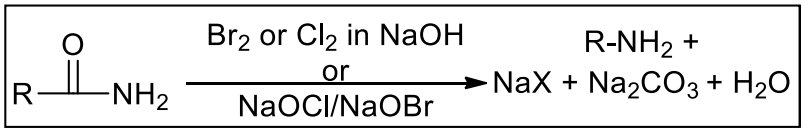
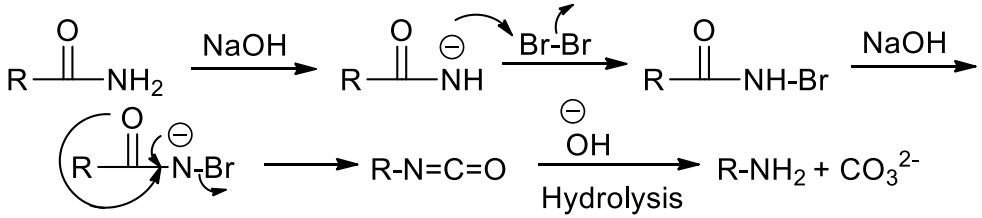
Rearrangement to electron-deficient nitrogen

HOFMANN REACTION
or
HOFMANN AMIDE DEGRADATION

- Hofmann reaction/Hofmann amide degradation is a technique to convert an ***alkyl/aryl/ heteroaryl amides*** into ***primary alkyl/aryl/heteroaryl amines*** by removing the -CO group.

- Its basically an oxidation reaction by Br_2 or Cl_2 or NaOCl or NaOBr in alkaline condition.

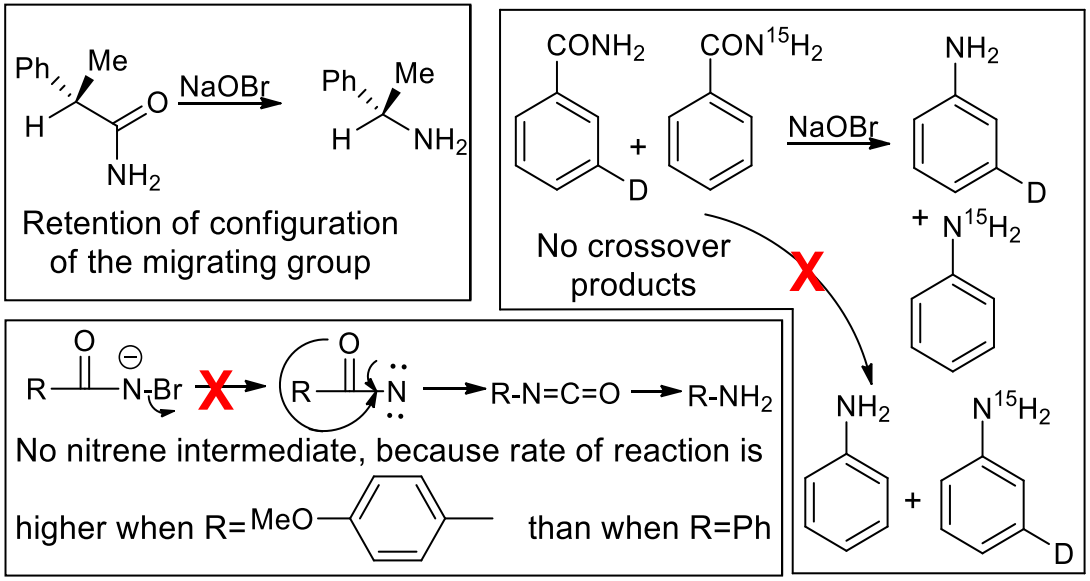




- The reaction begins with deprotonation of the amide proton, forming an anion, which immediately attacks the halogen present and gets converted into a N-halogenated amide.

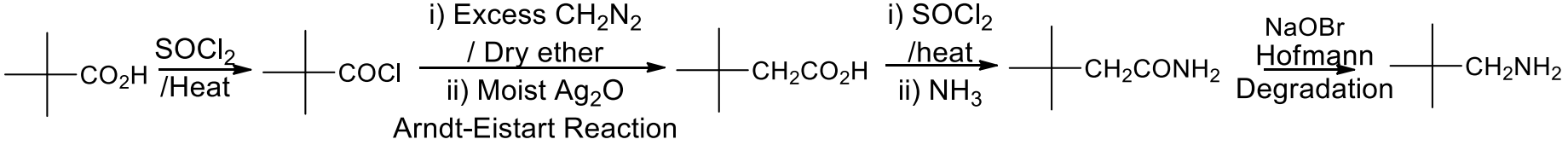
- The base present in the system, further deprotonates it, which then rearranges to an isocyanate and finally hydrolyses to a primary amine and carbonate anion.

- This mechanistic course is established by a) isolation of a number of intermediates such as, RCONHBr, $[RCONBr]^-K^+$, RNCO etc; b) retention of configuration of the migrating group in Hofmann reaction of an optically active amide; c) formation of no cross-over products; d) enhancement of rate, when the migrating group is electron-releasing.

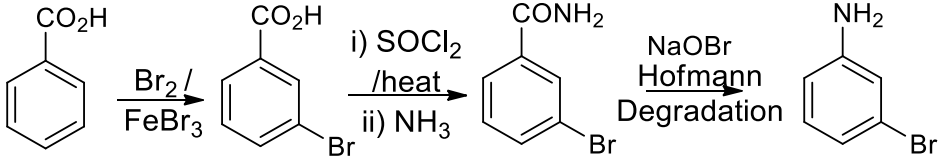


Problems:

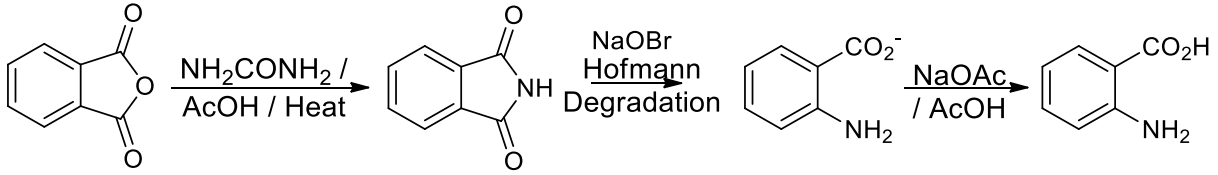
1. *How would you Synthesize neopentylamine?*



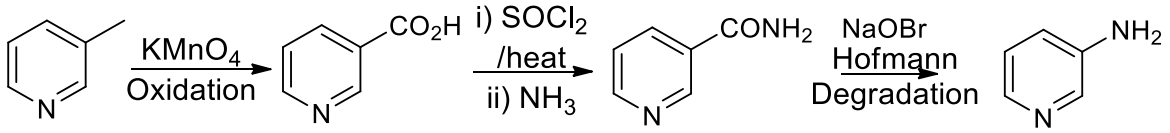
2. *Convert benzoic acid into m-bromoaniline:*



3. *Convert phthalic anhydride into anthranilic acid:*



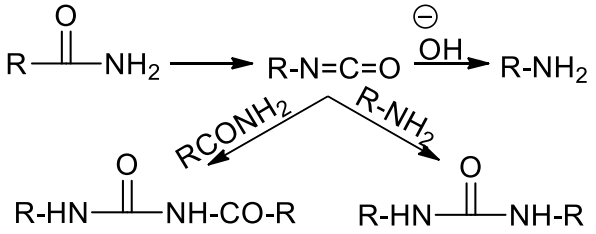
4. *Convert 3-methylpyridine into 3-aminopyridine:*



5. *What is the side product in Hofmann Reaction? How could you make it major product?*

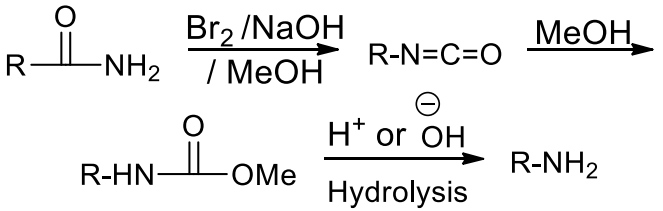
As the reaction proceeds, hydroxide alone doesn't remain the nucleophile. It has to compete with the nucleophilic -NH_2 of the starting amide as well as that of the product amine. So, we get ureas and acylureas as the side product.

Of course, they could be made the major products, if we increase the competition. This could be done by using half amount of Br_2/NaOH.

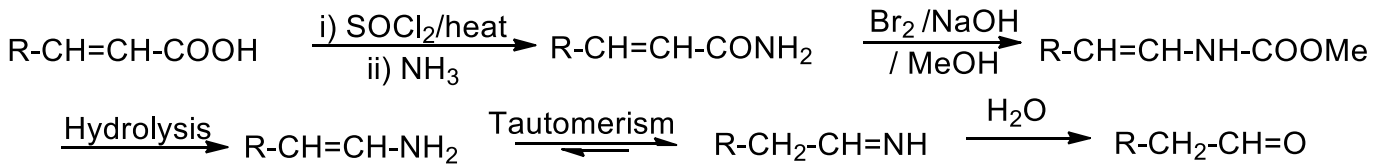


6. Why high mol. wt. amides give poorer yield? How could you overcome this problem?

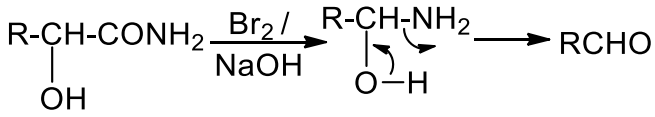
High mol.wt. amides have large hydrophobic parts, that makes them less soluble in aq. medium, causing low yield. But, if we use methanolic NaOH, then the solubility issue will not persist and in stead of directly leading to the amine, the isocyanate will be attacked by methanol, to give a methylcarbamate, which could then easily be hydrolysed to amine. Note that, urea side product formation is also avoided in this modification.



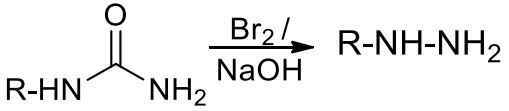
7. R-CH=CH-CONH$_2$ on reaction with Cl$_2$/NaOMe/MeOH, followed by hydrolysis, produces RCH$_2$CHO. Explain.



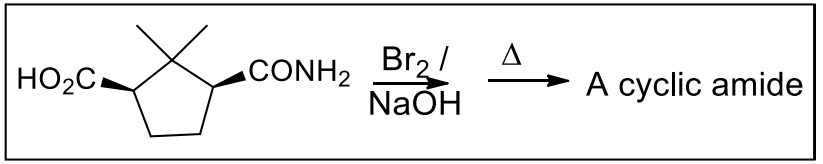
8. R-CH(OH)-CONH$_2$ on reaction with Br$_2$/NaOH, produces RCHO. Explain.

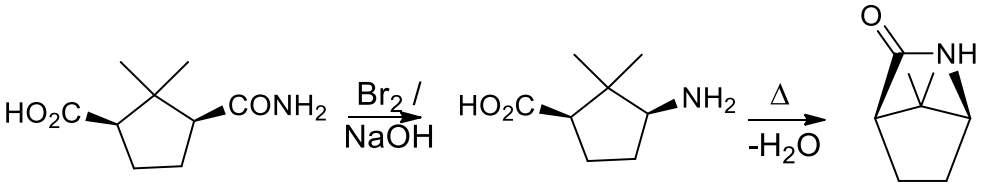


9. How could you convert urea or N-alkylureas into hydrazines?



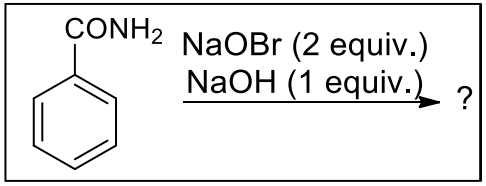
10. Complete the following and explain which property of Hofmann reaction is established in this result?



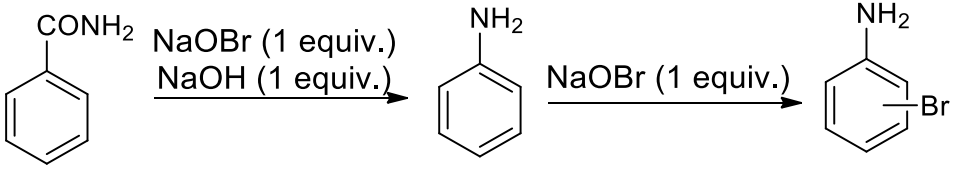


The first step shows retention of configuration of the migrating group, an important feature of Hofmann Reaction

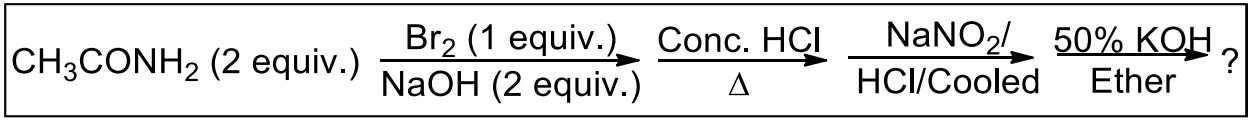
11. Complete the following:



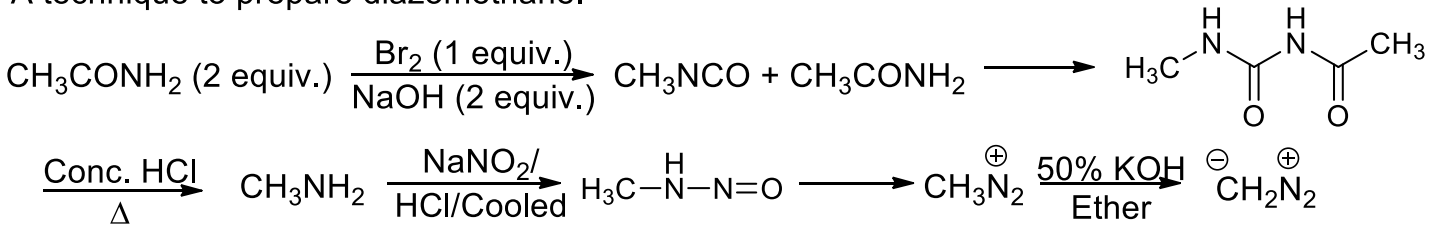
Of course, the Hofmann degradation requires only one equiv. of NaOBr. The extra NaOBr is used for bromination of the produced aniline.



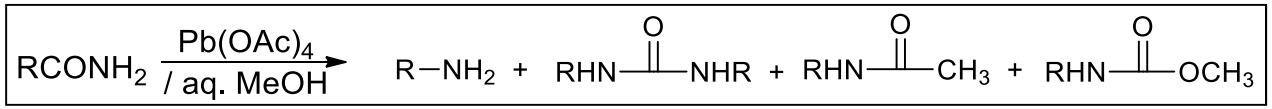
12. Complete the following:

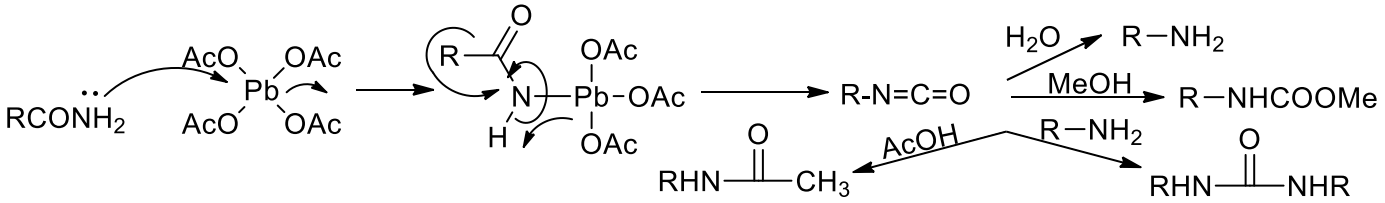


A technique to prepare diazomethane.



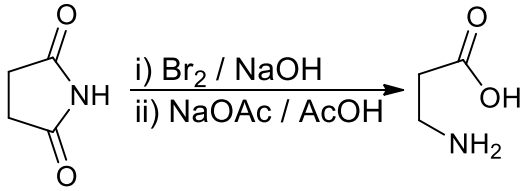
13. Explain mechanistically:





14. How would you synthesize β-alanine?

By Hofmann degradation of phthalimide



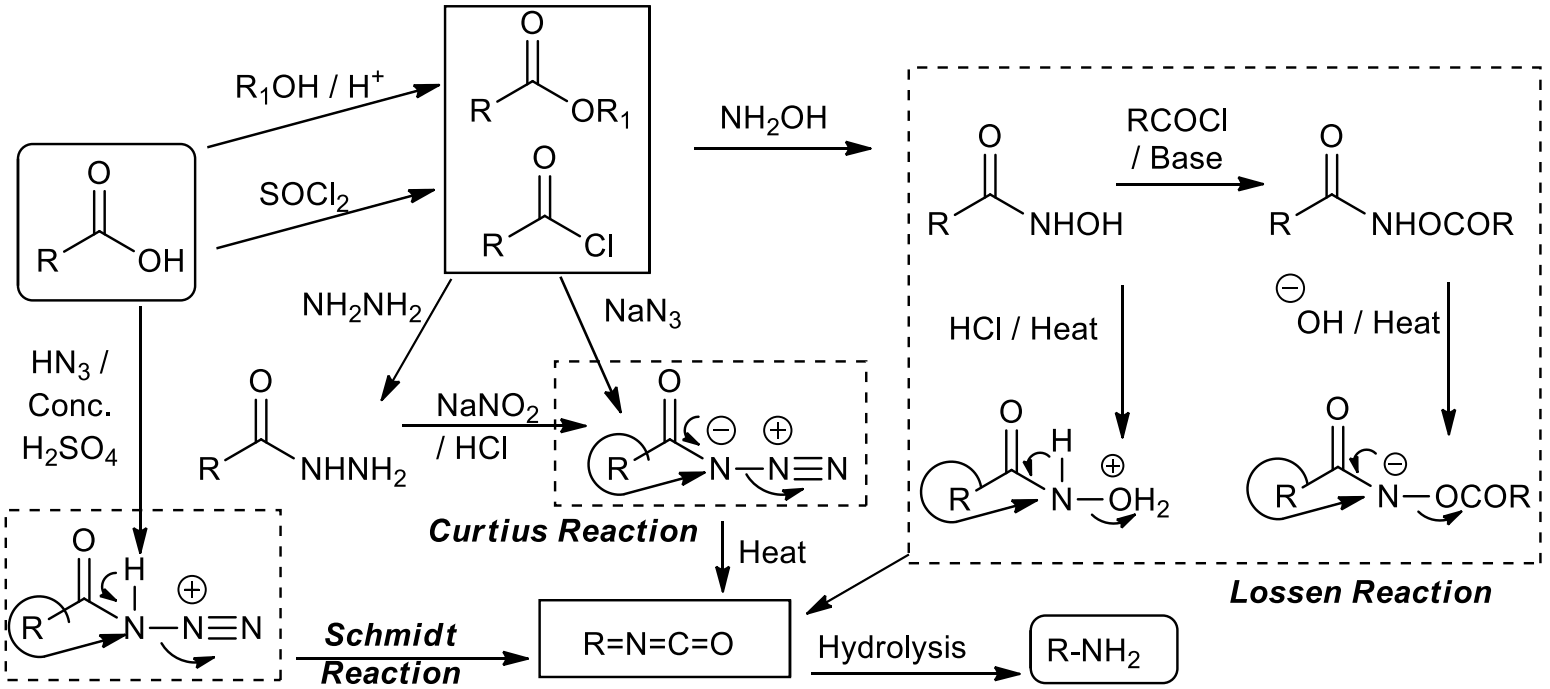
LOSSEN, CURTIUS and SCHMIDT REACTION

- These three reactions are degradation techniques to convert a ***carboxylic acid*** into ***primary amine***, having one less carbon.

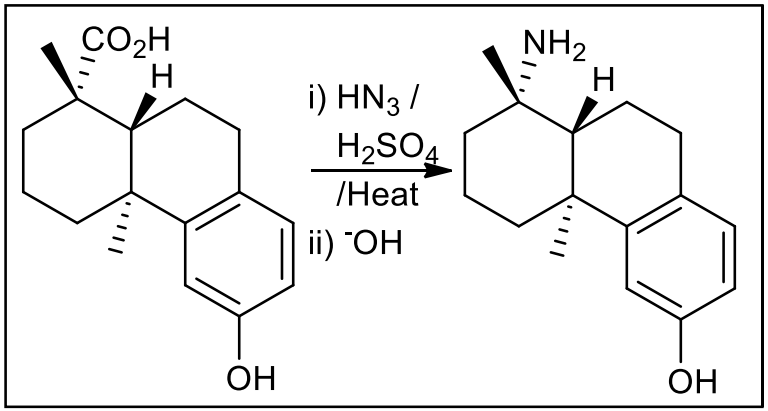
- In ***Lossen Reaction***, hydroxamic acid / O-acylated hydroxamic acid, rearranges to isocyanate.

- In ***Curtius Reaction***, acyl azide rearranges to isocyanate and in ***Schmidt Reaction***, protonated acyl azide rearranges to isocyanate.

- Finally, hydrolysis of isocyanate produces the primary amine.

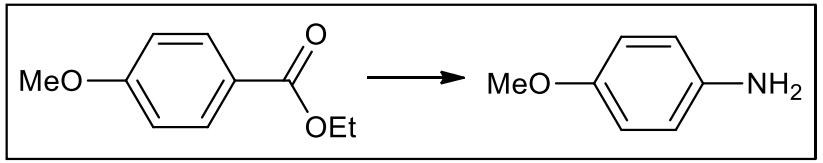


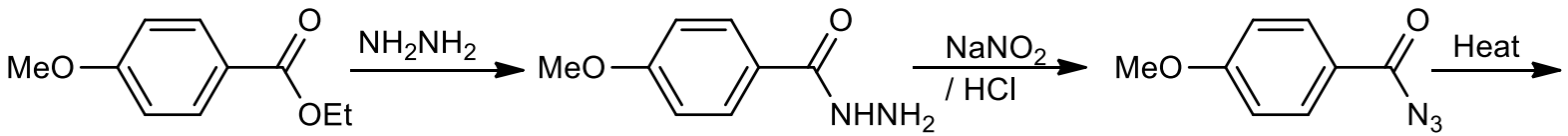
- All these three reactions proceed with retention of configuration of the migrating group.

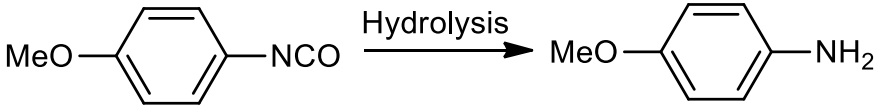


Problems:

1. Carry out the following conversion:

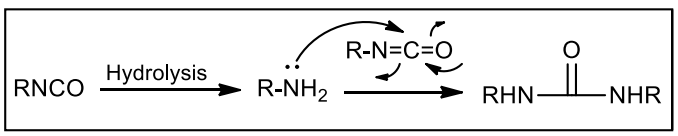


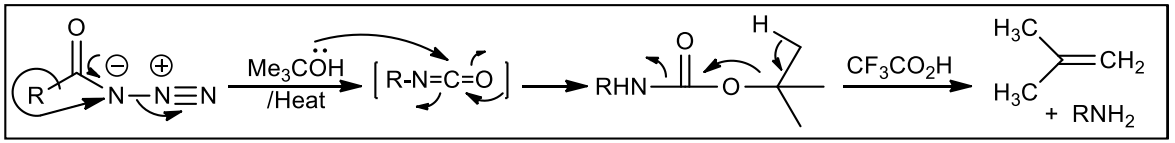




2. *Why urea derivative side product is formed in Curtius reaction? How could it be avoided?*

On hydrolysis, the produced amine react with unrected isocyanate, to produce the urea derivative. It can be avoided by carrying out the reaction in tert-butanol, followed by treatment of CF_3CO_2H.

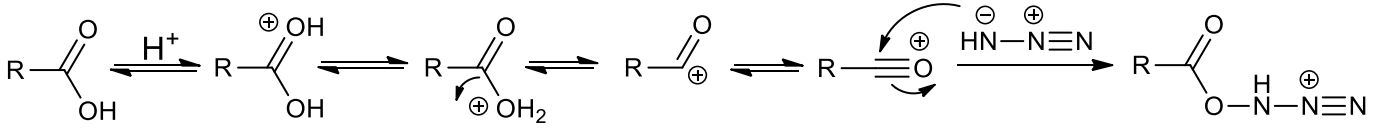


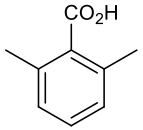
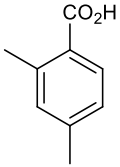


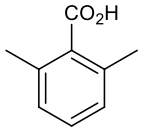
3. *Why urea derivative side product doesn't form in Schmidt reaction?*

Schmidt reaction is carried out under strongly acidic condition. So, the isocyanate gets hydrolysed autometically, forming the amine. Under this strongly acidic medium, the amine gets protonated and becomes unable to attack the isocyanate to form urea derivative.

4. *Show mechanistically, how HN_3 converts RCO_2H into $RCO\text{-}NH\text{-}N_2^+$ in Schmidt reaction?*



5.  *undergoes Schmidt Rearrangement at faster rate than*  *. Explain.*

Formation of acyl cation is the r.d.s. during Schmidt reaction. Here hybridization state of the carbonyl carbon changes from planar SP^2 to linear SP. So, strain is released. For more hindered substrate, this relief is more and therefore rate is higher. Of course,  is more hindered and therefore undergoes Schmidt Rearrangement at faster rate.

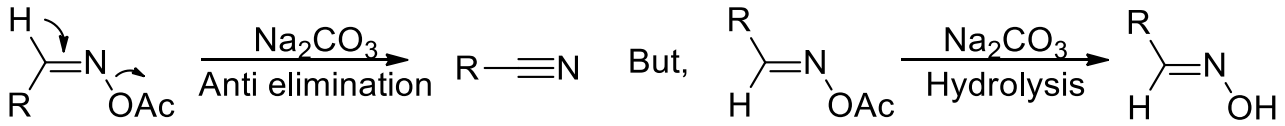
BECKMANN REARRANGEMENT

- Oximes are prepared from aldehydes/ketones using CH_3COONa/CH_3COOH buffer. Buffer is required to maintain an ***optimum pH***, necessary for the two-step reaction. The first step, where nucleophilic attack by NH_2OH at the carbonyl center occurs, requires a high pH so that, amine lone pair remains free. Under low pH it gets blocked as NH_3^+OH, which slows the first step down. The second step is a dehydration process and works faster at lower pH. Under high pH, dehydration slows down. Due to the above two opposing factors, none of the extreme pH conditions could be used. So, an optimum pH around 4 to 5, a slightly acidic condition, was found to be the best condition and was maintained by CH_3COONa/CH_3COOH buffer.

- Further dehydration of aldoximes (obtained from the reaction of aldehyde with NH_2OH) into nitriles is generally performed using acetic anhydride as the dehydrating agent. However, Ethyl othoformate/H^+ or PPh_3/CCl_4 are also used sometimes.

- Direct conversion of aldehyde into nitrile is also done by $NH_2OH.HCl/HCOOH$ or NH_2OSO_3H.

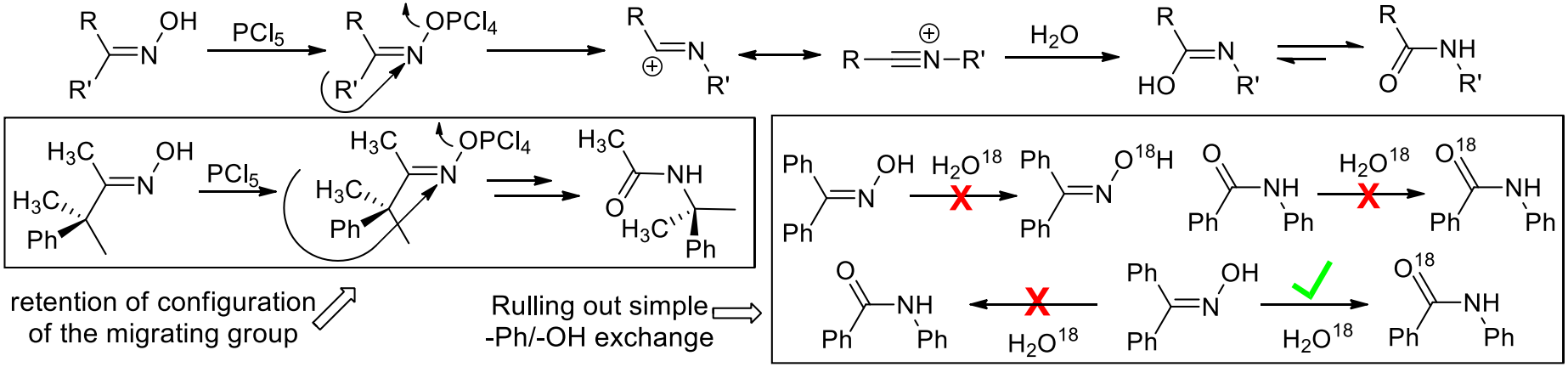
- The stereochemical requirement for such dehydration is anti-orientation of –H and –OH, which is easily established from the behavior of acetyl-derivatives of their syn- and anti-isomer with aq. Na_2CO_3. ***Z-isomer*** rapidly produces nitrile, but the ***E-isomer*** gives back aldoxime. It's a technique to distinguish isomeric aldoximes too.



- Ketoxime, on the other hand, on treatment with dehydrating agents like PCl_5, Conc. H_2SO_4, HCOOH, $SOCl_2$, P_2O_5, HCl/AcOH/Ac_2O, polyphosphoric acid etc., rearranges to substituted amide. This is known as ***Beckmann Rearrangement***.

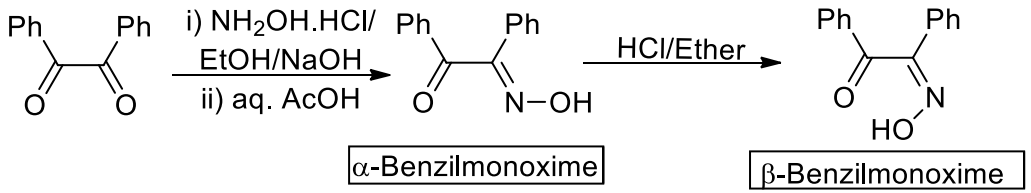
- Direct conversion of ketone into amide is done by NH_2OSO_3H / HCOOH.

- The mechanism involves migration of the group, anti to the –OH group, with retention of its configuration. The argument was proved from the retention of configuration of the migrating group in beckmann rearrangement of an optically active ketoxime.

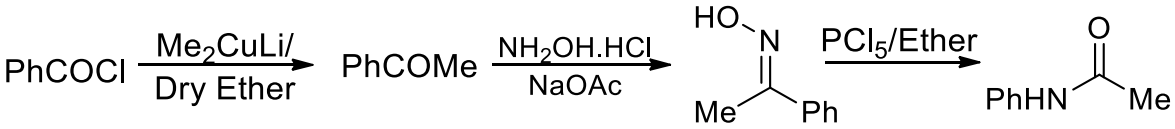


- Also, possibility of a simple exchange between the –R' and –OH was ruled out by carrying out the reaction of benzophenone ketoxime in H_2O^{18}. Studies proved that, neither starting material or product exchanges O/O^{18} in H_2O^{18}. So, If its a simple exchange, then product amide should not contain any O^{18}. But, O^{18} proportion was found to be the same in both H_2O^{18} and in product benzanilide, which is only possible if the –OH of ketoxime is lost from the starting material and $–O^{18}H$ was reintroduced from H_2O^{18}.

- However, there are examples where *syn*- group appears to have migrated (when both migrating groups are alkyl), resulting in either exclusive *syn*-migrated product or a mixture. Actually, in most of those cases, the starting ketoxime itself isomerises first, before Beckmann Rearrangement. This competitive isomerization was found to be least likely, when PCl_5 is used as the reagent for Beckmann Rearrangement.



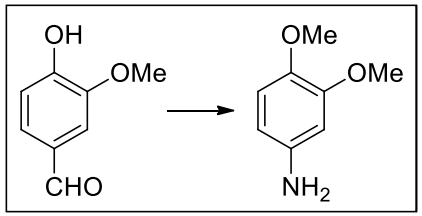
- Another interesting fact is that, in oximes of aryl alkyl ketones, always aryl group migrates during Beckmann Rearrangement, indicating preferential formation of anti-aryl ketoxime during the reaction of aryl alkyl ketones with hydroxylamine. So, we have,-

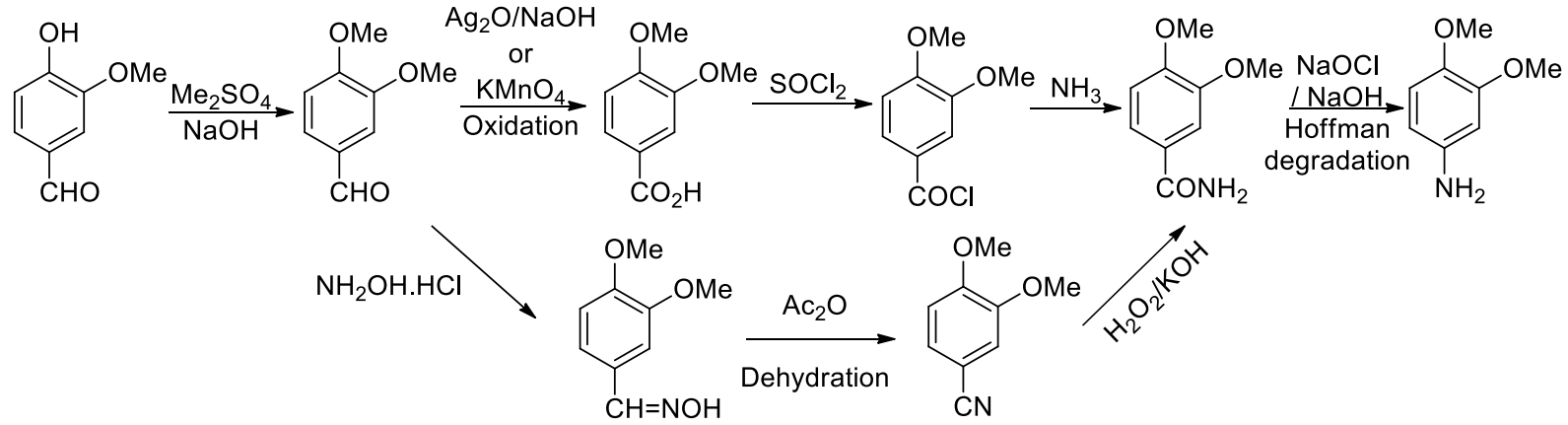


- Its worth mentioning that, Beckmann Rearrangement is often used to determine the configuration of the oxime, since always anti-group migrates in this reaction.

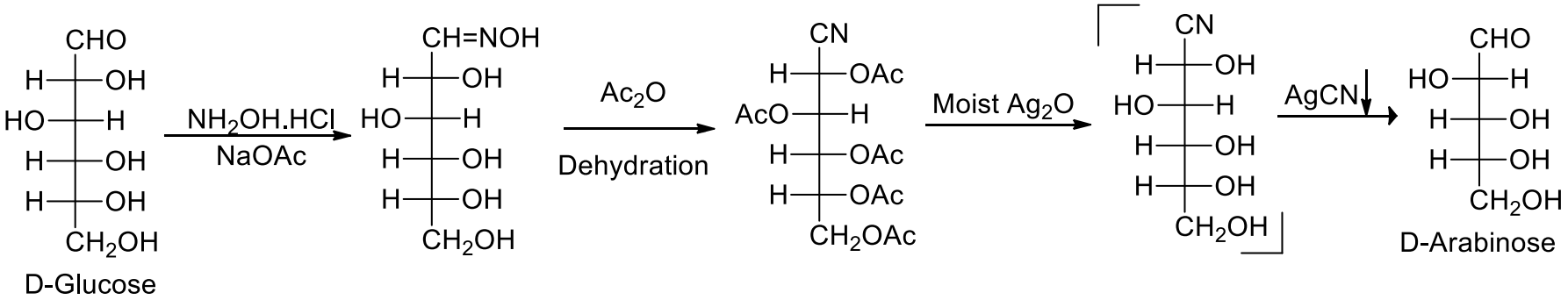
PROBLEMS:

1. ***Perform the following conversion:***





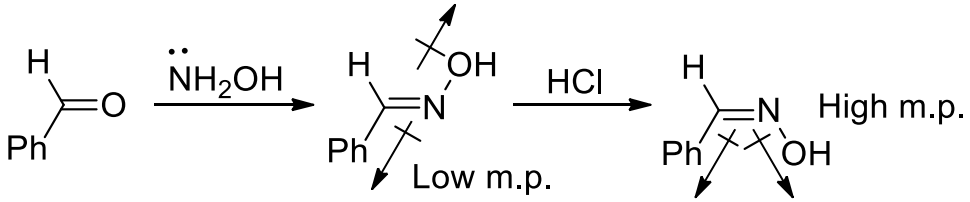
2. ***Show how glucose can be degraded to arabinose:***



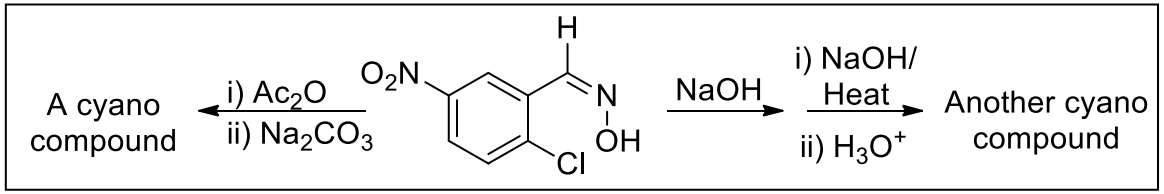
3. ***Among the isomeric aldoximes of benzaldehyde, the one having high m.p. undergoes rapid dehydration to PhCN. Explain.***

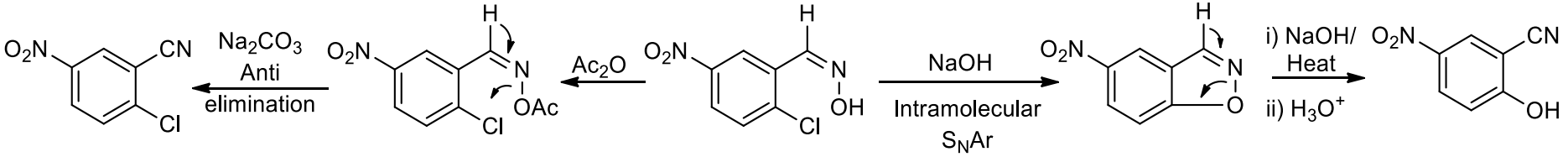
The initial aldoxime obtained from hydroxylamine treatment of benzaldehyde is the syn-hydrogen aldoxime. Here, the phenyl group and hydroxyl groups are anti to each other and therefore, their bond moments cancels out each other to some extent, causing an

overall low dipole moment and eventually low m.p. As, in this compound, -H and –OH are syn-to each other, the dehydration on treatment with Ac_2O, is sluggish. But when this syn-aldoxime is treated with acid it rearranges to anti-hydrogen aldoxime. Here, the phenyl group and hydroxyl groups are syn to each other and therefore, their bond moments gets added up, causing an overall high dipole moment and eventually high m.p. As, in this compound, -H and –OH are anti-to each other, the dehydration on treatment with Ac_2O occurs rapidly.

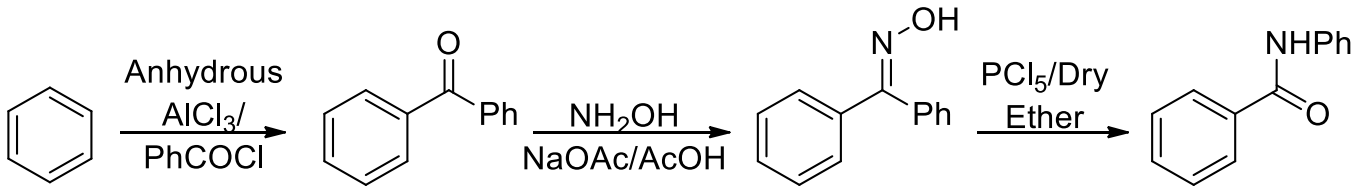


4. Complete the following:

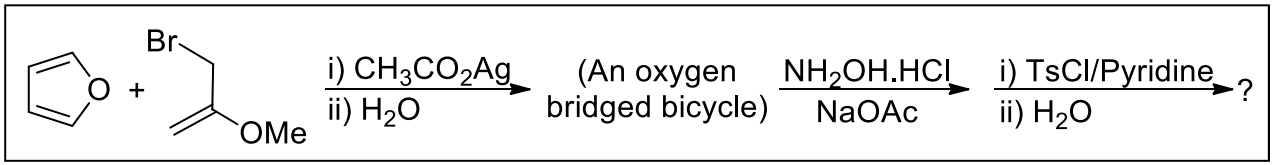


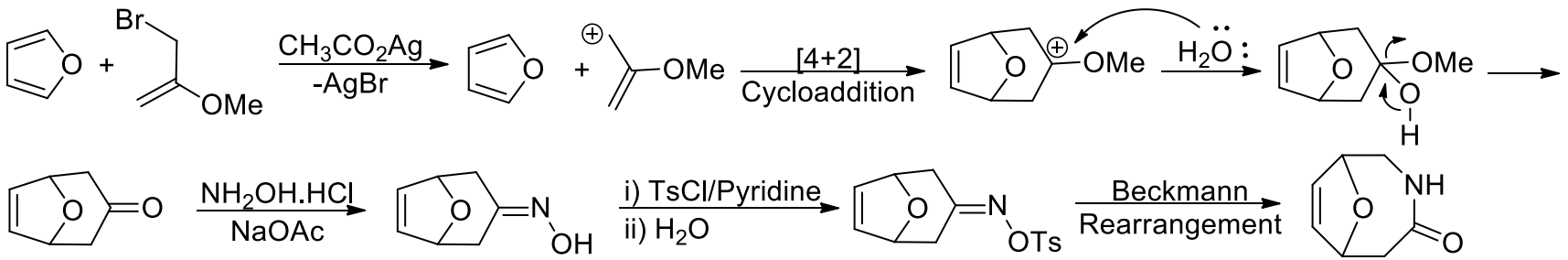


5. How would you convert benzene in to benzanilide?

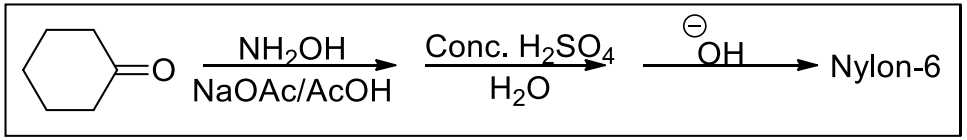


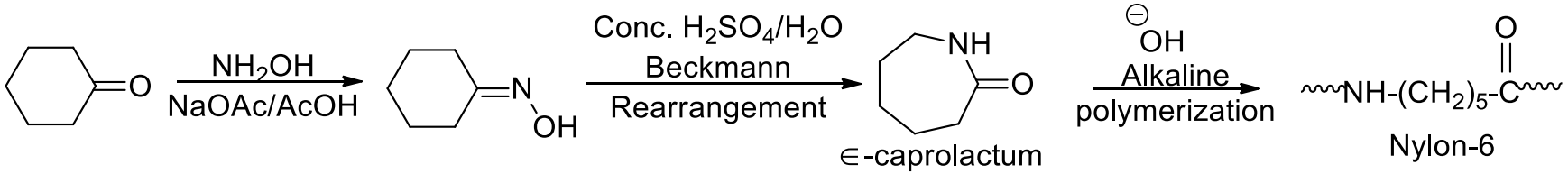
6. Complete the following:



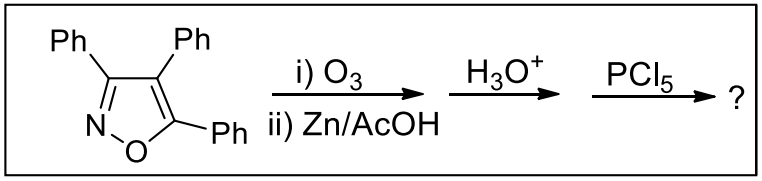


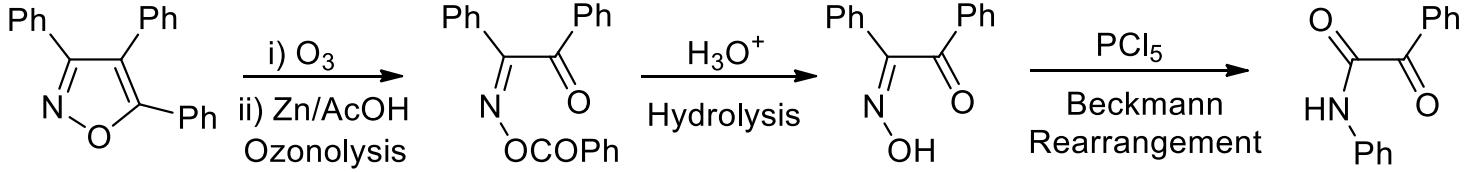
7. Complete the following:





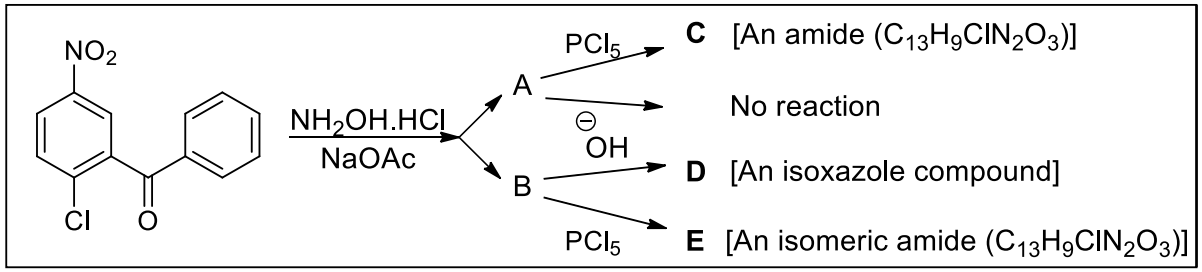
8. Complete the following:

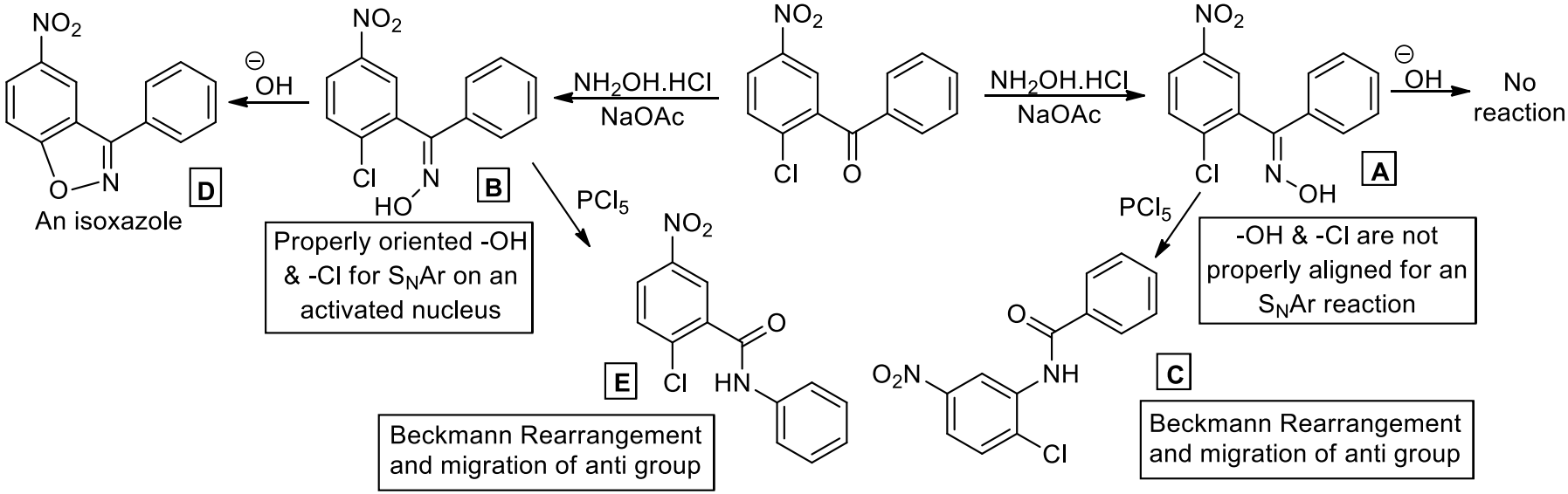




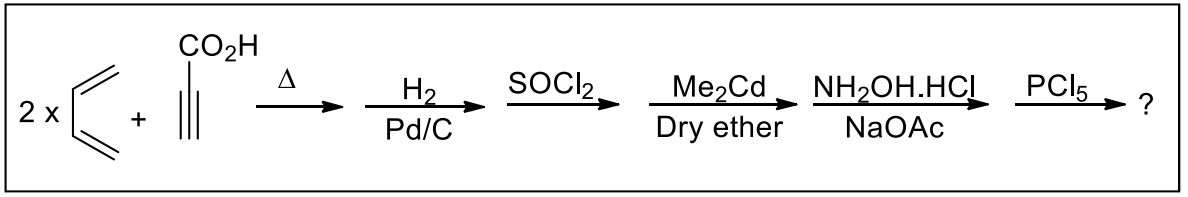
This reaction sequence is a proof of migration of the anti group, during Beckmann Rearrangement.

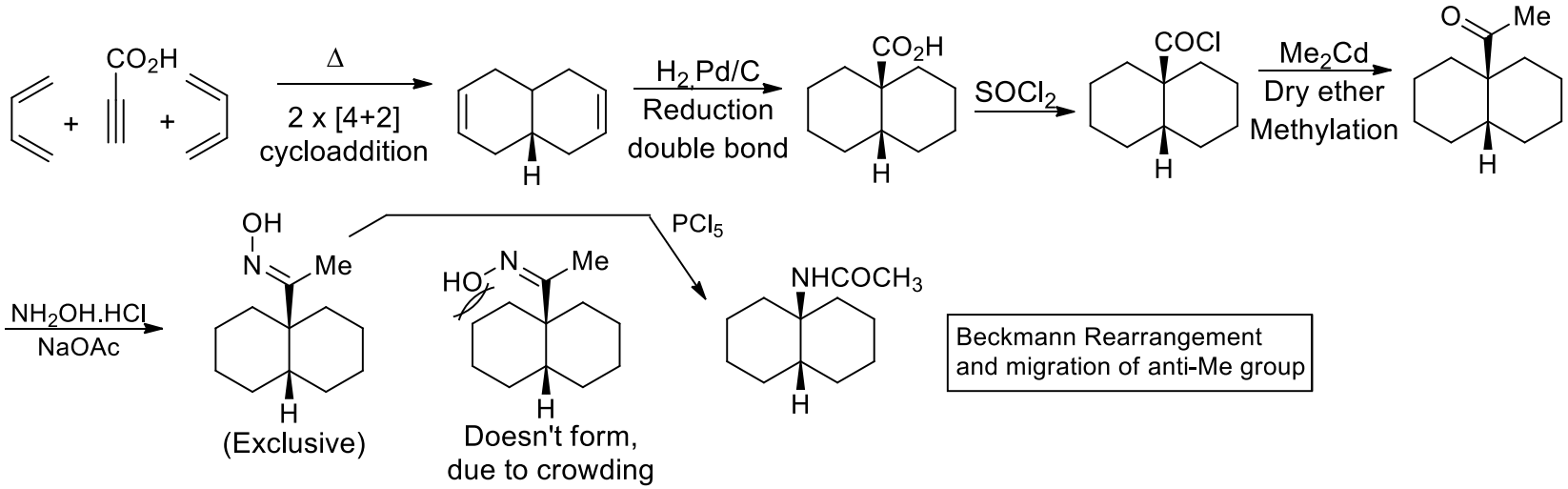
9. Identify A-E:



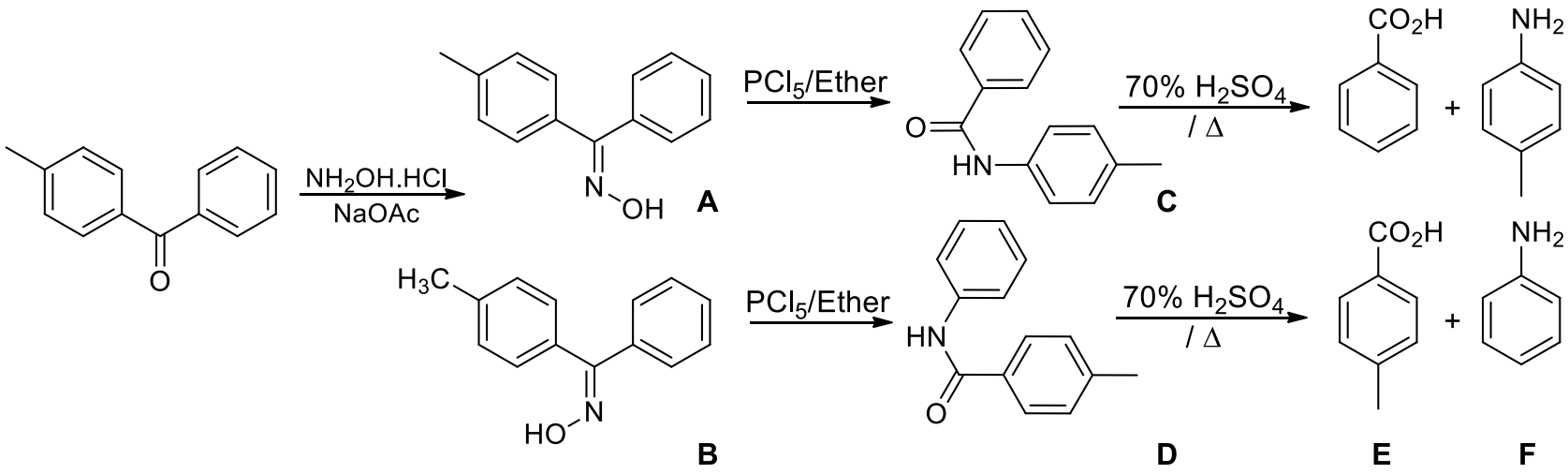


10. Complete the following:



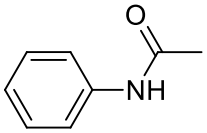


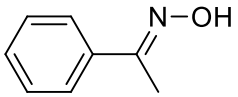
11. Identify A-F:

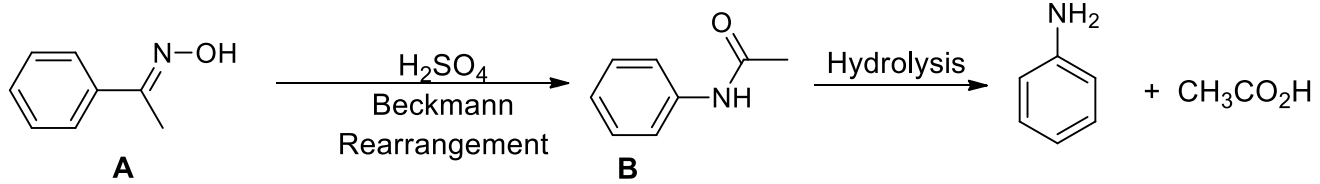


12. An organic compound "A" of formul C_8H_9ON, on treatment with H_2SO_4 isomerises to "B", which on hydrolysis gave aniline and acetic acid. Identify A, B with explanation.

Of course, aniline and acetic acid are the hydrolysis products of $PhNHCOCH_3$.

So, B =  Since, its an amide, it could have isomerised from the corresponding anti-phenyl ketoxime via

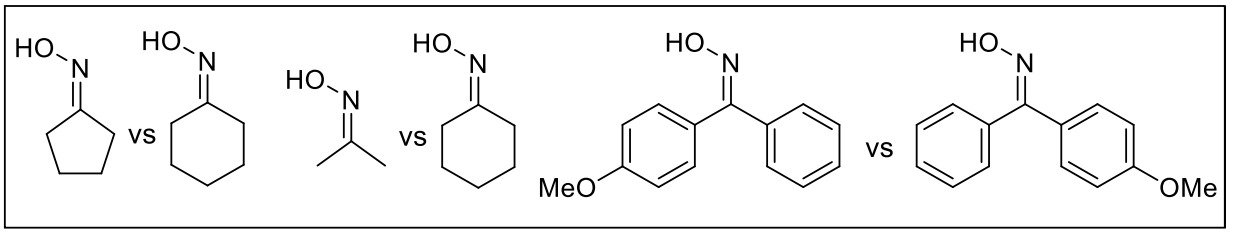
Beckmann Rearrangement. So, A = 

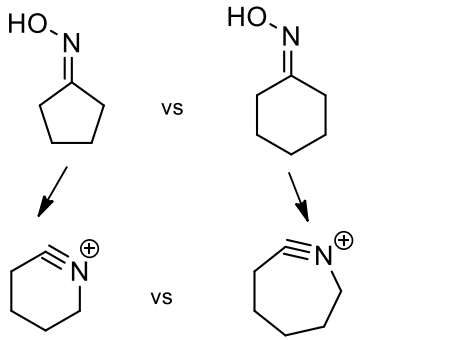


A **B**

Chemical Formula: C_8H_9NO

13. Find out the more reactive entity in each pair:



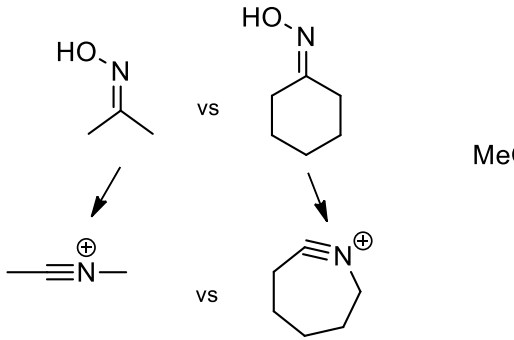


More strained SP hybridised system, due to smaller ring size

Less strained SP hybridised system, due to larger ring size

Less reactive

More reactive

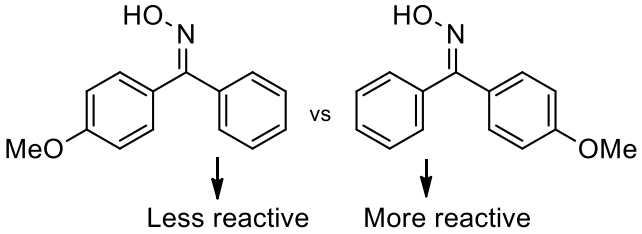


No strain, as SP hybridised system is linear here, perfectly

More Strained, as SP-hybridised system is forced to be in ring form

More reactive

Less reactive



As, the intermediate in Beckmann Rearrangement is a nitrilium ion, electron-donating migrating group stabilizes it, thereby increasing the rate. Of course, the anti-*p*-methoxyphenyl isomer will have a more electron-donating migrating group, making it more reactive.

14. An aliphatic ketone (molecular weight = 86) on reaction with hydroxylamine, gave a pair of oximes, which on reduction produces a resolvable amine and via Beckmann Rearrangement forms non-resolvable amides. Identify them.

Since, carbonyl group accounts for 28 mass unit (Mass of C + Mass of O = 12+16 = 28) of the aliphatic ketone, the remaining part, i.e. (86 - 28) = 58 mass unit accounts for the combined mass of the two alkyl groups (R_1 and R_2).
Of course, if both of them are saturated then on clubbing them hypothetically, they will form an alkane of molecular formula C_nH_{2n+2}.
The abobe arguement will only be valid if, on solving the following euation, **"n"** turns out to be an integer :

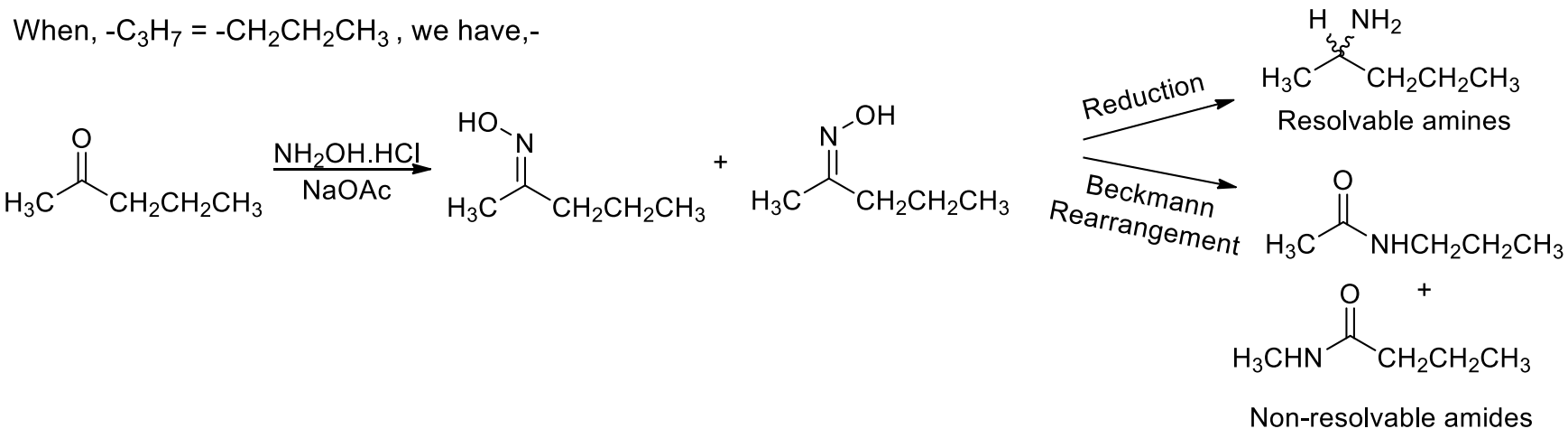
$12n + 2n + 2 = 58$; Or, $14n = 56$; Or, $n = 4$

So, the total number of alkyl carbons = 4, which could either be divided as (2+2) or (1+3).

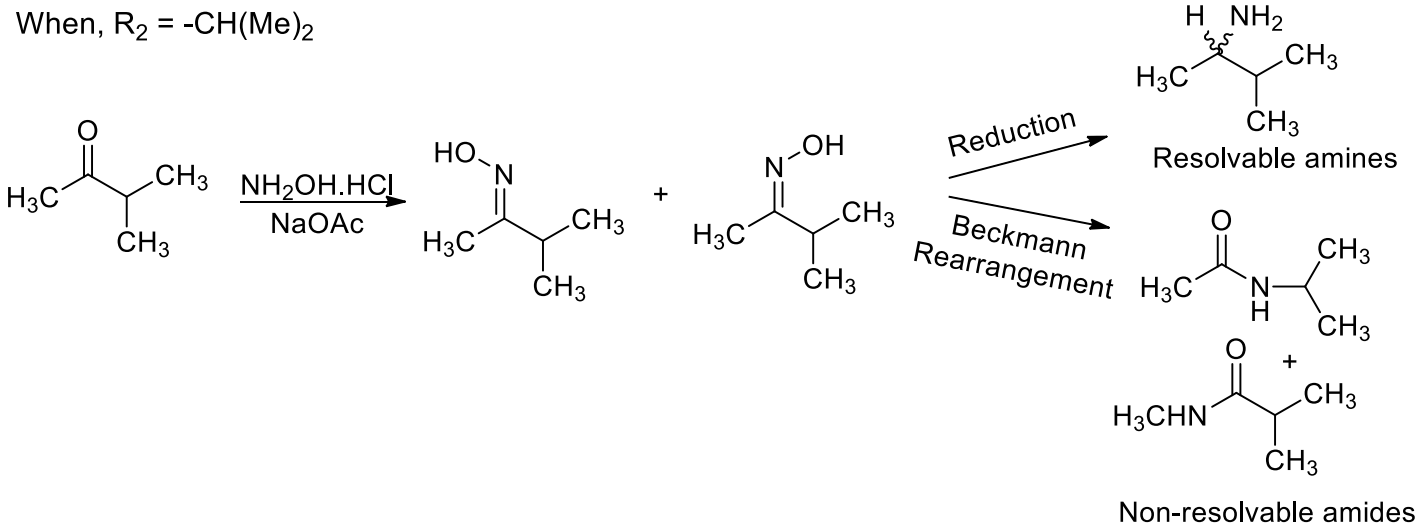
Of course, the first option implies, $R_1 = R_2$ = Ethyl. But, thats not possible, as diethyl ketone will produce only one type of ketoxime.

So, we must go with the second option, i.e. $R_1 = -CH_3$ and $R_2 = -C_3H_7$
Now, $-C_3H_7$ = either, $-CH_2CH_2CH_3$ or $-CH(CH_3)_2$.

When, $-C_3H_7 = -CH_2CH_2CH_3$, we have,-

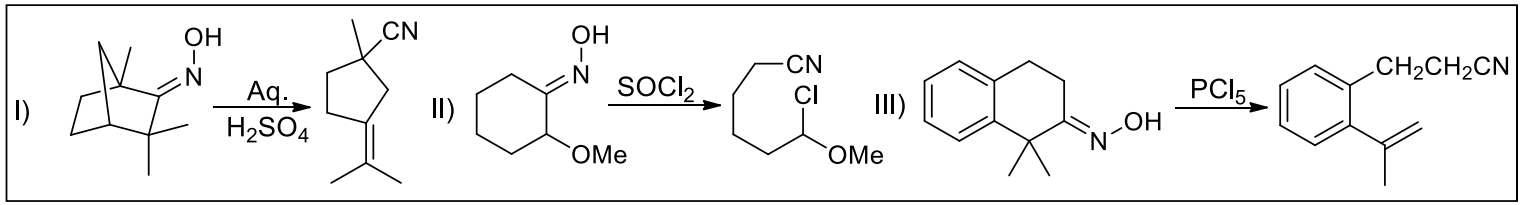


When, R_2 = -CH(Me)$_2$

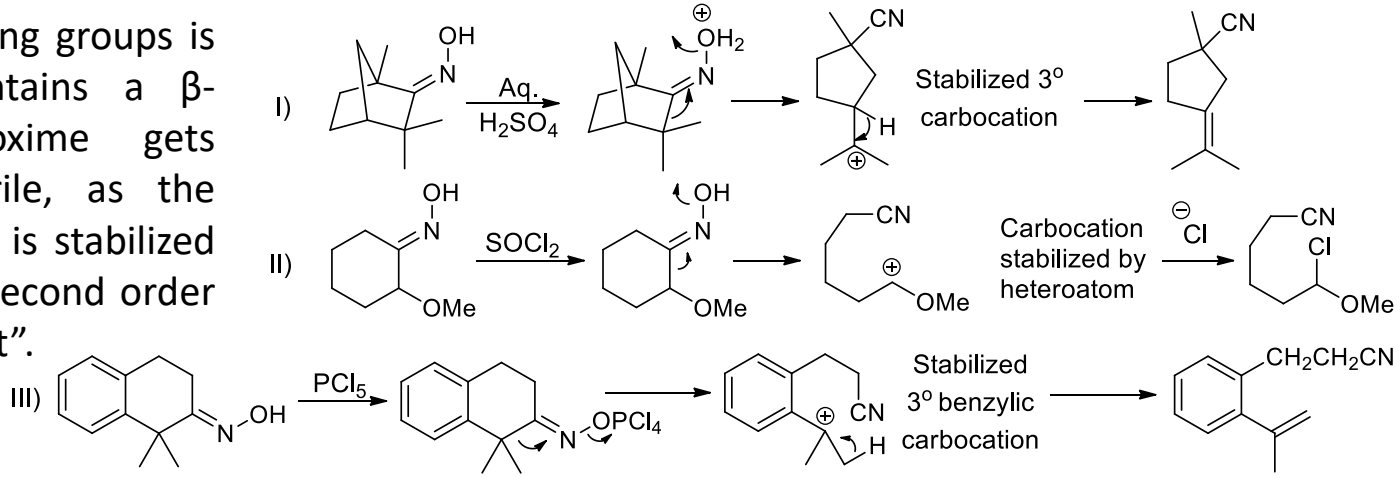


- Note that, since both the migrating groups are alkyl, we get mixture of amides.
- Both ketones produce resolvable amines and non-resolvable amides.
- So, both the structures are possible.

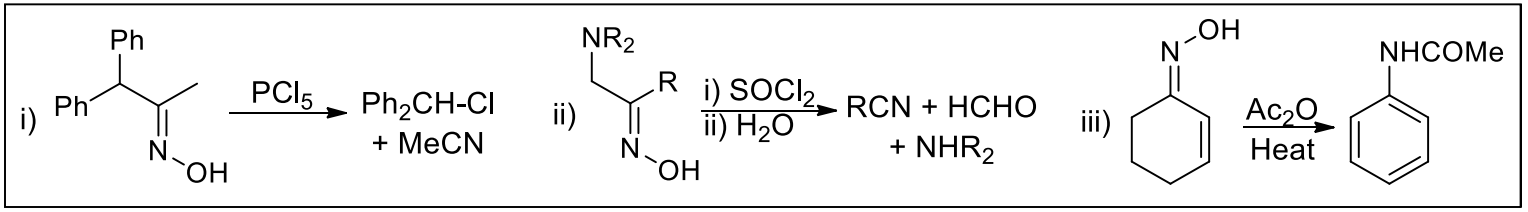
15. Explain the following:

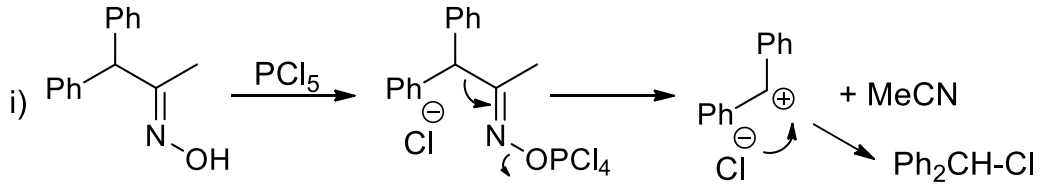


When one of the migrating groups is 3° or benzylic or contains a β-heteroatom, the ketoxime gets fragmented into a nitrile, as the intermediate carbocation is stabilized that way. Its known as "Second order Beckmann Rearrangement".

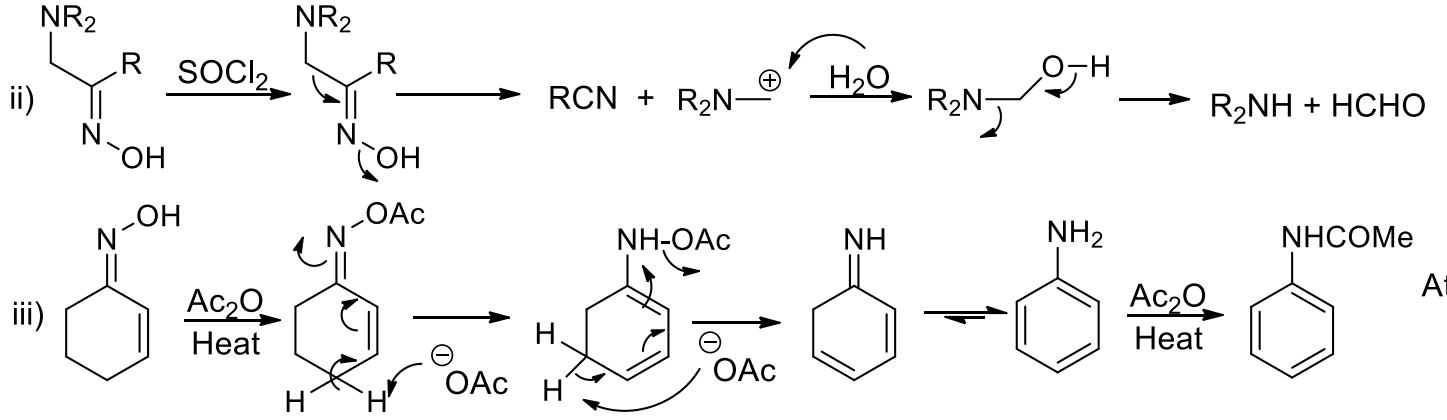


16. Explain the following:





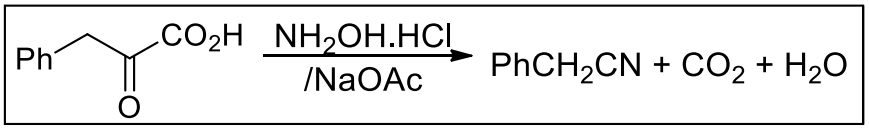
Stability of benzylic carbocation is the driving force here



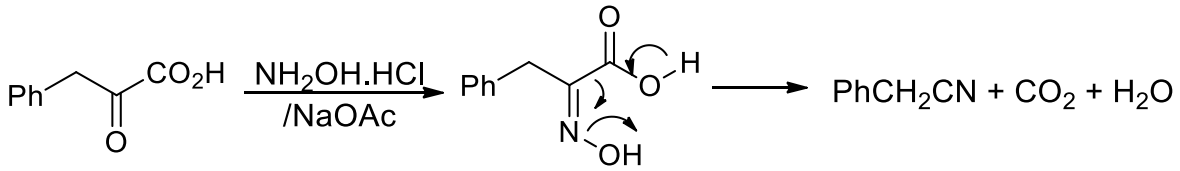
Stability of β-heteroatom containing carbocation is the driving force here

Attainment of aomaticity is the driving force

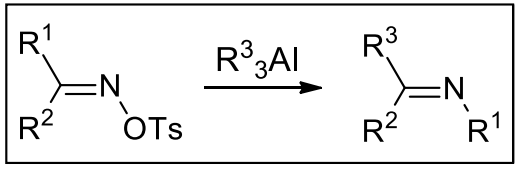
17. Explain the following:

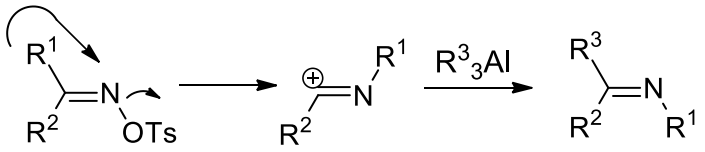


Its a general method to prepare cyanides.



15. Explain the following:





A technique to convert oximes into imine