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

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata

email: chiralkaushik@gmail.com

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 nitrogen: Schmidt rearrangement

A general reaction of ketones, aldehydes, and carboxylic acids with HN₃ to give amides, nitriles, and amines, respectively.

Mechanism:

1. For carboxylic acid:

Proof of mechanism:

This is similar to esterification of mesitoic acid or hydrolysis of mesitoate ester, both of which proceed via the A_{Ac}1 pathway, not the more usual $A_{Ac}2$ or $B_{Ac}2$ routes.

2,6-Dimethylbenzoic acid forms the acylium ion faster than the 2,4-dimethyl isomer, because of the greater relief of steric strain for the former that is associated with such isonisation:

relief of steric congestion is more important for the 2,6-dimethylated ring than for the 2,4-dimethylated isomer

Migration from carbon to electron-deficient nitrogen: Schmidt rearrangement

$$\begin{array}{c} O \\ R \\ H \\ \text{aldehyde} \end{array} \xrightarrow{N_3H, \text{ c. } H_2SO_4} \begin{array}{c} R \\ \\ O \\ \text{substituted} \end{array} + \begin{array}{c} R \\ \\ \text{cyanide} \end{array}$$

Mechanism for carbonyl compounds:

a) Baeyer-Villiger-like pathway:

N₂ leaves, R migrates, oxygen stabilises the incipient cation
R and N₂ anti

O R₁ N H The group that migrates from C to N, ends up with N in the product amide

b) Beckmann-like pathway:

The loss of water from azidoalcohol usually places the more voluminous of R and R_1 groups *trans* to the leaving group, so eventually that group migrates. For aryl alkyl ketones, the aryl group migrates (size of aryl > alkyl).

diastereoisomeric pair

(protonated form)

nitrilium ions
$$\begin{array}{c} & & & \\ & \downarrow \\ & & \\$$

HÖR
$$N_2$$
H N_2
H N_3
H N_4

Migration from carbon to electron-deficient nitrogen: Schmidt rearrangement

For aryl alkyl ketones, the aryl group migrates.

The bulky group tends to be anti to the leaving group, that is the one that migrates.

$$R = Me$$
 [bulk: Ph > Me] $R = t-Bu$

product of.... aryl migration alkyl migration 95

Migration of tertiary carbon more efficient than secondary one, this is a migration to an e-deficient N - more subst. side migrates

Migrating group retains stereochemistry, as expected in case of an intramolecular migration.

$$MsOH = \frac{OOO}{Me^{OH}}$$

phenyl migrates better

$$\begin{array}{c} O \\ \hline \\ NaN_3, H_2SO_4 \\ \hline \\ CHCl_3 \end{array}$$

aryl with EWG migrates less effectively

of the migrating group

$$\begin{array}{c|c}
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\$$

product of.... aryl migration

alkyl migration

ÓН 61%

In general hydrazoic acid reacts much faster with ketones than it does with esters or carboxylic acids; and thus ketones can be converted to amides/lactams in presence of these functional group.

5

100

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

The conversion of ketoximes to the corresponding amides in acidic medium. The reaction is usually carried out under forcing conditions (high temperatures >130 °C, large amounts of strong Brönsted acids) and it is non-catalytic. The applied Brönsted acids are: H₂SO₄, HCl/Ac₂O/AcOH, etc., which means that sensitive substrates cannot be used in this process. Early examples made use of PCl₅ as well.

Stereochemistry: The stereochemical outcome of this rearrangement is predictable: the R group *anti* to the leaving group on the nitrogen will migrate. If the oxime isomerizes under the reaction conditions, a mixture of the two possible amides is obtained.



E. O. Beckmann (1853-1923)

Mechanism:

e-deficient N

LG leaves, R migrates, nitrogen stabilises the incipient cation R and N₂ anti

[1,2]-shift intramolecular, concerted - E O H

(recall Schmidt reaction of ketones)

Proof for mechanism:

Ratio of isomeric amides same as that of starting amide mixture.

High stereoselectivity also points to concerted nature.

Retention of configuration of chiral migrating group proves the intramolecular nature of the migration.

via the conversion of OH to OPCl₄ which ultimately is lost as POCl₃ and Cl⁻

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

Proof for mechanism (contd.):

3. That a simple exchange b/w R and OH does not take place in the starting oxime has been established by the following experiment:

It has been verified independently that neither the starting oxime, nor the product amide exchanges ¹⁸O from the medium.

So, the inclusion of ¹⁸O must have been from the attack of the H₂O¹⁸ on the N-phenylnitrilium ion intermediate.

4. Crossover experiment: Generally there is no crossover product as the rearrangement in most cases is intramolecular. However, there are exceptions:

These carbocations are quenched by cyano compounds. the nucleophile is very poor, but the electrophiles are super reactive. All possible combinations should give us the four products.

[Recall Ritter reaction in this regard!]

nitrilium int. forms intermolecularly

direct fragmentation also possible

Page 14

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

More examples of Beckmann fragmentation:

nitrogen stabilises

the incipient cation C-C bond and H₂O anti

strained ring water leaves, C-C bond migrates,

EW, *m*-orienting

⊕ H₂O -

tertiary redraw

Note that in the course of hydrolysis of CN to COOH, CONH₂ is an intermediate; with proper adjustment of reaction conditions, the reaction can be tstopped at the amide stage. i.e., partial hydrolysis can be achieved.

Ph
$$\sim$$
 CN + H₂O + CO₂

a α-ketoacid

via:

(think how this is prepared?

fragmentation driven by increase in entropy

Interesting point:

acetoacetic acid

Note the structural similarity of the highlighted part with that of β -ketoacid, another system that is prone to decarboxylation.

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

A curious obervation:

cyclohexanecarboxylic acid cyclohexanone oxime

carboxylic acid

Another one:

oxime of aceta 2-cyclohexenone

Via:

OH

OH

OAC

HN

OAC

HN

OAC

HN

OAC

HN

AC2O

- ACOH

AC40

- ACOH

AC50

- ACOH

AC60

- ACOH

AC60

- ACOH

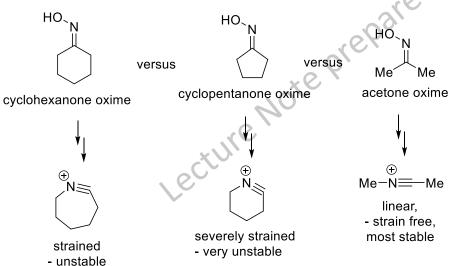
AC60

- ACOH

AC60

- AC60

Predicting the relative rates of Beckmann rearrangements:



We need to look at the intermediate nitrilium ion that forms after the [1,2]-shift. The more stable it is, faster it forms, faster is the reaction.

Thus we expect the following rate order for Beckmann rearrangement:

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

Predicting the relative rates of Beckmann rearrangements (contd.):

The group anti to the OH will migrate.

As this is a migration from carbon to e-deficient nitrogen centre, the more ER group will migrate more effectively, and reaction will be faster.

Therefore, Y is expected to react faster than X.

A problem in identification:

70% H₂SO₄, heat then work-up + H₂N Me

70% H₂SO₄, heat then work-up E + F (an amine) (a carboxylic acid)

The amide that on hydrolysis affords p-toluidine and benzoic acid must be:

The other oxime must be B, so, B is: (B is a diastereoisomer of A)

Ме

This arises from oxime A, so, A is:

B on Beckmann rearr. must give:

$$\begin{array}{c|c}
H & (D)
\end{array}$$

D on hydrolysis must give:

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

Beckmann rearrangement of aldehydes: Usually cyanides are formed, e.g. when treated with acetic anhydride, the following is observed:

The two diastereoisomers of aldoximes behave differently:

$$H$$
 and H OH R OH R Syn -alkyl isomer $Anti$ -alkyl isomer

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

via an elimination reaction:

$$\begin{array}{c|c} & & & & & & & \\ \hline OH & & & & & & \\ \hline OH & & & & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ OH & & \\ \hline OH & & \\ O$$

stereoelectronic requirement is the anti-periplanarity of eliminating groups, H, OAc antiperiplanar, hydroxide acts as a base

via a hydrolysis reaction:

H, OAc not anti-periplanar, so elimination via E2 not favourable, hydroxide behaves as a nucleophile.