A Two-Step Synthesis of Avobenzone.

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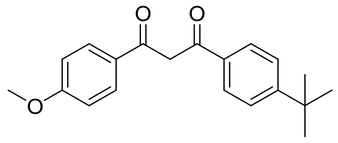
Abstract

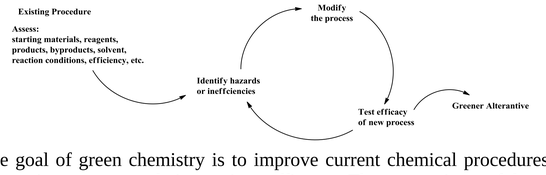
Avobenzone is an important agent in sunscreen that reacts with the full spectrum of UVA/UVB light. In Fact, avobenzone has one of the largest UV light absorbance ranges of all sunscreen agents. The wide absorbance range of avobenzone helps the sunscreen better protect the skin. This project involved two steps to synthesize avobenzone. Starting with 4-tert-butylbenzaldehyde, 4-methoxyacetophenone, and a base, an Aldol reaction was used to create a ketol intermediate. This step involved experimentation with several bases, including sodium hydroxide and potassium-tert-butoxide, to attempt to stop the product at this intermediate ketol form. Two different mixing methods were also compared in the synthesis of this ketol intermediate. The second step involved conversion of the ketol to the diketone avobenzone product after combination with an oxidizing agent. To make this synthesis more green a one-step synthesis relying on a Claisen reaction was also attempted.

Background on Avobenzone



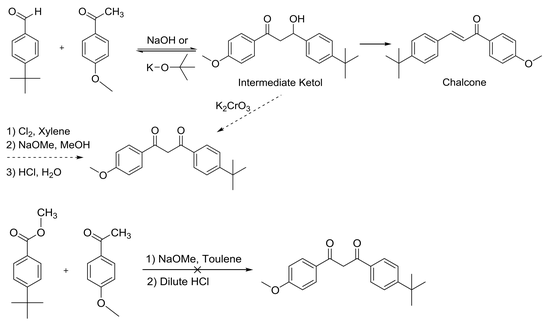
Avobenzone is a sunscreen agent that protects against the full spectrum of UV light. Of all sunscreen agents, avobenzone has one of the largest absorbance spectrums, absorbing light between 320 – 400 nm (peak absorption ~ 360 nm). Exposure to UV rays is a leading cause of skin cancer, and so use of an effective sunscreen, like avobenzone or avobenzone in combination with other agents, helps to lower risk of developing skin cancer. Avobenzone is specifically the most effective sunscreen agent against UVA rays. Avobenzone is susceptible to photodegredation, and therefore it is important that avobenzone be combined with photostabilizers in the final sunscreen product.

Background on Green Chemistry



The goal of green chemistry is to improve current chemical procedures by decreasing waste and increasing efficacy. The most impactful green chemistry changes make a reaction more efficient, followed by improving safety, improving the environmental fate, and decreasing cost. In this two step synthesis of avobenzone, green chemistry was incorporated by an alternate synthetic procedure with only one step. This increased the efficiency of the procedure. The two-step procedure is an aldol reaction, which produces a chalcone product after the first step. Chalcones have many biological implications, including its anticancer, antiulcer, antioxidant, and anti-inflammatory properties. The one-step procedure is a Claisen reaction, which creates diketones. Diketones are extremely useful starting materials for several reactions in research and in industry. These include use in polymer technology, as active pharmaceutical ingredients such as antidiabetic and antiasthmatic drugs, for monitoring of air pollution, and as fuel additives.

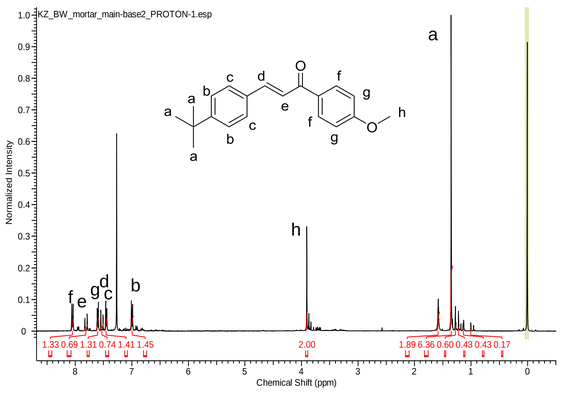
Synthetic Scheme

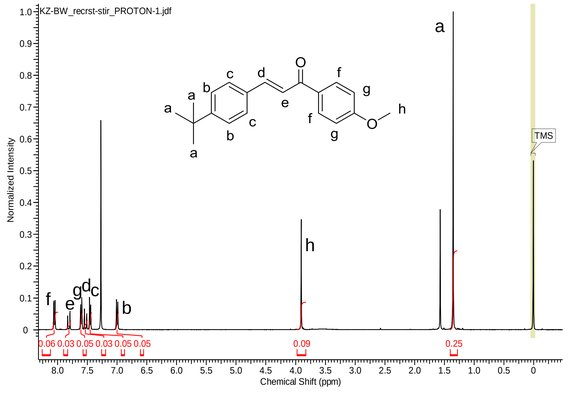


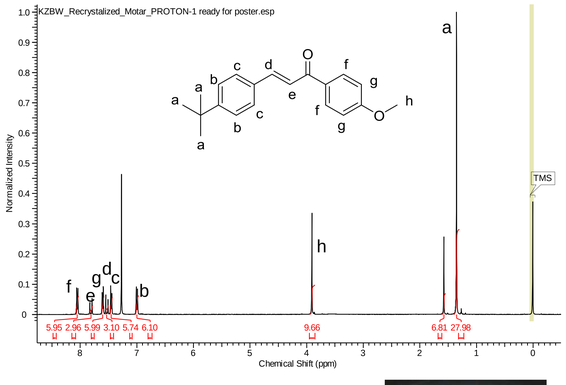
Green Chemistry Comparisons

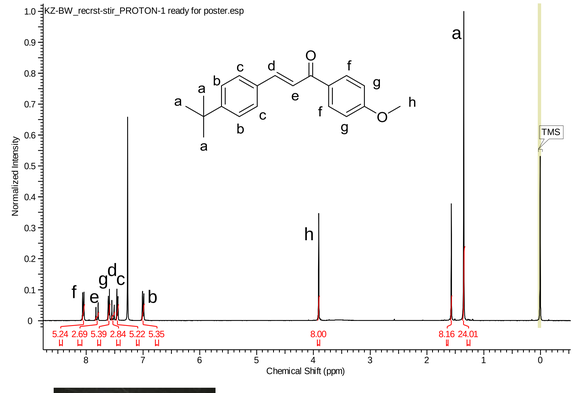
Comparison Parameters	4-tert-Butylbenzaldehyde (Mortar)	4-tert-Butylbenzaldehyde (Stir)	Methyl 4-tert-Butylbenzoate
Hazards	Acute toxicity, health hazard, environmental hazard (especially to aquatic life)	Acute toxicity, health hazard, environmental hazard (especially to aquatic life)	Not a hazardous substance
Cost	$1.86/g	$1.86/g	N/A
Percent Yield	69.06%	38.96%	N/D
E Factor	61.25%	71.43%	N/D
Reaction Time, Temp	4hours, room temperature	4hours, room temperature	17hours and 25minutes, 80˚ C
Product Purity, byproducts	Minimal Impurities	Minimal Impurities (easily separated)	N/D
Waste produced	15ml water, ~60ml ethanol, 0.010g 4-tert-Butylbenzaldehyde, 0.001g potassium tert-butoxide	Same as mortar product plus 0.001g potassium tert-butoxide 0.176 g white byproduct	0.214g 4-methoxyacetophenone, 2ml toluene, 0.093g sodium methoxide,0.274g methyl 4-tert-butylbenzoate

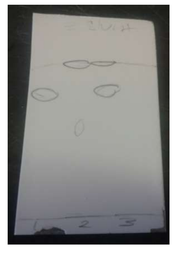
NMR Data and TLC pictures











Parts of Discussion

In the reaction involving 4-tert-butyl-benzaldehyde, an attempt was made to stop the reaction at the ketol intermediate. One trial utilized potassium tert-butoxide, rather than sodium methoxide, because it is a bulkier base and potentially less likely to deprotonate the alpha hydrogen to initiate ECB1. In this trial the reaction still produced the chalcone product. This could have been the result of the alpha hydrogen being very acidic and ECB1 occurring despite a bulkier base. Kinetic conditions could decrease the likelihood of ECB1. An alternative one step reaction was tried to make avobenzone directly. The methyl 4-tert-butylbenzoate reaction was inconclusive because it did not go to completion. This may have been the result of switching the original base, sodium amide, for sodium methoxide. Literature indicates similar reactive properties for both bases, so it should have worked. The original solvent (toluene) was used with sodium methoxide, and therefore a different solvent (methanol) could have produced better results. The addition of a catalyst could have also been helpful. In addition, the reaction could be attempted at a lower temperature for an extended period of time. Methyl 4-tert-butylbenzoate has a boiling point range of 110-112˚ C, close to the reaction temperature (80˚ C). Since the reaction was done overnight, the temperature was not monitored and may have fluctuated closer to 110˚ C causing the reagent to evaporate, interfering the reaction process. Another way the reaction may have gone to completion would have been to use the original base.

Conclusion

In the first step of the two step synthesis of avobenzone, the chalcone product was formed. In the alternative one step synthesis of avobenzone with a modified procedure using sodium methoxide in lieu of sodium amide, no reaction occurred. The greener synthesis of the two syntheses was the first step of the two step synthesis because this reaction went to completion. The 4-methyl-tert-butyl-benzaldehyde is a more toxic chemical than methyl 4-tert-butyl benzoate, which is one key area in which the one step synthesis is more green.

Future Directions

- Synthesize avobenzone from the chalcone product using potassium chromate
- Attempt the first step of the two step synthesis under kinetic conditions to favor the ketol product
- Attempt the one step synthesis with sodium amide, the base used originally in the literature
- Attempt the one step synthesis at a lower temperature for an extended period of time

References

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Acknowledgements

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