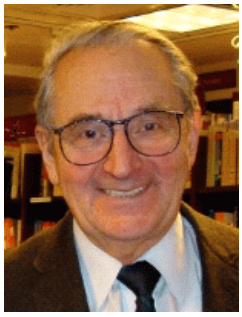
Fig. 18-1



Experiment 18

STEREOCHEMISTRY OF NUCLEOPHILIC SUBSTITUTION

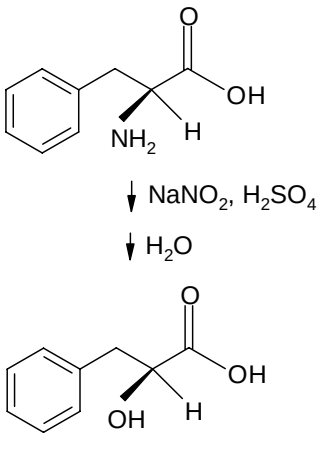
Elias James Corey (1928 - present)
Received 1990 Nobel prize for synthetic organic chemistry work
http://nobelprize.org/nobel_prizes/chemistry/laureates/1990/corey-autobio.html

Text Topics

Nucleophilic substitution reactions, nucleophilicity.

Discussion

Wouldn't it be wonderful and enlightening if we could record a video of the progress of a reaction as it proceeds from starting material to products? Unfortunately, because of size and timing limitations of our current technology, it is not yet possible to capture the mechanism of a reaction on video. Instead, significant information about reaction mechanisms can be accumulated by using several techniques. By determining the kinetics of a reaction and the effects of variables such as concentrations, temperature, isotope effects, solvent effects and structural changes on reaction rates, it is often possible to piece together a good description of the mechanism of a reaction. The symbols S_N1 and S_N2 represent two possible extremes for the mechanisms of nucleophilic substitution reactions at a saturated carbon. Ideally, the two mechanisms can be distinguished by determining the rate expression as S_N1 reactions should be independent of the concentration of the nucleophile and S_N2 reactions should be proportional to the concentration of the nucleophile. In practice, it is not always easy to make this distinction. For example, when the nucleophile is the solvent (e.g., water or methanol), varying the concentration of the nucleophile is not practical. Another method to distinguish between the two mechanisms involves a study of the stereochemistry of the reaction. See the **Discussion** in ***Experiment 15*** for more information. Admittedly, a stereochemistry study is only useful when the carbon at the center of the reaction is stereogenic (a chirality center). Studies of sterochemical outcomes are often complicated by the time and expense involved in obtaining optically pure starting materials. Today's experiment involves the study of the stereochemistry of a sequence of reactions starting with the relatively inexpensive and readily available enantiomer, *(S)*-(-)-phenylalanine. *(S)*-(-)-Phenylalanine is available because it is a naturally occurring amino acid. However, humans do not synthesize *(S)*-(-)-phenylalanine and it must be in your diet if health problems are to be avoided.



L-(-)-3-phenyllactic acid or
D,L-3-phenyllactic acid

The objective will be to convert *(S)*-(-)-phenylalanine via a sequence of two substitution reactions to 2-hydroxy-3-phenylpropanoic acid (common name 3-phenyllactic acid). If either substitution goes via an S_N1 mechanism, the product should be racemic. If, however, both go by S_N2 mechanisms, the stereogenic center should end up with retention of the original configuration.

As indicated in the ***Prelaboratory Questions***, you should propose a mechanism for the conversion of *(S)*-(-)-phenylalanine to either L-(-)-3-phenyllactic acid/or D,L-3-phenyllactic acid. To help you formulate a mechanism, the sodium nitrite should diazotize the amino group. Following this, a lactone could be formed as a result of displacement by the carboxyl group. The next step is a hydrolysis.

The biggest challenge in this experiment is to determine if the reaction goes with retention or inversion of configuration at the steroeogenic center. The most straightforward method to do this would seem to be determination of the optical activity of the product. However, the experiment will be performed with small amounts and it will probably be necessary to pool the products of many groups of students to accumulate enough product for a polarimetery study. If the optical rotation cannot be conveniently measured, an alternative method involves determination of the melting range of the product. A racemic mixture consists of equal amounts of two enantiomers. You are well aware that impurities depress melting points and it is often the case that a racemic mixture melts substantially lower than either enantiomer. In other words, the racemate often behaves the expected way for a mixture. By determining the melting range of your product, you should be able to determine if it is a racemic mixture (literature melting range 95-98^{o}C) or predominantly one enantiomer (literature melting range 120-121^{o}C). A mixed melting point determined for a mixture of your product and one of the enantiomers could also provide additional evidence. However, the enantiomers are very expensive and should be used sparingly.

An H-nmr of the product should also be obtained in DMSO-d_6. The benzlic hydrogens in the product are diastereotopic and should resonate at different field strengths and show coupling with each other and the α hydrogen.

Procedure

For the first step of the reaction, hazardous nitrogen dioxide will be emitted. If the addition is performed at a very slow rate, the emission should be slow. To minimize risk, the reaction should be performed in a hood. Add 1.65 g of *(S)*-(-)-phenylalanine to a 25 mL Erlenmeyer flask equipped with a magnetic stirring bar. Carefully add 10 mL of 1 M H_2SO_4 to the flask at room temperature and stir until the mixture is homogeneous. Cool the mixture in an ice bath to <5^{o}C while continuing the stirring. Add 5 mL of a 3.0 M aqueous $NaNO_2$ solution dropwise over a 45 minute period keeping the temperature <5^{o}C. Record all observations especially of different gases emitted and relate your observations to your proposed mechanism. After the addition is complete, remove the ice bath but continue stirring until your laboratory session is over. Crystals should start to form. Lightly cork the flask and store safely until your next lab period. Because the second step is very slow, the reaction must be allowed to sit for at least 24 hours to produce a reasonable yield.

At the beginning of the next laboratory period, to maximize the crystalline yield, once again cool the mixture with an ice bath until the temperature <5^{o}C. Vacuum filter to collect the product. With the crystals still in the Büchner funnel, turn off the vacuum and add 5 mL of ice-cold water. Mix to make a slurry. Turn on the vacuum to remove the water and allow the crystals to dry at least overnight. Determine the melting range of the product along with the H-nmr spectrum and optical rotation if possible.

References

Van Draanen, N. A.; Hengst, S. *J. Chem. Educ.*, **2010**, *87*, 623.

Prelaboratory Preparation - *Experiment 18*

First, be sure to list all the goals of the experiment. Calculate the theoretical yield of the product. Propose a mechanism for the conversion of *(S)*-(-)-phenylalanine to either L-(-)-3-phenyllactic acid/or D,L-3-phenyllactic acid.

Observations

Report all relevant observations including masses, melting ranges and ^{1}H-nmr.

Conclusions

This section should include the following:

1. Were the goals of the experiment achieved? Explain your answer.
2. Report your experimental yield and give reasons for any losses.
3. Based on your melting range results, did the reaction result in racemization or retention of configuration? Explain your answer in detail.
4. Based on your answer to #3 above, was the mechanism you proposed in the ***Prelaboratory Questions*** consistent with the results? If not, suggest a different mechanism.
5. Discuss the possible observations that could result if a melting point is determined for a mixture of one of the enantiomers and your product. Does it make any difference which enantiomer is used for the test? Explain your answer.