Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation, Dakin oxidation, cumene-phenol reaction

Baeyer-Villiger oxidation/rearrangement: The transformation of ketones into esters and cyclic ketones into lactones or hydroxy acids by peroxyacids.

Cyclic ketones to lactones: ring expansion

Ketones to esters:

Aldehydes to carboxylic acids:

1,2-diketones to mixed anhydrides:

Oxygen insertion at the marked bonds. Note the retention of configuration of the asymmetric centres.

A. von Baeyer  V. Villiger
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation, Dakin oxidation, cumene-phenol reaction

Baeyer-Villiger oxidation/rearrangement: Mechanism:

For R migration:

\[
\begin{align*}
\text{carboxylate leaves, } R \text{ migrates,} \\
\text{oxygen stabilises the incipient cation} \\
\text{R and OCOAr anti}
\end{align*}
\]

Which group migrates?

As this is a migration to an e-deficient centre, it is expected that the group that has the better ER ability should migrate better. Consider the following data:

<table>
<thead>
<tr>
<th>R</th>
<th>90</th>
<th>0</th>
<th>87</th>
<th>6</th>
<th>33</th>
<th>63</th>
<th>2</th>
<th>77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et</td>
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<tr>
<td>i-Pr</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>t-Bu</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Migratory aptitude: \( \text{t-alkyl > sec. alkyl > phenyl > prim. alkyl > methyl} \)

The role of steric bulk: Let the size of \( R \) < that of \( R_1 \)

\[\text{viewing through C-O} \]

\[\text{IM H-bonding} \]

\[\text{more severe crowding} \]

\[\text{less severe crowding} \]

\[\text{IM H-bonding} \]

\[\text{tert-butyl has unusually high tendency for migration}\]
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

The identity of the peracid:

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \quad \overset{\text{PhCO}_3\text{H}, \overbrace{\text{CH}_2\text{Cl}_2, \text{heat}}}{} \overset{\text{Me}}{\text{O}} \overset{\text{O}}{\text{Ph}} & + \overset{\text{Me}}{\text{O}} \overset{\text{O}}{\text{Ph}} \quad \text{(trace)} \quad \text{carboxylic acid by-product} \\
& \quad \text{(90\%)} \quad \overset{\text{HO}}{\text{O}} \overset{\text{Ph}}{\text{Ph}} \quad \text{phenyl migrates in preference to methyl}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \quad \text{Me} \quad \overset{\text{CF}_3\text{CO}_3\text{H}, \text{CF}_3\text{CO}_2\text{H}}{} \overset{\text{Na}_2\text{HPO}_4, \text{CH}_2\text{Cl}_2}{} \overset{\text{Me}}{\overset{\text{O}}{\text{Me}}} \overset{\text{O}}{\text{Ph}} & + \overset{\text{Me}}{\overset{\text{O}}{\text{Me}}} \overset{\text{O}}{\text{Ph}} \quad \text{(major)} \quad \text{carboxylic acid by-product} \\
& \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \overset{\text{HO}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \quad \text{t-butyl migrates in preference to phenyl} \\
& \quad \text{(minor)} \quad \overset{\text{HO}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \quad \text{carboxylic acid by-product} \\
& \quad \overset{\text{pK}_a \ 0.52, \text{much stronger acid}}{}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \overset{\text{CF}_3\text{CO}_3\text{H}, \text{CF}_3\text{CO}_2\text{H}}{} \overset{\text{Na}_2\text{HPO}_4, \text{CH}_2\text{Cl}_2}{} \overset{\text{Me}}{\overset{\text{O}}{\text{Ph}}} & + \overset{\text{cyclohexyl}}{\overset{\text{O}}{\text{Me}}} \overset{\text{O}}{\text{Ph}} \quad \text{(71\%)} \quad \text{carboxylic acid by-product} \\
& \quad \overset{\text{Me}}{\text{Me}} \quad \overset{\text{O}}{\text{Ph}} \quad \overset{\text{HO}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \quad \text{we get mixture, both migrate} \\
& \quad \overset{\text{(44\%)} \quad \overset{\text{HO}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \quad \text{carboxylic acid by-product}}{}
\end{align*}
\]

Conclusion:

\[
\overset{\text{O}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \quad \text{is more stable than} \quad \overset{\text{O}}{\text{O}} \overset{\text{Ph}}{\text{CF}_3} \\
\overset{\text{O}}{\text{O}} \overset{\text{Ph}}{\text{CF}_3} \quad \text{is a better LG than} \quad \overset{\text{O}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \\
\overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{R}} \overset{\text{O}}{\text{CF}_3} \quad \text{is faster than} \quad \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{R}} \overset{\text{O}}{\text{Ph}}
\]

So CF\(_3\)CO\(_3\)H should be the reagent of choice. But there is a trade-off. TFA is a very strong acid in organic standard.

It may lower the pH of the medium to such levels where the following transesterification reaction may take over, leading to the formation of undesired side products:

\[
\begin{align*}
\overset{\text{Me}}{\overset{\text{O}}{\text{Me}}} \overset{\text{O}}{\text{Ph}} & + \overset{\text{HO}}{\text{O}} \overset{\text{CF}_3}{\text{Ph}} \overset{\text{H}^+}{\leftrightarrow} \overset{\text{Me}}{\overset{\text{O}}{\text{Me}}} \overset{\text{O}}{\text{CF}_3} + \overset{\text{Me}}{\overset{\text{O}}{\text{Me}}} \overset{\text{O}}{\text{Ph}} \\
\end{align*}
\]

So, the pH must be controlled from getting too low. For that a buffer like Na\(_2\)HPO\(_4\) is used that consumes the CF\(_3\)CO\(_2\)H produced in situ. Recall that Na\(_2\)HPO\(_4\) is a salt derived from the strong base NaOH and weak acid H\(_3\)PO\(_4\).
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

Proof in favour of the mechanism:

1. The fate of the carbonyl oxygen is determined by isotopic labelling study:

   \[
   \begin{align*}
   &\text{Ph} - \text{Ph} \quad [\* = ^{18}\text{O}] \\
   &\text{R} - \text{O} - \text{O} - \text{H} \\
   &\text{Ph} - \text{O} - \text{O} - \text{Ph} \\
   &\text{LiAlH}_4 \quad \text{the work-up} \\
   &\text{Ph} - \text{O} - \text{H} + \text{O} - \text{Ph} \\
   \end{align*}
   \]

   The isotopically labelled oxygen ends up in the benzyl alcohol. Consistent of the mechanism proposed.

2. Intramolecular migration is proved by complete retention of configuration for chiral migrators:

   \[
   \begin{align*}
   &\text{Ph} - \text{Me} - \text{H} - \text{Me} - \text{H} \\
   &\text{mCPBA, CH}_2\text{Cl}_2 \quad \text{heat} \\
   &\text{Ph} - \text{Me} - \text{H} - \text{Me} - \text{O} - \text{Me} \\
   &\text{PhCO}_3\text{H, CH}_2\text{Cl}_2 \quad \text{heat} \\
   &\text{EtO}_2\text{C} - \text{Ph} - \text{Me} - \text{H} - \text{Me} - \text{O} - \text{Me} \\
   \end{align*}
   \]

   Note the regioselectivity in each case

3. When steric bulk does not matter, the more ER group migrates preferentially - indicates e-deficient nature of the RDS TS:

   \[
   \begin{align*}
   &\text{C}_{6}\text{H}_4\text{NO}_2 \\
   &\text{MeCO}_3\text{H, MeCO}_2\text{H, H}_2\text{SO}_4 \\
   &\text{C}_{6}\text{H}_4\text{O} - \text{C}_{6}\text{H}_4\text{NO}_2 \\
   \end{align*}
   \]

   Electron-rich phenyl ring migrates preferentially. The e-deficient red aryl ring does not migrate, \text{NO}_2 is an -I, -R effect exerting group.
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

For aldehydes, hydrogen migrates, leading to the formation of carboxylic acid:

\[
\begin{align*}
\text{PhCHO} & \quad \xrightarrow{\text{RCO}_2\text{H}} \quad \text{PhCO}_2\text{H} \\
\text{benzaldehyde} & \quad \text{benzoic acid}
\end{align*}
\]

However, if the aryl group has a strong ERG then it may compete with H when migrating, consider the following:

\[
\begin{align*}
\text{PhCHO} & \xrightarrow{\text{PhCO}_2\text{H}, \text{aq. MeOH}, \text{r.t.}} \quad \text{PhCO}_2\text{H} + \text{Z-PhOH} \\
\text{Z} & = \text{H, 90%} \\
\text{Z} & = \text{OMe, 19%}
\end{align*}
\]

Thus it is a trade-off b/w stabilising the e-deficient TS and the protonated ester product. H-migration is driven by the second factor here.

Aerial oxidation of benzaldehyde proceeds via a Baeyer-Villiger oxidation mechanism:

\[
\begin{align*}
\text{PhCHO} + \cdot\text{O-O}^- & \xrightarrow{\text{hv}} \text{PhCO}_2\text{H} + \text{H}_2\text{O} \\
\text{PhO}^- + \cdot\text{O-O}^- & \xrightarrow{} \text{PhCO}_2\text{O}^- \\
\text{PhCO}_2\text{O}^- + \text{PhCHO} & \xrightarrow{} \text{perbenzoic acid generated in situ}
\end{align*}
\]

Appears as white powder on the threads of bottles containing benzaldehyde.
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

For a 1,2-dicarbonyl compounds, a mixed anhydride results:

\[ RCOOR_1 + ArCOOH \rightarrow \text{mixed anhydride} \]

via:

\[ RCOOR_1 + ArCOOH \rightarrow \text{mixed anhydride} \]

alternative outcome:

\[ RCOOR_1 + ArCOOH \rightarrow \alpha\text{-ketoester} \]

Therefore, the acyl migration is favourable because the alternative leaves the same EW acyl group right next to the positively-charged carbon - a species rather unstable and difficult to form.

Compare this situation with an earlier example seen for dienone-phenol rearrangement:

\[ \text{Ph} \overset{\text{acid medium steps}}{\rightarrow} \text{Ph} \]

Ph has a greater migratory apt. than CO\(_2\)Et, then?

Answer:

CO\(_2\)Et migrates because phenyl migration leaves the postively-charged carbon right next to EW CO\(_2\)Et, that is bad.
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Baeyer-Villiger oxidation

Presence of C=O in the substrate for B-V oxidation:

Epoxidation can be a seriously competing side reaction, particularly so if the C=O is e-rich in nature. The reactivity of ketones and olefins towards peracids are comparable, so a mixture of products is expected. However, careful control of reaction condition and judicious selection of reagents can favour one reaction over the other. Thus,

And also the following examples:

Recall that for epoxidation of α,β-unsaturated carbonyl compounds, peracids are not recommended. The reason is two-fold - a) peracid is an electrophilic epoxidizer and the C=O of enones are also electrophilic; so it is not a compatible combination, and b) there is a possibility of Baeyer-Villiger oxidation. The epoxidation is conveniently carried out by alkaline H₂O₂, which proceeds via the hydroperoxide anion - a nucleophilic epoxidizer.

B-V oxidation of an enone:

Thus,

regioselective epoxidation of the electrophilic alkene

Take home lesson: It is difficult to predict exactly which reaction will dominate. However, for enones, alk. H₂O₂ is the best bet for effecting epoxidation. using peracid will probably give more B-V oxidation.
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Cumene-phenol process

Stepwise conversion of benzene and propylene into phenol and acetone via cumene and cumene hydroperoxide.

\[
\text{benzene} + \text{prop-1-ene} \xrightarrow{\text{H}_3\text{PO}_4, 250^\circ\text{C}, \text{pressure}} \text{cumene} \xrightarrow{\text{O}_2, \text{OH}, 130^\circ\text{C}, 5 \text{ atm.}} \text{cumene hydroperoxide} \xrightarrow{\text{dil. H}_2\text{SO}_4, 100^\circ\text{C}} \text{phenol} + \text{acetone}
\]

Stage-1: formation of cumene
Stage-2: oxidation of cumene to cumene hydroperoxide
Stage-3: conversion of cumene hydroperoxide to acetone and phenol

This is the rearrangement step.

Mechanism:

Stage-1: formation of cumene: a $S_{\text{E}2}\text{Ar}$ reaction

Stage-2: formation of cumene hydroperoxide: an oxidation via radical mechanism

What is/are the possible side reaction(s) that may happen here? How may you prevent those? [Hint: this is a Friedel-Crafts alkylation.]

Rearrangements in organic Chemistry

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\[
\begin{align*}
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& & \quad \text{cumene} & \quad \text{O}_2, \text{OH, 130}^\circ \text{C} & \quad 5 \text{ atm.} \\
& & & \quad \text{cumene hydroperoxide} & \quad \text{dil. H}_2\text{SO}_4, 100^\circ \text{C} \\
& & & \quad \text{phenol} & \quad + \quad \text{acetone}
\end{align*}
\]

Stage-1 : formation of cumene
Stage-2 : oxidation of cumene to cumene hydroperoxide
Stage-3 : conversion of cumene hydroperoxide to acetone and phenol

Mechanism:

Stage-2 : formation of cumene hydroperoxide:
Support for mechanism via formation of side product such as \textit{t}-cumyl alcohol:

Molecular oxygen is a diradical

\[
\begin{align*}
\text{abstraction of tertiary, benzylic H} & \quad \text{combination with O}_2 \\
\text{O-O bond is weak} & \quad \text{abstraction of tertiary, benzylic H} \\
\text{t-cumyl alcohol} & \quad \text{a side product}
\end{align*}
\]
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Stage-1: formation of cumene
Stage-2: oxidation of cumene to cumene hydroperoxide
Stage-3: conversion of cumene hydroperoxide to acetone and phenol

Mechanism:

Stage-3: Rearrangement of cumene hydroperoxide: Migration of an aromatic ring to an e-deficient, electrophilic oxygen atom

\[ \text{Me}^{-} \text{Me}^{+} \text{OH} \xrightarrow{\text{H}^+} \xrightarrow{[1,2]-\text{shift, intramolecular, concerted, -H}_2\text{O}} \xrightarrow{\text{H}_2\text{O}} \text{protonated hemiacetal} \]

H$_2$O leaves, Ph migrates, oxygen stabilises the incipient cation
Phenyl has a higher migratory aptitude than methyl

Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Dakin reaction/oxidation:

The oxidation of aromatic aldehydes and ketones to the corresponding phenols by peroxo compounds.

\[
\begin{align*}
\text{R} = & \text{H or alkyl} \\
\text{R}_1 = & \text{H or alkyl} \\
\text{R} = & \text{-OH, -NH}_2, \text{-NHR, -OR, alkyl, i.e. ERG, preferably o- and/or p- w.r.t. COR}_1
\end{align*}
\]

Mechanism: Illustrated using salicylaldehyde as example:

\[
\begin{align*}
\text{H}_2\text{O}_2, \text{alkali} & \text{ or RCO}_2\text{H} \\
\text{phenyl ester} & \text{ - may not be isolated} \\
\text{hydrolysis and work-up} & \text{ substituted phenol}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \text{OH} \\
\text{catechol} & \text{H}_2\text{O}, \text{NaOH} \\
2\text{-hydroxybenzaldehyde} & \text{formate}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{O}_2, \text{alkali} & \text{ or RCO}_2\text{H} \\
\text{phenyl ester} & \text{ - may not be isolated} \\
\text{hydrolysis and work-up} & \text{ substituted phenol}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \text{O} \text{O} \text{H} + \text{OH} \rightarrow \text{H} \text{O} \text{O} \text{H} + \text{H} \text{OH} \\
nucleophilic & \text{epoxidizer}
\end{align*}
\]

2-hydroxybenzaldehyde \( \text{pK}_a \text{ ca. 8.5} \)

\[
\begin{align*}
\text{Ar} & \text{OH} + \text{H}_2\text{O} \\
\text{Hydroxide leaves, aryl migrates, oxygen stabilises the incipient cation} \\
\text{Ar and OH anti} & \text{formate ester of catechol}
\end{align*}
\]

\[
\begin{align*}
\text{catechol} + \text{formate} & \rightarrow \text{catechol} + \text{formate}
\end{align*}
\]
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Dakin reaction/oxidation:

The oxidation of aromatic aldehydes and ketones to the corresponding phenols by peroxo compounds.

Migration of aryl versus hydrogen: aryl migrates in preference to H

\[ \text{is better than} \]

\[ \text{i.e. the migration of aryl can be assisted by the ortho substituent in the following way:} \]

For this +R effect to operate, the ERG must be at the o- or at the p-position.

If this reasoning were true, then - a) absence of such ER group should prompt H to migrate in presence of the aryls in such substrates, and b) placing the ER group at the m-position should also result in preferential migration of H as the +R effect of the ERG would not operate in that case. Both are observed.

a) \( \text{O} = \text{H} \)

benzaldehyde

\[ \text{NaOH, H}_2\text{O}_2 \]

benzoate results from H-migration

\[ > 99\% \]

phenol results from Ph-migration

\[ > 1\% \]

via:

\[ [1,2]-\text{H-shift} \]

No ERG present

Compare this with the B-V oxidation of benzaldehyde. Benzoic acid is the product there as well. A 4-methoxy group encourages aryl migration.

b) \( \text{O} = \text{H} \)

3-hydroxybenzaldehyde

ERG at m-position

\[ \text{NaOH, H}_2\text{O}_2 \]

3-hydroxybenzoate

Homework: What is the Dakin oxidation product of p-nitrobenzaldehyde?
Rearrangements in organic Chemistry

Migration from carbon to electron-deficient oxygen: Dakin reaction/oxidation:

Synthetic utility: Accessing functionalised phenols

In general, aldehydes are more reactive than ketones because the keto carbonyl carbon is less electrophilic than the carbonyl carbon of an aldehyde.

o-Hydroxyphenyl aldehydes and ketones oxidize faster than the corresponding p-hydroxy isomers in weakly basic conditions.

An important application of these rearrangements (B-V, cuemene-phenol, Dakin) is the introduction of an electrophilic oxygen atom into an aryl ring, thereby making substituted phenols easily accesible. Ordinarily, electrophilic hydroxylation on aromatic ring is not very successful, because introduction of OH powerfully activates the α- and ρ- positions of the ring it towards further hydroxylations. Polyphenolic compounds are formed which are converted to quinones resulting in subsequent rapture of the ring.

The method is however, successful on substrates where those α/ρ-positions are already occupied, e.g.

2,4,6-trimethylphenol aka mesitol

Homework:
Recall the other methods available for synthesising phenols.
Propose an alternative route for converting meitylene to mesitol.