals confirmed the formation of the product and were observed at 7.05 (multiplet, 2H), 7.55 (triplet, 1H), 7.79 (doublet, 1H), 8.15 (doublet, 1H), 9.21 (doublet, 1H), 12.17 (singlet, 1H). The reaction was repeated with increasing the amount of water in the reaction environment.

The first trial of the reaction with 10% water produced thiazolyl salicyl ketone (**6**), a yellow compound, was isolated via preparative TLC with a 13% yield. The ^{1}H NMR signals confirmed the formation of the product and were observed at 7.04 (multiplet, 2H), 7.58 (triplet, 1H), 7.80 (doublet, 1H), 8.15 (doublet, 1H), 9.21 (doublet, 1H), 12.19 (singlet, 1H). These were reasonably the same signals observed in the previous reaction so the product was confirmed to be produced. To test whether the reaction yield could be increased, production of the thiazolyl salicyl ketone (**7**) was repeated after manipulating the order that each of the reagents were added to the reaction tube. After isolating the reaction compound via preparative TLC, the reaction yield was 56%. The ^{1}H NMR signals confirmed the formation of the product and were observed at at 7.04 (multiplet, 2H), 7.52 (triplet, 1H), 7.76 (doublet, 1H), 8.15 (doublet, 1H), 9.17 (doublet, 1H), 12.20 (singlet, 1H). An almost identical ^{1}H NMR to those previously observed for the thiazolyl salicyl ketone increased our confidence that the ketone was formed in good yield. A summary of the ketones produced and their various yields can be seen (Figure 3).

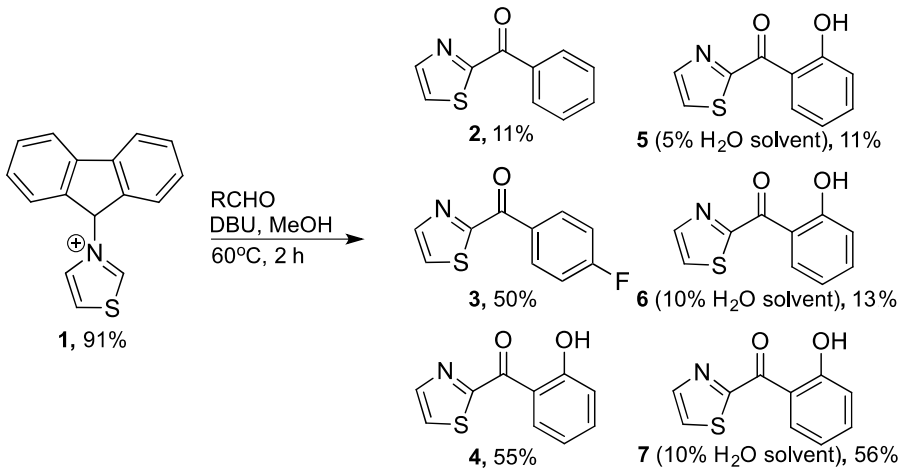


Figure 3. The figure shows the various compounds produced in the study, including the reactant salt, along with each of their percent yields.

Discussion

The purpose of this study was to analyze a two-step synthetic technique for producing thiazolyl aryl ketones. The main findings of the study were that this method was successful in the production of ketones using aldehyde reactants of various levels of nucleophilicity with moderate yields. Further analysis of the synthetic method provided promising data to show that water could also be introduced into the solvent and the reaction could still proceed again with moderate yields. In the first step of the method, the production of the salt proved to deliver good yields with easily reproducible methods along with the minimization of solvent waste. The results showed that the highest yields for this reaction were in the production of the 4-fluorophenyl ketone and the thiazolyl salicyl ketone, and lower in the production of the thiazolyl phenyl ketone. One explanation for the much lower yield of the thiazolyl phenyl ketone is the possibility of rearrangement products. In another study conducted by Ayinuola, a reaction with the 3-fluorenylthiazole salt with benzaldehyde under similar conditions produced a 20% yield and three rearrangement products (2015). In contrast to the study by Ayinuola, the ketone was only being isolated in this study, and the possibility of the appearance of rearrangements was not analyzed. These possible rearrangement products could be the subject of further study in order to determine their impact of reaction yield. Previously identified rearrangement possibilities can be seen in (Figure 4) (Ayinuola, 2015). Also, reactions with aldehydes 3-pyridinecarboxylaldehyde and ortho-tolualdehyde resulted in complex reaction mixtures that did not result in a clear ketone band in column chromatography to be isolated. As compared to a synthesis method using a Weinreb Amide, which could deprotonate the hydrogen in salicylaldehyde forming an unwanted product, this synthesis method can combat this unnecessary byproducts.

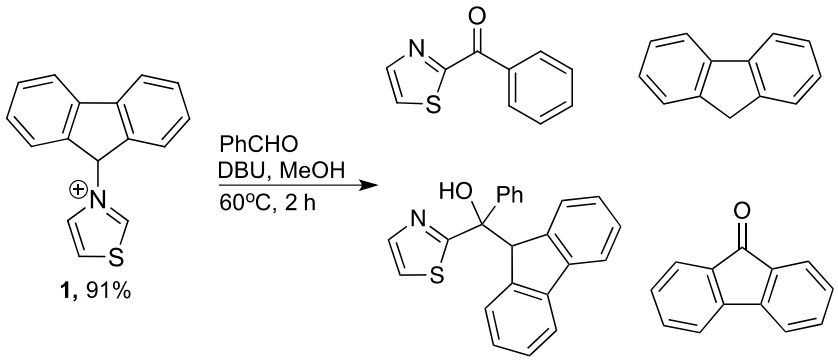


Figure 4. The figure shows possible rearrangement products that could have formed and caused the thiazolyl benzyl ketone produced in the study to have a lower yield than expected (Ayinuola, 2015).

Finally, the introduction of water into the solvent produced interesting results. In the first trial, the salicylaldehyde and the base were added before the salt and solvent thereby producing much lower yields than in Trial 2. It seems that 10% water solvent yields were optimized only when the salt and salicylaldehyde were added before the solvent and the base. These reaction conditions were repeated with 5% water and again produced a low yield of ketone. The hypothesis was that with a lower amount of water, the reaction would behave more like the trial with no water and would produce closer to moderate yields. This was not observed, and more experimentation needs to be done in order to optimize conditions for a reaction with water and to consider how the introduction of water into the reaction environment affects the ketone formation. Even so, one successful trial after adding water to the solvent provides promising resulting that the method may be able to be conducted while substituting methanol for water. By substituting water for substantial amounts of methanol, the cost of synthesis could be dramatically decreased. The success of the 10% trial provides promising data to suggest that water could be substituted for methanol without dramatically effecting the reaction. Along with a cost benefit, substituting water for methanol could provide a safety advantage if enough water was added so that the solvent is no longer flammable. An increase in safety and cost decrease

would prove beneficial with more widespread production of these compounds for their ultimate pharmaceutical uses, and would make this synthetic technique more desirable for commercial uses.

Limitations

A limitation in this study is human error when isolating the ketone product. In purification by column chromatography and preparative TLC, the remaining aldehyde band and the product band are extremely close together. It takes precision to isolate the band from the remaining reactants. This involves manipulation of solvent polarity when conducting column chromatography in order to collect the ketone without any aldehyde contaminant.

Conclusion

The purpose of this study was to determine if the two-step proposed synthetic technique was successful in producing medicinally relevant thiazolyl aryl ketones. We found that while the synthesis technique is successful in producing the desired ketones, more research needs to be done in order to optimize the reaction yield. Still, this study helped to analyze a technique that minimizes solvent waste and is conducted under less harmful conditions than previously utilized. These methods could potentially make the production of thiazolyl ketones a more effective synthetic process that produces fewer unwanted byproducts and is more tolerant of functional groups than existing methods. Also, the success of a trial after the addition of water into the solvent provides promising results suggesting that the reaction could be conducted while substituting water for methanol. This could make the production of these pharmaceutical intermediates more suited for commercial production due to reduced production costs and an added safety advantage. Overall, the results provide the conclusion that the synthetic technique could be used to produce thiazolyl aryl ketones under mild conditions.

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