Solvent-Free Synthesis of Chalcones

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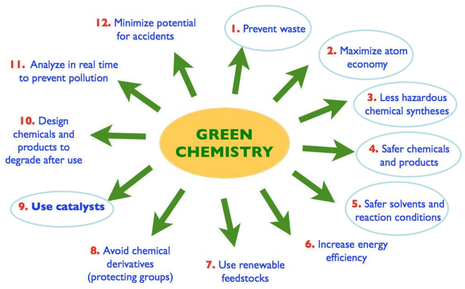
Green Chemistry



http://ccvc.research.mcgill.ca/research/research.html. Accessed on April 3, 2017

Figure 1. Green chemistry is a concept that aims to reduce, if not eliminate, the use or generation of hazardous materials in the design, manufacture, and application of chemical products. The synthesis of chalcones is a typical preparation included in introductory organic chemistry laboratories that proceeds with high atom economy. Atom economy is a comparison evaluating how many atoms in the reactants end up in the product. In the aldol condensation reaction, all the atoms in the reactants go into the desired product except for two hydrogen atoms and one oxygen atom. This well-known reaction was performed under unusual experimental conditions where heating under reflux was replaced by the grinding of solids with mortar and pestle in the absence of a solvent. Solvents are a significant component of industrial chemical waste. Making a reaction solventless significantly minimizes excessive waste.

Chalcones

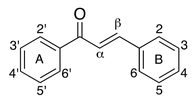
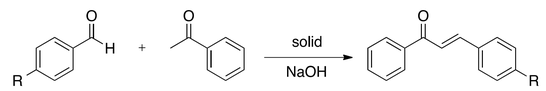


Figure 2. Chalcone (1,3-diphenylprop-2-propen-1-one) is a generic term given to compounds in which two aromatic rings are linked by a three-carbon 〈,®-unsaturated carbonyl framework. The numbering of the carbon atoms and aromatic rings (A/B) is shown.



Palleros et al., *J Chem Ed*. **2004**, 81, 1345-1347

Figure 3. Chalcones constitute an important class of natural products that display a wide spectrum of biological activities including antioxidant activity. Chalcones are readily synthesized by the base-catalyzed Claisen-Schmidt aldol condensation of an aldehyde and a ketone. The goal is to understand how the chemical structure influences its ability to be reduced by a hydrogenating reagent. In order to contribute to an extensive structure-activity relationship study, a series of mono substituted chalcones were prepared with either electron-donating or electron-withdrawing substituents at the ortho-, meta-, or para- positions.

Solventless Aldol Condensation

Concepts/techniques:
Carbonyl chemistry; the aldol reaction; melting points of solids and mixtures; recrystallization.
Green chemistry messages:
Solventless reaction between solids; atom economy; catalysis.

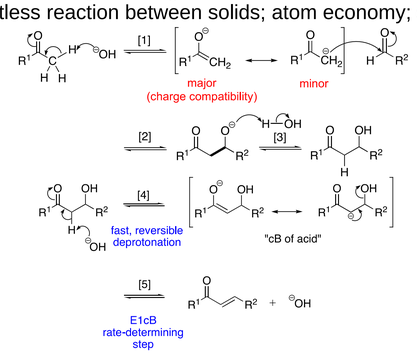


Figure 4: In Step [1], the hydroxy anion removes a proton from the 〈-carbon of the ketone to form a resonance-stabilized enolate. In Step [2], the nucleophilic enolate attacks the electrophilic carbonyl carbon of the aldehyde, forming a new carbon-carbon bond. In Step [3], the alkoxide anion is protonated to form the corresponding ®-hydroxy ketone. In Step [4], the hydroxide anion removes a proton from the 〈-carbon, thus forming a resonance stabilized enolate. In Step [5], the electron pair of the enolate forms the □-bond as the hydroxide anion is eliminated to give the corresponding 〈,®-unsaturated ketone.

Chalcone Visual

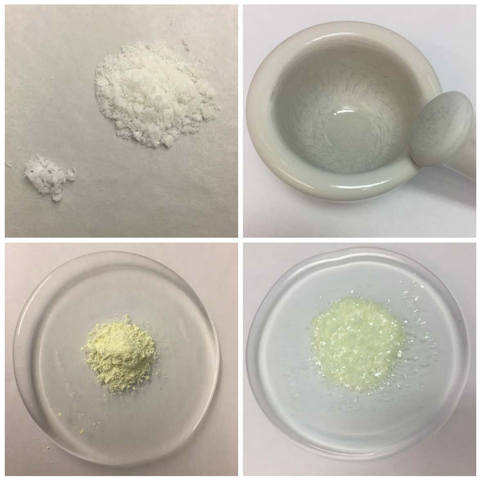


Figure 5. The four pictures shown above provide a visual representation of the various steps in the synthesis of biphenylchalcone. The first picture (clockwise from top left) shows solid NaOH and biphenyl-4-carboxaldehyde. The second picture shows the ketone, acetophenone, in the mortar and pestle before the other reagents are added. After ~10 minutes of mixing, water was added to the mixture. The separated solid, seen in the third picture, was collected by filtration and recrystallized from 95% ethanol. The final product can be seen in the fourth picture.

Synthesis of Mono-substituted Chalcones

Compound	R	mp (°C)	Yield (%)
Biphenylchalcone	Ph	112.8 - 116.1	47.8
4-Nitrochalcone	NO_2	157.9 - 158.8	57.0
3-Nitrochalcone	NO_2	143.0 - 143.8	36.2
2-Nitrochalcone	NO_2	123.7 - 124.1	39.9
4-Methylchalcone	CH_3	91.0 - 94.0	58.0
4-Trifluoromethylchalcone	CF_3	231.4 - 234.4	24.7
4-Fluorochalcone	F	86.0 - 89.0	31.5
4-Chlorochalcone	Cl	111.9 - 113.1	75.4
4-Bromochalcone	Br	126.1 - 127.0	59.3

Figure 6. The preparation of substituted chalcones were prepared according to the method of Daniel Palleros at the University of California, Santa Cruz. Previous researchers in our lab prepared substituted chalcones in yields of 25-75%. We tried many additional hydrophobic aldehydes substituted at the para- position (e.g. ethyl, iso-propyl, propyl, iso-butyl) but we were only successful with the biphenyl substituent. All compounds were purified via recrystallization from 95% ethanol and were characterized by TLC and melting point determination.

Bacteria Used

Staphylococcus aureus
- Gram-positive coccus
- It is a member of the normal flora of the body
- Commonly found in the nose, respiratory tract and skin

Escherichia coli
- Gram-negative bacillus
- Part of the normal human gut flora
- Cause of most urinary tract infections
- Certain strains are associated with food-born illness

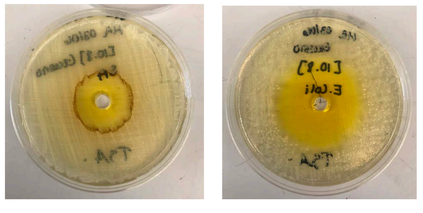
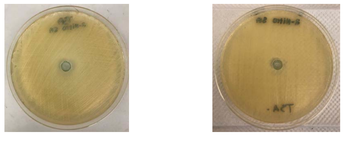


Figure 7. The bacteria used to determine the antibiotic properties of some of the chalcones were tested against Guanofuracin as a control. The ring of inhibition shows that Guanofuracin (10.8 mg/mL) stopped the bacteria from growing.

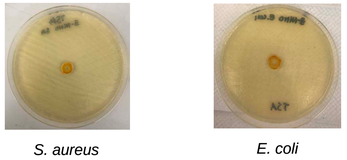
Bacterial Zones of Inhibition

2-Nitrochalcone



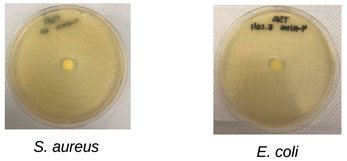
S. aureus *E. coli*

3-Nitrochalcone



S. aureus *E. coli*

4-Nitrochalcone



S. aureus *E. coli*

Figure 8. 2-Nitrochalcone, 3-Nitrochalcone and 4-Nitrochalcone were tested against the bacteria. The chalcone concentration was 10 mg/mL.

Conclusions

- The generality of the method of Palleros is supported by our syntheses, aimed at extending the method to the analogous biphenyl-, trifluoromethyl-, bromo-, fluoro- and nitro-substituents, which were not previously prepared by Palleros.

Future Goals

1) Reduction of monosubsitiuted chalcones by transfer hydrogenation with Wilkinson's Catalyst in 2-propanol in colaboration with Dr. Stephen Anderson.
2) Assess the growth inhibitory activity of the chalcones in cervical epithelial carcinoma (HeLa) cell lines by antiproliferative activity studies.
3) Characterization of chalcone products via nuclear magnetic resonance (NMR) spectroscopy.
4) Test remaining chalcones for antibiotic activity against *Staphylococcus aureus* and *Escherichia coli*.

Acknowledgments

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