

An Aldol Condensation to synthesize Chalcones

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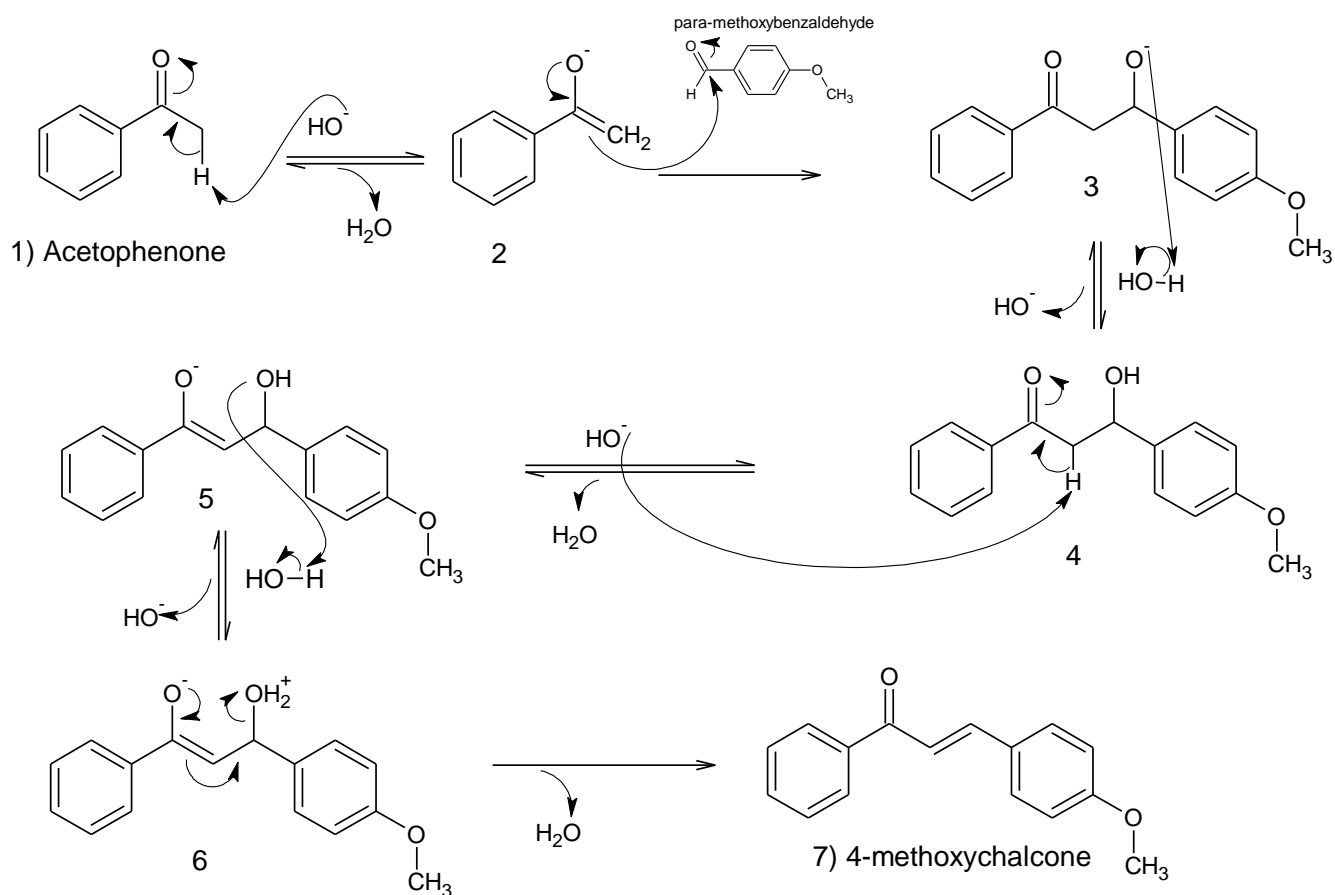
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Introduction

A chalcone is a molecule formed by two core functional groups: an aromatic ketone and an enone. Chalcones are found naturally in plants, fruits, and vegetables, and the organisms containing chalcones benefit from their antimicrobial properties. The reactive alpha, beta-unsaturated functional groups found in chalcones are responsible for their antimicrobial effects, and these effects can be tweaked by changing the substituents on the aromatic ring. Results from an experiment showed para-substituted nitro and halogen groups had good antifungal activity.¹

Not only do chalcones have good antimicrobial effects, but they can also be used to fight the triggers of coronary heart disease. Pre-factors indicating possible heart disease are represented by low high-density lipoprotein cholesterol (HDL-C) levels and high levels in low-density lipoprotein cholesterol (LDL-C), triglycerides, and total cholesterol. Chalcones belong to the flavonoid family, which consists of “two aromatic rings joined by a three-carbon alpha, beta-unsaturated carbonyl system.” Flavonoids inhibit the synthesis of ergosterol, which is a type of cholesterol. Determined experimentally, chalcones cause a decrease in triglycerides, LDL-C, and total cholesterol levels.²

Chalcones have many uses, some of which are preventative of microbial diseases and coronary heart disease, but chalcones can also be used as intermediates in the synthesis of more complex compounds. By adding sodium borohydride, methanol, and THF to 4-methoxychalcone, the carbonyl can be reduced to an alcohol, while further treatment with NBS and methyl cyanide results in 2,4-diphenyloxetane. This three-step synthetic route obtained high yields, and the procedure was completed in a single day. The new mechanism of obtaining 2,4-diphenyloxetane may allow for more advanced studies of this molecule and allow for new scientific breakthroughs relating to this molecule.³



Scheme 1: Synthesis of 4-methoxychalcone via an Aldol condensation mechanism

As the first step, hydroxide deprotonates the carbon alpha to the carbonyl on acetophenone, which creates an alkoxide bonded to an alkene. The carbon-carbon double bond in (2) nucleophilically attacks the carbonyl carbon in para-methoxybenzaldehyde to form (3); during this step the carbonyl is reformed. To form (4), the alkoxide in (3) deprotonates water to give hydroxide. Hydroxide then deprotonates the carbon alpha to the carbonyl in (4) to give another alkoxide attached to an alkene. The alcohol in (5) is protonated by water to give (6), which then forms a carbonyl to release water and give 4-methoxychalcone.

Chalcones have many uses as antimicrobial and anti-coronary heart disease pharmaceuticals as well as functioning as intermediates for more complex molecules. The purpose of this experiment was to synthesize and purify 4-methoxychalcone via an Aldol condensation mechanism. The product was then

analyzed by NMR spectroscopy, IR spectroscopy, and melting point analysis. Quantification of the product was obtained by observing the yield.

Experimental

4-Methoxychalcone. Acetophenone (1mL), para-methoxybenzaldehyde (1mL), and ethanol (95%, 3mL) was added to a test tube and stirred. Solid sodium hydroxide (2.5g, 62.5mmol) was added to distilled water (5mL), and this sodium hydroxide solution (0.5mL) was added to the test tube. The reaction was shaken, stirred, and monitored by TLC (25% Ethyl Acetate in Hexanes, then 50% Ethyl Acetate in Hexanes) to yield a dark yellow solution. After one hour, the reaction was placed in an ice bath (-4°C) for ten minutes and then vacuum filtered. The yellow solid was recrystallized (30% water in ethanol) to yield an off-white flakey solid (0.924g, 67% yield) mp 73 - 76°C, 74 - 76°C⁴; ¹HNMR (400MHz, CDCl₃) δ (ppm) 8.0 (d, 2H), 7.8 (d, 1H), 7.60 (d, 2H), 7.55 (d, 1H), 7.50 (t, 2H), 7.4 (d, 1H), 6.9(d, 1H), 3.8 (s, 3H); ¹³CNMR (400MHz, CDCl₃) δ (ppm) 190.5, 161.6, 144.6, 138.4, 132.5, 130.1, 128.4, 128.3, 127.5, 119.6, 114.3, 55.3; IR (ATR) ν_{max} (cm⁻¹) 3016, 1655, 1574, 1504, 1465, 1206.

Results and Discussion

Synthesis of 4-methoxychalcone utilized an Aldol condensation mechanism. The reaction was monitored by TLC for one hour, and it was stopped at a little over half completion. The crude product was recrystallized and identified using ¹HMR, ¹³CNMR, IR, and melting point. The following will give a detailed overview of the results.

Figure 1b shows the 400MHz ¹HNMR of 4-methoxychalcone. The protons on methyl ether are identified by the peak at 3.8 ppm, and the protons in the range from 8.0ppm to 6.9ppm can be viewed in more detail in figure 1c. Since the peaks at 8.0ppm are integrated to a value of two, these protons must be attached to a symmetric aromatic ring and subjected to a lot of de-shielding. Since the ring system both magnifies the intensity of the applied magnetic field and the carbonyl carbon is extremely electron

withdrawing, it can be concluded as the proton labeled 'a'. By applying similar arguments (integration values and distance from the carbonyl), the order of protons with decreasing ppm values are as follows: a, d, b, e, f, c, g. The 'g' proton is last because the adjacent ether group is electron donating, hence the huge shift in ppm relative to the other proton shifts. The peak at 7.2ppm is the solvent peak (CDCl₃).

Figure 2 shows the 400MHz ¹³CNMR of 4-methoxychalcone. The peaks at 77ppm are solvent peaks (CDCl₃), and once accounted for, there are twelve unique carbon atom peaks and twelve identifiable unique carbons in the molecule. Carbon 'l' is at 55.3ppm because it is next to an electron donating oxygen atom. The carbon labeled 'e' has a shift of 190.5ppm because it is a carbonyl carbon and is extremely de-shielded. The ten peaks up field with respect to the 'e' carbon are the following carbons: a, b, c, d, f, g, h, I, j, and k. Since these ten unique carbons are represented by ten unique peaks, it is simply enough to conclude the carbons above are represented by the peaks since predicting the order can become almost impossible. All in all, the ¹³CNMR spectrum in figure 2 is conclusive of 4-methoxychalcone.

In figure 3, the IR spectrum of 4-methoxychalcone is represented. The peak at 3016 cm⁻¹ is representative of an alkyl hydrogen, and the peaks at 1574cm⁻¹, 1504cm⁻¹, and 1465cm⁻¹ are representative of aromatic double bonds. The peak at 1655cm⁻¹ is representative of a carbonyl while the peak at 1206cm⁻¹ is representative of an ether; the peak at 1440cm⁻¹ is representative of an alkyl stretch. By the peaks listed above, the IR spectrum in figure 3 supports the synthesis of 4-methoxychalcone.

The melting point of 4-methoxychalcone was found to be 73-76 °C, which in comparison with literature is 74-76 °C.⁴ Therefore, since the melting point has a small range and is not depressed, it can be concluded there are almost no impurities in the sample. Based on figure 1b, however, there are small unidentifiable peaks throughout and a small peak at 1.6ppm. These peaks may be due to residue on the inside of a beaker, which did not completely exit the sample during recrystallization or some residue

was in the NMR sample. These peaks may also be a reactant, and they can also be, and most likely are, noise. The peak at 1.6ppm, however, cannot be noise and is something unidentifiable.

Above, it was noted the reaction was stopped at a little over half completion; therefore the percent yield will be lower than one-hundred percent. Also, during recrystallization there was a huge amount of solvent used to dissolve the entire crude product. Since the product was constantly oiling out (due to product with a lower melting point than the boiling point of the solvent), there may have been an issue with solubility, and hence more solvent than necessary may have been used. In order to raise the yield from 47 percent, a different solvent system should be used in order to efficiently dissolve the product without oiling out. The reaction should be run for a much longer time also, in order to allow the reaction to proceed to completion, and the reaction may also be run at a higher temperature in order to lower the activation energy and allow a faster rate of reaction.

Chalcones are commonly found in plants, vegetables, and fruits. They have uses in preventing coronary heart disease, and they also have antimicrobial uses. Chalcones are used as intermediates in order to make more complex molecules. Even though the yield of the synthesis above was low, the yield was pure. By implementing some different procedures, the yield can be improved to give a very useful reaction.

References

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