Principles of Organic synthesis
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Molecular Rearrangements
Lecture 22
Rearrangement to Electron Deficient Carbon
Carbon Migration

Welcome you all to Principles of Organic Synthesis. So far, we studied the aliphatic C-C/C-N bond formation, organometallic reagent, electrophilic/nucleophilic aromatic substitution and aromatic diazonium salt. Today, we will start the new module on molecular rearrangement. If you look at the lectures that we studied so far the basic skeleton was intact. In case of the molecular rearrangement, the basic skeleton rearranges, which can take place within the molecule or between two molecules. In this lecture, we will study the rearrangement to electron deficient carbon.

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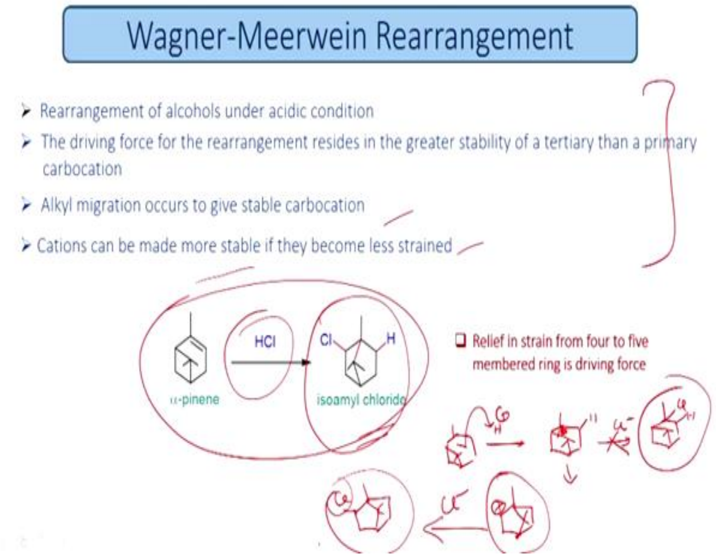

Wagner-Meerwein Rearrangement

- Rearrangement of alcohols under acidic condition
- The driving force for the rearrangement resides in the greater stability of a tertiary than a primary carbocation
- Alkyl migration occurs to give stable carbocation
- Cations can be made more stable if they become less strained

☐ Relief in strain from four to five membered ring is driving force

Here is the Wagner-Meerwein rearrangement. For example, α-pinene rearranges to isoamyl chloride. The driving force for the rearrangement is the relief in strain from four to five membered ring. Addition of the double bond with proton leads to the formation of tertiary carbocation, which rearranges to secondary carbocation due to relief of strain from four to five membered ring, which reacts with chloride anion. The reaction involves addition of HCl with rearrangement of the basic skeleton via the carbocation.

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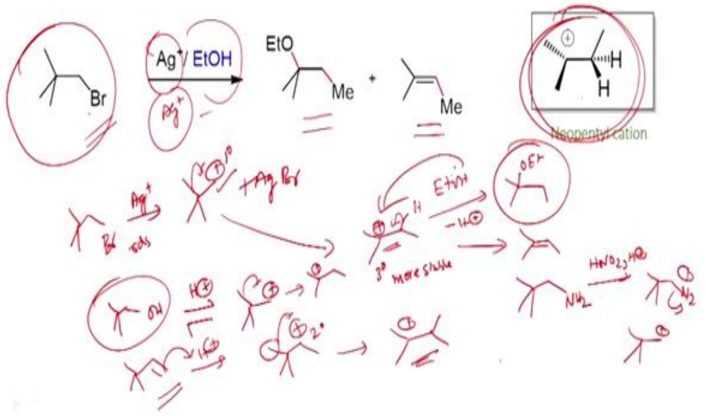
Wagner-Meerwein Rearrangement



Here look at the rearrangement of neopentyl bromide using silver salt in ethanol. Driving force for this rearrangement is the transformation of primary to tertiary carbocation. Neopentyl bromide with silver salt converts to primary carbocation. 1,2-Methyl shift to the carbocation results in the formation of tertiary carbocation. Which can react with solvent to give ether. Alternatively, the carbocation can convert to alkene by deprotonation.

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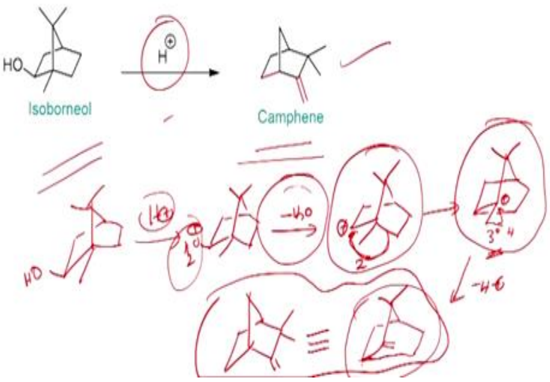
Wagner-Meerwein Rearrangement

- The earliest example of Wagner-Meerwein rearrangement was noticed in bicyclic terpenes



Here is the rearrangement of isoborneol to camphene. Protonation of isoborneol followed by removal of water molecule gives the isobornyl secondary carbocation, which rearranges to the tertiary carbocation that loses a proton to give camphene.

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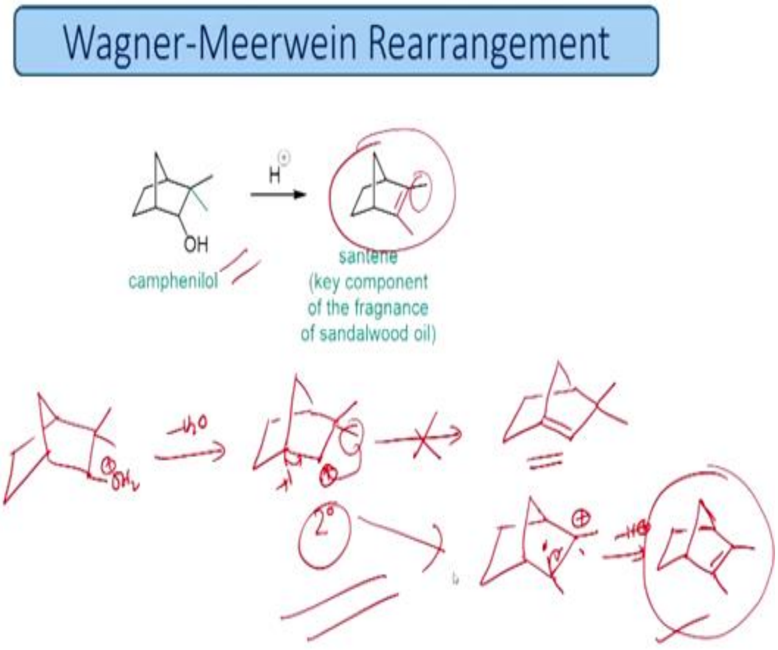

Wagner-Meerwein Rearrangement

camphenilol

santene (key component of the fragnance of sandalwood oil)

Here is the acid-catalyzed rearrangement of camphenilol to santene. Protonation followed by the removal of water molecule produces the secondary carbocation. Deprotonation will produce the bridge head double bond, which is not feasible. On the other hand, migration of the methyl group produces the tertiary carbocation, which converts to the bicyclic alkene via the E1 elimination.

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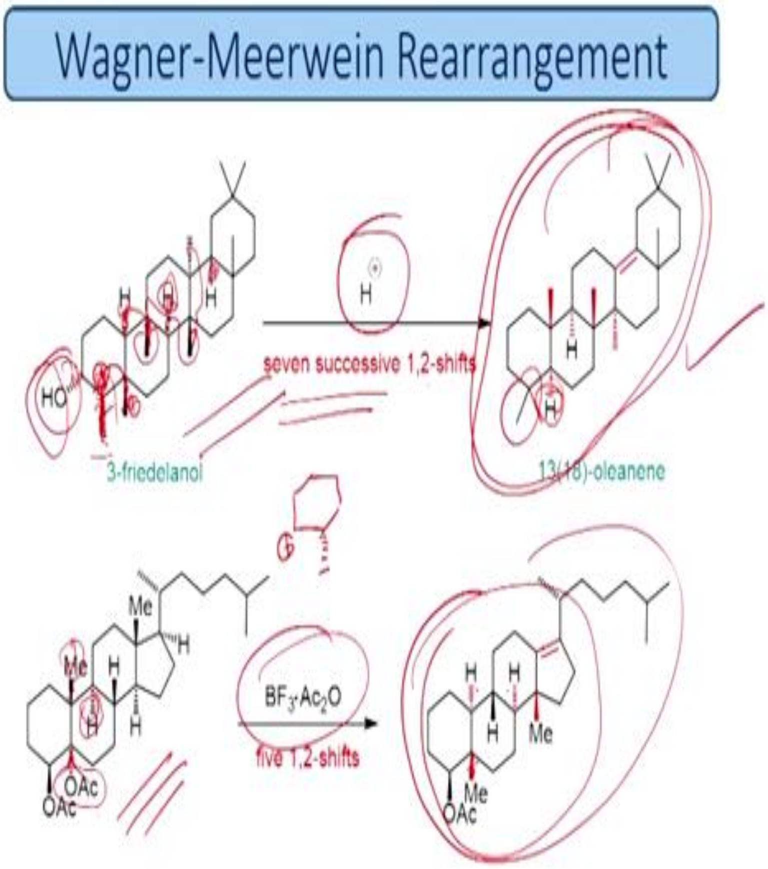

Wagner-Meerwein Rearrangement

Now let us see the rearrangement of polycyclic compounds. Protonation of 3-friedelanol with acid followed by seven S_N2 1,2-migrations lead to a tertiary carbocation, which loses proton to give oleanene via E1 elimination. Similarly, in the second example, OAc makes chelation with BF_3, which leads to five S_N2 1,2-migrations to give a tertiary carbocation, that loses proton to give the polycyclic alkene via E1 elimination.

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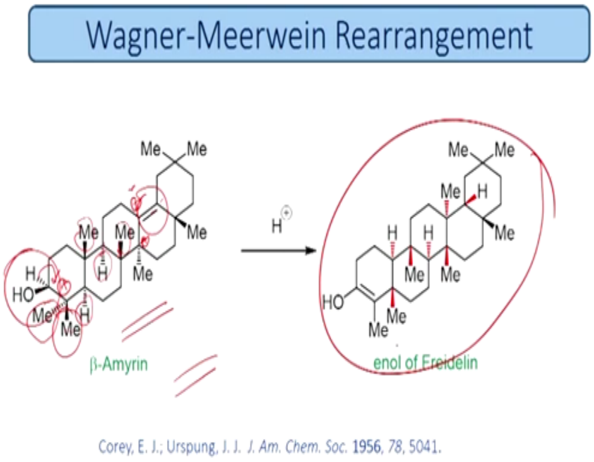

Wagner-Meerwein Rearrangement

Corey, E. J.; Urspung, J. J. *J. Am. Chem. Soc.* **1956**, *78*, 5041.

In this example, the double bond adds to proton to produce a tertiary carbocation, which leads to six S_N2 1,2-migrations to produce a tertiary carbocation. Removal of proton gives the enol via E1 elimination.

So far, we have seen the tandem stereospecific 1,2-migration of polycycles. Now let us look at the rearrangement that involves the neighboring group participation.

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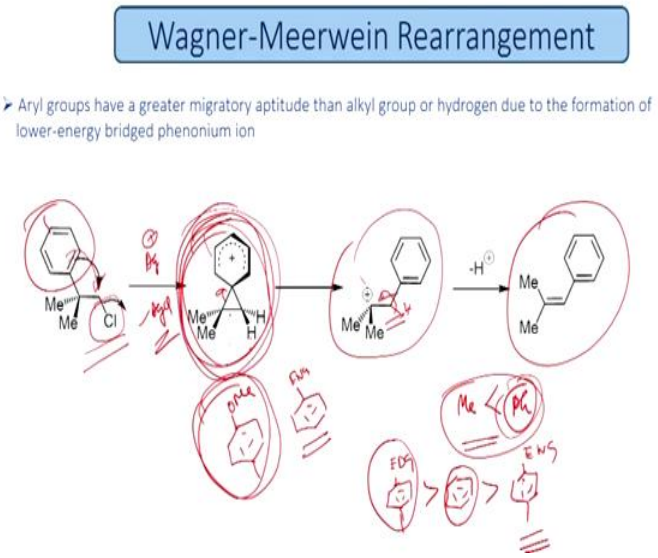

Wagner-Meerwein Rearrangement

- Aryl groups have a greater migratory aptitude than alkyl group or hydrogen due to the formation of lower-energy bridged phenonium ion

Aryl group has more migratory aptitude compared to alkyl group due to the formation of lower-energy bridged phenonium ion. For example, the alkyl chloride with silver salt produces the phenonium ion via the neighboring group participation. Which opens to tertiary carbocation that loses a proton to give the styrene derivative via E1 elimination.

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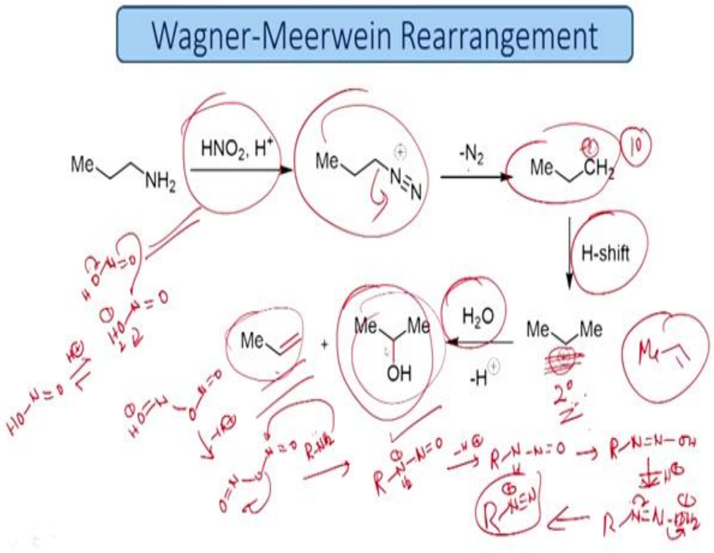
Wagner-Meerwein Rearrangement

Here is the diazotization of propylamine followed by the rearrangement of the carbocation. Diazotization using nitrous acid produces the diazonium salt, which converts to propyl carbocation due to the acidic reaction medium. 1,2-Hydrogen shift produces the secondary carbocation, which can react with water molecule to give 2-propanol. Alternatively, loss of proton can give the propene via E1 elimination.

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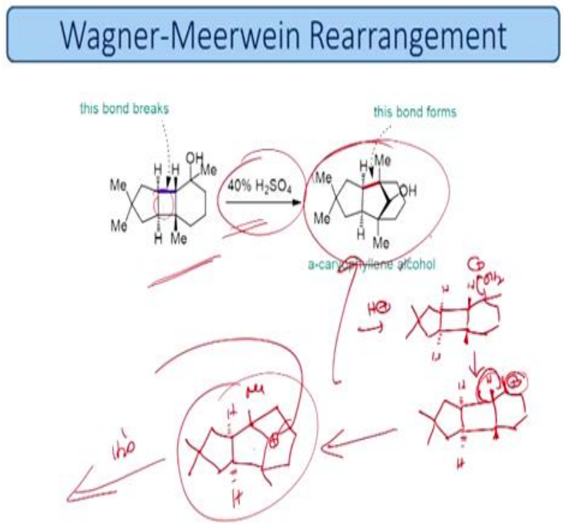
Wagner-Meerwein Rearrangement

The tricyclic alcohol rearranges in the presence of 40% sulfuric acid. Protonation of the OH group followed by loss of water molecule gives the tertiary carbocation. Which rearranges to secondary carbocation due to relief from the strain of four to five membered ring. Reaction with water molecule produces the cyclic secondary alcohol. Thus, tertiary alcohol rearranges to secondary alcohol and the main driving force is the conversion of more strained four to five membered ring.

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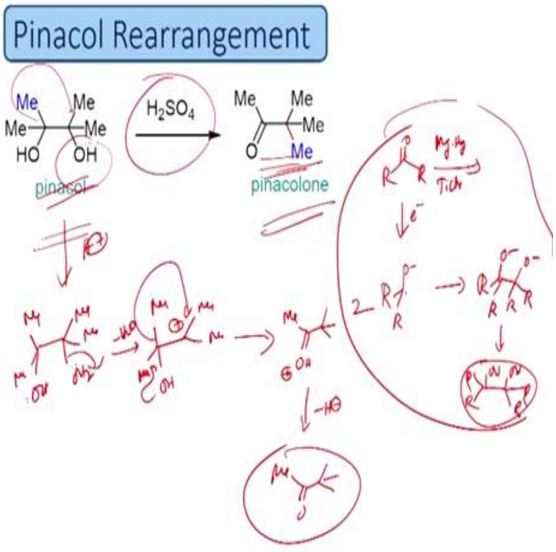

Pinacol Rearrangement

Now let us look at the pinacol rearrangement. Protonation of the OH group followed by the 1,2-migration of the methyl group gives butyl methyl ketone as the product. The feature of this rearrangement is similar to that of Wegner Meerwein rearrangement.

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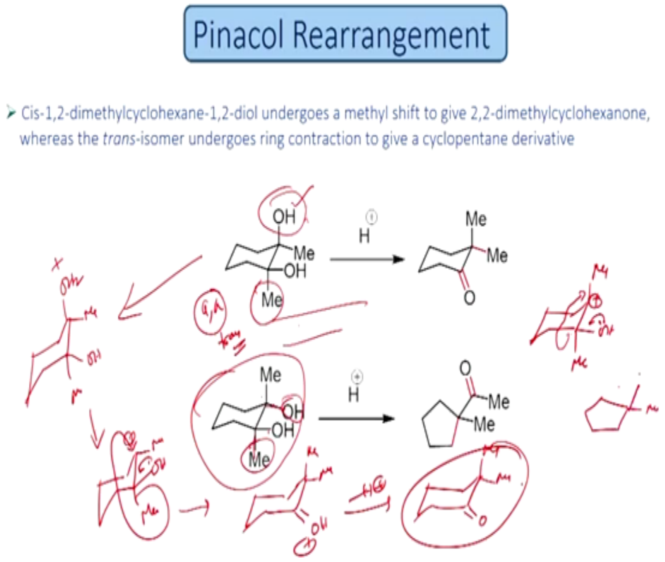

Pinacol Rearrangement

- Cis-1,2-dimethylcyclohexane-1,2-diol undergoes a methyl shift to give 2,2-dimethylcyclohexanone, whereas the *trans*-isomer undergoes ring contraction to give a cyclopentane derivative

Here is the acid catalyzed rearrangement of 1,2-dimethylcyclohexane-1,2-diols. *Cis*-1,2-diol leads to the formation of 2,2-dimethylcyclohexanone via 1,2-migration of *trans*-methyl group. While *trans*-1,2-diol rearranges to methyl 1-methylcyclopentyl ketone due to the migration of cyclohexyl CH_2. The reactions are stereospecific and can selectively be converted to the respective ketones.

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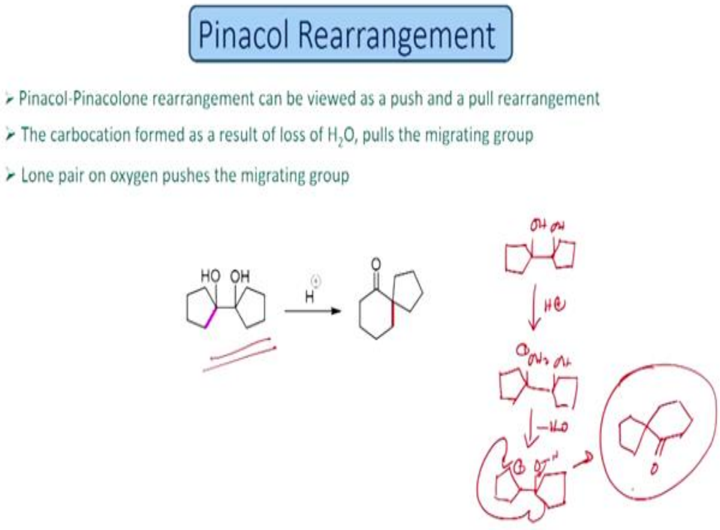

Pinacol Rearrangement

- Pinacol-Pinacolone rearrangement can be viewed as a push and a pull rearrangement
- The carbocation formed as a result of loss of H_2O, pulls the migrating group
- Lone pair on oxygen pushes the migrating group

Now, let us look at the rearrangement of 1,1’-bis(cyclopentane)-1,1’-diol to spiro[4.5]decan-6-one. Protonation followed by loss of water molecule gives the tertiary carbocation, which converts to the spirocyclic ketone by ring expansion.

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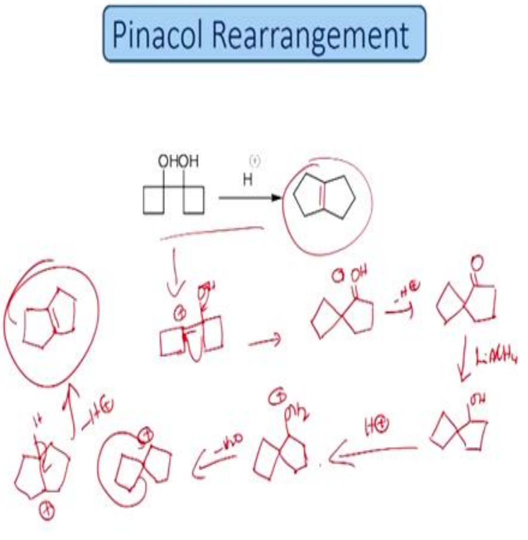

Pinacol Rearrangement

As the previous example, acid catalyzes the rearrangement of 1,1’-bis(cyclbutane)-1,1’-diol to spiro[3.4]octan-5-one, which can be reduced using $LiAlH_4$ to give the alcohol. Treatment with acid can produce the secondary carbocation, which can rearrange to more stable tertiary carbocation via ring expansion. Loss of proton can produce 1,2,3,4,5,6-hexahydropentalene.

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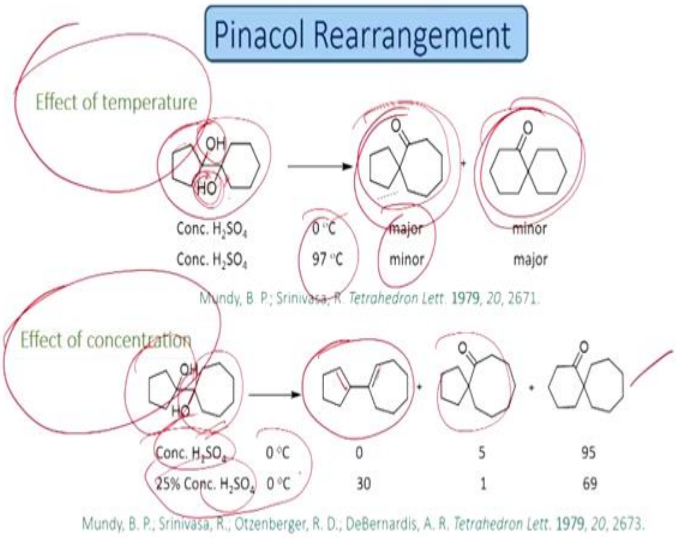

Pinacol Rearrangement

Effect of temperature

Conc. H_2SO_4	0 °C	major	minor
Conc. H_2SO_4	97 °C	minor	major

Mundy, B. P.; Srinivasa, R. *Tetrahedron Lett.* 1979, *20*, 2671.

Effect of concentration

Conc. H_2SO_4	0 °C	0	5	95
25% Conc. H_2SO_4	0 °C	30	1	69

Mundy, B. P.; Srinivasa, R.; Otzenberger, R. D.; DeBernardis, A. R. *Tetrahedron Lett.* 1979, *20*, 2673.

Pinacol rearrangement depends on the reaction temperature as well as concentration of the acid. The first example shows the role of temperature for the rearrangement of 1-(1-hydroxycyclopentyl)cyclohexan-1-ol. At 0 °C, spiro[4.6]undecan-6-one forms as the major product due to the formation of cyclopentyl carbocation. While at 97 °C, spiro[5.5]undecan-1-one is formed as the major product due to the formation of cyclohexyl carbocation.

The second example shows the effect of the concentration of sulfuric acid in the catalysis. Concentrated sulfuric acid gives the rearranged spirocyclic ketone as the product, whereas dilute sulfuric acid facilitates the dehydration to produce diene along with the rearranged spirocyclic ketone. Thus, the reaction conditions play the crucial role in the selectivity of the products.

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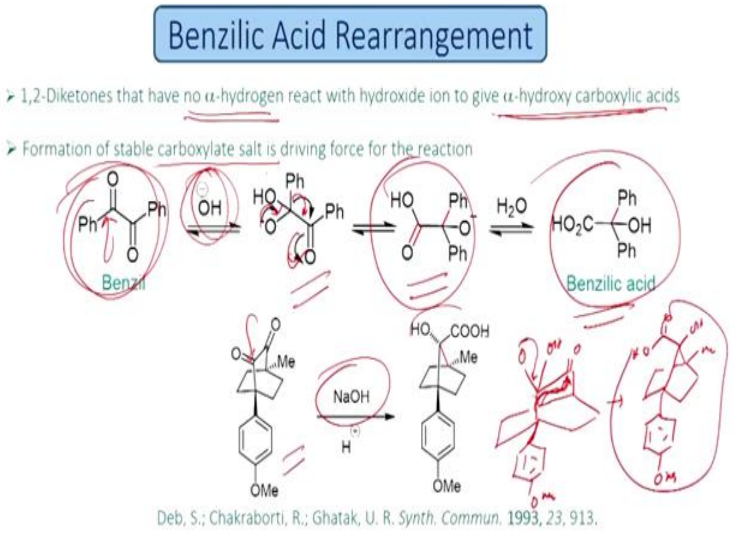

Benzilic Acid Rearrangement

- 1,2-Diketones that have no α-hydrogen react with hydroxide ion to give α-hydroxy carboxylic acids
- Formation of stable carboxylate salt is driving force for the reaction

Deb, S.; Chakraborti, R.; Ghatak, U. R. *Synth. Commun.* 1993, *23*, 913.

So far we have seen the acid catalyzed rearrangements. Now, let us focus on the hydroxide-mediated benzylic acid rearrangement. 1,2-Diketones, that don’t have α-hydrogen, undergo addition with hydroxide, which leads to the rearrangement to produce α-hydroxy carboxylic acid due to the formation of stable carboxylate. The first example shows the rearrangement of benzoin with hydroxide to benzylic acid. Addition of hydroxide to the carbonyl group followed by 1,2-migration of the phenyl group gives α-hydroxy carboxylic acid. Similarly, the second example with bicyclic diketone rearranges to α-hydroxy carboxylic acid via the migration of aryl substituted tertiary carbon.

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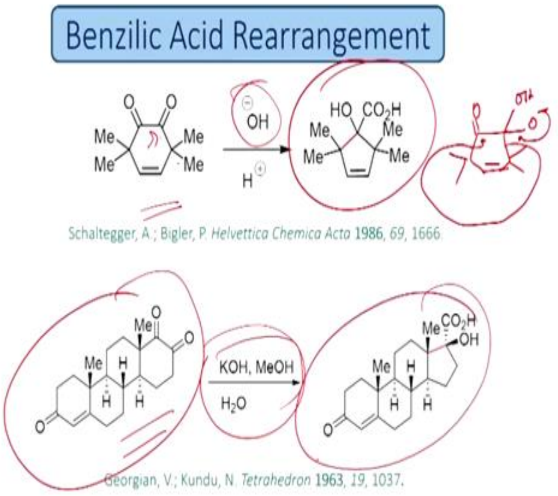

Benzilic Acid Rearrangement

Schaltegger, A ; Bigler, P. *Helvettica Chemica Acta* 1986, *69*, 1666.

Georgian, V.; Kundu, N. *Tetrahedron* 1963, *19*, 1037.

The rearrangement of six membered 1,2-diketones readily take place to produce the respective five membered α-hydroxy carboxylic acids. The last example shows that the reaction can be utilized for the rearrangement of functionalized 1,2-diketones.

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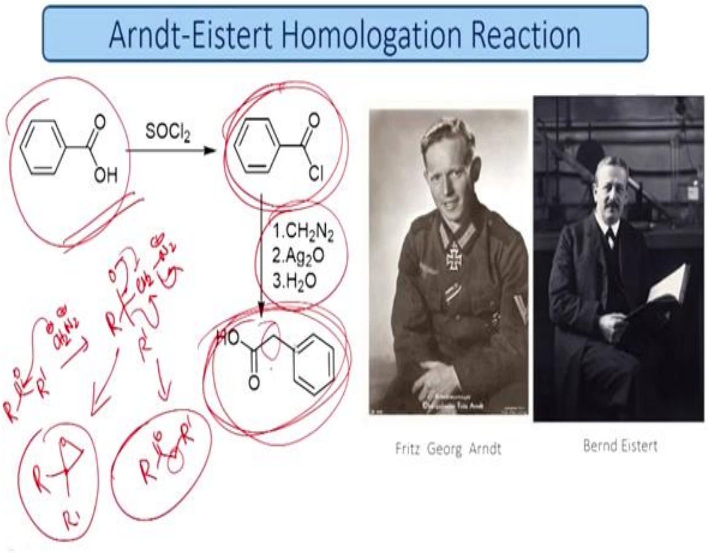

Arndt-Eistert Homologation Reaction

Now, let us move to the Arndt-Eistert synthesis. This reaction involves the homologation of the carboxylic acid. For example, benzoic acid is converted to benzoyl chloride, which is further reacted with diazomethane to produce phenylacetic acid. Overall, benzoic acid is converted to phenylacetic acid, which is known as the Arndt-Eistert synthesis.

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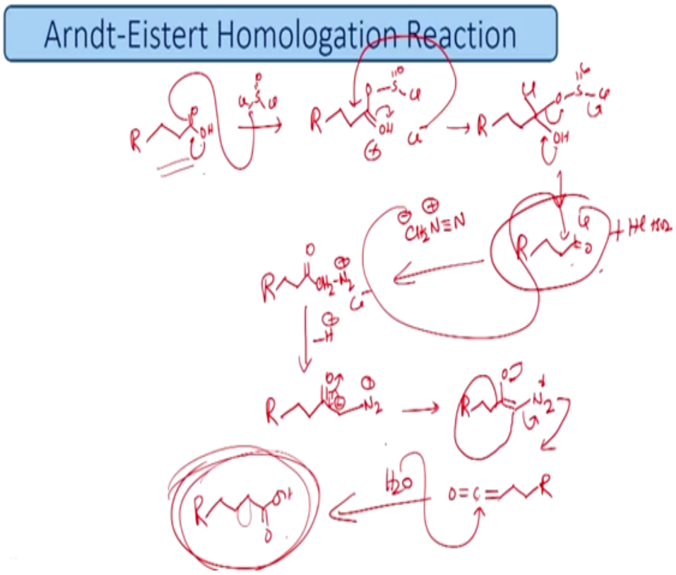

Arndt-Eistert Homologation Reaction

Carboxylic acid is converted to more reactive carboxyl chloride using $SOCl_2$, which undergoes addition reaction with diazomethane. Removal of nitrogen and 1,2-migration of the substituent produces isocyanate, which undergoes addition reaction with water to produce the carboxylic acid. The isocyanate can be reacted with a variety of nucleophiles to produce the respective addition products.

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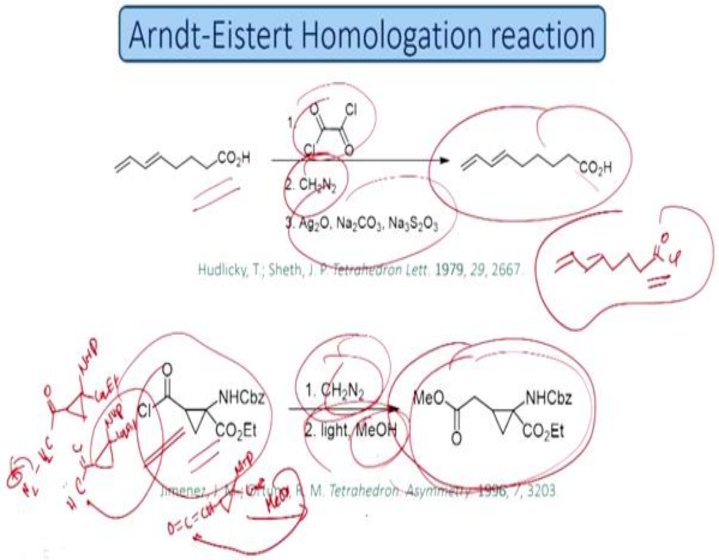

Arndt-Eistert Homologation reaction

Hudlicky, T.; Sheth, J. P. *Tetrahedron Lett.* 1979, *29*, 2667.

Jimenez, J. M.; Ortuno, R. M. *Tetrahedron: Asymmetry* 1996, *7*, 3203

Here the first example involves the transformation of linear carboxylic acid to acid chloride using oxalyl chloride, which reacts with diazomethane to form carbene that rearranges to isocyanate and reacts with water to produce the homologues carboxylic acid.

The second example shows the reaction of acid chloride with diazomethane, which under light converts to carbene that rearranges to isocyanate and reacts with methanol to give the methyl ester.

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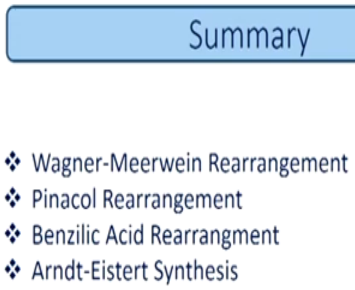

Summary

- Wagner-Meerwein Rearrangement
- Pinacol Rearrangement
- Benzilic Acid Rearrangment
- Arndt-Eistert Synthesis

In summary, we have studied four types of rearrangements. Acid catalyzes the Wagner-Meerwein and Pinacol rearrangements. The driving force for these reactions is the formation of the more stable carbocation or relief of ring strain to give the more stable compounds.

Subsequently, we have seen the hydroxide mediated 1,2-diketone rearrangement. The driving force is the formation of the more stable carboxylate.

Finally, we have discussed the homologation of carboxylic acid. In this reaction, acid chloride reacts with diazomethane and migration takes to the carbene to produce isocyanate that reacts with nucleophile. These are fundamental and important organic transformations. We have covered their synthetic and mechanistic aspects. With this we conclude this lecture. Thank you very much.