Cis-Cinnamonic Nitriles: Synthesis, Separation, and Reaction with Diphenylphosphine
An Honors Thesis (HONRS 499)
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Purpose of Thesis

The series of experiments described here was done in an attempt to study the reaction of diphenylphosphine with the cis isomer of variously substituted cinnamionitriles. This discussion begins with the synthesis of the cinnamionitriles and how they are characterized using various instruments. Also, the characterization of the diphenylphosphine is described. Next, the method of separation of the two isomers of the cinnamionitrile is illustrated. Lastly, the results of the diphenylphosphine addition to p-chlorocinnamionitrile is discussed.
Cis-Substituted Cinnamonnitriles: Synthesis, Separation, and Reaction with Diphenylphosphine

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Introduction:

Substituted cinnamonnitriles contain an electron poor alkene group which allows for the reaction with diphenylphosphine. The reaction of diphenylphosphine with this sort of alkene was first studied in the case of diphenylphosphine and acrylonitrile which yields 3-diphenylphosphino-propanonitrile. That reaction was conducted with acetonitrile as the polar solvent with aqueous potassium hydroxide added. Later, the reaction of cinnamonnitriles with diphenylphosphine was carried out with deuterated chloroform as the non-polar solvent and without the necessity of basic catalyst. We present here a series of experiments dealing with variously substituted cinnamonnitriles in an attempt to understand this apparently polar reaction that takes place in a non-polar and non-basic environment of deuterated chloroform.
Synthesis of Substituted Cinnamonic Acid:

A Knoevenagel condensation reaction with a benzaldehyde of chosen substitution and an equal molar ratio of cyanoacetic acid in a solvent system containing both pyridine and piperidine produced the necessary cinnamonic acid. (Figure 1)

The reaction was run under an argon blanket at reflux which was set up in a round-bottomed flask equipped with condensor and an extraction apparatus with extraction thimble containing barium hydroxide (to remove excess water). As the reaction proceeded, the doubly substituted acid nitrile was decarboxylated to the substituted cinnamonic acid. The yield from this synthesis was fairly high -- about 60 percent. Also, the ratio of cis and trans products was usually about 50/50.

Although some of these substituted cinnamonic acid were available at a reasonable expense through chemical distribution companies, the amount of cis- isomer in the commercially produced product was very small. For unsubstituted cinnamonic acid, the commercially produced product is 99 percent trans while the product we synthesized by the above procedure was 55 percent trans. All of the substituted cinnamonic acid synthesized experimentally had a higher cis- percentage than the commercial
product from Aldrich.

The chosen substituent for the synthesis depended on what kind of electron effect was needed. Electron donating groups such as \( p \)-methyl- and \( p \)-methoxy-, donate electrons to the ring and affect the reactivity of the compound. Electron withdrawing groups, such as \( p \)-nitro-, \( m \)-nitro-, \( p \)-trifluoromethyl-, \( p \)-fluoro-, and \( p \)-cyano-, withdraw electrons from the ring structure thus affecting the reactivity in the opposite manner. Due to the electron differences in the substituents, the syntheses of the cinnamonitriles containing electron donating groups gave slightly higher yields. (Figure 2 & 3)

Characterization of Product:

The two instruments used to characterize the product were the nuclear magnetic resonance spectrometer (NMR) and the mass spectrometer. For the NMR, the peak with the most analytical utility was that corresponding to the vinylic hydrogen adjacent to the nitrile. The chemical shift of this set of two peaks (cis/trans) was between 5 and 6 parts per million. (Figure 3) Also, the two peaks not only distinguished the cis- and trans-isomers with the trans-isomer being shifted farther downfield but allowed estimation of relative amounts of the two isomers. A plot showing the correlation between the chemical shift of the vinylic hydrogen and the Hammett's Sigma value for the effect of substituents on the benzene ring has been plotted. A plot of this data shows a distinctly, separate linear correlation for
the cis- and trans- isomers. (Graph 1)

When looking at the spectrum of the cinnamonitrile, the two peaks corresponding the cis- and trans- isomers could be easily distinguished. By integrating these individual peaks, the relative amounts of cis and trans isomer available in that sample can be determined. Usually, the downfield peak representing the trans- isomer was of greater intensity in the samples. (Figure 3)

The mass spectrometer was also used to characterize the products. When using the chemical ionization feature of the mass spectrometer, the cinnamonitrile behaved as expected as only pseudomolecular ions and their complexes with common neutrals were observed. (Figure 4) For the p-methylcinnamonitrile, molecular weight 143 amu, the peak at m/e = 144 corresponds to the molecular weight of the compound and a proton. The peak at m/e = 185 corresponds to the molecular weight of the compound and the solvent, acetonitrile. Lastly, the peak at m/e = 287 corresponds to 2 molecular weights and one proton. All of these peaks are what was expected for the chemical ionization of p-methlycinnamonitrile. The chemical ionization of p-nitrocinnamonitrile followed a similar pattern. (Figure 5) However, additional peaks were found in that spectrum because of a mixture of two solvents were used to dissolve the sample.

Another type of ionization method in mass spectrometry is electron ionization. This method usually produces an extensive fragmentation pattern of the compound. For the unsubstituted cinnamonitrile, the major fragmentation is a loss of -HCN.
Further fragmentation results in a benzene ring peak at m/e = 78. (Figure 6) For p-chlorocinnamoniitrile, two major fragmentation types were discovered. (Figure 7) One fragmentation, similar to the unsubstituted cinnamoniitrile, was -HCN. The other fragmentation was chlorine loss. Because chlorine has two isotopes -- chlorine-35 and chlorine-37 -- two different peaks were found in a three to one ratio for the loss of chlorine. Although this pattern was different than the unsubstituted, the fragmentation pattern was what was expected.

To further this study on cinnamonitriles using the mass spectrometer, we plan to determine any differences in the fragmentation patterns for cis- and trans-isomers of the variously substituted cinnamonitriles.

Separation of Cis- and Trans- Isomers:

Once the substituted cinnamoniitrile was synthesized, the compound was separated using a GOW-MAC series 550P gas chromatograph equipped with quarter inch column. This instrument model was chosen for its ejection port on the rear of the instrument, non-destructive detector type, quarter inch column, and other locational conveniences. Since a GC separates all the components of a mixture, the substances used on this instrument did not have to be pure to be separated into their respective isomers.

To begin separation, the given substituted cinnamoniitrile had to be in liquid or solution form. Solids and gooey liquids
were dissolved in acetone. More fluid liquids were used without addition of solvent. The sample was injected into the instrument using a syringe containing an appropriate amount of sample. The amount of injection depended on the consistency of the sample. For example, the p-chlorocinnamonicitrile flowed through the column in a reasonable amount of time; therefore, the injection amount was approximately 30 μL. However, for the p-nitrocinnamonicitrile, the injection amount was lowered to approximately 5 μL to ensure that no compound corrupted the column. Table 1 shows the parameters for the running of the gas chromatograph with cinnamonicitroles.

As the sample flows across the detector, the integrator connected to the GC graphs the relative amount of that component in the sample. Also, the more volatile components go through the column first. The first component eluted was the solvent, acetone, which gave a strong peak on the integrator approximately two seconds after injection. A given while later, the substituted

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Gas Chromatogram

Figure 8

Small peak on left corresponds to the cis. While the taller peak on the right is the trans.
cinnammonitrile travels across the detector. (Figure 8) Since the cis- isomer is the more reactive isomer, it elutes before the trans- isomer. Therefore, the cis- isomer can be collected from the ejection port as the integrator is graphing the cis- peak. Also, the trans- isomer may be collected in the same manner.

The collection of the cis-isomer was done with a glass disposable Pasteur pipette with a little bit of glass wool in the larger end. The pipette was placed against the insulated ejection port and the sample was collected. The glass wool produces turbulence in the flowing gases which helped catch the liquid as the gas condenses. Since a very minuscule amount of sample was injected, a very small amount of each isomer was collected. Therefore, many collections of each isomer must be done to gain a sufficient sample for analysis.

The sample was removed from the pipette by rinsing deuterated chloroform through the pipette and into an NMR tube. The sample was analyzed for purity using NMR. (Figure 9) This technique allowed for high purity of separation with little expense.

Figure 9
This NMR is of cis-p-chlorocinnammonitrile. The peak at 5.5 corresponds to the cis isomer. The purity of this technique is found by looking at the absence of a peak at 6 signifying nearly pure cis isomer.
Characteristics Diphenylphosphine:

The reagent used to react with the variously substituted cinnamionitriles was diphenylphosphine (DPP). This reagent reacts violently with air and water, has a very nasty odor, and is light sensitive. Therefore, the handling of this reagent is very important. This nasty chemical is always stored in dark glass containers and stored and handled under argon.

Diphenylphosphine gives two distinct peaks on the NMR spectrum due to the spin-spin splitting of the phosphorous. (Figure 10) Also, a small peak farther downfield between 9 and 10 ppm corresponds to the partially oxidized portion of the molecule. When the spectrum is integrated, if the two sharp peaks are not eight times the oxidized peak, then the reagent cannot be used until the impurities of the oxidation have been removed or reduced.

The reaction of diphenylphosphine with variously substituted cinnamionitriles was done in an NMR tube with deuterated chloroform as the solvent. Since diphenylphosphine is so nasty, the protocol for addition of the reagent is important. (Figure 11) Water in the deuterated chloroform can cause the diphenylphosphine to react with the water instead of the cinnamo-
nitrile. Therefore, water must be avoided in the deuterated chloroform. Of course, the addition of diphenyl-phosphine must be done under an argon blanket. Therefore, the NMR tube with deuterated chloroform and cinnamonicnitrile must be swept with argon before addition of the diphenylphosphine. Also, the Epindorf Pipetter used to add the diphenylphosphine must have argon in the tip. Lastly, the diphenylphosphine must be kept under an argon blanket during the whole procedure.

Results of DPP Addition to Cinnamonicnitrile:

The reaction of diphenylphosphine with \( p \)-chloro-cinnamnicnitrile was done in deuterated chloroform with many NMR scans taken over the period of the reaction. (Figure 12) An equal molar ratio of the cinnamonicnitrile to the diphenylphosphine was used. The initial \( p \)-chlorocinnamonicnitrile had about 75 percent trans- isomer. The addition of DPP showed the characteristic two peaks of DPP. Over time, those peaks disappeared into the base line. Also, the mole fraction of the cis- decreases as the reaction proceeds. Lastly, a broad peak began to form at about 5.5 ppm. That peak became sharper as the reaction proceeded.
Discussion about DPP addition to p-Chlorocinnamnitrile:

Since the mole fraction of cis- decreased as the reaction progressed over time while the mole fraction of trans increased, then the cis isomer is reacting with the DPP. (Figure 13) This scheme suggests that DPP adds to the double bond of the cis-cinnamnitrile in a Michael type fashion. The possible equilibrium between the DPP-cis-cinnamnitrile complex and the trans-cinnamnitrile suggests that the DPP could be acting as a catalyst in the isomerization reaction.

Also, the change in shape of the peak corresponding to the possible product suggests something about the rate of reaction. Since the peak is very sharp when an abundance of cis is present and as the relative amount of cis declines the peak becomes broader, then the cis- could be the limiting factor for the reaction of DPP to cinnamnitriles.
References:
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Chemical Shift (ppm)

Trans-isomer
- p-methyl
- p- trifluoromethyl
- p-chloro
- p-cyano
- p-nitro

Cis-isomer
- p-methoxy
- p-methyl
- p-trifluoromethyl
- p-chloro
- p-cyano
- m-nitro
Figure 2
This NMR shows the unsubstituted cinnamonicnitrile from Aldrich. Only the trans peak is apparent at 5.85 ppm.
Figure 3
This NMR shows the unsubstituted cinnamonic acid that we synthesized. The peak 5.49 represents the cis peak while the peak at 5.85 corresponds to the trans peak.
Figure 4
This mass spectra shows the chemical ionization of p-methylcinnamonicnitrile with acetonitrile as solvent.
Figure 5
This mass spectrum show the chemical ionization of p-nitrocinnamonnitrile with methanol and acetonitrile as solvents.
Figure 6
This mass spectrum shows the fragmentation pattern of unsubstituted cinnamonic acid by electron ionization.
Figure 7
This electron ionization mass spectrum shows the fragmentation pattern of p-chlorocinnamonnitirile.
Figure 10
This NMR is of DPP with ethyl crotonate. The characteristic peaks of DPP are at 4.6 and 5.7 ppm.

87 μL DPP plus 100 μL D2O (20x) in DMSO