

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

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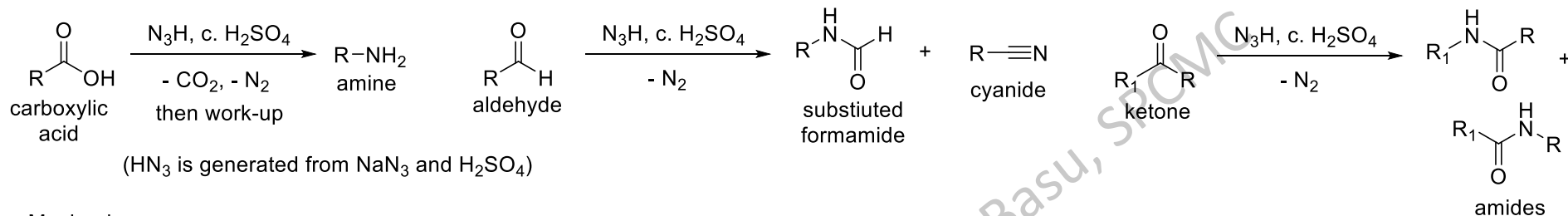
Recommended texts:

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

Rearrangements in Organic Chemistry

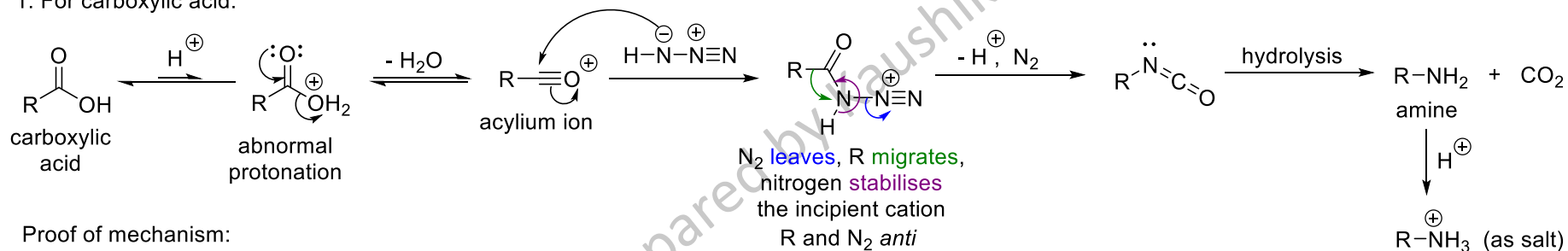
Migration from carbon to electron-deficient nitrogen: Schmidt rearrangement

A general reaction of ketones, aldehydes, and carboxylic acids with HN_3 to give amides, nitriles, and amines, respectively.

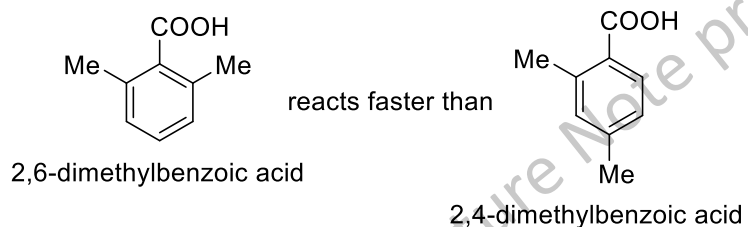


Mechanism:

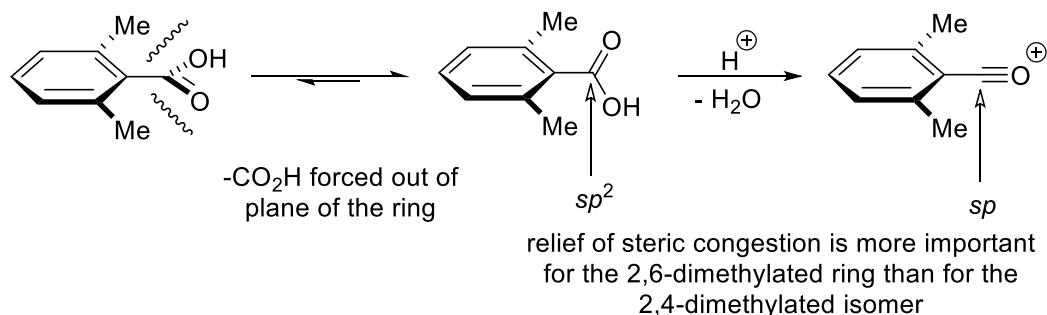
1. For carboxylic acid:



Proof of mechanism:



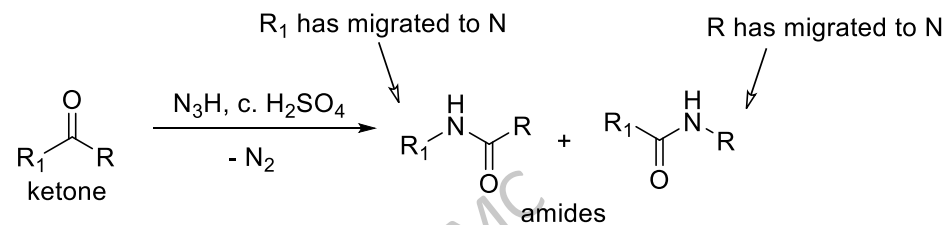
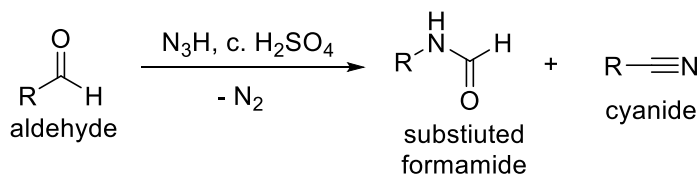
2,6-Dimethylbenzoic acid forms the acylium ion faster than the 2,4-dimethyl isomer, because of the greater relief of steric strain for the former that is associated with such isonisation:



This is similar to esterification of mesitoic acid or hydrolysis of mesitoate ester, both of which proceed via the $\text{A}_{\text{AC}}1$ pathway, not the more usual $\text{A}_{\text{AC}}2$ or $\text{B}_{\text{AC}}2$ routes.

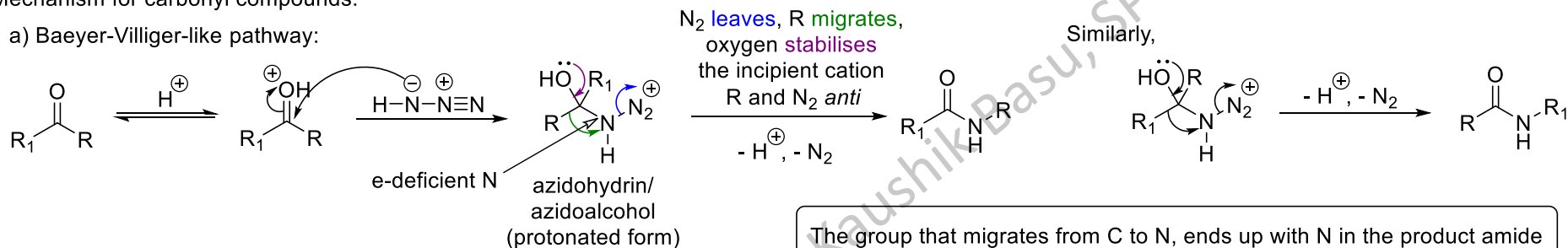
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Schmidt rearrangement

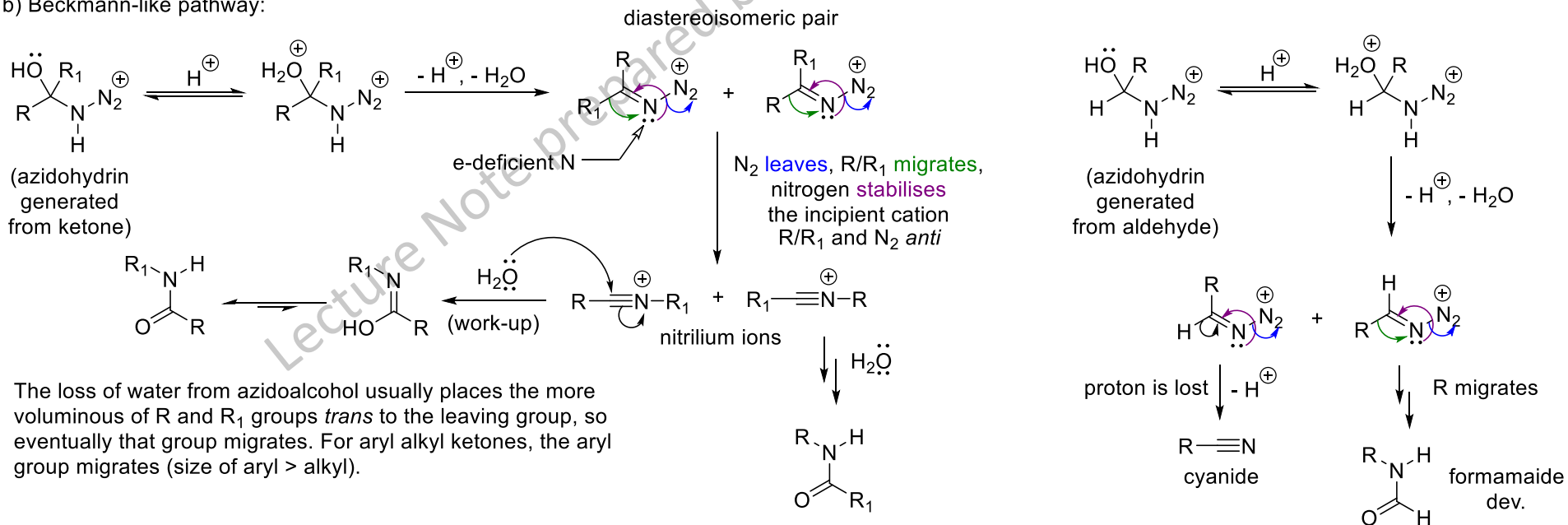


Mechanism for carbonyl compounds:

a) Baeyer-Villiger-like pathway:



b) Beckmann-like pathway:

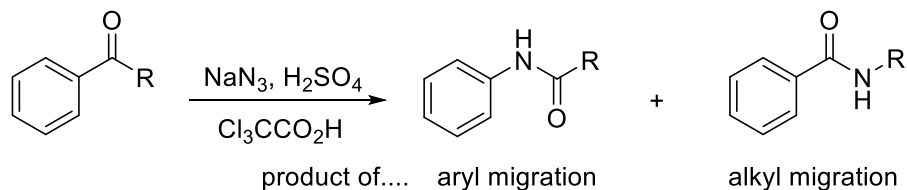


The loss of water from azidoalcohol usually places the more voluminous of R and R₁ groups *trans* to the leaving group, so eventually that group migrates. For aryl alkyl ketones, the aryl group migrates (size of aryl > alkyl).

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Schmidt rearrangement

For aryl alkyl ketones, the aryl group migrates.

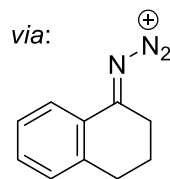
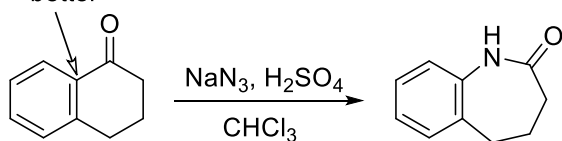


The bulky group tends to be anti to the leaving group, that is the one that migrates.

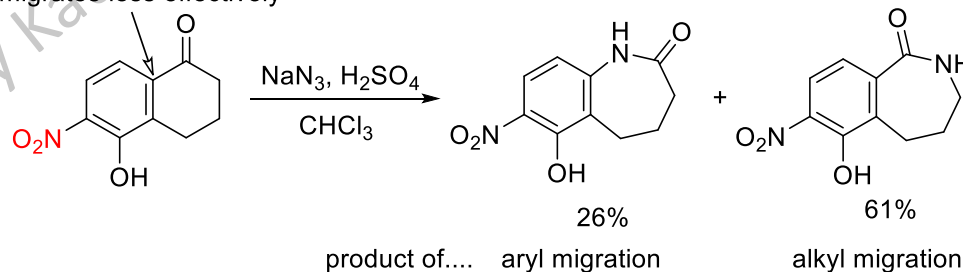
R = Me	95	5
[bulk: Ph > Me]		
R = <i>t</i> -Bu	0	100
[bulk: <i>t</i> -Bu > Ph]		



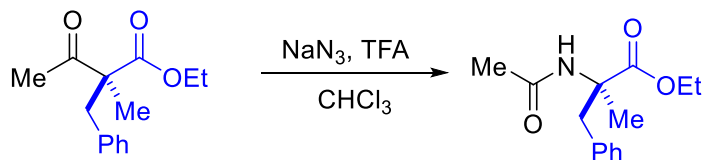
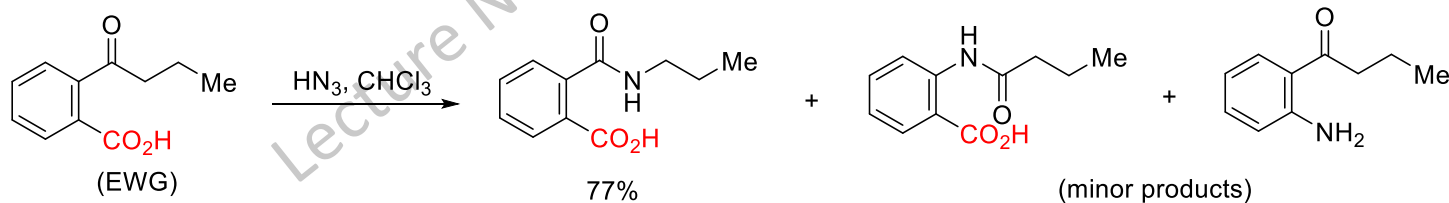
phenyl migrates better



aryl with EWG migrates less effectively



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.

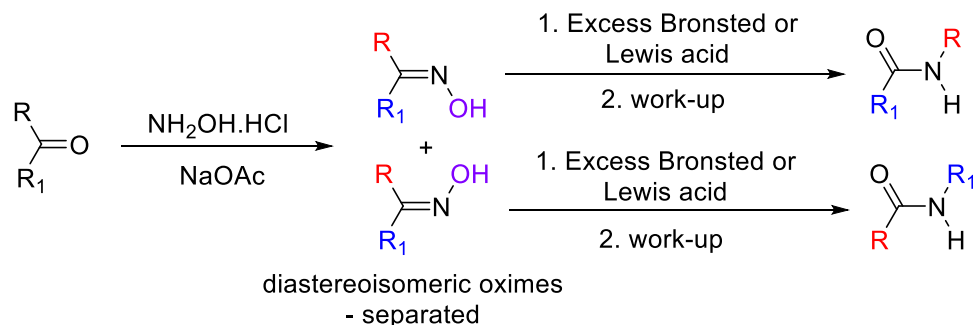


Note the retention of configuration of the migrating group

Rearrangements in Organic Chemistry

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 Brønsted acids) and it is non-catalytic. The applied Brønsted 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.

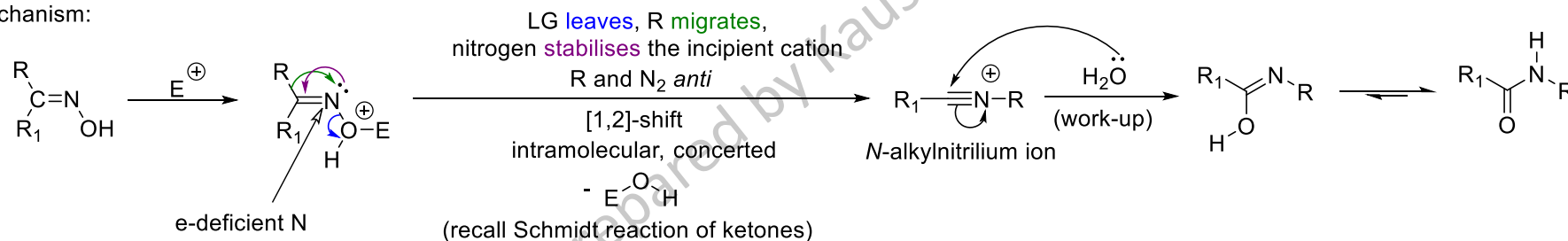


Stereochemistry: The stereochemical outcome of this rearrangement is predictable: the R group *anti* to the leaving group on the nitrogen will migrate. If the oxime isomerizes under the reaction conditions, a mixture of the two possible amides is obtained.

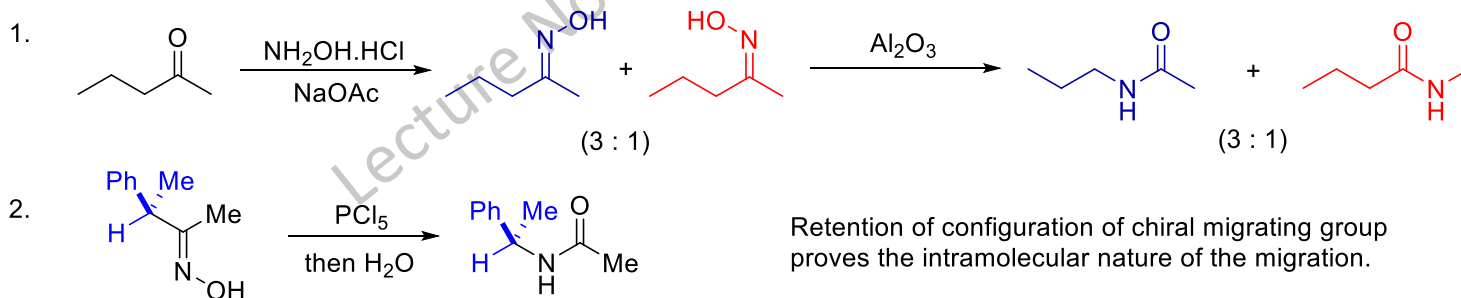


E. O. Beckmann
(1853-1923)

Mechanism:



Proof for mechanism:



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

High stereoselectivity also points to concerted nature.

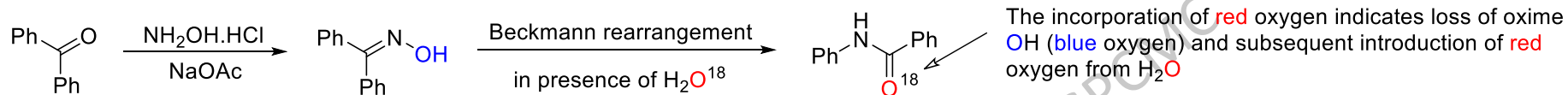
via the conversion of OH to OPCl₄ which ultimately is lost as POCl₃ and Cl⁻

Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

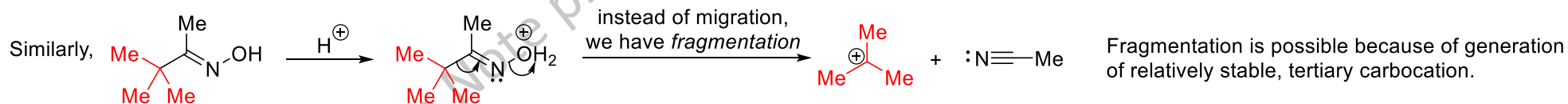
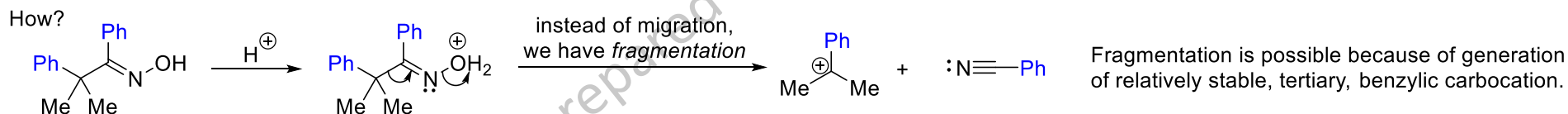
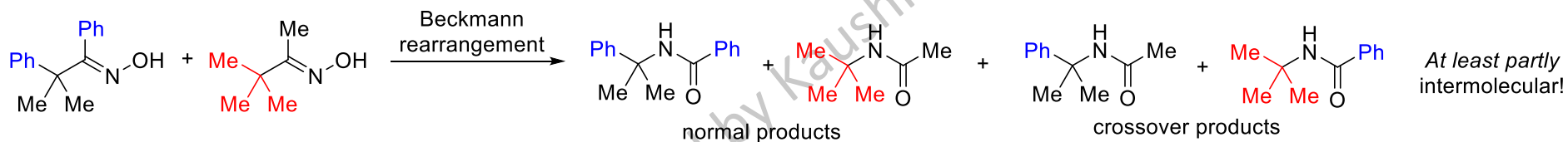
Proof for mechanism (contd.):

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:

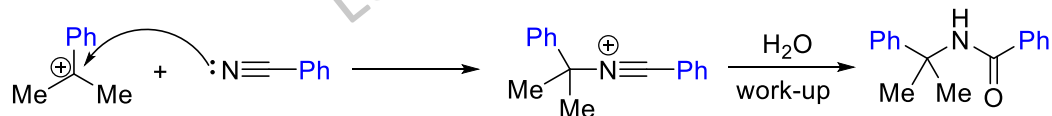


It has been verified independently that neither the starting oxime, nor the product amide exchanges ¹⁸O from the medium. So, the inclusion of ¹⁸O must have been from the attack of the H₂O¹⁸ on the N-phenylnitrilium ion intermediate.

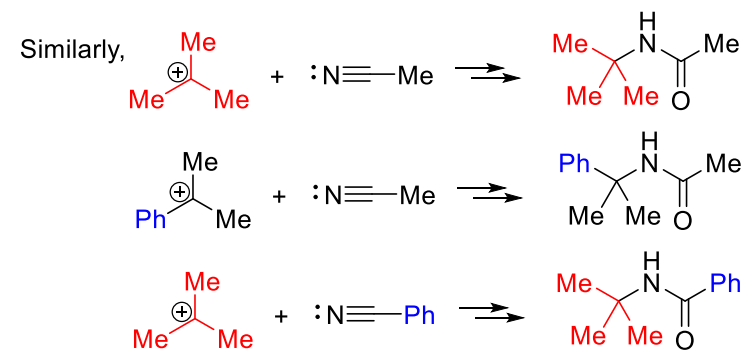
4. Crossover experiment: Generally there is no crossover product as the rearrangement in most cases is intramolecular. However, there are exceptions:



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.



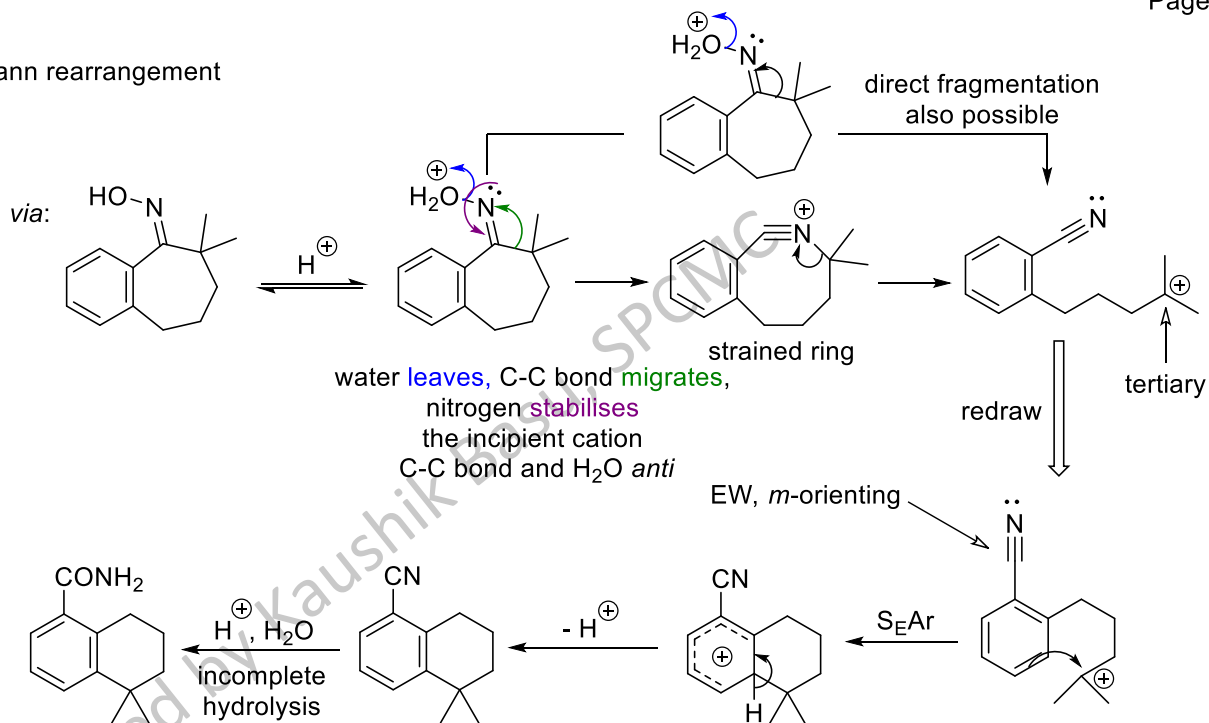
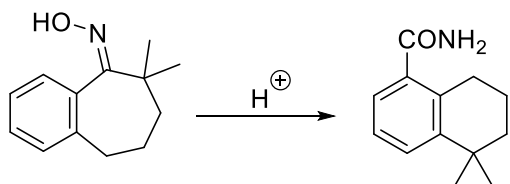
[Recall Ritter reaction in this regard!] nitrilium int. forms *intermolecularly*



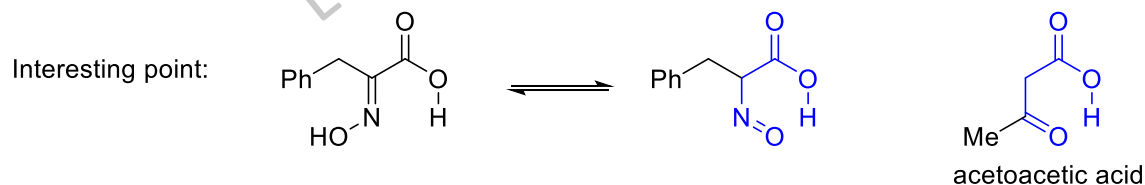
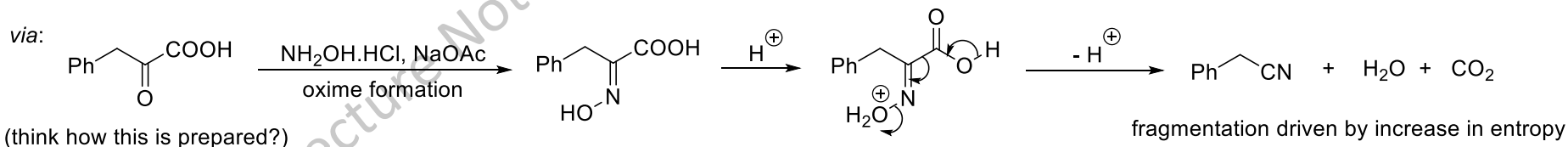
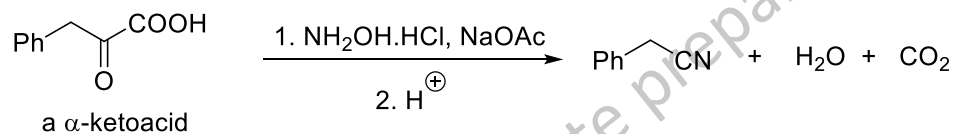
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

More examples of Beckmann fragmentation:



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 stopped at the amide stage. i.e., partial hydrolysis can be achieved.

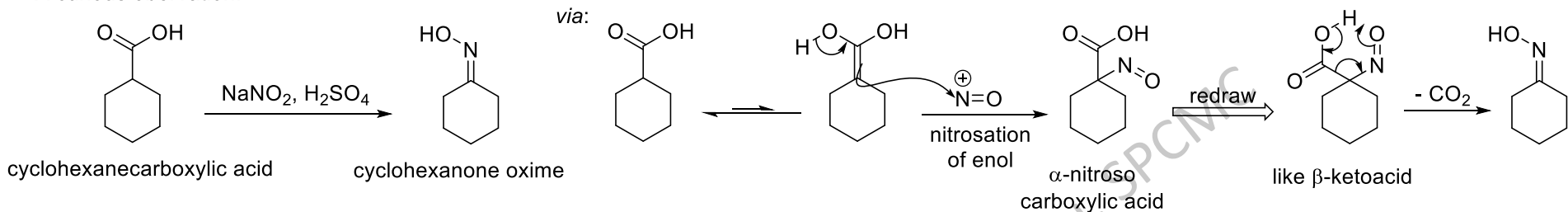


Note the structural similarity of the highlighted part with that of β -ketoacid, another system that is prone to decarboxylation.

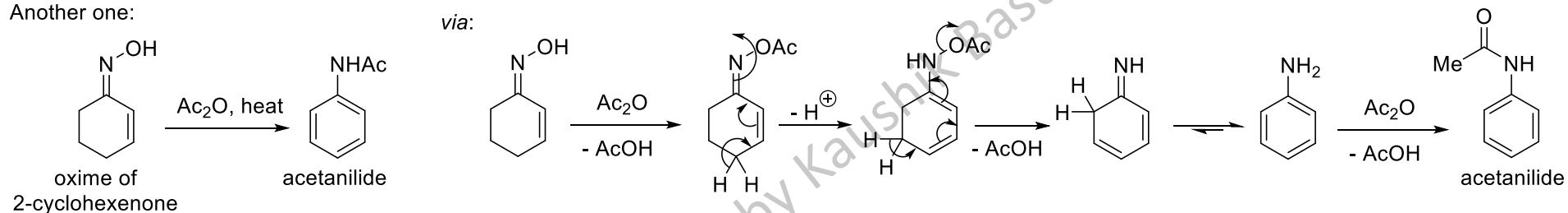
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

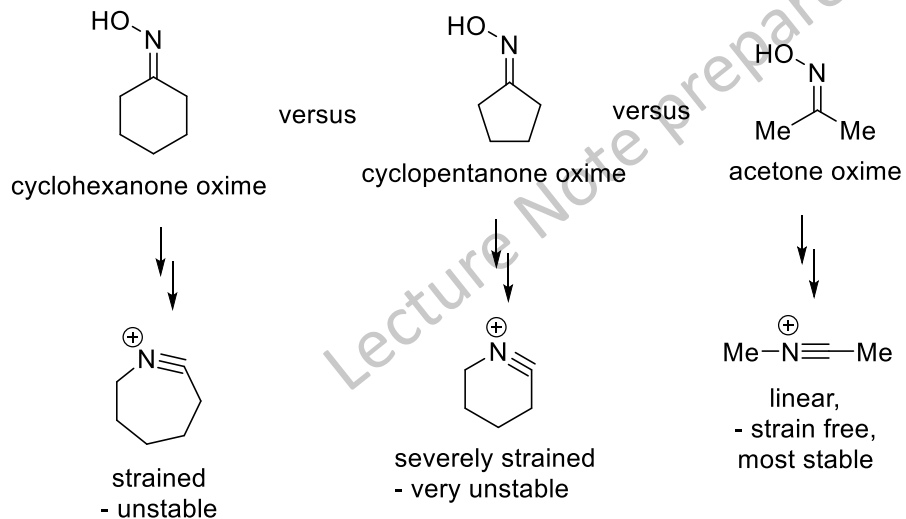
A curious observation:



Another one:

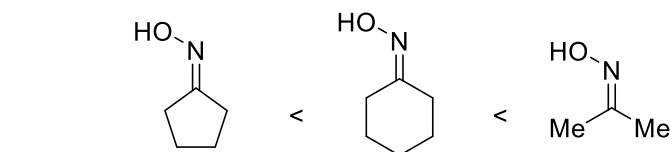


Predicting the relative rates of Beckmann rearrangements:

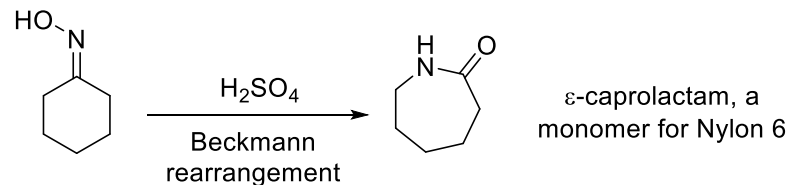


We need to look at the intermediate nitrilium ion that forms after the [1,2]-shift. The more stable it is, faster it forms, faster is the reaction.

Thus we expect the following rate order for Beckmann rearrangement:



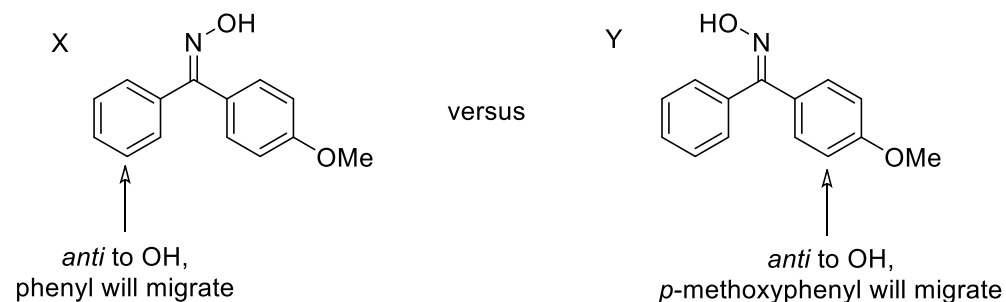
Note:



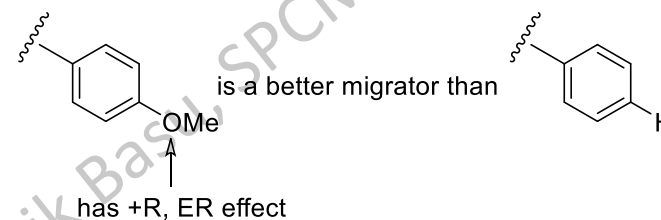
Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Beckmann rearrangement

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

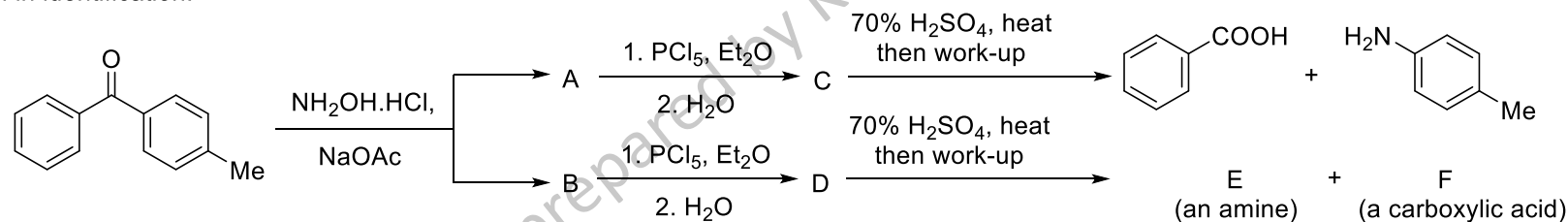
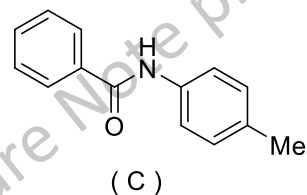
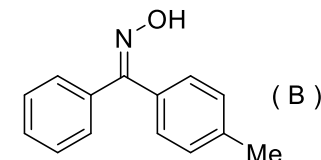
The group *anti* to the OH will migrate.

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.

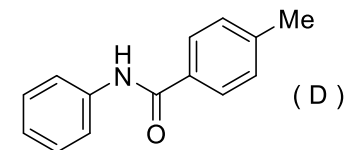


Therefore, Y is expected to react faster than X.

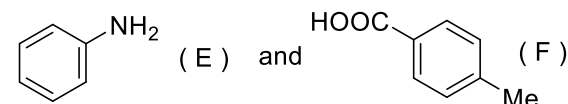
A problem in identification:

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)

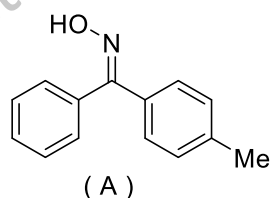
B on Beckmann rearr. must give:



D on hydrolysis must give:



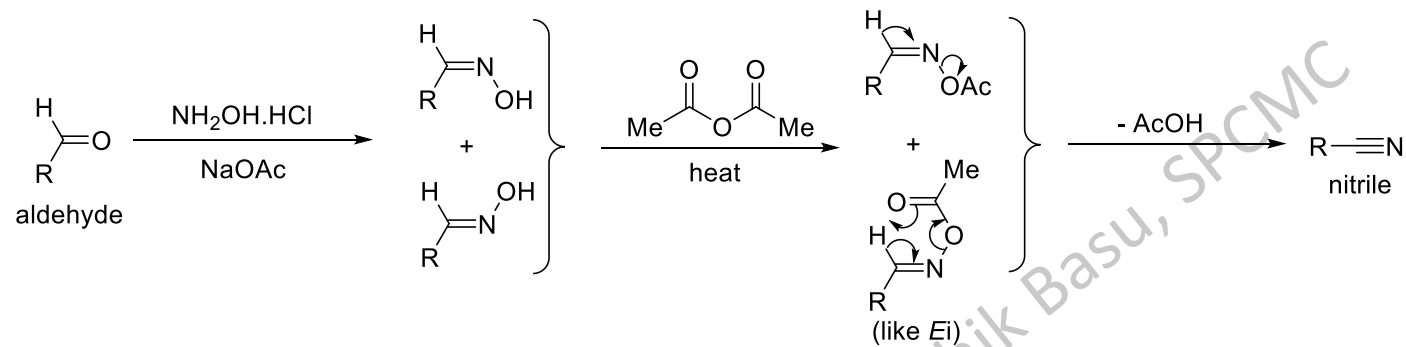
This arises from oxime A, so, A is:



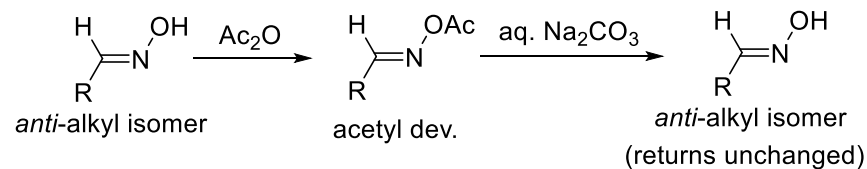
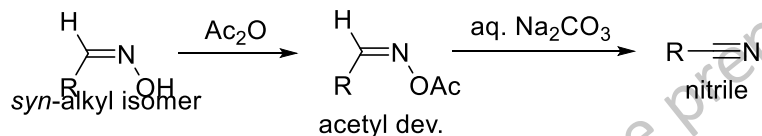
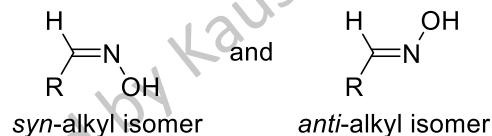
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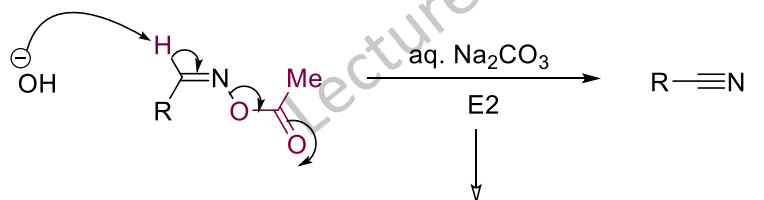
Beckmann rearrangement of aldehydes: Usually cyanides are formed, e.g. when treated with acetic anhydride, the following is observed:



The two diastereoisomers of aldoximes behave differently:

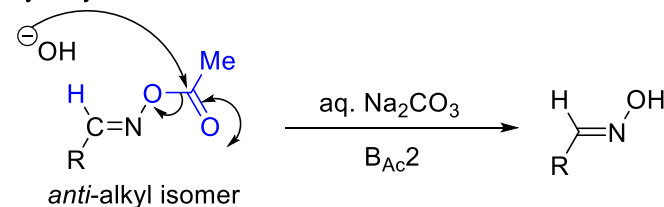


via an elimination reaction:



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.