Cole Curtis, Chemistry 213

Synthetic #1 FFR

Synthesis and Characterization of 4-methoxychalcone

Introduction

Recrystallization is a very effective technique commonly used by chemists to purify solids contaminated with small amounts of impurities. Chemists can synthesize a desired product and utilize recrystallization in order to purify that product from unwanted starting material and intermediates that are still present. The crude product is simply dissolved in a solvent of similar polarity and as it slowly cools, the pure organic compound forms a crystal lattice structure leaving impurities behind in solution. This is an important process, especially in respect to synthesis of molecules with beneficial biological properties. For example, chalcones are synthesized in this experiment via a mixed aldol condensation reaction and then purified by recrystallization. Aldol condensation reactions are important in synthetic organic chemistry because they offer a pathway to form new carbon-carbon bonds.[1] This particular aldol condensation reaction is known as the Claisen-Schmidt reaction which is a very common method used in the synthesis of chalcones. This mixed aldol condensation reaction involves an aldehyde, a ketone and a strong base. Using this reaction, several beta-unsaturated chalcones can be synthesized through the condensation of acetophenone with aromatic aldehydes. The aldehyde is more reactive than the ketone, so it reacts with the ketone anion yielding a beta-hydroxyketone which undergoes a base catalyzed dehydration to form the desired chalcone product.

Scheme 1. Synthesis of 4-methoxychalcone **3** from acetophenone **1** and z-methoxybenzaldehyde **2**

Chalcones belong to a class of natural products known as flavonoids which are found in a variety of fruits and vegetables.[2] Chalcones and their many derivatives have several biological features that give them a lot of potential to be a powerful tool in the pharmaceutical industry. These biological activities include anti-microbial, anti-inflammatory, analgesic, anti-cancer, anti-viral, antioxidant, and many more.[3] In a study done by Ugwu, David. I et al, around 200 derivatives of chalcones were shown to have antimalarial activities similar to chloroquine, a drug used in the prevention and treatment of malaria.[4]

Scheme 2. Mechanism of base catalyzed Claisen-Schmidt condensation of acetophenone and z-methoxybenzaldehyde to 4-methoxychalcone

In the first step of the mechanism, acetophenone is deprotonated by the base sodium hydroxide, leaving a ketone anion. This anion then attacks methoxybenzaldehyde forming a 1, 3-dicarbonyl intermediate which is protonated by ethanol, forming a beta-hydroxyketone. Next, an alpha hydrogen is deprotonated from the beta-hydroxyketone forming a carbanion which then forces off the alcohol group leaving the final product, a 4-methoxychalcone.

The purpose of this lab was to synthesize chalcones via the base catalyzed Claisen-Schmidt condensation reaction with acetophenone and z-methoxybenzaldehyde and to utilize recrystallization to purify the chalcones from left over starting material and intermediates. The product was then characterized by melting point analysis, IR and NMR.

Experimental

4-Methoxychalcone. Acetophenone (1 mL, 8.57 mmol) was mixed with z-methoxybenzaldehyde (1 mL, 8.218 mmol) and ethanol (3 mL, 95%). Sodium hydroxide solution (50% w/v, 0.5 mL) was added and solution mixed until homogenous mixture was obtained. The reaction was stirred occasionally at room temperature for 30 minutes. TLC of the reaction was run at 30 minutes (25% ethyl acetate/75% hexanes). Upon completion, the reaction tube was placed in a -4 ^{o}C ice bath (ice in saturated sodium chloride) for 10 minutes to crystallize. Formed crystals were isolated via vacuum filtration yielding a yellow crystal structure. Crude product was recrystallized in ethanol (70%) and cooled. Pure product was isolated via vacuum filtration yielding white crystals (1.341 g, 68.5%) mp 73.4 – 75.5 ^{o}C; H^1 NMR (60 MHz, $CDCL_3$) d (ppm) 8.096-6.852 (m, 11H), 3.845 (s, 3H); H^1 NMR (400 MHz, $CDCL_3$) d (ppm) 8.0216-8.0002 (d, 2H), 7.8103-7.7712 (d, 1H), 7.6117-7.5898 (d, 2H), 7.5709-7.5526 (d, 1H), 7.5124-7.4753 (t, 2H), 7.4387-7.3996 (d 1H), 6.9437-6.9218 (d, 2H), 3.8445 (s,

3H); ^{13}C NMR (400 MHz, CDCL^{3}) d (ppm) 190.6127, 161.7009, 144.7499, 138.5084, 132.6084, 130.2778, 128.5995, 128.4457, 127.6065, 119.7498, 114.4396, 77.4023, 77.0841, 76.7668, 55.4357, 0.0366; IR (ATR) y_{max} (cm^{-1}) 3018.37, 1655.41, 1207.50.

Results and Discussion

4-Methoxychalcone was synthesized in a Claisen-Schmidt mixed aldol condensation reaction using acetophenone and z-methoxybenzaldehyde along with sodium hydroxide to facilitate the dehydration. TLC was used to verify the reaction had completed, crude product was cooled, and crystals isolated using vacuum filtration. Recrystallization was utilized using 70:30 ethanol/water to purify the pure chalcone product from leftover starting material and intermediates. The pure chalcone product was isolated once again by vacuum filtration and characterized by melting point, IR, 60 MHz, ^{1}H 400 MHz and ^{13}C 400 MHz NMR.

Acetophenone and paramethoxybenzaldehyde were first mixed with ethanol. A solution of sodium hydroxide was prepared by dissolving NaOH pellets in water and was then added to the reaction. The sodium hydroxide acted as a base which enabled the dehydration of the acetophenone. The reaction was run at room temperature for approximately 30 minutes until completion, determined using TLC in 25% ethyl acetate in hexanes. The reaction tube was placed in a -4 ^{o}C ice bath of saturated aqueous sodium chloride over ice. The product crystallized in the ice bath for 10 minutes and the crystals were isolated via vacuum filtration. The crude product was then dissolved using 70:30 ethanol/water as the solvent while heating on hot plate. Once the crude product was fully dissolved, the mixture was cooled to room temperature and finally placed on ice for 10 minutes to recrystallize, yielding pure chalcone crystals which were isolated via vacuum filtration.

Percent yield of 4-methoxychalcone was determined to be 68.5%, and the melting point determined experimentally to be 73.4-75.5 ^{o}C. Literature reported melting point is 73-76 ^{o}C.[5] In a study done by Kumar, B et al in which several derivatives of chalcones were synthesized using the Claisen-Schmidt condensation reaction, product yield ranged from 69 % to 81%,[6] indicating that 68.5% is a successful yield of product.

The chalcone product was characterized by IR analysis. A peak occurred at 3018.37 cm^{-1}, which is in the stretch for aromatic structures, and also for an alkene C-H bond which is specific to the chalcone product. Peaks also occurred at 1655.41 cm^{-1} and 1207.50 cm^{-1} which represent the carbonyl group and ether group respectively. The starting materials also contain aromatics, a carbonyl group and an ether meaning that the IR analysis does not necessarily support that the desired product was synthesized and purified.

NMR analysis on the other hand, gives stronger evidence for the indication of a successful synthesis and purification of the chalcone product. ^{1}H NMR was very useful in determining that the characterized compound was the desired product. The first key feature of the characterization is that the total number of protons present is 14, which is consistent with the structure of 4-methoxychalcone. A cluster of peaks occurred as a multiplet between 8.096-6.852 ppm with a total of 11 protons, which represent all of the benzylic protons as well as the alpha and beta protons. A singlet also occurred at 3.845 ppm, with an integration value of three representing the methyl in the ether group.

400 MHz ^{1}H NMR was consistent with the data found in the 60 MHz analysis. Again, a total of 14 protons were present. The defining peaks that support a successful synthesis of 4-methoxychalcone occurred at 7.8103-7.7712 ppm as a doublet with 1 proton, and at 7.5709-

7.5526 ppm, another doublet with 1 proton. These peaks represent the alkene that formed on the chalcone product in the final step of the mechanism as seen in Scheme 2. A singlet with 3 protons at 3.8445 ppm represents the methyl of the ether group. The other 9 protons representing the benzylic hydrogens all fall between 8.0216 ppm and 6.9218 ppm.

400 MHz ^{13}C NMR was also a strong indicator that synthesis and purification of 4-methoxychalcone was successful. The analysis shows a total of 16 carbons which is consistent with the structure of 4-methoxychalcone. The peaks at 144.7499 ppm and 119.7498 ppm confirm the formation of the alkene in the last step of the mechanism seen in Scheme 2 where the anion forces off the alcohol leaving group to form the final product. The carbonyl carbon is also seen by the appearance of a peak at 190.6217 ppm. The methyl on the ether group is represented by the peak at 55.4357 ppm. The other 12 carbons are found between 161.7009 ppm and 0.0366 ppm.

Melting point analysis, IR and NMR all give strong evidence to support a successful synthesis and purification of 4-methoxychalcones from acetophenone and z-methoxybenzaldehyde with no major impurities. The melting point, 73.4-75.5 ^{o}C, fell within an accepted range of 73-76 ^{o}C[5] and the percent yield of product was 68.5% which is comparable to yields found in literature ranging from 69% to 81%.[6] Sources of error include moving into the workup before the reaction has finished, which would cause the percent yield to be significantly lower. One improvement that could be made to this experiment would be to use a microwave irradiation method which will reduce synthesis time and increase the overall percent yield of chalcones.[4]

References

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Supplemental Information:

Figure 1. FTIR of 4-methoxychalcone

Figure 2. 60 MHz ^{1}H NMR of 4-methoxychalcone

Figure 3. 400 MHz ^{1}H NMR of 4-methoxychalcone

Figure 4. 400 MHz ^{13}C NMR pf 4-methoxychalcone