

Synthesis and Characterization of 4-Ethylbenzophenone

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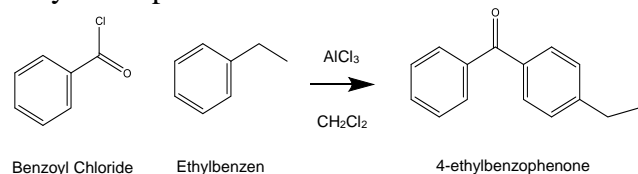
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4-Ethylbenzophenone was synthesized utilizing the Friedel-Crafts acylation from the precursors of ethylbenzene and benzoyl chloride, catalyzed by aluminum chloride. Characterization was achieved via refractometry, GC-MS, IR and HNMR. Refractometry yielded a refractive index of 1.5932 ± 0.0001 , notably higher than literature value indicating the presence of impurities. GC-MS detected the presence of all three isomers of ethylbenzophenone, including the ortho form (2%), the meta form (7%) and the para form (78%). GC-MS also revealed the presence of diethylbenzophenone impurities which totaled 13% of the product. IR spectroscopy identified characteristic phenol stretching around 3030 cm^{-1} and alkyl stretching around 2900 cm^{-1} and ketone $\text{C}=\text{O}$ stretching at 1655 cm^{-1} . HNMR experienced instrumentation difficulties however sufficient data was collected to identify characteristic ethyl triplet and quartet peaks at 1.3 and 2.7 ppm, respectively. Although the product was not pure, utilizing the data gained via GC-MS the yield was determined to be 60% of the targeted 4-ethylbenzophenone.

Introduction

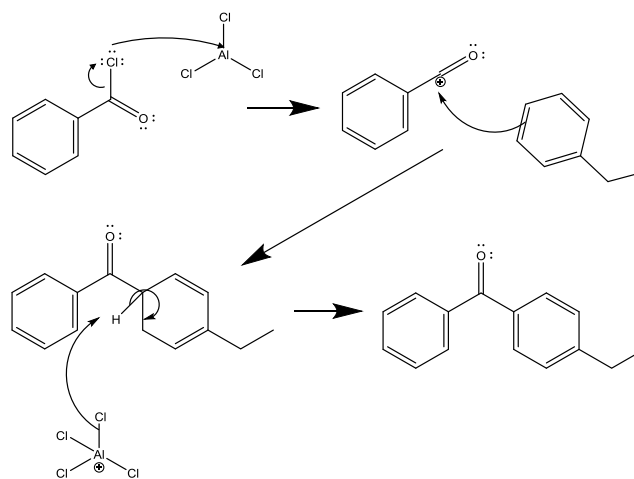
The Friedel-Crafts acylation offers a simple method to synthesize benzophenones. In this experiment 4-ethylbenzophenone was synthesized from benzoyl chloride and ethylbenzene precursors, catalyzed by aluminum chloride as depicted in Scheme 1.

Scheme 1. Friedel-Crafts acylation of benzoyl chloride and ethylbenzene to produce 4-ethylbenzophenone.



A closer examination of the reaction mechanism, as seen in Scheme 2, shows the para directing nature of the Friedel-Crafts acylation. This reaction is para directing due to the conjugation effects of the alkyl group making the para position on the ethylbenzene most favorable. Once synthesized and purified the resulting product was characterized on a variety of instruments. Refractometry, infrared spectroscopy (IR), gas chromatography coupled mass spectrometry (GC-MS) and proton nuclear magnetic resonance (HNMR) were used for detailed characterization.

Scheme 2. Friedel-Crafts acylation mechanism using regenerative aluminum chloride as a catalyst.



Experimental

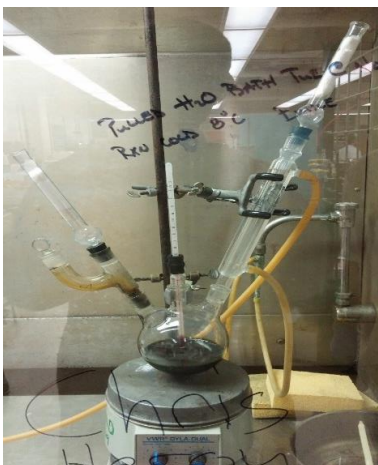
The reaction procedure followed the general procedure proposed by Suhana and Srinivasan¹. Reported reaction yields vary from 78%¹ to 55%². For this experiment a 50% reaction yield was expected and thereby used in reagent quantity calculations.

A reaction apparatus, as shown in Figure 1, was assembled with a 500 mL 3 neck round bottom flask. The glassware used for the reaction

apparatus was stored in a drying oven overnight and quickly assembled after removal from the oven to ensure minimum atmospheric H_2O contamination. Drying tubes loosely packed with approximately two inches of CaCl_2 were used to mitigate atmospheric H_2O from entering the reaction vessel post assembly. Water was continually flowing through the condenser throughout the addition phase of AlCl_3 as described below.

25 mL of ethylbenzene (200 mmol) was mixed with 51 mL dichloromethane (800 mmol) in the reaction vessel. 24 mL of benzoyl chloride (200 mmol) was then added to mixture. With the solution submerged in an ice bath, 29.2 g of AlCl_3 (220 mmol) was inserted into the Claisen adapter. It should be noted that not all of the AlCl_3 was added to the reaction mixture due to sticking on the walls of the Claisen adapter which caused an estimated loss of 1-2 g of AlCl_3 . Over the course of three hours, with vigorous stirring, the AlCl_3 was slowly added to the reaction mixture by rotating the Claisen adapter until a small portion of the solid dropped in. The insertion of the AlCl_3 resulted in visible bubbling in the reaction mixture and the evolution of acidic gas (believed to be HCl), as measured by litmus paper held above the drying tubes.

Figure 1. Reaction apparatus set up with a 500 mL 3-neck round bottom flask with magnetic stirring. Drying tubes with CaCl_2 were inserted in the top of both the condenser and the Claisen adapter. The image lacks a metal bowl filled with ice water, which the round bottom flask was submerged in, that was used during the AlCl_3 addition phase of the reaction.



Throughout the addition process the reaction mixture stayed liquid and visually changed color from clear to yellow to green and finally to brown. After the final addition of AlCl_3 the mixture was allowed to slowly warm up in a water bath (after the ice melted) with continued stirring for an additional hour. Stirring and condenser water were discontinued and the reaction mixture was allowed to sit in a water bath at approximately 8°C for 4 days before being removed from the water bath and warmed to 15°C for an additional 24 hours. Stirring was then resumed for an additional 4 hours at 15°C while thin layer chromatography (TLC) was being examined using a 1:3 ethyl acetate/hexane mixture.

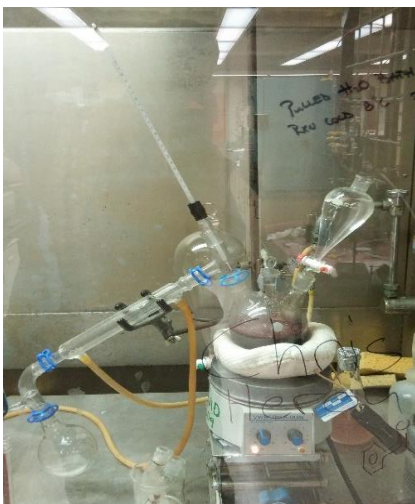
TLC results obtained following the initial addition of AlCl_3 showed no distinction between the reaction mixture and benzoic acid (benzoyl chloride was acidified with HCl to mimic condition in the reaction mixture). Both showed an R_f value of 0.47. After the second day of mixing however, TLC showed a distinct reaction progression with the benzoic acid's R_f of 0.30 compared to the reaction mixture's R_f of 0.77 which was believed to be the ketone product. This data was used to determine the reaction had reached completion and was ready for quenching.

To quench the reaction acid hydrolysis was used. 200 mL of ice was added into a 1L beaker and 20 mL of concentrated HCl was poured onto the ice followed by the slow addition of the reaction mixture with magnetic stirring. The solution was then transferred to a separatory funnel with an additional 25 mL of diethyl ether (anhydrous). After mixing and venting, the aqueous and organic layers were allowed to separate, and the aqueous layer was discarded.

The organic layer, now black in color, was transferred back to the 3-neck round bottom flask for steam distillation. See Figure 2 for steam distillation apparatus setup. With stirring and water flowing through the condenser, heat was applied through a heating mantle powered by a variac. An initial setting of 40 V produced slight boiling and collection of the organic solvent with a vapor temperature of 35°C . As the organic solvents were co-distilled the color of the mixture turned from black to dark purple.

With the collection of approximately 70mL of solvent over 2.3 hours, equivalent to the quantity of solvent in the reaction mixture, the vapor temperature began to fall with only minimal amounts of distillate being collected. To distil the water, the variac was incrementally increased to 70 V with a vapor temperature of 98°C to distil and collect water. Over 2.5 hours, an additional 25 mL (approximately) of water was collected before steam distillation was terminated.

Figure 2. Steam distillation apparatus setup. Distilled H₂O was kept in the dropping funnel and added to the solution at a rate concurrent with distillate collection rate.



The remaining solution was treated with 10% NaOH until basic conditions were met as determined via litmus paper. The solution was then worked up using DCM in a 1000 mL separatory funnel until clear distinction could be made between aqueous and organic layers. The organic layer was then rotovaped to remove the majority of the DCM solvent. The crude product remained liquid with a purple color.

Purification was preformed utilizing mechanical vacuum distillation. Recrystallization was not an option owing to 4-ethylbenzophenone's melting point of 20.2 °C¹. The crude product was transferred to a 250 mL round bottom flask for vacuum distillation. Figure 3 shows the vacuum distillation apparatus used. Under a mechanical vacuum of 0.1 Torr the variac was slowly increased to 50 V. Upon thermal equilibrium, the vapor temperature rose and stabilized at 122 °C and noticeable steam began to show at the base of the condenser. With the stable

temperature, distillate began condensing and collecting in the receiving flask. Fractions were not taken due to the consistent temperature at which distillate began collecting at. It is believed that any solvent in the crude product bypassed the collection flask and condensed in the cold trap. Distillate was collected for one hour and thirty minutes before temperature rise occurred indicating the end of the distillation.

Figure 3. Vacuum distillation apparatus. The final distillation included wrapping the apparatus in thermal insulation and aluminum foil for even temperature over the column.



Results

Product obtained from vacuum distillation was 32.54 g suggesting a percent yield of 77%, purity depending. To test the purity of the product a variety of characterization methods were utilized including TLC, refractometry, IR, GC-MS and proton NMR.

TLC of the distilled product was measured with a 1:3 ethyl acetate/hexane mixture. Two distinct spots formed with R_f values of 0.65 and 0.70. The two distinct spots suggest the possibility of impurities in the distillate. Refractometry, sampled 12 times, yielded a temperature corrected refractive index of 1.5932 ± 0.0001. This value contrasts with literature's value of 1.5585³ further supporting the likelihood of impurities present in the product. In order to gain more insight to the character of the impurities more powerful characterization techniques were employed.

The instrument utilized for GC-MS was an Agilent Technologies 7820A GC coupled to a 5975 series electron impact MS of the same manufacture. GC-MS yielded three distinct peaks

containing the desired product ethylbenzophenone. Figure 4 shows the GC trace of the product. The first peak, at 9.8 minutes, contains 6.7% of the product and is likely the meta arrangement while the peak at 10.2 minutes contains 2.1% of the product and is likely the ortho arrangement. The largest peak, at 10.5 minutes contained 78.1% of the crude product and is believed to be the desired para form of the ethylbenzophenone. A higher resolution image of Figure 4 can be found in Appendix 1.

Figure 4. GC trace of the distilled product. The large peak belongs to the targeted 4-ethylbenzophenone (78%) while two to its left belong to its meta (6.7%) and ortho (2.1%) isomers. The two rightmost peaks are believed to belong to two diethylbenzophenones isomers (2.6% and 9.7%). Note the x-axis labeled time is in the form of minutes.

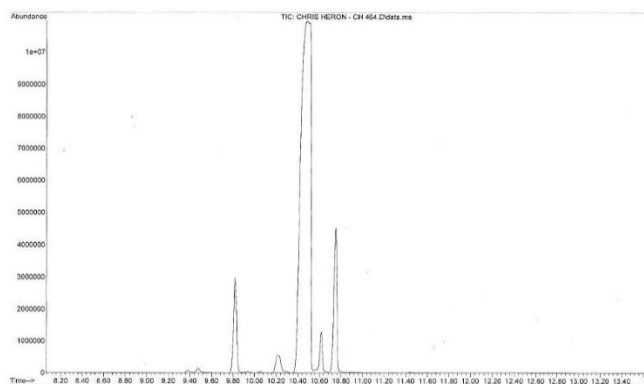
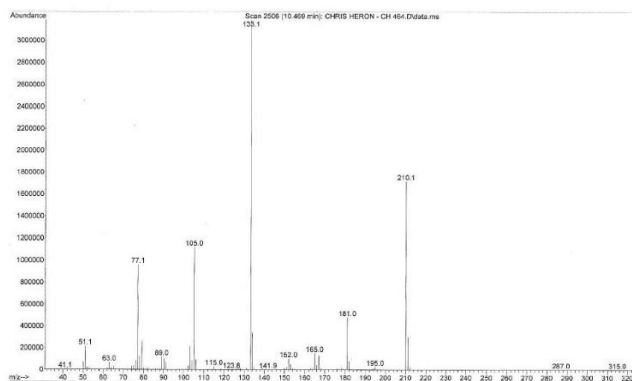


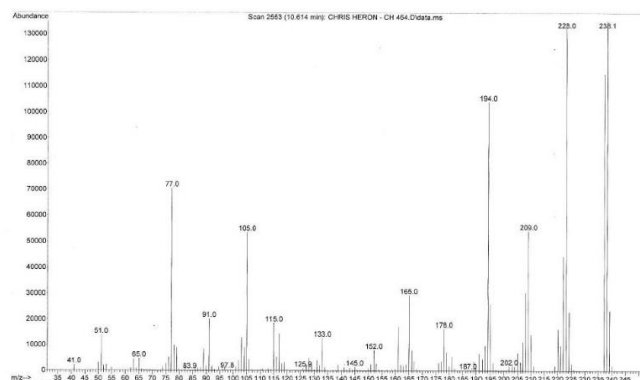
Figure 5 shows the fragmentation pattern of the GC peak corresponding to 10.5 minutes. The M^+ peak correlates with ethylbenzophenone's molecular mass of 210 amu. Noteworthy peaks include the benzene ion at 77 amu, ethyl benzene ion and benzoyl ion at 105 amu and the ethyl benzyol ion at 133 amu. The three MS histograms belonging to the three ethylbenzophenone isomers share similar fragmentation patterns and high resolution images of each can be found in Appendix 2-4.

Figure 5. GC-MS fragmentation pattern of 4-ethylbenzophenone. This was the dominant species within the distillate comprising 78% which eluted from the GC column at 10.5 min. The other two isomers owing to the ortho and meta configurations produced nearly identical fragmentation patterns at 9.8 and 10.2 min, respectively. Note that m/z listed on the x-axis of the histogram represents amu.



Two impurities within the distillate, aside from the para and meta forms of the ketone product, were identified using the GC-MS. The impurities are believed to be two isomers of diethylbenzophenone as shown by the two latest peaks in Figure 4. The peaks at 10.6 minutes, composing 2.6 % of the product, and 10.7 minutes composing 9.7 % of the product. Figure 6 shows the MS of the species which eluted at 10.6 minutes which shares nearly identical MS fragmentation pattern as with the peak which eluted at 10.7 minutes. Both have an M^+ mass of 238 amu, indicative of different isomers of diethylbenzophenone. Further support of this is found with fragmentation lying at 223 amu, suggesting a diethylbenzophenone missing one methyl group (15 amu) and another fragmentation peak at 209 amu which corresponds to diethylbenzophenone missing an ethyl substituent (29 amu). All fragmentation below 209 amu are commiserate with the MS pattern obtained of the single substituent ethylbenzophenone. The difference in GC retention time concerning the two diethylbenzophenones can be attributed to the existence two different isomers in the sample. High resolution images of the impurities' MS histograms can be found in Appendix 5-6.

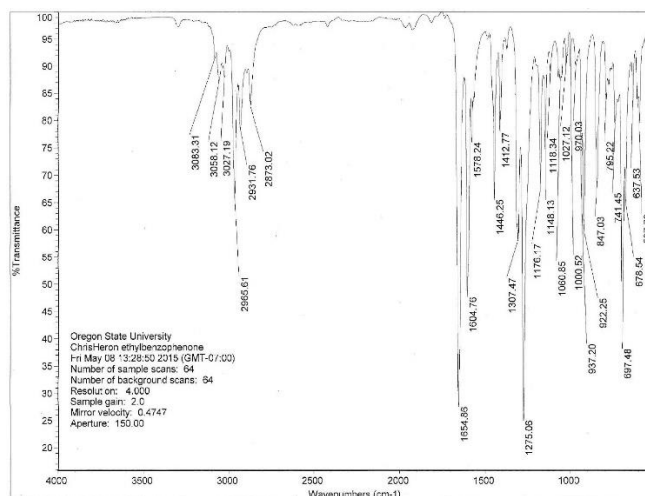
Figure 6. GC-MS fragmentation pattern of diethylbenzophenone impurities obtained at 10.6 minutes. This molecule and the one collected at 10.7 minutes contain nearly identical fragmentation patterns. Note that m/z listed on the x-axis of the histogram represents amu.



Using the information gained by the GC-MS the purity of the distilled product is determined to be 78.1% giving a 4-ethylbenzophenone yield of the 25.51 g or a 60 % yield.

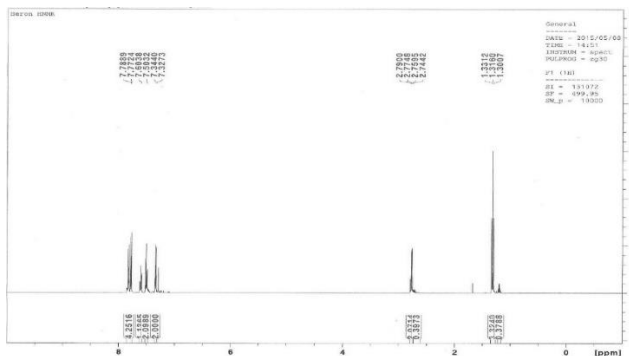
Infrared absorption spectra was collected via a Thermo Scientific Nicolet 6700 FT-IR with 4 cm^{-1} resolution scanning 64 times both background and sample. As show in Figure 7, characteristic vibrational behavior of phenol rings and alkyl groups are seen at the higher wave numbers. The highest wave number behavior, belonging to the aromatic ring stretching, exist as the top three peaks, 3027 cm^{-1} , 3058 cm^{-1} and 3083 cm^{-1} . Adjacent to those peaks are the alkyl peaks owing to C-H stretching at 2873 cm^{-1} , 2931 cm^{-1} and 2966 cm^{-1} . Of particular importance in the IR spectrum is the peak at 1655 cm^{-1} which represents the ketone's C=O stretching that would only exist in the product. A high resolution image of the IR spectra is available in Appendix 7.

Figure 7. IR spectra of the product. Noteworthy peaks belong to the ketone C=O stretching at 1655 cm^{-1} , alkyl C-H stretching centered around 2932 cm^{-1} and phenol stretching around 3030 cm^{-1} .



HNMR spectra was obtained on a Bruker Ascend 500 m/z NMR. Unfortunately only one image of the NMR spectra, shown in Figure 8, was recorded and lacks sufficient details to gain meaningful insight of the details residing in the conformation of the aromatic region centered around 7.5 ppm. The presence of the ethyl substituent is identifiable by the presence of a triplet at 1.3 ppm, suggesting a CH₂ group, and a quartet centered 2.7 ppm suggesting the presence of a neighboring CH₃ group thus supporting the presence of ethyl substituent(s). A full sized image of Figure 8 can be found in Appendix 8.

Figure 8. HNMR spectra recorded with a 500 m/h NMR. The presence of the ethyl subsibuent is easily identifiable by the presence of a triplet centered at 1.3 ppm and a quatet centered at 2.7 ppm. Unfortunutly insificent detail was not abaible for detailed analysis of the the aromatic region for isomer identification.



Further theoretical characterization was carried out utilizing Hyperchem to identify the heat of formation. Bond angles regarding the phenol groups were rotated out of plane from each other to establish the angle at which the lowest heat of formation (ΔH_f) exists at. Numerous tests were carried out until the lowest ΔH_f was established at a phenyl group's rotation of 37.6° out of plane with the other phenyl producing a ΔH_f of $-33.49 \text{ kJmol}^{-1}$.

Discussion

The prolificacy of impurities in the sample establishes that vacuum distillation was insufficient for obtaining pure product with the desired 4-ethylbenzophenone product composing 78% of the distillate. Although the vacuum distillation was sufficient for the characterization methods utilized in this experiment, high purity product would be best attained via a silica column or high theoretical plate distillation, such as spinning band, following the initial vacuum distillation⁴.

The presence of the impurities was identifiable throughout the characterization process, notably TLC, refractometry and GC-MS. The two spots that were visible on the TLC are likely belonging to the ethylbenzophenone and the diethylbenzophenone. Likewise, the index of refraction was 0.0347 higher than literature value suggesting the presence of impurities. Whereas TLC and refractometry suggest the presence of impurities³, GC-MS explicitly identified the impurities and their abundance.

Of the impurities identified in GC-MS, the presence of the ortho and meta ethylbenzophenones were not surprising. The Friedel-Crafts acylation is para directing, favored by the presence of an electron withdrawing substituent, in this case ethyl. The ethyl substituent, however, is not likely to eliminate the formation of the other isomers. With only mild conjugation character of the ethyl group it is easy to speculate that the other isomers would readily form, particularly the meta isomer. The formation of the ortho isomer is likely drastically slowed by both steric hindrance and the conjugation effects of the ethyl substituent. It is therefore conceived that GC the peak containing 2% (10.2 min.) of the product belongs to the ortho ketone while the peak containing 8.6% (9.8 min.) of the product belongs

to the meta isomer and the peak containing 78% (10.5 min.) of the product belonging to the para isomer.

The presence of diethylbenzophenones is, however, surprising. To better understand their presence requires a close examination of the reaction environment. Ethyl benzene, in the presence of a strong acid source, facilitates an intermolecular transalkylation-dealkylation mechanism⁵. Due to the high quantities of eluded HCl as the reaction proceeded, some ethylbenzene likely went through rearrangement resulting in the formation diethyl benzene and benzene. The diethyl benzene then undergoes Friedel-Crafts acylation presumably more favorably than reaction with the benzene as a result of the electron withdrawing effects of the substituted benzene. This means that both ethyl groups are likely arranged on the same phenol ring with the two peaks showing latest in the GC plot, Figure 4, belonging to the two diethylbenzophenone isomers.

The ketone IR peak shown in Figure 7 is located at 1655 cm^{-1} . This is at a lower wavenumber than what would be normally considered a ketone peak. Ketones typically fall between $1750\text{--}1680 \text{ cm}^{-1}$. By considering the ketones environment an understanding of the lower than normal wavenumber can be attained. The ketones in the product are surrounded by phenol groups. Conjugation of the carbonyl group with the surrounding aromatic rings results in a higher absorption frequency, and thus lower wavenumber. The peak at 1655 cm^{-1} is therefore confidently believed to be the ketone peak indicating a successful Friedel-Crafts acylation.

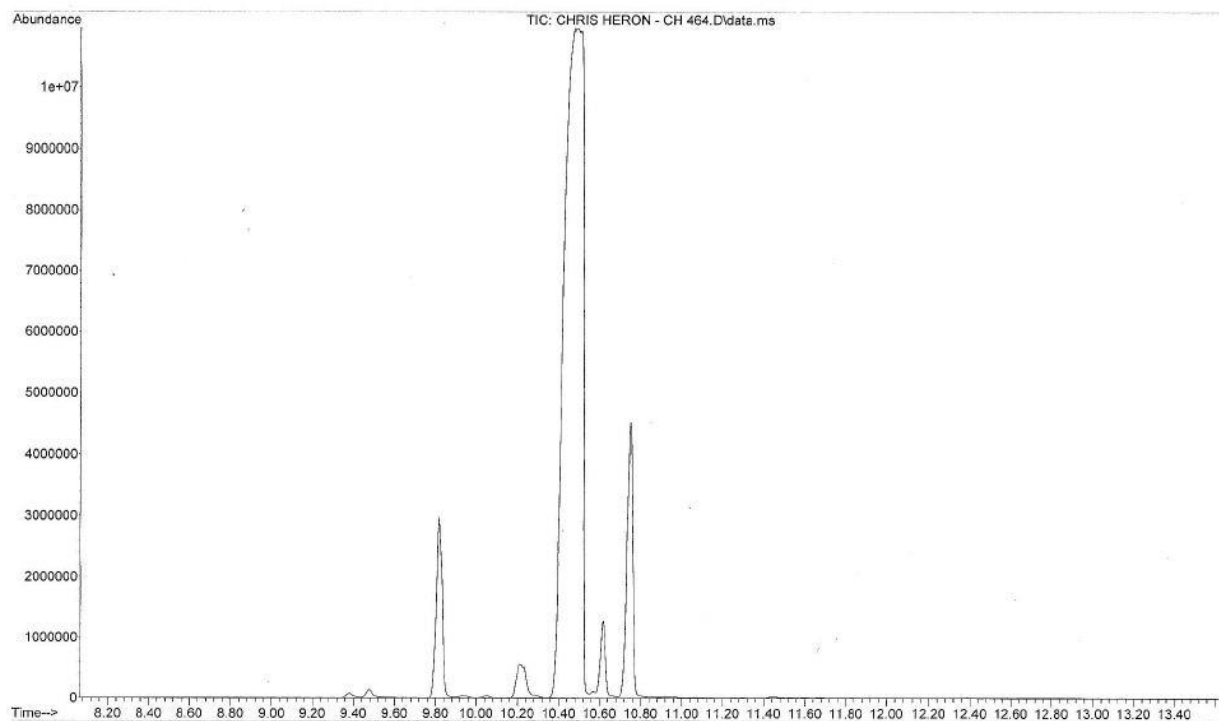
NMR was intended to be employed to identify the arrangement of substituents on both the product and the impurities. Unfortunately, only one low detailed full spectrum image was received. The intention was to receive high resolution ^{13}C and 2D NMR spectra but instrument complications precluded analysis. Further complications arose when the file containing the spectra from the 500 m/z HNMR was lost while simultaneously the 500 m/z instrument malfunctioned and was rendered inoperable. This made an enlarged view of the aromatic region of the product impossible which may have helped identify the arrangements of the product and the impurities. Nonetheless logic can be utilized along

with spectra obtained by IR and GC-MS to obtain the identity and likely arrangement of the species present.

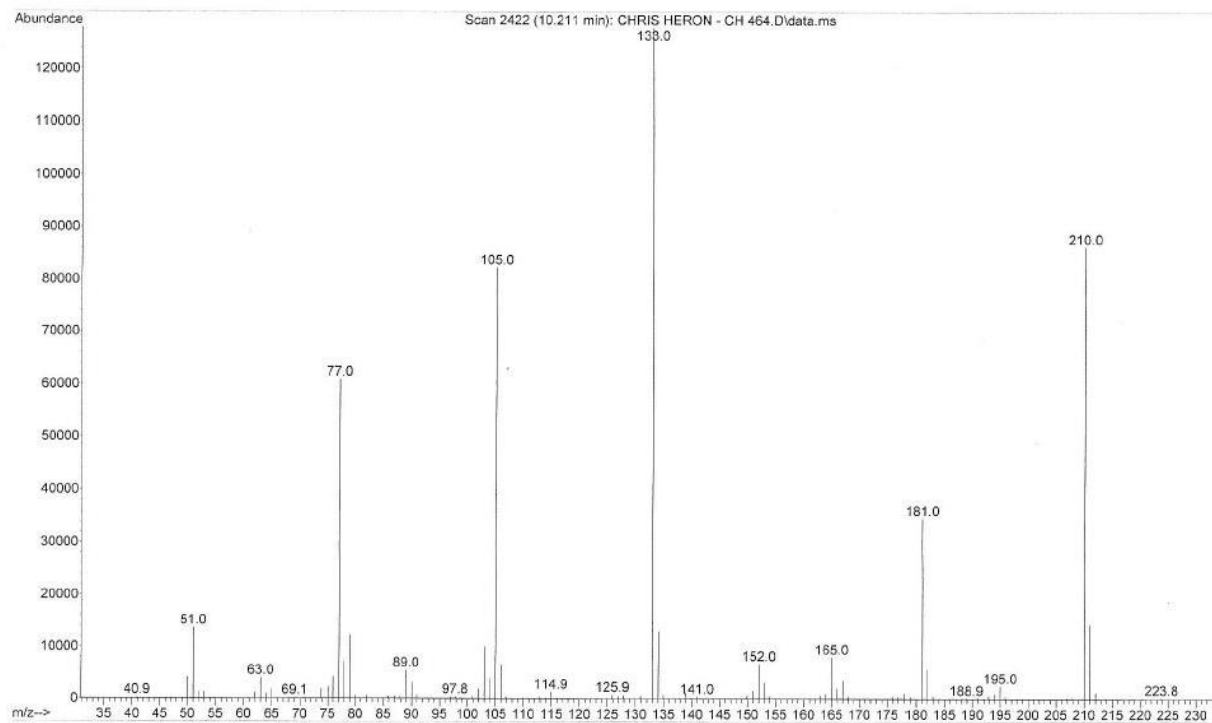
References

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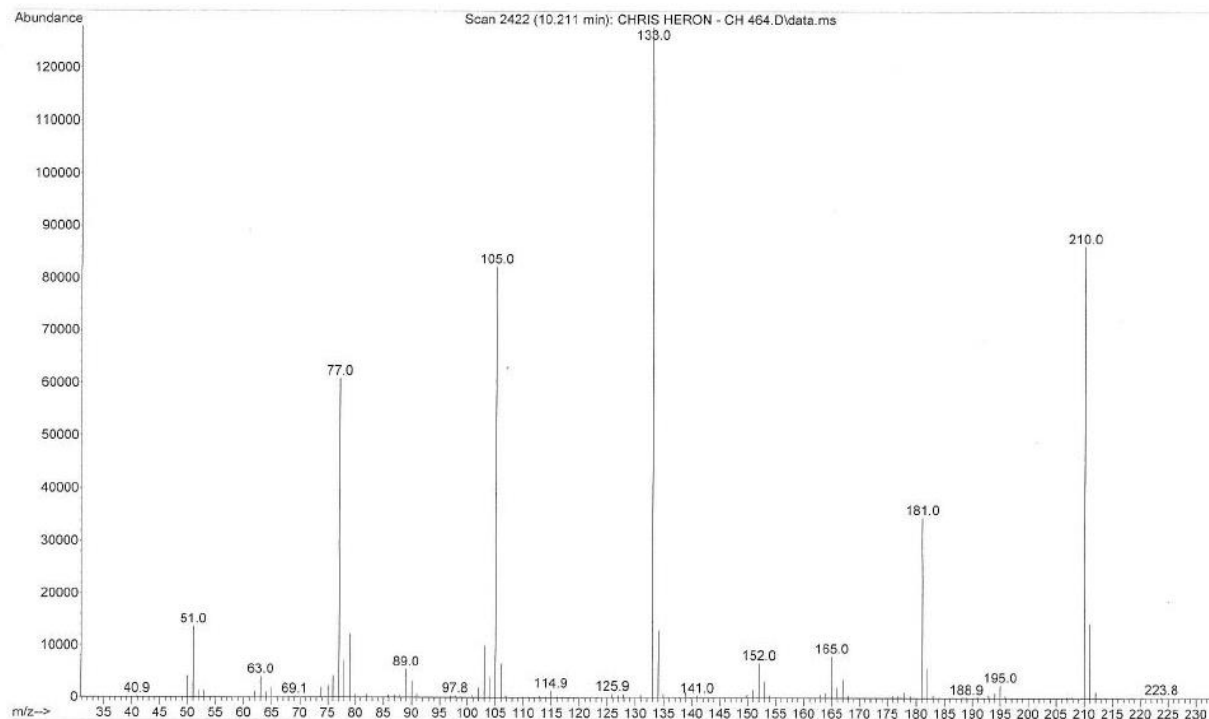
Appendix 1. GC plot of product. Retention times on x-axis are listed as minutes.



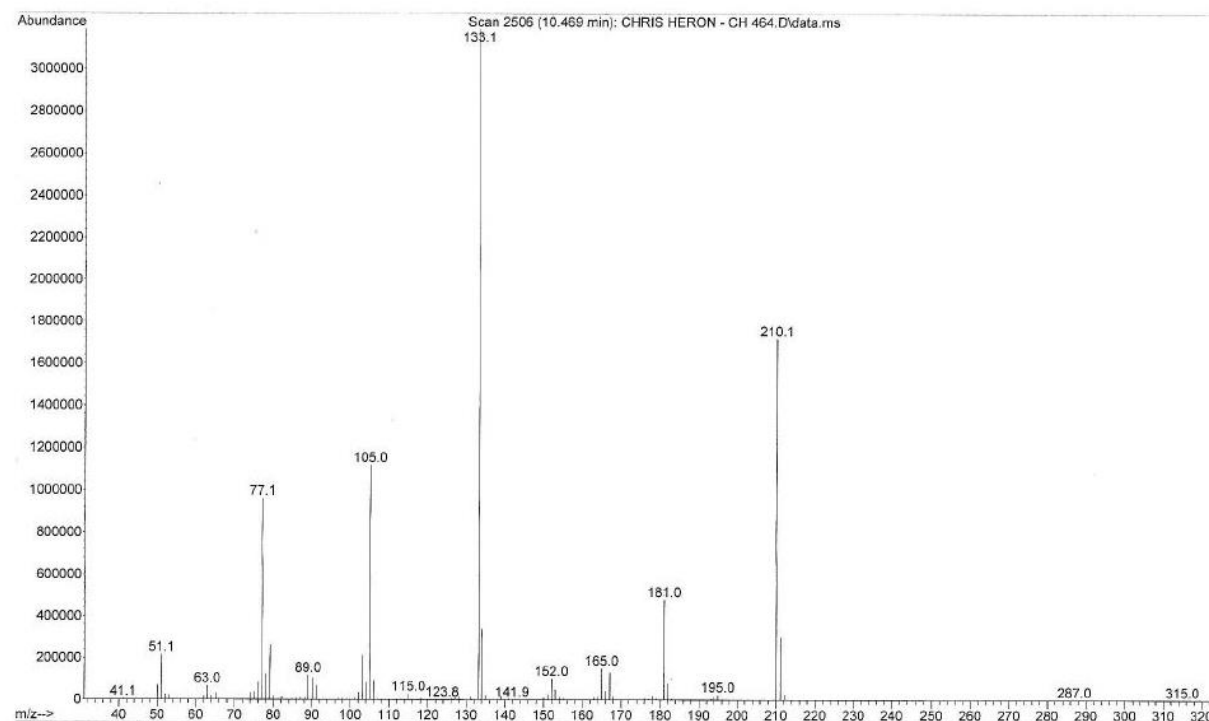
Appendix 2. MS histogram of GC peak at 9.8 minutes belonging to meta ethylbenzophenone.



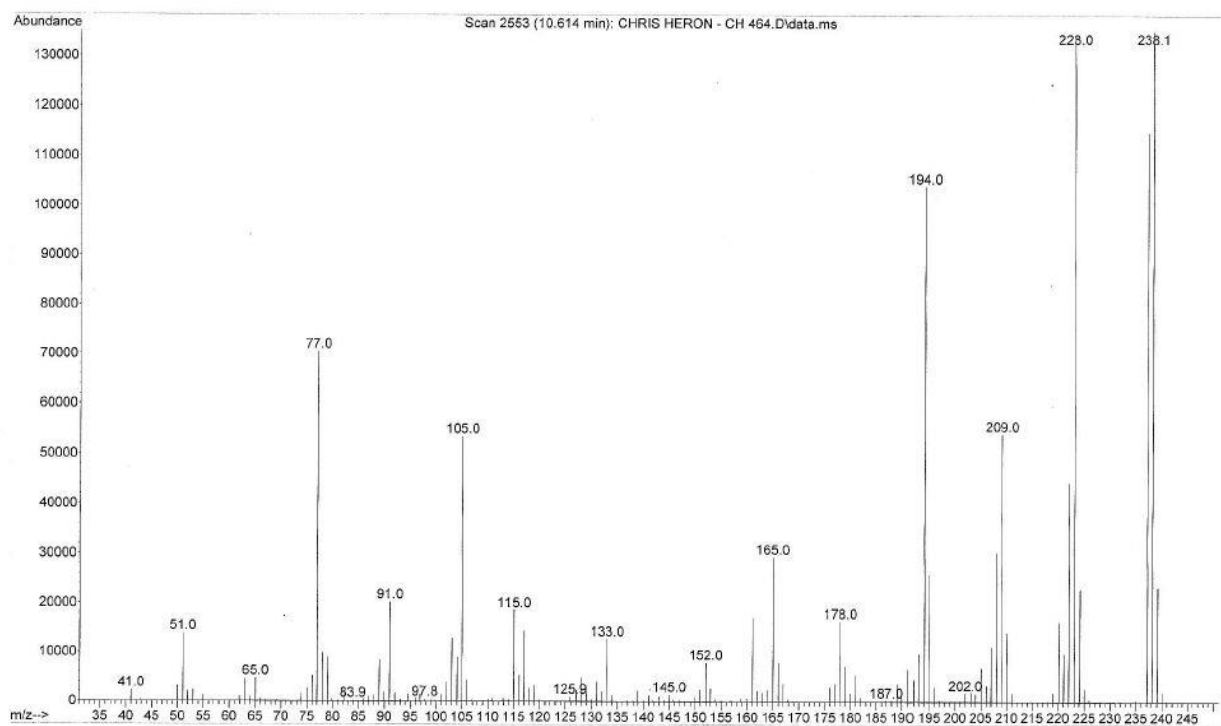
Appendix 3. MS histogram of GC peak at 10.2 minutes belonging to ortho ethylbenzophenone.



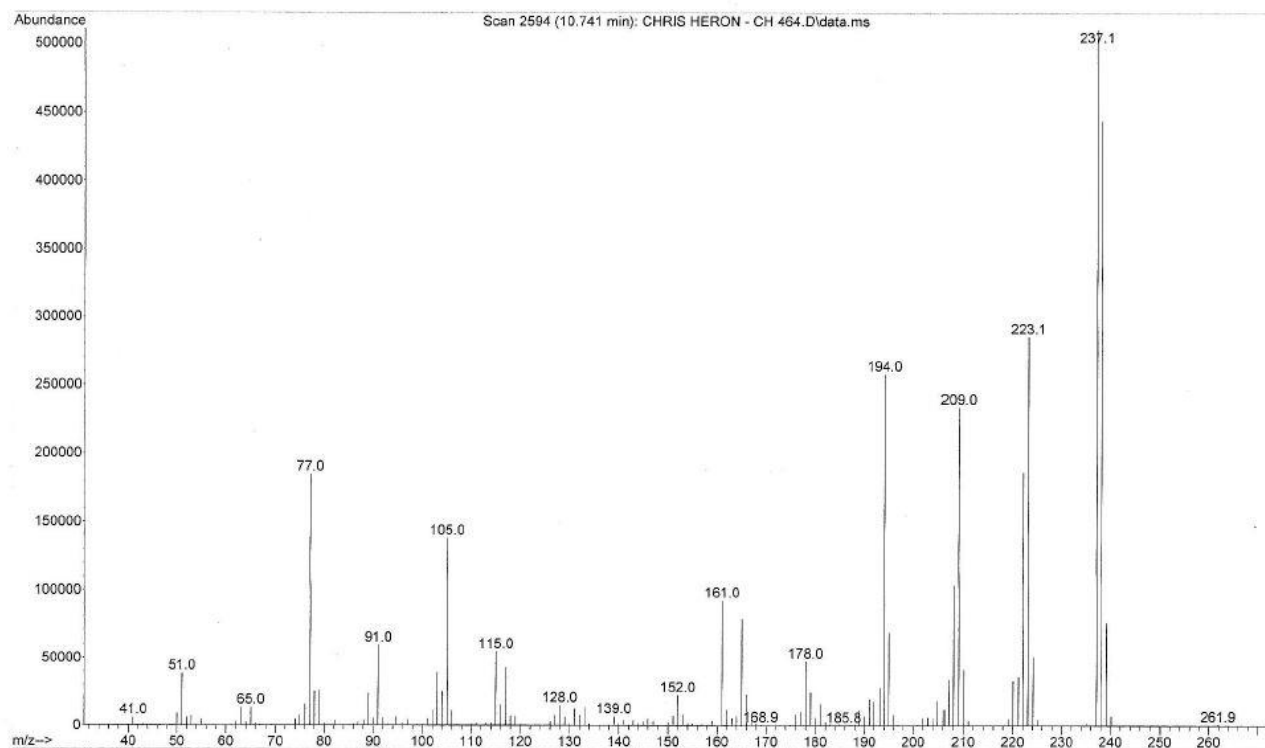
Appendix 4. MS histogram of GC peak at 10.5 minutes belonging to para ethylbenzophenone.



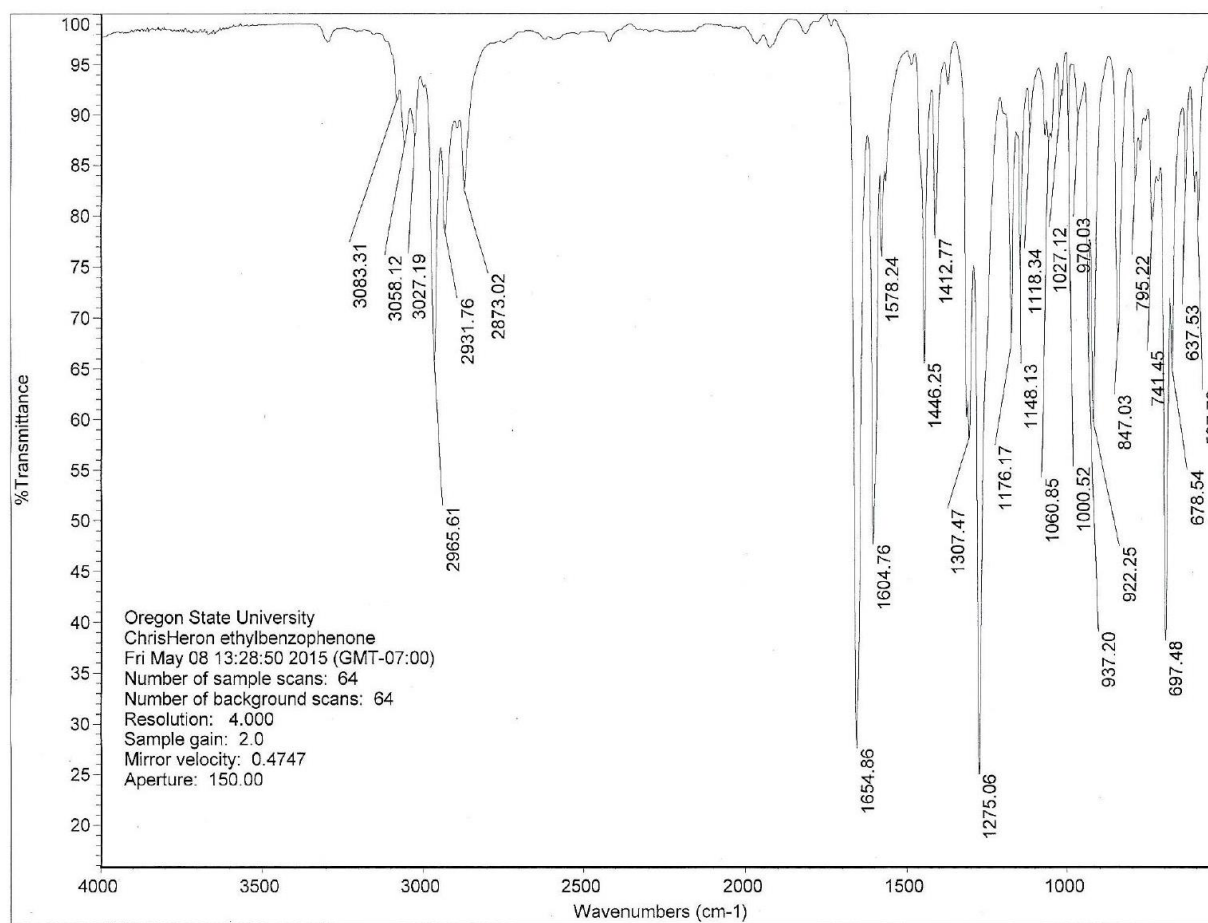
Appendix 5. MS histogram of GC peak at 10.6 minutes belonging to diethylbenzophenone.



Appendix 6. MS histogram of GC peak at 10.7 minutes belonging to diethylbenzophenone.



Appendix 7. IR spectra of product.



Appendix 8. 800 m/z HNMR spectra of product.

