

Lab 5: Chiral Reduction of Ethyl Acetoacetate

I. Purpose: The purpose of this experiment is gain knowledge on how to use the NMR to determine the ratio of enantiomers formed from a stereoselective reaction involving baker's yeast.

II. Description of Experimental Approach: By reacting the ester created by the baker's yeast with acid, we can create a chiral ester that will contain the original stereogenic centers and can be differentiated by NMR. The ratio of products will be determined via integration of specific points in the NMR spectra.

III. Summary of Results: It has been determined that a 1.17:1 ratio of S,S to S,R ester was created, and therefore the reaction of ethyl acetoacetate with baker's yeast primarily yields the S stereoisomer. However, the ratio is not overpowering to one side or the other; the final product is almost a racemic mixture.

IV. Data and Analysis:

Compound	Ethyl acetoacetate	Ethyl 3-hydroxybutanoate	(S)-methoxyphenyl-acetic acid	S,R/S,S Chiral Ester
Molecular formula	C ₆ H ₁₀ O ₃	C ₆ H ₁₂ O ₃	C ₉ H ₁₀ O ₃	C ₁₅ H ₂₀ O ₅
Molecular weight	130.133 g/mol	132.147 g/mol	166.166 g/mol	270.23 g/mol
Moles used (grams used)	0.023 mol (3.0g)	0.014 mol (1.83g)	0.4 mmol (0.065g)	0.3 mmol (0.083g)
Product yield	--	60.8%	--	77 %

Long involved lab, this was! The baker's yeast procedure went off without a hitch – nothing much to say about that. Filtration via Buchner funnel and cheesecloth effectively filtered all the large particles out of the solution, and a steri-cup filtration apparatus helped further to remove fine particles from the solution, making it much less cloudy.

During the extractions, emulsions occurred. I was able to minimize the emulsions by poking the emulsion with a spatula and coaxing the air bubbles to the top. As such, centrifuging was not necessary to break up the emulsion. Rotary evaporation of the solvent yielded 1.83g of ethyl 3-hydroxybutanoate. The IR spectra was misprinted (as it only shows up to 1800 cm⁻¹), but we can clearly see ester/carboxyl group combined stretching making a broad peak at 1722 cm⁻¹. A GC-MS analysis of this compound yields a library match to the structure illustrated in the text of the procedure (see attached).

The procedure for day three (adding the acid to the ester to create the final product) went well except for one major mishap. After completing the extractions, I placed the extracted methylene chloride solution with the product inside into a 100mL beaker. It quickly evaporated since a large surface area of the solvent was exposed. I hastily added ~5mL of methylene chloride and quickly moved the solution to a closed vial to prevent total evaporation again. I was pretty convinced that I'd lost my product, but adding methylene chloride to the beaker retrieved the product stuck to the bottom of the beaker. My NMR readings came out fine, so this didn't seem to effect too much outside of my yield! I recovered 0.083g product after evaporating with an air stream.

NMR analysis: For the ethyl 3-hydroxybutanoate, there are seven different types of hydrogens. The peak around 4.0 relate to the (a) and (b) hydrogens, a multiplet and quartet, respectively. The multiplet comes from the (a) hydrogen coupling with the 6 hydrogens scattered around it, while the (b) hydrogens get a quartet from the nearby methyl group. At 3.4, the (c) hydrogen (the O-H hydrogen) forms a blob due to the oxygen and couples with the (a) hydrogen. The peak at 2.2 represents the (d) and (e) hydrogens coupling to the (a) and (c) hydrogens. It forms a doublet of doublet of sorts, due to the separate coupling constants to the (a) and the O-H (c) hydrogen. The final peaks around 1.0 correspond to the terminal methyl groups on either end. The (f) hydrogens couple to the nearby two (b) hydrogens while the (g) hydrogens couple with the (a) hydrogen.

For the ester, it's significantly harder to decipher the diagram. We know that the first peak at 7.4 consist of the benzene's hydrogens, (a). The quartet at 5.4 corresponds to the chiral hydrogen (d) coupling with the nearby methyl group, (e) as well as its proximity to an oxygen. The peak at 4.8 is a singlet, as the (c) hydrogen is not able to couple with any other hydrogen. Meanwhile, the peak at 4.3 is a quartet as the (f) hydrogens couple with the nearby terminal methyl group, (g). The tall peak at 3.5 is a singlet of three (b) hydrogens that are unable to couple with other hydrogens. The multiplet at 2.6 has the (h) hydrogens coupling with the (d) hydrogen. There exists some stereoselectivity at this position, so the two (h) hydrogens do not couple congruent to each other, making a messy multiplet.

The two remaining groups of hydrogens, (e) and (g) are shown in detail on the next page. These two groups depend on the stereoisomerism of the carbon molecule that the (e) hydrogen is attached to. Without divulging too much into what makes the chemical shifts different, the (e) hydrogens form a doublet with the nearby chiral hydrogen (d). The terminal methyl group's hydrogens, (g), make a triplet with the nearby two (f) hydrogens.

We can see the ratio of the two stereoisomers made by looking at the ratio of the S,S peaks against the S,R peaks.

V. Questions:

1. Done. I actually enjoyed learning how to actually decipher a NMR spectra to find the ratio of stereoisomers. It is a very neat application!

2. By dividing the integral of the peaks from 1.31 to 1.2 by the sum of the integrals of the peaks from 1.4 to 1.31 and 1.2 to 1.08, we can find the ratio of the products, S,S/S,R. (see attached NMR for details).

3.

4. On the ethyl 3-hydroxybutanoate NMR spectra, it is essentially impossible to tell stereoisomers apart because of the mess that the O-H bond does to hydrogen coupling. By adding onto this alcohol/ester and 'replacing' the hydroxyl group with an ether, the chemical shifts between the two stereoisomers become significant and can be differentiated based upon the integration of the now separate peaks since the O-H hydrogen has been eliminated. Phenyl acetic acid could work enough to differentiate the peaks, but it doesn't contain as many electron withdrawing groups as the acid that we added, so the chemical shift between the enantiomers may not be so significant.

5. Since Karl has added a racemic mixture of the acid to be used in the synthesis of the final product, there are four stereoisomers that can be formed, up from the original two. R,R and R,S isomers can now be formed. This will just clutter up the NMR spectra and make it extremely difficult to differentiate what peaks correspond to each isomer. As a result, it will be hard to determine the exact ratio of stereoisomers in the original product. Maybe we should stop picking on poor Karl – he might even be proficient in physics! Chemistry just isn't his strong point at all. :o)

** attached pages: 1pg GC-MS, 2pg IR spectra (reactant and synthesized ester from yeast), and 3pg NMR spectra.*