Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

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Recommended texts:

- 1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
- 2. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259, 3. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

A general rtransformation for acyclic and cyclic vicinal diols (also known as glycols or 1,2-diols), which, upon treatment with catalytic amounts of acid, undergo dehydration with concomitant [1,2]-alkyl,- aryl- or hydride shift to afford ketones or aldehydes. This acid-catalyzed transformation of vicinal diols is also known as the pinacol rearrangement.

First reported by R. Fittig in 1860:

structure elucidated by A. M. Butlerov in 1874

2,3-dimethylbutane-2,3-diol

aka pinacol;

from Greek pinax, meaning tablet

3,3-dimethylbutan-2-one aka pinacolone



W. R. Fittig (1835-1910)

A. M. Butlerov (1828-1886)

Pinacol preparation: by reductive coupling of acetone

2 Me Me SET Me Me Me Me Me Me ketyl radical anion

Mg
O coupling
Me Me Me Me

Pinacol can undergo an alternative double dehydration:

Me Me Me Me

2,3-dimethylbuta-1,3-diene

Point to note that pinacol rearrangement is also a dehydration accompanied by a rearrangement of carbon skeleton:

2,3-dimethylbutane-2,3-diol Chemical Formula: C₆H₁₄O₂

3,3-dimethylbutan-2-one Chemical Formula: C₆H₁₂O Alternative reagents:

Protic acids: HCIO₄, H₃PO₂, TFA, TsOH;

Lewis acid: BF₃-OEt₂

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basically, a combination of dehydration and skeletal rerrangement

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility of pinacol rearrangement: pinacolone is an important synthetic intermediate

2,3-dimethylbutane-2,3-diol

aka pinacol

3,3-dimethylbutan-2-one aka pinacolone

deoxygenation is driven by formation of the strong P=O bond

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility of pinacol rearrangement: pinacolone is an important synthetic intermediate

Br₂, NaOH

2,3-dimethylbutane-2,3-diol aka pinacol

3,3-dimethylbutan-2-one aka pinacolone

Pinacol rearrangement is an excellent method to synthesise <u>targets</u> <u>containing the <u>tert-butyl</u> <u>group</u>. The following examples are illustrative:</u>

1. SOCl₂,

2. MeOH

Hofmann degradation

2-methylpropan-2-amine aka tert-butylamine

1. LAH, dry THF
2. work-up
reduction

Me Me
NH₂

NH₂

2-methylpropan-2-amine aka tert-butylamine

Me Me
NH₂

NH₂

2,2-dimethylpropan-1-amine aka neopentylamine

P₂O₅, heat Me Me
dehydration

Me Me

Baeyer-Villiger oxidation CI O H O H O Me Me O Me

tert-butyl acetate

Me Me Me Me OH

O 2,2-dimethylpropan-1-ol aka neopentyl alcohol

1. LAH, dry THF

2. work-up

reduction

Me Me COOH

3,3-dimethylbutanoic acid aka *tert*-butylacetic acid

Hunsdie

1. SOCl₂,

2. CH₂N₂ (excess)

3. Ag(I), H₂O

Arndt-Eistert reaction

Me COOAg

Ag(I)-salt

Hunsdiecker reaction Br₂, CCl₄

pivalonitrile

aka tert-butylcyanide

Me Me Me Br neopentyl bromide

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Mechanism:

A dehydration followed by elimination

(Me and OH2 must be anti-periplanar)

[1,2]-shift,

conjugate acid of

pinacolone

regenerated

e-deficient

carbon

aka pinacol

Mé Me pinacolone

2,3-dimethylbutane-2,3-diol

3M H₂SO₄, distilled

3,3-dimethylbutan-2-one aka pinacolone

correct orbital overlap required for migration

H

$$\sigma_{C-C}$$
 to vacant p

 σ_{C-C} to vacant p

 σ_{C-C}

The driving force of the reaction is the formation of the strong C=O bond via rearrangement to a resonance-stabilised oxocarbenium ion:

Proof of intramolecular migration:

Crossover experiment:

normal products

crossover products

Absence of crossover products indicates that the rearrangement is strictly intramolecular, be it concerted or stepwise.

Question:

Why are the following not formed in this reaction?

i.e. why don't the phenyls migrate?

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

The issue of regioselectivity: when all four substituents of the diol are identical (as in pinacol), the rearrangement yields a single product (as in pinacolone) and there is no debate about which group should migrate (Me migrates); however, when the glycol substrate is unsymmetrical the product is usually formed via the *most stable carbocation intermediate*:

Therefore the protonation in such cases is regioselective, so it is *pre-determined* which group should migrate.

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

The issue of regioselectivity: when the glycol substrate is symmetrical but contains two different groups at one end the product is usually formed via the migration of the group that has a higher migratory aptitude. As this is a migration to an e-deficient centre, that group should have a greater migratory aptitude which has a better ER capacity:

is eqv. to

: R F HO HO

HO HO

HO_⊕

shows +R effect

The 1,1-sigma bond breaks and new bond forms b/w 1 and 2, this is why it is called [1,2]-shift of R. The migration is assisted by

This implies that the group that can sustain the postive charge better will also have a greater migration tendency. Thus:

Aryl > tert. alkyl > sec. alkyl > prim. alkyl > methyl

particularly those bearing ERGs

H's position is debatable, as we have already discussed

migration tendency decreases

Thus,

the oxygen l.p.

$$\begin{array}{c} \text{Ar Ph} \\ \text{HO} \\ \text{Ar Ph} \end{array} \begin{array}{c} \text{H}_2\text{SO}_4 \\ \\ \hline \\ \text{Ar = } \end{array} \begin{array}{c} \text{OMe} \\ \end{array}$$

Ph should be the major product and not

Ph Ph Ar O

TS-Ar:

• OMe Ph

is more stable than

No regioselectivity issue regarding protonation, both end similar, can protonate any one OH

same carbocation

n Ar [1,2]-shift ⊕ Oh Of phenyl

TS-Ph:

major product

p-methoxyphenyl has a higher migratory aptitude than phenyl, so it migrates in preference * The possibility of NGP via phenonium intermediate cannot be ruled out.

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Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Importance of reaction condition in dictating the product composition: The outcome of pinacol rearrangement may completely alter from one reaction condition to the other. Consider the following:

Thus,

Ph Ph heat

Ne Me Me

AcOH, cat. H₂SO₄

Me Ph

Ne Me

AcOH, cat. H₂SO₄

Me Ph

Ne Me

No Me Me

Conjugation of C=O

with phenyl ring

With H₂SO₄:

reaction outcome determined by regioselective protonation that leads to the formation of the more stable carbocation int. (which is benzylic and tertiary); phenyl is a better migrator but it does not matter.

With AcOH, cat. H₂SO₄:

Reaction outcome determined by regioselective acetylation of the less hindered OH group that leads to the formation of the *less stable* carbocation int. (which is only tertiary but not benzylic); phenyl now migrates.

Take home lesson: It is rather difficult to predict which group will migrate and what will be the major product. Along with the relative migratory aptitude of the different groups, reaction condition may also dictate the outcome.

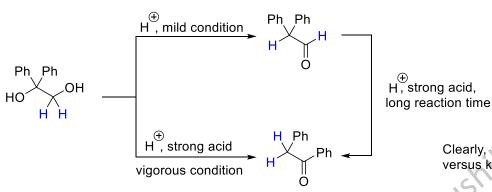
hybridization changes from \mbox{sp}^2 to \mbox{sp}^3 during acetylation

- reaction susceptible to steric crowding
- less hindered -OH reacts at a faster rate leading to regioselective acetylation $A_{Ac}2$ mechanism

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Importance of reaction condition in dictating the product composition: The outcome of pinacol rearrangement may completely alter from one reaction condition to the other. Consider the following:

Thus,



OH

is more stable than

Ph Ph H O

conjugation of C=O with phenyl ring

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Clearly, this is a case of thermodynamic versus kinetic control.

Ph Ph H H

is the TCP

Ph Ph H O

is the KCP

Under milder conditions:

Reaction outcome determined by which carbocation forms fastest as it is under kinetic control. A regioselective protonation leads to formation of the more stable carbocation int. (which is benzylic and tertiary). This eventually dictates that hydride shift will take place.

Under more vigorous conditions, all reactions are reversible and the KCP interconverts to the TCP, via:

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

A curious observation regarding ring contraction is the following:

The same observation for the *cis*-isomer

Mechanism:

trans-isomer

(··OH [1,2]-shift Ring contraction: ′′Ph ′′′Ph ring contraction OH - H₂O Ph⊕ Ph (··OH νŎΗ² H₂O [1,2]-shift Phenyl migration: "Ph "Ph of phenyl OH OH OH Ph cannot migrate until carbocation is formed, as Ph is syn to the OH being eminated!

Note:

C=O has conjugation with phenyl sp^2 carbon outside

the strained ring

C=O has no conjugation with phenyl sp^2 carbon inside the strained ring

no relief from ring strain that exists in the starting diol

i) The species resulting from the phenyl shift will be just as strained as the precursor; also, an unsaturated appears inside the four-membered ring in this pathway.

The four-membered ring contracts to a three-membered ring. This is unusual because the three-membered ring should be

We have seen the opposite happen, rings expanding to release the

This is even more surprising, considering the relatively high migratory

more strained than the four-membered one.

strain, but here the outcome is different.

aptitude of phenyl group.

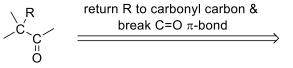
So why is this happening?

- ii) Ring contraction introduces ring strain but also provides stabilisation by bringing the unsaturated carbon outside the strained ring system.
- iii) There is also the matter of conjugative stabilisation of the C=O in the product ketone in the phenyl in the ring contraction product...

All these factors operating in unison decides the optimum outcome which is ring contraction and not phenyl migration.

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility: How to think of pinacol rearrangement retrosynthetically



structural fragment accessible by pinacol rearrangement

synthon

neutralise O and

(need dihydroxylation, recall methods?)

or

via reductive coupling of ketones

For

You can return any one of the three groups to the carbonyl carbon to get...

choice is guided by...

point to remember that the forward reaction proceeds via the more stable carbocation; and relative migratory aptitude varies in the following way:

three possible precursors

particularly those bearing ERGs

Aryl > tert. alkyl > sec. alkyl > prim. alkyl > methyl migration tendency decreases

H's position is debatable, as we have already discussed

Example:

is a bad choice, because - a) carbocation formation may not be entirely regioselective, and ii) even if the secondary benzylic carbocation forms selectively, H and Me both can migrate - leading to a mixture of products.

and make necessary

What happens if we return phenyl?!

is a better choice, because - a) carbocation formation will be entirely regioselective, forming the more stable tertiary, benzylic cation, and ii) only H will migrate - there is no other choice, leading to a single product.

[1,2]-shift of methyl

then - H

Me wrong product

mixture

right product

Ph Me

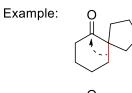
right product, only product

SM-2

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility: How to think of pinacol rearrangement retrosynthetically

Synthesis of spirocyclic ketone targets:



return the marked C-C & make necessary adjustments

return the marked C-C & make necessary adjustments



redraw

starting diol not so easily obtained

OH

anti

Question: Why not take:

Thus we have the following synthesis:

via:
$$\begin{array}{c} OH \\ HO \end{array}$$

$$\begin{array}{c} H^{\oplus} \\ H_{2}O\oplus \end{array}$$

$$\begin{array}{c} OH \\ H_{2}O\oplus \end{array}$$

$$\begin{array}{c} -H_{2}O \\ \hline \end{array}$$

$$\begin{array}{c} OH \\ \hline \end{array}$$

$$\begin{array}{c} I1,2]\text{-shift} \\ \hline \text{ring} \\ \text{expansion} \end{array}$$

no regioselectivity issue - diol is symmetrical

aside: LAH

Think of a suitable mech.

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Synthetic utility: How to think of pinacol rearrangement retrosynthetically

return R to carbonyl carbon & break C=O π -bond

, `Ph Ph

Note:

⊕ R - C O O Synthon

neutralise O and add OH to carbocation

HO C R OH vic-diol

structural fragment accessible by pinacol rearrangement

B good choice: carbocation formation regioselective, only ring expansion feasible

A) bad choice: leads to mixture

stepwise

Ph

OH HO Ph - H₂O O rearrange Ph Ph Ph Vic-diol epoxide is the dehydrated form of vic-diol pinacol-pinacolone - dehydration and rearrangement

Therefore, epoxide is one step ahead of *vic*-diol towards the ketone target

regioselective epoxide ring-opening is guided by formation of the more stable tertiary, benzylic cation

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Cultivating epoxide-involvement in pinacol rearrangement:

There is always a possibility of involvement of an epoxide in the pinacol rearrangement pathway:

Possible driving force of conversion of epoxide to ketone:

a) release of ring strain, b) formation of strong C=O, c) gain in entropy on going to the acyclic product from cyclic precursor.

Thus, pinacol rearrangement and acid-catalysed epoxide ring-opening are two closely related transformations. If the epoxide ring-closing is faster than the 1,2-shift then the vic-diol and the epoxide are, in all purposes, equivalent. If we use strongly acidic medium and stabilizing substituents, the two pathways will merge. OTOH, if we use milder acids with good nucleophiles present in the medium, epoxide ring-opening leads not to rearrangement, but to covalent bond-forming reactions, such as halohydrin formation.

or any other nucleophile around.

possible, if X is good nucleophile, like bromide etc.; ring-opening and ncuelophilic capture also proceeds in dilute acid where there's lots of water which acts as the nucleophile.

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in strongly acidic medium, not much water

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

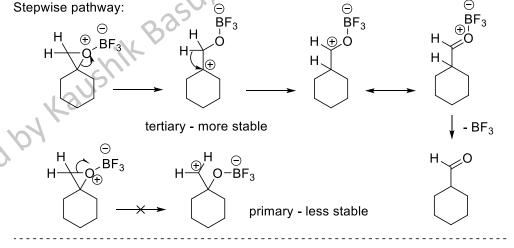
Cultivating epoxide-involvement in pinacol rearrangement:

- proceeds via incipient tertiary cation

Alternative ways to achieve this transformation:

hemiacetal hydrolysis

OMe



2.

CO₂Et

ketone

rearrange

cyclopentanecarbaldehyde

epoxide is the dehydrated

form of vic-diol

pinacol-pinacolone - dehydration and rearrangement

Therefore, epoxide is one step ahead of *vic*-diol towards the ketone target

vic-diol

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Cultivating epoxide-involvement in pinacol rearrangement:

unexpected, rearranged product

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Pinacol rearrangement under basic condition: Complementing the acid condition

Reaction preceds via formation of the more stable carbocation:

H migrates leaving behind R to stabilise the rearranged carbocation.

protonation of OH is regioselective

+I effect stabilises the adjacent cationic centre

But what if the target is:

? For this we need to selectively make the secondary hydroxyl group a better leaving group and keep the more hindered, tertiary hydroxyl unreacted.

We have already seen that regioselective acetylation of the less hindered OH can solve this problem. The same feat can be achieved by tosylation

When one of the hydroxyl groups is converted to a good leaving group, one of the two possible products can be generated regionselectively. Similarly, selective generation of carbocations can be realized when 2-heterosubstituted alcohols (e.g., halohydrins and 2-aminoalcohols etc.) are used as substrates. The pinacol-type rearrangement of these compounds is referred to as the semipinacol rearrangement, a term first coined by M. Tiffeneau. Owing to its predictability and the mild reaction conditions, the semipinacol rearrangement is almost exclusively utilized in complex molecule synthesis.

Migration from carbon to electron-deficient carbon: Pinacol-pinacolone rearrangement

Semipinacol rearrangement:

1. Me Ph AgNO₃ O Ph Me pre-destined to leave, 1-phenylpropan-2-one

1-iodo-2-phenylpropan-2-ol a halohydrin

+ NaOMe

no ambiguity

Under the given condition, it is pre-ordained which heteroatom-substituted carbon would lose the leaving group. There is no ambiguity.

Outcome just opposite to pinacol rearr. of

2. Pinacolic demination of β-aminoalcohols: Tiffeneau-Demjanov rearrangement:

via:

Stereoci e nical outcome indicates both stepwise and concerted paths are operating:

migration terminus

Tiffeneau-Demjanov rearr. is preferred than Demjanov rearr. Demjanov rearr. gives an alcohol, while T-D gives a ketone. Demjanov rearrangement is mainly reliable for five-to-sevenmembered rings, the T-D rearrangement works perfectly also for rings of four-to-eight members. In addition, T-D rearr. is free from the side reactions commonly associated with Demjanov rearrangement.

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migration terminus