Year 2 Organic Chemistry

Dicarbonyl Chemistry – Dr Wyatt

1,3-dicarbonyls

Introduction

- 1,3-dicarbonyls have many synthetic uses due to the two carbonyl groups present.
    - 1,3-dicarbonyls, e.g. diethylmalonate (Figure 1 - diethyl malonate)

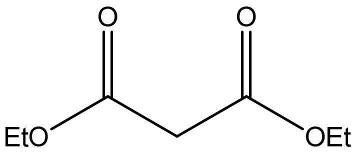
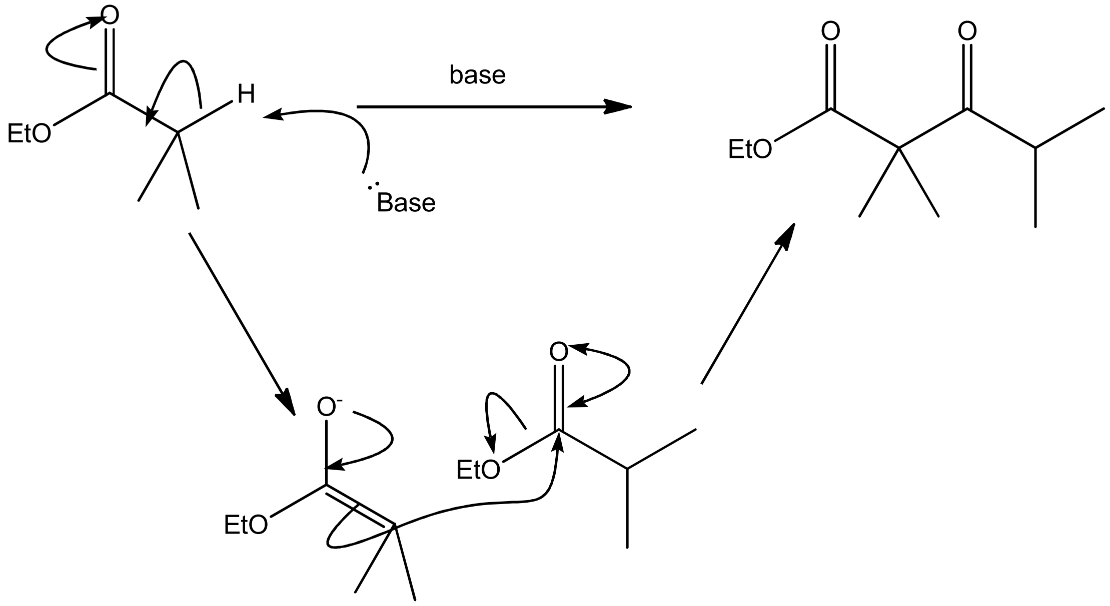


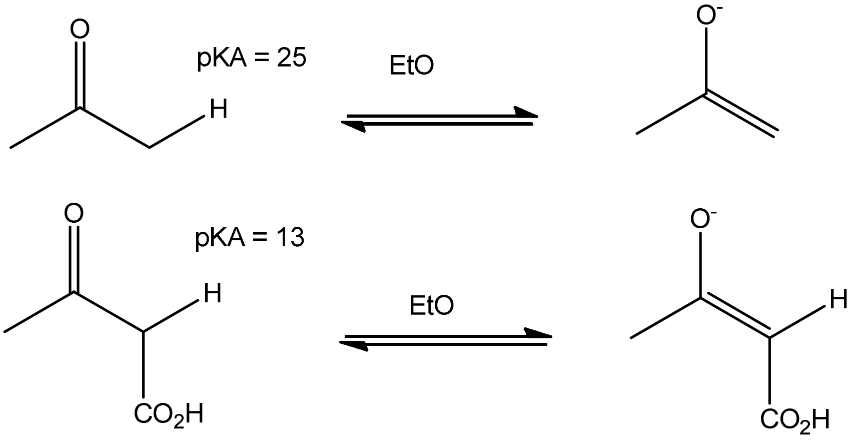
Figure 1 - diethyl malonate

- Malonates are cheap and readily available as starting materials, and can easily be synthesised from mono-carbonyl compounds.(Scheme 1 - Synthesis of a 1,3-dicarbonyl)



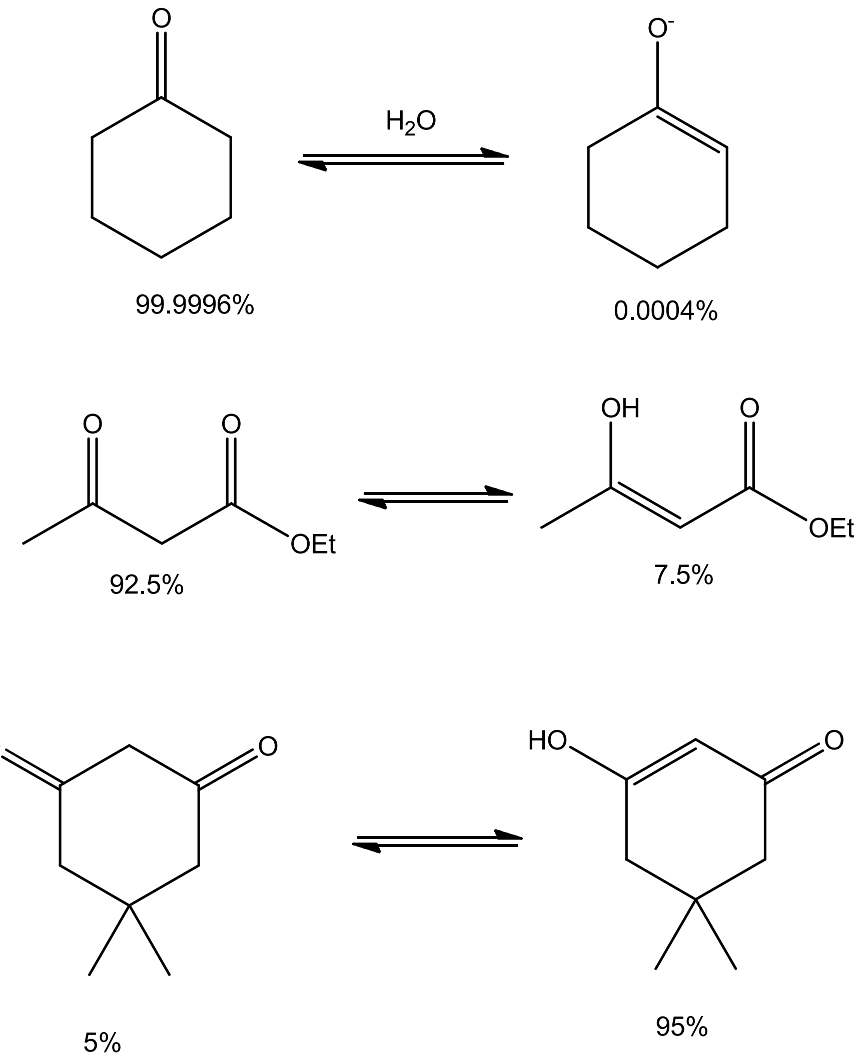
Scheme 1 - Synthesis of a 1,3-dicarbonyl

pK_A values



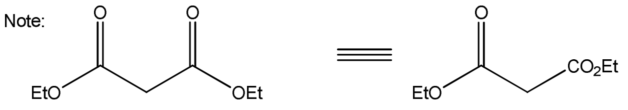
Scheme 2-pKA values of mono- and di- carbonyls

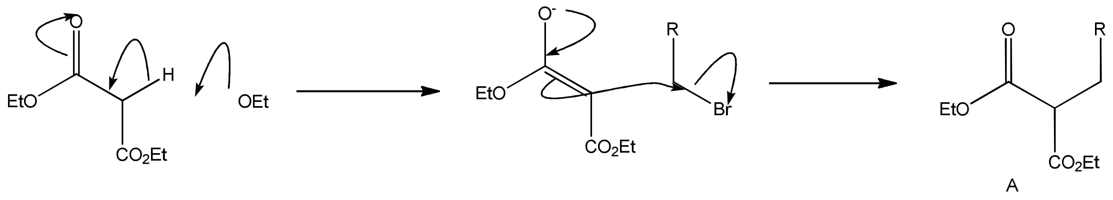
- Addition of a second carbonyl makes the adjacent proton much more acidic, so it can be removed by weaker bases.
- Alternatively, the anion produced by deprotonation is more stable when two carbonyl oxygens are present due to conjugation of the enolate (Scheme 2-pKA values of mono- and di- carbonyls)



Scheme 3 - effect of structure on existence of deprotonated (enol) form

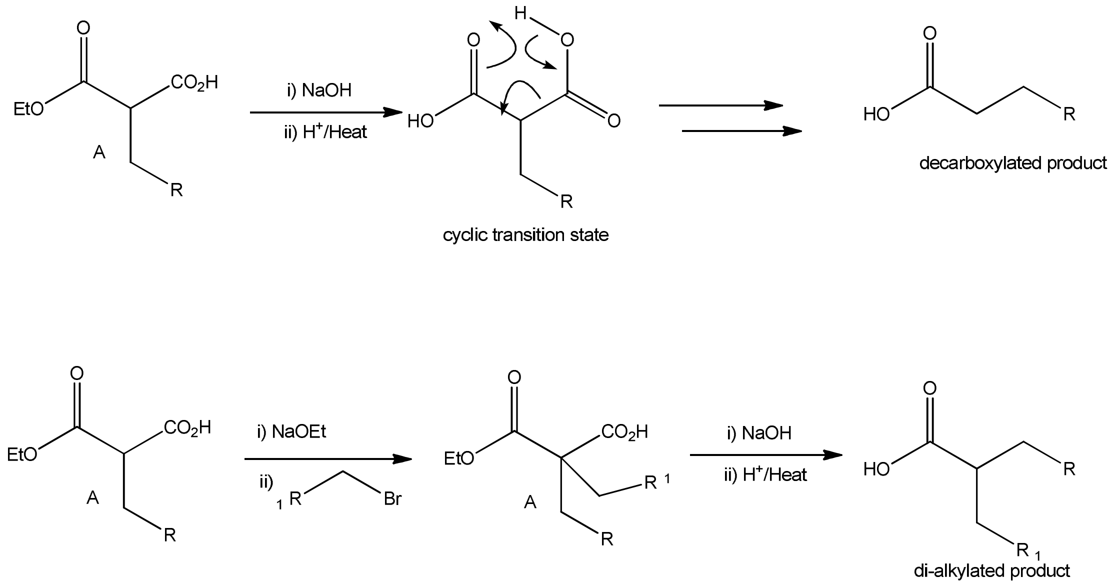
Alkylation of 1,3-dicarbonyls





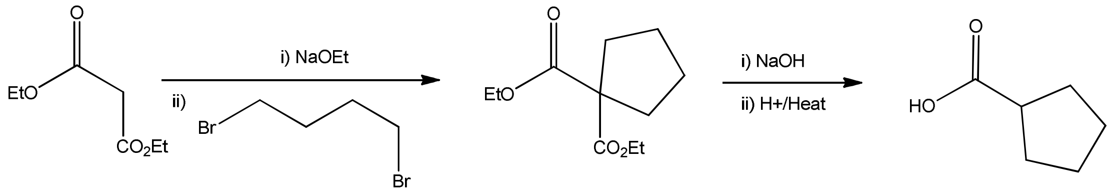
Scheme 4 - Alkylation of 1,3-dicarbonyl

- Mild base may be used to form enolate which can then react with electrophiles giving the alkylated product A. Scheme 4 - Alkylation of 1,3-dicarbonyl
- Further reactions can then be done (Scheme 5 - decarboxylation of 1,3-dicarbonyls)



Scheme 5 - decarboxylation of 1,3-dicarbonyls

- Alkylation of 1,3-dicarbonyls can be used to synthesise rings



Scheme 6 - Ring synthesis by alkylation of 1,3-dicarbonyls

- Other control groups are available:

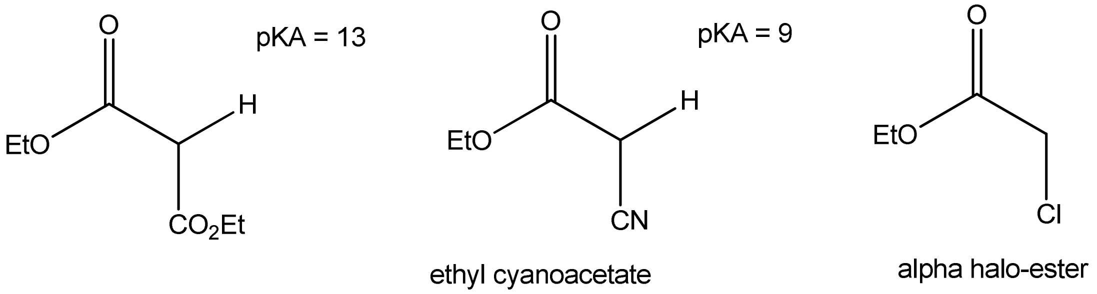
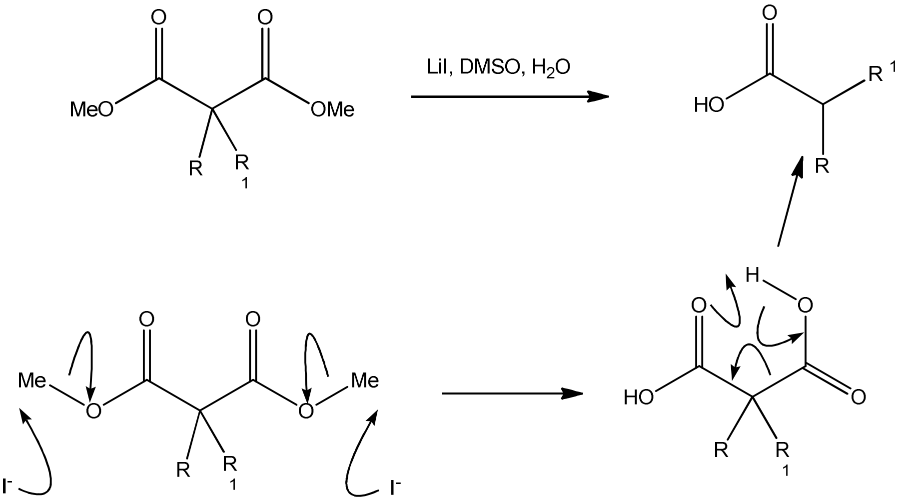


Figure 2 - other groups available and their pKA values

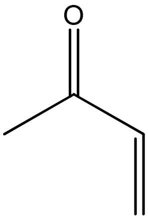
- Other ways to decarboxylate:



Scheme 7 – decarboxylation

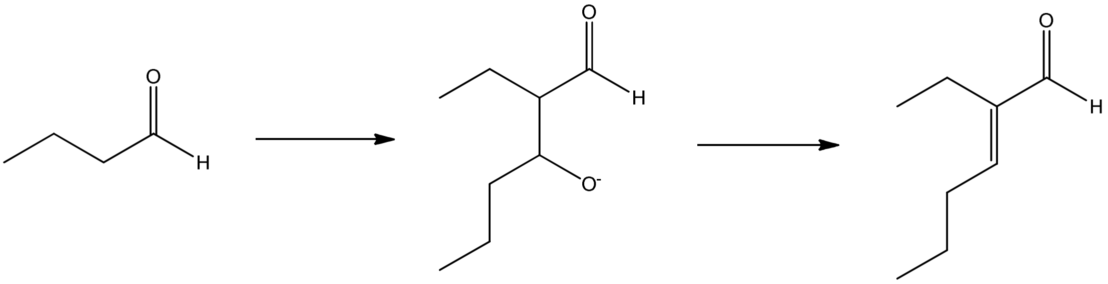
Enones

Introduction and Synthesis

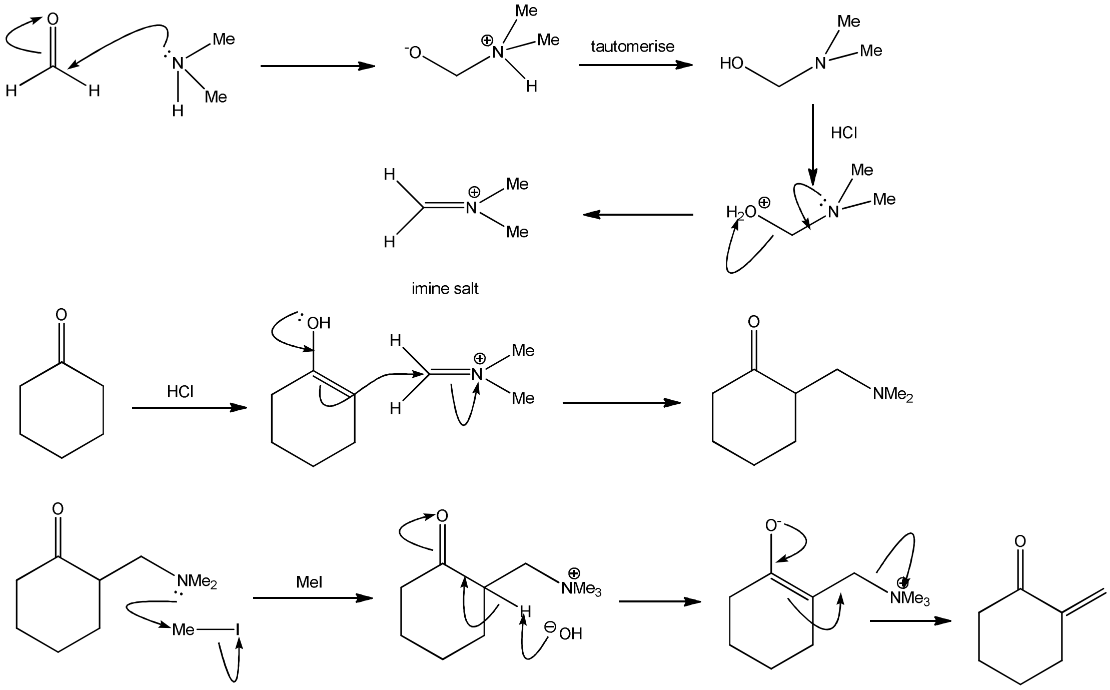


An enone

- Enones are α,β-unsaturated carbonyl compounds.
- Enones can be made in several ways:
  - Self condensation of aldehydes:

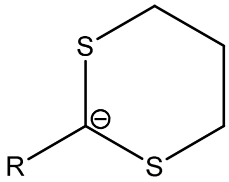
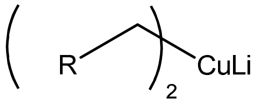


  - Mannich reaction:

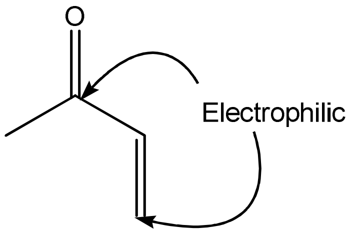


Scheme 8 - Mannich Reaction

1,2 vs 1,4 attack

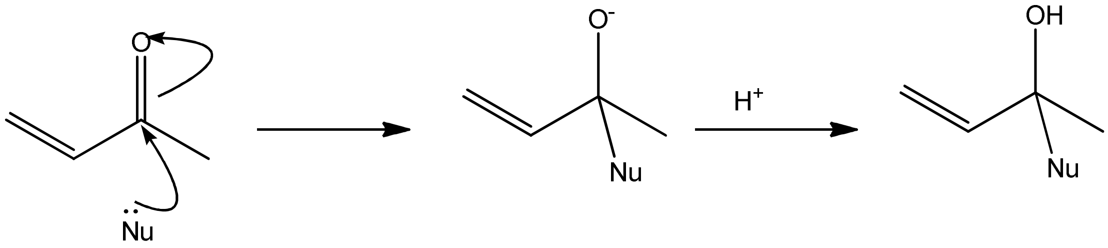
1,2 attack (direct)	1,4 attack (conjugate, Michael addition)
• Occurs with more reactive nucleophiles and nucleophiles with unstabilised charges, i.e. hard nucleophiles. • E.g.  • Organometallics • E.g. organolithium	• Occurs with nucleophiles with no charge or stabilised charge, i.e. soft nucleophiles • E.g. Stable enols Enamines Silyl enol ethers Amines • Organometallics • E.g. organocuprates 

Reactivity of enones



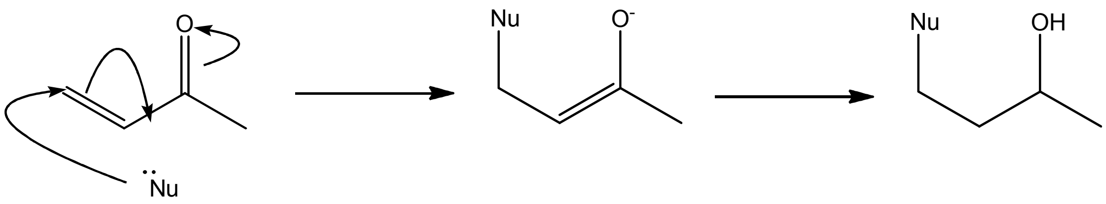
- Double bond present in enones is not as in a normal alkene due to conjugation with carbonyl

- 1,2 addition (direct):



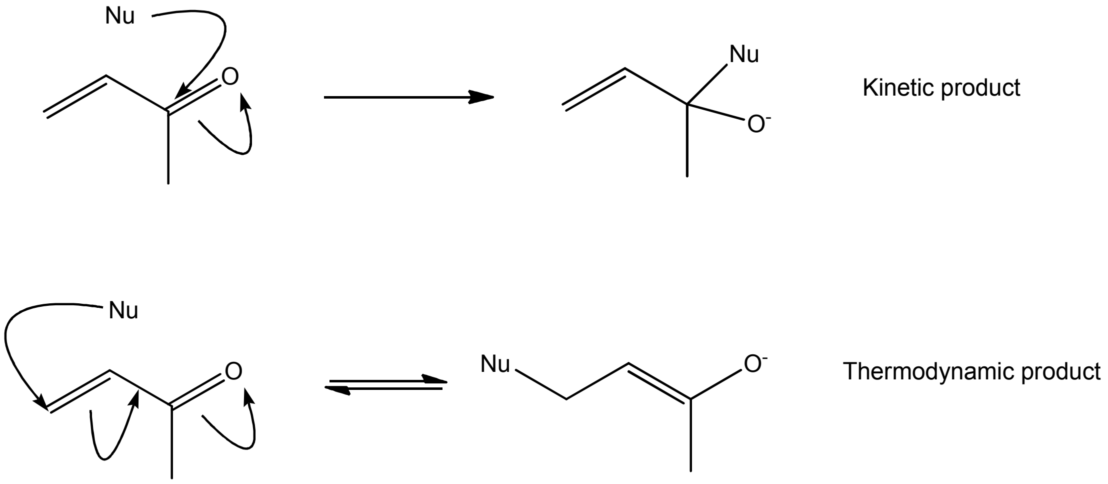
Scheme 9 - Direct attack on an enone

- 1,4 addition (Michael/conjugate addition)



Scheme 10 - 1,4 attack

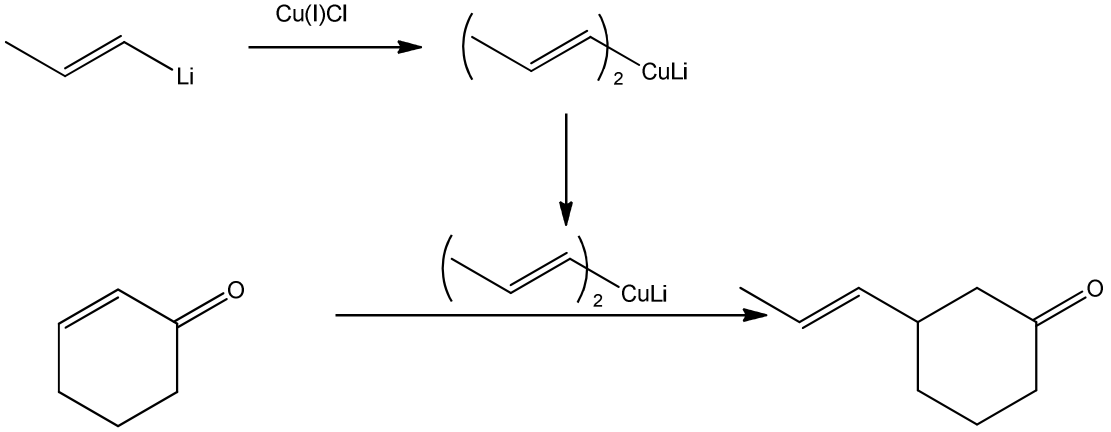
- 1,4 and 1,2 attack are often in competition, leading to two possible products (thermodynamic and kinetic products)
  Thermodynamic vs. Kinetic



Scheme 11 - thermodynamic (1,4 addition) and kinetic (1,2) products

Cuprates

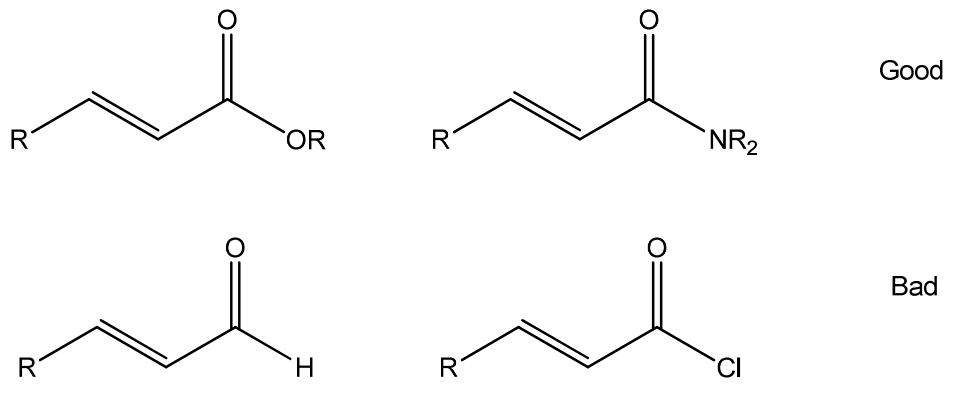
- Organometallic reagents are very reactive and can undergo 1,2 and 1,4 addition.
- Organocuprates are used to achieve smooth 1,4 addition.



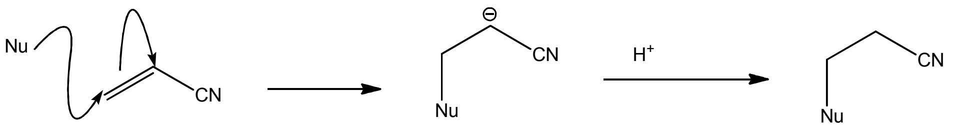
Scheme 12 - 1,4 addition with organocuprate

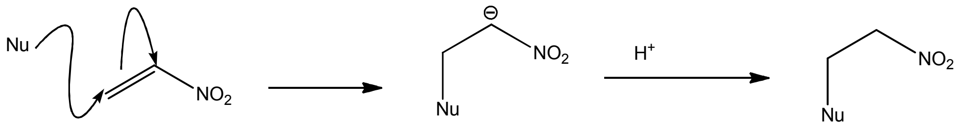
Michael acceptors

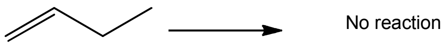
- Less electrophilic carbonyls make better substrates for Michael addition:



- Anything that stabilises negative charge has potential to be a good Michael acceptor, e.g. NO_2 group.

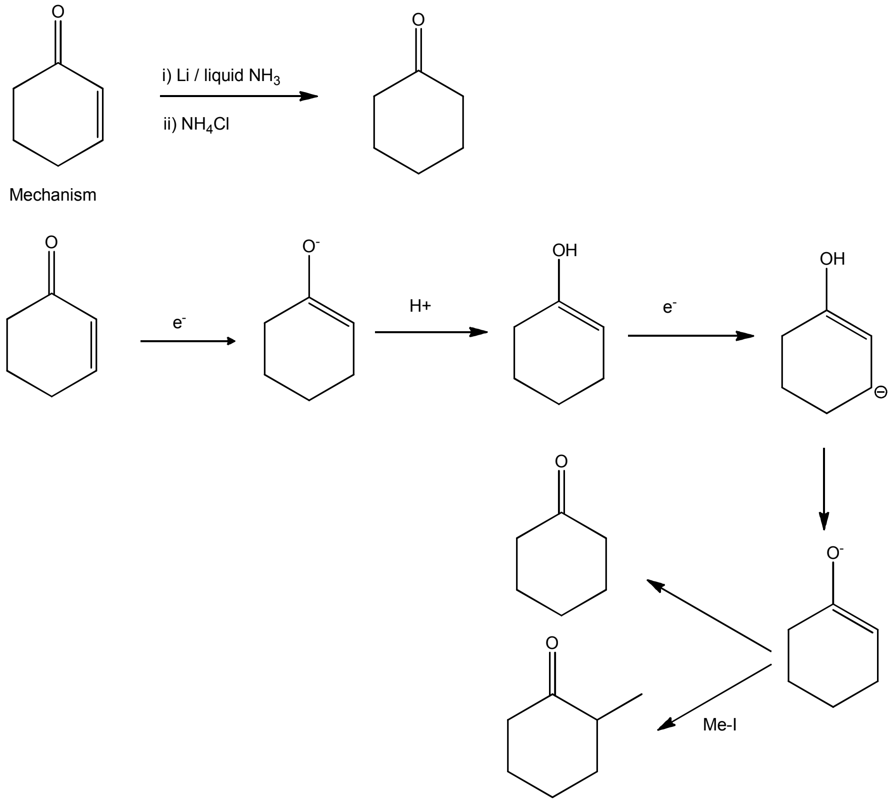






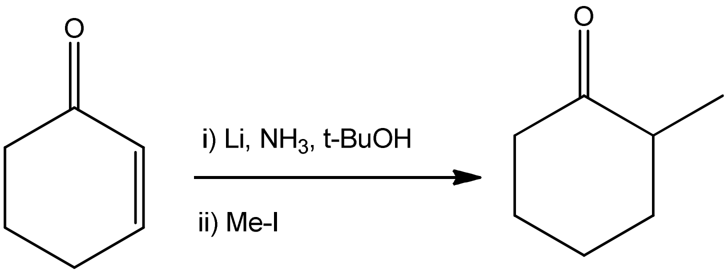
Lithium metal

- Lithium provides a way to reduce enones:



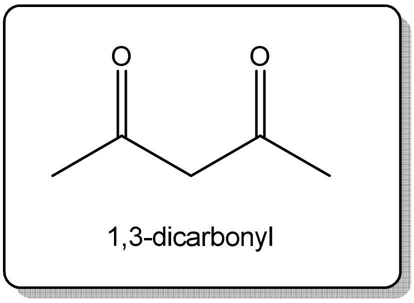
Scheme 13 - reduction of enones by Li

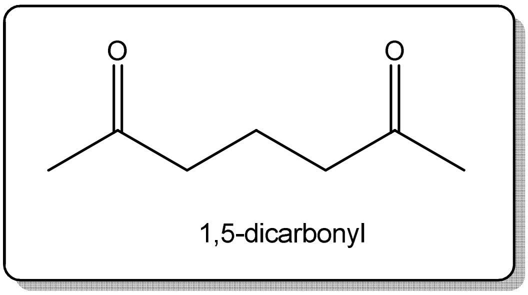
- This is a useful way of making enones react as a nucleophile rather than undergoing direct or conjugate addition.



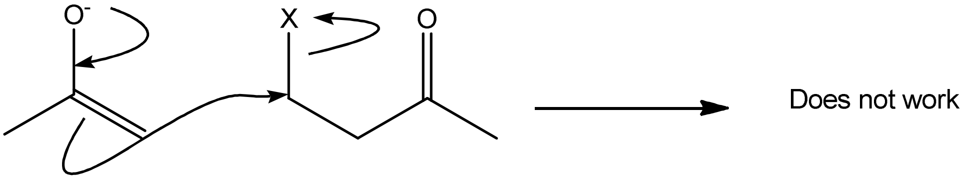
Scheme 14 - reaction of enone with electrophile

1,5-dicarbonyl chemistry

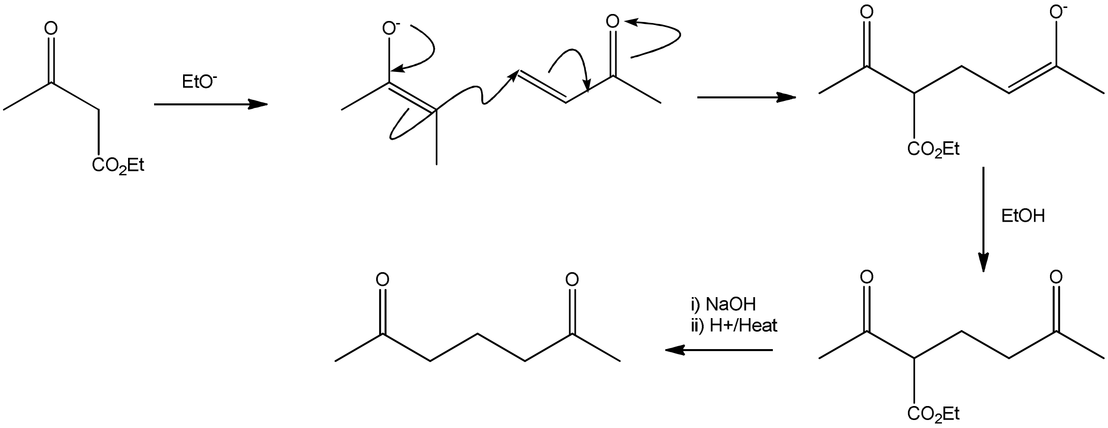




Synthesis:



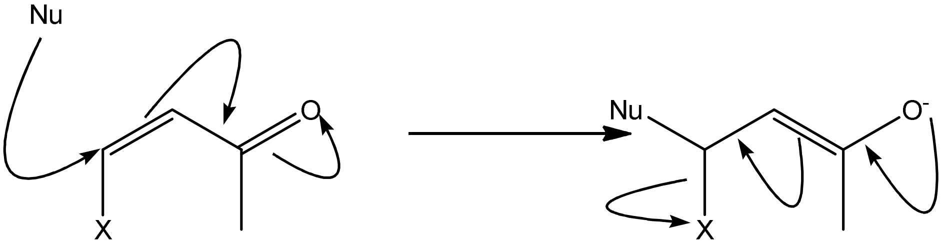
- Instead, to synthesis 1,5-dicarbonyls, use α,β-unsaturated carbonyl (enone)



- Enones can be made using Mannich reaction, 1,3-dicarbonyls can be prepared using Claisen chemistry. Alternatively, enamines can be used.

Advanced conjugate addition

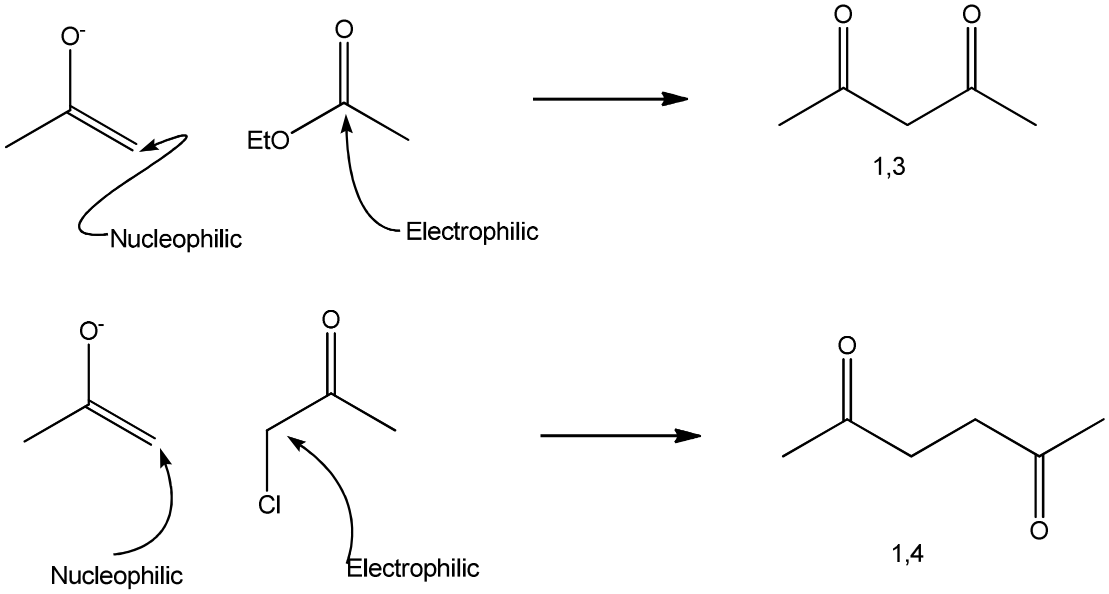
- Conjugate addition with preservation of the enone can be achieved using a leaving group to allow enone to re-form.



1,n-dicarbonyl chemistry

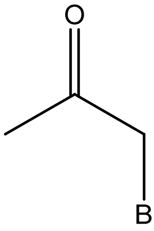
1,4-dicarbonyl chemistry

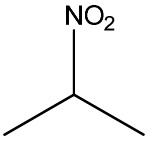
- Preparation of 1,4-dicarbonyls requires reversing the natural polarity of the carbonyl group, so is more tricky.

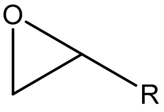


Scheme 15 - Synthesis of 1,4 dicarbonyl

- Reagents which reverse natural polarity of carbonyl group:

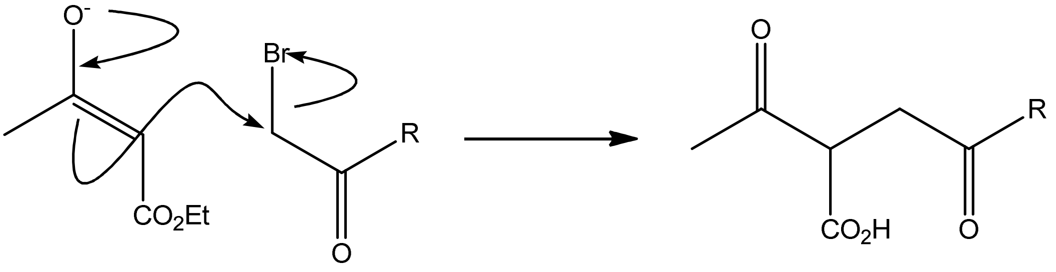




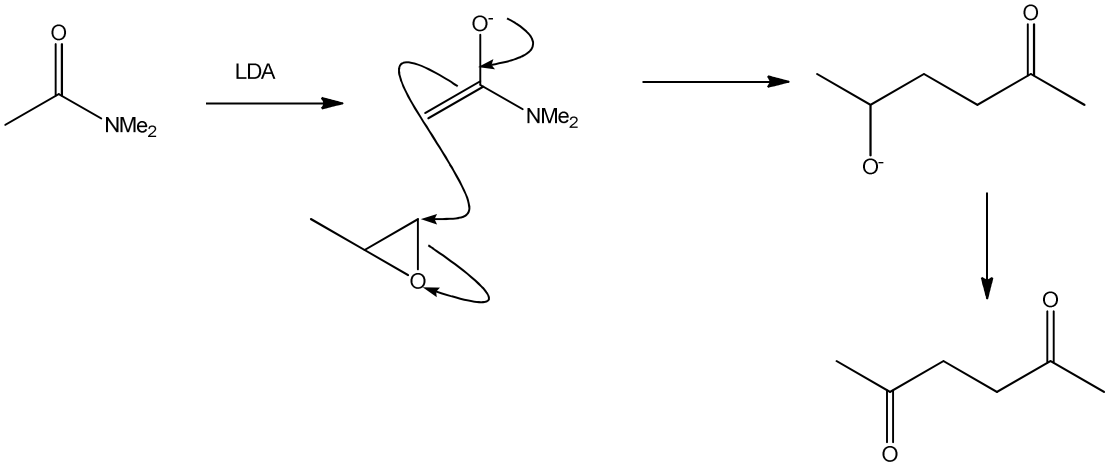


α-halo carbonyls

- Very reactive compounds, need special care.

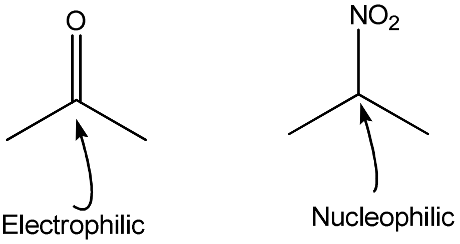


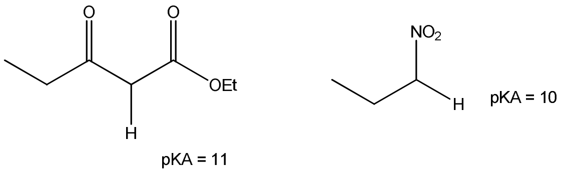
Epoxides

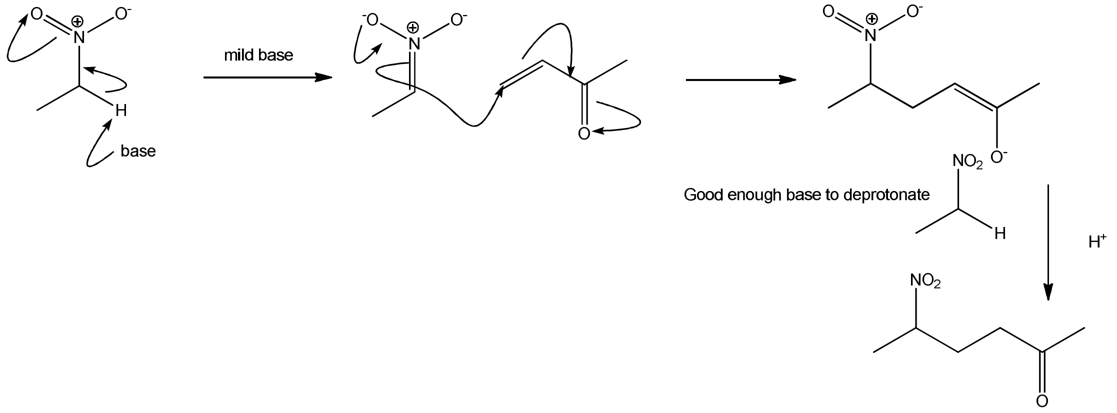


Nitro compounds

- Carbonyl is normally electrophilic at carbon, so to make it nucleophilic, replace carbonyl oxygen with a nitro group.

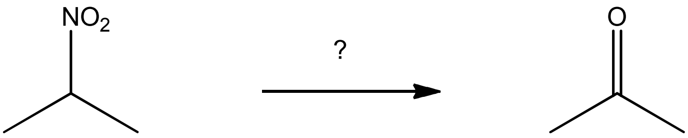


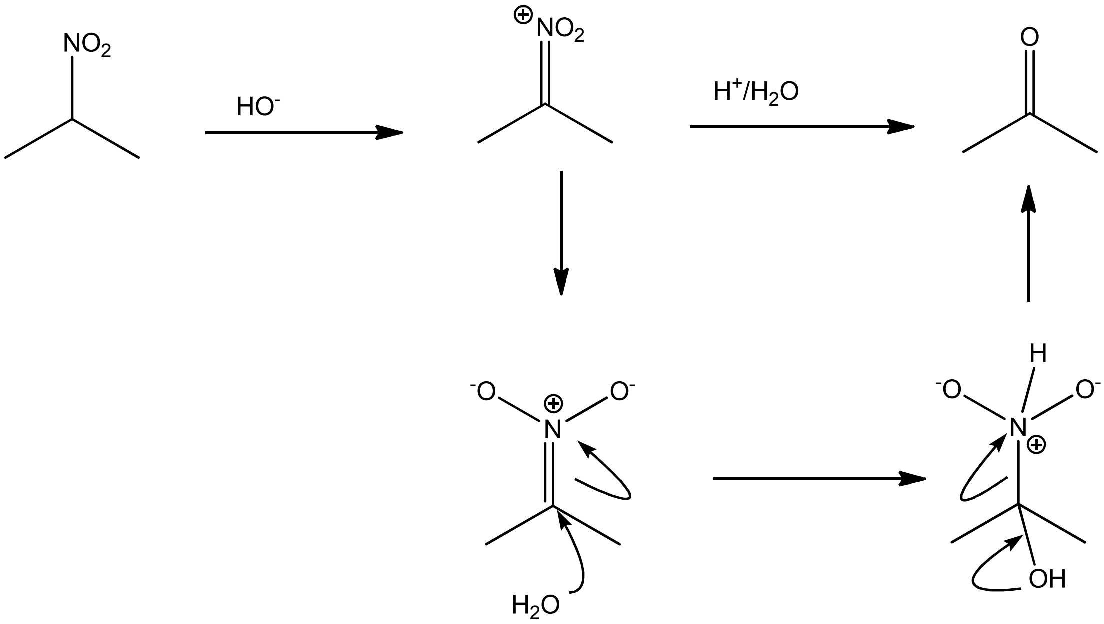




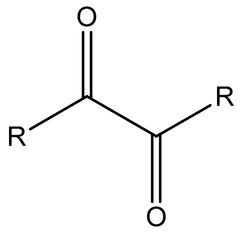
- To re-form the carbonyl from a nitro group, there are 2 main routes: the Nof and McMurray reactions:

Nof reaction:

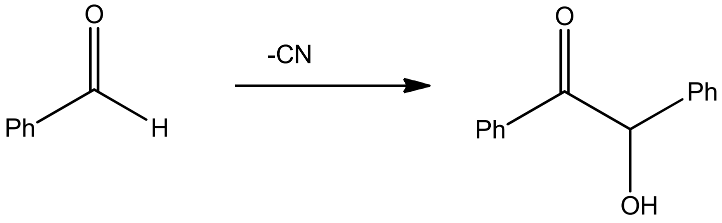




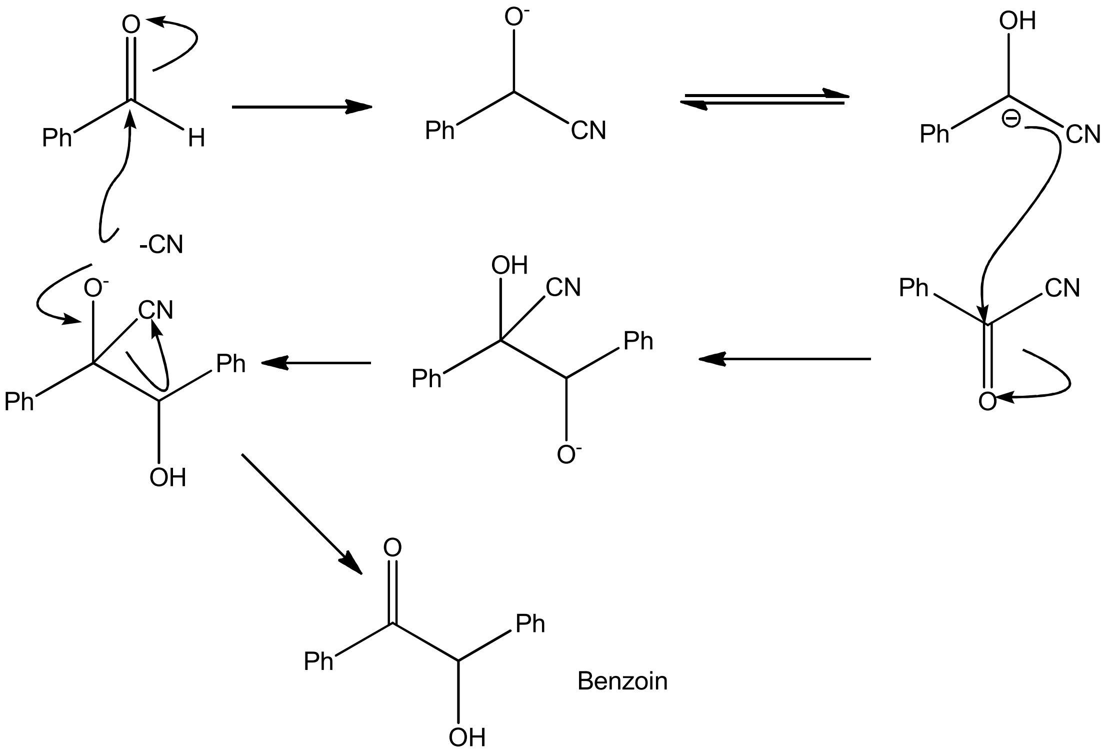
1,2-dicarbonyl chemistry



Benzoin condensation

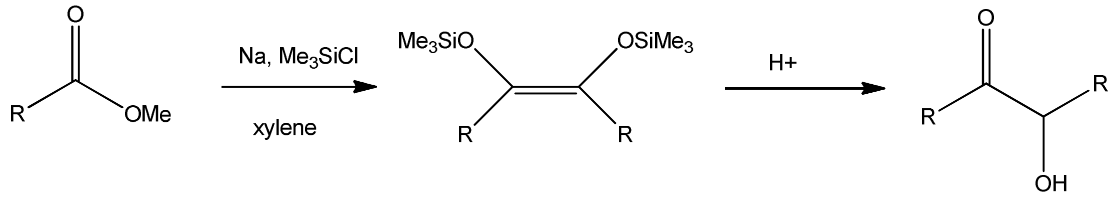


Mechanism



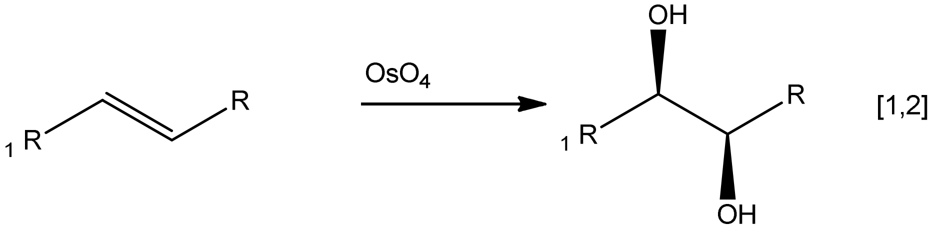
Scheme 16 - The benzoin condensation

Acyloin Reaction



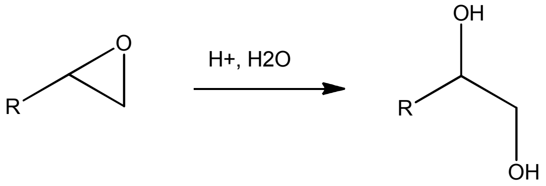
Scheme 17 - The acyloin reaction

Osmylation (dihydroxylation)

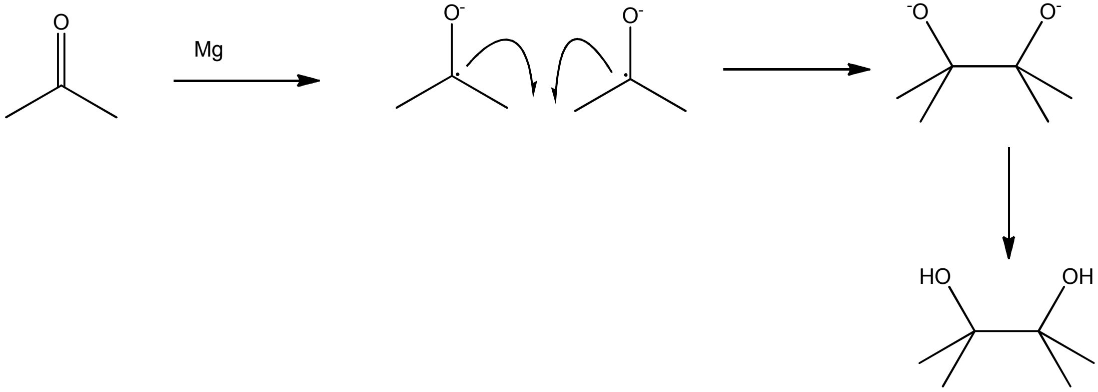


- Other ways to 1,2 dicarbonyls:

Epoxides:



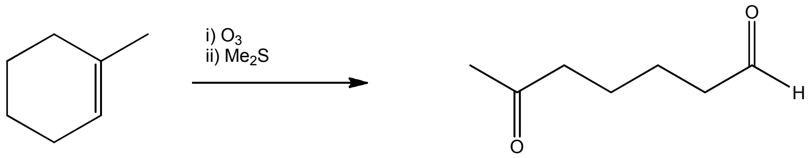
Pinacol:



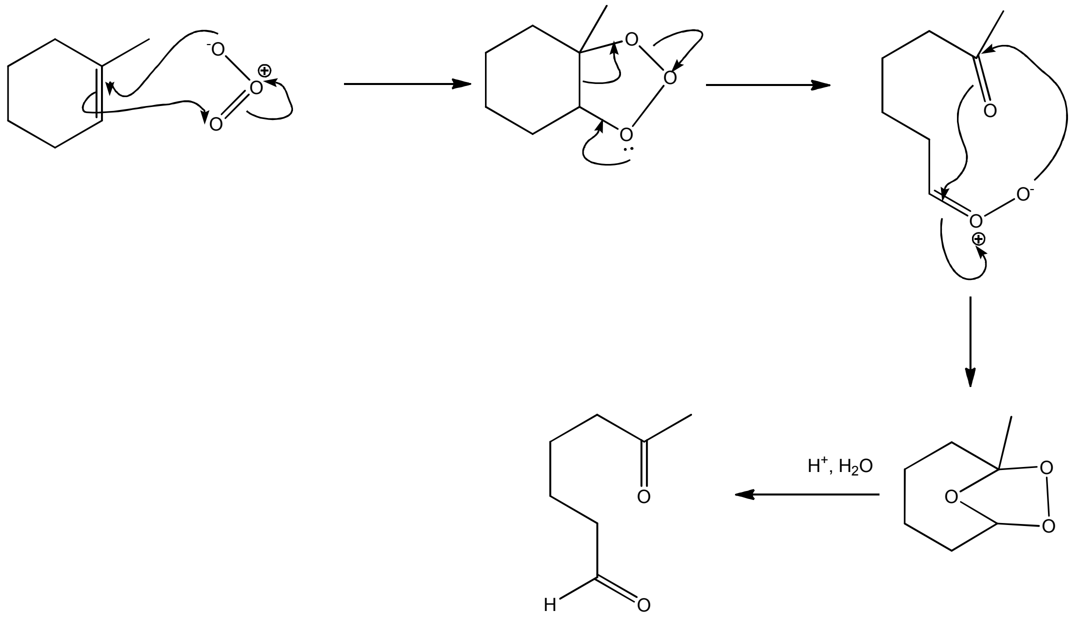
1,6-dicarbonyl chemistry

Ozonolysis

- Reaction of an alkene with ozone splits the alkene double bond leaving two aldehydes.



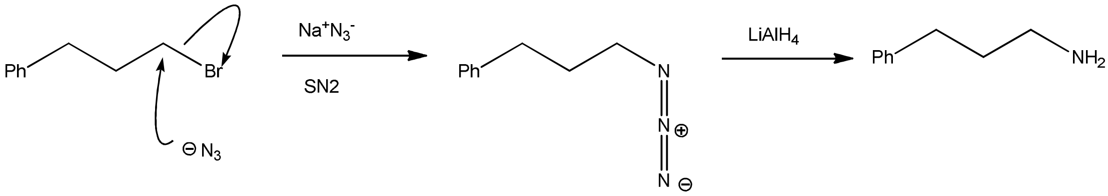
Mechanism



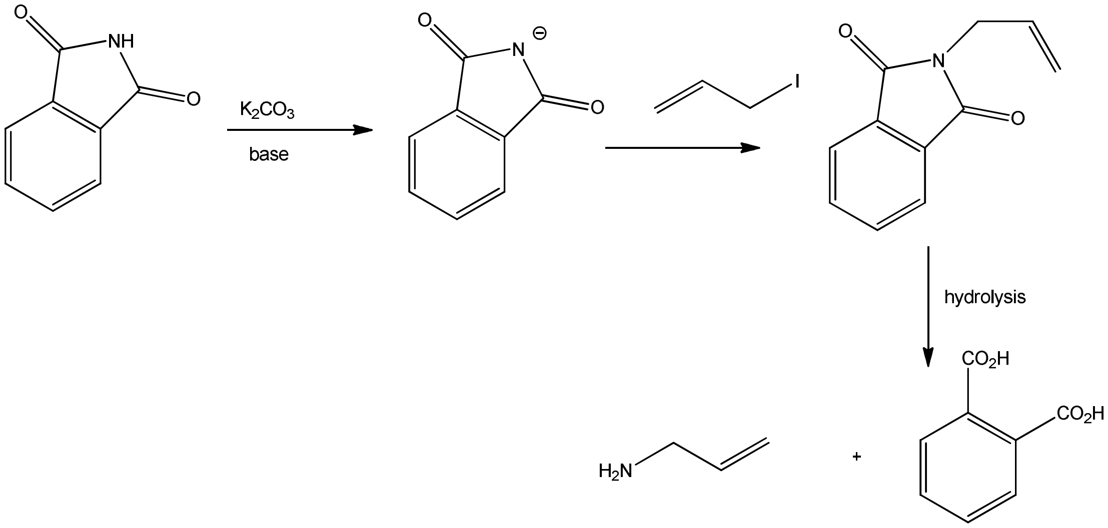
Amines – Professor Willis

Synthesis of amines

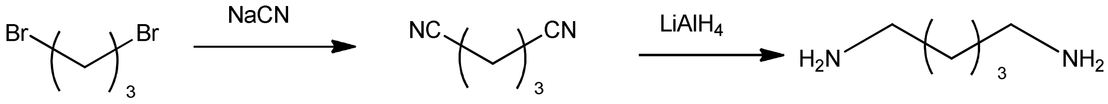
- Amines can be synthesised using azides:



- Gabriel amine synthesis:

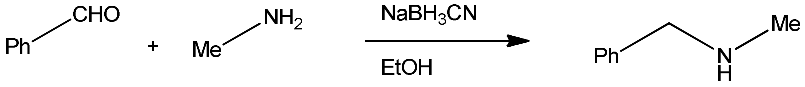


- With the use of cyanide

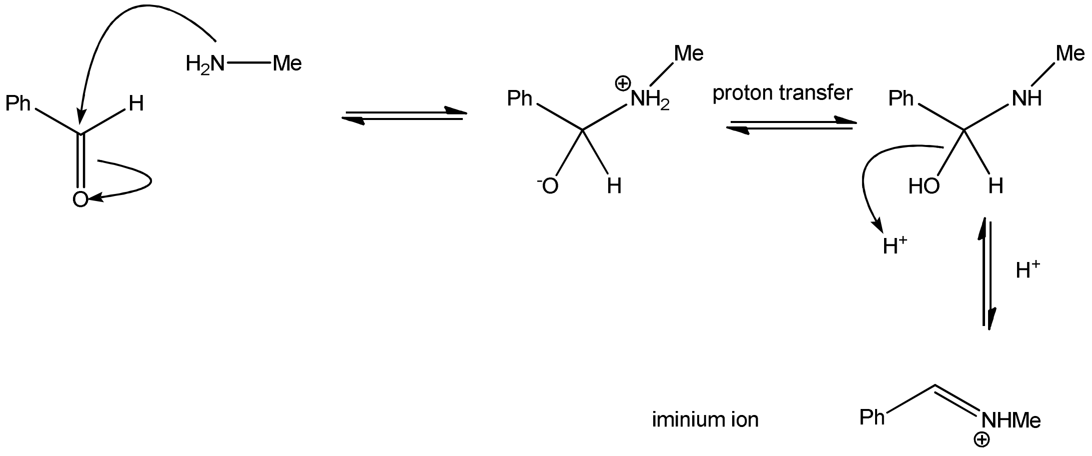


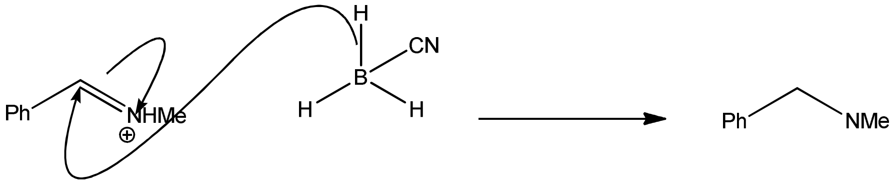
Reductive amination

- Via formation of an iminium ion

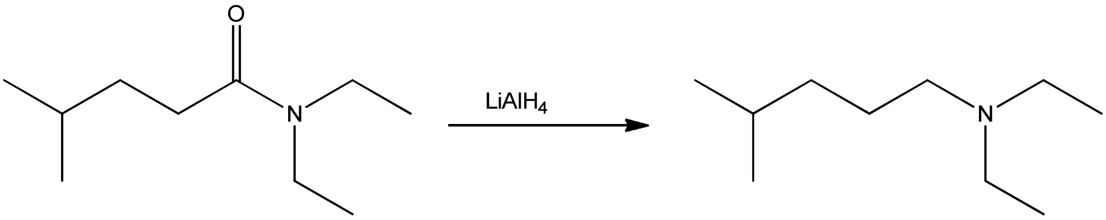


Iminium ion formation

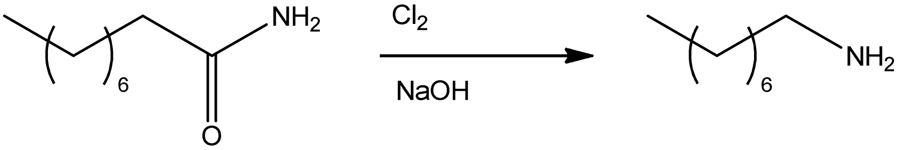




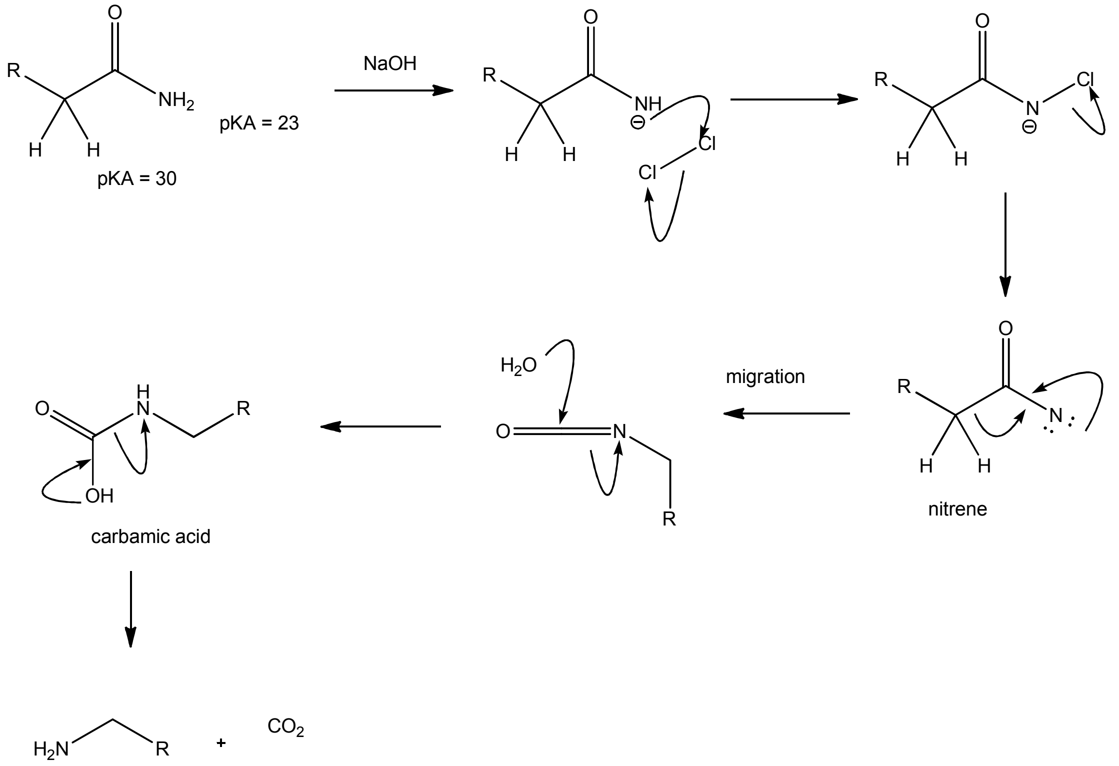
Reduction of amines



Hofmann Rearrangement

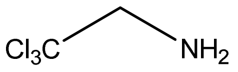


- Mechanism:



- The basicity of nitrongen's lone pair is affected by the environment around nitrogen.
- The lone pair will be less available for protonation (and therefore the nitrogen less basic) if:
  - The lone pair is in an sp or sp^2 hybridised orbital
  - The lone pair is involved in the aromaticity of the molecule
  - The nitrogen is bonded to an electron-withdrawing group.

Example:



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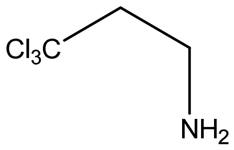

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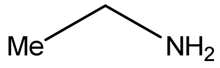
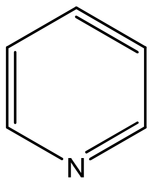
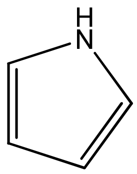


pKB = 3.3

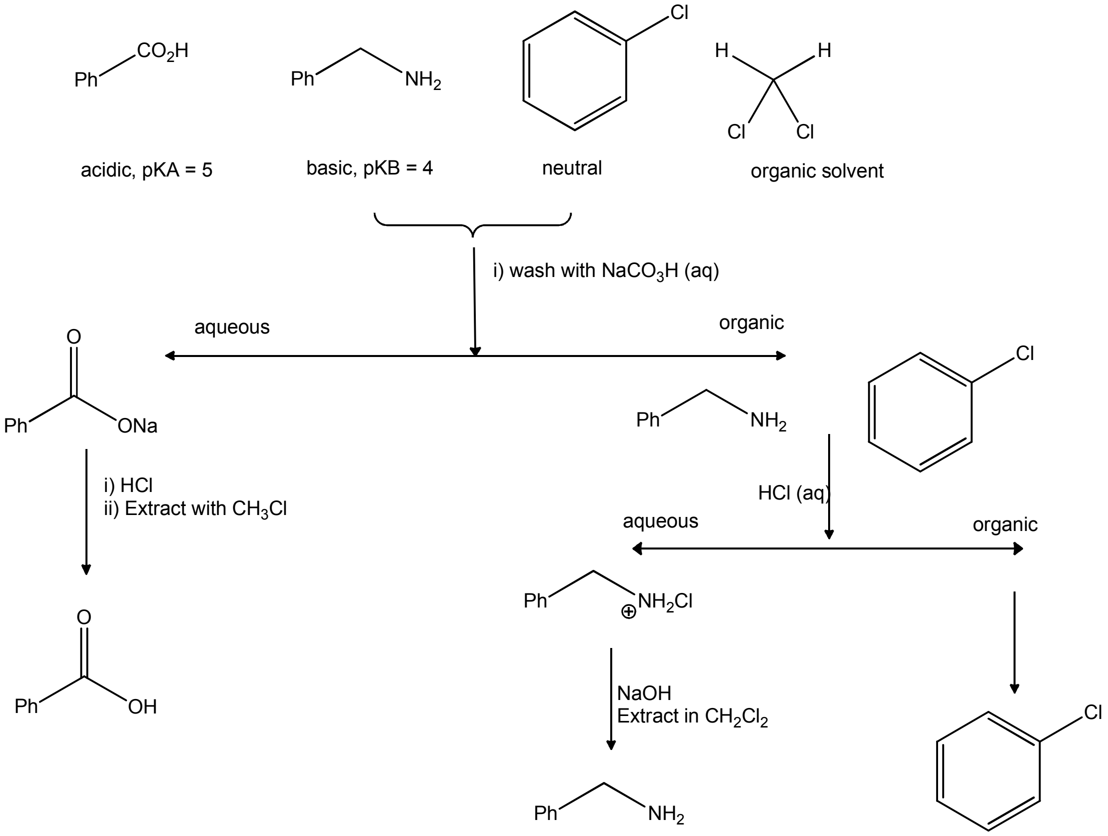


pyridine - pKB = 8.71



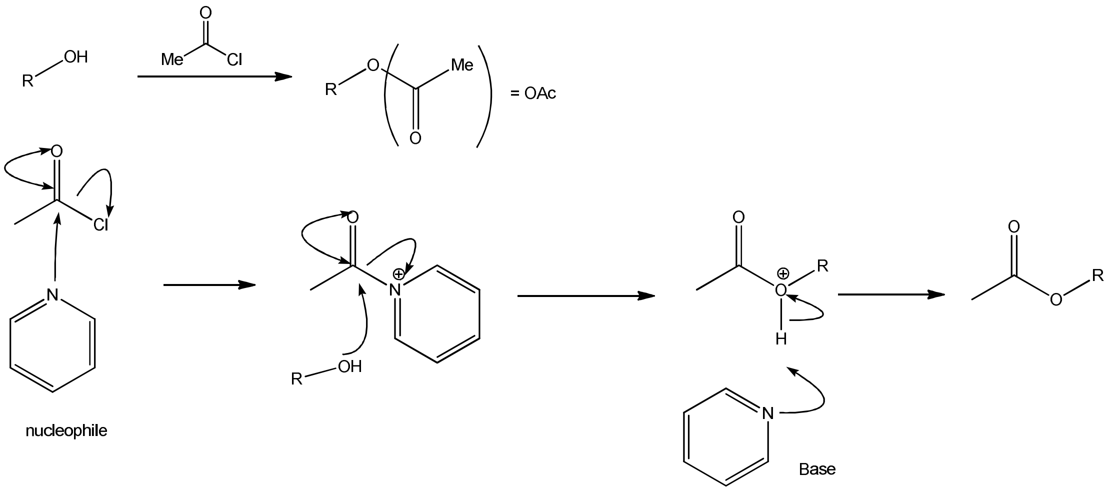
pyrrole - pKB - 18.4

- It is possible to separate mixtures of compounds based on their differing acidity/basicity:



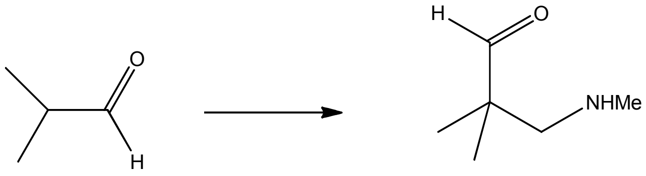
Conversion of alcohol to acetate

- Using pyridine as both base and nucleophile

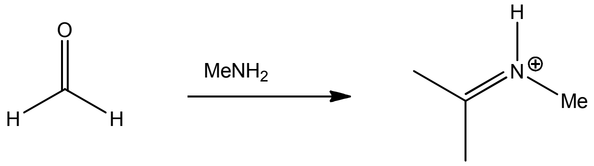


Mannich Reaction

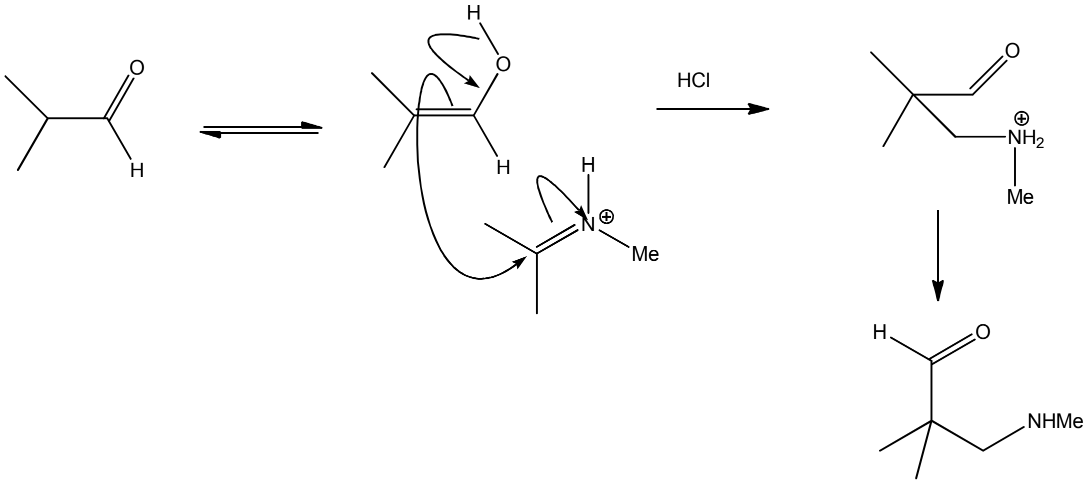
- Uses formaldehyde and $HNMe_2$ to form a reactive iminium ion which is used to add an amine.



Iminium ion:

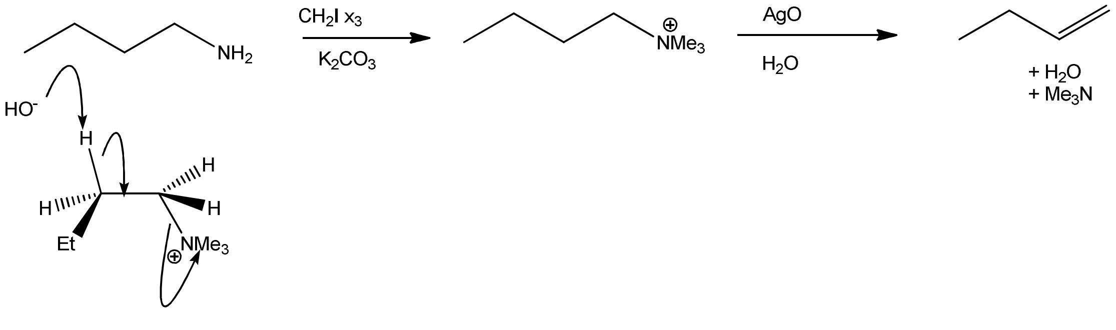


Mannich reaction

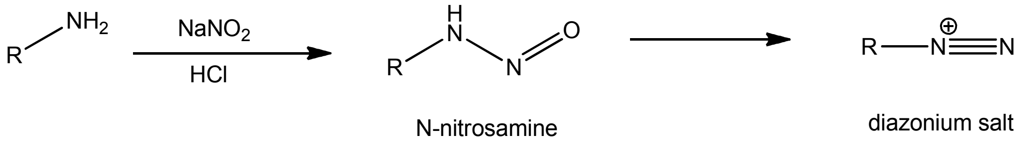


Hofmann Elimination

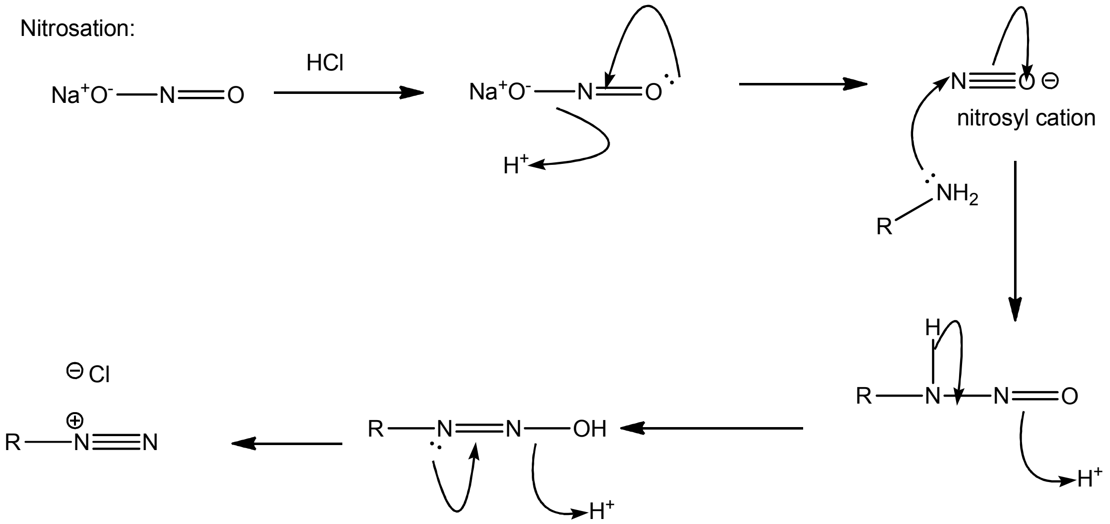
Generation then elimination of tertiary amine (good leaving group) to produce alkene.



Nitrosation of amines

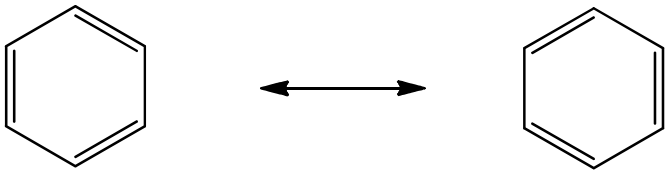


Nitrosation:

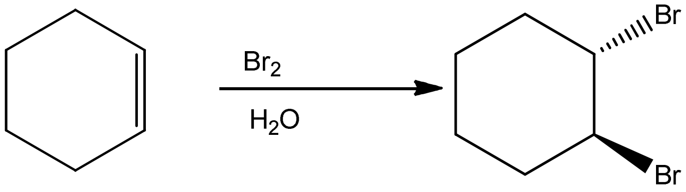


Electrophilic Substitution of Benzene – Professor Simpson

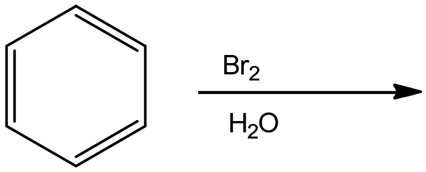
Introduction



- Benzene has delocalisation or resonance stabilisation, making it more stable than the analogous non-delocalised ‘cyclohexatriene’
- Reactions of benzene are different from the typical alkenes, for example:

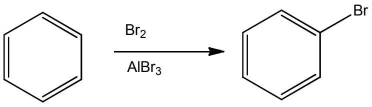


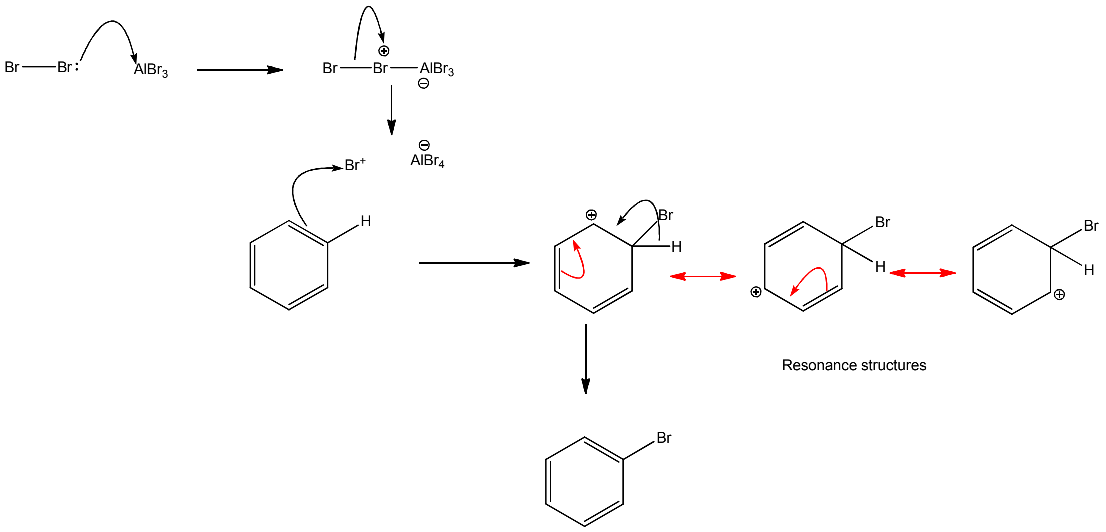
Electrophilic addition



No reaction

- A Lewis acid must be used to brominate benzene

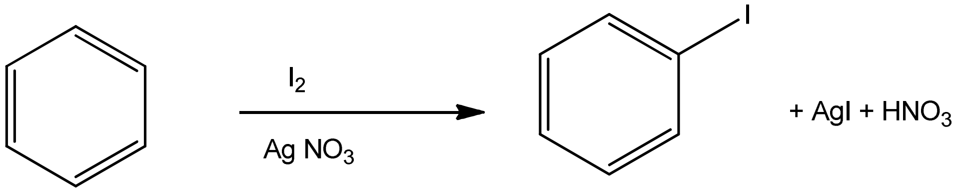




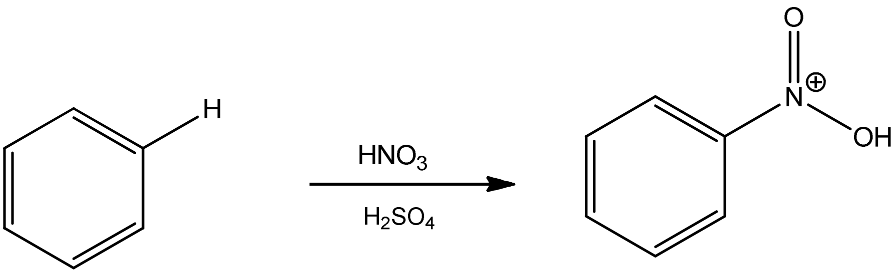
- All reactions with benzene occur in the order:
    - Addition + Elimination = Substitution

Halogenation

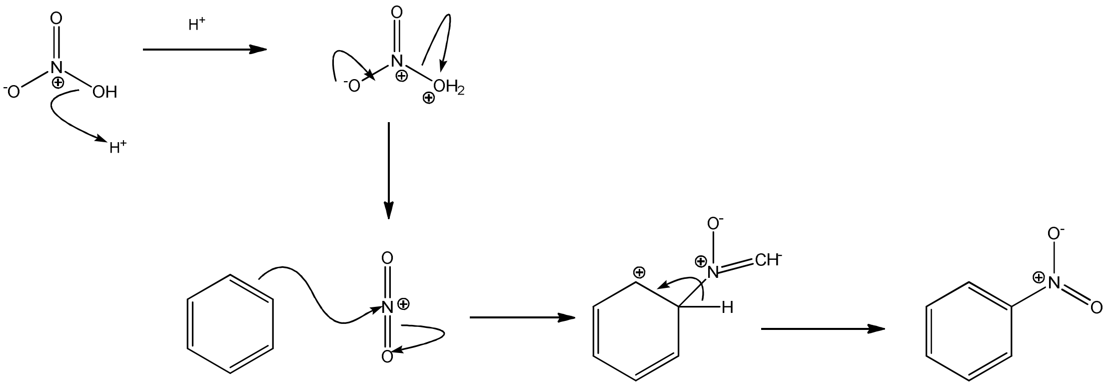
- The Lewis acid method works for:
    - Cl - exothermic
    - Br – exothermic
    - I - endothermic



Nitration

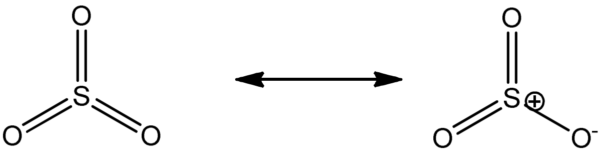


- Reaction occurs via a reactive nitro cation

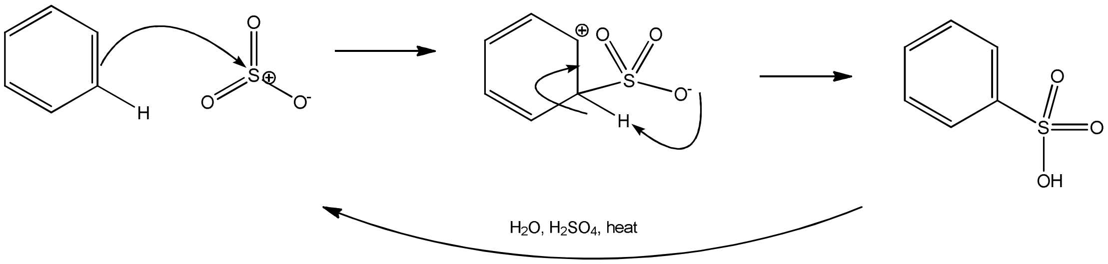


- Trinitrophenol (picric acid) is explosive
- Nitrobenzene can be reduced with $LiAlH_4$ to aniline

Sulphonation

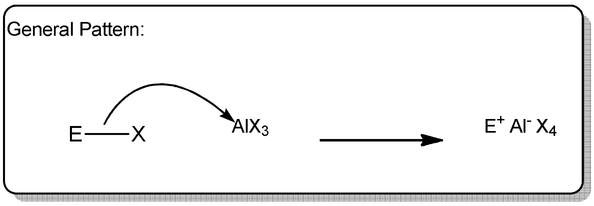


- Sulphonation is reversible

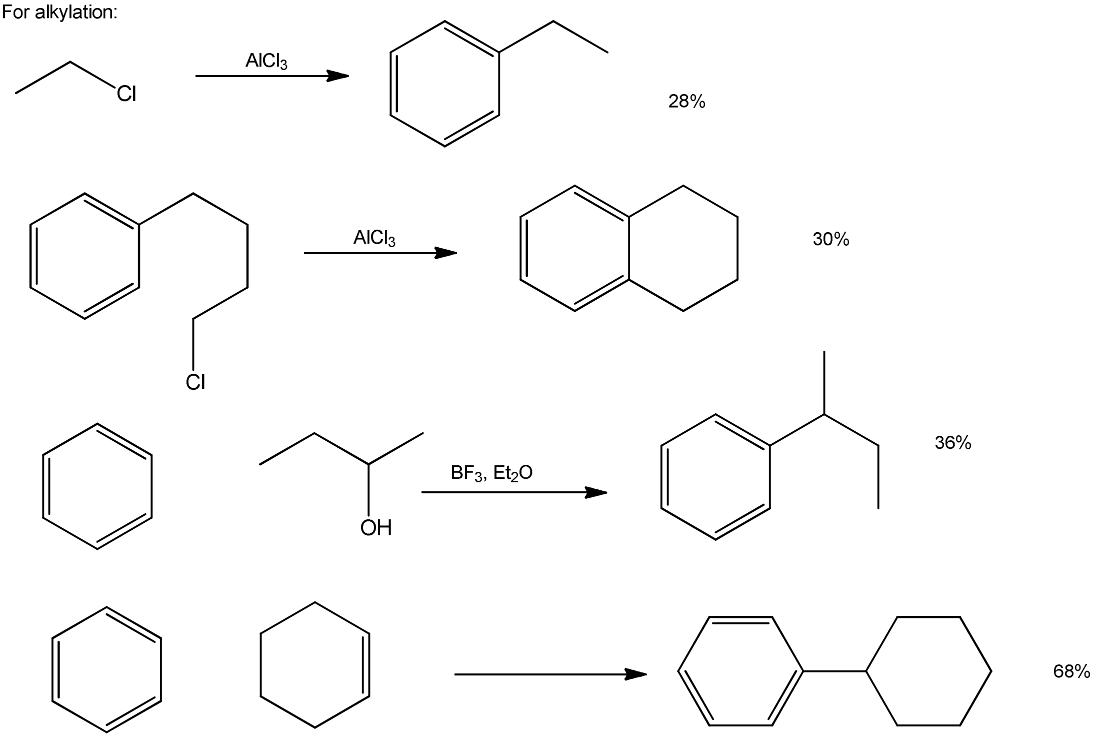


Friedel-Crafts alkylation

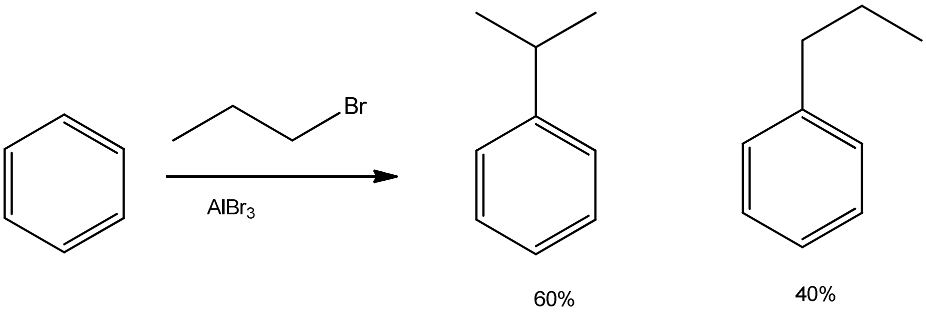
- Method of bonding alkyl chains to aromatic rings

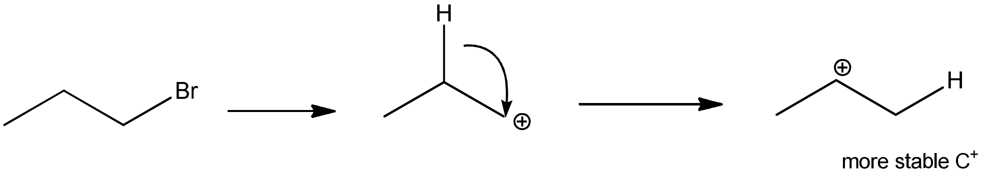


For alkylation:

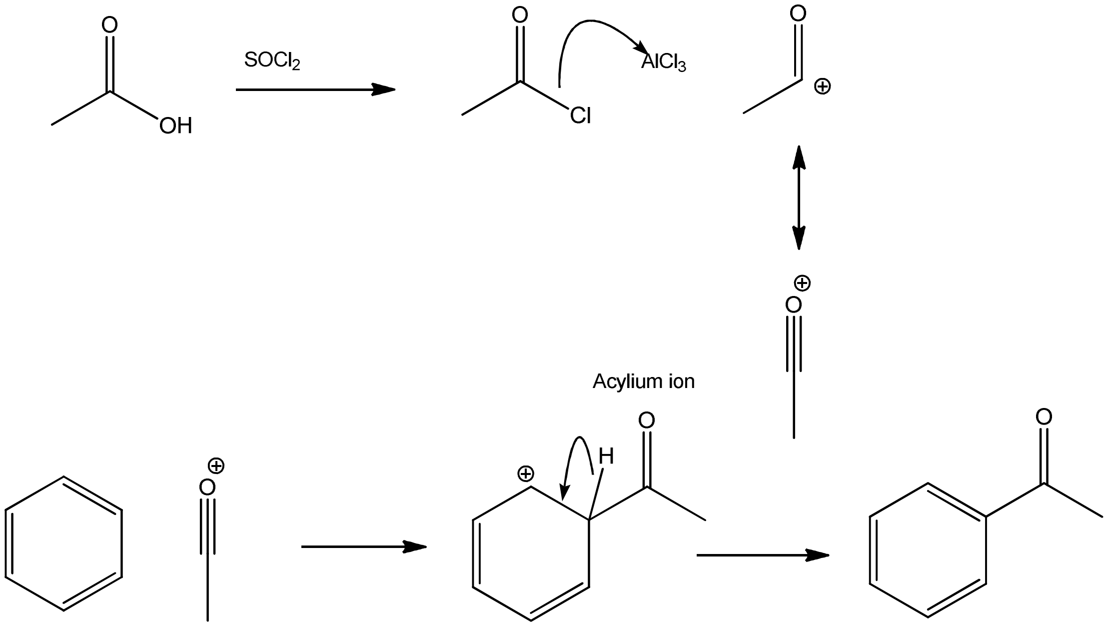


- Limitations:
  - Alkyl group activity, caused by positive induction effect, means that the product is more reactive than the starting material, so multi-alkylations can occur
  - Carbocation rearrangement – alkyl chain will rearrange to give most stable carbocation, meaning desired alkylation will not always occur.
- Example: n-propyl benzene:

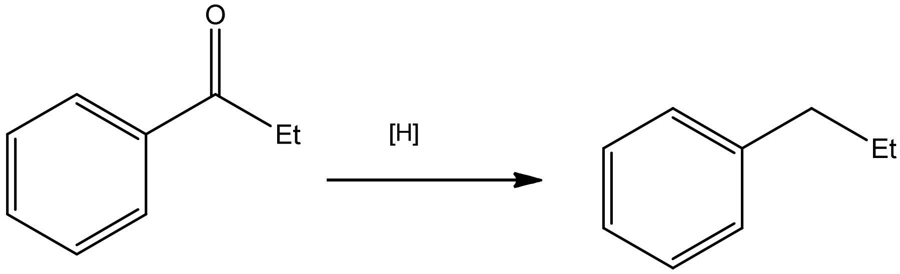




Friedel Crafts Acylation

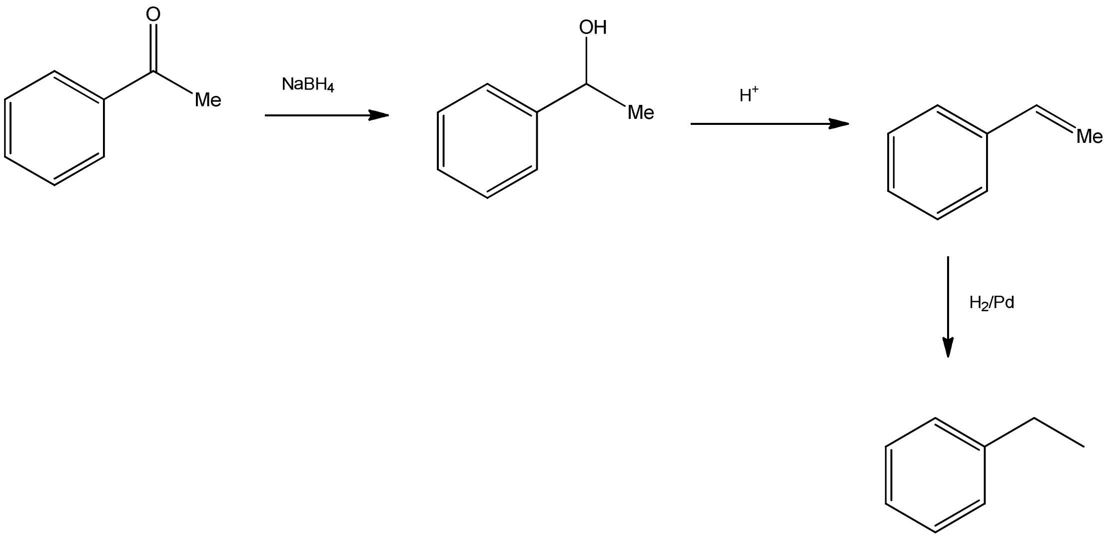


- Using acylation prevents the effects of carbocation rearrangements, allowing, for example, n-propyl benzene.
- Acyl groups are deactivating, so poly alkylation is avoided.

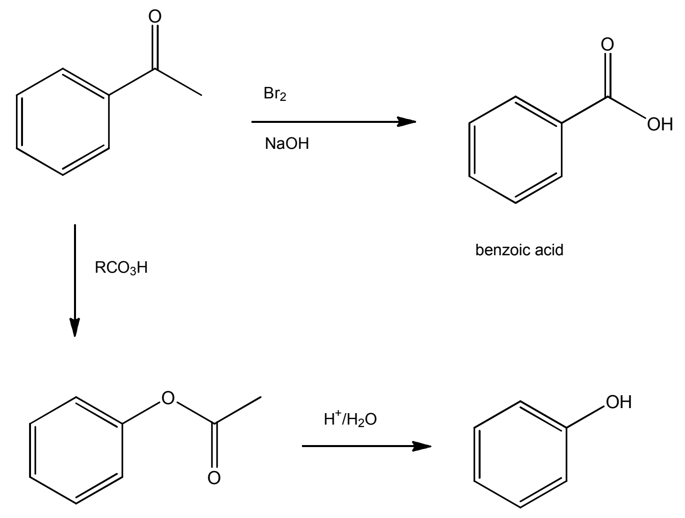


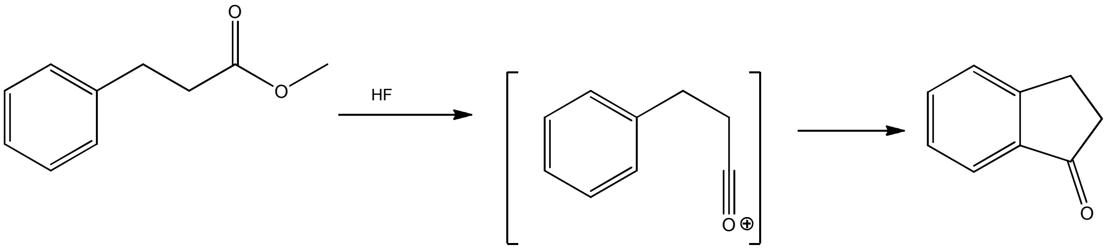
- Reduction of the carbonyl can be done in several ways:
  - Elemmensen: Zn (Hg) / HCl
  - Wolff-Kischner reduction: $H_2N\text{-}NH_2$, KOH, ethylene glycol

Reduction:



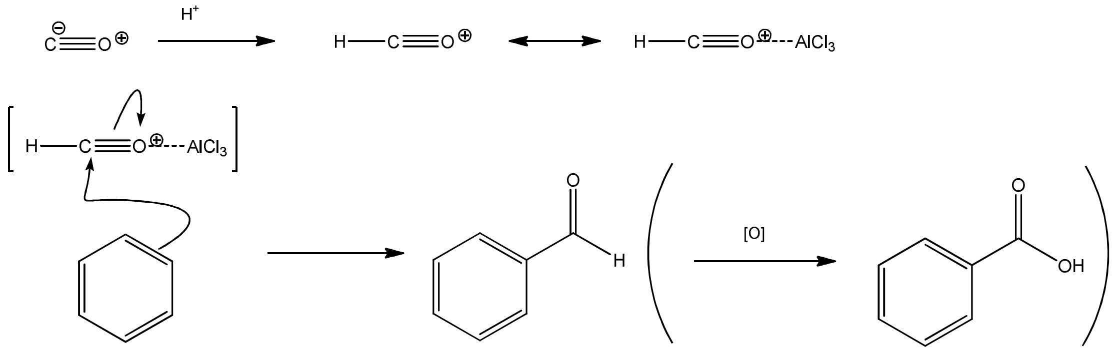
- Acylated benzene is very versatile:



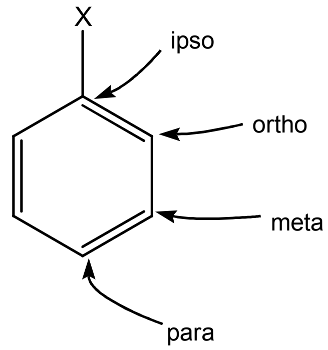


Gatterman-Koch reaction

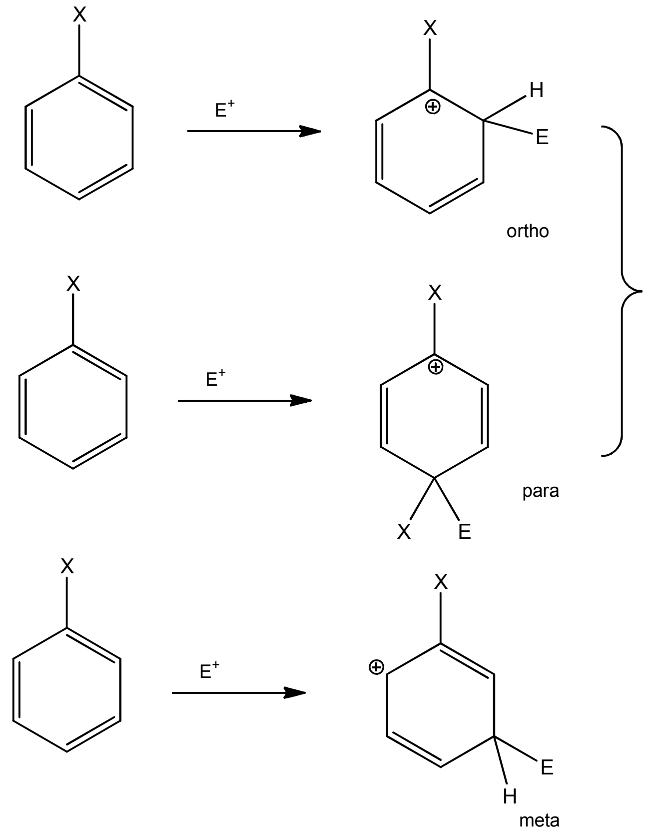
- Produces benzaldehydes using carbon monoxide and HCl in a Friedel-Crafts acylation-type method.



Further substitution of mono-substituted benzene



- Substituent X has two main effects:
  - Activate or deactivate
  - Direct position of future substitution
- Substituents are divided into two types depending on their effects on further substitution:
  - Those that activate/deactivate by inductive effects
  - Those that activate/deactivate by resonance effects



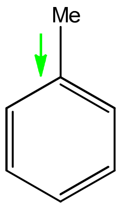
Ortho/Para directing

For ortho/para direction,
must have resonance form
with +ve charge at ipso

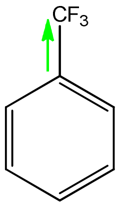
Meta directing

+ve charge can't delocalise onto ipso position

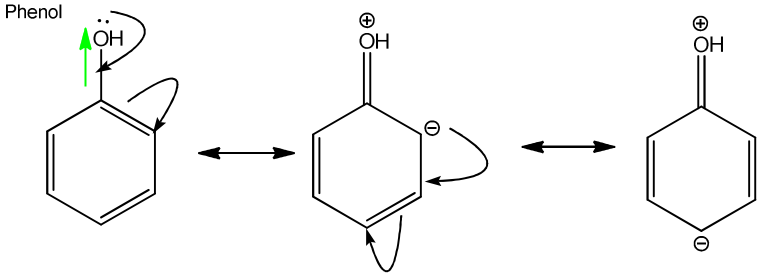
- If X donates electrons: destabilisation and therefore o/p directing
- If not, then m directing



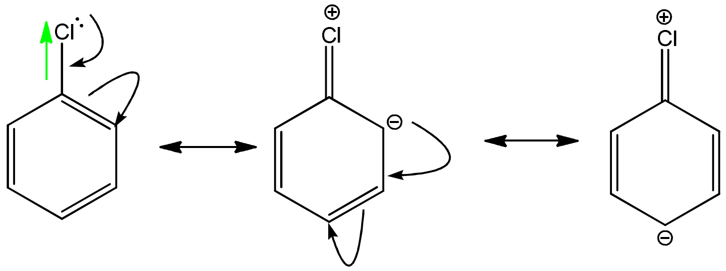
Activating (o/p)



Deactivating (m)



- In the case of phenol, the resonance effects >> inductive effects, making phenol a very activating substituent.
- Halogens are deactivating due to their electronegativity but can donate lone pairs. The resonance effects this causes mean halogens direct o/p

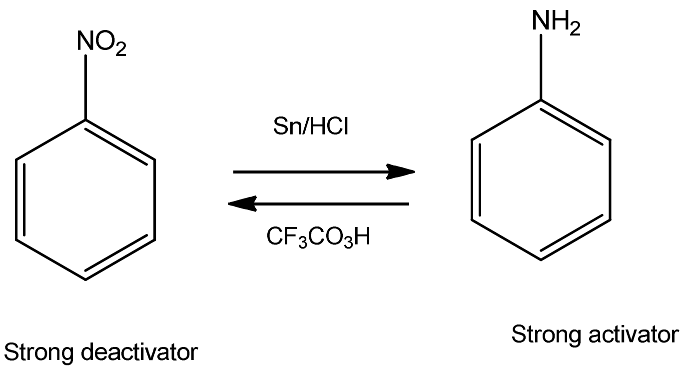


- Other activating groups (o/p directing)
  - NH_2, NHR, NR_2, OH, OR

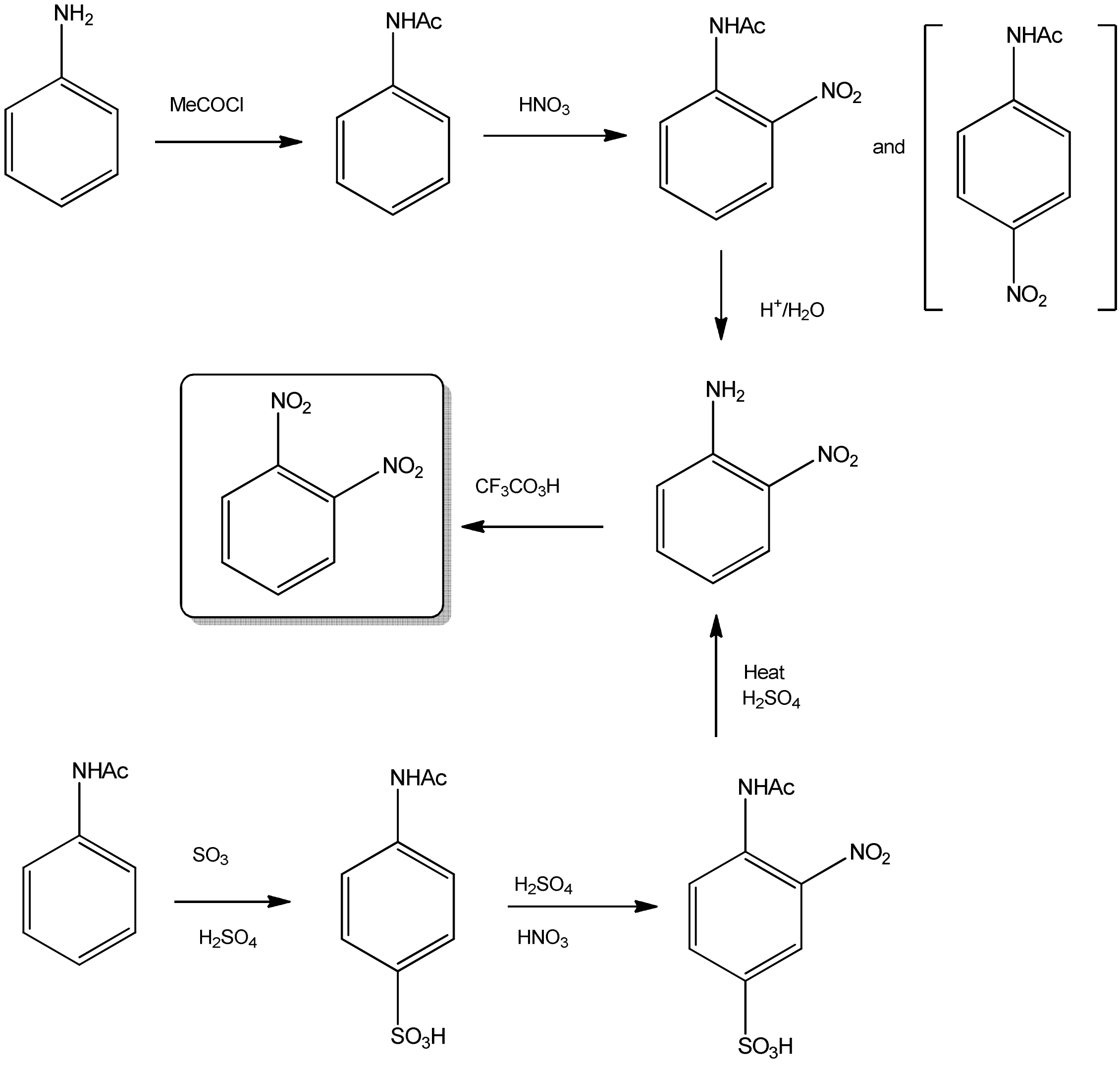
- Other deactivating groups (m directing)
  - CO_2H, NO_2

Substituent effects when more than one substituent is present

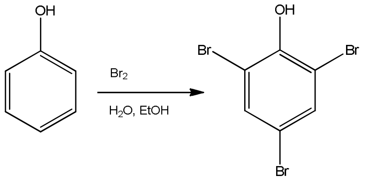
- If substituent effects reinforce each other, i.e. two o/p directing groups, then no problems arise.
- If there is a clash, strongly activating/deactivating groups will dominate over weak activating/deactivating groups.
- It can be useful to manipulate the substituents and use blocking groups to achieve the desired product if substituent effects cause a problem.



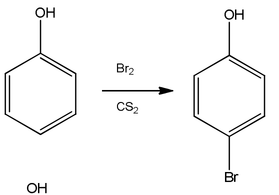
- How do you make *o,m*-nitrobenzene?



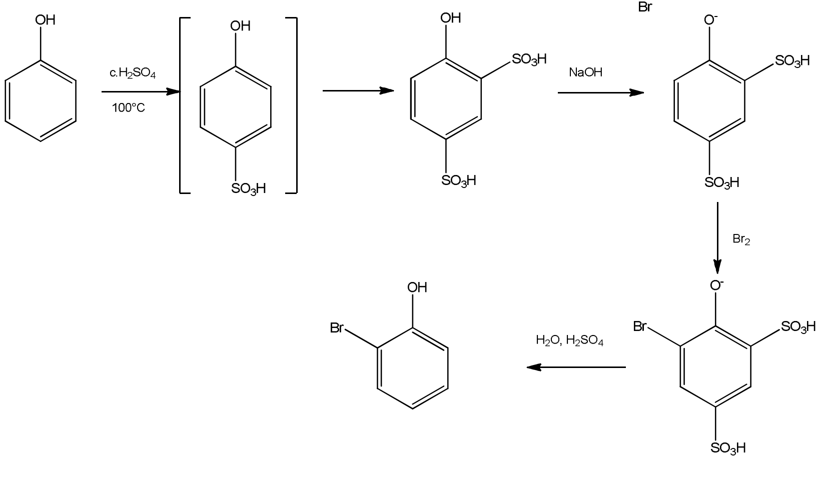
- Use of blocking groups can improve the yield. Sulphonic acid groups can be removed easily and in the case above block the para position from substitution under nitration, meaning only ortho nitration can occur.
- For example, in bromination:



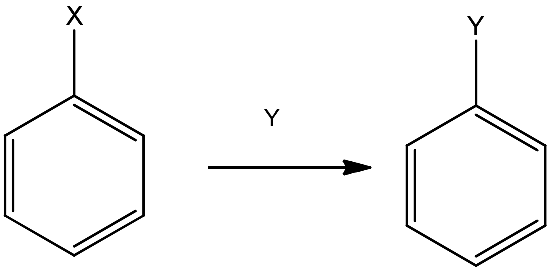
How can only p-bromophenol be made?



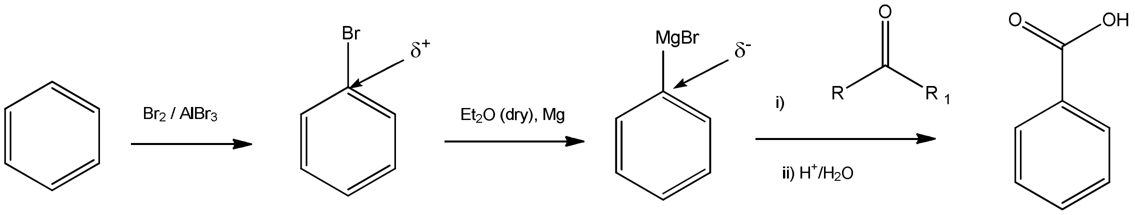
How can only m-bromophenol be made?



Ipso substitution

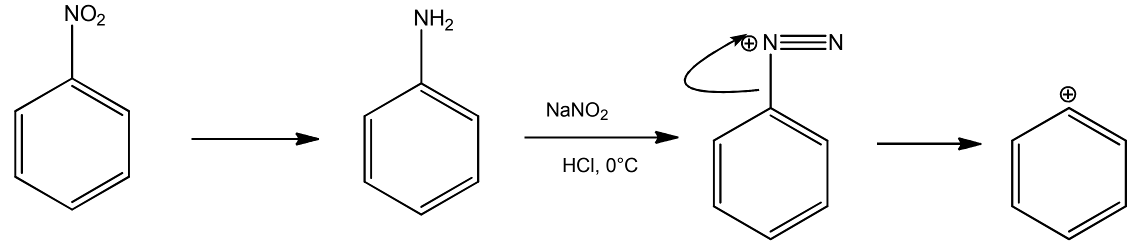


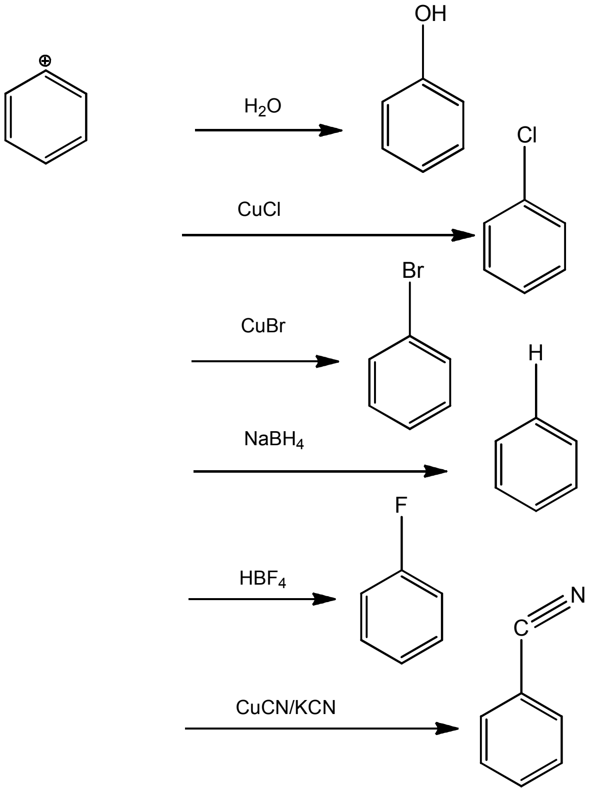
Grignards



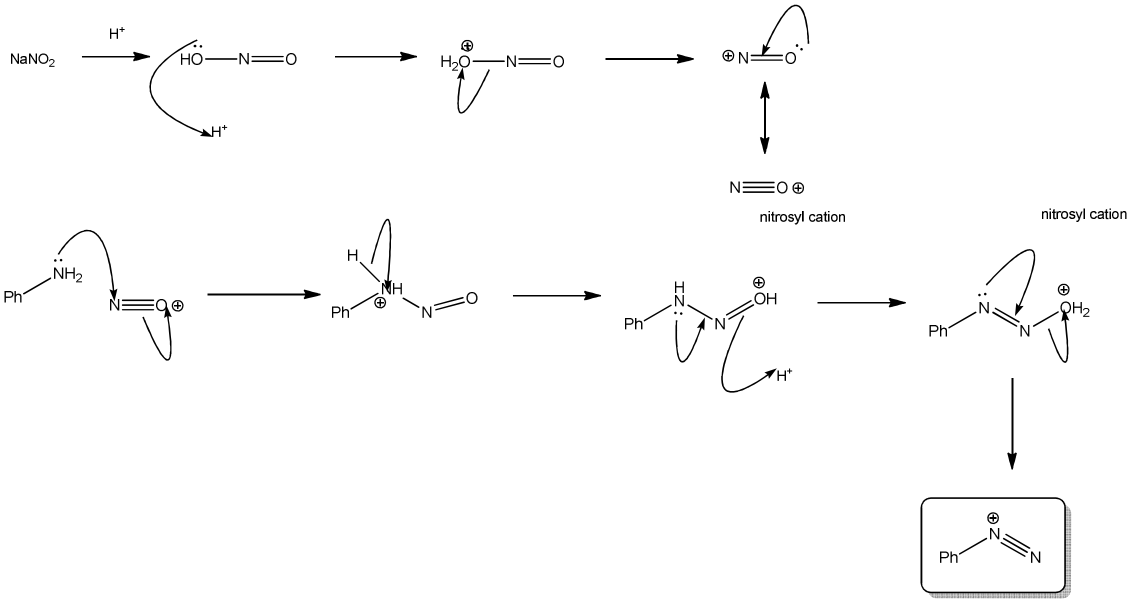
Substitution via diazonium salts

- Diazonium salts provide a means of achieving a range of substitutions selectively.



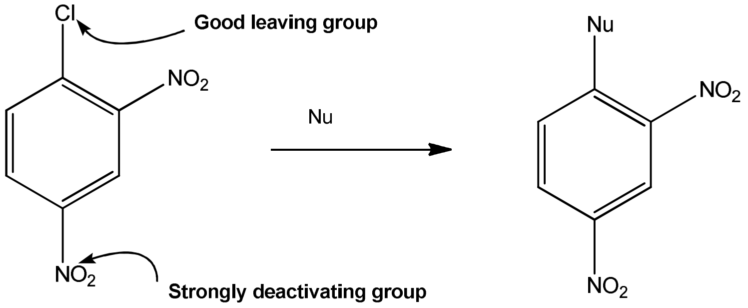


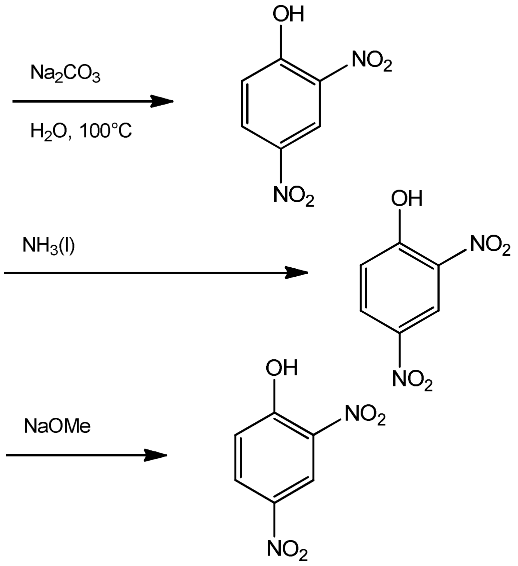
- Mechanism:



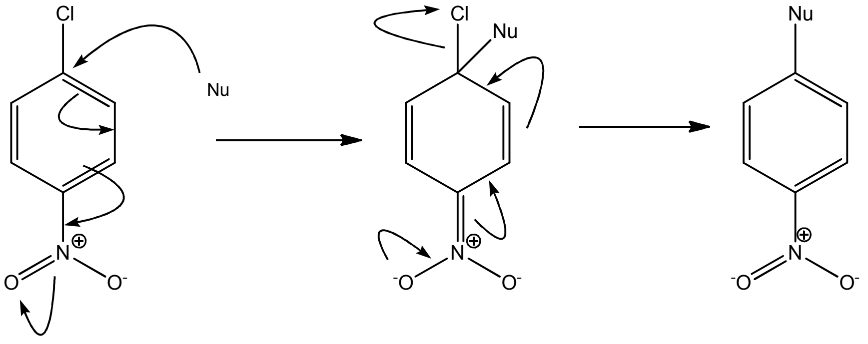
Aromatic Nucleophilic Substitution

- Can be done when a good leaving group is present with a deactivating (electron withdrawing) group which can stabilise the anion.



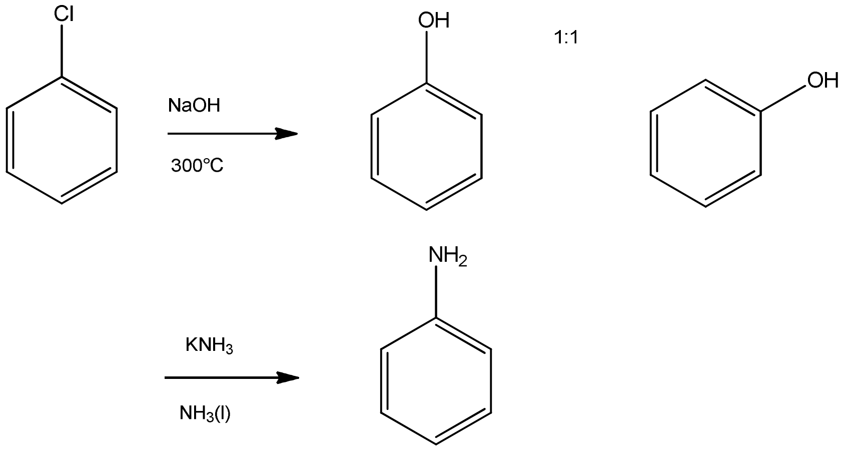


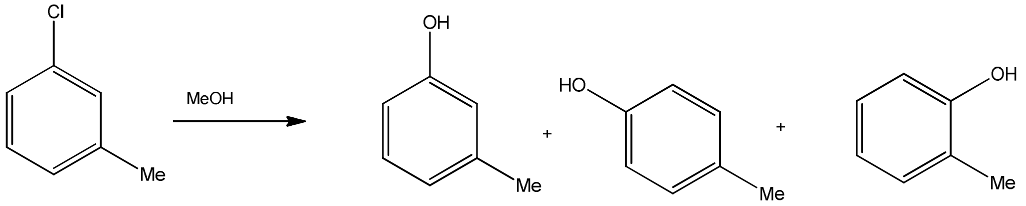
- Mechanism:

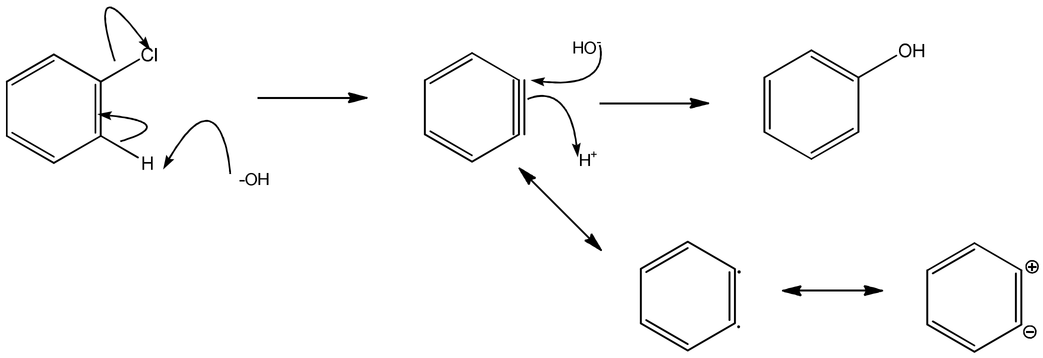


Benzyne

- Elimination can yield an alkyne-type triple bond in a ring:

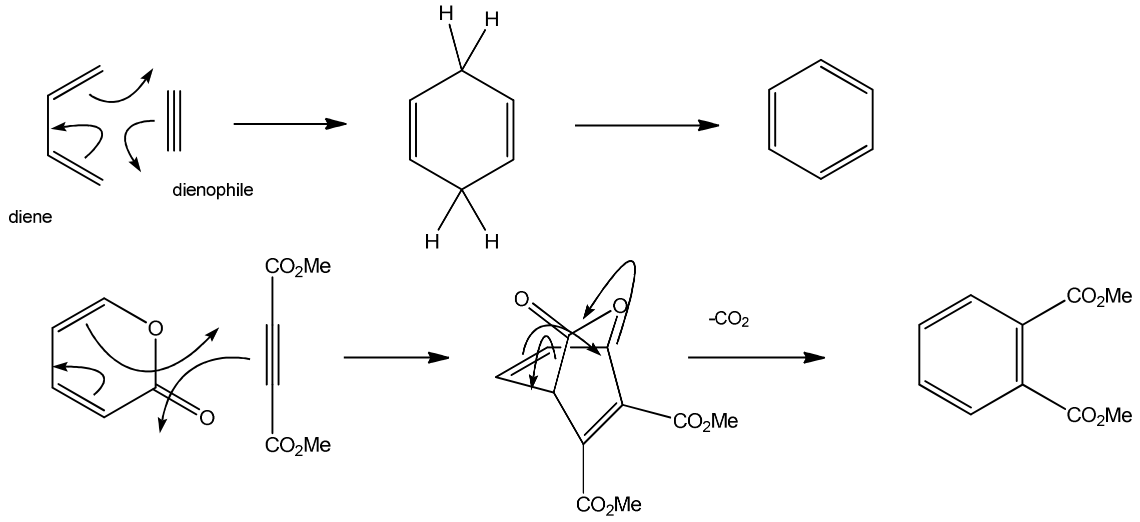




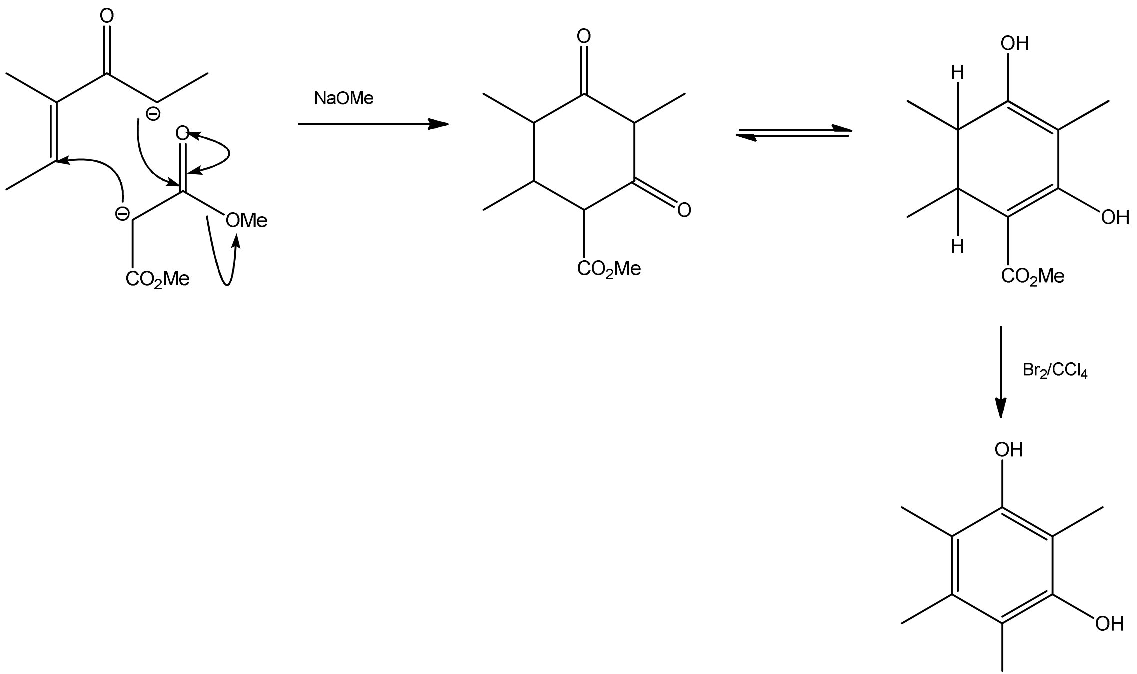


Other methods of synthesising benzene derivatives

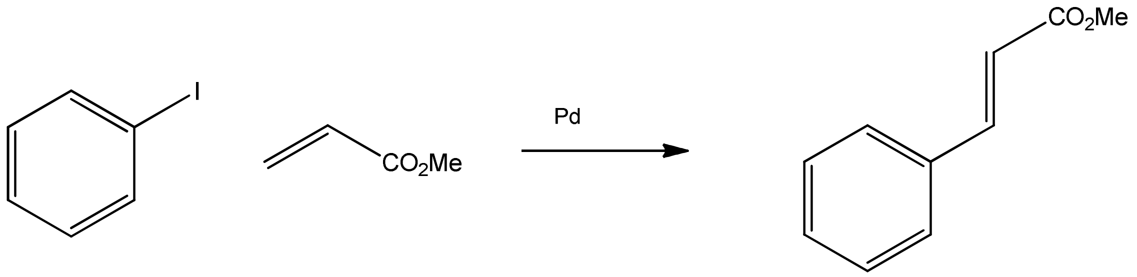
- Diels-Alder (cycloaddition)



- Carbonyl condensation chemistry:

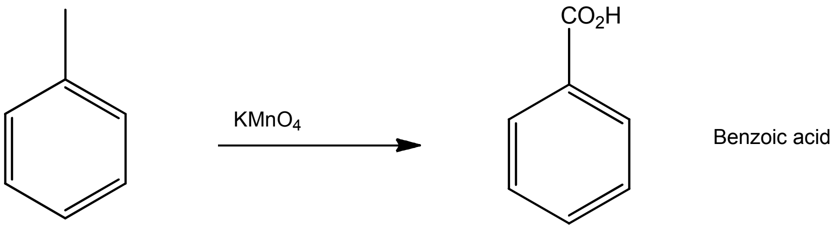


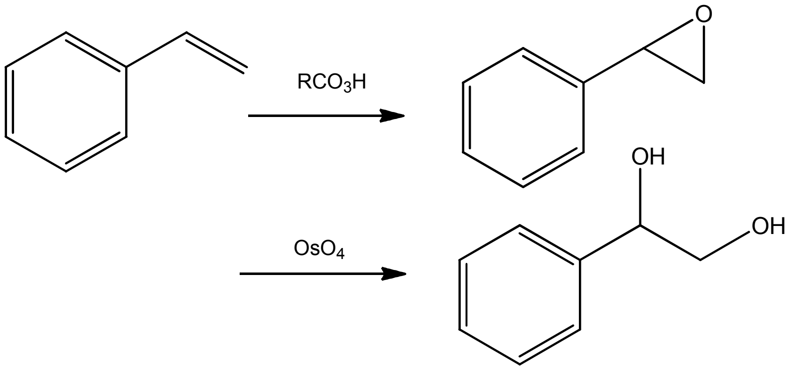
- Pd catalysis

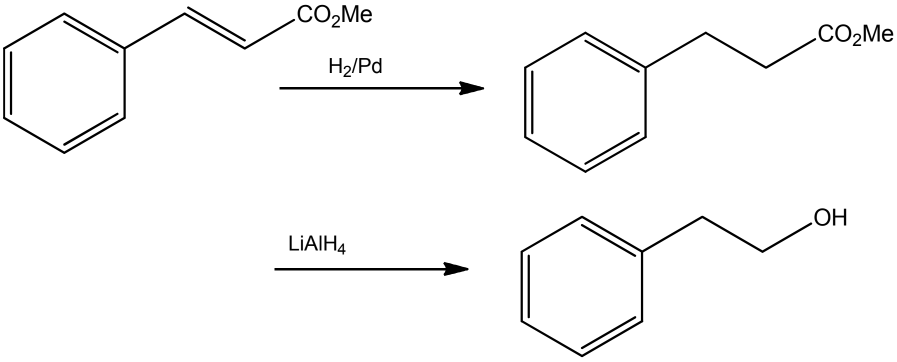


Miscellaneous Reactions

- Aromatic rings are resistant to reduction and oxidation

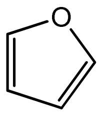


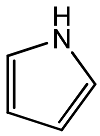


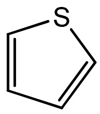


Heterocyclic Chemistry – Professor Booker-Milburn

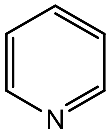
- Two classes of heterocycles:
  - Aromatic:
    - 5-membered:


Furan

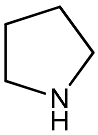

Pyrrole

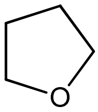

Thiophene

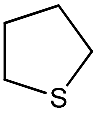
    - 6-membered:

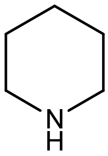

Pyridine

  - Saturated:


pyrollidine

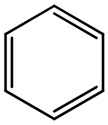

THF

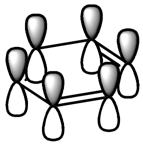

tetrahydrothiophene


piperidine

Heteroaromaticity

- Recall benzene:



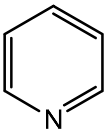


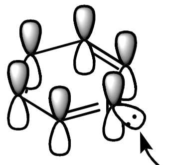
6 pi-electrons in a
delocalised cyclic pi-cloud

- For a system to be aromatic, Huckel's rule must be obeyed:

Number of conjugated pi-electrons = 4n + 2

- Pyridine:

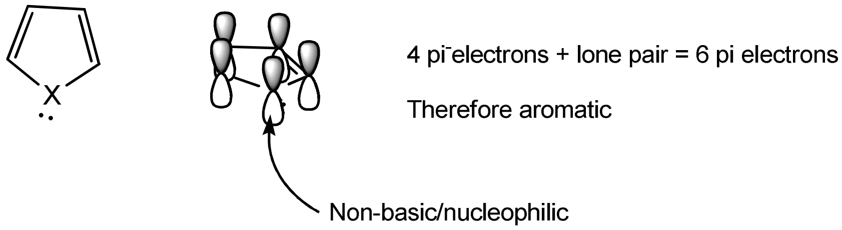




Lone pair is at 90° to the pi-cloud,
therefore is not involved in aromaticity

Basic/nucleophilic

- 5 membered heteroaromaticity:



4 pi electrons + lone pair = 6 pi electrons

Therefore aromatic

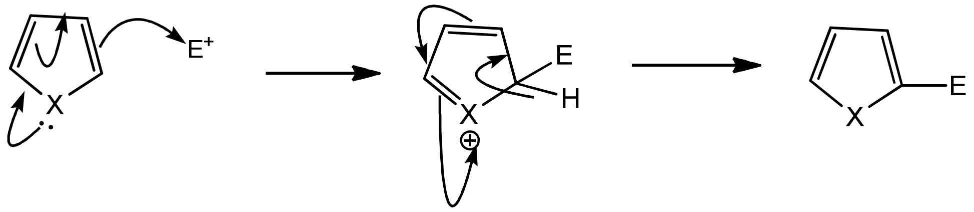
Non-basic/nucleophilic

- 5-membered heterocycles are more electron-rich than benzene – “pi-excessive” heterocycles
- These heterocycles are much more reactive than benzene in aromatic substitution

Pyrrole > Furan > Thiophene >> Benzene

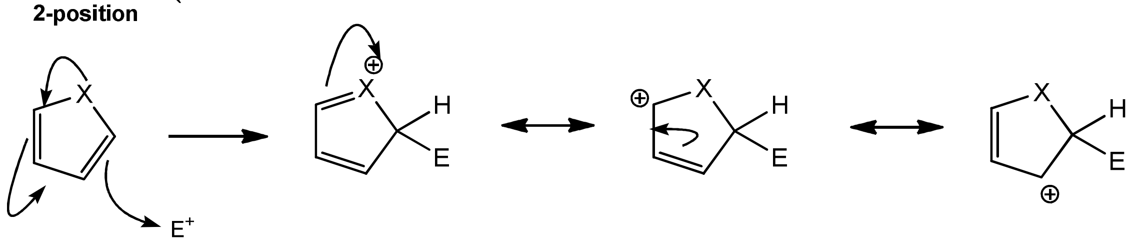
Electrophilic Substitution

- Reaction occurs at the 2 position in first instance

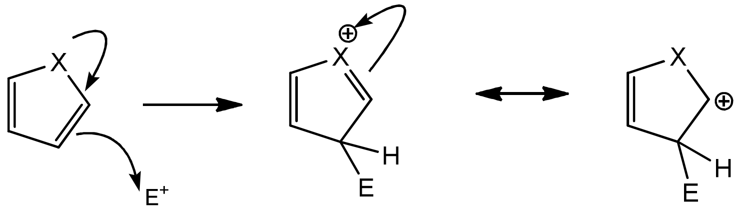


- It is possible to predict that the 2 position is favoured for reaction over the 3 position by considering resonance forms.

2-position

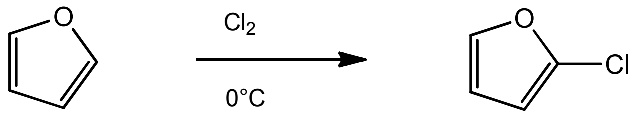


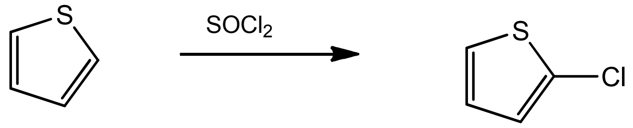
3 position

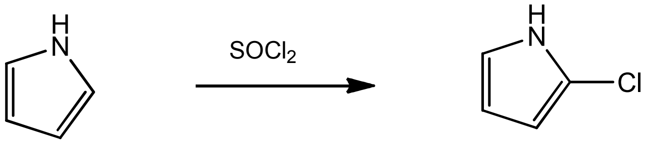


- The 2 position is favoured because there are 3 ways of delocalising the positive charge around the ring compared with only 2 when substitution occurs at the 3 position

Halogenation

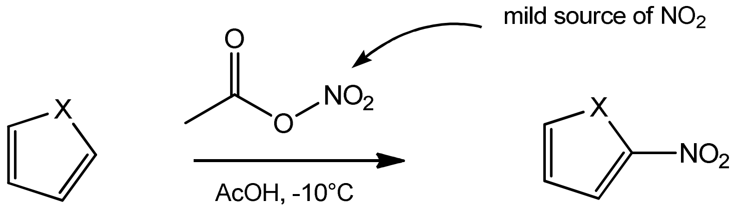






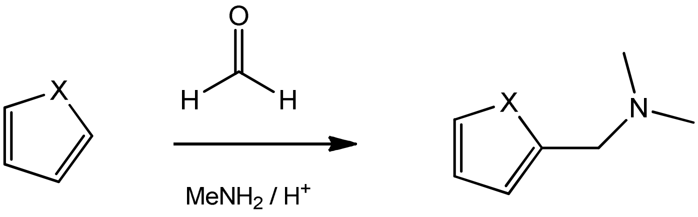
- Since these heterocycles are more reactive than benzene, a Lewis acid catalyst is not needed.

Nitration



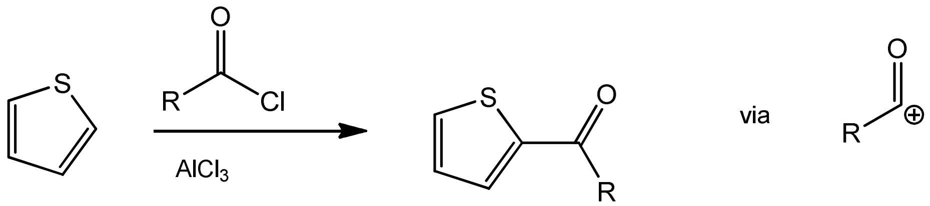
mild source of NO_2

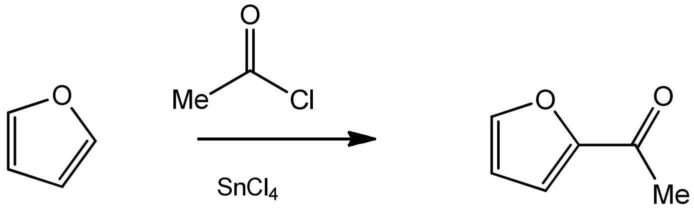
Mannich reaction



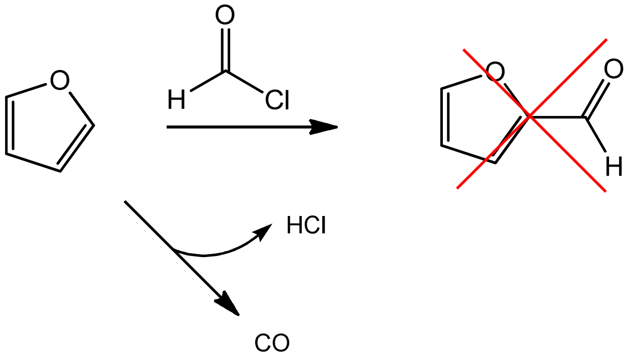
Via $Me_2N{=}CH_2$

Friedel-Crafts Acylation



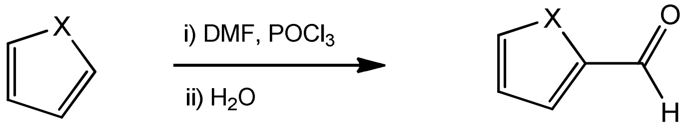


- No Friedel-Crafts reaction exists for R = H, i.e. aldehydes cannot be made via a Friedel-Crafts reaction

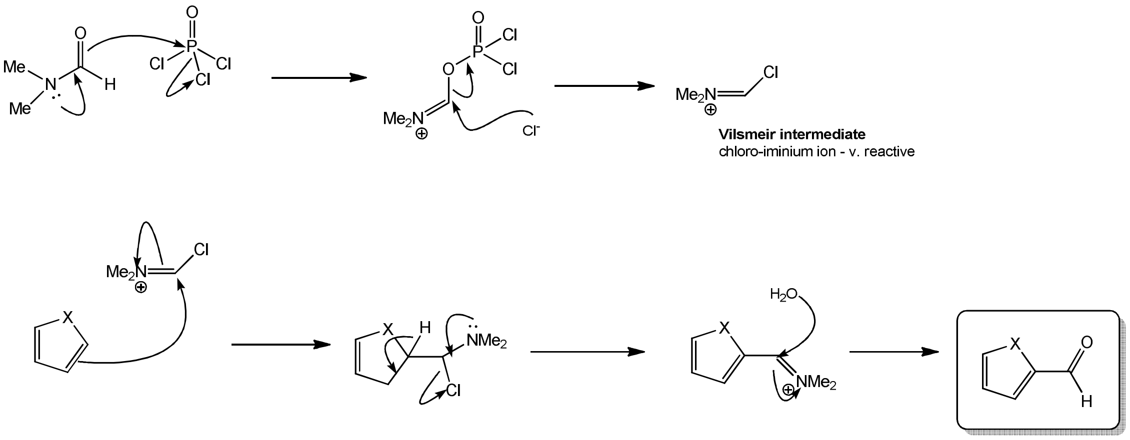


- Instead, the Vilsmeir reaction must be used

Vilsmeir reaction

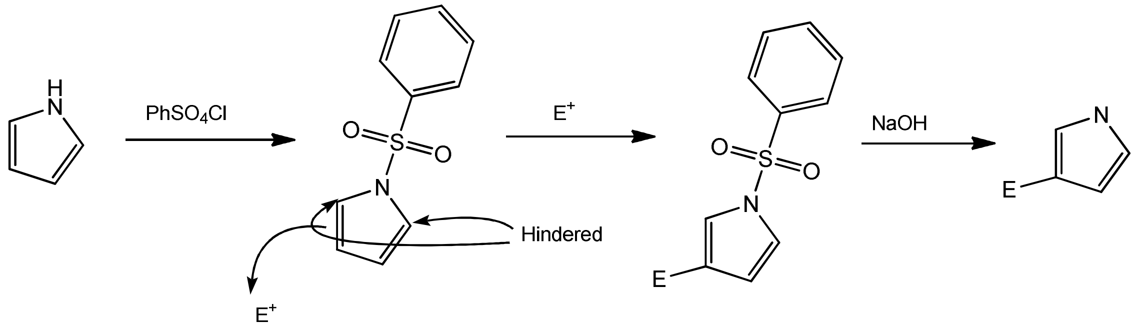


Mechanism:



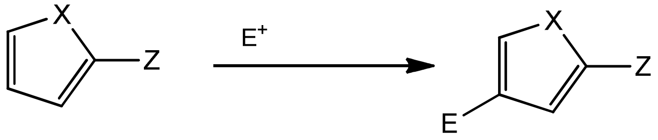
Selective 3-substitution

- Large bulky groups can be used to block the 2 position so only 3-substitution can occur

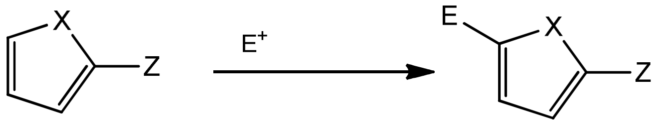


Substituted aromatics

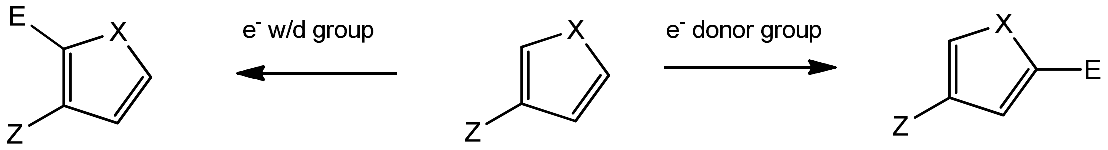
- Similar to benzene, already-present substituents on heteroaromatics direct the position of further substitution.
- For 2-substituted heteroaromatics:
  - Electron-withdrawing groups favour 4 position substitution



  - Electron-donating groups favour 5 position substitution

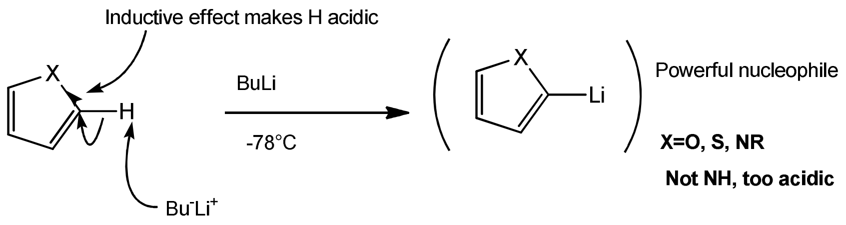


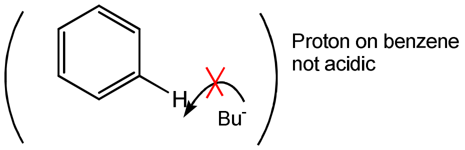
- For 3-substuted aromatics:
  - Electron donating groups favour 2 position
  - Electron withdrawing groups favour 5 position

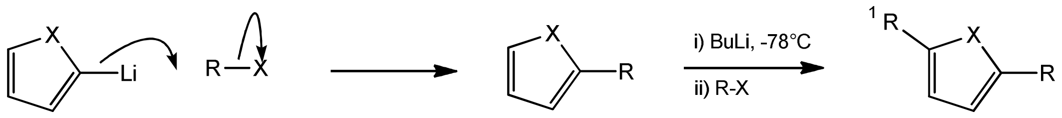


- These results can be predicted by considering resonance structures.

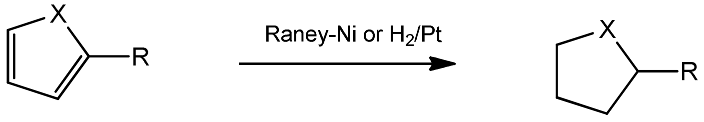
Metallation



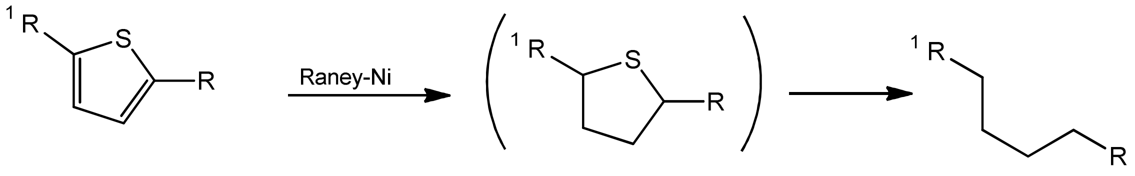




Reduction

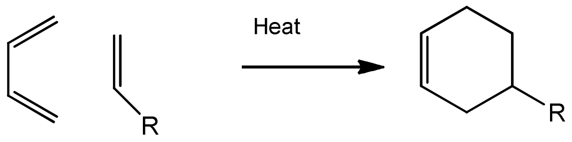


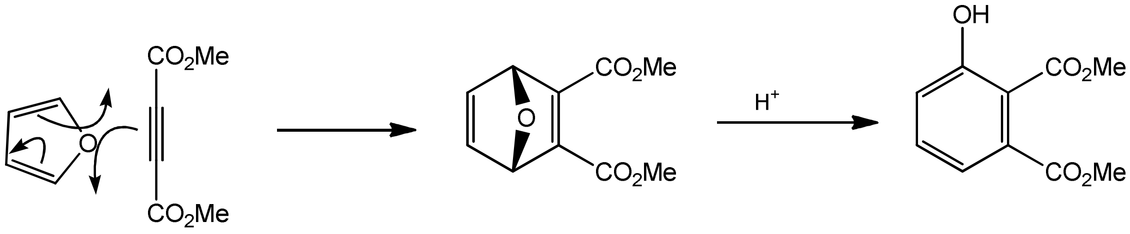
Thiophene



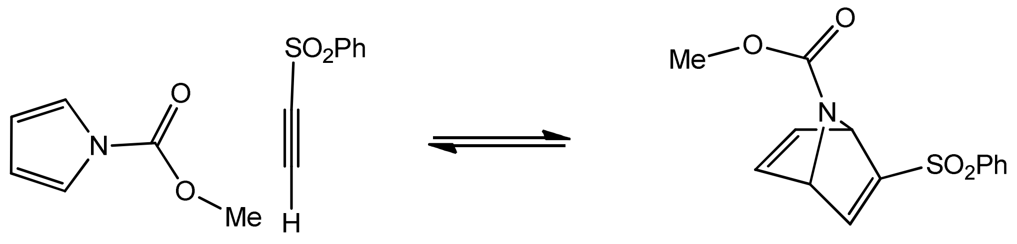
Cycloaddition

- Furan readily participates in cycloaddition reactions; for pyrrole and thiophene it is much harder to achieve.



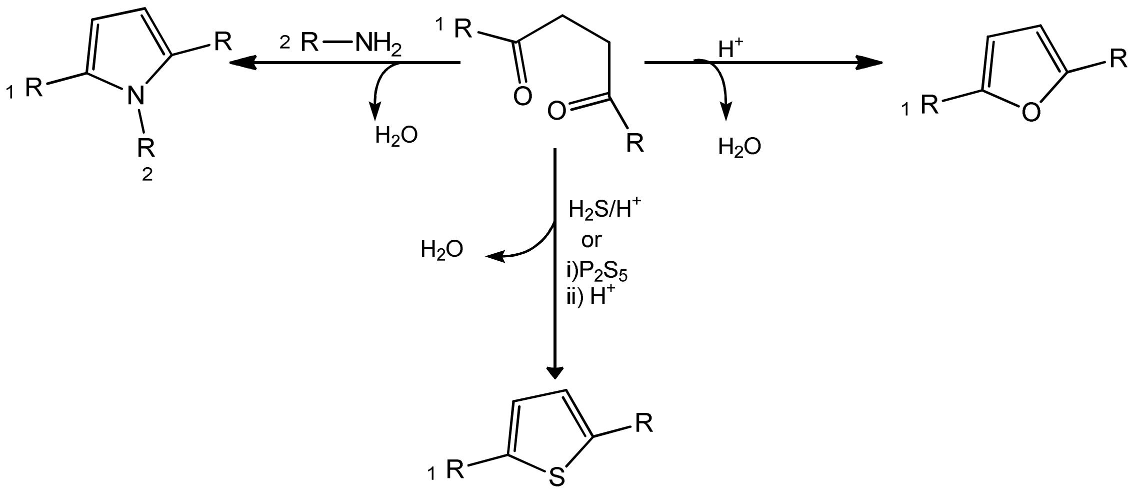


- Pyrrole:



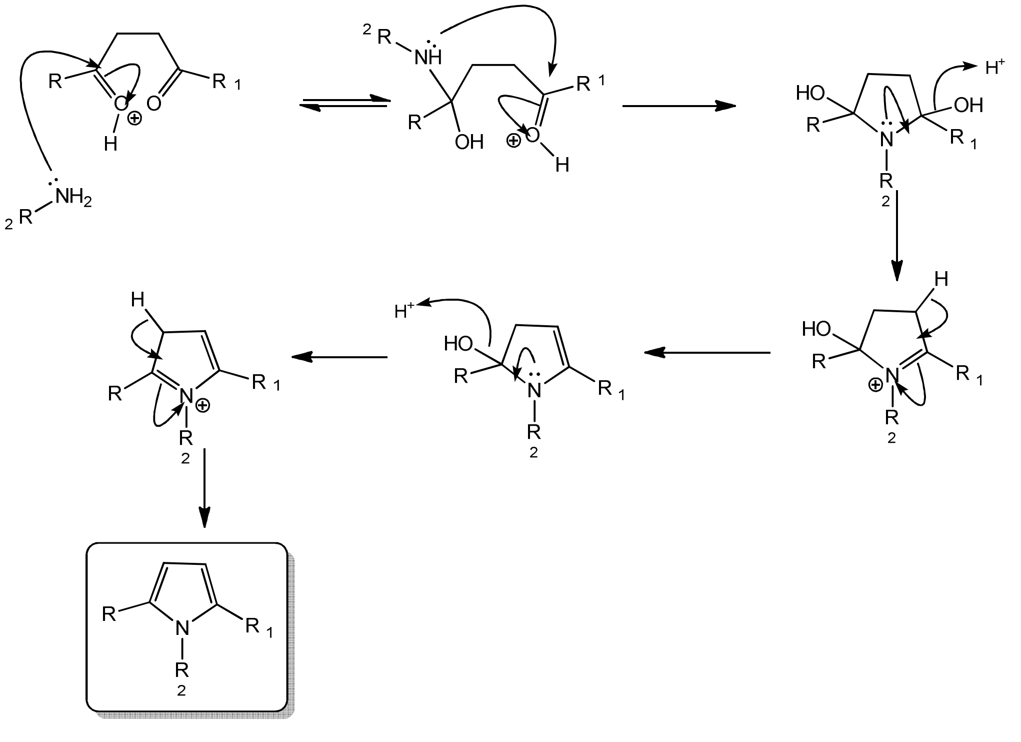
Synthesis of Heterocycles

Paal-Knorr Synthesis

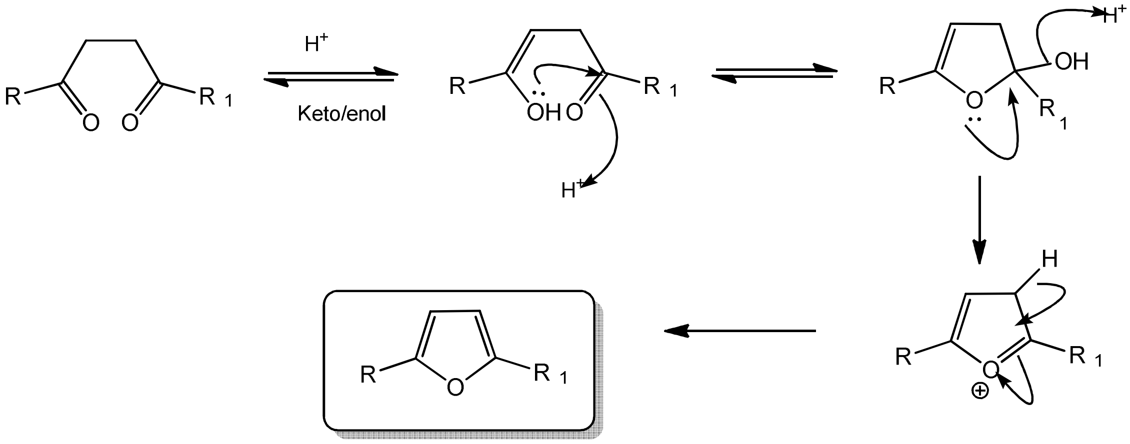


- Advantages: one common starting material
- Disadvantages: availability of starting material

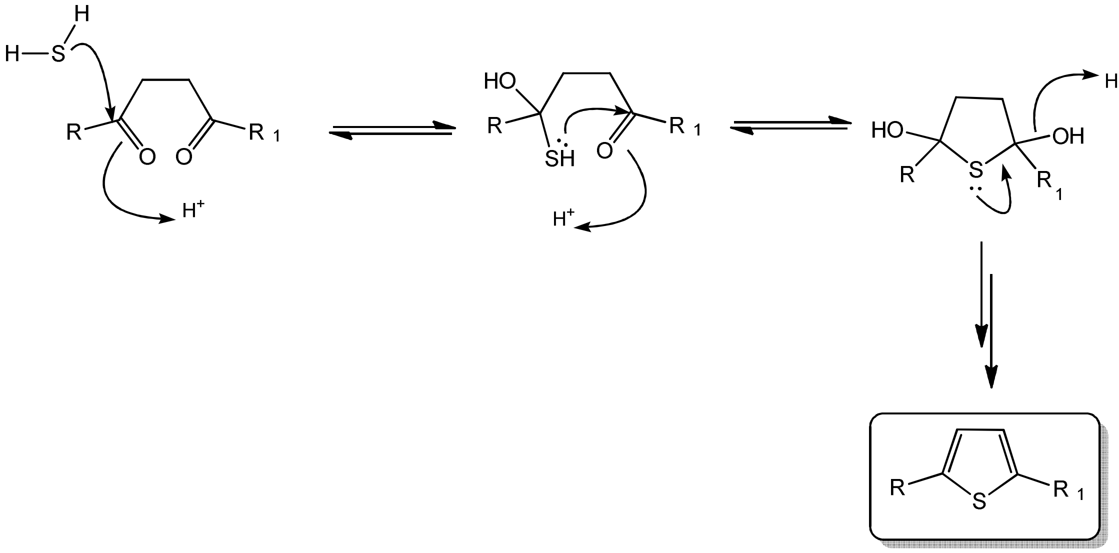
- Mechanism – Pyrrole:



- Mechanism – furan:

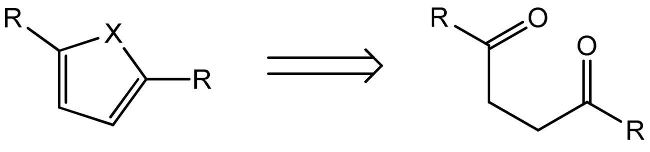


- Mechanism – thiophene:



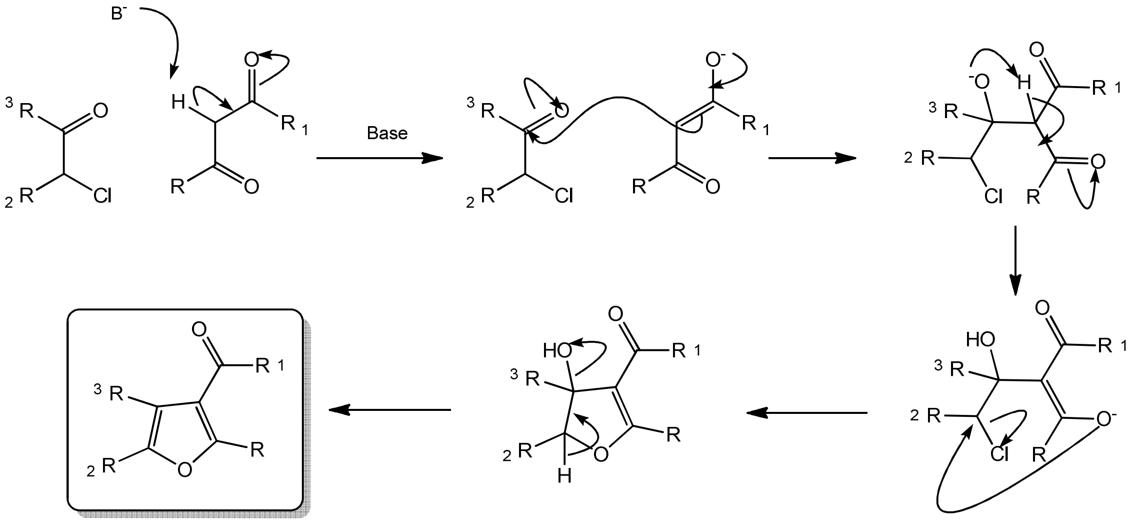
Paal-Knorr retrosynthesis

- Break bonds to go from product to starting material

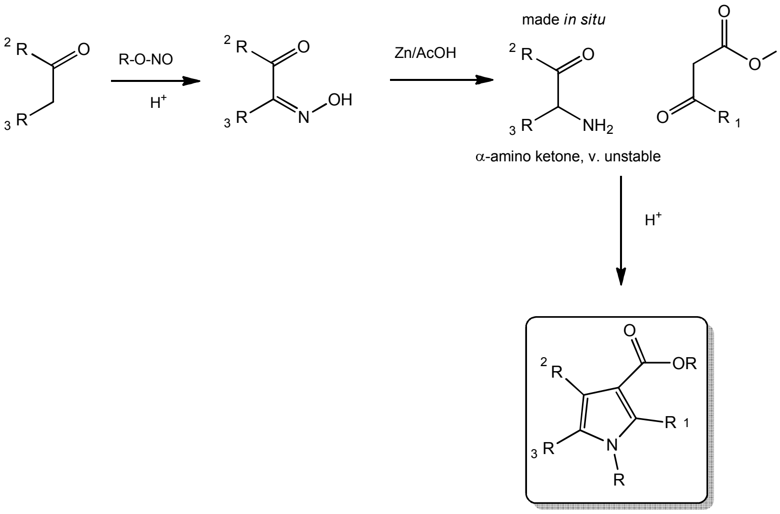


Furans – Feist-Benary synthesis

- Condensation of a dicarbonyl with an alpha-halo carbonyl



Pyrroles – Knorr synthesis

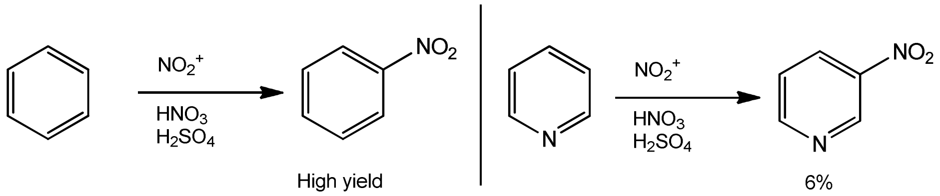


Pyridine and derivatives

- Pyridine is very stable and unreactive around the ring. It is soluble in water and organic solvents, and has an unpleasant odour.
- The lone pair on nitrogen is not involved in the aromaticity of the ring and so is available for bonding.

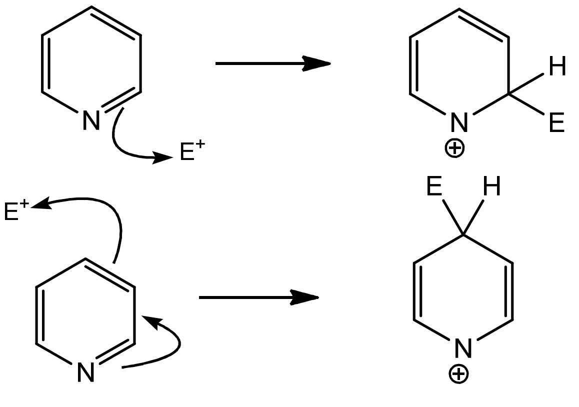
Reactions with electrophiles:

- Pyridine is very unreactive compared to benzene – “pi-deficient” heterocycle, c.f. “pi-excessive” heterocycles mentioned earlier.



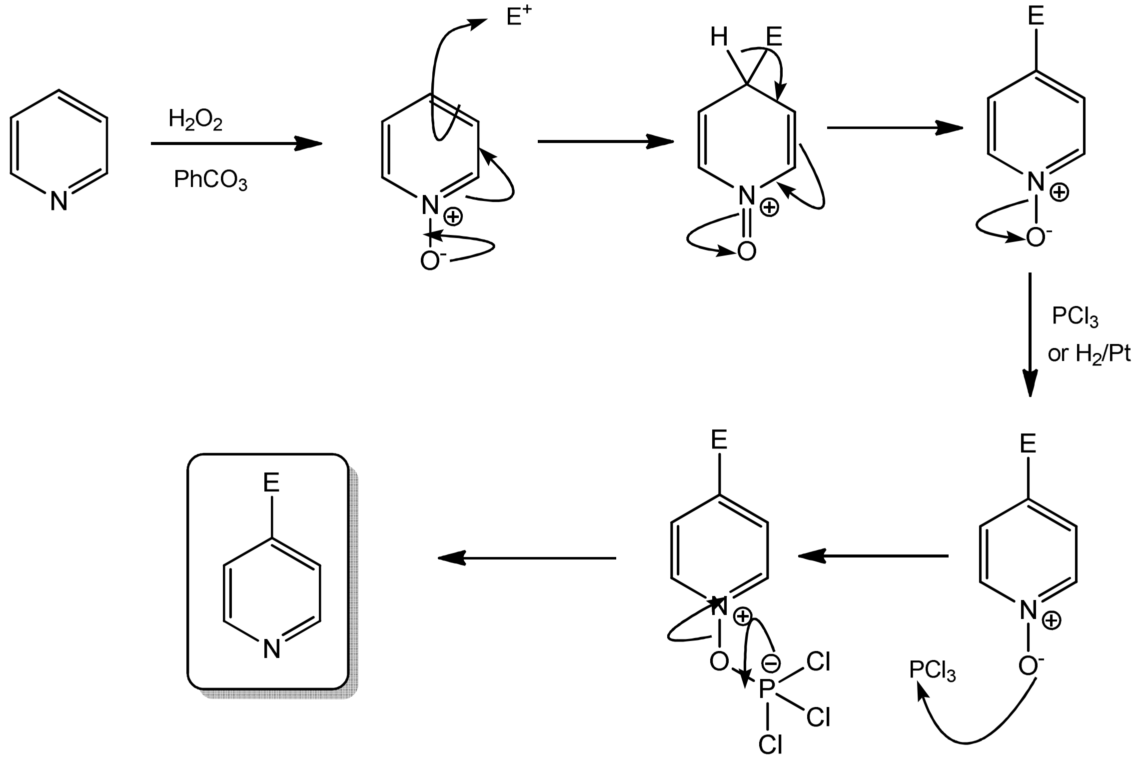
- There are 3 problems which have to be overcome to make pyridine react in high yield:

  1. Frequently the lone pair on nitrogen rather than the ring reacts with the electrophile, forming a salt.
  2. Due to electronegativity of nitrogen, the ring is electron deficient compared to benzene.
  3. Resonance structures show that positive charge must be delocalised onto a divalent nitrogen when substitution on the ring occurs – very high energy and highly unfavourable.



Indirect substitution methods

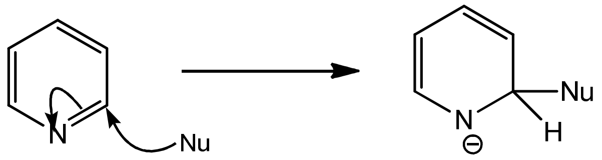
- Oxidising the nitrogen lone pair makes nitrogen more able to support the positive charge after substitution:



- This method has the same scope as do substitutions on benzene, e.g. bromination, Friedel-Crafts, nitration etc.

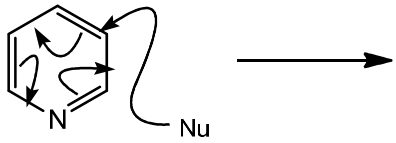
Nucleophilic substitutions

- 2 position:



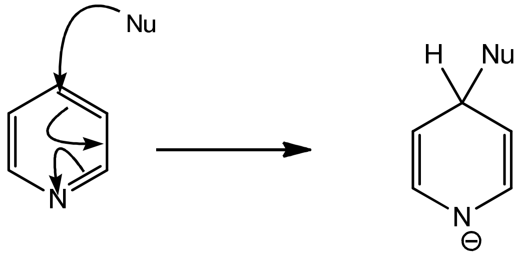
negative charge stabilised on N

- 3 position:



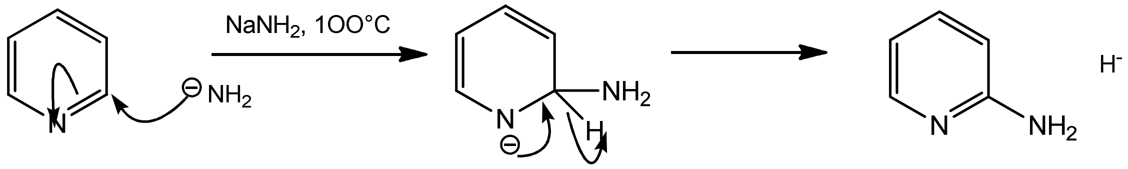
Not favourable
as negative charge doesn't reside on N

- 4 position:



favourable
as negative charge resides on N

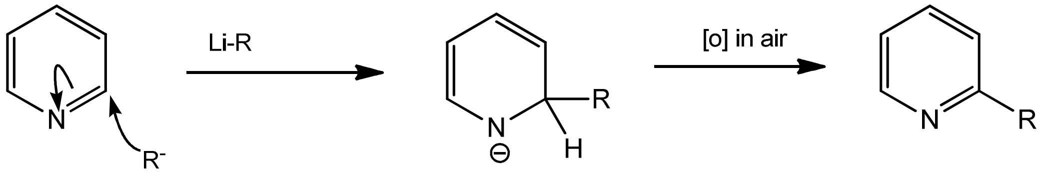
Chichibaben reaction



- The mechanism of this reaction is not known for certain, however needs some more explanation as hydride is not a good leaving group.

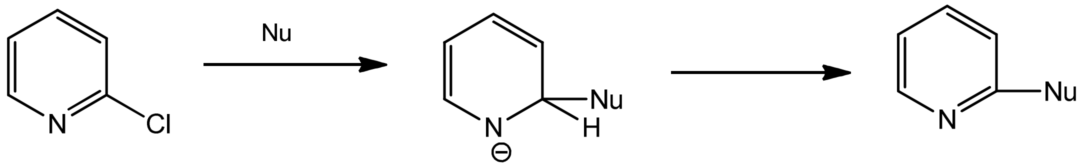
Use of Lithium

- Organolithium compounds can be used to do nucleophilic substitution with pyridine:

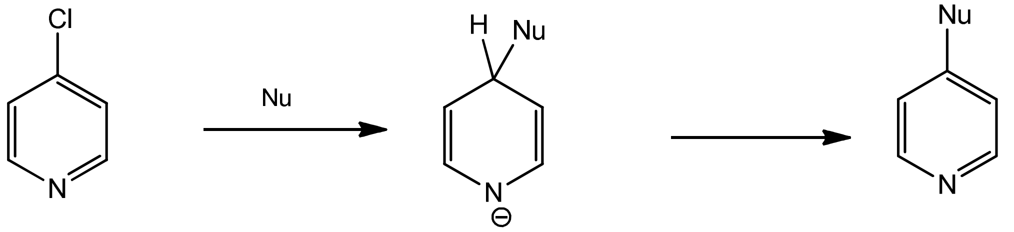


Leaving group in 2/4 positions

- 2 position



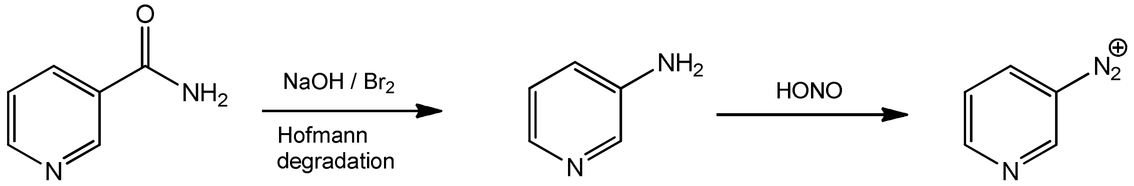
- 4 position



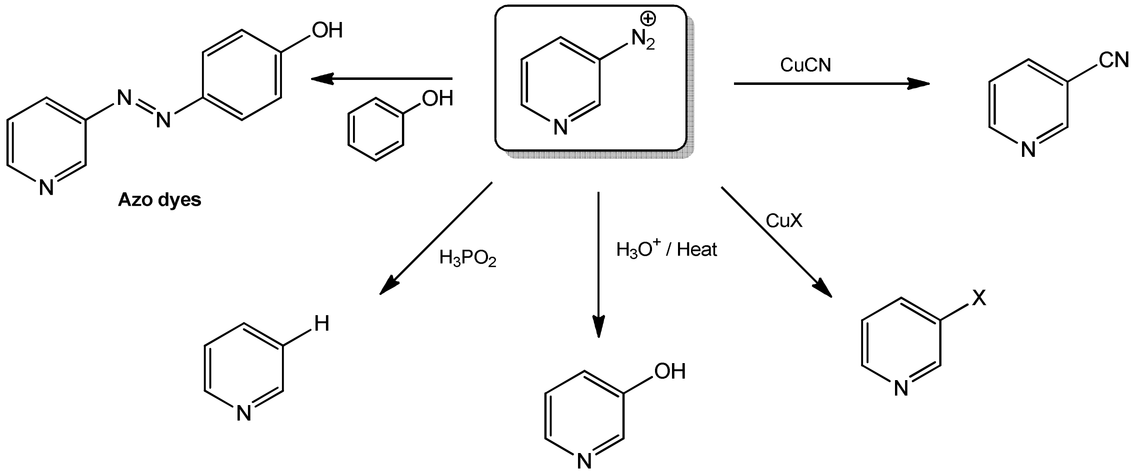
- The presence of the leaving group makes the substituted position much more electrophilic, and the addition/elimination mechanism of aromatic nucleophilic substitution occurs.
- The 3 position however cannot be substituted in this way, as charge cannot reside on N

Substitution of the 3 position

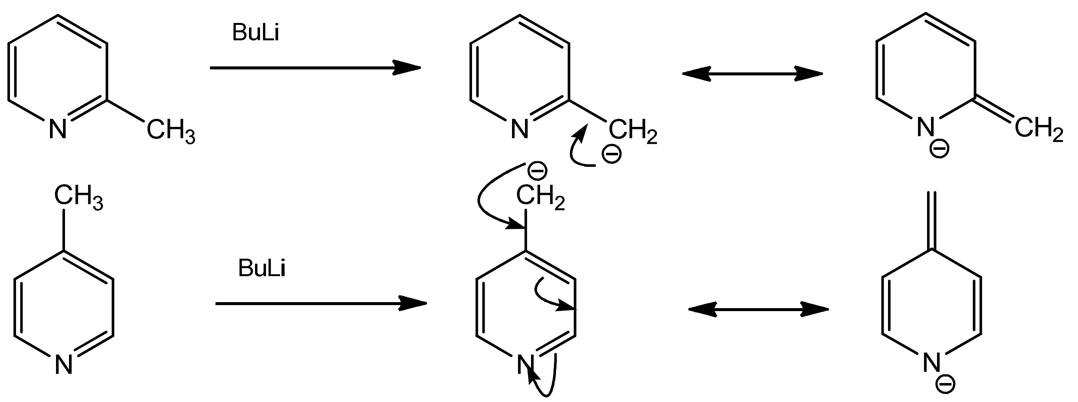
- Substitution can be done via diazonium salts formed from nicotinic acid or nicotinamide.



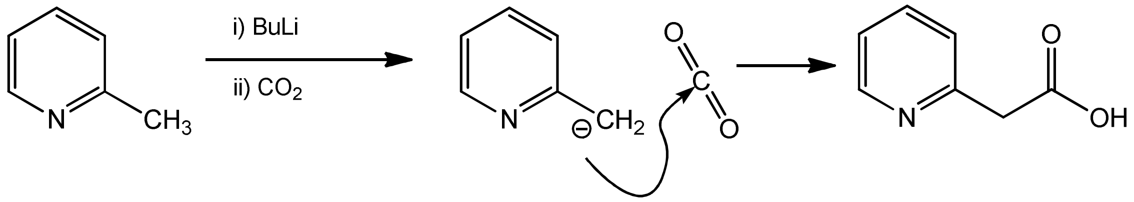
- Diazonium salts have a large variety of reactions leading to many substituents.



Alkyl pyridines

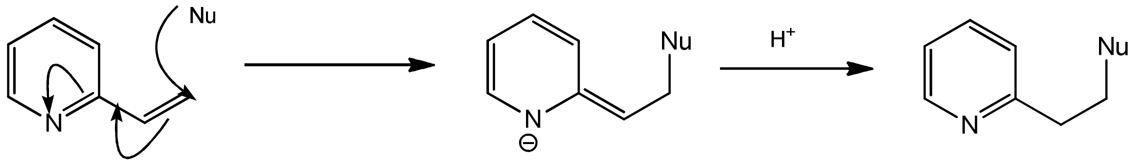


- This resonance stabilisation makes the intermediates stable and so further reactions can be done on the alkyl chain

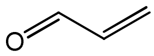


- The same reactions can occur at the 4 position, and any good electrophile can be used.

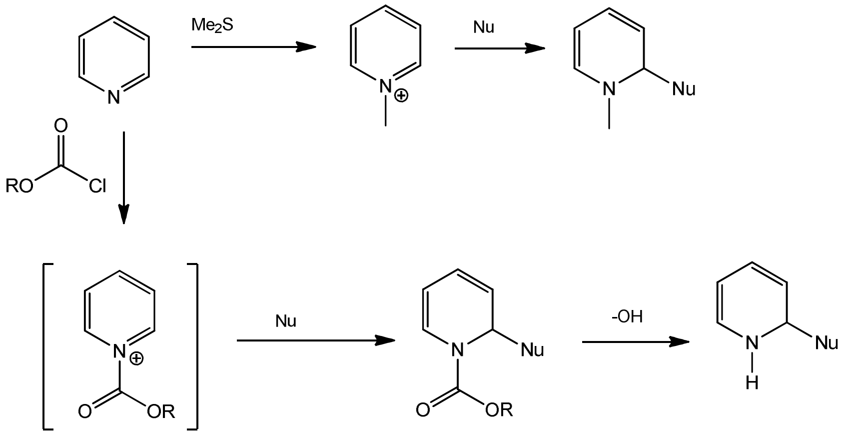
Vinyl Pyridines



c.f.

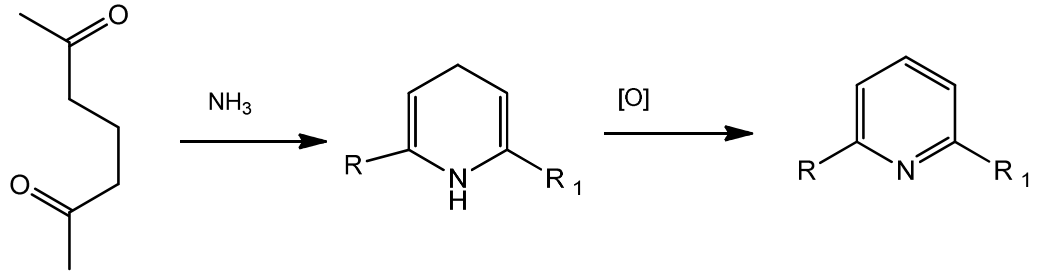


Pyridinium salts

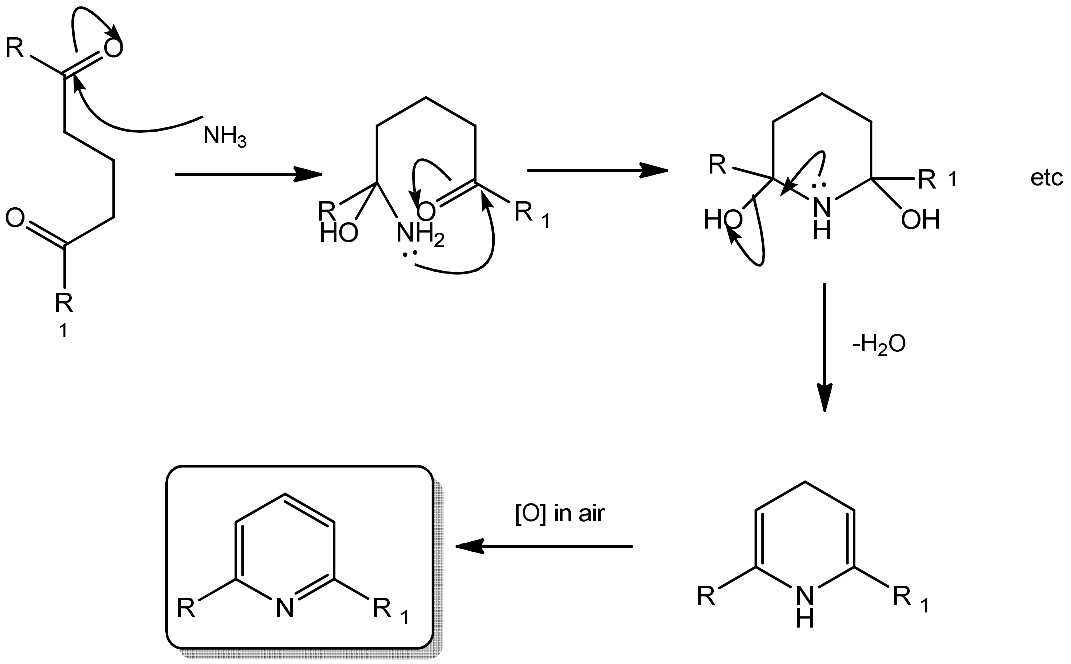


Synthesising pyridine rings

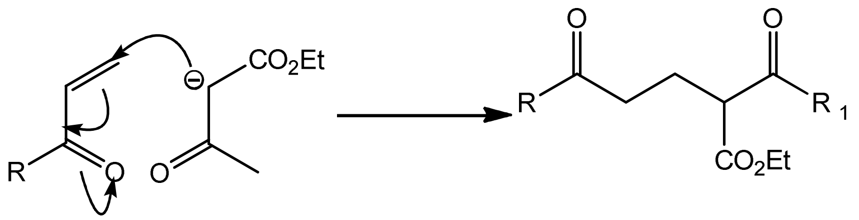
- From 1,5-dicarbonyls (comparable to Paal-Knorr)



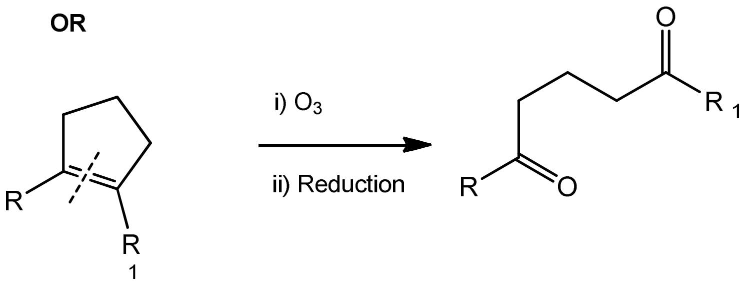
Mechanism:



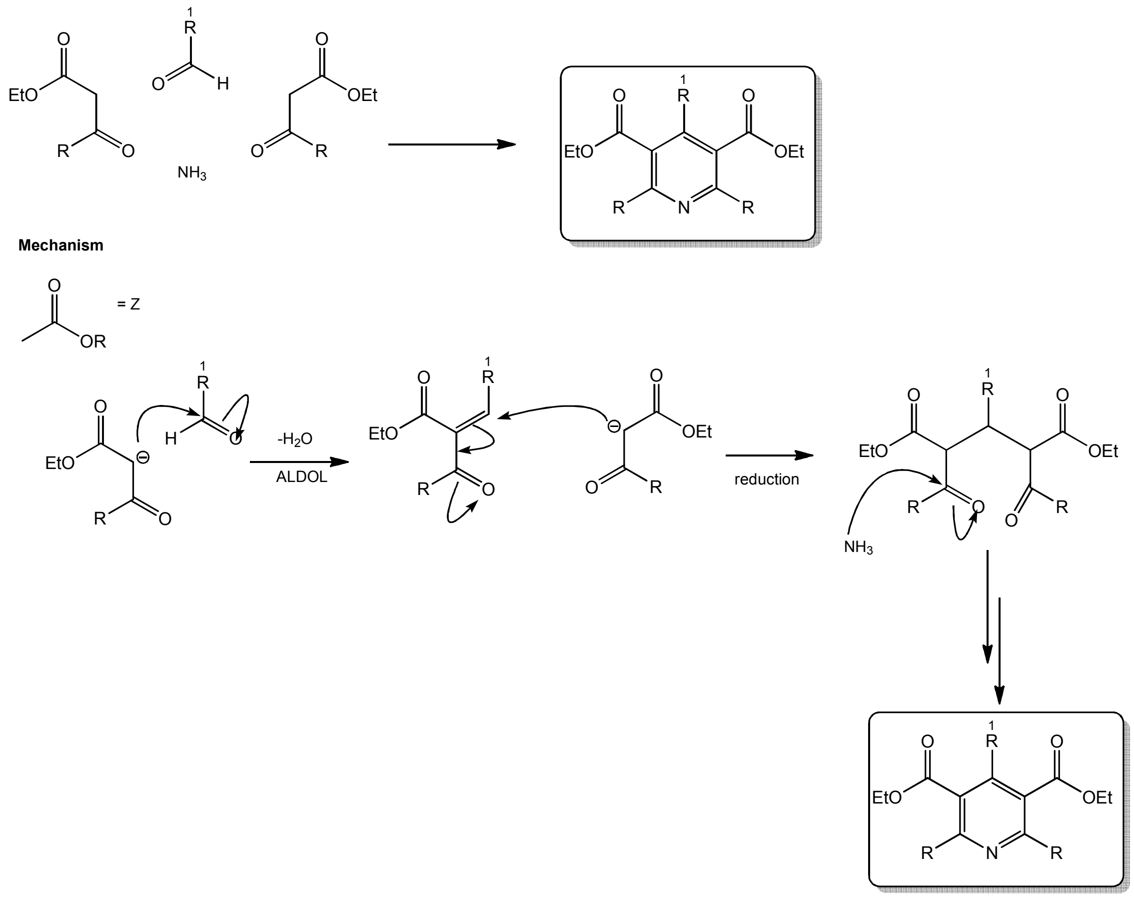
- 1,5 dicarbonyls may be produced in several ways:



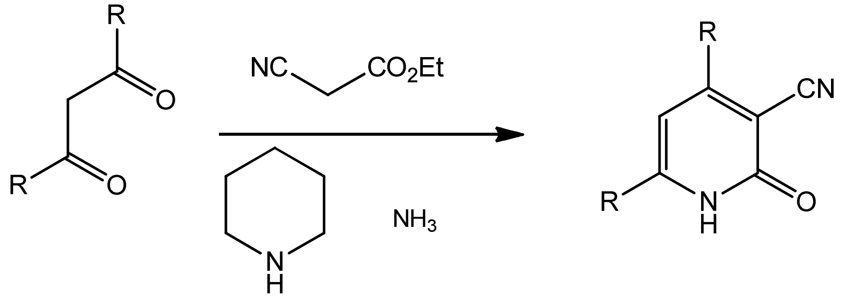
OR



Hantzch pyridine synthesis



Gaureschi-Thorpe Pyridone synthesis

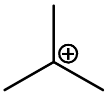


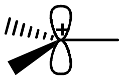
- The mechanism proceeds via an aldol reaction and then intramolecular attacks.

Carbocations and Rearrangements – Dr Craig Butts

Introduction

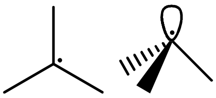
Carbocations





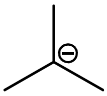
- Composed of 3 filled bonding orbitals and 1 vacant sp^2 hybridised orbital.
- Planar.
- Stabilised by electron donors, destabilised by electron withdrawing groups

Radicals



- 6 electrons in bonding orbitals
- 1 electron in a non-bonding orbital
- Sp^3 hybridiised – tetrahedral
- Stabilised by electron donors
- Destabilised by electron withdrawing groups

Carbanions



- 3 filled bonding orbitals, one filled non-bonding orbital
- Sp^3 hybridised orbitals, tetrahedral
- Stabilised by electron withdrawing groups
- Destabilised by electron donating groups.

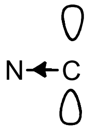
Substituent effects

- N is electron donating via its lone pair
- N is also electron withdrawing
- Overall effect is a combination of these effects.

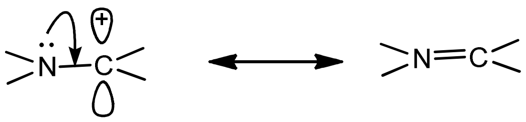
Inductive effect

- Depends on relative electronegativity

H	2.20	O	3.44	Br	2.96
C	2.55	F	3.98	I	2.66
N	3.04	Cl	3.16	Si	1.90

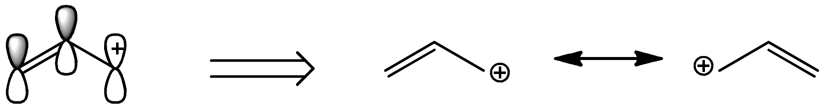


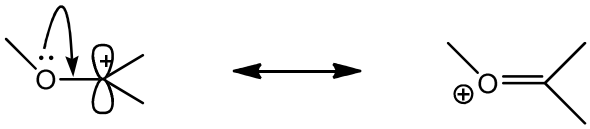
- Short range effect (1-2 bonds)
- N also has lone pair:

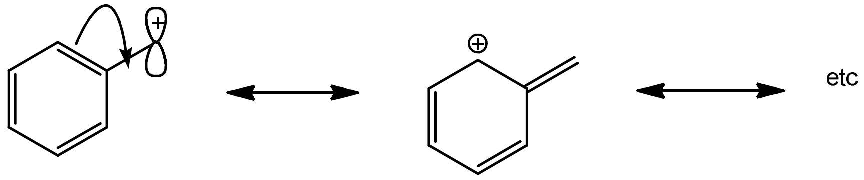


Resonance Stabilisation

- Pi-electron donation/withdrawl – mesomeric effects



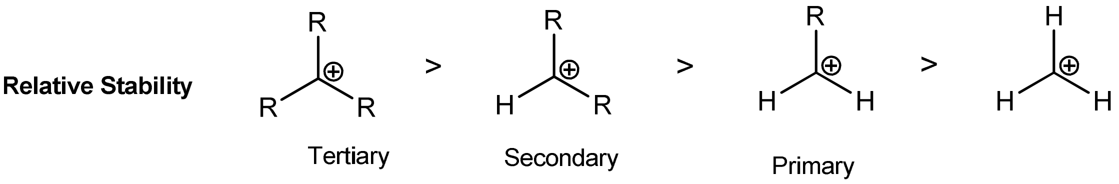




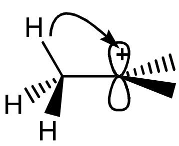
- Mesomeric effects effectively spreads/delocalises the +ve charge over one or more atoms
- Much stronger effect than inductive effect BUT the donor must be conjugated with the accepting orbital.
- Also depends on the ability of the atom to donate their lone pair, i.e. depends on electronegativity. So N > O > F

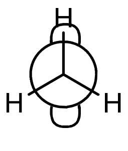
Hyperconjugation

- How do you explain stability of carbocations?



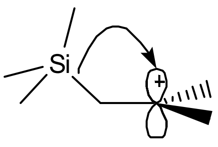
- Not inductive or mesomeric!
- Caused by hyperconjugation.
- This is the donation of a pair of bonding electrons into an unfilled or partially filled orbital.



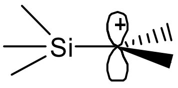


- Only occurs when the C-H bond aligns with the carbocation orbital.
- Weaker than pi-donation as the electrons are localised in a bond.
- The donor bond must be able to overlap with the acceptor orbital, so rigid structures that hold the donor out of alignment are less stable.
- Silicon is very good at stabilising β-carbocations.

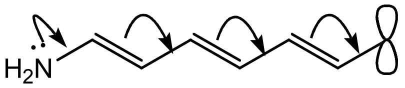
Beta-Si effect



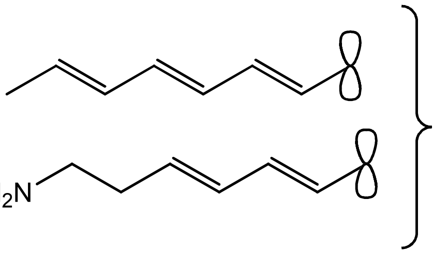
alpha-Si effect



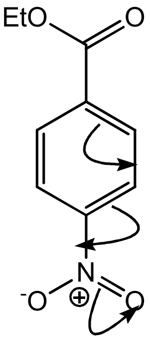
- β-silyl carbocation is very stable because Si is electropositive relative to C, therefore it is able to donate electrons into the bond, making it 'electron rich'.
- α-silyl carbocations is actually destabilised relative to β-Si effect.



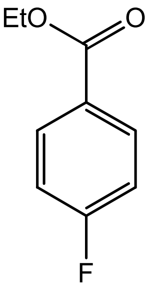
can pi-donate



Can't pi-donate

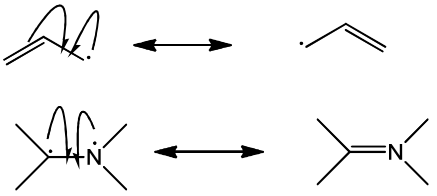


pi withdrawal

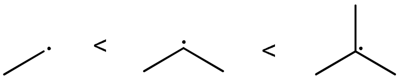


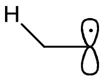
sigma-withdrawal not long range

Radicals



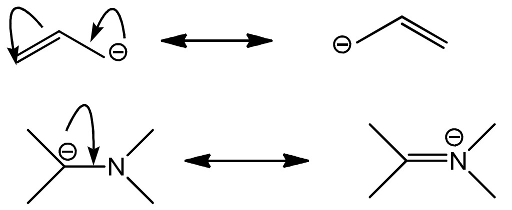
Radical Stability:



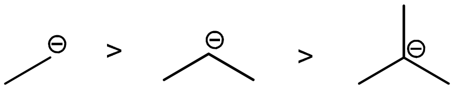


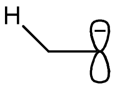
Stabilised by hyperconjugation

Carbanions



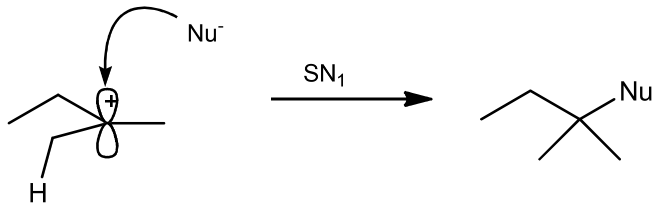
Carbanion Stability:

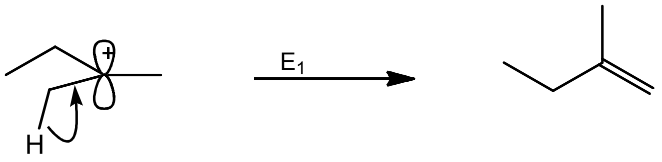


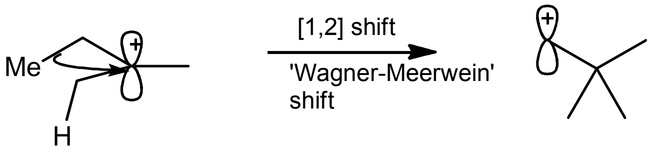


Destabilised by hyperconjugation

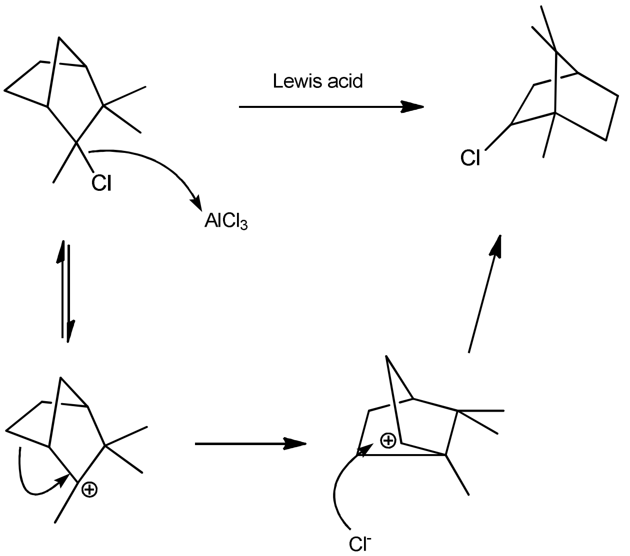
Reactions of carbocations



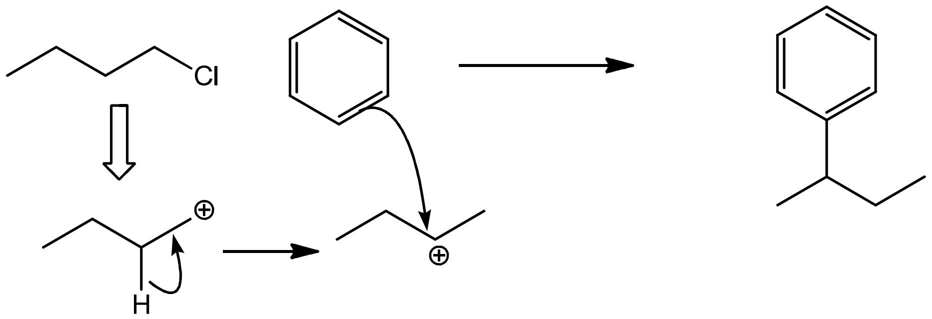




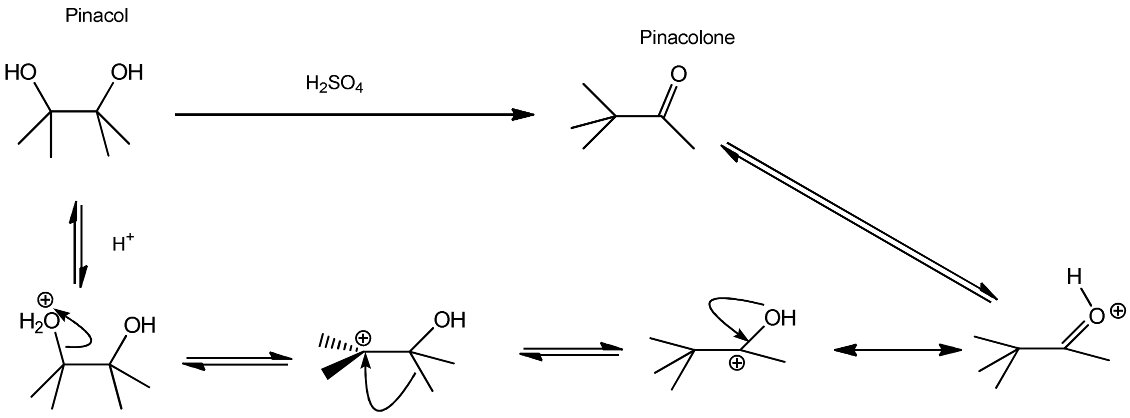
- It is possible for the electrons in a C-C bond to migrate into the unfilled carbocation orbital, forming a new C-C bond and a new carbocation where the old C-C bond was.
- For example, the rearrangement of camphene hydrochloride:



- This is the reason why Friedel-Crafts alkylation cannot reliably synthesise n-propyl benzene:



Pinacol rearrangement

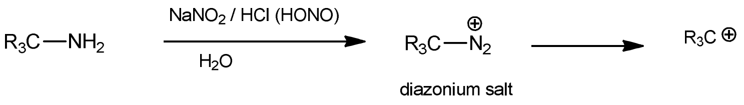


Driving Force - oxonium ion much more stable than carbocation

- Rearrangement reactions usually occurs by the formation of a more stable carbocation, so the mechanism must be one that takes a less stable C+ to a more stable C+

More Wagner-Meerwein shifts

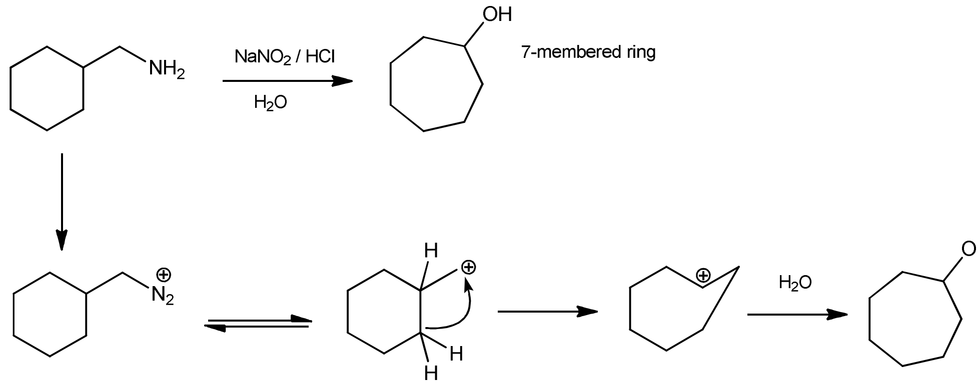
Demjanov reaction



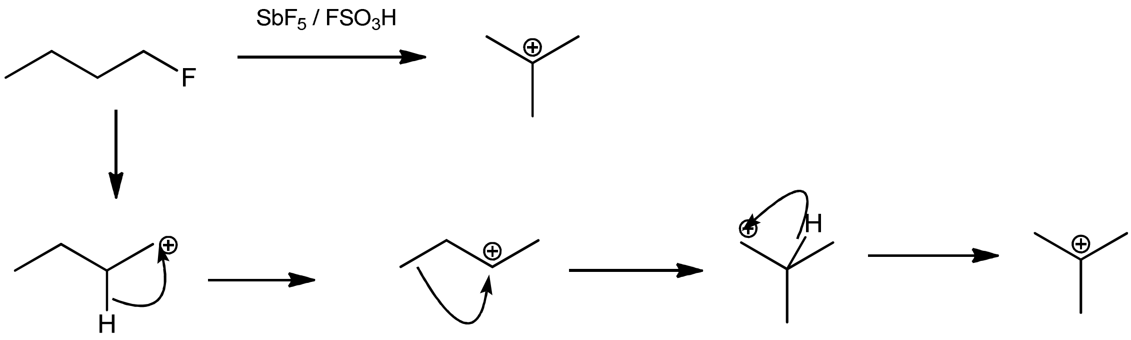
$$R_3C-NH_2 \xrightarrow[H_2O]{NaNO_2 / HCl\ (HONO)} R_3C-\overset{\oplus}{N_2} \longrightarrow R_3C^{\oplus}$$

diazonium salt

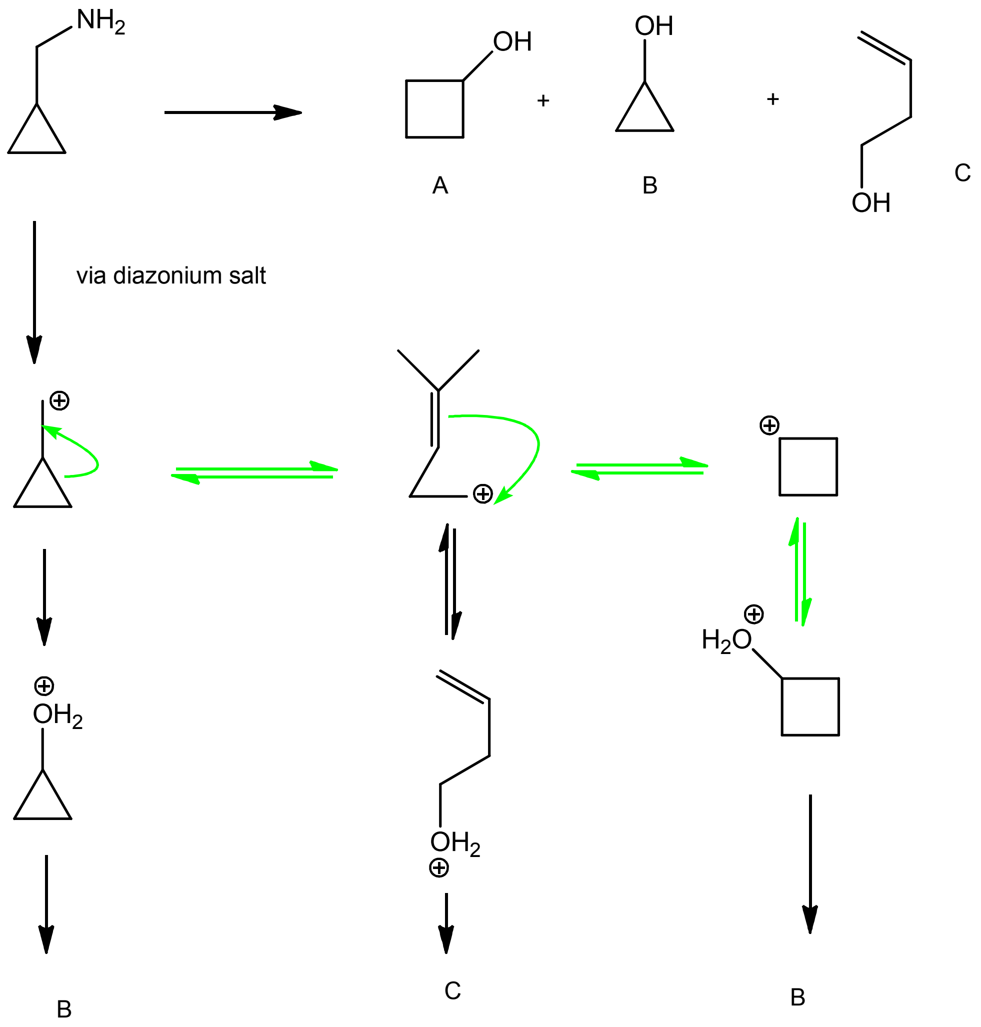
Example



- Another example:

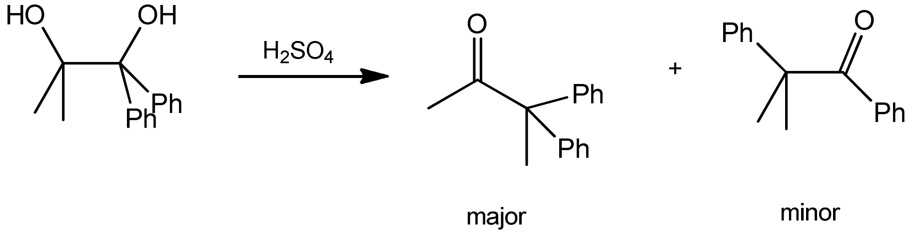


- Variations:

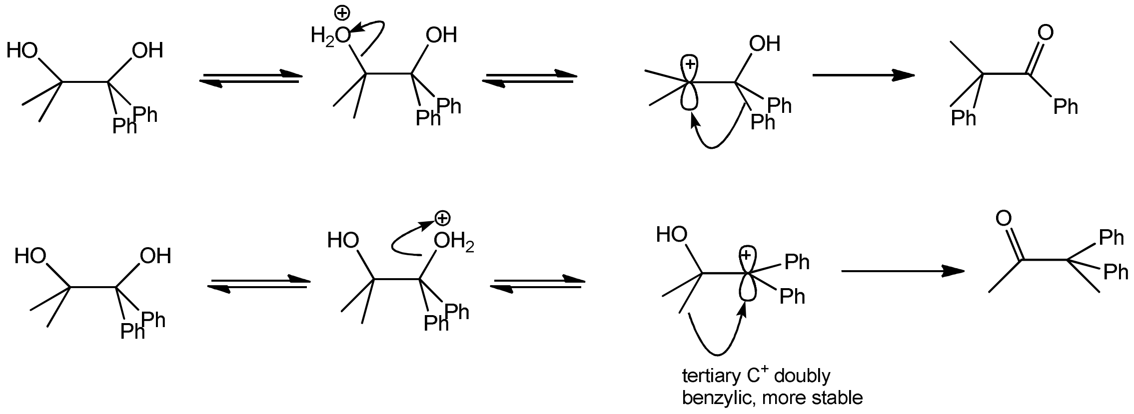


Asymmetric examples

- Example:



Mechanism:

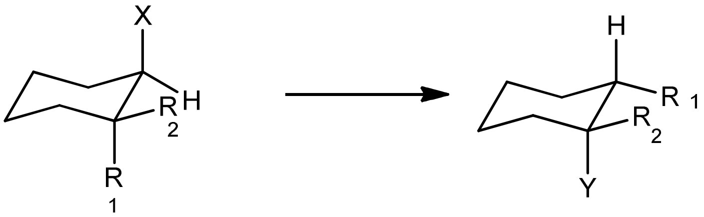


Control features

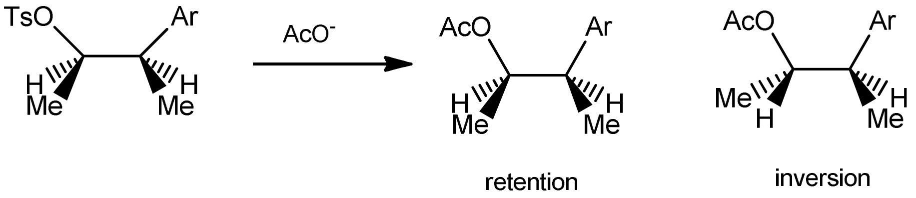
- Migratory aptitude:
  - In general, more electron donating groups migrate faster
  - i.e. $R_3C > R_2CH > RCH_2 > CH_3$

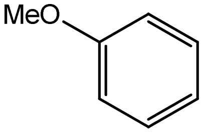
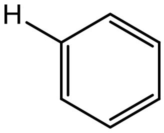
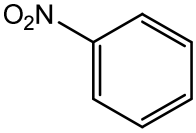
Stereoelectronic factors

- Generally, migrating group must be anti-periplanar to the C+ orbital, e.g.:



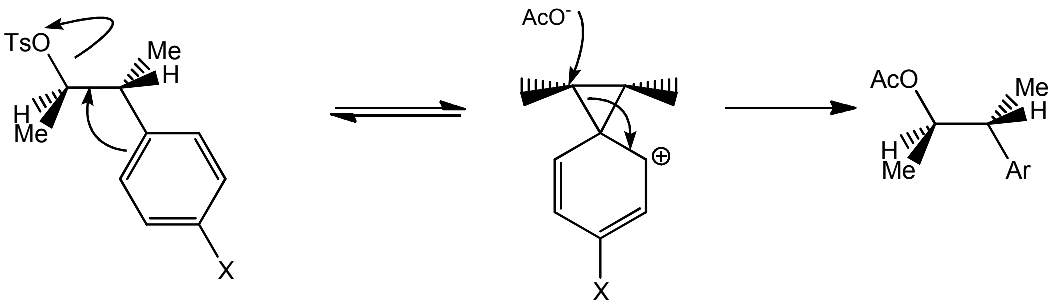
- R_1 will always migrate in preference to R_2 because it is anti-periplanar to the C-X bond.



Ar	Retention	Inversion	Rate
	100%	0%	Fast
	60%	40%	↓
	1%	99%	Slow

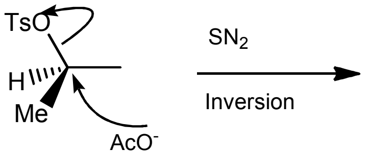
- Acyl group can act as a participating neighbour:

Retention



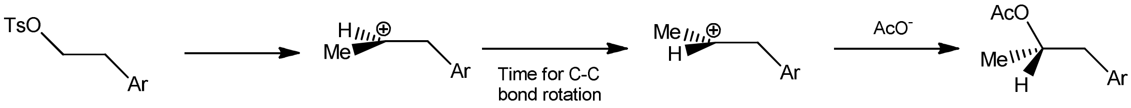
Stabilised more by resonance
if X is an e- donor.
Destabilised by e- withdrawing
groups

Inversion



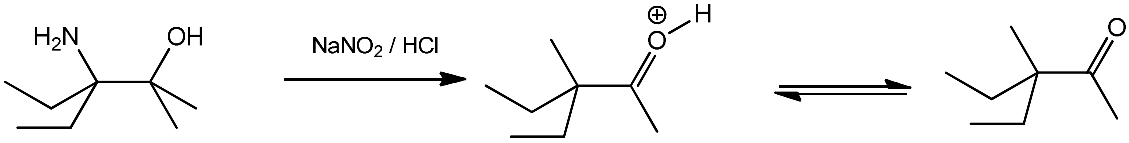
Timing / Synchronicity of rearrangements (concerted or stepwise)

- The reaction shown above is synchronous, i.e. Ar forms a bond as TsO leaves.
- Corresponding asynchronous (stepwise) reaction:

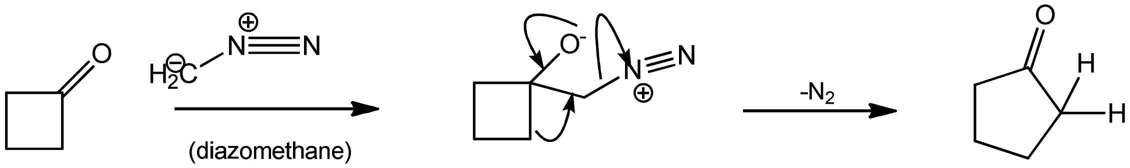


- Time for bond to rotate leads to inversion of configuration, so product is a racemate.

Compare pinacol rearrangement to Tiffeneau/Denjanov



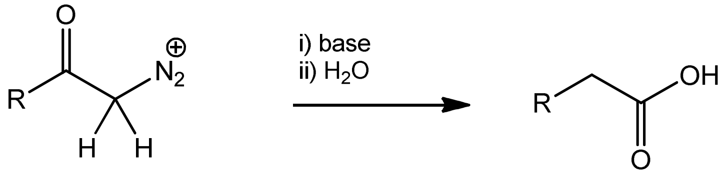
- Pinacol is non-selective for regiochemistry, but is synchronous, giving stereochemical control.
- A superior alternative:



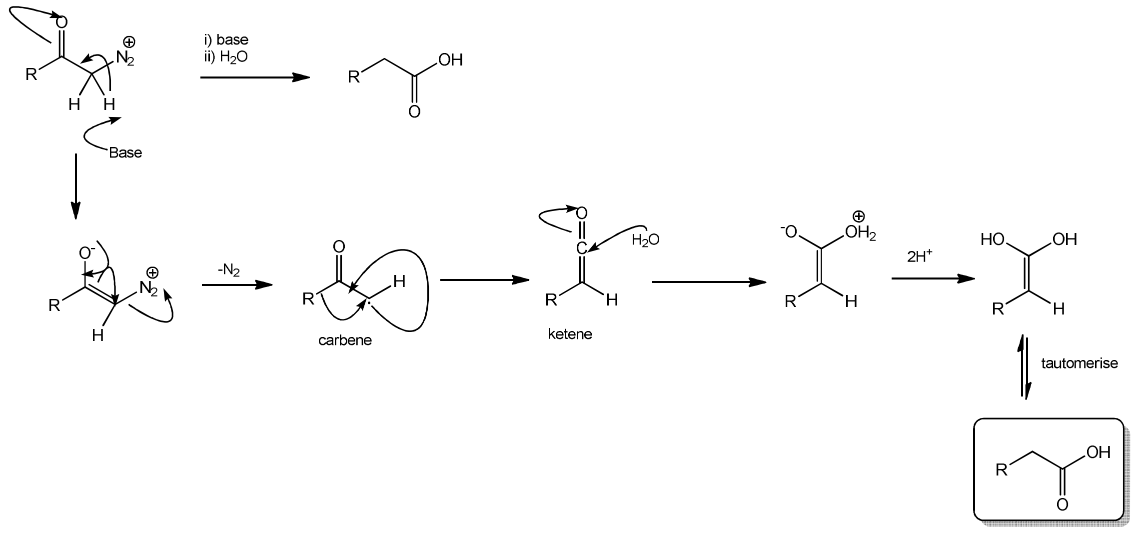
- This homologation of a ketone Is driven by ring strain in the 4-membered ring.

Common rearrangements – migrations to e^- deficient C

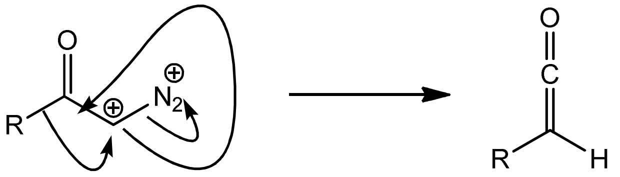
Wolff rearrangement



- There are 2 possibilities for the mechanism:
  - Stepwise:

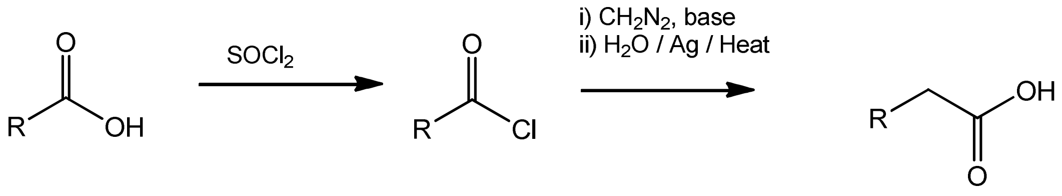


- Concerted:

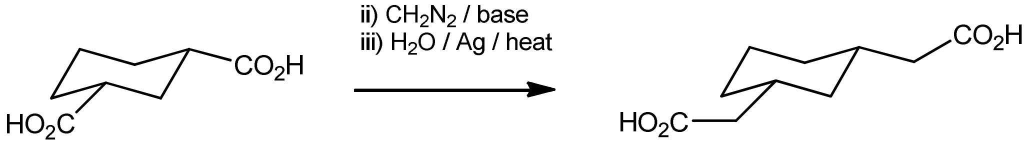


Arndt-Eistert homologation

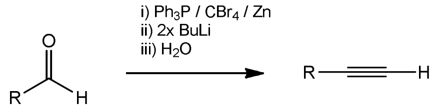
- Used to convert carboxylic acids into a higher carboxylic acid homologue, i.e. contains one additional carbon atom with <u>retention of stereochemistry</u>



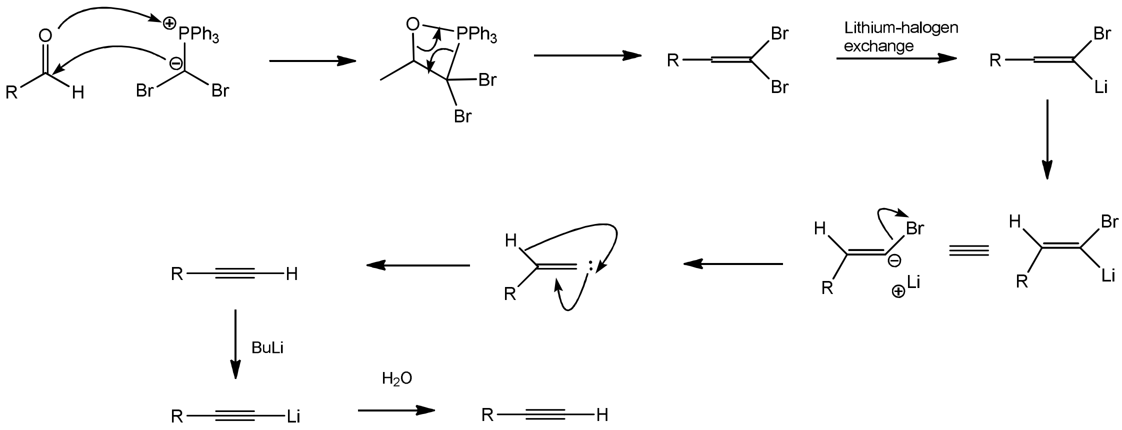
Example



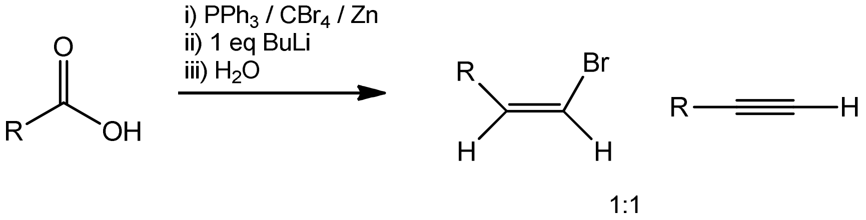
Corey-Fuchs reaction



Mechanism

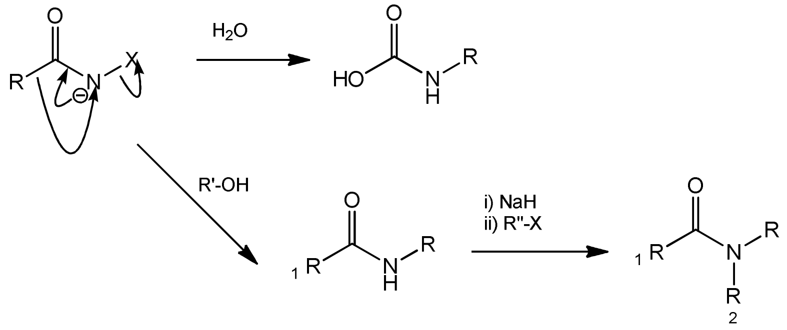


- Need 2 equivalents of BuLi to prevent mixture of products forming:

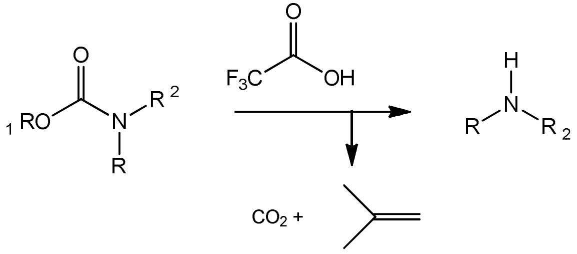


Migrations to e$^-$ deficient N

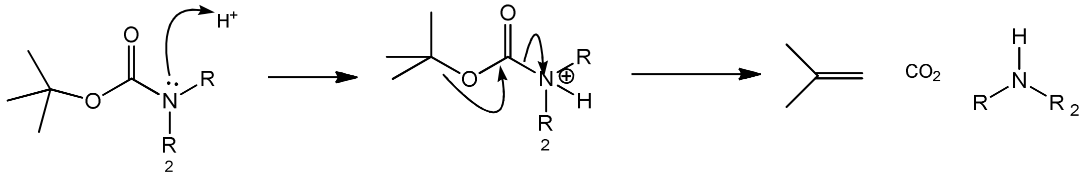
- One common mechanism applies to several named rearrangements:



If R_1 = tBu:

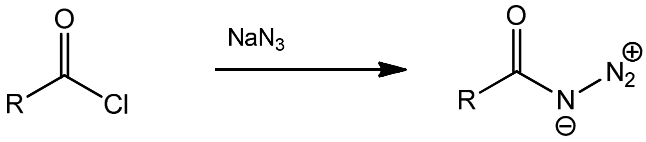


Mechanism:



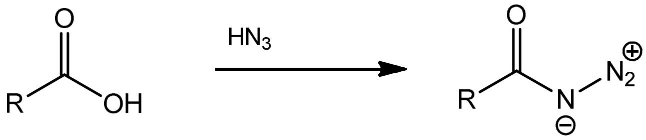
Curtius rearrangement

- X = N_2^+



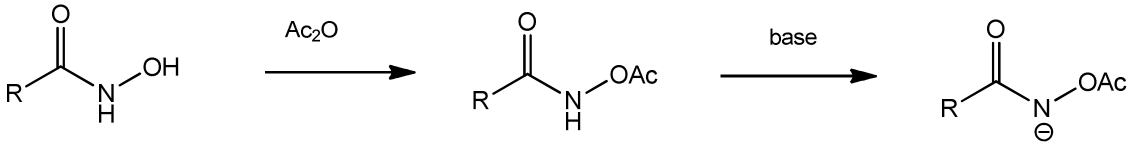
Schmidt rearrangement

- X = N_2^+

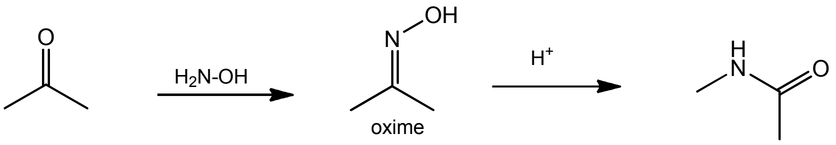


Lossen rearrangement

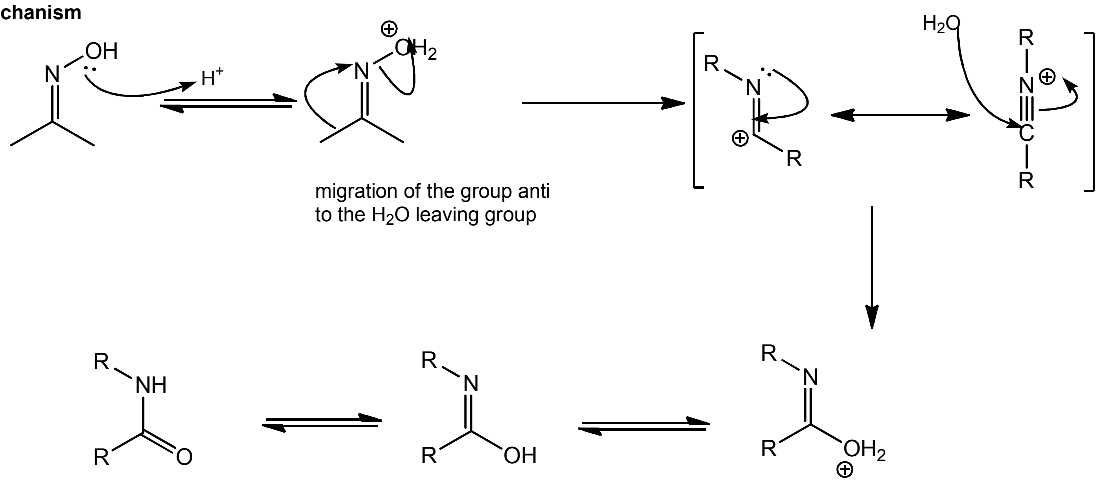
- X = OAc



Beckmann rearrangement

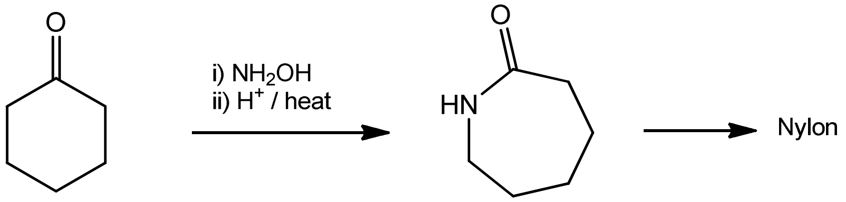


Mechanism



migration of the group anti to the H$_2$O leaving group

- One application of this is in the manufacture of nylon:



Migration to e^- deficient O

Baeyer-Villiger rearrangement